TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)
A REFERENCE MODEL IN PERCUTANEOUS CARDIOVASCULAR INTERVENTIONS
(VOLUME II)

RUI CAMPANTE TELES

A thesis submitted in fulfillment of the requirements for the Doctoral Degree in Medicine,
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TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI). A REFERENCE MODEL IN PERCUTANEOUS CARDIOVASCULAR INTERVENTIONS

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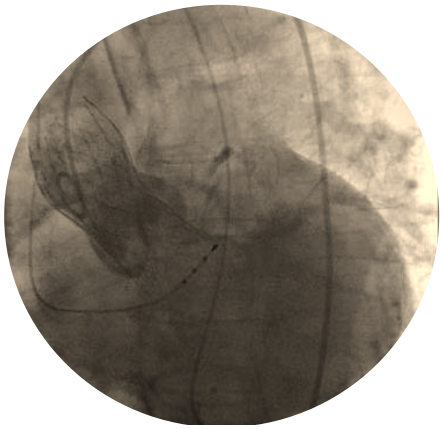


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PUBLICATIONS

11. Publications

Manuscript #1

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Case Reports in Cardiology
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Case Report

Surgical Bailout Therapy after Implantation of a Medtronic CoreValve Bioprosthesis

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Moderate-to-severe paraprosthesic leak causing hemodynamic deterioration and left ventricular remodeling can occur after transcatheter aortic valve implantation (TAVI). We present the case of a 75-year-old woman who underwent TAVI with a 26 mm CoreValve prosthesis complicated with an acute left ventricle dilatation due to a severe paravalvular leak. Patient was unresponsive to elective balloon post-dilatation, and therefore she was successfully treated with open-heart surgery to remove the malfunctioning CoreValve bioprosthesis and perform standard aortic valve replacement.

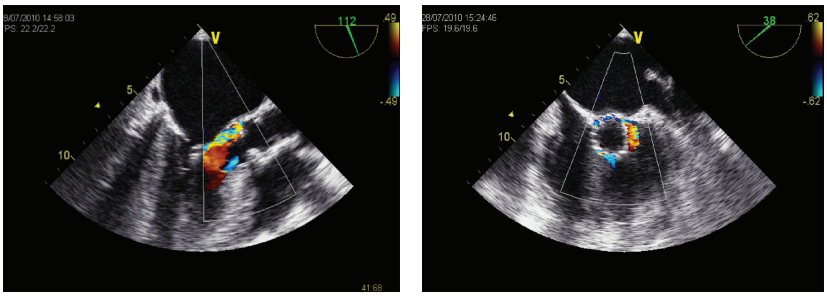
1. Introduction

Moderate-to-severe paraprosthesic leak causing hemodynamic deterioration and left ventricular remodeling can occur after transcatheter aortic valve implantation (TAVI) [1]. There are several percutaneous techniques already described to manage early implant failure [2]. Nevertheless, the surgical bailout therapy has not been described after TAVI using the Medtronic Core Valve bioprosthesis (Medtronic, Minneapolis, MN).

2. Case Report

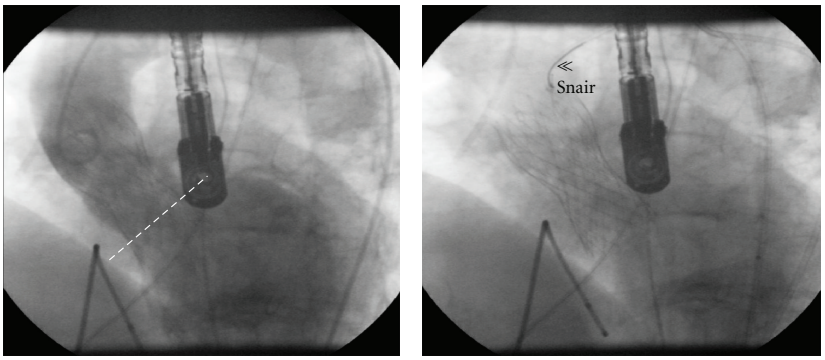
A 75-year-old female with worsening exertional dyspnea and angina for the previous 10 months was referred for cardiology evaluation. She had several cardiovascular risk factors (hypertension, diabetes, hiperlipidaemia and a morbid obesity with a BMI of 40), chronic lung disease, and renal chronic insufficiency with a calculated creatinine clearance of 38 mL/min. On the transthoracic echocardiogram, a severe stenosis aortic was diagnosed with an aortic orifice area of 0,7 cm^2 and a systolic left ventricle dysfunction with an ejection fraction of 38%. Coronary angiography showed coronary arteries without lesions and good femoral accesses. The intraoperative transesophageal echocardiogram confirmed a heavy calcified aortic valve with an annulus of 21 mm. The transfemoral implantation of the 26 mm CoreValve prosthesis was complicated with acute moderate aortic leak (Figure 1) and moderate mitral regurgitation associated to a deep prosthesis implantation. Repositioning the prosthesis with a snair was performed to reduce the severity of mitral regurgitation with slight improvement (Figure 2). The postoperative course was uneventful, and the patient was discharged eight days later.

One month later the patient developed a progressive dyspnea and was readmitted with acute pulmonary edema. Transthoracic echocardiography evidenced a moderate-to-severe aortic paraprostesic leak (which occupies a quarter of the sewing ring, with a steep jet deceleration slope of 6,3 m/s^2 and a holodiastolic flow reversal in the descending thoracic aorta) [3] associated with a severe left ventricle dilatation and dysfunction (left ventricle diastolic dimensions in paraesternal long axis increased from 53 to 70 mm by M-mode tracing preprocedure and postprocedure, respectively). She performed angiotomography which suggests an adequate position prosthesis although underexpansion (Figure 3). For that reason a postdilatation with a Nucleus NuMED balloon



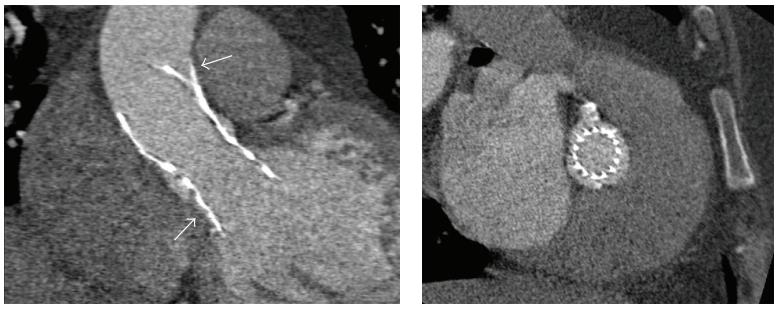
(a) (b)

Figure 1: Transesophageal echocardiography images (intercomissural long axis view (a), short axis view (b)) after transcatheter valve implantation demonstrated a moderate paravalvular aortic regurgitation.



(a) (b)

Figure 2: Fluoroscopy and angiographic images showing a deep implantation of the 26 mm CoreValve prosthesis (a) and its repositioning with a snair (b).

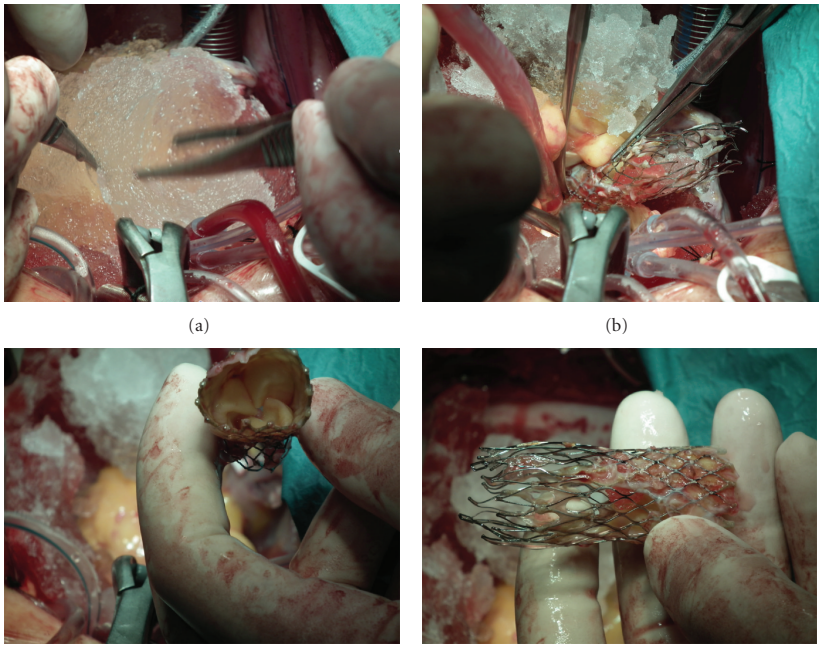


(a) (b)

Figure 3: Angiotomography view showing a 26 mm CoreValve prosthesis in long-axis (a) and short-axis view (b) in an adequate position although underexpansion (white arrows).

22 mm was done without clear clinical or echocardiography improvement. The patient had a decompensated heart failure refractory to medical treatment and, despite the high-operative risk, we decided to perform an aortic valve replacement via standard median sternotomy. The 26 mm CoreValve prosthesis was removed and replacement of the aortic valve using 21 mm Mitroflow was done (Figure 4).

The postoperative period was complicated by worsened renal failure requiring dialysis and paroxysmal atrial fibrillation but the patient was discharged without dyspnea two months later. Transthoracic echocardiography at discharged showed a normal prosthetic valve function and a slight improvement on left ventricle dimensions and function, although not completely normal.



(a) (b) (c) (d)

Figure 4: Intraoperative images. Ice was applied (a) to reduce the size of the prosthesis in order to remove it completely (b), (c) and (d).

3. Discussion

After TAVI, a significant paravalvular leak can occur for several reasons: undersized prosthesis, malposition of the device (very deep or high implantation), prosthesis underexpansion, the presence of heavily calcified stenotic aortic valve or a bicuspid valve [4]. With the currently available devices, it is very difficult to fully reposition the bioprosthesis after initial deployment. Several bailout transcatheter techniques have been described to manage suboptimal prosthesis deployment: a postdilatation, snair repositioning, or valve-in-valve technique with implantation of a second device inside the first one [2, 4–7]. In the present case, there was more than one possible mechanism for the development of this severe paravalvular leak: the first explanation was deep valve implantation, but this was resolved intraprocedure by repositioning the prosthesis with a snair and documented by angio-CT. A second possible mechanism was underexpansion, as angiotomography scan evidenced, but a postdilatation did not improve clinical or echocardiography status. This was probably related to insufficient oversizing of the transcatheter valve with respect to the patient's aortic annulus and the severity and asymmetric distribution of valve calcification. The implantation of a second valve might be associated with an increase of the radial force [6], although "valve-in-valve" procedure, eventually with a balloon expandable, is mainly indicated to acutely manage device malposition.

Despite the absence of such case reports, our heart team decided to undergo an open-heart surgery, to remove the malfunctioning CoreValve bioprosthesis and perform standard aortic valve replacement. Cardiac surgery was successful, although complicated by acute renal failure requiring dialysis. We can also discuss percutaneous valve-in-valve procedure as an alternative strategy.

Presently there is scarce data on paravalvular leak predictors. As other authors have already suggested [4, 6], there is a need to better predict and assess ominous prognosis caused by paravalvular leaks after TAVI and to determine the role of different strategies for the treatment of each mechanism.

4. Conclusion

The surgical bailout therapy by implanting a second aortic bioprosthesis through conventional surgery after removing the first malfunctioning CoreValve bioprosthesis in a high-risk patient is possible, with good results and without major complications. In the future, the development of percutaneous bioprosthesis that reduce paravalvular leaks and allow valve retrieval and reposition after suboptimal deployment could avoid the need of surgical bailout therapy.

Conflict of Interests

The authors have no conflict of interests to declare.

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Manuscript #2

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Rev Esp Cardiol. 2012;65(4):350–355

Artículo original

Implante percutáneo de válvula aórtica: seguridad y eficacia del tratamiento del homoinjerto aórtico disfuncionante

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Palabras clave:
Estenosis valvular aórtica
Prótesis valvular
Homoinjerto aórtico

RESUMEN

Introducción y objetivos: El implante percutáneo de válvula aórtica, como tratamiento de la estenosis aórtica severa con elevado riesgo quirúrgico, está actualmente bien establecido. Pretendemos comunicar la experiencia en términos de seguridad y eficacia del implante percutáneo de válvula aórtica, sobre una serie de homoinjertos aórticos disfuncionantes.
Métodos: Presentamos la experiencia inicial acumulada en cuatro centros, sobre 5 pacientes portadores de un homoinjerto aórtico degenerado, todos con insuficiencia aórtica severa y rechazados para cirugía por un equipo multidisciplinario, sometidos a implante de una prótesis aórtica CoreValve®.
Resultados: Se incluyó a 3 varones y 2 mujeres, con una media de edad de 70 ± 3,5 años, severamente sintomáticos en clase funcional III o IV de la *New York Heart Association.* El procedimiento se llevó a cabo por vía femoral en todos los casos, y mediante sedación en 4 pacientes. El implante se realizó con éxito en todos los casos. Ningún paciente presentó complicaciones mayores durante el procedimiento o el ingreso, y en todos ellos se resolvió la deficiencia valvular. No hubo mortalidad hospitalaria ni durante el seguimiento. Todos los pacientes presentaron mejoría clínica en el seguimiento, con una disminución de al menos 2 grados en la escala de la *New York Heart Association.*
Conclusiones: En nuestra experiencia, el tratamiento de homoinjerto disfuncionante e insuficiencia aórtica se ha demostrado seguro y eficaz. El reto actual es trasladar los buenos resultados del implante percutáneo de válvula aórtica en la estenosis aórtica severa degenerativa del anciano a pacientes con alto riesgo quirúrgico y otras afecciones de la aorta. Es posible que en el futuro el implante percutáneo de válvula aórtica abarque cada vez mayor número de enfermedades aórticas y pacientes de menor riesgo quirúrgico.
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Transcatheter Aortic Valve Implantation: Safety and Effectiveness of the Treatment of Degenerated Aortic Homograft

Keywords:
Aortic valve stenosis
Valvular prosthesis
Aortic homograft

ABSTRACT

Introduction and objectives: Percutaneous aortic valve implantation for patients with severe symptomatic aortic stenosis and a high surgical risk is currently well established. We report our experience in terms of safety and effectiveness of transcatheter aortic valve implantation in other clinical context like the degenerated aortic homografts.
Methods: We report our initial experience in four hospitals and five patients with degenerated aortic homograft and severe aortic regurgitation, refused for surgery for a heart team, that underwent percutaneous implantation of CoreValve® aortic prosthesis.
Results: We included three males and two females. The mean age was 70 (3.5) years. All patients were symptomatic in New York Heart Association class III or IV. Procedures were performed through one of the femoral arteries in all patients and under sedation in three patients. The implant was successfully carried out in all cases. There were no major complications during the procedure or admission and the valvular defect was solved in all cases. In-hospital and 30-days mortality was 0. All patients had clinical improvement during follow-up with a reduction in at less two grades in the New York Heart Association functional scale.
Conclusions: In our experience the treatment of degenerated aortic homografts and aortic insufficiency with transcatheter aortic valve implantation showed to be safe and effective. The current challenge is to

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convey the good results of transcatheter aortic valve implantation in symptomatic aortic stenosis and high surgical risk to others disorders of the aortic valve. In the future, it is possible that transcatheter aortic valve implantation will expand its indications to majority of aortic valve disorders and patients with less surgical risk.

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Abreviaturas

EAS: estenosis aórtica severa
HI: homoinjerto
IAo: insuficiencia aórtica
IPVA: implante percutáneo de válvula aórtica

INTRODUCCIÓN

La estenosis aórtica severa (EAS) es la valvulopatía degenerativa más prevalente en el mundo occidental; el recambio valvular mediante cirugía es el tratamiento de elección, por la amplia experiencia existente y sus buenos resultados[1]. En los últimos 10 años, el implante percutáneo de válvula aórtica (IPVA) en pacientes inoperables, bien por elevado riesgo quirúrgico (EuroSCORE logístico > 20%), bien por contraindicaciones técnicas para la cirugía, ha experimentado un importante avance, avalado por los buenos resultados de los registros[2] y la simplificación de la técnica. Ya se ha convertido en una alternativa reconocida para este tipo de pacientes[3], y se ha demostrado su superioridad respecto al tratamiento conservador[4]. Incluso en pacientes de alto riesgo, se ha demostrado recientemente en el estudio PARTNER A que el IPVA es un tratamiento de igual eficacia que la cirugía de recambio valvular, sin diferencias significativas en la supervivencia a 1 año, aunque con mayor incidencia de ictus[4]. Así, hasta el momento se ha sometido a este tipo de terapia a más de 15.000 pacientes en todo el mundo. Actualmente disponemos de dos tipos de válvula percutáneas, la Medtronic CoreValve® System y la Edwards-SAPIEN® System, ambos portadores de una prótesis biológica, pero con distinto soporte. Para su implante, se ha utilizado mayoritariamente el acceso femoral, pero también el transapical y el axilar[5], con las prótesis SAPIEN® y CoreValve® respectivamente.

Animados por el buen resultado de estos dispositivos implantados en la EAS degenerativa, ha aparecido recientemente una serie de publicaciones en las que se ensaya con buenos resultados el IPVA sobre otras enfermedades de la válvula aórtica en pacientes con elevado riesgo quirúrgico. Entre estas, destacan la EAS en presencia de aorta bicúspide[6] y la disfunción de bioprótesis aórtica, tanto con estenosis como con insuficiencia aórtica (IAo)[7]. Sin embargo, en otras afecciones de la aorta la experiencia con este tipo de prótesis es muy escasa; ese es el caso los homoinjertos (HI), cuyo deterioro estructural es la principal causa de reoperación en estos pacientes, para los que la cirugía es actualmente el tratamiento de elección cuando degeneran de gravedad. También se está investigando la posibilidad de ampliar la indicación de IPVA a pacientes con EAS y riesgo quirúrgico intermedio; así, se está poniendo en marcha el estudio SURTAVI, un estudio aleatorizado que pretende demostrar la no inferioridad del IPVA frente a la cirugía convencional en este tipo de pacientes. Aun así, todavía persisten ciertos obstáculos para su extensión a pacientes de menor riesgo quirúrgico, como son su durabilidad, que todavía no está bien clarificada, o la mayor incidencia de ictus e implante de marcapasos con respecto a la cirugía convencional. En esta línea de indicaciones, que podríamos denominar *off-label* en el uso de IPVA, presentamos la mayor serie publicada en el tratamiento de la disfunción de HI aórticos, mediante el implante percutáneo de una prótesis CoreValve®.

MÉTODOS

Pacientes

Se seleccionó a 5 pacientes en cuatro centros hospitalarios nacionales e internacionales, portadores de un HI aórtico disfuncionante, con elevado riesgo quirúrgico valorado mediante EuroSCORE logístico o con contraindicaciones técnicas para una reoperación. La selección se realizó en todos los casos por un equipo multidisciplinario formado por cardiólogos clínicos e intervencionistas y cirujanos cardiacos.

Procedimiento

Previamente a la intervención, se realizaron ecocardiograma transtorácico y/o transesofágico, coronariografía, estudio angiográfico de los vasos aortoiliacos y estudio de la raíz aórtica, aorta ascendente y válvula aórtica mediante angiografía y/o tomografía computarizada (TC).

Todos los procedimientos se realizaron en centros con cirugía cardiaca disponible; se llevaron a cabo en el laboratorio de hemodinámica, con sedación profunda en 4 pacientes y anestesia general en 1, e infiltración de anestesia local en la zona de punción. El acceso fue totalmente percutáneo, a través de la arteria femoral derecha en todos los casos, con cierre percutáneo mediante el dispositivo Prostar XL®. Los pacientes estaban pretratados con 100 mg de ácido acetilsalicílico y 75 mg de clopidogrel al día. Previamente al inicio de la intervención, se administró profilaxis antibiótica siguiendo el protocolo habitual en cada hospital para cirugía cardiaca convencional y se implantó un marcapasos temporal en ventrículo derecho por vía yugular o femoral. El implante de la válvula se llevo a cabo según técnica estándar, como ya está descrito ampliamente en la literatura[8,9], a excepción de la valvuloplastia, que no fue necesaria en los pacientes con disfunción del HI por IAo. Que durante el procedimiento se realizara o no ecografía transesofágica se dejó a elección del operador.

Para la elección del tamaño de la prótesis, se tuvo en cuenta el diámetro del anillo aórtico del HI según su ficha técnica, aunque se realizó un estudio *ad-hoc* según protocolo de cada hospital. Como norma general, y siguiendo las especificaciones para el tratamiento de la EAS degenerativa, donde hay abundante calcio valvular que proporciona un sustrato ideal para el correcto anclaje de la válvula, se implantó una prótesis CoreValve® n.º 29 en los anillos ≥ 23 mm y una n.º 26 si se trataba de un anillo < 23 mm. En los casos de calcificación poco importante y medida del anillo en el límite (21-22 mm), quedó a criterio del operador utilizar una prótesis n.º 29 para conseguir más fijación y estabilidad tras el implante.

Definiciones

Seguridad: ausencia de complicaciones derivadas de la prótesis o el procedimiento.

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Tabla 1
Características basales de los pacientes

	Paciente 1	Paciente 2	Paciente 3	Paciente 4	Paciente 5
Edad (años)	65	69	76	70	74
Sexo	Varón	Varón	Mujer	Mujer	Varón
EuroSCORE log (%)	8,6	10,8	34,8	31,2	14,6
Clase NYHA	IV	III	III	III	III
Intervenciones cardiacas previas	3	1	1	2	1*
Bypass aortocoronario	Sí	Sí	Sí	Sí	No
Indicación HI	EIP	AAA	EAS	EAS	EAS y rotura Ao
Tipo cirugía HI	SRA	SC	SC	SC	SRA
Edad HI (años)	9	2	12	14	11
Tipo de disfunción	IAo	IAo	IAo	IAo	IAo
FEVI (%)	65	50	60	17	41
Diámetro de anillo aórtico (mm)	24	26	24	23	22
Calcificación HI	III/IV	II/IV	I/IV	II/IV	I/IV
ETE	Sí	Sí	No	Sí	Sí
TC	Sí	Sí	Sí	No	Sí

AAA: aneurisma de aorta ascendente; Ao: aorta; EAS: estenosis aórtica severa; EIP: endocarditis infecciosa protésica; ETE: ecocardiograma transesofágico; EuroSCORE log: *European System for Cardiac Operative Risk Evaluation;* FEVI: fracción de eyección del ventrículo izquierdo; HI: homoinjerto; IAo: insuficiencia aórtica; NYHA: *New York Heart Association;* SC: subcoronaria; SRA: sustitución de raíz aórtica; TC: tomografía computarizada.
* Fue una intervención, pero se complicó con sangrado y se reoperó en dos ocasiones durante el mismo ingreso. Por este motivo fue rechazado para cualquier actuación quirúrgica en el seguimiento.

Eficacia: combinación de ausencia de complicaciones y la consecución de un beneficio clínico medible para el paciente.

Éxito del implante: implantación correcta y normofuncionante de la prótesis (valorado por angiografía y ecocardiograma), en ausencia de mortalidad durante el procedimiento.

Complicaciones: siguiendo los criterios establecidos en el documento de consenso de la *Valve Academic Research Consortium*[10], se registró la presencia de muerte por cualquier causa, muerte cardiovascular, accidente cerebrovascular, hemorragia, fallo renal agudo, complicaciones vasculares, IAo severa tras el implante, trombosis o endocarditis de prótesis, necesidad de implante de marcapasos y obstrucción coronaria tras el implante.

RESULTADOS

Se incluyó a 5 pacientes, 3 varones y 2 mujeres, con una media de edad de 70 ± 3,5 años, con un HI disfuncionante por IAo severa y disnea en clase funcional avanzada en todos los casos, cuyas características basales se muestran en la tabla 1. El EuroSCORE logístico medio fue del 20%. Destaca la elevada prevalencia de cardiopatía isquémica; todos los casos menos uno tenían *bypass* aortocoronario previo y, además, 2 pacientes presentaban más de una intervención cardiaca previa. La indicación de IPVA se estableció en 3 pacientes por contraindicaciones técnicas para la cirugía, y por elevado riesgo quirúrgico en los otros 2.

Tabla 2
Características y resultado del procedimiento. Mortalidad y seguimiento clínico

	Paciente 1	Paciente 2	Paciente 3	Paciente 4	Paciente 5
Anestesia	Sedación	Sedación	General	Sedación	Sedación
Éxito del implante	Sí	Sí	Sí	Sí	Sí
Número de intentos	1	1	1	1	2
Número de prótesis	29	29	29	29	29
IAo residual	0	I	0	0	II
Acceso	Femoral	Femoral	Femoral	Femoral	Femoral
Éxito del cierre percutáneo	Sí	Sí	Sí	Sí	Sí
Tiempo de escopia (min)	18,3	24,7	19,4	11,3	22,5
Volumen de contraste (ml)	315	243	180	270	200
ETE intraprocedimiento	Sí	Sí	Sí	Sí	No
Complicaciones VARC	No	No	No	No	Sí*
Migración de la prótesis	No	No	No	No	No
Muerte hospitalaria	No	No	No	No	No
Muerte a 30 días	No	No	No	No	No
Muerte al final del seguimiento	No	No	No	No	No
Disminución en NYHA ≥ 2 grados	Sí	Sí	Sí	Sí	Sí

ETE: ecocardiograma transesofágico; IAo: insuficiencia aórtica; NYHA: *New York Heart Association*; VARC: *Valve Academic Research Consortium.*
* Implante de marcapasos definitivo en un paciente con bloqueo de rama derecha + bloqueo auriculoventricular de primer grado en el electrocardiograma basal.

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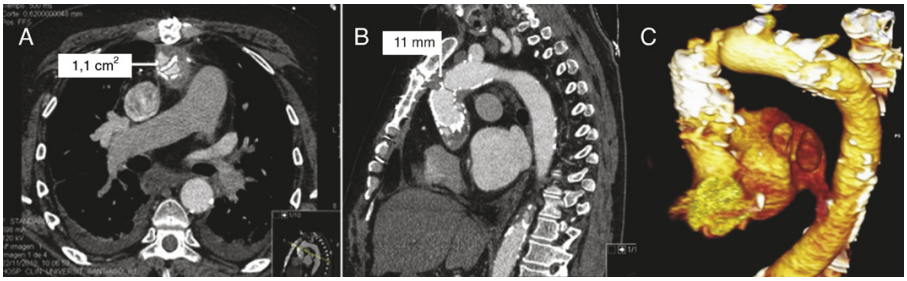


Figura 1. Imagen de tomografía computarizada (A y B) y reconstrucción en 3 dimensiones (C), del paciente 1, con importante estenosis en la anastomosis entre el homoinjerto y la aorta nativa.

En la tabla 2 mostramos los datos relativos al procedimiento y el seguimiento. El implante se concluyó con éxito y se resolvió el problema valvular en todos los pacientes, sin que se presentaran complicaciones en el procedimiento o durante el ingreso, a excepción de la necesidad de implante de marcapasos en uno de los pacientes que previamente presentaba bloqueo de la rama derecha y bloqueo auriculoventricular de primer grado. En uno de los pacientes, antes del liberar la prótesis se decidió retirarla para recolocarla, pues estaba demasiado baja, en la maniobra de recaptura; la prótesis se soltó del catéter liberador y se alojó, parcialmente desplegada, a nivel de la aorta infrarrenal. Se procedió a dilatar la válvula a ese nivel para poder avanzar una nueva válvula hasta la válvula aórtica, y el procedimiento finalizó con éxito.

En el paciente 1, la indicación por la que se había implantado años antes el HI era una endocarditis infecciosa; en este caso, la extrema friabilidad del tejido de la aorta ascendente en la anastomosis terminoterminal, entre el HI y la aorta nativa, observada durante la intervención, obligó a reforzarla con bandas de pericardio bovino y pegamento biológico. Con los años, el resultado fue una anastomosis muy restrictiva que incluso producía gradiente a ese nivel (fig. 1). En este caso, el implante de la válvula tenía dos dificultades añadidas. La primera, atravesar este pequeño orificio calcificado de 11 mm de diámetro con la válvula, teniendo en cuenta que el calibre de la vaina dispensadora es de 6 mm. Para ello, se exploró de forma invasiva cuál sería la mejor vía de acceso de entre la arteria femoral y la arteria axilar izquierda. En el acceso femoral resultó más adecuado, por alinearse mejor con el eje de la estenosis. La segunda dificultad estribó en conseguir un correcto posicionamiento de la prótesis, que debía quedar por debajo de la estenosis para conseguir una expansión completa de la nueva válvula, pero que al mismo tiempo no quedase implantada muy baja en el ventrículo izquierdo, con lo que se produciría una IAo severa. Para esto, fue muy importante la adecuada medición de la distancia entre el anillo aórtico y la anastomosis restrictiva, para lo que se realizaron varias mediciones en distintos planos mediante TC. Teniendo en cuenta que la prótesis mide 5 cm en su eje largo y que la distancia anillo-estenosis resultó ser 5,6 cm, el margen de error en su posicionamiento era muy pequeño. Además, una vez iniciado el despliegue de la válvula, la maniobra para recapturarla en caso de posicionamiento incorrecto sería extremadamente dificultosa o imposible, al tener que atravesar en la retirada el pequeño orificio anastomótico con la válvula parcialmente desplegada. Como contrapartida, una vez desplegada la prótesis por debajo de la estenosis, esta misma ayudó a fijarla en su posición, impidiendo su dislocación distal (fig. 2).

En el paciente 5 con un anillo de 22 mm, se implantó una válvula n.º 29, ya que la escasa calcificación que presenta el HI no garantizaba un correcto anclaje de la prótesis n.º 26; se consiguieron las óptimas fijación, expansión y funcionalidad de la prótesis, que no mostraba gradiente transavalvular significativo al final del procedimiento.

Con un seguimiento medio de 322 ± 168 días, todos los pacientes permanecen vivos, con una importante mejoría clínica y al menos una disminución de 2 grados en la escala clase funcional de la *New York Heart Association* para disnea.

DISCUSIÓN

Aunque se ha publicado alguna experiencia individual aislada[11], nuestra serie es hasta la fecha la primera que comunica el tratamiento de pacientes con un HI degenerado, por lo general pacientes con elevado riesgo quirúrgico, mediante el implante de prótesis vía percutánea.

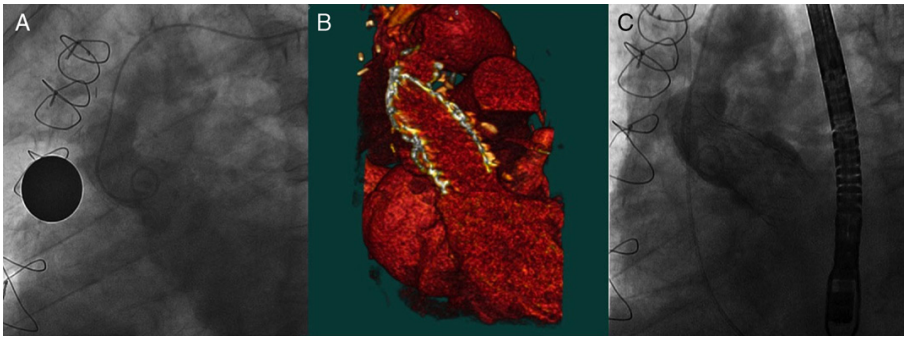


Figura 2. A: aortografía previa al procedimiento. B: reconstrucción de tomografía computarizada en 3 dimensiones. C: angiografía tras el implante de la válvula en el paciente 1.

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En la actualidad, existe un grupo creciente de pacientes en los que se asocia una alteración de la válvula aórtica y la aorta ascendente. En estos pacientes, desde hace más de tres décadas debido a sus buenos resultados tanto a corto como a largo plazo, se ha usado la técnica quirúrgica de Bentall y De Bono[12], consistente en el recambio de la raíz y la aorta ascendente con un injerto tubular valvulado, al que posteriormente se reimplantan las arterias coronarias. Sin embargo, existe otro tipo de intervención que está actualmente al alza, que consiste en el uso de HI criopreservados como sustitutos de la raíz y/o la válvula aórtica, especialmente indicados en el caso de endocarditis infecciosa sobre válvula protésica o cuando se extiende produciendo destrucción de la raíz aórtica[13].

Entre las ventajas que se postulan para este tipo de intervención, se incluye un comportamiento más fisiológico de la raíz aórtica en su relación con el ventrículo izquierdo, con lo que se consiguen mayores tasas de regresión de la masa que con el recambio valvular convencional[14]. Otras ventajas son menor incidencia de endocarditis infecciosa y enfermedad tromboembólica y la ausencia de necesidad de tratamiento anticoagulante[15]. Existen dos técnicas quirúrgicas para el tratamiento con HI aórtico, una es mediante implantación subcoronaria, y la otra mediante sustitución de la raíz aórtica (SRA). Aunque no hay diferencias en cuanto a su durabilidad a largo plazo, el implante subcoronario presenta mayor tasa de incompetencia precoz, como vemos representado en el paciente 2, en el que la disfunción apareció tan sólo 2 años después de la cirugía, mientras que la SRA tiene mayor incidencia de reintervención precoz y mortalidad perioperatoria por problemas relacionados, entre otros, con el reimplante de las arterias coronarias[16]. La SRA ofrece también un mejor comportamiento hemodinámico que la subcoronaria, por lo que se considera la técnica de elección.

El deterioro estructural de los HI es la principal causa de reoperación en estos pacientes. La edad del paciente en el momento del implante es uno de los elementos que más fuertemente se asocian a este deterioro estructural y a la necesidad de nueva reintervención, que es más frecuente cuanto más joven es el paciente, como se pone manifiesto en un estudio ya clásico de O'Brien et al, donde la tasa de reintervención a los 10 años en pacientes menores de 20 años era casi 20 veces mayor que en los pacientes mayores de 65 años[14].

La forma de disfunción más habitual, como ocurre en nuestra casuística, es la calcificación y la insuficiencia valvular, que parece estar en relación con procesos degenerativos[17]; actualmente la cirugía es el tratamiento de elección.

Tanto el EuroSCORE como el STS *score,* las dos escalas de riesgo más usadas para la cirugía cardiaca, incorporan la reintervención como un elemento que eleva el riesgo quirúrgico, siendo mayor todavía si se trata de una segunda o tercera reintervención, elemento este último, sólo valorado en el STS *score*. Aunque el efecto de la reintervención sobre la mortalidad siempre es importante, este es más alto según avanza la edad; así, la reintervención multiplica por 6 el riesgo de muerte a los 30 días tras una cirugía valvular aórtica en pacientes mayores de 80 años, y se converte en el mayor predictor de mortalidad[18].

Por todo esto, los pacientes con un HI aórtico disfuncionante tienen, en primer lugar, elevado riesgo quirúrgico y en segundo, con casi toda probabilidad, IAo. En este contexto, IAo y válvula no nativa, la indicación de IPVA está todavía sin establecer. En nuestra breve experiencia inicial en el tratamiento de los HI disfuncionantes, el uso de IPVA mostró ser seguro, no se produjo ninguna complicación importante, y eficaz, pues se corrigió el defecto valvular en todos los casos y se obtuvo beneficios clínicos para el paciente. Hemos identificado una serie de consideraciones previas al procedimiento y durante el procedimiento, distintas del implante en la EAS, para adaptar la técnica a la afección que

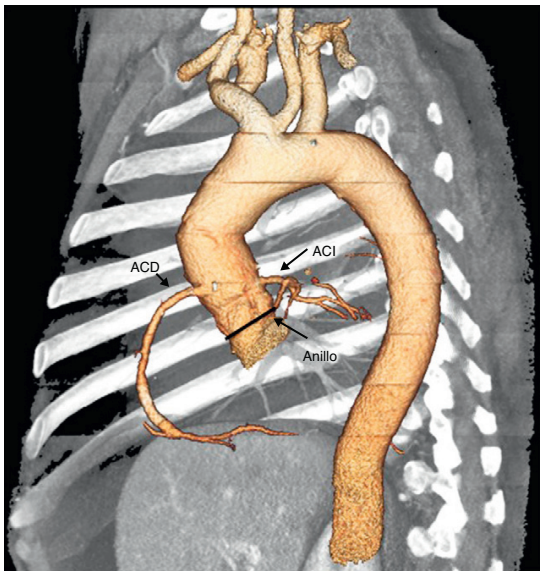


Figura 3. Reconstrucción de tomografía computarizada en 3 dimensiones para la correcta identificación de los *ostia* coronarios antes de la intervención. ACD: arteria coronaria derecha; ACI: arteria coronaria izquierda.

queremos tratar. Así, en la evaluación previa al implante, una TC de aorta puede resultar muy valiosa para una correcta evaluación del HI, valorando especialmente su grado de calcificación y el de la zona de implante, que nos ayudará al correcto anclaje de la prótesis. Es importante también evaluar la zona de la anastomosis entre el HI y la aorta ascendente, que en ocasiones, como hemos visto en el paciente 1, puede llegar a ser muy restrictiva. Si es así, se debe de medir su distancia al anillo para asegurarnos una correcta expansión de la corona de la prótesis. Otro aspecto que tener en cuenta en estos pacientes es la adecuada identificación del origen de ambos *ostia* coronarios, sobre todo cuando el HI se halla implantado mediante técnica de SRA. Habitualmente estarán en su lugar anatómico, ya que para el reimplante de las arterias coronarias se usan los propios *ostia* de HI, pero en ocasiones, por cuestiones técnicas, estas se reimplantan en otra localización (fig. 3).

A diferencia de lo propuesto en el IPVA en bioprótesis disfuncionantes[6] para la elección del tamaño de la prótesis, el diámetro del anillo medido en el HI antes de su implante puede servirnos de guía, pero se deberá de realizar una medición *ad-hoc* siguiendo el mismo protocolo que el tratamiento de la EAS, pues la degeneración del propio HI puede haber conllevado la dilatación del anillo. El tamaño de la aorta ascendente en estos pacientes, en que la degeneración del HI puede llevar aparejada una dilatación de esta, puede ser una limitación a la hora de seleccionar a los pacientes para implante de una CoreValve®, ya que su diámetro a 5 cm del anillo debe de ser < 41 mm si se implanta una válvula n.º 26 y de 43 mm si la válvula es de los números 29 o 31. Esto será especialmente importante en los pacientes con un HI poco calcificado y, por lo tanto, con un anclaje más débil a nivel del anillo aórtico.

En cuanto al procedimiento en sí, obviamente, en los pacientes con disfunción por IAo no habrá que realizar valvuloplastia. Una dificultad añadida a la hora del implante, es la estabilidad del catéter *pig-tail* que se ubica en el seno coronario posterior, marcando la posición del anillo y que sirve como referencia a la hora de colocar la prótesis, así como para la medición de presión arterial y la realización de angiografías de control. En los pacientes con disfunción por IAo, el *pig-tail* está muy inestable, lo que dificulta su labor de marca, por lo que habrá que ayudarse de otras

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marcas radiológicas guiadas por la realización de aortografía y de la realización de angiografías más frecuentes, así como de ecocardiografía transesofágica intraprocedimiento. En principio, no hemos encontrado otras diferencias con respecto al implante en la EAS degenerativa y, como en esta, lo importante es realizar una buena valoración individualizada previa a la intervención para idear la estrategia más adecuada en cada paciente.

CONCLUSIONES

Los resultados obtenidos en nuestra serie indican que el IPVA en HI disfuncionantes podría ser una alternativa segura y eficaz a corto plazo, resultados que en un futuro nuevos registros deberán avalar. Actualmente, se puede considerar que el tratamiento de la EAS en pacientes de alto riesgo quirúrgico mediante el IPVA ya se ha consolidado en la práctica habitual, con excelentes resultados tanto en mortalidad intrahospitalaria y a los 30 días como en una importante mejoría en la clase funcional de los pacientes. Una vez superada esta fase inicial, cada vez con mayor frecuencia, se ensayan este tipo de terapias en indicaciones *off-label*, con esperanzadores resultados iniciales, aunque con muy poca experiencia acumulada para extraer resultados consistentes. Se están realizando nuevos estudios en pacientes de menor riesgo, en el intento de ampliar la indicación de IPVA a gran parte de las enfermedades de la valvular aórtica y a sectores de población más jóvenes. Sin embargo, para esto aún se tendrá que demostrar su superioridad con respecto a la cirugía convencional en estos pacientes y resolver algunas de su importantes limitaciones, como la mayor incidencia de necesidad de marcapasos e ictus y la presencia de diferentes grados de IAo residual, que si bien es permisible en pacientes sin otra alternativa, no lo es si se quiere extender a pacientes con bajo riesgo quirúrgico.

CONFLICTO DE INTERESES

Ninguno.

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The Ibero-American transcatheter aortic valve implantation registry with the CoreValve prosthesis. Early and long-term results

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is the recommended therapy for patients with severe aortic stenosis who are not suitable candidates for surgery. The aim of this study was to describe early experience and long-term follow-up with the CoreValve self-expanding aortic prosthesis at 42 Ibero-American hospitals.
Methods: Multiple centre observational study including 1220 consecutive patients with symptomatic severe aortic stenosis who are not suitable candidates for surgery and underwent transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System between December 2007 and May 2012.
Results: The registry included 1220 consecutive patients with a mean age of 80.8 ± 6.3 years and a mean logistic euroSCORE of 17.8% ± 13%. The procedural success rate was 96.1%. Hospital mortality was 7.3% and combined end-point was 21.3%. Aortic regurgitation after TAVI was present in 24.5% (Sellers grade ≥ 2). The estimated 1-year and 2-year survival rates were 82.1% and 73.4% respectively. The following issues were significant independent risk factors for hospital mortality: acute kidney failure (odds ratio 3.55); stroke (odds ratio 5.72); major bleeding (odds ratio 2.64) and euroSCORE (odds ratio 1.02). Long-term predictors of mortality were diabetes mellitus (hazard ratio 1.59, 95% confidence interval 1.09–2.31), severe chronic obstructive pulmonary disease (hazard ratio 1.85, 95% confidence interval 1.85–2.88), and functional classes NYHA III–IV (hazard ratio 1.31, 95% confidence interval 1.01–1.70).
Conclusions: Transcatheter aortic valve implantation constitutes a safe and viable therapeutic option for high operative risk patients with severe aortic stenosis. Long-term prognosis is conditioned by associate comorbidities.
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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

The incidence of aortic stenosis in developed countries has grown in recent decades due to increased life expectancy. Between 30 and 50% of patients with severe aortic stenosis do not undergo surgery for a variety of reasons including age, associated comorbidities or high surgical risk [1]. Percutaneous therapy for severe aortic stenosis, transcatheter aortic valve implantation (TAVI), has become a recognised alternative treatment for inoperable or high surgical risk patients [2–5], and has been included as a therapeutic option in recent European guidelines on the management of valvular heart disease [6].

TAVI has a high implantation success rate with hospital mortality lower than 10% according to initial series [7,8]. Several studies have reported clinical and haemodynamic improvements in the mid-term, reaching survival rates of 81% and 74% at one and two years respectively [9–11].

Various registries have analysed the results of TAVI in different European countries and Canada [12–18]. However, except for a cooperative study carried out by three Spanish hospitals [8], no further information has been published on the results of this technique in Spain, Portugal and Ibero-America.

The purpose of this paper is to report the early and long-term results, in addition to the factors that are predictive of hospital and late mortality of patients with severe aortic stenosis treated with CoreValve prosthesis in a multi-centre study: the *Registro Ibero-Americano* [Ibero-American Registry].

2. Material and methods

2.1. Study design

The CoreValve Registry coordinating committee for Spain and Portugal was set up in 2008 and in 2010 Ibero-America was included. The proposed objective was to find out the indications, early results and survival of TAVI patients in our population. An online form for data entry was created (https://protesisaorticas.org) in compliance with the Spanish Data Protection Law, and Medtronic made unrestricted funding available. Between December 2007 and May 2012, the registry included a total of 1291 patients from 43 centres in 9 European and Ibero-American countries; the data from 1220 patients was analysed, and 71 patients were excluded due to incomplete information.

2.2. Patients

All of the participating centres included consecutive patients with symptomatic severe aortic stenosis with a valve area $<1\ cm^2$ ($<0.6\ cm^2/m^2$) with or without aortic regurgitation (AR) in addition to some of the following criteria:

A) Inoperable or high surgical risk by consensus of a multidisciplinary team with:
   - a logistic euroSCORE ≥ 15
   - or the presence of at least one of the following comorbidities:
     - Advanced cirrhosis.
     - Restrictive or obstructive ventilatory insufficiency (FEV1 < 1 L).
     - Prior heart surgery with graft permeability (left mammary artery to anterior descending).
     - Porcelain aorta.
     - Morbid obesity (body mass index ≥ 40)
     - Immunodeficiencies
     - Neoplastic pathology with life expectancy greater than 1 year.
     - Thoracic radiotherapy

B) Patients over 75 years who reject surgery.

C) Anatomical criteria:
   - Diameter of aortic annulus ≥19 mm and ≤29 mm
   - Diameter of the ascending aorta ≤40 mm (prosthesis 26 mm) or ≤43 mm (prosthesis 29 and 31 mm).
   - Diameter of the femoral artery and/or left subclavian artery ≥6 mm.

All patients signed informed consent. Clinical evaluation, transthoracic echocardiogram, coronarography and aortography were carried out to assess the aortic root, in addition to an angiography or computed tomography (CT scan) for the aorto–iliac–femoral axis.

2.3. Description of the device

The CoreValve aortic prosthesis (Medtronic, Irvine, CA, USA) consists of a trileaflet bioprosthetic pericardial porcine tissue valve that is mounted and sutured in a self-expanding nitinol stent. The sizes used were: a 26 mm prosthesis for aortic annuli between 19 and 23 mm, a 29 mm prosthesis for annuli between 23 and 27 mm and a 31 mm prosthesis for annuli between 27 and 29 mm.

2.4. Procedure

43.5% of the procedures were carried out under general anaesthesia. The approach was femoral in 1155 (94.7%) cases, with percutaneous access and closure performed using the Prostar XL 10 Fr device (Abbott Vascular Devices, Redwood City, California) in 88% of patients, and with surgery in 12%. In 64 (5.3%) the approach was subclavian and there was one case of direct aortic access.

Delivery of the aortic prosthesis was made with angiographic control and fluoroscopic guidance. After implantation of the CoreValve prosthesis, an aortography was made to quantify the degree of regurgitation and at 48–72 h a transthoracic echocardiography was carried out.

2.5. Definitions

A patient was considered as high surgical risk by consensus of the multidisciplinary team, based on perioperative risk indices such as the logistic euroSCORE and associated comorbidities.

Success of the procedure was defined as the correct implantation and normal working of the aortic prosthesis in the absence of mortality during the procedure.

The criteria used for the definition are those established by the Valve Academic Research Consortium [19]. We considered major cardiovascular events to be: death from any cause, acute myocardial infarction (AMI), a cerebrovascular event (CVE), repeat intervention and vascular complications (aortic dissection, iliac or femoral rupture, haemorrhage requiring surgery).

The presence and severity of AR were quantified using Sellers classification (absent = 0; mild = 1+; moderate = 2+; moderate-severe = 3+; severe = 4+).

It was decided to implant a definitive pacemaker in advanced AV block, in accordance with European Society of Cardiology recommendations for patients with acquired AV block in special situations [20]. Other indications for pacemakers were left to the criterion of each researcher. Functional class was assessed using the NYHA (New York Heart Association) classification. Acute kidney failure was defined as creatinine ≥ 2.5 mg/dL. Implantation position was defined as ideal, high or low according to the criterion of the operator, taking an aortogram with the three sinuses of Valsalva aligned on the same plane as a reference, and measuring the distance between the annulus at the level of the noncoronary sinus and the lower part of the CoreValve prosthesis [21].

3. Statistical analysis

Data is expressed as a mean ± standard deviation in the case of continuous variables and as an absolute number and percentage for categorical variables. A basic descriptive statistical analysis and a survival study were made by means of a Kaplan–Meier analysis and the log-rank test. We used the χ^2 or Fisher test for comparison of qualitative variables and Student's *t*-test for continuous variables depending on their distribution. A multivariate analysis was used with a multiple logistic regression model and a Cox regression analysis to identify independent variables predictive of hospital and late mortality respectively; these were staggered to show the association of different risk factors more clearly. This model included variables that reached a significance level of <0.05 in the univariate analysis or those recognised in literature as predictors. Results are presented as an odds ratio (OR) and a confidence interval (CI) of 95% for analysis of logistic regression and as a hazard ratio (HR) and a CI of 95% for the Cox regression model. A value of $p < 0.05$ was considered statistically significant. Data was analysed with the SPSS statistical programme, version 15.0 (Chicago, Illinois).

4. Results

1220 patients were analysed with a median follow-up of 238 days (percentile 25 and 75, 50 and 480 days respectively). The patients included by each centre are listed in Appendix A.

The mean age was 80.8 ± 6.3 years (range, 49–95) with a predominance of females (54.7%). The mean logistic euroSCORE was 17.8 ± 13% and there was a coexistence of relative contraindications for surgery such as porcelain aorta (7%), or prior CABG (9.5%) or valve surgery (4.4%). 26.5% presented chronic moderate to severe respiratory failure. Baseline clinical characteristics are summarised in Table 1.

79.4% had NYHA functional classes III–IV and 1.7% was in cardiogenic shock. In accordance with indications, 78.5% were considered inoperable

Table 1
Basal clinical characteristics.

Age (years)	80.7 ± 6.3
Sex (female)	667 (54.7%)
Peso (kg)	70.3 ± 13
NYHA functional classification	
Class I	13 (1.%)
Class II	238 (19.5%)
Class III	760 (62.3%)
Class IV	209 (17.1%)
Angina	393 (32.2%)
Syncope	140 (11.5%)
Prior valve surgery	54 (4.4%)
Aortic bioprosthesis	29 (2.4%)
Coronary artery disease	441 (36.1%)
Prior bypass graft surgery	116 (9.5%)
PCI prior to procedure	152 (20.7%)
Logistic euroSCORE (%)	17.8 ± 13
Prior AMI	140 (11.5%)
Acute kidney failure (creatinine > 2.5 g/dL)	289 (23.7%)
COPD	
Mild	106 (8.7%)
Moderate	164 (13.4%)
Severe	160 (13.1%)
Prior CVE	136 (11.1%)
Pulmonary hypertension > 60 mm Hg	229 (18.8%)
Porcelain aorta	85 (7.6%)
Cardiovascular risk factors	
Diabetes mellitus	380 (31.2%)
Hypercholesterolemia	670 (54.9%)
Arterial hypertension	969 (79.4%)
Smoking	198 (16.2%)
Echocardiographic parameters	
Maximum gradient, mm Hg	82.9 ± 24
Mean gradient, mm Hg	51.6 ± 18
AVA, cm^2	0.62 ± 0.18
Aortic annulus, mm	22.4 ± 2
Septal thickness	14.7 ± 4.8
Ejection fraction, %	55.8 ± 14
LVEF ≤ 40%	222 (18.2%)

NYHA: New York Heart Association; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease; CVE: cerebrovascular events; AVA: aortic valve area; LVEF: left ventricular ejection fraction.

Table 2
Basal clinical characteristics per approach used.

	Transfemoral N = 1155	Subclavian N = 65	p
Age	80.9 ± 6	77.5 ± 7	0.001
Sex (male)	506 (43.8%)	47 (72.3%)	0.001
Logistic euroSCORE	17.6 ± 13	22.5 ± 15	0.011
Diabetes mellitus	354 (30.7%)	26 (40%)	0.404
Porcelain aorta	73 (6.3%)	12 (18.1%)	<0.001
Weight (kg)	70.1 ± 13	73 ± 13	0.051
Extracardiac arteriopathy	124 (10.7%)	43 (66.2%)	0.001
Intermittent claudication	75 (6.5%)	33 (50.8%)	<0.001
Carotid occlusion	37 (3.2%)	7 (10.8%)	<0.001
Aortic abdominal surgery	8 (0.7%)	4 (6.2%)	<0.001

or high surgical risk with a mean age of 80 ± 6 years and a logistic euroSCORE of 19.6 ± 14%, while the group of patients who rejected surgery had a lower logistic euroSCORE of 11.4 ± 2%, p < 0.001 and a higher age, 81 ± 6 years, although without significant differences.

Forty patients (3.3%) had severe AR. Mitral regurgitation was severe in 23 patients (1.9%) and moderate in 202 (16.6%).

4.1. Characteristics of the procedure

The mean time for the procedure was 107 ± 48 min. Patients undergoing a subclavian approach were predominantly male, with more peripheral arteriopathy and porcelain aorta than those treated via the femoral (see Table 2) approach.

The success rate of the procedure was 96.1%. It was not possible to implant the prosthesis in 4 cases (0.3%), 223 patients underwent post-dilation (18.3%) and a second prosthesis was implanted in 49 (4%). The implantation depth was considered ideal in 969 (79.4%), low in 191 (15.7%) and high in 60 (4.9%) cases. Patients with a low implantation more frequently presented impaired atrioventricular conduction, both in the need for pacemakers (39.3%) and in development of left bundle branch block (LBBB) (22.5%). Patients with a high implantation presented greater obstruction of the origin of coronary arteries (6.7%) and migration of the prosthesis to the ascending thoracic aorta (16.7%) (Table 3).

After TAVI, the maximum aortic transvascular gradient diminished from 82.9 ± 24 to 5.81 ± 4.8 mm Hg and AR in the angiography was: absent, 240 patients (19.7%), grade 1+ in 681 (55.8%), grade 2+ in 252 (20.7%), grade 3+ in 37 (3%) and grade 4+ in 10 (0.8%).

4.2. Complications and survival at 30 days

Hospital mortality was 7.3% and the combination of death, vascular complications, AMI or CVE was 21.3% (Table 4).

A definitive pacemaker was needed by 303 patients (24.8%), 81.8% of which were for advanced AV block, 7.64% for new onset LBBB, 6.6% for trifascicular block and 3.96% for bifascicular block. Incidence of CVE was 2.8% and associated factors were prior CVE (25% vs. 10.8%, p = 0.002), migration of the prosthesis during the procedure (9.4% vs. 2.4%, p = 0.047) and aortic dissection (3.1% vs. 0.2%, p = 0.001) with no differences between the approach (subclavian artery 6.3% vs. 5.3%) or with a porcelain aorta (9.4% vs. 2.4%, p = 0.047).

The echocardiogram showed a discrete improvement in the ejection fraction (LVEF) from 55.8 ± 14 to 59 ± 11%, p < 0.01. 78.4% were discharged with a double antiaggregant therapy and 20.1% with oral anticoagulants.

Table 3
Complications based on the position of the prosthesis in relation to the valvular annulus.

	High N = 60	Low N = 191	Ideal N = 969	p
Prosthesis size				
26 mm	27 (45%)	95 (49.7%)	548 (56.5%)	0.190
29 mm	31 (51.7%)	94 (49.2%)	412 (42.5%)	
31 mm	1 (1.7%)	2 (1%)	6 (0.6%)	
Degree of residual regurgitation				
0	4 (6.7%)	32 (16.8%)	204 (21.1%)	0.001
1+	33 (55%)	86 (45%)	562 (58%)	
2+	17 (28.3%)	53 (27.7%)	182 (18.8%)	
3+	3 (5%)	16 (8.4%)	18 (1.9%)	
4+	3 (5%)	4 (2.1%)	3 (0.3%)	
In-hospital death	10 (16.7%)	12 (6.3%)	67 (6.9%)	0.041
Conversion to surgery	1 (1.7%)	4 (2.1%)	2 (0.2%)	0.015
Cardiac tamponade	2 (3.3%)	2 (1%)	16 (1.7%)	0.476
Valve migration	10 (16.7%)	6 (3.1%)	16 (1.7%)	0.001
Coronary obstruction	4 (6.7%)	1 (0.5%)	3 (0.3%)	0.001
Cardiac arrest	6 (10%)	2 (1%)	23 (2.4%)	0.006
Annulus rupture	1 (1.7%)	0%	4 (0.4%)	0.211
Need to implant 2nd prosthesis	9 (15%)	18 (9.4%)	22 (2.3%)	0.001
Post-dilation	9 (15%)	50 (26.2%)	164 (16.9%)	0.012
AV block during procedure	9 (15%)	66 (34.6%)	170 (17.5%)	0.035
CVE	1 (1.7%)	5 (2.6%)	13 (1.3%)	0.744
Need for pacemaker	5 (8.3%)	75 (39.3%)	223 (23%)	0.001
New onset LBBB	5 (8.3%)	43 (22.5%)	173 (17.9%)	0.002

A–V block: atrio–ventricular block; LBBB: left bundle branch block.

Table 4
Complications during procedure and in-hospital.

Conversion to surgery	7 (0.6%)
Cardiac tamponade	20 (1.6%)
Migration, implant in aorta	32 (2.6%)
Coronary ostial stenosis	8 (0.7%)
Cardiac arrest during procedure	31 (2.5%)
Aortic annulus rupture	5 (0.4%)
Aortic dissection	3 (0.2%)
AMI < 72 h post implantation	12 (1%)
Vascular complications	
Major	47 (3.9%)
Minor	77 (6.3%)
Haemorrhage	
Major	54 (4.4%)
Minor	67 (5.5%)
Transient ischemic attack	15 (1.2%)
CVE	19 (1.6%)
Acute kidney failure	
Stage 1	58 (4.8%)
Stage 2	30 (2.5%)
Stage 3	35 (2.9%)
Atrioventricular block post valvuloplasty	101 (8.3%)
AV block during procedure	144 (11.8%)
Definitive pacemaker	303 (24.8%)
Hospital mortality	89 (7.3%)

AMI: acute myocardial infarction.

The clinical characteristics and procedures of the patients with mortality at 30 days, compared to those who survived, are shown in Table 5. In the multivariate analysis, the factors associated with hospital mortality were complications after TAVI (acute kidney failure, CVE and haemorrhage), the logistic euroSCORE and coronary artery disease (Table 6).

4.3. Late survival

Survival at one and two years was 82.1% and 73.4% respectively. 89.7% of patients were NYHA functional classes I–II (see Fig. 1).

Cumulative mortality during follow-up was 17%. Of the 118 patients who died after 30 days, 49 (41.5%) were from cardiovascular causes and the rest were related with comorbidities. The clinical characteristics and characteristics of the procedures for patients with late mortality compared to those who survived are shown in Table 7; and in the multivariate analysis, the factors associated with late mortality were secondary to comorbidities (severe COPD, diabetes mellitus, kidney failure in dialysis), a worse LVEF and a NHYA functional classes of III–IV (Table 8).

Survival at one year for patients without AR, Sellers grade 1+, 2+, 3+ and 4+ was: 86% vs. 82.9%, vs. 83.6% vs. 62.3% vs. 33.3% respectively, $p < 0.001$ (see Fig. 2).

5. Discussion

This collaborative project between hospitals in Spain, Portugal and several Ibero-American countries was conducted following the recommendations of the scientific societies of the countries [22] by means of a multicentre registry with data about practice in the real world of patients with symptomatic severe aortic stenosis treated consecutively with TAVI using the CoreValve aortic prosthesis.

Our series has contributed the following findings: firstly, it confirms that TAVI is safe and effective, and identifies that post procedural complications predict mortality at 30 days; secondly, long-term survival is conditioned by the patient's basal state and comorbidities.

Table 5
Clinical and procedure characteristics of the patients with mortality at 30 days compared to those who survived.

	Deaths N = 89	Alive N = 1129	p
Age	81.7 ± 5,4	80.6 ± 6.4	0.133
Sex (male)	51 (57.3%)	616 (54.5%)	0.605
Risk factors			
Arterial hypertension	71 (79.8%)	898 (79.4%)	0.933
Diabetes mellitus	28 (31.4%)	152 (31.2%)	0.683
Dyslipidemia	47 (52.8%)	623 (55.1%)	0.678
Smoking	15 (16.9%)	183 (16.2%)	0.868
Prior CVE	10 (11.2%)	126 (11.1%)	0.978
Weight	67 ± 11	70 ± 13	0.028
Prior AMI	13 (14.6%)	127 (11.2%)	0.336
Severe COPD	15 (16.9%)	145 (13.8%)	0.250
Peripheral arteriopathy	17 (19.1%)	150 (13.3%)	0.123
LVEF	53 ± 15	56 ± 14	0.058
Acute kidney failure	26 (9%)	263 (23.3%)	0.203
Logistic euroSCORE	24.3 ± 14	17.3 ± 12	0.001
Coronary artery disease	24 (27%)	417 (36.9%)	0.061
Prior PCI			
<6 months	12 (13.1%)	154 (13.4%)	0.719
>6 months	9 (10.1%)	80 (7.1%)	
Prior valve surgery	4 (4.5%)	50 (4.4%)	0.974
Prior CABG	7 (7.9%)	109 (9.6%)	0.719
Bioprosthesis	1 (1.1%)	28 (2.5%)	0.420
Porcelain aorta	5 (5.6%)	80 (7.1%)	0.604
Clinical presentation			
NYHA class IV	27 (30.3%)	182 (16.1%)	0.002
Syncope	8 (9%)	132 (11.7%)	0.445
Angina	32 (36%)	361 (31.9%)	0.433
Cardiogenic shock	7 (7.9%)	14 (1.2%)	0.001
Inotropes	13 (14.6%)	29 (2.6%)	0.001
Mechanical ventilation	7 (7.9%)	17 (1.5%)	0.001
Oliguric renal failure	5 (5.6%)	17 (1.5%)	0.005
High surgical risk	78 (87.6%)	880 (77.8%)	0.030
Rejection of surgery	11 (12.4%)	251 (22.2%)	0.038
Severe pulmonary hypertension	21 (23.6%)	208 (18.4%)	0.226
Moderate–severe MI	22 (22.7%)	203 (18%)	0.565
General anaesthesia	48 (53.9%)	483 (42.7%)	0.040
Axillary-subclavian access	4 (4.5%)	61 (5.4%)	0.716
Prosthesis size			
26 mm	54 (60.6%)	616 (54.5%)	0.002
29 mm	33 (37.1%)	504 (44.6%)	
31 mm			
Post-dilation	15 (16.9%)	208 (18.4%)	0.718
Procedure duration	122 ± 55	106 ± 47	0.003
Need for 2nd prosthesis	9 (10.1%)	40 (3.5%)	0.002
Post implantation AR			
0	12 (13.5%)	228 (20.2%)	0.001
1	49 (55.1%)	632 (55.9%)	
2	15 (16.9)	237 (21%)	
3	8 (9%)	29 (2.6%)	
4	5 (5.6%)	5 (0.4%)	
AR ≥ 2	28 (31.5%)	270 (23.9%)	0.109
Implantation position			
High	10 (11.2%)	50 (4.4%)	0.016
Low	12 (13.5%)	179 (15.8%)	
Ideal	67 (75.3%)	902 (79.8%)	
Conversion to surgery	3 (3.4)	4 (0.4%)	0.001
Cardiac tamponade	7 (7.9%)	13 (1.2%)	0.001
AMI	3 (3.4%)	9 (0.8%)	0.001
Haemorrhage	14 (15.7%)	40 (3.5%)	0.001
CVE	8 (9%)	11 (1%)	0.001
Acute kidney failure			
Stage 1	7 (7.9%)	51 (4.5%)	0.001
Stage 2	7 (7.9%)	23 (2%)	
Stage 3	18 (20.2%)	17 (1.5%)	
New onset LBBB	13 (14.6%)	208 (18.5%)	0.538
Pacemaker	16 (18%)	287 (25.5%)	0.001
Vascular complications			
Major	11 (12.4%)	36 (3.2%)	0.001
Minor	5 (5.6%)	72 (6.4%)	

Table 6
Predictors of hospital mortality (multivariate analysis).

	OR	HF 95%	p
Acute kidney failure	3.55	1.92–6.54	<0.001
CVE	5.75	2.22–14.84	<0.001
Haemorrhage	2.64	1.37–5.08	0.003
Prosthesis on prosthesis	−0.25	0.11–0.6	0.002
Post-implantation aortic regurgitation	1.19	0.94–1.5	0.144
Vascular complications	1.69	0.815–3.53	0.157
LVEF	1.002	0.98–1.02	0.875
Logistic euroSCORE	1.02	1.001–1.04	0.008
Conversion to surgery	−0.35	0.04–2.59	0.305

The success rate of the procedure (96.1%) is slightly higher than that of the initial series with CoreValve prosthesis [4], and similar to the rate reported by Webb et al. [7] with the Edwards-Sapien prosthesis (97%), and the rates of recent French (96.9%) and Italian (98%) registries [13,15].

Unlike other registries [12–18], in our series there was an "off label" category for octogenarian patients who rejected surgery, a group characterised by lower surgical risk and the predominance of women (64.1%). Updated VARC criteria emphasise the selection of patients by a multi-disciplinary team, the "heart team", which assesses surgical risks, other circumstances and comorbidities [23].

Impaired AV conduction is more frequent with the CoreValve prosthesis [24]. The need for a pacemaker was 24.8%, similar to other series with the CoreValve prosthesis [13,14,17]. The main indication for implantation was third-degree AV block (81.8%). The need for definitive pacemaker implantation and the development of LBBB were more prevalent in patients with a low implant; this supports the studies that identify prosthesis depth as a predictive factor for needing a pacemaker and reduction of this rate by carrying out higher implantation, which is made easier by the new *Accutrak* delivery system [21,25,26]. It has been reported that patients who develop LBBB present worse survival after a mean follow-up of 449 days, with LBBB as a predictor of late mortality [27]. In our series, we found no difference in one year survival among patients who required or did not require a pacemaker, 82.2% vs. 84.2%, p = 0.134 and in those who developed LBBB (81 vs. 85.6%, p = 0.337), data similar to that reported by Urena, M. et al. [28].

A mortality rate at 30 days of 7.3% is within the intervals of the different studies and registries, with 8.1% for high surgical risk patients and

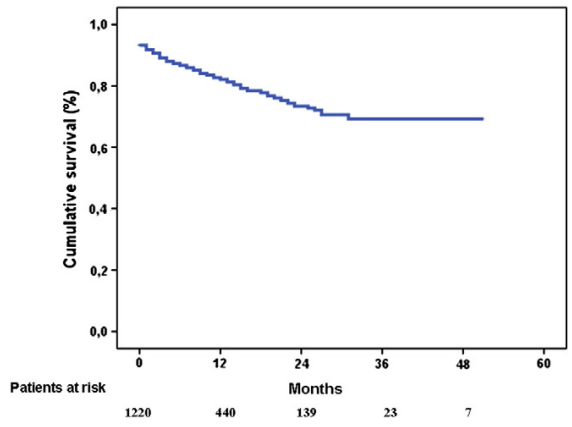


Fig. 1. Estimation of survival at one and two years for the population studied (n = 1220) using Kaplan–Meier survival analysis.

Table 7
Clinical characteristics related with late mortality.

	Deaths N = 118	Alive N = 998	p
Age	79.9 ± 6	80.8 ± 6.3	0.167
Sex (male)	59 (50%)	448 (44.9%)	0.292
Risk factors			
Arterial hypertension	84 (71.2%)	803 (80.5%)	0.018
Diabetes mellitus	50 (42.4%)	300 (30.1%)	0.007
Dyslipidemia	61 (51.7%)	555 (55.6%)	0.419
Smoking	23 (19.5%)	158 (15.8%)	0.308
Prior CVE	13 (11%)	109 (10.9%)	0.975
Weight	71.4 ± 15	70.5 ± 12	0.496
Prior AMI	17 (14.4%)	108 (10.8%)	0.243
Severe COPD	25 (21.2%)	119 (11.9%)	0.005
Peripheral arteriopathy	24 (20.3%)	125 (12.5%)	0.018
LVEF	52 ± 16	56.6 ± 13	0.001
Acute kidney failure	26 (22%)	234 (23.4%)	0.731
Dialysis	7 (5.9%)	8 (0.8%)	0.001
Cirrhosis	7 (5.9%)	20 (2%)	0.009
Logistic euroSCORE	21.5 ± 14	16.7 ± 11	0.001
Coronary artery disease	57 (48.3%)	355 (35.6%)	0.007
Two-vessel disease	16 (13.6%)	78 (7.8%)	0.034
Prior PCI			
<6 months	20 (16.9%)	129 (12.9%)	0.133
>6 months	9 (7.6%)	71 (7.1%)	
Prior valve surgery	5 (4.2%)	42 (4.2%)	0.988
Prior CABG	17 (14.4%)	90 (9%)	0.112
Aortic bioprosthesis	4 (3.4%)	23 (2.3%)	0.468
Porcelain aorta	8 (6.8%)	69 (6.9%)	0.957
Clinical presentation			
NYHA classes III–IV	104 (88.2%)	773 (77.4%)	0.001
Syncope	11 (9.3%)	121 (12.1%)	0.373
Angina	31 (26.3%)	325 (32.6%)	0.165
Cardiogenic shock	1 (0.8%)	13 (1.3%)	0.674
Oliguric renal failure	2 (1.7%)	15 (1.5%)	0.551
High surgical risk	100 (84.7%)	768 (77%)	0.054
Rejection of surgery	17 (14.4%)	210 (21%)	0.090
Severe pulmonary hypertension	34 (28.8%)	173 (17.3%)	0.02
Mitral regurgitation			
Mild	47 (39.8%)	453 (45.4%)	0.179
Moderate	25 (21.2%)	156 (15.6%)	
Severe	5 (4.2%)	15 (1.5%)	
General anaesthesia	50 (42.9%)	422 (42.3%)	0.985
Axillary-subclavian access	10 (8.5%)	50 (5%)	0.115
Prosthesis size			
26 mm	60 (50.8%)	542 (54.3%)	0.440
29 mm	58 (49.2%)	442 (44.3%)	
31 mm	0%	9 (0.9%)	
Post-dilation	22 (18.6%)	184 (18.4%)	0.956
Need for 2nd prosthesis implantation	8 (6.8%)	32 (3.2%)	0.048
Post-implantation regurgitation			
0	17 (14.4%)	205 (20.5%)	0.271
1	64 (54.2%)	561 (56.2%)	
2	32 (27.1%)	203 (20.3%)	
3	4 (3.4%)	25 (2.5%)	
4	1 (0.8%)	4 (0.4%)	
AR ≥ 2	37 (31.4%)	233 (23.3%)	0.055
Position			
High	2 (1.7%)	48 (4.8%)	0.005
Low	30 (25.4%)	148 (14.8%)	
Ideal	86 (72.9%)	802 (80%)	
Conversion to surgery	0%	4 (0.4%)	0.639
Cardiac tamponade	1 (0.8%)	12 (1.2%)	0.593
AMI	1 (0.8%)	7 (6.7%)	0.951
Major haemorrhage	6 (5.1%)	34 (3.4%)	0.055
CVE	3 (2.5%)	8 (0.8%)	0.183
Acute kidney injury			
Stage 1	8 (6.8%)	43(4.3%)	0.035
Stage 2	2 (1.7%)	21 (2.1%)	
Stage 3	5 (4.2%)	12 (1.2%)	
New onset LBBB	17 (14.4%)	190 (19%)	0.204
Pacemaker	29 (24.6%)	256 (25.7%)	0.911

(continued on next page)

Table 7 (*continued*)

	Deaths N = 118	Alive N = 998	p
Vascular complications			
Major	4 (3.4%)	32 (3.2%)	0.855
Minor	6 (5.1%)	66 (6.6%)	

Table 8
Independent prediction factors for late mortality after TAVI (multivariate analysis).

	HR	CI 95%	p
Diabetes mellitus	1.59	1.092–2.319	0.016
Severe COPD	1.85	1.185–2.887	0.007
Prior LVEF	−0.97	0.962–0.985	0.001
NHYA classes II–IV	1.1	1.016–1.705	0.038
Acute kidney injury	1.73	0.985–3.039	0.057
Prior dialysis	−0.24	0.111–0.524	0.001
Coronary artery disease	1.35	0.924–1.984	0.120
Cirrhosis	0.57	0.237–1.389	0.218
Peripheral arteriopathy	0.78	0.462–1.348	0.387
Arterial hypertension	1.25	0.822–1.928	0.290
Logistic euroSCORE	1.01	0.989–1.023	0.499
Major haemorrhage	1.13	0.588–2.198	0.702
Aortic regurgitation > 2+	1.31	0.937–1.365	0.201
Severe pulmonary hypertension	0.84	0.525–1.351	0.477
Prosthesis on prosthesis	0.50	0.244–1.044	0.065
Prosthesis position	1.04	0.679–1.607	0.844

4.2% for patients who rejected surgery. In the PARTNER study, mortality was 3.4% and 5% respectively in cohorts A and B [29,30]. Mortality varies greatly in the different registries (5.4%–12.4%) although only the Italian registry is with CoreValve, while the others include Edwards-Sapien and CoreValve prosthesis [12–18]. The differences in the percentage of the transapical approach, which has higher mortality, may explain the variability in hospital mortality.

In our series, predictors of mortality at 30 days were post-TAVI complications (acute kidney failure, CVE, haemorrhage) and the logistic euroSCORE. The Italian registry also indicates the complications of the procedure (conversion to surgery, tamponade or haemorrhage) and prior valvuloplasty, EF <40% and diabetes mellitus [15].

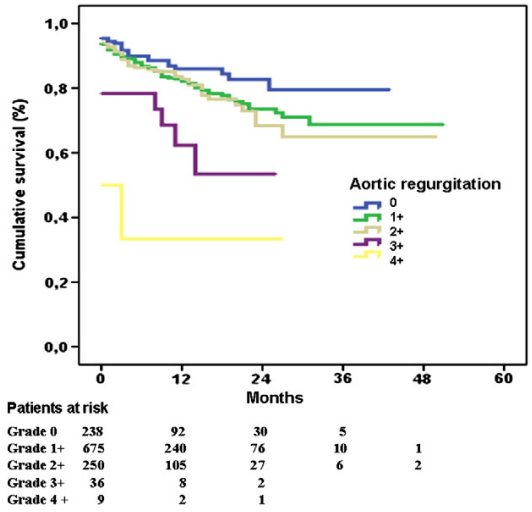


Fig. 2. Survival curve based on residual aortic regurgitation after TAVI, log-rank 34.9, p < 0.001.

Rodes et al. [18] analysed the predictors of mortality at 30 days in the Canadian experience with the Edwards-Sapien prosthesis and found predictors to be pulmonary hypertension, severe mitral regurgitation and the need for haemodynamic support. Buellesfeld et al. [16] showed that the patient's basal functional state, evaluated using the Karnofsky Index, was the only independent predictor of hospital mortality.

Although the incidence of CVE in our series is low (2.8%), there are other series such as the PARTNER A cohort that reach 5.5% at thirty days. In our series, associated factors were prior CVE, migration of the prosthesis during the procedure and aortic dissection. Nombela-Franco L et al. [31] reported that the presence of atrial fibrillation, peripheral arteriopathy or prior CVE was predictive factors for CVE.

Mortality at one and two years was 17.9% and 26.6%, figures that are slightly lower than those reported in the French and British registries, where one year mortality were 24% and 21.4% respectively [13,17], and similar to the Italian registry, 15% at one year [15]. Predictors of mortality in our series were related to prior comorbidities (severe COPD, diabetes mellitus or kidney failure in prior dialysis) in addition to a depressed LVEF or NYHA functional classes of III–IV. This data has been confirmed by other registries, with the addition of other comorbidities such as prior CVE or the presence of AR ≥ 2+ [15,18,32].

In the PARTNER study, at two years the presence of moderate or severe AR after TAVI was a factor associated with late mortality, with an effect on mortality proportional to the severity of the AR [33]. In our series, the presence of moderate or severe AR was not associated with mortality at 30 days, but there was an association with late mortality, presenting worse survival at one year than the patients with mild or no AR (Fig. 2), however, the presence of an AR ≥ 2+ was not an independent predictor of late mortality.

5.1. Limitations

This study presents limitations. Although patients were consecutively included, this was a voluntary registry, with each participating centre carrying out inclusion of data, and with events that were not independently adjudicated, even though patients with incomplete data were excluded. The participating centres are widely heterogeneous with regard to the volume of procedures carried out and follow-up periods. Definition of prosthesis position in relation to the aortic annulus was a subjective parameter left to the criterion of the operator.

6. Conclusions

The results of this registry reflect that in our environment, percutaneous treatment of high surgical risk aortic stenosis with the CoreValve prosthesis is a safe and effective therapeutic option with a high success rate that allows long-term clinical improvement. Survival during follow-up is conditioned by associated comorbidities.

Acknowledgment

We would like to acknowledge the members of the Ibero-American Registry without whose work this paper could not have been written. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Disclosures

Doctors Hernández-García, Morís, Trillo and Alonso-Briales are proctors for Medtronic Incorporation. The other authors present no conflict of interests to declare.

Appendix A. List of participants by centre, with the number of patients included

Centre	Researcher	No. of cases
Hospital Clínico Universitario Virgen de la Victoria, Málaga	José María Hernández	229
Hospital Central de Asturias	César Morís	115
Hospital Clínico Universitario de Santiago	Ramiro Trillo	101
Hospital Universitario Gregorio Marañón	Jaime Elízaga	85
Hospital Clínico Universitario de Valladolid	Federico Gimeno	70
Hospital Clínico San Carlos	Rosana Hernández	64
Hospital Santa Cruz, Lisbon	Rui Campante Teles	52
Hospital de Gaia, Oporto	Vasco de Gama Ribeiro	41
Hospital Universitario Virgen de las Nieves	Eduardo Molina	38
Hospital de Bellvitge	Angel Cequier	36
Hospital Carlos Haya	Cristóbal Urbano	33
Hospital Clínico de Salamanca	Ignacio Cruz	31
Hospital Fernández, Buenos Aires, Argentina	Miguel Oscar Payaslian	31
Hospital Santa Marta, Lisbon	Lino Patricio	22
ICBA, Buenos Aires, Argentina	Fernando Cura	22
Sanatorio Guemes, Buenos Aires, Argentina	Matías Sztejfman	21
Hospital Do Meixoeiro, Vigo	Andrés Iñiguez	20
Hospital Clínico de Caracas, Venezuela	Victor Rodríguez	18
Hospital Español, Buenos Aires, Argentina	Antonio Scuteri	18
Clinica Las Condes, Santiago de Chile, Chile	Carlos Caorsi	17
Hospital Juan Ramón Jimenez, Huelva	José F Díaz	16
Hospital General de Valencia	Alberto Berenguer	15
CEDIMAT, Santo Domingo, Dominican Republic	Pedro Ureña	15
Fundación Jimenez Díaz	Felipe Navarro	14
Fundación Cardioinfantil de Bogotá, Colombia	Mauricio Pineda	14
Fundación Cardiovascular de Colombia, Bucaramanga, Colombia	Sebastián Balestrini	13
Hospital de León	Felipe Fernández	11
Hospital del Tórax, Santiago de Chile, Chile	Fernando Pineda	10
Instituto Cardiovascular de Rosario, Argentina	Aníbal Damonte	8
Hospital Rebagliati, Lima, Peru	Gustavo Miranda	7
Hospital Privado de Cordoba, Argentina	Miguel Ballarino	6
Sanatorio Modelo Burzaco, Buenos Aires, Argentina	Pablo Marina	5
Hospital General Universitario de Albacete	Jesús Jiménez	4
Hospital de Navarra, Pamplona	Román Lezaun	4
Hospital Miguel Servet, Zaragoza	Isabel Calvo	2
Hospital General Yagüe, Burgos	Juan Manuel Durán	2
Hospital Fundación Alcorcón	Javier Botas	2
Hospital de Valme, Sevilla	Pastor Perez Santigosa	2
Hospital D. F. Santojanni, Buenos Aires, Argentina	Rubén Keborkian	2
Hospital Universitario de Maracaibo, Venezuela	Pedro Hidalgo	1
Hospital Privado Del Sur, Bahía Blanca, Argentina	Alejandro Álvarez	1

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Heart Valve Disease

Transcatheter Aortic Valve Replacement in Europe

Adoption Trends and Factors Influencing Device Utilization

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Montreal, Canada; Galway, Ireland; Rotterdam, the Netherlands; Bern and Basel, Switzerland; Massy, France; Milan, Italy; London and Belfast, United Kingdom; Copenhagen, Denmark; Wilrijk, Belgium; Lisbon, Portugal; Madrid, Spain; and Munich, Germany

Objectives The authors sought to examine the adoption of transcatheter aortic valve replacement (TAVR) in Western Europe and investigate factors that may influence the heterogeneous use of this therapy.

Background Since its commercialization in 2007, the number of TAVR procedures has grown exponentially.

Methods The adoption of TAVR was investigated in 11 European countries: Germany, France, Italy, United Kingdom, Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland. Data were collected from 2 sources: 1) lead physicians submitted nation-specific registry data; and 2) an implantation-based TAVR market tracker. Economic indexes such as healthcare expenditure per capita, sources of healthcare funding, and reimbursement strategies were correlated to TAVR use. Furthermore, we assessed the extent to which TAVR has penetrated its potential patient population.

Results Between 2007 and 2011, 34,317 patients underwent TAVR. Considerable variation in TAVR use existed across nations. In 2011, the number of TAVR implants per million individuals ranged from 6.1 in Portugal to 88.7 in Germany (33 ± 25). The annual number of TAVR implants performed per center across nations also varied widely (range 10 to 89). The weighted average TAVR penetration rate was low: 17.9%. Significant correlation was found between TAVR use and healthcare spending per capita ($r = 0.80$; $p = 0.005$). TAVR-specific reimbursement systems were associated with higher TAVR use than restricted systems (698 ± 232 vs. 213 ± 112 implants/million individuals ≥75 years; $p = 0.002$).

Conclusions The authors' findings indicate that TAVR is underutilized in high and prohibitive surgical risk patients with severe aortic stenosis. National economic indexes and reimbursement strategies are closely linked with TAVR use and help explain the inequitable adoption of this therapy. (J Am Coll Cardiol 2013;62:210–9) © 2013 by the American College of Cardiology Foundation

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Transcatheter aortic valve replacement (TAVR) gained Conformité Européenne (CE) mark approval in 2007, and the number of patients undergoing TAVR in Europe has increased exponentially in subsequent years. Despite the encouraging results from randomized, controlled trials and registries (1–4), there is anecdotal evidence that the use of TAVR varies markedly across European nations.

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Disparate adoption of medical technology is pervasive and results in inequitable patient access (5). Adoption kinetics of a novel medical technology such as TAVR and the factors influencing these variables have not been previously described. Regional differences in TAVR adoption are likely to have emerged because of variations in social, regulatory, economic, and political circumstances, as well as disease prevalence and longevity. This information may be of interest to patients, healthcare professionals, regulatory authorities, the medical device industry, and healthcare payers. In addition, these data may have implications for healthcare resource allocation, service development planning, assessment of equitable patient access, and physician training.

We sought to address this information gap by examining the trends in both the number of TAVR implants and number of centers across 11 European countries since CE mark approval. In addition, we investigated factors that may influence the heterogeneous adoption of this novel technology across nations.

Methods

Data sourcing. We investigated TAVR use in 11 European countries: Germany, France, Italy, United Kingdom (including Northern Ireland), Spain, the Netherlands, Switzerland, Belgium, Portugal, Denmark, and Ireland. Data were collected from 2 distinct sources. First we identified data from published national registries and large databases in countries in which reimbursement is linked to registry inclusion (3,4,6–8). Lead physicians from each nation submitted data from national registries regarding the annual number of patients treated with TAVR and the annual number of implanting centers from 2007 to 2011. Lead physicians take responsibility for the integrity of the data (Online Table 1).

Secondly, we present data from BIBA MedTech (London, United Kingdom), a cardiovascular market analysis group tracking TAVR use since mid-2009. These data were gathered through specifically designed questionnaires and prearranged telephone interviews with an extensive research panel comprising interventional cardiologists, cardiac surgeons, and administrators from a large number of TAVR centers throughout Europe. National implant estimates were extrapolated using an algorithm that incorporated the following variables: device pricing, national guidelines, national reimbursement policies, portfolio, spread, and trend. This final data set was cross-referenced with published registries.

Abbreviations and Acronyms

CE = Conformité Européenne
DRG = diagnosis-related group
GDP = gross domestic product
TAVR = transcatheter aortic valve replacement

Nation-specific data were combined with European Union–derived year-end population estimates (9) to calculate the: 1) annual and cumulative number of TAVRs performed in each nation; 2) annual number of TAVR implants per million population and TAVR implants per million population of age ≥75 years; 3) annual and cumulative number of TAVR centers in each nation; 4) number of TAVR centers per million population; and 5) mean number of TAVR implants per center for each nation.

TAVR penetration. The penetration rate of a therapy is a descriptor of the use of that therapy among eligible patients. Thus, TAVR penetration in each nation was determined as a measure of actual TAVR use relative to potential use. The numerator for calculating penetration was the number of living TAVR recipients at year end in each country. This was calculated as the sum of patients receiving TAVR in that calendar year and the number of living TAVR recipients from previous years. Annual mortality rates at 1, 2, 3, and 4 years following TAVR were assumed to be 24%, 33%, 49%, and 57%, respectively (10). The denominator was an estimate of the prevalence of patients with symptomatic severe aortic stenosis at high or excessive surgical risk that could potentially be treated with TAVR (11). Briefly, the proportion of elderly inhabitants of each country of age ≥75 years with severe aortic stenosis (3.4%) was determined by a random-effects meta-analysis. Among these patients, 75.6% were estimated to be symptomatic, 40.5% were deemed to be inoperable due to excessive surgical risk, and 5.2% were determined to be at high operative risk among the patients who received surgical aortic valve replacement (Society of Thoracic Surgeons risk of mortality ≥10%). Finally, 40.3% of inoperable patients and 80.0% of the high-risk patients were deemed to be potential TAVR candidates.

Economic indexes. National economic indexes and healthcare parameters for 2011 were obtained from European Union and Organisation for Economic Co-operation and Development databases (12). To establish economic factors associated with TAVR use, we correlated the number of TAVR implants per million population (age ≥75 years) to the volume indexed gross domestic product (GDP) per capita in purchasing power standards. GDP per capita in purchasing power standards is obtained by converting GDP per capita to a fictive currency using purchasing power parities that eliminate differences in currency and price levels between countries, thereby allowing meaningful volume comparisons of GDP. In addition, we correlated the number of TAVR implants per million population (age ≥75 years) with the percentage of GDP spent on health care and the purchasing power parities–adjusted total healthcare expenditure per capita (U.S.$). In Europe, health care is funded

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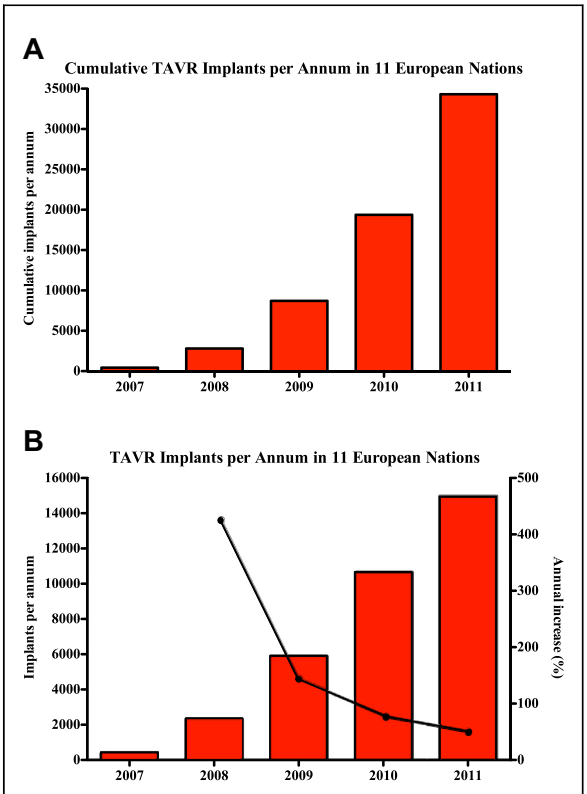


Figure 1 TAVR Adoption in Europe

(A) Cumulative transcatheter aortic value replacement (TAVR) implants in 11 Western European nations between 2007 and 2011. **(B)** TAVR implants per annum and percentage annual increase **(solid line)**.

either by taxation or by social insurance institutions, which are largely outside the commercial marketplace. We classified healthcare financing in each country according to the principal source of funding and compared TAVR use between these systems.

TAVR reimbursement. Medical device reimbursement in Europe is inconsistent because healthcare regulators with diverse policies dictate the method of reimbursement (12). We divided existing 2011 TAVR reimbursement into 2 categories and compared TAVR use between these schemes: 1) "TAVR-specific" systems, in which TAVR is completely reimbursed via a therapy-specific national diagnosis-related group (DRG) tariff; and 2) "constrained" systems, in which TAVR reimbursement is only partially funded by an existing national DRG tariff or the cost is borne by a local healthcare trust or hospital budget.

Statistics. Continuous variables are presented as mean ± SD or median with interquartile range according to distribution. Normally distributed variables were compared with the Student *t* test and nonnormally distributed variables compared with the Wilcoxon rank-sum test. Categorical variables are presented as numbers and percentages. Bland-Altman plots were used to graphically compare the 2 sources of TAVR implant data. Correlation between economic indexes and TAVR implants per million population (age ≥75 years) was assessed using the Pearson or Spearman correlation according to distribution. A probability value <0.05 was considered to indicate statistical significance. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois).

Results

Data sourcing. With the exception of 1 small center (<30 TAVR implants per annum) in both the Netherlands and Belgium, complete data were available from the 11 study nations. Herein, we report the results from the national databases which include TAVR implant data since CE mark approval in 2007. The BIBA MedTech data set includes data from 2009 to 2011 and is presented in the Online Appendix.

Implantation rates. Between January 2007 and December 2011, 34,317 patients underwent TAVR in the 11 study nations (Fig. 1A). Almost half of all implants were performed in Germany (45.9%), with Italy (14.9%) and France (12.9%)

Table 1 TAVR Implants in Each Nation

	TAVR Implants per Annum, % increase					Cumulative TAVR	Cumulative TAVR, %
	2007	2008	2009	2010	2011		
Germany	157	921 (487)	2,566 (179)	4,859 (89)	7,252 (49)	15,755	45.9
France	58	82 (41)	320 (290)	1,523 (376)	2,447 (61)	4,430	12.9
Italy	71	450 (534)	1,138 (153)	1,581 (39)	1,879 (19)	5,119	14.9
United Kingdom	66	295 (347)	561 (90)	778 (39)	1,037 (33)	2,737	8.0
Spain	12	151 (1,158)	426 (182)	655 (54)	770 (18)	2,014	5.9
the Netherlands*	40	123 (208)	226 (84)	329 (46)	438 (33)	1,156	3.4
Switzerland	18	127 (606)	277 (118)	382 (38)	501 (31)	1,305	3.8
Belgium*	10	100 (900)	163 (63)	257 (58)	289 (12)	819	2.4
Portugal	4	13 (225)	52 (300)	67 (29)	65 (-3)	201	0.6
Denmark	9	81 (800)	126 (56)	190 (51)	239 (26)	645	1.9
Ireland	0	12	61 (408)	34 (−44)	29 (−15)	136	0.4
Total (% increase)	445	2,355 (429)	5,916 (151)	10,655 (81)	14,946 (40)	34,317	100

Values are n (%). *Excludes 1 low-implant volume center (<30 TAVR implants per annum) in both the Netherlands and Belgium.
TAVR = transcatheter aortic valve replacement.

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the next most frequent implanters (Table 1). Ireland accounted for the smallest proportion of implants (0.4%). In 2011, the highest annual increases in procedural volume were observed in France (61%) and Germany (49%), whereas Ireland (−15%) and Portugal (−3%) were the only nations to experience declines. The annual number of implants increased 33-fold from 455 in 2007 to 14,946 in 2011 (Fig. 1B). Although the annual procedural volume growth rate decreased from 429% in 2008 to 40% in 2011, it remained positive.

We observed a wide variation in the number of TAVR implants per million population (Figs. 2A and 2B). Germany (88.7) and Portugal (6.1) accounted for the highest and lowest number of TAVR implants per million population

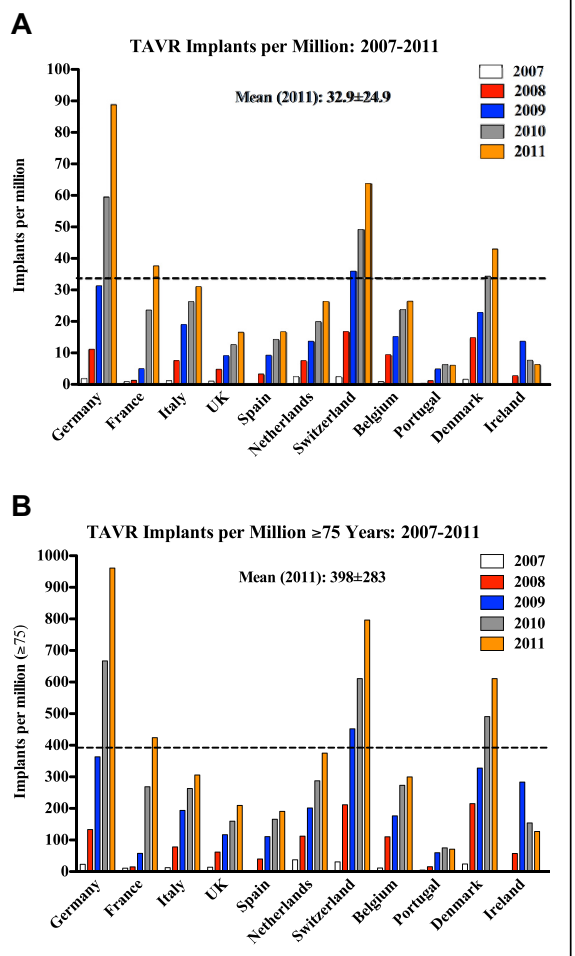


Figure 2 TAVR Implants per Million Population in the Study Nations

TAVR implant dynamics in the study nations between 2007 and 2011. **(A)** TAVR implants per million population. **(B)** TAVR implants per million population age ≥75 years. **Broken line** represents mean. Abbreviation as in Figure 1.

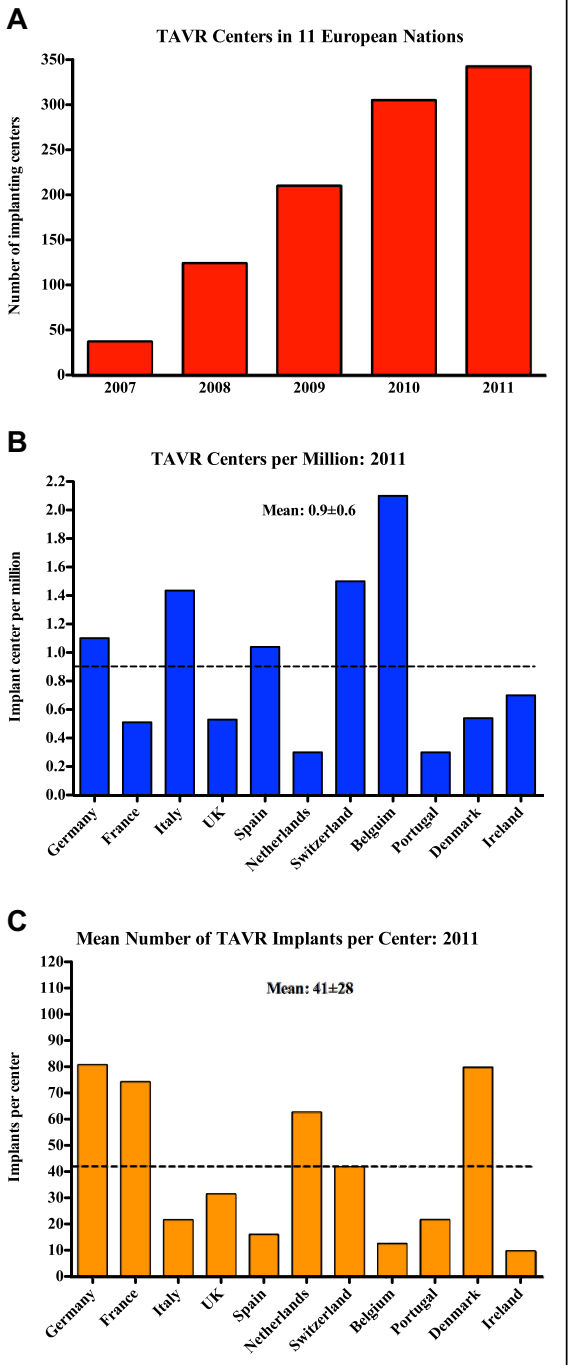


Figure 3 TAVR Centers in Europe

(A) Cumulative TAVR centers in 11 Western European nations from 2007 to 2011. **(B)** TAVR centers per million population in 2011. **(C)** Mean number of TAVR implants per center in each nation in 2011. **Broken line** represents mean. Abbreviation as in Figure 1.

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in 2011, respectively. Among the 11 study nations, the mean number of TAVR implants per million population was 32.9 ± 24.9 and the mean number of TAVR implants per million population age ≥75 years was 398 ± 283.

Implanting centers. The number of centers performing TAVR increased approximately 9-fold from 37 in 2007 to 342 in 2011 (Fig. 3A). In 2011, Germany (90) and Italy (87) had the highest number of TAVR centers, whereas Portugal, Denmark, and Ireland (3 each) had the lowest (Table 2). Belgium had the highest number of TAVR centers per million population (2.1) and Portugal (0.3) the lowest (Fig. 3B). On average, there were 0.9 ± 0.6 TAVR centers per million population. These numbers led to an average of 41 ± 28 TAVR implants per center in 2011, with estimates in individual countries ranging from 10 in Ireland to 89 in Germany (Fig. 3C). On account of the high number of TAVR centers per million population, Belgium had the second lowest number of TAVR implants per center (13).

TAVR penetration. In 2011, we estimated that there were 28,400 living TAVR recipients and 158,371 potential TAVR candidates in the 11 study nations (Table 3). Thus, the calculated weighted average TAVR penetration rate in 2011 was 17.9%. The estimated collective and nation-specific TAVR penetration rates are presented in Figures 4A and 4B. Germany (36.2%) and Switzerland (34.5%) had the highest TAVR penetration rates; Portugal (3.4%) and Spain (8.4%) had the lowest penetration rates.

Economic indexes. We assessed the association between several economic indexes and TAVR use (Table 4). The volume-indexed GDP per capita, which is considered to be a reliable indicator of a country's standard of living, was not associated with TAVR use ($r = 0.53$; $p = 0.10$) (Fig. 5A). In contrast, a significant linear correlation was found between the number of TAVR implants per million population (age ≥75 years) and healthcare spending as a percentage of GDP ($r = 0.68$; $p = 0.025$) (Fig. 5B) and healthcare spending per capita ($r = 0.80$; $p = 0.005$) (Fig. 5C). We also found an association between the principal source of healthcare funding and the number of TAVR implants per million population (Fig. 5D). Although not statistically significant, there was a trend toward increased TAVR use in those nations in which healthcare was funded principally by social insurance (Germany, France, the Netherlands, Switzerland, and Belgium) than those principally funded by taxation (Italy, United Kingdom, Spain, Portugal, Denmark, and Ireland) (571 ± 290 vs. 252 ± 192 implants per million population age ≥75 years; $p = 0.056$).

TAVR reimbursement. TAVR reimbursement strategies across the study nations were heterogeneous (Fig. 6, Table 4). TAVR-specific national DRG-based reimbursement occurs in Germany, France, Switzerland, and Denmark. Constrained reimbursement systems were noted for the United Kingdom, Spain, the Netherlands, Belgium, Portugal, and Ireland, where the cost of TAVR is borne by a local healthcare trust (United Kingdom) or by the hospital budget. Reimbursement systems evolved over the course of the study. For example, a TAVR-specific DRG was introduced in Germany in January 2008 as opposed to France, where it was introduced in December 2009.

We investigated the association between reimbursement system and both TAVR use (implants per million population age ≥75 years) and the number of TAVR implants per center. Italy was excluded from the analysis because reimbursement strategies varied across provinces. TAVR-specific reimbursement systems were associated with a 3.3-fold higher number of TAVR implants per million population (age ≥75 years) than constrained systems (698 ± 232 vs. 213 ± 112; $p = 0.002$) (Fig. 5E). Furthermore, TAVR-specific reimbursement systems were associated with 2.5 times more TAVR implants per center than constrained systems (69 ± 18 vs. 26 ± 20 implants per center; $p = 0.008$) (Fig. 5F).

Comparison between registry and BIBA data sets. The correlation between national registry and BIBA MedTech data sets for TAVR implant numbers is presented in a

Table 2 Implant Centers

	Cumulative TAVR Centers					TAVR Centers, 2011, %	TAVR Centers per Million Population, 2011	TAVR Implants per Center, 2011
	2007	2008	2009	2010	2011			
Germany	6	36	61	80	90	26.3	1.1	81
France	6	12	16	33	33	9.6	0.5	74
Italy	8	21	50	75	87	25.4	1.4	22
United Kingdom	6	19	26	31	33	9.6	0.5	31
Spain	2	10	20	39	48	14.0	1.0	16
the Netherlands	3	6	7	7	7	2.0	0.4	63
Switzerland	1	7	8	11	12	3.5	1.5	42
Belgium	2	7	13	20	23	6.7	2.1	13
Portugal	1	2	3	3	3	0.9	0.3	22
Denmark	2	3	3	3	3	0.9	0.5	80
Ireland	0	1	3	3	3	0.9	0.7	10
Total	37	124	210	305	342	100	0.9 ± 0.6	41 ± 28

Values are n or mean ± SD, unless otherwise indicated.
Abbreviation as in Table 1.

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Table 3 TAVR Penetration, 2011

	Total Population, 2011	Population Age ≥ 75 years, 2011	Severe AS (3.4%)	Symptomatic Severe AS (75.6%)	Ineligible for SAVR		Eligible for SAVR			Total TAVR Eligible	TAVR Penetration, 2011, %
					Ineligible for SAVR (40.5%)	TAVR Eligible (40.3%)	Eligible for SAVR (59.5%)	High Risk (5.2%)	TAVR Eligible (80%)		
Germany	81,751,602	7,546,760	256,590	193,982	78,563	31,661	115,419	6,002	4,801	36,462	36.2
France	65,048,412	5,771,830	196,242	148,359	60,085	24,214	88,274	4,590	3,672	27,887	13.9
Italy	60,626,442	6,147,116	209,002	158,005	63,992	25,789	94,013	4,889	3,911	29,700	13.8
United Kingdom	62,498,612	4,947,416	168,212	127,168	51,503	20,756	75,665	3,935	3,148	23,903	9.1
Spain	46,152,926	4,031,995	137,088	103,638	41,947	16,915	61,665	3,207	2,565	19,481	8.4
the Netherlands	16,655,799	1,166,868	39,647	29,993	12,147	4,895	17,846	928	742	5,638	16.3
Switzerland	7,870,134	629,004	21,386	16,168	6,548	2,639	9,620	500	400	3,039	34.5
Belgium	10,951,266	954,607	32,457	24,537	9,938	4,005	14,600	759	607	4,612	14.1
Portugal	10,529,255	964,125	32,780	24,782	10,037	4,045	14,745	767	613	4,658	3.4
Denmark	5,560,628	391,138	13,299	10,054	4,072	1,641	5,982	311	249	1,890	27.1
Ireland	4,569,864	227,917	7,749	5,858	2,373	956	3,486	181	145	1,101	9.2
Total	376,049,328	32,778,776	1,114,478	842,546	341,230	137,516	501,315	26,068	20,855	145,962	Weighted average: 17.9

Population data derived from EU sources (9). Estimates of TAVR-eligible patients derived from Osnabrugge (11).
AS = aortic stenosis; SAVR = surgical aortic valve replacement; other abbreviation as in Table 1.

Bland-Altman plot (Online Fig. 1). There was satisfactory agreement between the 2 sources of information, and both provided similar results and conclusions (Online Figs. 2 to 6, Tables 2 to 4).

Discussion

This study described the adoption of TAVR in 11 Western European nations since the 2007 CE mark approval of the Edwards Sapien (Edwards Lifesciences Inc., Irvine, California) and Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) systems. The main findings are: 1) more than 34,000 patients received TAVR between 2007 and 2011; 2) there is substantial variation in the adoption of TAVR across nations; 3) there is disparity in the annual number of TAVR implants per center across nations (mean 41 ± 28); 4) TAVR remains greatly underutilized, with an estimated weighted penetration rate of 17.9%; and 5) economic and reimbursement indexes may help explain the variability in TAVR adoption across nations.

We found considerable variation in TAVR use across nations. Germany had more than 2 times the implant rate of all other nations except Switzerland and 14 times the implant rate of Ireland and Portugal. Regional variation in the adoption of medical technology is not unique to TAVR. In Europe, disparate use of drug-eluting stents and implantable cardioverter-defibrillators (ICDs) has previously been described (5,14,15). The identification of inequitable access to medical technologies is important because it generates discussion and initiatives to address inequalities and the corresponding impact on patient outcomes through payer- and physician-led programs (e.g., Stent for Life initiative [16]).

Explanations for the divergence in TAVR adoption among countries are numerous and varied. The economic challenge of providing progressive care for an aging population has mandated that the use of new medical device technologies be not only determined by the expectation of improved clinical outcomes but also by cost effectiveness. It is axiomatic, therefore, that the magnitude of healthcare resources influences the adoption of new medical device technology. Consistent with our findings that healthcare expenditure correlated with TAVR use, the use of ICDs in Europe has also been associated with national economic performance (5,14). Not surprisingly, the lowest TAVR implantation rates were found in Spain, Portugal, and Ireland, who are currently experiencing substantial economic hardship. In these nations, the medical device industry could provide additional support to develop and maintain TAVR programs. As was the case with drug-eluting stents and ICDs, the introduction of competitive TAVR systems should decrease procedural costs and consequently increase TAVR adoption.

Procedural reimbursement and healthcare funding are critical factors in determining the adoption of new medical device technology. Previously, these factors were shown to influence the use of ICDs and coronary stents. In the current study, TAVR use and the number of TAVR implants per

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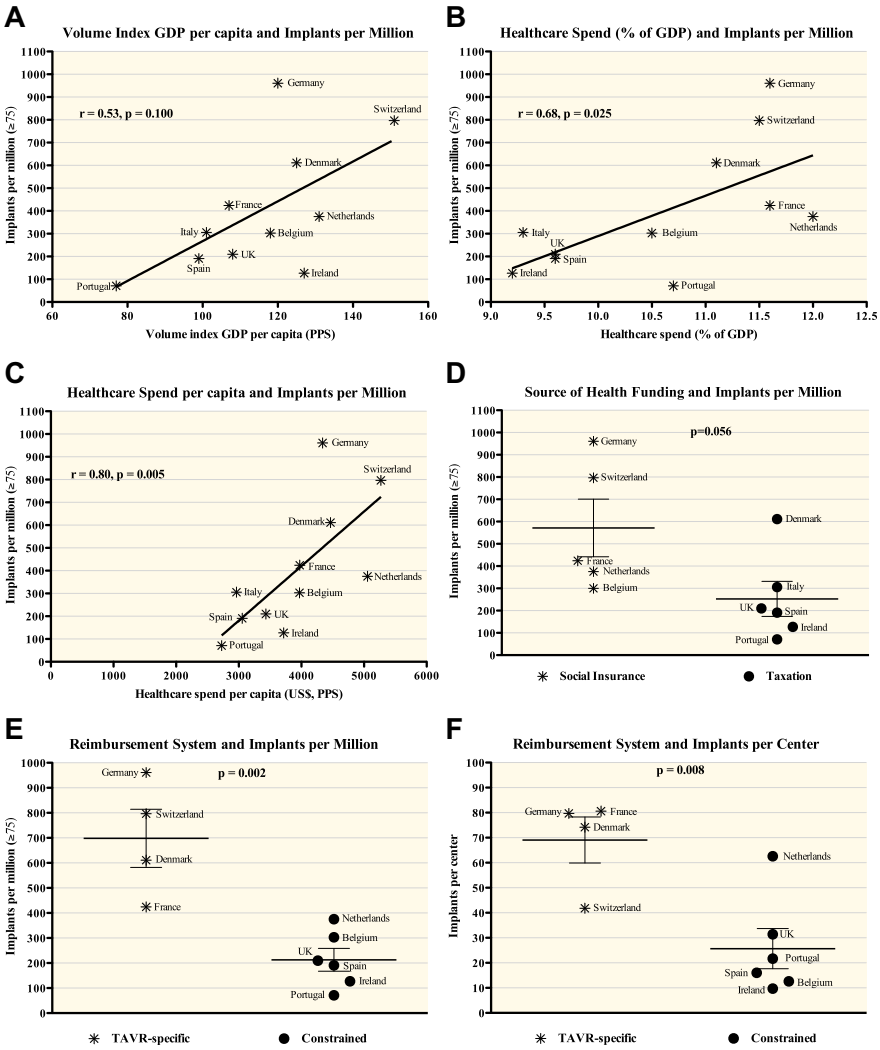


Figure 5 **Factors Influencing TAVR Adoption in Europe**

Correlation between TAVR implants per million population (age ≥75 years) and **(A)** volume-indexed gross domestic product (GDP); **(B)** healthcare expenditure (% of GDP); and **(C)** annual healthcare spend per capita (U.S.$). Number of TAVR implants per million population (age ≥75 years) according to **(D)** the principal source of healthcare funding (social insurance or taxation) and **(E)** the system of reimbursement (TAVR specific or constrained). **(F)** The average number of TAVR implants per center in 2011 and the system of reimbursement. DRG = diagnosis-related group; PPS = purchasing power standards; other abbreviation as in Figure 1.

volume for these complex procedures (26–28). National health technology assessments and position papers have suggested that each center perform a minimum of 24 TAVR procedures per annum (27,29,30). We observed centers with low procedural volume and therefore nonadherence to these criteria in several nations. In particular, centers in Ireland, Belgium, and Spain performed on average less than 20 implants in 2011. Two distinct observations explain the low procedural volume: 1) low number of TAVR implants per million population (Ireland); and 2) excessive number of TAVR centers (Belgium and Spain). The reasons for the variation in the number of TAVR centers per million population and center volume across nations are unclear. National political and financial concerns, healthcare policy, population density and profile, reimbursement strategy, and cultural factors may be important in determining the number of centers in each nation.

The way complex medical technology is disseminated has been revolutionized by TAVR. Clinical site selection, mandatory physician and team training, and detailed

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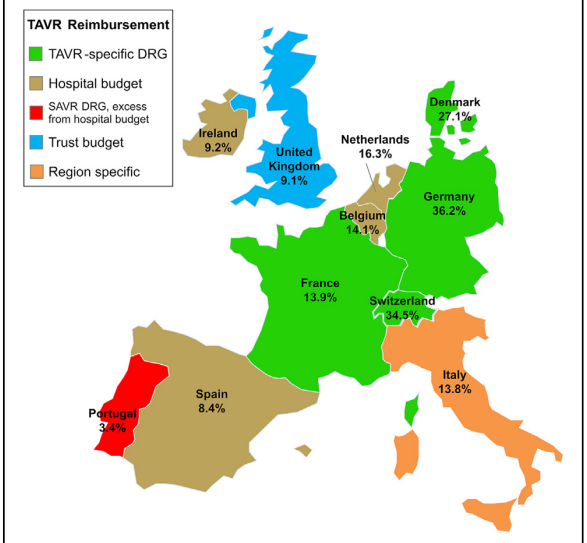


Figure 6 Reimbursement Systems and TAVR Penetration Across Europe

Map of the 11 study nations depicting estimated TAVR penetration rate and the 2011 TAVR reimbursement systems. SAVR = surgical aortic valve replacement; other abbreviations as in Figures 1 and 5.

algorithms outlining patient selection have become the standard of care. Nevertheless, the variation in the adoption of TAVR in Western Europe is clear. Physicians, medical societies, the medical device industry, and other stakeholders have a responsibility to ensure the appropriate use and sensible dispersion of this innovative technology.

Study limitations. Several limitations are of note. First, although every attempt was made to ensure the validity of the implant data, both data sources should be considered to be estimates. Registry data may underestimate the true scale of TAVR use because some cases or small implant centers may not have been included. Secondly, the estimates of TAVR use are likely to have included patients treated for off-label indications, such as patients at lower surgical risk, which may have affected the estimates of TAVR penetration.

Conclusions

Despite the rapid adoption of TAVR across Europe, our findings indicate that a sizeable treatment gap remains for high/prohibitive surgical risk patients with severe aortic stenosis. National economic indexes and reimbursement strategies are closely linked with TAVR use and may explain the inequitable adoption of TAVR across nations.

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Key Words: aortic stenosis ▪ transcatheter aortic valve implantation ▪ transcatheter aortic valve replacement.

APPENDIX

For supplemental tables and figures, please see the online version of this article.

Manuscript #5

Research

Original Investigation

Transcatheter Aortic Valve Implantation in Failed Bioprosthetic Surgical Valves

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IMPORTANCE Owing to a considerable shift toward bioprosthesis implantation rather than mechanical valves, it is expected that patients will increasingly present with degenerated bioprostheses in the next few years. Transcatheter aortic valve-in-valve implantation is a less invasive approach for patients with structural valve deterioration; however, a comprehensive evaluation of survival after the procedure has not yet been performed.

OBJECTIVE To determine the survival of patients after transcatheter valve-in-valve implantation inside failed surgical bioprosthetic valves.

DESIGN, SETTING, AND PARTICIPANTS Correlates for survival were evaluated using a multinational valve-in-valve registry that included 459 patients with degenerated bioprosthetic valves undergoing valve-in-valve implantation between 2007 and May 2013 in 55 centers (mean age, 77.6 [SD, 9.8] years; 56% men; median Society of Thoracic Surgeons mortality prediction score, 9.8% [interquartile range, 7.7%-16%]). Surgical valves were classified as small (≤21 mm; 29.7%), intermediate (>21 and <25 mm; 39.3%), and large (≥25 mm; 31%). Implanted devices included both balloon- and self-expandable valves.

MAIN OUTCOMES AND MEASURES Survival, stroke, and New York Heart Association functional class.

RESULTS Modes of bioprosthesis failure were stenosis (n = 181 [39.4%]), regurgitation (n = 139 [30.3%]), and combined (n = 139 [30.3%]). The stenosis group had a higher percentage of small valves (37% vs 20.9% and 26.6% in the regurgitation and combined groups, respectively; *P* = .005). Within 1 month following valve-in-valve implantation, 35 (7.6%) patients died, 8 (1.7%) had major stroke, and 313 (92.6%) of surviving patients had good functional status (New York Heart Association class I/II). The overall 1-year Kaplan-Meier survival rate was 83.2% (95% CI, 80.8%-84.7%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 95% CI, 68.9%-83.1%; 34 deaths; 86 survivors) in comparison with the regurgitation group (91.2%; 95% CI, 85.7%-96.7%; 10 deaths; 76 survivors) and the combined group (83.9%; 95% CI, 76.8%-91%; 18 deaths; 66 survivors) (*P* = .01). Similarly, patients with small valves had worse 1-year survival (74.8% [95% CI, 66.2%-83.4%]; 27 deaths; 57 survivors) vs with intermediate-sized valves (81.8%; 95% CI, 75.3%-88.3%; 26 deaths; 92 survivors) and with large valves (93.3%; 95% CI, 85.7%-96.7%; 7 deaths; 73 survivors) (*P* = .001). Factors associated with mortality within 1 year included having small surgical bioprosthesis (≤21 mm; hazard ratio, 2.04; 95% CI, 1.14-3.67; *P* = .02) and baseline stenosis (vs regurgitation; hazard ratio, 3.07; 95% CI, 1.33-7.08; *P* = .008).

CONCLUSIONS AND RELEVANCE In this registry of patients who underwent transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves, overall 1-year survival was 83.2%. Survival was lower among patients with small bioprostheses and those with predominant surgical valve stenosis.

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Surgical aortic valve replacements increasingly use bioprosthesis implants rather than mechanical valves.[1] Structural valve deterioration can result in leaflet degeneration and failure, as evidenced by valve stenosis, regurgitation, or a combination of both.[2-4] Owing to a considerable shift toward bioprosthesis implantation, it is expected that patients will increasingly present with degenerated bioprostheses. Treatment of patients with failed bioprostheses is a clinical challenge. Although reoperation is considered the standard of care, these patients are frequently elderly, and repeat cardiac surgery carries significant morbidity and mortality risks.[5,6]

Transcatheter aortic valve replacement has become an alternative, less invasive treatment for patients at high surgical risk with severe symptomatic native aortic valve stenosis.[7-11] Previous reports have demonstrated the feasibility of treating degenerated bioprostheses with transcatheter heart valves inside failed surgical valves (eFigure 1 in the Supplement).[12-16] Preliminary data from the Valve-in-Valve International Data (VIVID) Registry revealed that although procedural success was achieved in 93.1% of patients, the valve-in-valve procedure included several safety and efficacy concerns.[17] However, a comprehensive long-term evaluation of valve-in-valve procedures of a larger group of patients with considerable follow-up has not yet been performed.

Methods

Registry Design

The VIVID Registry was initiated in December 2010 and was designed to collect data on valve-in-valve procedures using mainly self-expandable CoreValve (Medtronic) and balloon-expandable Edwards SAPIEN devices (Edwards Lifesciences). Valve-in-valve procedures performed using other transcatheter devices or implanted in positions other than the aortic valve were not included in the current analyses. We collected data retrospectively for cases performed before registry initiation and prospectively thereafter. A total of 55 centers from Europe, North America, Australia, New Zealand, and the Middle East contributed data (eTable 1 in the Supplement). Data were collected for cases performed between 2007 and May 2013 using a dedicated case report form. All inconsistencies were resolved directly with local investigators and on-site data monitoring. All patients gave written informed consent to a transcatheter aortic valve-in-valve procedure. The inclusion of patients was approved in each center by a local ethics committee.

Definitions

Prediction of patient operative mortality after conventional surgical valve replacement was calculated using the Society of Thoracic Surgeons (STS) score (http://riskcalc.sts.org/de.aspx) and the LogEuroSCORE (http://www.euroscore.org/calcold.html). Mechanism of bioprosthetic valve failure (ie, stenosis, regurgitation, or combined) was evaluated according to the criteria of the American Society of Echocardiography.[18] Patients with at least a moderate degree of both stenosis and regurgitation were included in the combined group. Other patients were categorized according to the primary mechanism of failure, either in the stenosis group or in the regurgitation group. Body surface area was calculated using the Mosteller formula. Internal diameter of a surgical valve was derived from its label size and manufacturer charts.[19] In cases for which label size was unknown, internal diameter was defined according to available imaging modes, such as computed tomography or transesophageal echocardiography. Major clinical end points were assessed according to the Valve Academic Research Consortium criteria.[20] Early postimplantation hemodynamic data were obtained from either intraprocedural or first postprocedural echocardiogram. Post-valve-in-valve severe prosthetic-patient mismatch (PPM) was defined in cases that had a postprocedure effective aortic orifice area divided by body surface area of less than 0.65 cm^2/m^2.[21]

Statistical Analysis

Results are presented as mean (standard deviation) for continuous variables with normal distribution, as median (interquartile range) for continuous variables without normal distribution, and as number (percentage) for categorical data. The *t* test was used to compare normally distributed continuous variables between the devices used during the valve-in-valve procedure and the Wilcoxon rank sum test was used for variables not normally distributed. One-way analysis of variance was used to compare the stenosis, regurgitation, and combined groups for normally distributed continuous variables and the Kruskal-Wallis test was used for non-normally distributed data. The χ^2 and Fisher exact tests were used to compare categorical variables. Time-to-event curves using the Kaplan-Meier method were calculated. Results were compared using the log-rank statistic. High postprocedural gradients were defined as those having mean gradients of at least 20 mm Hg.[20] Variables entered into bivariable models included sex, age, baseline echocardiographic parameters (ie, left ventricular ejection fraction), STS score, baseline renal failure, bioprosthetic type (stented vs stentless) and size, device used during the valve-in-valve procedure, and procedural access. Three semiparametric Cox proportional hazards regression analyses were conducted. The first was an overall analysis and the others were time-segmented analyses. For the latter, the hazard function was used as a guide to determine approximate time points for the end of the early phase of hazard and the beginning of the late phase. This occurred at approximately 30 days. Therefore, piece-wise time-segmented Cox analyses were performed for 2 periods. For one pair of analyses, deaths occurring within the first 30 postoperative days were analyzed, with follow-up beyond that time set to 30 days; then deaths beyond 30 days were analyzed. Characteristics included in the multivariable model for 1-year death were bioprosthesis label size, mechanism of failure, procedural access, and STS score. The results of the multivariable analysis are presented as hazard ratios (HRs) for 1-year mortality with 95% confidence intervals. A 2-sided $P<.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 20.0 statistical software (IBM SPSS Inc).

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Table 1. Baseline Characteristics at the Time of Valve-in-Valve Procedure

Characteristics	All (n = 459)	Mechanism of Surgical Valve Failure				Device Used		
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	*P* Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	*P* Value
Age, mean (SD), y	77.6 (9.8)	78.8 (7.8)	77.1 (10.6)	76.6 (11.1)	.10	77.6 (10)	77.6 (9.7)	.95
Men, No. (%)	257 (56)	87 (48)	93 (66.9)	77 (55.4)	.002	113 (53.1)	144 (58.5)	.25
Height, mean (SD), cm	167.2 (9.8)	167.1 (9.9)	168.1 (9.7)	166.5 (9.8)	.20	166.9 (10)	167.4 (9.7)	.59
Weight, mean (SD), kg	73.9 (15.2)	77.6 (16.5)	72 (13.3)	70.8 (14.1)	<.001	73.7 (15)	74 (15.4)	.84
BMI, mean (SD)[a]	26.4 (4.8)	27.7 (4.8)	25.4 (3.9)	25.5 (4.2)	<.001	26.4 (4.6)	26.3 (4.4)	.78
BSA, mean (SD), m^2	1.85 (0.22)	1.89 (0.24)	1.83 (0.2)	1.8 (0.21)	.002	1.84 (0.22)	1.85 (0.23)	.76
LogEuroSCORE, median (IQR), %[b]	29 (19.1-42.3)	29.8 (20-39.9)	25.7 (16-41.9)	30.3 (22.3-44.7)	.18	29 (18.6-38.7)	29 (19.3-44.2)	.48
STS score, median (IQR), %[b]	10 (6.2-16.1)	9.9 (6.1-13.9)	9.9 (5.8-15.6)	10.8 (7.1-18.4)	.33	11 (6.2-17.3)	9.3 (6.1-14.1)	.13
Diabetes mellitus, No. (%)	125 (28.7)	69 (40.1)	28 (21.2)	28 (21.4)	.001	62 (31.1)	63 (26.5)	.29
Peripheral vascular disease, No. (%)	114 (26.1)	53 (30.6)	31 (23.5)	30 (22.9)	.22	37 (17.4)	77 (31.3)	<.001
Chronic renal failure, No. (%)[c]	224 (48.8)	80 (44.2)	71 (51.1)	72 (51.8)	.37	81 (38)	140 (56.9)	<.001
Previous stroke/TIA, No. (%)	51 (11.7)	23 (13.3)	17 (12.8)	12 (9.2)	.52	24 (12.2)	27 (11.3)	.76
>1 Previous SAVR, No. (%)	62 (13.5)	16 (8.8)	23 (16.5)	23 (16.5)	.06	27 (12.7)	35 (14.2)	.63
NYHA functional class, No. (%)								
II	35 (7.8)	14 (7.7)	10 (7.2)	11 (7.9)	.97	15 (7)	20 (8.1)	.66
III	283 (61.9)	130 (71.8)	78 (56.1)	75 (54)	.001	124 (58.2)	159 (64.6)	.16
IV	141 (30.3)	37 (26.2)	51 (36.7)	53 (38.1)	.001	74 (34.7)	67 (27.2)	.08
Left ventricular ejection fraction, mean (SD), %	50.3 (13.1)	51.7 (12.9)	49.0 (13.1)	49.7 (13.3)	.16	49.1 (13.4)	51.2 (12.8)	.08

Abbreviations: BMI, Body mass index; BSA, body surface area; IQR, interquartile range; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Prediction of operative mortality after conventional surgical valve replacement (STS score: http://riskcalc.sts.org/de.aspx; LogEuroSCORE: http://www.euroscore.org/calcold.html). Range of scores is 0% to 100%; higher score indicates greater patient risk.

[c] Calculated glomerular filtration rate <60 mL/min.

Results

Patient Demographics

Table 1 shows clinical characteristics of the 459 patients included in the registry. Mean age was 77.6 (SD, 9.8) years (range, 25-92 years) and 56% were men. The mechanism of failure of surgical bioprostheses was stenosis in 181 patients (39.4%), regurgitation in 139 (30.3%), and combined in 139 (30.3%). The balloon-expandable device was used in 246 patients (53.6%) and the self-expandable in 213 patients (46.4%). The distribution of failure mode differed between the balloon-expandable device group (stenosis, n = 106 [43.1%]; regurgitation, n = 61 [24.8%]; combined, n = 79 [32.1%]) and the self-expandable device group (stenosis, n = 75 [35.2%]; regurgitation, n = 78 [36.6%]; combined, n = 60 [28.2%]), as more regurgitant bioprostheses were treated by self-expandable device implantation (*P* = .02). There were no significant differences in surgical risk scores when patients were stratified according to mechanism of failure or according to the device used during the valve-in-valve procedure. The stenosis group had more women and higher patient body weight, body mass index, and body surface area levels in comparison with the other groups (Table 1).

Degenerated Bioprosthetic Valves and Characteristics of Valve-in-Valve Procedures

Patients included in the registry had 1 to 4 previous cardiac surgeries (**Table 2** and eTable 2 in the Supplement). Surgical valve sizes were characterized as small (label size ≤21 mm; n = 133 [29%]), intermediate (>21 mm and <25 mm; n = 176 [38.3%]), large (≥25 mm; n = 139 [30.3%]), and unknown (n = 11 [2.4%]). Bioprostheses were either stented (n = 366 [79.7%]) or stentless (n = 93 [20.3%]). The stenosis group had more stented valves (95.6% vs 60.4% in the regurgitation group and 78.4% in the combined group; *P* < .001) and more small valves (37% vs 20.9% and 26.6%, respectively; *P* = .005). There was no significant difference between the self-expandable and balloon-expandable device groups in the rate of valve-in-valve procedures performed in small bioprostheses (31.9% vs 26.4%, respectively; *P* = .19).

Devices used included balloon-expandable 20-mm, 23-mm, 26-mm, and 29-mm sizes (58.9% SAPIEN XT) and self-expandable 23-mm, 26-mm, 29-mm, and 31-mm sizes. eTable3 in the Supplement shows data on valve-in-valve procedural characteristics. Device delivery access included transfemoral (n = 270 [58.8%]), transapical (n = 171 [37.3%]), transaxillary (n = 13 [2.8%]), and direct aortic (n = 5 [1.1%]). The main ac-

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Table 2. Surgical Valve Characteristics at the Time of Valve-in-Valve Procedure

Characteristics	All (n = 459)	Mechanism of Surgical Valve Failure				Device Used		
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	*P* Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	*P* Value
Time since last SAVR, median (IQR), y[a]	9 (6-12)	8 (5-11)	10(7-14)	10 (7-14)	.04	9 (7-13)	9 (6-12)	.08
Type, No. (%)					<.001			<.001
Stented	366 (79.7)	173 (95.6)	84 (60.4)	109 (78.4)		152 (71.4)	214 (87)	
Stentless	93 (20.3)	8 (4.4)	55 (29.6)	30 (21.6)		61 (28.6)	32 (13)	
Label size, No. (%)								
≤21 mm	133 (29)	67 (37)	29 (20.9)	37 (26.6)	.005	68 (31.9)	65 (26.4)	.19
>21 mm and <25 mm	176 (38.3)	74 (40.9)	43 (30.9)	59 (42.4)	.09	83 (39)	93 (37.8)	.80
≥25 mm	139 (30.3)	34 (18.8)	65 (46.8)	40 (28.8)	<.001	53 (24.9)	86 (35)	.02
Unknown	11 (2.4)	6 (3.3)	2 (1.4)	3 (2.2)	.54	9 (4.2)	2 (0.8)	.02
Internal diameter, No. (%)								
<20 mm	126 (27.5)	53 (29.3)	32 (23)	41 (41.7)	.37	66 (31)	60 (24.4)	.11
≥20 mm and <23 mm	230 (50.1)	102 (56.4)	64 (34.5)	64 (46)	.10	100 (46.5)	130 (52.8)	.21
≥23 mm	103 (22.4)	26 (14.4)	43 (30.9)	34 (24.5)	.002	46 (21.6)	57 (23.2)	.69
AV area, mean (SD), cm^2	0.95 (0.48)	0.69 (0.21)	1.48 (0.6)	0.91 (0.31)	<.001	0.99 (0.49)	0.91 (0.46)	.04
AV index, mean (SD), cm^2/m^2[b]	0.51 (0.28)	0.38(0.13)	0.83 (0.37)	0.51(0.19)	<.001	0.55 (0.31)	0.49 (0.25)	.05
AV maximum gradient, mean (SD), mm Hg	60.8 (27.4)	75.2 (23.1)	34.3 (17.7)	64.6 (22.8)	<.001	59.7 (27.2)	61.8 (27.6)	.44
AV gradient, mean (SD), mm Hg	36.2 (18.4)	46.4 (16.1)	18.0 (10.1)	37.6 (14.9)	<.001	35 (18.5)	37.3 (18.3)	.21
AV regurgitation of at least moderate degree, No. (%)[c]	296 (64.5)	22 (12.2)	139 (100)	135 (97.1)	<.001	143 (67.1)	153 (63)	.27

Abbreviations: AV, aortic valve; IQR, interquartile range; SAVR, surgical aortic valve replacement.

[a] Time interval between last SAVR and valve-in-valve procedure.

[b] AV index = AV area (cm^2)/patient body surface area (m^2).

[c] Evaluated according to the criteria of the American Society of Echocardiography.[18]

cess route in the self-expandable device group was transfemoral (n = 197 [92.5%]) while in the majority of the balloon-expandable device group was transapical (n = 171 [69.5%]; *P* < .001). Device retrieval was attempted in 10.3% of self-expandable procedures. A second transcatheter device was implanted in 5.7% of the total patients (self-expandable, 7.5% vs balloon-expandable, 4.1%; *P* = .05). Ostial coronary obstruction following valve-in-valve implantation occurred in 2% and was more frequent in the stenosis group (3.9%; *P* = .02).

Clinical Outcomes

The median duration of hospital stay after the procedure was 8 days (interquartile range, 5-12 days). At 30 days, 35 patients (7.6%) had died. **Table 3** includes data on procedural outcomes. Patients in the stenosis group had a higher 30-day mortality rate (10.5% vs 4.3% in the regurgitation group and 7.2% in the combined group; *P* = .04). There were no differences between the self-expandable and balloon-expandable device groups in terms of mortality or stroke rates. The balloon-expandable device group had more major/life-threatening bleeding and more acute kidney injury events, while the self-expandable device group had more permanent pacemaker implantation. Aortic regurgitation of at least moderate degree was evident in 25 cases (5.4%) after valve-in-valve procedure and was more common in the regurgitation group (9.4% vs 2.8% in the stenosis group and 5% in the combined group; *P* = .04) and in the self-expandable device group (8.9% vs 2.4% in the balloon-expandable device group; *P* = .002).

The degree of postprocedure residual aortic stenosis was higher in the stenosis group, manifested by lower mean orifice area and higher mean gradient (orifice area, 1.37 [SD, 0.33] cm^2 and mean gradient, 18.5 [SD, 9.8] mm Hg vs 1.56 [SD, 0.51] cm^2 and 12 [SD, 6.7] mm Hg in the regurgitation group and 1.56 [SD, 0.65] cm^2 and 16.1 [SD, 8.3] mm Hg in the combined group, respectively; *P* < .001 for each comparison). Postprocedural gradients were assessed in 429 patients. Moderately elevated postprocedural gradients (mean gradients ≥20 mm Hg) were recorded in 115 patients (26.8%) (eFigure 2 in the Supplement). Elevated postprocedural gradients were more common with balloon-expandable devices in comparison with self-expandable devices (HR, 1.87; 95% CI, 1.21-2.9; *P* = .005); for small surgical valves, 41.2% vs 23.4% (*P* = .04) and for intermediate-sized valves, 35.8% vs 19.4% (*P* = .01), respectively. Severe PPM occurred in 31.8% of patients surviving aortic valve-in-valve procedure. The incidence of severe PPM was lower in patients with predominantly bioprosthesis regurgitation at baseline (19.3% vs 36.1% and 36.4% in those with predominant stenosis and combined failure, respectively; *P* = .03) and higher in patients who received a balloon-expandable device vs a self-expandable device (43.8% vs 15.2%, respectively; *P* < .001). One-year survival was not affected by having severe PPM (86.7% [95% CI, 77.6%-95.8%] vs 89.1% [95% CI, 82.2%-96%] in patients without severe PPM; *P* = .69).

Time-to-event curves are depicted in **Figure 1**. No patients were lost to follow-up. Median follow-up time was 301

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Table 3. Clinical Outcomes

Outcomes	All (n = 459)	Mechanism of Surgical Valve Failure, No. (%)				Device Used, No. (%)		
		Stenosis (n = 181)	Regurgitation (n = 139)	Combined (n = 139)	*P* Value	Self-Expandable (n = 213)	Balloon-Expandable (n = 246)	*P* Value
Duration of hospital stay, median (IQR), d	8 (5-12)	7 (5-11)	7 (5-12)	8 (6-13)	.21	7 (5-12)	8 (6-13)	.07
Thirty-day outcomes								
Death, No. (%)	35 (7.6)	19 (10.5)	6 (4.3)	10 (7.2)	.04	15 (7)	20 (8.1)	.66
Cardiovascular death, No. (%)	30 (6.5)	16 (8.8)	5 (3.6)	9 (6.5)	.06	12 (5.6)	18 (7.3)	.47
NYHA functional class, No. (%)								
I/II	313 (92.6)	126 (91.3)	100 (94.3)	87 (92.6)	.83	160 (93)	153 (93.3)	.94
III/IV	25 (7.4)	12 (8.7)	6 (5.7)	7 (7.4)	.83	12 (7)	13 (7.8)	.94
Major stroke, No. (%)[a]	8 (1.7)	1 (0.6)	3 (2.2)	4 (2.9)	.26	2 (0.9)	6 (2.4)	.22
Death or major stroke, No. (%)	42 (9.2)	19 (10.5)	9 (6.5)	14 (10.1)	.42	17 (8)	25 (10.2)	.22
Major vascular complication, No. (%)[a]	42 (9.2)	14 (7.7)	10 (7.2)	18 (12.9)	.11	16 (7.5)	26(10.6)	.26
Major/life-threatening bleeding, No. (%)[a]	37 (8.1)	20 (11)	5 (3.6)	12 (8.6)	.01	10 (4.7)	27 (11)	.01
Acute kidney injury type II/III, No. (%)[a]	34 (7.4)	16 (8.8)	10 (7.2)	8 (5.8)	.58	9 (4.2)	25 (10.2)	.02
Permanent pacemaker implantation, No. (%)	38 (8.3)	17 (9.4)	12 (8.6)	9 (6.5)	.63	26 (12.2)	12 (4.9)	.005
AV area, mean (SD), cm^2	1.47 (0.5)	1.37 (0.33)	1.56 (0.51)	1.56 (0.65)	.01	1.58 (0.41)	1.38 (0.54)	.001
AV index, mean (SD), cm^2/m^2[b]	0.77 (0.25)	0.71 (0.15)	0.82 (0.23)	0.84 (0.35)	.004	0.83 (0.19)	0.74 (0.28)	.004
AV maximal gradient, mean (SD), mm Hg	28.3 (14.1)	32.2 (14.7)	22.4 (11.6)	29.1 (13.6)	<.001	26.2 (12.1)	30.3 (15.4)	.002
AV mean gradient, mean (SD), mm Hg	15.8 (8.9)	18.5 (9.8)	12 (6.7)	16.1 (8.3)	<.001	14.1 (7.3)	17.2 (9.7)	<.001
AV regurgitation of at least moderate degree, No. (%)[c]	25 (5.4)	5 (2.8)	13 (9.4)	7 (5)	.04	19 (8.9)	6 (2.4)	.002
Left ventricular ejection fraction, mean (SD), %	51.6 (11.5)	53.7 (9.9)	48.9 (11.6)	51.2 (12.9)	.002	51.2 (12.2)	51.7 (10.8)	.66
One-year outcomes								
Death, No. (%)	62 (16.8)	34 (23.4)	10 (8.8)	18 (16.1)	.01	25 (15)	37 (18.7)	.44
NYHA functional class, No. (%)								
I/II	163 (86.2)	62 (84.9)	46 (85.2)	55 (88.7)	.34	88 (81.6)	75 (82.4)	.89
III/IV	26 (13.8)	11 (15.1)	8 (14.8)	7 (11.3)	.34	10 (18.4)	16 (17.6)	.89
AV area, mean (SD), cm^2	1.38 (0.42)	1.28 (0.29)	1.51 (0.48)	1.36 (0.45)	.01	1.55 (0.41)	1.29 (0.39)	.006
AV maximal gradient, mean (SD), mm Hg	30 (14.7)	32.3 (14.9)	25.2 (15.4)	32.1 (12.5)	.005	25.3 (11.9)	33.3 (16)	<.001
AV mean gradient, mean (SD), mm Hg	16.9 (9.1)	18.3 (9.5)	13.8 (8.9)	18.4 (8)	.001	13.5 (7)	19.4 (9.6)	<.001

Abbreviations: AV, aortic valve; IQR, interquartile range; NYHA, New York Heart Association.

[a] According to the Valve Academic Research Consortium definition.

[b] AV index = AV area (cm^2)/patient body surface area (m^2).

[c] Evaluated according to the criteria of the American Society of Echocardiography.[18]

days (interquartile range, 53-504 days). Overall 1-year Kaplan-Meier survival rate was 83.2% (95% CI, 80.8%-84.7%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 95% CI, 68.9%-83.1%; 34 deaths; 86 survivors) vs the regurgitation group (91.2%; 95% CI, 85.7%-96.7%; 10 deaths; 76 survivors) and the combined group (83.9%; 95% CI, 76.8%-91%; 18 deaths, 66 survivors) (*P* = .01). Similarly, patients with small valves had worse 1-year survival after valve-in-valve procedure (74.8%;95% CI, 66.2%-83.4%; 27 deaths; 57 survivors) vs with intermediate-sized valves (81.8%; 95% CI, 75.3%-88.3%; 26 deaths; 92 survivors) or with large valves (93.3%; 95% CI, 85.7%-96.7%; 7 deaths; 73 survivors) (*P* = .001) (Figure 1, A and B). There was no significant difference in survival between patients undergoing self-expandable and balloon-expandable valve-in-valve procedures (Figure 1C). One-year mortality was higher among patients undergoing transapical procedures, those with STS scores higher than 20%, and those with a baseline left ventricular ejection fraction of less than 45% (eFigures 3-8 in the Supplement).

Figure 2 includes data on correlates for mortality within 1 year after valve-in-valve procedures. Independent correlates included small surgical bioprostheses (HR, 2.04; 95% CI, 1.14-3.67; *P* = .02), baseline surgical bioprosthesis stenosis (vs re-

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gurgitation; HR, 3.07; 95% CI, 1.33-7.08; P = .008), transapical access (HR, 2.25; 95% CI, 1.26-4.02; P = .006), and STS score (per 1% increment; HR, 1.01; 95% CI, 1.00-1.01; P < .001). Independent correlates for early mortality (≤30 days) included small surgical bioprostheses (HR, 2.25; 95% CI, 1.03-4.93; P = .04) and for late mortality (>30 days) included baseline surgical bioprosthesis stenosis (HR, 3.33; 95% CI, 1.00-11.31; P = .05).

Discussion

The VIVID Registry is a multinational comprehensive evaluation of transcatheter valve implantations for failed surgical aortic bioprostheses. Survival after valve-in-valve procedures was associated with surgical valve size and mechanism of failure. Patients with baseline stenosis and those with small surgical valves had worse clinical outcomes after valve-in-valve procedures.

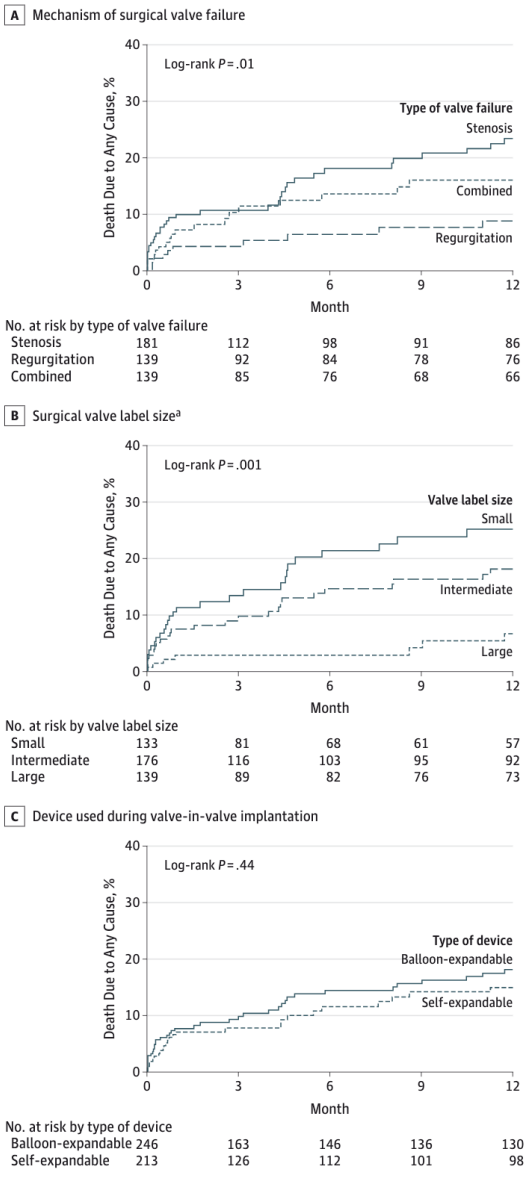
Mechanism of Failure of Bioprosthetic Valves and Valve-in-Valve Procedures

Valve-in-valve implantation should be considered a heterogeneous group of procedures, performed in widely diverse surgical valves with different degeneration modes.[22] Bioprosthesis failure may present as stenosis that occurs as a consequence of calcification, pannus, or, less commonly, thrombosis. Failure may also present as regurgitation secondary to wear and tear or infection.[23,24] The mode of failure in the VIVID registry was relatively balanced among stenosis, regurgitation, and a combination of both. Although there was no difference in patient age or calculated risk scores among the groups, clinical outcomes differed significantly. Higher mortality in the stenosis group could partially be attributed to higher rates of specific life-threatening procedural complications, such as ostial left main obstruction. Nevertheless, long-term dissimilarity between the groups could be a result of differences in baseline characteristics and postprocedural hemodynamics. After valve-in-valve implantation, patients with baseline stenosis had a lower valve area and higher gradients. Prosthetic-patient mismatch occurs when the effective orifice area is physiologically too small in relation to patient body size.[21] In the current analysis, patients with predominantly surgical valve stenosis had larger body size measures (body weight, body mass index, and body surface area); nevertheless, they had smaller surgical valves implanted compared with the other groups. In patients undergoing surgical aortic valve replacement, lower effective orifice area in relation to body size is associated with lower left ventricular mass regression, less recovery in ventricular systolic function, and lower long-term survival.[21,25-28]

Evaluation of Patients for Valve-in-Valve Procedures

Thorough assessment of candidates for valve-in-valve implantation is a key step to obtain optimal results.[22] The current analysis highlights the need for meticulous evaluation of bioprosthesis mechanism of failure before attempting a valve-in-valve procedure. Patients who are diagnosed as having failed surgical valves secondary to stenosis should be further separated into those with degenerated valves and those who have elevated gradients and small effective orifice area as a result of severe PPM with their surgical valve. Occasionally, it is clinically difficult to differentiate between

Figure 1. Time-to-Event Curves in Patients Undergoing Valve-in-Valve Procedures



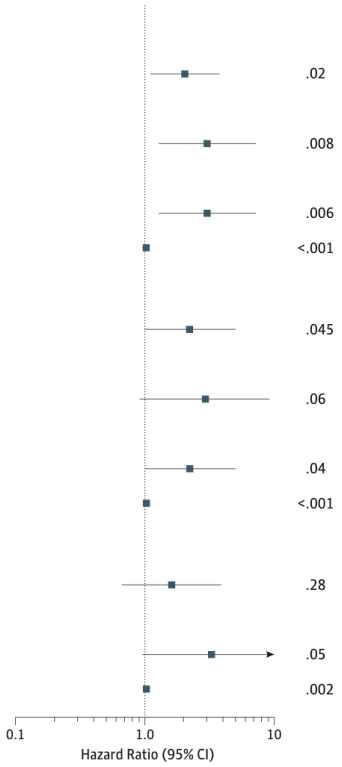
[a] Surgical valve sizes were as follows: small, label size ≤21 mm; intermediate, >21 mm and <25 mm; and large, ≥25 mm. In 11 patients (2.4%), label size was unknown.

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Figure 2. Results of Multivariable Analyses for Correlates for 1-Year Mortality After Valve-in-Valve Implantation

	No. of Events	Total	Hazard Ratio (95% CI)	P Value
Overall mortality				
Surgical valve label size				
≤21 mm	28	133	2.04 (1.14-3.67)	.02
>21 mm	34	315		
Type of valve failure				
Stenosis	34	181	3.07 (1.33-7.08)	.008
Regurgitation	12	139		
Transapical access				
Yes	34	171	2.25 (1.26-4.02)	.006
No	30	288		
STS score (per 1% increment)[a]			1.01 (1.00-1.01)	<.001
Early mortality, ≤30 d				
Surgical valve label size				
≤21 mm	15	133	2.25 (1.02-4.98)	.045
>21 mm	17	315		
Type of valve failure				
Stenosis	18	181	2.97 (0.94-9.37)	.06
Regurgitation	6	139		
Transapical access				
Yes	19	171	2.25 (1.03-4.93)	.04
No	15	288		
STS score (per 1% increment)[a]			1.01 (1.00-1.01)	<.001
Late mortality, >30 d				
Surgical valve label size				
≤21 mm	13	133	1.61 (0.68-3.80)	.28
>21 mm	17	315		
Type of valve failure				
Stenosis	16	181	3.33 (1.00-11.31)	.05
Regurgitation	6	139		
STS score (per 1% increment)[a]			1.01 (1.00-1.04)	.002



[a] The Society of Thoracic Surgeons (STS) score is a prediction of operative mortality after conventional surgical valve replacement (http://riskcalc.sts.org/de.aspx).

those entities, and a patient may have a combination of both. Small bioprostheses (label size ≤21 mm) have small effective orifice areas and the gradients across them are commonly high, even in the absence of structural degeneration, such as impaired leaflet mobility, significant calcification, or pannus.[29] Therefore, markers for stenosis in bioprostheses should lead to a more detailed assessment of previous echocardiographic examinations and changes in clinical status over years. It seems that the valve-in-valve approach should only be rarely offered to patients after implantation of small surgical valves without signs of valve degeneration, for which gradients are relatively stable over time.

Candidates with surgical valve regurgitation should be evaluated for the location of the leak. Significant paravalvular leak should not be treated by valve-in-valve implantation since no considerable change is expected in regurgitation severity.[22] The current registry reveals an elevated rate of residual leak in the group of patients with baseline regurgitation (9.4%) in comparison with patients with predominantly stenosis (2.8%). Significant postprocedural regurgitation could be attributed to improper treatment of patients with predominantly paravalvular leak at baseline. Transesophageal echocardiography is a key mode during this screening process and should be routinely performed for evaluating leak origin.

Implications for Cardiac Surgery

Increasing global valve-in-valve experience may affect cardiac surgery practice. The valve-in-valve approach may offer an effective, less invasive treatment for patients with failed surgical bioprostheses and, therefore, the trend toward implantation of bioprostheses in younger patients is expected to grow.[1] It is difficult to define an optimal cutoff age for bioprostheses implantation rather than mechanical valves.[30] However, surgeons should be aware that their technique is crucial to allow for the possibility of successful valve-in-valve implantation when bioprosthesis failure occurs years later. According to the VIVID Registry analysis, valve-in-valve outcomes are worse in patients with small surgical valves (label size ≤21 mm) and those with stenosis as the mechanism of failure; an attempt to address these limitations may possibly be made during the index procedure by providing the largest effective orifice area achievable. However, annular enlargement and other related techniques must balance the potential benefit of larger valve against described increase in operative complications.[31-33]

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Limitations

The valve-in-valve therapeutic approach represents a widely diverse heterogeneous group of procedures; hence, it is difficult to stratify patients according to each type of the numerous surgical valves treated. Nevertheless, stratification according to mechanism of failure and bioprostheses size showed a major influence on clinical outcomes after valve-in-valve implantation. Since specific label sizes of surgical valves such as the 19 mm were not common (2.4%), we were not powered to compare different surgical valve sizes without clustering cases into subgroups. Nevertheless, dividing surgical bioprostheses into small, intermediate, and large valve sizes, in accordance with previous reports, is clinically relevant and showed clinical significance when defining small valve size as those having a label size of 21 mm or smaller.[34,35]

Study results reveal that PPM of the implanted transcatheter heart valve device during valve-in-valve procedures did not influence 1-year survival. However, analyses were limited by lack of echocardiographic data immediately after surgical implantation (median of 9 years before the valve-in-valve procedure) that would have enabled evaluation of PPM of the implanted surgical valve. Therefore, a clear differentiation between degeneration of the surgical bioprosthesis and PPM is challenging.

Although dozens of baseline medical and echocardiographic parameters were included in the analyses (Table 1, Table 2, and Table 3 and eTables 2 and 3 in the Supplement), analyses is limited by lack of several parameters known to be related to clinical outcomes in patients with structural aortic valve disease, including left ventricular mass index, diastolic function, ischemic cardiomyopathy, and frailty.

Conclusions

In this registry of patients who underwent transcatheter valve-in-valve implantation for degenerated bioprosthetic aortic valves, overall 1-year survival was 83.2%. Survival was lower among patients with small bioprostheses and those with predominant surgical valve stenosis.

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Acquisition, analysis, or interpretation of data: Dvir, Webb, Pasic, Waksman, Kodali, Barbanti, Latib, Schaefer, Rodés-Cabau, Treede, Piazza, Hildick-Smith, Himbert, Walther, Hengstenberg, Nissen, Bekeredjian, Presbitero, Ferrari, Segev, Weger, Windecker, Moat, Napodano, Wilbring, Cerillo, Brecker, Tchetche, Lefèvre, De Marco, Fiorina, Petronio, Teles, Testa, Laborde, Leon, Kornowski.
Drafting of the manuscript: Dvir, Webb, Pasic, Laborde, Leon, Kornowski.
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Manuscript #6

Catheterization and Cardiovascular Interventions 00:00–00 (2015)

Original Studies

Neurologic Complications after Transradial or Transfemoral Approach for Diagnostic and Interventional Cardiac Catheterization: A Propensity Score Analysis of 16,710 Cases From a Single Centre Prospective Registry

Luis Raposo,* MD, Sérgio Madeira, MD, Rui Campante Teles, MD, Miguel Santos, MD, Henrique Mesquita Gabriel, MD, Pedro Gonçalves, MD, João Brito, MD, Silvio Leal, MD, Manuel Almeida, MD, and Miguel Mendes, MD

Background and aim: Transradial approach (TRA) is being used increasingly as the preferential vascular access site for both diagnostic and interventional procedures. However, concerns have risen about the risk of clinically meaningful neurologic complications. We aimed to assess the association between the risk of stroke/transient ischemic attack (TIA) and the transradial (vs. transfemoral) approach. Methods and Results: Data from 16,710 cases included in a single centre prospective registry between January 2006 and November 2012 was analyzed. Radial procedures were considered as those in which the radial access was used either primarily ($n = 4,195$) or after conversion ($n = 36$). Potential cases with neurologic events were targeted by cross-referencing patients who underwent both cardiac catheterization and cranial-computed tomography (cranial-CT) during the same admission episode ($n = 67$). Procedure-related events were defined as a definitive non-CABG related stroke/TIA occurring within 48 hr of the procedure. TRA increased from 0.7% in 2006 to 75% in 2012. Total incidence of stroke/TIA was 0.16% and did not change over the study period ($P = 0.26$). There was no significant difference in stroke/TIA rates between groups (0.165% vs. 0.160%; $P = 1.0$). After correction for baseline differences and propensity score matching, TRA was not an independent predictor of stroke/TIA (OR 1.21; 95% CI 0.49–2.98 and 1.3; 95% CI 0.55–3.54, respectively). Results were consistent in pre-specified sub-groups according to age (≥65 y.o. vs. younger), gender, interventional vs. diagnostic and ACS vs. stable. Conclusion: Rates of documented stroke/TIA were low. Our observational study suggests that widening the use of the TRA is not associated with an increased risk of clinically relevant procedure-related neurologic complications. © 2015 Wiley Periodicals, Inc.

Key words: percutaneous coronary intervention; coronary angiography; transradial; stroke

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Conflict of interest: Nothing to report.

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INTRODUCTION

Invasive techniques have attained a primordial role as part of the investigation and management of most forms of cardiac and vascular disease, particularly coronary artery disease. Nowadays, millions of cardiac and other endovascular procedures are performed worldwide every year for both diagnostic and therapeutic purposes. Several techniques for arterial access have been described and developed [1–7]. Despite the transfemoral approach (TFA) has become largely preferred by interventional cardiologists, it has been demonstrated that a very significant proportion of clinically relevant periprocedural complications, particularly bleeding, are ultimately related to the femoral vascular access site, and have been held responsible for prolonged admission times, and both increased morbidity and mortality [8–14].

The radial artery has several anatomical characteristics that make it an attractive site for vascular access for both cardiac and non-cardiac procedures. It is promptly accessible in the anterior aspect of the forearm (even in those markedly obese) [15,16], vessel calibre is sufficient in most patients for the majority of the procedures, radial artery occlusion, despite not uncommon, is generally well tolerated, and other significant vascular complications are seldom [17–24]. Meanwhile, data is accumulating that reinforces the benefits of the TRA in various clinical settings, including reduced mortality, especially in the high-risk subset of patients with acute coronary syndromes (ACSs), in which bleeding complications may offset the benefits of both coronary revascularization itself and currently used potent anti-thrombotic therapy [8,10,12–14,25–27]. In addition, the use of the radial artery as the vascular access site has been shown to be associated with lower procedural-related costs, both early and mid-term [28–30]. Finally, the improvements made in vascular access materials and the use of dedicated catheters have also definitely contributed to facilitate TRA adoption, allowing its implementation as the access site of choice, without compromising overall procedural success [31,32].

Periprocedural stroke, resulting from manipulation with dislodgment of debris made up of thrombus, calcific material, or cholesterol particles from atherosclerotic plaques, the formation and embolization of fresh thrombus at catheter and guidewire tips themselves or intra-cranial bleeding [33], is a rare but potentially devastating event. Historically, rates of periprocedural stroke have been kept acceptably low— around one per thousand patients overall, perhaps higher in interventional procedures (up to 0.6%)—and have not decreased further in recent years [34,35]. With the increase in the use of the TRA, concerns have risen regarding the risks associated with the manipulation of the subclavian arteries—and specifically the right brachiocephalic artery (in which both the right vertebral and carotid arteries originate) - and also the ascending aorta, that could potentially increase cerebral embolization during TRA procedures. Jurga et al., have reported a significantly higher rate of micro-embolization to the brain, detected by transcranial Doppler, in patients undergoing cardiac catheterization via the radial artery [36], although these findings have not been confirmed in larger randomized trials and registries [37–39]. The very low incidence of periprocedural stroke/TIA and the fact that no trial has been specifically designed to assess differences between transradial and TFAs concerning it's occurrence, renders these studies largely underpowered to detect clinically meaningful differences in this endpoint.

To further address this issue, we performed an analysis of a large database from a single centre prospective registry in which a very significant shift from femoral-to-radial access has occurred, making it possible to look at the evolution of stroke/TIA rates over time and it's relation to the TRA.

METHODS

Study Design, Population and Selection Criteria

We designed an observational study based on the single centre *A*ngiography and *C*ardiovascular Inte*R*venti*O*n at *S*anta Cruz Ho*S*pital (ACROSS) Registry, in which anthropometric, demographic, clinical and procedural-related variables are prospectively collected in a dedicated database (Cardiobase®, Infortucano®, Lisbon, Portugal). All invasive procedures involving an arterial vascular access performed at our unit between January/2006 and November/2012 were initially screened ($n = 19{,}691$). Entry criteria were as follows: (1) age at least 18-year old and (2) procedures involving any manipulation of the ascending aorta or the aortic arch. Patients undergoing selective carotid catheterization for diagnostic or interventional purposes, mitral or aortic balloon valvuloplasty, percutaneous aortic valve implantation, atrial septal defect or persistent *foramen ovale* percutaneous closure and peripheral diagnostic or interventional procedures in which no manipulation of the proximal aorta was undertaken were excluded from the analysis. The final study population consisted of 16,710 diagnostic and interventional procedures. Radial artery was used as the primary vascular access site in 4,195 cases (25%) and in 36 additional patients after conversion from femoral-to-radial (final transradial cohort $n = 4{,}231$ patients). The overall radial-to-femoral crossover rate was 7% ($n = 296$).

Catheterization Technique and Anticoagulation

Catheterization technique, including the calibre of the introducer sheath and of the catheters that were used,

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was chosen in each case by individual operator decision. According to our institution's protocol (which has not changed significantly during the study period), unfractionated heparin is used in all diagnostic procedures—at a standard dose of 2,500 to 5,000 U in transradial and 2,500 U in transfemoral cases—unless specifically contra-indicated or if the patient has been previously treated with therapeutic doses of low molecular weight heparin. In interventional procedures, total heparin dose is ACT-guided, according to recommended international standards. Glicoprotein IIb/IIIa inhibitors were used at the discretion of treating physicians.

Definition of the Study Endpoint

The study endpoint was the occurrence of clinically significant stroke or TIA presumably related to endovascular manipulation. At our hospital, suspected cases of neurologic complications are universally submitted to brain imaging and, additionally, all medical procedures are coded in the institution's database. Thus, to increase the probability of correctly identifying potential target cases, a cross-reference search of patients who underwent both cardiac catheterization and cranial-CT during the same admission episode was undertaken. Subsequently, clinical files from each of the identified cases were reviewed. Procedure-related events were finally adjudicated according to a definite diagnosis of stroke or TIA established by a clinician, preferably a neurologist, using both imaging and clinical criteria, as those occurring within 48 hr of the procedure and that were unrelated to coronary artery bypass grafting. For patients discharged or transferred to other institutions before the 48-hr period, subsequent reporting registered in the cath-lab database (Cardiobase®, Infortucano, Lisbon, Portugal) was used instead.

Statistical Analysis

In this observational study, all patients meeting the specified criteria were included. All the performed analyses were retrospective. Continuous variables with normal distribution were expressed as means and standard deviation. Normality was tested with the Kolmogorov-Smirnov test and/or Q-Q Plot visual assessment. Discrete variables were expressed as frequencies and percentages. Statistical comparison of baseline characteristics and outcomes was performed using the chi-square test or Fisher's exact test, when appropriate, for categorical variables and the *t*-Student's test or the Satterthwaite test for continuous variables. Corrected risk estimates were performed using a logistic regression model, in which all the variables found to differ significantly in the univariate analysis were included (Table I). Model calibration was assed by the Hosmer and Lameshow goodness-of-fit test.

To improve similarity between study groups, 4,231 procedures in which the TRA was ultimately used were matched to 8,462 transfemoral procedures using a propensity score methodology. The propensity variable was calculated using binary logistic regression with any use of the transradial access (either primarily or after conversion) as the dependent variable and, as independent variables, all the demographic, clinical and procedural-related information available in the database, irrespective of the differences between groups found in the baseline model. Matching was performed in a 1:2 fashion using a nearest neighbourhood algorithm with a 0.2 calliper.

To assess heterogeneity, a pre-specified descriptive sub-group analysis was performed in the baseline cohort according to age (≥65 year-old *versus* younger), gender, procedure type (diagnostic *versus* interventional) and clinical setting (ACS/urgent procedure *versus* stable). Odds ratios (OR) were corrected by including the propensity score variable in the regression model. Interaction tests between each baseline covariate, the vascular access type and the risk of stroke/TIA were performed. Two-tailed tests of significance are reported. For all comparisons, a P value of <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CI) were calculated. Statistical analysis was performed with IBM® SPSS® Statistics version 19.0 (SPSS, Chicago, IL) and R version 2.10.0 (The R Foundation for Statistical Computing).

Data Management and Funding

In the *A*ngiography and *C*ardiovascular Inte*R*venti*O*n at *S*anta Cruz Ho*S*pital (ACROSS) Registry, data is prospectively collected and stored in a dedicated computer database (Cardiobase®, Infortucano, Lisbon, Portugal). Per-protocol, all patients must provide written informed consent for data collection at the time of the procedure. The authors were entirely responsible for the design, data collection, all statistical analyses, the drafting and editing of the manuscript, and its final content. No external funding was involved.

RESULTS

TRA over the Study Period

The study time frame encompassed two representative periods. From 2006 to 2008, virtually all procedures (>99%) were performed using the TFA. Afterwards, particularly since 2010, a steep increase occurred in radial access use, which led to its clear predominance in both diagnostic and interventional procedures (Fig. 1,

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TABLE I. Population Baseline Characteristics

Variable (%)	Transradial ($n = 4.231$)	Transfemoral ($n = 12.479$)	P value
Demographic			
Age (years) [average ± SD]	66.1 ± 11.3	65.7 ± 11.6	0.029
Male gender	67.3	66.4	0.281
BMI (Kg/m^2) [average ± SD]	27.59 ± 4.15	27.27 ± 3.99	<0.001
Cardiovascular risk factors			
Diabetes mellitus	27.5	28.4	0.258
Hypertension	72.0	73.4	0.730
Smoking (current or former)	38.2	39.9	0.450
Dyslipidemia	59.9	60.2	0.743
Prior clinical history			
MI	16.5	23.0	<0.001
PCI	21.4	24.2	<0.001
CABG	2	11.6	<0.001
Stroke/TIA	6.3	8.1	<0.001
PAD	5.8	7.6	<0.001
Non-CABG surgery	2.1	2.7	0.05
Moderate/severe CRD	2.0	3.6	<0.001
Renal transplant	0.1	0.5	<0.001
Clinical setting and procedural characteristics			
Interventional procedure	36.3	43.6	<0.001
Acute coronary syndrome	38	36.8	0.185
Aortic valvulopathy	10.5	6.2	0.001
Blood pressure (mmHg) [average ± SD][a]			
Systolic	132.5 ± 26.1	141.6 ± 28.5	<0.001
Diastolic	72.0 ± 13.3	72.3 ± 12.8	0.243
Coronary artery disease extension[b]	1.2 ± 1.1	1.4 ± 1.2	<0.001
Number of treated segments[c]	1.31 ± 0.59	1.48 ± 0.76	<0.001
Fluoroscopy time (min)	10.78 ± 9.22	9.65 ± 9.11	<0.001
Contrast volume (mL) [average ± SD]	125.3 ± 87.5	140.1 ± 96.8	<0.001
Number of catheters used [average ± SD]	2.75 ± 1.3	2.79 ± 1.4	0.155

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; MI: Myocardial infarction; PAD: Peripheral Artery Disease; PCI: Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction; IQR: Interquartile Range (P25;P75).
Radial access included those in whom primary vascular access site was the radial artery and those ($n = 36$) who converted from femoral-to-radial.
[a]Blood pressure recorded invasively at the beginning of the procedure.
[b]number of vessels with stenosis ≥50 to 70%.
[c]Refers to patients in whom percutaneous coronary intervention was performed ($N = 6.973$).

Vertical Bars). Nowadays, at our institution, femoral artery puncture is reserved for patients with non-palpable radial arteries, those with previously known failure of the radial approach, the relatively seldom cases of severe spasm or extreme tortuosity, lack of adequate mechanical support during PCI, severe chronic renal failure or arterial-venous fistulae and, finally, some patients with prior bypass grafting.

Population Baseline Characteristics

Population baseline characteristics are depicted in Table I. Briefly, approximately 57% of the patients were at least 65 years old and mean age did not differ between groups. There was a high prevalence of interventional procedures (41.7%) and 37% of the patients were enrolled in the high-risk setting of an ACS. Although the observed differences between groups tended to dissipate over the study period, overall, transradial patients had a more benign clinical profile: they were less likely to have had a prior myocardial infarction, any revascularization procedure (PCI or CABG), moderate to severe renal failure or a renal transplant and also a history of peripheral artery disease or prior stroke. In addition, transradial patients were more likely to undergo purely diagnostic procedures (63.7% *vs.* 56.4%; $P < 0.001$). In line with the higher prevalence of interventional procedures and more extensive PCI being performed, the total volume of contrast was superior in transfemoral patients, although fluoroscopy time was slightly, but significantly, lower and the average number of catheters used was roughly the same as in transradial procedures.

Incidence of Stroke and TIA

Sixty-seven patients (0.4% of the entire cohort) underwent brain-CT and cardiac catheterization during the same admission episode (Table II). Of these, twenty examinations were performed after CABG. Over the entire study period, the incidence of brain-CT was significantly higher in transradial than in

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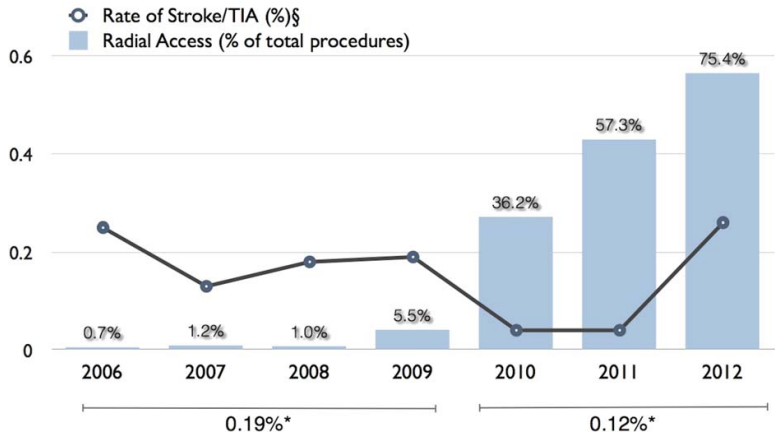


Fig. 1. Transradial approach and crude incidence of stroke/TIA during the enrolment period in the entire 16.710 patient cohort. § $P = 0.404$ for the change in stroke/TIA rates over the study period. *$P = 0.202$ for the comparison of stroke/TIA rates between 2006 to 2009 and 2010 to 2012. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

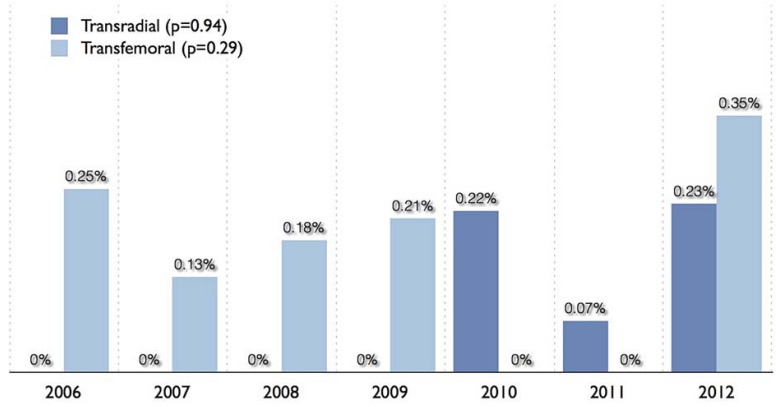


Fig. 2. Annual incidence of stroke/TIA according to vascular access site. *P* values are for the comparison between years. All *P* values > 0.1 for the association between Stroke/TIA and vascular access within each year. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

transfemoral procedures (0.56% *vs.* 0.34%; $P = 0.048$); also, despite there was a trend towards an increase in the proportion of patients undergoing brain-CT in the 2010 to 2012 period, relative to the first 4 years of the registry (0.5% *vs.* 0.32%; $P = 0.079$), the incidence of imaging procedures within the 48-hr time frame after the index procedure was similar (0.18% *vs.* 0.14%; $P = 0.42$) (Fig. 3).

Stroke was confirmed in 19 cases (0.11%) and TIA in eight additional patients (0.05%); thus, the diagnosis of a clinically meaningful acute neurologic event was ultimately established in 27 of the initially targeted cases (0.16% of the entire cohort). All confirmed events, according to study definition, were non-haemorrhagic in nature and were adjudicated in patients who underwent brain-CT within 48 hr after catheterization. Characteristics of the index event, radiological findings and clinical outcome (both functional and vital) of the 27 patients diagnosed with a neurological complication are described in detail on Supporting Information Table IV. Mortality among patients with stroke/TIA was 14.8% (four deaths out of 27 patients) and no stroke-related deaths occurred, either during hospitalization or later during long term follow-up.

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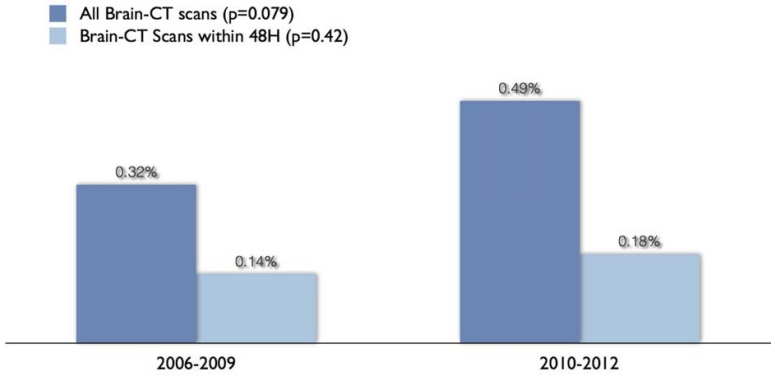


Fig. 3. Incidence of brain-CT performed during the same hospital admission in two representative periods. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE II. Timing and Reasons for Cranial-CT Scan Performed During the Same Hospital Admission

Timing of cranial-CT	Reason	Frequency
Before procedure	Stroke/TIA Suspicion	3
	Neurological dysfunction after Cardiorespiratory arrest	1
	Syncope	2
Within first 48 hr following the procedure	Stroke/TIA Suspicion (non-CABG related)	27
	Neurological dysfunction after cardiorespiratory arrest	1
More than 48 hr following the procedure	Stroke/TIA suspicion (non-CABG related)	2
	Seizure	1
	Altered Mental Status	3
	Neurological dysfunction after cardiorespiratory arrest	7
	Stroke/TIA suspicion after cardiac surgery	20
Total CT scans		67

CABG: Coronary Artery Bypass Graft; CT: Computed tomography; TIA: Transient ischemic attack.

Overall, the study primary endpoint occurred in seven of 4,231 transradial procedures and in 20 of the 12,479 transfemoral cases (0.165% versus 0.160%, respectively; $P = 1.0$).

Confirmed Stroke/TIA rates were unrelated to the proportion of radial access site cases performed during each year of the study period ($P > 0.1$ for all comparisons between transradial and transfemoral; Figs. 1 and 2). There was no significant difference in the rate of neurologic events when the period comprised between 2006 and 2009 was compared with the period from 2010 to 2012, during which radial procedures markedly increased (0.19% *vs*. 0.12%; $P = 0.202$; Fig. 1). Although there was a significant increase ($P = 0.013$) in stroke/TIA rates within the latest period (from 2010 to 2012) the difference was driven by a sharp increase in 2012, rather than a progressive rise in event rates and, importantly, most of the events occurred in transfemoral patients (Figs. 1 and 2). After correction for baseline differences between groups, using a logistic regression model, the TRA was not independently associated with an increased risk of stroke/TIA (OR = 1.21; 95% CI = 0.49–2.98; *P* value for Goodness-of-fit Hosmer and Lameshow test = 0.88).

Propensity Score Matching and Risk of Stroke/TIA

As previously described, to minimize the observed differences between study groups, a propensity score based comparison was performed. Sample size was reduced to a total number of 12,693 cases (4,231 transradial and 8,462 transfemoral procedures). After matching, small, but statistically significant, differences persisted in the type of procedure (diagnostic *versus* interventional), aortic valvulopathy as the indication for catheterization, fluoroscopy time, total contrast volume and systolic blood pressure (Table IIII); these variables were subsequently included in the final regression model for calculation of the corrected risk estimate in the matched cohort. All other covariates that potentially could have influenced the initial choice

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TABLE III. Baseline Characteristics of the Study Groups, After Propensity Score Matching

Variable (%)	Transradial ($n = 4.231$)	Transfemoral ($n = 8.462$)	P value
Demographic			
Age (years) [average ± SD]	66.1 ± 11.4	65.7 ± 11.4	0.101
Gender	67.3	67.6	0.747
BMI (Kg/m^2) [average ± SD]	27.6 ± 4.15	27.6 ± 4.08	0.843
Cardiovascular risk factors			
Diabetes mellitus	27.4	27.1	0.687
Hypertension	72.0	71.5	0.543
Smoking (current or former)	38.2	39.2	0.286
Dyslipidemia	59.8	59.7	0.892
Prior clinical history			
	16.5	16.8	0.760
PCI	21.3	21.9	0.449
CABG	1.9	2.0	0.943
Stroke/TIA	6.3	6.2	0.786
PAD	5.8	5.9	0.903
Non-CABG Surgery	2.1	2.2	0.793
Moderate/severe CRD	2.1	1.9	0.497
Renal transplant	0.1	0.1	0.532
Clinical setting and procedural characteristics			
Aortic valvulopathy	10.4	8.4	<0.001
Blood pressure (mmHg) [average ± SD][a]			
Systolic	132.5 ± 25.9	134.9 ± 25.9	<0.001
Diastolic	72.1 ± 13.3	71.0 ± 12.3	0.093
Acute coronary syndrome	37.9	38.3	0.668
Interventional procedure	36.2	43.6	<0.001
Coronary artery disease extension[b]	1.19 ± 1.09	1.17 ± 1.12	0.293
Number of treated segments[c]	1.31 ± 0.59	1.32 ± 0.61	0.807
Fluoroscopy time (min)	10.4 ± 9.2	8.0 ± 8.3	<0.001
Contrast volume (mL) [average ± SD]	122.6 ± 90.3	129.0 ± 91.9	0.009
Number of catheters used [average ± SD]	2.75 ± 1.3	2.67 ± 1.3	0.092

ACS: Acute Coronary Syndrome; CABG: Coronary Artery Bypass Graft; MI: Myocardial infarction; PAD: Peripheral Artery Disease; PCI: Percutaneous Coronary Intervention; STEMI: ST-Elevation Myocardial Infarction.
Radial access included those in whom primary vascular access site was the radial artery and those ($n = 36$) who converted from femoral-to-radial.
[a]Blood pressure recorded invasively at the beginning of the procedure.
[b]number of vessels with stenosis ≥50 to 70%.
[c]Refers to patients who underwent percutaneous coronary intervention ($N = 4.395$).

of the vascular access site were very well balanced between study groups. Nineteen events were finally left for comparative analysis, an incidence that was similar to the overall population (0.15%). Consistent with the baseline model, there was no statistically significant difference in stroke/TIA rates between groups: 0.165% in transradial *versus* 0.141% in transfemoral patients ($P = 0.4$). After correction for the remaining differences, the *odds ratio* for the occurrence of stroke or TIA associated with the TRA was 1.3 (95% CI = 0.55–3.54; $P = 0.49$).

Sub-Group Analysis

A sub-group analysis was performed to explore potential differences in stroke/TIA rates in pre-specified groups perceived to be clinically relevant. There were no statistically significant differences in the incidence of the study endpoint regarding gender (male versus female), older versus younger patients (age cut-off set at 65-year old), interventional versus diagnostic procedures and, finally, stable patients versus urgent/ACSs (Fig. 4). All P values for the interaction between sub-group variables and TRA concerning the incidence of stroke/TIA were non-significant.

DISCUSSION

In this large single centre observational registry, we demonstrated that the use of TRA for both diagnostic and interventional procedures, in various settings, was not associated with a statistically significant increase in the risk of stroke or TIA. To our knowledge, only one registry has been published, that has specifically addressed the issue of periprocedural neurologic complications and their relation to transradial versus TFA, for that purpose analysing a nationwide unselected

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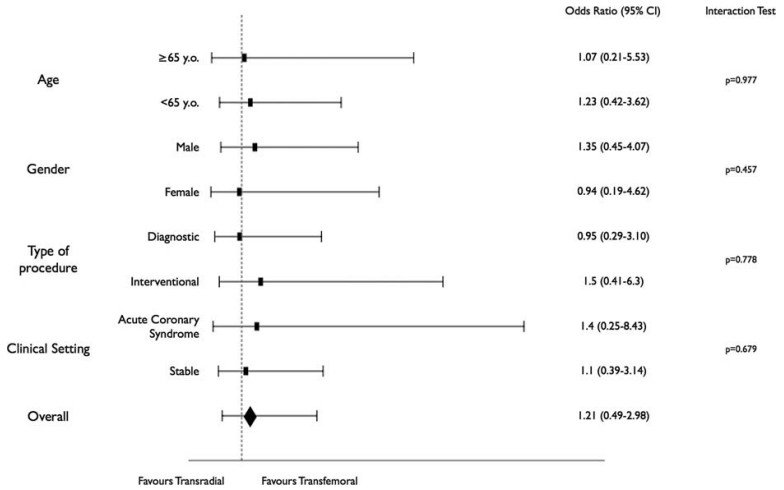


Fig. 4. Sub-group analysis. Forest plot representing the ORs for the occurrence of the study primary endpoint (stroke or TIA) in pre-specified sub-groups and in the entire cohort. ORs were calculated with TFA as the reference category.

population submitted to percutaneous coronary intervention (PCI) [39].

Stroke in association with PCI is a seemingly infrequent but devastating event that has been associated with markedly increased hospital mortality [40], although in our cohort, all deaths occurred later than 30 days after the index procedure and were unrelated to the neurological complication (see Supporting Information). Most of the previous studies (including the one by Ratib et al. [39]) and meta-analysis addressing this issue [40,41] have focused on the particular subset of patients undergoing PCI. Despite the overall smaller population size, our study also included patients undergoing purely diagnostic (coronary and non-coronary) procedures. Although the point estimate of the *odds ratio* appeared to favor the TFA, the 95% CI was wide (Fig. 4). In addition to multivariable logistic regression, a robust propensity score based methodology was used to properly match patient's baseline characteristics, allowing for a better correction of risk estimates.

The choice of cranial-CT for targeting potential cases was based on the assumption that imaging procedures are less likely to miss adequate codification than clinical observations alone and even discharge diagnoses. Although a positive brain scan was not mandatory for final diagnosis (as radiological signs may lag behind clinical features), having had a CT-scan performed increased the likelihood of correctly identifying patients with events. Importantly, cases were ultimately adjudicated according to a clinician's unbiased observation (a neurologist in most cases), based on both imaging data and clinical features.

Overall, our findings are in line with previous observations in the literature, both concerning the observed very low rates of stroke/TIA and the fact that a significant association between TRA and the probability of occurrence of neurologic complications could not be found [12,31,41]. However, in the sub-analysis focussing on the last 3-year period of the study, during which transradial procedures increased significantly, an increase in the overall stroke/TIA rates was observed, which was statistically significant. The observation that the event rate in 2012 was roughly similar to 2006, when TRA was seldom used (<1%), suggests that this may have been largely a matter of chance or the result of an association with some other unknown factor not taken into consideration in the available dataset. In addition, within this timeframe, the proportion of neurologic events was actually higher (although non-significantly) in transfemoral patients, thus reinforcing that the apparent association with the growing use of TRA is most likely a spurious finding. In our population, the relationship between baseline characteristics known to increase the risk of procedure-related stroke (like old age, hypertension, clinically overt cardiovascular disease, prior stroke, previous CABG, interventional procedure, ACS and increased procedure complexity) [33,40] and the actual event rate was not straightforward. The prevalence of these high-risk features varied significantly over the entire study period in both study groups and there was no statistically significant association with stroke/TIA rates. For instance, relative to the remaining study years, patients undergoing TFA procedures during 2010 and 2011 (in

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whom no events were observed), actually had a more adverse risk profile. In fact, the area under the curve of a score derived from the regression coefficients of the aforementioned variables for predicting the primary endpoint was poor, both in the baseline and in the matched model (data not shown), indicting that, in our cohort, risk factors other than these important, largely non-modifiable, baseline characteristics (like, for instance, operator volume or the adequacy of antithrombotic therapy), may have been relevant factors for the occurrence of neurologic complications.

Significant associations have been found between PCI-related stroke and several measures of procedural complexity [41,42]. Consistent with the higher prevalence of interventional procedures being performed, the average dose of contrast delivered, the number of coronary segments receiving treatment and the number of catheters used (all of which have been shown to bee associated with increased stroke rates) was higher in TFA patients (Table I). Conversely, fluoroscopy time (a surrogate of radiation exposure) was slightly but significantly longer in TRA procedures. A more extensive manipulation of catheters, to reach the aortic root and the coronary *ostia*, without necessarily using contrast injection is a plausible explanation for this finding. At least in part, this could justify why, despite a more benign risk profile and a significantly lower incidence of interventional procedures in TRA procedures, the incidence of stroke/TIA was the same in both groups, and actually the point estimate of the *odds ratio* appeared to favor the TFA, particularly in the matched model (although without statistical significance).

Limitations

We consider the limitations of our study to be related mainly to the observational and retrospective design and to the methodology of event adjudication. The possibility that some cases of neurologic complications might have been undetected, thus underestimating the actual event rate, cannot definitely be ruled out, despite it seems unlikely that true procedure-related neurologic complications would have occurred long after the 48-hr period considered for the purpose of this analysis. To minimize this bias, a database search was performed to detect patients with subsequently reported events that might have been discharged or transferred to other institutions before that period, ultimately without undergoing any imaging procedure. As previously stated, all the events reported in the cathlab database also underwent brain-CT. In addition, the fact that the incidence of stroke/TIA in our study is in consonance with the recent report by Ratib et al. [39] also suggests that the number of potentially undetected events, if any, may have been marginal. Importantly, asymptomatic patients with embolism or those with atypical presentations (thought not to be clinically relevant and thus not prompting brain imaging) are not represented in this analysis. Importantly, patients with transient or non-specific symptoms (that could not be definitely interpreted as typical embolic events) may also have suffered from contrast-induced neurotoxicity [43,44], medication side effects (i.e., sedation) or even diffuse micro-embolization. It must be recognized that in some of these cases a definite diagnosis of TIA might either have been missed or, on the opposite, inappropriately adjudicated.

Finally, despite adequate statistical corrections and propensity score matching, unmeasured confounders that affected the decision to use either vascular approach may not have been well represented in the database, thus precluding a more robust correction of risk estimates.

CONCLUSION

In conclusion, in this contemporary "real-world" large cohort, the incidence of stroke or TIA was low with the radial vascular access. Our study confirms prior observations and shows that, when compared with transfemoral, the preferential use of the TRA for both diagnostic and interventional procedures does not increase the risk of clinically significant neurologic embolism.

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Manuscript #7

Original Article

Predictors of Conversion from Radial Into Femoral Access in Cardiac Catheterization

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Abstract

Background: Fewer bleeding complications and early ambulation make radial access a privileged route for cardiac catheterization. However, transradial (TR) approach is not always successful, requiring its conversion into femoral access.

Objectives: To evaluate the rate of conversion from radial into femoral access in cardiac catheterization and to identify its predictors.

Methods: Prospective dual-center registry, including 7632 consecutive patients undergoing catheterization via the radial access between Jan/2009 and Oct/2012. We evaluated the incidence of conversion into femoral access and its predictors by logistic regression analysis.

Results: The patients' mean age was 66 ± 11 years, and 32% were women. A total of 2969 procedures (38.4%) were percutaneous coronary interventions (PCI), and the most used first intention arterial access was the right radial artery (97.6%). Radial access failure rate was 5.8%. Independent predictors of conversion from radial into femoral access were the use of short introducer sheaths (OR 3.047, CI: 2.380-3.902; p < 0.001), PCI (OR 1.729, CI: 1.375-2.173; p < 0.001), female sex (OR 1.569, CI: 1.234-1.996; p < 0.001), multivessel disease (OR 1.457, CI: 1.167-1.819; p = 0.001), body surface area (BSA) ≤ 1.938 (OR 1.448, CI: 1.120-1.871; p = 0.005) and age > 66 years (OR 1.354, CI: 1.088-1.684; p = 0.007).

Conclusion: Transradial approach for cardiac catheterization has a high success rate and the need for its conversion into femoral access in this cohort was low. Female sex, older age, smaller BSA, the use of short introducer sheaths, multivessel disease and PCI were independent predictors of conversion into femoral access. (Arq Bras Cardiol. 2015; 104(5):401-408)

Keywords: Radial Access; Femoral Access; Cardiac Catheterization.

Background

For the last decades, transfemoral approach in cardiac catheterization has been the preferred access for invasive cardiac procedures. However, recent evidence favors transradial approach in several observational and randomized trials. It has been shown that radial artery access decreases vascular complications with fewer access site bleeding complications, early patient ambulation, shorter length of hospital stay and lower hospital costs[1-8]. Recently, the large RIFLE study, on patients with ST elevation myocardial infarction (STEMI), has reported a statistically significant benefit from radial approach on cardiac mortality[9]. Despite its proven clinical benefit, many interventional cardiologists perceive that the decrease in vascular complications is balanced by technical difficulties and a longer learning curve, which might explain why the transradial approach is still underemployed[5,10]. On the other hand, when radial access fails, the most common alternative route is the femoral one[11,12].

In this study, we aimed to evaluate the rate of conversion from radial into femoral access in cardiac catheterization and to identify its clinical, demographic and procedural predictors.

Methods

Study design and patient population

In a prospective registry of 14750 consecutive patients from two centres, who underwent cardiac catheterization for diagnostic or interventional coronary procedures, between January 2009 and October 2012, we selected for the purpose of this analysis all consecutive patients in whom the first intention was to use the radial artery (n = 7664). Of these patients, we excluded those in whom the radial access failed, and the alternative choice was the contralateral radial (n = 26), the humeral (n = 4) and the cubital artery (n = 2) (Figure 1).

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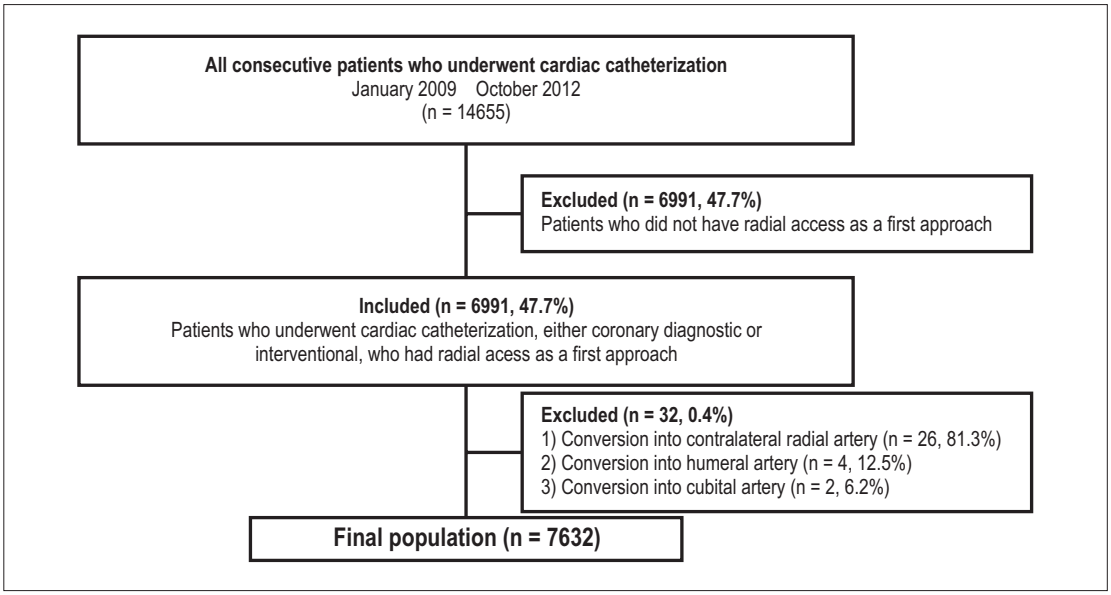


Figure 1 – *Patient selection and study design.*

Baseline characteristics, indication for and type of the procedure performed, procedural devices, details of coronary intervention, need for access site crossover and chosen alternative access were prospectively recorded.

Written informed consent was obtained from all patients as per protocol.

Transradial technique

During the study period, in the two institutions involved in this study, there were nine invasive cardiologists with high experience (> 100 procedures/year) in radial artery catheterization and three fellows in training. The choice of the arterial access was left at each operator's discretion. Either Allen's test or oximetry/plethysmography (Barbeau test) was used, as per protocol, in all patients to access the radial artery patency and adequacy of dual hand blood supply[13,14].

Using a dedicated arm board, with the patient's wrist slightly hyperextended, the right or left radial artery was cannulated with a short 20-gauge needle after administration of 2 to 3 mL of local anaesthetic. A straight 0.025-inch guide wire was then advanced into the radial arterial lumen through the needle, and a specific transradial 5F or 6F hydrophilic introducer sheath (Terumo Medical Corporation, Elkton, MD) was placed into the radial artery. Both long (25-cm) and short introducer (10-cm) sheaths were used at the operator's discretion.

Following sheath insertion, whenever radial spasm was suspected, verapamil (2 mg) and/or isosorbide dinitrate (2 mg) were administered.

An initial intra-arterial bolus of 5000 U of unfractionated heparin was administered to all patients. Monitoring of coagulation with activated clotting time (ACT) was used routinely during percutaneous coronary intervention (PCI) in the centers included in this registry. In case of ad hoc PCI, additional bolus of unfractionated heparin was given to achieve an ACT > 250 seconds. The use of additional glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. The radial sheath was removed immediately in the catheter laboratory following completion of procedure, and hemostasis was achieved by application of an adjustable plastic clamp on the radial artery (TR Band™, Terumo Co., Tokyo, Japan). The clamp was gradually released over 2 to 3 hours, while monitoring for access site bleeding or hematoma, and removed after satisfactory access site hemostasis had been achieved.

As per our routine, all patients undergoing elective or ad hoc PCI were preloaded with clopidogrel before the procedure (75 mg in the case of chronic treatment with clopidogrel > 10 days, or 600 mg, if not).

Definitions and statistical analysis

Procedural success was defined as successful completion of the coronary procedure (diagnostic or interventional) via the initial radial access.

Categorical variables are expressed as absolute values and percentages, and continuous variables, as mean ± SD or median (interquartile range). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov's test and for equality of variances using the Levene's test.

Baseline and procedural characteristics were compared using Fisher exact test or Chi-square test for categorical variables and Student *t* test for continuous variables. Multivariate analysis

regression was used to determine the independent predictors of conversion from radial into femoral access. The independent variables for entry into the multivariate model were selected according to their significance in univariate testing (included those with $p < 0.1$ in univariate analysis). The final model was built by forward stepwise variable selection with entry and exit criteria at the $p = 0.05$ and $p = 0.1$ levels, respectively. The goodness of fit of the model was evaluated by calculating the Hosmer-Lemeshow statistic.

A significance level of 0.05 with two-sided test was used, and all analyses were done with the *Statistical Pack for Social Sciences* (SPSS) software, version 19.

Results

A total of 7632 patients were included in the study. The baseline clinical and procedural characteristics are described in Table 1. The mean age of the study population was 66 ± 11 years, and 32% were women. About one third were diabetic, 73.3% had hypertension, 62.7% had hypercholesterolemia and 41.9% had smoking habits. The incidence of prior PCI was 22.2%, whereas 1.7% had had prior coronary artery bypass grafting. Of the total, 2969 procedures (38.4%) were PCIs and the right radial access was the first choice in most patients (97.6%).

Conversion from initial radial access into femoral access occurred in 5.8% of all patients. Univariate predictors of conversion from radial into femoral access are described in Table 1. Comparing with the successful transradial access group, the transradial access failure group patients were significantly older (mean age of 69 ± 12 years vs. 65 ± 11 years, $p < 0.001$), more likely to be women (46.7% vs. 30.7%, $p < 0.001$), to have chronic kidney disease (7.0% vs. 4.0%, $p = 0.002$) and a smaller body surface area (mean BSA of 1.82 ± 0.18 vs. 1.87 ± 0.19, $p < 0.001$). Conversion into femoral access was also more frequent when the procedure was a PCI (7.4% vs. 4.8% in diagnostic procedures, $p < 0.001$), in patients with multivessel disease (8.8% vs. 5.2%, $p = 0.001$) and when shorter introducers were used (8.0% vs. 3.6% with long introducers, $p < 0.001$). Smoking was associated with lower radial access failure (4.2% vs. 7.0% in non-smokers, $p < 0.001$), as well as the use of 6F introducers compared to 4F or 5F (5.5 % vs. 7.6%, $p = 0.009$). All patients who had an intra-aortic balloon pump needed the conversion into femoral access (2.7% vs. 0.0%, $p < 0.001$).

After multivariable adjustment (Figure 2), independent predictors of conversion from radial access into femoral access were female sex (OR 1.569, CI: 1.234-1.996, $p < 0.001$), age > 66 years (OR 1.354, CI: 1.088-1.684, $p = 0.007$), BSA ≤ 1.938 (OR 1.448, CI: 1.120-1.871, $p = 0.005$), multivessel disease (OR 1.457, CI: 1.167-1.819, $p = 0.001$), the use of short introducer sheaths (OR 3.047, CI: 2.380-3.902, $p < 0.001$) and PCI (OR 1.729, CI: 1.375-2.173).

Discussion

In this study, we sought to identify possible predictors of conversion from radial into femoral access in cardiac catheterization.

Our main findings were: (1) a very low radial access failure (5.8%) in contemporary practice by intermediate (60-100 procedures/year) and high (> 100 procedures/year) volume transradial operators with standard radial sheaths and catheters; (2) the most common alternative access was the femoral artery; (3) independent predictors of radial access failure were the use of short introducers, PCI, female sex, multivessel disease, lower BSA and older age; and (4) both a smoking history and the use of larger sheaths (≥ 6F) were associated with radial access success.

Several aspects make radial access a privileged route. It is feasible, being superficial and easy to puncture and to compress, causing fewer complications at the vascular access site compared to femoral access. Likewise, it offers superior comfort for the patient in the post-procedural period, with earlier ambulation and higher cost-effectiveness[15]. Recent studies have shown a mortality benefit in STEMI patients[1,9]. Nevertheless, potential procedural difficulties still intimidate some operators and radial access success is highly dependent on the operator's experience and skills.

Failure can be due to inability to gain radial artery access or inability to successfully engage the coronary arteries, owing to radial spasm, anatomic variations or severe tortuosity in the radial, brachial, or subclavian arteries[11,16-18].

Over the years, as expected, the use of radial access had a gradual increase: 25% in 2009 to 76% in 2012 (Figure 3A). Focusing on radial access failure rates, one could anticipate a decrease with greater experience. Nonetheless, failure rate was higher in the last years and this could be explained by the fact that higher operator experience could have been offset by a widespread use of the technique, even in less favorable situations to the transradial approach (Figure 3B).

Procedural failure lessens with experience, and ultimately occurs with a frequency of less than 5%[19-21]. Our higher failure (5.8%) could be partly justified by the fact that we have fellows-in-training. Moreover, in the acute coronary syndrome setting, as in the RIVAL trial[1], a higher radial access failure rate has been reported (about 7%). After a systematic review of 23 randomized studies published up to 2007, comparing radial with femoral access in diagnostic and/or therapeutic coronary procedures, Jolly et al.[3] reported a transradial approach failure rate of 5.9%. Our radial access failure rate (5.8%) was similar, although we must consider that, in that meta-analysis, 85.3% of the procedures were PCIs, whereas in our population, the percentage is substantially lower (38.4%). In line with this remark, a non-randomized study performed in 2009[12], including 2100 patients undergoing PCI in the acute coronary syndrome setting, reported a radial access failure rate of 4.6%.

Comparing with the Brazilian experience, the study by Andrade et al.[21] showed a very low failure rate (2.5%), but with a substantially reduced use of the radial access (< 15%), which implies a highly selected population in which this approach was used and may justify the high success rate.

The choice of the catheterization approach (femoral, radial or brachial) is usually a function of the operator, institution, and patient preference. Despite some advantages related to radial access, femoral approach is still widely used since many

Table 1 – Baseline and procedural characteristics

Variables	Prevalence			
	Overall n = 7632	Conversion n = 445	RA success n = 7187	p
Clinical characteristics				
Age (years)	66 ± 11	69 ± 12	65 ± 11	< 0.001
Female, n (%)	2416 (31.7)	208 (46.7)	2208 (30.7)	< 0.001
Weight (Kg)	76 ± 13	74 ± 13	77 ± 13	< 0.001
Height (cm)	166 ± 9	163 ± 9	166 ± 9	< 0.001
BMI (Kg/m^2)	28 ± 4	28 ± 4	28 ± 4	0.479
BSA (m^2)	1.87 ± 0.19	1.82 ± 0.18	1.87 ± 0.19	< 0.001
CKD (GFR < 60 mL/min/1.73 m^2), n (%)	316 (4.1)	31 (7.0)	285 (4.0)	0.002
Heart failure, n (%)	343 (4.5)	17 (3.8)	328 (4.6)	0.464
COPD, n (%)	328 (4.3)	14 (3.1)	314 (4.4)	0.208
Peripheral arterial disease, n (%)	389 (5.1)	17 (3.8)	372 (5.2)	0.191
Previous valvular surgery, n (%)	1053 (13.8)	75 (16.9)	978 (13.6)	0.052
Previous myocardial infarction, n (%)	1312 (17.2)	88 (19.8)	1224 (17.0)	0.136
Previous cerebrovascular accident, n (%)	442 (5.8)	28 (6.3)	414 (5.7)	0.623
Previous revascularization				
Previous PCI, n (%)	1694 (22.2)	93 (20.9)	1601 (22.2)	0.510
Previous CABG, n (%)	130 (1.7)	10 (2.2)	120 (1.7)	0.374
Cardiac risk factors				
Hypertension, n (%)	5593 (73.3)	340 (76.4)	5253 (73.1)	0.131
Hypercholesterolemia, n (%)	4782 (62.7)	298 (67.0)	4484 (62.4)	0.053
Smoking, n (%)	3201 (41.9)	135 (30.3)	3066 (42.7)	< 0.001
Diabetes mellitus, n (%)	2317 (30.4)	139 (31.2)	2178 (30.3)	0.692
Clinical context / Procedural characteristics				
ACS, n (%)	2850 (37.3)	184 (41.3)	2666 (37.1)	0.077
PCI, n (%)	2970 (38.9)	221 (49.7)	2749 (38.2)	< 0.001
Multivessel disease, n (%)	412 (5.4)	39 (8.8)	373 (5.2)	0.001
Right RA, n (%)	7452 (97.6)	438 (98.4)	7014 (97.6)	0.261
Caliber ≥ 6F, n (%)	6666 (87.4)	374 (84.0)	6292 (88.2)	0.009
Longer sheats, n (%)	3718 (48.7)	132 (29.7)	3586 (49.9)	< 0.001
Intra-aortic balloon pump, n (%)	12 (0.2)	12 (2.7)	0 (0.0)	< 0.001

RA: radial access; BMI: body mass index; BSA: body surface area; CKD: chronic kidney disease; GFR: glomerular filtration rate; CODP: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; ACS: acute coronary syndrome.

operators were initially trained in this access and it has also several advantages, such as allowing the use of larger sheaths (useful for procedures in need of higher catheter support and/or bulkier devices). In addition, the femoral access has been associated with less radiation time and contrast[22-26].

We found that the use of short introducers was linked to radial access failure. This could be explained by a potential selection bias (center preference concerning introducer choice) or by the fact that long sheaths, once inserted, provide protection to almost the entire length of the radial artery from further manipulation. Nevertheless, in a previous study, no association was found between sheath length and radial artery spasm[27]. We also found that the need for PCI and the presence of multivessel disease were associated with radial access failure, which are surrogates for a more challenging procedure, with more catheter manipulation and exchanges, which would probably be more difficult in transradial approach, and this was also found in other studies[28-30].

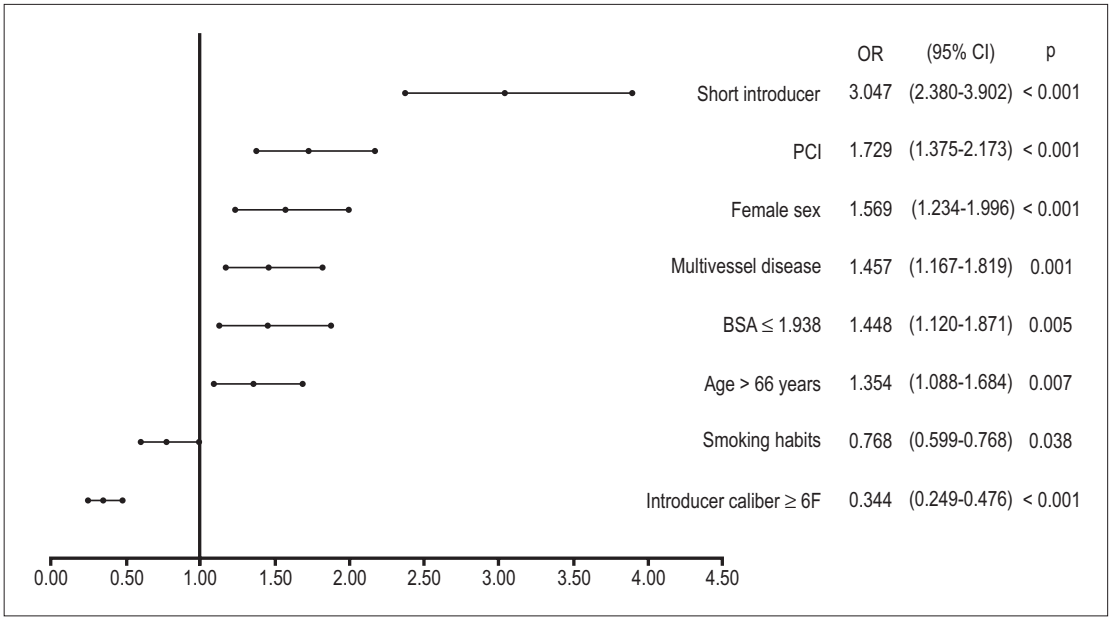


Figure 2 – *Predictors of conversion from radial access into femoral access.*
PCI: percutaneos coronart interventions; BSA: body surface area; CI: confidence interval.

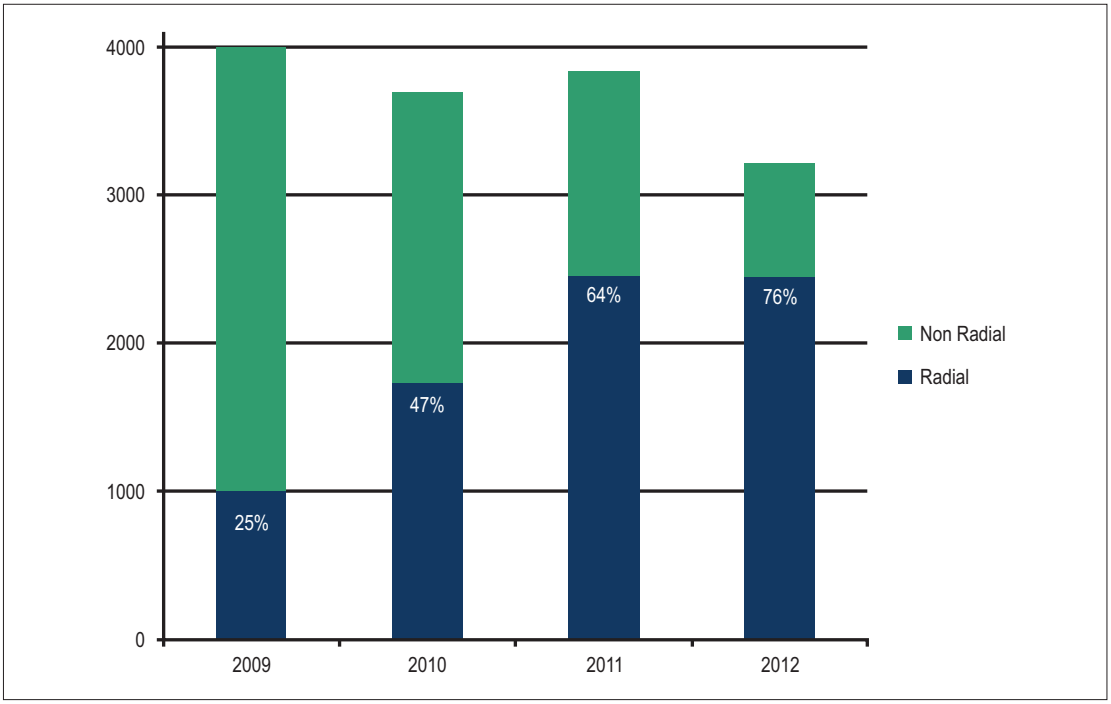


Figure 3A – *Radial access use over the years.*

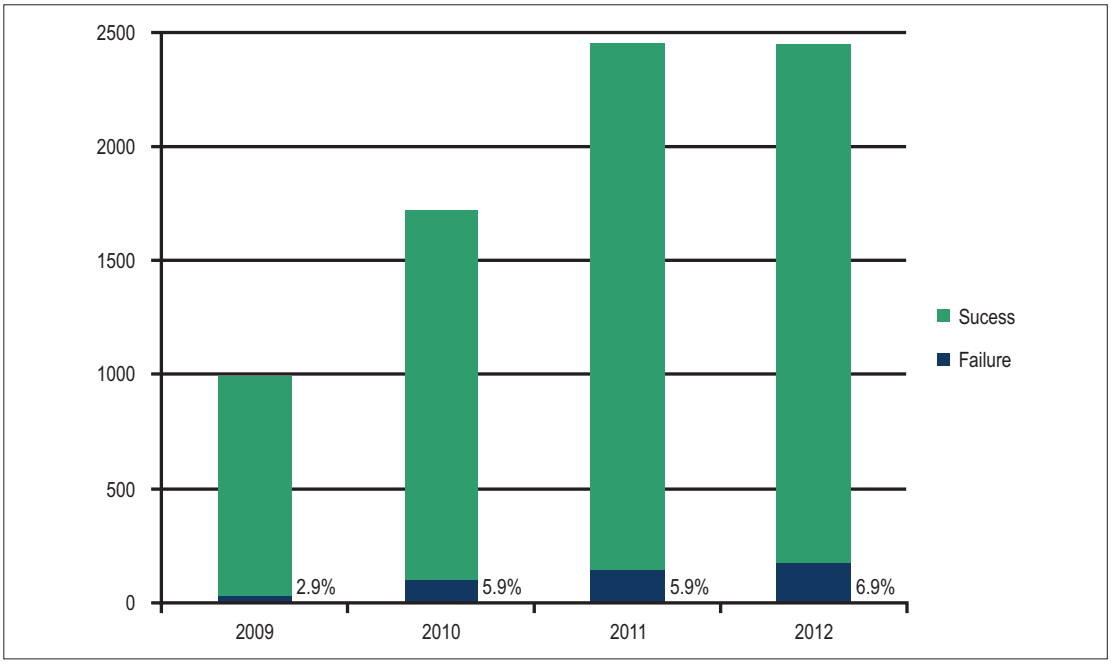


Figure 3B – *Radial access failure over the years.*

Female sex, as well as shorter BSA and older age, were found to be independent predictors of transradial cardiac catheterization failure. This is likely related to smaller size of radial artery, increased subclavian tortuosity, small aortic roots and short ascending aortas, preventing steady guide catheter coronary cannulation during the procedure, as previously described by other authors[1,11,19].

One interesting finding in our results was the association between smoking history and a lower radial access failure. In line with the smoking paradox for coronary artery disease this could also be explained by the younger age of smoking patients submitted to catheterization (in our study, the mean age of the smoking patients was 61 ± 11 vs. 69 ± 11 years, $p < 0.001$) and this has also been found in other studies[31]. Nevertheless, smoking remained an independent predictor of radial access success after multivariate analysis.

Finally, the association between larger sheaths (≥ 6F) and radial access success might be due to selection bias, because the operator would select smaller diameter sheaths for patients in which he would anticipate a more difficult radial access procedure, such as smaller and older patients, in line with International recommendations[27].

Study limitations

The present study is a registry from two high-volume centers, with bias in the selection of patients for radial access. The procedures were performed by different operators, with variable degrees of experience, and it was not possible to evaluate the impact of the operator's experience on failure rate.

Our results reflect radial access learning curve, since, in the first 2 years, less than 50% of the procedures were performed via radial access, and thus, predictors of radial access failure in more experienced centers/operators might be different.

Conclusions

Transradial approach for cardiac catheterization was associated with a high success rate. The predictors of conversion into femoral access were female sex, older age, smaller BSA, multivessel disease, PCI and the use of short introducers.

These findings could contribute to improve patient selection and increase radial access success.

Author contributions

Conception and design of the research: Carvalho MS, Calé R. Acquisition of data: Carvalho MS, Calé R, Gonçalves PA, Vinhas H, Raposo L, Teles R, Martins C, Gabriel HM, Pereira H, Almeida M. Analysis and interpretation of the data: Carvalho MS, Calé R, Almeida M. Statistical analysis: Carvalho MS, Calé R. Writing of the manuscript: Carvalho MS, Calé R. Critical revision of the manuscript for intellectual content: Gonçalves PA, Almeida M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Study Association

This study is not associated with any thesis or dissertation work.

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Manuscript #8

122 Original research

Impact of complete revascularization in patients with ST-elevation myocardial infarction: analysis of a 10-year all-comers prospective registry

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Background **The benefit of complete revascularization (CR) during a primary percutaneous coronary intervention (PCI) in patients with multivessel disease (MVD) is still not clear. The aim of the present study was to evaluate the impact of CR in a nonselected population from an all-comers prospective registry of patients with ST-elevation myocardial infarction (STEMI) over a long period of time.**

Methods and results **Between 2004 and 2014, 671 noncardiogenic shock STEMI patients with MVD were included in the present study, of whom 522 were subjected to incomplete revascularization and 149 were subjected to CR. Patients in the CR group were younger [61 (SD 12) vs. 64 (SD 12.4) years old, $P = 0.001$], more often subjected to femoral access (79.4 vs. 67.1%, $P = 0.002$), and had a lower number of segments with lesion [2 (2.2) vs. 3 (3.4), $P = 0.001$]. The CR group tended to have a lower 1-year major adverse cardiac event (MACE) rate (17.8 vs. 25.7%; $P = 0.05$) that reached statistical significance at 2 years (19.4 vs. 28.5%, $P = 0.03$). The rates of the individual endpoints were not different between groups. Independent predictors of 2-year MACE were age, femoral access, and previous PCI. Index CR was associated with lower MACE (hazard ratio 0.5, 0.36–0.79). MACE-free survival was higher in the CR group throughout the 2 years of follow-up.**

Conclusion **In patients with STEMI and MVD undergoing culprit lesion PCI, preventive PCI in noninfarct coronary arteries with significant stenosis was associated with a lower risk of MACE compared with incomplete revascularization in this all-comers prospective registry.** *Coron Artery Dis* **27:122–127** **Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.**

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Keywords: complete index revascularization, multivessel disease, ST-elevation myocardial infarction

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Introduction

ST-segment elevation myocardial infarction (STEMI) remains a major cause of morbidity and mortality worldwide, and according to contemporary guidelines, timely reperfusion of the culprit lesion with a percutaneous coronary intervention (PCI) is considered the treatment of choice [1,2].

At angiography, 40–65% of STEMI patients have multivessel disease (MVD), which is associated with a poorer prognosis [3–7]. The best revascularization strategy, especially in terms of PCI of nonculprit arteries, is still not clear [7–11]. Until recently, except for patients in cardiac shock, PCI of nonculprit lesions during primary PCI was not recommended, but guidelines are mainly based on nonrandomized studies, susceptible to important biases [1,2,5, 12–14]. Recently, three randomized studies, Complete versus Lesion only Primary-PCI Trial (CvLPRIT), preventive angioplasty in myocardial infarction (PRAMI), and DANAMI3-PRIMULTI, suggested some benefit from complete revascularization (CR) [15–18].

The aim of the present study was to evaluate the potential clinical impact of CR in a nonselected population from an all-comers prospective registry of STEMI patients over a long period of time.

Methods

Population and design

The present analysis is based on the single-center Angiography and Coronary revascularization Registry of Santa Cruz Hospital (ACROSS Registry) in which demographic, clinical, angiographic, and procedure-related variables are prospectively collected using a dedicated lab-based computer database (Cardiobase; Infortucano, Lisbon, Portugal). This study was investigator driven and independent of any commercial funding. Between January 2004 and January 2014, all consecutive

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STEMI patients subjected to primary PCI ($N=1433$) were initially screened for the presence of MVD (defined as the presence of a stenosis of $\geq 50\%$ in one or more coronary arteries other than the infarct artery).

Patients with single-vessel disease ($N=527$), those with previous coronary artery bypass graft ($N=25$), presenting postcardiac arrest ($N=20$), or in cardiac shock ($N=85$) were excluded. Of the remaining 784 patients with MVD, patients subjected to staged revascularization ($N=113$) were also excluded. Study groups were finally defined according to whether index CR (defined as treatment of all lesions with $\geq 50\%$ stenosis during primary PCI) was performed: 22% of the remaining 671 patients were subjected to index CR and 77.8% ($N=522$) were subjected to incomplete revascularization (IR) (Fig. 1).

Endpoints

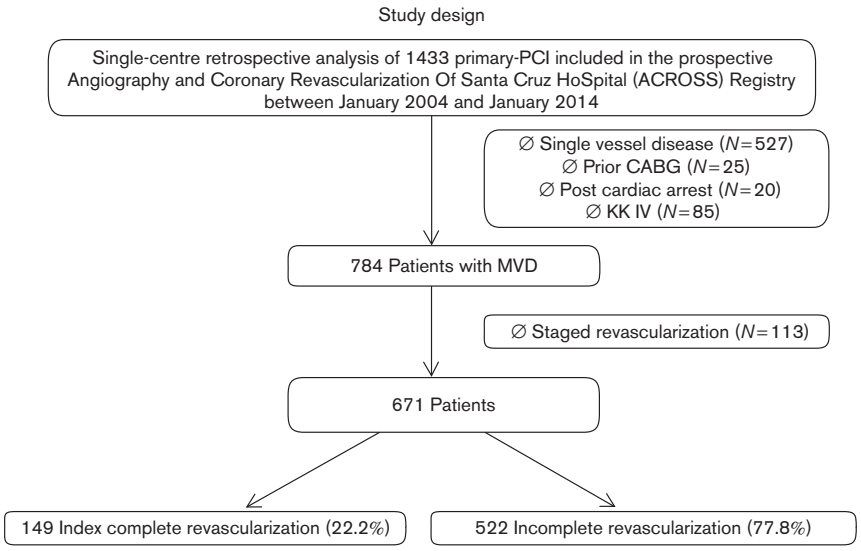
The primary outcome was the occurrence of major adverse cardiac events (MACE) at 30 days, 1, and 2 years. MACE was defined as a composed endpoint of all-cause death, nonfatal myocardial infarction (MI), and repeated revascularization. Mortality was defined as death from any cause. Nonfatal MI and repeated revascularization were adjudicated by clinical file review or telephone interview and without knowledge of the initial revascularization strategy. For all-cause mortality, our national social security database was also used. Repeated revascularization was considered if the patient was electively subjected to PCI at the discretion of the clinician (because of persistent angina despite medical therapy or documented ischemia), who was not blinded to the revascularization status of the patient, and nonfatal MI was defined according to the 2014 universal definition of MI of the European Society of Cardiology [2].

The choice of treatment strategy was at the discretion of the operator for each individual case. All patients underwent PCI using standard interventional techniques in accordance with our department's protocol at each time point; the type of stent used and the steps performed for angiographic optimization were according to the physician's preference. Postdischarge therapy followed international standard-recommended regimens.

Statistical analysis

Continuous variables with a normal distribution are expressed as mean ± SD. Discrete variables are expressed as frequencies and percentages. Statistical comparison of baseline characteristics and outcomes was performed using the χ^2-test or Fisher's exact test, when appropriate, for categorical variables and Student's t-test or the Mann–Whitney test for continuous variables (Table 1). All analyses were retrospective. The Kaplan–Meier method was used to plot time-to-event curves. Independent predictors of MACE were estimated using Cox proportional hazard regression analysis, adjusted for baseline characteristics (Table 2). The following variables were included as covariates: index CR, age, drug-eluting stent, chronic kidney disease, femoral access, previous MI, and previous PCI. All reported P-values are two sided and a value lower than 0.05 was considered statistically significant. When appropriate, the 95% confidence interval was calculated. Statistical analysis was carried out using the

Fig. 1



Patient flow diagram. CABG, coronary artery bypass grafting; KK, Killip Kimbal; MVD, multivessel disease; PCI, percutaneous coronary intervention.

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Table 1 Demographics and baseline clinical characteristics

	Total ($N=671$)	IR ($N=522$)	CR ($N=149$)	P value
Age (years) [mean (SD)]	63.7 (12.5)	64.4 (12.4)	61 (12.0)	0.001
Male sex	519 (77.4)	399 (76.6)	120 (80)	0.39
Hypertension	378 (56.3)	302 (57.9)	76 (50.9)	0.13
Diabetes mellitus	144 (21.4)	117 (22.4)	27 (18.2)	0.28
Dyslipidemia	332 (49.5)	261 (50.1)	71 (47.3)	0.54
Smokers	376 (56)	285 (55.5)	91 (61.1)	0.18
Family history of CV disease	56 (7.5)	42 (7.3)	14 (8.5)	0.61
Previous MI	112 (16.7)	83 (15.9)	29 (19.4)	0.28
Previous PCI	94 (14)	68 (13)	26 (17.6)	0.16
Peripheral vascular disease	28 (4.2)	22 (4.3)	6 (3.6)	0.44
CKD-stage 5	15 (2.2)	14 (2.4)	1 (1.2)	0.27
Cerebrovascular disease	36 (5.3)	29 (5.5)	7 (4.2)	0.69
Chronic pulmonary disease	18 (2.7)	15 (2.8)	3 (2.4)	1.00
Rescue-PCI	67 (10.1)	56 (10.7)	11 (7.9)	0.3
Femoral access	468 (69.8)	350 (67.1)	118 (79.4)	0.002
Drug-eluting stent	274 (40.8)	216 (41.4)	58 (38.8)	0.59
Culprit-LM	20 (3)	17 (3.3)	3 (1.8)	0.44
Culprit-LAD	325 (48.5)	249 (47.7)	76 (51.5)	0.43
Culprit-Cx	122 (18.2)	95 (18.2)	27 (18.2)	1.00
Culprit-RCA	203 (30.3)	161 (30.8)	42 (28.5)	0.63
Number of segments with lesion	3 [2–3]	3 [2–4]	2 [2–2]	<0.001
Number of treated segments	1 [1–2]	1 [1–2]	2 [2–2]	<0.001

Values are n (%) or median [25th to 75th percentile].
CKD, chronic kidney disease; CR, complete revascularization; CV, cardiovascular; Cx, circumflex; IR, incomplete revascularization; LAD, left anterior descending; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery.

Table 2 Clinical outcomes at 30 days, 1, and 2 years

	Total	IR	CR	P value
MACE (30 days)	53 (7.9)	46 (8.6)	7 (5.2)	0.21
MACE (1 year)	162 (24)	138 (25.7)	24 (17.8)	0.05
MACE (2 years)	182 (27)	156 (28.5)	26 (19.4)	0.03
Repeated PCI	68 (37)	58 (10.8)	10 (7.4)	0.25
Nonfatal MI	60 (33)	52 (9.7)	8 (5.9)	0.26
All-cause mortality	54 (30)	46 (8.6)	8 (5.9)	0.38

Values are expressed in n (%).
CR, complete revascularization; IR, incomplete revascularization; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; R, revascularization.

SPSS software (version 21.0; SPSS Inc., Chicago, Illinois, USA).

Results

Of 1433 STEMI patients initially screened, 671 were included in the analysis: 522 (77.8%) subjected to IR and 149 (22.2%) subjected to CR, as shown in Fig. 1. Patients in the CR group were younger [61 (SD 12) vs. 64.4 (SD 12.4) years, $P=0.001$], were more often subjected to femoral access (79.4 vs. 67.1%, $P=0.002$), and had a lower number of segments with lesion [2 (2.2) vs. 3 (3.4), $P=0.001$]. The remaining baseline characteristics were similar between both groups: 77.4% men; 21.4% diabetic; 56% were current or previous smokers; and 16.7% had previous MI (Table 1). The distribution of the culprit lesions was comparable between groups. In terms of the primary endpoint, the 30-day MACE rate was not statistically different between groups (5.2% in the CR group vs. 8.6% in the IR group, $P=0.21$). The CR group tended to show a significantly lower 1-year MACE rate (17.8 vs. 25.7%; $P=0.05$) that reached statistical significance at 2 years (19.4 vs. 28.5%; $P=0.03$). Individual endpoint rates did not differ between the different approaches (Table 2). By multivariate analysis, the independent predictors of a higher 2-year MACE were age [hazard ratio (HR) 1.01, 1–1.02; $P=0.012$], femoral access (HR 1.61, 1.10–2.36; $P=0.014$), and history of a previous PCI (HR 1.57, 1.005–2.46; $P=0.048$). In contrast, index CR was associated with a lower MACE rate (HR 0.5, 0.36–0.79; $P=0.002$) (Table 3). MACE-free survival was higher in the CR group early in the follow-up and this difference remained throughout the 2 years of follow-up because of a constant rate of MACE (Fig. 2).

Discussion

In this single-center registry analysis, index CR was associated with a lower 2-year MACE rate. As patients were not randomized, some differences between the two subgroups should be taken into consideration. As expected, patients in the CR subgroup had less disease burden, with a lower number of segments with significant stenosis. This feature itself could imply a lower MACE risk in this subgroup and may lead to the operator's decision to treat nonculprit lesions during the same procedure because of the lower level of anatomy complexity. Patients in the CR subgroup were also younger, which could also be associated with this lower burden of disease. Femoral access was more often used in the CR subgroup and it was an independent predictor of 2-year MACE. Radial access is associated with a lower risk of bleeding complications [19] and for this reason our center progressively changed from a predominantly femoral to radial access. In this way, radial access is linked to more contemporary PCI practice, which can be associated with better outcomes. In addition, this could also be related to the fact that femoral access is more often decided on unstable or complex patients, some of whom were not excluded from this analysis (higher Killip class, left main

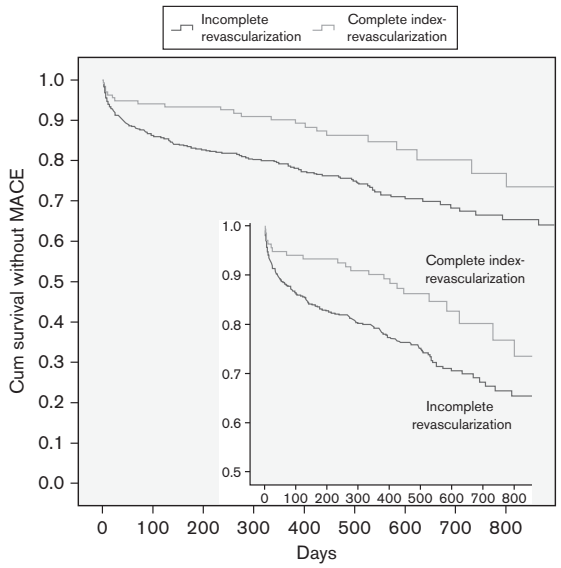
Table 3 Independent predictors of 2-year MACE

Variables	HR (95% CI)	P value
Index complete revascularization	0.5 (0.36–0.79)	0.002
Age	1.01 (1.00–1.02)	0.012
DES	0.89 (0.65–1.22)	0.47
CKD	1.41 (0.68–2.92)	0.43
Femoral access	1.61 (1.10–2.36)	0.014
Previous MI	1.05 (0.68–1.62)	0.82
Previous PCI	1.57 (1.005–2.46)	0.048

CI, confidence interval; CKD, chronic kidney disease; DES, drug-eluting stent; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

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Fig. 2



Cumulative event-free survival. MACE, major adverse cardiovascular events.

disease, cardiac arrest, worst left ventricle function, or transient intraprocedure instability). The other independent predictors of MACE in our multivariate analysis were age and previous PCI, probably representing patients with more advanced coronary disease burden.

Despite our wide inclusion time and real-world population, the significantly lower rate of MACE 1 and 2 years in the CR group is in accordance with the latest randomized trials, CvLPRIT and PRAMI [15,16], and a recent meta-analysis [20–22].

In addition, at 30 days, the MACE rate was similar between the two subgroups, suggesting the safety and feasibility of the CR index, which is in line with previous studies [4,5,23].

An STEMI population with MVD represents a heterogeneous population, complex to randomize in a prospective study. Therefore, the search for a standardized universal approach to these patients is hampered [24].

Revascularization guidelines were traditionally based mostly on small, single-center nonrandomized studies, susceptible to important treatment selection bias [5,12,13,25]. Accordingly, CR in STEMI with MVD is recommended only when hemodynamic instability is present [1,2] and this strategy is currently being evaluated in the CULPRIT-SHOCK trial. Until recently, there was limited evidence for the implications of treatment of 'bystander' lesions (associated with higher mortality) identified during primary PCI [6]. STEMI patients have more lesions with an unstable phenotype than patients with stable coronary disease [10]. Moreover, STEMI and MVD are most likely to have a worse prognosis because of increased cardiovascular morbidity and mortality compared with those with single-vessel disease [3,4,7,23,26]. CR, performed during the index procedure, could limit the infarct size, reduce ischemic burden and the risk for further PCI, MI, and heart failure, stabilize unstable 'bystander' plaques, and decrease overall costs and perhaps mortality. However, it can increase the risk of stent thrombosis because of a thrombotic and inflamed acute state, prolong the duration of a procedure during which there may always be some instability, and increase the risk of contrast-induced nephropathy and overestimation of lesion severity leading to unnecessary stenting and its complications [24,27]. Nevertheless, there is no difference in costs (balanced by earlier discharges and less procedures in the future), rate of stroke, major bleeds, or in-hospital mortality [15,16,18,28,29].

Three recent randomized studies challenged the classic strategy of revascularization in this setting [15–17]. The randomized trial of PRAMI study compared primary preventive PCI with culprit-only PCI in 465 patients and was stopped early because of a significant between-group difference ($P < 0.001$) in the incidence of the primary outcome (cardiac death, nonfatal MI, or refractory angina) favoring preventive PCI [16]. In the CvLPRIT, MACE was significantly lower (driven mainly by subsequent revascularization) in the CR arm (10 vs. 21.2%) [15]. The individual components of MACE were also lower, but did not achieve statistical significance. These studies were limited by a lack of statistical power and a reliance on repeat revascularization and refractory angina as an outcome, which may be subject to bias in nonblinded trials [15].

The DANAMI3-PRIMULTI study, which included 627 patients with STEMI and MVD, compared culprit-only PCI with CR using fractional flow reserve, also showing a protective effect of CR (HR 0.56, 95% confidence interval 0.38–0.83; $P = 0.004$) [17].

Four recent meta-analyses including only randomized studies (most with over a 1-year follow-up) showed beneficial outcomes of primary multivessel PCI [21,22, 30,31]. Preventive index PCI was associated with a significantly reduced incidence of MI, refractory angina, and repeated revascularization. Cardiac and all-cause death were reduced, and this was not statistically significant.

Ongoing larger studies, such as the COMPLETE: complete versus culprit-only revascularization to treat MVD after primary PCI for STEMI (COMPLETE) trial, may yield important information on who will benefit from CR as well as the optimal timing of the staged procedure.

In our single-center prospective registry in an all-comers population over a long period of time (10 years), preventive PCI in noninfarct coronary arteries in patients with STEMI and multivessel coronary artery disease was associated with a lower risk of adverse cardiovascular

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events. Our results are in agreement with recent randomized trials that have questioned the traditional guidelines and reinforce the potential benefits from complete index revascularization, which needs to be confirmed by broader randomized trials.

Limitations

Our study should be assessed in the context of its limitations, many of which are inherent to registry studies, such as treatment selection bias. These as well as other potentially relevant clinical features that could have impacted both the choice to use multivessel PCI (e.g. use of fractional flow reserve) and the outcomes could have influenced the results as these differences cannot be completely corrected by multivariate analysis. The use of medication in secondary prevention was not accounted for in this analysis, but patients were treated in accordance with the available guidelines, independent of the revascularization status. In addition, if such differences would occur, these would probably be in favor of a higher drug use (number or dosage) in patients in the IR subgroup, which could have had a positive impact on cardiovascular events and therefore lead to an underestimation of the benefit of CR.

In addition, as this analysis covered a 10-year span, it also reflects changes in the PCI technique with progressive adoption of newer stents/drugs that could have a positive impact on outcomes, but the small sample size prevented us from proceeding with further subanalysis over different time intervals.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Manuscript #9

EXPERIMENTAL RESEARCH
INTERVENTIONS FOR VALVULAR DISEASE AND HEART FAILURE

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In vitro evaluation of implantation depth in valve-in-valve using different transcatheter heart valves



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KEYWORDS

- aortic valve replacement
- circulatory *in vitro* studies
- haemodynamics
- heart valve prosthesis
- valve-in-valve

Abstract

Aims: Transcatheter heart valve (THV) implantation in failed bioprosthetic valves (valve-in-valve [ViV]) offers an alternative therapy for high-risk patients. Elevated post-procedural gradients are a significant limitation of aortic ViV. Our objective was to assess the relationship between depth of implantation and haemodynamics.

Methods and results: Commercially available THVs used for ViV were included in the analysis (CoreValve Evolut, SAPIEN XT and the Portico valve). THVs were implanted in small surgical valves (label size 19 mm) to simulate boundary conditions. Custom-mounted pulse duplicators registered relevant haemodynamic parameters. Twenty-eight experiments were performed (13 CVE, 5 SXT and 10 Portico). Ranges of depth of implantation were: CVE: –1.2 mm to 15.7 mm; SXT: –2.2 mm to 7.5 mm; Portico: 1.4 mm to 12.1 mm. Polynomial regression established a relationship between depth of implantation and valvular mean gradients (CVE: $p<0.001$; SXT: $p=0.01$; Portico: $p=0.002$), as well as with EOA (CVE: $p<0.001$; SXT: $p=0.02$; Portico valve: $p=0.003$). In addition, leaflet coaptation was better in the high implantation experiments for all valves.

Conclusions: The current comprehensive bench testing assessment demonstrates the importance of high device position for the attainment of optimal haemodynamics during aortic ViV procedures.

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Abbreviations

EOA effective orifice area
THV transcatheter heart valve
ViV valve-in-valve
VIVID Valve-in-Valve International Data Registry

Introduction

Biological prostheses are increasingly preferred over mechanical valves, due to the lower rate of thrombotic complications[1]. Unfortunately, these tissue valves have limited durability and commonly fail within 10-20 years[2-4], resulting in a high-risk patient population in need of repeat valve implantation[5-8]. Recent evidence suggests that transcatheter heart valve (THV) implantation in failed surgical valves (valve-in-valve [ViV]) is an appealing alternative to reoperation[9,10]. However, elevated post-procedural gradients related to THV underexpansion are unfortunately common following ViV, and possibly related to poor long-term device durability[11].

Evidence suggests that THV devices with a supra-annular functional valve position are associated with lower gradients after ViV[12,13]. It seems that a THV that has a functional valve operating above the surgical valve annulus is unencumbered by the non-elastic portion of the original surgical bioprosthesis. Full expansion of the valve level of the THV can be expected in these cases, thus maximising the orifice area and lowering transvalvular gradients. Nevertheless, there are considerable design differences among the commercially available THVs, and each one functions in a different way. Some are supra-annular by design, while others tend to operate inside the surgical valve annulus **(Figure 1)**. It is possible that a higher implantation of any THV would enable better expansion and lower gradients[14]. However, excessively high implantation could increase the risk of device malposition. Therefore, it is necessary to determine an optimal depth of implantation of THV devices in ViV procedures. The current *in vitro* study aimed to examine whether high implantation of three commonly used THV devices (i.e., aiming to achieve a supra-annular position of the THVs) would demonstrate improved haemodynamics after ViV.

Methods

THV MODELS AND VIV DEPLOYMENT

In vitro bench testing was performed with multiple implantation depths of three different THV devices implanted inside small surgical bioprostheses (label size 19 mm). Each position was assessed by X-ray imaging for its implantation depth prior to *in vitro* haemodynamic testing.

COREVALVE EVOLUT

CoreValve® Evolut® (Medtronic, Minneapolis, MN, USA) 23 mm devices were implanted in a 19 mm Epic™ Supra (St. Jude Medical, St. Paul, MN, USA) with a true internal diameter of 16.5 mm. Small and gradual changes in implantation depth were attempted between each experiment (13 positions). For the determination of implantation depth, the bottom diamond of the CoreValve Evolut was used as the reference for a scale. One straight line, starting at the surgical valve ring, was traced on each side of the device. The two values obtained were added together and their average was considered the final depth of implantation for each case.

SAPIEN XT

SAPIEN XT (Edwards Lifesciences, Irvine, CA, USA) 23 mm devices were implanted in a 19 mm Carpentier-Edwards PERIMOUNT valve (Edwards Lifesciences) with a true internal diameter of 17 mm. Small and gradual changes in implantation depth were attempted between each experiment (five positions). For the determination of implantation depth, one straight line was traced on each side of the SAPIEN XT. The values obtained were added and their average was considered the height of the device. Another line was traced at each side of the THV, starting from the surgical valve ring to the bottom of the THV. The values from both lines were added and their average was considered the depth numeric value. Finally, the depth was then defined as the percentage of the THV height below the stented surgical valve ring. Device height in millimetres was estimated by multiplying the depth value by the height of the expanded device (14.3 mm for the 23 mm device).

PORTICO VALVE

Portico™ (St. Jude Medical) 23 mm devices were implanted in a 19 mm Trifecta™ valve (St. Jude Medical) with a true internal diameter of 16 mm. Small and gradual changes in implantation

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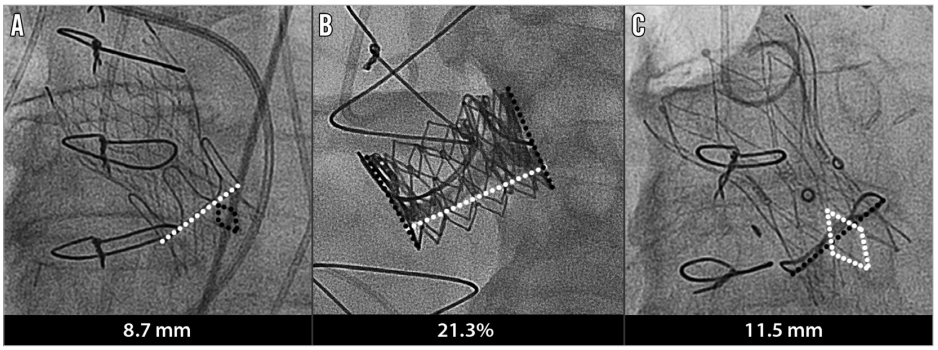


Figure 1. *Examples of depth of implantation measurement for each of the transcatheter devices. A) CoreValve. B) SAPIEN XT. C) Portico valve.*

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depth were attempted between each experiment (10 positions). For Portico ViV procedures, the bottom diamond of the THV device was used as the reference for the creation of a scale. One straight line was traced on each side of the device. The two values obtained were added together and their average was considered as the final depth of implantation.

HAEMODYNAMIC MEASUREMENTS

THVs were tested at a temperature of 37°C in a custom-built pulse duplicator system. Heart rate, blood pressure, and cardiac output were used as control parameters for the waveform generator controlling a servo pump. Pressure was measured in the left atrium, left ventricle, left ventricular outflow tract, and ascending aorta with strain gauge pressure transducers (Deltran®; Utah Medical Products, Inc., Midvale, UT, USA). An electromagnetic flowmeter (CME 500 Series; Carolina Medical Electronics Inc., East Bend, NC, USA) was used to measure aortic valve flow rate. In addition, normal saline solution was used as recirculating fluid for the haemodynamic measurements. Pulse duplicator input parameters were used to match ISO 5840-1:2015 standard and Food and Drug Administration (FDA) specifications for testing heart valves: heart rate of 70 beats/min (bpm), 35% systolic duration of cycle period, mean atrial and aortic pressures of 10 and 100 mmHg, and cardiac output 5 litres/minute. These haemodynamic parameters were maintained constant throughout the study. Valvular mean pressure gradient, effective orifice area (EOA), and regurgitation volume were determined by the pulse duplicator software. EOA was calculated using the Gorlin equation. In addition, short-axis images of the opening and closing of the devices were recorded by a high-speed camera (FASTCAM SA4; Photron USA, Inc., San Diego, CA, USA) during the entire cardiac cycle at a rate of 1,000 frames per second. Relative haemodynamic values for pressure gradient, EOA, and regurgitation volume in comparison with the deepest THV position were reported.

Statistical analysis

Polynomial regression was performed for each THV device, with three correlations performed: implantation depth and final mean gradient, implantation depth and EOA, and implantation depth and regurgitation volume. F-tests were used to assess the fit of the data to linear, quadratic and cubic equations. F-tests were also used to test the significance of an increase in R^2 between linear and quadratic equations, and also between quadratic and cubic equations. A two-tailed $p<0.05$ was considered statistically significant. Statistical analysis was performed using Microsoft Excel for Mac (Microsoft Corporation, Redmond, WA, USA).

Results

COREVALVE EVOLUT

Thirteen *in vitro* experiments were performed at varied implantation depths from –1.2 mm to 15.7 mm **(Figure 2)**. **Online Table 1** shows the relative haemodynamic values for pressure gradient, EOA, and regurgitation volume. The relative values were calculated based on the case with the lowest implantation depth. Cubic regression demonstrated a correlation between higher implantation and lower mean gradients ($p<0.001$) **(Figure 3)**. Supra-annular positioning of the CoreValve Evolut THV (0.7 to 3 mm depth of implantation) resulted in an average 17.2% lower mean transvalvular pressure gradient than in the common deeper position (6.1 to 8.2 mm depth of implantation). The reduction in mean transvalvular pressure gradient with increasingly supra-annular ViV deployment was due primarily to increases in valve orifice area. As shown in **Figure 3**, there was a correlation between higher implantation and larger EOAs ($p<0.001$). Furthermore, visual evaluation showed improved leaflet movement and closing morphology in high-implanted devices with lower transvalvular gradients **(Moving image 1, Moving image 2)**. However, regurgitation volume increased considerably with higher implantation depth **(Figure 3)**. Regurgitation volume was found to be lowest at the normal implantation depth, with a minimum value at 8.2 mm implantation depth. The largest regurgitation volume was found in the case with the lowest implantation depth (i.e., 15.7 mm implantation depth).

SAPIEN XT

Five *in vitro* experiments were performed at varied implantation depths. The depth range was from –2.2 mm to 7.5 mm **(Figure 4)**. **Online Table 1** shows the relative haemodynamic

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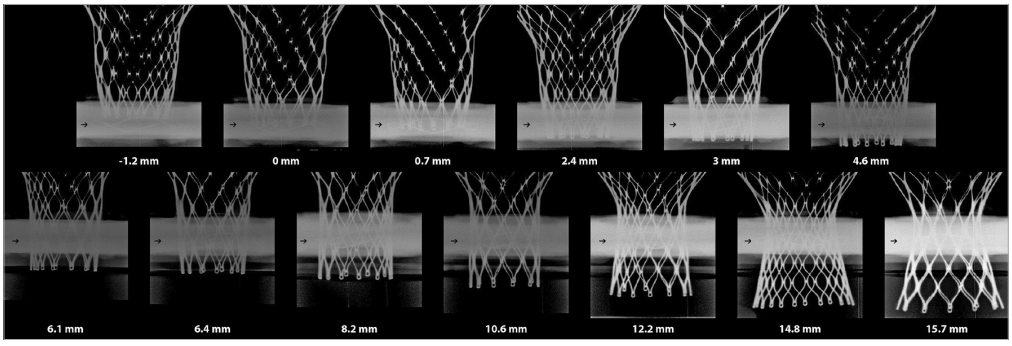


Figure 2. *Thirteen CoreValve Evolut in vitro experiments with respective implantation depths.*

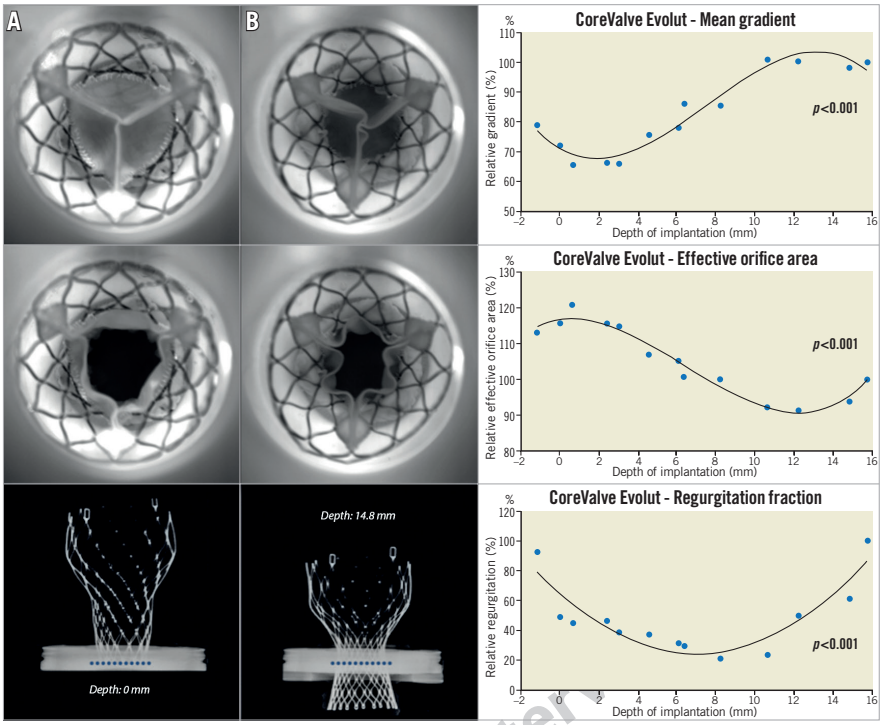


Figure 3. *Thirteen 23 mm CoreValve Evolut in 19 mm St. Jude Epic experiments with respective depths. The first graph demonstrates the relationship between depth of implantation and EOA. The second graph demonstrates the correlation between depth and post-procedural gradients. Finally, the third graph shows the correlation between depth and relative regurgitation. Relative gradient is based on the gradient of the case with the lowest implantation. Experiment A demonstrates a high implantation of CoreValve Evolut. There was symmetric leaflet closure and larger orifice area, whereas experiment B demonstrates smaller orifice area. Notice the different implantation depths between the devices (the dotted line represents the surgical valve ring position).*

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values for pressure gradient, EOA, and regurgitation volume of SAPIEN XT THV at varied implantation depths. Similar to the CoreValve Evolut THV, the relative values were calculated based on the case with the lowest implantation depth. Cubic regression demonstrated a relationship between higher implantation depth and lower pressure gradients (p=0.01) **(Figure 5)**. Supra-annular positioning of the SAPIEN XT THV (i.e., –2.2 mm depth of implantation) resulted in a 3.7% lower mean transvalvular pressure gradient than a deeper ViV position (i.e., 1 mm depth of implantation). The mean transvalvular pressure gradient increased as the depth of implantation increased, as the top portion of the THV could not be fully expanded to the manufactured size. In addition, as shown in **Figure 5**, a correlation between higher implantation depth and larger EOA was present (p=0.01). Visual evaluation showed that the oversized THV was constrained by the rigid bioprostheses, resulting in leaflet distortion at lower implantation

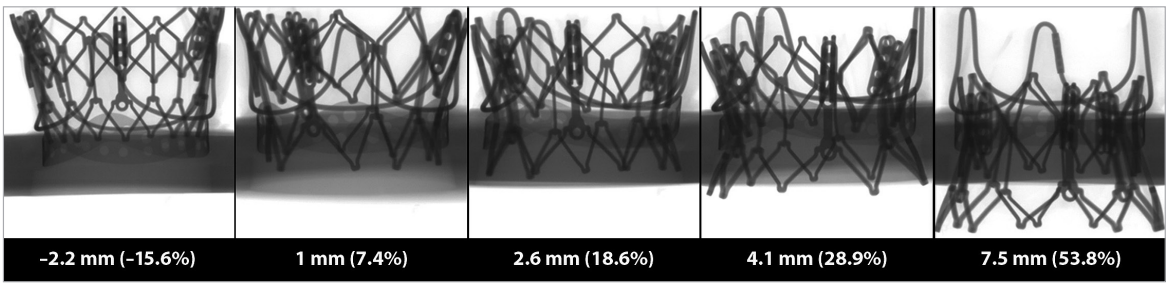


Figure 4. *Five SAPIEN XT in vitro experiments with respective implantation depths.*

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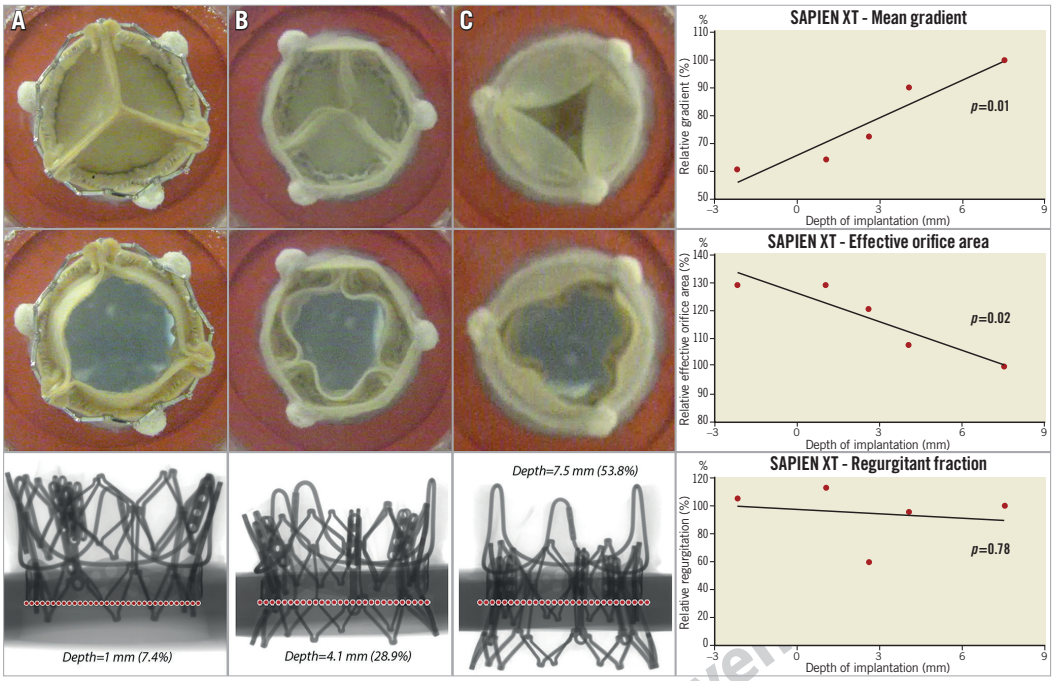


Figure 5. *Five 23 mm SAPIEN XT in 19 mm PERIMOUNT with respective depths. The first graph demonstrates the relationship between depth of implantation and EOA. The second graph demonstrates the correlation between depth and post-procedural gradients. Finally, the third graph shows the correlation between depth and relative regurgitation. Relative gradient is based on the gradient of the case with the lowest implantation. Experiment A demonstrates a high implantation of SAPIEN XT. Notice the adequate closing of the leaflets and larger orifice area, whereas experiment B demonstrates smaller orifice area. Experiment C had a very deep implantation, resulting in leaflet overhang.*

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depths **(Figure 5)**. Better leaflet coaptation was visually evident in case of higher implantation **(Figure 5, Moving image 3, Moving image 4)**. Moreover, excessively low implantation demonstrated leaflet overhang, resulting in two functional sets of leaflets, the original surgical leaflet and the THV leaflet **(Figure 5, Moving image 5)**. Furthermore, regurgitation volume was found to be lowest at the 2.6 mm implantation depth.

PORTICO VALVE

Ten experiments were performed *in vitro* at varied implantation depths **(Figure 6)**. **Online Table 1** shows the relative haemodynamic data for depth range of –1.4 mm to 12.1 mm. The relative values were calculated based on the case with the lowest implantation depth. A correlation was found between higher implantation and lower gradients ($p<0.001$) **(Figure 7)**, as well as between higher implantation and larger EOA ($p<0.001$) **(Figure 7)**. The lowest mean gradient and the largest EOA were observed at the highest THV implantation depth (i.e., –1.4 mm implantation depth). The reduction in mean transvalvular pressure gradient with increasingly supra-annular ViV deployment was due to increases in valve orifice area **(Figure 7A, Figure 7B)**. Leaflet movement videos demonstrate better closing position in high-implanted devices **(Moving image 6, Moving image 7)**. The largest regurgitation volume was found in the case with the lowest implantation position (i.e., 12.1 mm implantation depth). Regurgitation volume was found to be lowest at the 6.5 mm implantation depth.

Discussion

Transcatheter ViV is an alternative to conventional surgical valve replacement. Currently, the major limitation of ViV procedures is residual stenosis, which is common in this setting as surgical valve rings generally constrict THVs and do not allow full expansion. The current analysis is the largest comprehensive *in vitro* evaluation of the effect of positioning on ViV outcomes. Results suggest that supra-annular implantation of the three commonly used THVs within small bioprostheses can lead to lower gradient and larger EOA after ViV implantation. Visual evaluation of the three THVs showed improved leaflet movement and coaptation in high-implanted devices. The current analysis is in agreement with a previous *in vivo* analysis on the importance of depth of implantation in ViV procedures[12].

Optimal THV function and leaflet coaptation require full device expansion to the manufactured size[15]. In addition to supra-annular positioning of THVs, ViV haemodynamics and leaflet

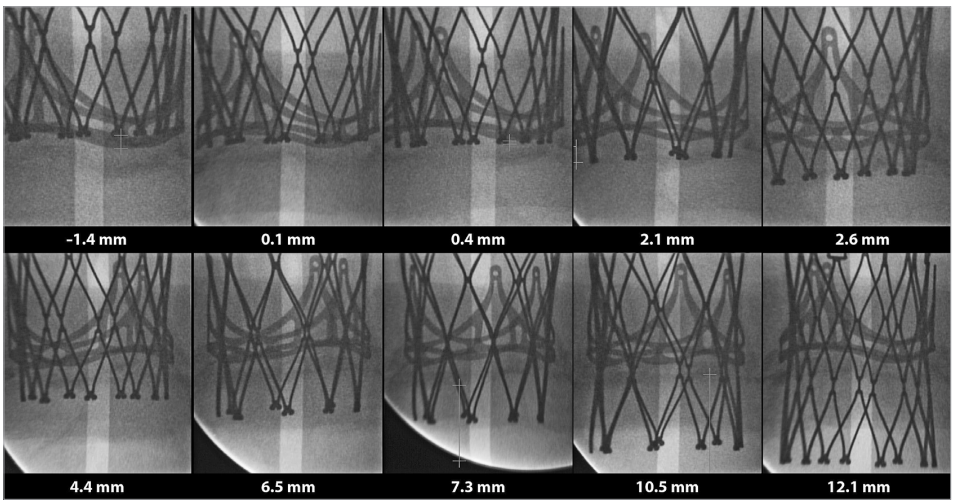


Figure 6. *Ten Portico in vitro experiments with respective implantation depths.*

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coaptation in small degenerated bioprostheses may hypothetically be improved by using size-specific THVs that match bioprosthetic valve size[15,16]. Azadani et al[16] evaluated the haemodynamic performance of 20 mm THVs created based on the Edwards SAPIEN valve design within 19 and 21 mm degenerated Carpentier-Edwards PERIMOUNT and Carpentier-Edwards porcine bioprostheses. ViV within the 19 mm PERIMOUNT and 21 mm porcine degenerated bioprostheses significantly reduced transvalvular pressure gradient and improved valve area. However, the 20 mm THVs migrated retrogradely into the left ventricle after ViV in 21 mm degenerated PERIMOUNT bioprostheses. Furthermore, ViV within the 19 mm porcine bioprosthesis was ineffective, with no reduction in pressure gradient.

The long-term durability and failure modes of THV devices in the ViV setting are unknown. The two distinct yet synergistic processes that contribute to the durability limitations of bioprosthetic valves are widely considered to be: 1) calcification, and 2) fatigue-induced structural deterioration[17]. Calcification is initiated primarily within residual connective tissue cells that have not been removed by fixation pretreatment procedure[18-20]. Furthermore, collagen and elastin fibres can serve as nucleation sites for calcification[21,22]. Alternatively, non-calcific tissue degeneration is due to fatigue-induced structural deterioration, induced by fibre debonding and shearing[23].

Several studies have shown that high stress regions on bioprosthetic leaflets correlate with regions of calcification and mechanical damage due to fatigue[17,19,23-27]. A recent article by Abbasi et al[11] demonstrated that incomplete deployment of a THV induced localised high stress regions within the belly of the THV during diastole. Generally, the stress is localised at the commissures during the diastolic phase of the cardiac cycle with complete THV expansion to the manufactured size. The computational simulations demonstrated that incomplete expansion of THVs would induce localised high stress regions within the leaflets, which over time may accelerate valve tissue degeneration. In addition, elevated gradients, more common in incompletely expanded devices, could be associated with a reduction in valve durability[28]. Therefore, long-term results of structural valve degeneration using the under-expansion strategy may possibly be related to poor device durability. In a recent analysis of a multicentre registry of 1,521 patients who underwent transcatheter aortic valve replacement, a ViV procedure was an independent predictor of valve haemodynamic deterioration, defined as a ≥10 mmHg increase in transprosthetic mean gradient during follow-up compared with discharge assessment[29]. However, as was shown in the current analysis, supra-annular position of THV leaflets potentially improves the haemodynamics of THVs constrained within the inexpansible bioprosthetic ring, with a reduction in leaflet coaptation distortion. It could be suggested that a high THV position during ViV may therefore improve long-term THV durability. Long-term assessment after ViV implantations when performed in the future may answer this question.

The VIVID Registry has recently evaluated the *in vivo* aspects of depth of implantation in ViV[12]. A total of 292 patients were included in that analysis, utilising core lab assessment of implantation depth. Optimal depth cut-offs were determined for the SAPIEN XT (0% to 10% of the device frame height, approximately 0 to ~2 mm) and for the CoreValve (0 to 5 mm). Low implantation was associated with a much higher rate of elevated gradients (mean ≥20 mmHg): 43.5% in the SAPIEN XT and 34.2% in the CoreValve vs. 18.5% and 15% in the high implantation group, respectively.

The present *in vitro* analysis further elucidates the pathophysiology of elevated mean gradients in low implantation ViV and validates the *in vivo* findings. Bench testing is especially important because it allows evaluation in controlled conditions. This permits a direct insight into valve functioning and the isolated effects of positioning on haemodynamics.

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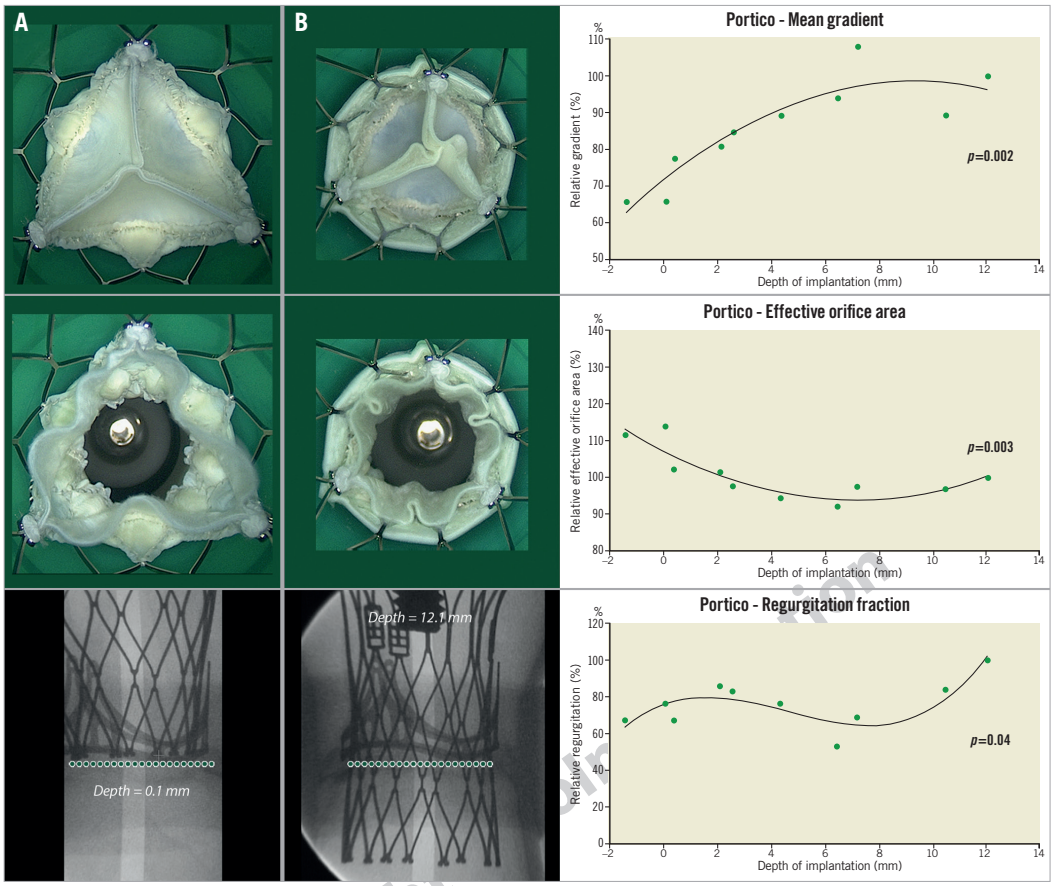


Figure 7. *Ten 23 mm Portico in 19 mm St. Jude Trifecta with respective depths. The first graph demonstrates the relationship between depth of implantation and EOA. The second graph demonstrates the correlation between depth and post-procedural gradients. Finally, the third graph shows the correlation between depth and relative regurgitation. Relative gradient is based on the gradient of the case with the lowest implantation. Experiment A demonstrates a high implantation of the Portico valve. There was symmetric leaflet closure and larger orifice area, whereas experiment B demonstrates smaller orifice area.*

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It is evident that high implantation could potentially benefit the vast majority of patients. Nevertheless, there are specific situations that could be considered as especially deserving of a more careful implantation. Most importantly, patients with small surgical valves have a more constricted valvular environment, in which high position may alleviate the risks of elevated gradients.

Limitations

The present study was limited to testing in *in vitro* conditions. The importance of THV depth of implantation on ViV haemodynamics has already been analysed in cases included in the VIVID Registry with similar findings that validate the importance of those revealed in the current analysis[12]. Nevertheless, the current *in vitro* analysis should be considered as similarly important for testing the significance of depth implantation, as these bench tests were performed in similar controlled conditions, something that could never be performed while assessing real-world *in vivo* clinical cases which differ in their left ventricular ejection fraction, pressures within the different cavities and in many other aspects. The SAPIEN 3 heart valve was not included in this analysis. Further studies in the future should address the effects of depth of implantation in novel THV devices. In addition, in the current study, we have only considered stented surgical bioprostheses for ViV. Therefore, extrapolating the current findings to stentless surgical bioprostheses would be inadequate. Our analysis was limited in testing one THV model per surgical valve. We also utilised different surgical valves for the different THV experiments. Distinct surgical valves could potentially affect haemodynamic outcomes. Future experiments could potentially test different THVs in each of the surgical valves, providing information about each specific model. Different surgical valve sizes could also provide more important information in future experiments. Furthermore, the bioprosthetic valves that were used in our experiments were not degenerated. Previous data suggest that an important predictor for having elevated gradients

after ViV is significant stenosis of the failed surgical valve[12]. As a consequence, we needed to test the importance of implantation depth in very small surgical valves (label size 19 mm) that simulate conditions of valves with small effective orifice area.

Conclusion

The current analysis is the largest comprehensive *in vitro* evaluation of the effect of THV position on ViV outcomes. Our results demonstrate the importance of high device position for achieving optimal haemodynamics post procedure and support specific implantation targets for different THV devices during ViV procedures. Clinicians must carefully weigh the benefit of supra-annular THV implantation in reducing post-procedural gradients against the potential risk of malposition in potential ViV candidates.

Impact on daily practice

Elevated post-procedural gradients are relatively common in transcatheter valve-in-valve procedures. Comprehensive bench testing experiments show that high position of different types of transcatheter heart valve may improve haemodynamics after aortic valve-in-valve. *In vitro* results validate *in vivo* findings related to the importance of implantation depth.

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Conflict of interest statement

D. Dvir reports consulting for Edwards Lifesciences and Medtronic. J. Webb reports consulting for Edwards Lifesciences. A. Petronio reports clinical proctoring for Medtronic and Boston Scientific, membership of the speaker's bureau and consulting for Abbott Laboratories and Eli Lilly. A. Vahanian reports speaker's fees and honoraria from Edwards Lifesciences, Abbott Laboratories and Valtech. The other authors have no conflicts of interest to declare.

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Supplementary data

Online Table 1. The relative haemodynamic values of 23 mm CoreValve Evolut, SAPIEN XT, and Portico for pressure gradient, EOA, and regurgitation volume.

Moving image 1. Short-axis view of the CoreValve Evolut 23 mm implanted low (depth=14.8 mm). Leaflet closure is asymmetrical, with a whorled pattern in coaptation. This situation demonstrates incomplete device expansion.

Moving image 2. Short-axis view of the CoreValve Evolut 23 mm implanted high (depth=0 mm). Leaflet coaptation is fully symmetrical, without whorls or imperfections. The device is fully expanded, with a gradient approximately 30% lower and an EOA 15% greater than the reference low implantation experiment.

Moving image 3. Short-axis view of the SAPIEN XT 23 mm implanted low (depth=28.9%, 4.1 mm). A deep implantation is demonstrated, with improper leaflet contact and a whorled pattern, demonstrating incomplete expansion.

Moving image 4. Short-axis view of the SAPIEN XT 23 mm implanted high (depth=7.4%, 1 mm). This high implantation case has adequate and symmetrical leaflet coaptation, a consequence of full device expansion. This is reflected in the haemodynamic results, with a gradient 36% lower and an EOA almost 30% greater than the reference low implantation case.

Moving image 5. Short-axis view of the SAPIEN XT 23 mm implanted extremely low (depth=53.8%, 7.5 mm). This video exemplifies the leaflet overhang phenomenon, which consists in two functional sets of leaflets. In this situation, the XT frame did not compress the surgical valve leaflets against the stent posts.

Moving image 6. Short-axis view of the Portico 23 mm valve implanted low (depth=12.1 mm). The device in question has very poor leaflet coaptation, with an evident asymmetrical whorled pattern that shifts with each cycle.

Moving image 7. Short-axis view of the Portico 23 mm valve implanted high (depth=0.1 mm). The leaflets close in a much more symmetrical manner than the previous experiment, demonstrating the positive effects of high implantation. The gradient was 35% lower and the EOA 14% greater than the reference low implantation case.

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Supplementary data

Online Table 1. The relative haemodynamic values of 23 mm CoreValve Evolut, SAPIEN XT, and Portico for pressure gradient, EOA, and regurgitation volume.

Valve	Case #	Depth of implantation (mm)	Relative gradient (%)	Relative effective orifice area (%)	Relative regurgitation (%)
CoreValve Evolut	1	–1.2	78.9%	113.0%	92.5%
CoreValve Evolut	2	0	72.2%	115.7%	48.8%
CoreValve Evolut	3	0.7	65.7%	120.9%	45.0%
CoreValve Evolut	4	2.4	66.4%	115.7%	46.2%
CoreValve Evolut	5	3.0	66.1%	114.8%	38.7%
CoreValve Evolut	6	4.6	75.7%	107.0%	37.2%
CoreValve Evolut	7	6.1	78.2%	105.2%	31.4%
CoreValve Evolut	8	6.4	86.2%	100.9%	29.3%
CoreValve Evolut	9	8.2	85.6%	100.0%	20.9%
CoreValve Evolut	10	10.6	100.9%	92.2%	23.6%
CoreValve Evolut	11	12.2	100.4%	91.3%	49.8%
CoreValve Evolut	12	14.8	98.2%	93.9%	61.1%
CoreValve Evolut	13	15.7	100.0%	100.0%	100.0%
SAPIEN XT	1	–2.2 (–15.6%*)	60.7%	129.3%	134.8%
SAPIEN XT	2	1 (7.4%*)	64.4%	129.3%	144.9%
SAPIEN XT	3	2.6 (18.6%*)	72.6%	120.7%	76.4%
SAPIEN XT	4	4.1 (28.9%*)	90.1%	107.8%	122.5%
SAPIEN XT	5	7.5 (53.8%*)	100.0%	100.0%	100.0%
Portico	1	–1.4	65.7%	111.6%	67.3%
Portico	2	0.1	65.7%	114.0%	76.6%
Portico	3	0.4	77.5%	102.3%	67.3%
Portico	4	2.2	80.8%	101.6%	86.0%
Portico	5	2.6	84.5%	97.7%	83.2%
Portico	6	4.4	89.2%	94.6%	76.6%
Portico	7	6.5	93.9%	92.2%	53.3%
Portico	8	7.3	108.0%	97.7%	69.2%
Portico	9	10.5	89.2%	96.9%	84.1%
Portico	10	12.1	100.0%	100.0%	100.0%

* percentage of the THV height below the stented surgical valve ring.

Manuscript #10

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CASE REPORT

Transcatheter tricuspid valve-in-valve replacement: one-year results

Alternative to surgery in high-risk patients

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Abstract Although rheumatic heart disease is becoming uncommon in industrialized countries, its global burden is still significant. We report the case of a 70-year-old male with rheumatic heart disease, who underwent 4 previous heart valve replacement surgeries, and presented to our hospital with refractory heart failure (NYHA functional class IV) due to severe stenosis of a previously implanted tricuspid bioprosthesis. The Heart Team deemed the patient as inoperable/high-risk for surgery. As an alternative, a transcatheter tricuspid valve-in-valve replacement was decided upon and later executed through the right femoral vein, with the insertion of an Edwards SAPIEN XT 29 no. (Edwards Lifesciences, Irvine, CA, USA) through the inferior vena cava, towards the RV, followed by direct implantation in the tricuspid bioprosthesis (valve-in-valve), under rapid pacing, without complications. A substantial clinical and echocardiographic improvement was noted after the procedure and the patient was subsequently discharged in NYHA functional class II. These favourable outcomes persisted through the 1-year follow-up period. This case report adds to the current body of evidence that tricuspid valve implantation stands as a viable and reliable alternative in the treatment of degenerated bioprosthesis in high-surgical-risk patients.

Keywords Tricuspid valve · Bioprosthesis · Heart failure · Structural heart intervention

Introduction

Rheumatic heart disease (RHD) remains associated with a significant global cardiovascular burden [1]. Although aortic and mitral valves are usually the main focus of diagnostic and therapeutic concerns, tricuspid valve disease is not uncommon amongst these patients [2].

Until the last decade, heart surgery was the only viable treatment option for patients with heart failure (HF) due to valvular heart disease [3]. However, after several trials reported transcatheter valve implantation as a viable therapeutic approach for high-risk surgical patients presenting with symptomatic aortic stenosis [4–9], the procedure began to be performed in other clinical settings, namely in high-surgical-risk/inoperable patients with degenerated aortic and mitral bioprosthesis, with varying but generally positive outcomes [10–14]. Nevertheless, there is still an important call for additional data regarding the Heart Team clinical and evidence-based decision-making, procedural characteristics and follow-up of these patients.

Case report

We report the case of a 70-year-old male with a history of rheumatic heart disease, who initially underwent a double mitral and aortic bioprosthesis [Carpentier-Edwards

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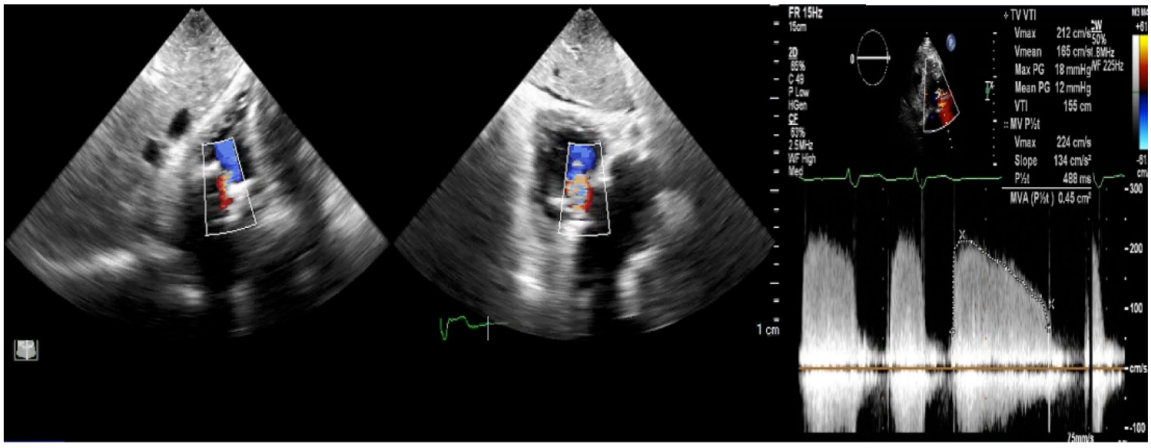


Fig. 1 TTE images showing severe tricuspid stenosis with flux acceleration and mild leak

(Edwards Lifesciences, Irvine, CA, USA)] implantation in 1980 owing to refractory HF. Due to severe regurgitation, both bioprostheses were replaced in 1991 with St. Jude (St. Jude Medical Inc., Minnesota, USA) mitral (27 no.) and aortic (23 no.) mechanical prosthesis, respectively. A tricuspid valve annuloplasty (28 no. ring) was also performed because of tricuspid regurgitation. Furthermore, in 2007, both mitral and tricuspid dysfunctional prosthesis were replaced with a St. Jude (27 no.) and a tricuspid bioprosthesis (31 no.), correspondingly. Permanent atrial fibrillation (AF) and hepatitis C (secondary to a blood transfusion in 1980) had been previously documented.

The patient presented to the hospital with worsening dyspnoea, asthenia and excessive tiredness [New York Heart Association (NYHA) class IV], for the previous 3 weeks. Metallic heart sounds and a loud holosystolic murmur on the left sternal border (increasing with inspiration) were noted. Distended jugular veins (positive Kussmaul's sign), abdominal (positive fluid wave test), scrotal and inferior limb oedema (Godet's sign +++) were observed. His admission weight was 82 kg.

The electrocardiogram (EKG) showed AF with a 62-bpm ventricular response rate. Blood tests revealed haemoglobin 10.7 g/dl, creatinine 1.7 mg/dl, INR 3.2 and an NT-proBNP value of 1350 pg/ml. The first transthoracic echocardiogram (TTE) evidenced a non-hypertrophied, non-dilated left ventricle, with a preserved ejection fraction. A severe stenosis of a degenerated tricuspid bioprosthesis was identified (peak gradient = 13 mmHg and mean gradient = 8 mmHg) along with a mild leak. Both mitral and aortic mechanical prosthesis presented normal prosthetic valve pressure gradients, without significant regurgitation. The pulmonary artery systolic pressure (PASP) was 53 mmHg (moderate pulmonary hypertension) and the right ventricle (RV) ejection fraction was mildly reduced (Fig. 1). A transesophageal echocardiogram (TEE) was performed to further characterize the tricuspid bioprosthesis dysfunction, showing an elevated mean gradient of 12–20 mmHg, with a pressure half-time (PHT) >170 ms and mild regurgitation. The estimated PASP was 50–55 mmHg and a reduced RV systolic function was noted. A mild mitral periprosthetic leak was observed (mean gradient 5–6 mmHg) (Fig. 2).

The patient was admitted to our Cardiology ward with decompensated heart failure (HF), exhibiting a poor response to intravenous (IV) furosemide and metolazone, with limited weight reduction (2 kg in 10 days).

The Heart Team thoroughly discussed this case, deeming the patient inoperable—4th heart surgery procedure, Euroscore II 5.5% (STS score did not apply). Since this was a previously autonomous patient whose decline for surgery was mainly based on the number of previous procedures, the tricuspid valve-in-valve percutaneous intervention was decided upon as the best therapeutic option. Further investigation was conducted to determine patient's eligibility for the procedure:

Catheterization and angiography: the coronarography showed normal coronary arteries, without significant lesions. The venous angiography showed a dilated vena cava and no obstructions from the right femoral vein to the right atria (RA). Right ventriculography revealed a preserved RV function (lower limit), without tricuspid bioprosthesis regurgitation. The distance from the bioprosthesis to the RV apex was 70–73 mm. The RA/RV gradient was 25 mmHg.

An MSCT angiography was performed to determine the size of the new valve (using OsiriX and 3mensio software) and a levophase venogram (contrast injected through

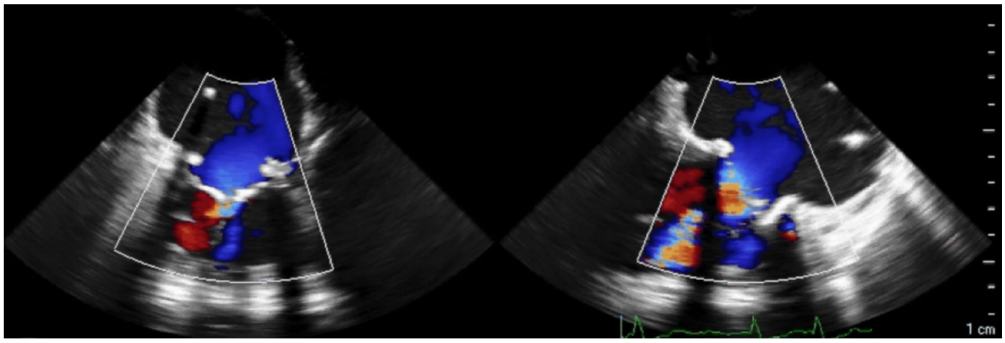


Fig. 2 TEE images showing severe tricuspid stenosis and mild leak

the antecubital vein with late venous phase image acquisition) was done to evaluate vascular access suitability for the valve-in-valve procedure: (1) the degenerated prosthesis inner diameter of 27.8 mm (average) was assessed on multi-planar reconstructed images (Fig. 3) and (2) large venous distensible vessels, suitable for the procedure, were noted (inferior vena cava diameter of 24 mm; both left and right femoral veins diameters of 15 mm).

The size of the new valve (SAPIEN XT 29 no.) was chosen according to CT-angio measurements (inner diameter) and manufacturer's indications regarding expanded annulus size coverage.

Endovascular tricuspid procedure (30 April, 2014)

The percutaneous intervention was performed under general anaesthesia. The right femoral vein (20F) was exposed with Kocher's surgical tweezers and used as the primary vascular access. An additional access through the right radial artery (6F) was established for continuous haemodynamic assessment.

An arrow (Teleflex Incorporated, Wayne, PA, USA) 5F balloon-pacing catheter (lead for temporary pacing) was placed in the coronary sinus though the left subclavian vein.

A standard guidewire (0.35) was advanced through the inferior vena cava into the right atria. A JR4 Super Torque Plus was used to cross the degenerated bioprosthesis and was subsequently replaced with an extra-stiff that remained wrapped in a pigtail conformation inside the RV. To avoid injuring the RV, the angiographic study was orthogonally aligned with the wire frame of the degenerated bioprosthesis. It is important to note that although the pulmonary artery usually confers greater wire support, in this case, the RV was regarded as a better option, allowing for a more accurate alignment of the new valve with the failing bioprosthesis, thereby preventing further complications such as valve embolization.

The Edwards SAPIEN XT 29 no. (Edwards Lifesciences, Irvine, CA, USA) progression was carefully handled, avoiding the hepatic veins, and placed within the degenerated bioprosthesis, under angio and echocardiographic guidance. Since this was a degenerated bioprosthesis, the risk of debris release during pre-dilation was significant, which led us to directly implant the new valve. To maximize ventricular stability, the SAPIEN XT 29 was deployed (valve-in-valve) under rapid ventricular pacing (180 bpm). Due to mild prosthesis frame underexpansion, an ad hoc post-dilation under rapid ventricular pacing (180 bpm) was performed, resulting in a successful implant (angio and echocardiographic control), after which the sheath was withdrawn (Figs. 4, 5).

The procedure had no complications and the patient was then transferred to a CCU, where he remained clinically stable (weighing 79 kg). On the 5th day, he was transferred to the Cardiology ward.

On the first week after the procedure, a limited response to IV furosemide persisted. Nonetheless, over the following month, the patient displayed a slow but steady weight loss with peripheral oedema regression. When metolazone was reinitiated, weight loss (74–60 kg in 2 weeks) and NYHA functional class significantly improved (IV–II). Two weeks after the procedure, a control TTE was performed: tricuspid stent valve (valve-in-valve) with preserved morphology and function (peak gradient = 8 mmHg and mean gradient = 5 mmHg) with minor periprosthetic regurgitation (unchanged). Slightly lower PASP (52 mmHg). Mitral and aortic valves had no significant abnormalities. Preserved LV function with concentric hypertrophy. RV function improved modestly. Dilated inferior vena cava, without inspiratory collapse. No mechanical complications from the procedure were observed. The patient was discharged on the 87th day, in NYHA functional class II, with mild malleolar oedema and jugular vein regurgitation (3 cm). Blood tests showed Hb 10.5 g/dl, creatinine 1.44 mg/dl (creatinine clearance Cockcroft-Gault = 40.5 ml/min/1.73 m^2).



Fig. 3 Degenerated prosthesis inner diameter assessed by multi-planar reconstruction imaging

On the 6th and 9th months of follow-up, the patient remained in NYHA functional class II, weighing 63 kg, with laboratory and echocardiographic results comparable to those of his hospital discharge. During the first year of follow-up, he developed a urinary tract infection to *Enterococcus faecalis*, refractory to the first and second lines of treatment, during which he presented to the hospital with decompensated congestive HF (NYHA class III-IV, weighing 81 kg, with marked peripheral oedema and periods of mental confusion). The TTE showed no changes in comparison to the previous evaluations: tricuspid stent valve with preserved morphology and function and both mitral and aortic mechanical prosthesis showing no new/acute signs of degeneration. He was started on IV antibiotics, with a good clinical response. Albeit the infection was eliminated and the patient improved modestly, he still remained in NYHA class III, with significant peripheral oedema. Kidney and hepatic failure were excluded as causes of the refractory fluid retention, and eventually, the patient was started on continuous veno-venous haemofiltration (CVVH), after which he improved markedly. He was discharged in NYHA functional class II-III, weighing 64 kg, with mild oedema. Nonetheless, as expected, a deterioration of his kidney function was noted after the initiation of CVVH (basal creatinine 1.7→2.4).

Discussion

High-risk surgical patients, who require reintervention for severe valvular heart disease, represent a complex challenge for interventional cardiology. Previously, there was no alternative to surgery, but the technological advances, paired with the increasing clinical experience, led to the development of new and reliable alternatives for inoperable individuals [6, 15].

Even though long-term data for transcatheter tricuspid valve replacement are still being evaluated, several case reports and meta-analyses clearly show a trend for positive outcomes [12, 13, 16].

In this case report, we have demonstrated and thoroughly discussed how a transcatheter tricuspid valve-in-valve replacement represents a valid alternative to surgery in high-risk surgical patients with refractory HF secondary to a dysfunctional prosthesis. The observed outcome is encouraging and adds to the currently scarce body of available data.

Nevertheless, we consider that these should not yet be considered routine procedures and must remain only as an alternative for inoperable patients.

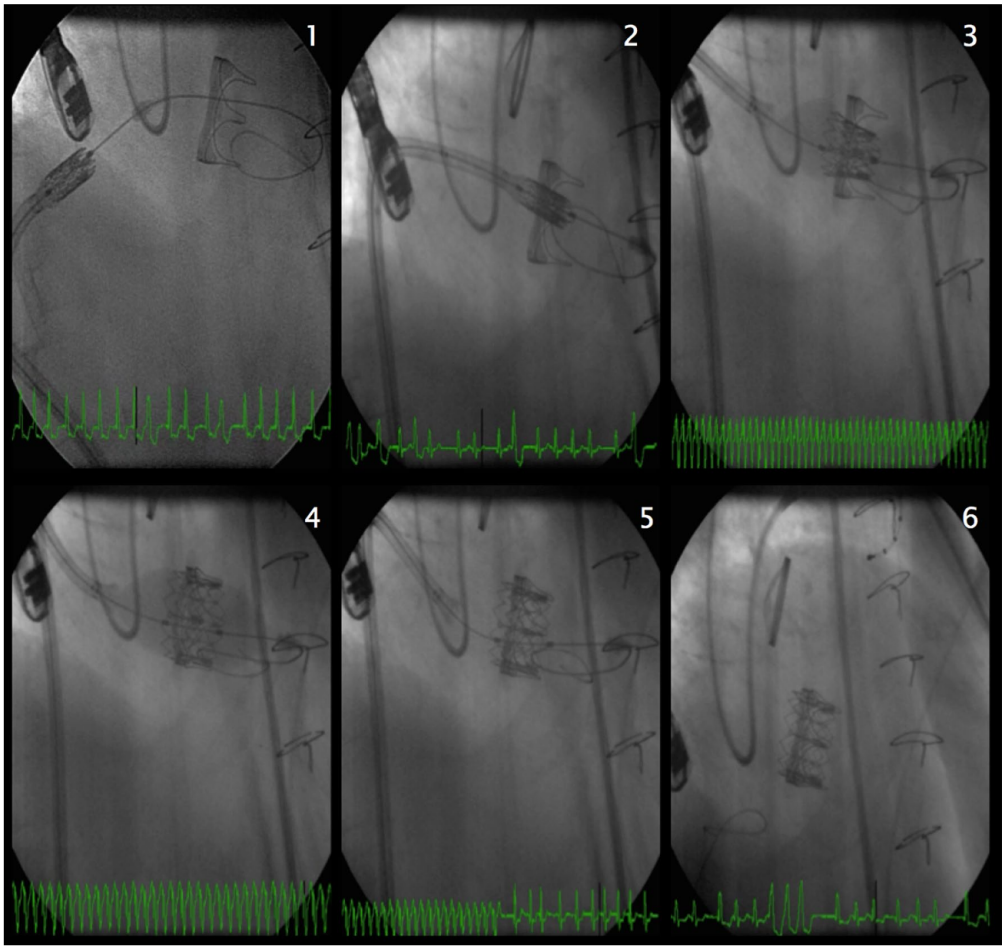


Fig. 4 The stages depicting the transcatheter tricuspid valve-in-valve replacement procedure (1–6). The balloon post-dilation because of stent underexpansion is depicted in (4). The vascular accesses used were the right femoral vein (18F) and left subclavian vein (catheterization of coronary sinus—electrocatheter)

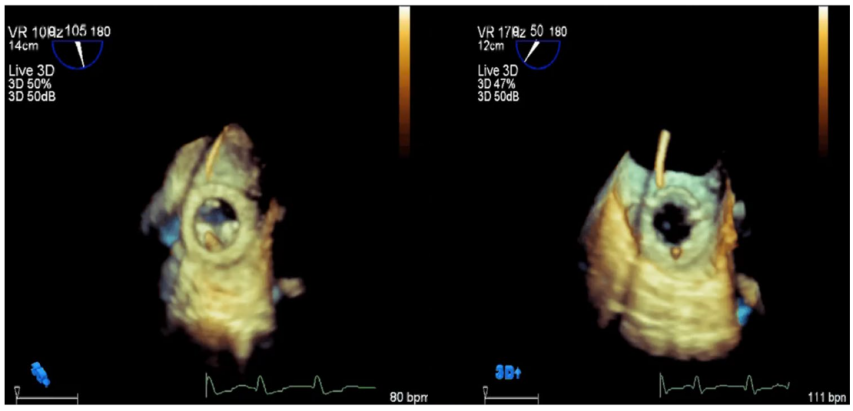


Fig. 5 3D TEE images displaying the degenerated tricuspid bioprosthesis (**a**) in comparison to the final outcome of the transcatheter valve-in-valve replacement (**b**). The fusion between the leaflets is evident in (**a**) (one of the leaflets is retracted by the catheter) as in (**b**) the leaflets are mobile and no stenosis is noted

Conclusion

Percutaneous tricuspid valve implantation stands as a viable and reliable alternative in the treatment of degenerated bioprosthesis in high-surgical-risk/inoperable patients.

Compliance with ethical standards

This human study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The patient signed an informed consent both for the procedure and publication of any relevant data.

Conflict of interest The authors report no conflicts of interest regarding the content herein.

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Transcatheter mitral valve interventions for mitral regurgitation, with special focus on MitraClip: The position of Spanish, Portuguese and Italian interventional societies

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ABSTRACT

Mitral regurgitation is a common valvular heart disease and its prevalence is expected to increase with population ageing. In the recent years we have witnessed the evolution of several transcatheter devices to correct mitral regurgitation in patients at high-risk for surgery. Most of the evidence of the safety and efficacy of this new therapy comes from MitraClip studies. However, new alternatives have emerged with promising results. The aim of this position paper is to review the current evidence regarding patient selection, expected results and timing for transcatheter mitral valve interventions from the perspective of three European interventional societies.

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1. The necessity of transcatheter mitral valve interventions (TMVI)

Mitral regurgitation (MR) is the second most common symptomatic valvular disease worldwide [1]. The presence of MR after myocardial infarction or with dilated cardiomyopathy is associated with an increased risk of cardiac insufficiency and death [2–4].

Mitral valve (MV) surgery is the treatment of choice for patients with severe MR; however, 50% of patients [5] referred for MV surgery are not operated on, predominantly because of comorbidities, LV dysfunction or advanced age [6]. Noteworthy, the proportion of functional MR (FMR) patients undergoing surgical treatment is even lower [7], due to high surgical risk, the lack of clear survival benefit and the high recurrence rate of significant MR 1 year after surgery. Notwithstanding, patients with FMR when medically managed are burdened with substantial morbidity, mortality, and cost of care [8,9]. In this setting, catheter-based interventions have emerged to fill a large unmet need.

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2. Summary of current available devices for TMVI

In the last few years, important innovations have been developed in this field, with several percutaneous devices under investigation [10]. In Table 1 the most promising devices for TMVI are displayed. Some of them have gained approval for human use and have been tested in small clinical trials (Fig. 1). A detailed description of all these devices is beyond the scope of this position paper and their clinical application is still limited. We will focus in the device with the largest use to date in order to overview the role of TMVI in current clinical practice. However, one of the lessons learned from heart valve surgery is that a combination of diverse techniques addressing different mechanisms of MR may improve long-term outcomes [11] and we will foresee a place for combination therapy in early future.

2.1. Annuloplasty devices

Annuloplasty is the most common surgical repair performed to treat MR [12]. This technique is widely used as a stand-alone procedure to enhance MV coaptation in FMR or added to leaflet repair in degenerative MR in order to improve durability [11]. Based on prior large surgical experience, some percutaneous novel devices have tried to reproduced

undersized MV annuloplasty to address dilatation of the mitral annulus (MA). A reliable transcatheter mitral valve annuloplasty (TMVA) has the potential to improve outcomes in combination with edge-to-edge repair in selected patients and to increase therapeutic alternatives in patients with anatomic ineligibility for MitraClip®. As a further potential advantage, unlike to MitraClip®, this approach preserves the native valve anatomy, thus keeping the option for future valve implantation open. In fact, some of the annuloplasty rings may actually serve as a dock for the anchoring of some available transcatheter aortic valves ("valve-in-ring" procedure). Carillon®, Cardioband® and Mitralign® have shown promising results and they will have a place in the mitral space in the near future.

2.2. Neochord®

Neochord® (Neochord, Minnesota, MN) are the first ePTFE chordal loops conceived to be implanted on the MV leaflets to correct flail or prolapse [13]. Colli et al. reported the results of transapical off-pump mitral valve implantation of Neochord in 62 patients with MV prolapse [14]. Thirty-day major adverse events included 1 acute myocardial infarction (2%) and 2 cases of sepsis (3%). MR at 30 days was grade 1 + or 2 + in 55 patients (88.7%).

2.3. Transcatheter mitral valve replacement (TMVR)

The simpler structure of the aortic valve (AV) has probably facilitated the success of a stent-like transcatheter approach for treatment of the AV disease. On the contrary, the much more complex structure of the MV may explained the slower way to find a safe and effective alternative for TMVR. Many companies have completed first-in-human cases; however, no devices are currently approved beyond compassionate use, and several others remain in preclinical development. These percutaneous MV prostheses vary either in the access site, the design and the anchoring technology within the MA or the subvalvular apparatus [15]. Currently, several devices have been already implanted in-human since 2012 (CardiAQ®, Neovasc Tiara®, Edwards Fortis®, Tendyne®, Twelve®, Navigate®, Highlife®, Caisson®, M-Valve®). These initial experiences showed heterogeneous rates of morbidity and mortality across different platforms and pointed out some important challenging issues that might be determinant in the development of this technique: the LV outflow obstruction, the thrombotic risk, the delivery profile and the access route (transapical vs transeptal). Interestingly, patients with poor ejection fraction presented the higher rates of adverse outcomes and might not benefit from this procedure.

2.4. MitraClip®

Among all CE approved devices, only MitraClip (Abbott Vascular, Abbott Park, IL) has gained wide clinical use. The first generation MitraClip device consists of two clip arms and opposing grippers, which can be opened and closed against each other in order to grasp and coapt the leaflets at the origin of the regurgitant jet. Recently, an evolution of the device has been released, MitraClip NT. Main changes are the improved steerability of the device in the left atrium (LA), allowing a more precise position over the mitral valve, and more flexible grippers that can be deployed at 120°. This feature translates into an improved grasping by increasing the leaflet insertion and thus the reduction of MR with a single clip.

In the randomized EVEREST II trial, 184 patients were designated (2:1) to receive MitraClip therapy and 95 patients to undergo surgical repair or replacement [16]. In this trial MitraClip was less effective than surgery but safer. In those patients with an initial successful repair no differences in mortality or reoperation compared to surgery were observed at 5 year follow-up [17]. In these study, stringent echo criteria were used to guide the feasibility of device insertion and deployment. However, with increasing experience more complex valve pathologies can be treated with acceptable results [18].

3. Patient selection for TMVI

The vast majority of clinical evidence in TMVI derives from MitraClip studies and patient selection and the potential benefits of the therapy mentioned in this document are related to this device. The current guidelines, based only on the limited experience of the EVEREST II trial, stated that percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary MR who fulfill the echo criteria of eligibility, are judged inoperable or at high surgical risk by a 'heart team', and have a life expectancy >1 year (recommendation class IIb, level of evidence C). With the commercial use in Europe, the limited clinical and anatomical EVEREST criteria have constantly been expanded. Therefore, the prototype of patient candidate for TMVI can be derived from the patients included in the main European registries of MitraClip [19–23]. Summary of the characteristics of those patients are shown in Table 2. Typical MitraClip patient has advanced age, high-surgical risk, highly symptomatic, FMR, frequent ischemic history, LVD and a significant proportion of carriers of defibrillators and/or resynchronization devices. However, there are other scenarios of heart failure patients where the potential utility of the device that must be taken into account. Notwithstanding, the properly patient selection represents the result of the heart team tailored management.

3.1. High risk degenerative MR

High surgical risk or inoperable DMR is one of the main indications of MitraClip therapy. The EVEREST II REALISM study is a registry designed for continued data collection under more "real world" conditions after the completion of enrollment in the pivotal EVEREST trials. In this study relevant results were achieved with MitraClip including reduction

Table 1
Devices in pipeline for transcatheter mitral valve interventions.

Anatomic target					
Leaflet/chordae	Indirect annuloplasty	Direct or LV annuloplasty	Hybrid surgical	LV remodeling	Replacement
MitraClip	Carillon XE2 Mitral Contour System	Mitralign	Adjustable Annuloplasty Ring	The Basal Annuloplasty of the Cardia Externally (BACE)	CardiaQ
Neochord DS1000 System	Kardium MR	GDS Accucinch system	EnCor Dinaplasty ring	Tendyne repair	Caisson
Mitra-Spacer	Cerclage annuloplasty	Cardioband	Cardinal ring	Bioventrix	Tendyne
Mitra-Flex		Milipede			Tiara
Middle Peak Medical		TASRA			Intrepid
V-Chordal					M-Valve
PASCAL					Cephea
Harpoon					Sinomed
					High-life
					endovalve

Device	Target of therapy	Year of CE mark	Current number of patients treated	Surgical background	Vascular access
	Leaflet coaptation	2008	> 40.000	Edge-to-edge repair	Transfemoral
	Chordae implantation	2013	> 300	Chordae implantation	Transapical
	Indirect annuloplasty	2009	> 100	No	Transjugular
	Direct annuloplasty	2015	> 100	Flexible ring	Transfemoral
	Direct annuloplasty	2016	> 100	Commissuroplasty	Transarterial retrograde

Fig. 1. Current devices for mitral regurgitation with CE mark.

in rehospitalization, functional improvement, and favorable ventricular remodeling at 1 year after MitraClip procedure in DMR patients [24].

3.2. CRT non-responders

MitraClip has also been proved to be a useful tool for those patients with heart failure not responding to CRT therapy [25]. The authors published their experience with 51 patients who were severely symptomatic despite CRT therapy. They showed that MitraClip implantation was associated with significant reduction in MR that was progressive during median follow-up of 14 month, with clinical improvement and favorable remodeling parameters on echocardiographic follow-up.

3.3. End-stage heart failure

Franzen et al. reported the effect of MitraClip in patients with end-stage heart failure [26] analyzing the treatment of 50 patients in 7 European centers with LVEF ≤25%, MR ≥ 3+ and advanced functional class (NYHA III or IV). The authors reported an acute procedural success (APS) of 94%, and 92% of patients were discharged with MR ≤ 2+. The 30-day mortality was 6% in this high-risk group (mean EuroScore 34%). Other registries reported symptom improvement and reduction of re-hospitalizations [27,28]. The beneficial effects in this subgroup of patients may be related to the positive hemodynamic changes observed after the device implantation and the favorable inverse remodeling in left ventricle [29]. However, patients with very poor LV function are at high risk of mortality even with MitraClip treatment and the selection of these candidates should be very careful and based on operator's experience, probability of success and expected benefits [21].

3.4. Acute MR following acute myocardial infarction

Acute ischemic MR is a life-threatening complication associated with high rates of morbidity and mortality even when surgically corrected. Small series have proved that MitraClip is a safe and effective alternative to surgical intervention in these unstable patients [30,31]. Potential advantages of this therapy are rapid hemodynamic improvement after MR correction [32] and the avoidance of the LV damage induced by the inflammatory response associated with cardiopulmonary bypass in an ischemic myocardium [33].

3.5. Failing annuloplasty rings

Patients treated with annuloplasty rings suffering from FMR (mainly ischemic MR) are at high risk for recurrence in >50% at 2 years [34]. Frequently, these patients are symptomatic and reoperation may carry an unacceptable risk [34]. Series from Italy and Spain have proved that the use of the device is safe and produces a persistent reduction in MR, hemodynamic improvement and symptom relief [35,36], and MitraClip must be taken into consideration in such cases. Table 3 summarizes the type of patients that should be considered for MitraClip therapy.

Table 2
Clinical profile in main registries of MitraClip implantation.

	ACCESS-EU	TVT SENTINEL	TRAMI	GRASP
n	567	628	1064	117
Age (years)	74	74	75	72
logES, %	23	20	STS 9.2	12
FMR, %	77	72	79	76
Previous MI, %	32	31	28	28
NYHA III/IV, %	85	86	87	80
LVD	52% EF < 40%	33% EF < 30%	33% EF <30%	Mean 38%
ICD/CRT, %	27%	NA	21%	NA

EF: ejection fraction; FMR: functional mitral regurgitation; logES: logistic EuroScore; LVD: left ventricular dysfunction; MI:myocardial infarction; ICD: implantable cardiverter-defibrillator; CRT: cardiac resynchronization therapy.

Table 3
Candidates for TMVI following interventional societies criteria.

Appropriate candidates
Severe FMR + LVEF ≤ 30% + no CABG planned
Severe MR (DMR or FMR) + previous grafts with patent LIMA
Severe DMR and high-surgical risk or inoperable
Severe MR after CRT
Consider
Failing surgical rings
Acute MR following MI if high-risk or inoperable
Ischemic FMR with surgical repair unlikely to offer durable repair (several characteristics indicating high probability of failure; as a less invasive step to avoid replacement).
Bridge-to-transplant option in severe MR patients
Systolic anterior movement of MV

3.6. Systolic anterior motion (SAM) of MV and MR

In those patients with hypertrophic obstructive cardiomyopathy with SAM and severe MR that are judged not candidates for septal myectomy, MitraClip may serve as an alternative. Small experiences have been published with reduction of MR and significant decrease in left ventricular outflow tract obstruction [37,38].

4. Expected benefits from TMVI

4.1. Persistent MR reduction

Persistent MR reduction is one of the main goals of this therapy. The goal proposed since the EVEREST trials is to maintain a MR ≤ 2+ and this is what is considered a procedural success and an acceptable result during follow-up [39]. Interestingly, the study that settled the basis for the take-off of the therapy was the one with the lower procedural success presented (77%) [16]. With increasing experience PS has raised to a >95% of cases [19–21] and highly impacts the prognosis of patients. A persistent MR reduction is linked to a better outcome and "the less MR possible" should be used as a rule of thumb [40]. Recurrence of significant MR is observed in 6 to 21.1% of cases at one year [19,20]; similarly, surgical repair techniques presented comparable percentages of MR recurrence in ischemic FMR [41].

4.2. Symptom improvement

After treatment with MitraClip there is a significant recovery in the functional capacity with patients presenting on NYHA functional classes I–II in a range of 63.3% to 86% [19–21,42,43]. Beyond this variable, patients also experience improvement in 6MWT [19], quality of life [42,44] and reduced the BNP levels [26]. And, notably, there is a significant reduction in re-hospitalizations for heart failure, which it probably will turn into an improved prognosis and will reduce costs of patients' care [9,24,42].

4.3. Survival advantage over medical therapy

The available evidence to date regarding this issue relies mainly on retrospective studies. In a study by Swaans et al. [45] 139 patients treated with MitraClip were compared to 59 patients medically treated. At one-year transcatheter repaired patients showed better prognosis than those treated only medically with a relative reduction in the risk of mortality of 59% compared to medical therapy alone. In a recent paper, Velazquez et al. [46] compared the outcomes of 351 patients included in the EVEREST high-risk registry and historic comparator cohort from the Duke Echocardiography Laboratory Database medically managed. After propensity matching MitraClip was associated with a 1-year improved survival (mortality 22.4% MitraClip vs. 32% stand-alone medical therapy, $p = 0.043$). Finally, a recent report by Giannini [47] included 60 patients treated with MitraClip and propensity matched with 60 patients conservatively managed. All patients presented FMR. Patients treated with TMVI showed less mortality, less cardiac mortality and less readmissions due to heart failure. While we eagerly wait for the confirmation of these results in the properly designed randomized trials, this information encourages increasing the application of the therapy.

4.4. Effect on heart remodeling: annulus and LV

Data derived from EVEREST trial have demonstrated that there is an inverse remodeling after a successful MitraClip procedure in patients with FMR [48] that affects both LV and left atrium (LA). And, interestingly, the magnitude of the remodeling is greater with greater reduction in MR. This positive effect is maintained at 5 years follow-up [17].

MitraClip offers not only a heart chamber remodeling effect but also an annulus effect. Recent studies have demonstrated that in secondary MR annulus size (posteroanterior diameter), annulus area and tenting area significantly decrease after device implantation [49]. And interestingly this reduction is associated with an improved functional status at 6 month after the procedure [50]. Conversely, in primary MR annulus parameters remain stable after clipping.

5. Timing for TMVI

It is difficult to establish the perfect time-point for TMVI taking into account that patients usually present in a pretty advanced stage of the disease. However, several factors have been associated with an impaired prognosis after MitraClip implantation, such as, NYHA functional class IV, advanced age, NT-pro-BNP >10,000 pg/ml, right ventricular dysfunction, significant tricuspid regurgitation, significant pulmonary hypertension, ischemic MR, severely dilated LV or severe renal dysfunction. It is likely that if patients would be treated earlier, although not curative, a significant change in the natural history of the LV disease might be obtained.

Conflict of interest

Dr. Rodrigo Estévez-Loureiro, Dr. Xavier Freixa and Dr. Dabit Arzamerdi are consultants and proctors for Abbott Vascular. Dr. Pan and Dr. Melica have received speaker fees from Abbott Vascular. The rest of authors have no conflict of interest to disclose.

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Manuscript #12

PORTUGUESE ASSOCIATION OF CARDIOVASCULAR INTERVENTION

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Portugal: coronary and structural heart interventions from 2010 to 2015

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Abstract

The aim of the present paper is to report trends in Portuguese interventional cardiology from 2010 to 2015. We studied data from the prospective multicentre Portuguese National Registry of Interventional Cardiology (RNCI) to analyse percutaneous coronary intervention (PCI) procedures and structural heart interventions from 2010 to 2015. A total of 73,977 PCIs and 780 transcatheter aortic valve implants were performed during the study period. Since 2010 there has been a 60% increase in PCI procedures and a twofold increase in primary angioplasty rates reaching 316 per million population. Significant PCI trends were observed, notably the increase of radial access, a reduction in restenosis indications, as well as an increase in stent use, including DES, in imaging and in functional techniques. Importantly, there was a fourfold increase in the TAVI rates reaching 29 per million population.

Introduction

The aim of the present paper is to report trends in the percutaneous treatment of heart disease in Portugal, based on the description of the demographics and health system organisation and on the data analysis from the Portuguese National Registry of Interventional Cardiology (RNCI) of the Associação Portuguesa de Intervenção Cardiovascular (APIC, www.apic.pt).

We performed a transversal analysis regarding the 2015 cathlab status and studied the prospective multicentre data from the RNCI to analyse percutaneous coronary intervention (PCI) procedures and structural heart interventions from 2010 to 2015.

Demographics and organisation

The Portuguese population is 10.3 million and there is a total of 27 catheterisation laboratories, seven of them private. A total of 19 public hospitals operate 24h/7d and run the primary PCI (pPCI)

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programme (Via Verde Coronária). A total of seven public centres have permanent on-site surgical departments of which five run valvular heart team programmes.

Since 2008, interventional cardiology has become a subspecialty whose certification is issued by the Ordem dos Médicos (Portuguese Medical Association) based upon the curriculum vitae and two years of training, ensuring a minimum number of procedures (250 therapeutic catheterisations, half of them as first operator).

Access to the public health system in Portugal is universal. Although the system itself is tax-funded, users may be required to pay an admission fee to emergency departments, to consultation clinics, for hospital admission or for specific examinations.

The majority of hospitals with fully operational catheterisation laboratories are part of the public health system and are thus financed by the yearly state budget for healthcare. The Portuguese public healthcare system is not reimbursement policy-based. Each year hospitals individually prepare a budget concerning the estimated expenditure for inpatient and outpatient diagnostic and treatment techniques. In matters of interventional cardiology, estimate numbers of diagnostic and percutaneous coronary intervention procedures, of special techniques – pressure wires and intracoronary imaging, atherectomy and ventricular assist devices – and a specific estimate of the number of structural intervention techniques must be determined. The yearly budget report is submitted to the office of the Ministry of Health for evaluation, including an analysis of any deviation from the budget of previous years. Hospital funding per procedure is also influenced by whether the patient was referred by another hospital or if the patient was admitted for a duration over twenty-four hours; if this is the case, the hospital will receive a different preset hospital admission fee. Final yearly funding to each hospital is established based on the individual analysis and discussion with the submitting hospitals. The growth of transcatheter aortic valve implantations (TAVI) has been subject to a specific analysis, and a national plan for specific funding of structural heart disease is underway.

The increasing number of private hospitals in Portugal has carried out growing numbers of interventional cardiology procedures in the private sector. The private sector receives payment from individual private insurances, and is not subject to state funding except under specific circumstances. As is typical of private insurance systems, the contracted individual policy may limit the type or extent of treatment. Reimbursement is made according to preset values for each procedure, special techniques utilised and the extent of hospital admission. Insurance coverage for interventional cardiology procedures is a growing field.

The RNCI was established in 2002 and is centralised in the National Centre for Data Collection in Cardiology (CNCDC, http://www.spc.pt/CNCDC/), under the aegis of the Portuguese Society of Cardiology (Sociedade Portuguesa de Cardiologia, www.spc.pt)[1]. The aim of this multicentre, voluntary, prospective patient registry is to provide a continuous record of percutaneous procedures and patient characteristics in Portugal, based on the Cardiology Audit and Registration Data Standards (CARDS). Data are continuously introduced and are available online at: http://www.spc.pt/RegistosNacionaisSPC[2-4].

Coronary interventions

Changes in PCI characteristics of the population treated by PCI in Portugal between 2010 and 2015 are shown in **Table 1.** The number of PCI has increased 56% since 2010, paralleled by the number of procedures per operator. In absolute terms, pPCI rates almost doubled in this period, with a steady rise to 316 pPCIs per million **(Figure 1)**.

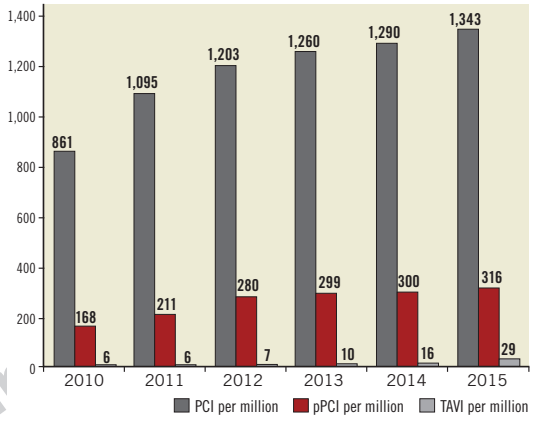


Figure 1. *Evolution of procedures per million population. PCI: percutaneous coronary intervention; pPCI: primary PCI; TAVI: transcatheter aortic valve implantation*

The predominant arterial access has inverted from femoral to radial, reaching 62.8%. In-stent restenosis (ISR) and chronic total occlusion (CTO) indications have decreased progressively. Several variables also increased their frequency, namely stent and DES use, respectively 92.9% and 85.5%. The rate of DES use was 66.4% initially and, since 2012, bioresorbable stents have reached 6.5%. Atherectomy peaked in 2010 (12.7%), followed by a steep fall (to 4.0% in 2015). Imaging and functional techniques have regained ground, reaching 3.5% and 3.3%, respectively, in 2015.

Structural heart interventions

Structural heart disease interventions are depicted in **Table 2.** TAVI procedures remained steady at around 7 per million population until 2012 and increased thereafter, reaching 29 per million in three years. MitraClip® (Abbott Vascular, Santa Clara, CA, USA) procedures started in 2013 and are evolving quickly. The left atrial appendage closure registry is next in line but as yet there are no reliable registries for adult congenital procedures.

Discussion and limitations

The Portuguese PCI network is wide and covers most of our territory, in particular for pPCI[5]. Operator productivity increased

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Table 1. Coronary interventions between 2010 and 2015 in Portugal.

	2010	2011	2012	2013	2014	2015	*p*-value
PCI (total), n	9,093	11,559	12,702	13,307	13,425	13,891	–
Primary PCI, n	1,773 20.9%	2,230 20.5%	2,952 23.8%	3,155 24.2%	3,121 23.6%	3,267 23.9%	<0.001
Femoral/radial access, n (%)	5,578 (62.5%)/ 3,218 (36.1%)	6,253 (55.2%)/ 4,901 (43.3%)	5,842 (46.0%)/ 6,681 (52.6%)	5,403 (40.6%)/ 7,627 (57.3%)	4,772 (35.6%)/ 7,742 (57.7%)	4,150 (29.9%)/ 8,718 (62.8%)	Femoral: <0.001 Radial: <0.001
PCI in CTO, n	1,024 16.1%	1,124 14.5%	1,157 14.0%	1,211 14.1%	1,106 13.3%	1,126 13.0%	<0.001
PCI in unprotected LM, n	93 1.0%	115 1.0%	137 1.1%	118 0.9%	135 1.0%	172 1.3%	0.497
PCI for in-stent restenosis, n	404 5.7%	430 4.4%	531 4.8%	599 5.3%	504 4.5%	543 4.8%	QQ trend: 0.129 QQ: <0.001
Average PCI per cathlab, n	337	428	508	532	537	556	<0.001 Pearson corr. coef.: 0.904
Average PCI per operator, n	107	136	149	157	158	163	<0.001 Pearson corr. coef.: 0.900
PCI without stent, n	1,372 16.5%	1,686 16.1%	1,757 15.2%	1,002 8.5%	902 7.7%	843 7.1%	<0.001
Total PCI with stent, n	6,933 83.2%	8,625 82.8%	9,713 83.8%	10,622 90.3%	10,753 91.9%	10,915 92.3%	<0.001
Total PCI with DES, n	4,341 66.4%	5,130 62.4%	6,072 65.6%	7,426 72.6%	8,066 77.4%	9,050 85.5%	<0.001
Total PCI with BRS, n	0 0.0%	0 0.0%	275 0.8%	446 2.6%	680 6.5%	693 6.5%	<0.001
Total IC imaging techniques (IVUS, OCT, NIRS, etc.), n	232 2.8%	261 2.6%	231 2.0%	327 2.7%	359 3.0%	441 3.5%	<0.001
Total IC flow/pressure techniques (CFR, FFR, iFR, etc.), n	274 3.3%	335 3.3%	328 2.9%	316 2.6%	340 2.8%	421 3.3%	QQ trend: 0.459 QQ: 0.008
Total rotational or orbital atherectomy, n (Rotablator)	183 12.7%	180 8.8%	136 4.4%	128 4.1%	127 4.1%	120 4.0%	<0.001
Haemodynamic support devices (IABP, Impella, LVAD, etc.)*, n	97 1.2%	122 1.1%	124 1.0%	98 0.8%	72 0.6%	106 0.8%	<0.001

*Both as stand-alone or during complex interventions (e.g., TAVI). BRS: bioresorbable scaffold; CFR: coronary flow reserve; CTO: chronic total occlusion; DES: drug-eluting stent; FFR: fractional flow reserve; iFR: instantaneous wave-free ratio; IABP: intra-aortic balloon pump; IVUS: intravascular ultrasound; LM: left main; NIRS: near-infrared spectroscopy; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

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during the reported time period, leading to a higher number of PCIs, creating the hypothesis of lesser complexity as the ISR and CTO percentages diminished. Of particular note is the growing proportion of use of the radial approach and the decreasing rate of atherectomy procedures, which implies a change in terms of training and organisation. These indicators show the advantage of registries based upon patient-level data that allow hypothesis generation, as such variables enable a deeper and more comprehensive interpretation. It is also interesting to note the changing role of adjunctive diagnostic media, namely fractional flow reserve (FFR) and imaging, that seem to be regaining popularity.

Structural heart disease data are still scarce and the registry is undergoing data transfer from a spreadsheet to a specific and dedicated electronic platform. Available data currently demonstrate the preference for the transfemoral route for TAVI procedures.

Table 2. Structural heart interventions between 2010 and 2015 in Portugal.

	2010	2011	2012	2013	2014	2015	*p*-value
Valvular devices, n	67	65	71	109	178	359	–
MitraClip procedures, n	0	0	0	4	10	45	<0.001
Total TAVI, n	67	65	71	105	168	304	–
Transfemoral TAVI, n	58	57	53	92	151	280	0.009
Valve-in-valve percutaneous implantation, n	3	2	1	4	5	13	QQ trend: 0.692 QQ: 0.879

TAVI: transcatheter aortic valve implantation

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This analysis has important limitations. Inclusion of data from all centres was achieved only in 2013, and the figures presented here are based on the patients included in the registry for specific years, which ranged between 97% in 2010 and 99% in 2015. Patients are not followed systematically, and the RNCI does not currently have either internal or external auditing.

Future projects

Having considered the relevance of data collection in cardiology, APIC plans on implementing additional electronic national registries. The planned registries will include left atrial appendage closure and coronary chronic total occlusions.

Conclusion

In 2013 all Portuguese interventional cardiology centres were participating in the National Registry of Interventional Cardiology. PCI increased by twofold per million population and concomitantly we observed the growing importance of primary angioplasty and of the radial approach. Valvular percutaneous procedures increased by fourfold. Portuguese operator volume increase caused a generalised expansion of main percutaneous cardiac interventions from 2010 until 2015.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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The Addenda and Questions and Answers companion documents of these guidelines are available at: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of

For the Web Addenda which include background information and detailed discussion of the data that have provided the basis for the recommendations see https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehx095#supplementary-data

Click here to access the corresponding chapter in ESC CardioMed - Section 49 Peripheral arterial diseases.

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What is new in the 2017 PAD Guidelines?

CHANGE IN RECOMMENDATIONS

2011	2017
Carotid Artery Disease	
EPDs in carotid stenting	
Asymptomatic 60–99% carotid stenosis	
• Surgery for all	• Surgery for high stroke risk[116]
• Stenting as an alternative	• Stenting in high surgery risk[129, 135-137]
	• Stenting in average surgical risk
Upper Extremity Artery Disease	
Revascularization for symptomatic subclavian artery stenosis	
Subclavian stenosis revascularization	
• Endovascular first	• Stenting or surgery
Revascularization for asymptomatic subclavian stenosis in patients with/planned for CABG	
Renal Artery Disease	
Stenting for symptomatic atherosclerotic stenosis >60%[229,231,232]	
Lower Extremity Artery Disease	
Aorto-iliac lesions	
• Primary endovascular therapy for "TASC-D"	• Surgery for aorto-iliac or aorto-bi-femoral occlusions
	• Endovascular as an alternative in experienced centres
Infra-popliteal lesions	
• Endovascular first	• Bypass using GSV
	• Endovascular therapy[320-326]

2017 NEW RECOMMENDATIONS

All Peripheral Arterial Diseases (PADs)

- Screening for heart failure (BNP, TTE)
- Stable PADs + other conditions requiring anticoagulants (e.g. AF): anticoagulation alone[91]

Carotid Artery disease

- Coronary angiography before elective carotid surgery[383]
- Routine prophylactic revascularization of asymptomatic carotid 70-99% stenosis in patients undergoing CABG

Mesenteric Artery Disease

- D-dimers to rule out acute mesenteric ischaemia
- No delay for re-nutrition in case of symptomatic CMI

Renal Artery Disease

- Fibromusuclar dysplasia: balloon angioplasty with bailout stenting

Lower Extremity Artery Disease (LEAD)

- Statins to improve walking distance[30,278]
- LEAD + AF: Anticoagulation if CHADS-VASc >2
- Angiography in CLTI with below-the-knee lesions
- Duplex screening for AAA[258, 259]
- In case of CABG: screen LEAD with ABI, limit vein harvesting if LEAD
- Screening for LEAD in CAD patients[366–368, 375–379]
- Screening for LEAD in HF patients
- Clopidogrel preferred over aspirin[a]
- Antiplatelet therapy in isolated[b] asymptomatic LEAD[66, 67]

I IIa IIb III

2017 NEW / REVISED CONCEPTS

PADs in general:
- "Vascular Team" for a multidisciplinary management.
- Best medical therapy: drugs and non pharmalogical interventions for optimal outcome. A specific chapter addresses antithrombotic therapies in different PADs presentations, including when anticoagulants are needed.

Carotid disease:
- Risk stratification for asymptomatic carotid disease.
- In patients undergoing CABG, revascularization of severe carotid stenosis is not systematic.

Lower extremity artery disease:
- Masked LEAD should be individualized from asymptomatic disease.
- Modern management of claudication: statins and (supervised) exercise therapy always prescribed, even after revascularization. In this context, the benefit from "vaso-active" drugs to improve walking distance is uncertain.
- "Chronic limb-threatening ischaemia (CLTI)" defines the most severe form of LEAD. Beyond ischaemia, wound and infection should be evaluated to stratify the amputation risk (new WIfI classification). TASC classification excluded from the guidelines.
- Beyond concomitant CAD, patients with PADs have often other cardiac conditions (e.g. HF, AF). The major scenarios have been addressed in a specific new chapter.

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AAA = abdominal aorta aneurysm; ABI = ankle-brachial index; AF = atrial fibrillation; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting surgery; CAD = coronary artery disease; CLTI = chronic limb-threatening ischaemia; EPD = embolic protection devices; HF = heart failure; GSV = great saphenous vein; TASC = Trans-Atlantic InterSociety Consensus; TTE = transthoracic echocardiography.

[a]Recent data from COMPASS trial need further analyses and will be addressed in the future.

[b]Without any other clinical condition requiring antiplatelet therapy.

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13. Gaps in evidence

Rapid changes in therapeutic techniques create the situation in which clinical practice tends to follow technical developments without evidence from RCTs. In addition, RCTs often yield conflicting results because of technical evolution. Moreover, PADs may involve multiple sites, creating a large number of clinical scenarios to investigate. All these contribute to the broad spectrum of gaps in evidence, of which the most relevant are listed in *Table 10*. The current background information and detailed discussion of the data for the following section of these Guidelines can be found in ESC CardioMed.

Table 10 Main gaps in evidence in the management of patients with peripheral arterial diseases

Epidemiology
Data on epidemiology of PADs in Europe are scarce.
Important challenges are associated with PADs in women. This group has classically been underrepresented in research studies. Therefore, several sex-related challenges regarding diagnosis and management issues should be acknowledged.
Carotid artery disease
The benefits of new antiplatelet drugs for the management of asymptomatic carotid artery disease should be assessed by RCTs.
A multifactorial and standardized score is necessary to stratify the risk of stroke in patients with asymptomatic carotid artery stenosis, to determine the subgroup who may benefit from revascularization, in addition to best medical therapy.
The efficacy of embolic protection devices during CAS has not been studied in adequately powered RCTs, and the available evidence is conflicting.
The optimal duration of dual antiplatelet therapy after CAS is not well established.
The timing of carotid revascularization in the acute phase of stroke after intra-cerebral thrombolysis/thrombectomy is not yet defined and should be investigated.
Vertebral artery disease
Almost no data are available on the comparison between surgical and endovascular revascularization in symptomatic patients.
Upper extremity artery disease
Little is known about the natural course in upper extremity artery disease.
Almost no data are available on the long-term clinical benefit of revascularization (and the optimal mode) of symptomatic subclavian artery stenosis/occlusion.
Optimal duration for DAPT after subclavian artery stenting is unknown.
Mesenteric artery disease
The potential benefits of prophylactic revascularization for asymptomatic mesenteric artery disease involving multiple vessels needs investigations.
In case of symptomatic mesenteric artery disease, no data are available on the potential benefit of covered vs. bare stents.
Optimal duration for DAPT after mesenteric stenting is unknown.
Renal artery disease
The role of renal artery stenting for patients with pulmonary flash oedema remains to be demonstrated by RCT.
Appropriate treatment of in-stent renal artery restenosis is not yet defined.
Risk stratification would be necessary to clarify whether a subgroup of patients with RAS may benefit from renal revascularization. In case of renal stenting, optimal duration for DAPT is unknown.
Lower extremity artery disease
The role of drug-eluting stents and drug-eluting balloons in superficial femoral artery and below-the-popliteal artery interventions has to be established.
Optimal treatment for popliteal artery stenosis needs to be addressed.
Clinical studies on self-expanding stents, drug-coated balloons and drug-eluting stents for below-the-knee interventions in patients with CLTI should include amputation-free survival, wound healing and quality of life in addition to standard-patency outcomes.
Optimal duration of DAPT after stenting, as well as the potential benefit of its long-term use in patients with CLTI, should be further investigated.
The rationale of the angiosome concept to decide on modality of revascularization in patients with CLTI remains to be demonstrated.
There is a need to develop European registries for patients with LEAD in order to provide "real world" assessment of clinical outcomes and practices.
There is a need to validate improved classification systems for CLTI that incorporate wound, ischaemia and foot infection such as the WIfI classification.
Multisite artery disease
Whether the screening for other sites of atherosclerosis (e.g. CAD) in patients with PADs may improve their outcome needs further investigation.
Cardiac conditions in patients with PADs
The impact of heart failure screening and treatment and its impact on outcome of patients with PADs requires further investigations.
The optimal strategy of antithrombotic treatment in patients with atrial fibrillation and PADs requires specific RCTs.

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CAD = coronary artery disease; CAS = carotid artery stenting; CLTI = chronic limb-threatening ischaemia; DAPT= dual antiplatelet therapy; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; RAS = renal artery stenosis; RCT = randomized clinical trial.

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14. To do and not to do messages from the Guidelines

Recommendations	Class[a]	Level[b]
General recommendations on the management of patients with PADs		
In healthcare centres, it is recommended to set up a multidisciplinary Vascular Team to make decisions for the management of patients with PADs.	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases.	I	C
Recommendations in patients with PADs: best medical therapy		
Smoking cessation is recommended in all patients with PADs.	I	B
A healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.	I	A
In patients with PADs, it is recommended to reduce LDL-C to < 1.8 mmol/L (70 mg/dL) or decrease it by ≥ 50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C[c]
In patients with PADs and hypertension, it is recommended to control blood pressure at < 140/90 mmHg.	I	A
Recommendations on antithrombotic therapy in patients with PADs		
In patients with symptomatic carotid stenosis, long-term SAPT is recommended.	I	A
Dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least 1 month after CAS.	I	B
Long-term SAPT is recommended in symptomatic patients.	I	A
Long-term SAPT is recommended in all patients who have undergone revascularization.	I	C
SAPT is recommended after infra-inguinal bypass surgery.	I	A
Because of the lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD.	III	A
In patients with PADs and AF, OAC is recommended when the CHA_2DS_2-VASc score is ≥ 2	I	A
Recommendations for imaging of extracranial carotid arteries		
DUS (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.	I	B
When CAS is being considered, it is recommended that any DUS study be followed either by MRA or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation.	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated either by MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).	I	B
Recommendations on revascularization in patients with symptomatic carotid disease[e]		
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is < 6%.	I	A
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.	I	A
Revascularization is not recommended in patients with a < 50% carotid stenosis.	III	A

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Recommendations for management of vertebral artery stenoses		
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C
Recommendations on the management of acute mesenteric ischaemia		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended.	I	C
Recommendations for management of chronic mesenteric artery disease		
In patients with suspected CMI, DUS is recommended as the first-line examination.	I	C
In patients with symptomatic multivessel CMI, revascularization is recommended.	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.	III	C
Recommendations for diagnostic strategies for RAD		
DUS (as first-line), CTA[f] and MRA[g] are recommended imaging modalities to establish a diagnosis of RAD.	I	B
Renal scintigraphy, plasma renin measurements before and after ACEI provocation and vein renin measurements are not recommended for screening of atherosclerotic RAD.	III	C
Recommendations for treatment strategies for RAD		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral renal artery stenosis.	I	B
Calcium channel blockers, beta-blockers and diuretics are recommended for treatment of hypertension associated with RAD.	I	C
Routine revascularization is not recommended in renal artery stenosis secondary to atherosclerosis.	III	A
Recommendations for ABI measurement		
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated.	I	C
Recommendations on imaging in patients with LEAD		
DUS is indicated as a first-line imaging method to confirm LEAD lesions.	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.	I	C
The data from an anatomical imaging test should always be analysed in conjunction with symptoms and haemodynamic tests prior to a treatment decision.	I	C
Recommendations for the management of patients with intermittent claudication		
On top of general prevention, statins are indicated to improve walking distance.	I	A
In patients with intermittent claudication, supervised exercise training is recommended.	I	A
In patients with intermittent claudication, non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Recommendations on revascularization of aorto-iliac occlusive lesions[h]		
An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions.	I	C
Recommendations on revascularization of femoro-popliteal occlusive lesions[g]		
An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions.	I	C
In patients who are not at high risk for surgery, bypass surgery is indicated for long (i.e. ≥25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is > 2 years.	I	B
The autologous saphenous vein is the conduit of choice for femoro-popliteal bypass.	I	A

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Recommendations on revascularization of infra-popliteal occlusive lesions		
In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage.	I	C
For revascularization of infra-popliteal arteries, bypass using the great saphenous vein is indicated.	I	A
Recommendations on the management of CLTI		
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.	I	C
In patients with CLTI, assessment of the risk of amputation is indicated.	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended.	I	C
For limb salvage, revascularization is indicated whenever feasible.	I	B
In patients with CLTI, stem cell/gene therapy is not indicated.	III	B
Recommendations for the management of patients presenting with acute limb ischaemia		
In the case of neurological deficit, urgent revascularization is indicated.[i]	I	C
In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case-by-case decision.	I	C
Heparin and analgesics are indicated as soon as possible.	I	C
Recommendations on screening for carotid disease in patients undergoing CABG surgery		
In patients undergoing CABG, DUS is recommended in patients with a recent (<6 months) history of TIA/stroke.	I	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C
Recommendations on the management of carotid stenosis in patients undergoing CABG surgery		
It is recommended that the indication (and, if so, the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with a recent (<6 months) history of TIA/stroke, carotid revascularization is not recommended in those with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG, routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.	III	B
Recommendations for screening and management of concomitant LEAD and CAD		
In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention.	I	C
Recommendations on the management of cardiac conditions associated with PADs		
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation.	I	C
In patients with LEAD and atrial fibrillation, OAC is recommended with a CHA_2DS_2-VASc score ≥2.	I	A
Screening for LEAD and UEAD is indicated in patients undergoing TAVI or other structural interventions requiring an arterial approach.	I	C

ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy; CLTI = chronic limb-threatening ischaemia; CMI = chronic mesenteric ischaemia; CTA = computed tomography angiography; DUS = duplex ultrasound; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography; OAC = oral anticoagulation; PADs = peripheral arterial diseases; RAD = renal artery disease; SAPT = single antiplatelet therapy; TAVI = transcatheter aortic valve implantation; TIA = transient ischaemic attack; UEAD = upper extremity artery disease. CHA_2DS_2-VASc score is calculated as follows: congestive heart failure history (1 point), hypertension (1 point), age >75 years (2 points), diabetes mellitus (1 point), stroke/TIA or arterial thromboembolic history (1 point), vascular disease history (1 point), age 65–74 years (1 point), sex category (1 point if female).

[a]Class of recommendation.

[b]Level of evidence.

[c]Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding sections.

[d]Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multisite artery diseases).

[e]Stroke or TIA occurring within 6 months.

[f]When eGFR is ≥ 60 mL/min.

[g]When eGFR is ≥ 30 mL/min.

[h]These recommendations apply for patients with intermittent claudication and severe chronic limb ischaemia.

[i]In this case, imaging should not delay intervention.

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15. Web addenda and companion document

All Web figures and Web tables are available at the European Heart Journal online and also via the ESC Web site at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Peripheral-Artery-Diseases-Diagnosis-and-Treatment-of

The questions and answers companion document for these guidelines is available via this same link.

16. Appendix

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Manuscript #14

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Image in cardiology

Successful Clinical and Therapeutic Approach for Valve-in-valve Leaflet Thrombosis

Exitoso abordaje clínico y terapéutico de trombosis en procedimiento valve-in-valve

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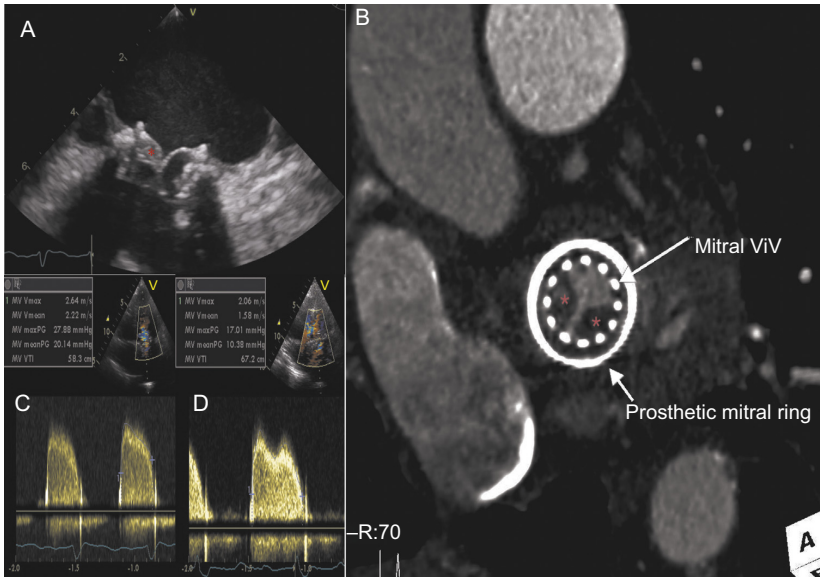


Figure.

An 87-year-old woman with rheumatic valve disease underwent aortic, mitral (Hancock II 27) and tricuspid biological prosthetic valve implantation in 2010.

In 2016, a transapical mitral valve-in-valve procedure (ViV; Edwards Sapien 26) was performed because of prosthesis degeneration with predominant intraprosthetic regurgitation. The patient was in sinus rhythm and a long-term clopidogrel antithrombotic regimen was started.

She was admitted in December 2017 with a 3-week history of exertional dyspnea and orthopnea. A transthoracic echocardiogram (TTE) revealed a severely obstructed mitral prosthesis (mean gradient of 20 mmHg and right ventricle-right auricle gradient of 96 mmHg). A transesophageal echocardiogram suggested the presence of a prosthetic thrombosis (asterisk), as hypoechoic material overlapped the atrial surface of the posterior leaflet (Figure A).

Restrictive motion of the prosthetic leaflets, covered by hypodense thrombotic material (asterisk), was also depicted by computed tomography (Figure B). Given the patient's hemodynamic stability and high surgical risk, a conservative strategy with unfractionated intravenous heparin and clopidogrel was attempted. The clinical course was favorable with a gradual increase in exercise tolerance and normalization of prosthetic gradients at the first month, confirmed by transthoracic echocardiography (Figure C and Figure D).

The incidence of transcathether heart valve thrombosis after mitral ViV procedures remains largely unknown and scarcely reported, with uncertain treatment and undefined antithrombotic regimens. It is particularly interesting in the era of the upcoming percutaneous mitral bioprosthesis. We found this case notable for its rarity and favorable outcome under anticoagulation and antiplatelet therapy. Complementary use of multimodality imaging improved our confidence in its diagnosis and the treatment strategy selected.

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Mid-Term Valve-Related Outcomes After Transcatheter Tricuspid Valve-in-Valve or Valve-in-Ring Replacement

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ABSTRACT

BACKGROUND Transcatheter aortic and pulmonary valves have been used to treat stenosis or regurgitation after prior surgical tricuspid valve (TV) replacement or repair. Little is known about intermediate-term valve-related outcomes after transcatheter tricuspid valve replacement (TTVR), including valve function, thrombus, and endocarditis.

OBJECTIVES The authors sought to evaluate mid-term outcomes in a large cohort of patients who underwent TTVR after surgical TV repair or replacement, with a focus on valve-related outcomes.

METHODS Patients who underwent TTVR after prior surgical TV replacement or repair were collected through an international registry. Time-related outcomes were modeled and risk factors assessed.

RESULTS Data were collected for 306 patients who underwent TTVR from 2008 through 2017 at 80 centers; 52 patients (17%) had a prior history of endocarditis. Patients were followed for a median of 15.9 months after implantation (0.1 to 90 months), with 64% of patients estimated to be alive without TV reintervention or a valve-related event at 3 years. The cumulative 3-year incidence of death, reintervention, and valve-related adverse outcomes (endocarditis, thrombosis, or significant dysfunction) were 17%, 12%, and 8%, respectively. Endocarditis was diagnosed in 8 patients 2 to 29 months after TTVR, for an annualized incidence rate of 1.5% per patient-year (95% confidence interval: 0.45% to 2.5%). An additional 8 patients were diagnosed with clinically relevant valve thrombosis, 3 in the short term, 2 within 2 months, and 3 beyond 6 months. Only 2 of these 8 patients received anticoagulant therapy before thrombus detection ($p = 0.13$ vs. patients without thrombus). Prior endocarditis was not a risk factor for reintervention, endocarditis, or valve thrombosis, and there was no difference in valve-related outcomes according to TTVR valve type.

CONCLUSIONS TV dysfunction, endocarditis, and leaflet thrombosis were uncommon after TTVR. Patients with prior endocarditis were not at higher risk for endocarditis or other adverse outcomes after TTVR, and endocarditis occurred with similar frequency in different valve types. Though rare, leaflet thrombosis is an important adverse outcome, and further study is necessary to determine the appropriate level of prophylactic therapy after TTVR.
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Transcatheter valve replacement has altered the therapeutic landscape for individuals with native and post-operative stenosis or regurgitation of the aortic, pulmonary, mitral, and tricuspid valves (1–11). In recent reports of data from the international VIVID registry (Valve-in-Valve International Database Registry), it was shown that transcatheter tricuspid valve (TV) implantation after prior surgical repair or bioprosthetic valve replacement can be performed successfully and safely, with good short-term outcomes in most patients (6–8). Although those early findings were encouraging, there is relatively little information about intermediate outcomes or associations between patient-related factors and valve-related outcomes after transcatheter TV replacement (TTVR). In patients who have undergone transcatheter aortic valve replacement, long-term durability, valve thrombosis, and to a lesser degree, endocarditis have emerged as important concerns (12–15), whereas recurrent obstruction and endocarditis are the most prominent adverse outcomes that have been observed after transcatheter pulmonary valve replacement (16,17). These observations are not surprising, insofar as all patients with a prosthetic valve

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are at risk for endocarditis (18–20). Given these findings, it is important to understand valve-related outcomes after TTVR, including the epidemiology of post-intervention endocarditis and the impact of prior endocarditis. Therefore, we undertook the present study to evaluate mid-term outcomes in a large international cohort of patients who underwent TTVR after surgical TV repair or replacement.

METHODS

PATIENTS AND PROCEDURES. Data were collected through the voluntary unsponsored Valve-in-Valve International Database Registry, for patients with acquired or congenital heart disease (CHD) who underwent TTVR after prior TV repair (valve-in-ring) or replacement (valve-in-valve) surgery, as described previously (6–8). TTVR procedures were performed clinically at the discretion of the implanting physician. Post-procedural antiplatelet or antithrombotic therapy was also determined by the treating clinicians. Data collected included basic demographic, historical, and diagnostic variables, procedural details, and follow-up information, as reported in prior studies (6–8). Follow-up data were actively collected through January 2018, when the database was locked for analysis. Patients with <3 years follow-up who were alive, reintervention-free, and had no follow-up visit entered in our database within the past 2 years were defined as lost to follow-up for this study. Patients who underwent transcatheter valve implantation in the tricuspid position of a modified Bjork Fontan (i.e., right atrium-to-right ventricle connection) were reported separately (21) and were not included in this study. For this follow-up outcomes study, we excluded patients who underwent catheterization with intention, but no attempt, to implant a valve (n = 5) or an unsuccessful attempt to deliver a valve to the implant site (n = 1), which were included in a prior report (6). Institutional review boards at participating centers approved submission of data.

OUTCOMES AND DATA ANALYSIS. The primary outcomes evaluated for this study were TV function,

ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease
CI = confidence interval
HR = hazard ratio
TR = tricuspid regurgitation
TS = tricuspid stenosis
TTVR = transcatheter tricuspid valve replacement
TV = tricuspid valve
TVR = tricuspid valve replacement

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reintervention (surgical or transcatheter) on the TV, and endocarditis or valve thrombus after TTVR. Early post-implantation TV function was assessed using transesophageal or transthoracic echocardiographic according to methods described previously, with significant tricuspid regurgitation (TR) defined as moderate or greater in severity or reintervention for a stated indication of TR, and significant tricuspid stenosis (TS) defined as a mean Doppler gradient ≥10 mm Hg or reintervention for a stated indication of TS (6,7). Reinterventions included surgical or transcatheter intervention on the TTVR or for paravalvar regurgitation, or removal of the TTVR during surgery for another indication, as a separate procedure (i.e., implantation of a second valve or closure of paravalvar leaks during the primary TTVR procedure were not considered reinterventions). Indications for reintervention were at the discretion of treating physicians and were not standardized. Diagnosis of endocarditis was also determined by the treating physicians. Valve function and valve thrombosis were also reported. A composite valve-related adverse outcome metric was also defined as reintervention, endocarditis, thrombus, or significant TS or TR. Valve-related outcomes were compared according to prior history and valve-related factors.

Data were presented as frequency (%), median (minimum to maximum), or mean ± SD. Differences between groups were assessed using chi-square analysis, Fisher exact test, independent samples Student's *t*-test, or Wilcoxon rank sum test as appropriate. Cumulative incidence functions were estimated from competing risk data using Gray's method (22), and time-related outcomes were depicted with cumulative incidence competing outcome curves. Survival analysis was performed with Cox regression, and univariable analysis of time-related outcomes other than death was performed by fitting proportional subdistribution hazards regression model with death as a competing risk using the method of Fine and Gray (23). Multivariable modeling was performed only for analysis of death, with ≤1 variable included for every 10 events. In analyses of time-related outcomes, several early post-implantation variables (immediate post-TTVR mean TS gradient, significant residual TR/TS or paravalvular leak, and type of anticoagulation/antiplatelet therapy) were considered in addition to historical pre-implantation data. For Cox and Fine-Gray regression, hazard ratios (HRs) were presented with 95% confidence intervals (CIs). Cumulative incidence estimates were presented as proportion with 95% CI. All p values were 2-sided and were considered significant if <0.05. R (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22 (IBM, Armonk, New York) were used for statistical analyses.

RESULTS

PATIENTS. From 2008 through 2017, 306 patients from 80 centers underwent TTVR after prior surgical TV replacement (valve-in-valve n = 284; 93%) or repair (valve-in-ring n = 22) and were included in this analysis. Fifty-two of these patients (17%) had a prior history of endocarditis, which was the underlying cause of TV dysfunction that ultimately led to replacement or repair in most cases (**Table 1**). In 11 of the 52 patients with prior endocarditis, CHD with TV involvement or intervention-related TV injury was the underlying reason for TVR or repair, and in 8 others, it was endocarditis in the setting of nonvalvar CHD. TTVR was performed with a Melody valve in 138 patients (45%) (Medtronic, Dublin, Ireland) or a Sapien valve in 168 (55%; Sapien in 19, Sapien XT in 82, and Sapien 3 in 67) (Edwards Lifesciences, Irvine, California). Intraprocedural echocardiography was performed in 84% of patients, including transesophageal in 164 (54%), intracardiac in 57 (19%), transthoracic in 26 (8%), and multiple modalities (usually intracardiac and transesophageal) in 9 (3%). Additional interventions were performed at the same catheterization in 47 patients (15%) (Online Table 1).

SHORT-TERM OUTCOMES. In 7 patients, the implanted valve (Sapien in 3 patients, Sapien XT in 3 patients, Melody in 1 patient) was malpositioned or embolized; 4 of these patients had a second valve implanted during the same catheterization resulting in elimination of paravalvular regurgitation, 2 had the valve repositioned to the right atrium or inferior vena cava in the catheterization lab and underwent surgery emergently (n = 1) or several months later (n = 1), and 1 with a stable valve but paravalvular leakage underwent surgical TVR later during the same hospitalization.

After TTVR, the mean TV inflow gradient and TR grade measured by echocardiography improved significantly (both p < 0.001). The mean Doppler TV gradient was reduced from a median of 9 mm Hg (0 to 29, 9.0 ± 4.5 mm Hg) to 4 mm Hg (0 to 16, 3.8 ± 2.0 mm Hg). In the 298 patients with a valve in place and a reported measurement, TR was trivial or none in 83% (n = 251), mild in 16% (n = 49), and moderate in 1% (n = 3). Five patients (1.3%) had important residual TV dysfunction: moderate TR in 3 patients and significant TS in 2. There was no difference in the early post-intervention gradient according to

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TABLE 1 Demographic and Diagnostic Data (N = 306)

Patient age, yrs	40 (1-86)
Etiology of original TV disease (before TV surgery)	
Congenital	181 (59)
Ebstein anomaly	100 (33)
Other CHD, abnormal TV, or secondary TR	62 (20)
TV injury related to CHD surgery or catheter intervention	15 (5)
Other	4 (1)
Acquired	125 (41)
Endocarditis	36 (12)
Associated with intravenous drug use	10 (3)
Rheumatic heart disease	39 (13)
TV injury related to biopsy, trauma, PM lead, or other	20 (7)
Functional TR with left heart disease	16 (5)
Other	14 (4)
Number of prior cardiac surgeries	2 (1-10)
Prior TV surgery type	
Replacement	284 (93)
Repair with annuloplasty ring	22 (7)
Age of current TV bioprosthesis or repair, yrs	8 (0.1-40)
Other prosthetic valves, aortic, mitral, pulmonary	107 (35)
Clinical status and comorbidities	
NYHA functional class III or IV	193 (63)
Acutely ill, hospitalized before procedure	36 (12)
Atrial fibrillation or flutter	135 (44)
Acute/chronic renal insufficiency	33 (11)
Liver disease	27 (9)
Chronic lung disease	24 (8)
Existing permanent PM	17 (38)
Epicardial	55 (18)
Transvenous	62 (20)

Values are median (minimum-maximum range) or n (%).
CHD = congenital heart disease; NYHA = New York Heart Association; PM = pacemaker; TR = tricuspid regurgitation; TV = tricuspid valve.

hemodynamic indication for TTVR, transcatheter valve type, underlying congenital versus acquired TV disease, or prior endocarditis history. Patients with a surgical TV prosthesis size 29 mm or larger had a slightly but significantly lower post-TTVR gradient than those with smaller valves (3.6 ± 1.8 mm Hg vs. 4.2 ± 2.3 mm Hg; p = 0.024).

The median post-catheterization hospital stay was 2 days (1 to 81 days). All but 9 patients were placed on some form of antiplatelet/anticoagulant therapy, with 135 on aspirin or another antiplatelet agent only, 61 treated with warfarin alone, 9 on another anticoagulant, and 82 on both antiplatelet and anticoagulant agents (15 unknown). Of the 135 patients with a history of atrial fibrillation or flutter, 93 were discharged on anticoagulant therapy.

FOLLOW-UP. Survival. Patients were followed for a median of 15.9 months after implantation (0.1 to 90 months), with a total of 541 patient-years of follow-up. During that time, 36 patients died, 8 within 30 days (2.6%). The cumulative incidence of death on competing outcomes analysis, accounting for all of the competing risks depicted in the **Central Illustration**, was 0.18. Death was related to procedural complications in 2 patients, cardiovascular causes unrelated to the procedure in 20, and noncardiovascular causes in 14. All but 5 of the patients who died were in New York Heart Association functional class III or IV pre-TTVR, and 11 had been hospitalized and acutely ill before the procedure. By multivariable Cox regression analysis, older age (HR: 1.03 per year; 95% CI: 1.02 to 0.05 per year; p < 0.001) and patient acutely ill and hospitalized before TTVR (HR: 4.4; 95% CI: 2.1 to 9.1; p < 0.001) were associated with higher risk of death over time. When patients hospitalized pre-TTVR were excluded from the analysis, only older age (HR: 1.03; 95% CI: 1.01 to 1.05; p < 0.001) was significant. Prior history of endocarditis and other baseline or procedural factors were not associated with shorter survival.

Among the 244 patients who were alive and had not undergone reintervention, 184 had been followed for <3 years, 56 of whom were considered lost to follow-up according to the definition used for this study. Thirty-nine patients who were alive and reintervention-free had been followed for <1 year.

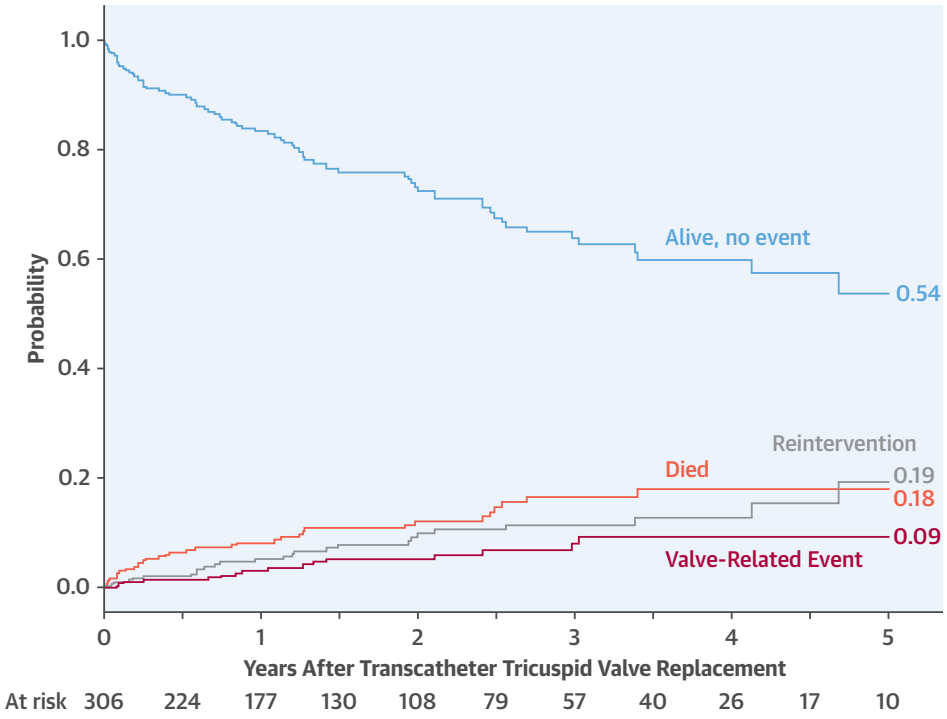
Valve-related outcomes. Valve-related adverse outcomes, including TV reintervention, endocarditis, thrombosis, and significant TS or TR, are depicted in the competing outcomes curve shown in the **Central Illustration**.

TV reintervention. Thirty-one patients (10%) underwent reintervention on the TV during follow-up: surgical TVR in 18 patients, a second TTVR within the first for malposition or dysfunction in 8 patients, redilation of the original TTVR in 3 patients, and device closure of paravalvar leak in 2 patients. Two other patients had the TTVR removed due to heart transplantation. Indications for reintervention are summarized in **Table 2**. Four reinterventions were within the first month after TTVR and 10 were during the first 6 months. Five patients died after reintervention, 3 within 30 days and 2 at 6 to 7 months later. The cumulative incidence of reintervention was 5% at 1 year, 12% at 3 years, and 19% at 5 years (**Central Illustration**). By Fine-Gray regression, higher early post-TTVR inflow gradient was associated with shorter freedom from reintervention (HR: 1.14 per mm Hg; 95% CI: 1.04 to 1.25 per mm Hg; p = 0.005).

Endocarditis. During follow-up, endocarditis was diagnosed in 8 patients 2 to 29 months after TTVR. Six of these patients had underlying CHD (4 with Ebstein

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CENTRAL ILLUSTRATION **Competing Outcomes Over Time After Transcatheter Tricuspid Valve Replacement**



McElhinney, D.B. et al. J Am Coll Cardiol. 2019;73(2):148–57.

These competing outcomes curve depicts cumulative incidences of death, tricuspid valve (TV) reintervention, and valve-related adverse outcomes (endocarditis, thrombosis, significant tricuspid stenosis [TS], or significant tricuspid regurgitation [TR]) over time after transcatheter tricuspid valve replacement. Estimated probability of survival without an event was 0.83 at 1 year, 0.64 at 3 years, and 0.54 at 5 years. The estimated 1-year, 3-year, and 5-year probability of death was 0.08, 0.17, and 0.18; of TV reintervention 0.05, 0.12, and 0.19; and of valve-related adverse outcomes (endocarditis, thrombosis, or significant TS or TR) 0.03, 0.08, and 0.09.

anomaly), and 1 had a prior history of endocarditis associated with intravenous drug use. Causative organisms are listed in Table 3. By competing risk analysis, the estimated cumulative incidence of endocarditis was 0.017 (0.006 to 0.040) at 1-year post-TTVR and 0.042 (0.019 to 0.079) at 3 years and beyond, and the annualized incidence rate was 1.5% per patient-year (95% CI: 0.4% to 2.5%). On univariable analysis, there were no significant associations between endocarditis and potential risk factors, including prior history of endocarditis, method of anticoagulant/antiplatelet therapy, and immediate post-TTVR right ventricular inflow gradient. One of the 8 patients had a pre-existing transvenous pacing system, and 2 with a prosthetic pulmonary valve or conduit had also undergone transcatheter pulmonary valve replacement, but none had evidence of lead or pulmonary valve involvement. TTVR had been performed with a Melody valve in 5 of these patients and a Sapien valve in 3 (Sapien XT in 2, Sapien 3 in 1). Four of these patients had been discharged on antiplatelet therapy only, 1 on warfarin only, and 3 on both.

No patient died as a result of or in the context of an endocarditis episode. Four patients underwent reintervention for endocarditis, including surgical TVR in 3 patients and balloon TV valvuloplasty for moderate TS in 1 patient. In the other 4 patients, the endocarditis was not associated with deterioration of valve function and was treated medically without reintervention.

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TABLE 2 Indications for TV Reintervention After TTVR

TV dysfunction	13
Stenosis	4
Regurgitation	4
Both stenosis and regurgitation	5
Paravalvar leak	4
Endocarditis	4
Valve thrombosis*	3
Concurrent with reintervention for another reason†	3
Acute valve embolization	2
Persistent atrial flutter plus exercise-induced stenosis	1
Persistent multiorgan failure with suspected TV dysfunction	1

Values are n. *Early in 2 patients, late in 1 patient. †Transcatheter pulmonary valve replacement, mitral valve replacement, pericardiectomy in 1 patient each.
TTVR = transcatheter tricuspid valve replacement; TV = tricuspid valve.

TABLE 3 Details of Patients Who Developed Endocarditis

Organism	N	Duration After TTVR, Months	Prior Endocarditis History	Valve Type	Management
Staphylococcus aureus	2	2	No	Melody	Surgical TVR
		13	No	Sapien 3	Medical therapy only
Enterococcus	1	29	No	Melody	Medical therapy only
Candida albicans	1	14	No	Melody	Surgical TVR
Kingella	1	8	No	Sapien XT	Medical therapy only
Haemophilus influenzae	1	8	No	Melody	Balloon valvuloplasty
Unknown/culture negative	2	7	Yes	Sapien XT	Surgical TVR
		16	No	Melody	Medical therapy only

TTVR = transcatheter tricuspid valve replacement; TVR = tricuspid valve replacement.

Among the 184 patients who had been followed for <3 years, the proportion with a prior history of endocarditis (i.e., as a potential risk factor for post-TTVR endocarditis) did not differ significantly from those with >3 years follow-up (p = 0.23). Of the 56 patients defined in the preceding text as lost to follow-up, 29% had a prior history of endocarditis, which was less than in the cohort not lost to follow-up (17%; p = 0.056), and 1 had been diagnosed with post-TTVR endocarditis before being lost to follow-up.

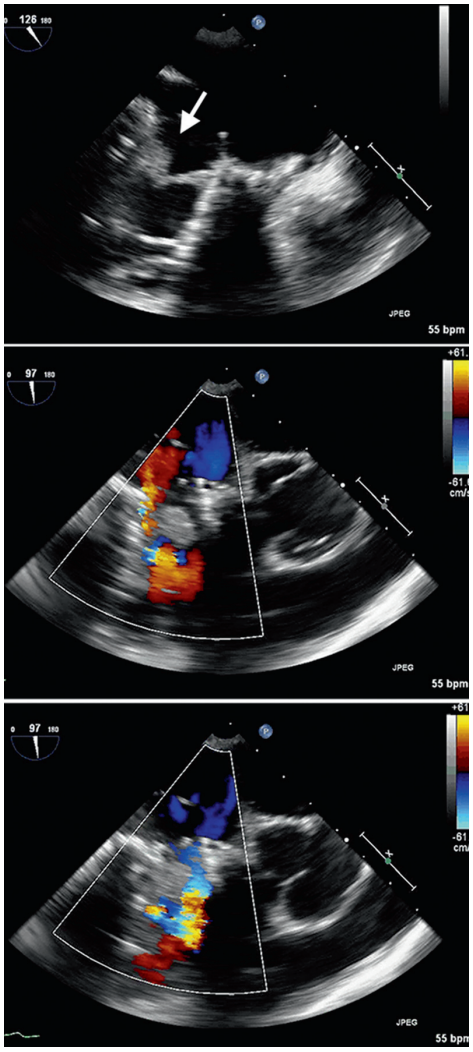
VALVE THROMBOSIS. An additional 8 patients (Melody n = 5, Sapien n = 3) were diagnosed with clinically relevant valve thrombosis (n = 4) or presumed thrombus (immobility or thickening of the leaflets; n = 4), 3 within several days of TTVR, 2 within 2 months (early), and 3 beyond 6 months (late). The cumulative incidence of thrombosis on competing risk analysis was 0.033 (0.015 to 0.061) at 3 years and beyond, and higher immediate post-TTVR inflow gradient was associated with increased risk of thrombosis (HR: 1.38 per mm Hg; 95% CI: 1.13 to 1.70 per mm Hg; p = 0.002). Examples are depicted in **Figures 1 and 2** and Online Videos 1A and 1B. None of these patients had a prior history of endocarditis, 3 had a transvenous pacing system, 3 had atrial fibrillation/flutter, and 2 had other cardiac valve prostheses (1 mitral, 1 pulmonary)—these factors were not significantly associated with thrombosis. All 3 patients with acute thrombosis were treated with anticoagulation after diagnosis, with resolution of the thrombus in 2 patients; 1 patient also had a balloon valvuloplasty at the time, and the other 2 patients underwent surgical TVR 8 and 41 months later for TR or mixed TR and TS, respectively. Of the 2 patients with early thrombus, 1 underwent surgical TVR, and the other (who had a second valve implanted at the time of TTVR due to distal implantation and moderate regurgitation around the first) was started on warfarin, with resolution of thrombus and good TV function 48 months later. Notably, the patient who underwent surgical TVR for early thrombosis also developed early thrombosis of the surgical valve, which was treated medically and left with severe TR and moderate TS. All 3 patients with late thrombosis underwent reintervention, 1 patient at the time of diagnosis and 2 patients later for progressive TS or TR. Thus, at the most recent follow-up, 2 of the 8 had the original TTVR in place with good function.

The 3 patients with acute thrombus were discharged on both anticoagulant and antiplatelet therapy after the immediate treatment, but 2 of the 3 patients had not been on post-procedural anticoagulant before the thrombus; 4 of 5 patients with subacute or late thrombus were discharged from the original TTVR procedure on antiplatelet therapy alone and 1 on a nonwarfarin oral anticoagulant. Thus, only 2 of the patients who developed a thrombus (p = 0.13 by log-rank test), and 1 of the 5 with an acute or early (within 2 months) thrombus (p = 0.15 by Fisher exact test), were on anticoagulant therapy.

TTVR function. Follow-up echocardiographic data were available for all but 25 of the surviving patients who had not undergone reintervention, 17 patients of whom had been followed for <1 year. In addition to the patients who underwent TV reintervention, significant TR (moderate or severe, n = 7), TS (mean Doppler gradient ≥10 mm Hg; n = 6), or combined TS and TR (n = 1) was diagnosed in 14 patients after TTVR, 4 within 6 months of implantation (immediate n = 1). The mechanisms of TS or TR were not reported in detail. Missing data limited the analysis, but only 32% of patients who were diagnosed with significant TR or TS during follow-up were discharged on antithrombotic agents, compared with 52% of those who did not develop significant TV dysfunction. There was no apparent difference in TV dysfunction

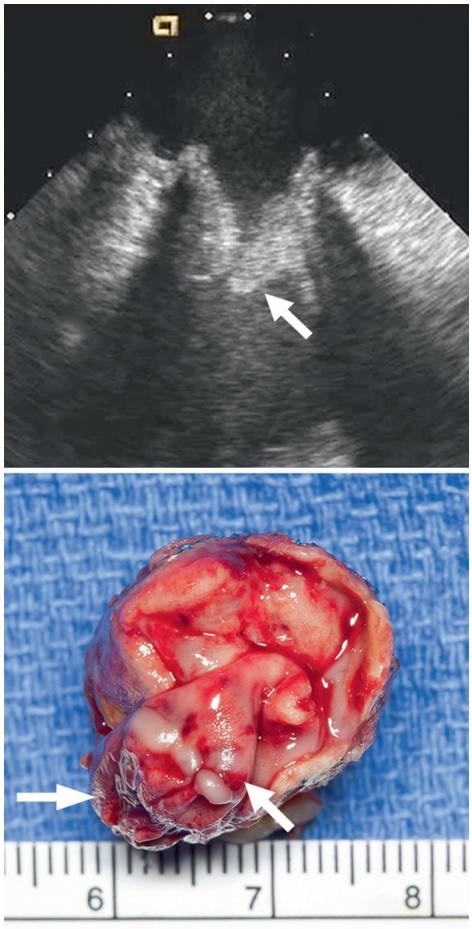
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FIGURE 1 Leaflet Thrombus Early After TTVR With a Sapien Valve



This series of transesophageal echocardiographic images taken 6 weeks after TTVR shows a Sapien valve in the TV position with **(top)** thickening of 1 leaflet and a mass on another **(arrow, middle)** a large thrombus and color Doppler evidence of regurgitation, and **(bottom)** the thrombus restricting inflow and resulting in stenosis **(color)**. After treatment with warfarin, the thrombus and gradient resolved, and the patient is doing well with the valve in place 48 months later. TV = tricuspid valve; TTVR = transcatheter tricuspid valve replacement.

FIGURE 2 Leaflet Thrombus After TTVR With a Melody Valve



(Top) this intracardiac echocardiogram image shows thrombosis of the Melody valve leaflets **(arrow)** 1 month after TTVR. **(Bottom)** this photograph viewed from the right ventricular aspect shows the explanted Melody valve in the same patient, with thrombus indicated by the **arrows**. This patient experienced acute right ventricular failure after TTVR, possibly related to increased flow through the right heart after closing a left superior vena cava draining to the left atrium at the time of TTVR, and was supported with a right ventricular assist device for 5 days before undergoing surgical TVR with a homograft valve, which also failed early by the same mechanism and remains in place (Online Videos 1A and 1B). Abbreviations as in **Figure 1**.

according to transcatheter valve type; of the valves with TR, 4 were Melody and 3 were Sapien, and of the valves with TS or mixed dysfunction, 6 were Sapien and 1 was Melody.

DISCUSSION

TTVR OUTCOMES AND IMPLICATIONS. In prior reports from this international multicenter registry, we showed that TTVR after prior surgical TV replacement or repair was associated with a high

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rate of technical success and few serious procedural complications, restoration of good TV function, and clinical improvement in most patients (6–8). In particular, given the importance of endocarditis and thrombosis after other transcatheter valve therapies (12–16,18,19,24,25), we undertook this study to assess the burden of these outcomes after TTVR, to evaluate whether there were patient-related or procedural factors associated with greater risk of endocarditis and thrombosis after TTVR, and to determine whether prior endocarditis history was associated with post-TTVR outcomes.

TV ENDOCARDITIS. Compared with left-sided endocarditis, relatively little is known about endocarditis affecting the right-sided valves. In studies of surgical TV replacement, endocarditis was a common comorbidity and underlying cause of TV dysfunction (20,26). However, there was no information in those studies regarding the causes and details of the original endocarditis episode. Similarly, in the present cohort, a prior history of endocarditis was reported in 17% of patients, most of whom underwent TV replacement as a consequence. In patients undergoing surgery for endocarditis, investigators have observed several pathological differences between right- and left-sided endocarditis (27), and it has been reported that TV involvement is associated with worse survival (28). Although there is limited information on endocarditis after TV repair or replacement, regardless of the underlying pathology, it appears to be an uncommon, but nontrivial, late complication that more often affects mechanical than bioprosthetic valves (29–32).

In this large unselected cohort, endocarditis was reported in 8 of 306 patients after TTVR, with various organisms affecting both valves similarly. Diagnostic criteria for tricuspid or pulmonary valve endocarditis are less clear than for the more common left-sided infection, and it was recently reported that right-sided endocarditis is less likely to be invasive than left-sided disease (27), so there may be some ambiguity about the certainty of diagnosis. As also noted in this study, noninfectious thrombus may be observed after TTVR, and may be difficult to distinguish from endocarditis with echocardiography. Two of the 8 cases in this series were presumed to have endocarditis but without an identified organism. Although the available data are insufficient to draw firm conclusions, on the basis of the published reports and this study, there does not appear to be an obvious difference between endocarditis risk after surgical TVR and TTVR. Although small numbers precluded robust assessment of risk factors, only 1 of the 8 cases of endocarditis (16%) had a prior history of endocarditis, similar to the 17% prior prevalence in the overall cohort. Thus, prior endocarditis does not appear to confer substantial risk of post-TTVR endocarditis and should not exclude patients from this therapy. Given the pathogenesis of endocarditis and experimental data suggesting a benefit of thromboprophylaxis (33,34), it will be important to assess whether and what type of anticoagulant/antithrombotic therapy and hemodynamic factors after TTVR are associated with the risk of endocarditis.

TV THROMBUS. The issue of leaflet thrombosis after transcatheter aortic valve replacement, often subclinical, has emerged as an important consideration in that population (15), and there is ongoing debate about the proper approach to post-implantation thromboprophylaxis. In this study, valve thrombus was not investigated systematically with computed tomography to detect subtle or minor cases, which may have been missed, but 8 patients were found to have hemodynamically significant thrombus confirmed by transesophageal or intracardiac echocardiography, leading to surgical TVR or redo TTVR in 6. Three of these cases were acute, and may have been related to hemodynamic factors unique to transcatheter valve implantation in the TV position, including large dilated right atrial and ventricular chambers, impaired right ventricular function, and consequently, sluggish flow across the new valve. A higher immediate post-TTVR inflow gradient was associated with greater risk of both leaflet thrombosis and TV reintervention. Although these findings should be considered preliminary, they suggest that implanters should strive for maximal gradient relief during the implant, and perhaps consider post-dilation of the implanted TTVR even for relatively minor residual gradients.

Only 2 of the 8 patients with a clinically evident thrombus, and 1 of the 5 with acute or early valve thrombosis, were on anticoagulation at the time, less than patients who did not develop a thrombus, although this finding should be interpreted with caution due to the small number of events. In addition, there have been anecdotal cases in which rising TV inflow gradients were reversed with initiation of anticoagulation. Thus, whereas frank thrombosis was uncommon in this series, the importance of thrombus prevention after TTVR may not yet be fully appreciated, and it is worth considering whether conditions after TTVR merit utilization of anticoagulant or dual antiplatelet therapy rather than a single antiplatelet

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agent. Over one-half of the patients in this series were discharged on some form of anticoagulant therapy, with or without an antiplatelet medication, whereas almost all of the others were on antiplatelet therapy alone. We did not collect data on changes in or compliance with these therapies, and the absolute number of clinically detected thrombotic episodes was small, precluding analysis that might provide insight into risks and benefits associated with different approaches.

TV FUNCTION. As we reported previously, TV function remained stable in the majority of patients who underwent TTVR. At most recent follow-up, which was beyond 3 years in a substantial number of patients, the mean Doppler inflow gradient was typically in the 4 to 5 mm Hg range, and TR was mild or less. This is similar to gradients observed across newly implanted surgical bioprosthetic valves in the TV position (35), but as we discussed in a prior report, the magnitude of gradient across a TTVR that should be considered significant has not been determined (6). As discussed in the preceding text, the hemodynamic implications of subtle leaflet thrombus were not investigated in this study. Subclinical thrombosis has emerged as an important concern after transcatheter aortic valve replacement (15), and insofar as the valves employed for TTVR are often transcatheter aortic valves used off-label, it is reasonable to hypothesize that this may be a relevant concern with TTVR as well. Accordingly, it will important to examine this issue in depth, particularly because small increases in the TV inflow gradient can translate into significant symptoms and sequelae.

METHODOLOGICAL CONSIDERATIONS AND STUDY LIMITATIONS. In addition to the issues addressed in the preceding text, there were several important limitations to this study. Data were collected as part of a voluntary unsponsored retrospective registry with no core labs, no auditing of data, and no standardized criteria for anticoagulation/antiplatelet therapy or reintervention. Similarly, assessment of TV function by echocardiography depends on a number of factors, which were not standardized or analyzed in this study, and further studies will be necessary to characterize post-TTVR hemodynamics more rigorously. Details of prior endocarditis episodes, including the organism, duration before TTVR, involvement of the native or prosthetic TV, and number of episodes were unknown for this study, so we cannot make inferences about risks related to specific circumstances. Incomplete follow-up is also an important limitation: in most surviving patients, follow-up was available for <3 years, limiting our ability to assess freedom from valve-related events over time. The disparity of loss to follow-up among patients with a prior history of endocarditis may confound assessment of this as a potential risk factor for post-TTVR adverse outcomes. Thus, these findings should be considered preliminary, and more robust estimates will require longer evaluation in a larger cohort of patients. There were few patients with underlying functional TR related to left-heart disease or valve-in-ring TTVR procedures, so future studies will be required to provide insight into these important cohorts.

CONCLUSIONS

TTVR was hemodynamically and clinically beneficial in patients of various ages and underlying disease states. Adverse valve-related outcomes were relatively uncommon in this high-risk cohort, and valve function remained excellent in the vast majority of patients followed beyond 3 years post-TTVR. Although a history of endocarditis and prosthetic material in the heart are both risk factors for subsequent endocarditis, patients with prior endocarditis were not at higher risk for adverse valve-related outcomes after TTVR. Endocarditis after TTVR was uncommon, and occurred with similar frequency in patients with both valves. Leaflet thrombosis was also an uncommon but important adverse outcome. Further study is necessary to determine the appropriate level of thromboprophylactic therapy after TTVR.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Early experience suggests that TTVR can be associated with favorable mid-term clinical outcomes in patients with bioprosthetic tricuspid stenosis and/or regurgitation.

TRANSLATIONAL OUTLOOK: Potential relationships between hemodynamic factors and valve leaflet thrombosis after TTVR require further study to guide antithrombotic therapy.

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KEY WORDS endocarditis, percutaneous valve, stenosis, thrombus, transcatheter valve implantation

APPENDIX For a list of additional centers and investigators participating in the VIVID registry as well as a supplemental table and videos, please see the online version of this paper.

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REVIEW PAPER

Usefulness of skeletal muscle area detected by computed tomography to predict mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis study

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Abstract
Measures of sarcopenia, such as low muscle mass measured from the readily available preoperative computed tomography (CT) images, have been recently suggested as a predictor of outcomes in patients undergoing transcatheter aortic valve replacement (TAVR). However, results of these studies are variable and, therefore, we performed a systematic review of current literature to evaluate sarcopenia as a predictor of outcome post TAVR. The search was carried out in electronic databases between 2008 and 2018. We identified studies that reported CT-derived skeletal muscle area (SMA) and survival outcomes post TAVR. Studies were evaluated for the incidence of early (≤ 30 days) and late all-cause mortality (> 30 days) post TAVR. Eight studies with 1881 patients were included (mean age of 81.8 years ± 12, 55.9% men). Mean body mass index was (28.2 kg/m^2 ± 1.1), mean Society of Thoracic Surgeons risk score (7.0 ± 0.6), and mean albumin level was (3.8 g/dL ± 0.1). Higher SMA was associated with lower long-term mortality [odds ratio (OR) 0.49, 95% confidence interval (CI) 0.28–0.83, p = 0.049], compared with low SMA. Also, higher SMA was associated with lower early mortality but was not statistically significant (OR 0.72; 95% CI 0.44–1.18; p = 0.285). CT-derived SMA provides value in predicting post-TAVR long-term outcomes for patients undergoing TAVR. This is a simple risk assessment tool that may help in making treatment decisions and help identifying and targeting high-risk patients with interventions to improve muscle mass prior to and following the procedures.

Keywords Transcatheter aortic valve replacement · Skeletal muscle area · Computed tomography · Frailty · Mortality

Introduction

The Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation are frequently used as risk stratification tools before transcatheter aortic valve replacement (TAVR) in order to evaluate a patient's risk for such interventions [1]. In recent years, there was an increasing interest in frailty as a predictor of outcomes after surgical aortic valve replacement/TAVR, thus guiding risk stratification of those patients before the procedure [2]. Nevertheless, most of the proposed frailty indicators are difficult to measure objectively and are often estimated on the basis of subjective clinical judgment and questionnaires of patient functionality as well as relying heavily on physical performance tests which can be less feasible in very frail patients [2, 3]. In the aging population, frailty is often associated with sarcopenia, which is defined as an age-related disease described by a significant loss of muscle mass [4, 5]. Low

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muscle mass as a measure of sarcopenia is easily measured from preoperative computed tomography (CT) images and has garnered interest as an objective quantitative measure of frailty. Moreover, recent small reports suggested skeletal muscle mass as an independent predictor of outcomes in patients undergoing TAVR. We sought, therefore, to perform a meta-analysis of the available body of literature to examine the effect of low muscle mass on the clinical outcomes post TAVR.

Methods

Search strategy

With the help of an experienced librarian at MedStar Washington Hospital Center (F.K.), the search was carried out in three electronic databases, Medline/Ovid, Embase, and Scopus, between January 2008 and February 2018. This was done entirely as a keyword search because (1) we wanted to include results from Ovid Medline's non-indexed segments, and (2) the keyword search included all the citations found using MeSH terms ("Sarcopenia" and "transcatheter aortic valve replacement").

The pre-defined search terms were: "sarcopenia", "muscle mass", or "muscle area" and "TAVI" or "TAVR" or "transcatheter aortic valve implantation" or "transcatheter aortic valve replacement". In addition, conference abstracts and presentations were considered using the Google search engine to ensure further that pertinent articles were not missed. The reference lists of included studies were screened as well for any eligible studies. This search was not limited by any language filters. The search strategy and search terms used are detailed in the Online Data Supplement.

Inclusion criteria

Eligible studies would have fulfilled all of the following inclusion criteria: (1) randomized controlled trials or observational studies (cohort, cross-sectional, or case-control studies) published as original articles or conference abstracts that evaluated and compared the effect of sarcopenia in patients undergoing TAVR; (2) sufficient quantitative data such as contingency tables, OR, relative risks, or hazard ratios with 95% confidence intervals (CIs); and (3) a reference group composed of non-sarcopenic patients. The outcomes of interest were short- and long-term mortality after TAVR.

Data extraction and outcome measures

Independent duplicate data extraction was done by two reviewers (G.H. and M.S.). The following data were extracted: first author, article title, study design, year of study, country of origin, year of publication, and tools used to assess muscle mass and muscle strength. Eligible studies were examined for the short-term (≤ 30 days) and long-term mortality (> 30 days). For continuous variables, we collected the means and standard deviations whenever possible. For dichotomous variables, we abstracted effect measures [relative risks, odds ratios (OR), or hazard ratios] and 95% CIs. Alternatively, we collected the event rates and populated a contingency table to calculate the effect measures.

Statistical analysis

The findings were evaluated in a descriptive manner based on the information provided by each of the included studies. Quantitative study results were expressed as OR with 95% CI. When available, ORs were reported. Otherwise, crude ORs were computed from the available results in the paper.

We assessed heterogeneity of the study using Chi square tests ($p > 0.1$ showed no significant heterogeneity among studies) and I^2 statistic ($I^2 > 25$, > 50, and $> 75\%$ showed low, moderate, and high heterogeneity, respectively). Statistical analyses were conducted using OpenMetaAnalyst [6]. All values are two-tailed, and $p < 0.05$ was set as the threshold for statistical significance.

Quality and bias assessment

The quality of the included studies was assessed by two authors independently based on the modified Newcastle-Ottawa-scale in this meta-analysis [7]. Modified Newcastle-Ottawa-scale uses a rating system to determine the quality of studies based on two categories, which include selection of participants, comparability between groups, and assessment of exposure or outcome. Modified Newcastle-Ottawa-scale is widely used and recommended by the Cochrane collaboration to assess the quality of nonrandomized studies, especially in cohort and case-control studies. Eight items relevant to the evaluation of quality were applied to this meta-analysis (online data supplement). Disagreements were resolved through discussion.

We intended to assess publication bias using funnel plot techniques, Begg's rank test and Egger's regression test, as appropriate given the known limitations of these methods.

Results

Eight studies with 1881 patients were included (Fig. 1) [8–15]. Long-term outcome data were available for six studies [8, 10–13, 15]. Based on the available information, 55.9% of the included patients were males, and the mean age of the enrolled patients was 81.8 years $\pm$ 12. The body mass

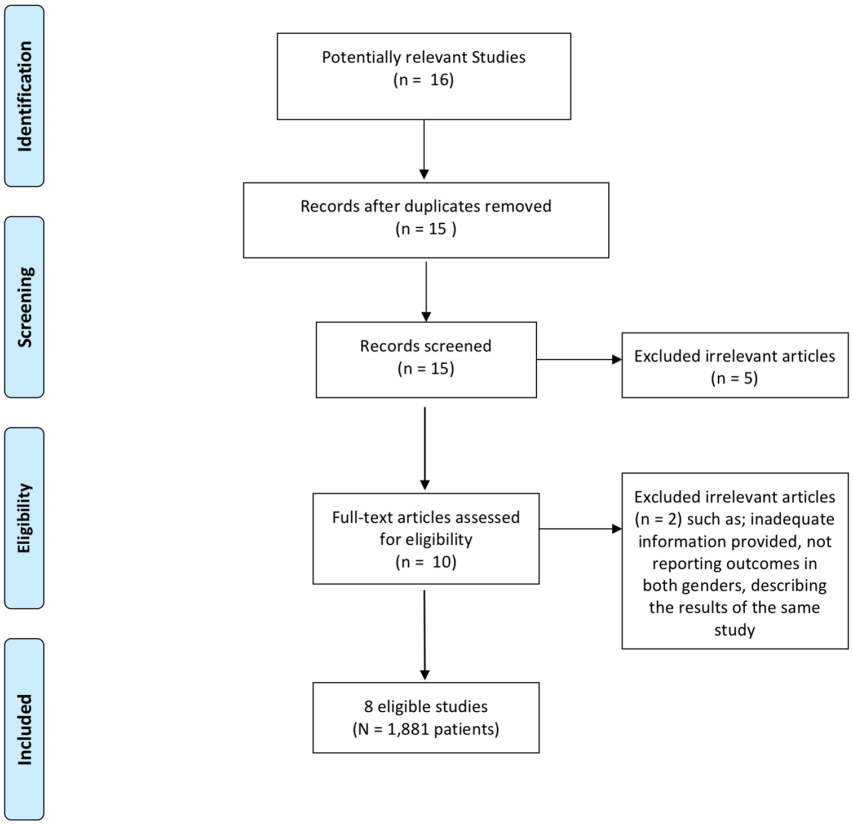


Fig. 1 Flow diagram of the meta-analysis with algorithm for the literature search results and inclusion into the study

index was 28.2 kg/m^2 ± 1.1, STS risk score was 7.0 ± 0.6, and albumin level was 3.8 g/dL ± 0.1. Roughly one-third (37.4%) of patients had diabetes, two-thirds (64.2%) had hyperlipidemia, and 81.4% had hypertension.

Five studies used the psoas muscle area to assess muscle mass [8, 9, 11–13]. One study used psoas muscle area indexed to body mass index [14], and two studies used the skeletal muscle index [10, 15]. Characteristics of the studies included in the analysis are described in Table 1.

We were unable to assess the publication bias as there were inadequate numbers of included studies to properly assess a funnel plot or more advanced regression-based assessments. The information regarding the intra/interobserver variability were available only from two studies [8,

Table 1 Characteristics of included studies

Study	Year	Study design	Sample size	Follow-up (months)	Country	Outcomes
Garg [8]	2017	Retrospective cohort	152	12	USA	Early poor outcome 30 days, 1-year mortality, high-resource utilization
Saji [12]	2016	Retrospective cohort	154	6	USA	All-cause mortality at 30 days and 6 months
Paknikar [11]	2016	Retrospective cohort	139	24	USA	late mortality, high-resource utilization
Mok [10]	2016	Prospective cohort	460	12	Canada	Mortality at 30 days and cumulative mortality
Garg [9]	2016	Retrospective cohort	103	12	USA	Early poor outcome 30 days, 1-year mortality, high resource utilization
Lindman [14]	2016	Retrospective cohort	330	1	USA	All-cause mortality at 30 days
Mamane [13]	2016	Prospective cohort	386	12	Canada	Length of stay, disability, all-cause mortality
Nemec [15]	2017	Retrospective cohort	157	12	USA	Postprocedural complications, length of stay 30 days and 1-year mortality

12]. Both inter-observer and intra-observer reproducibility for muscle area assessment were satisfactory, with a coefficient of variability ranging from < 2–5%.

Primary and secondary outcomes

When compared with sarcopenic patients, non-sarcopenic individuals have a lower risk for long-term mortality following TAVR OR 0.49, 95% CI 0.28–0.83, p = 0.049; Fig. 2a). Similarly, short-term mortality after TAVR was reduced in non-sarcopenic patients; however, it was not statistically significant (OR 0.72; 95% CI 0.44–1.18; p = 0.285; Fig. 2b). Despite all efforts, we were unable to eliminate the overall substantial statistical heterogeneity ($I^2 > 50\%$).

Discussion

We demonstrated that aortic stenosis patients with low muscle mass, measured on the preoperative CT images, had a 50% lower long-term mortality rate when compared to their peers with normal skeletal muscle mass. This summarizes the growing body of evidence on frailty in TAVR and offers better insight into the various scales that were developed and adapted to the highly frail and complex TAVR population in order to predict post-procedural poor outcomes [2, 16, 17].

In order to obtain a more objective evaluation to identify frail patients, preprocedural serum albumin level as a simple marker that is not subject to inter- or intraobserver bias was found to be independently associated with mortality in patients who undergo TAVR [18, 19]. Recently, the FRAILTY-AVR study compared different frailty scales in a prospective cohort of 646 patients undergoing TAVR and demonstrated a four-items scale encompassing lower-extremity weakness, cognitive impairment, anemia, and hypoalbuminemia to outperform other frailty scales [2]. Nevertheless, albumin is considered an acute-phase protein that has a relatively short half-life, with levels that are largely influenced by vascular injury, renal injury, and various cytokine levels which can reflect acute changes rather than representing a true frailty syndrome [20, 21].

Several tools are available for valid and reliable measurements of muscle strength and performance [22]. Tests such as handheld dynamometer, short physical performance battery, and gait speed over a short distance are frequently used as screening tools, and when scores on these parameters are below normal, further assessment of muscle mass might be more useful. In this current era of TAVR, CT remains the standard method for sizing the aortic annulus and assessing the access route patency before the procedure; therefore, muscle area measurement on CT images is readily accessible in almost all patients [23, 24].

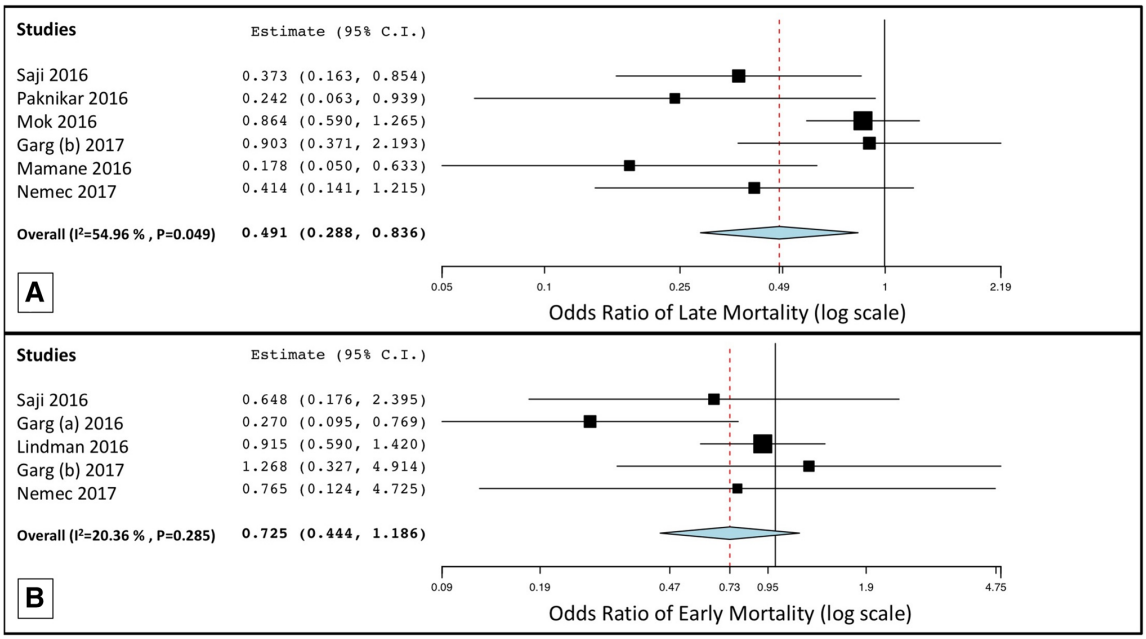


Fig. 2 Forest plots for the long-term (**a**) and short-term (**b**) mortality for non-sarcopenic patients who underwent TAVR compared to their sarcopenic counterparts. Heterogeneity across trials was evaluated with I^2 statistic. *CI* confidence interval

Table 2 Features of the tools that were used to assess muscle area in the included studies

Study	Vertebra level(s)	Density thresholds (Hounsfield unit)	Tool used to assess muscle mass	Comment(s)
Garg [8]	L3	n/a	BSA indexed PMA mm^2/m^2	PMA obtained from axial cuts on CT as a surrogate for global muscle mass Sarcopenia was defined as PMA indexed to body surface area less than the median
Saji [12]	L4	− 30 to 150	BSA indexed PMA mm^2/m^2	Three tertiles according to indexed PMA for each gender (men: tertile 1, 1708–1178 mm^2/m^2; tertile 2, 1176–1011 mm^2/m^2; and tertile 3, 1009–587 mm^2/m^2; women: and tertile 1, 1436–962 mm^2/m^2; tertile 2, 952–807 mm^2/m^2; and tertile 3, 806–527 mm^2/m^2
Paknikar [11]	L1 – L4	n/a	TPA	The areas of the left and right psoas muscles were summed to compute the TPA. TPA was standardized by gender to control for differences in body habitus
Mok [10]	L3	− 29 to 150	SMMI cm^2/m^2	Muscles that can be identified at L3 are psoas (major and minor), erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis Sarcopenia was defined as an SMMI 2 SDs less than the mean SMMI of young, healthy gender-specific reference ranges
Garg [9]	n/a	n/a	BSA indexed IPA	n/a
Lindman [14]	L4L5	n/a	PMABMI	Right and left psoas muscle area indexed to BMI
Mamane [13]	n/a	n/a	PMA	n/a
Nemec [15]	L3	− 29 to 150	SMI	The measurements included the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles For diagnosing sarcopenia, cutoff values of L3 muscle area of ≤ 52.4 cm^2/m^2 in men and ≤ 38.9 cm^2/m^2 in women were used

BSA body surface area, *PMA* psoas muscle area, *CT* computed tomography, *TPA* total psoas area, *SMMI* skeletal muscle mass index, *IPA* iliopsoas muscle area, *BMI* body mass index, *PMABMI* PMA indexed to BMI, *SMI* skeletal muscle index

Muscle mass has garnered interest as an objective quantitative measure of frailty that is independent of illness acuity and day-to-day changes in functional status required by other performance-based on frailty assessments, which may be unrelated to operative risk factors. Previous studies showed a prognostic value of skeletal muscle assessment in noncardiac as well as cardiothoracic surgeries [25]. The relationship between muscle mass and other known frailty markers is not well studies. A study by Cesari et al. [26] investigated the relation of the frailty syndrome with muscle, as assessed by computerized tomography scan, and found strong associations between that the different frailty syndrome component and muscle mass measurement.

The mechanism that links skeletal muscle mass and post-TAVR mortality is thought to be related to the central role of skeletal muscle in the frailty syndrome. Skeletal muscle is the main reservoir for amino acids in the body, which, when depleted, impairs several vital functions necessary for recovery [27]. Frail patients with low muscle mass have impaired muscle protein synthesis and a high risk of deconditioning after an invasive procedure; this is compounded by the vicious cycle of inadequate nutrition and decreased physical activity [28].

The impact of lower muscle mass after the procedure is not only limited to its undesirable effect on survival following TAVR, patients with SMA were found to be more likely to require discharge to rehabilitation facilities [8]. Therefore, CT-derived skeletal mass measurement might be considered a screening tool to identify vulnerable sarcopenic patients who might be targeted for specific interventions (e.g., protein supplementation and physical rehabilitation) to optimize their frailty status after the TAVR procedure [29, 30].

Limitation

Our study has several evident limitations. Inherent to all meta-analyses is the potential for heterogeneity among selected studies. However, heterogeneity testing did not indicate significant heterogeneity for the overall OR of mortality. The measurement of muscle mass and the definition of sarcopenia are not uniformed, and our analysis included

studies with several tools that were used to assess muscle area with different threshold to define sarcopenic patients. These differences are highlighted in Table 2.

Conclusion

Our meta-analysis of all the available literature to date is suggestive of a benefit of CT-derived skeletal muscle area in providing a prognostic value and predicting post-TAVR long-term outcomes.

This method is a simple risk assessment tool that may improve risk stratification for TAVR procedure and guide clinical decisions and may perhaps be integrated into the STS score. It might also help identifying and targeting high-risk patients with nutritional and exercise interventions to improve muscle mass prior to and following the procedure.

More research is needed to validate these results with a prospective analysis of a larger cohort of patients or even through extracting data from the prior published randomized TAVR studies.

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Compliance with ethical standards

Conflict of interest Ron Waksman: Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips Volcano, Pi-Cardia Ltd.; Grant Support: Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance. All other authors declared that they have no conflict of interest.

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Manuscript #17

Original Article

Impact of Transcatheter Aortic Valve Implantation on Kidney Function

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Abstract

Background: Chronic kidney disease (CKD) is frequently present in patients with aortic valve disease. Decreased kidney perfusion as a consequence of reduced cardiac output may contribute to renal dysfunction in this setting.

Objective: Given the potential reversibility of kidney hypoperfusion after valve repair, this study aimed to analyze the impact of percutaneous transcatheter aortic valve implantation (TAVI) on kidney function.

Methods: We performed a retrospective analysis of 233 consecutive patients who underwent TAVI in a single center between November 2008 and May 2016. We assessed three groups according to their baseline estimated glomerular filtration rate (eGFR) (mL/min/1.73 m²): Group 1 with eGFR ≥ 60; Group 2 with 30 ≤ eGFR < 60; and Group 3 with eGFR < 30. We analyzed the eGFR one month and one year after TAVI in these three groups, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to calculate it.

Results: Patients from Group 1 had a progressive decline in eGFR one year after the TAVI procedure (p < 0.001 vs. pre-TAVI). In Group 2 patients, the mean eGFR increased one month after TAVI and continued to grow after one year (p = 0.001 vs. pre-TAVI). The same occurred in Group 3, with the mean eGFR increasing from 24.4 ± 5.1 mL/min/1.73 m² before TAVI to 38.4 ± 18.8 mL/min/1.73 m² one year after TAVI (p = 0.012).

Conclusions: For patients with moderate-to-severe CKD, kidney function improved one year after the TAVI procedure. This outcome is probably due to better kidney perfusion post-procedure. We believe that when evaluating patients that might need TAVI, this 'reversibility of CKD effect' should be considered. (Arq Bras Cardiol. 2019; 113(6):1104-1111)

Keywords: Aortic Valve Stenosis/complications;renal Insufficiency,Chronic; Calcinosis; Renal Dialysis; Diabetes Mellitus; Cardyomyopathies; Hypertension.

Introduction

Since Bright[1] first described the association between chronic kidney disease (CKD) and heart disease in 1836, many epidemiological studies have confirmed and extended this finding.

With higher life expectancy, the prevalence of valvular heart disease, such as aortic valve disease, is increasing, and patients needing intervention are older and display multiple comorbidities.[2] Surgical intervention is the most effective therapeutic option, but transcatheter aortic valve implantation (TAVI) has become an important treatment choice for inoperable or high-risk patients.[2-4]

Many studies show poor short- and long-term outcomes in patients with CKD submitted to TAVI.[5,6] Other studies on this field focus on acute kidney injury (AKI) after TAVI, showing that AKI is not merely an independent predictor of adverse outcome but also predisposes to the development of CKD. Cases of AKI requiring dialysis have a poor prognosis (50% in-hospital mortality), and a significant proportion of patients progress to end-stage kidney disease.[7-9]

Aortic valve disease is frequently seen in CKD patients[10] due to progressive and accelerated leaflet calcification, a well-known complication of kidney failure. The key modulators in this field have not been totally identified, but might include calcification inhibitors (e.g., fetuin-A and matrix Gla protein), calcification promotors (e.g., hyperphosphatemia, calcium-phosphate product, parathyroid hormone), and leptin. On the other hand, long-standing aortic stenosis may contribute to CKD by impairing forward blood flow from the heart, causing chronic hypoperfusion and resulting in organ damage, and by increased renal venous pressure associated with right-sided heart failure.[11,12] Hypothetically, these pathological CKD mechanisms can be reversed after correction of aortic valve stenosis.

Little is known about the reversibility of CKD after aortic valve replacement. The dynamic changes in kidney function after TAVI have not been described and are not fully understood.

Given the potential reversibility of the pathological CKD mechanism after the correction of aortic valve disease, this study aimed at analyzing the variations in kidney function after TAVI.

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Methods

We performed a retrospective analysis of patients submitted to TAVI at the Hospital de Santa Cruz – Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, between November 2008 and May 2016. We excluded patients under dialysis prior to the procedure and those with a follow-up of less than one month in our center (Figure 1).

Demographic and clinical data were collected from patient chart review. All patients met standard indications for aortic valve replacement.

TAVI was performed mainly by a transfemoral approach. Transapical, subclavian, and transaortic accesses were used in case the former approach was not adequate due to calcification, tortuosity, or caliper. Delivery catheters between 14 F and 20 F sizes were used for valve delivery after previous aortic valve stenosis crossing with a guidewire. Preparation by valvuloplasty with an undersized aortic valve balloon was left to the discretion of the operators, as well as post-dilation valvuloplasty. Several types of valves were selected according to anatomic, valvular, and clinical characteristics based on computed tomography angiography and/or transesophageal echocardiogram (TEE): self-expandable, balloon, and mechanically expandable devices were implanted (respectively Corevalve®/Corevalve Evolut®/Portico®, Edwards®, and Lotus®) in the cath lab by a team including an experienced interventional cardiologist and cardiac surgeons, under fluoroscopic guidance and discretionary intraprocedural TEE. The protocol of the center determined the type (Iomeron® or Visipaque®) and volume (mL) of the iodine contrast selected.

Patient baseline characteristics included demographic data and comorbidities, such as diabetes, coronary artery disease, peripheral vascular disease, hypertension, chronic heart failure, and obesity (Body Mass Index ≥ 30 kg/m^2). Comorbidities found in patient charts were classified in accordance with the International Classification of Diseases, Ninth Revision (ICD-9). Kidney function was assessed by estimated glomerular filtration rate (eGFR), which was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[13] using the closest serum creatinine (sCreat) within 5 days prior to the procedure and after 1 and 12 months (1 year). Based on pre-TAVI eGFR, we evaluated three groups according to the categories suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines:[13] Group 1 with eGFR ≥ 60 mL/min/1.73 m^2 (patients without CKD or CKD G1-2); Group 2 with 30 ≤ eGFR < 60 mL/min/1.73 m^2 (CKD G3a-b); and Group 3 with eGFR<30 (CKD G4-5). Start of renal replacement therapy (RRT) and mortality during follow-up were also considered.

Categorical variables were expressed as frequency distributions and percentages, and continuous variables as mean ± standard deviation. Continuous variables as median values were tested using the paired Student's t-test, and categorical variables were compared with the chi-square test. Differences in eGFR among the three groups over time were analyzed using repeated measures ANOVA. Sphericity was determined by the Mauchly's test when the p-value > 0.05. When the Mauchly's test did not identify sphericity, we used repeated measures ANOVA with Greenhouse-Geisser correction. Multivariate logistic regression was generated for analyses predictors of eGFR improvement.

All statistical tests used the software SPSS version 22.0 (IBM Corp., Armonk, NY, USA). We considered p < 0.05 statistically significant.

Results

We analyzed data from 233 consecutive patients submitted to TAVI in a single center in Lisbon, Portugal, from November 2008 to May 2016.

Table 1 summarizes the baseline characteristics of the patients. The mean age of the patients was 81.8 ± 7.5 years (47 to 94 years), and 56.7% were females. Among all patients, 30.5% had diabetes; 40.3%, coronary artery disease; 22.3%, peripheral vascular disease; 69.5%, hypertension; 35.2%, chronic heart failure; and 17.2% were obese. The mean sCreat was 1.2 ± 0.49 mg/dL, and the mean eGFR was 55.2 ± 19.9 mL/min/1.73 m^2. During the follow-up period, 26.6% of patients died.

Before the TAVI procedure, 100 patients were in Group 1, 101 in Group 2, and 32 in Group 3. The three groups did not present differences regarding gender, incidence of comorbidities, and mortality (Table 1).

Mean eGFR in Group 1, Group 2, and Group 3 before TAVI was 74.6 ± 9.5 mL/min/1.73 m^2, 45.3 ± 8.4 mL/min/1.73 m^2, and 25.0 ± 4.5 mL/min/1.73 m^2, respectively (p < 0.001).

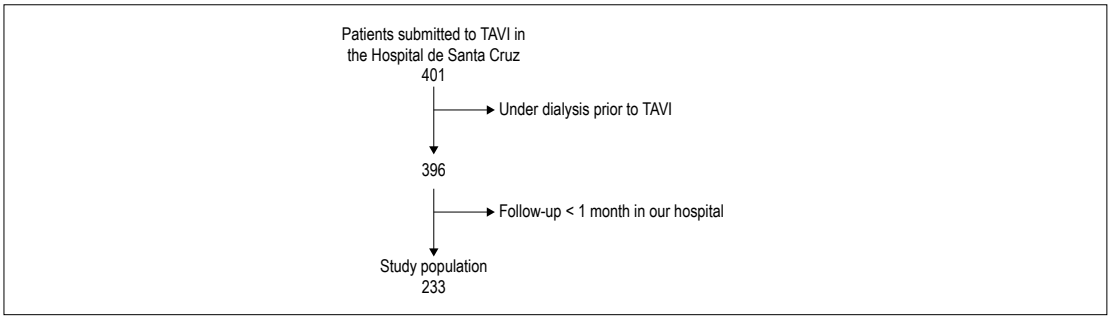


Figure 1 – *Flowchart of the patient population. TAVI: transcatheter aortic valve implantation.*

Table 1 – Baseline characteristics

	All patients (n = 233)	Group 1 (n = 100)	Group 2 (n = 101)	Group 3 (n = 32)	P-value
Females, n (%)	132 (56.7)	49 (49)	66 (64.7)	17 (54.8)	0.078
Age (years, mean ± SD)	81.8 ± 7.5	80.0 ± 9.2	83.5 ± 5.6	81.7 ± 4.9	0.003
Diabetes, n (%)	71 (30.5)	27 (27)	31 (30.4)	13 (41.9)	0.30
Coronary artery disease, n (%)	94 (40.3)	36 (36)	45 (44.1)	13 (41.9)	0.46
Peripheral vascular disease, n (%)	52 (22.3)	18 (18)	28 (27.5)	6 (19.4)	0.23
Hypertension, n (%)	162 (69.5)	73 (73)	70 (68.6)	19 (61.3)	0.46
Chronic heart disease, n (%)	82 (35.2)	30 (30)	37 (36.7)	15 (48.4)	0.16
Obesity, n (%)	29 (17.2)	14 (14)	14 (13.7)	1 (5.9)	0.43
sCreat	1.2 ± 0.49	0.85 ± 0.16	1.26 ± 0.26	2.13 ± 0.45	< 0.001
eGFR	55.2 ± 19.9	74.6 ± 9.5	45.3 ± 8.4	25.0 ± 4.5	< 0.001
Iodine contrast volume (mL)	144.8 ± 82.8	152.7 ± 101.2	139.9 ± 65.1	134.5 ± 64.7	0.434
Dead n (%)	62 (26.6)	29 (29)	21 (20.6)	12 (38.7)	0.11

sCreat: serum creatinine; eGFR: estimated glomerular filtration rate.

The mean volume of iodine contrast was 144.8 ± 82.8 mL, with no differences in the three groups (p = 0.434). Out of all patients, 54.5% received Iomeron®, and 45.5% received Visipaque®. In Group 1, 65.0% of patients received Iomeron®, and 35.0% received Visipaque® (p = 0.004). In Group 2 and Group 3 patients, there was no difference between the iodine contrast used (p = 0.092 and p = 0.151, respectively) (Table 2).

The TAVI procedure had a significant effect on kidney function in the three groups. Sphericity was assumed by Mauchly's test in Group 1 and Group 3 [χ^2 (2) = 4.34, p = 0.144, χ^2 (2) = 0.54, p = 0.763[. Greenhouse-Geisser correction was used in Group 3 [χ^2 (2)=6.93, p = 0.031].

Patients from Group 1 showed a progressive decrease in eGFR after TAVI [F (2-118) = 12.77, p < 0.001], reaching a value of 63.4 ± 19.2 mL/min/1.73 m^2 one year after the procedure (Table 3 and Table 4). The decline in kidney function was more significant in the first month after the TAVI procedure (Table 4 and Figure 2-A).

Patients from Group 2 presented an increase in eGFR [F (2-94) = 6.25, p = 0.003] one month and one year after TAVI (Table 5). The difference between eGFR means was higher one month after the procedure (Figure 2-B). Group 3 had the same results, that is, the mean eGFR increased over time after the procedure [F (2-32) = 5.91, p = 0.014], and the improvement in kidney function was greater in the first month (Table 6 and Figure 2-C).

A multivariate analysis adjusted for gender, age, and comorbidities did not change the variations in eGFR across the three groups.

In a logistic regression model for patients whose kidney function worsened after one month and one year, the contrast administered was a predictor of worsening. Administration of Iomeron® was a predictor of worsening in renal function after one year (HR 4.397, 95%CI 1.584–7.286, p = 0.002). On the other hand, the volume administrated was not a predictor of worsening in eGFR after one month (HR 0.997, 95%CI 0.994–1.001, p = 0.125) and one year (HR 0.999, 95%CI 0.995–1.002, p = 0.476).

The incidence of patients needing to initiate dialysis twelve months after the TAVI procedure was 2.4% (five patients). Before TAVI, one of these patients was in Group 1; two were in Group 2; and two were in Group 3. We did not find a statistically significant difference in mortality among the three groups (p=0.11). All of these patients had chronic heart failure, and four died.

Discussion

This analysis contains data from patients who underwent TAVI in a single center from November 2008 to May 2016. The present results suggest that kidney function might improve in patients with CKD G3-5 after the correction of aortic stenosis. However, in patients with no CKD or with CKD G1-2 (eGFR ≥ 60 mL/min/1.73 m^2), the eGFR decreased during the follow-up. This study also shows a low incidence of new dialysis – 2.4% (five patients).

Several studies address the prognosis and factors that influence mortality and other poor outcomes in patients with CKD undergoing aortic valve replacement, but little is known about the effect of the treatment of aortic valve disease on kidney function.

This study reveals that our patients with CKD G3-5 (eGFR < 60 mL/min/1.73 m^2) had an improvement in kidney function one month after aortic valve replacement, maintaining the improvement after one year of follow-up. Other studies have also indicated this potential reversibility of CKD, both early and after one year of follow-up.[2,14–16]

A study with 69 patients from a single center in Brazil[14] showed an acute kidney recovery after the TAVI procedure. After one year of follow-up, all patients who had an acute recovery remained with improved levels of sCreat. This work also suggests that kidney recovery is more frequent in patients who had more severe renal

Table 2 – Iodine contrast administered to the three groups

	Iomeron® (n; %)	Visipaque® (n; %)	p-value
Group 1	65; 65.0%	35;35.0%	0.004
Group 2	42; 41.2%	62; 58.8%	0.092
Group 3	20; 64.5%	11; 35.5%	0.151

Table 3 – Evolution of kidney function after TAVI

	N patients	eGFR pre-TAVI (mL/min/1.73 m²)	eGFR 1 month after TAVI (mL/min/1.73 m²)	eGFR 1 year after TAVI (mL/min/1.73 m²)	p-value
Group 1	60	74.9 ± 9.0	65.6 ± 20.0	63.4 ± 19.2	<0.001
Group 2	48	45.4 ± 8.5	50.1 ± 15.1	52.6 ± 16.4	0.001
Group 3	17	24.4 ± 5.1	34.9 ± 18.1	38.4 ± 18.8	0.012
All patients	125	56.7 ± 20.5	55.5 ± 20.9	55.8 ± 19.9	0.51

*eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation. *p-value between eGFR pre-TAVI and eGFR 1 year after TAVI.*

Table 4 – Repeated Measures ANOVA: pairwise comparisons (Group 1)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	9.276*	2.533	0.002	3.034	15.518
	eGFR 1 year after TAVI	11.521*	2.612	< 0.001	5.084	17.958
eGFR 1 month after TAVI	eGFR pre-TAVI	-9.276*	2.533	0.002	-15.518	-3.034
	eGFR 1 year after TAVI	2.245	2.072	0.849	-2.861	7.351
eGFR 1 year after TAVI	eGFR pre-TAVI	-11.521*	2.612	<0.001	-17.95	-5.084
	eGFR 1 month after TAVI	-2.245	2.072	0.849	-7.351	2.861

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

dysfunction before aortic valve replacement. Azarbal et al.[15] have found similar results. In their work, acute kidney recovery (defined as a positive change in eGFR of ≥ 25% 48 hours after TAVI) was strongly associated with baseline CKD: 8.9% in patients with eGFR > 60 mL/min/1.73 m² compared to 26.6% in patients with eGFR < 60 mL/min/1.73 m². Also, in a multivariate logistic regression model, lower baseline eGFR was highly predictive of acute kidney recovery (OR 3.27, 95%CI 1.84–5.82, p < 0.001).[15]

Najjar et al.[16] showed that patients with moderate and severe CKD (30 ≥ eGFR > 60 and eGFR < 30, respectively) had initial improvement in eGFR, peaking one week after the aortic valve replacement. The improvement was maintained after one year for patients with moderate CKD and after six months in patients with severe CKD compared with the pre-TAVI eGFR value. The group with severe CKD also presented a better short- and long-term survival in this study.

We believe that these results are due to an improvement in cardiac output and a reduction in venous congestion after aortic valve replacement, leading to better kidney perfusion, and therefore an improvement in kidney function. These data suggest that a better kidney function can be expected in patients with CKD G3-5, which may have important implications in the selection of individuals for the treatment of aortic valve diseases.

The short- and long-term prognosis of aortic valve replacement in patients with CKD prior to the procedure often calls into question the benefit of valve repair in these patients. Recently, some studies have shown that the poor prognosis associated with CKD is influenced by the stage of the disease.[5,6,15,16] Gibson and his work group[19] revealed that eGFR < 60 mL/min/1.73 m² is an important predictor of mortality post-TAVI (HR 5.0, 95%CI 1.87–13.4, p = 0.001) as well as in short-term follow-up (HR 2.98, 95%CI 1.85–4.80, p < 0.001). Other recent study[20] shows that for patients with eGFR < 60 mL/min/1.73 m², a variation as small as 5 mL/min/1.73 m² in eGFR could make a measurable difference in risk of death, RRT, or both at 30 days and 1 year of follow-up. Nguyen et al.[21] showed that a worsening in renal function was associated with increased in-hospital mortality, hospital length of stay, and intensive care unit length of stay in surgical aortic valve replacement patients, but not in TAVI patients. Our study contradicts these data. We found no difference in mortality among patients with CKD G3-5 compared to those who had CKD G1-2 or no CKD before TAVI.

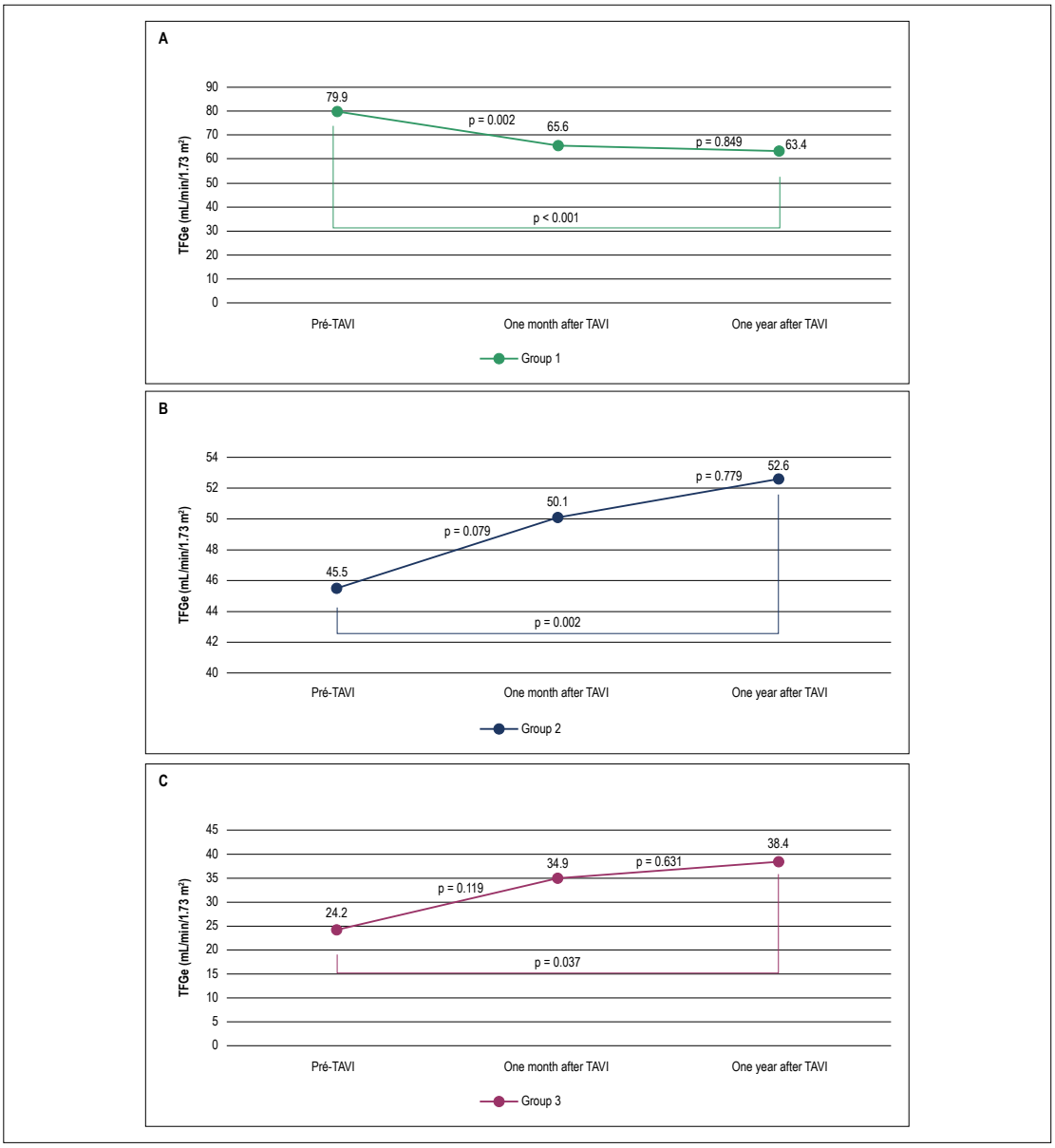


Figure 2 – *Comparison of eGFR between groups after the TAVI procedure. A: Group 1; B: Group 2; C: Group 3. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

Regarding the administration of contrast, the three groups showed no differences regarding the volume received; thus, volume was not a predictor of worsening in eGFR after one month and one year. The predictive value of contrast volume for kidney dysfunction after TAVI is controversial:[15,22,23] in a meta-analysis with over 3,800 patients post-TAVI, higher contrast use was not clearly associated with a greater risk of AKI.[24]

However, we found a difference in the type of contrast administered in Group 1: most patients with CKD G1-2 at baseline received Iomeron® and this iodine contrast was a predictor of worsening in eGFR. Iodine contrast is divided into three groups according to their osmolarity. Iomeron® is a low-osmolar contrast characterized by values within 300–900 mOsm/kg H_2O.[25] Visipaque® is iso-osmolar, having an osmolarity level similar to that of blood (290 mOsm/kg H_2O)

Table 5 – Repeated Measures ANOVA: pairwise comparisons (Group 2)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	-4.716	2.019	0.079	-9.728	0.295
	eGFR 1 year after TAVI	-7.201*	2.007	0.002	-12.184	-2.219
eGFR 1 month after TAVI	eGFR pre-TAVI	4.716	2.019	0.071	-0.295	9.728
	eGFR 1 year after TAVI	-2.485	2.178	0.779	-7.893	2.923
eGFR 1 year after TAVI	eGFR pre-TAVI	7.201*	2.007	0.002	2.219	12.184
	eGFR 1 month after TAVI	2.485	2.178	0.779	-2.923	7.893

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

Table 6 – Repeated Measures ANOVA: pairwise comparisons (Group 3)

(I) eGFR	(J) eGFR	Mean Difference (I-J)	Std. Error	Sig.†	95% Confidence Interval for Difference†	
					Lower Bound	Upper Bound
eGFR pre-TAVI	eGFR 1 month after TAVI	-10.453	4.670	0.119	-22.938	2.031
	eGFR 1 year after TAVI	-13.923*	4.944	0.037	-27.138	-0.708
eGFR 1 month after TAVI	eGFR pre-TAVI	10.453	4.670	0.119	-2.031	22.938
	eGFR 1 year after TAVI	-3.470	2.658	0.631	-10.576	3.636
eGFR 1 year after TAVI	eGFR pre-TAVI	13.923*	4.944	0.037	0.708	27.138
	eGFR 1 month after TAVI	3.470	2.658	0.631	-3.636	10.576

**The mean difference is significant at the 0.05 level. † Adjusted for multiple comparisons: Bonferroni. eGFR: estimated glomerular filtration rate; TAVI: transcatheter aortic valve implantation.*

and dimeric structure opposed to monomeric low-osmolar contrast media.[25] Despite the many years of experience in the use of iodine contrast, the exact pathogenesis of contrast-induced nephropathy (CIN) remains unknown. The causes might include the osmotic effect of contrast media on the kidneys, the increased levels of vasoconstrictive factors, such as adenosine or endothelin, the reduced levels of vasodilators, such as nitric oxide or prostacyclin, and the toxic effect of contrast molecules on renal tubules.[25] According to the American College of Radiology guidelines, iso-osmolar iodixanol has no evident superiority over low-osmolar contrast with respect to the incidence of CIN.[26] Regardless, the difference in the contrast administrated may be one of the factors contributing to the poorer results in patients from Group 1, although there are not enough data to prove this supposition, namely whether these patients had AKI after the procedure. Another hypothesis that could explain the kidney function variation in patients with CKD G1-2 is that, prior to the aortic valve repair, they could not tolerate the angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor antagonists (ARA-II), and as such, the therapeutic could be optimized after the procedure, thus explaining the GFR variation.

We found an incidence of new dialyses of 2.4% (five patients) after a year of follow-up in all categories of CKD without statistical difference between them. A recent study in this field showed a difference in new-dialysis patients according to their CKD stage, with an incidence of 1.2%, 3.74%, 14.6%, and 60.1% in CKD 1-2, CKD 3, CKD 4, and CKD 5, respectively.[18] Given the low incidence of patients who started dialysis in the follow-up period after TAVI, drawing statistically relevant conclusions would not be accurate; nevertheless, we believe that some of these results stand out: (i) the mean age of these patients was 80 ± 5.96 years, similar to the mean age of all the analyzed population (81.8 ± 7.5 years); (ii) almost all patients died (4 out of 5); (iii) all patients had chronic heart failure, which probably contributed to the outcome.

The main limitations of this study concern its retrospective and observational nature. The use of patient charts for data collection is also a limitation, as some data might be missing or incorrectly coded. In addition, a significant number of patients were excluded, which could introduce a systematic bias toward the patients included in the study. Also, sCreat fluctuates often day-to-day, as it is influenced by numerous factors, such as hydration state, medication, or comorbidities. These variations in sCreat significantly affect the estimated kidney function. The present study also has some limitations regarding the patients' follow-up: short follow-up period (one year); the decline in kidney function with age may be a confounding factor for the true benefit of aortic valve

replacement in these patients; and other important covariates not included in this study (such as the severity of aortic stenosis, intra-procedure events, including hypotension, and AKI after the procedure).

Summarizing, the association between worse outcomes in CKD patients undergoing TAVI is well-established, while the potential reversibility of kidney function after aortic valve replacement has not been well-investigated. Despite the limitations, our study provides some significant evidence of reversibility of CKD after aortic valve replacement, probably due to improved renal perfusion post-procedure. Further randomized controlled studies involving more patients and longer follow-up periods are necessary to evaluate the reversibility of CKD after aortic valve replacement.

Conclusions

Our study suggests that the correction of aortic stenosis is associated with an improvement in kidney function in patients with moderate to severe CKD, showing some significant evidence of reversibility of CKD after aortic valve replacement. The confirmation of this 'reversibility of CKD' effect is clinically important insofar as it may help to improve the decision-making process, refining risk stratification in these challenging groups of patients, and perhaps become one of the indications for TAVI.

Author contributions

Conception and design of the research and Writing of the manuscript: Calça R; Acquisition of data: Calça R, Teles RC, Brito J, Nolasco T, Almeida MD; Analysis and interpretation of the data and Statistical analysis: Calça R, Teles RC, Branco P, Weigert A; Critical revision of the manuscript for intellectual content: Teles RC, Branco P, Gaspar A, Neves JP, Mendes M, Weigert A, Machado DS.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Diagnostic accuracy of computed tomography angiography for the exclusion of coronary artery disease in candidates for transcatheter aortic valve implantation

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Coronary CT angiography (CTA) is currently considered a reliable method to exclude obstructive coronary artery disease (CAD) before valvular heart surgery in patients with low pretest probability. However, its role in excluding obstructive CAD before transcatheter aortic valve implantation (TAVI) is less well established. Single-center retrospective study where patients with severe symptomatic aortic stenosis underwent both CTA and invasive coronary angiography (ICA) as part of TAVI planning. CTA exams were conducted on a 64-slice dual source scanner, with a median interval of 45 days to ICA (IQR 25–75 [13–82]). In both tests, obstructive CAD was defined as a ≥50% stenosis in an epicardial vessel ≥2 mm diameter. Per-patient, per-vessel and per-proximal segment analyses were conducted, excluding and including non-evaluable segments. The study included 200 patients (120 women, mean age 83 ± 6 years). The prevalence of obstructive CAD on ICA was 35.5% (n = 71). On a per-patient analysis (assuming non-evaluable segments as stenotic), CTA showed sensitivity of 100% (95% CI, 95–100%), specificity of 42% (95% CI, 33–51%), and positive and negative predictive values of 48% (95% CI, 44–51%) and 100% (95% CI, 92–100%), respectively. CTA was able to exclude obstructive CAD in 54 patients (27%), in whom ICA could have been safely withheld. Despite the high rate of inconclusive tests, pre-procedural CTA is able to safely exclude obstructive CAD in a significant proportion of patients undergoing TAVI, possibly avoiding the need for ICA in roughly one quarter of the cases.

The prevalence and prognostic significance of coronary artery disease (CAD) among patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) warrant the systematic evaluation of the coronary anatomy[1–3]. Cardiac computed tomography angiography (CTA) is usually performed before TAVI for procedure planning, but may also provide valuable information about the coronary arterial tree[4]. Despite several limitations in this setting, pre-procedural CTA may be sufficient to exclude significant CAD, thus avoiding the risks and costs of invasive coronary angiography (ICA)[5–11].

The purpose of this study was to evaluate the diagnostic performance of pre-procedural CTA for excluding significant CAD in patients with severe AS assessed for TAVI, and to determine the proportion of patients where ICA could safely be avoided.

Results

The baseline characteristics of the 200 selected patients with severe symptomatic AS are presented in Table 1.

Overall, 71 patients (35.5%) had obstructive CAD on ICA. These patients were more often male, had a higher prevalence of peripheral artery disease, higher coronary artery calcium (CAC) score values, and a higher

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	Total	Invasive coronary angiography		p value
		No obstructive CAD	Obstructive CAD	
No. of patients	200	129 (64.5%)	71 (35.5%)	
Female gender	120 (60.0%)	85 (65.9%)	35 (49.3%)	**0.02**
Age, years	83.4 ± 5.9	83.1 ± 5.6	83.9 ± 6.2	0.50
BMI, Kg/m^2	26.6 ± 4.7	26.7 ± 5	26.2 ± 4.2	0.09
Arterial hypertension	185 (92.5%)	118 (91.5%)	67 (94.4%)	0.58
Dyslipidemia	147 (73.5%)	94 (72.9%)	53 (74.6%)	0.87
Diabetes mellitus	56 (28.0%)	36 (27.9%)	20 (28.2%)	1.00
Smoking history	43 (21.5%)	24 (18.6%)	19 (26.8%)	0.21
PAD	14 (7.0%)	4 (3.1%)	10 (14.1%)	<**0.01**
Stroke/TIA	19 (9.5%)	12 (9.3%)	7 (9.9%)	1.00
Previous pacemaker	20 (10.0%)	13 (10.1%)	7 (9.9%)	1.00
AFib	67 (33.5%)	46 (35.7%)	21 (29.6%)	0.44
Hemoglobin, g/dl	12 ± 1.7	12.2 ± 1.3	11.8 ± 2.1	0.06
COPD	33 (16.5%)	24 (18.6%)	9 (12.7%)	0.32
Cr Cl (EPI), ml/min/1.73 m^2	55.8 ± 22.4	58.6 ± 20.5	51 ± 24.9	0.08
Euroscore II	4.0 ± 2.8	3.9 ± 3	4.2 ± 2.3	0.79
AVA, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.98
MG, mmHg	50.6 ± 15.2	51.4 ± 15.6	49 ± 14.8	0.84
Reduced LVEF	48 (24.0%)	28 (21.7%)	20 (28.2%)	0.31
CAC score, median and IQR [25–75]	596 [173–1308]	442 [99.5–940.8]	1178 [499–1893]	<**0.01**
Inconclusive CTA	135 (67.5%)	70 (54.3%)	65 (91.5%)	<**0.01**

Table 1. Baseline characteristics of the patients included in the study. AFib - atrial fibrillation; AVA - aortic valve area; BMI - body mass index; CAC score - coronary artery calcium score; COPD - chronic obstructive pulmonary disease; Cr Cl - creatinine clearance; CTA - cardiac computed tomography angiography; IQR - interquartile range; LVEF - left ventricular ejection fraction; MG - mean gradient; PAD - peripheral artery disease; TIA - transient ischemic attack.

frequency of inconclusive CTA. The prevalence of one, two and three-vessel disease was 23.0%, 11.0% and 1.5%, respectively.

On CTA, 31 patients (15.5%) had obstructive CAD and 54 (27.0%) had no significant CAD. The remainder 115 patients (57.5%) had no clearly obstructive CAD but had at least one non-evaluable coronary segment. The main reason for classifying segments as nonevaluable was severe vessel calcification. When considering non-evaluable segments as positive for a significant stenosis in a patient-based analysis, obstructive CAD was present in 146/200 patients (73.0%). Results for the diagnostic performance of CTA for obstructive CAD are presented in Table 2. CTA correctly ruled out significant CAD in 54/200 patients (27.0%), with no false-negative results.

In vessel-based analysis, CTA correctly excluded significant CAD in 401/789 vessels (50.8%), but failed to identify obstructive CAD in 3/789 vessels (0.3%). All three cases of false-negative results involved the ostium of the right coronary artery (RCA). Only one of these three patients underwent percutaneous coronary intervention previous to TAVI due to the severity of the stenosis.

Regarding CTA's procedural data, 18.5% of the patients were in atrial fibrillation (AFib) when CTA was performed, and the mean heart rate in the entire cohort was 72.7 ± 17.0 beats per minute. The effective radiation dose was 993 ± 378 mGy.cm. The presence of AFib did not correlate with a higher number of nonevaluable segments ($p = 0.87$).

Sensitivity analysis. Cardiac CTA was performed before ICA in 79 cases (39.5%). The median number of days between CTA and ICA was 45 (IQR 25–75 [13–82]). To assess the likelihood of potential bias from the fact that CTA readers were not necessarily blinded to ICA results, we performed a sensitivity analysis, where the 121 patients who underwent ICA before CTA were excluded. Specificity and positive predictive values were lower in this subset, but sensitivity and negative predictive values remained high (Table 3).

Finally, regarding the clinical outcome data of the 34 patients without obstructive CAD on CTA who were excluded from the main analysis for not undergoing ICA (mean age 84.0 ± 7.0 years; 79.4% male), at one year there were 3 cases of sudden cardiac death (all in patients awaiting TAVI) and no cases of hospital admission for acute coronary syndrome.

Discussion

CTA is nowadays accepted as a reasonable alternative method to exclude significant obstructive CAD before valve surgery in selected patients with a low or intermediate pretest probability of CAD[12,13]. Its use to rule out obstructive CAD in AS patients with a higher pretest probability of coronary atherosclerosis is not so firmly established. The age of patients with AS (mostly octogenarians), their high prevalence of advanced calcified CAD, the high prevalence of atrial fibrillation during scanning, and the relative contra-indication to administer beta-blockers

	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Patient-based analysis (n = 200)								
>Including those with NE segments	69	76	55	0	100% (94.8–100%)	42% (33.4–50.9%)	47.6% (44.0–51.2%)	100% (92.2–100%)
>Excluding those with NE segments	10	5	55	0	100% (69.2–100%)	91.7% (81.6–97.2%)	66.7% (46.4–82.2%)	100% (92.2–100%)
Vessel-based analysis (n = 789)								
>Including those with NE segments	91	294	401	3	96.8% (91–99.3%)	57.7% (53.9–61.4%)	23.6% (22.0–25.4%)	99.3% (97.8–99.8%)
>Excluding those with NE segments	17	23	401	3	85% (62.1–96.8%)	94.6% (92.0–96.5%)	42.5% (32.3–53.4%)	99.3% (98.0–99.7%)
Patient-based proximal segment analysis (n = 200)								
>Including those with NE segments	34	90	76	0	100% (89.7–100%)	45.8% (38.0–53.7%)	27.4% (24.7–30.3%)	100% (94.2–100%)
>Excluding those with NE segments	7	8	76	0	100% (59–100%)	90.5% (82.1–95.8%)	46.7% (31.2–62.9%)	100% (94.2–100%)

Table 2. Diagnostic accuracy of computed tomography angiography compared with invasive coronary angiography in the patient-based, vessel-based and patient-based proximal segment analyses. FN - false negative; FP - false positive; NPV - negative predictive value; TN - true negative; TP – true positive; PPV - positive predictive value.

	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Patient-based analysis (n = 79)								
>Including those with NE segments	29	36	14	0	100% (88.1–100%)	28% (16.2–42.5%)	44.6% (40.4–48.9%)	100% (74.9–100%)

Table 3. Diagnostic accuracy of computed tomography angiography compared in the patient-based analysis, excluding patients that underwent invasive coronary angiography before computed tomography. FN - false negative; FP - false positive; NPV - negative predictive value; TN - true negative; TP - true positive; PPV - positive predictive value.

and nitrates are among the reasons that make coronary CT particularly challenging in this population[14]. Our results suggest that, despite these limitations, pre-procedural CTA can also be used to opportunistically screen for obstructive CAD before TAVI, potentially avoiding the unnecessary risks and costs of ICA in roughly one quarter of patients. Despite its relatively low diagnostic yield, this information comes at no additional cost in terms of contrast and radiation exposure, since CTA has become mandatory before TAVI and no change in protocol is required.

The high number of inconclusive CTA results (67.5%) comes as no surprise considering the advanced age, high prevalence of cardiovascular risk factors and high CAC score in this study population. The fact that CTA acquisition was not routinely performed under nitrates or beta-blockers could also have increased the number of inconclusive results.

In a patient-based, vessel-based and proximal segment patient-based analysis, sensitivity and, particularly NPV, remained high, even when including those patients with non-evaluable segments. These results were also not significantly affected by the fact that CTA readers were not blinded to ICA results.

To our knowledge, seven previous studies have addressed the diagnostic performance of CTA for CAD before TAVI, with study populations ranging from 60 to 475 patients[5–11]. Overall, despite different methodologies, NPV values remained roughly over 90% throughout these studies. The reported prevalence of significant CAD in patients undergoing TAVI ranges between 40–75%[15], and similar results are stated in the studies described above. Our patients displayed a slightly lower prevalence of obstructive CAD on ICA (35.5%), possibly due to the fact that known CAD was an exclusion criterion. Our study adds to the current body of evidence showing that CTA is useful for excluding obstructive CAD before TAVI.

As for safety concerns, there were three cases of false negative results on a per-vessel analysis (0.4%), all of them related to RCA ostial lesions which were considered non-significant on CTA. The time interval between CTA and ICA was small (<10 days for all three lesions), ruling out the possibility that the coronary stenosis could have progressed between the two tests. Reassessment of these three lesions in CTA suggested calcification of the aortic root wall as the cause for the misjudgement. False negative results were also not exclusive to our study, with previous studies reporting up to 1.5% false negative results in vessel-based analysis[8,10,11].

Our study has several limitations. First, this was a retrospective study, conducted in a single center, with a limited sample size, and as such, its results may not be applicable to other populations and may not represent the exact accuracy of CTA in TAVI patients. Second, interventional cardiologists and imaging cardiologists were sometimes aware, beforehand, of the results of the ICA or CTA. However, significant bias seems unlikely since our sensitivity analysis displayed similar results to the global analysis. Third, a follow-up for the occurrence of vascular complications and contrast nephropathy resulting from ICA was not performed, and so we can only speculate on the potential harm of conducting a potentially unnecessary ICA. Fourth, the 6-month time interval

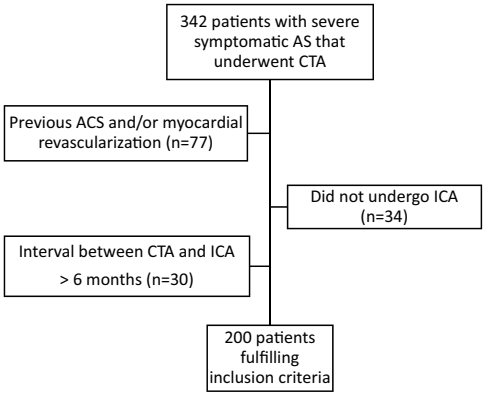


Figure 1. Patient selection flowchart. ACS - acute coronary syndrome; AS - aortic stenosis; CAD - coronary artery disease; CTA - computed tomography angiography; ICA - invasive coronary angiography.

between CTA and ICA defined as cut-off is wider than that stated in previous studies. However, this did not seem to affect CTA's diagnostic performance.

In our population of elderly patients with severe symptomatic aortic stenosis, coronary CT angiography was able to safely exclude obstructive coronary artery disease in roughly one quarter of the cases. The clinical implications of these findings, taken together with similar studies, may include changes in institutional protocols for transcatheter aortic valve implantation planning. Heart teams involved in patient selection and procedure planning should consider performing coronary CT angiography as a first-line test and withholding invasive coronary angiography whenever the absence of significant stenoses can be demonstrated non-invasively. Although beyond the scope of our study, it can be speculated that such an approach might avoid the risks and costs of some unnecessary invasive angiographies without compromising patient safety.

Methods

Patient selection. In this single-center longitudinal retrospective study, all potential candidates for TAVI undergoing both pre-procedural CTA and ICA between October 2015 and March 2018 were included. Patients were considered potential candidates for TAVI based on the presence of severe symptomatic AS, estimated life expectancy greater than one year, and intermediate or high surgical risk. The TAVI screening protocol included both CTA and ICA[16]. Candidates with a time interval between CTA and ICA greater than six months were excluded. Patients with previous history of acute coronary syndrome and/or previous coronary revascularization (percutaneous or surgical) were also excluded. The patient selection flowchart did not exclude patients with poor image quality (Fig. 1). Informed consent was obtained from all subjects. The study was given approval by the *Comissão de Ética para a Saúde* of *Centro Hospitalar Lisboa Ocidental*.

Scan protocol and image analysis. Cardiac CTA was used to assess the aortic annulus size and shape, the aortic valve anatomy and degree of calcification, the distance between the annulus and coronary ostia, the aortic and iliofemoral dimensions, and the coronary anatomy. Coronary CTA was performed on a dual source 64-slice CT (*Siemens Somatom Definition®*, *Siemens Healthineers*, Erlangen, Germany) according to the Society of Cardiovascular Computed Tomography guidelines[14].

Briefly, a bolus of 80–100 mL of iodinated contrast was injected at 4.5 mL/s in an antecubital vein, followed by a 30–50 mL saline flush. A bolus-tracking technique was employed, with a region of interest placed into the ascending aorta, set to detect a predefined threshold of 120 HU. For cardiac imaging, an ECG-gated retrospective scan with tube current modulation was used, with full tube current applied at 25% to 70% of the R-R interval. Tube potential was set at 100 kV by default, and increased to 120 kV in patients with body mass index greater than 30 Kg/m^2. Cardiac imaging was immediately followed by a non-gated scan of the entire aorta and femoral arteries. For the cardiac dataset, transaxial images were reconstructed with a slice thickness of 0.6 mm in at least two points of the cardiac cycle (systole and diastole). The vascular dataset was reconstructed with a slice thickness of 1.0 mm.

Coronary artery calcium (CAC) was determined using the *Agatston* score. Given the presence of severe symptomatic AS, no routine beta-blockers or nitrates were given before CTA, regardless of baseline heart rate or blood pressure. All CTA scans were analyzed by a cardiologist or radiologist with level III experience, on an *Aquarius®* workstation (*Terarecon® Inc*., USA), using axial images, multiplanar reconstructions and maximum intensity projections, as appropriate. ICA exams were performed using standard techniques and projection planes, and analysed by experienced interventional cardiologists. Coronary atherosclerotic lesions on CTA and ICA were assessed by visual estimation. Obstructive CAD was defined as the presence of any plaque with $\leq$50% diameter stenosis in an epicardial vessel with $\geq$2 mm diameter. This threshold was chosen since patients without $\geq$50% stenosis usually warrant no further testing[17]. The same definition was used for ICA. The diagnostic performance of coronary CTA was assessed using ICA results as gold standard on a per-patient, per-vessel and per-proximal segment basis (where only the left main and proximal segments of the three epicardial coronary arteries were

considered for analysis). On the per-vessel analysis, if more than one obstructive stenosis was present in the same vessel, the most severe lesion was considered as representative of the vessel. Segments located distally to a chronic total occlusion were also excluded from the analysis. In order to deal with the presence of non-evaluable segments (segments where the scan reader could not reliably evaluate the degree of stenosis), we conducted two separate analyses: first, assuming that all non-evaluable segments had obstructive CAD, and second, excluding all non-evaluable segments from the analysis. In the vessel-based analysis of the right coronary artery, non-dominant vessels were excluded. Finally, since ICA was sometimes performed before coronary CTA and scan readers were not sistematically blinded to ICA results, we performed a sensitivity analysis excluding these patients in order to assess the likelihood of significant bias.

All methods were carried out in accordance with relevant guidelines and regulations.

Statistical analysis. Continuous variables are presented as means and standard deviations for data with normal distribution, and as median and interquartile range for non-normally distributed data. Normal distribution of continuous data was assessed with the Kolmogorov-Smirnov test. Categorical variables are expressed as frequencies and percentages. Fisher's exact test and unpaired t test were used to compare categorical and normally distributed continuous data, respectively. The diagnostic performance of CTA is expressed as sensitivity, specificity, positive predictive value and negative predictive values, with corresponding 95% confidence intervals, using ICA results as the reference standard. All analyses were performed using IBM SPSS software version 23. Two-tailed p values < 0.05 were considered statistically significant.

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Author contributions

C.S. and A.F. conceived the idea of the study; A.F., J.A., G.C., P.F., S.G., A.S., C.S. performed the pre-procedural CT angiography and interpreted the exam; L.R., J.B., P.G., H.M.G., R.T. and M.A. performed the pre-procedural invasive coronary angiography and interpreted the exam; C.S. and G.M. collected the data; C.S., A.F. and M.M. analysed the results; all authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Transcatheter Self-Expandable Valve Implantation for Aortic Stenosis in Small Aortic Annuli

The TAVI-SMALL Registry

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate and compare the outcomes of transcatheter self-expandable prostheses in patients with small annuli.

BACKGROUND Transcatheter aortic heart valves appear to have better performance than surgical valves in terms of prosthesis-patient mismatch, especially in patients with aortic stenosis with small aortic annuli.

METHODS TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) is a retrospective registry of patients with severe aortic stenosis and small annuli (annular perimeter <72 mm or area <400 mm^2 on computed tomography) treated with transcatheter self-expandable valves (n = 859; Evolut R, n = 397; Evolut PRO, n = 84; ACURATE, n = 201; Portico, n = 177). Primary endpoints were post-procedural mean aortic gradient, indexed effective orifice area, and rate of severe prosthesis-patient mismatch.

RESULTS Pre-discharge gradients were consistently low in every group, with a slight benefit with the Evolut R (8.1 mm Hg; 95% confidence interval [CI]: 7.7 to 8.5 mm Hg) and Evolut PRO (6.9 mm Hg; 95% CI: 6.3 to 7.6 mm Hg) compared with the ACURATE (9.6 mm Hg; 95% CI: 8.9 to 10.2 mm Hg) and Portico (8.9 mm Hg; 95% CI: 8.2 to 9.6 mm Hg) groups ($p < 0.001$). Mean indexed effective orifice area was 1.04 cm^2/m^2 (95% CI: 1.01 to 1.08 cm^2/m^2) with a trend toward lower values with the Portico. No significant differences were reported in terms of severe prosthesis-patient mismatch (overall rate 9.4%; $p = 0.134$), permanent pacemaker implantation (15.6%), and periprocedural and 1-year adverse events. Pre-discharge more than mild paravalvular leaks were significantly more common with the Portico (19.2%) and less common with the Evolut PRO (3.6%) compared with the Evolut R (11.8%) and ACURATE (9%) groups.

CONCLUSIONS Transcatheter self-expandable valves showed optimal clinical and echocardiographic results in patients with small aortic annuli, although supra-annular functioning transcatheter heart valves seemed to slightly outperform intra-annular functioning ones. The role of transcatheter aortic valve replacement with self-expandable valves for the treatment of aortic stenosis in patients with small annuli needs to be confirmed in larger trials.
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Transcatheter aortic valve replacement (TAVR) in patients affected by aortic stenosis has been shown to have good clinical results in a wide range of patients, from inoperable subjects to those at high surgical risk (1-5), and furthermore in patients at moderate (6-8) and even low (9-11) predicted risk for surgical complications.

Nevertheless, some technical aspects may reduce the efficacy of percutaneous procedures, despite progressive technological improvements (newer generation valves and delivery systems, detailed pre-procedural imaging and planning) (12) and increasing operator expertise. One of the most relevant anatomic features that could influence hemodynamic and clinical outcomes after TAVR is aortic annular size, which may play a major role in determining post-procedural gradients, effective orifice area, and paravalvular leak (PVL) (13,14).

Previous studies suggested that surgical aortic valve replacement (SAVR) (15) is associated with a high risk for prosthesis-patient mismatch (PPM) in patients with small annuli, which in turn may result in worse prosthetic performance and eventually in worse mid-term clinical outcomes. A post hoc analysis of pivotal trials that compared TAVR with surgery showed that transcatheter bioprostheses offered better hemodynamic results and a reduced risk for developing PPM (16,17). In addition, a few studies compared outcomes after implantation of balloon-expandable valves (BEVs) and self-expandable valves (SEVs) in patients with small aortic annuli, suggesting improved hemodynamic performance with SEVs compared with BEVs (18,19).

However, no direct comparisons of the performance of SEVs in this subgroup of patients are available. Therefore, the aim of the present study was to assess hemodynamic and clinical outcomes of patients affected by severe aortic stenosis with small aortic annuli undergoing TAVR with SEVs.

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METHODS

STUDY DESIGN AND DEFINITIONS. Between June 2011 and October 2018, consecutive patients with aortic stenosis and small aortic annuli treated with transcatheter implantation of current-generation SEVs at 9 high-volume, experienced European centers (Online Figure 1), were included in the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry.

Key inclusion criteria were the use of a current-generation SEV (CoreValve Evolut R [EvR] and Evolut PRO [EvPRO], Medtronic, Minneapolis, Minnesota; ACURATE [ACU], Boston Scientific, Marlborough, Massachusetts; and Portico [POR], Abbott Vascular, Santa Clara, California) in native aortic stenosis (both tricuspid and nontricuspid anatomies) in patients with small aortic annuli. A small aortic annulus was defined as annular area <400 mm^2 and/or annular perimeter <72 mm on computed tomography; these thresholds were selected on the basis of previous studies on this topic (17-20).

Main exclusion criteria were valve-in-valve procedures, TAVR for pure aortic regurgitation, and a lack of pre-procedural computed tomographic data. No limits were set with respect to age, comorbidities, risk class, and access site. The ACU TransApical transcatheter heart valve, which is no longer commercially available, was included because it was still marketed at the time of data collection.

Local multidisciplinary heart teams evaluated all patients and confirmed the indications for TAVR. All patients underwent pre-procedural screening by means of clinical assessment (patient demographic features, New York Heart Association functional class, history of angina and/or syncope, comorbidities, laboratory examinations, surgical risk, and frailty evaluation), echocardiography, and multidetector computed tomography.

Aortic annular, leaflet, and left ventricular (LV) outflow tract calcifications were classified and graded using a semiquantitative scoring system, as previously described (21). Prosthesis type and size

ABBREVIATIONS AND ACRONYMS

ACU = ACURATE
BEV = balloon-expandable valve
CI = confidence interval
EvPRO = CoreValve Evolut PRO
EvR = CoreValve Evolut R
iEOA = indexed effective orifice area
LV = left ventricular
OR = odds ratio
PM = pacemaker
POR = Portico
PPM = prosthesis-patient mismatch
PVL = paravalvular leak
SAVR = surgical aortic valve replacement
SEV = self-expandable valve
TA = transapical
TAVR = transcatheter aortic valve replacement
TF = transfemoral

Bronx, New York. *Drs. Regazzoli and Chiarito contributed equally to this paper and are joint first authors. Dr. Barbanti is a consultant for Edwards Lifesciences; and serves as an advisory board member for Biotronik. Dr. Stefanini has received a research grant (to the institution) from Boston Scientific; and has received speaking and consulting fees from B. Braun, Biosensors, and Boston Scientific. Dr. Pagnotta is a proctor for Cardia and Boston Scientific. Dr. Kim is a proctor for Boston Scientific and Abbott; and has received speaking fees from Boston Scientific, Abbott, Medtronic, and Edwards Lifesciences. Dr. Tamburino has received speaking fees from Boston Scientific and Abbott. Dr. Reimers has received speaking honoraria from Boston Scientific. Dr. Latib serves on the advisory boards of Medtronic and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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selection, as well as implantation technique and subsequent antithrombotic therapy, were left to discretion of the treating physician at each center.

This study complied with the Declaration of Helsinki and was approved by local ethics committees. Each patient provided written informed consent for the procedure and subsequent data collection.

DATA COLLECTION AND FOLLOW-UP PROCEDURES. Dedicated databases were used for data collection. Active follow-up was performed by means of telephone interviews or follow-up visits.

ENDPOINTS. Coprimary endpoints were short-term mean aortic valve gradient, indexed effective orifice area (iEOA), and rate of severe PPM. PPM was defined as moderate in case of post-procedural iEOA <0.85 cm^2/m^2 and severe in case of post-procedural iEOA <0.65 cm^2/m^2 (22).

Secondary procedural endpoints were short-term rate of more than mild PVL, need for permanent pacemaker (PM) implantation, and major vascular complications. Secondary clinical endpoints included the 1-year rate of all-cause death, rehospitalization for heart failure, ischemic stroke, myocardial infarction, and major bleeding.

Echocardiographic and clinical endpoints were defined according to the Valve Academic Research Consortium-2 (23). Bleeding events were defined according to the Bleeding Academic Research Consortium. Major bleeding was defined as Bleeding Academic Research Consortium grade ≥3 bleeding events (24).

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD and were compared using Student's *t*-test or the Mann-Whitney *U* or Wilcoxon test in case of 2-group comparisons on the basis of normality of data distribution, verified using the Kolmogorov-Smirnov goodness-of-fit test. In case of a skewed distribution, variables are reported as median (interquartile range). In case of continuous variable comparisons between more than 2 groups, analysis of variance was performed. Bartlett's test for equal variances was performed to assess if the variances were comparable between groups. For the primary endpoints of pre-discharge gradient and iEOA, 95% confidence intervals (CIs) are also reported. Categorical variables are reported as number (percentage) and were compared using the chi-square test without Yates' correction for continuity or the Fisher exact test as appropriate. A subgroup analysis was performed to assess eventual differences in terms of post-procedural mean gradient among patients with very small aortic annuli, defined as perimeter- or area-derived diameter <20 mm (25). Furthermore, linear regression was performed to assess the correlation between mean gradient and iEOA with annular perimeter. Last, we performed a multivariate binary logistic regression to assess if the implantation of any SEVs could be independently associated with moderate or severe PPM. All variables associated (with p values < 0.1) with the outcome at univariate analysis were included in the model. Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. Two-sided p values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24 (SPSS, Chicago, Illinois) and Stata version 13.1 (StataCorp, College Station, Texas).

RESULTS

STUDY POPULATION AND CLINICAL CHARACTERISTICS. A total of 859 patients with small aortic annuli treated with TAVR were included: EvR, n = 397; EvPRO, n = 84; ACU, n = 201; and POR, n = 177.

Baseline features of the study population stratified by SEV type are shown in **Table 1**. The mean age was 82.4 ± 0.23 years. The vast majority of patients were women (89.9%). Mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 5.7 ± 0.15%. At baseline, 72.9% of patients were in New York Heart Association functional class III or IV. No significant differences were noted between groups in terms of clinical history, with the exception of chronic obstructive pulmonary disease (which was more common in the EvR and ACU compared with EvPRO and POR groups) and previous percutaneous coronary interventions (less frequent in patients treated with the EvPRO).

Baseline echocardiographic and computed tomographic features are shown in **Table 2**. There were no differences among groups in terms of echocardiographic variables, with the exception of slightly lower LV end-diastolic volume and pre-procedural mean and peak aortic gradients in the POR group compared with the other groups. Mean aortic annular area was 347.23 mm^2, while mean aortic annular perimeter was 67.3 mm.

PROCEDURAL OUTCOMES. Procedural outcomes are shown in **Table 3**. The majority of patients were treated by transfemoral (TF) access (87.3%), with a significantly lower percentage of patients reported in the ACU group (69.7%; $p < 0.001$) compared with the other groups because of the use of the transapical

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TABLE 1 Baseline Clinical Characteristics

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Age, yrs	82.4 ± 0.2	82.0 ± 0.4	83.5 ± 0.7	82.7 ± 0.4	82.7 ± 0.5	0.244
Male	87 (10.1)	43 (10.8)	9 (10.7)	21 (10.5)	14 (7.9)	0.747
BMI, kg/m^2	26.6 ± 0.2	26.8 ± 0.4	26.5 ± 0.9	26.6 ± 0.4	26.2 ± 0.4	0.763
BSA, m^2	1.7 ± 0.01	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.141
Weight, kg	65.1 ± 0.5	64.7 ± 0.7	63.7 ± 1.4	66.5 ± 1	65 ± 1	0.347
Height, cm	158.3 ± 0.2	158.7 ± 0.3	156.8 ± 0.8	158.7 ± 0.6	157.6 ± 0.5	**0.044**
Hypertension	719 (83.8)	339 (85.4)	68 (81.9)	162 (80.6)	150 (84.8)	0.459
Diabetes mellitus	234 (27.3)	104 (26.2)	20 (24.1)	55 (27.4)	55 (31.1)	0.584
Dyslipidemia	418 (48.8)	202 (51)	40 (48.1)	86 (42.8)	90 (51.1)	0.253
COPD	93 (10.9)	52 (13.1)	3 (3.6)	26 (12.9)	12 (6.8)	**0.015**
Peripheral artery disease or prior PTA	140 (16.3)	72 (18.1)	16 (19.1)	30 (14.9)	22 (12.6)	0.321
Cerebrovascular disease	76 (8.9)	34 (8.6)	8 (9.5)	15 (7.5)	19 (10.8)	0.708
Previous BAV	21 (2.5)	14 (3.5)	1 (1.2)	3 (1.5)	3 (1.7)	0.300
Previous CABG	56 (6.5)	27 (6.8)	4 (4.8)	15 (7.5)	10 (5.7)	0.089
Previous PCI	203 (23.7)	87 (21.9)	12 (14.5)	53 (26.4)	51 (29)	**0.043**
Previous MI	93 (11.3)	42 (11.1)	8 (9.6)	24 (12.9)	19 (10.8)	0.857
Coronary artery disease	318 (37.1)	152 (38.4)	24 (28.6)	80 (39.8)	62 (35.2)	0.285
PM or ICD	87 (10.2)	37 (9.4)	12 (14.5)	19 (9.5)	19 (10.9)	0.538
Atrial fibrillation	200 (23.3)	82 (20.6)	21 (25.0)	47 (23.4)	50 (28.3)	0.249
Angina	140 (19)	79 (20.1)	10 (12.1)	27 (19)	24 (19.8)	0.395
NYHA functional class III or IV	626 (72.9)	294 (74.1)	68 (81.0)	135 (67.2)	129 (72.9)	0.095
STS-PROM, %	5.7 ± 0.2	5.9 ± 0.3	5.5 ± 0.4	5.7 ± 0.3	5.3 ± 0.2	0.337
Hemoglobin, g/dl	11.6 ± 0.1	11.5 ± 0.1	11.4 ± 0.2	11.9 ± 0.1	11.8 ± 0.2	0.064
NT-proBNP, pg/ml	2,842.3 ± 393.6	2,746 ± 571.0	3,655 ± 1,331.0	4,035 ± 1,436.0	2,000 ± 384.0	0.406

Values are mean ± SD or n (%). The values in **bold** represent statistical significant differences between groups.

ACU = Acurate; BAV = balloon aortic valvuloplasty; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EvPRO = Evolut PRO; EvR = Evolut R; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PM = pacemaker; POR = Portico; PTA = percutaneous transluminal angioplasty; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

(TA) approach in 60 patients (29.9%). Mean nominal bioprosthesis diameter was 25.1 ± 1 mm (EvR, 25.8 ± 1 mm; EvPRO, 25.8 ± 0.4 mm; ACU, 23.6 ± 1 mm; POR, 24.7 ± 1 mm; p < 0.001). Pre-dilatation was significantly more common in the ACU and POR groups compared with the EvR and EvPRO groups (p = 0.001) because of manufacturers' recommendations to perform valvuloplasty prior to valve implantation, especially in the early phase of marketing. No differences were observed in terms of post-dilatation rate (p = 0.711). Procedural complications were rare, with no differences observed between groups in terms of the need for second valve implantation (2.3%), major vascular complications (5%), and major bleeding (5.2%). Three cases of annular rupture were reported (0.5%). In all 3 cases, post-dilation was performed and likely led to annular damage that was treated conservatively and did not result in major adverse clinical events.

ECHOCARDIOGRAPHIC AND CLINICAL OUTCOMES. Pre-discharge echocardiographic and 1-year follow-up data are shown in Table 4. Lower mean gradients were observed in the EvR (8.1 mm Hg; 95% CI: 7.7 to 8.5 mm Hg) and EvPRO (6.9 mm Hg; 95% CI: 6.3 to 7.6 mm Hg) groups compared with the ACU (9.6 mm Hg; 95% CI: 8.9 to 10.2 mm Hg) and POR (8.9 mm Hg; 95% CI: 8.2 to 9.6 mm Hg) groups (p < 0.001). Mean iEOA was 1.04 cm^2/m^2 (95% CI: 1.01 to 1.08 cm^2/m^2), with a trend toward lower values in the POR group (0.95 cm^2/m^2 [95% CI: 0.89 to 1.01 cm^2/m^2]; EvR, 1.07 cm^2/m^2 [95% CI: 1.01 to 1.13 cm^2/m^2]; EvPRO, 1.08 cm^2/m^2 [95% CI: 1.01 to 1.16 cm^2/m^2]; ACU, 1.04 cm^2/m^2 [95% CI: 0.98 to 1.11 cm^2/m^2]; p = 0.06) compared with the other groups (Figure 1), leading to a significantly higher rate of moderate PPM in the POR group (38.7%; EvR, 24.5%; EvPRO, 20.5%; ACU, 32.7%; p = 0.037). No significant differences were reported in terms of severe PPM (overall rate

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TABLE 2 Echocardiographic and Procedural Characteristics

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Baseline echocardiographic features						
Mean AV gradient, mm Hg	50.1 ± 0.6	50.6 ± 0.8	51.6 ± 1.9	51.5 ± 1.2	46.5 ± 1.2	**0.015**
Maximum AV gradient, mm Hg	80.3 ± 0.9	82.1 ± 1.3	83.9 ± 2.9	81.4 ± 1.8	73 ± 2	**0.001**
EOA, cm^2	0.64 ± 0.01	0.65 ± 0.01	0.61 ± 0.02	0.64 ± 0.01	0.65 ± 0.02	0.401
iEOA, cm^2/m^2	0.39 ± 0.004	0.39 ± 0.01	0.37 ± 0.12	0.38 ± 0.01	0.39 ± 0.01	0.415
sPAP, mm Hg	41.4 ± 0.5	41 ± 0.8	39.3 ± 1.5	42.4 ± 1	42.1 ± 1.3	0.416
RV dysfunction*	119 (13.9)	54 (13.6)	13 (15.5)	19 (9.5)	33 (18.6)	0.076
Bicuspid AV	27 (3.9)	16 (5.5)	0 (0.0)	5 (2.6)	6 (3.5)	0.177
Moderate or greater MR	90 (10.5)	45 (11.3)	13 (15.5)	16 (8.0)	16 (9.0)	0.231
Moderate or greater AR	58 (6.8)	31 (7.8)	8 (9.5)	11 (5.5)	8 (4.5)	0.302
Moderate or greater TR	50 (5.8)	29 (7.3)	2 (2.4)	8 (3.4)	11 (6.2)	0.195
LVEF <40%	71 (8.3)	38 (9.6)	9 (10.7)	16 (7.8)	8 (4.5)	0.183
LVEDV, ml	80.2 ± 1.6	82.4 ± 2.3	74.9 ± 6.9	85.0 ± 2.9	69.7 ± 3.1	**0.006**
LVESV, ml	34.8 ± 1.3	34.7 ± 1.8	35.6 ± 5.3	38.5 ± 3.1	31.8 ± 1.9	0.414
Baseline MDCT features						
Mean annular diameter, mm	21.3 ± 0.05	21.2 ± 0.1	21.4 ± 0.1	21.5 ± 0.1	21.2 ± 0.1	0.061
Maximum diameter, mm	23.6 ± 0.1	23.4 ± 0.1	23.7 ± 0.2	23.8 ± 0.1	23.9 ± 0.1	**0.039**
Minimum diameter, mm	18.9 ± 0.1	18.9 ± 0.1	19.0 ± 0.2	19.1 ± 0.1	18.4 ± 0.1	**0.003**
Mean aortic annular perimeter, mm	67.3 ± 0.2	67.1 ± 0.2	68.0 ± 0.4	67.3 ± 0.3	67.4 ± 0.4	0.335
Mean aortic annular area, mm^2	347.2 ± 1.4	346.1 ± 2.3	346.02 ± 4.6	351.5 ± 2.7	344.7 ± 2.6	0.307
Severe AV calcification	84 (9.8)	42 (10.6)	8 (9.5)	23 (11.4)	11 (6.2)	0.324
LMCA distance	11.9 ± 2.7	12 ± 0.2	12.4 ± 0.7	11.7 ± 0.2	11.8 ± 0.3	0.557
RCA distance	14.3 ± 2.8	14.4 ± 0.2	15.8 ± 0.6	13.9 ± 0.2	14.5 ± 0.2	**0.032**
Sinotubular junction diameter	26.1 ± 2.5	26 ± 0.2	25.7 ± 0.5	26.1 ± 0.3	26.2 ± 0.2	0.780
Sinus of Valsalva diameter	29.1 ± 2.5	29 ± 0.2	30.2 ± 0.4	29 ± 0.2	29 ± 0.2	0.077
Ascending aorta diameter	32.1 ± 4.1	31.5 ± 0.3	32.3 ± 0.7	32.3 ± 0.4	32.8 ± 0.4	**0.014**
Porcelain aorta	34 (4.1)	6 (1.5)	4 (5.7)	15 (7.8)	9 (5.3)	**0.002**

Values are mean ± SD or n (%). *Defined as tricuspid annular plane systolic excursion <17 mm. The values in **bold** represent statistical significant differences between groups.

AV = aortic valve; AR = aortic regurgitation; EOA = effective orifice area; iEOA = indexed effective orifice area; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end systolic volume; LVESV = left ventricular end systolic volume; MDCT = multidetector computed tomographic; MR = mitral regurgitation; sPAP = systolic pulmonary artery pressure; RCA = right coronary artery; RV = right ventricular; TR = tricuspid regurgitation; other abbreviations as in Table 1.

9.4%; p = 0.134) (Online Figure 2). Mean gradients, iEOA, and rate of PPM in patients treated via TF access are reported in Online Table 1. In the TF cohort, pre-discharge mean gradients were significantly higher in the POR group and slightly but significantly lower in the EvPRO group compared with the EvR and ACU groups. Considering only the ACU group, the rates of moderate and severe PPM were considerably lower in patients treated via TF access compared with the entire group (moderate PPM, 11.1% vs. 32.7%; severe PPM, 6.4% vs. 10.6%, respectively) (**Central Illustration**, Online Table 2).

POR and TA ACU implantation was found to be independently associated with moderate PPM (EvR, odds ratio [OR]: 0.75 [95% CI: 0.33 to 1.68; p = 0.480]; EvPRO, OR: 0.54 [95% CI: 0.11 to 2.68; p = 0.448]; ACU TF, OR: 0.27 [95% CI: 0.07 to 1.07; p = 0.062]; ACU TA, OR: 3.05 [95% CI: 1.17 to 7.93; p = 0.022]; POR, OR: 3.00 [95% CI: 1.46 to 6.16; p = 0.003]), while no significance associations with severe PPM were found for any SEVs. When patients with very small annuli (n = 175) were analyzed, we found a significant inverse correlation between post-procedural gradients and annular perimeter (β = −0.07; p = 0.042) (Online Figure 3). Consistently, mean gradients in this subset were slightly but significantly higher compared with those in patients with annular diameters >20 mm (8.1 vs. 10 mm Hg, mean difference 1.9 mm Hg; 95% CI: 1.1 to 2.6 mm Hg). However, the difference may not be clinically relevant, and only 13.7% of patients with very small annulus had severe PPM, without differences among valve groups (p = 0.291).

Pre-discharge more than mild PVLs were significantly more common in the POR group (19.2%) and significantly less common in the EvPRO group (3.6%) compared with the EvR (11.8%) and ACU (9%) groups. Conversely, there were no differences between groups in terms of more than moderate PVL (overall rate 1.6%; p = 0.257). The permanent PM implantation

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TABLE 3 Procedural Outcomes

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	ACU (n = 201)	POR (n = 177)	p Value
Access						
Transaortic	7 (0.8)	4 (1.0)	1 (1.2)	0 (0.0)	2 (1.1)	0.532
Percutaneous axillary/subclavian	11 (1.3)	6 (1.5)	1 (1.2)	0 (0.0)	6 (3.4)	0.159
Surgical axillary/subclavian	29 (3.4)	20 (5.0)	4 (4.8)	1 (0.5)	4 (2.3)	**0.022**
Apical	62 (7.2)	0 (0.0)	0 (0.0)	60 (29.9)	0 (0.0)	**<0.001**
Femoral	749 (87.3)	367 (92.4)	77 (91.7)	140 (69.7)	165 (93.2)	**<0.001**
Valve size, mm	25.1 ± 0.06	25.8 ± 0.08	25.8 ± 0.14	23.6 ± 0.07	24.7 ± 0.09	**<0.001**
Pre-dilatation	422 (49.3)	123 (31.1)	27 (32.5)	151 (75.5)	121 (68.4)	**<0.001**
Post-dilatation	312 (36.6)	141 (35.7)	35 (42.2)	71 (35.5)	65 (37.1)	0.711
Contrast medium, ml	139.5 ± 2.8	147.5 ± 4.0	132.4 ± 6.8	119.6 ± 6.0	145.7 ± 6.9	**<0.001**
Annular rupture	3 (0.5)	2 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	0.830
Any vascular complication	124 (14.4)	52 (13.1)	8 (9.5)	35 (17.4)	29 (16.4)	0.244
Major vascular complication	43 (5.0)	20 (5.0)	2 (2.4)	10 (5.0)	11 (6.2)	0.652
Need for second valve implantation	19 (2.3)	11 (2.9)	1 (1.2)	1 (0.5)	6 (3.5)	0.143

Values are n (%) or mean ± SD. The values in **bold** represent statistical significant differences between groups.
Abbreviations as in Table 1.

rate was 15.6%, with a numeric trend toward lower risk in the ACU group. Hemorrhagic events were rare, with a Bleeding Academic Research Consortium major bleeding rate of 5.23%, without significant differences among groups (p = 0.161).

Median follow-up duration was 342.5 days (interquartile range: 80 to 478 days). No differences were observed in terms of all-cause mortality, stroke or transient ischemic attack, myocardial infarction, hospitalization for heart failure, valve dysfunction, New York Heart Association functional class III or IV, and major bleeding.

DISCUSSION

The aim of the present study was to provide a direct comparison, although not randomized, of SEVs in a real-world cohort of patients with aortic stenosis with

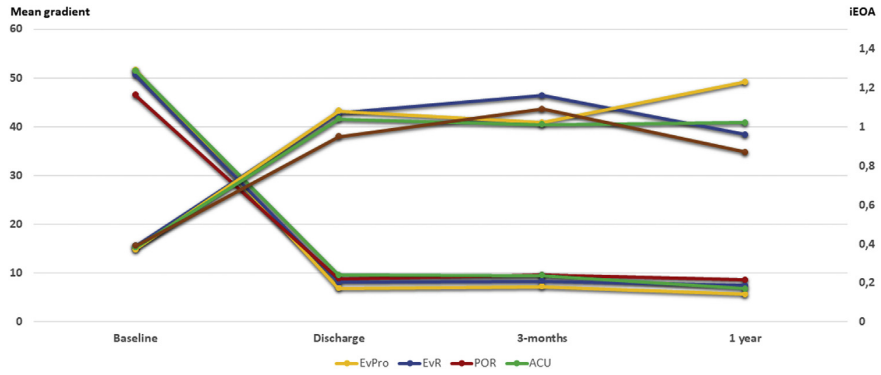
TABLE 4 Pre-Discharge Outcomes and 1-Year Follow-Up Data

	Overall (N = 859)	EvR (n = 397)	EvPRO (n = 84)	NEO (n = 201)	POR (n = 177)	p Value
Pre-discharge outcomes						
Mean AV gradient, mm Hg	8.5 ± 0.15 (8.2–8.8)	8.1 ± 0.2 (7.7–8.5)	6.9 ± 0.3 (6.3–7.6)	9.6 ± 0.3 (8.9–10.2)	8.9 ± 0.3 (8.2–9.6)	**<0.001**
Maximum AV gradient, mm Hg	15.1 ± 0.3	14.7 ± 0.4	14.1 ± 0.8	15.9 ± 0.7	16.0 ± 0.9	0.196
iEOA	1.04 ± 0.02	1.07 ± 0.03	1.08 ± 0.04	1.04 ± 0.05	0.95 ± 0.03	0.058
Moderate PPM	129 (29.0)	50 (24.5)	9 (20.5)	34 (32.7)	36 (38.7)	**0.039**
Severe PPM	42 (9.4)	17 (8.3)	1 (2.2)	11 (10.6)	13 (14.0)	0.134
New permanent PM	132 (15.6)	70 (18.1)	11 (13.3)	25 (12.6)	26 (14.7)	0.330
More than mild PVL	102 (11.9)	47 (11.8)	3 (3.6)	18 (9.0)	34 (19.2)	**0.001**
More than moderate PVL	14 (1.6)	5 (1.3)	0 (0.0)	6 (3.0)	3 (1.7)	0.285
BARC major bleeding	38 (5.2)	23 (7.4)	2 (4.1)	6 (3.1)	7 (4.0)	0.161
1-yr follow-up data						
Follow-up, days	343 (80–478)	283.5 (66–468)	104 (42–244)	364 (128–516)	372 (170–541)	**<0.001**
All-cause death	71 (11.1)	29 (10)	6 (9.5)	18 (11.7)	18 (13.6)	0.705
MI	5 (0.9)	2 (0.7)	0 (0.0)	1 (0.8)	2 (1.9)	0.659
TIA/stroke	21 (3.9)	15 (5.2)	3 (4.3)	2 (1.9)	1 (1.3)	0.342
Acute kidney injury	18 (4.8)	9 (4.1)	3 (7.1)	4 (7.3)	2 (3.3)	0.532
Hospitalization for HF	29 (5.5)	11 (3.8)	4 (6.2)	8 (7.7)	6 (7.9)	0.257
NYHA functional class III or IV	31 (3.6)	13 (3.3)	2 (2.4)	9 (4.5)	7 (4.0)	0.804

Values are mean ± SD (95% confidence interval), mean ± SD, n (%), or median (interquartile range). The values in **bold** represent statistical significant differences between groups.
BARC = Bleeding Academic Research Consortium; HF = heart failure; PPM = prosthesis patient mismatch; PVL = paravalvular leak; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

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FIGURE 1 **Indexed Effective Orifice Area and Mean Gradient From Baseline to 1 Year**



ACU = Acurate; EvPRO = Evolut PRO; EvR = Evolut R; iEOA = indexed effective orifice area; POR = Portico.

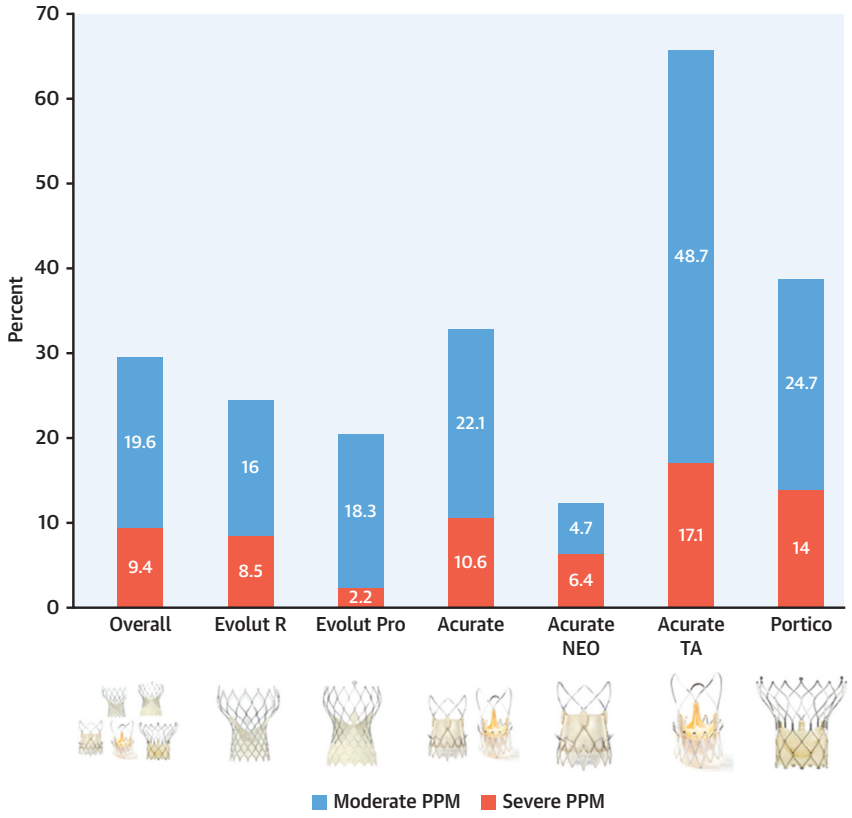
small aortic annuli. We decided to focus our attention on this specific subgroup, considering that patients with small aortic annuli showed the highest benefit in terms of valve forward hemodynamic and PPM in those studies comparing outcomes after TAVR and SAVR, especially in case of SEV implantation. The main findings can be summarized as follows. 1) Currently available SEVs showed excellent acute and mid-term clinical results, with a low incidence of adverse events and with no differences among groups. 2) The use of SEVs proved to be effective and showed good hemodynamic results in patients with small and very small annuli. An inverse correlation between annular perimeter and post-procedural gradients was found, but its clinical relevance is not clear, because the incidence of severe PPM was low in patients with both small (9.4%) and very small (13.7%) annuli. 3) The POR valve showed a significantly higher mean gradient, lower iEOA, and consequently higher rates of moderate (but not severe) PPM compared with the EvR and EvPRO valves, with intermediate valve performance shown by the ACU valve. 4) More than mild PVLs were rare with the EvPRO and significantly more common with the POR valve, with intermediate rates shown by the EvR and ACU valves. 5) No differences were noted in terms of need for PM implantation, despite a nonsignificant favorable trend in the ACU group.

This large retrospective registry of consecutive patients treated with SEVs showed low rates of in-hospital and 1-year adverse events in terms of procedural complications, death, and stroke or transient ischemic attack. These data, comparable with those observed in other contemporary TAVR studies (26), are consistent between groups, suggesting good procedural planning and implantation technique, irrespective of the selected device.

The main aim of the study was to evaluate the hemodynamic performance of currently available SEVs, with a focus on PPM. PPM was initially defined as an effective prosthesis area lower than that of the normal human valve (27). According to this definition, all patients undergoing aortic valve replacement should present some degree of PPM. In any case, no clinical implications may present until mismatch exceeds a critical threshold (28), especially in the absence of those factors (e.g., reduced LV ejection fraction, severe LV hypertrophy, significant mitral regurgitation, and low-flow, low-gradient aortic stenosis) that exacerbate the detrimental effect of PPM (29). Significant PPM is recognized as one of the most important predictors of valve dysfunction, persistence of LV hypertrophy, heart failure rehospitalization, and mortality among patients undergoing SAVR (15,30), and its impact on hemodynamic valve function and on clinical outcomes is progressively more recognized also among patients treated percutaneously (13,16,17,31). Post hoc analysis of the pivotal trials comparing surgical and transcatheter therapies (namely PARTNER [Placement of Aortic Transcatheter Valves] and the U.S. CoreValve High Risk Study) have shown a lower rate of PPM with TAVR than with SAVR (16,17). This is probably due to the thin struts and the lack of a sewing ring and because with TAVR larger valves are implanted compared with SAVR. Of note, the rate of PPM is higher after SAVR than after TAVR in cases of implantation of both stentless and stented surgical valves (32).

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CENTRAL ILLUSTRATION **Moderate and Severe Prosthesis-Patient Mismatch in Patients With Aortic Stenosis and Small Aortic Annuli Treated With Self-Expandable Valves**



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PPM = prosthesis-patient mismatch.

The improved hemodynamic performance of transcatheter prostheses, first noted with the SAPIEN XT BEV (Edwards Lifesciences, Irvine, California), seemed to be more pronounced in patients with small compared with large annuli (16). In contrast, the newer-generation SAPIEN 3 was designed with an outer skirt that decreased the incidence of PVL but increased the occurrence of PPM (10). Indeed, the recent PARTNER 3 trial, which compared TAVR of the SAPIEN 3 valve and SAVR in patients at low surgical risk, was the first study comparing transcatheter and surgical valve replacement showing higher gradients and a higher rate of PPM in patients treated percutaneously (10).

Conversely, SEVs proved to consistently reduce PPM incidence (compared with SAVR) across all annular size dimensions (17), with a greater reduction among patients with small annuli.

Consistently, when directly compared with each other in the CHOICE trial and in the extended CHOICE registry, CoreValve and EvR SEVs showed lower post-procedural mean gradient and larger iEOA compared with SAPIEN 3 BEVs, with a consequent lower rate of PPM (18). Similarly, in a propensity score-matched analysis involving 246 patients with aortic stenosis and small aortic annuli, the ACU SEV showed lower gradients and a lower rate of PPM compared with the SAPIEN 3 BEV (19). The aforementioned SEVs share some important structural features that could explain the lower transvalvular gradient and higher iEOA compared with BEVs, such as the supra-annular leaflet position. Also, the supra-annular leaflet

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position of these SEVs may avoid the additional constraints by native annulus combined to leaflets and stent, resulting in larger effective orifice area compared with intra-annular transcatheter valves.

Conversely, recently published data showed that the POR SEV had similar post-procedural gradients and PPM rate compared with the SAPIEN XT. Among currently available SEVs, the POR is the only one with intra-annular leaflets, which may explain this result and the findings in our study of slightly higher gradients and lower iEOA compared with the supra-annular SEVs (33).

The EvPRO was the most recent valve to be marketed, and there is still a paucity of data about its outcomes and hemodynamic performance (34,35), with no available data in patients with small annuli. This prosthesis is based on the EvR platform, with the implementation of an external porcine pericardial wrap for the reduction of PVL (35). This additional feature raised concerns regarding the risk for higher post-procedural gradients, which were not confirmed by preliminary studies (34).

The results of the present study are consistent with those in the published research, with good and comparable hemodynamic performance of the EvR, EvPRO, and ACU valves and slightly worse results achieved with the POR valve. As aforementioned, these findings could be at least partially explained by the POR's intra-annular leaflet design. This hypothesis is further corroborated by the post-procedural echocardiographic data observed in the ACU group in our study: we reported higher mean gradients, smaller iEOA, and consequently a higher rate of PPM in patients treated with the ACU TA device (which had intra-annular leaflets) compared with those treated with the ACU neo TF device (with a supra-annular design). Importantly, the ACU TA device is no longer available but was included in the present analysis because it was still available at the time of data collection.

Last, our findings regarding patients with very small annuli favorably compare with those observed after SAPIEN XT implantation in the OCEAN-TAVI registry; indeed, post-procedural mean gradients in patients with very small annuli ranged from 12.2 ± 4.8 mm Hg with the 23-mm SAPIEN XT to 15.4 ± 4.1 mm Hg with the 20-mm SAPIEN XT, compared with 10 ± 0.4 mm Hg observed in our studies, further suggesting the better forward hemodynamic function of SEVs compared with BEVs in patients with small annuli and at high risk for significant PPM (25).

With regard to PVL, the incidence of severe insufficiency was very low and consistent among groups. Conversely, the overall rate of more than mild regurgitation was significantly higher in the POR group than in the other SEV groups. This may be explained by the low radial force and absence of an external skirt of this device.

Of note, the prognostic role of residual PVL and of PPM is still debated; although both were identified as predictors of worse outcomes, the relative weight of each is unclear in patients with small annuli. However, the incidence of significant PVL seems to be lower in patients with small than in those with larger aortic annuli (18), which may provide a rationale to aggressively prevent PPM, thus making SEVs a good choice in this specific setting.

Finally, the permanent PM implantation rate seemed to be reasonable and with a nonsignificant trend in favor of the ACU. These findings are consistent with those reported in a large series assessing the rates of PM implantation after TAVR with new-generation valves (36).

The recently published PARTNER 3 and Evolut Low Risk trials showed that TAVR is noninferior to SAVR also in patients with low surgical risk (9,10). These results should lead to a reduction of the threshold for TAVR and further highlight the importance of the choice of the right device for each patient. Our results shed light on the different hemodynamic performance provided by commercially available SEVs in patients with small aortic annuli, showing slightly worse performance of the POR compared with the other SEVs. However, considering the small (although significant) differences, it remains uncertain if current results in terms of different hemodynamic valve performance could have an impact on long-term prognosis. Large-scale randomized trials are necessary to confirm our findings, and long-term follow-up is warranted to assess the impact of PPM and PVL on patients with aortic stenosis and small aortic annuli treated with SEV.

STUDY LIMITATIONS. The first limitation is the nonrandomized and retrospective design of our study. Therefore, we cannot exclude some source of selection bias that in turn could have influenced our results, although we did not observe important baseline differences among SEV groups.

Second, a certain level of underreporting or missing echocardiographic and follow-up data could exist, even if most of the relevant events were prospectively reported by the investigators in the course of the clinical follow-up or derived from an ad hoc database. Furthermore, in the present analysis we did not assess the impact on outcomes of oversizing, or computed tomographic and procedural data, such as those regarding implantation depth and calcification distribution. Additional analyses of the TAVI-SMALL registry focusing on these topics are foreseen.

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Third, our study lacked dedicated core laboratory adjudication of echocardiographic outcomes. Moreover, Doppler velocity index was available only for a limited number of patients and therefore was not reported.

Fourth, although the ACU TA device is no longer commercially available and despite the aforementioned differences with the ACU neo TF valve, we included in the ACU cohort also those patients treated with the ACU TA valve, because it was still marketed at the time of data collection.

Fifth, the decision to focus our attention on patients with small aortic annuli, therefore not including all aortic annular sizes, could have reduced the power of our analysis and results interpretation. Hence, this study was not powered for clinical outcomes and does not allow any inferential speculation on important clinical events such as stroke and mortality.

Nevertheless, the present evaluation of commercially available SEVs in a real-world population of patients with aortic stenosis and small aortic annuli represents an important piece of evidence by confirming favorable outcomes of these devices in this setting.

CONCLUSIONS

In this multicenter retrospective registry, SEVs showed optimal clinical and echocardiographic results in patients with small aortic annuli, although supra-annular functioning devices (EvR, EvPRO, and ACU) seemed to slightly outperform the intra-annular functioning POR valve. The promising role of TAVR with SEVs for treatment of aortic stenosis in patients with small annuli and the impact of supra-annular versus intra-annular valve design must be confirmed in larger trials.

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PERSPECTIVES

WHAT IS KNOWN? Patients with small aortic annuli are common in clinical practice among patients with aortic stenosis. A post hoc analysis of pivotal trials that compared TAVR with surgery showed that transcatheter prostheses offered better hemodynamic results and a reduced risk for developing PPM, especially with SEV implantation.

WHAT IS NEW? This direct comparison among SEVs shows that these devices have good hemodynamic performance in patients with aortic stenosis and small annuli, with low post-procedural gradients, large orifice areas, and a low incidence of severe PPM. The EvR, EvPRO, and ACU seemed to slightly outperform the POR regarding hemodynamic function, while similar rates of severe PVL and need for PM implantation were reported.

WHAT IS NEXT? The possible role of SEVs as first-line therapy in patients with aortic stenosis and small annuli and the impact of supra-annular versus intra-annular valve design need to be confirmed in large-scale randomized trials.

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KEY WORDS self-expandable valves, small annuli, TAVR

APPENDIX For supplemental figures and tables, please see the online version of this paper.

Manuscript #20

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Letters

TO THE EDITOR

The Spotlight Is on Secondary Access for TAVR

Radial Versus Femoral Revisited

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The evolution of transcatheter aortic valve replacement since its introduction in 2002 has been astonishing. Classically, contralateral ancillary femoral artery (FA) access was used. More recently, the radial artery (RA) has been proposed for angiography and iliac crossover (1).

Khubber et al. (2) described an innovative approach, reporting their experience with ipsilateral FA secondary access. In a consecutive cohort of patients, 1,007 (83.4%) had contralateral secondary FA access, and 201 (16.6%) had ipsilateral access. The investigators hypothesized that ipsilateral FA access might improve patient comfort, facilitate bailout interventions by having access to the distal lumen, and avoid the need for an iliac crossover, which is switching from a routine technique to a bailout intervention.

The small sample size of the ipsilateral group precludes drawing definitive conclusions. However, it is reassuring to note that vascular complications are equally rare in both groups—10.7% with contralateral access and 8.4% with ipsilateral access—and bailout interventions were successfully performed (2).

The investigators acknowledge that RA access constitutes a viable alternative, although noting that the adoption of cerebral protection devices could be a limitation. Current protection devices use the right RA, leaving the left RA available for angiography and staged bailout peripheral interventions with dedicated equipment (3).

With decreasing rates of vascular complications, the advantage of FA access for peripheral interventions might be overshadowed by lower vascular complication rates and improved patient comfort with RA access (4). This debate revisits the discussion of arterial access in percutaneous coronary intervention (5). Prospective randomized trials are needed to address the pros and cons of each strategy.

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REPLY: The Spotlight Is on Secondary Access for TAVR

Radial Versus Femoral Revisited

We would like to thank Dr. Felix-Oliveira and colleagues for bringing up a very important alternative for contralateral access. The idea of using the radial artery as an alternative access site for crossover is appealing, and the initial data from a small number of patients (N = 46) showed no difference in major vascular and bleeding complications between the 2 techniques (1). As appropriately pointed out, the limitation of this approach is the need to use right radial access for the only currently Food and Drug Administration-approved embolic protection device.

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ORIGINAL STUDIES

Transcatheter aortic valve implantation (TAVI) in cardiogenic shock: TAVI-shock registry results

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Abstract

Objectives: Aim of this study is to evaluate safety, feasibility, and mid-term outcome of transcatheter aortic valve implantation (TAVI) in cardiogenic shock (CS).

Background: Balloon aortic valvuloplasty in patients with severe aortic valve stenosis (SAS) complicated by CS is indicated but associated with a grim prognosis. TAVI might be a more reasonable treatment option in this setting but data are scant.

Methods: From March 2008 to February 2019, 51 patients with severe aortic valvulopathy (native SAS or degenerated aortic bioprosthesis) and CS treated by TAVI in 11 European centers were included in this multicenter registry. Demographic, clinical, and procedural data were collected, as well as clinical and echocardiographic follow-up.

Results: The mean age of our study population was 75.8 ± 13, 49% were women, and mean Society of Thoracic Surgeons (STS) score was 19 ± 15%. Device success was achieved in 94.1%, with a 5% incidence of moderate/severe paravalvular leak. The 30-day events were mortality 11.8%, stroke 2.0%, vascular complications 5.9%, and acute kidney injury 34%. Valve Academic Research Consortium-2 early safety endpoint was reached in 35.3% of cases. At 1-year of follow-up, the mortality rate was 25.7% and the readmission for congestive heart failure was 8.6%.

Conclusions: TAVI seems to be a therapeutic option for patients with CS and SAS or degenerated aortic bioprosthesis in terms of both safety and efficacy at early and long-term follow-up.

KEYWORDS
aortic stenosis, aortic valve disease, cardiogenic shock, transcatheter aortic valve implantation

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1 | INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has a class I indication in symptomatic patients with severe aortic valve stenosis (SAS) deemed at prohibitive or high surgical risk.[1-3] Even though cardiogenic shock (CS) represents a high-risk surgical condition, it was an exclusion criterion in randomized controlled trials comparing TAVI to surgery.[3,4] Similarly, SAS was an exclusion criterion in the setting of studies focused on CS complicated acute coronary syndrome.[5-7] Accordingly, data on TAVI in CS setting are scant.

Balloon aortic valvuloplasty (BAV) in patients with SAS complicated by CS is indicated but associated with a grim prognosis in terms of morbidity and mortality.[8] For this reason, it is considered a palliation. On paper, TAVI might be a more reasonable treatment option in this setting, but data on CS patients, with SAS, treated by TAVI are limited to case reports and small series[9,10] and, more important, there are no guideline's recommendation. Another unexplored field is on TAVI in the setting of degenerated aortic bioprosthesis complicated by CS.[11-13] We aimed to investigate safety and feasibility at early and long-term follow-up of TAVI in patients with SAS/bioprosthesis dysfunction and CS.

2 | MATERIAL AND METHODS

2.1 | Study population and design

This is a retrospective multicenter registry (TAVI-SHOCK) including all urgent/emergent TAVI performed for severe aortic valvulopathy (native SAS or degenerated aortic bioprosthesis) during CS in 11 European centers. The inclusion criteria were an ongoing CS status at the time of TAVI including also patients in whom the clinical deterioration occurred after a plain balloon valvuloplasty. CS was defined as: (a) systolic blood pressure < 90 mmHg for >30 min or vasopressors required to achieve a blood pressure ≥ 90 mmHg; (b) pulmonary congestion or elevated left-ventricular filling pressures; (c) signs of impaired organ perfusion with at least one of the following criteria: (i) altered mental status; (ii) cold, clammy skin; (iii) oliguria (urine output <30 ml/hr); and (iv) increased serum-lactate. Patients receiving mechanical cardiac support (MCS) as bridge to TAVI were also included. The following patients were excluded from our study population: (a) elective TAVI patients in whom CS followed a procedural complication; (b) patients in CS receiving successful BAV, in which TAVI was staged after hemodynamic stabilization; and (c) elective TAVI patients receiving planned MCS during TAVI according to clinical judgment. Patients included in the registry provided written informed consent for the procedure and for anonymous processing of their data. Demographic, clinical, and procedural data were collected in a dedicated database, as well as clinical and echocardiographic follow-up at 30-day, 1-year, and longer whenever available.

2.2 | TAVI procedure

TAVI procedures were performed according to standard practice at each respective participating site. The decision to perform TAVI and the choices of approach and device used were made on the basis of multidisciplinary heart team assessment at each participating center. The decision-making process for valve sizing was thoroughly analyzed. It was based upon multislice computed tomography (MSCT) measurements following the manufacturer's guidelines, whenever a MSCT was available. In the other cases, a multiparametric evaluation by using other imaging modalities (ultrasound and X-rays) was pursued. Procedures and postprocedural management were performed in accordance with each site's routine protocol.

2.3 | Endpoints and definitions

Primary endpoints were device success, 30-day mortality, and early safety defined according to Valve Academic Research Consortium (VARC)-2 definitions.[14] Other secondary endpoints were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, bleeding, and recurrence of congestive heart failure within the first year. Complications were classified using VARC-2 criteria.

All data, including in-hospital complications and follow-up, were site reported according to the definitions within the dedicated dataset. In cases of missing, extreme, or inconsistent values, centers were contacted and asked to verify and modify records as appropriate.

2.4 | Statistical analysis

Continuous variables are summarized as mean ± *SD* or median (interquartile range) and categorical variables as absolute frequencies and percentages. Comparisons of continuous variables were performed using the *t* test or appropriate nonparametric test (the Wilcoxon test for paired samples and the Mann–Whitney *U* test for independent samples). Categorical variables were compared using the Chi-squared test. Repeated measures of continuous variables at different time points were compared by repeated-measures analysis of variance. All probability values were two-tailed, and a value of $p < .05$ was considered significant. Kaplan–Meier estimates were used to construct the survival curves on the basis of all available follow-up data for the time-to-event analyses. Statistical analysis was performed with SPSS Statistics 25.

3 | RESULTS

3.1 | Study population

From March 2008 to February 2019, 51 patients met the criteria to be included in the TAVI-SHOCK registry. The mean age of the study population was 76 ± 13, half (49%) of them were female, Society of

TABLE 1 Baseline characteristics

Variables	
Age, years	75.81 ± 12.93 (range 31–93) (51) median 79.54
Female sex	49.0% (26/51)
BSA, mq	1.76 ± 0.24 (47)
BMI, kg/mq	26.03 ± 6.36 (47)
CCS ≥ 1	12% (6/50)
History of syncope	14% (7/50)
DM	21.6% (11/51)
Hypertension	74.5% (38/51)
Smoke	24% (12/50)
Dyslipidemia	46% (23/50)
CAD	33.3% (17/51)
Single vessel	19.6% (10/51)
2 vessel	9.8% (5/51)
3 vessel	3.9% (2/51)
Previous MI	11.8% (6/51)
Previous PCI	19.6% (10/51)
Previous CHF	65.3% (32/49)
LVEF ≤ 35%	29.4% (15/51)
Previous CVA	5.9% (3/51)
CKD	64.7% (33/51)
1	21.6% (11/51)
2	7.8% (4/51)
3	19.6% (10/51)
4	5.9% (3/51)
5	9.8% (5/51)
Renal replacement therapy	3.9% (2/51)
COPD	17.6% (9/51)
Extracardiac arteriopathy	21.6% (11/51)
Previous cardiac surgery	31.4% (16/51)
Previous CABG	7.8% (4/51)
Previous BAV	13.7% (7/51)
Neurological dysfunction	3.9% (2/51)
Liver dysfunction	6.4% (3/47)
Porcelain aorta	8.0% (4/50)
Hostile thorax	5.9% (3/51)
Active cancer	0% (0/47)
AF	19.6% (10/51)
PPM	7.8% (4/51)
Mechanical ventilation	31.4% (16/51)
Cardiac resuscitation	15.7% (8/51)
Concomitant STEMI	2.0% (1/51)
Inotropic support	86.3% (44/51)
IABP	7.8% (4/51)
ECMO	3.9% (2/51)
Impella device	2.0% (1/51)
EuroSCORE II	27.89 ± 22.85 (49)
STS score	19.24 ± 15.03 (48)
Hb level, gr/dl	11.15 ± 1.96 (48)

Abbreviations: AF, atrial fibrillation; BAV, balloon aortic valvuloplasty; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCS, Canadian Class Society; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; ECMO, extra corporeal membrane oxygenator; Hb, hemoglobin; IABP, intra-aortic balloon pump; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPM, permanent pace-maker; STEMI, ST-elevation myocardial infarction; STS, society of thoracic surgeons.

Thoracic Surgeons (STS) Score was 19 ± 15%, and EuroSCORE II was 28 ± 23%. Baseline characteristics and hemodynamic parameters are listed in Table 1. Patients had a SAS in 26 cases (51%), mixed aortic stenosis/regurgitation in 12 (23.5%), and aortic bioprosthesis dysfunction in 13 (25.5%). Out of 51 patients, 10 (19.6%) had a mean aortic gradient <40 mmHg. Using the SCAI CS definition, 39 patients were in class C, 4 in class D, and 8 in class E. The majority of them were on vasopressors (86.3%), mechanical ventilation (31.4%), intra-aortic balloon pump (7.8%), extracorporeal membrane oxygenator (3.9%), or Impella assist device (Abiomed Inc., Danvers, MA) (2.0%). More details about patients with MCS are showed in Table 2. In nine cases, the patients had a STEMI or were resuscitated from a cardiac arrest.

3.2 | TAVI procedure and valve sizing

Patients were treated mostly in Cath Lab (86.3%), by transfemoral vascular access (88.2%) and under general anesthesia (54.9%). A TAVI combined percutaneous coronary intervention was performed in 15.7% of cases. Self-expandable transcatheter aortic valves, mostly CoreValve iterations, were used in 76.6%. MSCT (previously available) based sizing was done in 33 cases (64.7%). On the contrary, for patients without MSCT, sizing process included: transthoracic and/or transesophageal evaluation measurements (6 cases), aortic angiography before and after BAV (11 cases), and use of valve-in-valve aortic app in case of degenerated surgical bioprosthesis (3 cases).

Other procedural characteristics were detailed in Table 3.

3.3 | Procedural and 30-day outcome

Device success was achieved in 48/51 cases (94%). The mean transvalvular gradient was reduced from 45 ± 18 to 12 ± 6 mmHg, with an increase of the aortic valve area (AVA) from 0.7 ± 0.2 to 2 ± 0.8 cm^2. Three patients had a procedural failure: one patient presented with prevalent severe aortic regurgitation and had device embolization

TABLE 2 Details about patients with MCS

Pt#	Type of MCS	Age	Male sex	OTI	Same session PCI	Valve-in-valve	THV	Device success	30-Day mortality	In-hospital mortality	1-Year mortality
#2	ECMO	31	1	1	1	1	EDW	1	0	1	-
#4	IABP	81	1	1	0	0	MCV	1	1	1	-
#5	Impella	81	1	1	0	0	MCV	1	1	1	-
#6	IABP	79	0	0	1	0	Acu	1	0	0	0
#7	IABP	66	0	1	0	0	Acu	1	1	1	-
#21	IABP+ECMO	77	1	1	0	0	EDW	1	0	0	0

Abbreviations: Acu, acurate neo valve; ECMO, extracorporeal membrane oxygenator; EDW, Edwards valve; IABP, intra-aortic balloon pump; MCS, mechanical cardiac support; MCV, Medtronic CoreValve; OTI, orotracheal intubation; PCI, percutaneous coronary intervention; Pt, patient; THV, transcatheter heart valve.

TABLE 3 Procedural characteristics

Variables	
Same session PCI	15.7% (8/51)
Valve-in-valve	25.5% (13/51)
Hybrid/OR	13.7% (7/51)
General anesthesia	54.9% (28/51)
TEE monitoring	41.2% (21/51)
Transfemoral access	88.2% (45/51)
Transaxillary access	2.0% (1/51)
Transapical access	7.8% (4/51)
Transaortic access	2.0% (1/51)
Percutaneous access	84.3% (43/51)
Procedural length, min	107.42 ± 69.56 (26)
Exposure time, min	25.99 ± 20.59 (26)
Exposure dose, Gy/cmq	140.58 ± 110.32 (17)
Contrast dye amount	142.44 ± 99.83 (32)
Device type	
Balloon expandable (Edwards family)	23.5% (12/51)
CoreValve family	58.8% (30/51)
Acurate	13.7% (7/51)
Portico	4.1% (2/51)
Predilation	31.6% (12/38)
Postdilation	21.6% (11/44)

Abbreviations: OR, operating room; PCI, percutaneous coronary intervention; PVL, paravalvular leak; TEE, transesophageal echocardiography.

with intraprocedural death; another patient treated with a valve-in-valve (CoreValve 31 mm) developed a severe paravalvular leak (PVL) and in-hospital death; the last one had a prosthesis-patient mismatch after a valve-in-valve with a CoreValve Evolut R 23 mm in a Mitroflow 19 mm. In this case, the final mean gradient was 34 mmHg, without residual PVL, but the clinical status of patient improved significantly and he remained free from events at 3-year follow-up.

The 30-day mortality was 11.8% (6/51). Thirty-day mortality was lower (6.5%) in patients presenting with a baseline mean transvalvular aortic gradient >40 mmHg, rather than in those presenting with low flow low gradient AS or prevalent aortic regurgitation (20%). The 30-day mortality rate of the patients with C SCAI class was 7.7%, while for class D and E was 25%. Mean hospital stay was 15 ± 15 days (range 0–70 days). Thirty-day events are shown in Table 4 in overall population and according to the use of balloon-expandable versus self-expandable devices.

3.4 | Follow-up

One-year follow-up was available in all but one patient (97%). The mean length of follow-up was 15 ± 16 months (range 1–74 months). Survival curve is shown in Figure 1—the overall survival rate at 1 year was 74.3% (26/35); 91.4% of patients were in NYHA class I or II. The mortality was noncardiovascular in all but two patients. The rehospitalization due to heart failure was 8.6%. There were no stroke, myocardial infarction, or reintervention on aortic valve. The hemodynamic performance of the device was stable over time both for gradient and AVA (see Table S1 for details).

"Time-related valve safety" was 5.7%—in one case, there was an increase of the mean gradient to 30 mmHg following an endocarditis; in the second case, CoreValve Evolut 23 mm in a Mitroflow 21 mm, there was an increase in prosthesis gradient from 14 to 25 but the patients did not have readmission for heart failure.

4 | DISCUSSION

The main findings of this multicenter registry including patients with severe aortic valve disease and CS treated by TAVI are the following: (a) emergent TAVI by transfemoral access in patients in CS is feasible, with a device success rate of 94%; (b) The 30-day mortality is higher (12%) than that of elective patients but significantly lower than that predicted by surgical scores; (c) the event rate at long-term follow-up is low, confirming the value of TAVI also in the emergent clinical setting of CS.

It is well known that patients with severe aortic valve disease and CS have a poor prognosis with high morbidity and mortality (50–

TABLE 4 Thirty-day outcome in overall population and according to the use of balloon-expandable (BEV) versus self-expandable (SEV) valves

Variables	Overall	BEV (12/51)	SEV (39/51)
Device success	94.1% (48/51)	100% (12/12)	92.3% (36/39)
Conversion to surgery	0% (0/51)	-	-
Device embolization	2.0% (1/51)	0% (0/12)	2.6% (1/39)
TAVI-in-TAVI	0% (0/51)	-	-
PVL			
None/trivial	55.0% (22/40)	66.7% (8/12)	50% (14/28)
Mild	25.0% (10/40)	25.0% (3/12)	25% (7/28)
Moderate	15.0% (6/40)	8.3% (1/12)	17.9% (5/28)
Severe	5.0% (2/40)	0% (0/12)	7.2% (2/28)
Final gradient	9.89 ± 6.97 (31)	11.27 ± 8.53 (11)	9.13 ± 6.05 (20)
Procedural death	2.0% (1/51)	0% (0/12)	2.6% (1/39)
Intraprocedural AVB	0% (0/51)	-	-
VT/FV	5.9% (3/51)	8.3% (1/12)	5.1% (2/39)
Coronary flow impairment	3.9% (2/51)	8.3% (1/12)	2.6% (1/39)
Tamponade	2.0% (1/51)	0% (0/12)	2.6% (1/39)
CVA	2.0% (1/50)	0% (0/12)	2.6% (1/38)
MI	2.0% (1/50)	0% (0/12)	2.6% (1/38)
Vascular complication			
Minor	2.0% (1/50)	0% (0/12)	2.6% (1/38)
Major	3.9% (2/50)	16.7% (2/12)	0% (0/38)
Bleeding			
Minor	9.8% (5/50)	0% (0/12)	13.2% (5/38)
Major	3.9% (2/50)	8.3% (1/12)	2.6% (1/38)
Life threatening	0% (0/50)	0% (0/12)	0% (0/38)
Transfusion	24.0% (12/50)	16.7% (2/12)	26.3% (10/38)
AKI			
Stage 1	20.0% (10/50)	66.7% (8/12)	5.3% (2/38)
Stage 2	8.0% (4/50)	0% (0/12)	10.5% (4/38)
Stage 3	6.0% (3/50)	0% (0/12)	7.9% (3/38)
Sepsis	4.0% (2/50)	8.3% (1/12)	2.6% (1/38)
New PPM[a]	10.9% (5/46)	10.0% (1/10)	11.1% (4/36)
In-hospital death	13.7% (7/51)	8.3% (1/12)	15.4% (6/39)
30-day death	11.8% (6/51)	0% (0/12)	15.4% (6/39)
VARC-2 early safety	35.3% (18/51)	16.7% (2/12)	41% (16/39)

Abbreviations: AKI, acute kidney injury; AVB, atrio-ventricular block; BEV, balloon-expandable valve; CVA, cerebrovascular accident; MI, myocardial infarction; PPM, permanent pace-maker; SEV, self-expandable valve; TAVI, transcatheter aortic valve implantation; VARC, valve academic research consortium; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]New PPM is calculated as the amount of new PPM over the patient without a PPM, a baseline (n = 47) considering one missing data.

75%).[15,16] Critical hemodynamic status may increase the risk for surgical aortic valve replacement up to prohibitive (≈25% operative mortality).[17,18] Otherwise by guidelines, BAV is an option in severely decompensated AS, both as palliative treatment or as bridge to definite surgical or transcatheter intervention.[19] However, even after successful BAV, the mortality rate is high (up to 71%) because of the final suboptimal hemodynamic result, the risk of regurgitation, and the high rate of complications.[20-22] TAVI could be reasonable in these emergent and high-risk settings due the more stable and durable hemodynamic improvements when compared to BAV. Notwithstanding, very few reports are available on this field and mostly on the role of the Valve-in-Valve TAVI in patients with degenerated aortic bioprosthesis and CS.[11-13]

To the best of our knowledge, the current study is the largest European multicenter series reporting on safety and feasibility of TAVI in patients in CS (Table S2). Previous study like the STS/ACC

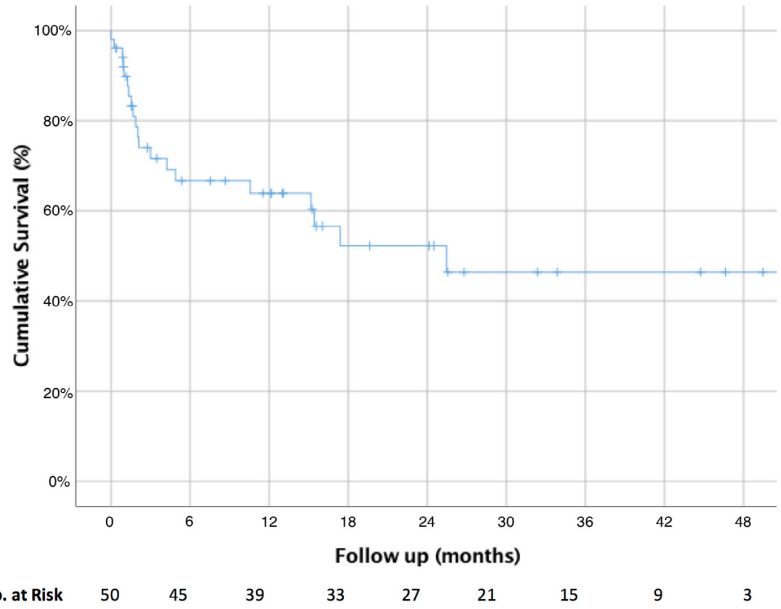


FIGURE 1 Estimated total survival by Kaplan–Meier of patients in CS receiving a TAVI. CS, cardiogenic shock; TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

TVT Registry sub-analysis reported on urgent and/or emergent TAVI, but the inclusion criteria were less restrictive including also ACS without hemodynamic instability.[23]

We found a similar device success rate compared to the TVT registry that actually was not significantly different from that reported in literature for elective case.[23,24] Interestingly, this rate of procedural success was reached despite a CT scan was not available in about one third of our patients because of the clinical conditions. Notwithstanding, our data suggest that, in high-volume centers and experienced operators, an emergent TAVI procedure can be conducted safely by the use of echocardiography and angiography.[25] The use of new generation devices, with improved design and smaller delivery sheaths have simplified the procedure and improved in-hospital outcomes in terms of both PVL and vascular complications.[26-28] In our series, with also a limited use of old-generation devices, mostly CoreValve iterations, the rate of severe PVL was only 5.0%. Related to the vascular access, it was transfemoral in 90% of the cases with a vascular complication rate as low as 5.9%. We cannot exclude that this finding was related also to the entry selection bias of excluding patients for emergent TAVI when the peripheral vasculature prevented an emergent transfemoral TAVI. Thus, differently from BAV series,[8,21,22] we found also a better 30-day mortality rate due to the more rapid stabilization of the acute clinical conditions of the patients that came along with the immediate hemodynamic improvement (lower gradient and lower aortic regurgitation) after TAVI. In BAV series, the reduction of the gradient is partial, almost never complete, as well as severity of aortic stenosis that remain (<1.0 cmq) in most of the cases.[8,19] The observed 30-day mortality in our series was similar to that reported in the TVT registry and significantly lower than that predicted by the STS score model.[23] Differently, Frerker et al. reported a three times higher 30-day (33%) mortality rate after emergent TAVI, with sepsis as prevalent cause of death.[24] Similarly, another multicenter study on 23 emergent TAVI performed in patients with CS, reported a high (24%) 30-day mortality without detailing specific reasons.[29] The most important complication we found was the acute kidney injury present in 34% of patients and cardiac death was the main cause of death.

Finally, we found that more than two third of the CS patients treated by successful TAVI who survive at 30 days survived during follow-up with a NYHA functional class I or II. The one-year mortality of our patients was numerically inferior to that reported in TVT Registry[23] (25.7 vs. 29.1%) and interestingly inferior to that reported in Partner I trial cohort B (30.7%)[30] that excluded CS. To note, the 1-mortality rate reported in case of BAV in CS patients, was over 70%.[8,19,22]

Accordingly, although the optimal treatment of patients with severe aortic valve disease complicated by CS is not completely defined yet, we propose a practical flow algorithm that may be reasonable in this setting (Figure 2).

5 | LIMITATIONS

Our study has several limitations. This is a retrospective multicenter registry that covers 10 years of patients' inclusion during which have had different transcatheter valve systems iterations, and changes in technicalities and standards of the TAVI procedures. All data are center-reported, and no Clinical Endpoint Committee was available for events adjudication. Moreover, we cannot exclude that some centers have included also patients in preshock (such as for example severe decompensation with pulmonary edema, NYHA IV) and not in overt shock conditions (hypotension <90 mmHg with impaired end-organ perfusion). This fact might explain our low 30-day mortality, more

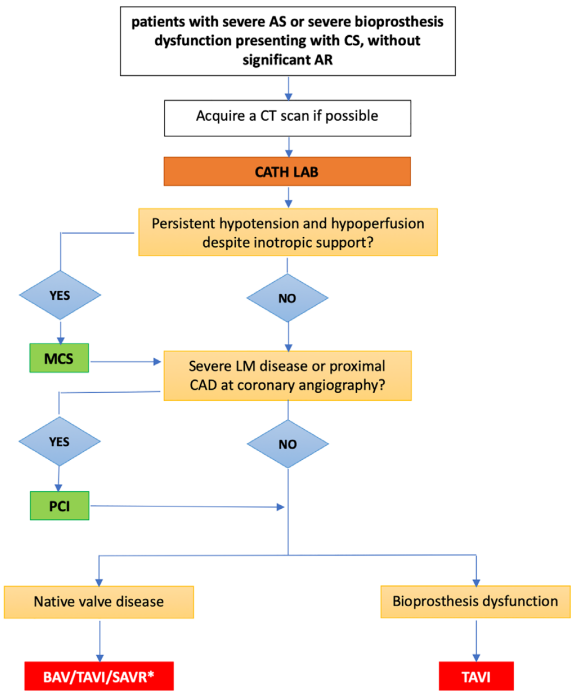


FIGURE 2 Suggested flow algorithm for the management of patients with SAS or severe bioprosthesis dysfunction presenting with CS, and without significant AR. *The choice between BAV, TAVI, or SAVR depends on multiple patient-related factors (age, comorbidities, frailty, and peripheral vascular disease) and hemodynamic status (LVEF and mean transaortic gradient). AR, aortic regurgitation; BAV, balloon aortic valvuloplasty; CS, cardiogenic shock; CT, computed tomography; LVEF, left-ventricular ejection fraction; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; SAS, severe aortic stenosis; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

similar to that reported in TVT registry[23] rather than by other studies.[24,29] To note, among the unmeasured variables, we should acknowledge hemodynamic data like cardiac output, biochemical parameters (such as lactate), type and number of vasopressors, duration of ischemia and/or shock before intervention, that may have had an impact on the observed outcome are missing. No control group is available. In addition, because of the low number of patients and events, we did not make any multivariate analysis to explore predictors of outcomes as well as further analysis on the role of baseline transvalvular gradient or different classification of shock[31] on outcome. The vast majority of our patients had a higher transvalvular gradient. Given that, we do not have the real number of total SAS patients presented in CS in study centers as well as details on the number of patients not treated at all. We cannot totally exclude some selection bias related to the exclusion of older patients with severe LV dilatation and contractile dysfunction and very low gradient. Notwithstanding, we cannot exclude that the rate of patients with SAS and higher gradients and CS are not differently distributed compared to the overall population of patients with SAS and severe LV dysfunction without CS.[32] To this regard, our patients experienced a reduction in LV volume and a significant increase in LVEF after TAVI, a finding more typical of SAS with afterload mismatch rather than significant myopathy. Finally, we cannot make inferences on predictors of intervention versus palliative care in these patients leaving out the future need to improve the patient's selection to avoid futility in this setting.

6 | CONCLUSION

In conclusion, a systematic approach with TAVI in CS still remains a matter of concern, also in terms of cost-effectiveness, and larger data are needed to support our evidences. In the meantime, urgent TAVI seems to be a reasonable therapeutic option only in very selected patients, in experienced hands and high-volume centers. In fact, compared to published series in elective conditions, TAVI in CS seems to have a similar procedural success rate, a still higher 30-day mortality (but lower than BAV alone in CS), and an otherwise good long-term outcome.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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2020 EAPCI Core Curriculum for Percutaneous Cardiovascular Interventions

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KEYWORDS

• miscellaneous

Abstract

The proposed 2020 Core Curriculum for Percutaneous Cardiovascular Interventions aims to provide an updated European consensus that defines the level of experience and knowledge in the field of percutaneous cardiovascular intervention (PCI). It promotes homogenous education and training programmes among countries, and is the cornerstone of the new EAPCI certification, designed to support the recognition of competencies at the European level and the free movement of certified specialists in the European Community. It is based on a thorough review of the ESC guidelines and of the EAPCI textbook on percutaneous interventional cardiovascular medicine. The structure of the current core curriculum evolved from previous EAPCI core curricula and from the "2013 core curriculum of the general cardiologist" to follow the current ESC recommendations for core curricula. In most subject areas, there was a wide - if not unanimous - consensus among the task force members on the training required for the interventional cardiologist of the future. The document recommends that acquisition of competence in interventional cardiology requires at least two years of postgraduate training, in addition to four years devoted to cardiology. The first part of the curriculum covers general aspects of training and is followed by a comprehensive description of the specific components in 54 chapters. Each of the chapters includes statements of the objectives, and is further subdivided into the required knowledge, skills, behaviours, and attitudes.

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Introduction

The present version of the Core Curriculum for Percutaneous Cardiovascular Interventions was organised and developed by the Education and Training Committee (ETC) of the European Association of Percutaneous Coronary Interventions (EAPCI), under the leadership of EAPCI Presidents Michael Haude and Andreas Baumbach.

In most countries, the prevalence of coronary artery disease (CAD), valvular heart disease (VHD), peripheral vascular disease (PVD) and heart failure (HF) is increasing. This relates both to the progressive ageing of the population and to a better identification of these diseases. To date, cardiovascular disease remains the leading cause of death worldwide. In Europe, ischaemic heart disease now accounts for almost 1.8 million annual deaths while VHD is becoming a pressing clinical issue[1,2].

The main areas of the percutaneous cardiovascular interventional field, as covered by the interventional cardiologist (IC), are percutaneous coronary interventions (PCI), transcatheter valvular interventions, percutaneous interventions for PVD (including those for ischaemic stroke), and percutaneous interventions for HF (including those for cardiogenic shock).

The broad use of these interventions is supported by overriding scientific evidence and has been associated with durable benefits for both individuals and populations[3-12]. In this context, ensuring quality of patient care, and clinical excellence in percutaneous cardiovascular interventions are of the utmost importance. The completion of a dedicated curriculum provides the IC with the knowledge, skills, behaviours and attitudes to act as an expert in the invasive physiological and anatomic assessment, diagnosis, and management of coronary and structural heart diseases as well as in the invasive management of HF and PVD.

The first and only "Curriculum and syllabus for Interventional Cardiology subspecialty training in Europe" was published in 2006 by di Mario et al on behalf of the "Working Group 10 of the ESC" (which later became the EAPCI) and a panel of experts in education including the chairmen of the national interventional societies, coordinated by the European Board for the Specialty of Cardiology (EBSC)[13]. This document was very ambitious and addressed the need for a certified, uniform, training programme, before cardiologists engage in interventional procedures that carry a potential risk. It was divided into several parts: rationale and aims of the curriculum, structure of the training programme, assessment methods, organisation of the training and, importantly, a syllabus-specific programme content with several chapters (basic science, pharmacology, imaging, indication for treatment and patient selection, procedural techniques, management of complications of percutaneous intervention and miscellaneous). Some procedures were not considered to be part of the core curriculum but rather an "optional" part of the training.

The 2006 visionary document set the European standards although these were not broadly adopted. The present approach intends to overcome the main limitations identified in the previous document, namely its endorsement and promotion by the interventional and general cardiology societies. The proposed core curriculum aims to support the educational requirements and to fill the gap of an updated European consensus that defines the level of competences in the field of percutaneous cardiovascular intervention. It promotes homogenous education and training programmes in interventional cardiology among countries, and is the cornerstone of the new EAPCI certification, designed to support the recognition of knowledge, skills, behaviours and attitudes of newly trained interventional cardiologists.

Considering the distinct realities among European and other countries and because numbers are not sufficient *per se* to describe the proficiency of an IC, the present document is not recommending minimal procedural volume for trainees or for training centres. It is rather providing guidance on the "achievements" and on the "levels of competence" which have to be acquired by the trainees **(Table 1-Table 3)**. We also provide detailed information on how a training centre will have to be organised, including the

Table 1. Summary of the general aspects of training in interventional cardiology.

Area of training	General aspects of training
Continuous medical education	Structured learning under supervision, including explicit learning and implicit learning.
Supervision and mentoring	Acute and elective cases with direct supervision, progressing from second, to first and ultimately independent operator status.
Research	Participation in clinical/translational research to enhance critical appraisal of evidence.
Evaluation	Clearly defined for each individual, with regular review/ appraisal of their progress and formal assessment.
Out-patient care	Preprocedural and post-procedural assessment.
Acute coronary syndrome, STEMI	Appropriate mix of in-patient/emergency and out-patient/ elective care, including patients with "acute coronary syndrome" and "out-of-hospital cardiac arrest".
Percutaneous coronary interventions	Experience with different arterial accesses and exposure to several complex techniques.
Structural interventions	Exposure to structural intervention is strongly recommended.
Heart Team	Regular participation in the Heart Team meetings.

Table 2. Description of levels translating competence into investigational or procedural skills (adapted from EPA).

Technique	Description of competence
Level I*	No performance, even with direct supervision. Observation is recommended
Level II*	Performance as second operator and/or with direct, proactive supervision
Level III	Performance as first operator with reactive supervision, i.e., on request and quickly available
Level IV	Performance as first operator without supervision. Possibility of *post hoc* supervision.
Level V**	Performance as first operator without supervision and ability to teach/supervise more junior colleagues

* Level I and II intervention skills may be acquired outside the primary training centre, as part of a cooperation programme. ** Level V intervention skills are not expected in all areas at the end of the two years of training in interventional cardiology.

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Table 3. Level of competence translating into interventional cardiology skills.

Technique	Description of competence	Level of competence
Peripheral venous access	Performance as first operator and teaching/supervision to more junior colleagues	V
Radial access	Performance as first operator and teaching/supervision to more junior colleagues	V
Femoral access <10 Fr	Performance as first operator and teaching/supervision to more junior colleagues	V
Femoral access ≥10 Fr	Performance with reactive supervision, i.e., on request and quickly available	III
Closure devices <9 Fr	Performance as first operator and teaching/supervision to more junior colleagues	V
Closure devices ≥9 Fr	Performance with reactive supervision, i.e., on request and quickly available	III
Pericardiocentesis	Performance as first operator without supervision	IV
Right and left haemodynamic assessment	Performance as first operator and teaching/supervision to more junior colleagues	V
Coronary angiography	Performance as first operator and teaching/supervision to more junior colleagues	V
Ventricular angiography	Performance as first operator and teaching/supervision to more junior colleagues	V
Peripheral angiography	Performance with reactive supervision, i.e., on request and quickly available	III
Cerebral angiography	No performance, even with direct supervision. Observation is recommended	I
PCI in simple lesions	Performance as first operator without supervision	IV
PCI in STEMI	Performance as first operator without supervision	IV
PCI in NSTE-ACS	Performance as first operator without supervision	IV
PCI in multivessel disease	Performance as first operator without supervision	IV
PCI in bypass grafts	Performance as first operator without supervision	IV
PCI in bifurcation lesions	Performance as first operator without supervision	IV
PCI in LM	Performance as first operator without supervision	IV
PCI in CTO	Performance as second operator and/or with direct, proactive supervision	II
PCI with rotablator	Performance as second operator and/or with direct, proactive supervision	II
Invasive physiology (FFR, iFR, RFR and others)	Performance as first operator without supervision	IV
OCT/OFDI	Supervision at a distance and/or post hoc	IV
IVUS	Supervision at a distance and/or post hoc	IV
Endomyocardial biopsy	No performance, even with direct supervision. Observation is recommended	I
Use of percutaneous mechanical haemodynamic support	Performance with reactive supervision, i.e., on request and quickly available	III
Balloon aortic valvuloplasty	Performance as second operator and/or with direct, proactive supervision	II
TAVI	Performance as second operator and/or with direct, proactive supervision	II
Balloon mitral valvuloplasty	Performance as second operator and/or with direct, proactive supervision	II
Transcatheter mitral valve repair	No performance, even with direct supervision. Observation is recommended	I
Transcatheter mitral valve implantation	No performance, even with direct supervision. Observation is recommended	I
Transcoronary ablation of septal hypertrophy	No performance, even with direct supervision. Observation is recommended	I
Transcatheter pulmonary valve interventions	No performance, even with direct supervision. Observation is recommended	I
Left atrial appendage occlusion	Performance as second operator and/or with direct, proactive supervision	II
Atrial septal defect closure or patent foramen ovale closure	Performance as second operator and/or with direct, proactive supervision	II
Closure of ventricular septal defect	No performance, even with direct supervision. Observation is recommended	I
Percutaneous treatment of paravalvular leaks	No performance, even with direct supervision. Observation is recommended	I
Transcatheter myocardial stem cell therapy	No performance, even with direct supervision. Observation is recommended	I
Cardiac catheterisation in "grown-up congenital heart" patients	Performance as second operator and/or with direct, proactive supervision	II
Supra-aortic interventions including acute ischaemic stroke treatment	No performance, even with direct supervision. Observation is recommended	I
Aortic disease interventions (thoracic endovascular repair of aorta/ endovascular repair of aortic aneurysm)	No performance, even with direct supervision. Observation is recommended	I
Infra-aortic arterial disease interventions	No performance, even with direct supervision. Observation is recommended	I
Renovascular interventions for arterial hypertension	No performance, even with direct supervision. Observation is recommended	I
Transseptal puncture	Performance as second operator and/or with direct, proactive supervision	II
Interpretation of multislice CT for TAVI	Performance as second operator and/or with direct, proactive supervision	II
Interpretation of transoesophageal echocardiography for mitral procedure	Performance as second operator and/or with direct, proactive supervision	II
Percutaneous direct treatment for acute pulmonary embolism	No performance, even with direct supervision. Observation is recommended	I
Balloon pulmonary angioplasty for "chronic thromboembolic pulmonary hypertension"	No performance, even with direct supervision. Observation is recommended	I

need to involve at least two ICs with more than five years' experience dedicated to the percutaneous cardiovascular interventional field **(Table 4)**.

The EAPCI has designed a new two-part certification process: part A (theoretical) and part B (practical). Part A is a multiple choice question (MCQ) exam held twice a year, based on the present core curriculum, as well as the EAPCI Textbook of Interventional Cardiology, the ESC General Cardiology Core Curriculum and the content of the Fellows Course of the EAPCI. The exam was successfully launched at EuroPCR 2018 in Paris. Part B, which

Table 4. Characteristics and requirements of training centres.

Basic characteristics (mandatory)	– Number of trainees should not exceed number of trainers – Catheterisation laboratory conferences, at least monthly – Regular electronic database, audited by the national interventional association/working group – Research programme – Performance measures at least annually – Quality programme – Radiation safety programme – Compliance with local standards according to national regulation bodies, including minimal procedural volumes
Standard centre	– PCI including complex procedures (mandatory) – Intracoronary imaging (IVUS and/or OCT, others) and invasive physiological assessment (FFR, iFR, RFR and others) (mandatory) – CTO programme (recommended) – Rotational atherectomy (recommended) – Percutaneous mechanical circulatory support devices (encouraged) – TAVI (encouraged)
Advanced centre	– PCI including complex procedures (mandatory) – Intracoronary imaging (IVUS and/or OCT, others) and invasive physiological assessment (FFR, iFR, RFR and others) (mandatory) – CTO programme (mandatory) – Rotational atherectomy and lithotripsy (mandatory) – Percutaneous mechanical circulatory support device programme (recommended) – TAVI (mandatory) – Transseptal procedures (mandatory) – Other structural procedures (recommended)

is currently under final development, is based on the recognition of acquisition of the competencies listed in **Table 4** of the present document. To prevent duplication, and simplify the process, it will preferably be conducted through a very strong interaction with national certification programmes when such programmes exist (i.e., mutual recognition process) and/or a direct interaction with training centres. The model of the present EAPCI certification, in which full certification requires acquiring the two parts, is very similar to those developed by the other subspecialty associations of the European Society of Cardiology (ESC).

The EAPCI ETC Committee launched the project under the auspices of Professors Michael Haude and Andreas Baumbach. A total of 10 groups, consisting of two to three interventional cardiologists each, developed, circulated and improved the document under the direction of the successive Chair and Co-Chair of the ETC, Professors Dariusz Dudek and Eric Van Belle and Doctor Rui Campante Teles. The document was revised by the Chair and Co-Chair of the ETC, Professor Eric Van Belle and Doctor Rui Campante Teles, as well as the current EAPCI President, Professor Andreas Baumbach, and President Elect, Professor Dariusz Dudek.

The 2020 Core Curriculum underwent a thorough review process based on the template of the review of the ESC guidelines and of the EAPCI textbook on percutaneous interventional cardiovascular medicine. The document does not include minimum or optimal numbers of procedures to be undertaken, and does not address periodic evaluation or revalidation. It defines the clinical, patient-oriented, training of the IC. The structure of the current core curriculum has been drastically modified as compared to the previous version and has evolved from the "2013 Core Curriculum of the general cardiologist" to follow the current ESC recommendations for core curriculums. In most subject areas, there was a wide if not unanimous consensus among the task force members on the training required for the IC of the future. The document recommends that acquisition of competence requires at least two years of training in interventional cardiology, in addition to four years devoted to cardiology.

The first part of the curriculum covers general aspects of training and is followed by a comprehensive description of the specific components in 54 chapters. Each of the chapters includes statements of the objectives, and is further subdivided into the required knowledge, skills, behaviours, and attitudes.

The core curriculum for the interventional cardiologist

THE CLINICAL FIELD OF INTERVENTIONAL CARDIOLOGY

The clinical specialty of interventional cardiology aims to deliver expert interventional care for patients presenting with disorders of the heart, the systemic, and the pulmonary circulations. This core curriculum provides the standards for training in interventional cardiology, as well as a template for the maintenance of competence for qualified cardiologists.

The IC is the subspecialist who performs percutaneous interventional cardiovascular procedures. He/she is primarily a medical specialist with a thorough basic training in internal medicine who has completed an approved cardiology fellowship programme incorporating the knowledge demanded by the ESC Core Curriculum for the general cardiologist[14]. Interventional cardiologists perform general cardiac investigation and management of patients with suspected or established cardiovascular disease using non-invasive methods and are involved in the comprehensive management of the patient and treatment of the underlying disease, not only focused on procedural considerations. They have the ability to consider and apply interventional techniques to the global care of patients. They are team workers who interact closely with other cardiologists and other medical specialties, nurses, paramedics and other healthcare professionals.

In order to master the invasive techniques, there are skills in several general fields which are important for the IC and require special differentiation that complement basic general cardiology skills. It is recommended that an operator be able to interpret the most advanced cardiology imaging techniques required for periprocedural assessment, especially echocardiography, computed tomography and endovascular studies. A high level of cardiac intensive care experience is requested, with a special emphasis on acute heart failure and arrhythmia management[14].

As simulators have shown benefit in the progress of novice operators, they are progressively being incorporated into training programmes and courses[15,16]. While the exact role of these simulators in most advanced technical skills still needs to be clarified, with their progressive sophistication their use in the training of ICs will continue to increase.

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A key role of the IC is to perform emergency procedures for reperfusion of acute myocardial infarction in 24/7 PCI-capable centres. Regarding PCI, any operator is expected to be fully competent regarding the entire spectrum of patient evaluation, information, techniques and follow-up, including all advanced techniques such as imaging, physiology, adverse clinical presentations and anatomies and adverse lesion scenarios, incorporating calcification, degenerated grafts, simple chronic total occlusions (CTOs) and bifurcations in general. An IC is expected to be fully skilled in the management of any procedural complications.

Concerning the increasing importance of transcatheter aortic valve implantation (TAVI), any operator should be prepared to conduct complete preprocedural evaluation of TAVI candidates and collaborate with a valvular Heart Team to select the most suitable treatment.

Concomitantly, these fields are continuously expanding and, in certain cases, a very specific training to master a procedure or technique is required. Help from a proctor is recognised as advantageous or an appropriate referral to a more skilled centre might be advisable, especially in certain areas that, depending on the individual and the centre, require a particular expertise, namely complex coronary interventions, stroke, PVD, grown-up congenital heart (GUCH) disease, mitral or tricuspid valve disease, left atrial appendage occlusion (LAAO), etc.

The spectrum of expertise is broad and, in addition to the procedures, includes a comprehensive patient risk assessment that is fundamental for patient information and integrates medical decision making. A multidisciplinary management strategy is essential including a heart failure specialist, imaging specialist, surgeons, geriatrician, anaesthetist and cardiac rhythm specialists[17].

Because these interventions are applied to a very large population of patients, their economic impact has become significant. The IC must be conscious of this economic burden and responsible for the appropriate utilisation of devices and therapies.

The process for medical decision making and patient information is guided by the "four principles" approach to healthcare ethics - autonomy, beneficence, non-maleficence and justice. The IC represents the patient's best interest and therefore the medical decision process must be independent and be performed according to the best available evidence, in order to deliver optimal patient-centred care. Moreover, because this is a very technological and continuously demanding evolving medical area, it requires lifelong learning and continuous updating of his/her knowledge. The IC is expected to be engaged in structured clinical investigation programmes and to collaborate actively in patient follow-up.

GENERAL ASPECTS OF TRAINING IN THE SPECIALTY

Candidates for interventional training should be physicians licensed to practise in the country of training. The trainee must have the necessary linguistic ability to communicate with patients and colleagues in the country of training and later in the country of practice. The trainee should have completed a minimum of four years of full-time training in general cardiology.

The recommended minimum duration of dedicated subspeciality training should be two years of full-time and exclusive training in interventional cardiology.

To gain sufficient experience, the trainee should gain exposure to all aspects of interventional cardiology, with an appropriate mix of in-patient/out-patient and emergency/elective care, including the elements described below and summarised in **Table 1**:

- Participation in the clinical management of in-patients, with an emphasis on patients presenting acutely to the coronary care unit (CCU) and acute medical unit (AMU) with acute coronary syndromes (ACS).
- Regular on-call commitment providing a primary PCI service for patients presenting with ST-elevation myocardial infarction (STEMI) and/or out-of-hospital cardiac arrest (OHCA).
- Regular attendance and/or coordination of Heart Team meetings.
- Bedside patient care, including preprocedural and post-procedural assessment.
- Structured learning, under the direct supervision of educational supervisors/nominated trainers, which may include (a minimum of two hours/day is suggested):
  - explicit learning: journal club, postgraduate teaching, exercises in evidence-based medicine, discussion of guidelines for clinical practice, national/international symposia/congress attendance.
  - implicit learning: ward rounds, case-based discussions, supervised acquisition of diagnostic and interventional skills.
- Interventional training should include a mix of acute and elective cases with direct supervision, progressing from second, to first and ultimately independent operator status by the end of the training period.
- Interventional training should guarantee experience with arterial access (femoral and radial), and with the most frequent of the complex techniques, including bifurcation strategies, treatment of calcified vessels, intravascular imaging, and functional assessment of coronary stenoses (FFR, iFR, etc.).
- Exposure to chronic total occlusion (CTO) strategies, with both antegrade and retrograde approach, atherectomy techniques including rotablation, haemodynamic support/mechanical circulatory support, is required.
- Exposure to structural intervention including TAVI, mitral and tricuspid valve treatment, atrial septal defect/patent foramen ovale/left atrial appendage closure, and paravalvular leak/ventricular septal defect closure is strongly recommended.
- The training programme should be clearly defined for each individual, with regular review/appraisal of their progress and formal assessment of their knowledge and procedural competencies.
- Participation in clinical/translational research in interventional cardiology is recommended to enhance critical appraisal of evidence.

Learning objectives should be clearly defined and are preferred to recommendations based solely on the time spent in a particular department or on the number of procedures performed. The objectives should include knowledge, and specific and generic skills

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including communication and appropriate behaviours, competencies and attitudes that will be further reinforced during ongoing training.

LEARNING OBJECTIVES

These are specific aims which demonstrate skills acquired by the trainee at the end of the course. They are based on the trainee's capabilities in certain tasks. Specific objectives are classified according to knowledge, skills, and behaviours and attitudes.

– Knowledge: describes requirements for trainees. The subject matter is defined by the EAPCI Core Curriculum chapters. This knowledge includes pathology of diseases as the rational basis for long-term learning.
– Skills: a practical application of knowledge acquired from experience and training to solve practical problems, make clinical decisions and perform specific procedures.
– Behaviours and attitudes: refer to those attitudes and behaviours that lead to optimal clinical performance.

CATEGORIES AND LEVELS OF COMPETENCE

First-hand exposure and practical experience are crucial in the learning of techniques. However, the number of procedures performed by trainees is not considered an exclusive measure of performance. The authors acknowledge the variability of the learning curve among individuals and the impact of the training centre volumes on the learning process. Thus, this document focuses on the acquisition of competencies rather than on procedural volume.

This section describes the levels to translate competencies into investigational or procedural skills. Their ascending order is defined as follows and summarised in **Table 2**. It has been adapted from the description of Entrustable Professional Activities (EPA)[18]:

– Levels I and II. The trainee must have acquired experience in selecting an appropriate diagnosis or therapy and in interpreting results or choosing an appropriate treatment for a referred patient.
  – Level I does not require any procedural skills, yet participation in related procedures during training may be valuable.
  –Level II of competency indicates acquisition of some procedural skills as operator, usually as assistant/second operator, obtained in the primary or external training centres.
– Level III. The trainee must be able to interpret clinical data, recognise treatment indications, and perform the technique or procedure and manage related complications, as first operator, but still requires to work under the direct supervision of a senior IC operator.
– Level IV. The trainee must be independent in the ability to interpret clinical data, recognise treatment indications, perform the technique or procedure and manage related complications, as first operator without the direct supervision of a senior IC operator. *Post hoc* supervision including case review with more senior colleagues is possible.
– Level V. Same as level IV. In addition, it includes the ability to teach and supervise the technique or procedure to more junior colleagues.

Table 3 summarises the level of competence translating into interventional cardiology skills that the EAPCI considers desirable for a trainee in interventional cardiology to achieve at the end of his/her two years of training[19-24]. Although organisation of cardiac services and resources for training are not uniform across Europe and ESC member countries, the core curriculum aspires to an optimal, rather than a minimal standard. In countries or centres that are currently unable to deliver training in all aspects required, the core curriculum should be used as a benchmark to promote policies for improvement. Also, rotation of trainees between different centres may provide an adequate solution.

REQUIREMENTS FOR TRAINING INSTITUTIONS AND TRAINERS

REQUIREMENTS FOR TRAINING INSTITUTIONS

General aspects

We believe that training institution profile and performance are as important as trainers' profile and expertise in order to provide objective and quality interventional training. In order to comply with EAPCI standards, the institutions must be standardised using procedural volume reports and performance measures.

A training institution/centre for interventional cardiology should include a cardiac catheterisation laboratory with on-call 24-hour PCI availability and a dedicated cardiology unit, department or ward, in order to manage patients throughout hospitalisation. The trainee should be able to be educated to manage patients from their admission, through the invasive procedure, to discharge from the ward. Institutional workflow allowing the interventional cardiology programme attendees to follow the patient throughout their hospitalisation is mandatory.

The training centre should have an independent interventional cardiology unit, allowing the trainee to follow the patient from the beginning to the completion of interventional treatment. Units not integrated into a cardiology department (run as a service without dedicated beds) can exceptionally be considered if they demonstrate a well-developed structured co-operation with cardiology wards where the patients are admitted, allowing the interventional cardiology programme attendees to follow the patient throughout their hospitalisation.

Training centres should be encouraged to incorporate on-site interventional cardiology simulators or to provide simulation sessions during the IC training, especially during the early phases of training of the trainee and/or the techniques[15,16].

Training centres should have the following basic characteristics (summarised in **Table 4**):

1) Active clinical research programme and/or involvement in clinical trials is mandatory for both types of centre.
2) Number of trainees per institution should not exceed the number of faculty members/trainers.
3) Heart Team meetings, including participation by clinical cardiologists, interventional operators, and cardiothoracic surgeons should be planned regularly (i.e., weekly or bimonthly).

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4) Regular database - electronic database of diagnostic and interventional procedures regularly audited by the national interventional society is recommended to ensure centre quality.
5) Performance measures report of the institution (periodic, at least annual): in-hospital mortality in acute, elective PCI and diagnostic catheterisation.
6) Regular "quality assessment and quality improvement" (QA/QI) programme including radiation safety programme.

We further define two types of training centre: standard and advanced training centre **(Table 4)**.

– Standard centre: must have a (mandatory) programme of 24 hours a day availability of PCI on call for STEMI/NSTEMI patients and a working hours regular programme for all kinds of patients. Availability of IVUS and/or OCT and assessment of intracoronary pressure-based physiology indices such as FFR/iFR is mandatory. It is strongly recommended that these centres are involved in complex PCI, including left main and multivessel disease. Availability of left ventricular assist devices such as IABP/Impella® (Abiomed, Danvers, MA, USA) is desirable but not mandatory as well as a CTO programme, rotational atherectomy and similar procedures. Institutional coronary and structural Heart Teams are also encouraged, even if the centre does not perform TAVI.
– Advanced centres: these have similar requirements to standard centres and should have a structural heart programme including at least TAVI according to national regulation, transseptal procedures and a structured CTO programme. Other structural procedures (stroke, carotid, peripheral, GUCH, septal ablation, left atrial appendage occlusion, paravalvular leak closure, etc.) are recommended. The presence of a Heart Team is mandatory.
– A centre may develop other programmes for peripheral interventions (stroke, carotid stenting, aorta, peripheral limb), treatment of adult congenital heart disease, performance of septal ablation for hypertrophic cardiomyopathy, etc.

Procedural volumes and public metric reporting

It has been established that the procedural volumes of centres have a significant impact on the availability of training opportunities and on performance measures and intervention outcomes, but numbers are insufficient to define the quality of a centre and their ability to train interventional fellows. Public reporting of centre training programmes, procedural volumes and clinical outcomes is advisable to guide trainee choice of the training centre. While the present document does not make recommendations on specific procedural volumes, training centres should comply with local standards according to national regulation bodies, including minimal procedural volumes.

REQUIREMENTS FOR TRAINERS

General aspects and levels of competence

Trainers should be graded as trainers in standard institutions (standard trainers) and trainers in advanced institutions (advanced trainers). Trainers should be experts for levels of competence III, IV and V **(Table 2, Table 3)**. It is not required that every trainer be expert in those techniques for which a level of competence I or II **(Table 2, Table 3)** is required, provided trainees can rotate to train with an IC (in the same or different institution) with the necessary expertise.

Ideally, the number of trainers (full-time equivalent) should match or exceed the number of trainees. Delivery of the curriculum may be facilitated by a structure that includes a director of training (national/regional), a cath lab director (or supervisor), a training mentor (or educational mentor), and multiple clinical trainers (or clinical mentors).

The training mentor (or someone else involved in the organisation of training) should be responsible for organising the training programme in interventional cardiology, coordinating external rotations to referral centres, attendance at courses and congresses, and organising structured learning. It is necessary that both trainee and training mentors be subject to periodic assessment.

Number of trainers and their expertise

At least two trainers (supervisors) must be available, with more than five years' experience dedicated to interventional cardiology as their main clinical activity. These trainers should be members of the permanent staff and should be able to deliver the procedural skills associated with levels of competence III, IV and V in the learning objectives **(Table 2, Table 3)**.

In advanced centres, trainers should have experience of more than five years performing advanced heart interventions.

Trainers without personal expertise in these additional skills described in the learning objective (levels of competence I and II, **Table 2**, **Table 3**) should make them available to trainees through a cooperation programme with other trainers (or other institutions) who will deliver the formal training on these techniques. A similar five years of experience is required for the trainers delivering training on each one of those additional procedural skills.

The cath lab director must be responsible for the interventional unit and should ensure that the trainee fulfils his/her learning objectives. The training mentor must also ensure that the trainee attends the formal training courses and is involved in the research and educational activities of the department.

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Conflict of interest statement

A. Baumbach received institutional research support from Abbott Vascular, consultation and speaker fees from AstraZeneca, Sinomed, MicroPort, Abbott Vascular, Cardinal Health, KSH, and Medtronic. R. Estevez-Loureiro reports grants and personal fees from Abbott Vascular and personal fees from Boston Scientific, outside the submitted work. A. Geppert reports lecture fees from Medtronic, Abbott and Abiomed, consulting fees from Abbott and Abiomed, congress grants from Asahi and Terumo, outside the submitted work. J. Kefer reports proctorship and speaker fees from Medtronic and Abbott, and speaker fees from Servier. D. Milasinovic reports personal fees from Abbot, Biosensors, Terumo, AstraZeneca and Sanofi, outside the submitted work. D. Muir is a proctor and advisory board member for Abbott Vascular, and received proctor, advisory board and speaker fees from Edwards Lifesciences. A.S. Petronio received proctor and advisory board fees from Abbott Vascular, and received proctor, advisory board and speaker fees from Edwards Lifesciences. G. Pires-Morais received speaker fees from Abbott Vascular. S. Pyxaras received consultancy fees from Abiomed and Boston Scientific and proctor fees from Boston Scientific. R. Parma received speaker fees from Boston Scientific, Edwards Lifesciences and Medtronic. F. Saia reports personal fees from Abbott Vascular, Boston Scientific, Edwards, Medtronic, Biotronik, Amgen, AstraZeneca, Daiichi Sankyo, Bayer and Boehringer-Ingelheim, outside the submitted work. N. Van Mieghem reports advisor fees from PulseCath BV and Abiomed. S. Windecker reports grants from Abbott, Amgen, BMS, Bayer, Boston Scientific, Biotronik, Cardinal Health, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Johnson and Johnson, Medtronic, Quebert, Polares, Sanofi and Terumo, outside the submitted work. E. Van Belle reports personal fees from HeartFlow and Philips, outside the submitted work. The other authors have no conflicts of interest to declare.

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FASTTRACK CLINICAL RESEARCH

Long-term outcomes after transcatheter aortic valve implantation in failed bioprosthetic valves

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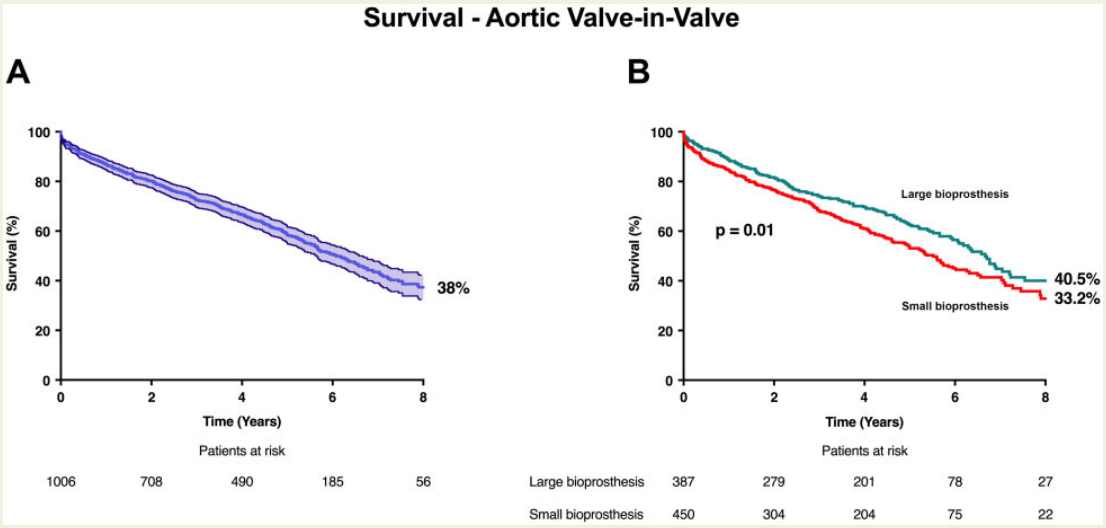
Aims Due to bioprosthetic valve degeneration, aortic valve-in-valve (ViV) procedures are increasingly performed. There are no data on long-term outcomes after aortic ViV. Our aim was to perform a large-scale assessment of long-term survival and reintervention after aortic ViV.

Methods and results A total of 1006 aortic ViV procedures performed more than 5 years ago [mean age 77.7 ± 9.7 years; 58.8% male; median STS-PROM score 7.3% (4.2–12.0)] were included in the analysis. Patients were treated with Medtronic self-expandable valves (CoreValve/Evolut, Medtronic Inc., Minneapolis, MN, USA) ($n = 523$, 52.0%), Edwards balloon-expandable valves (EBEV, SAPIEN/SAPIEN XT/SAPIEN 3, Edwards Lifesciences, Irvine, CA, USA) ($n = 435$, 43.2%), and other devices ($n = 48$, 4.8%). Survival was lower at 8 years in patients with small-failed bioprostheses [internal diameter (ID) ≤ 20 mm] compared with those with large-failed bioprostheses (ID > 20 mm) (33.2% vs. 40.5%, $P = 0.01$). Independent correlates for mortality included smaller-failed bioprosthetic valves [hazard ratio (HR) 1.07 (95% confidence interval (CI) 1.02–1.13)], age [HR 1.21 (95% CI 1.01–1.45)], and non-transfemoral access [HR 1.43 (95% CI 1.11–1.84)]. There were 40 reinterventions after ViV. Independent correlates for all-cause reintervention included pre-existing severe prosthesis–patient mismatch [subhazard ratio (SHR) 4.34 (95% CI 1.31–14.39)], device malposition [SHR 3.75 (95% CI 1.36–10.35)], EBEV [SHR 3.34 (95% CI 1.26–8.85)], and age [SHR 0.59 (95% CI 0.44–0.78)].

Conclusions The size of the original failed valve may influence long-term mortality, and the type of the transcatheter valve may influence the need for reintervention after aortic ViV.

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Graphical Abstract



Keywords TAVR • Aortic valve-in-valve • Reintervention • Severe prosthesis–patient mismatch • SAPIEN valve

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Introduction

An increase in the use of bioprosthetic tissue valves has been observed in the last decades.[1,2] Although bioprostheses offer the advantage of avoiding lifetime anticoagulation, their durability is limited.[3] A rapidly growing number of bioprostheses will thus require reintervention over time for the treatment of structural valve degeneration (SVD). Transcatheter aortic valve-in-valve (ViV) implantation in failed bioprosthetic valves is an effective therapy with a large worldwide experience.[4–6] Nevertheless, aortic ViV is associated with several adverse events including residual stenosis and coronary obstruction.[7–11] Long-term transcatheter aortic ViV outcome data, beyond 3 years of follow-up, are limited. The objective of this study was to perform a large-scale comprehensive assessment of long-term survival and reintervention outcomes after transcatheter aortic ViV, with the goal of identifying independent correlates for these endpoints following the procedure.

Methods

Data collection and registry

The VIVID Registry is an international multicentre collaboration including over 180 centres from the Americas, Europe, Middle East, Asia, Africa and Oceania.[4] Patient information is collected in a secure online form. All patients gave informed consent to a ViV procedure and were included in the VIVID Registry after local institutional review board approval. The study was conducted in accordance to the Declaration of Helsinki. Inconsistencies and missing information in the dataset were resolved with local investigators after direct contact from Registry personnel.

The current analysis was a retrospective cross-sectional evaluation and was designed after several investigator-directed meetings [Paris (May 2018), San Diego (September 2018), and Paris (May 2019)]. Between July and December 2019, we contacted all centres included in the VIVID Registry that performed ViV cases before 31 December 2014 (i.e. 5 years before 2019) requesting recent clinical follow-up and echocardiographic data using a dedicated case report form.

Definitions

The primary endpoint for this analysis was patient survival, and the main secondary endpoint was all-cause reintervention. All-cause reintervention was defined as all-cause repeat transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) after the index ViV procedure, regardless of the aetiology. Structural reintervention included only patients who underwent redo TAVR or SAVR for degeneration of the implanted tissue valve after excluding cases with either endocarditis and/or thrombosis. The mechanism for bioprosthetic valve failure was classified according to criteria from the American Society of Echocardiography.[12] Cases with at least a moderate degree of both stenosis and regurgitation were included in the mixed category. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate ≤60 mL/min/1.73 m^2. Edwards balloon-expandable valves (EBEV, $n = 435$) in the current analysis included the Cribier-Edwards, SAPIEN, SAPIEN XT and the SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA). Medtronic self-expandable valves (MSEV, $n = 523$) included the CoreValve and the Evolut valve (Medtronic Inc., Minneapolis, MN, USA). Other valves ($n = 48$) included Portico ($n = 19$; Abbott Vascular, Menlo

Park, CA, USA), Engager ($n = 10$; Medtronic Inc.), Symetis Acurate ($n = 9$; Boston Scientific, Marlborough, MA, USA), JenaValve ($n = 7$; JenaValve Technology Inc., Munich, Germany), Melody ($n = 2$; Medtronic Inc.), and Lotus ($n = 1$; Boston Scientific). Major clinical endpoints were assessed according to the Valve Academic Research Consortium II (VARC II) criteria.[13] Body surface area (BSA) was calculated according to the Mosteller formula.[14] Pre-existing severe prosthesis–patient mismatch (PPM) of the bioprosthetic valve was also defined according to VARC II criteria, namely: indexed effective orifice area (EOA) ≤0.65 cm^2/m^2 for non-obese patients (body mass index < 30 kg/m^2) and indexed EOA ≤0.60 cm^2/m^2 for obese patients (body mass index ≥ 30 kg/m^2). The predicted EOA of bioprosthetic valves was derived from the normal reference values for different models and sizes previously published.[15] True internal diameter (ID) for each bioprosthetic valve, when available, was derived from previous publications.[16] Malposition was operator-reported and defined as inadequate final position of the transcatheter heart valve (THV) for any cause. Small bioprosthetic valves were defined as true ID ≤20 mm and, conversely, large bioprosthetic valves were defined as true ID >20 mm.[17] Structural valve degeneration was defined according to current standardized definitions.[18,19]

Statistical analysis

Results are presented as mean ± standard deviation for continuous variables with normal distribution, median [interquartile range (IQR), 25th to 75th percentiles] for continuous variables without normal distribution, and number (percentage) for categorical data. Student's *t*-test was used to compare normally distributed continuous variables between two groups. When more groups were involved, one-way analysis of variance (ANOVA) was used. Tukey's honest significant difference test was used for *post hoc* evaluation of ANOVA results, as appropriate. The Mann–Whitney *U* test (two groups) and the Kruskal–Wallis test (three groups) were used for non-normally distributed variables. The χ^2 and Fisher's exact tests were used to compare categorical variables as appropriate. Time-to-event curves utilized the Kaplan–Meier method, and results were compared with the log-rank statistic. Time-to-event curves were truncated at the last time-point with ≥5% of patients still at risk. Cox regression was utilized to establish independent correlates for long-term survival. A Fine and Gray[20] cause-specific subdistribution hazards model was used for reintervention analysis, given the competing risk of mortality. The following parameters were evaluated in the univariable analyses: age, gender, New York Heart Association (NYHA) functional class IV, stented bioprosthetic valve (vs. stentless), pre-existing severe PPM, stenosis as the mechanism of bioprosthetic valve failure, diabetes mellitus (DM), permanent pacemaker at baseline, peripheral vascular disease (PVD), CKD, history of stroke, EBEV (vs. MSEV), transfemoral access, general anaesthesia, malposition, height, weight, BSA, BMI, age, true ID, baseline EOA, echocardiographic baseline peak gradient, echocardiographic baseline mean gradient, and baseline left ventricular ejection fraction (LVEF). Parameters with a *P*-value of <0.1 in the univariable analysis were included in the multivariable model with a forward likelihood ratio method. Collinearity was evaluated with variance inflation factors (VIF), and parameters with a VIF of >5 were not included in the multivariable analyses. Proportional-hazards assumption was confirmed through testing based on Schoenfeld residuals. Multivariable correlates are presented as hazard ratios (HRs), subhazard ratios (SHRs), and 95% confidence intervals (CIs). Bootstrapping was used to consider non-parametric data distribution. A two-sided *P*-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23 (IBM Corporation, Armonk, New York, NY, USA) and Stata 14.1 (StataCorp, College Station, TX, USA) statistical software.

Results

Baseline demographics and echocardiographic characteristics

A total of 1006 cases were included in the analysis. Cases were performed from 24 April 2007 to 29 December 2014. *Table 1* describes the baseline characteristics of this population. The patient mean age was 77.7 ± 9.7 years, and 58.8% of them were male. Patients were highly symptomatic, with 90.1% reporting NYHA class III or IV symptoms. Common comorbidities included CKD (54.5%), DM (27.3%), and PVD (22.3%). The majority of bioprosthetic valves was stented (81.3%) and mixed stenosis and regurgitation were the most common mechanisms of valve failure (44.7%). The median STS score was 7.3% (IQR 4.2–12.0). Almost half of the patients had aortic regurgitation ≥moderate-to-severe, and the baseline mean gradient was 35.5 ± 17.5 mmHg.

Baseline characteristics differed according to the THV deployed and also according to the size of the original failed bioprosthetic valve by true ID: EBEV cases were more commonly male (63.9% vs. 54.9% MSEV, $P = 0.02$) and had been more frequently utilized in stented bioprosthetic valves (85.8% vs. 77.4% MSEV, $P = 0.005$). Patients with small bioprosthetic valves were significantly older (80.3 ± 7.0 vs. 76.8 ± 9.3 years, $P < 0.001$), included predominantly stented valves (95.8% vs. 81.7%, $P < 0.001$), and had significantly more pre-existing severe PPM (10.6% vs. 0.3%, $P < 0.001$).

Procedural characteristics and early results

Table 2 details key procedural characteristics for all patients. Transfemoral technique was the most common access utilized (69.5%). Bioprosthetic valve ring fracture was not utilized in this cohort. For patients with small surgical valves (true ID ≤ 20 mm), there was no difference in age or STS score when comparing patients by THV type. However, patients with small surgical valves who underwent MSEV implantation had greater prevalence of pre-existing severe PPM (14.1% vs. 6.8% EBEV in small valves, $P = 0.022$), more transfemoral access (91.7% vs. 45.9% EBEV in small valves, $P < 0.001$), and PVD (36.1% vs. 19.3% EBEV in small valves, $P < 0.001$). After the procedure, the patients with small surgical valves in the MSEV group had larger EOA (1.51 ± 0.49 vs. 1.18 ± 0.39 cm^2 EBEV in small valves, $P < 0.001$) and lower mean gradients (16.5 ± 8.7 vs. 21.1 ± 10.4 mmHg EBEV in small valves, $P < 0.001$). There were 10 intraprocedural deaths (1.0%), with no significant difference between MSEV, EBEV, or other valves (0.8% vs. 1.4% vs. 0.0%, $P = 0.49$). The rate of coronary obstruction was similar between MSEV and EBEV or other devices (2.3% vs. 2.1% vs. 4.4%, respectively; $P = 0.61$).

Long-term follow-up and echocardiographic data

The median absolute follow-up was 3.9 years (IQR 1.5–5.4 years; total range 0–11.7 years). Clinical follow-up at 1000 days was available for 85.4% of patients. *Take home figure* depicts the Kaplan–Meier survival curve for all patients. Estimated survival at 8 years was 38.0% (95% CI 32.9–43.1%) with a median survival of 6.2 years (95% CI 5.7–6.7 years). In the multivariable analysis, smaller bioprosthetic valves [1 mm decrease in true ID, HR 1.07 (95% CI 1.02–1.13)], age [per 10-

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year increase, HR 1.21 (95% CI 1.01–1.45)], lower baseline LVEF [per 10% decrease, HR 1.25 (95% CI 1.14–1.36)], CKD [HR 1.36 (95% CI 1.06–1.74)], non-transfemoral access [HR 1.43 (95% CI 1.11–1.84)], and DM [HR 1.57 (95% CI 1.22–2.03)] were independently associated with decreased patient survival (*Figure 1A* and Supplementary material online, *Table S1*). Bootstrapping did not change results substantially (Supplementary material online, *Table S2*). There was no difference in long-term survival according to post-procedural mean gradient ≥20 mmHg or residual aortic regurgitation ≥moderate (Supplementary material online, *Figure S1*). Supplementary material online, *Table S3* describes selected long-term echocardiographic data.

Reintervention

Forty patients required reintervention during follow-up. Freedom from reintervention at 8 years was 93.2% (95% CI 90.5–95.9%); 16 (40.0%) patients underwent a new TAVR and 23 (57.5%) underwent SAVR. One patient underwent balloon valvuloplasty. The most common reason for reintervention was severe transvalvular stenosis (60.0% of cases, Supplementary material online, *Table S4*). Thirty-day mortality after the reintervention was not different between procedures (9.1% TAVR vs. 4.8% SAVR, $P = 0.63$). Pre-existing severe PPM [SHR 4.34 (95% CI 1.31–14.39)], malposition [SHR 3.75 (95% CI 1.36–10.35)], EBEV [SHR 3.34 (95% CI 1.26–8.85)], and age [per 10-year increase, SHR 0.59 (95% CI 0.44–0.78)] were independent correlates for all-cause reintervention (*Figure 1B* and Supplementary material online, *Table S5*). An alternative model for structural reintervention is available in Supplementary material online, *Table S5*. *Figure 2A and B* represent all-cause reintervention cumulative incidence function curves for the type of THV and pre-existing severe PPM, respectively.

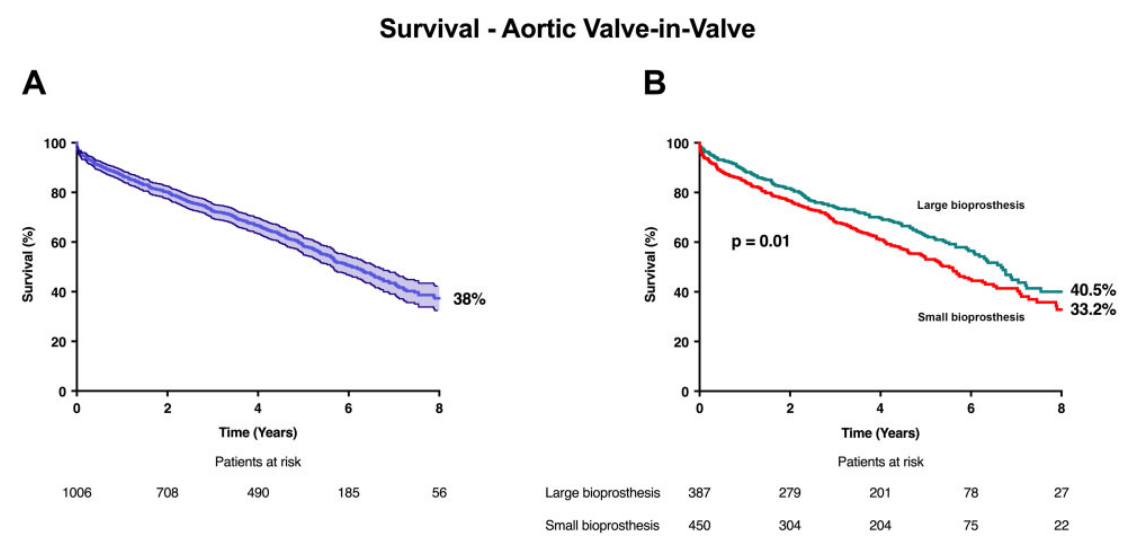
Discussion

Aortic ViV represents a significant proportion of TAVR procedures[21] and, given the increase in the use of bioprosthetic tissue valves,[2] the procedure is expected to continue to grow in numbers.[22] This is the first comprehensive long-term evaluation of aortic ViV. Our analysis shows that the size of the original failed valve may influence long-term mortality and the type of the transcatheter valve may influence the need for reintervention after aortic ViV. Hence, operator decisions during the original tissue valve implantation and/or during the ViV procedure may influence meaningful clinical outcomes.

Survival after aortic valve-in-valve

Survival after aortic ViV was recently reported in a smaller cohort of high-risk patients from the PARTNER trial.[23] Patients had a mean age of 78.9 ± 10.2 years with a mean STS score of 9.1 ± 4.7%. The estimated 3-year survival rate was 67.3%,[23] similar to the results of the present study: 73.0%. An analysis from the CoreValve US Expanded Use Study with a total of 226 extreme-risk patients was also recently published[24] and reported a 3-year survival rate of 72.3%. A small multicentre assessment of 116 aortic ViV patients (76.0 ± 11.0 years, STS score 8.0 ± 5.1%) reported a 5-year survival rate of 67.9%.[25] The current data from the VIVID Registry include a much larger number of high-risk patients ($n = 1006$) with longer follow-up and reveal an 8-year survival rate of 38.0% after ViV.

Having a small bioprosthesis represents an important risk factor for mortality after ViV procedure, both at 1 year[4] and over long-term



Take home figure Kaplan–Meier model of survival after aortic valve-in-valve. (*A*) All patients included in the analysis. (*B*) Patients with small bioprostheses (i.e. true internal diameter ≤20 mm) had worse survival at 8 years. Note that bioprosthetic valves without a known standard for internal diameter size, such as homografts, were not included.

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Table I **Baseline characteristics of the aortic valve-in-valve cohort**

	Aortic ViV (*n* = 1006)	Medtronic self-expandable valves (*n* = 523)	Edwards balloon-expandable valves (*n* = 435)	Other valves (*n* = 48)	*P*-value	Large bioprosthetic valves (*n* = 387)[a]	Small bioprosthetic valves (*n* = 450)[a]	*P*-value
Age (years), mean ± SD	77.7 ± 9.7	78.2 ± 9.3	77.2 ± 10.0	76.9 ± 10.4	0.25	76.8 ± 9.3	80.3 ± 7.0	<0.001
Male gender, *n*/*N* (%)	590/1004 (58.8)	286/521 (54.9)	278/435 (63.9)	26/48 (54.2)	0.02	294/385 (76.4)	194/450 (43.1)	<0.001
Height (cm), mean ± SD	167.4 ± 9.4	166.8 ± 9.4	168.2 ± 9.5	167.5 ± 9.0	0.07	170.7 ± 9.2	164.5 ± 8.6	<0.001
Weight (kg), mean ± SD	74.8 ± 16.6	74.2 ± 16	75.4 ± 17.4	76.3 ± 15.7	0.45	79.1 ± 18.4	71.5 ± 14.5	<0.001
BSA (m^2), mean ± SD	1.86 ± 0.23	1.85 ± 0.22	1.87 ± 0.24	1.88 ± 0.22	0.30	1.93 ± 0.23	1.8 ± 0.21	<0.001
BMI (kg/m^2), mean ± SD	26.6 ± 5.6	26.7 ± 5.3	26.6 ± 6.0	27.2 ± 5.0	0.80	27.2 ± 6.7	26.3 ± 4.6	0.04
Valve type, *n*/*N* (%)					0.005			<0.001
Stented	806/992 (81.3)	398/514 (77.4)	369/430 (85.8)	39/48 (81.3)		316/387 (81.7)	431/450 (95.8)	
Stentless	186/992 (18.8)	116/514 (22.6)	61/430 (14.2)	9/48 (18.8)		71/387 (18.3)	19/450 (4.2)	
Label size (mm), mean ± SD	23.2 ± 2.2	22.9 ± 2.2[b]	23.6 ± 2.11[b]	23.3 ± 1.9	<0.001	24.9 ± 1.6	21.7 ± 1.3	<0.001
True ID (mm), mean ± SD	19.9 ± 2.4	19.7 ± 2.5[b]	20.3 ± 2.2[b]	19.8 ± 2	0.001	22.0 ± 1.6	18.1 ± 1.2	<0.001
Predicted indexed EOA (cm^2), mean ± SD	0.83 ± 0.16	0.81 ± 0.17[b]	0.85 ± 0.16[b]	0.84 ± 0.13	0.008	0.93 ± 0.17	0.75 ± 0.11	<0.001
Pre-existing severe PPM, *n*/*N* (%)	46/739 (6.2)	34/369 (9.2)	12/331 (3.6)	0/39 (0.0)	0.002	1/314 (0.3)	45/425 (10.6)	<0.001
Mechanism of bioprosthetic valve failure, *n*/*N* (%)					0.46			<0.001
Regurgitation	172/989 (17.4)	93/514 (18.1)	68/431 (15.8)	11/44 (25.0)		80/379 (21.1)	37/442 (8.4)	
Stenosis	375/989 (37.9)	197/514 (38.3)	161/431 (37.4)	17/44 (38.6)		134/379 (35.4)	190/442 (43.0)	
Mixed	442/989 (44.7)	224/514 (43.6)	202/431 (46.9)	16/44 (36.4)		165/379 (43.5)	215/442 (48.6)	
NYHA class, *n*/*N* (%)					0.81			0.24
I	12/997 (1.2)	8/523 (1.5)	4/426 (0.9)	0/48 (0.0)		2/383 (0.5)	5/449 (1.1)	
II	87/997 (8.7)	48/523 (9.2)	35/426 (8.2)	4/48 (8.3)		38/383 (9.9)	31/449 (6.9)	
III	626/997 (62.8)	322/523 (61.6)	270/426 (63.4)	34/48 (70.8)		243/383 (63.4)	279/449 (62.1)	
IV	272/997 (27.3)	145/523 (27.7)	117/426 (27.5)	10/48 (20.8)		100/383 (26.1)	134/449 (29.8)	
Diabetes mellitus, *n*/*N* (%)	274/1004 (27.3)	146/522 (28.0)	115/434 (26.5)	13/48 (27.1)	0.88	94/386 (24.4)	135/450 (30.0)	0.07
Peripheral vascular disease, *n*/*N* (%)	220/986 (22.3)	84/514 (16.3)	127/424 (30.0)	9/48 (18.8	<0.001	76/379 (20.1)	114/439 (26.0)	0.05
Chronic kidney disease, *n*/*N* (%)	537/986 (54.5)	275/507 (54.2)	237/431 (55.0)	25/48 (52.1)	0.92	186/376 (49.5)	272/447 (60.9)	0.001
History of stroke, *n*/*N* (%)	123/957 (12.9)	64/515 (12.4)	51/398 (12.8)	8/44 (18.2)	0.55	39/370 (10.5)	61/430 (14.2)	0.12
Permanent pacemaker, *n*/*N* (%)	127/892 (14.2)	77/506 (15.2)	48/359 (13.4)	2/27 (7.4)	0.44	47/348 (13.5)	61/396 (15.4)	0.46
EuroSCORE (%), median (IQR)	27.3 (17.9–40.0)	27.3 (18–38.9)	27.3 (17.8–41.5)	29.6 (18.4–37.8)	1.00	25 (16.0–36.4)	31.2 (21.5–43.5)	<0.001
EuroSCORE II (%), median (IQR)	12.7 (8.7–18.4)	13.3 (8.8–19.6)	12.4 (8.6–17.9)	11.6 (6.8–17.7)	0.14	11.3 (7.7–16.7)	14.7 (10.7–20.2)	<0.001
STS score (%), median (IQR)	7.3 (4.2–12.0)	7.8 (4.4–12.9)	7.2 (4.2–11.7)	5.5 (2.4–8.3)	0.001	6.2 (3.8–10.7)	8.6 (5.6–13.1)	<0.001
Baseline haemodynamics								

Continued

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Table I *Continued*

	Aortic ViV ($n = 1006$)	Medtronic self-expandable valves ($n = 523$)	Edwards balloon-expandable valves ($n = 435$)	Other valves ($n = 48$)	*P*-value	Large bioprosthetic valves ($n = 387$)[a]	Small bioprosthetic valves ($n = 450$)[a]	*P*-value
LVEF (%), mean ± SD	51.8 ± 13.1	52.0 ± 13.6	51.2 ± 12.7	56.2 ± 11.8	0.06	50.7 ± 12.9	53.3 ± 12.8	0.005
EOA (cm^2), mean ± SD	0.94 ± 0.46	0.95 ± 0.48	0.92 ± 0.43	0.97 ± 0.4	0.70	1.00 ± 0.49	0.83 ± 0.36	<0.001
Peak gradient (mmHg), mean ± SD	60.8 ± 27.1	60.7 ± 27.6	61.6 ± 27	54.3 ± 21.2	0.35	60.5 ± 29	64.8 ± 24	0.04
Mean gradient (mmHg), mean ± SD	35.5 ± 17.5	34.9 ± 17.6	36.4 ± 17.7	33.3 ± 14.2	0.36	35.2 ± 18.7	37.8 ± 15.7	0.05
Aortic regurgitation, *n/N* (%)					0.01			0.009
None	140/961 (14.6)	91/508 (17.9)	46/411 (11.2)	3/42 (7.1)		48/363 (13.2)	71/437 (16.2)	
Mild	213/961 (22.2)	104/508 (20.5)	97/411 (23.6)	12/42 (28.6)		71/363 (19.6)	115/437 (26.3)	
Moderate	130/961 (13.5)	59/508 (11.6)	65/411 (15.8)	6/42 (14.3)		47/363 (12.9)	66/437 (15.1)	
Moderate to severe	200/961 (20.8)	99/508 (19.5)	87/411 (21.2)	14/42 (33.3)		84/363 (23.1)	92/437 (21.1)	
Severe	278/961 (28.9)	155/508 (30.5)	116/411 (28.2)	7/42 (16.7)		113/363 (31.1)	93/437 (21.3)	

BMI, body mass index; BSA, body surface area; EOA, effective orifice area; ID, internal diameter; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, prosthesis–patient mismatch; SD, standard deviation; ViV, valve-in-valve.
[a]Bioprosthetic valves without a known standard for ID size, such as homografts, were not included.
[b]Significant differences by *post hoc* Tukey's honest significant difference test after the analysis of variance.

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Table 2 Procedural characteristics, early outcomes, and haemodynamics of the aortic valve-in-valve cohort

	Aortic ViV ($n = 1006$)	Medtronic self-expandable valves ($n = 523$)	Edwards balloon-expandable valves ($n = 435$)	Other valves ($n = 48$)	*P*-value	Large bioprosthetic valves ($n = 387$)[a]	Small bioprosthetic valves ($n = 450$)[a]	*P*-value
THV label size (mm), median (IQR)	23 (23–26)	26 (23–26)	23 (23–26)	23 (23–25)	<0.001	26 (23–26)	23 (23–26)	<0.001
Access, *n/N* (%)					<0.001			0.25
Transfemoral	698/1004 (69.5)	477/523 (91.2)	198/433 (45.7)	23/48 (47.9)		256/386 (66.3)	325/450 (72.2)	
Transapical	250/1004 (24.9)	0/523 (0.0)	226/433 (52.2)	24/48 (50)		111/386 (29.3)	100/450 (22.2)	
Subclavian	19/1004 (1.9)	16/523 (3.1)	3/433 (0.7)	0/48 (0.0)		7/386 (1.8)	8/450 (1.8)	
Transaortic	23/1004 (2.3)	16/523 (3.1)	6/433 (1.4)	1/48 (2.1)		10/386 (2.6)	12/450 (2.7)	
Other	14/1004 (1.4)	14/523 (2.7)	0/433 (0.0)	0/48 (0.0)		0/386 (0.0)	5/450 (1.1)	
General anaesthesia, *n/N* (%)	649/914 (71.0)	293/478 (61.3)	317/388 (81.7)	39/48 (81.3)	<0.001	268/356 (75.3)	271/416 (65.1)	0.002
TEE, *n/N* (%)	549/875 (62.7)	233/476 (48.9)	282/356 (79.2)	34/43 (79.1)	<0.001	234/339 (69.0)	216/398 (54.3)	<0.001
Pre-dilation, *n/N* (%)	237/947 (25)	82/518 (15.8)	138/389 (35.5)	17/40 (42.5)	<0.001	93/363 (25.6)	98/422 (23.2)	0.44
Malposition, *n/N* (%)	62/952 (6.5)	45/493 (9.1)	15/415 (3.6)	2/44 (4.5)	0.003	38/365 (10.4)	15/421 (3.6)	<0.001
Post-dilation, *n/N* (%)	128/894 (14.3)	100/475 (21.1)	18/383 (4.7)	10/36 (27.8)	<0.001	39/343 (11.4)	66/401 (16.5)	0.05
Second THV, *n/N* (%)	53/995 (5.3)	35/523 (6.7)	17/424 (4.0)	1/48 (2.1)	0.11	28/381 (7.3)	19/446 (4.3)	0.06
Permanent pacemaker needed, *n/N* (%)	63/844 (7.5)	38/427 (8.9)	23/373 (6.2)	2/44 (4.5)	0.26	20/328 (6.1)	29/374 (7.8)	0.39
Vascular complications, *n/N* (%)					0.001			0.07
Minor	66/972 (6.8)	49/496 (9.9)	16/428 (3.7)	1/48 (2.1)		24/373 (6.4)	38/438 (8.7)	
Major	33/972 (3.4)	19/496 (3.8)	14/428 (3.3)	0/48 (0.0)		8/373 (2.1)	20/438 (4.6)	
Major bleeding, *n/N* (%)	70/910 (7.7)	27/456 (5.9)	38/413 (9.2)	5/41 (12.2)	0.11	21/345 (6.1)	34/420 (8.1)	0.29
Major stroke, *n/N* (%)	18/954 (1.9)	10/489 (2.0)	7/419 (1.7)	1/46 (2.2)	0.91	9/368 (2.4)	5/426 (1.2)	0.17
Acute kidney injury, *n/N* (%)	72/918 (7.8)	38/458 (8.3)	31/415 (7.5)	3/45 (6.7)	0.86	24/351 (6.8)	36/423 (8.5)	0.39
Coronary obstruction, *n/N* (%)	22/957 (2.3)	11/487 (2.3)	9/425 (2.1)	2/45 (4.4)	0.61	10/370 (2.7)	9/434 (2.1)	0.56
Post-procedural haemodynamics								
LVEF (%), mean ± SD	51.6 ± 11.9	51.7 ± 12.3	51.3 ± 11.4	53.8 ± 12.0	0.45	50.7 ± 12.0	53.1 ± 11.3	0.005
EOA (cm^2), mean ± SD	1.49 ± 0.51	1.59 ± 0.50[b]	1.39 ± 0.51[b]	1.40 ± 0.57	<0.001	1.55 ± 0.47	1.38 ± 0.47	<0.001
Max. gradient (mmHg) mean ± SD	29.0 ± 14.9	27.1 ± 13.6[b]	30.8 ± 15.8[b]	34.7 ± 16.8[b]	<0.001	26.5 ± 13.0	32.3 ± 15.6	<0.001
Mean gradient (mmHg), mean ± SD	16.3 ± 9.1	14.7 ± 8.2[bb]	17.7 ± 9.5[b]	20.3 ± 10.9[b]	<0.001	14.8 ± 8	18.3 ± 9.6	<0.001
Aortic regurgitation, *n/N* (%)					<0.001			0.49
None	586/925 (63.4)	268/479 (55.9)	288/403 (71.5)	30/43 (69.8)		223/361 (61.8)	277/411 (67.4)	
Mild	284/925 (30.7)	169/479 (35.3)	104/403 (25.8)	11/43 (25.6)		117/361 (32.4)	116/411 (28.2)	
Moderate	41/925 (4.4)	31/479 (6.5)	8/403 (2.0)	2/43 (4.7)		17/361 (4.7)	14/411 (3.4)	
Moderate to severe	10/925 (1.1)	8/479 (1.7)	2/403 (0.5)	0/43 (0.0)		2/361 (0.6)	3/411 (0.7)	
Severe	4/925 (0.4)	3/479 (0.6)	1/403 (0.2)	0/43 (0.0)		2/361 (0.6)	1/411 (0.2)	

EOA, effective orifice area; IQR, interquartile range; LVEF, left ventricular ejection fraction; SD, standard deviation; TEE, transesophageal echocardiography; THV, transcatheter heart valve; ViV, valve-in-valve.
[a]Bioprosthetic valves without a known standard for internal diameter size, such as homografts, were not included.
[b]Significant differences by *post hoc* Tukey's honest significant difference test after the analysis of variance.

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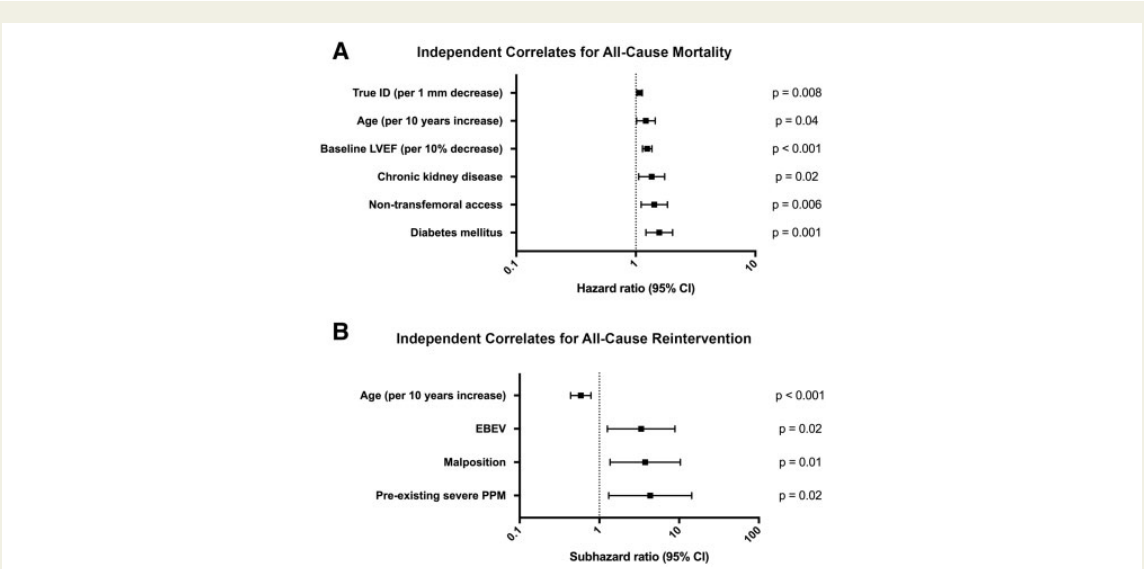


Figure 1 Independent correlates of (*A*) all-cause mortality and (*B*) all-cause reintervention in aortic valve-in-valve. Small bioprosthetic valves were independently associated with decreased survival. In addition, prosthesis–patient mismatch and balloon-expandable valves were associated with all-cause reintervention. CI, confidence interval; EBEV, Edwards balloon-expandable valves; ID, internal diameter; LVEF, left ventricular ejection fraction; PPM, prosthesis–patient mismatch.

follow-up. This is a novel finding since bioprosthetic valve size was not included in the multivariable analysis of the CoreValve US Expanded Use Study[24] and patients with label size <21 mm were excluded in the PARTNER study[23] and these studies did not report long-term outcomes beyond 3 years of follow-up. Furthermore, these studies included only one THV type, while the VIVID data allow 'real-world' analysis of the impact of different devices, including the need for reintervention.

Valve reintervention

In the present study, the 8-year reintervention rate after ViV was 6.8%, mainly for valve stenosis. Three-year reintervention rates were 4.4% in the CoreValve US Expanded Use Study[24] and 1.9% in the PARTNER ViV trial.[23] Consistent with our own findings of an almost five-fold increased risk for reintervention with the presence of pre-existing severe PPM, the authors of the CoreValve US Expanded Use Study identified a significant association between reintervention and pre-existing severe PPM (14.8% vs. 1.6% moderate PPM vs. 4.4% no PPM, $P = 0.02$).[24] As THVs may be under-expanded when implanted in small bioprosthetic valves, which may be further modified by the depth of implantation,[26] the final result may be postulated to be even worse. Severe PPM at baseline is a known independent correlate of mortality at 1-year follow-up,[8] although post-procedural PPM did not appear to affect outcomes.[27] Severe PPM has previously been associated with the increased risk of SVD following biological SAVR.[28–30] Taken together with prior findings, our study adds further evidence and insight into the fact that small bioprostheses, which frequently exhibit severe PPM, bear a high risk for worse outcomes after ViV procedures. In addition, the issue of valve thrombosis should be considered. In prior analyses, thrombosis is resolved with anticoagulation in the majority of cases without a need for reintervention.[11] In the current data, we have identified two cases requiring reintervention due to valve thrombosis. There are no specific protocols for anticoagulation in ViV patients and further evaluation is needed.

The type of THV was also associated with a greater rate of all-cause reintervention. Intra-annular THV devices tend to develop higher transvalvular gradients after the ViV procedure,[4] a finding that has been replicated in the current study. The implantation of a THV with intra-annular design in a small bioprosthetic valve with severe PPM may result in leaflet pin-wheeling,[26] increased mechanical stress, and highly turbulent flow that may increase the risk of valve thrombosis and SVD.[31] There is evidence of a higher SVD rate with the SAPIEN XT beyond 5 years compared with the self-expandable CoreValve[32] and also of a higher reintervention rate in the SAPIEN XT when compared with SAVR in the PARTNER II trial.[33]

Implications for aortic valve surgery

This large-scale long-term analysis emphasizes the adverse impact of small bioprostheses and pre-existing severe PPM on mortality and reintervention rates. Surgeons should therefore aim to avoid implanting small bioprostheses whenever possible (i.e. label size <23 mm, or with predicted severe PPM). When evaluating a patient with a failing small bioprosthetic valve, patients should understand the additional surgical risk of redo open heart surgery, especially when root enlargement is performed, and also the limitations of a ViV procedure with regard to residual stenosis.

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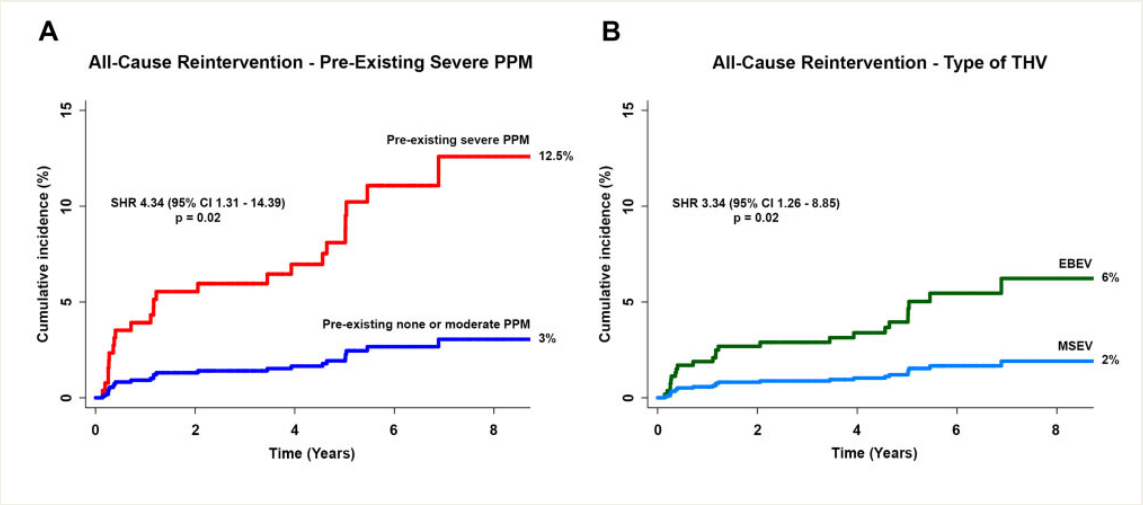


Figure 2 Fine and Gray cumulative incidence function curves showing the adjusted cumulative subhazard of all-cause reintervention. Model according to (*A*) the presence or absence of pre-existing severe prosthesis–patient mismatch and (*B*) the type of transcatheter heart valve implanted. CI, confidence interval; EBEV, Edwards balloon-expandable valves; MSEV, Medtronic self-expandable valves; PPM, prosthesis–patient mismatch; SHR, subhazard ratio; THV, transcatheter heart valve.

During ViV procedures, the operator should make every effort to avoid residual stenosis. Relevant strategies may include THV selection, precise device positioning and novel procedural techniques, such as bioprosthetic valve ring fracture.[7,9]

Limitations

Our study has several limitations. There was no control group of conventional surgery, although many patients were considered very high risk for redo open heart surgery as demonstrated by the elevated surgical scores. Echocardiographic follow-up was performed without a centralized core-lab and at the discretion of the operator. Without serial evaluations, we were unable to obtain SVD and bioprosthetic valve failure rates. However, our principal findings are based on actual reintervention events and not on echocardiographic parameters. The regression analysis regarding mortality is one of the many plausible models that likely fit the data equally as well and the individual variables selected may not be completely independent. Similarly, those not selected may not be any less important than those selected had alternative modelling taken place. As in all observational analyses, the possibility of unmeasured confounders in the models exists. The mode and methods of follow-up assessment differed among centres, as some centres routinely perform follow-up visits, while other centres performed active (through direct patient contact) or passive (through administrative or governmental data) assessment of the current health state specifically for this study. In addition, first-generation devices were most common in our population, with a lower representation of currently used valves (SAPIEN 3 and Evolut R) and the EBEV and MSEV groups differed significantly in procedural access. The EBEV group more commonly had alternative access for the TAVR procedure, which is associated with inferior early survival after TAVR procedures in comparison to transfemoral approach. Nevertheless, the clinical outcomes after EBEV ViV procedures were inferior to MSEV in several outcomes that do not seem to be related to the procedural access. EBEV cases were associated with higher post-procedural gradients and were an independent correlate of the need for reintervention. Finally, no cases of bioprosthetic valve ring fracture were included in our cohort and it is still unknown how patients with pre-existing PPM, who undergo ring fracture, will clinically perform over the long term.

Conclusions

The size of the original failed valve may influence long-term mortality, and the type of the transcatheter valve may influence the need for reintervention after aortic ViV.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data sharing

Data sharing with qualified researchers may be considered after submission of a proposal to the board of the Institute of Valvular Research.

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Low rate of invasive coronary angiography following transcatheter aortic valve implantation: Real-world prospective cohort findings

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ABSTRACT

Aim: To evaluate the real need for coronary access after transcatheter aortic valve implantation (TAVI).
Methods and results: Prospective observational single center registry, including 563 consecutive patients that underwent TAVI between April 2008 and November 2018, with both self and balloon expandable valves in a tertiary European center. Mean age was 82.4 ± 6.9 years, 53.3% were female, 16% had previous history of CABG, 33% of previous PCI and 16.6% of MI. Twenty four percent of the patients were revascularized within one year before TAVI in preparation for the procedure. Median STS Score was 4.82 (IQ 2.84).
In a median follow up of 24 months (IQ 21.5), 18 patients (3.2%) were identified as potentially in need for ICA: 9 (1.6%) in the setting of stable coronary artery disease and 9 (1.6%) for an acute coronary syndrome.
A total of 11 PCI were performed in 9 patients, with a complete success rate of 63.6%. Procedures that were unsuccessful or partially unsuccessful were due to the inability to cross the stent or the drug eluting balloon through the valve struts or misplacement within the coronary artery due to lack of catheter's support.
Conclusion: In this population, a strategy of previous guideline guided revascularization before transcatheter aortic valve implantation was associated with a low rate of myocardial infarction and repeated need of coronary access, with a scattered distribution over time. Assuring future access to coronary arteries in patients at increased risk may depend on the revascularization strategy rather than device selection.

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1. Introduction

It is known that coronary artery disease is prevalent among patients with severe aortic stenosis, ranging from 70% in intermediate and high risk patients to 30% in low risk patients [1–3]. Transcatheter aortic valve implantation (TAVI) procedures are increasing at a high rate in Europe with approximately 180,000 patients annually being considered potential TAVI candidates in the European Union and in Northern-America, a number that could increase up to 270,000 with the widespread of indications to low-risk patients [4]. Revascularization strategies before TAVI differ [5,6] and concerns about future coronary intervention influence strategy and device selection.

With the high prevalence of coronary artery disease, the lowering age of patients and the increasing life expectancy after TAVI it is expected that acute coronary syndromes may occur, with reported rates as high as 10% at two years [7–9]. Intraprocedural need for coronary access is a major concern and coronary ostial obstruction due to valve

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; DES, drug eluting stent; ICA, invasive coronary angiography; LVEF, left ventricular ejection fraction; LAD, left anterior descending artery; LCX, left circumflex coronary artery; LM, left main; MI, myocardial infarction; NSTEMI, non ST segment elevation myocardial infarction; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; PAP, pulmonary artery pressure; RCA, right coronary artery; SHID/SAP, stable angina pectoris; SOV, sinus of Valsalva; STEMI, ST segment elevation myocardial infarction; STJ, sinotubular junction; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VCROSS, Valve Catheter Restorative Operation on Santa Cruz hospital; ViV, valve-in-valve.

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leaflets or calcium displacement can be as high as 0.8% [10] and 3.5% when valve-in-valve procedures are accounted [11,12].

With the increasing number of procedures, coronary access can become a challenge [13,14] for interventional cardiology operators and so, real world data about the incidence of acute coronary events after TAVI, the need for coronary reassessment and success rate of consequential procedures should be shared.

We therefore aimed to evaluate the incidence of myocardial infarction (MI), rate of invasive coronary angiography (ICA) and percutaneous intervention (PCI) after TAVI during a median follow up of 24 months (IQ 21.5).

2. Methods

2.1. Population

This is an observational study from a prospective cohort of 605 patients considered for TAVI in a European academic tertiary care center, between April 2008 and November 2018. The patients were enrolled in the VCROSS (Valve Catheter Restorative Operation on Santa Cruz hospital) registry created to obtain all demographic, clinical, procedural and follow up data from patients undergoing TAVI in our hospital for severe aortic stenosis.

A total of 36 patients were excluded due to incomplete follow up data and there were 5 patients undergoing a second procedure due to primary access failure (converting from transfemoral to subclavian or transapical approach). One patient only underwent balloon valvuloplasty due to transfemoral vascular access failure with no further access attempted. Overall, 93.1% of all patients enrolled in the VCROSS registry were eligible for this analysis ($n = 563/605$).

All patients signed informed consent approved by the ethical committee. Mortality status was collected from electronic medical records and/or civil registries until November 2019. Complications and follow up data were obtained from patient's clinical files (manual and electronic records) or the national platform of medical records when available.

Patients were considered for TAVI if they had symptomatic severe aortic stenosis, defined by a jet velocity > 4.0 m/s, mean gradient >40 mmHg and valve area < 1.0 cm^2 or index < 0.6 cm^2/m^2, being referred to our hospital from primary or secondary centers. Indication for TAVI was assessed by a multidisciplinary heart team composed of clinical and interventional cardiologists together with cardiac surgeons.

2.2. Procedure

Coronary artery disease was ruled in or out either by coronary computed tomography angiography (CCTA) or ICA. Patient's revascularization was performed after heart team's decision for TAVI on a case-by-case basis, before TAVI procedure, generally whenever there was prove of ischemia or a > 70% stenosis on a proximal or mid segment from one of the main branches (>50% for left main (LM)).

The following access were performed: transapical and subclavian by a hybrid team with interventional cardiologists and cardiac surgeons and transfemoral mainly by interventional cardiologists and permanent bail-out background support from cardiac surgery.

Several TAVI valves were implanted namely CoreValve©, CoreValve Evolut©, CoreValve Evolut R©, CoreValve Evolut Pro© (Medtronic), SAPIEN©, SAPIEN XT©, SAPIEN 3©, SAPIEN 3 Ultra© (Edwards), Portico© (Abbott), Lotus©, Accurate Neo© (Boston Scientific) both on native and prosthetic valves.

Most of the procedures were performed under patient's conscious sedation and analgesia with use of anesthesia for cases guided by transesophageal echocardiogram or when severe complications occurred during valve implantation.

Pacing for balloon-expandable valves was performed on the left ventricle wire or through a temporary transvenous pacing in cases where conduction disturbances like right bundle branch block were already present, and a few cases with patient's own pacemaker.

Pre-emptive coronary protection was performed in a case-by-case level taking in account: 1) Anatomical features: cases where i) the sino-tubular junction (STJ) size was close to the selected device at that level and/or ii) coronary ostia height was less than 10 mm based on CCTA curved multiplanar reconstructions and/or when there was a difference of less than 3 mm between the sinus of Valsalva (SOV) mean diameter and the bioprosthetic diameter in valve in valve (ViV) procedures, especially in surgical heart valve with leaflets sutured outside the stent. 2) LM significant disease defined as ≥50% angiographic stenosis not previously revascularized. A total of seven patients underwent pre-emptive LM protection (with a wire in the left anterior descending artery (LAD)), and one of the right coronary artery (RCA), seven of them during valve-in-valve procedures (all TAVI-in-SAVR). In five of these patients, a provisional stent was also positioned in the LAD and one case in the RCA. Two of these patients underwent emergent PCI due to acute coronary obstruction, one patient in both the LM and a non-protected RCA and the second patient in the previously protected RCA.

Vascular closing devices used were Prostar©, Angioseal©, Proglide© and Manta©.

After TAVI, patients were admitted in a cardiac care unit for the first hours until clinically stable to move to the cardiology ward with telemetry.

2.3. Endpoints

Need for coronary revascularization was chosen as the main endpoint and secondary endpoints were acute coronary syndrome, all-cause mortality at the time of follow up, 1-year all-cause mortality and cardiovascular mortality.

2.4. Definitions

All definitions were obtained from PARTNER III [2], or were otherwise specified.

Acute coronary syndrome was defined as an ischemic event associated with clinically significant myocardial necrosis such as new ischemic symptoms (e.g. chest pain, shortness of breath) or signs (new ST segment changes, imaging evidence of new loss of viable myocardium) and elevated cardiac biomarkers consisting of at least one sample with a peak value exceeding the 99th reference limit of high sensitivity troponin T and a significant 3 h delta or a further increase of at least 50% post-procedure for patients with baseline elevated values. Type 2 MI was defined according to the 4th Universal Definition of MI European Guidelines [15], requiring evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary athero-thrombosis. Post-procedural MI was defined if the previous occurred within 72 h from the procedure.

Coronary obstruction was defined by angiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications or dissection, occurring during or after valve deployment.

PCI success was defined according to clinical success. Procedural success was defined as a reduction to residual stenosis of <50% by balloon angioplasty or successful stent or drug eluting balloon (DEB) deployment at the desired position with a residual stenosis <30% by visual assessment in two orthogonal projections. Clinical success was defined as procedural success plus the absence of major adverse cardiac events while in hospital for the index PCI—that is, myocardial infarction, the need for repeated revascularization, coronary artery bypass grafting (CABG), or death.

Non cardiovascular mortality was defined as any death which is due primarily to an identifiable non-cardiovascular cause or etiology. Cardiac death was defined by all procedure-related deaths, device related

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deaths including valve dysfunction or other valve related adverse events and death preceded by cardiovascular symptoms (such as chest pain). Unknown death cause was defined by unwitnessed death or unavailable information.

2.5. Statistical analysis

Descriptive statistics are presented as median and interquartile range or mean and standard deviation for continuous variables and frequencies and percentages for categorical variables. All *P* values are 2-sided and were considered significant if <0.05. Continuous variables were compared using Student *t*-test, and categorical variables were compared using Pearson chi-square test or Fisher exact test as appropriate. All analyses were performed using IBM SPSS Statistics version 21.

3. Results

3.1. Population

A number of 563 patients undergoing TAVI were included in this analysis (Fig. 1).

Baseline characteristics from the population are presented in Table 1. Mean age was 82.4 ± 6.9 years, 53.3% were female, 16.2% had previous CABG history, 33.2% of previous PCI and 16.6% of MI. Twenty four percent of the patients were revascularized within one year before TAVI procedure, in preparation for the procedure and according to the criteria previously defined in the methods section. There were 12 patients presenting bicuspid valves. Twenty one patients underwent valve-in-valve procedures (all previously submitted to surgical replacement). Median STS Score was 4.82 (IQ 2.84).

3.2. Procedure

In a median follow up of 24 months (IQ 21.5), 18/563 (3.2%) patients were identified as potentially in need for ICA (21 events, 16 ICAs performed) (see Table 2). Mean age was 80 ± 6.6 years-old and 44.4% were female. PCI previous to TAVI was performed in 55.6% (10/18) and 44.4% (8/18) had a history of CABG. None of them presented a TAVI-in-TAVI or TAVI-in-SAVR. The distribution in time of these events was scattered (Fig. 2).

Within the patients identified, 9/563 (1.6%) were in the setting of stable coronary artery disease and 9/563 (1.6%) had an acute coronary syndrome.

From the 9 patients presenting an acute coronary syndrome, 5 underwent ICA (all were non-ST segment elevation MI) and the other 4 were considered for medical therapy (classified as type 2 MIs, with recognized secondary causes. One patient died before invasive angiography due to unexplained hemodynamic instability and cardiac arrest occurring in the first 24 h after the procedure.

The 7 patients referred due to stable pectoris angina (refractory angina or with documented ischemia) and 1 referred for risk stratification before noncardiac surgery, proceeded with ICA. Four of them had no new significant lesions and were considered for medical therapy. Three underwent successful PCI. One patient underwent two

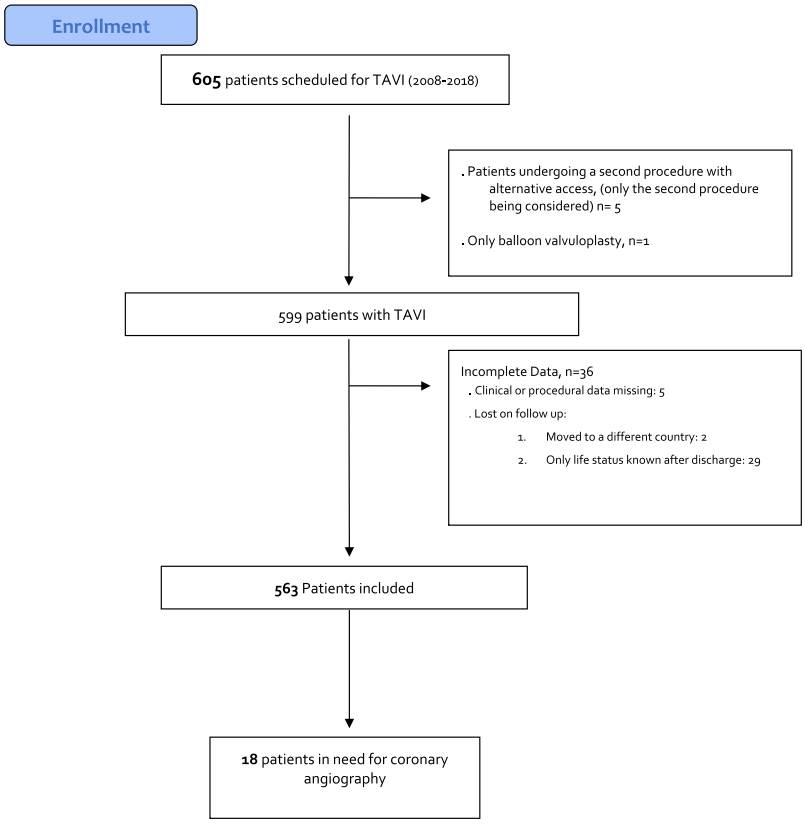


Fig. 1. Patient selection flow diagram. TAVI means transcatheter aortic valve implantation.

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Table 1
Baseline characteristics of the population.

Population baseline characteristics	(N = 563) (%)
Demographic	
Age (yr)	82.4 ± 6.9
Clinical	
Female gender	53.3
Diabetes	31.8
Hypercholesterolemia	66.4
Hypertension	86.7
Smoking habits	22.6
Peripheral artery disease	19.0
BMI	26.1 ± 4.2
Atherosclerotic burden	
Previous MI	16.6
Previous PCI	33.2
Previous CABG	16.2
Previous stroke	12.4
Comorbidities	
NYHA class III or IV	66.4
NT-proBNP (pg/mL) (median)	2164 (IQ 4319)
Euroscore II (median)	4.90 (IQ 3.59)
STS Score for mortality (median)	4.82 (IQ 2.84)
PAP (mmHg) (mean)	42.8 ± 12.6
LVEF	54.0 ± 14.1
CKD (Cr Cl < 45 mL/Kg/min or HD)	27
Chronic pulmonary disease (>moderate)*	17.1
Atrial fibrillation	32.5
Procedural characteristics	
Balloon expandable valve	29.1
Self expandable valve	67.7
Mechanically expandable valve	2.7
Non-TF access	17.4
Coronary obstruction during TAVR	0.5
Outcomes after discharge (%)	
Myocardial infarction	1.6
1st year all cause mortality	13.0
All cause mortality	35.2
Non cardiovascular mortality	7.6
Cardiovascular mortality	9.1
Death of unknown cause	18.5

BMI – body mass index; CABG – coronary artery bypass graft; CKD – chronic kidney disease; LVEF – left ventricular ejection fraction; MI – myocardial infarction; PCI – percutaneous coronary intervention; PAP – pulmonary artery pressure; TAVI – transcatheter aortic valve implantation; TF - transfemoral.
* Chronic obstructive pulmonary disease with FEV1< 80%, predicted FVC < 75% or under bronchodilator or oxygen home therapy.

independent procedures: in the first, PCI was unsuccessful due to the inability to cross DEB through valve struts; in the second, PCI was only partially successful as, although it was possible to cross the struts, DEB was misplaced. One patient had an unsuccessful attempt of PCI of the distal LDA due to distal vessel dissection, with no further clinical instability, and being the patient considered for medical therapy.

Median time for ICA since TAVI was 288 (IQ 774) days.

Overall, 13 patients underwent 16 invasive coronary angiographies. There were 2 patients requiring a second procedure on the same clinical event, one due to the inability to perform selective coronary angiography on the first attempt and the other due to maximal contrast dose attained for patient's renal function (recent acute renal lesion). In these 13 patients, 6/13 (46.1%) had received a supracoronary supra-annular self-expandable valve with slender tab diameter, 4/13 (30.8%) a balloon expandable valve, 2/13 (15.4%) a supracoronary supra-annular self-expandable valve with larger tab diameter and 1/13 (7.7%) a supracoronary intra-annular self-expandable valve.

Procedural details are summarized in Table 3. Arterial femoral access was used in 68.8% (11/16) of the ICAs. Overall, mean ICA/PCI procedural time was 48 (±22) min, mean fluoroscopy time 16 ± 8 min, median effective radiation dose was 1036 (IQR 1092) mGy and contrast dose was 158 mL (IQ 195).

Mean number of diagnostic catheters used for LM was 1.25 (min 1 max 3) and for RCA was 1.83 (min 1 max 4). Mean number of guide catheters was 2.4 (min 1 max 4). Not all the cases aimed to access both coronary arteries. Complete catheter's engagement on the LM was achieved in 87% (13/15) of the cases, and on the RCA in 66.7% (8/12). The JR4 catheter was the main diagnostic catheter chosen for the RCA followed by 3DRC and both JL 3.5 and 4 were well succeeded for the LM (see Table 2).

Most cases did not need special techniques to engage the catheters but in one case the use of a guide catheter extension (GuidelinerTM©) was helpful to reach the ostia and in others a guidewire was first positioned in the coronary artery to drive the catheter with a global success rate of 77.8% (21/27 coronary ostia engaged). No difficulties were reported on disengaging the catheter from the valve frame. In patients where pre-emptive coronary protection was performed, no complications were observed while removing the wire or the stent from the vessel after TAVI, namely wire entrapment or stent dislodgement.

A total of 9/563 (1.6%) patients underwent 11 PCI procedures. Despite a high rate of catheter intubation, the success rate of the PCI procedure was lower in self than in balloon expandable valves: 4/4 (100%) balloon expandable valves, 3/7 (42.8%) in self expandable valves and partial success in 2/7 (28.6%) self-expandable valves. These procedures were unsuccessful due to the inability to cross the stent or the DEB through the valve struts, misplacement within the coronary artery due to lack of catheter's support and one case due to distal vessel dissection with no hemodynamic compromise. Left anterior descending artery OCT was performed in 1 case and PCI with rotational atherectomy in another case (see Table 3).

There were additional three cases (0.53%) that presented the need for coronary access immediately after valve deployment and were successfully treated. These patients are not included in this report.

3.3. Outcomes

All-cause death rate at 30-days was 3.6% ($n = 20$), at 1 year was 13% ($n = 73$) and in a median follow up of 24 months was 35.2% ($n = 198$). At the end of follow up, cardiovascular death accounted for 25.8% of the deaths ($n = 51$) and a non-cardiovascular was identified in 21.7% of the cases ($n = 43$). In the remaining 52.5% of the patients, no access to death cause registries was possible due to data protection laws (unknown cause) ($n = 104$).

4. Discussion

Our findings show that, when following a strategy of ischemia driven PCI together with a case-by-case analysis of the coronary disease anatomic severity before TAVI, both for prevention of ischaemic instability during TAVI and for prevention of late coronary events and procedures, these patients present a low rate of need for ICA during follow up. The rate of MI was lower than the ones previously reported [7,16], even when including patients at high risk and with a long follow up (from 1 to 10 years of follow up) like the population described by *Vilalta* et al. The indications for revascularization in preparation for TAVI diverge between centers and our population is in between the reported range of 13% to 31% [17–19].

The distribution in time was scattered, with almost half of the events occurring in the first six months, which is consistent with the findings previously reported by *Mentias* et al. [16].

Many factors can impact on catheter engagement on the coronary ostia. First, native aortic valve anatomy can present characteristics, such as extensive calcification and long leaflet length, in favor of partial or complete coronary ostia obstruction and, so, impairing fully engagement of the catheter. Interestingly, not accounting for acute coronary obstruction, *Katsanos* et al. [20] reported that in a population of 142 patients who underwent TAVI with a balloon expandable valve and were assessed by cardiac CT, there were no differences in troponin T levels

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Table 2
Characteristics of patients identified as potentially in need for invasive coronary angiography and respective indications.

	Age	Valve implanted	Size of the valve implanted	Days after TAVI	Indication	Previous PCI	Previous CABG	Patent Grafts
Balloon expandable valves								
Patient A	87	Edwards Sapien	26	4	Type 2 MI	No	LIMA-LAD SVG-RCA	LIMA-LAD SVG-RCA
Patient B	72	Edwards Sapien 3	23	35	Stable angina pectoris	LAD	No	–
Patient C	71	Edwards Sapien	29	96	Type 2 MI	No	LIMA-LAD SVG-OM2 SVG-PDA	LIMA-LAD
Patient D	88	Edwards Sapien 3	23	419	Stable angina pectoris	No	No	–
Patient E #1	87	Edwards Sapien 3	23	642	NSTEMI	LM, LCX, RCA, LAD	No	–
Patient E #2	74	Edwards Sapien 3	23	766	2nd attempt	LM, LCX, RCA, LAD	No	–
Patient F	88	Edwards Sapien	23	1172	Type 2 MI	No	No	–
Patient G #1	72	Edwards Sapien XT	26	1485	NSTEMI	RCA, LCX	LIMA-LAD RA-RCA	LIMA-LAD
Patient G #2	72	Edwards Sapien XT	26	1638	Planned percutaneous intervention	RCA, LCX	LIMA-LAD RA-RCA	LIMA-LAD
Self expandable valves								
Patient H	82	Corevalve Evolut R	29	1	Cardiogenic shock	No	No	–
Patient I	80	Corevalve Evolut Pro	26	16	NSTEMI	LAC, RCA, LCX	No	–
Patient J	85	Corevalve Evolut R	29	21	Type 2 MI	LCX	No	–
Patient K	67	Corevalve	29	104	Stable angina pectoris	LCX, 1st Diag	LIMA-LAD SVG-OM	LIMA-LAD
Patient L #1	77	Corevalve	29	358	Stable angina pectoris	OM2	LIMA-LAD SVG-1st Diag	LIMA-LAD
Patient L #2	80	Corevalve	29	1142	Stable angina pectoris	OM2	LIMA-LAD SVG-1st Diag	LIMA-LAD
Patient M	77	Corevalve	29	517	Stable angina pectoris	RCA	No	–
Patient N	74	Corevalve Evolut R	26	765	NSTEMI	RCA	LIMA-LAD	LIMA-LAD
Patient O	83	Corevalve Evolut R	34	1017	Before non-cardiac surgery	RCA	LIMA-LAD	LIMA-LAD
Patient P	86	Neo Accurate	25	145	NSTEMI	LAD, LCX	No	–
Patient Q	81	Neo Accurate	27	219	Stable angina pectoris	LAD-1st Diag	LIMA-LAD SVG-OM SVG-PDA	LIMA-LAD
Patient R	83	Portico	25	928	Stable angina pectoris	LM, LCX, RCA	No	–

CABG – coronary bypass graft surgery; LAD – left anterior descending artery; LCX – left circumflex coronary artery; LIMA – left internal mammary artery LM – left main; MI – myocardial infarction; NSTEMI – non ST segment elevation myocardial infarction; PCI – percutaneous coronary intervention; RCA – right coronary artery; SHID/SAP – stable angina pectoris; SVG - Saphenous vein graft; TAVI – transcatheter aortic valve implantation; — represents unavailable data; # represents patients undergoing more than one procedure.

between patients with fully covered ostia versus patients with partly or non-covered ostia, and that subsequent PCI rate at 30 months was similar between patients with any covered and non-covered ostia. Second, also for consideration are the anatomic issues related to aortic root, such as coronary ostia height, sinus of Valsalva and STJ dimensions. Intuitively, lower and narrower sinus are more prone to be attained by native

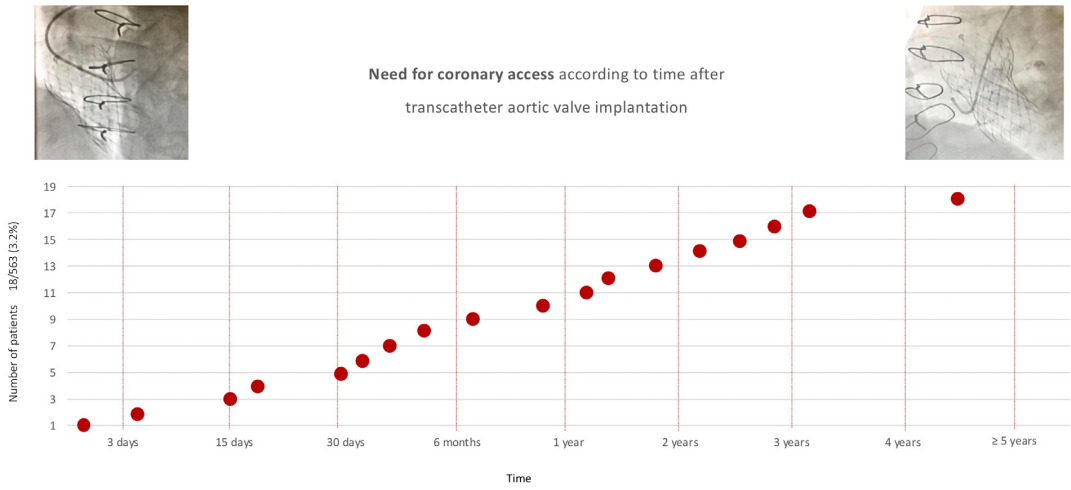


Fig. 2. Distribution of invasive coronary angiography need according to time after transcatheter aortic valve implantation.

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Table 3
Procedural characteristics of the patients undergoing invasive coronary angiography after transaortic valve implantation.

	New lesions	Success of catheter engagement (number of catheters)	Diagnostic catheters	Guide catheters	PCI lesions	PCI success	Duration of the procedure (min)	Time of fluoroscopy (min)	Contrast (mL)
Balloon expandable valves									
Patient B	None	Complete on LM [1]; RCA not attempted	CLS 3.75	CLS 3.75	Distal LM Bifurcation	Successful [1]	52	29	190
Patient D	pLAD	Complete on LM [1] Complete on RCA [1]	JL 4; JR 4	CLS 3.75	pLAD	Successful [1] (R)	63	21	150
Patient E	pLAD, oCX	Complete on LM [3] Complete on RCA [1]	JL 3.5; AL 1; XB 3.5 JR 4	XB 3.5	pLAD	Successful [1]	33	12	60
Patient G #1	mRCA	Complete on LM [1] Complete on RCA [1]	JL 4; JR 4	–	–	–	45	11	160
Patient G #2	mRCA	–	–	JR 3.5	mRCA	Successful [1]	50	14	475
Self expandable valves									
Patient I	LCX LAD	Complete on LM (Guideliner) [1][b] Complete on RCA [2][b]	JL 4[a] JR 4; 3DRC[a]	XB 3; JL 4; MP A1; JR 4 ± Guideliner	Distal LM Bifurcation + dLAD	Successful LM stenting; but unsuccessful – impossibility to cross DES to dLAD [4]	54	–	197
Patient K	LCX and OM1	Complete on LM [2]; RCA not attempted	EBU 3.75; EBU 4	EBU 3.75; EBU 4	LCX and OM1	Successful [2]	69	19	–
Patient L #1	OM	Complete on LM [1] Complete on RCA [2]	JL 4 JR4; 3DRC	EBU 3.75; XB3; AL2; JL 3.5	OM	Partially successful – impossibility to cross DEB [4]	95	37	390
Patient L #2	LCX	Complete on LM [2] Complete on RCA [2]	JL 4 5F; JL 4 6F JR 4; 3DRC	XB 3.5; JL 3.5; JL 4	LCX	Partially successful in mLCX –DEB misplacement; Unsuccessful on dLCX [3]	90	50	215
Patient M	None	Complete on LM [1] Partial on RCA [4]	JL 4; JR 4; AR; AR II; AL I	–	None	–	–	14	320
Patient N	None	Unsuccessful [2]	JL 4; JR 4	–	None	–	33	10	30
	None	Unsuccessful [2]	JL 3,5; JR 4	–	None	–	11	3	40
Patient O	None	Complete on LM [1] Complete on RCA [4]	JL 4; BLK; AR 2; JR 4; IM	–	None	–	90	21	158
Patient P	dLAD	Complete on LM [1] Complete on RCA [1]	JL 3.5; JR 4	XB 3.5; JL 3.5; AL 2; AL 1	dLAD	Unsuccessful – distal vessel dissection [4]	100	44	–
Patient Q	LM-LAD	Complete on LM [1] Partial on RCA and LCX (origin in RCC) [2]	JL 4; JR 4; MP	XB 3.5; XB 3	LM-LAD	Successful [2]	55	21	300
Patient R	None	Complete on LM [2] RCA not attempted	JL 3.5 5F; JL 4 6F	XB 3; XB 3.5	None	OCT [2]	–	13	141

DEB – drug eluting balloon; DES – drug eluting stent; dX – distal; LAD – left anterior descending artery; LCX – left circumflex coronary artery; LM – left main; MI – myocardial infarction; mX – mid; OCT – optical coherence tomography; PCI – percutaneous coronary intervention; pX-proximal; (R) means rotational atherectomy; RCA – right coronary artery; RCC – right coronary cusp; TAVI – transcatheter aortic valve implantation; — represents unavailable data.
[a] Underlined catheters were the successful ones used for coronary angiography or intervention.
[b] Number of catheters used until successful engagement in each coronary ostia.

valve's leaflets and to be faced by a frame. There was only one case in our series in which nor left or right ostium engagement was possible but no cardiac CT was performed to evaluate valve position. In self expandable valves, due to the presence of a newly created aortic root, reports advise the use of smaller catheters [8] but in our series 9/13 of the complete LM engagement was achieved with a JL 4.0. For balloon expandable valves, no significant differences in procedural aspects were identified in our experience, like previously suggested by wider cohorts [21].

Third, procedural details such as height of implantation and commissural tab alignment with coronary ostia can influence ostial access. CT has been suggested [9] to locate the ostia in relation to the stent frame, however, commissural posts identification is still limited [22]. None of our patients underwent cardiac CT before ICA to verify device's commissural tab alignment.

Forth, time after implant and frame apposition to the aortic wall may also be related to difficulties in crossing valve's diamonds. The endotheliazation period has been described to last around 3 months in surgically implanted valves [23–25], never though, transcatheter valves have wider frame area to be endothelialized and apposition to the aortic wall and annulus may not be as complete as in sutured valves, foreseeing longer periods. This aspect is relevant because it would suggest that catheter engagement after the first 3 months would become more challenging. This did not seem to be an important factor for engagement success in our population, nor did times of fluoroscopy or success rate differ when considering procedures with >3 months after TAVI.

Lastly, valve design related concepts: waist and frame diameter, thickness of metallic struts, number and size of diamonds, planned valve position according to the annulus, commissure and skirt height and commissural tab orientation are all aspects refined by the devices' companies. Despite some previous reports describing challenges and a low rate of selective intubation after self-expandable valves [13,14] against balloon expandable valves, in our experience diagnostic images were obtained in most of patients, with different types of valves. In spite of this, the rate of successful PCI in self-expandable valves was actually lower than expected [26]. Htun et al. [8] and Allali et al. [27] reported a coronary selective angiography of 97% in the LM and 90% in the RCA in patients with a Medtronic™ self-expandable valve. In our population, the rate of catheter engagement success was higher in the LM than in the RCA and in balloon expandable than self-expandable valves. In proportion there was a higher rate of patients undergoing ICA with a balloon expandable valve, which probably reflects already the preemptive operators' choice of this device in patients with more complex coronary disease. Never though, the choice of device did not seem to

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influence management strategy once 3/4 patients considered for medical therapy had balloon-expandable valves.

Proposed algorithms [9] may help to overshoot some of the obstacles in these complex procedures and for more easily educational purposes a mobile phone app TAVRCathAID©[2018 Icahn School of Medicine at Mount Sinai] is also presently available.

4.1. Limitations

Due to patient's data protection law, cause of death was unspecified in a percentage of patients, resulting in underreporting of cardiovascular deaths.

The threshold for invasive coronary angiography referral was left at the description of each patient's referral doctors comprising a wide range of clinical reasoning.

These patients continued medical follow up in their referral hospitals after discharge. Coronary angiographic data were obtained from each five centers. Thirty-one patients were lost on follow up and may have had invasive coronary procedures in private setting or out of the country hospitals for which we have no access. The small number of cases limits the feasibility of comparisons and cannot obviate the heterogeneity in procedural execution and rate of catheter engagement success. Never though, it is a real-world experience report, that also takes in account the results of smaller centers without TAVI experience.

5. Conclusion

In this population, a less restrictive strategy of previous guideline guided revascularization before transcatheter aortic valve implantation (TAVI) was associated with low rates of myocardial infarction and repeated coronary angiography, with a scattered distribution over time. Assuring future access to coronary arteries in patients at increased risk may depend on the revascularization strategy rather than on choosing the valve type, nevertheless new approaches are required to improve coronary access after TAVI.

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CRediT authorship contribution statement

Mariana Gonçalves: Investigation, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Pedro de Araújo Gonçalves:** Conceptualization, Investigation, Visualization, Supervision, Writing - review & editing. **Rui Campante Teles:** Investigation, Data curation, Writing - review & editing. **Manuel de Sousa Almeida:** Investigation, Writing - review & editing. **Afonso Félix de Oliveira:** Data curation, Writing - review & editing. **João Brito:** Investigation, Writing - review & editing. **Luís Raposo:** Investigation, Writing - review & editing. **Henrique Mesquita Gabriel:** Investigation, Writing - review & editing. **Tiago Nolasco:** Investigation, Writing - review & editing. **José Pedro Neves:** Writing - review & editing. **Miguel Mendes:** Writing - review & editing. **Hector M. Garcia-Garcia:** Visualization, Formal analysis, Supervision, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors do not have any conflict of interest to declare regarding this manuscript.

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Manuscript #25

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ESC Report

ESC Core Curriculum for the Cardiologist

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Abbreviations and acronyms

2D	Two-Dimensional
3D	Three-Dimensional
AAT	Audit Assessment Tool
ABI	Ankle Brachial Index
ACAT	Acute Care Assessment Tool
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AR	Aortic Regurgitation
AS	Aortic Stenosis
AV	node AtrioVentricular node
AVNRT	AtrioVentricular Node Reentry Tachycardia
AVRT	AtrioVentricular Reentry Tachycardia
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CanMEDS	Canadian Medical Education Directives for Specialists
Cardiac	MR Cardiac Magnetic Resonance
CbD	Case-based Discussion
CHF	Congestive Hear Failure
CICU	Cardiac Intensive Care Unit
CKD	Chronic Kidney Disease
CME	Continuing Medical Education
CMR	Cardiac Magnetic Resonance
CPD	Continuing Professional Development
CRT	Cardiac Resynchronisation Therapy
CRT-D	Cardiac Resynchronisation Therapy Defibrillator
CT	Computed Tomography
CTCA	Cardiac Computed Tomography Angiography
CV	CardioVascular
CVD	CardioVascular Disease
DOPS	Direct Observation of Procedural Skills
DVT	Deep Venous Thrombosis
EbD	Entrustment-based Discussion
EC	European Community
ECG	ElectroCardioGraphy
ECLs	ExtraCorporeal Life support
eCPR	extracorporeal CardioPulmonary Resuscitation
EEGC	European Exam in General Cardiology
EHRA	European Heart Rhythm Association
EPA	Entrustable Professional Activity
ESC	European Society of Cardiology
EU	European Union
FFR	Fractional Flow Reserve
GDMT	Guideline Directed Medical Therapy
HDL	High Density Lipoproteins
HF	Heart Failure
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICCU	Intensive Coronary Care Unit
ICD	Implantable Cardioverter-Defibrillator
ICU	Intensive Care Unit
IE	Infective Endocarditis
iFR	instantaneous wave-Free Ratio
IVUS	IntraVascular Ultrasound
LAA	occlusions Left Atrial Appendage occlusion
LDL	Low Density Lipoproteins
LGE	Late Gadolinium Enhancement
Lp(a)	Lipoprotein (a)
LQT	Long QT

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Table 1 Chapters

1	The Cardiologist in the wider context
2	Imaging
3	Coronary artery disease
4	Valvular heart disease
5	Rhythm disorders
6	Heart failure
7	Acute cardiovascular care
8	Prevention, rehabilitation, sports
9	Cardiac patients in other settings

The ESC Core Curriculum for the Cardiologist is organized around nine chapters. Chapters 2–9 are based on EPAs.

3. Entrustable professional activities

Trust is central for the provision of good care and an essential component of healing. Patients and other health professionals need to trust their physician, physicians need to have trust in each other, and healthcare systems rely on the trustworthiness of their specialists. Trainers develop increasing trust in a trainee during their training. To capture this often subconscious process, EPAs provide defined units of professional activity.[4] When a trainee can be trusted to perform a professional activity at the expected level of independence, the EPA is completed. Hence, a completed EPA documents the ability of a trainee to safely, effectively, and independently perform the professional activity.

EPAs have a particular focus on clinical skills, but incorporate the related knowledge, adequate attitudes, and professional roles in a holistic clinical context. Moreover, EPAs can be overseen, assessed, monitored, documented, and certified. For these reasons, EPAs are an excellent instrument for assessing a trainee repetitively during the training period.

Taken together, the EPAs contained in this core curriculum describe the requirements for independent professional cardiology practice. The curriculum thus constitutes a framework for acquiring the clinical competencies required for working as a cardiologist in Europe. All 62 EPAs in this core curriculum share a common structure (*Figure 1*). The clinical competence is defined in the title and specified in the description. This is followed by the knowledge, skills, and attitudes the trainee should possess to perform the professional activity. Tools are suggested for the assessment of each professional activity. Each EPA also indicates the minimal required level of independence a trainee is expected to reach when training is completed.

Since all these professional activities concern patients, and are performed in a social context, the relevant roles are described in the CanMEDS Roles section of each EPA.[5] They have been adapted for this core curriculum as described in Chapter 1 but remain consistent with the definitions in the CanMEDS Physician Competency Framework. This framework was adapted from: Frank, JR, Snell L and Sherbino J eds. The CanMEDS 2015 physician competency framework. Ottawa: Royal College of Physicians and Surgeons of Canada; 2015. Adapted with permission. Hence, these roles are important for all the professional activities and are part of all EPAs (*Figures 1 and 2*).

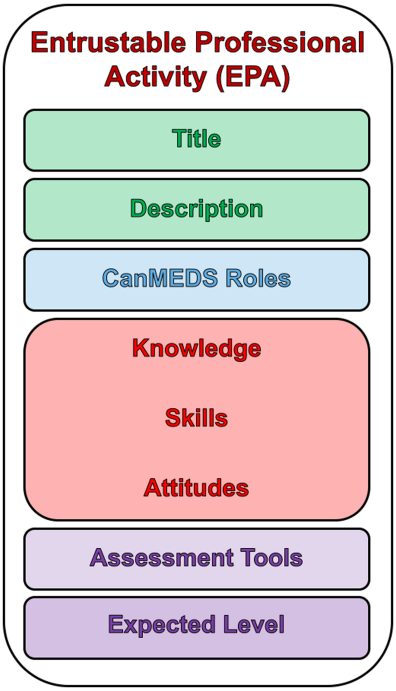


Figure 1 All 62 EPAs in this core curriculum share a common structure. The clinical competence is defined in the title and specified in the description. The CanMEDS Roles required for being competent are mentioned as well. This is followed by the knowledge, skills, and attitudes the trainee should possess to perform the professional activity. Tools are suggested for the assessment of each professional activity. Each EPA also indicates the level of independence a trainee is expected to reach when training is completed.

4. Level of independence

Each EPA defines a clinical activity. The required level of independence for executing this activity, however, is not identical for all the professional activities performed by a cardiologist. *Table 2* defines the five levels of entrustment or independence, starting from 'able to observe' (level 1) to 'able to perform the activity and supervise others (level 5)'. *Table 3* defines the level of independence for each EPA and *Table 4* for each investigation.

5. Assessment of clinical competencies using entrustable professional activities

Each entrustable activity requires knowledge, skills, integrity, reliability, and humility.[6] Assessment of clinical competencies is a very important aspect of the EPA concept. Entrustable professional activities enable easy, formative, and repeated assessment during the training period until the trainers are satisfied that the trainee is able to execute the professional activity in an independent manner and they can

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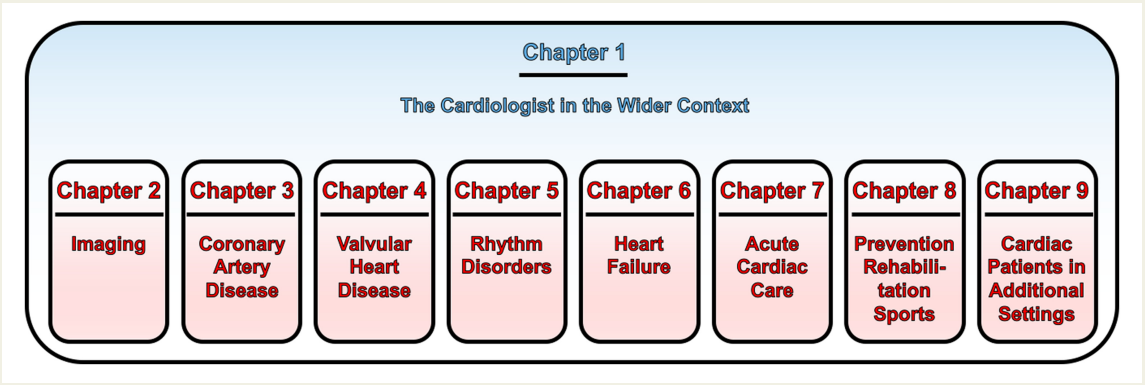


Figure 2 This core curriculum consists of 9 chapters. The professional roles of the cardiologist - based on the CanMEDS framework - are described in Chapter 1 and are all represented, to a variable extent, within each EPA of Chapters 2–9. The EPAs are arranged in eight chapters (Chapters 2–9) reflecting the major clinical topics in current cardiological practice.

Table 2 Levels of independence

Level 1: Trainee is able to observe
Level 2: Trainee is able to perform the activity under direct supervision proactive, close supervision, supervisor in the room
Level 3: Trainee is able to perform the activity under indirect supervision reactive, on-demand supervision, trainee has to ask for help, supervisor readily available, within minutes
Level 4: Trainee is able to perform the activity under distant supervision reactive supervision available remotely, e.g. within 20–30 min, on the phone or *post hoc*
Level 5: Trainee is able to supervise others in performing the activity

Five different levels of independence defined for a professional activity.

Table 3 Level of independence for each EPA

EPA	Level of independence				
	1	2	3	4	5
2. Imaging					
2.1. Assess a patient using one or multiple imaging modalities					
2.2. Assess a patient using echocardiography					
2.3. Assess a patient using cardiac magnetic resonance					
2.4. Assess a patient using cardiac computed tomography					
2.5. Assess a patient using nuclear techniques					
3. Coronary artery disease					
3.1. Manage a patient with symptoms suggestive of coronary artery disease					
3.2. Manage a patient with acute coronary syndrome					
3.3. Manage a patient with chronic coronary syndrome					
3.4. Assess a patient using coronary angiography					
4. Valvular heart disease					
4.1. Manage a patient with AR					
4.2. Manage a patient with AS					
4.3. Manage a patient with mitral regurgitation					
4.4. Manage a patient with mitral stenosis					
4.5. Manage a patient with tricuspid regurgitation					
4.6. Manage a patient with tricuspid stenosis					
4.7. Manage a patient with pulmonary regurgitation					
4.8. Manage a patient with pulmonary stenosis					

Continued

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Table 3 ***Continued***

EPA	Level of independence				
	1	2	3	4	5
4.9. Manage a patient with multivalvular disease					
4.10. Manage a patient with a prosthetic valve					
4.11. Manage a patient with endocarditis					
5. Rhythm disorders					
5.1. Manage a patient with palpitations					
5.2. Manage a patient with transient loss of consciousness					
5.3. Manage a patient with atrial fibrillation					
5.4. Manage a patient with atrial flutter					
5.5. Manage a patient with supraventricular tachycardia					
5.6. Manage a patient with ventricular arrhythmia					
5.7. Manage a patient with bradycardia					
5.8. Manage a patient with a cardiac ion channel dysfunction					
5.9. Manage a patient with a pacemaker					
5.10. Manage a patient with an ICD					
5.11. Manage a patient with a CRT device					
6. Heart failure					
6.1. Manage a patient with symptoms and signs of heart failure					
6.2. Manage a patient with heart failure with reduced ejection fraction					
6.3. Manage a patient with heart failure with preserved ejection fraction					
6.4. Manage a patient with acute heart failure					
6.5. Manage a patient with cardiomyopathy					
6.6. Manage a patient with pericardial disease					
6.7. Manage a patient with right heart dysfunction					
6.8. Manage a patient with a cardiac tumour					
6.9. Manage cardiac dysfunction in oncology patients					
7. Acute cardiovascular care					
7.1. Manage a patient with haemodynamic instability					
7.2. Manage a patient with survived cardiac arrest					
7.3. Manage a critically ill cardiac patient					
7.4. Manage a patient after a percutaneous cardiovascular procedure					
7.5. Manage a patient after cardiac surgery					
7.6. Manage end-of-life care in a cardiac patient					
8. Prevention, rehabilitation, sports					
8.1. Manage cardiovascular aspects in an athlete (Sport Cardiology)					
8.2. Manage a patient with arterial hypertension					
8.3. Manage a patient with dyslipidaemia					
8.4. Manage cardiovascular aspects in a diabetic patient					
8.5. Manage a cardiac patient in primary prevention					
8.6. Manage a cardiac patient in secondary prevention					
8.7. Prescribe a prevention and rehabilitation programme for a cardiovascular patient					
9. Cardiac patients in other settings					
9.1. Manage a patient with aortic disease					
9.2. Manage a patient with trauma to the aorta or the heart					
9.3. Manage a patient with peripheral artery disease					
9.4. Manage a patient with thromboembolic venous disease					
9.5. Manage a patient with pulmonary thromboembolism					
9.6. Manage a patient with pulmonary hypertension					
9.7. Manage a patient with adult congenital heart disease					
9.8. Manage a pregnant patient with cardiac symptoms or disease					
9.9. Perform a cardiological consultation					

Each EPA is assigned an expected level of independence from level 1 to level 5: (1) Observe; (2) Direct supervision; (3) Indirect supervision; (4) Distant supervision; and (5) Able to teach (no supervision).

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Table 4 Level of independence for each investigation

Investigations	Levels of independence				
	1	2	3	4	5
ECG					
Ambulatory ECG					
Exercise ECG testing					
Cardiopulmonary exercise testing					
Ambulatory BP monitoring					
Transthoracic echocardiography					
Trans-oesophageal echocardiography					
Stress echocardiography					
Vascular ultrasound					
Coronary CT					
Cardiac CT					
Cardiac MR					
Nuclear imaging					
Right heart catheterization					
Endomyocardial biopsy					
Coronary angiography					
Percutaneous interventions					
Structural interventions					
Cardiac surgery					
Pacemaker programming					
ICD/CRT programming					
Temporary pacemaker implantation					
Permanent pacemaker implantation					
ICD/CRT implantation					
Electrophysiological studies					
Electrophysiological interventions					
Electrical cardioversion					
Pericardiocentesis					

Each investigation is assigned an expected level of independence from level 1 to level 5: (1) Observe; (2) Direct supervision; (3) Indirect supervision; (4) Distant supervision; and (5) Able to teach (no supervision).

entrust him/her with this clinical activity. We strongly encourage that assessment is integrated into routine clinical care. It is important to recognize that the competence of the trainee will further increase after completion of training due to continued learning, gaining of additional clinical experience, and continued medical education. Consistent with this clinical reality, knowledge when to consult more experienced colleagues or other experts is integrative to all EPAs. The key question for trainers assessing a trainee by an EPA, therefore, is whether the trainee is ready to (i) execute the respective professional activity in an independent manner and (ii) assume the expected professional responsibilities.

The tools for assessment depend on the nature of the professional activity; suitable tools are proposed in the assessment section of each EPA. To facilitate assessment with EPAs in the clinical context, *Table 5* indicates what should be aimed at and what should be avoided in the assessment situation. When the competence of a trainee is evaluated by EPAs, the assessment focuses on clinical skills, even though knowledge and attitudes are also tested. Nevertheless, assessment of the trainee should usually be complemented by a specific knowledge centred examination, such as the European Examination in General Cardiology (EEGC) (*Figure 3*). Similarly, attitudes should be additionally evaluated by multi-source feedback given by healthcare professionals and patients, helping trainees to develop the appropriate attitudes for clinical practice (*Figure 3*).

6. Role of the trainers

Entrustable professional activities are an opportunity for trainers. In the past, training was based on a syllabus, and the training level was often 'counted' by the number of investigations and procedures performed by the trainee.[7] That system was convenient to administer, but the quality of a trainee's clinical performance, their attitudes and their ability to work independently were not assessed. Entrustable professional activities , in contrast, capture how far a trainee can be trusted to perform a professional activity considering his or her skills, knowledge, and attitudes. It is the responsibility of the trainer to provide an environment in which the trainee can reach the expected level of independence during the training period. If a trainee does not reach this goal, however, EPAs provide a framework to extend the

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Table 5 Do's and Don'ts for the EPAs of the ESC Core Curriculum

Do's	Don'ts
For trainers	
Define the EPAs that are feasible and relevant for your setting; any clinical situation is an opportunity for an assessment	Don't think you are on your own; share challenges, tips, and tricks with peers
Use the Knowledge/Skills/Attitudes section of the EPAs as a resource for specific feedback	Don't use the Knowledge/Skills/Attitudes section as a checklist
Integrate the assessment real time in your daily work	Don't postpone the assessment
When observing a trainee always look for knowledge and attitudes, not only skills	Don't assess manual/technical skills only
Use your expert judgement to rate the level of the trainee's independence	Don't worry about subjectivity
For trainees	
Integrate the assessment in the workflow	Don't postpone assessments
Ask your trainer to rate the level of independence for every EPA you perform - and the reason for the level	Don't only ask for ratings in EPAs you are already competent in
Ask all your trainers to rate you at several occasions	Don't only ask for ratings from your favourite trainer
Identify the relevant EPAs for each setting	
Use your EPA profile for driving your learning and completing your competence	
Use Knowledge/Skills/Attitudes section of the EPAs to guide you in your training	

What should be aimed at and avoided by trainers and trainees in the assessment situation.

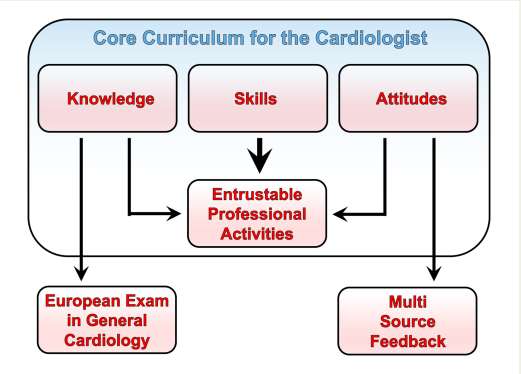


Figure 3 Entrustable professional activities define the knowledge, skills, and attitudes required for the respective clinical competencies. Due to their focus on skills, they are particularly useful for assessments in a clinical context. The latter should be complemented with a knowledge-based examination such as the European Exam in General Cardiology as well as with multisource feedback.

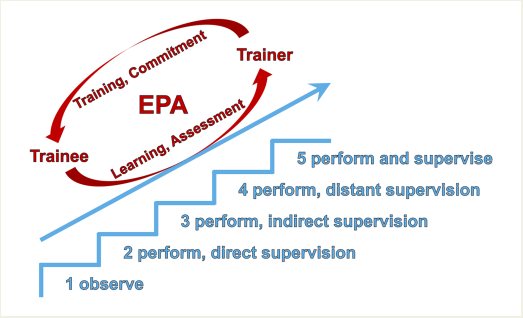


Figure 4 Trainees develop an increasing degree of independence during their training. In parallel, trainers develop increasing trust in the competence of their trainees. This process requires the commitment of both sides involved. Commitment of the trainers for teaching and assessing the trainees is essential since the trainers need to be able to confirm that the trainees can be trusted to perform the professional activities at the expected level of independence.

training until the trainers are able to confirm that the trainee can be trusted to perform the professional activity independently. With the adoption of EPAs, trainers may have greater demands on their time and energy for education, but they are rewarded with more meaningful assessments and defined responsibility for their trainees (*Figure 4*). The authors of this core curriculum hope that it is used in clinical practice for assessing clinical competencies and that it inspires both trainees and their trainers to reach responsible entrustment decisions.

Union of European Medical Specialists European Training Requirements

1. Preamble

The Union of European Medical Specialists (UEMS) is a non-governmental organization representing national associations of medical specialists at the European Level. With a current

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Skills

- Perform an individualized cardiac risk assessment by applying risk stratification indices according to the patient's underlying CVD and the type and urgency of non-cardiac surgery
- Select, perform, and interpret the non-invasive diagnostic tests before surgery (ECG, echocardiography, and stress testing)
- Perform and interpret the following diagnostic modalities before surgery:
  - ECG
  - Exercise ECG
  - Transthoracic echocardiography
- Interpret the following diagnostic modalities:
  - Chest X-ray
  - Trans-oesophageal echocardiography
  - Vascular ultrasound screening of carotid arteries
  - Cardiac catheterization
- Liaise with the anaesthetist over perioperative management and surveillance appropriate for the type of surgery and the anaesthetic technique
- Implement pharmacological and non-pharmacological interventions that can reduce cardiac risk during surgery
- Decide on the optimal timing and the anti-thrombotic regimen in a patient following a recent myocardial revascularization procedure, in whom non-cardiac surgery cannot be delayed
- Optimize the control of all risk factors for long-term CVD prevention
- Identify the need for cardiac follow-up after non-cardiac surgery
- Use echocardiography, including trans-oesophageal echocardiography, and other techniques to search for potential sources of embolism
- Define the need for further diagnostic work-up to search for other atherosclerotic manifestations, and advise on appropriate therapy
- Implement secondary prevention strategies, including lifestyle and pharmacological therapies
- Prevent, identify, and stratify the risk of CVD with specific reference to the elderly patient

Attitudes

- Stimulate multidisciplinary team discussions on preoperative CVD assessment and perioperative management strategies
- Consider the current cardiovascular prognosis of a patient for whom non-cardiac surgery is planned
- Work closely with neurologists and radiologists to determine the best management strategy for patients with ischaemic and non-ischaemic neurological conditions
- Use the cardiac consultation as an opportunity to identify cardiovascular risk factors and provide recommendations to the patient on lifestyle and medical therapy

Assessment tools

- Direct observation/WBA (e.g. DOPS, Mini-CEX, fieldnotes)
- CbD (case-based discussion)/EbD (entrustment-based discussion)

Level of independence

- 5. Able to teach (no supervision)

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Manuscript #26

Circulation

ORIGINAL RESEARCH ARTICLE

Transcatheter Mitral Valve Replacement After Surgical Repair or Replacement

Comprehensive Midterm Evaluation of Valve-in-Valve and Valve-in-Ring Implantation From the VIVID Registry

Editorial, see p 117; Article see p 178

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BACKGROUND: Mitral valve-in-valve (ViV) and valve-in-ring (ViR) are alternatives to surgical reoperation in patients with recurrent mitral valve failure after previous surgical valve repair or replacement. Our aim was to perform a large-scale analysis examining midterm outcomes after mitral ViV and ViR.

METHODS: Patients undergoing mitral ViV and ViR were enrolled in the Valve-in-Valve International Data Registry. Cases were performed between March 2006 and March 2020. Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions. Significant residual mitral stenosis (MS) was defined as mean gradient ≥10 mm Hg and significant residual mitral regurgitation (MR) as ≥ moderate.

RESULTS: A total of 1079 patients (857 ViV, 222 ViR; mean age 73.5±12.5 years; 40.8% male) from 90 centers were included. Median STS-PROM score 8.6%; median clinical follow-up 492 days (interquartile range, 76–996); median echocardiographic follow-up for patients that survived 1 year was 772.5 days (interquartile range, 510–1211.75). Four-year Kaplan-Meier survival rate was 62.5% in ViV versus 49.5% for ViR (P<0.001). Mean gradient across the mitral valve postprocedure was 5.7±2.8 mm Hg (≥5 mm Hg; 61.4% of patients). Significant residual MS occurred in 8.2% of the ViV and 12.0% of the ViR patients (P=0.09). Significant residual MR was more common in ViR patients (16.6% versus 3.1%; P<0.001) and was associated with lower survival at 4 years (35.1% versus 61.6%; P=0.02). The rates of Mitral Valve Academic Research Consortium–defined device success were low for both procedures (39.4% total; 32.0% ViR versus 41.3% ViV; P=0.01), mostly related to having postprocedural mean gradient ≥5 mm Hg. Correlates for residual MS were smaller true internal diameter, younger age, and larger body mass index. The only correlate for residual MR was ViR. Significant residual MS (subhazard ratio, 4.67; 95% CI, 1.74–12.56; P=0.002) and significant residual MR (subhazard ratio, 7.88; 95% CI, 2.88–21.53; P<0.001) were both independently associated with repeat mitral valve replacement.

CONCLUSIONS: Significant residual MS and/or MR were not infrequent after mitral ViV and ViR procedures and were both associated with a need for repeat valve replacement. Strategies to improve postprocedural hemodynamics in mitral ViV and ViR should be further explored.

The full author list is available on page 114.

Key Words: heart valve disease ■ hemodynamics ■ mitral valve ■ mitral valve insufficiency ■ mitral valve stenosis

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Clinical Perspective

What Is New?

- Residual stenosis is common after mitral valve-in-valve/valve-in-ring procedures, especially in patients with small devices and large body size, and is associated with a need for repeat mitral valve replacement.
- Residual regurgitation was especially common in mitral valve-in-ring procedures.
- The suboptimal survival of patients having mitral valve-in-ring procedures extends to 4 years with ≈50% mortality.

What Are the Clinical Implications?

- Suboptimal hemodynamics of mitral valve-in-valve and mitral valve-in-ring should lead to procedural strategies to improve postimplantation hemodynamics, aiming to optimize device durability.
- Alternative therapies to mitral valve-in-ring in patients with mitral valve failure after surgical repair should be considered.

Mitral valve (MV) disease is associated with substantial morbidity and mortality.[1] Patients with severe MV disease are increasingly treated with bioprosthetic valves or repaired with annuloplasty rings.[2] Bioprosthetic tissue valves and native valves that were surgically repaired are prone to failure over time because of tissue degeneration and disease progression, and some patients may require reoperation.[3–6] Almost half of patients may be denied an intervention because of high surgical risk.[7] Reoperation by itself is associated with increased surgical risk,[8,9] particularly in those with heart failure and nonelective operations.[8]

The use of transcatheter heart valves in failed bioprosthetic surgical valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]) is a less invasive alternative approach to conventional surgical reoperation for high-risk patients only.[10–13] However, the current literature is limited by small number of patients and/or short follow-up. In addition, there is paucity of data on the prognostic significance of postprocedural hemodynamics; in particular, the impact of significant residual mitral stenosis (MS) and mitral regurgitation (MR) after these procedures is uncertain. Our objectives were to perform a large-scale analysis examining midterm clinical, hemodynamic, and echocardiographic outcomes after transcatheter mitral ViV and ViR procedures and to evaluate the clinical significance of postprocedure residual MS and MR.

METHODS

Data Collection

The Valve-in-Valve International Data Registry is a multicenter collaboration and has been previously described in detail.[14] Cases were performed between March 2006 and March 2020 in 90 centers worldwide. Anonymized data were collected through the use of a centralized and secure electronic case report form. All included patients provided informed consent for a ViV or ViR procedure. Cases were included in the Registry after local institutional review board approval. Inconsistencies and missing information in the dataset were resolved through direct contact with the participating investigators by the Registry team. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the board of the Institute of Valvular Research at registry@valveinvalve.org.

Definitions

The primary endpoint of this analysis was patient survival and the main secondary endpoints were significant residual MS (defined as immediate postprocedure mean gradient ≥10 mm Hg), significant residual MR (defined as regurgitation ≥ moderate), and rate of repeat MV replacement ([MVR] either transcatheter or surgical). The mechanism of bioprosthetic valve failure was defined according to European Association of Echocardiography and American Society of Echocardiography criteria.[15] The presence of at least moderate MR and MS was defined as mixed failure. Surgical risk was estimated by the Society of Thoracic Surgeons (STS) MVR score. Chronic kidney disease was defined as estimated glomerular filtration rate ≤60 mL/min·1.73 m^2 (ie, stage III and above). Clinical endpoints are reported according to the Mitral Valve Academic Research Consortium (MVARC) definitions (Expanded Methods).[16] Body surface area was calculated with the Mosteller formula.[17] Severe prosthesis-patient mismatch was defined as indexed effective orifice area ≤0.9 cm^2/m^2 for patients with body mass index <30 kg/m^2 and indexed effective orifice area ≤0.75 cm^2/m^2 for those with body mass index ≥30 kg/m^2.[18] Left ventricular outflow tract (LVOT) obstruction was defined as outflow mean gradient ≥10 mm Hg[16] or cardiogenic shock that was clinically related to that complication as reported by the center. The true internal diameter for each model and size of surgical valve/ring was derived from previously published tables, when available.[19] Malposition was reported by the principal operator and defined as inadequate final position of the transcatheter heart valve for any cause, according to MVARC definitions.

Statistical Analysis

Results are presented as mean±SD for continuous variables with normal distribution, median (interquartile range [IQR]; 25th–75th percentiles) for nonnormally distributed continuous variables and number (percentage) for categorical data. Student's *t* test was used to compare means of normally distributed continuous variables between 2 groups. The Mann–Whitney U-test was used to compare distributions of nonnormally distributed continuous variables between 2 groups and the Kruskal–Wallis test was used to compare nonnormally distributed continuous variables between 3 or more groups. χ^2 and Fisher's exact tests were used to compare proportions of categorical variables, as appropriate. Time-to-event curves were truncated at the last point with ≥10% of patients at risk for the primary endpoint (4-year follow-up).

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Logistic regression was utilized to establish independent correlates of significant residual MS and significant residual MR. Cox regression was utilized to establish independent correlates of survival. Given the competing risk of mortality in the evaluation of repeat MVR, a Fine and Gray cause specific subdistribution hazards model was used.[20] The following variables were included in univariable models for significant residual MR and MS: body mass index, age, label size, true internal diameter, baseline MV area, baseline mean mitral gradient, baseline left ventricular ejection fraction, transcatheter heart valve diameter, male sex, mitral ViR (versus ViV), and MR versus MS as the mechanism of failure. In addition to the aforementioned variables, the following were also included in the survival and repeat MVR models: diabetes, peripheral vascular disease, chronic kidney disease, cerebrovascular disease, chronic lung disease, baseline New York Heart Association (NYHA) class IV symptoms (versus others), immediate postprocedural residual mean gradient ≥10 mm Hg, residual MR ≥ moderate, baseline pulmonary artery systolic pressure, transseptal access, and LVOT obstruction, as well as if the case was performed before or after the tenth mitral ViR/ViV of a center (ie, median number of cases performed per center). The proportional hazards assumption was tested for each covariate of the Cox regression and for the final model. A center effect was included in the Cox proportional hazards model in the form of a shared frailty variable. Variables with a *P* value <0.1 in the univariable model were considered for inclusion in the multivariable model, with consideration also given to collinearity and overfitting. Odds ratio (OR), hazard ratio (HR), and subhazard ratio (SHR) are reported for binary logistic, Cox and Fine and Gray models, respectively, with the associated 95% CI. The first author and the corresponding author had full access to the data and vouch for its integrity. A 2-tailed *P* value <0.05 was considered statistically significant. Statistical analyses were performed with SPSS 23 (IBM Corporation, Armonk, NY) and Stata 14.1 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 1079 patients were included: 857 mitral ViV and 222 mitral ViR (Figure I in the Data Supplement). Average age was 73.5±12.5 years, 40.8% of patients were male, and median STS score was 8.6% (IQR, 5.4%–14.1%). As shown in Table 1, mitral ViR patients were younger and more commonly male compared with mitral ViV patients. At baseline, mitral ViR patients had lower ejection fraction, and the proportion of failure by pure MR was significantly higher than in ViV patients. Mitral ViR patients were more frequently in NYHA III/IV than mitral ViV patients (94.9% versus 89.5%, respectively; *P*=0.02). Incomplete rings were present in 9.4% of ViR patients. Table I in the Data Supplement includes detailed information on failed surgical valve and ring models and their characteristics.

Out of 1079 patients, 314 patients (29.1%) underwent their operation between the years of 2006 to 2013, 390 patients (36.1%) between 2014 and 2016, and 375 patients (34.8%) between 2017 and 2020. Baseline and procedural details stratified by procedural year are presented in Tables II and III in the Data Supplement. While the proportion of ViV and ViR cases was not significantly different across the years, there was a significant and progressive decrease in the median STS score (Figure 1). There was also a significant increase in the proportion of transseptal access in more recent years (15.6% in 2006–2013, 30.7% in 2014–2016, and 62.7% in 2017–2020; *P*<0.001). The trend of rates of LVOT obstruction throughout the years (1.6% in 2006–2013, 2.8% in 2014–2016, 3.2% in 2017–2020) was not statistically significant (*P*=0.39). There were also decreases in the rate of major bleeding and acute kidney injury in more recent procedures. Finally, patients in the 2006 to 2013 cohort had a trend toward lower survival (*P*=0.05; Figure II in the Data Supplement).

Procedural Characteristics and Outcomes

Patients were most frequently treated with SAPIEN 3 (Edwards Lifesciences, Irvine, CA; n=446; 41.8%). The most frequent access routes were transapical (n=625; 61.6%) and transseptal (n=375; 36.9%). ViV patients were treated with larger transcatheter heart valves and a lower rate of transseptal access than ViR patients. In terms of procedural complications, ViR patients had higher rates of malposition (7.0% versus 2.4% ViV; *P*=0.001), increased need for second transcatheter valve implantation (10.1% versus 2.8% ViV; *P*<0.001), and higher rates of LVOT obstruction (5.9% versus 1.8% ViV; *P*=0.001).

Clinical Outcomes and Survival

As shown in Table 2, MVARC-defined technical success was higher in ViV than in ViR (93.5% versus 82.0%; *P*<0.001). The rates of MVARC-defined device success were low for both procedures (39.4% total; 32.0% ViR versus 41.3% ViV; *P*=0.01). Immediate postprocedural mean gradient ≥5 mm Hg was the most common cause of device failure (present in 95.9% of unsuccessful ViV cases and 88.4% of unsuccessful ViR cases). Causes of absent procedural success are detailed in Table IV in the Data Supplement. With a modified definition of device failure requiring an immediate postprocedural mean gradient ≥10 mm Hg (instead of ≥5 mm Hg), ViR still had lower rates of device success (63.1% versus 84.0% ViV; *P*<0.001). Finally, when excluding the hemodynamic component of the success definition (ie, residual stenosis or regurgitation), success in mitral ViV was 92.5% and in mitral ViR was 81.5% (*P*<0.001). Almost all included patients were discharged on antiplatelets or anticoagulants (96.2%) after the procedure. The rate of anticoagulation was 71.9% and was not significantly different between mitral ViV and ViR (70.8% versus 76.6%; *P*=0.15).

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Table 1. Baseline Clinical and Echocardiographic Characteristics of the 2 Groups

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
Clinical features				
Male	40.8%	50.9%	38.2%	0.001
Age, y	73.5±12.5	71.2±12.8	74.1±12.4	0.002
Height, cm	165.5±9.7	168.0±9.3	164.9±9.8	<0.001
Weight, kg	70.1±16.7	73.8±17.2	69.1±16.4	<0.001
Body mass index, kg/m2	25.5±5.3	26.1±5.6	25.3±5.2	0.07
New York Heart Association class				0.05
I	0.5%	0.0%	0.6%	
II	9.0%	5.1%	10.0%	
III	59.3%	65.6%	57.7%	
IV	31.3%	29.3%	31.8%	
Time to index surgery, y	9.2 (5.8– 12.8)	6.8 (3.2–10.4)	9.8 (6.5–13.1)	<0.001
Mechanism of failure				<0.001
Regurgitation	15.4%	35.6%	10.2%	
Stenosis	27.6%	15.3%	30.7%	
Mixed	57.1%	49.1%	59.1%	
Label size, mm	28.4±2.1	28.9±2.5	28.2±2.0	<0.001
True internal diameter, mm	25.3±2.6	28.2±2.8	24.7±2.1	<0.001
Diabetes	22.5%	27.6%	21.2%	0.04
Peripheral vascular disease	13.8%	16.1%	13.2%	0.27
Chronic kidney disease	53.4%	62.5%	50.9%	0.003
Atrial fibrillation	49.9%	40.8%	52.3%	0.006
Cerebrovascular disease	15.8%	12.1%	16.7%	0.10
Chronic lung disease	26.9%	29.6%	26.2%	0.32
Permanent pacemaker	26.9%	39.7%	23.6%	<0.001
STS replacement score, %	8.6 (5.4–14.1)	7.4 (4.6–13.0)	9.0 (5.6–14.3)	0.006
Baseline echocardiographic data				
Left ventricular ejection fraction, %	53.2±12.7	45.1±14.8	55.2±11.3	<0.001
Pulmonary artery systolic pressure, mm Hg	59.0±17.8	56.8±17.7	59.5±17.8	0.08
Mitral valve area, cm^2	1.50±0.91	1.87±1.09	1.41±0.83	<0.001
Maximum gradient, mm Hg	22.6±9.9	17.4±11.1	23.8±9.2	<0.001
Mean gradient, mm Hg	10.7±5.9	7.8±5.0	11.4±5.9	<0.001
Mitral regurgitation				<0.001
None/trace	13.5%	6.8%	15.2%	
Mild	13.7%	8.2%	15.1%	
Moderate	12.5%	12.3%	12.6%	
Moderate to Severe	17.4%	25.0%	15.3%	
Severe	43.0%	47.7%	41.7%	

Median absolute follow-up was 492 days (IQR, 76–996) and was similar in the ViV and ViR groups (519 days [IQR, 95.5–1007] versus 426 days (IQR, 40.8–895), respectively; *P*=0.11). Figure 2A shows the Kaplan-Meier survival estimates according to procedure type. Thirty-day mortality was 6.5% in the ViV group and 8.6% in the ViR group (*P*=0.29), while 1-year survival was 86.2% in the ViV group and 76.8% in ViR group (*P*=0.004). In unadjusted analysis, compared with ViV, patients undergoing ViR had significantly lower survival at 4 years (62.5% ViV versus 49.7% ViR; *P*=0.002). Patients at high risk for repeat open-heart surgery (STS score ≥8%) also had significantly worse survival at 4 years (Figure 2B). There was no significant survival difference between patients with transseptal access versus those with other accesses (Figure III in the Data

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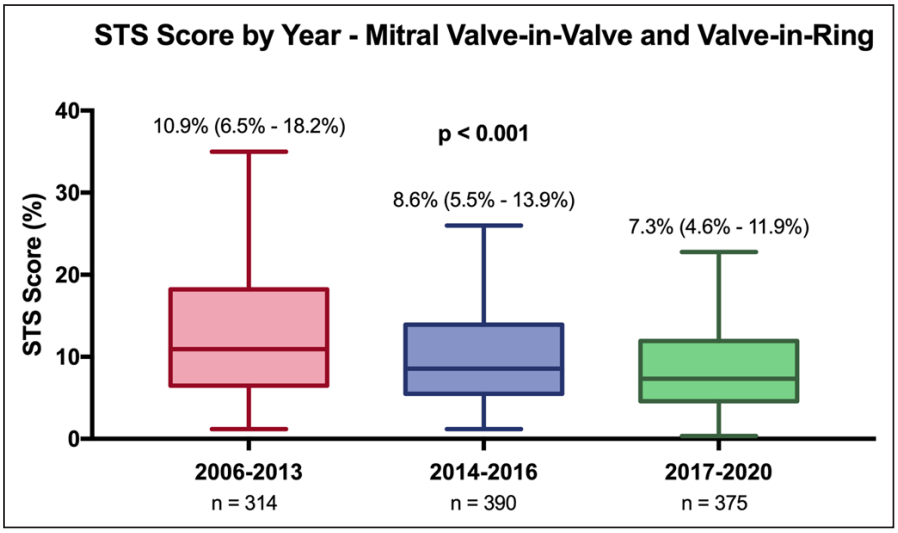


Figure 1. Median Society of Thoracic Surgeons (STS) score across time.
There was a significant decrease in median STS score across the different time periods, indicating a tendency toward the selection of lower risk patients. Numbers represent median and interquartile range.

Supplement). There were no significant 4-year survival differences between mitral ViR patients with semirigid rings and those with rigid/flexible rings (51.1% versus 47.3%, respectively; *P*=0.79), and also no differences between those with complete and incomplete rings (49.5% versus 56.1%, respectively; *P*=0.93). Rates of technical success (81.9% semirigid versus 82.7% rigid/flexible; *P*=0.89) and device success (29.4% semirigid versus 40.4% rigid/flexible; *P*=0.14) were similar between ring types. The overall rate of repeat MVR at 4 years was 2.7% (18 events: 13 open heart surgery, 5 transcatheter), with a higher rate in ViR (5.9% versus 1.9% ViV; *P*<0.001). There was no difference in the 4-year rate of repeat MVR for patients with immediate postprocedural mean gradient ≥5 mm Hg (3.8% versus 1.6% others; *P*=0.64), but the unadjusted 4-year rate of repeat MVR was higher in patients with immediate postprocedural mean gradient ≥10 mm Hg (13.4% versus 2% others; *P*<0.001).

Echocardiographic Follow-Up

An immediate postprocedural mean gradient ≥5 mm Hg was present in 61.4% of all patients, including 67.5% of ViR and 59.9% of ViV patients (*P*=0.05). Significant residual MS (immediate postprocedural mean gradient ≥10 mm Hg) was present in 12.0% of ViR and 8.2% of ViV patients (*P*=0.09). Postimplant significant residual MR was also more common after ViR than ViV (16.6% versus 3.1%; *P*<0.001). Significant residual MR was associated with lower survival at 4 years in unadjusted analysis (35.1% versus 61.6% no residual MR; *P*=0.02; Figure 1C). No such association was found for significant residual MS (66.1% versus 60.5% immediate postprocedural mean gradient <10 mm Hg; *P*=0.89; Figure 1D). Severe postprocedural prosthesis–patient mismatch was present in 24.5% of cases, with no association to 4-year survival (72.7% versus 60.5% no/moderate prosthesis-patient mismatch; *P*=0.13), 4-year repeat MVR (1.3% versus 2.4% no/moderate prosthesis-patient mismatch; *P*=0.83), and/or postprocedural NYHA III/IV functional class (19.4% versus 17.9%; *P*=0.76).

Echocardiographic follow-up of more than 1 year (median time, 772.5 days [IQR 510 – 1211.75]) was available for 446 patients (70.0% of those alive at 1 year). Both mitral ViV and ViR were associated with immediate significant increases in mitral valve area that remained stable during follow-up (Figure 3A). Mitral ViV and ViR procedures immediately reduced mean gradients (Figure 3B). There was, however, a slight but statistically significant increase in mean MV gradients during the follow-up period after ViV (*P*<0.001), but none after ViR (*P*=0.20; Figure 3B). Similar results were obtained when only patients with more than 1 year of echocardiographic follow-up were included in the analysis (Figure IV in the Data Supplement). The rates of significant residual MS were higher in patients with baseline stenosis and smaller true internal diameter (Figure V in the Data Supplement), but at the same time patients with small valves (true internal diameter ≤23 mm) did not have a significant increase in their gradients in follow-up (Figure VI in the Data Supplement). There was a trend for a greater rate of NYHA III/IV symptoms when the immediate postprocedural residual mean gradient was ≥10 mm Hg (26.1% versus 17.8% others; *P*=0.09), but no difference was found when the immediate postprocedural residual mean

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Table 2. Procedural Outcomes of the 2 Groups

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
Transcatheter heart valve diameter, mm	27.1±2.0	26.7±2.0	27.1±2.0	0.01
Access				0.002
Transapical	61.6%	50.7%	64.4%	
Transseptal	36.9%	46.4%	34.5%	
Right thoracotomy	1.0%	1.9%	0.7%	
Other	0.5%	0.9%	0.4%	
General anesthesia	97.4%	96.4%	97.6%	0.36
Transesophageal echocardiography	97.3%	98.0%	97.1%	0.50
Preinflation	19.0%	24.0%	17.8%	0.05
Postinflation	12.4%	28.8%	8.4%	<0.001
Vascular complications				0.06
Minor	2.3%	1.4%	2.5%	
Major	2.7%	0.5%	3.2%	
Major bleeding complication	8.0%	4.7%	8.8%	0.05
Acute kidney injury	9.6%	13.0%	8.8%	0.07
Success and components				
Technical success*	91.1%	82.0%	93.5%	<0.001
Device success†	39.4%	32.0%	41.3%	0.01
Modified device success‡	79.7%	63.1%	84.0%	<0.001
Device success without hemodynamics criteria§	90.3%	81.5%	92.5%	<0.001
Malposition/embolization/migration	3.3%	7.0%	2.4%	0.001
Second transcatheter heart valve needed	4.3%	10.1%	2.8%	<0.001
Mean gradient ≥5 mm Hg	61.4%	67.5%	59.9%	0.05
Mean gradient ≥10 mm Hg	8.9%	12.0%	8.2%	0.09
Mitral regurgitation ≥moderate	5.8%	16.6%	3.1%	<0.001
Major stroke	1.2%	0.5%	1.4%	0.27
Left ventricular outflow tract obstruction	2.6%	5.9%	1.8%	0.001
Procedural mortality	1.8%	0.5%	2.1%	0.10
30-day mortality	7.0%	8.6%	6.5%	0.29
Discharge medications				0.01
Single antiplatelet alone	12.7%	10.8%	13.2%	
Single antiplatelet and anticoagulation	38.2%	46.8%	36.1%	
Double antiplatelet	11.4%	10.1%	11.8%	
Double antiplatelet and anticoagulation	2.8%	5.1%	2.2%	
Warfarin/coumadin alone	26.8%	19.6%	28.6%	
Novel oral anticoagulants alone	4.2%	5.1%	3.9%	
Other	0.1%	0.6%	0.0%	
None	3.8%	1.9%	4.2%	
Immediate postprocedural echocardiographic data				
Left ventricular ejection fraction, %	52.1±12.8	45.2±15.4	53.8±11.4	<0.001
Mitral valve area, cm^2	2.04±0.74	2.13±0.74	2.01±0.74	0.17
Severe patient–prosthesis mismatch	24.5%	26.9%	23.8%	0.54
Maximum gradient, mm Hg	12.6±5.6	12.1±5.6	12.7±5.6	0.24
Mean gradient, mm Hg	5.7±2.8	6.0±2.8	5.6±2.7	0.08
Mitral regurgitation				<0.001

(*Continued*)

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Table 2. Continued

	Total (n=1079)	Mitral valve-in-ring (n=222)	Mitral valve-in-valve (n=857)	*P* value
None/trace	71.7%	50.7%	77.0%	
Mild	22.5%	32.7%	19.9%	
Moderate	5.0%	12.8%	2.9%	
Moderate to Severe	0.5%	2.4%	0.0%	
Severe	0.4%	1.4%	0.1%	

*Technical success: absence of procedural mortality, and successful access, delivery and retrieval of the device delivery system, successful deployment and correct positioning of the first intended device, and freedom from emergency surgery or reintervention related to the device or access procedure.

†Device success: absence of procedural mortality or stroke, proper placement and positioning of the device, freedom from unplanned surgical or interventional procedures related to the device or access procedure, continued intended safety and performance of the device, including no evidence of structural or functional failure, no specific device-related technical failure issues, and complications and reduction of mitral regurgitation to either optimal or acceptable levels without significant mitral stenosis (ie, postprocedure effective regurgitant orifice area is ≥1.5 cm^2 with a transmitral gradient <5 mm Hg), and with no greater than mild (>1) paravalvular MR (and without associated hemolysis).

‡≥10 mm Hg considered as a cut-off.

§Only the components of device success not related to hemodynamics (ie, procedural death, malposition/embolization/migration, second transcatheter heart valve, left ventricular outflow tract obstruction, and stroke) considered.

gradient was ≥5 mm Hg (17.8% versus 19.9% others; *P*=0.48). As shown in Figure 4, there were significant postprocedural decreases in MR severity after both ViV and ViR procedures. The distribution of MR severity remained stable during follow-up after ViR procedures. In contrast, the proportion of cases with MR severity of moderate or more increased over time in the ViV group.

Multivariable Analyses

In a Cox regression model, mitral ViR as compared with ViV was independently associated with mortality (HR, 1.52; 95% CI, 1.03–2.25; *P*=0.04; Figure 5). The 4-year adjusted survival was 66.7% for mitral ViV and 53.8% for mitral ViR (Figure VII in the Data Supplement). In addition, both significant residual MS (SHR, 4.67; 95% CI, 1.74–12.56; *P*=0.002) and significant residual MR (SHR, 7.88; 95% CI, 2.88–21.53; *P*<0.001) were independent predictors of the need for repeat MVR (Figure 5; Figure VIII in the Data Supplement). Independent predictors for significant residual MS were small device true internal diameter, young age, and a larger body mass index (Figure 5). Finally, the only independent predictor of significant residual MR was a ViR procedure (OR, 7.90; 95% CI, 4.01–15.56; *P*<0.001; Figure 5). Table V in the Data Supplement contains further details on the univariable and multivariable models.

DISCUSSION

ViV and ViR procedures are increasingly performed to treat failing mitral valves after open heart surgery. The current analysis is the largest and most comprehensive evaluation of mitral ViV and ViR procedures to date with the longest follow-up reported. This is also the first analysis to extensively detail echocardiographic findings at ≥1 year. The major findings include: (1) transcatheter heart valve implantation in failed surgical mitral valves has acceptable safety and clinical outcomes over the medium-term in a selected group of high-risk patients; (2) 4-year survival was low after both procedures, and was especially notable after ViR (49.7% survival within 4 years for patients with an average age of 71 years), which was also associated with a higher rate of significant residual MR and LVOT obstruction; (3) significant residual MR was associated with lower 4-year survival (35.1% versus 61.6% other patients); (4) both ViV and ViR were commonly associated with residual stenosis (immediate postprocedural mean gradient ≥5 mm Hg in 61% of cases and ≥10 mm Hg in 9% of cases), which was associated with need for repeat MVR and a trend toward worse heart failure symptoms, but not 4-year survival (66.1% versus 60.5% other patients); and (5) the severity of MS and MR increased in ViV procedures, but not in ViR, with a significant loss of echocardiographic follow-up. It is apparent that the durability of these mitral procedures should be further explored, as other major findings were a significant shift towards treating lower risk patients, and an increasing utilization of transseptal access over time.

Survival Analysis

Until recently, the mitral ViV and ViR reports in the literature were limited to single center or small multicenter studies, mainly reporting 30-day and 1-year outcomes.[13,21–24] A small study with 91 patients from a single center reported 35.7% 2-year mortality.[25] The largest cohort to date with more than 30 days follow-up (463 mitral ViV and ViR patients) showed that 1-year mortality was significantly higher in mitral ViR patients at 30.6%, compared with 14% in mitral ViV patients.[10] These results are similar to our own 1-year mortality findings of 23.2% and 13.8%, respectively. In terms of

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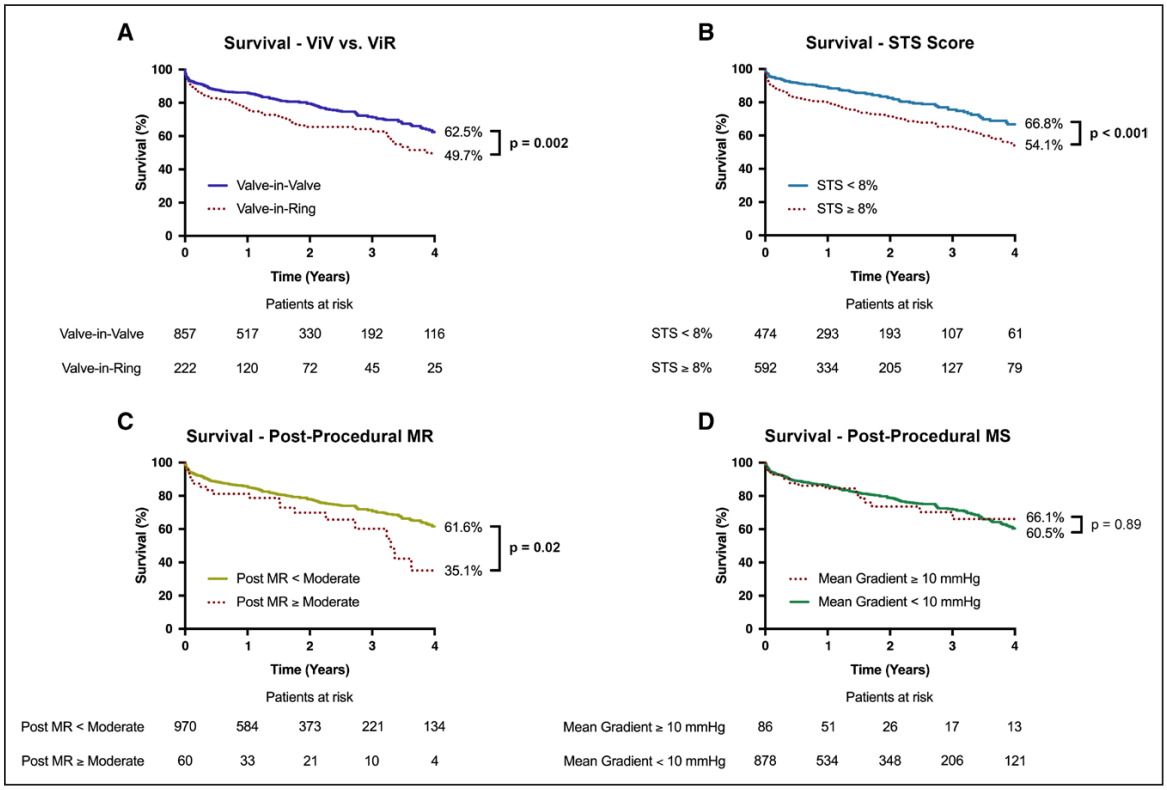


Figure 2. Kaplan-Meier survival curves in different patient subgroups.
A, ViV vs ViR. **B**, STS MVR score <8% vs ≥8%. **C**, Postprocedural MR ≥ moderate vs < moderate. **D**, Immediate postprocedural mean mitral gradient ≥10 mm Hg vs <10 mm Hg. ViR patients, those with STS score ≥ 8% and postprocedural MR ≥ moderate had lower survival at 4 years. No difference in 4-year survival was found for those with mean gradients ≥10 mm Hg. MR indicates mitral regurgitation; MS, mitral stenosis; STS, Society of Thoracic Surgeons; ViR, valve-in-ring; and ViV, valve-in-valve.

predictors of all-cause mortality, our study is in agreement with previous analyses showing the association of mitral ViR and chronic lung disease with clinical outcomes.[10] While that study chose to include STS score in multivariable analyses,[10] our evaluation shows the predictive importance of individual components of this score, including age, chronic kidney disease, baseline functional class, and others that are not included in this score, such as baseline pulmonary hypertension.

The present large-scale study demonstrates that the worse survival in mitral ViR patients persists at 4 years and that approximately half of these patients have died within that time frame. While the 37.5% 4-year mortality of mitral ViV patients is also of concern, the markedly decreased survival after mitral ViR procedures emphasizes the need for alternative therapies geared toward patients with failed surgical ring annuloplasty, including surgical reoperation.[26] It also highlights the need for improved patient selection. Comparison of mitral ViV and ViR results with surgical reoperation outcomes is challenging, given the dissimilarity in risk profile in patients referred for transcatheter strategy, in comparison to those having redo open heart surgery. One study with 1627 Medicare beneficiaries undergoing mitral valve reoperation reports 3-year survival of 68.1%.[8] Our results were comparable, with 3-year survival of 64.2% and 71.6% for mitral ViR and ViV patients, respectively. Although this surgical registry did not report STS scores, these naturally represented a cohort who were deemed operable. This is consistent with higher baseline comorbidity rates in our population of chronic kidney disease, peripheral vascular disease and history of cerebrovascular disease compared with the surgical study.[8] To date no head-to-head randomized comparison of transcatheter ViV/ViR versus surgical reoperation has been performed, and therefore objective contrasting is limited.

In our study, we identified a significant decrease in the risk scores of included patients, demonstrating that operators became progressively more comfortable in offering ViV and ViR to lower risk individuals. Additionally, we also saw an increase in the rates of transseptal access over time. While transapical access has been previously associated with worse outcomes in aortic procedures, we did not identify a survival difference in the current cohort. Our study confirms the findings of other studies that have not identified a survival advantage

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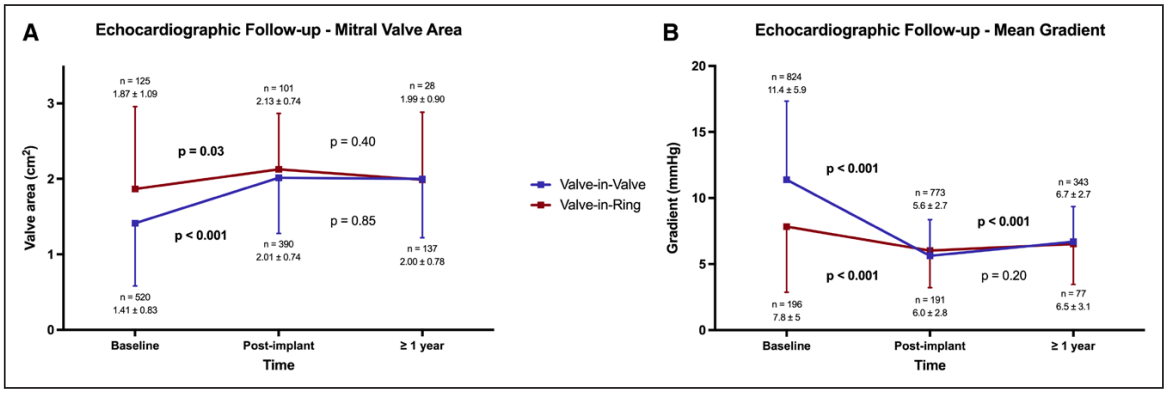


Figure 3. Echocardiographic findings at baseline and during follow-up after mitral ViV and ViR.
A, Mean mitral valve area. **B**, Mean mitral valve gradient. A slight increase in mean gradient occurred in mitral ViV patients. ViR indicates valve-in-ring; and ViV, valve-in-valve.

for transseptal access in transcatheter mitral ViV and ViR procedures, both at 30 days[12] and at 1 year.[10] Even though procedural invasiveness is reduced with transseptal access, it is likely that survival differences would be more closely related to patient characteristics and not as much to procedural aspects, especially considering that transapical access is performed for several years by experienced operators for this indication.

Specific Technical Challenges of Mitral ViR

There are several explanations for the worse outcomes after transcatheter ViR procedures. First, annuloplasty rings have many different shapes, not all of which are amenable to circular deformation.[27] Currently available transcatheter valves were all designed for use in the aortic valve, which is more circular in shape. The mismatch in the shape of the annulus and the transcatheter valve creates a greater likelihood for formation of gaps and consequently worse hemodynamics, particularly in rigid and noncircular rings, including more residual MR and device underexpansion.[12] This is less a concern with ViV, in that failed tissue valve rings are circular and more closely conform to the newly implanted valves. Second, mitral ViR is more prone to procedural complications than ViV. Malposition and need for a second transcatheter valve were significantly more common with ViR in our study. Transcatheter heart valves in the mitral position are subjected to higher closing pressures from the left ventricle during

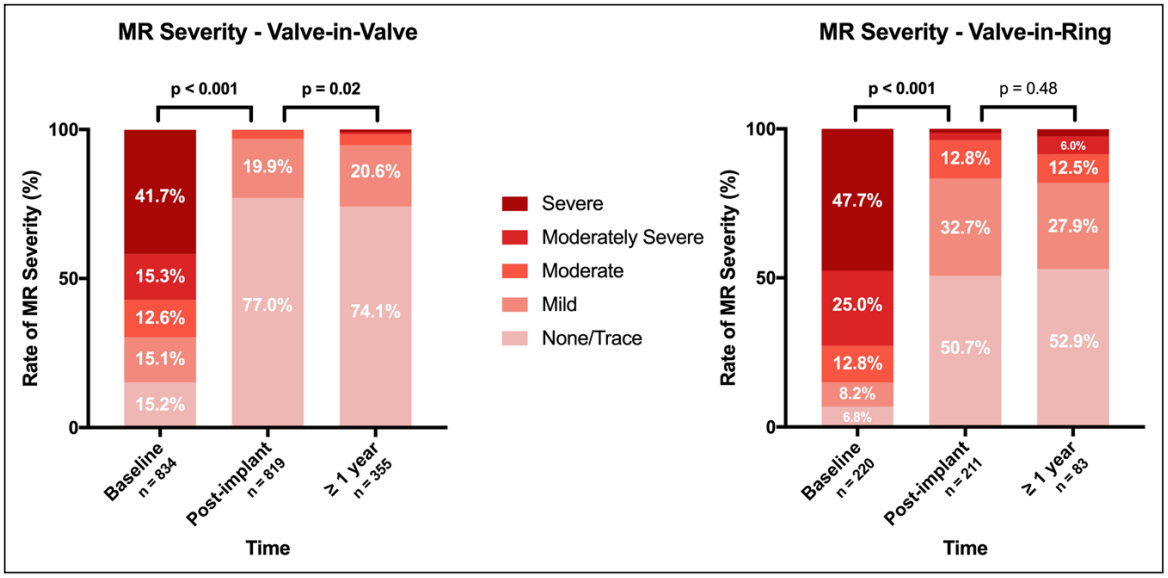


Figure 4. Echocardiographic follow-up of mitral regurgitation in mitral ViV and ViR patients.
Significant immediate decreases in mitral regurgitation severity occurred in both the ViV and ViR groups. The distribution of mitral regurgitation severity in ViR remained stable during follow-up, but there was a significant increase in the proportion of moderate and above mitral regurgitation in the ViV group. MR indicates mitral regurgitation; ViR, valve-in-ring; and ViV, valve-in-valve.

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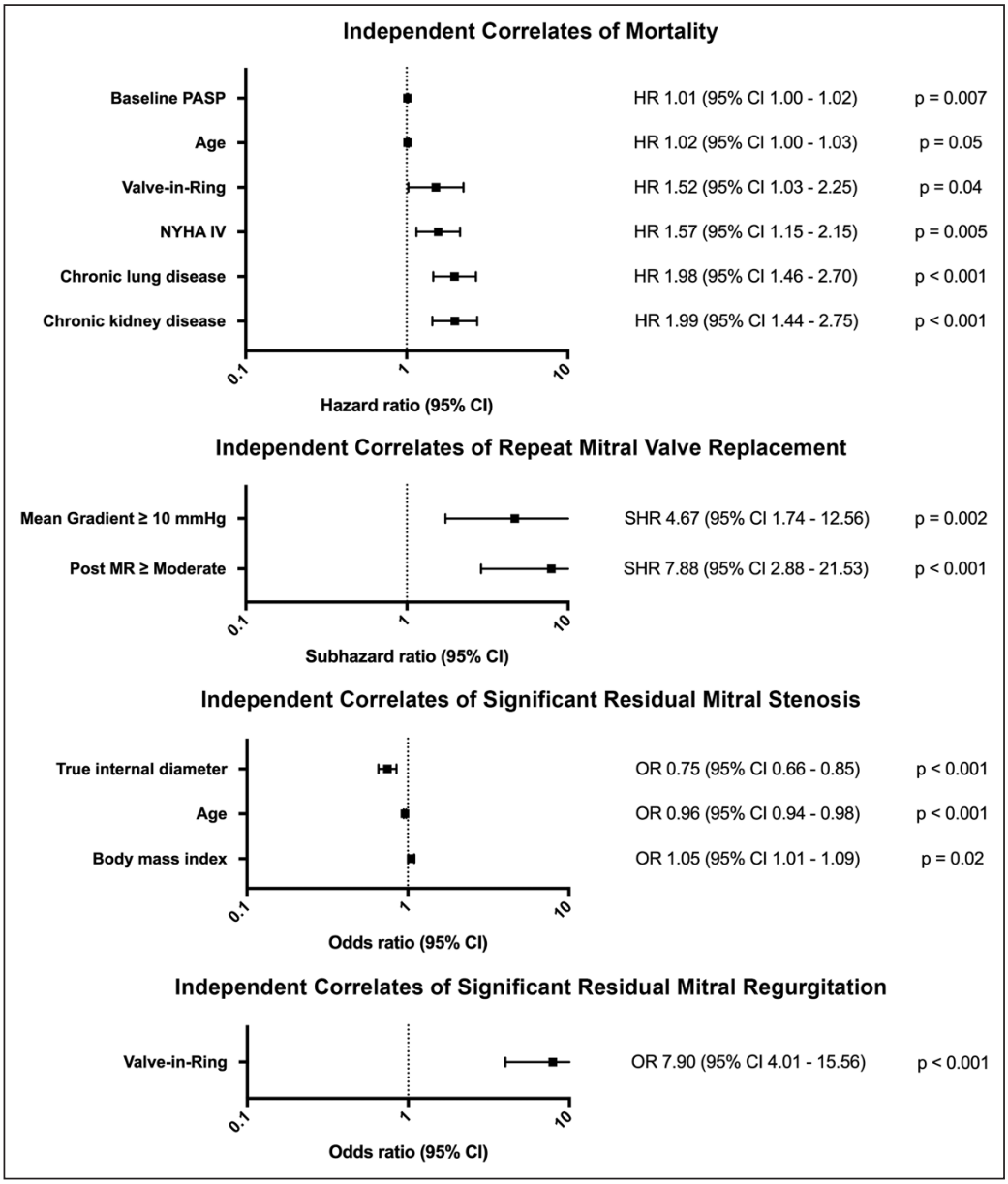


Figure 5. Multivariable models for mortality, repeat mitral valve replacement, residual mean gradient ≥10 mm Hg and residual mitral regurgitation ≥ moderate.

HR indicates hazard ratio; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; PASP, pulmonary artery systolic pressure; and SHR, subhazard ratio.

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systole that may lead to reduced anchoring.[28] The need for a second heart valve adds to procedure complexity and cost, and its suboptimal expansion may be associated with complications such as thrombosis or early degeneration. Another major complication that is much more common in ViR than ViV is LVOT obstruction. This complication is potentially life-threatening but may be predicted and prevented by one of several technical approaches.[29,30] The possibility of selection bias attributable to exclusion of patients with small neo-LVOT from mitral ViV and ViR procedures from the current cohort should be noted. Third, intrinsic characteristics of the ViR patient population at baseline, including worse left ventricular function and greater comorbidities than in patients undergoing ViV procedures, may also limit the potential benefits obtained by the procedure. Nonetheless, in multivariable analysis, ViR was associated with substantially greater mortality than ViV procedures.

Postprocedural Mitral Regurgitation and Stenosis After ViV and ViR Procedures

The consequences of postprocedural MR and MS after ViV and ViR procedures have not been previously explored in depth. Suboptimal postprocedure hemodynamics are known to influence clinical outcomes in other mitral interventions, such as MitraClip (Abbott Vascular, Menlo Park, CA).[31] Residual stenosis with mean gradients ≥5 mm Hg is common after ViV and ViR. This finding, revealed in our study, is reflected by relatively low rates of MVARC-defined device success. However, immediate postprocedural mean gradients 5 to 9.9 mm Hg were not associated with worse clinical outcomes, such as 4-year survival, 4-year repeat MVR, and NYHA functional class. Although significant residual MS (≥10 mm Hg) was not associated with increased 4-year mortality in our cohort, it was an independent predictor of the need for MVR, and a trend toward more severe heart failure symptoms. Therefore, 10 mm Hg may be a more appropriate cut-off for success in mitral ViV and ViR procedures. Mean gradient between 5 and 9.9 mm Hg after these procedures might be acceptable in selected patients. Strategies to reduce residual stenosis may include a more ventricular device position and, in selected cases, fracturing the bioprosthetic valve ring.[32,33] However, high pressure dilatation has limited value in mitral ViR and is potentially associated with several safety concerns. Postimplant significant residual MR was also associated with the later need for repeat MVR. The fact that there was a slight worsening in valve hemodynamics over follow-up (higher gradients and more significant regurgitation) is concerning. Longer follow-up is warranted to further evaluate the durability of implanted transcatheter valves after mitral ViV and ViR procedures.

Study Limitations

Our study has important limitations that should be taken into account. First, our study did not have a control arm of other possible alternative treatments for failed mitral valves or rings, such as repeat surgical MVR or repair. We have also not collected data on cases with failed surgical valves or rings that did not undergo ViV or ViR and were instead treated with medications alone. Second, it was a retrospective and nonrandomized study without core laboratory evaluation. Echocardiographic follow-up for 30% of patients confirmed alive at 1 year is missing from longer follow-up. As with many other retrospective and industry-independent studies, our study has some degree of missing data, although this issue is quite limited (commonly 2% to 3%; Table VI in the Data Supplement). Our data regarding MR does not differentiate between transvalvular and paravalvular MR. We have not systematically collected data on hemolysis or leaflet thrombosis. Small increases in gradients during follow-up may represent stroke volume improvement. However, we did not collect the additional echocardiographic parameters needed to evaluate this possibility. Although the case number is high, the included procedures are spread over 90 centers and a long period of time (14 years). Transapical access was utilized in the majority of cases. While we did not identify a survival difference, transapical access may add to procedural morbidity and is less commonly utilized nowadays. In addition, multiple device types have been included in the current analysis, as performed in real world practice, and our ability to examine clinical outcomes of several devices that are rarely utilized is limited. We have not systematically collected data on procedures to treat or prevent LVOT obstruction. We have also not collected LVOT gradients in patients not reported to have an LVOT obstruction per MVARC definition. The reasons for second valve implantation were not available in our database. Finally, while the currently available follow-up is the longest reported to date, longer-term follow-up (eg, 8–10 years) is required to assess late outcomes of ViV and ViR.

Conclusions

Mitral ViV has acceptable safety and clinical outcomes in a select group of high-risk patients. Mitral ViR may need further evaluation, as it is associated to lower success and survival rates, and higher rates of postprocedural MR. Significant residual MS and/or MR were not infrequent after mitral ViV and ViR procedures and were both associated with a need for repeat valve replacement. Strategies should be explored to prevent residual MR and MS, aiming to prolong device durability and patient symptom-free survival after ViV and ViR procedures.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Figures I–VIII
Data Supplement Tables I–VI

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Supplemental Materials

Data Supplement Figures I–VIII
Data Supplement Tables I–VI

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Impact of COVID-19 Pandemic on Mechanical Reperfusion for Patients With STEMI

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ABSTRACT

BACKGROUND The fear of contagion during the coronavirus disease-2019 (COVID-19) pandemic may have potentially refrained patients with ST-segment elevation myocardial infarction (STEMI) from accessing the emergency system, with subsequent impact on mortality.

OBJECTIVES The ISACS-STEMI COVID-19 registry aims to estimate the true impact of the COVID-19 pandemic on the treatment and outcome of patients with STEMI treated by primary percutaneous coronary intervention (PPCI), with identification of "at-risk" patient cohorts for failure to present or delays to treatment.

METHODS This retrospective registry was performed in European high-volume PPCI centers and assessed patients with STEMI treated with PPPCI in March/April 2019 and 2020. Main outcomes are the incidences of PPCI, delayed treatment, and in-hospital mortality.

RESULTS A total of 6,609 patients underwent PPCI in 77 centers, located in 18 countries. In 2020, during the pandemic, there was a significant reduction in PPCI as compared with 2019 (incidence rate ratio: 0.811; 95% confidence interval: 0.78 to 0.84; $p < 0.0001$). The heterogeneity among centers was not related to the incidence of death due to COVID-19. A significant interaction was observed for patients with arterial hypertension, who were less frequently admitted in 2020 than in 2019. Furthermore, the pandemic was associated with a significant increase in door-to-balloon and total ischemia times, which may have contributed to the higher mortality during the pandemic.

CONCLUSIONS The COVID-19 pandemic had significant impact on the treatment of patients with STEMI, with a 19% reduction in PPCI procedures, especially among patients suffering from hypertension, and a longer delay to treatment, which may have contributed to the increased mortality during the pandemic. (Primary Angioplasty for STEMI During COVID-19 Pandemic [ISACS-STEMI COVID-19] Registry; NCT04412655). (J Am Coll Cardiol 2020;76:2321–30) © 2020 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

DES = drug-eluting stent(s)

IRR = incidence rate ratio

PCI = percutaneous coronary intervention

PPCI = primary PCI

STEMI = ST-segment elevation myocardial infarction

The global pandemic of coronavirus disease-2019 (COVID-19) has dramatically affected health care, and the effects are ongoing. The outbreak was initially identified in Wuhan, China, in December 2019 (1), and recognized as a pandemic on March 11, 2020. As of May 26, 2020, more than 5.54 million cases of COVID-19 have been reported in 185 countries and territories, resulting in more than 348,000 deaths, especially in Europe and the United States.

During this pandemic period, health care resources have understandably been focused on the treatment of patients with COVID-19, with many clinical units converted to treat patients with COVID-19, limiting access for patients with chronic conditions while maintaining acute services for the treatment of acute coronary syndrome (ACS), particularly ST-segment elevation myocardial infarction (STEMI). Combined with this diversion of resource, lockdown rules, guidance on social distancing, and a public fear of coronavirus contagion appear to have affected patient willingness to present to hospital, as evidenced

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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by a reduction in percutaneous coronary intervention (PCI) procedures for ACS, including STEMI (2–7). The observation of extended time from symptom onset to treatment (8–10) is certainly expected to heavily affect mortality for acute myocardial infarction worldwide.

The ISACS-STEMI (International Study on Acute Coronary Syndromes-ST Elevation Myocardial Infarction) COVID-19 was established in response to the emerging outbreak of COVID-19 to provide a European snapshot and aims to estimate the true impact of the COVID-19 pandemic on the treatment and outcome of patients with STEMI treated by primary angioplasty, with identification of "at-risk" patient cohorts for failure to present or delays to treatment.

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METHODS

STUDY DESIGN AND POPULATION. This is a retrospective multicenter registry promoted by the Eastern Piedmont University, Novara, Italy, planned to include at least 40 European primary PCI (PPCI) centers, performing more than 120 PPCIs per year (with expected average >10/month), with the case load of STEMI not expected to be affected by a potential planned reorganization of the STEMI network. The inclusion period was 2 months (from March 1 to April 30). The data were compared with those retrospectively collected in the same time window (from March 1 to April 30) of 2019.

INCLUSION CRITERIA. STEMI treated by primary angioplasty (including mechanical reperfusion for failed thrombolysis).

DATA COLLECTION. Anonymized data were collected through a dedicated case report form (CRF). Each center identified a local principal investigator. We collected demographic, clinical, and procedural data, including total ischemia time, door-to-balloon time, referral to primary PCI facility, COVID positivity, PCI procedural data, and in-hospital mortality. After collection, each participating center submitted the CRF to the coordinating unit Eastern Piedmont University, in charge of reporting all data onto the central electronic database. Data were finally checked for missing or contradictory entries.

STUDY OUTCOMES. Study outcomes included: 1) number of patients with STEMI undergoing percutaneous revascularization; 2) proportion of patients with ischemia time >12 h; 3) proportion of patients with a door-to-balloon time >30 min; and 4) in-hospital mortality.

STATISTICS. Data were analyzed using SPSS Statistics Software 23.0 (IBM SPSS Inc., Chicago, Illinois) and R software (version 3.6.2) by an independent statistician (GC). Quantitative variables were described using median and interquartile range. Means and confidence intervals (CIs) were obtained assuming Poisson distributions for count data. Incidence rate ratio (IRR) was defined as the ratio between count data in 2019 and 2020, over the same population and time period. Poisson regression models (with log link function) were applied to compare the incidence rate of PPCI per million of residents per year in 2019 with the same rate in 2020, correcting for possible impact of major risk factors (11). Details are described in the Supplemental Appendix. Analysis was also conducted according to major European geographic areas (Supplemental Appendix) and subgroups of patients, such as according to age, sex, diabetes, and hypertension.

A subsequent analysis was based on individual data that were grouped according to the year of the intervention (2019 vs. 2020). Absolute frequencies and percentages were used for qualitative variables. Analysis of variance or Mann-Whitney *U* test and chi-square test were used for continuous and categorical variables, respectively. Normal distribution of continuous variables was tested by the Kolmogorov-Smirnov test.

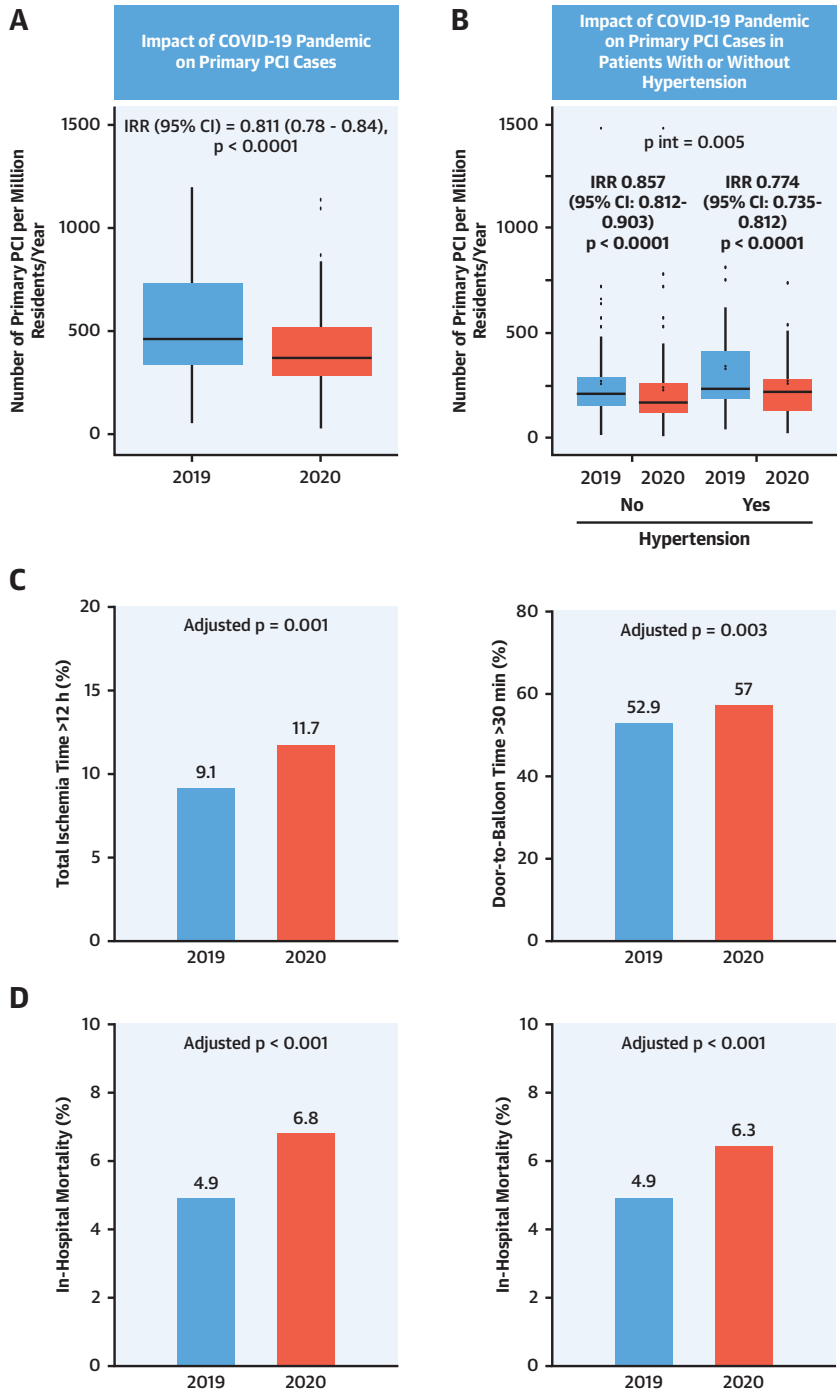
Multivariable logistic regression analyses were performed to identify the impact of the year of intervention on time delays and mortality after adjustment for baseline confounding factors between the 2 groups. All significant variables (set at $p < 0.10$) were entered in block into the model. A $p < 0.05$ was considered statistically significant. The data coordinating center was established at the Eastern Piedmont University.

SAMPLE SIZE CALCULATION. In view of the observational nature of this registry, no sample size calculations or statistical power analyses were performed. However, with the participation of at least 40 high-volume centers, with approximately 40 patients per center (based on average PPCI per month), we expected the inclusion of at least 1,600 patients with STEMI for 2019.

ETHICAL ISSUES. The study is a retrospective registry, with anonymized data collection, therefore

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CENTRAL ILLUSTRATION **Impact of Coronavirus Disease-2019 Pandemic Primary Percutaneous Coronary Intervention Cases, on Time Delays and Mortality**

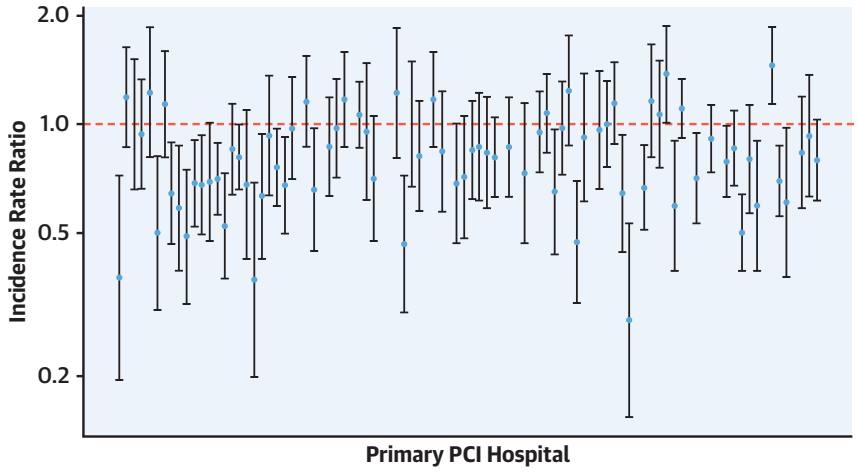


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FIGURE 1 Impact of COVID-19 Pandemic on Mechanical Reperfusion for STEMI



Forest plot of the incidence rate ratio on the log-scaled axis, with 95% confidence interval, across each hospital center. COVID-19 = coronavirus disease-2019; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

formal approval from the ethical committee was deemed not necessary; however, it was approved by the Ethical Committee of AOU Maggiore della Carità, Novara. The need to notify or ask for approval to the local ethical committees was left to each investigator's discretion according to local and national regulations.

RESULTS

A total of 77 European centers agreed to participate, including a total of 6,609 patients with STEMI undergoing mechanical reperfusion: 3,653 patients in 2019 and 2,956 patients in 2020. Characteristics of study centers are reported in Supplemental Table 1. Almost all European countries were represented (Supplemental Figure 1, Supplemental Table 1), especially Italy (n = 24), Spain (n = 13), and the Netherlands (n = 9). The number of STEMIs treated percutaneously per million residents had a consistent reduction, on average, from 595 (95% CI: 548 to 645) in 2019 to 494 (95% CI: 451 to 539) in 2020 (**Central Illustration**, Supplemental Figure 2). The IRR was 0.811 (95% CI: 0.78 to 0.84; $p < 0.0001$), showing a significant reduction of 18.9% in the number of STEMIs from 2019 to 2020. A significant heterogeneity was observed among centers (IRR had high variability between centers measured by SE = 0.18 in a random effect Poisson model; chi-square analysis of variance test with $p < 0.001$) (**Figure 1**). A significant reduction was observed in 39% of the centers under investigation, and was not related to the incidence of COVID disease, neither to the COVID mortality. In fact, the reduction in STEMI procedures was not associated with the number of COVID-positive patients, at both local ($p = 0.31$) (Supplemental Figure 3) and national levels ($p = 0.79$) (Supplemental Figure 4), neither with national ($p = 0.36$) (Supplemental Figure 5) nor local number ($p = 0.82$) (Supplemental Figure 6) of COVID-related deaths. Moreover, the reduction in STEMI procedures was not associated with the type of institutional center (private [1], academic [2], or

CENTRAL ILLUSTRATION Continued

Box-and-whisker plot showing the number of patients with STEMI treated by mechanical reperfusion per million of inhabitants/year in 2019 and 2020 in the overall population **(A)** and according to hypertension, the only clinical variable significantly affecting the number of cases **(B)**. **Bar graphs** show the association between the year of intervention with time delays (ischemia time longer than 12 h, **left graph**) and door-to-balloon time longer than 30 min, **right graph (C)**. **Bar graphs** show the association between the year of intervention with in-hospital mortality with (left graph) and without **(right graph)** COVID-positive patients **(D)**. CI = confidence interval; COVID-19 = coronavirus-2019; IRR = incidence rate ratio; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial intervention.

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TABLE 1 Baseline Demographic and Clinical Characteristics

	2019 (n = 3,484)	2020 (n = 2,811)	p Value
Age, yrs	64 (55-73)	64 (55-73)	0.64*
Age >75 yrs	758 (21.8)	598 (21.3)	0.65
Male	2,567 (73.7)	2,095 (74.5)	0.45
Medical history			
Diabetes mellitus			0.18
Type 1	130 (3.7)	81 (2.9)	
Type 2	629 (18.1)	516 (18.4)	
Hypertension	1,906 (54.7)	1,501 (53.4)	0.30
Hypercholesterolemia	1,445 (41.5)	1,195 (42.5)	0.40
Active smoker	1,438 (41.3)	1,155 (41.1)	0.89
Family history of CAD	837 (24.0)	658 (23.4)	0.57
Previous STEMI	327 (9.4)	272 (9.7)	0.73
Previous PCI	439 (12.6)	354 (12.6)	0.94
Previous CABG	59 (1.7)	55 (2.0)	0.43
Geographic area			0.037
Italy	964 (27.7)	779 (27.7)	
Iberian Peninsula	549 (15.8)	445 (15.8)	
Central Europe	910 (26.1)	742 (26.4)	
Balkan Peninsula	454 (13.0)	301 (10.7)	
Northeast Europe	607 (17.4)	544 (19.4)	
Referral to primary PCI hospital			
Type			0.005
Direct access to Hub	649 (18.6)	497 (17.7)	
Ambulance (from community)	1,893 (54.3)	1,639 (58.3)	
Transfer from spoke	942 (27.0)	675 (24.0)	
Time delays			
Total ischemia, min	181 (120-301)	200 (127-357)	0.004*
Total ischemia time, h			0.003
<6	2,732 (78.4)	2,109 (75.0)	
6-12	437 (12.5)	374 (13.3)	
12-24	196 (5.6)	193 (6.9)	
>24 h	119 (3.4)	135 (4.8)	
Total ischemia time >12 h	316 (9.1)	328 (11.7)	<0.001
Door-to-balloon time, min	34 (21-36)	36 (24-60)	0.007*
Door-to-balloon time, min			0.005
<30	1,640 (47.1)	1,209 (43)	
30-60	1,066 (30.6)	917 (32.6)	
>60	778 (22.3)	685 (24.4)	
Door-to-balloon time >30 min	1,843 (52.9)	1,602 (57)	<0.001
Clinical presentation			
Anterior STEMI	1,592 (45.7)	1,279 (45.5)	0.86
Out-of-hospital cardiac arrest	231 (6.6)	198 (7.0)	0.51
Cardiogenic shock	267 (7.7)	247 (8.8)	0.11
Rescue PCI for failed thrombolysis	124 (3.6)	95 (3.4)	0.70

Values are median (interquartile range) or n (%). *Mann-Whitney *U* test.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; IQR = interquartile range; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

nonacademic [3] hospitals; IRR: 0.989; 95% CI: 0.774 to 1.205; p = 0.925 type 2 vs. 1; IRR: 1.058; 95% CI: 0.843 to 1.273; p = 0.249 type 3 vs. 2). All participating geographic areas had a significant reduction in STEMI, especially the Balkans (Supplemental Figures 7 to 9). Furthermore, we used Poisson regression to investigate the reduction in STEMI in subgroups of subjects, by age (≤75, >75), sex, diabetes, and hypertension, and found a significant difference in this reduction (10%) only between subjects with (IRR: 0.857; 95% CI: 0.812 to 0.903; p < 0.0001) and without hypertension (IRR: 0.774; 95% CI: 0.735 to 0.812; p < 0.0001) (p interaction = 0.005) (Supplemental Figures 10 to 12). No significant differences were found for the other risk factors (Supplemental Figures 10 to 13).

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS. Individual data analysis was restricted to 6,295 patients with complete demographic, clinical procedural, and outcome data (complete cases, 95.2%), 3,484 in 2019 and 2,811 in 2020. Table 1 shows baseline characteristics of the 2 groups of patients according to the year of intervention. No difference was observed in baseline characteristics. We found a different distribution across the centers.

As shown in Table 1, we observed a significant difference in referral to primary PCI facility, with a larger number of patients reaching the primary PCI center by ambulance with direct transfer from community in 2020 as compared with 2019. Despite a greater proportion of patients presenting by the most efficient route, patients treated in 2020 had a significantly longer total ischemia and door-to-balloon time (Table 1, Central Illustration). The association between the COVID pandemic and ischemia time longer than 12 h was confirmed after correction for baseline clinical confounders (geographic area, direct access by ambulance, door-to-balloon, radial access, multivessel disease, use of drug-eluting stent [DES]) (adjusted odds ratio [OR]: 1.34; 95% CI: 1.13 to 1.58; p = 0.001). No significant interaction was observed for major risk factors (age, p = 0.11; sex, p = 0.65; diabetes, p = 0.83; hypertension, p = 0.13).

The association between the COVID pandemic and door-to-balloon longer than 30 min was confirmed after correction for baseline clinical confounders (geographic area, direct access by ambulance, ischemia time, radial access, multivessel disease, use of DES) (adjusted OR: 1.17; 95% CI: 1.05 to 1.29; p = 0.003, respectively). No significant interaction was observed for major risk factors (age, p = 0.83; sex, p = 0.49; diabetes, p = 0.55; with a significant interaction for hypertension, p = 0.044) (patients with hypertension had a shorter door-to-balloon time in 2019 [p < 0.001] but not in 2020 as compared with patients without hypertension).

No difference was observed in the rate of cardiogenic shock at presentation, infarct location, out-of-hospital cardiac arrest, or rescue procedures after failed thrombolysis.

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PROCEDURAL CHARACTERISTICS. Concerning procedural characteristics (Table 2), the use of DES was more frequent in 2020 (92.7% vs. 90.6%, p = 0.003), whereas no significant difference was observed in culprit vessel, lesion location, the rate of pre- and post-procedural Thrombolysis in Myocardial Infarction flow, use of intravenous antiplatelet therapies, thrombectomy, multivessel disease, and additional in-hospital coronary revascularization.

IN-HOSPITAL CLINICAL OUTCOME. A significantly higher mortality was observed in 2020 as compared with 2019 (192 deaths, 6.8% vs. 169 deaths, 4.9%, OR: 1.41; 95% CI: 1.15 to 1.71; p < 0.001) (Central Illustration). The mortality rate was extremely high among patients positive for COVID-19. In fact, a total of 18 of 62 positive patients died (29% vs. 5.5%, OR: 7.0; 95% CI: 4.1 to 12.3; p < 0.001).

The significantly poorer outcomes observed in patients with STEMI treated in 2020 persisted after correction for all potential confounding factors (geographic area, direct access by ambulance, ischemia time, door-to-balloon, radial access, use of DES) (adjusted OR: 1.46; 95% CI: 1.17 to 1.82; p <0.001), and even after exclusion of the patients positive for COVID (adjusted OR: 1.43; 95% CI: 1.15 to 1.79; p < 0.001) (Central Illustration).

TABLE 2 Angiographic and Procedural Characteristics

	2019 (n = 3,484)	2020 (n = 2,811)	p Value
Radial access	2,945 (84.5)	2,419 (86.1)	0.09
Culprit vessel			0.30
Left main	70 (2.0)	52 (1.8)	
Left anterior descending artery	1,590 (45.6)	1,264 (45.0)	
Circumflex	484 (13.9)	438 (15.6)	
Right coronary artery	1,312 (37.8)	1,029 (36.6)	
Anterolateral branch	11 (0.2)	6 (0.2)	
SVG	17 (0.5)	22 (0.8)	
Lesion location			0.78
Proximal	1,732 (49.7)	1,395 (49.6)	
Mid	1,386 (39.8)	1,134 (40.4)	
Distal	366 (10.5)	281 (10.0)	
In-stent thrombosis	150 (4.3)	128 (4.6)	0.63
Multivessel disease	1,594 (45.8)	1,346 (47.9)	0.092
Pre-procedural TIMI flow grade 0	2,114 (60.7)	1,754 (62.4)	0.16
Thrombectomy	652 (18.7)	489 (17.4)	0.17
Stenting	3,190 (91.6)	2,589 (92.1)	0.44
Drug-eluting stent	3,157 (90.6)	2,607 (92.7)	0.003
Post-procedural TIMI flow grade 3	3,212 (92.2)	2,567 (91.3)	0.21
Group IIb/IIIa inhibitors/cangrelor	776 (22.3)	671 (23.9)	0.13
Bivalirudin	24 (0.7)	11 (0.4)	0.11
Additional PCI			0.12
During the index procedure	500 (14.4)	442 (15.7)	
Staged	415 (11.9)	361 (12.8)	
DAPT therapy	3,453 (99.0)	2,777 (98.8)	0.21

Values are n (%).
DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; SVG = saphenous vein graft; TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

The ISACS-STEMI COVID-19 registry represents the largest study of patients with STEMI undergoing mechanical reperfusion during the COVID pandemic, to date. The main finding of the present study is that the number of primary PCI procedures is significantly reduced during the pandemic (in 2020) as compared with 2019, especially in patients suffering from arterial hypertension. Nevertheless, we found a significant heterogeneity among centers that was explained neither by the local or national spread of COVID-19 nor by the local or national deaths due to the pandemic. Importantly, a higher mortality rate was observed during the COVID pandemic period, and this is likely to reflect the significantly longer ischemia time associated with treatment during this challenging time.

As of now, the COVID-19 pandemic has rapidly spread around the world, resulting in an excess death toll of several hundreds of thousands of lives, especially in Europe and the United States. The true impact of COVID-19 on cardiovascular disease and mortality is still a matter of debate. In fact, COVID-19 may have increased cardiovascular mortality due to a direct and indirect effect on occurrence and management of acute heart disease. COVID-19 has been shown to cause acute cardiac injury that varies from acute heart failure or worsening of pre-existing systolic dysfunction, cardiogenic shock, tachyarrhythmias, myopericarditis, Tako-Tsubo syndrome, or ACS (12).

Reports about the presence of inflammatory pathophysiological mechanisms, triggering plaque disruption and generating a pro-thrombotic milieu (12–14) supported an anticipated increase in the number of patients presenting with ACS during the COVID-19 pandemic.

However, initial small reports from small-sized registries showed a remarkable reduction in the number of patients with ACS. Numerous factors are likely to contribute to the finding that the number of patients seeking help for chest pain and ACS-related symptoms have decreased, with huge national and regional differences varying from −20% to −70%, compared with pre-pandemic times (2–7). It has been speculated that during lockdown and with media attention highlighting the need to preserve health care resources for treatment of COVID-19, patients may have avoided acute treatment for fear of COVID infection, or avoidance of burdening an already overwhelmed clinical service. These behaviors may lead to increased morbidity and mortality, especially

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in patients with STEMI in whom a longer time delay has a significant negative impact on myocardial salvage, preservation of left ventricular function, and (short- and long-term) survival (8–10).

Furthermore, associated effects of social distancing and lockdown may have played a role, including less business-related stress, improved air quality, and a more sedentary lifestyle.

A recent small-sized report (7), including a total of 465 patients with STEMI in 54 Italian centers, showed a sizable reduction (26.5%) in STEMI procedures, more marked among women. Notably, patients with STEMI treated in 2020 had a tripled mortality rate (13.7% vs. 4.1%); however, this observation was restricted to no more than a single week, shortly after the lockdown, with fewer than 10 cases per center. An additional limitation of that study is the fact that it was not based on individual patient data, which prevents the correction for potential confounding factors.

As of now, the current study is the worldwide largest international multicenter registry in patients with STEMI who underwent mechanical reperfusion procedures, conducted in high-volume primary PCI centers. Therefore, it contributes relevant, reliable information to this controversial debate. Consistent with previous small-sized reports, we found a significant reduction in the number of patients with STEMI undergoing mechanical reperfusion; however, it was not consistent across all the centers. The results were not related to the local or national incidence of COVID or rates of death due to COVID-19.

We found a significant interaction with the decline in procedures in patients with hypertension, whereas no interaction was observed for age, sex, and diabetes. We may certainly speculate that due to the alarming message about the interplay between COVID-19 and the renin-angiotensin-aldosterone system, specifically with the use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) that could have increased the expression of ACE2 and patient susceptibility to COVID-19, in addition to the large prevalence of hypertension declared among patients affected by COVID 19, and the observation that hypertension had increased risk of COVID-19 mortality (15), may have impacted more relevantly in terms of fear of contagion in this group of patients. Professional societies have overcome this uncertainty by recommending that patients receiving ACE inhibitors and ARBs should continue taking their medication (16). Despite that, and because of the absence of data to unequivocally demonstrate the safety of these drugs, the entire discussion may have made hypertensive patients feel uneasy and it may have prevented some from promptly activating the emergency system in case of chest pain.

A significant reduction in patients with STEMI was observed in 39% of the centers under investigation and was not related to the incidence of COVID disease or to the COVID mortality. Moreover, the reduction in primary PCI was not associated with the type of institutional center and significant reduction in primary PCI was seen in all geographic areas. We cannot exclude local disparities among health care organizations and management of the COVID cardiovascular emergencies, which may have affected both the fear of contagion and the risk of out-of-hospital sudden death (17,18). Both factors may have contributed to the observed heterogeneity among centers.

Furthermore, we found that the COVID-19 pandemic was associated with a significantly longer ischemia time, with higher rates of late presentation and door-to-balloon beyond 30 min, both of which contribute to a longer ischemia time. The longer door-to-balloon time may certainly be explained by organizational delay because of the specific COVID-19 protocols for screening patients and preparing equipment and personnel in the catheterization laboratory. Several additional factors may play a role in the observed longer ischemia time during the COVID pandemic. A delayed time from symptoms to first medical contact may be a consequence of both direct patient delay or emergency system–related delay, as recently described (17). In fact, we observed in 2020 a longer ischemia time despite a higher proportion of patients who were transferred by ambulance from the community to PCI hospitals.

The longer delay to treatment contributes to the significantly higher mortality observed during this pandemic, as compared with 2019. This association persisted after correction for major differences and additionally for COVID positivity. Importantly, the COVID-positive population represented a very high-risk subgroup, with mortality exceeding 25%, confirming recent smaller reports (7,18).

Scientific societies and health authorities must adapt existing guidance for the public and health care professionals, highlighting the importance of recognition and response to characteristic symptoms of acute myocardial infarction, especially among patients suffering from hypertension. In fact, recent studies in different populations and with different designs arrived at the consistent message that the

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continued use of ACE inhibitors and ARBs is unlikely to be harmful in patients with COVID-19 and this may certainly reduce any fear of contagiousness for these patients (19–22).

STUDY LIMITATIONS. This study is limited by its retrospective design. It was conducted during a pandemic emergency, which was challenging and expected to encounter missing data. Nevertheless, our main data analysis and conclusions are based on counts and, therefore, the overall cohort of patients was included. Furthermore, even in the analysis based on full individual patient data, this limitation and the potential risk of type II error was largely overcome by the high complete case series (>95%) and the high statistical power due to the size of the study population. Finally, even though we did not find any difference in out-of-hospital cardiac arrest, we cannot exclude that the reduction in patients with STEMI observed in 2020 may have resulted from higher rates of prehospital death due to longer delays to first medical contact, as has been described during the COVID-19 pandemic (17,18).

CONCLUSIONS

The COVID-19 pandemic had a significant impact on the treatment of patients with STEMI, resulting in a reduction in primary PCI procedures, especially among patients suffering from hypertension, and in longer delay to treatment, which may have contributed to the increased mortality during this pandemic. Our data suggest that health authorities, supported by scientific societies, should take vigorous action to prevent patients from neglecting characteristic symptoms of an acute myocardial infarction, especially among patients who suffer from hypertension.

AUTHOR RELATIONSHIP WITH INDUSTRY

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The COVID-19 pandemic had a substantial impact on the management of patients with STEMI, resulting in a 19% reduction in primary PCI procedures, especially among patients with hypertension, and in longer delays to treatment, which could have contributed to increased mortality during the pandemic.

TRANSLATIONAL OUTLOOK: Health care authorities, supported by scientific societies, should implement strategies that deter patients from neglecting symptoms of acute myocardial infarction, and the impact of these measures should be assessed in regions where COVID-19 is prevalent.

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KEY WORDS COVID-19, primary angioplasty, STEMI

APPENDIX For a supplemental statistical analysis, tables, figures, and study organization details, please see the online version of this paper.

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Transcatheter Aortic Valve Replacement With the LOTUS Edge System

Early European Experience

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the short-term safety and efficacy of transcatheter aortic valve replacement (TAVR) with the LOTUS Edge system.

BACKGROUND The LOTUS Edge system was commercially re-released in April 2019. The authors report the first European experience with this device.

METHODS A multicenter, single-arm, retrospective registry was initiated to evaluate short-term clinical outcomes. Included cases are the first experience with this device and new implantation technique in Europe. Clinical, echocardiographic, and computed tomographic data were analyzed. Endpoints were defined according to Valve Academic Research Consortium-2 and were site reported.

RESULTS Between April and November 2019, 286 consecutive patients undergoing TAVR with the LOTUS Edge system at 18 European centers were included. The mean age and Society of Thoracic Surgeons score were 81.2 ± 6.9 years and 5.2 ± 5.4%, respectively. Nearly one-half of all patients (47.9%) were considered to have complex anatomy. Thirty-day major adverse events included death (2.4% [n = 7]) and stroke (3.5% [n = 10]). After TAVR, the mean aortic valve area was 1.9 ± 0.9 cm^2, and the mean transvalvular gradient was 11.9 ± 5.7 mm Hg. None or trace paravalvular leak (PVL) occurred in 84.4% and moderate PVL in 2.0%. There were no cases of severe PVL. New permanent pacemaker (PPM) implantation was required in 25.9% among all patients and 30.8% among PPM-naive patients.

CONCLUSIONS Early experience with the LOTUS Edge system demonstrated satisfactory short-term safety and efficacy, favorable hemodynamic data, and very low rates of PVL in an anatomically complex cohort. New PPM implantation remained high. Further study will evaluate if increasing operator experience with the device and new implantation technique can reduce the incidence of PPM implantation. (J Am Coll Cardiol Intv 2021;14:172–81)
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Transcatheter aortic valve replacement (TAVR) is a safe and effective alternative to surgical aortic valve replacement for the treatment of patients with symptomatic severe aortic valve stenosis across all surgical risk categories (1–7). The LOTUS aortic valve system (Boston Scientific, Marlborough, Massachusetts) is a mechanically expanding transcatheter heart valve (THV) with an intra-annular design and an adaptive seal to reduce the incidence of paravalvular leak (PVL). In the REPRISE III (Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement) trial, the LOTUS system was noninferior to the self-expanding CoreValve system (Medtronic, Minneapolis, Minnesota) for the coprimary safety and effectiveness composite endpoints (8). In this study, a lower incidence of PVL with the LOTUS system was offset by a higher rate of new permanent pacemaker (PPM) implantation. The LOTUS Edge system incorporated several iterative design improvements on its predecessor, including the Depth Guard technology to reduce the rate of new PPM implantation (**Central Illustration**). In 2017, the occurrence of important safety events mandated the commercial withdrawal of the LOTUS Edge device. In April 2019, the LOTUS Edge system received European Medicines Agency approval to recommence commercial implantation.

In this study, we present early short-term safety and efficacy results among an all-comers patient population treated with the re-released LOTUS Edge system in Europe.

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METHODS

STUDY DESIGN. This was an investigator-initiated, multicenter, single-arm, retrospective registry of consecutive patients who underwent TAVR with the LOTUS Edge aortic valve system across 18 European centers during the first 8 months after commercial release in April 2019. Clinical, echocardiographic, multislice computed tomographic (MSCT), procedural, and clinical outcome data were retrospectively collected using an electronic case report form. Participation in the registry was voluntary, but enrolling centers were mandated to include all patients treated with the LOTUS Edge system. Patient selection for TAVR was performed per standard practice at each center. All data were site reported and collected into an anonymized patient-level database. The study was approved by the local ethics committee at each participating site and was conducted in accordance with the Declaration of Helsinki.

DEVICE DESIGN. The LOTUS Edge aortic valve system is a bioprosthetic THV that includes a braided Nitinol frame with 3 bovine pericardial leaflets and a polymer adaptive seal. The system has an intra-annular design and is deployed via mechanical expansion. This repositionable and retrievable system allows complete deployment and functional assessment of the THV before final release. Novel features of this system include increased flexibility of the delivery catheter, enhanced visualization of the locking mechanism, and Depth Guard technology designed to reduce left ventricular outflow tract (LVOT) interaction and potentially reduce PPM implantation (**Central Illustration**). There are 3 valve sizes, 23, 25, and 27 mm, for native annular diameters of 20 to 23, 23 to 25, and 25 to 27 mm, respectively. The delivery system requires a minimal femoral artery diameter of 6.5 mm and is compatible with the large LOTUS introducer set. All operators were requested to follow a newly developed implantation technique whereby the expanding valve is maintained at a shallow depth (<8 mm below the annular plane) throughout deployment.

ENDPOINTS. The primary objective of this study was to investigate the 30-day safety and efficacy of this novel THV system. All individual and composite endpoints were defined according to the Valve Academic Research Consortium-2 criteria (9). 30-day all-cause mortality was further divided into cardiovascular and noncardiovascular death, and stroke was adjudicated as disabling or nondisabling, according to the Valve Academic Research Consortium-2 definitions. Surgical risk stratification was calculated using the Society of Thoracic Surgeons Predictor of Mortality (STS-PROM) score version 2.9 (10,11). We defined complex anatomy as the presence of 1 of

ABBREVIATIONS AND ACRONYMS

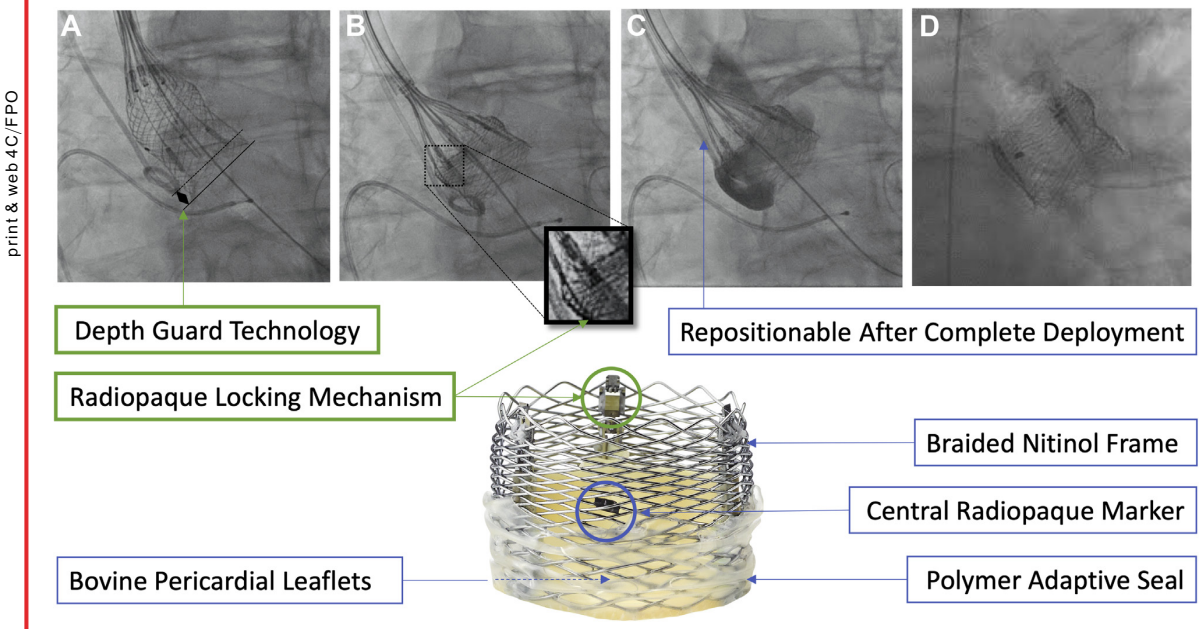
AVA = aortic valve area
AVB = atrioventricular block
LBBB = left bundle branch block
LVOT = left ventricular outflow tract
MG = mean transvalvular pressure gradient
MSCT = multislice computed tomographic
PPM = permanent pacemaker
PVL = paravalvular leak
RBBB = right bundle branch block
STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR = transcatheter aortic valve replacement
THV = transcatheter heart valve

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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CENTRAL ILLUSTRATION **The LOTUS Edge Aortic Valve System**



Armario, X. et al. J Am Coll Cardiol Intv. 2021;14(2):172-81.

The LOTUS Edge system is an intra-annular and mechanically expanding transcatheter heart valve (THV) that consists of a braided Nitinol frame, 3 bovine pericardial leaflets, and a polymer adaptive seal with a central radiopaque marker. Novel features of this device are displayed in the **green boxes**. **(A)** Depth Guard technology reducing the interaction between the stent frame and the left ventricular outflow tract during deployment. **(B)** Radiopaque markers improving the visualization of the locking mechanism. **(C,D)** Complete deployment and functional assessment of the THV before final release.

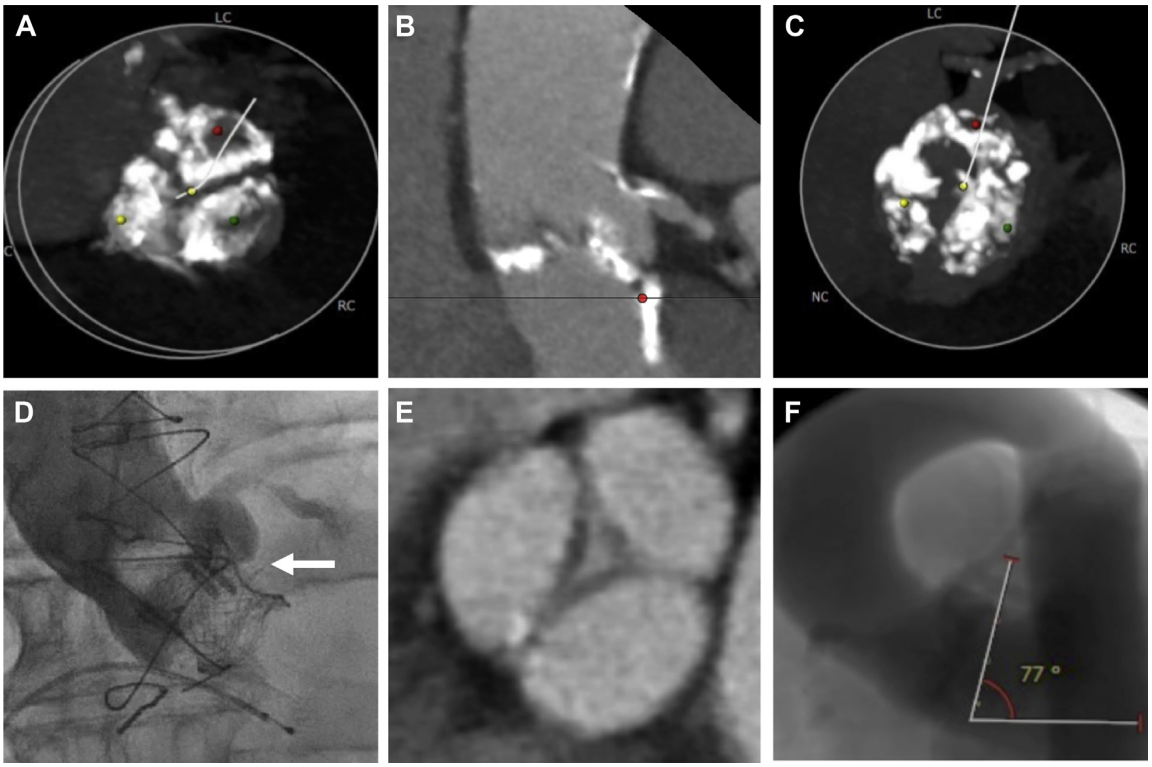
the following conditions: severe aortic valve calcification, moderate to severe LVOT calcification, bicuspid aortic valve morphology, degenerated surgical biological prosthesis, or pure aortic valve regurgitation (Figure 1). These characteristics were site reported. Aortic valve and LVOT calcification were defined semiquantitatively as mild, moderate, or severe on the basis of MSCT imaging (12). Porcelain aorta was defined semiquantitatively on the basis of MSCT imaging. THV repositioning was defined as partial or complete recapture of the valve in the ascending aorta, while THV retrieval was defined as complete removal of the THV from the patient. Prosthesis-patient mismatch was classified as moderate (indexed aortic valve area [AVA] 0.65 to 0.85 cm^2/m^2) or severe (indexed AVA <0.65 cm^2/m^2). We reported the incidence of new PPM implantation as the rate of post-TAVR new PPM implantation in the whole patient population and among patients who were PPM naive. The decision for new PPM implantation was at the discretion of the participating center.

STATISTICAL ANALYSIS. Categorical variables are reported as frequencies and percentages. Continuous variables are presented as mean ± SD for normally distributed variables or as median and interquartile range for skewed variables. The chi-square test was performed to compare categorical variables. Student's *t*-test and the Mann-Whitney *U* test were used to compare normally distributed and skewed continuous variables, respectively. A univariate analysis for predictors of 30-day stroke was performed using all baseline characteristics and procedural factors considered potentially relevant in the development of this endpoint. Multivariate analysis was subsequently performed using variables with p values <0.20 in the univariate analysis. All statistical analysis was performed using SPSS Statistics version 25.0 (IBM, Armonk, New York).

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FIGURE 1 Complex Anatomies



Examples of complex anatomies treated with the LOTUS Edge system. **(A)** Severe aortic valve calcification. **(B)** Moderate to severe left ventricular outflow tract calcification. **(C)** Bicuspid aortic valve morphology. **(D)** Degenerated surgical biological prosthesis. **(E)** Pure aortic valve regurgitation. **(F)** Horizontal aorta.

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. Between April and November 2019, 286 consecutive patients treated with the LOTUS Edge system at 18 European centers were included. Baseline clinical characteristics are reported in Table 1. The mean age was 81.2 ± 6.9 years, 41.6% were women, and the mean STS-PROM score was 5.2 ± 5.4%. Almost three-quarters of patients (n = 207 [72.4%]) were in New York Heart Association functional class III or IV. At the time of the procedure, 46 patients (16.1%) had undergone prior PPM implantation, including 22 patients (7.7%) who had undergone elective pre-procedural PPM implantation because of underlying conduction abnormalities: 16 patients had right bundle branch block (RBBB) and 6 patients had left bundle branch block (LBBB) with or without first-degree atrioventricular block (AVB).

Baseline echocardiographic and MSCT data are outlined in Table 2. The average AVA and mean transvalvular pressure gradient (MG) were 0.7 ± 0.2 cm^2 and 45.9 ± 13.8 mm Hg, respectively. Moderate to severe aortic regurgitation was present in 11.5% (n = 33). Nearly one-half of all patients (47.9%) were considered to have complex anatomy: severe aortic valve calcification was reported in 37.5% (n = 99), moderate to severe LVOT calcification in 23.5% (n = 61), and bicuspid aortic valve in 9.9% (n = 28). Four patients were treated for degenerated surgical bioprosthesis (1.4%) and 3 patients for pure aortic valve regurgitation (1.1%). Patients in the complex anatomy group were younger (80.1 ± 7.2 years vs. 82.3 ± 6.3 years; p = 0.006), and had higher MG (48.5 ± 14.6 mm Hg vs. 43.4 ± 12.5 mm Hg; p = 0.002) and more frequent PPM implantation (21.2% vs. 11.4%; p = 0.03) at baseline.

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TABLE 1 Baseline Characteristics

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Age, yrs	81.2 ± 6.9	82.3 ± 6.3	80.1 ± 7.2	0.006
Female	119 (41.6)	65 (43.6)	54 (39.4)	0.47
STS-PROM score, %	5.2 ± 5.4	5.9 ± 6.5	4.4 ± 3.6	0.03
NYHA functional class III or IV	207 (72.4)	110 (73.8)	97 (70.8)	0.57
Body mass index, kg/m^2	27.6 ± 5.6	27.7 ± 6.1	27.6 ± 5.1	0.93
Diabetes mellitus	69 (24.1)	33 (22.1)	36 (26.3)	0.42
Atrial fibrillation	87 (30.4)	49 (32.9)	38 (27.7)	0.34
Permanent pacemaker	46 (16.1)	17 (11.4)	29 (21.2)	0.03
Prior myocardial infarction	34 (11.9)	20 (13.4)	14 (10.2)	0.40
Prior PCI	57 (19.9)	36 (24.2)	22 (16.1)	0.09
Prior CABG	32 (11.2)	18 (12.1)	14 (10.2)	0.62
Prior SAVR	4 (1.4)	0 (0.0)	4 (2.9)	0.04
Prior cerebrovascular accident	35 (12.2)	20 (13.4)	15 (10.9)	0.52
Peripheral vascular disease	64 (22.4)	38 (25.5)	26 (19.0)	0.19
Chronic lung disease	48 (16.8)	23 (15.9)	25 (18.5)	0.56
Glomerular filtration rate <30 ml/min	29 (10.1)	16 (11.1)	12 (9.0)	0.56

Values are mean ± SD or n (%). p values represent comparisons between noncomplex and complex anatomies.

CABG = coronary artery bypass grafting; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

TABLE 2 Baseline Imaging

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Echocardiography				
Left ventricular ejection fraction, %	53.5 ± 11.5	53.6 ± 10.4	53.3 ± 12.6	0.79
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.25
Mean transvalvular gradient, mm Hg	45.9 ± 13.8	43.4 ± 12.5	48.5 ± 14.6	0.002
Peak transvalvular gradient, mm Hg	77.0 ± 21.9	73.7 ± 20.3	80.7 ± 23.1	0.008
Moderate to severe aortic regurgitation	33 (11.5)	22 (14.8)	11 (8.0)	0.08
Computed tomography				
Aortic annulus				
Minimum diameter, mm	22.4 ± 3.2	22.1 ± 2.7	22.7 ± 3.7	0.18
Maximum diameter, mm	27.2 ± 2.7	27.2 ± 2.6	27.1 ± 2.8	0.83
Mean diameter, mm	24.6 ± 2.8	24.4 ± 2.0	24.9 ± 3.6	0.14
Perimeter, mm	72.5 ± 18.5	73.6 ± 16.2	71.5 ± 20.4	0.37
Area, mm^2	427.9 ± 166.2	436.9 ± 143.3	418.8 ± 186.5	0.39
Sinus of Valsalva				
Mean diameter, mm	32.1 ± 3.9	31.2 ± 4.0	33.0 ± 3.7	0.002
Sinotubular junction				
Minimum diameter, mm	28.7 ± 3.6	28.3 ± 3.7	29.1 ± 3.6	0.13
Coronary arteries				
Left coronary artery height, mm	14.4 ± 3.3	14.4 ± 3.3	14.4 ± 3.4	0.89
Right coronary artery height, mm	16.4 ± 3.4	16.5 ± 3.4	16.4 ± 3.4	0.80

Values are mean ± SD or n (%). p values represent comparisons between noncomplex and complex anatomies.

Procedures were predominantly performed under local anesthesia (n = 278 [97.2%]) via transfemoral access (n = 282 [98.6%]) (Table 3). During TAVR, aortic valve pre-dilatation was performed in 54.2% (n = 155) and post-dilatation in 2.1% (n = 6). Both pre- and post-dilatation were performed more frequently in the complex anatomy group (65.0% vs. 44.3% [p < 0.001] and 2.1% vs. 0.0% [p = 0.01], respectively). THV repositioning occurred in 40.9% of cases (n = 61) with noncomplex anatomy and 38.7% of cases (n = 53) with complex anatomy (p = 0.70). In 1 case, a 27-mm LOTUS Edge was retrieved because of failure to achieve an optimal position, and a 26-mm SAPIEN 3 (Edwards Lifesciences, Irvine, California) was successfully implanted.

PROCEDURAL AND CLINICAL OUTCOMES. In-hospital mortality occurred in four patients (1.4%): 1 left ventricular guidewire perforation with cardiac tamponade and conversion to open surgery (day 0), 1 presumed left ventricular guidewire perforation with cardiac tamponade (day 1), 1 cardiac arrest of uncertain origin (day 1), and 1 stroke (day 2) (Table 4). There were 9 strokes (3.1%), of which 3 (1.0%) were categorized as disabling. No cases of myocardial infarction or stage 2 or 3 acute kidney injury were observed. Life-threatening and major bleeding occurred in 0.7% (n = 2) and 3.1% (n = 9), respectively, while the rate of major vascular complications was 2.1% (n = 6). No cases of valve malpositioning were reported.

Thirty-day follow-up was available in 99.3% (n = 284). Between hospital discharge and 30 days, 3 further deaths occurred: 1 myocardial infarction (day 25), 1 acute cholecystitis with septic shock (day 22), and 1 multiorgan failure of uncertain etiology (day 12). The 30-day mortality rate was consequently 2.4% (n = 7); 2.1% (n = 6) were classified as cardiovascular deaths (Table 5). One additional nondisabling stroke occurred on day 29, yielding a 30-day stroke rate of 3.5% (n = 10); 1.0% (n = 3) were classified as disabling strokes. Logistic regression did not identify any independent predictor of 30-day stroke (Supplemental Table 1).

At 30 days, 12.0% of patients remained in New York Heart Association functional class III or IV (Figure 2). The mean AVA and MG were 1.9 ± 0.9 cm^2 and 11.9 ± 5.7 mm Hg, respectively (Figure 3). Twenty-two patients (8.9%) had MG ≥20 mm Hg. The rates of severe and moderate prosthesis-patient mismatch were 7.5% (n = 13) and 26.4% (n = 46), respectively. None or trace PVL was reported in 84.4% (n = 211), and moderate PVL occurred in 2.0% (n = 5), with no cases of severe PVL (Figure 3).

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The incidence of new PPM implantation was 25.9% among all patients and 30.8% among PPM-naive patients. The indications for new PPM implantation were as follows: 66.2% developed third-degree AVB, 9.5% had second-degree AVB, 17.6% had first-degree AVB with LBBB or RBBB, and 6.8% had isolated LBBB.

Post-procedural antithrombotic therapy was diverse: 24.4% were treated with single-antiplatelet therapy, 38.7% with dual antiplatelet therapy, and 36.9% with oral anticoagulant agents with or without antiplatelet agents. There were 3 cases of clinical valve thrombosis after TAVR, treated successfully with oral anticoagulation.

Procedural and clinical outcomes at 30 days dichotomized according to noncomplex or complex anatomy were similar, except for significantly lower rates of new PPM implantation (18.2% vs. 32.9%; p = 0.005) and moderate PVL (0.0% vs. 3.6%; p = 0.04) in the complex group.

Overall Valve Academic Research Consortium-2 device success was 89.5% (n = 256), early safety was 92.7% (n = 265), and clinical efficacy was 75.2% (n = 215) (Supplemental Table 2).

TABLE 3 Procedural Characteristics

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p value
Local anesthesia	278 (97.2)	144 (96.6)	134 (97.8)	0.55
Transfemoral access	282 (98.6)	147 (98.7)	135 (98.5)	0.93
Valve size				
23 mm	74 (25.9)	41 (27.5)	33 (24.1)	0.51
25 mm	105 (36.7)	60 (40.3)	45 (32.8)	0.19
27 mm	107 (37.4)	48 (32.2)	59 (43.1)	0.06
Pre-dilatation	155 (54.2)	66 (44.3)	89 (65.0)	<0.001
Post-dilatation	6 (2.1)	0 (0.0)	6 (2.1)	0.01
Repositioning	114 (39.9)	61 (40.9)	53 (38.7)	0.70
Fluoroscopy time, min	19.2 ± 8.2	18.8 ± 8.1	19.6 ± 8.3	0.48
Contrast volume, ml	121.6 ± 54.3	127.2 ± 56.5	115.0 ± 50.9	0.12

Values are n (%) or mean ± SD. p values represent comparisons between noncomplex and complex anatomies.

DISCUSSION

Herein we present the first European clinical experience with the LOTUS Edge system among an all-comers patient population. The salient features of this initial experience with this new technology and implantation technique are that the LOTUS Edge system is associated with satisfactory clinical outcomes and hemodynamic results and very low rates of clinically significant PVL in an anatomically complex patient cohort. The requirement for new PPM implantation, however, remains high.

In this study, the LOTUS Edge system showed similar clinical outcomes at 30 days compared with its predecessor, the LOTUS valve, in the RESPOND registry despite operators' having to relearn how to use the device after a 2-year hiatus on commercial implantation (13). The rates of 30-day mortality (2.4%) and stroke (3.5%) in the present study were similar to those reported in RESPOND (2.6% and 3.0%, respectively), albeit with a slightly higher mean STS-PROM score in RESPOND (6.0 ± 6.9%), which could be attributed to changes in the STS-PROM calculator over time. Other clinical outcomes, such as acute kidney injury, life-threatening bleeding, and major vascular complications, occurred infrequently, with incidences similar to prior contemporary TAVR studies (4–7). We did not observe any severe device-related safety events that mandated the withdrawal of the previous LOTUS Edge system in 2017.

The hemodynamic outcomes at 30 days (AVA 1.9 ± 0.9 cm^2, MG 11.9 ± 5.7 mm Hg) were nearly identical to those reported in RESPOND (AVA 1.8 ± 0.4 cm^2, MG

TABLE 4 Procedural Outcomes

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Mortality	4 (1.4)	3 (2.0)	1 (0.7)	0.36
Stroke	9 (3.1)	6 (4.0)	3 (2.2)	0.37
Nondisabling	6 (2.1)	4 (2.7)	2 (1.5)	0.47
Disabling	3 (1.0)	2 (1.3)	1 (0.7)	0.61
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	–
Acute kidney injury	8 (2.8)	2 (1.3)	6 (4.4)	0.12
Stage 1	8 (2.8)	2 (1.3)	6 (4.4)	0.12
Stage 2 or 3	0 (0.0)	0 (0.0)	0 (0.0)	–
Bleeding	27 (9.4)	16 (10.7)	11 (8.0)	0.43
Minor	16 (5.6)	10 (6.7)	7 (5.1)	0.57
Major	9 (3.1)	6 (4.0)	3 (2.2)	0.37
Disabling or life threatening	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Vascular complications	22 (7.7)	16 (10.7)	6 (4.4)	0.04
Minor	16 (5.6)	11 (7.4)	5 (3.6)	0.17
Major	6 (2.1)	5 (3.4)	1 (0.7)	0.12
Valve malposition	0 (0.0)	0 (0.0)	0 (0.0)	–
Coronary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	–
Annular rupture	0 (0.0)	0 (0.0)	0 (0.0)	–
Ventricular perforation	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Cardiac tamponade	2 (0.7)	1 (0.7)	1 (0.7)	0.95
Surgical conversion	1 (0.3)	1 (0.7)	0 (0.0)	0.34
Hospitalization duration, days	5 (3-8)	5 (3-8)	5 (2-8)	0.49

Values are n (%) or median (interquartile range). p values represent comparisons between noncomplex and complex anatomies. All clinical outcomes are expressed according to the Valve Academic Research Consortium-2 definitions.

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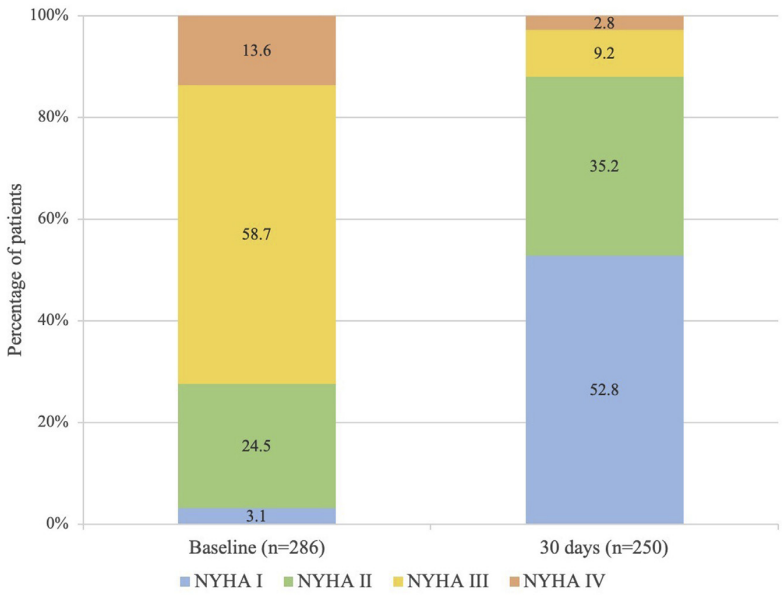
TABLE 5 Clinical Outcomes at 30 Days

	All Patients (N = 286)	Noncomplex Anatomy (n = 149)	Complex Anatomy (n = 137)	p Value
Mortality	7 (2.4)	3 (2.0)	4 (2.9)	0.62
Cardiovascular	6 (2.1)	3 (2.0)	3 (2.2)	0.92
Noncardiovascular	1 (0.3)	0 (0.0)	1 (0.7)	0.30
Stroke	10 (3.5)	6 (4.0)	4 (2.9)	0.61
Nondisabling	7 (2.4)	4 (2.7)	2 (1.5)	0.47
Disabling	3 (1.0)	2 (1.3)	2 (1.5)	0.93
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.7)	0.30
Clinical valve thrombosis	3 (1.0)	0 (0.0)	3 (2.2)	0.07
Valve endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	–
Repeated procedure for valve-related dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	–
New PPM implantation	74 (25.9)	49 (32.9)	25 (18.2)	0.005
Among PPM-naive patients	74 (30.8)	49 (37.1)	25 (23.1)	0.02
NYHA functional class III or IV (n = 250)	30 (12.0)	18 (13.4)	12 (10.3)	0.45
Aortic valve area, cm^2	1.9 ± 0.9	1.8 ± 0.5	2.0 ± 1.3	0.25
Mean transvalvular gradient, mm Hg	11.9 ± 5.7	11.4 ± 6.0	12.6 ± 5.3	0.11
Paravalvular leak (n = 250)				
None or trace	211 (84.4)	116 (84.7)	95 (84.1)	0.90
Mild	34 (13.6)	16 (11.7)	18 (15.9)	0.33
Moderate	5 (2.0)	5 (3.6)	0 (0.0)	0.04
Severe	0 (0.0)	0 (0.0)	0 (0.0)	–

Values are n (%) or mean ± SD. The p values represent comparisons between noncomplex and complex anatomies. All clinical outcomes are expressed according to the Valve Academic Research Consortium-2 definitions.

NYHA = New York Heart Association; PPM = permanent pacemaker.

FIGURE 2 Functional Class at Baseline and 30 Days



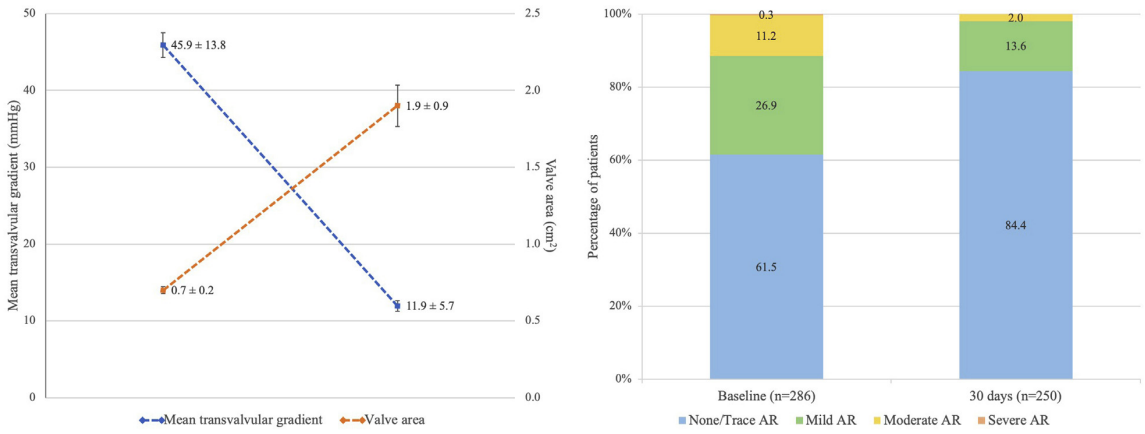
NYHA = New York Heart Association.

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FIGURE 3 Hemodynamic Data at Baseline and 30 Days



Values are mean ± SD. **Error bars** represent 95% confidence interval. AR = aortic valve regurgitation.

10.8 ± 4.6 mm Hg), in the same range as those reported for the balloon-expandable SAPIEN 3 Ultra valve (AVA 1.6 ± 0.4 cm², MG 11.6 ± 4.3 mm Hg), but less favorable compared with the self-expanding Evolut PRO valve (AVA 2.0 ± 0.5 cm², MG 6.4 ± 2.1 mm Hg) (13–15). The role of post-dilatation of the LOTUS valve and the impact of residual transvalvular gradients on long-term durability warrants further study. In contrast, as increasing PVL has proved to be associated with increasing mortality (16–19), the very low rate of moderate to severe PVL in the present study (2.0%) is clearly reassuring. Indeed, surgery-like results are observed in this cohort, with 84.4% of patients experiencing none or trace PVL post-TAVR. These data represent the best-in-class PVL data for THVs, especially when considering the anatomic complexity of the patient population (20).

The incidence of new PPM implantation with the LOTUS Edge remains high compared with other commercially available THVs (14,15). At 30 days, 25.9% of all patients and 30.8% of PPM-naive patients required new PPMs. This rate is numerically lower than that reported with the LOTUS valve in the RESPOND registry (30.0% among all patients, 34.6% among PPM-naive patients) (13) and in the REPRISE III study (29.1% among all patients, 35.5% among PPM-naive patients) (8). The Depth Guard technology was introduced to reduce the rate of PPM implantation by minimizing interaction between the stent frame and the LVOT during deployment. The Depth Guard system allows the majority of late THV foreshortening to occur at the outflow rather than the inflow, where greater LVOT interaction can lead to conduction system injury. However, 2 important aspects should be considered when interpreting the incidence of new PPM implantation in our study. First, the present study represents the first LOTUS Edge cases performed at each center in nearly 2 years. Thus, operators had to refamiliarize themselves with the device and integrate a new and unproven deployment protocol. Increasing operator experience with the device and ongoing evolution of the implantation technique have the potential to reduce the incidence of new PPM implantation. Second, in this retrospective study, the decision for PPM implantation was at the discretion of the participating center. In one-quarter (24.4%) of cases, new PPMs were implanted for first-degree AVB with LBBB or RBBB or even for isolated LBBB. According to the current European Society of Cardiology guidelines, such conduction disturbances would represent nonapproved indications for PPM implantation (21). If we excluded those patients with nonapproved indications, the incidence of new PPM implantation would be 19.6% among all patients and 23.3% among PPM-naive patients.

Anecdotal evidence would suggest that the LOTUS system is preferentially used in Europe for the most complex anatomies, including bicuspid aortic valve morphology and severe aortic valve calcification. Indeed, nearly one-half (47.9%) of the cases included in our study met the definition for complex anatomy. The LOTUS system has several unique features that favor its use in complex anatomy: 1) the valve can be

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completely deployed and subsequently recaptured, repositioned, and finally retrieved if the result is suboptimal; 2) the leaflets are functional early during deployment, so hemodynamic embarrassment is rare; 3) the adaptive seal adjusts to the surrounding anatomy giving very low rates of PVL, even in the presence of severe aortic valve or LVOT calcification; and 4) the gradual expansion of the THV yields a low risk for annular rupture. In the present study, complex anatomy was not associated with higher rates of peri-procedural complications, stroke, new PPM implantation, significant PVL, or elevated transvalvular gradients compared with noncomplex anatomy. The absence of any cases of valve malpositioning, coronary obstruction, or annular rupture along with favorable hemodynamic status and very low rates of PVL support the contention that the LOTUS Edge system is an important alternative for complex situations. The trade-off for these advantages, however, may be a higher rate of new PPM implantation.

STUDY LIMITATIONS. The relatively small sample size of the study population and the retrospective design with only 30-day follow-up limit the development of firm conclusions. Nevertheless, these short-term data are the first reported since the LOTUS Edge system was withdrawn from the market in April 2017 and include important safety and efficacy information for the community. Site-reported endpoints and the absence of an echocardiographic and MSCT core laboratory also represent important limitations. The decision for PPM implantation was at the discretion of the participating center. Thus, the indications for PPM implantation differ among centers and can be influenced by both patient and operational factors. Operator inexperience with the device and implantation technique may have influenced the rate of some adverse events. The ongoing RESPOND EDGE study (NCT04009720) will provide additional information regarding patient outcomes with this THV system.

CONCLUSIONS

Early European experience with the LOTUS Edge aortic valve system demonstrated satisfactory short-term safety and efficacy, favorable hemodynamic data, and very low rates of clinically relevant PVL in an anatomically complex patient cohort. The requirement for new PPM implantation remained high. Further study will evaluate whether increasing operator experience with the device and the new implantation technique can reduce the incidence of new PPM implantation.

AUTHOR DISCLOSURES

Dr. Khogali is a proctor for Medtronic and Boston Scientific. Dr. Van Mieghem has received research grant support from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, PulseCath BV, and Daiichi-Sankyo; and is a consultant for Abbott Vascular, Boston Scientific, PulseCath BV, Medtronic, and Daiichi-Sankyo. Dr. Cotton is a proctor for Boston Scientific; and has received speaker fees from Abbott Vascular and Medtronic. Dr. Frerker has received lecture honoraria and travel support from Boston Scientific, Abbott Vascular, Edwards Lifesciences, and Medtronic. Dr. Grygier is a consultant and proctor for Boston Scientific and Medtronic; and has received consulting fees and institutional research grants from Abbott Vascular, Boston Scientific, and Medtronic. Dr. Bjursten is a consultant and proctor for Boston Scientific; and has received institutional research grants from Boston Scientific. Dr. Jeger has received speaker honoraria and research support from B. Braun; and has received speaker honoraria from Cardionovum. Dr. Teles has received consulting fees and institutional research grants from Medtronic, Boston Scientific, and Abbott Vascular. Dr. Petronio is a consultant for Medtronic, Boston Scientific, and Abbott Vascular. Dr. Pilgrim has received research grants to the institution from Boston Scientific, Biotronik, and Edwards Lifesciences; has received speaker fees from Boston Scientific and Biotronik; and is a consultant for HighLife SAS. Dr. Søndergaard has received consulting fees and institutional research grants from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Medtronic, and Symetis. Dr. Mylotte is a consultant for Medtronic, Boston Scientific, and Microport. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? The LOTUS aortic valve system is a mechanically expanding THV for the treatment of symptomatic severe aortic valve stenosis. In 2017, the LOTUS Edge system was commercially withdrawn because of safety concerns.

WHAT IS NEW? In April 2019, the LOTUS Edge system was commercially relaunched. This study reports the first experience with this novel device in an all-comers population. These new data show satisfactory short-term safety and efficacy, with very low rates of clinically relevant PVL in an anatomically complex cohort. The requirement for new PPM implantation, however, remains high.

WHAT IS NEXT? Further study will evaluate whether the new implantation technique and an increasing operator experience can reduce the incidence of new PPM implantation.

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KEY WORDS aortic valve stenosis, transcatheter heart valve, transcatheter aortic valve replacement

APPENDIX For supplemental tables, please see the online version of this paper.

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ORIGINAL STUDIES

WILEY

Next-generation balloon-expandable Myval transcatheter heart valve in low-risk aortic stenosis patients

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Abstract

Objectives: We aimed to describe hemodynamic performance and clinical outcomes at 30-day follow-up of the balloon-expandable (BE) Myval transcatheter heart valve (THV) in low-risk patients.

Background: The results of the next-generation BE Myval THV in low-risk aortic stenosis (AS) patients are still unknown.

Methods: Retrospective registry performed in nine European centers including patients with low predicted operative mortality risk according to Society of thoracic surgeons (STS) and European system for cardiac operative risk evaluation (EuroSCORE-II) scores.

Results: Between September 2019 and February 2021, a total of 100 patients (51% males, mean age 80 ± 6.5 years) were included. Mean STS score and EuroSCORE-II were 2.4 ± 0.8% and 2.2 ± 0.7%, respectively. Intermediate sizes were used in 39% (21.5 mm: 8%, 24.5 mm: 15%, 27.5 mm: 15%). There were no cases of valve embolization, coronary artery occlusion, annulus rupture, or procedural death. A definitive pacemaker implantation was needed in eight patients (8%). At 30-day follow-up aortic valve area (0.7 ± 0.2 vs. 2.1 ± 0.6 cm^2) and mean aortic valve gradient (43.4 ± 11.1 vs. 9.0 ± 3.7 mmHg) improved significantly ($p < 0.001$). Moderate aortic regurgitation occurred in 4%. Endpoints of early safety and clinical efficacy were 3 and 1%, respectively.

Conclusions: Hemodynamic performance and 30-day clinical outcomes of the BE Myval THV in low-risk AS patients were favorable. Longer-term follow-up is warranted.

Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; BE, balloon-expandable; ES, European System for Cardiac Operative Risk Evaluation version II (EuroSCORE II); SE, self-expandable; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve; VARC-2, Valve Academic Research Consortium 2.

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KEYWORDS
aortic stenosis, balloon-expandable, TAVR

1 | INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is an established treatment for patients with calcified severe symptomatic aortic stenosis (AS).[1] Currently, new growing and robust evidence about the safety and efficacy of TAVR is emerging in low-surgical risk patients.[2] New challenges need to be covered in this population, characterized by long-life expectancy in which clinical outcomes are critical. Thus, over the last years, improvements in the devices and the development of new prostheses have been a priority.

The balloon-expandable (BE) Myval transcatheter heart valve (THV) is a new device with initial positive reports for the treatment of intermediate and high-risk AS patients.[3] Results from MYVAL-1 study include a 1-year all-cause mortality of 13% and a rate of new pacemaker of 2%,[4] and more recent research comparing alternative balloon expandable devices suggest favorable residual aortic regurgitation (AR) rate,[5] adequate residual gradients, similar mortality, and persistent lower rate of pacemaker need.[6] However, unlike more-frequently used self-expandable (SE) and BE TAVR systems, little is known on the outcomes of the Myval THV in low-surgical risk patients.

The aim of this multicenter European retrospective registry was to evaluate for the first time the hemodynamic performance and early outcomes of the next-generation BE Myval THV in low-risk patients with severe symptomatic AS.

2 | METHODS

2.1 | Study design and population

Multicenter retrospective registry performed at nine different sites across Europe, including Spain, Italy, Portugal, and the Netherlands. The study protocol was approved by the institutional ethics committees at each participating center.

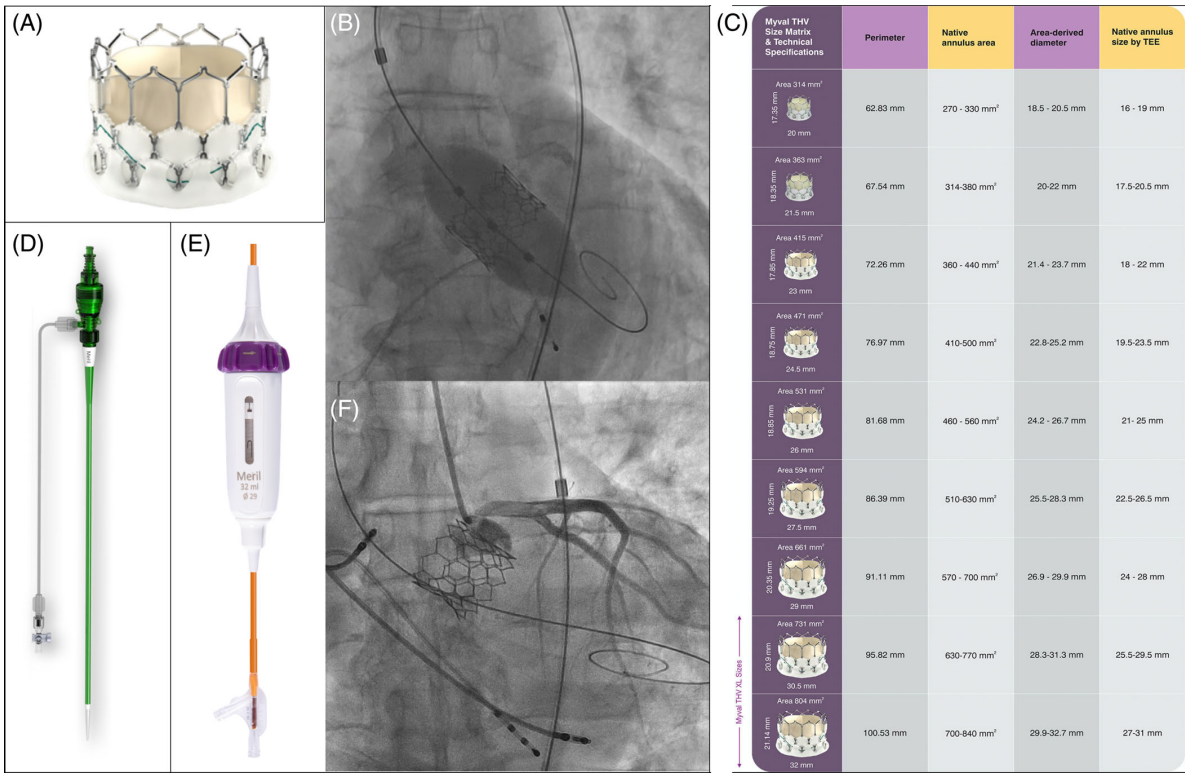


FIGURE 1 (A) Myval device. (B) Angiographic deployment of Myval THV. (C) Sizing chart. (D) Python 14 French sheath. (E) Handle of the Navigator delivery system. (F) Fully deployed Myval prosthesis demonstrating adequate access to left main coronary artery. THV, transcatheter heart valve [Color figure can be viewed at wileyonlinelibrary.com]

Patients with calcified severe AS who were treated with the implantation of the next-generation BE Myval THV were prospectively recruited. All cases were considered to have a low predicted operative mortality risk according to the Society of Thoracic Surgeons (STS) score and the European System for Cardiac Operative Risk Evaluation version II (EuroSCORE II). A Heart Team in each institution consisting of at least an imaging cardiologist, an interventional cardiologist and a cardiac surgeon assessed the suitability and eligibility for TAVR with the BE Myval THV. All patients provided written informed consent for the procedure.

TABLE 1 Clinical baseline characteristics

Variables	Myval (N = 100)
Age, years	80.0 ± 6.5
Male	51 (51)
BMI, Kg/m^2	27.7 ± 5.0
BSA, m^2	1.9 ± 0.2
STS score, %	2.4 ± 0.8
Logistic EuroSCORE II, %	2.2 ± 0.7
NYHA functional III-IV	44 (44)
Diabetes mellitus 2	30 (30)
Hypertension	74 (74)
Dyslipidemia	56 (56)
Smoking	15 (15)
Prior stroke or TIA	10 (10)
Peripheral vascular disease	8 (8)
Chronic kidney disease	11 (11)
Prior hemodialysis	0 (0)
Chronic lung disease	12 (12)
Extensively calcified aorta	3 (3)
Coronary artery disease	39 (39)
Prior open-heart surgery	4 (4)
Prior CABG	2 (2)
Prior valve surgery (mitral)	2 (2)
Electrocardiographic findings	
Sinus rhythm	72 (72)
Prior atrial fibrillation	12 (12)
Pre-existing pacemaker	5 (5)
Pre-existing LBBB	5 (5)
Pre-existing RBBB	7 (7)
First degree AV block	4 (4)

Note: Values are mean ± SD or n (%).
Abbreviations: AV, atrio-ventricular; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; EuroScore, European System for Cardiac Operative Risk Evaluation; LBBB, left bundle branch block; NYHA, New York Heart Association; RBBB, right bundle branch block; STS score, Society of Thoracic Surgeons score; TIA, transient ischemic attack.

2.2 | Study device and procedure

The Myval THV system, Conformité-Européenne approved since April 2019, is an Indian technology and globally the second-generation of BE TAVR prosthesis, whose design has been described previously by Sharma et al.[3] In summary, the device is characterized by a nickel-cobalt alloy frame, with bovine pericardium tissue that conforms a three leaflets valve. The lower cells are covered internally and externally with polyethylene terephthalate to minimize the potential for paravalvular leak (Figure 1). The device is available in conventional sizes (20, 23, 26, and 29 mm), intermediate sizes (21.5, 24.5, and 27.5 mm) and extra-large sizes (30.5 and 32 mm). All diameters are compatible with a 14Fr expandable introducer sheath. The Myval THV is crimped on its dedicated over-the-wire Navigator balloon catheter system (Meril Life Sciences Pvt. Ltd., India). Importantly, the sheath design allows complete withdrawal of the inserted delivery system if needed.

All procedures were performed under conscious sedation and by experienced interventional cardiologists using standard percutaneous techniques.

2.3 | Imaging analysis

Specially trained imaging cardiologists performed transthoracic echocardiograms (TTE) at baseline and at 30-day follow-up according to the guidelines of the American Society of Echocardiography. TTE images were centrally analyzed (www.icicorelab.es) by two independent imaging cardiologists. The hemodynamic performance of the

TABLE 2 Main imaging baseline characteristics

Variables	Myval (N = 100)
Echocardiography	
LVEF, %	57.9 ± 8.6
Aortic valve area, cm^2	0.7 (0.6–0.9)
Peak aortic gradient, mmHg	70 (60–79)
Mean aortic gradient, mmHg	43 (37–48)
>Moderate aortic regurgitation	15 (15)
>Moderate mitral regurgitation	16 (16)
>Moderate tricuspid regurgitation	14 (14)
Computed tomography	
Maximal AA diameter, mm	28.1 ± 2.6
Minimal AA diameter, mm	21.9 ± 2.9
Eccentricity index	0.22 ± 0.07
Mean AA diameter, mm	24.8 ± 2.7
AA area, mm^2	449.5 ± 100
AA perimeter, mm	57.9 ± 27.7
Moderate–severe AA calcification	36 (48.6)

Note: Values are mean ± SD or N (%).
Abbreviations: AA, aortic annulus; LVEF, left ventricle ejection fraction.

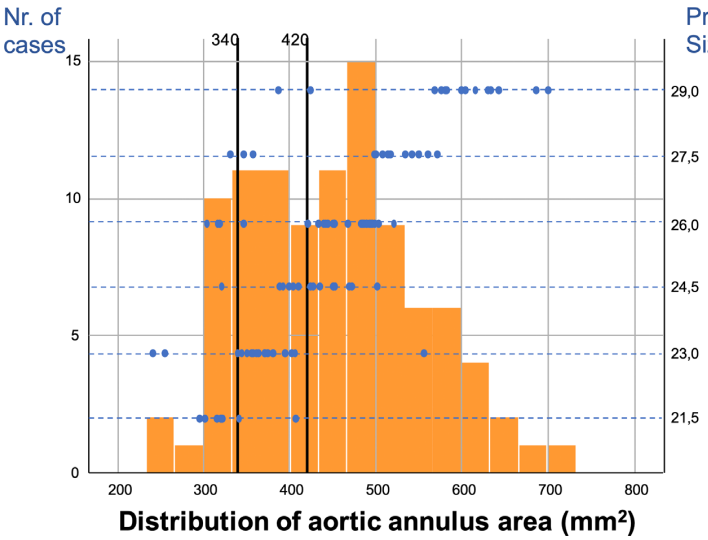


FIGURE 2 Aortic annular dimensions distributions and selected valve size [Color figure can be viewed at wileyonlinelibrary.com]

Myval THV was assessed by the degree of AR, residual transvalvular gradient, estimated aortic valve area, and prosthesis-patient mismatch defined as effective aortic orifice area ≤ 0.85 cm^2/m^2 (severe if <0.65 cm^2/m^2). The AR severity was classified following the Valve Academic Research Consortium-2 (VARC-2) recommendations.[7]

Multidetector computed tomography (CT) exams were performed according to the guidelines of the Society of Cardiovascular Computed Tomography. The following measures were obtained: aortic annulus (maximal, minimal, and mean diameter, area, and perimeter), eccentricity index (defined by 100 x [1 – {aortic annulus minimum diameter/maximum diameter}]) and degree of calcification (graded moderate–severe if >689 AU).

2.4 | Study endpoints

The primary endpoint of the study was to evaluate the hemodynamic performance, the peri-procedural, and the 30-day clinical outcomes according to VARC-2 criteria,[7] including early safety and clinical efficacy.

2.5 | Data collection and statistical analysis

All baseline, tomographic and procedural data of the study population were prospectively collected in a dedicated database at each participating center. Echocardiographic data were collected retrospectively and two independent imaging cardiologists analyzed the anonymized images. Correlation of findings was explored (Kappa index).

Categorical variables are presented as numbers and percentages. Continuous variables are expressed as mean ± SD. The change in aortic valve area and aortic mean gradient from baseline to 30-days follow-up was compared using the paired sample t test. A *p*-value <0.05 was considered to be statistically significant. All descriptive statistical analyses were performed using IBM SPSS Statistics version 25 (IBM, Armonk, New York).

3 | RESULTS

3.1 | Clinical baseline characteristics

Between September/2019 and February/2021, a total of 100 patients with symptomatic native severe AS (51% male) and mean age of 80.0 ± 6.5 years were included in the study. The mean STS-score was 2.4 ± 0.8% (range: 0.9–4%) and the mean logistic EuroSCORE-II was 2.2 ± 0.7% (range: 0.9–3.89%). A total of 39 subjects (39%) had history of coronary artery disease, but only 4% of the study population had prior open-heart surgery. The number of patients in sinus rhythm was 72 (72%) and five patients (5%) had a pre-existing definitive pacemaker. Further baseline clinical characteristics, including other conduction abnormalities, are summarized in Tables 1 and 2. In Figure 2, the aortic annulus area and the selected valve size for the study population is reported.

3.2 | Procedural and 30-day outcomes

The Myval THV was successfully implanted in all 100 subjects through transfemoral access. Procedural characteristics reported in Table 3. The most frequent implanted prosthesis were the conventional sizes: 23 mm (19%), 26 mm (27%), and 29 mm (15%). Intermediate sizes were used in 39 patients (39%), including 8% of the cases with 21.5 mm, 15% with the 24.5 mm prosthesis, and 15% with 27.5 mm device. Neither the 20 mm prosthesis nor the extra-large sizes (30.5 and 32 mm) prosthesis were used. Post-dilation

TABLE 3 Procedural and 30-day outcomes

Variables	Myval (N = 100)
Procedural outcomes	
Transfemoral access	98 (98)
Valve size implanted, mm	
20	0 (0)
21.5	8 (8)
23	19 (19)
24.5	15 (15)
26	27 (27)
27.5	16 (16)
29	15 (15)
30.5	0 (0)
32	0 (0)
Pre-dilation	43 (43)
Implantation of >1 prosthesis	0 (0)
Post-dilation	4 (4)
Valve embolization	0 (0)
Coronary artery occlusion	0 (0)
Annulus rupture	0 (0)
Cardiac tamponade	0 (0)
Conversion to surgery	0 (0)
Procedural death	0 (0)
In-hospital outcomes	
In-hospital death	0 (0)
Procedural success	99 (99)
Pacemaker implantation	8 (8)
New onset atrial fibrillation	3 (3)
Acute kidney injury	0 (0)
Minor vascular complications	4 (4)
Major vascular complications	3 (3)
Minor bleeding	1 (1)
Major bleeding	2 (2)
Life threatening bleeding	0 (0)
Cerebrovascular events	1 (1)
30-day outcomes	
Early safety[a]	3 (3)
Clinical safety[b]	1 (1)
30-day mortality	0 (0)
Cerebrovascular events	1 (1)
Pacemaker implantation after discharge	0 (0)
Need for readmission	1 (1)

Note: Values are N (%).
[a]Early safety was described as all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury (stages 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, or valve-related dysfunction requiring repeat procedure.
[b]Clinical efficacy was described as all-cause mortality, all stroke, requiring hospitalization for valve-related symptoms or worsening heart failure, NYHA III-IV, valve-related dysfunction.

TABLE 4 Echocardiographic findings at 30-day follow-up

Variables	Myval (N = 100)
LVEF, %	59.5 ± 8.3
Aortic valve area, cm^2	1.9 (1.7–2.2)
Peak aortic gradient, mmHg	17 (12–20)
Mean aortic gradient, mmHg	9 (6–12)
Severe mismatch	0 (0)
Moderate mismatch	4 (4)
Moderate–severe global aortic regurgitation	4 (4)
Moderate–severe central aortic regurgitation	0 (0)
Moderate–severe paravalvular aortic regurgitation	4 (4)
Moderate–severe mitral regurgitation	2 (2)
Moderate–severe tricuspid regurgitation	3 (3)

Note: Values are mean ± SD or N (%).
Abbreviations: AA, aortic annulus; LVEF, left ventricle ejection fraction.

was required in 4% of the cases. There were no cases of valve embolization, coronary artery occlusion, annulus rupture, or procedural death. The placement of a second valve was not required in any of the cases. A definitive pacemaker implantation was needed in 8 patients (8%). The rates of major and minor vascular complications were 3 and 4%, respectively.

At 30-day follow-up 97% of the patients were in New York Heart Association functional class I, one patient required hospitalization due to urinary infection, there were no cases of mortality, and one patient presented a cerebrovascular transitory ischemic attach leading to VARC-2 early safety and clinical efficacy rates of 3 and 1%, respectively.

3.3 | Echocardiographic findings

The echocardiographic findings at 30-day are summarized in Table 4. A good agreement was found between the two blinded operators performing the analysis (Kappa = 0.650). The correlation of aortic annular size and valve size is depicted in Figure 2; to remark, 14% of the patients presented an annular size below 340 mm^2 and 40% below 420 mm^2. Hemodynamic performance is shown in Figure 3. A significant improvement in aortic valve area (0.7 ± 0.2 vs. 2.0 ± 0.6 cm^2) and mean aortic valve gradient (43.4 ± 11.1 vs. 9.0 ± 3.7 mmHg) were found (Figure 3A,B), with no cases of severe prosthesis-patient mismatch. However, 11 patients presented some degree or prosthesis-patient mismatch (range: 0.83–0.70 cm^2/m^2) and the highest residual mean gradient was 16.5 mmHg. In patients presenting annulus size <420 mm (40%), the mean aortic gradient and valve area at baseline were 43.9 ± 10 mmHg and 0.71 ± 0.2 cm^2, respectively, and decreased to 10 ± 3 mmHg and 1.93 ± 0.4 at 30-day, with a rate of 5% of moderate mismatch but no cases of severe mismatch.

The rate of moderate AR was 4% with no cases of severe regurgitation (Figure 4).

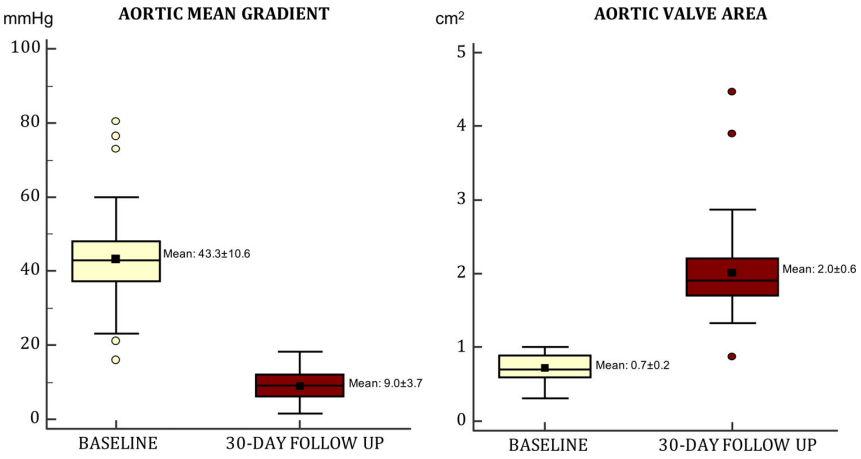


FIGURE 3 Aortic valve mean gradient (A) and estimated area (B) at baseline and 30-days follow-up (corelab analysis). Mean values have been added [Color figure can be viewed at wileyonlinelibrary.com]

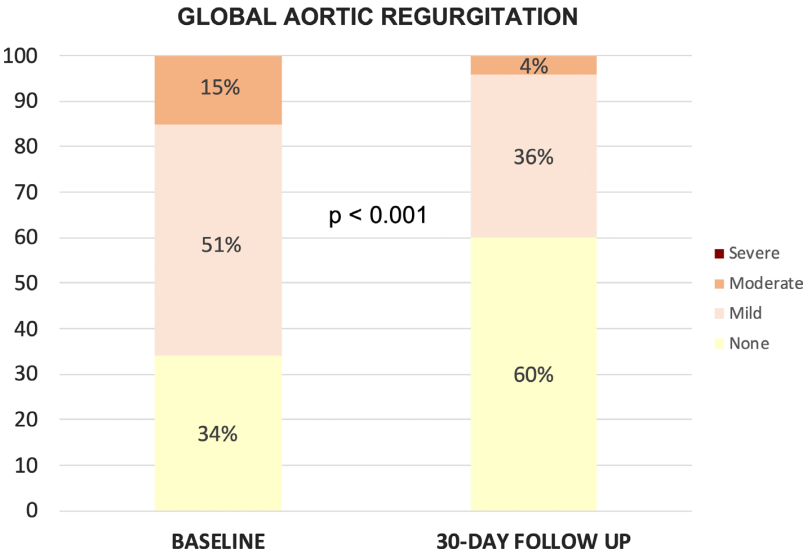


FIGURE 4 Total aortic regurgitation at baseline and at 30-days follow-up [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The main findings of the MYVAL low-risk study are: 1/Transfemoral Myval THV was successfully implanted in all low-risk patients with low rate of procedural-related complications and no mortality at 30 days; 2/intermediate sizes were used in 39% of the patients with no cases of annular rupture or coronary obstruction; 3/in a non-selected population, only 8% required new pacemaker implantation; and 4/hemodynamics, including transvalvular gradients and global AR, were optimal with no cases of severe mismatch.

PARTNER-3 trial demonstrated the superiority of TAVR with the BE SAPIEN 3 system (Edwards Lifesciences) compared to surgery among patients at low-surgical risk in terms of a lower rate of the composite endpoint of death, stroke or rehospitalization at 1 year (8.5 vs. 15.1%). The EVOLUT low-risk trial demonstrated non-inferiority of the composite endpoint of death or disabling stroke at 24 months (5.3 vs. 6.7%).[2] More recently, the NOTION trial has found no significant differences between TAVR with a SE prosthesis and SAVR for the composite rate of death, stroke or myocardial infarction after 1 year (13.1 vs. 16.3%)[5] in an all-comers patient cohort (81.8% with STS Score < 4%). In spite of these favorable data, concerns about other issues have emerged in these younger, lower-risk patients with longer life-expectancy, such as the long-term durability of TAVR prosthesis and the need for long-term pacemaker.[8] However, recent studies suggest that, compared with surgical bioprosthesis the rate of structural deterioration of TAVR might be lower.[8] On the other hand, the rate of paravalvular leak and the need for a new permanent pacemaker are still higher for TAVR. In this context, the next-generation BE Myval THV demonstrated in our exploratory study in low-risk patients a rate of only 8% of new permanent pacemaker need, excellent hemodynamic performance at 30 days follow-up, with no cases of severe mismatch, and the lack of severe residual AR with 4% of moderate paravalvular leak which is comparable to the best prior reports in low risk setting. Moreover, the use of intermediate-sized prosthesis might help to prevent aortic annular excessive overexpansion potentially reducing risk

of rupture. These finding are in agreement with preliminary reports suggesting no difference in terms of residual moderate or severe AR (Myval: 0.8%, Sapien 3: 2.5%, $p = 0.625$) and lower transvalvular mean gradients following Myval (Myval: 9 ± 4.7 mm Hg, Sapien 3: 12.1 ± 5.3 mmHg, $p < 0.001$), as well as a lower rate of permanent pacemaker (7.4 vs. 14.8%, $p = 0.042$).[6] Both, hemodynamics and conduction disturbances rate are part of the primary composite endpoint of the ongoing LANDMARK trial that will recruit 768 patients allocated in a 1:1 randomization to Myval, Sapien, or Evolut THV series.[9] The rate of mismatch has been traditionally higher with balloon- than with self-expandable devices due to intra-annular leaflets insertion; despite the more accurate sizing with Myval device, this higher rate will likely persist for small annuli since there is no additional feature in this particular scenario compared to Sapien-3.

The main limitation of this study is the retrospective data gathering, the small sample size that warrants future trials with larger populations and the evaluation only at short term on a selected patient population. Moreover, this is not a monitored study. Finally, the study was not powered for clinical endpoints but still represents the first hint of this new technology. Future randomized trials as the LANDMARK study (NCT04275726), that will compare the Myval THV to the most commonly used BE SAPIEN and SE Evolut prostheses will shed light on longer-term outcomes.[9]

5 | CONCLUSIONS

In this first-in-human experience with the BE Myval THV in a real-world low-risk AS population, the pacemaker rate, hemodynamic performance, and short-term clinical outcomes were favorable. Longer-term follow-up and randomized trials are necessary to confirm such findings.

CONFLICT OF INTEREST

Dr. Amat-Santos is proctor for Meril Life and Boston Scientific. Dr. Won-Keun is proctor for Boston Scientific, Meril Life Sciences, Abbott, speaker fees/advisory board from Boston Scientific, Abbott, Edwards, Medtronic, Meril Life Sciences, Shockwave Med. MATCH-BALL study protocol (NCT04548726).

DATA AVAILABILITY STATEMENT

Dataset is available for internal review and open to research proposals.

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ORIGINAL PAPER

Predictors of pacemaker implantation after TAVI in a registry including self, balloon and mechanical expandable valves

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Abstract
The need for permanent pacemaker implantation (PPMI) is a burdensome complication of transcatheter aortic valve implantation (TAVI). The aim of our study was to evaluate different anatomical, clinical, electrocardiographic, and procedural variables associated with the development of conduction abnormalities after TAVI across the entire device spectrum. Single-center prospective cohort of consecutive patients who underwent TAVI since March 2017. Final cohort was studied to detect areas of calcium within aortic valve characterized by leaflet sector and region. Membranous septum (MS) length was assessed throughout a modified coronal view. Device selection and positioning were performed according to the operator criteria. Device selection and positioning were performed according to the operator criteria. From the 273 patients included, 57 underwent PPMI (20.8%). Univariate analysis determined right bundle branch block (RBBB), QRS duration, MS length and calcium within LVOT of non-coronary cuspid as independent predictors. After multivariable logistic regression, both RBBB (OR 6.138; 95% CI 1.23–30.73, $P = 0.027$) and MS length (OR 0.259; 95% CI 0.164–0.399, $P < 0.005$) emerged as statistically significant. As a model, they could predict PPMI in 88.7%, independently of which valve used. Youden index analysis yielded 7.69 mm as the optimal cut-off with a negative and positive predictive value of 94.7 and 71.9%, respectively. In our experience, both RBBB pattern and short membranous septum (< 8 mm) were strongly and independently associated with new permanent pacemaker implantation, regardless of the device type. Our findings suggest that this simple evolved measure of MS length may guide device selection and implantation technique and facilitate early discharge.

Keywords Diagnostic testing · TAVI · Pacemaker · Cardiovascular computed tomography · Complications

Abbreviations

AVC	Aortic-valvular complex
AV	Atrioventricular
BEV	Balloon expandable valve
ICD	Implantable cardioverter-defibrillator
CT	Computed tomography
MS	Membranous septum
MEV	Mechanically expandable valve
MSCT	Multislice computed tomography
PPMI	Permanent pacemaker implantation
RBBB	Right bundle branch block
SEV	Self-expandable valve
TAVI	Transcatheter aortic valve implantation
THV	Transcatheter heart valve
SD	Standard deviation
ViV	Valve-in-valve

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Background

The occurrence of high degree atrioventricular conduction disturbances after transcatheter aortic valve implantation (TAVI) and the subsequent need of permanent pacemaker implantation (PPMI), is a present limitation that has not

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been effectively reduced with contemporaneous bioprosthesis [1–3].

Numerous risk factors for this outcome have been proposed and can generally be classified as clinical, electrocardiographic, prosthesis related, anatomic and intra-procedural variables [4–13].

In an era where image quality and process automation have greatly progressed, the anatomic landmarks [e.g. calcification patterns within aortic-valvular complex (AVC), membranous septum length (MS)] are attractive predictors for PPMI due to their consistency between observers. Both structures were only assessed in specific subsets of bioprosthesis, either balloon (BE) or self-expandable (SE) valves [12, 14, 17]. We sought to evaluate whether such pre-procedural association holds across the entire device spectrum and if these anatomical markers are independent from other well recognized predictors.

Methods

Study population

This is an observational study from a prospective cohort of 352 consecutive patients with symptomatic severe aortic stenosis that underwent elective TAVI in a European academic center between March 2017 and March 2020. Patients were enrolled in the VCROSS (Valve Catheter Restorative Operation on Santa Cruz Hospital) database created to obtain demographic, clinical, procedural and follow up data from our patients. Patients were excluded if pre-operative cardiac multislice CT (MSCT) image quality was not available or suitable, if patients had previous implantable cardiac defibrillator (ICD) or permanent pacemaker (PM), congenital bicuspid aortic valve, valve in valve (ViV) procedures or died within a 24 h period after the procedure (see Fig. 1). Final study population comprised 273 patients. PPMI was accountable as TAVI related if occurring within the first 30 days after the procedure. Multidisciplinary discussion was performed to decide indication and timing for PPMI. The study conforms with the principles outlined in the Declaration of Helsinki, and approval by the institutional ethics committee was obtained.

MSCT image acquisition and analysis

An electrocardiographically gated MSCT study was performed. Patients were evaluated using a Siemens™ Somatom Cardiac 64 using collimation of 0.6 mm at a fixed pitch of 0.2 with an injection of 80 to 100 ml of Iomeron®400. Image acquisition was mostly performed with retrospective ECG gating. Post processing was performed using 3mensio

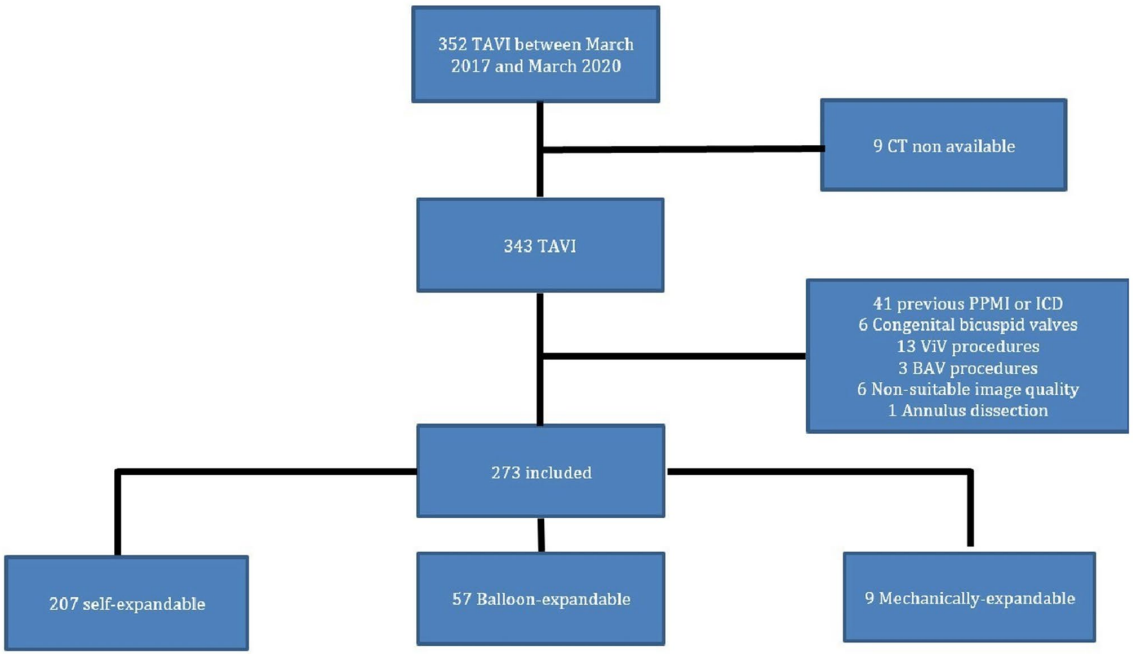


Fig. 1 Diagram illustrating study population. *PPMI* permanent pacemaker implantation, *ICD* implantable cardioverter-defibrillator, *CT* computed tomography, *TAVI* transcatheter aortic valve implantation, *ViV* valve-in-valve procedures, *BAV* balloon aortic valvuloplasty

Valves® software version 7.0 (Pie Medical Imaging, Maastricht, Netherlands). For reconstruction of midsystolic data, the cine or movie feature of this software was used to determine the point in the cardiac cycle when the aortic valve was maximally open.

Aortic annulus analysis

A MSCT virtual plane was aligned with the most basal attachment points of the three aortic valve cusps for aortic annulus defining. Throughout multiplanar reconstruction view (MPR), a line was generated through the centre point of the proximal ascending aorta, aortic valve, annulus, and LVOT. A plane perpendicular to this centre line and reaching the most basal leaflet attachment points defined the basal annular plane. Valve sizing derived from this annulus dimension.

Implantation depth

Implantation depth was angiographically assessed calculating the distance between the deepest THV end to the annulus.

Aortic-valvular complex calcium quantification

Regions of the aortic-valvular complex were separated in the craniocaudal axis of the left ventricular outflow tract (LVOT) and aortic valve into the following regions (Fig. 2A): total leaflet, device landing zone (DLZ), and LVOT. Segmental delimitations and calcium volume location were defined as depicted in Fig. 2B and C. An 850-Hounsfield unit threshold was used to detect areas of calcium in the region of interest [14, 17].

Membranous septum calculation

The MS calculation was acquired in the midsystolic phase and from the pure axial view. The acquisition is a stepwise MSCT approach (depicted in Fig. 3), starting with placement of the double cross reference planes in the left midventricular cavity and rotating it for LVOT obtainment. The reference plane is then placed in LVOT centre, just below the annular plane, and further rotated for MS obtention. From this modified coronal view, MS length is finally calculated at its longest, between the annular level and the muscular septum. The process was blinded for the study outcomes.

Statistical analysis

Continuous variables are described as mean ± SD or as median [interquartile range], while categorical variables are described as percentages. To compare variables, we used the chi-square test and the Fisher exact test as appropriate for categorical variables and the Mann–Whitney or Student's t-test for continuous variables.

Univariate logistic regression analysis was applied in the derivation cohort to relate a broad range of admission parameters to the study endpoint. After correction for multicollinearity, variables with a P-value < 0.05 were selected for multivariate analysis using a logistic regression model.

The associations were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). Sensitivity, specificity, negative predictive value, and positive predictive value were calculated using specific cut-offs by using the Youden index generated from the receiver operating characteristic (ROC) curve based on the predictive probability for PPMI.

All tests were 2-sided and statistical significance was accepted if $P < 0.05$. SPSS statistics software version 25.0 (SPSS, Chicago, Illinois) was used to perform all statistical evaluations.

Results

Patient Cohort

In our study population, 20.8% (n = 57) patients needed PPMI after TAVI. This was mainly due to third degree heart block (n = 52, 91.2%), the remaining with symptomatic first-degree AV block with concomitant left bundle branch block (n = 4, 7.1%) and second degree Mobitz II heart block (n = 1, 1.8%). Median time to implantation was 3.5 days (IQR:2–5) (Table 1).

Classic clinical and baseline findings

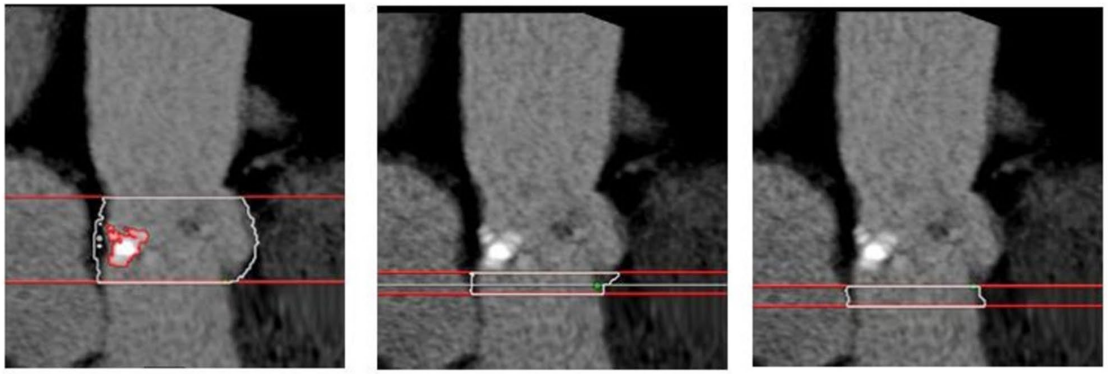
Both syncope (10.5% vs. 12.7%; $P = 0.821$) and a specific heart rate reducing therapy were not independently associated with the outcome. Both RBBB pattern (35.1% vs. 9.1%; $P < 0.005$) and QRS duration (120 ms vs. 100 ms; $P = 0.002$) independently predicted PPMI.

Computed tomography findings

The median total leaflet calcification was 353.3 mm^3 [200.5–607.4 mm^3]. Calcium volume was highest in the non-coronary cuspid (NCC) (152.2 mm^3, [71.9–247.6 mm^3]) and its presence within the LVOT region was the sole independent predictor for PPMI (0 mm^3, [0–5.5 mm^3] vs. 0 mm^3, [0–2.5 mm^3]; $P = 0.023$).

The MS length was significantly associated with the outcome (6.93 mm vs. 9.75 mm; $P < 0.005$). Youden index analysis yielded 7.69 mm as the optimal cut-off point with 80.7% sensitivity and 91.6% specificity (95%

A



B

Aortic valve complex	Landmarks
Total leaflet	15 mm above the annulus – annulus
DLZ	3 mm above the annulus – 2 mm under the annulus
LVOT	Annulus – 5 mm under the annulus

C

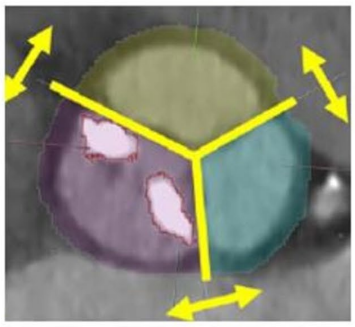


Fig. 2 Distribution of aortic valvular calcification methodology. **A** Craniocaudal axis of total leaflet, device landing zone and left ventricular outflow tract, respectively. **B** Landmarks used for calcium quantification within AVCM. **C** "Mercedes Benz" tool sign used for assessing calcium distribution according to leaflet

CI 87.1–95.0%) and with a positive and negative predicted value of 71.9 and 94.7% respectively (see Figs. 4, 5).

From a repeated measurement for a subset of 20 randomly selected patients, intraobserver and interobserver variability for MS length was satisfactory with an intraclass correlation coefficient of 0.95; $P < 0.005$ and 0.96; $P < 0.005$, respectively).

Transcatheter heart valve

Either prosthesis type or sizing were not independently associated with the outcome (Table 2).

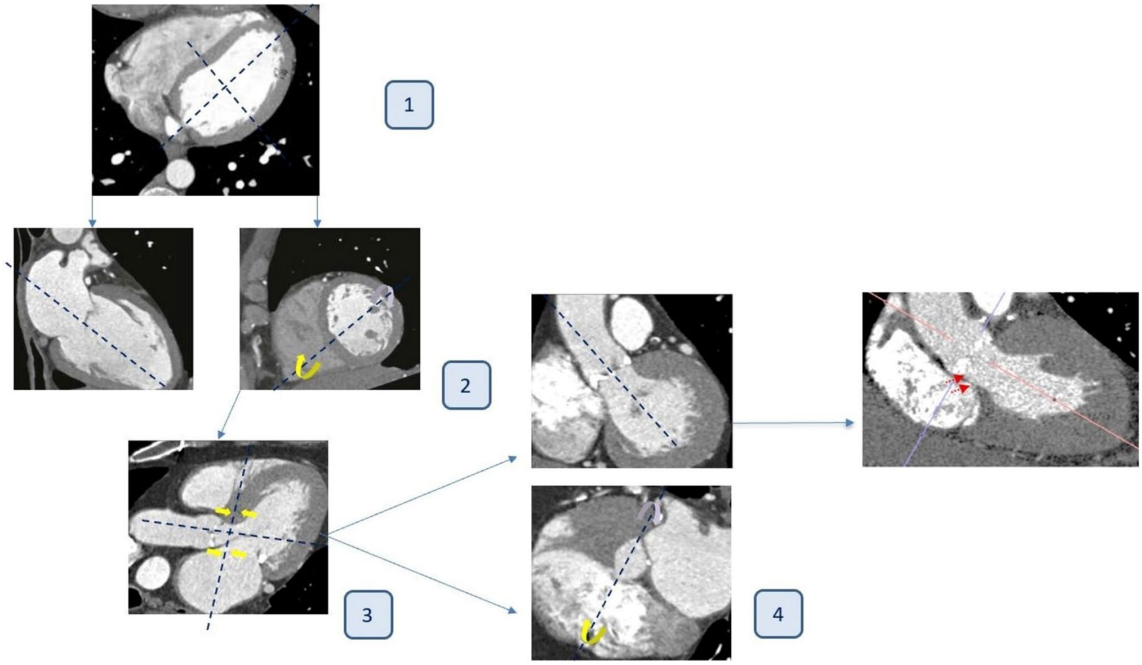


Fig. 3 Membranous septum (MS) calculation, a step-by-step approach: (1) double cross in left-midventricular; (2) turn reference plane for left ventricular outflow obtainment; (3) double cross in LVOT; (4) turn reference plane for MS assessment

Predictors of new permanent pacemaker implantation

Using previous variables that independently predicted PPMI, only RBBB pattern and MS length emerged as significant at multivariable logistic regression analysis (Table 3).

Interaction effect analysis among these variables yielded a trend towards significancy between MS length and QRS duration (OR 1.01; 95% CI 1.00–1.02; $P = 0.055$), meaning that patients are in risk for PPMI after TAVI when their baseline QRS is prolonged, even with a lengthy MS (Table 4). Additional interactions regarding MS length and other variables were examined (such as RBBB, LBBB, PR interval duration) but none of them arose as significant.

Both variables as a model could predict PPMI with a satisfactory area under the curve of 88.7%, independently of which valve used, as depicted in Table 5. This model was not used in ME valves due to very few included in this analysis and the discontinuation of the device.

Discussion

To our knowledge, this is the first study that extends the MS length as an independent predictor for PPMI through the entire device spectrum. In this group of patients, we found the combined use of ECG and an evolved MS length calculation, might predict this outcome with high accuracy.

As a model, both RBBB pattern and MS length strongly predicted the outcome throughout the entire device spectrum with an AUC of 88.7% (95% CI 82.6–94.9%). This model performed better than the Emory risk score. Such difference might be explained considering that anatomic landmarks were not assessed in the latter. On the other hand, as in our study, presence of RBBB pattern and QRS duration were highlighted as significant predictors. In addition, contrasting with this score, both previous syncope and oversizing did not predict the outcome. A now changing concept of oversizing benefits to prevent paravalvular leakage and the specificity of our center of choosing better suited bioprosthesis according to individual risk might have lessened the relative importance of such variable in the primary outcome prediction [6–8].

As for previous models that in fact assessed these anatomic surrogate markers, our model performed similarly and independently of implantation depth, with the difference that it could be applicable to all device spectrum [12, 14, 17].

Like other studies, 20.8% PPMI rate shows that even with contemporary bioprosthesis, executed in an experienced TAVI center, this complication remains an up-to-date drawback lacking an effective approach to prevent it [4, 15, 16, 21].

Table 1 Baseline population characterization

	Overall (n = 273)	No PPMI (n = 216)	PPMI (n = 57)	*P*-value
Demographics				
Age, (years)	84 (80–87)	84 (80–87)	85 (80–87)	0.580
Female, n (%)	166 (60.8)	127 (58.8)	39 (68.4)	0.223
CAD, n (%)	88 (32.2)	73 (33.8)	15 (26.3)	0.340
Clinical history				
Syncope, n (%)	33 (12.1)	27 (12.7)	6 (10.5)	0.821
Beta-blockers, n (%)	126 (46.2)	100 (47.6)	26 (46.4)	0.882
Antiarrhythmic, n (%)	19 (7.0)	15 (7.2)	4 (7.1)	1
Echocardiographic findings				
Mean gradient (mmHg)	48 (42–57)	48 (42–57)	48 (42–58)	0.832
NYHA functional class				
I, n (%)	2 (0.7)	2 (0.9)	0	0.649
II, n (%)	124 (45.4)	100 (46.7)	24 (42.1)	
III, n (%)	121 (44.3)	92 (43.0)	29 (50.9)	
IV, n (%)	24 (8.8)	20 (9.3)	4 (7.0)	
Laboratory findings				
Haemoglobin, g/dL	12.2 (11.0–13.3)	12.2 (10.9–13.2)	12.3 (11.4–13.7)	0.138
Creatinineh mg/dL	1.06 (0.87–1.40)	1.07 (0.88–1.40)	0.99 (0.84–1.31)	0.284
Pre-procedural ECG				
Atrial fibrillation				
Paroxysmic, n (%)	49 (17.9)	44 (20.4)	5 (8.8)	0.109
Persistent, n (%)	4 (1.5)	4 (1.9)	0	
Permanent, n (%)	37 (13.6)	30 (13.9)	7 (12.3)	
RBBB, n (%)	39 (14.3)	19 (9.1)	20 (35.1)	< 0.005
LBBB, n (%)	28 (10.3)	23 (11.1)	5 (8.8)	0.809
PR interval, ms	177 (160–199)	176 (160–199)	180 (155–199)	0.942
QRS interval, ms	102 (90–129)	100 (90–118)	120 (101–147)	0.002
Baseline heart rate, bpm	70 (62–77)	70 (63–76)	70 (59–77)	0.252
Vascular access				
Transfemoral, n (%)	258 (94.5)	201 (93.1)	57 (100)	0.123
Transubclavial, n (%)	19 (3.7)	5 (2.3)	0	
Transapical, n (%)	5 (1.8)	10 (4.6)	0	
Bioprosthesis				
Balloon-expandable, n (%)	57 (20.9)	48 (22.2)	9 (15.8)	0.140
Self-expandable, n (%)	207 (75.8)	163 (75.5)	44 (77.2)	
Mechanically-expandable, n (%)	9 (3.3)	5 (2.3)	4 (7.0)	
Oversizing (%)	17.2 (8.3–23.7)	16.3 (8.7–23.9)	17.4 (6.8–23.4)	0.942
Prosthesis size, mm	26 (25–29)	26 (25–29)	26 (25–29)	0.886
Device implantation depth, mm	5.3 (4.3–6.4)	5.3 (4.2–6.4)	5.5 (4.5–6.7)	0.704
Aortic valvular complex calcification				
Total leaflet, mm^3	353.3 (200.5–607.4)	348.1 (199.0—599.3)	417.1 (213.6–670.7)	0.457
LCC, mm^3	95.5 (46.4–177.6)	92.2 (45.3–177.1)	98.4 (53.5–200.0)	0.632
RCC, mm^3	96.1 (43.7–170.8)	93.7 (46.9–165.8)	103.3 (39.6–192.5)	0.786
NCC, mm^3	153.3 (71.9–247.6)	149.0 (66.4–241.1)	189.5 (79.9–285.9)	0.219
Device landing zone, mm^3	36.1 (13.8–72.2)	36.7 (14.1–78.1)	31.1 (11.0–66.9)	0.483
LCC, mm^3	11.6 (2.1–36.8)	11.6 (1.8–35.4)	11.7 (2.5–40.0)	0.517
RCC, mm^3	2.2 (0–13.5)	2.4 (0–13.8)	1.3 (0–6.0)	0.49
NCC, mm^3	5.8 (0.1–25.4)	5.8 (0.1–24.5)	6.2 (0.2–27.5)	0.537
LVOT, mm^3	3.0 (0–27.9)	3.1 (0–29.4)	2.1 (0–21.1)	0.207
LCC, mm^3	0.1 (0–14.7)	0 (0–14.5	0.3 (0–15.5)	0.836

Table 1 (continued)

	Overall (n = 273)	No PPMI (n = 216)	PPMI (n = 57)	*P*-value
RCC, mm^3	0 (0–0.4)	0 (0–0.4)	0 (0–0.6)	0.47
NCC, mm^3	0 (0–3.0)	0 (0–2.5)	0 (0–5.5)	0.023
Annulus diameter, mm	23.5 (22.0–25.5)	23.5 (22.0–25.5)	23.8 (22.1–25.5)	0.919
Membranous septum length, mm	9.11 ± 2.12	9.75 ± 1.71	6.93 ± 2.0	< 0.005

Values are mean ± SD if normal distributed

CAD coronary artery disease, *ECG* electrocardiogram, *NYHA* New York Heart Association, *RBBB* right bundle branch block, *LBBB* left bundle branch block

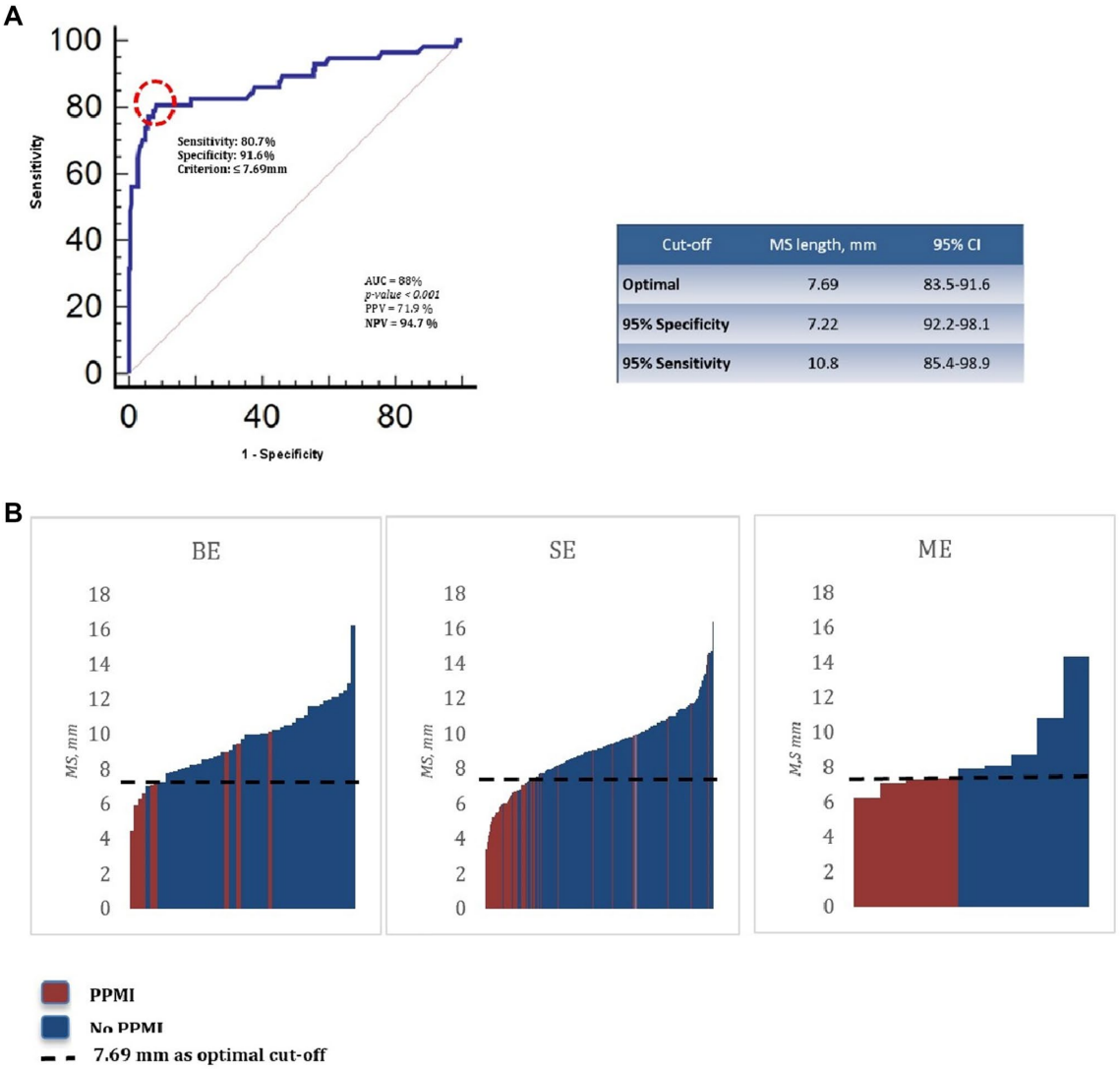


Fig. 4 MS discrimination ability for PPMI after TAVI. **A** Youden index analysis and different cut-off values yielded. **B** Waterfall graphic of MS length and its prediction for PPMI, **A** balloon-expandable valves, **B** self-expandable valves, **C** mechanically expandable valves. Dashed lines representing the optimal cut-off point of 7.69 mm

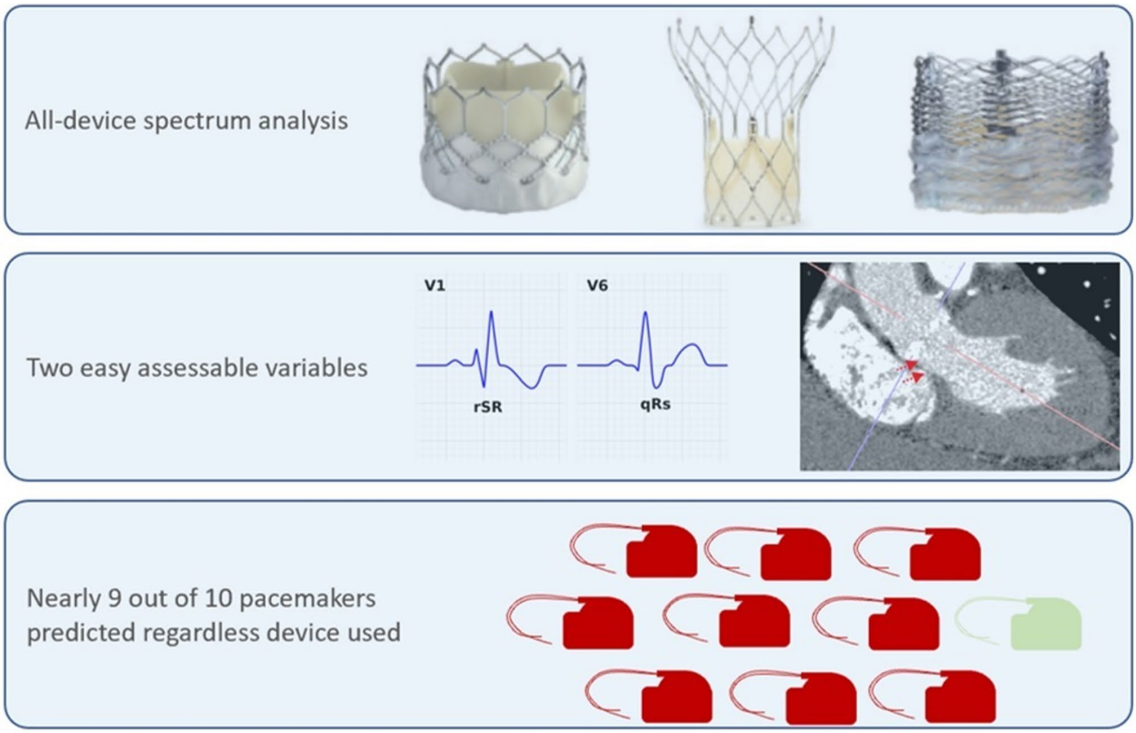


Fig. 5 Central illustration: **a** All-device spectrum analysis, **b** two easy assessable variables, **c** nearly 9 out of 10 pacemakers predicted regardless device used

Table 2 Baseline prosthesis characterization

	Overall (n = 273)	No PPMI (n = 216)	PPMI (n = 57)	*P*-value
Bioprosthesis type				
Corevalve®, n (%)	105 (38.5)	83 (38.4)	22 (38.6)	0.292
Portico®, n (%)	49 (17.9)	36 (16.7)	13 (22.8)	
Edwards®, n (%)	61 (22.3)	51 (23.6)	10 (17.5)	
Accurate®, n (%)	32 (11.7)	28 (13.0)	4 (7.0)	
Lotus®, n (%)	9 (3.3)	5 (2.3)	4 (7.0)	
Symetis®, n (%)	17 (6.2)	13 (6.0)	4 (7.0)	
Prosthesis ring size				
< 23 mm, n (%)	61 (22.3)	48 (22.2)	13 (22.8)	0.991
23–29 mm, n (%)	187 (68.5)	148 (68.5)	39 (68.4)	
> 29 mm, n (%)	25 (9.2)	20 (9.3)	5 (8.8)	

No statistically significant differences between bioprosthesis characteristics regarding study endpoint

In an exclusive SE bioprosthesis study, Hamdan et al. first hypothesized that MS length could effectively predict PPMI, and 7.4 mm arose as optimal cut-off. Both Maeno et al. and Jilaiwaihi et al. integrated MS length in predicting models for PPMI in studies for third generation BE and SE-valves, respectively. They also evaluated the difference between THV implantation depth and MS length with subsequent improvement of the discriminatory ability of both models. However, the concept and assessment of the depth of prosthesis implantation has measurement variability among studies and lacks reproducibility between

Table 3 Multivariate logistic regression showing RBBB and MS length as significant predictors of the outcome

Variable	Multivariable logistic regression			
	Wald	OR	95% CI	P-value
RBBB pattern	4.88	6.14	1.23–30.72	0.027
QRS duration	2.69	1.02	1–1.06	0.101
MS length	36.00	0.26	0.16–0.40	< 0.005
NCC LVOT CA	0.02	1.00	0.97–1.04	0.877

RBBB right bundle branch block, *MS* membranous septum, *NCC LVOT CA* non-coronary cuspid left ventricular outflow tract calcium volume

Table 4 Interaction effect. Patients with prolonged QRS complex tend pacemaker implantation even with lengthy MS

Variable	Multivariable		
	OR	95% CI	P-value
MS length	0.11	0.03–0.38	0.001
MS length × QRS duration	1.01	1–1.02	0.055
QRS duration	0.95	0.877–1.02	0.147
RBBB pattern	4.85	1.39–16.95	0.014

RBBB right bundle branch block, *MS* membranous septum, *NCC LVOT CA* non-coronary cuspid left ventricular outflow tract calcium volume

operators [17–20]. In our analysis, device implantation depth did not influence patient's outcome.

Most previous studies that incorporated MS length as a predictor for pacemaker implantation, obtained its dimension from pure standard coronal view [12, 17]. Although such approach was intended for decreasing intra- and inter-observer variability, it is quite difficult to standardize even among expert staff [14]. Another important consideration is that due to the patient postural differences, anatomical variability, the frequently extensive valvular calcification and tortuosity, in only a minority of patients full MS length is obtained. Our evolved methodology is easier and assures maximum MS length from a standardized double-cross reference plane positioning, which can be an improved surrogate marker due to anatomical variability of His bundle arising within the MS.

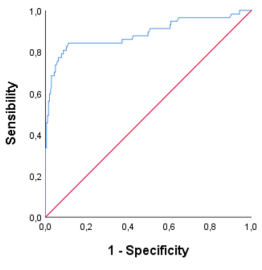
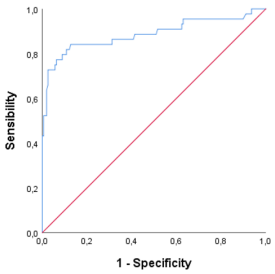
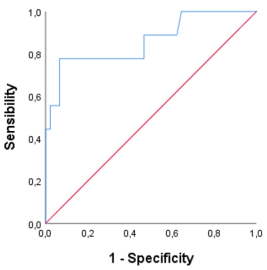
In our analysis, 7.69 mm emerged as the optimal MS length, with a negative and positive predictive value of 94.7 and 71.9%, respectively. Such sensitivity could safely prevent unnecessary transvenous PM and prolonged bed rest in often frail patients, prone for complications such as heart perforation or venous thromboembolism [21].

As for AVC calcification, even though previous studies showed a significant association with the outcome, its specific location within the aortic valve has been contradicting [13, 17]. In our study, this variable lost its significance after multivariate logistic regression analysis highlighting this variable's weakness.

Lastly, there was a trend towards significance for PPMI for those with prolonged baseline QRS even with lengthy MS. This stresses that outcome prediction should respect an all-inclusive approach, considering the cumulative probability for high-degree conduction disturbances.

The predictive ability of both RBBB and MS length as model had already impact in our daily practice allowing better risk stratification prior intervention and allowing early discharge for those low-risk patients (central illustration) [22].

Table 5 Receiving operator curves (ROC) showing good predictive ability of PPMI after TAVI of both right bundle branch block and membranous septum length as a model

Prosthesis type	**Any valve**	**Self-expandable**	**Balloon-expandable**
Graphic			
AUC (95% CI)	88.7 (82.6-94.9)	88.7 (81.5-95.8)	86.0 (70.7-100)

AUC area under the curve

Study limitations

First, this was a retrospective analysis restricting our ability to make mechanistic assumptions.

Second, the degree of selection bias could not be assessed. It is possible that for patients with apparent higher risks of developing high degree AV conduction block, operators were not that aggressive in the dilation phase, implantation depth, size selection, or type of THV. However, this would be expected to bias toward the null, and correcting for it would only serve to strengthen our findings.

Third, this was a single-center study. Although performed in a high-volume one, our results may suffer deviations in distinct patient populations with different procedure techniques. However, MS determination was blinded for clinical outcomes and performed with a MSCT analysis with tested variability.

Fourth, this study was performed in a moderate sample size population probably hampering the stablished association between self-expandable valves and PPMI outcome [23] in our study. In addition, risk assessment for mechanically expandable Lotus valves was underpowered due to limited sample size. As such, these might restrict universalization of the findings throughout overall device spectrum. Nonetheless, regardless the prosthesis, these variables consistently demonstrated good discriminatory ability for the outcome has illustrated in the waterfall graphic (Fig. 4) and Table 5. Particularly for the mechanically group, PM was only implanted in those with shorter MS length than the optimal cut-off point. Finally, although considering the modest sample size, it still represents the largest group of patients where combined evaluation of MS length and AVC calcification as predictors of PPMI after TAVI was performed.

Conclusions

Both right bundle branch block pattern and MS length were independent predictors of PPMI after TAVI, regardless of the THV type used. A computed tomography derived MS length cut-off of approximately < 8 mm predicts the risk of AV block after TAVI, and this parameter might be taken in consideration in risk stratification for earlier and safe home discharge.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL STUDIES

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Surgical versus transcatheter aortic valve replacement in low-risk patients: A long-term propensity score-matched analysis

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Abstract

Background: Recent studies suggest the use of transcatheter aortic valve implantation (TAVI) as an alternative to surgical aortic valve replacement (SAVR) in lower risk populations, but real-world data are scarce.

Methods: Single-center retrospective study of patients undergoing SAVR (between June 2009 and July 2016, $n = 682$ patients) or TAVI (between June 2009 and July 2017, $n = 400$ patients). Low surgical risk was defined as EuroSCORE II (ES II) < 4% for single noncoronary artery bypass graft procedure. TAVI patients were propensity score-matched in a 1:1 ratio with SAVR patients, paired by age, New York Heart Association class, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, creatinine clearance, and left ventricular ejection fraction < 50%.

Results: A total of 158 patients (79 SAVR and 79 TAVI) were matched (mean age 79 ± 6 years, 79 men). TAVI patients had a higher incidence of permanent pacemaker implantation (0% vs. 19%, $p < 0.001$) and more than mild paravalvular leak (4% vs. 18%, $p = 0.009$), but comparable rates of stroke, major or life-threatening bleeding, emergent cardiac surgery, new-onset atrial fibrillation, and need for renal replacement therapy. Hospital length-of-stay and 30-day mortality were similar. At a median follow-up of 4.5 years (IQR 3.0–6.9), treatment strategy did not influence all-cause mortality (HR 1.19, 95% CI 0.77–1.83, log rank $p = 0.43$) nor rehospitalization (crude subdistribution HR 1.56, 95% CI 0.71–3.41, $p = 0.26$). ES II remained the only independent predictor of long-term all-cause mortality (adjusted HR 1.40, 95% CI 1.04–1.90, $p = 0.029$).

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ES II, EuroSCORE II; HR, hazard ratio; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PPM, permanent pacemaker; PVL, paravalvular leak; RCT, randomized clinical trial; RRT, renal replacement therapy; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; 95% CI, 95% confidence interval.

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Conclusion: In this low surgical risk severe aortic stenosis population, we observed similar rates of 30-day and long-term all-cause mortality, despite higher rates of permanent pacemaker implantation and more than mild paravalvular leak in TAVI patients. The results of this small study suggest that both procedures are safe and effective in the short-term, while the Heart Team remains essential to assess both options on the long-term.

KEYWORDS
aortic valve disease, percutaneous intervention, surgery, transcatheter valve implantation, valvular

1 | INTRODUCTION

During the last decade, the treatment of patients with symptomatic severe aortic stenosis (AS) at increased surgical risk suffered an evidence-based paradigm shift from surgical aortic valve replacement (SAVR) toward transcatheter aortic valve implantation (TAVI). Several randomized clinical trials (RCTs), prospective matched studies, and observational registries over the years showed TAVI to be as safe and as effective as SAVR for the treatment of progressively lower risk patients.[1] In 2019, two additional landmark trials comparing contemporary TAVI and SAVR in severe AS patients at low surgical risk, the PARTNER 3 trial[2] and the Evolut Low Risk trial,[3] reinforced this trend.

Both trials randomized patients at low surgical risk (Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] < 4% for PARTNER 3 and STS-PROM < 3% for Evolut Low Risk) and were designed to show non-inferiority of TAVI compared to SAVR. In PARTNER 3, the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI; in Evolut Low Risk, TAVI was noninferior to surgery with respect to the composite endpoint of death or disabling stroke at 24 months.

Since 2008 the multidisciplinary Heart Team-based TAVI program at our center has led to the selection of patients whose risk-scores fall in the low surgical risk category for TAVI. The present study aimed to describe and compare the short- and long-term outcomes between TAVI and SAVR in a real world, single-center, and low surgical risk score population.

2 | MATERIALS AND METHODS

2.1 | Data collection

All baseline and procedure-related information respective to patients submitted to TAVI or SAVR at our center were prospectively collected in dedicated institutional percutaneous intervention registry (Valve Catheter Restorative Operation on Santa cruz hoSpital—VCROSS) and the cardiac surgery database (Cardiobase®, InforTUCANO SI®). Follow-up and outcome data were continuously registered during scheduled outpatient visits, and in case of fatalities, vital status was confirmed in the national health system registry.

EuroSCORE II (ES II) variables were prospectively collected, and risk estimation was retrospectively calculated. Completeness of data was adequate for all variables, except for systolic pulmonary artery pressure, missing in > 50% for the surgical cohort and 20% for the percutaneous cohort, and in which cases a normal value was assumed. Low surgical risk was defined as ES II < 4% for single noncoronary artery bypass graft procedure.

2.2 | Population

Low-risk patients were identified from an all-comers registry of patients undergoing TAVI between June 2009 and July 2017, accounting for 400 patients. For comparison between TAVI and SAVR, patients at low surgical risk were identified from a surgical

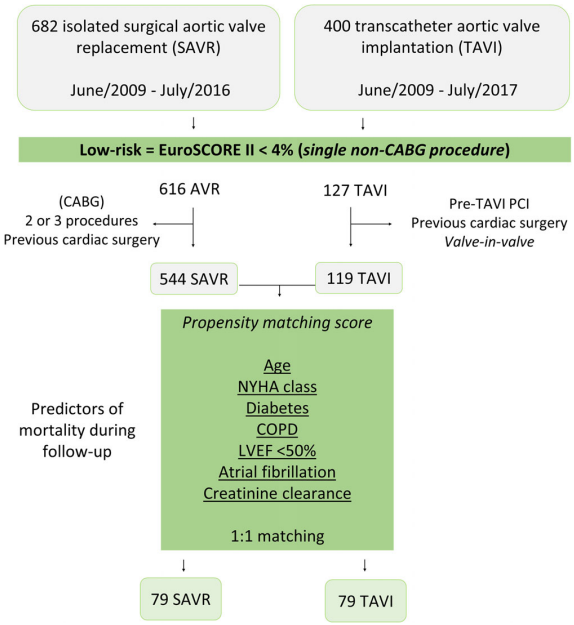


FIGURE 1 Flow chart of patient selection. CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline clinical characteristics of study cohort

	SAVR ($n = 544$)	TAVI ($n = 199$)	*p*-value
Age (years)	75 ± 6	81 ± 7	**<0.001**
Female	284 (52%)	56 (47%)	0.31
BMI (kg/m^2)	28 (24–31)	27 (24–29)	**0.006**
Tobacco use	89 (16%)	17 (14%)	0.679
Dyslipidemia	345 (63%)	39 (33%)	**<0.001**
Hypertension	451 (83%)	59 (50%)	**<0.001**
Diabetes mellitus	180 (33%)	20 (25%)	0.138
Insulin-treated	18 (3.3%)	1 (0.8%)	0.223
Coronary artery disease[a]	48 (9%)	27 (23%)	**<0.001**
Atrial fibrillation	58 (11%)	38 (32%)	**<0.001**
Stroke/TIA	42 (8%)	17 (14%)	**0.032**
COPD	53 (10%)	26 (22%)	**<0.001**
Hemoglobin (g/dl)	13.1 (12.1–14.2)	12.3 (11.1–13.6)	**0.002**
Creatinine clearance (ml/min)[b]	63 (50–81)	56 (43–68)	**<0.001**
<50 ml/min	109 (20%)	20 (25%)	0.215
Renal replacement therapy	10 (2%)	3 (2.5%)	0.712
NYHA class			
I	179 (32.9%)	5 (4.2%)	
II	265 (48.7%)	41 (34.5%)	**<0.001**
III	98 (18.0%)	69 (58%)	
IV	2 (0.4%)	4 (3.3%)	
NYHA class III/IV	110 (18%)	73 (61%)	**<0.001**
LVEF			
≥ 0%	489 (90%)	107 (90%)	
<50%	55 (10%)	12 (10%)	1.0
sPAP (mmHg)[c]	40 (33–47)	39 (31–46)	0.28
EuroSCORE II (%)	1.51 (1.12–2.18)	2.62% (1.98–3.21)	**<0.001**

Note: Values presented as number (percentage), mean (±standard deviation), or median (interquartile range). Bold represent statistically significant *p*-values.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; sPAP, systolic pulmonary artery pressure; TAVI, transcatheter aortic valve implantation.

[a]Coronary artery disease defined as previous history of myocardial infarction, chronic coronary syndrome or percutaneous coronary intervention.

[b]Creatinine clearance calculated according to the Cockcroft–Gault equation.

[c]Evaluation missing for 417 SAVR and 25 TAVI patients.

cohort of 682 patients undergoing isolated SAVR using a bioprosthesis between June 2009 and July 2016.

Population selection (Figure 1) applied the following exclusion criteria: ES II ≥ 4%, previous cardiac surgery, additional surgical interventions other than aortic valve replacement, pre-TAVI percutaneous coronary intervention (since only isolated SAVR was being considered), and valve-in-valve TAVI. Ultimately, the overall population comprised 544 SAVR and 119 TAVI patients.

In order to reduce the inherent selection bias of this type of analysis, a propensity score (PS)-based matching was performed to create a well-balanced dataset between groups regarding prognostically important baseline variables. TAVI patients were paired in a 1:1 ratio with a group of SAVR patients, matched for age, New York Heart Association (NYHA) class, diabetes mellitus, chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), creatinine clearance, and left ventricular ejection fraction < 50%. After matching, 158 patients (79 SAVR and 79 TAVI patients) were finally selected.

2.3 | Intervention

The TAVI treatment strategy was defined by the local Heart Team according to current guidelines and patient centered judgment, while SAVR was decided primary by the cardiothoracic surgeon.[4] For both interventions, prosthesis type was chosen at operator's discretion and suited clinical and anatomical features. TAVI access route, device type

TABLE 2 Intervention characteristics of study cohort

	SAVR ($n = 544$)	TAVI ($n = 119$)	*p*-value
Valve type	*Stented pericardial valves*	*Self-expandable: n = 72 (61%)*	
	Mitroflow ($n = 122$)	Evolut family ($n = 60$)	
	St. Jude Trifecta ($n = 127$)	Portico ($n = 11$)	
	St. Jude Trifecta GT ($n = 7$)	Acurate neo ($n = 1$)	
	Sorin Crown ($n = 24$)		
	Carpentier-Edwards ($n = 18$)		
	Perimount Magna ($n = 120$)		
	Stented porcine valves	*Baloon-expandable: n = 42 (35%)*	
	St. Jude Epic ($n = 110$)	Sapien family	
	Hancock II ($n = 2$)		
	Mosaic ($n = 14$)		
		Mechanically expandable: n = 5 (4%)	
		Lotus	
Main access		Transfemoral 85 (71%)	
		Trans-apical 26 (22%)	
		Trans-aortic 3 (3%)	
		Trans-axillary 5 (4%)	
Urgent procedure	22 (4%)	1 (0.8%)	0.597

Note: Values presented as number (percentage).
Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

and anesthesiology plan were selected at occasion of the Heart Team meeting.

2.4 | Outcomes

The matched population clinical outcomes were analyzed, comprising short- and long-term outcomes.

Short-term clinical outcomes were 30-day all-cause mortality, in-hospital complications, and hospital length of stay. Complications were adjudicated according to the Valve Academic Research Consortium-2 criteria[5] for stroke, major or life-threatening bleeding (Bleeding Academic Research Consortium, BARC types 3–5), emergent cardiac surgery, new-onset AF, permanent pacemaker (PPM) implantation, need for renal replacement therapy (RRT), and more than mild paravalvular leak (PVL). Short-term (< 1 month) valve hemodynamic performance indices were also assessed.

Long-term outcomes were all-cause mortality and all-cause rehospitalization during follow-up. End of follow-up was defined as April 15, 2020 and all included patients had their vital status available per end-of-study date. Median follow-up was 4.5 years (3.0–6.9).

2.5 | Statistical analysis

For SAVR and TAVI comparison, the PSs were calculated using a multivariable logistic regression, with treatment strategy as the dependent variable and the abovementioned baseline clinical characteristics as predictors. Such variables were chosen for exhibiting a *p*-value < 0.1 in the univariate Cox regression analysis for all-cause mortality during follow-up in the unmatched population. After estimation of the PS, a one-to-one matching protocol without replacement was performed using the nearest neighbor method and a caliper of 0.2 of the standard deviation of the logit of the PS. After matching, standardized mean differences were used to assess balance in matching variables before and after PS matching and found no

TABLE 3 Most frequent reasons for preferring TAVI over SAVR

	$n = 119$ (%)
Age	34 (28.5)
Frailty	20 (16.8)
Pulmonary disease	18 (15.1)
Porcelain aorta[a]	13 (11)
Chronic kidney disease	6 (5)
Poor mobility/osteoarticular pathology	4 (3.4)
Left ventricular dysfunction	3 (2.5)
Chronic liver disease/cirrhosis[a]	3 (2.5)
Anatomical issues of the thorax[a]	2 (1.7)
Other comorbidities[a]	14 (11.8)
Patient's preference	2 (1.7)

Note: Values presented as number (percentage).
Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.
[a]Potentially underestimated risk according to usual operative risk scores.

TABLE 4 Baseline clinical characteristics of propensity-matched population

	SAVR ($n = 79$)	TAVI ($n = 79$)	p-value
Age (years)	79 ± 4	81 ± 8	0.12
Female	38 (49%)	50 (51%)	0.31
BMI (kg/m^2)	27 (24–30)	27 (24–29)	0.65
Tobacco use	13	8	0.35
Dyslipidemia	55 (70%)	24 (30%)	**<0.001**
Hypertension	70 (89%)	35 (44%)	**<0.001**
Diabetes mellitus	23 (29%)	25 (32%)	0.94
Insulin-treated	1 (1.3%)	1 (1.3%)	1.0
Coronary artery disease[a]	11 (14%)	19 (24%)	0.16
Atrial fibrillation	14 (18%)	16 (20%)	0.84
Stroke/TIA	8 (10%)	9 (11%)	1.0
COPD	21 (27%)	14 (18%)	0.25
Hemoglobin (g/dl)	12.8 (11.6–14.1)	12.6 (11.1–13.8)	0.14
Creatinine clearance (ml/min)[b]	57 (41–72)	60 (47–74)	0.34
<50 ml/min	27 (34%)	18 (23%)	0.16
Renal replacement therapy	1 (1.3%)	2 (2.5%)	1.0
NYHA class			
I	8 (10.1%)	5 (6.3%)	
II	36 (45.6%)	36 (45.6%)	0.85
III	34 (43%)	37 (46.8%)	
IV	1 (1.3%)	1 (1.3%)	
NYHA class III/IV	35 (44%)	38 (48%)	0.75
LVEF			
≥50%	71 (90%)	72 (91%)	1.0
<50%	8 (10%)	7 (9%)	
sPAP (mmHg)[c]	40 (35–48)	37 (31–45)	0.40
EuroSCORE II (%)	2.11 (1.49–3.0)	2.43 (1.71–3.03)	0.18

Note: Values presented as number (percentage), mean (±standard deviation), or median (interquartile range). Bold represent statistically significant p-values.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonar disease; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; sPAP, systolic pulmonary artery pressure; TAVI, transcatheter aortic valve implantation.

[a]Coronary artery disease defined as previous history of myocardial infarction, chronic coronary syndrome or percutaneous coronary intervention.

[b]Creatinine clearance calculated according to the Cockcroft–Gault equation.

[c]Evaluation missing for 63 SAVR and 19 TAVI patients.

large imbalances, with the average absolute standardized mean difference being 0.49 before matching and 0.09 after matching.

Variables were described as number (%), mean (±standard deviation), or median (interquartile range). Baseline characteristics and short-term outcomes were compared through Student's t-test or Mann–Whitney U-test for continuous variables, and χ^2 test for categorical variables. Long-term all-cause mortality was assessed by Kaplan–Meier estimates and compared using the log rank test. Cumulative incidence of rehospitalization (with non-rehospitalization mortality as a competing event) was plotted and compared among groups by Gray's test. Fine-Gray subdistribution hazard model was used to estimate the effect of treatment strategy on rehospitalization, taking the competing risk of death into account. Predictors of mortality during follow-up were obtained with univariate and multivariate Cox regression analysis.

Statistical analyses were performed using the software SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY). Competing risk analysis was performed with "EZR" statistical software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html).[6] p-values < 0.05 (two-sided) were considered significant.

3 | RESULTS

3.1 | Overall population baseline and intervention characteristics

A total of 663 low-risk AS patients (544 SAVR patients and 119 TAVI patients) were included for analysis (Table 1). While SAVR patients were

TABLE 5 Intervention characteristics of propensity-matched population

	SAVR ($n = 79$)	TAVI ($n = 79$)	*p*-value
Valve type	*Stented pericardial valves*	*Self-expandable: n = 49 (62%)*	
	Mitroflow 34	Evolut family ($n = 41$)	
	St. Jude Trifecta 19	Portico ($n = 8$)	
	Sorin Crown 3		
	Carpentier-Edwards 2		
	Perimount Magna 6		
	Stented porcine valves	*Baloon-expandable: n = 28 (35%)*	
	St. Jude Epic 12	Sapien family	
	Mosaic 3		
		Mechanically expandable: n = 2 (3%)	
		Lotus	
Main access		Transfemoral 56 (71%)	
		Trans-apical 19 (24%)	
		Trans-aortic 1 (1%)	
		Trans-axillary 3 (4%)	
Urgent procedure	2 (2.5%)	1 (1.3%)	1.0

Note: Values presented as number (percentage).
Abbreviations: SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

TABLE 6 Short-term outcomes for the propensity-matched population

	SAVR ($n = 79$)	TAVI ($n = 79$)	*p*-value
30-day all-cause mortality	2 (2.5%)	2 (2.5%)	0.39
Stroke	2 (2.5%)	2 (2.5%)	0.65
Bleeding BARC 3–5	1 (1.3%)	6 (7.6%)	0.12
Emergent cardiac surgery	2 (2.5%)	1 (1.3%)	0.61
New-onset AF	11 (14%)	4 (5%)	0.10
New permanent pacemaker	0 (0%)	15 (19%)	**<0.001**
Need for RRT	1 (1.3%)	1 (1.3%)	0.75
Trans-prosthetic mean gradient (mmHg)[a]	15 (12–20)	9 (8–13)	**0.037**
>20 mmHg	11 (16%)	7 (11%)	0.45
Dimensionless velocity index[a]	0.52 (0.43–0.60)	0.60 (0.47–0.65)	0.625
Paravalvular leak[a]			
None/mild	66 (95.7%)	55 (79.8%)	**0.009**
More than mild PVL	3 (4.3%)	14 (20.2%)	**0.009**
Moderate	2 (2.9%)	13 (18.8%)	
Severe	1 (1.4%)	1 (1.4%)	
Length of stay (days)	8 (7–11)	7 (6–10)	0.38

Note: Values presented as number (percentage), mean (±standard deviation) or median (interquartile range). Bold represent statistically significant *p*-values.
Abbreviations: AF, atrial fibrillation; BARC, Bleeding Academic Research Consortium; PVL, paravalvular leak; RRT, renal replacement therapy.
[a]Echocardiographic data unavailable for 10 patients; percentages presented as valid percentage.

younger and had a higher prevalence of hypertension and dyslipidemia, TAVI patients were older, had lower body mass index, more comorbidities (coronary artery disease, AF, stroke/transient ischemic attack, and COPD), lower values of hemoglobin, and creatinine clearance, and were more symptomatic according to the NYHA classification. Accordingly, ES II was higher in TAVI patients (despite < 4% in all patients).

Nine different types of aortic bioprosthesis were used in SAVR patients. TAVI patients received self-expandable valves ($n = 72$, 61%) balloon-expandable valves ($n = 42$, 35%) and the remaining a mechanically expandable valve ($n = 5$, 4%). TAVI access was transfemoral in 85 patients, with alternative routes in the remainder 29% of patients (Table 2). Reasons to prefer TAVI over SAVR are outlined in Table 3.

TABLE 7 Long-term outcomes for the propensity-matched population

	SAVR ($n = 79$)	TAVI ($n = 79$)	p-value
All-cause mortality estimates at 1 year	10.1%	8.9%	0.78
All-cause mortality estimates at 2 years	15.2%	15.2%	0.98
All-cause mortality estimates at 3 years	25.3%	21.6%	0.62
Cumulative incidence of rehospitalizations during follow-up	15.4% (8.0–24.9)	23.6% (13.5–35.3)	0.23
Endocarditis	2	2	1.0
Valve thrombosis	0	0	NA

Note: Cumulative incidence of rehospitalizations presented as incidence (95% confidence interval).
Abbreviations: NA, not applicable; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

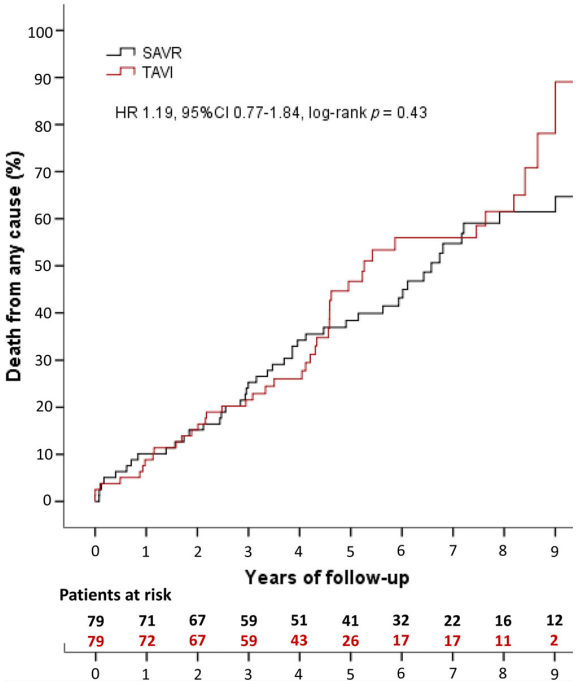


FIGURE 2 Kaplan–Meier curves for all-cause mortality according to the use of SAVR or TAVI. CI, confidence interval; HR, hazard ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

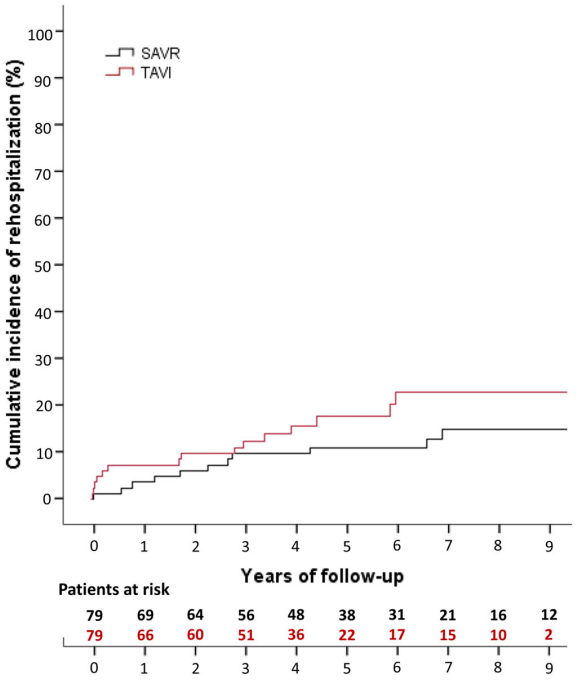


FIGURE 3 Cumulative incidence curves for rehospitalization (with all-cause mortality as competing risk event) grouped according to treatment strategy. SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Matched cohort baseline and intervention characteristics

After matching, demographic and clinical characteristics became well balanced between the 158 matched patients, except for a higher prevalence of hypertension and dyslipidemia in the SAVR group. The matched population clinical and procedural characteristics are shown on Tables 4 and 5.

3.3 | Short-term outcomes

In-hospital complications, namely stroke, major or life-threatening bleeding, emergent cardiac surgery, new-onset AF, and need for RRT after intervention were similar between groups (Table 6). The PPM implantation (0% vs. 19%, $p < 0.001$) and the presence of more than mild post-intervention PVL (4% vs. 18%, $p = 0.009$) were higher in the TAVI group.

TABLE 8 Predictors of long-term mortality (univariate and multivariate analysis after propensity score matching)

	Univariate analysis[a]			Multivariate analysis		
	Unadjusted HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
EuroSCORE II	1.51	1.16–1.98	**0.003**	1.40	1.04–1.90	**0.029**
Diabetes mellitus[b]	1.48	0.96–2.31	**0.079**			
Creatinine clearance (ml/min)[b]	0.99	0.98–1.00	**0.005**			
Need for RRT	7.77	1.87–32.39	**0.005**	1.82	0.23–14.36	0.57
Trans-prosthetic mean gradient (mmHg)	1.041	1.003–1.081	**0.036**	1.01	0.96–1.06	0.68
Dimensionless velocity index	0.65	0.009–0.486	**0.008**	0.11	0.009–1.368	0.09

Note: Bold represent statistically significant *p*-values.
Abbreviations: CI, confidence interval; HR, hazard ratio; RRT, renal replacement therapy.
[a]Only variables with a *p*-value < 0.1 in univariate analysis are presented.
[b]Not included in multivariate analysis given the presence of multicollinearity.

Hospital length of stay (8 [7–11] vs. 7 [6–10], $p = 0.39$) and 30-day all-cause mortality (2.5%, $n = 2$ in each group) did not differ between groups.

Regarding hemodynamic performance, higher trans-prosthetic mean gradients were found post-SAVR (15 [12–20] mmHg vs. 9 [8–13] mmHg, $p = 0.037$), but only a small percentage of patients in both groups had significantly elevated gradients (> 20 mmHg). Prosthesis dimensionless velocity indices were also comparable.

3.4 | Long-term outcomes

During a median follow-up of 4.5 years (3.0–6.9), 86 of the 156 patients died—45 in the AVR group and 41 in the TAVI group. The 1-, 2-, and 3-year all-cause mortality Kaplan–Meier estimates were similar between SAVR and TAVI patients (10.1% vs. 8.9%, 15.2% vs. 15.2%, and 25.3% vs. 21.6%, respectively, neither reaching statistical significance)—Table 7. Kaplan–Meier survival analysis showed no influence of treatment strategy on all-cause mortality during follow-up (HR 1.19, 95% CI 0.77–1.84, log rank $p = 0.43$)—Figure 2.

Eleven patients in the SAVR group and 15 patients in the TAVI group were hospitalized during follow-up. Four prosthesis endocarditis (two in each group) were diagnosed during follow-up and no clinically significant prothesis thrombosis was identified. Estimated cumulative incidence of any cause rehospitalization (with mortality as a competing risk event) remained similar between groups: 15.4%, (95% CI 8.0–24.9) in SAVR patients versus 23.6% (95% CI 13.5–35.3) in TAVI patients, truncated at 9-year follow-up (Gray's test $p = 0.23$)—Figure 3. TAVI treatment had no effect on rehospitalization incidence (crude sub-distribution HR 1.56, 95% CI 0.71–3.41, $p = 0.26$).

3.5 | Predictors of long-term mortality

Univariate Cox regression analysis (Table 8) showed ES II, diabetes and baseline creatinine clearance predicted long-term all-cause mortality. Likewise, need for RRT was the only periprocedural complication with long-term impact on mortality, while PPM implantation (HR 1.68, 95% CI 0.83–3.37, $p = 0.147$) and more than mild PVL (HR 1.27, 95% CI 0.55–2.46, $p = 0.48$) did not impact long-term prognosis. Higher post-intervention trans-prosthetic mean gradient and lower dimensionless velocity index influenced all-cause mortality during follow-up as well. After inputting these variables into a multivariate analysis model (excluding diabetes and creatinine clearance given the presence of multicollinearity with ES II), ES II was the only independent predictor of long-term all-cause mortality (adjusted HR 1.40, 95% CI 1.04–1.90, $p = 0.029$).

4 | DISCUSSION

The main findings of the present study can be summarized as follows: (1) early mortality, hospital length-of-stay, stroke, major/life-threatening bleeding, emergent cardiac surgery, new-onset AF and RRT did not differ significantly between treatment strategies; (2) TAVI was associated with increased rate of PPM implantation and more than mild PVL; and (3) long-term mortality and follow-up rehospitalizations were similar among groups. These findings are in line with randomized and non-randomized data showing safety and feasibility of both SAVR and TAVI for treating patients with severe AS at low surgical risk. To the best of our knowledge this is the longest follow-up of a real-world, low surgical risk patient cohort comparing TAVI with SAVR, in line with the PS-matched 5-year analysis by Schaefer et al.[7]

As expected, 30-day all-cause mortality was low (2.5%) and similar between groups, but slightly higher than the one predicted by the ES II—2.1% for SAVR and 2.4% for TAVI matched patients. While being recommended for risk evaluation,[4] the ES II has previously been shown to have a modest performance in early mortality prediction after TAVI, despite not being surpassed by other scores specifically derived from TAVI populations such as the FRANCE-2 score.[8] The observed higher-than-predicted short-term mortality captures the real cohort risk and recalls for the need to assess other factors besides risk scores during individual patient evaluation, as done by our Heart Team and described on Table 3. Aside its limitations, ES II remained

the only independent predictor for long-term all-cause mortality in our matched cohort, probably for considering comorbid conditions that influence not only early death after cardiac surgery but also longer-term survival. Since favorable data on long-term TAVI results is increasing, risk scores for mid- and long-term outcome prediction will be warranted, possibly considering not only baseline characteristics but also procedural TAVI features and complications.

Short-term clinical outcomes in RCTs for low-risk AS patients have reported lower incidence of disabling stroke,[2,3] major/life-threatening bleeding,[3,9] new-onset AF,[2,3,9] and acute kidney injury,[3,9] favoring TAVI over SAVR. While all these short-term clinical outcomes were similar between groups in our analysis, the low number of events in the matched population precludes further conclusions.

Concerning PPM implantation and more than mild PVL, both were higher in TAVI patients in our matched population. The Evolut Low Risk trial showed similar results (17.4% vs. 6.1% for PPM and 3.5% vs. 0.5% for more than mild PVL), as did the NOTION trial,[9] another landmark low risk TAVI versus SAVR RCT (34.1% vs. 1.6% for PPM implantation and 15.3% vs. 1.8% for more than mild PVL). Several risk factors for the need of PPM have been identified,[10] such as preexisting conduction disease, calcification of the aortic or mitral valve annulus, valve implantation depth, balloon post-dilatation, and using a self-expandable valve. More than mild PVL has been related mainly to the same predictive factors.[11] In our population, a self-expandable valve was used in 62% of the matched TAVI patients, which might partially explain why our PPM and PVL rates were in line with the Evolut Low Risk and the NOTION trials, which used a self-expandable valve for all procedures. Although PPM implantation and more than mild PVL did not predict all-cause mortality during follow-up in our cohort, PPM implantation was previously associated with adverse long-term outcomes in some populations,[12–14] while in others it did not influence mortality.[3] Likewise, significant PVL was also associated with worse outcomes.[15,16] Despite controversial results, the presumed impact of PPM implantation and PVL will continue to affect TAVI performance in the lower risk population, since their risk factors are independent from age and surgical risk and might become especially relevant in younger low-risk patients, whose longer life expectancy might allow device-related complications and aortic regurgitation impact to ensue.

Regarding long-term mortality, the PARTNER 3 and the Evolut Low risk trials showed non-inferiority of TAVI versus SAVR in low-risk patients, despite considering different composite primary endpoints at different time frames. Previously, the NOTION trial,[9] an all-comers randomized trial whose overall population comprised 82% of low surgical risk patients (mean ES II 2%), showed no differences between TAVI and SAVR regarding all-cause mortality, stroke, or myocardial infarction at 1 year. Analyzing the mortality outcome alone, all-cause mortality at 1 year was similar in all three trials (2.5% for SAVR vs. 1% for TAVI in the PARTNER 3 trial; 2.4% for SAVR vs. TAVI 3.0% for TAVI in the Evolut Low Risk trial; and 7.5% for SAVR vs. 4.9% for TAVI in the NOTION trial). Longer follow-ups also report comparable all-cause mortality at 2 years (4.5% in the Evolut Low Risk and 2.4% vs. 3.2% in the PARTNER 3 trial[17] and at 5 years (27.6% vs. 28.9% in the NOTION trial[18]). Our population showed similar all-cause mortality estimates at 1-, 2-, and 3-year analysis (10.1% vs. 8.9%, 15.2% vs. 15.2%, and 25.3% vs. 21.6%, respectively), and mortality during follow-up (median 4.5 years) was also similar between groups regardless of treatment strategy. These results reinforce RCTs' data on similar survival benefits between TAVI and SAVR in low-risk patients.

Higher mortality rates from our matched population compared to the former trials are probably related to the more stringent inclusion and exclusion criteria in RCT versus a real-world population. For instance, the PARTNER three trial excluded patients with clinical frailty, bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVR or surgery, while the NOTION trial excluded patients with severe renal failure requiring dialysis and significant pulmonary disease. All these features were present in both groups from our matched cohort. Excluding such comorbidities probably resulted in PARTNER 3 and Evolut Low Risk populations being significantly younger than ours—80 versus 74 years old—even though age was not an exclusion criterion per se. In addition, 99% of patients in the Evolut Low Risk trial and 96.5% in the NOTION trial used the transfemoral access and PARTNER 3 candidates were excluded if transfemoral route was unapproachable, while nearly one third of the patients in our series (29%) underwent TAVI implantation trough an access other than transfemoral. Comparing our results to other real-world PS-matched analysis, similar mortality rates at 1 year have also been reported—7.1% for SAVR versus 11.4% for TAVI in a single-center Spanish population[15] and 6.4% for SAVR versus 10.3% for TAVI in a single-center German population.[6] However, longer follow-ups report more favorable mortality outcomes for SAVR at 3 year (16.6% for SAVR versus 28% for TAVI in the multicenter Italian OBSERVANT study[19]) and at 5 years.[7] Despite such differences, one of the main strengths of our real-world data is conveying every-day information, reporting, despite with higher mortality, comparable TAVI, and SAVR results in low-risk patients outside the clinical trial environment and at a longer follow-up.

Other endpoints such as hospital length-of-stay were similar between TAVI and SAVR patients. The extended time frame of our study, encompassing different evolution stages of clinical assessment, patient selection, and technology might explain such similarities and make our results only fairly comparable to contemporary TAVI in some aspects. Similar hospitalization duration for both treatment strategies is an example of such discrepancies, as the evolution of prothesis and access closure devices reduced complications and allowed early post-TAVI discharge protocols to be implemented at our center starting 2018. Such progress allowed significantly shorter hospital admissions ever since, more in line with the PARTNER 3 and NOTION results for shorter hospitalizations for TAVI patients (median 3 vs. 7 days, $p < 0.001$ and mean 9 vs. 13 days, $p = 0.001$, respectively). The use of alternative access routes other than the transfemoral in 29% of patients might also explain longer hospitalizations for the matched TAVI population.

Lastly, regarding early hemodynamic valve profile, recent data report more favorable short-term echocardiographic evaluation for

TAVI when compared to SAVR.[3,16,19] Our results regarding immediate hemodynamic performance showed higher trans-prosthetic mean gradients for surgical valves but no significantly elevated gradients in both groups and comparable dimensionless velocity indices. As for most currently available RCTs and other real-world analysis, long-term echocardiographic follow-up was lacking, preventing clarification on TAVI durability and the impact of such initial differences on long-term valve degeneration.

Despite these differences, the main results of our study are in line with previously described short-term outcomes and long-term survival effects of SAVR and TAVI in low surgical risk patients, representing a true sample of the real-world practice. Long-term data regarding the impact of PVL and PPM implantation and valve durability is still necessary to inform low-risk patients about TAVI choice.

5 | LIMITATIONS

This study presents some limitations. Its retrospective, non-randomized nature, despite statistical correction with propensity matching, cannot exclude the impact of non-measured confounders in the decision-making process and selection of patients for each strategy by the Heart Team. The small sample size after the propensity matching process decreased this study's statistical power for accurately comparing long-term mortality outcomes and especially infrequent events (as mentioned for some of the short-term clinical outcomes); accordingly, our conclusions are adequate for supporting previous data on this subject but unfit for generalization to a broader population, for which large, randomized, clinical trials will bring more evidence. The study's long timeframe, encompassing considerable changes in TAVI standard of practice and technological development, as well as the use of different TAVI valves, with different performances and associated complications, might have influenced the reported PPM and PVL incidences, access complications and hospital length-of-stay. At last, there was relevant missing data regarding major vascular complications on SAVR patients, incomplete echocardiographic data on valve long-term performance, and unavailable pre- and post-intervention quality of life assessment.

6 | CONCLUSION

In this low surgical risk severe AS population, we observed similar rates of 30-day and long-term all-cause mortality, despite higher rates of permanent pacemaker implantation and more than mild paravalvular leak in TAVI patients. The results of this small study suggest that both procedures are safe and effective in the short-term for low-risk patients, while the Heart Team remains essential to assess and inform the patient about both options on the long-term.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Catarina Brízido, upon reasonable request.

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Manuscript #32

Original Contribution

Gender Differences and Mortality Trends After Transcatheter Aortic Valve Implantation: A 10-Year Analysis From a Single Tertiary Center

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Abstract

Aim. To evaluate gender differences and mortality trends in a population undergoing transcatheter aortic valve implantation (TAVI) and to analyze the correlates to all-cause mortality at follow-up. **Methods.** The study comprises a prospective cohort of 592 TAVI patients (53.4% female) treated between 2008 and 2018. Mortality differences between genders at different timepoints were assessed according to log rank test. Predictors of all-cause mortality at follow-up were identified using a univariate model and were then analyzed through multivariate Cox proportional hazard models. **Results.** Compared with female patients, males were younger (81 ± 7.5 years vs 84.3 ± 5.3 years) and presented more comorbidities. Twelve female and 8 male patients (3.5%) died in the first 30 days after TAVI. Despite a higher Society of Thoracic Surgeons (STS) score in women, all-cause mortality rates at 30 days and 1 year were comparable. At long-term follow-up, female patients demonstrated better survival rates, despite a higher number of periprocedural complications. Correlates identified in men were the presence of diabetes and previous history of coronary artery bypass grafting, New York Heart Association class III/IV, pulmonary artery systolic pressure, and non-transfemoral access. None of these variables remained significant in the multivariable analysis. In females, only peripheral artery disease was associated with mortality. Shock and need for renal replacement were predictors of mortality in both genders, as was heart failure readmission after discharge. STS score was also shown to correlate with long-term mortality in both genders. **Conclusion.** Despite a higher STS score in women, 30-day mortality was not significantly different from men, while women present better clinical outcomes at long-term follow-up.

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Key words: aortic stenosis, gender differences, TAVI mortality, transcatheter aortic valve implantation

Aortic stenosis is the most common valvular heart disease in developed countries, and its impact on public health and healthcare resources is expected to increase due to the aging population.[1]

Transcatheter aortic valve implantation (TAVI) is now an alternative to conventional cardiac surgery therapy for patients presenting symptomatic aortic stenosis in all settings of risk. In the European countries, predicted numbers point to 114,757 TAVI candidates annually and 58,556 in North America.[2]

Percutaneous valve treatment offers substantial reductions in mortality and improvement in quality of life compared with medical therapy[3,4] and has shown at least similar long-term outcomes compared with surgical aortic valve replacement (SAVR)[5-7] even in patients presenting low surgical risk.[8-10] Current mortality in TAVI trials with new-generation valves ranges from 1% to 2.4%[8,9] vs 3.5% in SAVR[11] in patients at low surgical risk, and 10%[12] in TAVI vs >12% in SAVR patients at high risk.[13] Long-term follow-up of TAVI cases from real-world tertiary European centers is not available, particularly in cohorts in which female patients are the majority. Female gender has been associated with higher operative mortality after SAVR,[14] yet previous reports are

inconsistent regarding the effect of gender on outcomes,[15] with the most frequent explanation being differences in preoperative risk profiles after propensity-matched assessment.[16-18] These findings do not seem to be extrapolatable for TAVI patients,[19] so we aimed to evaluate mortality trends over time and to identify correlates to mortality, outlining the differences between female and male patients.

Methods

Population. A largely female prospective cohort of 592 TAVI patients (53.4% female), treated between April 2008 and December 2018 was evaluated. The patients were enrolled in the VCROSS (Valve Catheter Restorative Operation on Santa Cruz hospital) registry, which was created to obtain all demographic, clinical, procedural, and follow-up data from patients undergoing TAVI in our hospital, for severe aortic stenosis.

All patients signed procedural informed consent approved by the ethics committee. Mortality status was collected from electronic medical records and/or civil registries through November 2019. Complications and follow-up data were obtained from patient's clinical files (handwritten and electronic records) or medical national platform records when available.

Patients were considered for TAVI if they had symptomatic severe aortic stenosis, defined by a jet velocity >4.0 m/s, mean gradient >40 mm Hg, and valve area <1.0 cm^2 or index <0.6 cm^2/m^2, being referred to our hospital from primary or secondary centers. Indication for TAVI was assessed by a multidisciplinary heart team comprised of clinical and interventional cardiologists together with cardiac surgeons.

Procedure. Coronary artery disease was ruled in or out either by coronary computed tomography angiography or invasive coronary angiography. Revascularization was performed after the heart team's decision for percutaneous approach, before TAVI procedure, whenever there was proof of ischemia or a >70% stenosis on a proximal or mid segment from one of the main branches (>50% for left main).

Transapical and subclavian procedures were performed by a hybrid team with interventional cardiologists and cardiac surgeons and transfemoral mainly by interventional cardiologists with background support from cardiac surgery.

Percutaneous valves included CoreValve, CoreValve Evolut R, and CoreValve Evolut Pro (Medtronic); Sapien 3, Sapien XT, Sapien 3 Ultra (Edwards Lifesciences); Portico (Abbott Vascular); and Lotus and Acurate Neo (Boston Scientific), and were implanted on both native and prosthetic valves.

After 2016, the procedures were performed mainly under conscious sedation and analgesia, with use of anesthesia for cases guided by transesophageal echocardiogram or when severe complications occurred during valve implantation. Pacing for balloon-expandable valves was performed on the left ventricular wire and through a temporary transvenous pacing in cases where conduction disturbances like right bundle-branch block were already present, or with the patient's own pacemaker. Vascular closure devices used were Prostar and ProGlide (Abbott Vascular), AngioSeal (Terumo), and Manta (Teleflex).

After TAVI, patients were admitted to a cardiac care unit for the first hours until clinically stable to move to the cardiology ward with continuous electrocardiographic monitoring.

Endpoints. The *primary endpoint* was all-cause mortality at 30 days and 1 year, and at a median follow-up of 24 months. *Secondary endpoints* were in-hospital complications, heart failure readmission, myocardial infarction (MI), stroke, and bleeding > type 2 according to the Blood Academic Research Consortium (BARC) definition[20] after discharge.

Definitions. All definitions were obtained from PARTNER III[8] or were otherwise specified. *Chronic kidney disease* was defined as baseline creatinine clearance <45 mL/kg/min as calculated by Cockroft-Gault equation and *chronic pulmonary disease* was defined as an established diagnosis of chronic obstructive pulmonary disease stage II or higher.

Reported in-hospital complications were: (1) emergent vascular surgery or percutaneous intervention due to vascular closure device failure; (2) femoral artery pseudoaneurysm diagnosed within 1 month after TAVI with or without the need for vascular surgery; (3) *emergent cardiac surgery*, defined as conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications, such as annular rupture or aortic dissection; (4) *pericardial effusion*, referring to evidence of a new pericardial effusion associated or not with hemodynamic instability and clearly related to the TAVI procedure; (5) > type 2 BARC bleeding with or without (6) *hemorrhagic shock*, defined by rapid and significant loss of intravascular volume, which may lead sequentially to hemodynamic instability, with decreases in oxygen delivery and tissue perfusion, cellular hypoxia, organ damage, and death; (7) *cardiogenic shock*, defined by decreased cardiac output (cardiac index <2.2) with evidence of end organ damage and increased filling pressures) in the presence of adequate intravascular volume, due to a cardiac cause; (8) myocardial infarction; (9) stroke; (10) need for mechanical invasive ventilation due to respiratory distress, pulmonary edema, or need of deep anesthesia due to procedure-related complications; (11) need for renal replacement therapy on patients with a previously preserved urinary output, caused by an acute renal injury (Acute Kidney Injury Network stage 3); (12) cardiac resuscitation due to cardiac arrest; and (13) *in-hospital death*, defined as death within the day the patient is admitted for valve implant procedure until the patient is discharged from the hospital.

Cardiovascular mortality was defined by proximate cardiac cause, all procedure- and device-related deaths including valve dysfunction, or other valve-related adverse events and

TABLE 1. Population baseline and procedural characteristics, complications, and outcomes in female and male patients after transcatheter aortic valve implantation.

Characteristics	Total Patients (n = 592)	Women (n = 316)	Men (n = 276)	*P*-Value
Demographics				
Age (years)	82.8 ± 6.6	84.4 ± 5	80.9 ± 7.6	<.001[a]
Clinical				
Diabetes	32.1%	29.7%	34.9%	.19
Hypercholesterolemia	67.7%	68.9%	66.2%	.61
Hypertension	85.9%	87.8%	83.6%	.22
Smoking habit	23.2%	5.0%	44.8%	<.001[a]
Peripheral artery disease	19.1%	14.6%	24.3%	<.01[a]
Body mass index (kg/m^2)	26.2 ± 4.2	26.3 ± 4.6	26.0 ± 3.8	.22
Atherosclerotic burden				
Previous myocardial infarction	16.7%	12.5%	21.5%	.01[a]
Previous percutaneous coronary intervention	33.3%	31.3%	35.5%	.30
Previous coronary artery bypass grafting	16.2%	7.6%	26.1%	<.001[a]
Previous stroke	12.0%	10.4%	13.8%	.25
Comorbidities				
New York Heart Association class III or IV	65.6%	68.1%	62.8%	.19
Median NT-proBNP (pg/dL)	2021	1967	2061	.41
Median EuroSCORE II	4.8 (IQR, 3.7)	4.9 (IQR, 3.5)	4.7 (IQR, 4.1)	.20
Median STS score for mortality	4.6 (IQR, 2.8)	5.1 (IQR, 3.0)	4.1 (IQR, 3.0)	<.001[a]
Pulmonary artery systolic pressure (mm Hg)	43 ± 13	43 ± 12	43 ± 14	.56
Left ventricular ejection fraction (%)	54 ± 14	56 ± 12	51 ± 15	<.001[a]
Chronic kidney disease (CrCl <45 mL/kg/min or HD)	27.4%	23.1%	32.2%	.02[a]
Chronic pulmonary disease (>moderate)	17.6%	14.6%	21.0%	.04[a]
Atrial fibrillation	33.8%	32.3%	35.5%	.43
Procedural characteristics				
Self-expandable	70.2%	77.4%	62.1%	<.001[a]
Non-transfemoral access	18.4%	15.2%	22.1%	.03[a]
General anesthesia	56.0%	56.5%	55.3%	.80
Periprocedural complications				
Emergent vascular surgery or peripheral angioplasty	5.9%	7.0%	4.7%	.30
Emergent cardiac surgery	1.5%	1.6%	1.4%	>.99
Pseudoaneurysm	2.7%	4.7%	0.4%	<.01[a]
>BARC 2 bleeding	12.3%	14.5%	9.8%	.10
Pericardial effusion	2.0%	3.5%	0.4%	<.01[a]
Hemorrhagic shock	1.2%	1.3%	1.1%	>.99
Cardiogenic shock	4.9%	6.0%	3.6%	.19

Continued on next page

TABLE 1. Population baseline and procedural characteristics, complications, and outcomes in female and male patients after transcatheter aortic valve implantation.

Characteristics	Total Patients (n = 592)	Women (n = 316)	Men (n = 276)	*P*-Value
Acute coronary obstruction	0.5%	0.9%	0.0%	.25
Stroke	2.5%	2.9%	2.2%	.79
Need for invasive ventilation	5.8%	5.4%	6.2%	.73
Need for renal replacement therapy	2.2%	1.6%	2.9%	.40
Cardiac resuscitation	3.4%	3.5%	3.3%	>.99
30-day mortality	3.4%	3.8%	2.9%	.65
Out-of-hospital events				
Heart failure admission	10.3%	10.2%	10.4%	>.99
Myocardial infarction	1.5%	1.9%	1.1%	.51
Stroke	5.5%	5.5%	5.6%	>.99
≥BARC-2 bleeding	5.0%	2.9%	7.5%	.01[a]
1-year mortality	13.0%	11.1%	15.2%	.14

Data presented as percentage, mean ± standard deviation, or median (interquartile range). [a]Denotes statistical significance, defined as *P*<.05.
BARC = Blood Academic Research Consortium; HD = hemodialysis; STS = Society of Thoracic Surgeons short-term risk score for adult cardiac surgery.

non-coronary vascular conditions, such as neurological events, pulmonary embolism, ruptured or dissecting aneurysm, or death preceded by cardiovascular symptoms (such as chest pain). *Non-cardiovascular mortality* was defined as any death that was due primarily to an identifiable non-cardiovascular cause or etiology. *Death of unknown cause* was defined by unwitnessed death or unprovided information.

MI was defined as an ischemic event associated with clinically significant myocardial necrosis, such as new ischemic symptoms (eg, chest pain, shortness of breath) or signs (new ST-segment changes, imaging evidence of new loss of viable myocardium) and elevated cardiac biomarkers consisting of at least 1 sample with a peak value exceeding the 99th reference limit of high sensitivity troponin T and a significant 3-hour delta (Δ) or a further increase of at least 50% post procedure for patients with baseline elevated values. *Postprocedural MI* was defined if the previous occurred within 72 hours from the procedure. *Type 2 MI* was defined according to the 4th Universal Definition of MI European Guidelines,[21] requiring evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis.

Heart failure readmission was defined as hospitalization >24 hours with clinical symptoms and objective signs of heart failure, including dyspnea, pulmonary edema, hypoperfusion, or anasarca, requiring a medical intervention like administration of intravenous diuretics, inotropic therapy, or institution of respiratory mechanical support. *Bleeding* was classified according to BARC criteria.[20]

Statistical analysis. Continuous variables were summarized as mean ± standard deviation or median (1st quartile, 3rd quartile) and compared with analysis of variance or Kruskal-Wallis test based on data distribution. Binary and categorical variables were calculated as frequencies (proportions) and were compared with the Chi-square test or Fisher's exact test if expected cell counts were <5. Survival curves were plotted for time-to-event variables with Kaplan-Meier estimates and compared using the log-rank test. Univariate and multivariate Cox proportional hazard models were used to calculate (un)adjusted hazard ratios (HRs) at follow-up. To determine covariates included in multivariate analysis, we performed univariate analyses for all patient-related baseline characteristics, procedural details, periprocedural complications, and postdischarge complications, namely, heart failure admission, stroke, MI, and bleeding. Variables evaluated are described in Table 1. We then used a Cox regression adjusted for covariates with a *P*-value <.20 at univariate analyses. For the Cox regression, 5 different models were used: (1) patient baseline and procedural characteristics; (2) including STS score and excluding overlapping characteristics (3) similar to the previous, using EuroSCORE II instead; (4) STS score; and (5) in-hospital complications. Model results are presented as HR, 95% confidence interval (CI), and *P*-values. Due to a low number of in-hospital complications resulting in wide CIs, HRs for these factors were not considered individually. The *P*-values were 2-sided and <.05 was considered statistically significant in all analyses. Statistical analyses were performed using SPSS Statistics, version 21 (IBM).

TABLE 2. Correlates to long-term mortality in a univariate and multivariate model in male and female patients after transcatheter aortic valve implantation.

Characteristics	Female				Male			
	Bivariate	Multivariate Analysis			Bivariate	Multivariate Analysis		
Preprocedural/procedural variables		*P*-Value	Hazard Ratio	Confidence Interval		*P*-Value	Hazard Ratio	Confidence Interval
Hypertension	.159				.465			
Diabetes	.270				.010			
Hypercholesterolemia	.127				.719			
Body mass index	.051				.752			
Peripheral artery disease	.042				.219			
Chronic kidney disease >3a	.185				.890			
Previous CABG	.772				.041			
Previous PCI	.141				.313			
Previous myocardial infarction	.555				.160			
Heart failure NYHA class III or IV	.053				.029			
Systolic pulmonary artery pressure	.916				.006			
EuroSCORE II	.023				<.001	<.001	1.13	1.06-1.19
STS score	<.001	<.001[a]	1.12	1.06-1.19	<.001	<.001	1.11	1.06-1.17
TAVI transfemoral access	.074				.001			
In-hospital complications								
Closing access failure	.120				.636			
Emergent cardiac surgery	.015				.005	.01		*
>BARC-2 bleeding or transfusion	.849				.096			
Hemorrhagic shock	.002	<.01[a]		*	.342			
Cardiogenic shock	.105				.001	<.001		*
Myocardial Infarction	<.001				<.001			
Stroke	.362				.176			
Invasive ventilation	.038				.031	.12		
Renal replacement	.001	<.001[a]		*	.005	.19		
Cardiac resuscitation	.002	<.01[a]		*	.018			
Out-of-hospital events								
Heart failure admission	.013				.001			
>BARC-1 bleeding	.106				.667			

*The number of events was <5, precluding hazard ratio and confidence interval interpretation. [a]Denotes statistical significance, defined as *P*<.05.
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons short-term risk score for adult cardiac surgery; TAVI = transcatheter aortic valve implantation.

Results

Patient characteristics are provided in Table 1. In the overall population, significant differences between gender were found with regard to age (81 ± 7.5 years in men vs 84.3 ± 5.3 years in women), as well as smoking habits and peripheral artery disease, chronic kidney and lung disease, previous MI and coronary artery bypass grafting, which were all significantly more prevalent in men. Notwithstanding, STS score was higher in women than in men (5.4% [IQ, 3.0%] vs 4.1% [IQ, 3.1%], respectively; *P*<.001).

TABLE 3. Causes of death at 30 days after transcatheter aortic valve implantation.

Age	Gender	STS PROM	Type of Valve Used	Year of Procedure	Day of Death	Access	Cause of Death	In-Hospital Death	Intra-procedural Death	Mortality Cause
91	female	9.7%	no valve implanted	2009	0	TA	cardiac	yes	yes	Cardiac arrest during anesthesia induction; balloon valvuloplasty performed with no clinical improvement.
91	female	6.9%	SE	2010	0	TF	cardiac	yes	yes	Acute aortic regurgitation.
83	male	6%	SE	2011	28	TF	cardiac	yes	no	Septic and cardiogenic shock (known reduced left ventricular ejection fraction with severe mitral regurgitation).
66	male	2.1%	BE	2011	0	TA	cardiac	yes	yes	Acute mitral regurgitation due to anterior leaflet entrapment in aortic prosthesis.
74	male	5.5%	BE	2011	20	TA	cardiac	yes	no	Cardiogenic shock due to unsuccessful valve implantation.
86	female	6.84%	SE	2012	0	TF	cardiac	yes	yes	Myocardial infarction due to intra-procedural coronary obstruction.
87	female	5.97%	SE	2012	0	TF	cardiac	yes	yes	Cardiac tamponade with need for emergent cardiac surgery – suspected left ventricular rupture.
72	male	18.28%	SE	2013	28	TF	cardiac	yes	no	Septic shock refractory endocarditis (already previous to procedure).
80	male	8.9%	BE	2014	23	TA	cardiac	Yes	No	Cardiac arrest in asystole. Never weaned from mechanical ventilation.
85	female	8.7%	SE	2015	2	TF	non-cardiac	Yes	No	Mesenteric ischemia due to aortic plaque embolization.
91	female	5.4%	ME	2015	22	TF	non-cardiac	No	No	Acute kidney failure superimposed in chronic kidney disease after low cardiac output period during TAVI.
77	male	2.65%	SE	2015	6	TF	cardiac	yes	no	Postprocedural ventricular fibrillation of unknown cause with cardiac arrest. No pulse recovery.
92	female	7.87%	SE	2016	0	TF	cardiac	yes	yes	Intraprocedural cardiac arrest in electromechanical dissociation with pericardial effusion and tamponade – Left ventricular rupture?
93	female	6.42%	SE	2016	13	TF	non-cardiac	yes	no	Hemorrhagic stroke (previously unknown neoplasia).
82	female	4.63%	SE	2017	1	TSC	cardiac	yes	no	Cardiogenic shock – autopsy revealed myocardial infarction.
87	female	5.96%	no valve implanted	2017	0	TF	cardiac	yes	yes	Left ventricular rupture.
71	male	6.9%	SE	2017	1	TF	cardiac	yes	no	Cardiogenic and hemorrhagic shock (previous reduced left ventricular ejection fraction and hemorrhagic dyscrasia).
86	female	7.34%	SE	2017	0	TF	non-cardiac	yes	yes	Hemorrhagic shock due to external and common iliac rupture.
87	female	2.97%	SE	2017	5	TF	non-cardiac	yes	no	Hemorrhagic shock due to closure device failure (surgery attempted).
80	male	2.53%	BE	2018	30	TF	non-cardiac	yes	no	Nosocomial pneumonia.

BE = balloon expandable; ME = mechanically expandable; SE = self-expandable; STS-PROM = Society of Thoracic Surgeons score predicted risk of mortality for adult cardiac surgery; TA = transapical; TF = transfemoral; TSC = transsubclavian.

TABLE 4. Differences on baseline and procedural characteristics, periprocedural, and postdischarge complications between alive and deceased patients on follow-up, after transcatheter aortic valve implantation.

	Alive (n = 389)	Deceased (n = 203)	*P*-Value
Population Baseline Characteristics			
Demographic			
Age (years)	83.3 ± 5.7	82.0 ± 7.6	.20
Female gender	57.1%	46.3%	.02[a]
Clinical			
Diabetes	28.5%	39.1%	.01[a]
Hypercholesterolemia	69.1%	62.7%	.23
Hypertension	86.4%	84.3%	.63
Smoking habit	22.6%	25.5%	.59
Peripheral artery disease	16.4%	24.1%	.03[a]
Body mass index	26.2 ± 4.2	26.1 ± 3.9	.27
Atherosclerotic burden			
Previous myocardial infarction	14.8%	21.8%	.06
Previous PCI	31.1%	37.9%	.10
Previous CABG	13.4%	21.7%	.01[a]
Previous stroke	11.1%	13.8%	.35
Comorbidities			
NYHA class III or IV	61.4	73.6%	<.01[a]
Median NT-proBNP (pg/dL)	1651 (IQR, 3338)	2405 (IQR, 6656)	.16
EuroSCORE II	5.06 ± 3.84	7.01 ± 5.04	<.001[a]
STS score for mortality	4.64 ± 2.54	6.34 ± 4.04	<.001[a]
PAP (mm Hg)	41.6 ± 12.5	43.6 ± 11.8	.06
Left ventricle ejection fraction (%)	54.6 ± 13	53.6 ± 14	.17
Chronic kidney disease (CrCl <45 mL/kg/min)	26.0%	30.0%	.33
Chronic pulmonary disease (>moderate)	16.2%	20.2%	.26
Atrial fibrillation	34.4%	32.5%	.648
Procedural characteristics			
Self-expandable valve	72.4%	66.0%	.11
Non-transfemoral access	14.7%	25.6%	<.01[a]
Periprocedural complications			
Emergent vascular surgery or peripheral angioplasty	5.4%	9.1%	.21
Emergent cardiac surgery	1.0%	6.7%	<.01[a]
Pseudoaneurysm	2.9%	1.3%	.41
≥BARC-3 bleeding	10.8%	22.7%	<.01[a]
Pericardial effusion	1.4%	6.5%	.01[a]
Hemorrhagic shock	0.2%	7.8%	<.001[a]

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TABLE 4. Differences on baseline and procedural characteristics, periprocedural, and postdischarge complications between alive and deceased patients on follow-up, after transcatheter aortic valve implantation.

	Alive (n = 389)	Deceased (n = 203)	*P*-Value
Cardiogenic shock	3.5%	14.3%	<.001[a]
Myocardial infarction	16.0%	23.3%	.13
Stroke	2.3%	3.9%	.43
Need for invasive ventilation	3.7%	20.0%	<.001[a]
Need for renal replacement therapy	1.0%	10.8%	<.001[a]
Cardiac resuscitation	1.6%	16.0%	<.001[a]
Out-of-hospital events			
Heart failure admission	6.5%	17.5%	<.001[a]
Myocardial infarction	1.0%	2.5%	.29
Stroke	4.7%	7.0%	.34
≥BARC-2 bleeding	4.7%	5.6%	.69

Data presented as percentage, mean ± standard deviation, or median (interquartile range). [a]Denotes statistical significance, defined as *P*<.05.
BARC = Blood Academic Research Consortium; CKD = chronic kidney disease; HD = hemodialysis; STS = Society of Thoracic Surgeons short-term risk score for adult cardiac surgery.

30-day and 1-year mortality rates. Twenty patients died (3.5%; 12 women and 8 men) in the first 30 days after TAVI (Figure 2A and Figure 3) despite the higher STS score in women. One-year mortality was 13% (77 patients; 35 women and 42 men), a rate that is statistically comparable between both genders (log-rank *P*=.11) (Figure 1A and Figure 2A.)

Longer-term mortality rates. Over a median follow-up of 23 months (IQ, 21 months), women demonstrated better overall survival rates (70.3% vs 60.5% in men; *P*=.01; log-rank *P*<.01) (Figure 1B and Figure 2B) suggesting a benefit in this population despite the higher absolute number of periprocedural complications (*P*=.08) (Table 1).

Correlates to mortality. In the univariate analysis, different correlates to all-cause mortality were identified in men and women (Table 2). When using a Cox regression model, none of the independent variables was correlated to death and only STS

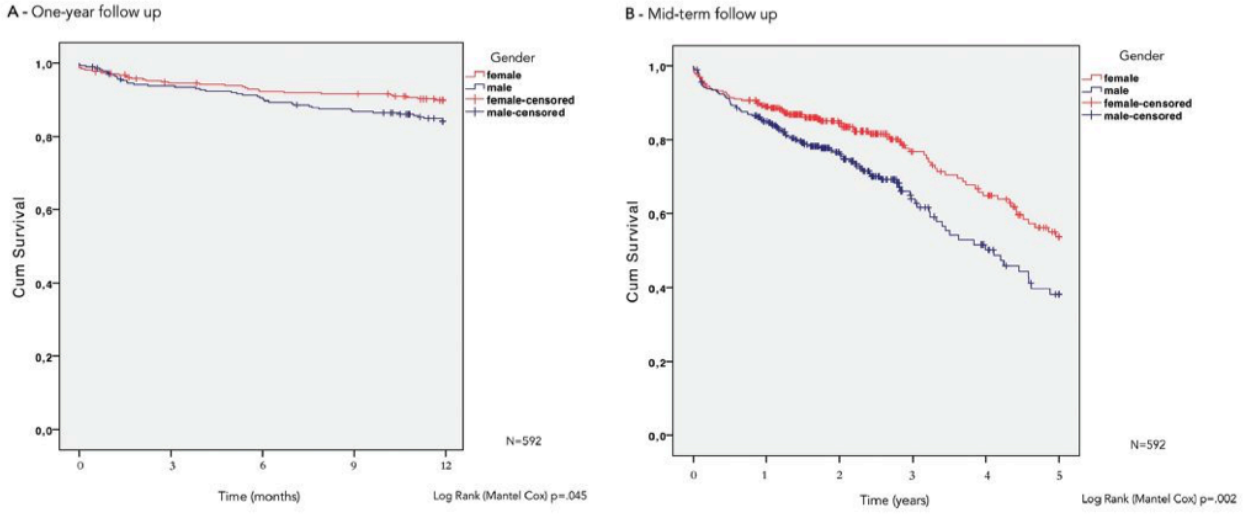


FIGURE 1. Kaplan-Meier curves for all-cause mortality according to gender, at (A) 1-year and (B) mid-term follow-up after transcatheter aortic valve implantation.

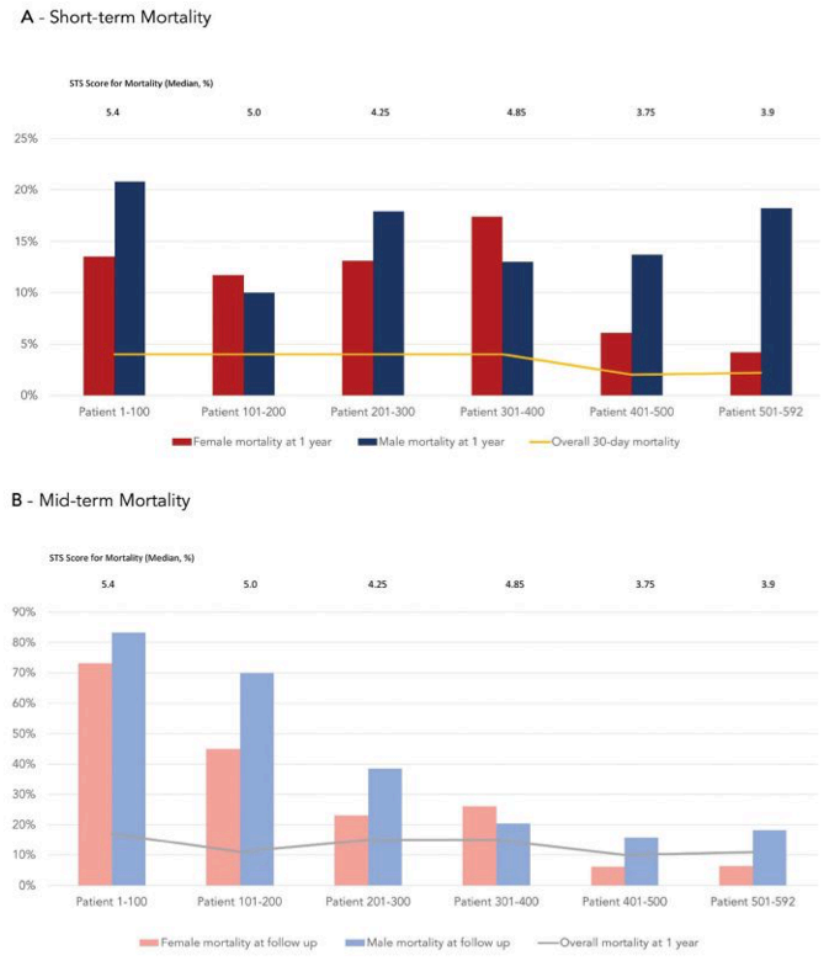


FIGURE 2. (A) Short-term and (B) mid-term mortality differences and trends according to gender in a 10-year spam cohort of patients after transcatheter aortic valve implantation.

score predicted long-term mortality (*P*<.001 for both women and men; HR, 1.12; 95% CI, 1.06-1.19 and HR, 1.11; 95% CI, 1.06-1.17, respectively).

When evaluating in-hospital complications and accounting for STS-predicted risk of mortality, the multivariable model identified hemorrhagic shock and cardiac resuscitation as independent predictors of long-term mortality in women, cardiogenic shock and need for prolonged invasive ventilation in men, and the need for renal replacement therapy in both genders.

Mortality trends. Thirty-day mortality seemed to decrease as the number of procedures increased (a 50% reduction in 30-day mortality from 4% in the first two-thirds of the patients to 2% in the last one-third) and it was lower than expected according to available risk predicting scores (Figure 2A).[22,23] The main 30-day mortality cause was cardiac (14/20 deaths; 70%), mostly because of refractory left ventricular systolic dysfunction leading to multiorgan failure and death (5/20 deaths; 25%) and left ventricular rupture (3/20 deaths; 15%), but also because of massive aortic regurgitation (1/20 deaths; 5%), acute mitral regurgitation due to anterior leaflet take up by the device (1/20 deaths; 5%), acute MI (2/20 deaths; 10%), and arrhythmias (cardiac arrest preceded by ventricular fibrillation in 1/20 deaths; 5%) (Table 3).

In the first subset of 100 patients treated, corresponding to the first 3 years of the program, mortality at 1 year increased and reached 20%, which likely reflects the inclusion of higher-risk patients, as confirmed by the highest STS scores (Figure 3). After that landmark, similar to 30-day mortality, mortality at 1 year also decreased from 20.0% to 10.9% in the last 100 patients (18.2% in men and 4.2% in women).

Discussion

Our results demonstrate that despite higher risk scores, female patients present short-term mortality similar to male patients and have better long-term survival after TAVI. Correlates to mortality identified in men and women are different, and contemporary risk scores may be inadequate to predict short- and long-term outcomes after TAVI in new lower-risk populations, especially when considering female patients. Trend evaluation shows a significant reduction in 30-day and 1-year mortality during the 10-year period of this study (Figure 3), despite no significant variation in the population's predicted risk, reflecting the improved patient clinical assessment (not mirrored in scores), in the technology and in operator performances, contributing to a significant improvement on patient outcomes.

In a large cohort of 1011 patients undergoing TAVI over a period of 8 years, Kesteren et al[24] reported a reduction of 50% in 1-year mortality between 2009 and 2016. This change was mainly attributed to a reduction in 30-day mortality and on the fact that STS-predicted risk of mortality also significantly decreased. In our cohort, STS score did not reduce significantly as we included patients at extreme high risk during the entire registry, but the rates of 30-day and 1-year mortality did decrease (Figure 2). This suggests that improvements in patient clinical assessment and multidisciplinary treatment assignment contributed to better outcomes, as did technological advances in



FIGURE 3. Trends of mortality at 30 days and at 1 year after transcatheter aortic valve implantation.

the valves and delivery systems, increasing operator experience and expertise, and procedure-related technical improvements.

To better understand this progress, one should start by analyzing short-term mortality. Terzian et al[25] reported a rate of 30-day mortality of twice the one observed in our cohort (7.5% vs 3.5%, respectively) in 600 patients between 2006 and 2014, with the deaths occurring in the catheterization laboratory or during the first 24 hours being the most frequent in agreement with our findings (33% and 38%, respectively) (Table 3). A decreasing rate of procedural death during the 8-year period was observed as in our experience, although no statistical analysis could be performed due to the low number of events. This improvement was mainly driven by a decrease in cases of postprocedural refractory congestive heart failure and major access complications, but also in the rate of cardiac rupture, reflecting better procedural planning and execution. To additionally enhance the role of operator experience on the outcomes, Beohar et al[26] compared the third tercile intervened vs the first tercile of a cohort with 1063 patients undergoing transfemoral TAVI in 2011. In our experience, device technology and procedural success improvement throughout the years allowed for a decrease in 30-day and long-term follow-up mortality, which was mainly attributed to better patient selection, valve sizing, and deployment. All-cause death at 1 year in this report was similar to the rate observed in our population (14.4% vs 13.0%, respectively).

Clinical assessment is a baseline step to define patient suitability and potential benefit for intervention, and is still a matter of debate. Different correlates have been identified in distinct populations. Recently, Overtchouk et al[27] studied a cohort of 11,469 patients and identified male sex, history of atrial fibrillation, and chronic renal failure as the strongest independent correlates to mortality. Beohar et al[28] identified serum creatinine, liver disease, coagulopathy, mental status, BMI, male gender, and STS score. Sabaté et al[29] also added peripheral vascular disease, lower ejection fraction, the need to convert to surgery, and at least moderate aortic regurgitation after TAVI as independent predictors of in-hospital and short-term (<1 year) mortality. These correlates diverge not only according to the population in the study, but also with the timing of the assessment (pre, peri, and post procedure), making it difficult to standardize risk definition tools. Furthermore, differences in gender have been outlined and start to suggest that different thresholds for TAVI should be established for female patients.[30,31]

Chieffo et al[32] described a 1-year mortality of around 12.5% in a female population at intermediate-to-high risk, which is not much higher than the rate observed in our female population, identifying EuroSCORE I, baseline atrial fibrillation, and prior percutaneous coronary intervention as independent predictors of 1-year death or stroke. The modest performance of contemporary risk scores in predicting early and long-term

mortality after TAVI has been described,[33,34] and in the present study, only STS (and not EuroSCORE II) was an independent predictor of mortality in both men and women (HR, 1.11 for men; HR, 1.12 for women).

No gender differences were observed in our cohort regarding survival at 30 days[30] or 1-year mortality,[19,30,35] contrary to previous findings,[36,37] which is perhaps due to the low rate of events observed in our population. Multiple registries point toward a higher number of procedural complications in women and we also observed significantly higher rates of procedural vascular complications[32–35] and pericardial effusion,[37–40] although these findings are inconsistent in higher-risk populations.[41] The differences in complications and cardiovascular events between men and women were nullified after hospital discharge. When considering longer-term follow-up, differences in mortality are apparent, with women surviving longer than men. Even considering the fact that, at any fixed age, women have a longer life expectancy than men, this would probably not explain the large significant difference between genders found in the study. Baseline characteristics differ between populations.[19,31,35,40,42] In our population, women were older and had a lower prevalence of coronary artery disease, peripheral artery disease, and chronic kidney disease, as well as higher baseline left ventricular ejection fraction,[39,42] paradoxically presenting a higher mean STS.[36,37] The effect of age in contemporary risk scores may become obsolete as older patients with fewer comorbidities are treated, and younger patients with higher-risk profiles are considered for TAVI. In our analysis, age was not a significant predictor of mortality.[39] Correlations to lower mortality have been established, eg, between lower prevalence of coronary artery disease, diabetes, and atrial fibrillation,[43] and higher baseline left ventricular ejection fraction.[44] In our population, these variables were not independent predictors when interpreted out of a multiparametric assessment like the STS score. Non-transfemoral access was significantly different between patients deceased or alive at follow-up (Table 4), more frequently used in male patients, and it was an independent predictor for mortality ($P<.01$ in men).[39,42] No differences were seen in mortality regarding the mechanism of the valve.[42]

Study limitations. After the 1-month follow-up visit, some of the study patients continued medical follow-up at referral hospitals. Due to patient data-protection laws, only live status could be assessed in every patient; thus, under-reporting of long-term follow-up cardiovascular events may have occurred. The cause of death was inaccessible in a percentage of patients, resulting in under-reporting of cardiovascular deaths.

Conclusion

Despite a higher STS score in women in a population undergoing TAVI, 30-day mortality was not significantly different between men and women, and it was largely lower than predicted. At long-term follow-up, women presented better outcomes.

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Predictors and Clinical Impact of Prosthesis-Patient Mismatch After Self-Expandable TAVR in Small Annuli

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ABSTRACT

OBJECTIVES The aim of this study was to define predictors of prosthesis-patient mismatch (PPM) and its impact on mortality after transcatheter aortic valve replacement (TAVR) with self-expandable valves (SEVs) in patients with small annuli.

BACKGROUND TAVR seems to reduce the risk for PPM compared with surgical aortic valve replacement, especially in patients with small aortic annuli. Nevertheless, predictors and impact of PPM in this population have not been clarified yet.

METHODS Predictors of PPM and all-cause mortality were investigated using multivariable logistic regression analysis from the cohort of the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry, which included patients with severe aortic stenosis and small annuli (annular perimeter <72 mm or area <400 mm^2 on computed tomography) treated with transcatheter SEVs: 445 patients with (n = 129) and without (n = 316) PPM were enrolled.

RESULTS Intra-annular valves conferred increased risk for PPM (odds ratio [OR]: 2.36; 95% confidence interval [CI]: 1.16 to 4.81), while post-dilation (OR: 0.46; 95% CI: 0.25–0.84) and valve oversizing (OR: 0.53; 95% CI: 0.28–1.00) seemed to protect against PPM occurrence. At a median follow-up of 354 days, patients with severe PPM, but not those with moderate PPM, had a higher all-cause mortality rate compared with those without PPM (log-rank p = 0.008). Multivariable Cox regression confirmed severe PPM as an independent predictor of all-cause mortality (hazard ratio: 4.27; 95% CI: 1.34 to 13.6).

CONCLUSIONS Among patients with aortic stenosis and small aortic annuli undergoing transcatheter SEV implantation, use of intra-annular valves yielded higher risk for PPM; conversely, post-dilation and valve oversizing protected against PPM occurrence. Severe PPM was independently associated with all-cause mortality.
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First described by Rahimtoola (1) in 1978, prosthesis-patient mismatch (PPM) is currently defined as a nonstructural valvular dysfunction relatively occurring when the effective area of an implanted prosthetic valve is too small relative to the patient's body size (2). PPM is associated with higher than expected gradients for a properly functioning bioprosthetic valve and seems fairly common with surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) (3).

The evidence of increased risk for short- and long-term mortality in patients with PPM after SAVR is well described (4-6), while its clinical impact in patients subject to TAVR is unclear (7). Recently, PPM has been associated with blunted left ventricular mass regression (8), increased risk for rehospitalization (9), and reduction in overall survival (10) and may vary according to the transcatheter heart valve platform (11).

Transcatheter bioprostheses seem to offer better hemodynamic status and a reduced risk for PPM compared with surgical valves (12-14). This applies particularly to the subset of patients with small aortic annuli (9,10), when using self-expandable valves (SEVs) (15,16). Data from the TAVI-SMALL (International Multicenter Registry to Evaluate the Performance of Self-Expandable Valves in Small Aortic Annuli) registry, which focused on this subgroup of patients, suggested that supra-annular SEVs seemed to slightly outperform intra-annular SEV in terms of transvalvular gradients (17). However, predictors of PPM and clinical outcomes in this context have not been investigated yet. Accordingly, the aim of this study was to evaluate predictors and clinical impact of PPM in patients with severe aortic stenosis and small annuli treated with self-expandable TAVR.

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METHODS

STUDY DESIGN AND DEFINITION. The study design of the observational, retrospective TAVI-SMALL registry has been previously described (17). Briefly, the registry included a total of 859 patients with severe native aortic valve stenosis and small aortic annuli (defined as annular area <400 mm^2 and/or annular perimeter <72 mm on computed tomography) treated with transcatheter implantation of current-generation supra-annular (Evolut R and Evolut PRO, Medtronic, Minneapolis, Minnesota; Acurate NEO, Boston Scientific, Marlborough, Massachusetts) and intra-annular (Acurate TransApical, Boston Scientific; Portico, Abbott Vascular, Santa Clara, California) SEVs between June 2011 and October 2018, at 9 high-volume European centers. This study complied with the Declaration of Helsinki and was approved by local ethics committees. All patients provided written informed consent for the procedure and subsequent data collection.

The present substudy was intended to focus on PPM; therefore, only patients with complete data (baseline computed tomographic measurements, baseline and follow-up echocardiographic parameters, and adequate clinical follow-up) were included, for a total of 445 cases.

Patients were then divided into groups according to the absence or presence of post-procedural PPM, defined as indexed effective orifice area (EOA) <0.85 cm^2/m^2; those with PPM were further divided into moderate (indexed EOA 0.65 to 0.85 cm^2/m^2) and severe PPM (indexed EOA <0.65 cm^2/m^2) groups (18). Additional analyses were conducted in groups divided according to body mass index (BMI)-adjusted PPM thresholds, that is, indexed EOA <0.70 and <0.60 cm^2/m^2 for moderate and severe PPM, respectively, in patients with BMI ≥30 kg/m^2 (19). EOA was calculated on pre-discharge echocardiography using the continuity equation method; stroke volume was estimated via left ventricular outflow tract (LVOT) diameter (outer to outer border of the valve stent) and velocity-time integral measured just underneath the ventricular margin of the valve stent (19).

ENDPOINTS. The primary objective of the study was to identify independent predictors of PPM. Secondary endpoints included 1-year all-cause mortality and ischemic stroke or transient ischemic attack; in addition, independent predictors of 1-year all-cause mortality were evaluated.

Clinical and technical endpoint definitions coincide with those of the original study (17); in addition, computed tomography-derived annular eccentricity (maximum/minimum annular diameter) and percentage of oversizing according to perimeter

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium
BEV = balloon-expandable valve
BMI = body mass index
CI = confidence interval
EOA = effective orifice area
HR = hazard ratio
LVOT = left ventricular outflow tract
OR = odds ratio
PPM = prosthesis-patient mismatch
SEV = self-expandable valve
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Demographic Characteristics According to Presence and Degree of PPM

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Age, yrs	82.5 ± 6.3	81.5 ± 7.7	**0.077**	82.5 ± 6.1	1.00	79.5 ± 10.0	**0.017**	**0.048**	**0.02**
Female	89.9 (284)	90.7 (117)	0.792	90.8 (79)	1.00	90.5 (38)	1.00	1.00	0.964
Weight, kg	63.1 ± 13.0	70.4 ± 13.9	**<0.001**	70.1 ± 13.1	**<0.001**	71.2 ± 15.5	**0.001**	1.00	**<0.001**
Height, cm	158.3 ± 6.9	159.5 ± 7.5	**0.052**	159.1 ± 7.6	1.00	160.3 ± 7.3	0.242	1.00	0.174
Body surface area, m^2	1.66 ± 0.18	1.78 ± 0.21	**<0.001**	1.78 ± 0.19	**0.001**	1.79 ± 0.25	**0.011**	1.00	**<0.001**
Body mass index, kg/m^2	25.9 ± 4.6	28.1 ± 5.5	**<0.001**	28.2 ± 5.2	**0.007**	28.0 ± 6.0	0.101	1.00	**0.003**
Hypertension	84.2 (266)	86.0 (111)	0.619	87.4 (76)	0.612	83.3 (35)	0.825	0.591	0.751
Diabetes mellitus	25.3 (80)	36.4 (47)	**0.062**	39.1 (34)	**0.024**	30.9 (13)	0.172	**0.060**	**0.018**
Dyslipidemia	44.1 (139)	45.0 (58)	0.872	48.3 (42)	0.543	38.1 (16)	0.510	0.346	0.568
COPD	11.1 (35)	7.8 (10)	0.302	9.2 (8)	0.844	4.8 (2)	0.284	0.496	0.427
Peripheral artery disease or previous PTA	16.8 (53)	16.3 (21)	0.888	16.1 (14)	0.871	16.7 (7)	0.979	0.934	0.987
Cerebrovascular disease	8,6 (27)	9.3 (12)	0.805	9.2 (8)	0.855	9.5 (4)	0.773	1.00	0.968
Previous BAV	3.2 (10)	3.9 (5)	0.695	4.6 (4)	0.510	2.4 (1)	1.00	1.00	0.741
Previous PCI	25.0 (79)	25.6 (33)	0.898	27.6 (24)	0.624	21.4 (9)	0.614	0.453	0.746
Previous CABG	6.6 (21)	11.6 (15)	**0.080**	11.5 (10)	0.133	11.9 (5)	0.217	0.946	0.216
Previous MI	10.7 (33)	13.2 (17)	0.467	14.9 (13)	0.282	9.5 (4)	1.00	0.580	0.510
Coronary artery disease	38.1 (120)	45.0 (58)	0.180	52.9 (46)	**0.013**	28.6 (12)	0.230	**0.009**	**0.013**
PM or ICD	9.2 (29)	13.2 (17)	0.208	11.5 (10)	0.517	16.7 (7)	0.129	0.416	0.301
Atrial fibrillation	22.8 (64)	28.1 (32)	0.266	27.6 (24)	0.147	19.0 (8)	0.941	0.345	0.331
Angina	20.7 (55)	15.5 (13)	0.294	6.9 (6)	0.114	16.7 (7)	0.805	0.169	0.261
NYHA functional class III or IV	73.2 (229)	89.8 (115)	**<0.001**	88.5 (77)	**0.001**	90.4 (38)	**0.015**	0.869	**0.001**
STS-PROM, %	5.87 ± 4.27	5.62 ± 2.97	0.559	5.77 ± 3.0	1.00	5.31 ± 2.9	1.00	1.00	0.704
NT-proBNP, pg/ml	2,638.8 ± 4,387.9	1,281.2 ± 2,209.0	0.100	1,449.2 ± 2,458.1	1.00	609.5 ± 702.1	1.00	1.00	0.617
Hemoglobin, g/dl	11.4 ± 2.10	11.5 ± 2.05	0.374	11.4 ± 2.03	1.00	11.8 ± 2.09	0.848	0.966	0.541

Values are mean ± SD or % (n). The p values in **bold** represent differences between groups with p values < 0.10.

BAV = balloon aortic valvuloplasty; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PM = pacemaker; PPM = prosthesis-patient mismatch; PTA = percutaneous transluminal angioplasty; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

([SEV perimeter/annular perimeter − 1]/100) were calculated.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (interquartile range) and were compared using Student's *t*-test or the Mann-Whitney *U* test or Wilcoxon test in case of 2-group comparisons on the basis of normality of data distribution, verified using the Shapiro-Wilk test. In case of continuous variable comparisons between more than 2 groups, analysis of variance was performed; Bartlett's test for equal variances was performed to assess if the variances were comparable between groups, and Bonferroni correction was applied to adjust for multiple comparisons. Categorical variables are reported as percentage (number) and were compared using the chi-square test without Yates's correction for continuity or the Fisher exact test, as appropriate. Univariable and multivariable logistic regression modeling for severe PPM included the following variables: severe annular calcification, oversizing ≥15% by perimeter, intra-annular valve, pre-dilation, and post-dilation. Results of the logistic regression analysis are presented as odds ratios (ORs) with 95% confidence intervals (CIs). The accuracy of logistic regression model was tested using C statistics; Hosmer-Lemeshow goodness-of-fit tests were performed to assess the fit of the model. Survival curves for all-cause mortality were constructed with the use of Kaplan-Meier estimates and compared using the log-rank test. Unadjusted and adjusted Cox proportional hazards models were generated for all-cause mortality. Hazard ratios (HRs) and 95% CIs are reported. The adjusted model includes characteristics we considered relevant: age, sex, BMI, diabetes mellitus, coronary artery disease, New York Heart Association functional class III or IV, moderate or more mitral regurgitation,

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TABLE 2 Baseline Echocardiographic and CT Characteristics According to Presence and Degree of PPM

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Echocardiographic data									
Mean AV gradient, mm Hg	51.7 ± 16.8	47.6 ± 17.1	**0.011**	47.4 ± 15.9	0.122	48.0 ± 19.5	0.553	1.00	**0.073**
Maximum AV gradient, mm Hg	82.8 ± 24.9	75.6 ± 26.5	**0.004**	74.7 ± 25.0	**0.035**	77.3 ± 29.4	0.606	1.00	**0.028**
EOA, cm^2	0,63 ± 0,19	0,64 ± 0,20	0.351	0.65 ± 0.19	1.00	0.62 ± 0.17	1.00	1.00	0.630
Indexed EOA, cm^2/m^2	0.38 ± 0.13	0.36 ± 0.11	0.565	0.36 ± 0.11	1.00	0.36 ± 0.10	1.00	1.00	0.689
sPAP, mm Hg	41.6 ± 14.3	43.3 ± 15.1	0.389	43.8 ± 14.9	0.726	42.1 ± 15.6	1.00	1.00	0.504
RV dysfunction*	12.3 (39)	13.2 (17)	0.809	9.2 (8)	0.418	21.4 (9)	0.104	**0.054**	0.141
Bicuspid AV	6.8 (16)	3.2 (3)	0.195	1.1 (1)	0.135	4.8 (2)	1.00	0.262	0.282
Moderate or greater AR	8.7 (27)	6.6 (8)	0.474	6.2 (5)	0.649	7.5 (3)	1.00	1.00	0.843
Moderate or greater MR	11.9 (36)	11.6 (14)	0.929	13.7 (11)	0.650	7.3 (3)	0.598	0.378	0.645
Moderate or greater TR	7.5 (18)	7.9 (7)	0.891	6.8 (4)	1.00	10.3 (3)	0.482	0.680	0.735
Ejection fraction, %	57.9 ± 9.9	58.1 ± 12.0	0.412	58.3 ± 11.8	1.00	57.8 ± 12.6	1.00	1.00	0.953
LVEF <40%	5.4 (17)	7.0 (9)	0.515	6.9 (6)	0.589	7.1 (3)	0.717	1.00	0.715
LVEDV, ml	85.8 ± 33.7	80.7 ± 31.8	0.178	77.8 ± 22.4	0.701	85.4 ± 43.3	1.00	1.00	0.489
LVESV, ml	36.3 ± 20.5	36.2 ± 30.0	0.487	35.4 ± 20.5	1.00	37.4 ± 40.0	1.00	1.00	0.962
CT data									
Mean annular diameter, mm	21.2 ± 1.3	21.1 ± 1.4	0.155	21.3 ± 1.4	1.00	20.7 ± 1.2	**0.057**	**0.083**	**0.053**
Maximum diameter, mm	23.4 ± 1.9	23.7 ± 2.0	**0.077**	23.9 ± 2.1	0.458	23.4 ± 1.7	1.00	0.461	0.131
Minimum diameter, mm	19.1 ± 1.9	18.5 ± 1.6	**0.001**	18.7 ± 1.7	0.250	18.1 ± 1.5	**0.004**	0.264	**0.003**
Annular eccentricity	1.24 ± 0.17	1.29 ± 0.14	**0.002**	1.29 ± 0.15	**0.058**	1.30 ± 0.13	**0.096**	1.00	**0.013**
Mean aortic annular perimeter, mm	67.4 ± 3.7	67.1 ± 3.5	0.182	67.4 ± 3.4	1.00	66.4 ± 3.6	0.324	0.546	0.272
Mean aortic annular area, mm^2	349.9 ± 38.0	338.8 ± 35.5	**0.007**	343.1 ± 34.8	0.583	330.4 ± 35.9	**0.015**	0.332	**0.013**
Area-derived diameter, mm	21.1 ± 1.1	20.7 ± 1.1	**0.007**	20.9 ± 1.09	1.00	20.5 ± 1.12	0.324	0.546	**0.014**
Perimeter-derived diameter, mm	21.5 ± 1.2	21.3 ± 1.1	0.182	21.4 ± 1.07	0.616	21.1 ± 1.17	**0.015**	0.320	0.272
Severe leaflet calcification	26.3 (31)	11.8 (4)	**0.077**	15.8 (3)	0.403	6.7 (1)	0.117	0.613	0.171
Severe annular calcification	12.0 (16)	4.8 (4)	**0.079**	3.8 (2)	0.106	6.4 (2)	0.531	0.624	0.219
Severe LVOT calcification	1.9 (6)	1.3 (1)	0.230	4.2 (1)	1.00	0.0 (0)	0.596	1.00	0.839
LMCA distance, mm	11.5 ± 2.6	11.4 ± 2.3	0.441	11.3 ± 2.1	1.00	11.8 ± 2.8	1.00	1.00	0.736
RCA distance, mm	14.1 ± 3.0	14.5 ± 2.1	0.153	14.4 ± 2.0	1.00	14.6 ± 2.3	1.00	1.00	0.579
Sinotubular junction diameter, mm	26.2 ± 2.4	26.0 ± 2.3	0.291	25.7 ± 1.9	0.501	26.8 ± 2.9	0.894	0.211	0.166
Sinus of Valsalva diameter, mm	29.5 ± 2.7	28.3 ± 2.2	**<0.001**	28.4 ± 1.9	**0.016**	28.3 ± 2.7	**0.066**	1.00	**0.004**
Ascending aorta diameter, mm	32.3 ± 4.1	31.8 ± 4.4	0.207	31.1 ± 3.9	0.120	33.7 ± 5.2	0.264	**0.015**	**0.014**
Porcelain aorta	3.8 (12)	7.7 (10)	**0.081**	10.3 (9)	**0.015**	2.4 (1)	1.00	0.165	**0.045**

Values are mean ± SD or % (n). The p values in **bold** represent differences between groups with p values < 0.10. *Defined as tricuspid annular plane systolic excursion <17 mm.

AR = aortic regurgitation; AV = aortic valve; CT = computed tomographic; EOA = effective orifice area; LMCA = left main coronary artery; LVEDV = left ventricular end systolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVOT = left ventricular outflow tract; MR = mitral regurgitation; PPM = prosthesis-patient mismatch; RCA = right coronary artery; RV = right ventricular; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

ejection fraction, transfemoral access, moderate PPM, and severe PPM. The interaction between severe PPM and BMI was assessed in the original cohort. Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. A 2-sided p value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using Stata version 13.0 (StataCorp).

RESULTS

STUDY POPULATION AND CLINICAL FEATURES. A total of 445 patients with aortic stenosis and small aortic annuli treated with transcatheter implantation of self-expandable bioprostheses were included in the analysis; of these, 316 patients did not develop PPM, while 87 (19.6%) and 42 (9.4%) patients had moderate and severe PPM, respectively, yielding a total of 129 patients with PPM (29.0%). When PPM thresholds were adjusted for BMI, 109 patients had PPM (24.5%); in particular, 71 (15.9%) had moderate and 38 (8.6%) severe PPM.

Table 1 reports baseline characteristics of patients according to presence and degree of PPM. Treated patients were mostly women (90%) and were at moderate surgical risk (mean Society of Thoracic Surgeons Predicted Risk of Mortality scores were

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TABLE 3 Procedural Characteristics

	No PPM (n = 316)	PPM (n = 129)	p Value No PPM vs. PPM	Moderate PPM (n = 87)	p Value No vs. Moderate PPM	Severe PPM (n = 42)	p Value No vs. Severe PPM	p Value Moderate vs. Severe PPM	p Value No vs. Moderate vs. Severe PPM
Access			**<0.001**		**<0.001**		**0.009**	0.632	**<0.001**
Femoral	90.2 (285)	69.8 (90)	**<0.001**	67.8 (59)	**<0.001**	73.8 (31)	**0.002**	0.487	**<0.001**
Apical	4.7 (15)	20.9 (27)	**<0.001**	23.0 (20)	**<0.001**	16.7 (7)	**0.003**	0.408	**<0.001**
Surgical axillary/subclavian	3.2 (10)	5.4 (7)	0.259	5.7 (5)	0.333	4.8 (2)	0.640	1.00	0.434
Percutaneous axillary/subclavian	0.3 (1)	3.1 (4)	**0.011**	3.4 (3)	**0.033**	2.4 (1)	0.221	1.00	**0.030**
Transaortic	1.6 (5)	0.8 (1)	0.503	0	0.590	2.4 (1)	0.530	0.326	0.372
Valve size			**<0.001**		0.135		**0.022**	0.706	**0.039**
≤25 mm	45.6 (144)	62.0 (80)	**0.002**	59.8 (52)	**0.020**	66.7 (28)	**0.011**	0.449	**0.006**
≥26 mm	54.4 (172)	38.0 (49)	**0.002**	40.2 (35)	**0.020**	33.3 (14)	**0.011**	0.449	**0.006**
Oversizing by perimeter	17.7 ± 7.7	16.0 ± 7.7	**0.019**	16.0 ± 7.7	0.176	16.2 ± 7.8	0.751	1.00	0.116
Oversizing by perimeter ≥15%	65.2 (206)	56.6 (73)	**0.089**	55.2 (48)	**0.087**	59.5 (25)	0.471	0.640	0.209
Valve type			**0.037**		0.179		**0.079**	0.602	0.110
Intra-annular valve	22.5 (71)	48.8 (63)	**<0.001**	49.4 (43)	**<0.001**	47.6 (20)	**<0.001**	0.847	**<0.001**
Evolut R	48.7 (154)	38.8 (50)	**0.055**	37.9 (33)	**0.074**	40.1 (17)	0.314	0.781	0.154
Evolut PRO	11.1 (35)	7.0 (9)	0.189	9.2 (8)	0.615	2.4 (1)	0.100	0.270	0.198
Acurate NEO	17.7 (56)	5.4 (7)	**0.001**	3.4 (3)	**<0.001**	9.5 (4)	0.270	0.214	**0.001**
Acurate TransApical	4.4 (14)	20.9 (27)	**<0.001**	23.0 (20)	**<0.001**	16.7 (7)	**0.002**	0.408	**<0.001**
Portico	18.0 (57)	27.9 (36)	**0.020**	26.4 (23)	**0.082**	30.9 (13)	**0.047**	0.592	**0.057**
Pre-dilation	48.6 (153)	50.4 (65)	0.728	47.1 (41)	0.477	54.8 (23)	0.685	0.416	0.677
Post-dilation	43.6 (137)	28.7 (37)	**0.003**	25.3 (22)	**0.002**	35.7 (15)	0.330	0.220	**0.007**
Contrast medium	135.6 ± 63.7	118.6 ± 57.7	**0.008**	115.0 ± 60.0	**0.037**	125.5 ± 52.9	1.00	1.00	**0.038**
Annular rupture	0.9 (2)	0.0 (0)	0.371	0.0 (0)	1.00	0.0 (0)	1.00	–	1.00

Values are % (n), mean ± SD, or % (n). The p values in **bold** represent differences between groups with p values < 0.10.
PPM = prosthesis-patient mismatch.

5.87 ± 4.27% and 5.62 ± 2.97% in patients without and with PPM, respectively). Mean age was lower in patients with severe PPM (79.5 ± 10.0 years) compared with those with no PPM (82.5 ± 6.3 years; p = 0.017) and moderate PPM (82.5 years; p = 0.048). As expected, weight and body surface area were higher in patients with any degree of PPM compared with those without PPM (70.4 ± 13.9 kg vs. 63.1 ± 13.0 kg [p < 0.001] and 1.78 ± 0.21 m^2 vs. 1.66 ± 0.18 m^2 [p < 0.001]); similarly, BMI was significantly higher in patients with moderate PPM. No significant differences were noted among groups with regard to traditional prognostic risk factors (such as diabetes, peripheral artery disease, and atrial fibrillation), with the exception of higher New York Heart Association functional class at baseline in patients who developed PPM (88.5% and 90.4% in class III or IV in patients with moderate and severe PPM compared with 73.2% in those with no PPM). Supplemental Table 1 includes baseline characteristics of cohorts derived from BMI-adjusted PPM thresholds.

ECHOCARDIOGRAPHIC AND COMPUTED TOMOGRAPHY FEATURES. Baseline echocardiographic and computed tomographic features are shown in **Table 2**. There were no relevant differences among groups in echocardiographic variables, except for slightly lower mean pre-procedural mean and peak aortic gradients in patients with PPM.

As expected, computed tomography-derived aortic annular area was lower in the PPM group (349.9 mm^2 vs. 338.8 mm^2; p = 0.007), especially in the severe PPM group (330.4 mm^2); similar differences were present in minimum annular diameter (19.1, 18.7, and 18.1 mm in the groups with no, moderate, and severe PPM, respectively; p = 0.003), annular eccentricity (p = 0.013), and sinus of Valsalva diameter (p = 0.004). Aortic annular perimeter did not significantly differ among groups (p = 0.272).

No significant differences were present in proportions of severe annular, leaflet, or LVOT calcifications, even though the former two tended to be more represented in patients without compared with those with PPM (12.0% vs. 4.8% [p = 0.079] and 26.3% vs. 11.8% [p = 0.077]). Baseline echocardiographic and computed tomographic features of BMI-adjusted PPM threshold cohorts are reported in Supplemental Table 2.

PROCEDURAL FEATURES. Procedural data are shown in **Table 3**. Most patients were treated by transfemoral access, but a significant difference in access-site

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TABLE 4 Post-Procedural Characteristics and Follow-Up

			p Value		p Value		p Value		
	No PPM (n = 316)	PPM (n = 129)	No PPM vs. PPM	Moderate PPM (n = 87)	No vs. Moderate PPM	Severe PPM (n = 42)	No vs. Severe PPM	Moderate vs. Severe PPM	No vs. Moderate vs. Severe PPM
Pre-discharge									
Any vascular complication	15.9 (50)	7.1 (9)	**0.014**	7.0 (6)	**0.034**	7.3 (3)	0.169	1.00	**0.052**
Major vascular complication	4.8 (15)	3.1 (4)	0.446	2.3 (2)	0.545	4.9 (2)	1.00	0.594	0.680
Need for second valve implantation	2.6 (8)	3.1 (4)	0.757	3.5 (3)	0.710	2.4 (1)	1.00	1.00	0.889
Mean AV gradient, mm Hg	8.4 ± 4.0	10.9 ± 4.7	**<0.001**	10.2 ± 3.8	**0.003**	12.3 ± 6.0	**<0.001**	**0.042**	**<0.001**
Maximum AV gradient, mm Hg	14.9 ± 7.0	17.7 ± 7.0	**0.002**	16.7 ± 7.1	0.354	19.2 ± 6.6	**0.006**	0.381	**0.005**
Indexed EOA, cm^2/m^2	1.18 ± 0.36	0.69 ± 0.12	**<0.001**	0.75 ± 0.06	**<0.001**	0.55 ± 0.09	**<0.001**	**0.001**	**<0.001**
More than mild PVL	9.3 (21)	10.6 (10)	0.711	13.6 (8)	0.334	5.7 (2)	0.749	0.312	0.431
More than moderate PVL	1.3 (3)	3.2 (3)	0.263	5.1 (3)	0.105	0	1.00	0.291	0.116
New permanent PM	15.6 (49)	18.1 (23)	0.528	19.8 (17)	0.363	14.6 (6)	0.865	0.482	0.627
BARC major bleeding	5.9 (15)	1.0 (1)	**0.043**	1.5 (1)	0.142	0	0.138	0.464	0.121
BARC bleeding			**0.095**		**0.092**		0.656	0.405	0.259
Type 1	10.3 (26)	20.0 (20)	**0.017**	22.7 (15)	**0.007**	14.3 (5)	0.478	0.311	**0.028**
Type 2	2.0 (5)	2.0 (2)	0.998	3.0 (2)	0.606	0	0.401	0.298	0.583
Type 3	5.9 (15)	1.0 (1)	**0.043**	1.5 (1)	0.142	0	0.138	0.464	0.121
Type 5	0	0	–	0	–	0	–	–	–
Follow-up									
All-cause mortality	6.6 (20)	10.5 (13)	0.176	8.4 (7)	0.567	14.6 (6)	**0.069**	0.289	0.191
Cardiovascular mortality	2.4 (7)	3.4 (4)	0.573	2.4 (2)	1.00	5.0 (2)	0.285	0.595	0.456
Myocardial infarction	0.7 (2)	0	0.365	0	1.00	0	1.00	–	1.00
TIA/stroke	1.8 (5)	3.5 (4)	0.298	3.9 (3)	0.376	2.6 (1)	0.533	1.00	0.441
Acute kidney injury	5.2 (9)	5.1 (2)	0.991	7.4 (2)	0.645	0	1.00	1.00	0.816
Hospitalization for HF	6.3 (13)	4.1 (2)	0.547	5.9 (2)	1.00	0	0.607	1.00	0.882
NYHA functional class III or IV	8.9 (12)	13.0 (3)	0.530	2.0 (3)	0.176	0	1.00	0.526	0.304

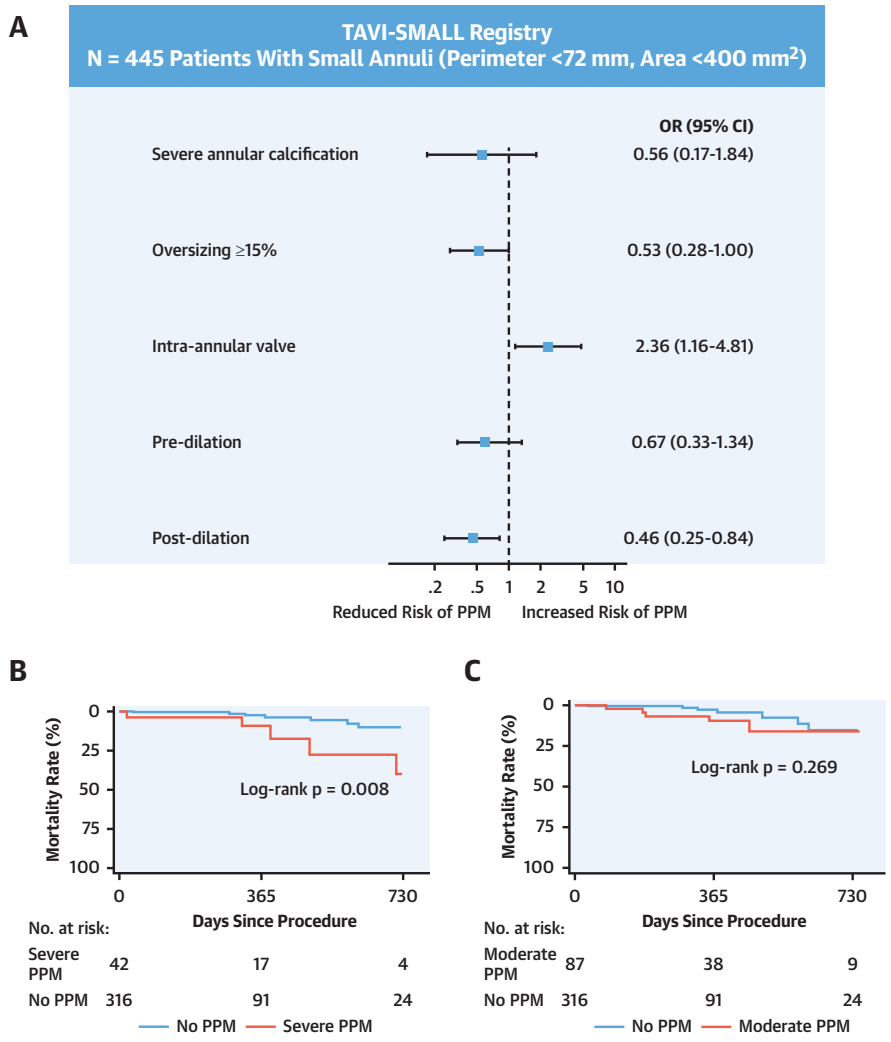
Values are % (n) or mean ± SD. The p values in **bold** represent differences between groups with p values < 0.10.
BARC = Bleeding Academic Research Consortium; HF = heart failure; PVL = paravalvular leak; TIA = transient ischemic attack; other abbreviations as in Tables 1 and 2.

selection was present, with a lower proportion of transfemoral procedures in the PPM group (90.2% vs. 69.8%; p < 0.001), a difference that was driven mainly by patients treated with the Acurate Trans-Apical device and by those treated via axillary or subclavian access. With respect to prosthesis selection, a higher proportion of SEVs with nominal diameter of 25 mm or less were implanted in patients with PPM than those without (62.0% vs. 45.7%; p = 0.002). A trend toward increased oversizing according to perimeter in the no PPM group was present (17.7% vs. 16.0% [p = 0.057], no PPM vs. PPM group, respectively; oversizing >15% in 65.2% vs. 56.6% [p = 0.089], no PPM vs. PPM group, respectively). Although the rate of pre-dilation was similar between groups, more patients in the no PPM group underwent post-dilation (43.6% vs. 28.7%; p = 0.003). A higher proportion of patients with PPM underwent implantation of an intra-annular SEV (48.8% vs. 22.5%; p < 0.001), driven by a higher use of Portico (27.9% vs. 18.0%; p = 0.012) and Acurate TransApical (20.9% vs. 4.4%; p < 0.001) devices. Similar results are reported in Supplemental Table 3.

PROCEDURAL AND CLINICAL OUTCOMES. Clinical and procedural outcomes in patient cohorts without and with BMI-adjusted PPM thresholds are reported in **Table 4 and** Supplemental Table 4, respectively. Acute complications were rare, with no differences observed between groups in need of second valve implantation, new permanent pacemaker implantation, and more than mild or more than moderate paravalvular leak; similarly, no significant difference regarding the incidence of annular rupture was observed; the only 2 events occurred in patients belonging to the no PPM group who had undergone post-dilation and were treated conservatively, with no resulting major adverse events. Although the incidence of major vascular complications did not differ between groups (4.8% vs. 3.1%; p = 0.446), vascular complications of any degree were more common in the no PPM group than the PPM group (15.9% vs. 7.1%; p = 0.014), and this was paralleled by higher Bleeding Academic Research Consortium type 3 bleeding in the former group (5.9% vs. 1.0%; p = 0.043). As expected, mean and maximum gradients were higher in patients with PPM than in those without (8.4 mm Hg vs. 10.9 mm Hg [p < 0.001] and 14.9 mm Hg vs. 17.7 mm Hg [p < 0.001]).

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CENTRAL ILLUSTRATION **Predictors and Impact on Mortality of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement With Self-Expandable Valves in Small Annuli**



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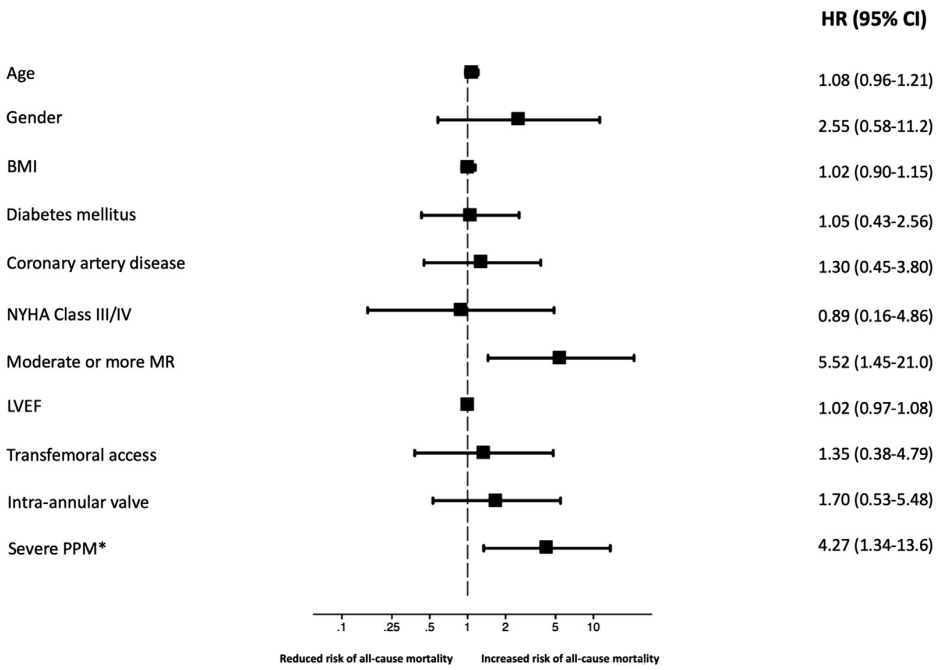
Forest plot illustrating predictive and protective factors toward the development of prosthesis-patient mismatch (PPM) after transcatheter aortic valve replacement with self-expanding valves in small annuli **(A)** and Kaplan-Meier analysis and log-rank test assessing all-cause mortality according to the presence of severe PPM **(B)** and moderate PPM **(C)**.

At a median follow-up of 354 days (interquartile range: 73 days-478 days), no differences were observed between patients with and those without PPM in terms of all-cause mortality, cardiovascular mortality, stroke or transient ischemic attack, myocardial infarction, hospitalization for heart failure, or New York Heart Association functional class III or IV.

Compared with no PPM on Kaplan-Meier analysis, moderate PPM did not result in increased risk for all-cause mortality ($p = 0.269$), while there was a significantly higher risk for all-cause mortality in the severe PPM group ($p = 0.008$), as shown in the **Central Illustration**. A higher risk for all-cause mortality was similarly present in patients with severe PPM compared with no or moderate PPM ($p = 0.008$), and

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FIGURE 1 Forest Plot Illustrating Predictors of 1-Year All-Cause Mortality After Transcatheter Aortic Valve Replacement With Self-Expanding Valves in Small Annuli



*Severe prosthesis-patient mismatch (PPM) versus no or moderate PPM. BMI = body mass index; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; OR = odds ratio; PPM = prosthesis-patient mismatch.

results were confirmed when comparing BMI-adjusted PPM threshold cohorts (Supplemental Figure 1).

Univariable and multivariable logistic regression results for PPM are shown in the **Central Illustration** and Supplemental Table 5. After multivariable adjustment, the risk for developing PPM was higher in patients implanted with intra-annular valves (adjusted OR: 2.36; 95% CI: 1.16-4.81). Conversely, post-dilation (HR: 0.46; 95% CI: 0.25-0.84) and relevant oversizing (>15%) according to perimeter (HR: 0.53; 95% CI: 0.28-1.00) were protective factors. Intra-annular valve implantation was a predictor of PPM development independently of its definition (Supplemental Table 6, Supplemental Figure 2).

After multivariable adjustment for clinically relevant baseline and procedural characteristics, severe PPM was independently associated with 1-year all-cause mortality (HR: 4.27; 95% CI: 1.34-13.6), as was moderate or more mitral regurgitation (HR: 5.52; 95% CI: 1.45-21.0), as seen in Supplemental Table 7 and **Figure 1**. Severe PPM predicted all-cause mortality independently of the PPM threshold accounted for (Supplemental Tables 7 and 8, Supplemental Figure 3), and no significant interaction with BMI was observed (p for interaction = 0.829).

DISCUSSION

The objective of the present study was to define predictors and clinical impact of PPM after TAVR with SEVs in patients with small aortic annuli. The main findings are the following: 1) intra-annular valves are associated with an increased risk for PPM, while post-dilation and valve oversizing reduced PPM occurrence; and 2) severe PPM, but not moderate PPM, conferred a higher risk for 1-year all-cause mortality.

To better understand PPM after TAVR, TAVI-SMALL focused on a population that is, by definition, at higher risk for developing this complication. Indeed, a small aortic annulus and body size were previously identified as the strongest clinical predictors of PPM (20). Notwithstanding the higher risk for developing PPM, patients with small annuli also appeared to benefit the most with respect to forward

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hemodynamic status in studies comparing TAVR with SAVR (9–11,16).

Overall, PPM after TAVR is not rare, but not as common as after SAVR; a recent meta-analysis revealed incidence rates of overall and severe PPM following TAVR of 32.0% and 10.0%, respectively, both lower compared with rates after SAVR (OR: 0.31 [95% CI: 0.20 to 0.50] and 0.38 [95% CI: 0.28 to 0.52], respectively) (14). It was hypothesized that this difference may derive from the intrinsic need for oversizing the annular dimensions with TAVR compared with SAVR (in which often the valve is true-sized or slightly undersized), from the thinner struts, and from the absence of a sewing ring. Nevertheless, this advantage seems to be preserved also when TAVR is compared with stentless surgical valves (21), which were originally developed to mitigate this issue (22).

Of note, commercially available transcatheter valves did not seem to perform equally in terms of risk for PPM. Indeed, although forward hemodynamic status after balloon-expandable valve (BEV) implantation seems to be extremely sensitive to minimal structural modifications made between different iterations of the same valve (12,23), not only have SEVs shown a consistent reduction in PPM incidence in both large and small annuli compared with SAVR (13), but also they have been associated with larger prosthetic valve EOA and lower transprosthetic gradient compared with BEVs (16,24). This was confirmed by 2 recently published studies comparing SEVs and BEVs (19,25), which suggested that supra-annular leaflets may be a key structural feature to produce a favorable hemodynamic profile. The larger EOA may be related to the fact that prosthetic leaflets lie in a different plane than bulky native annulus and native cusps. Preliminary data from the TAVI-SMALL registry supported this evidence (17), and the present subanalysis showed that an intra-annular design was independently associated with PPM. Supra-annular prostheses may therefore represent the first choice when treating patients with aortic stenosis and small aortic annuli, and the randomized SMART (Small Annuli Randomized to Evolut or SAPIEN Trial) trial (NCT04722250) is planned to further clarify this issue.

In addition, our data suggest that 2 procedural aspects may play a protective role in PPM reduction. First, larger oversizing seemed to be related to lower gradients and risk for PPM. Although oversizing (between 9% and 15%) was previously reported to have a favorable effect in SEV implantation (26), our results suggest that a perimeter ratio >15% protects against PPM development when patients with small annuli are treated. Moreover, post-dilation seemed to have a protective role against PPM too, confirming previous findings (27–29). Interestingly, data from the present registry confirmed that such degree of oversizing did not result in a higher risk for pacemaker implantation, coronary occlusion, or annular rupture (Supplemental Table 9).

We observed significantly higher 1-year all-cause mortality in patients with severe PPM compared with patients without PPM. Furthermore, severe PPM was an independent predictor of all-cause mortality, together with more than moderate mitral regurgitation. Whenever the aortic valve is replaced, in the absence of root reconstruction, the resulting EOA is necessarily smaller than the native EOA, as the prosthesis is inserted within the aorta with its own structural support. Thus, by definition in these cases, some degree of post-operative PPM is always present, but an impact on mortality seems to arise only when it exceeds a critical threshold (6,30–32). Recent studies showed an association between PPM after TAVR and reduced post-procedural functional class improvement, left ventricular mass, and diastolic dysfunction regression (8,33) and increased risk for rehospitalization for heart failure (9). Of note, although several studies have shown PPM to reduce overall survival, in particular when severe (10,24,34), others have confirmed such findings only in specific subsets of patients, namely, those without post-procedural aortic regurgitation (11) and those with left ventricular ejection fractions <40% (35). Also, although the analysis from the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry demonstrated that severe PPM is common after TAVR and is associated with greater 1-year mortality (HR: 1.19) (34), this may differ according to the type of transcatheter valve implanted (11,36,37). In line with the latter registry, our study did not find BMI to be a predictor of mortality on multivariable analysis, and no significant interaction with severe PPM was observed. It is in light of such evidence, in contrast to earlier reports of a more important impact of PPM on mortality in patients with smaller BMI (5), that PPM cutoff adjustment according to BMI might emerge apparently controversial (38).

In contrast, a meta-analysis revealed no statistically significant differences in late mortality between patients undergoing TAVR with at least moderate PPM and those without PPM (7), even though the investigators argued that concomitant paravalvular leak might represent a confounding bias. Whether this conflicting evidence stems from methodological differences, enrolled populations, or intrinsic limitations in the measurement of parameters needed to

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estimate EOA after implantation (including neo-LVOT diameter and pulsed-wave Doppler velocity-time integral estimation) (39) is a matter of debate.

Overall, we believe that the risk for developing PPM should be kept in consideration when evaluating patients for TAVR (40), particularly influencing transcatheter valve type and size choice and procedural planning.

STUDY LIMITATIONS. Selection bias cannot be excluded, because of the observational nature of our study; also, although the majority of relevant data were either prospectively reported during the course of clinical follow-up or derived from an ad hoc database, underreporting or missing echocardiographic and follow-up data need to be acknowledged. Furthermore, the semiquantitative scoring system used for aortic valve and LVOT calcification was derived from a study using a centralized computed tomographic data assessment (17), so reproducibility in the absence of core laboratory analysis might not have been optimal. Similarly, the lack of a centralized echocardiographic evaluation could have affected the assessment of procedural results. Finally, event rates did not allow us to conduct additional analyses according to valve type and design, which will need to be addressed in future studies.

CONCLUSIONS

The present multicenter observational retrospective registry of patients with aortic stenosis and small aortic annuli undergoing TAVR with SEVs suggests that the use of intra-annular functioning transcatheter valves is a risk factor for PPM, while valve post-dilation and oversizing play a protective role. In addition, severe PPM is associated with higher 1-year all-cause mortality. Randomized trials assessing long-term prognostic relevance of PPM and impact of strategies to prevent it are needed to confirm our hypothesis-generating data.

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PERSPECTIVES

WHAT IS KNOWN? The clinical impact of PPM after TAVR is not clear yet. Transcatheter valves have been shown to offer better hemodynamic status compared with surgical prostheses, especially in patients with small annuli. Findings from the TAVI-SMALL registry suggested that supra-annular SEVs slightly outperform intra-annular SEVs in this setting.

WHAT IS NEW? In this additional analysis of the registry, intra-annular valves were found to confer an augmented risk for PPM, while post-dilation and valve oversizing protect against PPM occurrence. Patients with severe PPM had higher 1-year all-cause mortality compared with those without PPM, and severe PPM was an independent predictor of all-cause mortality.

WHAT IS NEXT? As severe PPM seems to play a major role in mid- and possibly long-term survival after TAVR, larger trials assessing the impact of possible strategies to prevent it are awaited.

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KEY WORDS prosthesis-patient mismatch, self-expandable valves, small annuli, TAVR

APPENDIX For supplemental tables and figures, please see the online version of this paper.

Manuscript #34

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Transcatheter Aortic Valve Replacement for Degenerated Transcatheter Aortic Valves

The TRANSIT International Project

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BACKGROUND: Transcatheter aortic valve replacement (TAVR) has determined a paradigm shift in the treatment of patients with severe aortic stenosis. However, the durability of bioprostheses is still a matter of concern, and little is known about the management of degenerated TAV. We sought to evaluate the outcomes of patients with a degenerated TAV treated by means of a second TAVR.

METHODS: The TRANSIT is an international registry that included cases of degenerated TAVR from 28 centers. Among around 40 000 patients treated with TAVR in the participating centers, 172 underwent a second TAVR: 57 (33%) for a mainly stenotic degenerated TAV, 97 (56%) for a mainly regurgitant TAV, and 18 (11%) for a combined degeneration. Overall, the rate of New York Heart Association class III/IV at presentation was 73.5%.

RESULTS: Valve Academic Research Consortium 2 device success rate was 79%, as a consequence of residual gradient (14%) or regurgitation (7%). At 1 month, the overall mortality rate was 2.9%, while rates of new hospitalization and New York Heart Association class III/IV were 3.6% and 7%, respectively, without significant difference across the groups. At 1 year, the overall mortality rate was 10%, while rates of new hospitalization and New York Heart Association class III/IV were 7.6% and 5.8%, respectively, without significant difference across the groups. No cases of valve thrombosis were recorded.

CONCLUSIONS: Selected patients with a degenerated TAV may be safely and successfully treated by means of a second TAVR. This finding is of crucial importance for the adoption of the TAVR technology in a lower risk and younger population.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04500964.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: bioprosthesis ■ heart failure ■ transcatheter aortic valve replacement

See Editorial by Barbanti and Costa

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WHAT IS KNOWN

- Structural valve deterioration rarely occurs after transcatheter aortic valve replacement (TAVR).
- Considering the growing number of patients treated by means of TAVR, structural valve deterioration will become more frequent.
- The treatment of a degenerated TAV is still poorly investigated.

WHAT THE STUDY ADDS

- A second TAVR can be safely and successfully performed.
- The type of degenerated TAVR and the anatomy of the aortic root pose patient-specific issues (ie, coronary obstruction/sinus sequestration/difficult coronary access and patient-prosthesis mismatch).

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AS	aortic stenosis
CO	coronary obstruction
HR	hazard ratio
NYHA	New York Heart Association
PPM	patient-prosthesis mismatch
SVD	structural valve deterioration
TAV	transcatheter aortic valve
TAVR	transcatheter aortic valve replacement
VARC-2	Valve Academic Research Consortium 2
VIF	variance inflation factor

Transcatheter aortic valve replacement (TAVR) has determined a paradigm shift in the treatment of patients with severe aortic stenosis, at any level of surgical risk.[1–6] However, the durability of TAVR bioprostheses is still a matter of concern, although recent data show encouraging results at long-term follow-up.[7]

Although the rate of structural valve deterioration (SVD) and of bioprosthetic valve failure is very low,[7] it is likely that the expanding adoption of TAVR, in particular to patients with longer life expectancy, will result in an increasing number of degenerated TAV.[8]

In this scenario, a second TAVR is an obvious and intriguing option, however, its outcome is not yet fully elucidated.[9]

We thus sought to evaluate in a multicenter, international registry, the mode of failure of the index TAVR, the prosthesis selection criteria for the second TAVR, and its procedural and clinical outcomes.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

The TRANSIT project (Transcatheter aortic valve replacement for degenerated transcatheter aortic valves) is an investigator-initiated registry that started collecting data in January 2020. More than 60 centers worldwide have been initially contacted, however, 32 could not participate due to the lack of suitable cases despite a large volume of TAVR. As such, a final group of 28 centers took part to the project: 22 in Europe, 4 in North America, 1 in South America, and 1 in the Middle East. Among a total number of about 40 000 procedure performed since 2008, 172 cases of consecutive TAVR for a degenerated transcatheter aortic valve (TAV) have been collected.

Data concerning the first TAVR have been collected with a specific focus on the procedural results, echocardiographic parameters after the first TAVR, and mode of failure at last available follow-up before the second TAVR, as well as on the possible presence of patient-prosthesis mismatch (PPM). For the latter, we focused on the selection criteria of the specific type of transcatheter bioprosthesis as well as on the procedural results. Data concerning the last available follow-up thereafter were also collected. The study was approved by an institutional review committee and the subjects gave informed consent.

Definitions

The principal investigator at each center took responsibility of the data collection regarding the baseline demographics, clinical, and echocardiographic features, as well as of procedural and follow-up data. Importantly, cases of TAVR in TAVR due to a suboptimal implantation and result of the index TAVR (eg, implantation too deep or too high, insufficient expansion and so on) were not considered, as such, this registry exclusively collected cases of degenerated TAV which have been evaluated according to mode of failure (mainly stenotic, mainly regurgitant, and mixed cause when the 2 conditions were both at least moderate).

The Valve Academic Research Consortium 2 (VARC-2) definitions were adopted for procedural and clinical end points,[8] along with a modified classification of the European Society of Cardiology–European Association of Cardio-Thoracic Surgery consensus document described by Testa et al[7] for the definitions of SVD and bioprosthetic valve failure.

PPM after the first TAVR was classified on the basis of the discharge echocardiographic Effective Orifice Area (calculated with the continuity equation) Indexed to body surface area as severe (<0.65 cm^2/m^2), moderate (0.65–0.85 cm^2/m^2), or none (>0.85 cm^2/m^2).[8]

Statistical Analysis

Descriptive statistics are reported as mean and SD for normally distributed continuous variables, as median and 25th to 75th percentile otherwise. Absolute and relative frequencies are reported for categorical variables. For continuous variables, the comparisons were done either with ANOVA or with a nonparametric test (Kruskal-Wallis). For categorical variables, comparisons among groups were done with χ^2 tests or Fisher exact tests. All cause and CV death were reported using Kaplan–Meier estimates together with their 95% CI. Echocardiographic data have been reported throughout the

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overall follow-up by means of the most appropriate graphical representation. In addition, mean gradients and aortic regurgitation (AR) were presented in paired analysis for all time points after procedure and at postprocedure and longest follow-up. Wilcoxon signed rank-sum test was used for comparison of echo parameters in paired analyses. The cumulative incidences of clinical events at follow-up were assessed with the Kaplan-Meier method and log-rank test.

Parameters with a *P* value of <0.1 in the univariable analysis were included in the multivariable model with a forward likelihood ratio method. The variables tested at univariable analysis were age >75, male gender, end stage renal disease, chronic obstructive pulmonary disease, nontransfemoral access, age (per 10-year increase), reduced left ventricle ejection fraction (per 10% decrease), postprocedural mean gradient ≥20 mm Hg, residual AR ≥moderate, stenotic degenerated TAV, regurgitant degenerated TAV, mixed cause degenerated TAVR, degenerated TAV size <23.

Collinearity was evaluated with VIF (variance inflation factors), and parameters with a VIF of >5 were not included in the multivariable analyses. Proportional-hazards assumption was confirmed through testing based on Schoenfeld residuals. Multivariable correlates are presented as hazard ratios (HRs) and 95% CIs. A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23 (IBM Corporation, Armonk, New York, NY)

RESULTS

Among around 40 000 patients treated in the participating centers since the beginning of the TAVR program, 172 were treated for a degenerated TAVR. All patients had device success at the first TAVR implantation according to VARC-2 definitions, that is, no cases of high (>20 mm Hg) mean residual gradient nor of AR >1 were included.[8] Patients were grouped and analyzed according to the type of degeneration, as such, 57 (33%) had a mainly stenotic degenerated TAV, 97 (56%) a mainly regurgitant TAV, 18 (11%) a combined degeneration (Table 1). Six patients have been treated within a year since the first TAVR.

Overall, mean age was 79.9±7.9 and the male gender was slightly more frequent (57.6%) while the rate of New York Heart Association (NYHA) class III/IV was 73.5% with a consistent distribution across the groups. Euroscore I was 19.9±15.0, Euroscore II 8.8±3.4, and STS score 6.1±5.7 without statistically significant difference across the groups.

A moderate or severe PPM after the first TAVR was significantly less frequent in the group with a severely regurgitant TAV (Table 1). There was no difference in the time between the first and the second TAVR in patients with moderate PPM (597.5±132.2 days) or severe PPM (702±946.1) versus those without (980.6±906.7 days, *P*=0.4 and *P*=0.2, respectively).

Seven cases of valve thrombosis leading to a severe dysfunction of the first TAVR were recorded: 5 among patients presenting with a severely stenotic degenerated TAVR, 1 in the group of regurgitant TAVR, and 1 in the group with mixed cause. These patients were treated while on anticoagulation. The most frequent degenerated TAVR model was CoreValve (Medtronic, Minneapolis, MN; 84 [48%]) followed by Sapien XT (Edwards Lifesciences, Irvine, CA; 60 [35%]). Details concerning the valve size of the first and second TAVR are reported in Tables in the Data Supplement.

See Figure 1 for the mean and median time from implant to degeneration according to the valve type.

Procedural Results

For the second TAVR, the operators opted for a self-expanding valve in 104 cases (61%), the majority of them were Corevalve/Evolut (87, 83%). Of note, 53 (63%) cases of degenerated Corevalve were treated with an Evolut, 25 cases (29%) with an Edwards, while 33 cases (55%) of degenerated Edwards were treated with another Edwards, and 21 (35%) with an Evolut (See Tables in the Data Supplement). The choice of the second TAVR appears to be related to a case-by-case evaluation based on local experience and availability of the TAVR platforms. We could not find specific or generalizable criteria.

VARC-2 device success rate was 79%, as a consequence of residual gradient >20 mm Hg (24 patients, 14%) or AR >1+ (11 patients, 7%). No cases of valve malpositioning occurred. The group of patients with stenotic first TAV had a significantly higher residual mean gradient, while the group of regurgitant TAV had a significantly higher rate of AR >2 (Table 2).

Clinical Outcomes

In Hospital Events

The mortality rate was 4.1%, and all cases were due to cardiovascular causes without differences across the groups (Table 3). Overall, major vascular complications occurred in 2.3% of the cases, while the need for a permanent PM was 4.1%. The overall rate of cerebrovascular events was 3.5%, with a significant higher rate in the group with mixed degeneration, that is, 16.7%. An acute kidney injury occurred in 7% of the cases. No cases of valve thrombosis nor coronary obstruction (CO) were observed.

Thirty-Day Follow-Up

Cumulative overall mortality rate was 7%, no further cases of cardiovascular death were recorded (Table 4). Rates of NYHA class III/IV and hospitalization for HF were 7.0% and 3.6%, respectively, without differences across groups. No events of MI, stroke/TIA, CO were recorded after hospitalization (see Table 3), while 3 cases of valve thrombosis occurred (1.4%).

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Table 1. Baseline Characteristics of the Study Population

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
Age	79.9±7.9	77.5±8.8	77.9±7.2	79.4±8.8	0.669
Male	99 (57.6%)	28 (49.1%)	63 (64.9%)	8 (44.4%)	0.078
Hypertension	147 (85.5%)	50 (87.7%)	81 (83.5%)	16 (88.9%)	0.704
Dyslipidemia	114 (67.1%)	42 (73.7%)	59 (62.1%)	13 (72.2%)	0.300
Diabetes	48 (27.9%)	20 (35.1%)	23 (23.7%)	5 (27.8%)	0.357
Smoker	51 (29.7%)	17 (29.6%)	29 (30.1%)	5 (27.8%)	0.981
COPD	39 (22.7%)	18 (31.6%)	17 (17.5%)	4 (22.2%)	0.163
PM	54 (31.3%)	13 (22.8%)	35 (36.1%)	6 (33.3%)	0.185
Atrial fibrillation	63 (36.8%)	14 (24.6%)	42 (43.3%)	7 (38.9%)	0.076
Previous cardiac surgery	33 (19.4%)	10 (17.5%)	18 (18.6%)	5 (27.8%)	0.636
MI	43 (25.0%)	13 (22.8%)	25 (25.8%)	5 (27.8%)	0.882
Previous PCI	71 (41.3%)	27 (47.4%)	39 (40.2%)	5 (27.8%)	0.330
Severe renal failure	33 (19.2%)	10 (17.5%)	17 (17.5%)	6 (33.3%)	0.286
Creatinine	1.5±1.1	1.5±1.4	1.4±0.7	1.9±1.3	0.250
Dialysis	8 (4.7%)	3 (5.3%)	2 (2.1%)	3 (16.7%)	0.264
PAD	32 (18.6%)	10 (17.5%)	21 (21.6%)	1 (5.6%)	0.264
Stroke	9 (5.2%)	2 (3.5%)	6 (6.2%)	1 (5.6%)	0.770
NYHA III/IV	125 (73.5%)	39 (70.9%)	73 (75.3%)	13 (72.2%)	0.836
RBBB	8 (4.7%)	2 (3.5%)	6 (6.2%)	0 (0.0%)	0.510
LBBB	49 (28.5%)	17 (19.2%)	32 (33.0%)	6 (33.3%)	0.164
Euroscore I	19.9±15.0	21.0±17.0	18.1±13.1	24.7±17.0	0.266
Euroscore II	8.8 ±3.4	7.8±3.3	8.9±3.5	11.3±0.6	0.262
STS Score	6.1±5.7	6.0±4.1	5.8±5.4	8.3±9.8	0.307
SAPT	69 (40.1%)	26 (45.6%)	35 (36.1%)	8 (44.4%)	0.469
DAPT	47 (27.3%)	17 (29.8%)	27 (27.8%)	3 (16.7%)	0.543
NAO/Vka	56 (32.6%)	22 (21.1%)	26 (16.5%)	8 (33.3%)	0.243
Self-expanding TAVR	112 (65.1%)	30 (52.6%)	70 (72.2%)	12 (66.7%)	0.058
Balloon expanding TAVR	60 (34.9%)	27 (47.4%)	27 (27.8%)	6 (33.3%)	0.056
Moderate PPM	10 (5.8%)	6 (10.5%)	2 (2%)	2 (11.1%)	0.014
Severe PPM	5 (2.9%)	4 (7%)	0	1 (5.5%)	0.012

COPD indicates chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; LBBB, left bundle branch block; MI, myocardial infarction; NAO, novel oral anticoagulant; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PM, pace maker; PPM, patient prosthesis mismatch; RBBB, right bundle branch block; SAPT, single antiplatelet therapy; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; and vKa, vitamin K antagonist.

One-Year Follow-Up

The cumulative overall mortality rate was 10%, with a cardiovascular mortality rate of 5.8% (Table 5 and Figure 2). The rate of NYHA class III/IV was 12.8% (Figure 3) while that of new hospitalization for HF was 11%.

No differences across the groups were detected. Of note, no further cases of valve thrombosis, MI, stroke, or valve dysfunction requiring new intervention were recorded.

In the multivariable analysis, nontransfemoral access (HR, 1.53 [95% CI, 1.18–1.89]), age (per 10-year increase HR, 1.21 [95% CI, 1.03–1.48]), reduced left ventricle ejection fraction (per 10% decrease, HR, 1.45 [95% CI, 1.16–1.58]), severe renal failure (HR, 1.40 [95% CI, 1.16–1.94]) were independently associated with decreased patient survival. Postprocedural mean gradient ≥20 mm Hg or residual AR ≥moderate were not independent predictors of mortality from discharge to 1 year.

Clinical Events After 1 Year

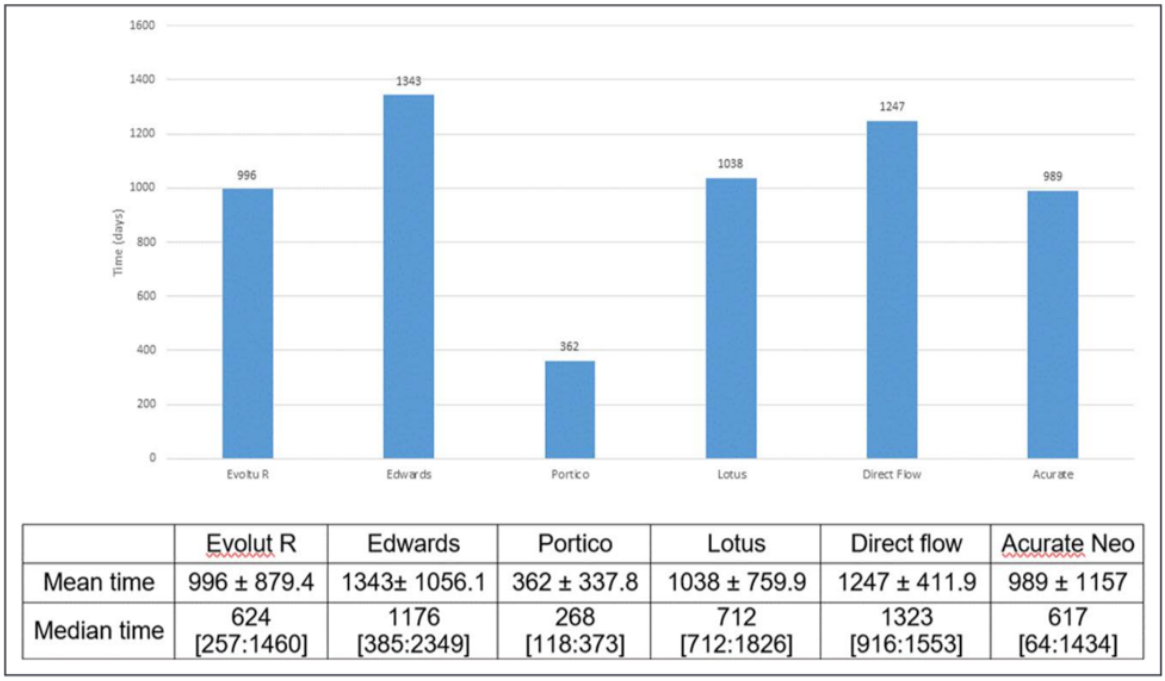
The clinical events have been reported up to 6-year follow-up, although concerning a limited number of patients (see Table VII in the Data Supplement).

Echocardiographic Findings

Echocardiographic data were available for 90% of the patients at 1 year.

Figure 4 shows the comparison between baseline (before the second TAVR), discharge and last available echocardiographic follow-up with respect to the rate of AR. After the second TAVR, the rate of AR 2 to 3 was

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	Evolut R	Edwards	Portico	Lotus	Direct flow	Acurate Neo
Mean time	996 ± 879.4	1343± 1056.1	362 ± 337.8	1038 ± 759.9	1247 ± 411.9	989 ± 1157
Median time	624 [257:1460]	1176 [385:2349]	268 [118:373]	712 [712:1826]	1323 [916:1553]	617 [64:1434]

Figure 1. Time from first to second transcatheter aortic valve replacement.
Corevalve Platform: 84 patients, Edwards-Sapien, Sapien S3, Sapien XT: 60 patients; Portico: 5 patients, Lotus: 5 patients, DirectFlow: 10 pts, Acurate: 8 patients.

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12.7%, while, at 1 month and 1 year it was 7% and 8.1%, respectively.

In paired analysis, the mean transprosthetic aortic gradient decreased significantly from baseline, that is, before the second TAVR (25±19 mm Hg) to discharge (11±5 mm Hg, $P<0.001$) but did not significantly change from discharge throughout follow-up (Figure 5).

DISCUSSION

Moderate or severe SVD rarely occurs after TAVR,[7] but its management is scarcely studied. A second TAVR appears to be a reasonable approach although the evidence is still very limited.

The international TRANSIT project collected the largest available registry exclusively concerning degenerated TAVR.[9–12] No cases of unsuccessful (according to VARC-2 definition) first TAVR implantation were included.[9] The results can be summarized as follows:

1. A second TAVR procedure was associated with a 79% rate of device success according to VARC-2 criteria.
2. Cases of unsuccessful second TAVR were mostly related to a residual significant gradient in patients with a severely stenotic degenerated TAV.
3. Severe and moderate PPM were significantly more frequent in patients with a stenotic degenerated TAV.
4. Rates of all cause as well as cardiac mortality were low within 1-year follow-up (10% and 5.8%, respectively).
5. The clinical benefit of a second TAVR, in terms of NYHA class, is significant regardless the mechanism of failure of the first TAVR, and sustained at 1 year.
6. No cases of CO were observed.

The indication to TAVR will conceivably expand to younger and lower risk patients, following recent encouraging results.[5,6] As such, a population with longer life expectancy will presumably experience a higher rate of moderate or severe SVD than that available from the literature,[7] considering that data on SVD mostly relate to a traditional elderly TAVR population, at high or prohibitive surgical risk. Indeed, a clearer understanding of how to manage cases of degenerated TAV is needed.[9–12]

Clinical Presentation

Degenerated TAV almost invariably presented with signs and symptoms of heart failure as documented by the high rate of NYHA class III/IV, and the prevalent mode of failure was regurgitation (56%), differently from what Landes et al[9] reported. In their overall cohort, the modes of failure were almost equally divided in the 3 groups; on the contrary, they actually found in patients treated within 1 year from the first TAVR a very high rate of severe

Table 2. Procedural Data

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
Transfemoral approach	158 (91.9%)	53 (93.0%)	88 (90.7%)	17 (94.4%)	0.809
Predilatation	36 (20.9%)	11 (19.3%)	20 (20.6%)	5 (27.8%)	0.738
Postdilatation	71 (41.3%)	24 (42.1%)	36 (37.1%)	11 (61.1%)	0.163
Contrast	95.3±57.1	98.4±68.9	95.4±53.6	83.4±25.4	0.708
Aortic dissection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Annulus rupture	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
Valve embolization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Myocardial infarction	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0.014
Emergency surgery	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
Coronary obstruction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Stroke/TIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Cardiac tamponade	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Major vascular complication	3 (1.7%)	2 (3.5%)	1 (1.0%)	0 (0.0%)	0.440
Ventricular arrhythmias	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Self-expanding TAVR	104 (61)	38 (67%)	53 (55%)	13 (72%)	0.09
Balloon expanding	68 (39)	19 (33%)	44 (45%)	5 (18%)	0.05
Device success	137 (79.7%)	45 (78.9%)	76 (78.4%)	16 (88.9%)	0.587
Mean gradient, mm Hg	10.9±5.3	12.5±6.0	10.1±2.8	10.2±3.0	0.029
AR 0–1	150 (87.2%)	54 (94.7%)	79 (81.4%)	17 (94.4%)	0.001
AR 2	19 (11.0%)	2 (3.5%)	16 (16.5%)	1 (5.6%)	0.008
AR 3	3 (1.7%)	1 (1.8%)	2 (2.1%)	0 (0.0%)	0.303

In the stenosis group, all patients without a device success had a residual mean gradient >20 mm Hg; in the regurgitation group, all 5 patients had a residual mean gradient >20 mm Hg, the remaining 18 had a residual AR >2; in the mixed group, 1 patient had a residual AR >2, 4 had a residual mean gradient >20 mm Hg. AR indicates aortic regurgitation; TAVR, transcatheter aortic valve replacement; and TIA, transient ischemic attack.

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regurgitation (73%). Of note, as explained by the authors, these cases were classified as possible first TAVR procedural failure, instead of a true degeneration. This may explain the difference between the 2 cohorts.

We observed a rate of baseline bioprosthetic valve thrombosis of 4%; however, a robust rate of clinical/subclinical leaflet thrombosis was not measurable as the computed tomography scan was not available in all cases.

In terms of transcatheter valve platform, a self-expanding valve, in particular, the first generation of the CoreValve is the most represented in this cohort and its most

Table 3. In-Hospital Events

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause mortality	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
Cardiovascular mortality	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
New onset LBBB	2 (1.2%)	0 (0.0%)	1 (1.0%)	1(5.6%)	0.157
Postprocedural LBBB	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
New onset AF	6 (3.5%)	4 (7.0%)	2 (2.1%)	0 (0.0%)	0.188
New PM	7 (4.1%)	5 (8.8%)	2 (2.1%)	0 (0.0%)	0.082
Stroke/TIA	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Major vascular complications	4 (2.3%)	1 (1.8%)	3 (3.1%)	0 (0.0%)	0.683
Major bleeding (≥BARC-3a)	9 (5.2%)	5 (2.9%)	4 (2.3%)	0 (0.0%)	0.263
Life-threatening bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Valve thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
AKI (≥AKIN-2)	12 (7.0%)	2 (3.5%)	9 (9.3%)	1 (5.6%)	0.386
Sepsis	8 (4.7%)	2 (3.5%)	5 (5.2%)	1 (5.6%)	0.880

AF indicates atrial fibrillation; AKI, acute kidney injury; BARC, Bleeding Academic Research Consortium; LBBB, left bundle branch block; MI, myocardial infarction; PM, pace maker; and TIA, transient ischemic attack.

Table 4. Cumulative Rates of Clinical Events at 30-Day Follow-Up

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause death	12 (7.0%)	5 (8.8%)	6 (6.1%)	1 (5.6%)	0.179
Cardiovascular death	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
NYHA III/IV	12 (7.0%)	5 (8.8%)	7 (7.2%)	0 (0.0%)	0.457
Hospitalization for HF	6 (3.6%)	1 (2.0%)	4 (3.9%)	1 (7.1%)	0.646
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Stroke/TIA	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Valve endocarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Valve thrombosis	3 (1.4%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	0.140
Valve dysfunction requiring reintervention	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…

HF indicates heart failure; MI, myocardial infarction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

frequent mode of failure seemed to be regurgitation. On the contrary, the degeneration of Edwards/Sapien valves tended to be equally distributed in stenosis or regurgitation. These data, however, do not infer on specific TAV platforms durability as this kind of analysis can only be done in a context of competing risk analysis.[7]

Patient Prosthesis Mismatch

A moderate or severe PPM after the first TAVR was more frequently associated with a stenotic degenerated TAV, while it was rarely observed in patients with a regurgitant first TAV: this finding was not previously reported in the literature,[9–12] and it is consistent with the physiopathology of the PPM as suggested since its first description by Rahimtoola.[14] Indeed, the mismatch between the hemodynamic performance of the prosthesis and the cardiac output requirements of the patient is largely related to the body size, and almost invariably leads to a stenotic prosthesis.

Key Procedural Observations

The second TAVR procedure was actually very safe considering the low rate of complications we observed, and the hemodynamic results were encouraging. The majority of the cases were treated with the same transcatheter valve platform (see Figure 6 for examples of same-platform second TAVR, and different–platform second TAVR). The rate of device success (79%) according to VARC-2 definition was lower than that of a traditional TAVR population,[1,2] mainly because of significant residual gradient: in some circumstances, a balloon aortic valvuloplasty alone to treat stenotic degenerated TAV might be considered; on the contrary, a surgical option to treat a degenerated TAV must obviously be weighted with its inherent risk of comorbidity and mortality.

Cerebral embolic protection devices may capture debris in the majority of patients undergoing TAVR.[13] We did not evaluate the use of cerebral embolic protection in this registry. Whether systematic use of cerebral embolic protection devices in the context of a failing transcatheter heart valve could reduce neurological event rate is intriguing and requires further study.

Clinical Benefit

Survival rate was very encouraging considering the clinical features of the population enrolled, reaching 10% at 1 year thus being quite consistent with the 11.7% of the late redo TAVR of the cohort of Landes et al[9] (Figure 2). The clinical benefit was also confirmed by the significantly improved NYHA classes distribution before and after the second TAVR (Figure 3). The neurological

Table 5. Clinical Events at 1-Year Follow-Up

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause death	17 (10.0%)	5 (8.6%)	10 (10.6%)	2 (11.1%)	0.942
Cardiovascular mortality	10 (5.8%)	1(1.8%)	8 (8.2%)	1 (5.6%)	0.535
NYHA III/IV	22 (12.8%)	6 (10.5%)	14 (14.4%)	2 (11.1%)	0.229
Hospitalization for HF	19 (11%)	8 (14%)	8 (8.2%)	3 (16.6%)	0.367
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Stroke	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Valve endocarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Valve thrombosis	3 (1.4%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	0.140
Valve dysfunction requiring reintervention	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…

HF indicates heart failure; MI, myocardial infarction; and NYHA, New York Heart Association.

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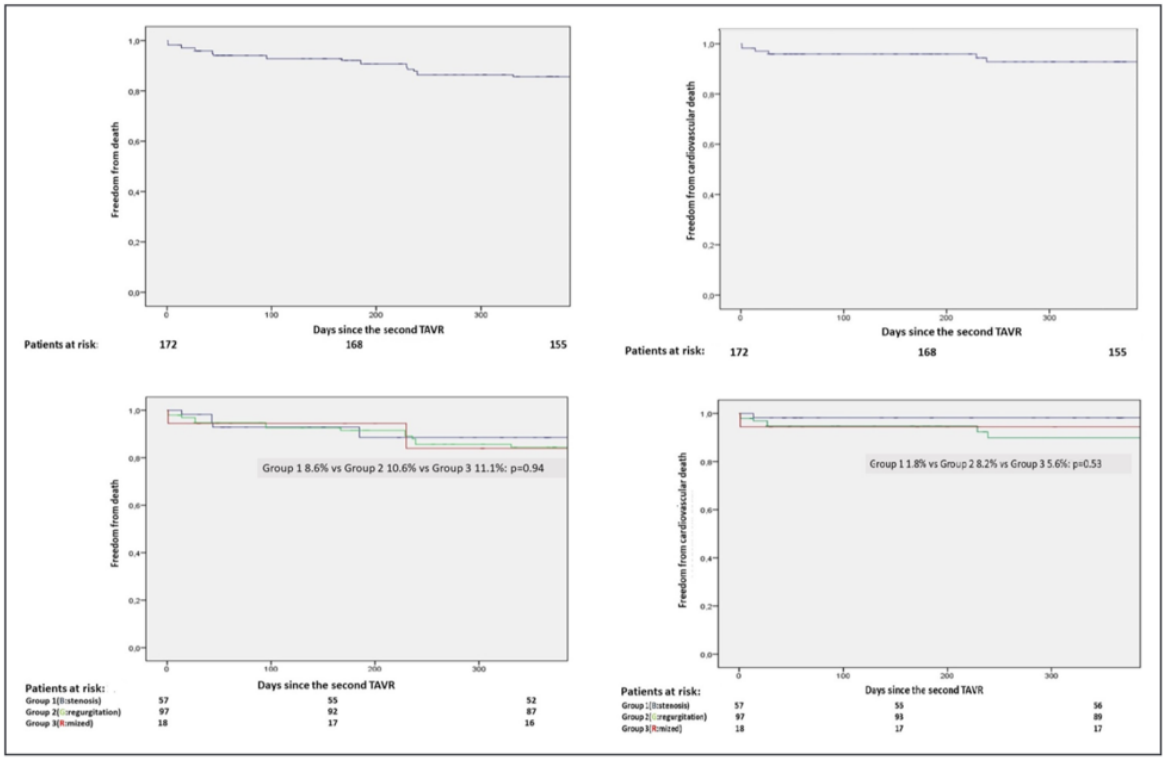


Figure 2. Survival analysis.
Top left: All cause mortality (overall). **Top right**: Cardiovascular mortality (overall). **Bottom left**: Overall mortality (subgroups). **Bottom right**: Cardiovascular mortality (subgroups). TAVR indicates transcatheter aortic valve replacement.

event rate was high in patients with a mixed mechanism of degeneration (Table 3): this signal should be evaluated in larger populations before deriving any conclusion.

Echocardiographic Findings

Echocardiographic parameters showed the expected reduction of moderate or severe AR after the second TAVR (Figure 4), as well as of the mean aortic gradient, and these results persisted at 1 year (Figure 5).

Unanswered Questions and Avenues for Future Research

It is conceivable that a percentage of patients with a degenerated TAV might be unsuitable for a second TAVR, in particular, for technical/anatomic reasons: we did not observe any case of CO, however, it cannot be excluded that this is a consequence of a selection bias, that is, patients with a prohibitive risk of CO might have been rejected for a second TAVR. A recent study from Ochiai et al[15] tried to evaluate the risk of CO due to sinus sequestration in redo TAVR using post-TAVR computed tomography. Redo TAVR was considered at risk of CO due to sinus sequestration if (1) the prior TAV commissure level was above the sinotubular junction and (2) the distance between TAV and sinotubular junction was <2.0 mm in each coronary sinus. The combination of a low sinotubular junction and high TAV commissures was found to increase the risk of CO. This conclusion, however, must be contextualized as it is based on a computed tomography scan derived model, not on clinical data. Moreover, in the setting of a degenerated TAVR, the risk of CO, a potentially lethal complication, should be evaluated along with the risk of coronary flow impairment and difficult/impossible coronary access[16]: it seems logic that small anatomies and self-expanding with high leaflet commissures TAV platforms might be the worst combination, however, self-expanding transcatheter aortic bioprostheses, with larger effective orifice areas, might potentially be associated with better durability.[17]

The PPM after a second TAVR should also be further investigated, as it will conceivably be even more relevant than after the first TAVR: theoretically, the balloon expandable platforms to treat a degenerated balloon expandable platform in a small anatomy seem to be the worst combination, however, as mentioned above, the issue of CO cannot be neglected, especially when evaluating a self-expanding platform to treat a degenerated TAV.

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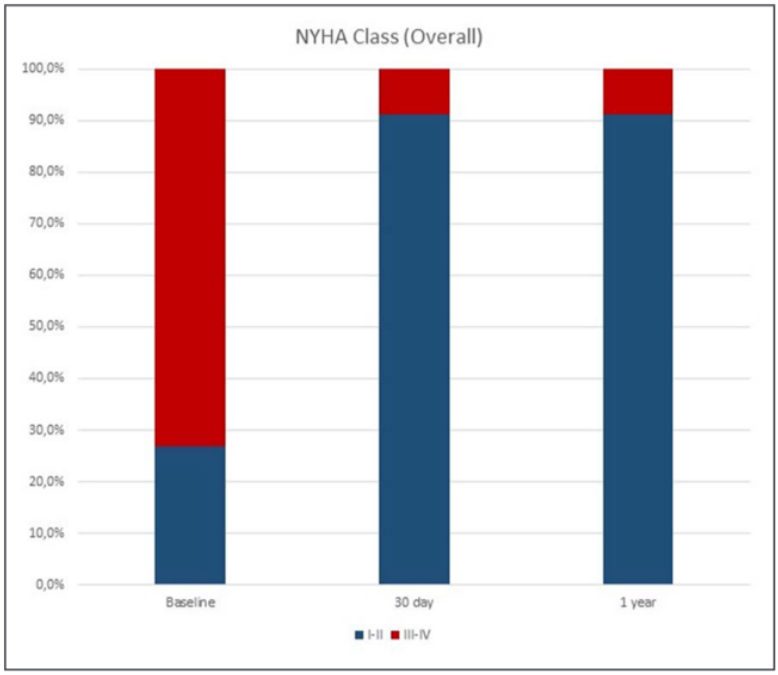


Figure 3. New York Heart Association (NYHA) class distribution before the second transcatheter aortic valve replacement, after and at follow-up.

Overall, a tailored approach at the time of the first TAVR, that is, when the aortic valve journey begins, is becoming critically important and the development of implantation techniques aiming at the commissure-to-commissure alignment should be pursued to minimize the subsequent risk of CO, coronary flow impairment and difficult coronary re-access.

This should also be kept into account in future TAV platforms iterations.

Finally, further research is needed to better depict the distinctive role of a second TAVR, the surgical approach despite its high mortality,[18] the balloon aortic valvuloplasty, and the optimized medical therapy.

Limitations

This is an investigator-initiated registry that involved high-volume centers in 3 continents, however, no central

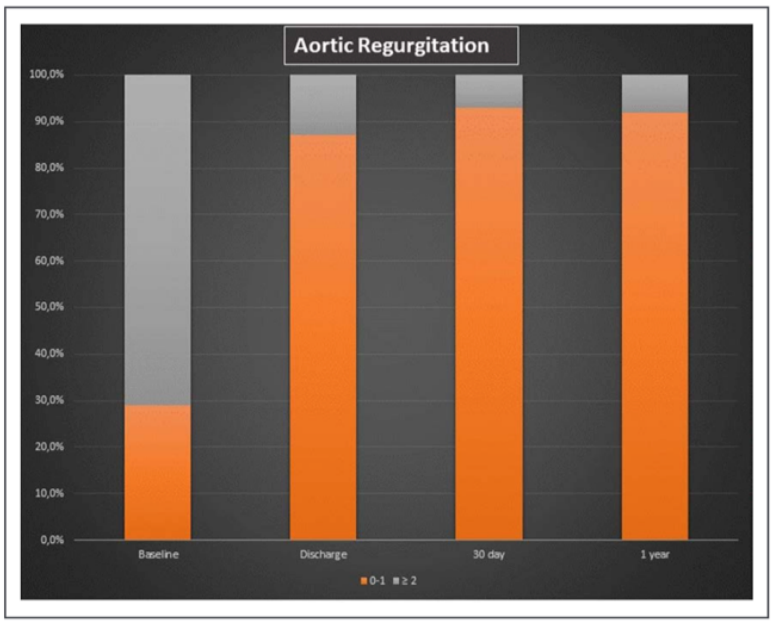


Figure 4. Temporal change of aortic regurgitation before the second transcatheter aortic valve replacement (TAVR), after the second TAVR, and at follow-up.

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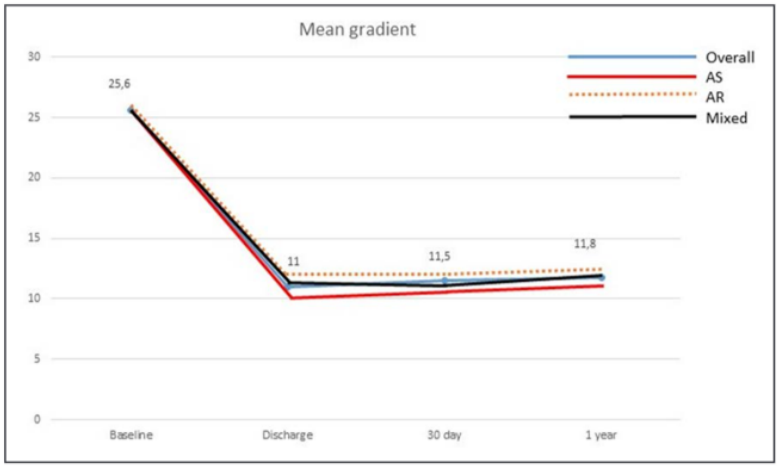


Figure 5. Temporal change of mean transaortic gradient before the second transcatheter aortic valve replacement (TAVR), after the second TAVR, and at follow-up.
Numbers are reported for the overall population (baseline: 25.6±12 mm Hg; discharge: 11±4 mm Hg; 30-day FU: 11.5±5 mm Hg; 1-year FU: 11.8±5 mm Hg). AR indicates aortic regurgitation; and AS, aortic stenosis.

adjudication of events has been performed, and we cannot rule out that results might be different in less experienced centers.

An Echo Core Lab is also lacking and the echo data have been collected by the participating centers: as such a reliable distinction between central AR and PVL was not possible. Likewise, a detailed analysis of PPM after the second TAVR was also unfeasible. A computed tomography scan analysis was not available in the majority of the cases, thus making the complete assessment of leaflet thrombosis actually impossible. As clearly stated, patients come from different countries and were treated with different devices thus mirroring the current real-world practice, however, differently from previous reports, they were all treated because of a degenerated TAV, that is, this is a relatively homogeneous population.

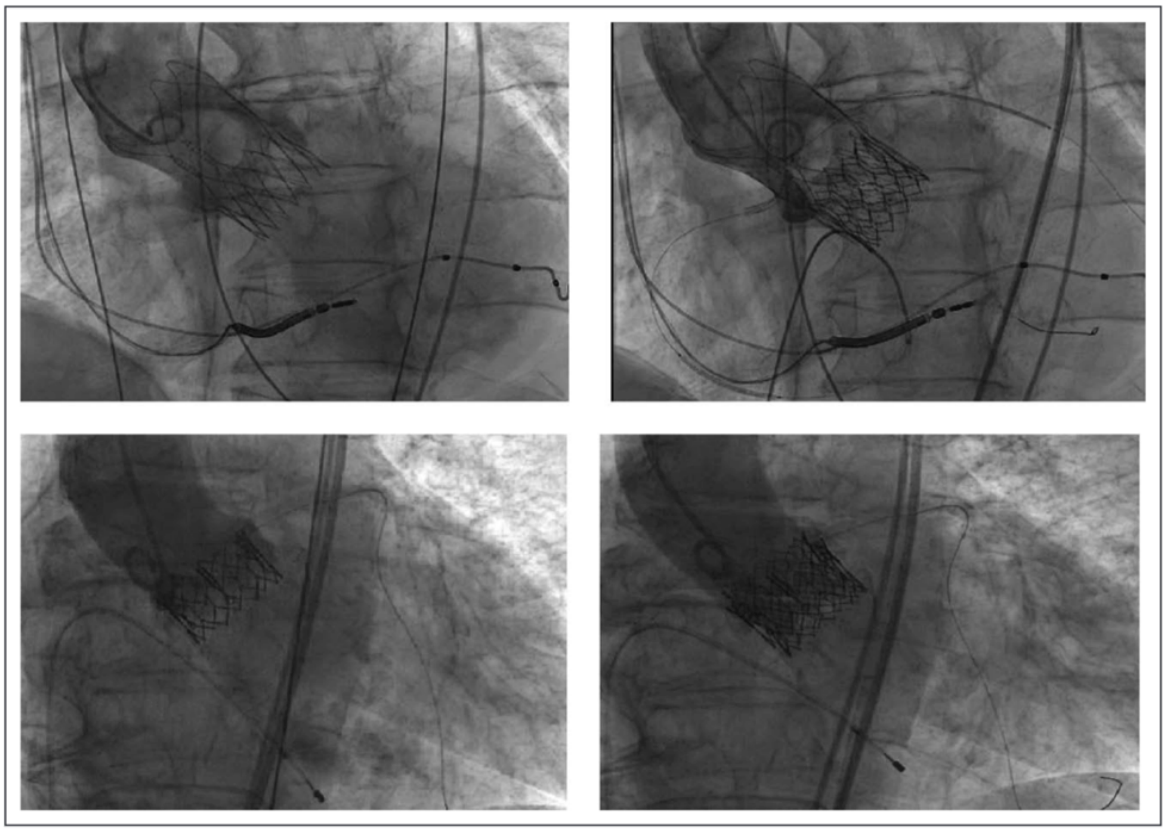


Figure 6. Examples of transcatheter aortic valve replacement (TAVR) in TAVR with same platform vs different platform.
Top left: Aortogram showing a severely regurgitant Acurate Neo valve, treated by means of MyVal (**top right**). **Bottom right**: Case of severely regurgitant Edwards Sapien XT, treated by means of an Edwards Sapien XT (**bottom right**).

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This registry did not consider those patients who were rejected for a second TAVR because of prohibitive risk of CO and treated surgically.

Conclusions

Selected patients with a degenerated TAV may be safely and successfully treated by means of a second TAVR. Notwithstanding some unanswered questions needing further investigations, these findings are of crucial importance for the adoption of the TAVR technology in a lower surgical risk and younger population.

ARTICLE INFORMATION

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Disclosures

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Supplemental Materials

Online Tables I–IV

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Percutaneous vs surgical axillary access for transcatheter aortic valve implantation: the TAXI registry

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is an established management strategy for severe aortic valve stenosis. Percutaneous axillary approach for TAVI holds the promise of improving safety without jeopardizing effectiveness in comparison to surgical access. We aimed at appraising the comparative effectiveness of percutaneous vs surgical axillary approaches for TAVI.

Methods: We performed an international retrospective observational study using de-identified details on baseline, procedural, and 1-month follow-up features. Valve Academic Research Consortium (VARC)-3 criteria were applied throughout. Outcomes of interest were clinical events up to 1 month of follow-up, compared with unadjusted and propensity score-adjusted analyses.

Results: A total of 432 patients were included, 189 (43.8%) receiving surgical access, and 243 (56.2%) undergoing percutaneous access. Primary hemostasis failure was more common in the percutaneous group (13.2% vs 4.2%, p<0.001), leading to more common use of covered stent implantation (13.2% vs 3.7%, p<0.001). Irrespectively, percutaneous access was associated with shorter hospital stay (-2.6 days [95% confidence interval: -5.0; -0.1], p=0.038), a lower risk of major adverse events (a composite of death, myocardial infarction, stroke, type 3 bleeding, and major access-site related complication; odds ratio=0.44 [0.21; 0.95], p=0.036), major access-site non-vascular complications (odds ratio=0.21 [0.06; 0.77], p=0.018), and brachial plexus impairment (odds ratio=0.16 [0.03; 0.76], p=0.021), and shorter hospital stay (-2.6 days [-5.0; -0.1], p=0.038).

Conclusions: Percutaneous axillary access provides similar or better results than surgical access in patients undergoing TAVI with absolute or relative contraindications to femoral access.

KEY-WORDS

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Access; Aortic stenosis; Axillary; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement

INTRODUCTION

The burden of structural heart disease continues to increase worldwide.(1) Among valvular disease, degenerative aortic stenosis continues to be a major challenge, despite remarkable breakthroughs in its minimally invasive management with transcatheter aortic valve implantation (TAVI, also commonly referred to as transcatheter aortic valve replacement, [TAVR]).(2-3) Indeed, TAVI has shown a favorable risk-benefit profile in subjects at prohibitive, high, moderate, and even relatively low surgical risk.(2,4-5)

Percutaneous femoral approach is the recommended routine access for TAVI, but several patients need an alternative access site due to severe peripheral artery disease (PAD) preventing femoral access.(6) Several non-femoral access sites have been proposed and used, including transapical, direct aortic, transcarotid, transcaval, and surgical axillary accesses.(7-8) Most recently, percutaneous access of the axillary artery has been employed for TAVI in patients with severe PAD, with favorable preliminary results.(9-11) This vascular access is technically more demanding than other access sites, but appears less invasive and therefore of potential benefit in elderly and frail patients.(6,12-13) Despite recent evidence supporting the acceptable risk-benefit profile of percutaneous axillary access for TAVI, there remains, however, ongoing uncertainty on the comparative effectiveness of percutaneous in comparison to surgical axillary access, as local vascular complications may also occur using such approach.(14-15)

We aimed at performing a multicenter retrospective observational study comparing percutaneous versus surgical axillary access in patients undergoing TAVI.

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METHODS

Design

The TAXI (Trans-AXillary Intervention) international registry was designed as a multicenter retrospective observational study aimed at comparing the acute and mid-term outcomes of patients undergoing TAVI in whom either percutaneous or surgical axillary access was attempted. Patients were recruited from 18 centers located in 8 countries. Institutional review boards granted the permission to accomplish this study in each of the participating centers as per local regulations.

Specifically, anonymized data from Italian centers were obtained through the dataset of the RISPEVA (Registro Italiano GISE sull'impianto di Valvola Aortica Percutanea) Study, an Italian prospective study based on formal ethical committee approval and written patient consent (trial registration: clinicaltrials.gov identifier NCT02713932).(16) Data from non-Italian centers were similarly obtained, after direct query to authors of previous published studies on percutaneous axillary TAVI or participating to previous multicenter studies on the same topic. Specifically, eligible patients included those with severe aortic stenosis, severe aortic regurgitation, and degenerated bioprosthesis in whom TAVI was indicated, including urgent and non-urgent cases (with urgent TAVI defined as procedures which could not be deferred to a subsequent elective hospitalization or required hospitalization within 30 days).(17) For each patient case, we sought baseline, procedural and outcome details as previously detailed using a dedicated dataset.(18)

Patients and procedures

Given the study design, patient selection for access strategy was chosen by the individual operator. Briefly, several baseline patient features were obtained, including medical, echocardiographic, and computed tomographic details. Several risk scores were obtained,

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including the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), and the Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, and Drugs or alcohol (HAS-BLED) scores. Similarly, procedural strategy was at the operator's discretion, including the choice of access site, type and size of device, post-dilation, and ancillary medical therapy.

For percutaneous axillary access, puncture was performed under duplex ultrasound or angiographic/fluoroscopic (after ascending aortogram) guidance, by using a micro puncture kit needle with a 0.018" guidewire, using the thoracoacromial branch as a landmark, enabling then upsizing from the kit cannula and 0.018" guidewire and deployment of a 0.035" guidewire. In case use of the ProGlide vascular closure device was planned (Abbott Vascular, Santa Clara, CA, USA), one or two ProGlides were then deployed, and the appropriate sheath was placed for TAVI device implantation. Postprocedural hemostasis was achieved using the Manta vascular closure device (Teleflex, Morrisville, NC, USA), multiple ProGlide devices, or ProGlide/Angioseal (Terumo, Tokyo, Japan) combo, at operator's discretion, and as described in detail elsewhere.(13,19-22) Notably, additional techniques for hemostasis included prolonged balloon occlusion and elective covered stent implantation in several institutions (in such cases evidently covered stent implantation does not represent a procedural complication or vascular event but simply part of the comprehensive hemostasis strategy). Conversely, covered stent implantation could also be performed as bail-out in case of failure of the primary hemostasis strategy. In the surgical group, a standard surgical cutdown approach was used for vascular access. Follow-up was based on direct patient visits and echocardiographic controls, typically performed every 1-3 months after discharge.

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Outcomes

Clinical and echocardiographic outcomes were defined according to international recommendations, including the Valve Academic Research Consortium (VARC)-3 statement.(23-24) In particular, we considered as key procedural outcomes/endpoints the following: device success, primary hemostasis failure, pacemaker dependency, device embolization, cardiac tamponade, emergency surgery, and procedure time. Key outcomes/endpoints at 1 month follow-up were: death, stroke, death or stroke, myocardial infarction, bleeding, access-related complication, major adverse event (defined as composite of death, stroke, myocardial infarction, type 3 or type 4 bleeding, or major access-related complication), brachial plexus impairment, permanent pacemaker implantation, New York Heart Association (NYHA) class, and length of hospital stay. Brachial plexus impairment was defined as impaired motility and/or sensory disturbances in the ipsilateral upper limb lasting 48 hours or more, and was considered also as a component of major vascular complication. Primary hemostasis failure was defined as failure of the planned hemostasis strategy causing a life-threatening bleeding, major vascular complication, requiring bail-out covered stenting or surgical access. As previously stated, elective/selective covered stenting was not considered a bleeding event or a vascular complication. The 1-month rate of major adverse events was chosen as primary outcome of the study.

Analysis

Descriptive analysis was based on mean±standard deviation for continuous variables, and count (%) for categorical variables. Bivariate analysis for hypothesis testing was based on unpaired Student t-test for continuous variables, and Fisher exact test for categorical variables, generating 2-tailed p values. Propensity scores were generated using a non-parsimonious logistic regression model, using as dependent variable the use of percutaneous axillary vs surgical access. Then,

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propensity score adjusted regression was used to test the independent impact of access site on outcomes, using a linear model for continuous variables, and a logistic model for categorical variables, generating 2-tailed p values and 95% confidence intervals without pairing. A sensitivity analysis using propensity score matching with a 0.1 caliper was also performed.

Specifically, the following variables were used to generate the propensity score: age, gender, hypertension, atrial fibrillation, diabetes mellitus, peripheral artery disease, estimated glomerular filtration rate, chronic obstructive pulmonary disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior right or left internal mammary artery graft, prior TAVI, prior surgical aortic valve replacement, prior aortic surgery, prior stroke, prior transient ischemic attack, prior pacemaker implantation, NYHA class, EuroSCORE II, STS-PROM, HAS-BLED, urgent indication, absolute contraindication to femoral access, LV ejection fraction, peak aortic valve gradient, mean aortic valve gradient, severe aortic stenosis, aortic valve area, aortic regurgitation, mitral regurgitation, tricuspid regurgitation, minimum axillary diameter, maximum axillary diameter, axillary tortuosity, axillary calcification, aorta-LVOT angle, aorta-LV inflow long axis angle, LVOT-LV inflow long axis angle, predilation, postdilation, and need for additional TAVI device. Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustment. Computations were performed with Stata 13 (StataCorp, College Station, TX, USA).

Neither patients nor the public were directly involved in any phase of this work.

RESULTS

Overall, 432 patients undergoing TAVI between January 2019 and May 2021 were included in the present analysis: 189 (43.8%) undergoing surgical access, and 243 (56.2%) undergoing percutaneous access (Table 1, Table 1S). Several baseline differences were observed favoring the

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percutaneous group, including age, hypertension, NYHA class, and urgent indication. Conversely, prior pacemaker or implantable cardioverter defibrillator implantation, prior stroke, and STS-PROM score were disfavoring the percutaneous group. Imaging features were also significantly different between the study groups (Table 2), with lower aortic valve gradients, larger aortic valve area, and LVEF, larger maximum axillary diameter, higher prevalence of moderate or severe aortic regurgitation, axillary tortuosity, axillary calcification, and larger aorta-left ventricular inflow long axis angle in the percutaneous group.

Focusing on procedural features (Table 3), significant differences included a higher proportion of local anesthesia, larger sheath size, smaller device size, and higher rate of predilation in the percutaneous group, where balloon-expandable TAVI devices were also more commonly used. Several closure devices/techniques were used, including the Manta vascular closure device, 2 or 3 Perclose ProGlide devices, or combination of ProGlide and Angio-Seal.

Device success was not significantly different in the 2 groups (179 [94.7%] in the surgical vs 218 [89.7%] in the percutaneous access groups, p=0.075), as was contrast volume (142±84 vs 146±102 mL, p=0.731) and procedure time (127±39 vs 130±65 minutes, p=0.614). Conversely, primary hemostasis failure occurred less frequently in the surgical access group (8 [4.2%], vs 32 [13.2%], p<0.001), and the same applied to the need for overall covered stent implantation (7 [3.7%] vs 32 [13.2%], p<0.001), despite similar and low rates of bailout covered stent implantation in both groups (5 [2.7%] vs 7 [2.9%], p=1).

Rates of death or stroke (18 [10.1%] vs 20 [7.9%], p=0.492), death (9 [5.0%] vs 10 [4.0%], p=0.638), and bleeding (29 [16.2%] vs 30 [11.9%], p=0.203) at 1 month follow-up were similar in the 2 groups (Table 4; Figure 1; Figure 2). However, major adverse events were more common in the surgical group (53 [28.0%] in the surgical group vs 47 [19.3%] in the percutaneous group, p=0.039), and the same applied to major access-site non-vascular complications (18 [9.5%] vs 8 [3.3%]).

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Propensity score adjusted analysis (Table 5) confirmed the lower risk of major adverse events (odds ratio=0.44 [95% confidence interval: 0.21; 0.95], p=0.036), and major access-site non-vascular complications (odds ratio=0.21 [0.06; 0.77], p=0.018) in patients undergoing percutaneous access, with the adjunct potential benefits of lower risk of brachial plexus impairment (odds ratio=0.16 [0.03; 0.76], p=0.021), lower NYHA class (odds ratio for 1 step increase=0.43 [0.19; 0.97], p=0.041) and shorter hospital stay (regression coefficient=-2.6 [-5.0; -0.1] days, p=0.038).

Additional analysis based on institutional experience with percutaneous access (distinguishing centers with or without 15 or more cases) suggested similar outcomes independent of caseload (Table 2S, Figure 3). Nonetheless, centers with more extensive experience reported lower contrast volume use (p<0.001), and shorter procedures (p<0.001). Comparison of right vs left percutaneous access also showed similar outcomes irrespective of the chosen side (Table 3S; Figure 4). Despite being limited by uneven use, comparative analysis focusing on vascular closure device suggested similar clinical outcomes in patients undergoing hemostasis with the Manta or ProGlide devices, despite more common need for covered stents when using the Manta device (p=0.007; Table 4S; Figure 5).

An exploratory analysis for predictors of adverse outcomes limited to the percutaneous group showed that the risk of major adverse events was significantly higher in women (odds ratio=2.09 [1.05; 4.06], p=0.035), patients with severe aortic stenosis (odds ratio=3.27 [1.27; 8.43], p=0.014), and higher STS-PROM score (odds ratio=1.06 [1.02; 1.10], p=0.002).

Finally, propensity score-matched analysis showed similar results for 1-month outcomes with percutaneous or surgical access, notwithstanding the smaller sample size and overall lower risk profile of this subsample of the dataset (totalling 100 patients)(Table 6S).

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with favorable results in terms of procedural success and short-term safety.(28-29) However, the need for open surgical access seems a limitation of this approach, and may lead to substantial peri-procedural complications, including bleeding, arterial thrombosis, infection, and nerve injury. More recently, improved device features and refined expertise have led to the proposal of percutaneous axillary access for TAVI.(12,20-21,30) Several studies have reported on the results with percutaneous axillary access, but these were limited either in size or in design (e.g. institutional series without control group).(9-12)

Important evidence on the comparative effectiveness of percutaneous vs surgical axillary access has been reported by Chung et al, exploiting the STS/ACC TVT Registry dataset, including a total of 4,219 patients, 1,140 receiving percutaneous axillary access.(14) After propensity score matching, significant differences were evident for fluoroscopy time, contrast volume, and rate major vascular complication disfavoring the percutaneous group. Conversely, effect estimates for intensive care unit stay, total hospital stay, rate of permanent pacemaker implantation significantly favored the percutaneous group). Evidently, our findings partly agree with this important analysis based on administrative data, especially in confirming the safety and efficacy of percutaneous axillary access for TAVI. However, we provide more ample appraisal of different clinical outcomes, capitalizing on the more accurate data collection and analysis, possibly suggesting indeed that the different permanent pacemaker implantation rates in Chung et al, not confirmed in our work, might be due to residual confounding, as indeed it may have limited pathophysiologic plausibility.

Furthermore, in our present analysis we found similarly favorable results were obtained by centers with extensive experience in percutaneous axillary access as well in less experienced ones, thus suggesting that adoption of this approach does not imply a challenging learning curve. The side of percutaneous axillary access seem being associated with similar success rates and safety, and the

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same equipoise might apply to the comparison between the Manta and ProGlide as vascular closure devices for achieving hemostasis.

While dedicated devices for percutaneous axillary TAVI are still lacking, we expect that their development and diffusion will improve operator confidence and clinical outcomes. In particular, the Achilles' heel of percutaneous axillary access is likely represented by the need for bail-out or elective covered stent implantation in almost one out of every 8 patients, and technological refinements are hopefully going to improve these figures. Indeed, while some cardiologists consider more liberally covered stenting of the axillary artery in case of suboptimal hemostasis, several operators aim to avoid covered stents in most cases, especially if access is rather lateral, as they can be in a high flex area with increased risk of late stent failure. In such cases extra vascular closure devices, internal balloon tamponade, and manual pressure may be helpful to minimize the long-term risks associated with axillary stenting. Furthermore, pectoralis nerve block may enable in case of challenging hemostasis the conversion to open surgical repair without the need for general anesthesia. Indeed, routine avoidance of general anesthesia is a major perk of percutaneous access and might translate into substantial clinical benefits in patients with comorbidities.

The strengths of this work include the multicenter design and the common set of data items used for descriptive and inferential purposes. In light of our findings, and pending the results of dedicated randomized trials, whenever femoral access is contraindicated, based on the present findings, we can recommend percutaneous axillary access as the default access for TAVI, given its favorable efficacy, effectiveness, and safety profile.

Limitations of this study include the observational design, retrospective nature, and lack of adjustment for multiple testing and type I error inflation. Even the sample size is only moderate, and a larger sample could provide more precise inferential estimates, as well as potentially more

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thorough adjustment for potential confounders. Furthermore, some institutions provided only data on percutaneous or surgical access, limiting within-center comparative analyses. Event rates associated with percutaneous axillary access were still relatively high, including peri-procedural strokes, confirming the recommendation shared by many guidelines that femoral access should continue to be the default access site for TAVI. Finally, the fact that propensity score-matched analysis was limited to a subset of patients highlights the evident differences between percutaneous and surgical access cases, reinforcing the mainly exploratory scope of this work. We also did not compare percutaneous axillary access, which has been suggested as safer than surgical axillary access, but recent reports from the STS/ACC TVT Registry support our present results favoring, at least for some endpoints, percutaneous access.(31-32)

In conclusion, this international registry suggests that percutaneous axillary access is at least equivalent to surgical access in patients undergoing TAVI with absolute or relative contraindications to femoral access, and can be adopted with relative ease by TAVI operators already skilled in femoral access.

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AUTHORS' CONTRIBUTION

Arturo Giordano designed the study, participated in data collection, participated in manuscript drafting, and finally approved it. Andreas Schaefer, Oliver D. Bhadra, Lenard Conradi, Dirk Westermann, Ole De Backer, Vilhelmas Bajoras, Lars Sondergaard, Waqas T. Qureshi, Nikolaos Kakouros, Summer Aldrugh, Ignacio Amat-Santos, Sandra Santos Martínez, Tsuyoshi Kaneko, Morgan Harloff, Rui Teles, Tiago Nolasco, Jose Pedro Neves, Miguel Abecasis, Nikos Werner, Michael Lauterbach, Jerzy Sacha, Krzysztof Krawczyk, Carlo Trani, Enrico Romagnoli, Antonio Mangieri, Francesco Condello, Ander Regueiro, Salvatore Brugaletta, Fausto Biancari, Matti Niemelä, Francesco Giannini, Marco Toselli, Rossella Ruggiero, Andrea Buono, Diego Maffeo, Francesco Bruno, Federico Conrotto, Fabrizio D'Ascenzo, Mikko Savontaus, Jouni Pykäri, Alfonso Ielasi, Maurizio Tespili, Nicola Corcione, Paolo Ferraro, Alberto Morello, and Michele Albanese, participated in study design, participated in data collection, critically reviewed the manuscript for important clinical and scientific content, and finally approved it. Giuseppe Biondi-Zoccai designed the study, performed the analysis, drafted the manuscript and finally approved it, and is responsible for the overall content as guarantor.

All authors read and approved the final version of the manuscript

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Original article

Iberian experience with PASCAL transcatheter edge-to-edge repair for mitral valve regurgitation

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ABSTRACT

Introduction and objectives: The PASCAL system is a novel device for transcatheter mitral valve repair based on the edge-to-edge concept. The unique features of this device might have a relevant impact on the repair outcomes. There are few data on clinical outcomes in real-life registries. The aim of this study was to report the early Iberian experience (Spain and Portugal) of the PASCAL system.
Methods: Procedural and 30-day outcomes were investigated in consecutive patients with symptomatic severe mitral regurgitation (MR) treated with the PASCAL system at 10 centers. Primary efficacy endpoints were technical success and degree of residual MR at discharge. The primary safety endpoint was the rate of major adverse events (MAE) at 30 days.
Results: We included 68 patients (age, 75 [68-81] years; 38% women; EuroSCORE II 4.5%). MR etiology was degenerative in 25%, functional in 65%, and mixed in 10%. A total of 71% of patients were in New York Heart Association (NYHA) functional class ≥ III. Technical success was achieved in 96% and independent capture was used in 73% of procedures. In the treated population, MR at discharge was ≤ 2+ in 100%, with no in-hospital deaths. At 30 days, the MAE rate was 5.9%, the all-cause mortality rate was 1.6%, 98% were in NYHA functional class ≤ II, and 95% had MR ≤ 2+ ($P < .001$).
Conclusions: Transcatheter mitral valve repair with the PASCAL system was safe and effective, with high procedural success and low rates of MAE. At 30 days, MR was significantly reduced, with a significant improvement in functional status.
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Experiencia ibérica con PASCAL para la reparación percutánea borde a borde en insuficiencia mitral

Palabras clave:
Insuficiencia mitral
Reparación percutánea borde a borde
Dispositivo PASCAL

RESUMEN

Introducción y objetivos: PASCAL es un dispositivo novedoso de terapia mitral transcatéter basada en la reparación borde a borde. Algunas características únicas podrían tener un impacto relevante en sus resultados. Hay pocos datos sobre los resultados clínicos en registros de la vida real. El objetivo de este estudio es publicar la experiencia ibérica precoz (centros de España y Portugal) del sistema PASCAL.
Métodos: Se incluyó prospectivamente a los pacientes tratados consecutivamente de insuficiencia mitral (IM) grave sintomática en 10 centros. El objetivo primario de eficacia fue el éxito técnico y el grado de regurgitación al alta. El objetivo primario de seguridad fueron los eventos adversos mayores (MAE) a 30 días.

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Resultados: Se incluyó a 68 pacientes (75 [68-81] años, 38% mujeres, EuroSCORE II 4,5%). La IM fue degenerativa en el 25% de los casos, funcional en el 65%, y mixta en el 10%. El 71% de pacientes estaban en clase funcional New York Heart Association (NYHA) ≥ III. El éxito técnico fue del 96% y la captura independiente se usó en el 73% de los procedimientos. Toda la población tratada obtuvo una IM al alta ≤ 2+ (100%) y no hubo muertes intrahospitalarias. A los 30 días, los MAE fueron del 5,9%, la mortalidad global del 1,6%, el 98% estuvieron en clase NYHA ≤ II y el 95% tuvieron IM ≤ 2+ ($p < 0,001$).
Conclusiones: El sistema PASCAL de terapia transcatéter mitral fue efectivo y seguro, con elevado éxito técnico y baja tasa de MAE. A los 30 días la IM se redujo significativamente, y hubo una mejoría en la clase funcional.
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Abbreviations

MR: mitral regurgitation
NYHA: New York Heart Association
TEER: transcatheter edge-to-edge repair

INTRODUCTION

Mitral regurgitation (MR) is a highly prevalent and undertreated valvular heart disease, which carries a poor prognosis if left untreated.[1–3] Transcatheter edge-to-edge repair (TEER) using the MitraClip system (Abbott Vascular, United States) has been consolidated as an effective therapy for high-risk patients with MR, with high procedural safety and producing rapid recovery.[4–7] However, residual MR after TEER with MitraClip is not uncommon and is associated with worse outcomes.[8]

The PASCAL valve repair system (Edwards Lifesciences, United States) is a novel device for TEER. It offers special characteristic features including a central spacer, broad paddles made of pliable nitinol and the possibility of independent leaflet capture.[9] PASCAL Ace is a new device designed with a narrow profile. Pivotal studies[10] and German real-world experience[11,12] demonstrated a low complication rate and high survival with sustained MR reduction. The present study assessed the real-world experience of a postapproval patient cohort treated at Spanish and Portuguese tertiary care centers.

METHODS

Study design and population

This article covers the initial experience of transcatheter edge-to-edge mitral valve repair with the PASCAL system in the Iberian Peninsula (Spain and Portugal). This was a multicenter study collecting individual data from an unselected all-comer population from 10 hospitals with initial access to the PASCAL and PASCAL Ace systems for the treatment of severe symptomatic MR from October 2019 to September 2021.

Demographics, baseline and procedural characteristic and clinical/echocardiographic outcomes at follow-up were prospectively collected in a dedicated, shared database at each participating center. All procedures were performed under general anesthesia and guided by transesophageal echocardiogram (TEE) and fluoroscopy. Periprocedural complications were noted during the index hospitalization. The study was conducted in accordance with the institutional ethics committee of each participating center, and all patients provided signed informed consent for the procedure.

Endpoints and definitions

Standardized definitions of all patient-related variables, clinical diagnoses, and in-hospital complications and outcomes were based on the Mitral Valve Academic Research Consortium criteria unless indicated otherwise.[13] MR was assessed using standard 2-dimensional color Doppler methods and were graded using a 4-class grading scheme: mild, moderate, moderate-severe, and severe.

The primary efficacy endpoints were technical success (device successfully deployed as intended, delivery system successfully retrieved without procedural mortality or need for surgery or reintervention) and severity of MR at discharge in the treated population.

The main safety endpoint was freedom from major adverse events (MAE) at 30 days, including all-cause mortality, cardiac tamponade, emergent surgery, vascular complications, severe bleeding (major, extensive, life-threatening, or fatal bleeding), stroke, and myocardial infarction.

Secondary endpoints included the severity of MR at discharge on an on-treatment basis (at least 1 PASCAL device implanted, alive and without reintervention), device success (at 30 days, defined as successful device implantation, MR ≤ 2+, mean gradient < 5 mmHg and freedom from mortality, stroke, unplanned surgical or interventional procedures, and device failure), clinical success (as defined in the CLASP[14] approval trial as successful device implantation, MR ≤ 2+, and freedom from mortality, stroke, unplanned surgical or interventional procedures, and device failure at 30 days), reintervention, and change in clinical evaluation of New York Heart Association (NYHA) functional class during follow-up.

Statistical analysis

Results are presented as mean ± standard deviation for continuous normally distributed variables, median [interquartile range] for continuous nonnormally distributed data, and as number (percentages) for categorical data. Analysis of normality was performed with the Kolmogorov-Smirnov and Shapiro-Wilks test. Categorical data and proportions were compared using the chi-square or Fisher exact test. Comparisons of continuous variables were analyzed using the unpaired *t*-test and the Mann-Whitney U-test as appropriate. The McNemar paired-test and Wilcoxon matched-pairs signed-rank test were used to compare differences resulting from treatment as appropriate. An alpha error level of .05 was established and Stata 12.1 software (College Station, United States) was used for all analyses.

RESULTS

Patient population and baseline characteristics

A total of 68 patients (median age 75 years, 62% men) with symptomatic MR underwent transcatheter mitral valve repair

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Table 1
Baseline characteristics

Baseline characteristics	Total (n = 68)	Functional MR (n = 44)	Degenerative MR (n = 17)
Age, y	75 [68-81]	72 [66-77]	84 [76-87]
Women	26 (38)	18 (41)	6 (35)
BSA	1.79 ± 0.18	1.79 ± 0.17	1.76 ± 0.20
Hypertension	57 (84)	36 (82)	15 (88)
Diabetes mellitus	22 (32)	17 (39)	3 (18)
Atrial fibrillation	40 (59)	26 (59)	10 (59)
CAD	30 (44)	19 (43)	6 (35)
PCI	22 (32)	14 (32)	5 (29)
CABG	9 (13)	4 (9)	3 (18)
Stroke/TIA	9 (13)	2 (5)	3 (18)
CKD	22 (32)	16 (36)	5 (29)
Previous valvular intervention	5 (7)	2 (5)	2 (12)
EuroSCORE II, mean	4.5 ± 3.6	4.6 ± 3.9	3.5 ± 2.6
STS, mean	4.1 ± 3.0	4.0 ± 3.4	4.2 ± 1.9
NYHA ≥ III	48 (71)	34 (77)	9 (53)
Previous heart failure admission	38 (56)	28 (64)	6 (35)
Medical treatment			
Beta-blockers	51 (75)	37 (84)	9 (53)
ACE-I /ARB	35 (52)	21 (48)	10 (59)
Sacubitril/Valsartan	24 (35)	22 (50)	0 (0)
Nitrates/Hidralazine	10 (15)	7 (16)	0 (0)
CRT	9 (13)	8 (18)	1 (6)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; BSA, body surface area; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy. NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons Score; TIA, transient ischemic attack.
Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

between October 2019 and November 2021. Baseline characteristics and center distribution are summarized in table 1 and figure 1. Patients were considered at high surgical risk, expressed by a mean EuroSCORE II of 4.5% and a relevant burden of comorbidities: 44% of patients had concomitant coronary artery disease, 13% had undergone surgical revascularization, and 7% had previous valve intervention. The prevalence of atrial fibrillation (59%) and chronic renal failure (32%) was high, most patients (71%) were in NYHA functional class III or IV and 38 patients (56%) had had a previous heart failure hospitalization in the last year.

Baseline echocardiographic parameters are shown in table 2. Most patients (96%) had moderate to severe (3+) or severe (4+) MR at baseline. MR etiology was classified as functional in 44 patients (65%), degenerative in 17 patients (25%), and mixed in the remaining 7 patients (10%). Median left ventricular ejection fraction was 43% and effective regurgitant orifice area 0.38 [0.30-0.49] cm^2. Optimal guideline-directed medical therapy in secondary MR was achieved in a high number of patients: 84% of patients were treated with beta-blockers, 98% with angiotensin inhibition (angiotensin converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor-neprilysin inhibitors, [ACE-I/ARB/ARNI:]), and 18% were treated with cardiac resynchronization therapy (CRT).

Procedural and intrahospital outcomes

Procedural outcomes are summarized in table 3. One PASCAL device was implanted in 52 patients (76%) and 2 devices in 16 patients (24%). Overall, technical success was achieved in 65 patients (96%). The procedure was aborted without PASCAL implantation in 3 patients (4%). One patient with a short posterior

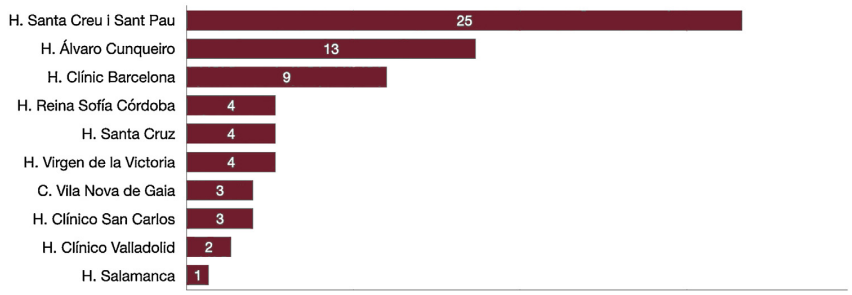


Figure 1. Distribution of cases performed by centers.

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Table 2
Baseline echocardiographic variables

Echocardiographic variables	Total (n = 68)	Functional MR (n = 44)	Degenerative MR (n = 17)
LVEF	43 [30-60]	35 [26-55]	60 [55-69]
LVEDD, mm	59 ± 9	62 ± 9	52 ± 5
LVESD, mm	46 ± 12	50 ± 12	37 ± 6
MR severity ≥ 3+	65 (96)	41 (93)	17 (100)
MR mechanism			
Functional	44 (65)		
Degenerative	17 (25)		
Mixed	7 (10)		
EROA, cm²	0.38 [0.30-0.49]	0.39 [0.32-0.50]	0.36 [0.28-0.55]
sPAP by echo, mmHg	48 ± 13	48 ± 14	48 ± 11
Mitral valve area, cm²	5.4 [4.5-6.3]	5.4 [4.4-6.2]	5.5 [5.1-7.0]
Mitral mean gradient, mmHg	1.7 ± 0.9	1.8 ± 1.0	1.6 ± 0.7

EROA, effective regurgitant orifice area; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic diameter; MR, mitral regurgitation; sPAP, systolic pressure pulmonary artery.
Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

Table 3
Procedural and in-hospital data

Procedural data	Total (n = 68)
Number of PASCAL per patient	
1	52 (76)
2	16 (24)
Type of PASCAL Ace/P10Ace	
Ace	22 (33)
P10	43 (64)
Both	2 (3)
Optimization	47 (73)
Technical success	65 (96)
Technical complications	
Partial detachment	0
Total detachment	0
Leaflet tear	1 (1)
Chordae rupture	0
MitraClip switch	1 (1)
Major adverse events	
Death	0
Cardiac tamponade	0
Emergent surgery	1 (1)
Vascular complications	0
Major bleeding	0
Stroke	2 (3)
Myocardial infarction	0
MR severity ≤ 2+ at discharge	65 ± 100
Mean gradient (mmHg) at discharge	2.7 ± 1.3
Admission days	2 [1-3]

MR, mitral regurgitation.
Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

leaflet had a tear with severe MR and underwent surgical repair. The second patient had leaflet tip calcification precluding appropriate PASCAL closure; the device was removed and a MitraClip was subsequently implanted. The third patient had worsening MR after leaflet clasping due to mitral valve distortion and the device was ultimately not released. Independent clasp optimization was applied in 47 patients (73%). Median procedural time was 121 [IQR: 83-168] minutes. There were no cases of intraprocedural single leaflet device attachment. Median length of stay after the procedure was 2 IQR: 1-3] days. There were no in-hospital deaths. In the treated population, residual MR at discharge was ≤ 2+ in 100% of the patients and ≤ 1+ in 77%. The mean transmitral gradient increased from 1.7 mmHg at baseline to 2.7 mmHg at discharge (P = .0001). Transmitral gradient was significantly lower in patients treated with a single device than in those requiring 2 devices (2.4 vs 3.5 mmHg, P = .0037). A mean gradient ≥ 5 mmHg was observed in 10% of patients (n = 6) and was not related to the number of devices (3 patients treated with 1 device, P = .27) nor to the type of device (4 patients treated with PASCAL, 1 treated with ACE, and 1 treated with both devices, P = .10).

Follow-up outcomes

Thirty-day survival status was available in all patients (median follow-up time 223 [IQR: 105-439] days). Clinical success was achieved in 86.7% (59 of 68 patients). The primary safety endpoint, defined as a freedom from composite MAE rate at 30 days, occurred in 64 of 68 patients (94%). One patient died from cardiovascular causes due to sudden death at 30 days and another patient died from cardiovascular causes at 12 months of follow-up. The Kaplan-Meier survival curve of freedom from mortality is shown in figure 2. In-hospital stroke occurred in 2 patients and 1 patient had surgical conversion due to leaflet tear. At 30 days, 96% of patients were in NYHA class I or II and 95% of patients had MR ≤ 2+, with significant clinical and echocardiographic improvement from baseline (P = .001, figure 3).

At 12 months, 5 patients were hospitalized for cardiovascular causes with a Kaplan-Meier curve for survival and cardiovascular hospitalization of 13.85% (figure 2).

DISCUSSION

We report the first Iberian experience of TEER with the PASCAL device in patients with symptomatic functional and degenerative MR. The main findings of the study are: *a)* technical success was achieved in 96%, and MR in the treated population was reduced to

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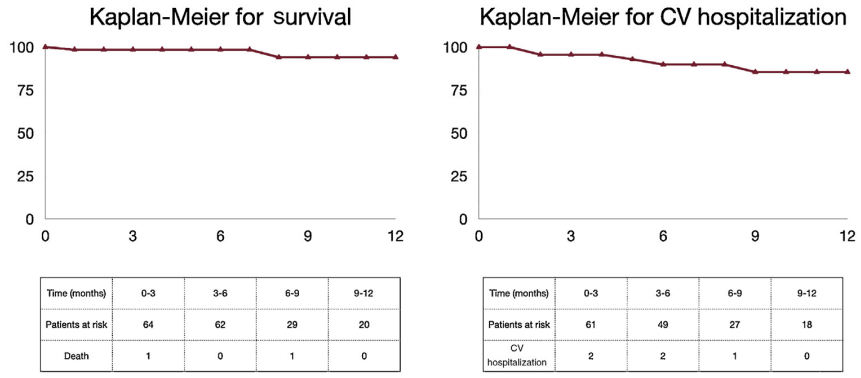


Figure 2. Kaplan-Meier curve for survival and cardiovascular hospitalization. CV, cardiovascular.

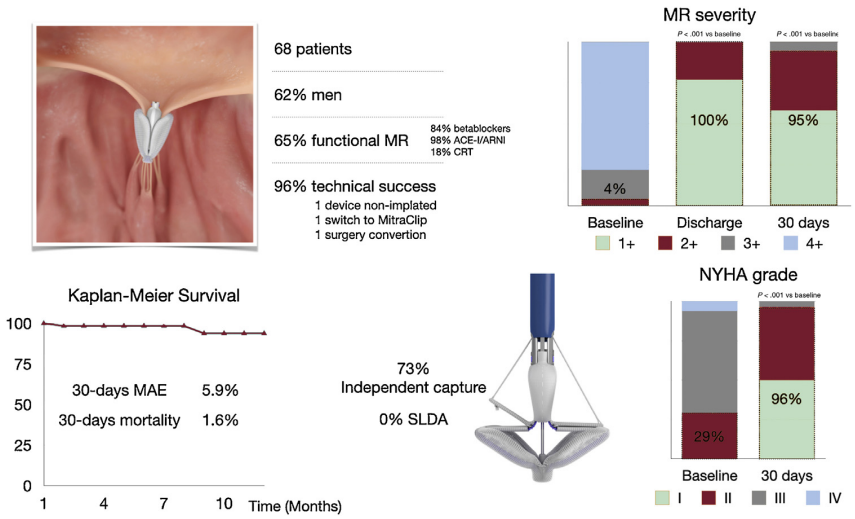


Figure 3. Central Illustration. Iberian experience with PASCAL for transcatheter mitral regurgitation repair. Baseline characteristics, procedural results, and follow-up. ACE-I/ARB/ARNI, angiotensin converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin receptor-neprilysin inhibitors; CRT, cardiac resynchronization therapy; MAE, major adverse events; MR, mitral regurgitation; NYHA, New York Heart Association; SLDA, single leaflet device attachment.

grade $\leq$ 2+ at discharge in 100% and to grade $\leq$ 1+ in 77% of patients; *b)* all-cause mortality and the MAE rate at 30 days were low at 1.6% and 5.9%, respectively; and *c)* the main reasons for technical failure were aborted procedures or a change to the MitraClip device due to worsening of MR (n = 2) or posterior leaflet tear (n = 1).

Our findings are derived from unselected real-world patients. In this initial experience, the suitability criteria for PASCAL were similar as previously used for MitraClip therapy.

Some special features differentiate the MitraClip and PASCAL devices:

- The central spacer seems to generate less leaflet tension in the mitral valve, and it could be useful in MR with atrial or ventricular tethering.
- Independent capture of leaflets. The independent capture allows 1 leaflet to be released while the other is captured. Until the development of the PASCAL system, capture of leaflets had been simultaneous and when trying to optimize the capture of one there was a risk of losing the other. The new G4 MitraClip system also incorporates this special feature. However, differences between the aggressivity of leaflet capture in the MitraClip system can reduce its use, reported in 49% of its initial experience.[15]

Baseline population characteristics were comparable with other real-world data from the German registry,[11,12] rather than the pivotal CLASP trial,[10,14] targeting a highly comorbid population with a mean EuroSCORE II of 4.5% and advanced NYHA functional class, > 70% in class III-IV.

Our results are in line with previous efficacy endpoints reported with the PASCAL repair system. The CLASP study achieved 95% technical success with MR $\leq$ 2+ in 96% of the patients at 30 days and real-world data from the German registry showed a technical success of 96% with residual MR $\leq$ 2+ in 93% of the patients. The results of this experience confirmed the safety profile of the PASCAL Repair system, with zero procedural mortality and a low rate of 30-day MAE (5.9%), similar to that reported in the CLASP and German studies (8.3% and 4.1%, respectively). Of note, there were no cases of intraprocedural single leaflet device attachment (1% in the German registry), which may be due to a higher rate of

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independent clasp optimization (after initial simultaneous clasping) in the present series (73% vs 48% in the German study).

Importantly, there was a significant NYHA functional class improvement at 30 days (96% NYHA I-II), which is much higher than that observed in the German registry (72%), CLASP study (81%), or in our first reported experience with TEER with MitraClip in 2014[16] (81%).

Learning effect

Since our first publication, the learning curve achieved with MitraClip in terms of patient selection and increased procedural experience may have strongly impacted on the positive results obtained with PASCAL in the present study. Indeed, patient selection has changed after the COAPT and Mitra-FR trials, which showed that patients with severe secondary MR with EROA $>$ 0.3 cm^2 and LVESD $<$ 70 mm under optimal medical treatment were more likely to benefit from TEER. Our data confirm these findings, with a median EROA value of 0.39 cm^2 [IQR: 0.32-0.50 cm^2], a mean LVESD of 50 mm and optimal guideline-directed medical therapy: 84% patients with beta-blockers, 98% with ACE-I/ARB/ARNI, and 18% with cardiac resynchronization therapy.

In addition, increased procedural skills over time have led to a significant reduction in transseptal puncture-related complications (0% vs 3% in our initial experience with MitraClip), as well as a lower ratio of devices required per patient ($\geq$ 2 devices required in 39% in MitraClip early-generation vs 24% in the present study).

Limitations

The present study was observational in nature. Because the study was designed as a registry, all echocardiographic and clinical data were site reported and lacked independent adjudication by a core laboratory or an event committee. The absence of a randomized control group limits conclusions and the results for efficacy and safety should be regarded in the context of the early phase of the learning curve with a new device.

CONCLUSIONS

Transcatheter mitral valve repair with the PASCAL device was safe and effective for treating severe MR, with a high technical success rate, a low rate of procedural complications, and sustained reduction in MR severity at 30 days. Larger studies with a longer-term follow-up are warranted.

FUNDING

There was no funding.

AUTHORS' CONTRIBUTIONS

C.-H.P. Li: concept/design, data collection, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics. R. Estevez-Loureiro: concept/design, data collection, critical revision of article, approval of article. X. Freixa: data collection, critical revision of article, approval of article. R. Teles: data collection, critical revision of article, approval of article. A. I. Molina-Ramos: data collection, approval of article. M. Pan: data collection, critical revision of article, approval of article. L. Nombela: data collection, critical revision of article, approval of article. B. Melica: data collection, critical revision of article, approval of article. I. J. Amat-Santos: data collection, critical revision of article, approval of article. I. Cruz-González: data collection, critical revision of article, approval of article. Ll. Asmarats: doncept/design, data analysis/interpretation, critical revision of article, approval of article, statistics. R. Alarcón: data collection, critical revision of article, approval of article. L. Sanchis: data collection, critical revision of article, approval of article.

E. Fernández-Peregrina: data collection, critical revision of article, approval of article. J. A. Baz: data collection, critical revision of article, approval of article. X. Millán: concept/design, data analysis/interpretation, critical revision of article, approval of article, statistics. I. Menduiña: data collection, critical revision of article, approval of article. D. Arzamendi: concept/design, data analysis/interpretation, critical revision of article, approval of article.

CONFLICTS OF INTEREST

C.-H.P. Li reports personal fees from Edwards and personal fees from Abbott, outside the submitted work. R. Estevez-Loureiro reports personal fees from Edwards, personal fees from Abbott, personal fees from Boston, outside the submitted work. L. Nombela has received consultant fees from Edwards Lifesciences and he is proctor for Abbott Vascular. L. Sanchis reports speaker honoraria from Abbott, Menarini, GE; she is proctor for MitraClip/TriClip implantation (Abbott) and associate editor of *Rev Esp Cardiol*. The journal's editorial procedure to ensure impartial handling of the manuscript has been followed. I. Cruz-González reports consultant fees for Edwards. Dr Melica reports personal fees from Abbott and Edwards, outside the submitted work. D. Arzamendi reports proctoring fees from Edwards Lifesciences.

WHAT IS KNOWN ABOUT THE TOPIC?

- The PASCAL system is safe and effective: the CLASP study achieved 95% technical success with MR $\leq$ 2+ in 96% of the patients at 30 days and real-world data from the German registry showed technical success of 96% with residual MR $\leq$ 2+ in 93% of the patients. MAE previously reported in CLASP and German studies were 8.3% and 4.1%, respectively.
- The PASCAL system allows independent capture of leaflets, and it was used in 48% of patients in the real-world data from the German registry.

WHAT DOES THIS STUDY ADD?

- The Iberian experience confirms the safety and effectiveness of the Pascal system: technical success was 96%, and MR in the treated population was reduced to grade $\leq$ 2+ at discharge in 100% and to grade $\leq$ 1+ in 77% of the patients. All-cause mortality and the MAE rate at 30 days were low at 1.6% and 5.9%, respectively.
- The main reasons for technical failure were aborted procedures or a change to the MitraClip device due to worsening of MR (n = 2) or posterior leaflet tear (n = 1).
- The independent capture rate was 73%, which was higher than in previous publications.
- The Iberian patient profile is adjusted to the COAPT trial with a high rate of optimal medical treatment.

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COMENTÁRIO EDITORIAL

Na cauda do cometa. Limitações para implantação de válvulas aórticas percutâneas transcatéter em Portugal

Trailing behind: Limitations on transcatheter aortic valve implantation in Portugal

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As válvulas aórticas percutâneas (VAP) transcatéter constituem uma inovação terapêutica sem paralelo na última década cardiológica. Desde a primeira válvula desenvolvida por Andersen em 1989 passaram duas décadas até ao primeiro estudo aleatorizado. Aos 24 meses de seguimento observou-se um decréscimo absoluto de mortalidade de 51% sob terapêutica médica para 31% após implantação de VAP[1–4]. Após a primeira implantação humana por Cribier em 2002, Webb introduziu a via retrógrada em 2005 e Walther a via transapical em 2006, verificando-se um crescimento meteórico da técnica desde então[5–7]. Este rápido progresso permitiu alcançar uma mortalidade aos 30 dias situada entre os 6,5 e os 9,7%[8–10], ainda em trajetória descendente, traduzida igualmente em ganhos significativos na qualidade de vida[11,12].

Na Europa há assimetrias consideráveis no acesso ao tratamento transcatéter desta patologia grave, com destaque para a realidade portuguesa[13,14]. A prevalência da estenose aórtica aumenta com a idade, pelo que, considerando uma prevalência de 3,4% de estenose aórtica nos 924 000 portugueses com mais de 75 anos, haverá cerca de 32 000 portadores de estenose grave, sendo 75% sintomáticos (n = 24 000)[15]. Admitindo que são elegíveis para VAP cerca de 40% dos doentes considerados inoperáveis e 80% dos doentes de alto risco, conclui-se que existem 4600 indivíduos nestas circunstâncias[16]. Os dados portugueses evidenciam que, nos últimos 5 anos, foram realizados 265 procedimentos, correspondentes a 5% dos candidatos.

Portugal apresenta a menor taxa anual de implantes por milhão de habitantes da União Europeia, 7 *versus* uma média 45. A adoção das recomendações conjuntas de 2012 de cardiologistas, cardiologistas de intervenção e cirurgiões para a doença valvular pode vir a reduzir este desfasamento paradigmático da mudança que estamos a viver[17]. Relativamente à estenose aórtica, há três áreas em que estas orientações revelam especial importância:

1. No rastreio e diagnóstico, que deve ser mais preciso e atempado:
   a. ao nível dos doentes e da medicina familiar, designadamente na valorização das queixas muito comuns nestas idades, tais como o dispneia de esforço, a astenia e as tonturas;
   b. no diagnóstico ecocardiográfico, viciado pela não realização de Doppler em muitos casos.
2. Nas indicações terapêuticas apropriadas, favorecendo a implantação cirúrgica ou percutânea de próteses em detrimento da terapêutica médica isolada:
   a. pela referenciação adequada pelos cardiologistas, podendo incluir estenoses valvulares aórticas graves que surgem em doentes que parecem «assintomáticos» e especialmente aqueles que têm demasiadas comorbilidades que limitam a sua qualidade de vida e/ou inibem a referenciação para a substituição valvular[18];

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   b. dos cirurgiões cardíacos, que estratificam o benefício potencial da cirurgia convencional e que definem o risco operatório que aumenta na presença de idade avançada, de disfunção ventricular esquerda, do género feminino, de comorbilidades, de uma classe funcional elevada, de disfunção ventricular esquerda, de hipertensão pulmonar, de doença coronária e no contexto de emergência[19];
   c. dos preditores de risco intrínsecos à opção alternativa transcatéter, alvo de intensa investigação sobre a avaliação anatómica para escolha do acesso vascular e do tipo de prótese, particularmente do anel aórtico, que raramente é circular e está frequentemente deformado pela calcificação exuberante.
3. Na organização e experiência das equipas multidisciplinares, que atuam nos limites da evolução tecnológica e das imposições orçamentais:
   a. na constituição de um *HEART TEAM* multidisciplinar englobando a cardiologia, a cirurgia cardíaca, a imagiologia, a hemodinâmica, a anestesiologia, a geriatria, a cardiopneumologia, a enfermagem e a reabilitação;
   b. na estrutura centrada no doente, disponibilizando individualmente as soluções, privilegiando a cirurgia convencional e procurando respeitar, quando apropriado, a preferência pela menor invasividade, tal como foi patente no PARTNER, em que 8% dos doentes do grupo da cirurgia convencional retiraram o consentimento informado, comparados com 0,3% do grupo VAP[2];
   c. nas características das próteses, que estão a evoluir rapidamente, formatadas nesta fase em duas formas de ancoragem e libertação (autoexpansível ou expansível por balão) e em dois tipos de tecido biológico (pericárdio bovino ou porcino), agora disponíveis em quatro tamanhos que cobrem anéis de 18 a 29 mm de diâmetro;
   d. na avaliação da sustentabilidade económica pela sociedade, com estudos direcionados para a área da avaliação da qualidade de vida e custo-eficácia[20].

O artigo de Sousa et al. é atual e debruça-se sobre o terceiro ponto. Conclui que, quando as equipas disponibilizam as soluções descritas - todas as abordagens vasculares e duas próteses com dois tamanhos, Medtronic Corevalve e Edwards Sapien - possuem alternativas anatómicas significativamente superiores e quase universais para o tratamento por VAP.

Trata-se uma população de dimensão apreciável, refletindo a experiência do grupo iniciada em agosto de 2007 no Centro Hospitalar de Vila Nova de Gaia, quando realizou o primeiro caso ibérico com implantação de uma válvula autoexpansível Corevalve por via transfemoral[21].

São apresentados escassos dados demográficos, indicando que a distribuição dos doentes se inclina para as menores dimensões, o que é concordante antropomorfometricamente com a população portuguesa que apresenta uma estatura média de 165,5 cm, inferior aos 169,9 cm dos habitantes da União Europeia[16].

O desenho do estudo foi retrospetivo e metodologicamente focado nos dados que tinham relação mais estreita com os objetivos do trabalho, baseado em dois métodos de imagem complementares.

De facto, a determinação do diâmetro do anel aórtico é crucial no planeamento, pois permite reduzir as regurgitações paravalvulares[22]. Alem disso, tem implicações na minimização da embolização (0,5-8%), da (rara) rotura do anel e da necessidade de *pacing* (3-40%) que parece aumentar com válvulas maiores[22–25]. Porém, como referido, a anatomia do anel é elíptica e, por isso, têm sido desenvolvidos inúmeros esforços e *softwares* que procuram aumentar a precisão das medições da área valvular, cada vez mais relevante na escolha do tamanho das próteses[26,27]. Nestes aspetos, o ecocardiograma transesofágico (ETE) 3 D tem vantagens relativamente ao ecocardiograma transtorácico (ETT) e o ETE 2D[28]. Sousa et al. utilizaram preferencialmente o ETE, não estando descrito se pré- ou intraprocedimento, nem qual a proporção de doentes que realizaram ETE 3 D. Os autores desvalorizaram relativamente a importância da anatomia da aorta ascendente e dos seios coronários, da proximidade das coronárias relativamente ao plano valvular, da quantidade e distribuição do cálcio aórtico e mitral e do diâmetro da câmara de saída do ventrículo esquerdo. De facto, não existem critérios inequívocos de exclusão. Porém, esta informação resulta relevante para os objetivos do trabalho, por poder excluir a implantação de pelo menos um dos tipos de válvulas, como os seios de Valsalva curtos ou a hipertrofia septal grave com gradientes intraventriculares.

As complicações vasculares *major* ocorrem em 4 a 20% dos casos e têm como principais preditores a relação entre o calibre dos introdutores e a artéria nativa, a calcificação dos vasos e a experiência dos operadores[29]. Sousa et al. analisam o calibre das femorais por angio-CT mas ignoram a importância – crítica – da calcificação, embora o centro reporte uma experiência nesta técnica de imagem mais completa[30]. Interessaria conhecer o equipamento, o tipo e a reprodutibilidade do protocolo, bem como outros dados em termos de quantidade e distribuição da calcificação – particularmente a circunferencial – e a avaliação em 3 D da anatomia aórtica e iliofemoral.

O mais importante é sabermos que temos soluções abrangentes em 98,6% dos doentes. Este trabalho evidencia que tal só é possível, por um lado, adotando uma estratégia multidispositivo, pois cada uma deles, isoladamente, não consegue tratar 2,8 a 6,2% dos casos. Por outro lado, a multiabordagem vascular acresce significativamente alternativas –que não existiam – em 5,2% dos casos.

Ressalve-se que o cenário «anatomicamente viável» está ligeiramente sobrevalorizado. Usualmente, na avaliação anatómica minuciosa realizada para planeamento, alguns doentes serão adicionalmente excluídos. Por exemplo, na abordagem femoral devido a tortuosidade vascular, ou na abordagem transapical pela associação do cálcio com uma distância diminuta às coronárias.

Na medida em que 98,6% dos casos foram realizados com um único tipo de prótese, nada se pode concluir da interligação destas variáveis anatómicas às implantações realizadas, designadamente do tipo de válvula e acesso efetivamente escolhidos. Seria interessante determinar as implicações prognósticas das variáveis analisadas na implantação e nos eventos adversos segundo as definições padrão propostas pelo *Valvular Academic Research Consortium*[29]. No sucesso do dispositivo, defi-

nido como o correto posicionamento de um dispositivo, com um gradiente anterógrado médio inferior a 20 mmHg, sem regurgitação moderada ou grave e, naturalmente, sem mortalidade[31]. E nos critérios de segurança precoce definidos aos 30 d, como a ausência de mortalidade, de qualquer acidente cerebrovascular, de uma hemorragia com risco de vida, de lesão renal aguda grau 2 ou mais (nefropatia de contraste), de oclusão coronária requerendo intervenção, de complicação vascular *major* e de disfunção protésica necessitando novo procedimento.

Em conclusão, o estudo de Sousa et al. é original porque evidencia que a anatomia não constitui um fator limitativo com as atuais válvulas aórticas percutâneas, desde que as equipas disponibilizem múltiplos dispositivos e abordagens vasculares. As condicionantes contemporâneas mais relevantes no tratamento da estenose aórtica são distintas e englobam o rastreio, o diagnóstico, a estratificação das comorbilidades, a orientação terapêutica multidisciplinar, as inovações tecnológicas e os custos. Cada uma delas é um desafio ao percurso a fazer até que porventura seja adequado tratar, também, indivíduos de risco intermédio ou baixo.

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POSITION STATEMENT

Position statement on transcatheter aortic valve implantation in Portugal☆

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KEYWORDS
Aortic stenosis;
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Working group

Abstract
Objective: To evaluate the clinical indications and guidelines for transcatheter aortic valve implantation (TAVI) and to propose adaptations for its use in Portugal.
Methods and Results: The working group analyzed the epidemiology of aortic stenosis and current clinical recommendations in the light of current evidence, taking into consideration their own experience in Portugal.

The evidence shows that TAVI significantly reduces mortality in patients with severe aortic stenosis considered unsuitable for surgery. This technique has a comparable safety profile, efficacy and quality of life improvement to conventional surgery in patients with high surgical risk, when carefully selected by multidisciplinary teams.

TAVI procedures should be performed within multidisciplinary programs in centers with on-site cardiac surgery by experienced teams treating no fewer than 50 cases per year in order to maintain proficiency.

The technique is little used in Portugal, with seven implantations/year per million population, a seventh of the European average and the lowest rate in Europe.

From a societal standpoint, it is important to evaluate clinical outcomes and analyze the incremental cost involved in order to define the situations in which the technique is appropriate and should be used.

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Conclusion: TAVI is the only treatment for severe aortic stenosis in patients unsuitable for surgery, and can also be applied in selected cases with high surgical risk.

Patients who are considered for this treatment should be evaluated in centers of excellence performing the technique and with a formal program of multidisciplinary team work. The first cases should be supervised until the team has established its routine. The program should perform the recommended minimum number of procedures per year in order to maintain proficiency and must keep a prospective clinical registry for monitoring purposes.
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PALAVRAS-CHAVE
Estenose aórtica;
Válvulas aórticas percutâneas transcatéter;
Recomendações;
Consenso;
Peritos;
Grupo de trabalho

Posição de consenso sobre válvulas aórticas percutâneas transcatéter em Portugal

Resumo
Objetivo: Avaliar as indicações e recomendações clínicas sobre a implantação de válvulas aórticas percutâneas (VAP) e propor adaptações para a sua aplicabilidade em Portugal.
Métodos e resultados: O grupo de trabalho analisou a epidemiologia da estenose aórtica, avaliou as recomendações clínicas existentes à luz da evidência científica conhecida e baseou-se na sua experiência em Portugal.

A evidência demonstra que as biopróteses valvulares percutâneas reduzem de forma muito significativa a mortalidade dos doentes com estenose aórtica grave considerados inoperáveis. Comparada com a cirurgia convencional, esta técnica apresenta um padrão comparável de segurança, de eficácia e de melhoria da qualidade de vida em doentes de elevado risco cirúrgico, devidamente selecionados por equipas multidisciplinares. Porém há preocupações relativamente à sua durabilidade e segurança a longo prazo.

De forma a ser proficiente, a implantação de válvulas aórticas percutâneas deve ser realizada no âmbito de programas multidisciplinares integrados desenvolvidos em centros médico-cirúrgicos com equipas experientes, em número não inferior a 50 casos por centro/ano.

Em Portugal observa-se uma utilização muito reduzida desta terapêutica, com sete implantes/ano por milhão de habitantes, o que corresponde a cerca de sete vezes menos do que a média europeia, constituindo a taxa mais baixa da mesma.

Para a sociedade, é necessário avaliar os resultados clínicos e estudar o custo incremental associado para definir quais as indicações em que esta técnica pode e deve ser selecionada.
Conclusão: A implantação transcatéter de válvulas aórticas percutâneas constitui a única terapêutica para doentes inoperáveis portadores de estenose aórtica grave. Em casos selecionados pode ser aplicada também em doentes considerados de alto risco cirúrgico.

Os doentes candidatos a este tratamento devem ser avaliados em centros de excelência que realizam estas técnicas e possuam um programa formal de funcionamento com uma equipa multidisciplinar. Esta deve ser assessorada nos primeiros casos, até estar rotinada. O programa deve assegurar o mínimo recomendado de casos anuais para manter a sua proficiência, elaborando um registo prospetivo monitorizável.
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Preamble

The prevalence of calcific aortic stenosis is growing due to the increase in degenerative valve disease, which affects 2.5% of people aged over 65; it is estimated that at least 32000 individuals in Portugal have the condition.[1]

The first-line treatment is surgical aortic valve replacement (SAVR).[2,3] Outcomes are adversely affected by the presence of certain comorbidities, and so transcatheter aortic valve implantation (TAVI) was developed for patients considered unsuitable for surgery.[4]

The 2012 guidelines published jointly by the European Society of Cardiology (ESC) and the European Association of Cardio-Thoracic Surgery (EACTS) assign a class I or IIa recommendation for TAVI according to clinical indications.[3]

National data for Portugal indicate an annual rate of TAVI of seven procedures per million population, a third of the rate in Spain and the UK and a seventh of the European Union average of 45 implantations.[5,6]

Current evidence on transcatheter aortic valve implantation and the situation in Portugal

The PARTNER trial, the only randomized study to date, reported a reduction in overall mortality in inoperable patients (cohort B) from 51% with optimal medical therapy to 31% with TAVI at one-year follow-up.[7]

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Table 1 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for the use of TAVI according to class of recommendation and level of evidence.[3]

ESC/EACTS recommendation	Class of recommendation	Level of evidence	Reference
TAVI should only be undertaken with a multidisciplinary 'heart team' including cardiologists and cardiac surgeons and other specialists if necessary.	I	C	
TAVI should only be performed in hospitals with cardiac surgery on-site.	I	C	
TAVI is indicated in patients with severe symptomatic aortic stenosis who are not suitable for SAVR and who are likely to gain improvement in their quality of life and to have a life expectancy of more than one year after consideration of their comorbidities.	I	B	7
TAVI should be considered in high-risk patients with severe symptomatic aortic stenosis who may still be suitable for surgery, but in whom TAVI is favored by a heart team based on the individual risk profile and anatomic suitability.	IIa	B	19

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Use of TAVI was further consolidated following publication of the second arm of the trial (cohort A), in which the percutaneous technique, via a transfemoral or transaortic approach, was compared with SAVR. Outcomes for TAVI tended to be better in terms of 30-day mortality (3.4% in the TAVI group vs. 6.5% in the SAVR group, p=0.07), but there was no significant difference in two-year mortality (33.9% TAVI vs. 35% SAVR),[8] both groups presenting significant functional improvement at two-year follow-up.[8,9]

Numerous registries have been published suggesting that the efficacy and safety of TAVI are generally good when performed outside of trials. Piazza et al.[14] published one of the first in 2008, reporting 30-day mortality of 8.0% and a combined major event rate – death, myocardial infarction and stroke – of 9.3%. Four years later, in the UK TAVI registry of 870 patients, 30-day mortality was 7.1%, but rose to 26.3% at two-year follow-up. The landmark FRANCE 2 registry, a mandatory official registry, with 3195 patients, covering all types of valve and approaches, including subclavian and transaortic, reports 30-day and one-year mortality of 9.7% and 24%, respectively.[10]

The only registry directly comparing TAVI with SAVR is an Italian one analyzing 618 patients that used three methods of statistical adjustment, including propensity scores. The annual major event rate based on the Valve Academic Research Consortium (VARC) criteria was 11.8%, with no significant differences between the two techniques in occurrence of death, stroke or myocardial infarction.[11]

The impact on quality of life has been the focus of much interest since the evidence consistently shows marked improvement from one month after TAVI.[9,12]

In general, the technique is used in patients who are judged inoperable or at high surgical risk due to older age, comorbidities, female gender, higher functional class, emergency operation, left ventricular dysfunction, pulmonary hypertension, coexisting coronary artery disease, or previous cardiac surgery, including for bioprosthetic valve failure.[3,13]

It should be stressed that implementation of TAVI programs has generally involved highly motivated teams with proctoring in the first 5–15 cases.[14]

Notwithstanding the good results obtained, certain aspects give rise to concern. Various periprocedural complications can require particular attention.[15,16] Periprosthetic regurgitation, mitral regurgitation and need for pacing appear to adversely affect long-term outcomes.[10,17–19] Medium-term non-cardiovascular mortality is high, reaching 59% in a study by Rodés-Cabau et al. of 339 patients followed for 42 months, which suggests that patient selection needs to be improved.[20]

SAVR can be a costly procedure in high-risk patients, with an additional cost of 2400 euros in hospital charges for each 1% increase in the Society of Thoracic Surgeons score,[21] but it is not known whether TAVI can reduce these costs. In the US, the additional cost of TAVI per life-year gained is around 40 000 euros compared with standard care in inoperable patients.[21,22] The PARTNER trial recently demonstrated that in 80% of cases the costs of SAVR and TAVI do not differ significantly at one year of follow-up.

It was against this background that the ESC/EACTS guidelines on the management of valvular heart disease were issued, which demonstrate the importance of this sophisticated and revolutionary technique in patients considered unsuitable for SAVR.[23]

Minimum technical conditions, clinical indications, additional costs, and outcome assessment

The Working Group recognizes the importance of TAVI programs being run by formally established multidisciplinary teams in centers of excellence with on-site cardiac surgery. Each team should include at least a cardiac surgeon, an interventional cardiologist, an anesthesiologist and a cardiologist experienced in echocardiography. The procedures should be performed in a hybrid operating room, a cardiac catheterization laboratory equipped as an operating room, or an operating room equipped with an imaging system of appropriate quality. Extracorporeal circulation should be available if required.

With regard to the clinical indications in the guidelines (Table 1), we should bear in mind the constraints of the International Monetary Fund financial bailout in Portugal and the publications suggesting that TAVI should only be performed in carefully selected patients in centers with

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a minimum annual volume of 50 procedures, in order to keep additional costs at an acceptable level and to maintain proficiency.[15]

It is therefore recommended that TAVI programs should preferentially treat inoperable patients with a class I recommendation.[3]

Patients with a class IIa recommendation should be considered for TAVI if:

- the risk-benefit ratio is favorable in terms of quality of life as assessed by the heart team;
- the center considers that the indication is compatible with the experience of the team and the predicted annual volume of procedures[15];
- the procedure is performed under the scope of investigational studies or registries.

The consensus is that the use of TAVI should be rigorously monitored, preferably through a national multicenter registry using the current VARC criteria to ensure quality and transparency.[24,25] It is recommended that all patients be followed for seven years and that nationwide studies be undertaken in Portugal to assess the costs of the technique.

The Working Group hopes that this document will be useful to health professionals, institutions, departments and decision-making bodies dealing with this important and rapidly developing treatment.

Conclusion

TAVI is the only effective treatment for patients with aortic stenosis who are considered unsuitable for surgery.

The technique should be performed in centers of excellence that have a formally established and trained multidisciplinary heart team, treat a minimum of 50 cases a year, have appropriate technical conditions, and keep a prospective registry for monitoring purposes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of interest

The authors have no conflict of interest to declare.

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CIRURGIA CARDIO-TORÁCICA

VÁLVULA AÓRTICA PERCUTÂNEA TRANSAPICAL: 5 ANOS DE EXPERIÊNCIA

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Trabalho galardoado com o Prémio Nacional Machado Macedo no decurso da XVª Reunião da Sociedade Portuguesa de Cirurgia Cardio-Torácica e Vascular, Santa Eulália, Algarve, Novembro de 2013

Resumo

Objectivos: A implantação de próteses valvulares transcatéter (VAP) por via transapical é uma terapêutica aceite para a estenose aórtica grave de alto risco para a cirurgia convencional. Reportam-se os resultados clínicos iniciais da técnica num centro de referência.

Métodos: Realizámos um estudo prospectivo longitudinal de centro único incluindo 54 doentes consecutivos (idade média 79±7,5 anos, 59% masculinos) submetidos, entre novembro 2008 e outubro 2013, a implantação de VAP Edwards Sapien por via transapical.

A indicação foi estenose aórtica nativa em 83% (gradiente médio=49±18,3mmHg e área=0,7cm^2), 11% doença aórtica e em 3 doentes próteses valvulares biológicas degeneradas, estando 65% em classe III/IV NYHA. As principais comorbidades eram doença coronária em 56% (status pós-cirurgia coronária em 37%), diabetes (37%), doença arterial periférica (31%) e insuficiência renal crónica (24%). O Euroscore logístico do grupo foi 19,8±11,2 e o Euroscore II 5,5%±3,5 com score STS mortalidade 5,1±3,7 e STS morbilidade 23,7±7,6.

Resultados: Análise seguindo os critérios VARC-2 (Valve Academic Research Consortium), com mortalidade aos 30 dias de 5,6%; EAM peri-procedimento 7,4%; acidente vascular cerebral incapacitante 1,9%; hemorragia grave 14,8%; complicações vasculares major 5,6%; implantação de pacemaker 11%. Utilizou-se circulação extra corporal não planeada em 5 casos e ocorreu disfunção protésica em 4 doentes (deslocamento de válvula em 2 casos). A mediana do internamento foi de 8,0 dias, com re-hospitalização em 12,2% dos casos. Os *endpoints* compostos VARC-2 foram: sucesso do dispositivo=90,7%; segurança precoce=75,9% e eficácia clínica após 30 dias=83,7%.

Conclusão: A abordagem transapical constituiu uma terapêutica eficaz para doentes de alto risco para a cirurgia convencional.

Summary

Transapical aortic valve replacement: A 5-years experience

Objectives: Transcatheter aortic valve replacement (TAVR) by transapical approach is accepted for severe aortic stenosis in patients with high risk for conventional surgical therapy. Herein is reported the initial clinical results of this technique in a reference center.

Methods: We conducted a longitudinal prospective single center study including 54 consecutive patients (mean age 79±7.5 years, 59% male) who underwent, between November 2008 and October 2013, TAVR with Edwards Sapien valves throught transapical approach.

The etiology was native aortic stenosis in 83% (mean gradient=49±18,3mmHg and area=0,7cm2), 11% aortic disease and 3 patients had degenerated biological valvular prostheses, being 65% in class III / IV NYHA. The major comorbidities were

coronary heart disease in 56% (status post-coronary surgery 37%), diabetes (37%), peripheral artery disease (31%) and chronic renal failure (24%). The logistic EuroSCORE was 19.8±11.2 and EuroSCORE II 5.5±3.5%, with STS mortality score 5.1±3.7 and 23.7±7.6 STS morbidity.

Results: Analysis following the VARC-2 criteria (Valve Academic Research Consortium), showed 30-day mortality of 5.6%; peri-procedural myocardial infarction 7.4%; disabling cerebral vascular accident 1.9%; severe haemorrhage 14.8%; major vascular complications 5.6%; pacemaker implantation 11%. Unplanned extracorporeal circulation was used in 5 cases and prosthetic dysfunction occurred in 4 patients (shift valve in 2 cases). The median hospital stay was 8.0 days, with re-hospitalization in 12.2% of cases. The composite VARC-2 endpoints were: device success=90.7%; early safety at 30 days =75.9% and clinical efficacy after 30 days=83.7%.

Conclusion: The transapical approach was found as an effective therapy for patients at high risk for conventional surgery.

INTRODUÇÃO

A implantação de prótese valvular aórtica transcatéter (TAVI) vulgarmente designada por válvula aórtica percutânea (VAP) é uma técnica que tem vindo a crescer internacionalmente nos últimos anos, oferecendo a doentes com estenose aórtica grave e alto risco cirúrgico ou com contraindicação para cirurgia convencional, uma opção terapêutica eficaz, com bom resultados clínicos comprovados.

Tem sido objecto de trabalho da ESC (European Society of Cardiology) e da EACTS (European Association for CardioThoracic Surgeons) e nomeadamente do consórcio VARC-2 (Valve Academic Research Consortium), definir critérios objectivos quer de seleção de doentes e quantificação das comorbilidades (Quadro 1 - comorbilidades), quer de padronização dos resultados obtidos de forma a serem possíveis estudos multicêntricos comparativos (Quadro 2 - *endpoints* VARC-2).

Todos estes esforços assentam na premissa da avaliação e decisão por uma equipa multidisciplinar (*Heart Team*), essencial para o sucesso do programa. Também em Portugal este consenso tem sido vinculado, de forma a ultrapassar os

Quadro 1 **Comorbilidades**[i]

Comorbilidades	Definição/Critério	Modalidade Diagnóstica
Aorta de porcelana ou aterosclerose severa	Calcificação marcada circunferencial ou placas ateromatosas graves de toda a aorta ascendente até ao arco, impossibilitando a clampagem da aorta	TAC sem contraste com avaliação segmentar ao nível: junção sino-tubular, aorta ascendente tubular, artéria inominada e todo o arco aórtico transverso
Fragilidade	Lentidão, fraqueza, exaustão, degradação e desnutrição, incapacidade e inatividade, dependência. Critérios: - tempo para percorrer 5 metros - força máxima do punho - IMC<20 e/ou perda >5Kg/ano - Albumina <3,5 g/dL - degradação cognitiva ou demência	História médica Exame físico Testes de performance física Avaliação cognitiva Testes laboratoriais
Doença hepática grave/ cirrose	Qualquer dos seguintes: - Child-Pugh classe C - Score MEDL ≥ 10 - Shunt porto-cava, espleno-renal ou transjugular intra-hepático - Cirrose documentada por biópsia com hipertensão portal ou disfunção hepatocelular	História médica Exame físico Testes laboratoriais Classificação de Child-Pugh Score MELD Biópsia hepática
Esterno adverso	Qualquer das seguintes ou outras razões que condicionem risco proibitivo para uma re-operação por esternotomia ou toracotomia anterior direita - deformação da parede torácica por cifoescoliose severa ou outra (como toracoplastia, doença de Pott) - complicações de cirurgia prévia - lesões de radioterapia (queimadura, destruição óssea, perda muscular, fibrose pulmonar ou estenose esofágica	História médica Exame físico Radiografia de tórax TAC tórax
Cirurgia coronária com artéria mamária interna ou outro conduto cruzando mediastino e/ou aderente a tábua interna do esterno	Doente com artéria mamária interna ou outro conduto aderente à tábua interna esternal, prevendo-se lesão na re-esternotomia. Pode ser considerada de alto risco nos seguintes casos: - os condutos são radiologicamente indistinguíveis da tábua interna do esterno - os condutos distinguem-se do esterno mas estão a 2-3mm da tábua interna	TAC axial ilustrando condutos a cruzar linha média de forma a ser possível medicação da distância ao esterno Angiografia com projeções laterais e/ou imagens de TAC 3D mostrando relação dos condutos e esterno
Hipertensão pulmonar severa **Disfunção ventricular direita severa**	Hipertensão primária ou secundária com pressão sistólica da Artéria pulmonar >2/3 da pressão sistémica Critério definido pelas recomendações (TAPSE<15mm, área tele-sistólica ventrículo direito>20cm^2, etc.)	Ecocardiografia, cateterização coração esquerdo e direito para documentar pressões da artéria pulmonar e sistémicas Documentar causas secundárias de hipertensão pulmonar

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Quadro 2 ***Endpoints* VARC-2**[ii]

Sucesso do dispositivo
Implantação de VAP segundo os critérios:
- Ausência de mortalidade
- Posicionamento apropriado de uma única válvula
- Funcionamento apropriado (gradiente médio < 20 mmHg e regurgitação < moderada)

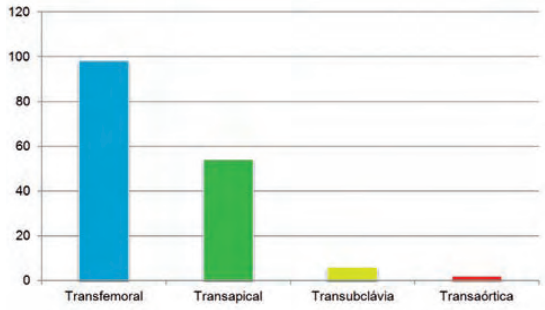
Segurança precoce
Incidência composta de eventos adversos major aos 30 dias:
- Mortalidade global
- Obstrução coronária requerendo ICP (EAM peri-operatório: novos sintomas isquémicos ou ECG + subida biomarcadores, preferível CK-MB x10)
- AVC qualquer tipo (sinais/sintomas e confirmação por neurologia ou imagiologia ou punção lombar)
- Lesão renal aguda grau 2-3 (AKIN) necessitando de técnica dialítica ou subida da creatinina ≥ 300% ou creatinina≥4,0mg/dL com subida 0,5mg/dL
- Hemorragia risco de vida (ou sequelas) ou hemorragia de órgão crítico (intracraneano, ocular, pericárdico com drenagem, síndrome Compartimental) ou choque hipovolémico com vasopressores ou necessitando cirurgia ou queda Hb≤5g/dL ou necessitando 4 ou mais transfusões
- Complicação vascular major
- Reintervenção por disfunção valvular

Eficácia (30 dias *ou mais*)
- Mortalidade de todas as causas
- AVC (qualquer, com ou sem sequelas)
- Rehospitalização por falência da terapêutica: por sintomas valvulares ou por insuficiência cardíaca
- Classe III ou IV NYHA
- Disfunção valvular protésica por válvula estenosada (gradiente médio ≥ 20 mmHg) e/ou regurgitação aórtica moderada ou grave

condicionantes inerentes à implantação de uma técnica nova (ver "Posição de Consenso").

Das vias de abordagem disponíveis, a via transfemoral é a mais frequente e atualmente na maioria dos centros a 1ª escolha, a via transapical normalmente é a 2ª escolha, sendo ainda possível a abordagem transubclávia e transaórtica. (Quadro 3)

O presente trabalho reporta os resultados clínicos, segundo os critérios do VARC-2, dos doentes sujeitos a implantação de válvulas aórticas percutâneas transapicais durante os primeiros 5 anos deste programa, no nosso centro.



Quadro 3 *Vias de abordagem: Experiência de 5 anos do nosso centro.*

MATERIAL E MÉTODOS

Realizámos um estudo prospectivo longitudinal de centro único (VCROSS - valvular and coronary revascularization at Hospital Santa Cruz) incluindo todos os doentes consecutivos que, entre novembro 2008 e outubro 2013, foram sujeitos a implantação de VAP por via transapical. Todos os doentes implantaram válvulas Edwards Sapien (n=21) ou Edwards Sapien XT (n=33).

Trataram-se 54 doentes com idade média 79±7,5 anos, 59% dos quais masculinos, e com IMC médio de 26±3,8 Kg.

Quanto à etiologia, 83% dos doentes apresentavam apenas estenose aórtica, 11% tinham doença aórtica e os restantes 3 doentes já tinham sido submetidos previamente a implantação de próteses valvulares aórticas biológicas, que se encontravam degeneradas.

Os critérios de inclusão incorporaram estenose aórtica grave sintomática com risco cirúrgico elevado (44,4%) ou inoperabilidade (53,7%) – admitidas como critérios as comorbilidades referidas no consenso VARC-2, nomeadamente os casos de aorta de porcelana, fragilidade, re-operação com artéria mamária interna sub-esternal, esterno adverso e insuficiência hepática (ver Tabela 1).

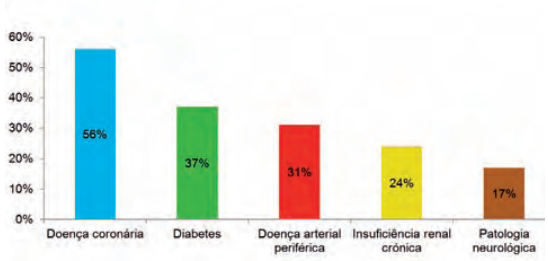
Tabela 1 **Comorbilidades englobadas nos critérios de seleção**

	n
Aorta de porcelana	7
Reoperação	12
CABG	9
Fragilidade	7
Radioterapia (esterno adverso)	5
Insuficiência hepática	2

Na apresentação clínica, o cansaço foi o sintoma predominante (78%), sendo que a classe funcional pré-operatória em 65% dos doentes era III/IV NYHA, seguida de 28% dos doentes em classe II/IV e 6% em classe IV/IV. O ritmo pré-operatório foi sinusal em 68% dos casos, mas 36% dos doentes apresentavam fibrilação auricular e 32% estavam sob anticoagulação oral.

No estudo ecocardiográfico, a média dos gradientes valvulares aórticos máximos era de 83±26,3mmHg e dos gradientes médios de 49±18,3mmHg, apresentando uma média de área valvular aórtica de 0,7cm2. A fração de ejeção era de 54,4±13,5%, sendo que em 11% dos doentes era inferior a 35%.

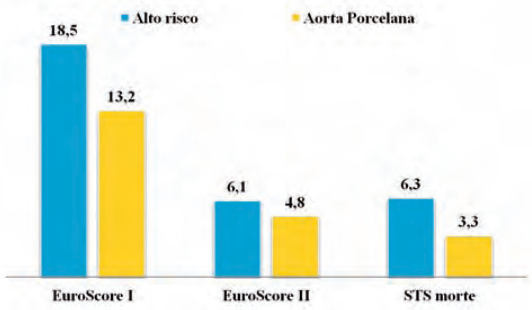
Apresentavam comorbilidades pré-operatórias 93% dos doentes, sendo as principais descritas no Quadro 2. De notar que 37% tinham sido previamente submetidos a cirurgia coronária e que 20% apresentavam história de neoplasia prévia.



Quadro 4 *Comorbilidades por percentagem de doentes.*

Analiticamente, a hemoglobina média pré-operatória era de 12,2±1,7 g/dL; do ponto de vista renal, os valores médios da ureia eram de 59±25 mg/dL e da creatinina de 1,4±1,4 mg/dL, apresentando uma *clearance* de creatinina de 50±26ml/min. A média do NT-proBNP era de 6354±8129 pg/mL , com uma mediana de 2500 pg/mL.

O cálculo médio do Euroscore logístico foi de 19,8±11,2% e Euroscore II 5,5±3,5% com STS score (Mortalidade) de 5,1±3,7% e 23,7±7,6 (Morbilidade). Salienta-se que nos doentes com contraindicação para cirurgia, nomeadamente os 7 casos com aorta de porcelana, os scores foram significativos mais baixos (Quadro 5).



Quadro 5 *Scores de risco.*

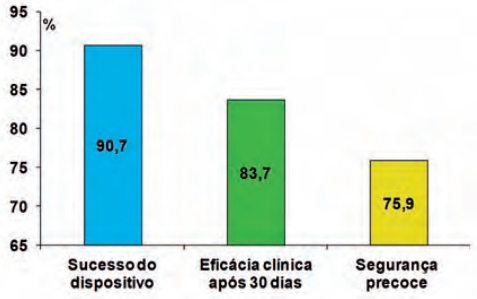
RESULTADOS

A mortalidade aos 30 dias foi de 5,6% (3 casos), todos de causa cardiovascular. A incidência de mortalidade a 1 ano situou-se nos 10,2%, e a 2 anos foi de 6,8%, demonstrando maior risco de mortalidade no 1º ano pós-procedimento.

A mediana da duração média de internamento foi de 8,0 dias, com uma média de 12,9±19,4 dias e com uma taxa de re-hospitalização aos 30 dias de 12,2%, predominantemente de causa respiratória. A média de seguimento foi de 529 dias.

Os *endpoints* compostos VARC-2 estão explícitos no Quadro 6.

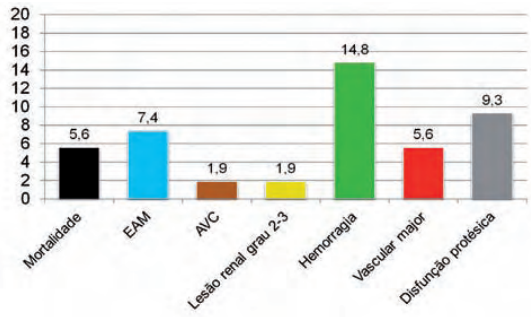
Ocorreu insucesso do dispositivo em 5 doentes: um



Quadro 6 *Endpoints compostos VARC-2.*

caso por óbito na indução anestésica com valvuloplastia aórtica emergente ineficaz; uma necessidade de reintervenção às 24h por cúspide valvular aórtica presa; um doente com insuficiência aórtica moderada intraprotésica e necessidade de revisão de hemostase; um doente com migração para o ventrículo esquerdo condicionando regurgitação mitral aguda por "*entrapment*" do folheto anterior pela VAP; e uma migração da prótese para a câmara de saída do VE com necessidade de reintervenção diferida e óbito ulterior.

A nível de segurança precoce do dispositivo, o valor de 75,9% engloba a ocorrência dos seguintes eventos VARC aos 30 dias (Quadro 7): EAM peri-procedimento (4 casos); 1 caso de acidente vascular cerebral com incapacidade; hemorragia grave em 8 casos; insuficiência renal AKIN 3 (1 caso); complicações vasculares major, 6 casos (11%) com implantação posterior de pacemaker. Em 5 destes casos foi necessária entrada em circulação extra corporal. Em 67% do total dos doentes houve necessidade de suporte transfusional, com mediana de uma transfusão de concentrado eritrocitário por doente.

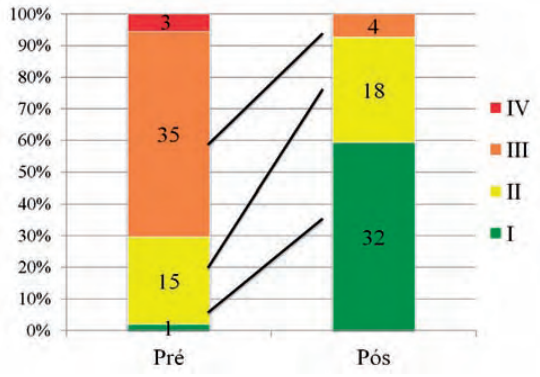


Quadro 7 *Eventos de segurança precoce VARC-2 a 30 dias (%).*

Quanto à eficácia clínica do dispositivo após 30 dias (83,7%), assistiu-se à seguinte evolução da classe funcional (Quadro 8).

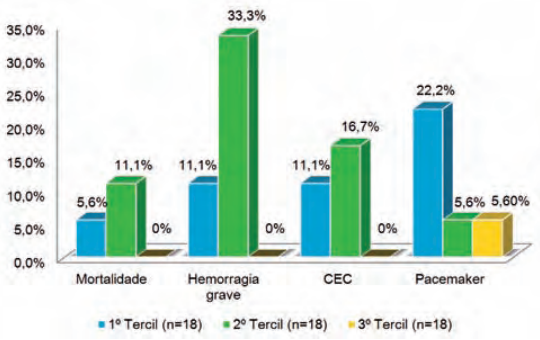
De modo a estudar a curva de aprendizagem optou-se por analisar alguns dos parâmetros já referidos por tercis

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Quadro 8 *Eficácia clínica VARC-2: Evolução de classe funcional NYHA.*

de grupos doentes (cada grupo com 18 doentes), conforme revela o Quadro 9, sendo evidente uma diminuição marcada no 3º tercil de todos os eventos.



Quadro 9 *Eventos por tercis de grupos de doentes.*

DISCUSSÃO

A nossa experiência com válvulas aórticas percutâneas evidencia uma curva de aprendizagem e a evolução desta técnica dando resposta a doentes com estenose aórtica, sem outras alternativas terapêuticas.

A via transapical tem constituído uma alternativa de primeira linha ao acesso transfemoral, excepto nos casos de ausência de acesso periférico, em que é a única escolha.

A análise do nosso programa segundo os critérios VARC-2 demonstrou excelentes resultados, pelo menos comparáveis com alguns dos principais estudos internacionais englobando os resultados das VAP, nomeadamente o PARTNER[3] e o FRANCE2[4].

É essencial uma seleção criteriosa dos doentes e da abordagem técnica mais apropriada para cada doente, através da interação de um *Heart Team* multidisciplinar, utilizando critérios padronizáveis que internacionalmente se têm vindo a definir.

A promoção de registos contínuos será essencial para promover a melhoria e a disseminação desta técnica.

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ORIGINAL ARTICLE

Late results (>10 years) of intracoronary beta brachytherapy for diffuse in-stent restenosis☆

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KEYWORDS
Beta radiation;
Brachytherapy;
Restenosis;
Coronary disease

Abstract
Introduction: Until the development of drug-eluting stents (DES), diffuse in-stent restenosis (ISR) was the main limitation of bare-metal stents in percutaneous coronary intervention (PCI). Among the different treatments available, intracoronary brachytherapy (BT) emerged as one of the most promising, although it was almost abandoned with the increasing use of DES.
Objective: To assess the Portuguese experience with $^{90}Sr/^{90}Y$ beta brachytherapy for the treatment of diffuse ISR regarding long-term (>10 years) major adverse cardiac events (MACE) and angiographic restenosis.
Methods: This single-center, retrospective, observational study included 12 consecutive patients treated between January and June 2001, mean age 58.6±9.9 years (range 43–77 years), 11 male. All had chronic stable angina, 75% had dyslipidemia, 58% had hypertension, 50% had peripheral arterial disease, 42% had diabetes and 50% had multivessel disease. Recurrent ISR was present in half of the patients and 11 had normal left ventricular function. After balloon dilatation, BT was performed using an $^{90}Sr/^{90}Y$ (Novoste Beta-Cath™) beta radiation source. All patients remained under dual antiplatelet therapy until scheduled nine-month follow-up angiography. Patients were followed for the occurrence of death (all-cause and cardiovascular), non-fatal myocardial infarction (MI), revascularization, stent thrombosis and angiographic restenosis. MACE were defined as the combined incidence of cardiac death, MI and urgent target vessel revascularization.
Results: In all cases there was both clinical and angiographic success. In a mean follow-up of 10.9±2.5 years, 19 events occurred in seven patients: death in three (25%), only one cardiac

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(8.3%); ST-elevation MI in one (related to a non-target vessel) (8.3%); and 15 revascularizations in five (42%), of which nine were of the target vessel (mainly in the first two years). There was only one case of probable stent thrombosis. Angiographic restenosis at nine months was 27% (three out of 11 patients), of which two were total occlusions. Ten-year MACE-free survival was 42% (5 patients).
Conclusions: Intracoronary beta brachytherapy for the treatment of diffuse ISR in this small cohort of patients proved to be safe and efficacious, with no late adverse events related to intracoronary radiation.
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PALAVRAS-CHAVE
Radiação beta;
Braquiterapia;
Restenose;
Doença coronária

Avaliação tardia (>10 anos) da braquiterapia intracoronária com radiação beta para reestenose difusa *intrastent*

Resumo
Introdução: No advento dos *stents* eluidores de fármaco (DES), a reestenose difusa (>20 mm) *intrastent* (RDIS) constituía a principal limitação ao uso de *stents* metálicos na intervenção coronária (PCI). Das várias soluções propostas para o seu tratamento, a braquiterapia intracoronária (BT) revelou-se uma das mais eficazes, sendo praticamente abandonada após a introdução dos DES.
Objetivo: Avaliar os resultados clínicos a longo prazo (>10 anos) do uso de BT beta com $^{90}Sr/Y^{90}$ para o tratamento RDIS, em termos de eventos cardíacos *major* (MACE) e reestenose angiográfica.
População e métodos: Estudo retrospetivo observacional de centro único incluindo 12 doentes (dts) consecutivos entre janeiro e julho de 2001, 11 homens, com a idade média de 58,6±9,9 anos (43-77 anos). Todos tinham angor estável. Os principais fatores de risco eram dislipidemia (75%), HTA (58%), doença arterial periférica (50%) e diabetes (42%). Havia doença multivaso em seis dts, tratava-se da 2.ª ou 3.ª reestenose em seis dts e a função ventricular era normal em 11. A BT foi feita após dilatação com balão, usando a fonte emissora de radiação beta $^{90}Sr/Y^{90}$ (Beta-Cath™/Novoste). Todos permaneceram sob dupla antiagregação pelo menos até à angiografia de controlo, programada para todos aos nove meses. Foi considerada a ocorrência de morte global e cardiovascular, enfarte do miocárdio não fatal (EAM), revascularização coronária, trombose de *stent* e reestenose angiográfica. Foi avaliada a incidência do evento hierárquico combinado (MACE) de: morte cardiovascular, EAM, revascularização coronária urgente do vaso alvo (TVRurg).
Resultados: Verificou-se sucesso angiográfico e clínico em 100% dos casos.
No seguimento médio de 10,9±2,5 anos, ocorreram 19 eventos em sete dts: morte em três dts (25%), apenas uma cardíaca (8,3%), EAM com elevação de ST (vaso não alvo) num dt (8,3%) e 15 novas revascularizações em cinco dts (42%): nove relacionadas com o vaso alvo (sobretudo nos primeiros dois anos). Apenas se verificou uma trombose de *stent*, provável. A reestenose angiográfica aos nove meses de seguimento foi de 27% (3/11 dts) com duas oclusões. A taxa de sobrevivência livre de MACE aos dez anos foi de 42% (cincodts).
Conclusões: A braquiterapia com radiação beta para RDIS, neste pequeno grupo de dts, demonstrou-se eficaz e segura, sem eventos tardios atribuíveis à radiação intracoronária.
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Introduction

Before the drug-eluting stent (DES) era, restenosis due to tissue proliferation in the neointima was the main limitation to wider use of bare-metal stents (BMS) in percutaneous coronary intervention (PCI). In their angiographic classification of in-stent restenosis (ISR), Mehran et al.[1] described diffuse ISR as having higher rates of recurrence and need for subsequent revascularization. Of the various methods used to control in-stent neointimal hypoplasia, intracoronary brachytherapy showed the strongest antiproliferative effect[2–6] and the best results, and its safety and efficacy were demonstrated in various randomized trials using gamma and beta radiation.[6–11] Following its approval by the US Food and Drug Administration in November 2000, the technique became established as an adjuvant to balloon angioplasty for the treatment of ISR and was incorporated into the guidelines on PCI.[12,13] However, the long-term

efficacy of brachytherapy has been questioned,[14] and there have been few studies with long-term follow-up after beta brachytherapy.[15–20]

The aim of the present study is to analyze the experience of the only Portuguese center using beta brachytherapy (in 2001) and to assess its late efficacy and safety in long-term follow-up (>10 years).

Methods

The study population consisted of 12 consecutive patients who underwent beta brachytherapy between January and July 2001 for diffuse ISR in BMS, defined as ≥50% stenosis and ≥20 mm in length.

Patients' mean age was 58.6±9.9 years (range 43–77 years), and 11 were male. The main cardiovascular risk factors were dyslipidemia in nine patients (75%), hypertension in seven (58%), and diabetes in five (42%). Six patients (50%) had concomitant peripheral arterial disease. All had chronic stable angina; four (33%) had previous myocardial infarction (MI) and three (25%) had previous coronary artery bypass grafting (CABG). There was multivessel disease in eight patients, and only one had left ventricular dysfunction. It was the first occurrence of ISR in six patients, the second in four, and the third in two. Only one case was proliferative ISR. All patients were under maximal tolerated medication with aspirin, statins, nitrates, beta-blockers, calcium channel blockers and angiotensin-converting enzyme inhibitors (Table 1).

Quantitative analysis of the coronary angiograms was performed with the CAAS II™ cardiovascular angiographic analysis system, using the diameter of the guiding catheter as a reference. The analysis included the reference vessel diameter, lesion length, degree of stenosis and minimal luminal diameter. Angiographic restenosis was defined as intraluminal ISR of ≥50%. The length of the lesions (40–90 mm) and the small diameter of the vessels treated (mean 2.5 mm) should be noted (Table 2).

Brachytherapy was performed using a $^{90}Sr/^{90}Y$ beta radiation source (Novoste Beta-Cath™). Beta radiation was chosen because, unlike gamma radiation, it did not require logistical changes to our catheterization laboratory. A protocol was established with the Francisco Gentil Portuguese Oncology Institute in Lisbon, including radiation therapists and medical physicists. All patients gave their informed consent and the treatment was approved by the ethics committee of Hospital de Santa Cruz.

All procedures were performed via femoral access using 8F guide catheters. Following control angiography and confirmation of ISR, the diagnostic catheter was replaced by the angioplasty guiding catheter and the lesion was crossed using a 0.014″ guidewire. The restenosed vessel was dilated with a balloon, the diameter and length of which were selected according to vessel diameter and lesion length. The 5F Beta-Cath™ delivery catheter has three lumens, one for the guidewire, one for delivery of the radiation source, and one to deliver saline solution. All catheters used were 40 mm in length. The catheter was advanced over the guidewire, radiation being applied from the distal to the proximal portion of the lesion, in all cases extending radiation coverage to the adjacent tissue without angiographically detectable disease. One or more applications were performed, depending on lesion length (one application in seven patients, two in three and three in two). Radiation dose and time varied in accordance with predefined tables for vessel and stent diameter (18.4 Gy for diameters ≥2.7 and <3.35 mm with radiation time 215 s and 23.0 Gy for diameters >3.35 and ≤4.00 mm with radiation time 268 s). When necessary, the lesions were redilated using the same balloon catheter. All maneuvers requiring handling of radiation (source, catheter and application) were performed by medical physicists and radiation therapists, while all other steps in the procedure were carried out by cardiologists. Quantitative analysis of angiograms was performed before, during and after the intervention. The initial heparin dose was 5000 U, with 2500 U being administered for each additional hour or according to activated coagulation time, which was monitored regularly. Prophylactic abciximab was administered in 11 of the 12 patients. Mean fluoroscopy time was 10.9±5 min (4.8–24.4) and mean procedural time was 50±16 min (33–79).

Angiographic success was defined as <50% final residual stenosis, and clinical success as angiographic success together with absence of clinical complications during hospital stay.

Table 1 Baseline characteristics of the study population.

Patients (n)	12
Age (years)	58.6±9.9
Male, n (%)	11 (92)
Risk factors	
Diabetes, n (%)	5 (42)
Dyslipidemia, n (%)	9 (75)
Hypertension, n (%)	7 (58)
PAD, n (%)	6 (50)
Smoking, n (%)	2 (17)
History	
MI, n (%)	4 (33)
CABG, n (%)	3 (25)
Clinical presentation	
Stable angina, n (%)	12 (100)
Positive ischemia test, n (%)	10 (83)
Multivessel disease, n (%)	8 (67)
Preserved LV function, n (%)	11 (92)
Indication for PCI	
First restenosis, n (%)	6 (50)
Second restenosis, n (%)	4 (33)
Third restenosis, n (%)	2 (17)
Medication before intervention	
Aspirin, n (%)	12 (100)
Statins, n (%)	9 (75)
Beta-blockers, n (%)	9 (75)
Calcium channel blockers, n (%)	9 (75)
ACE inhibitors, n (%)	7 (58)
Nitrates, n (%)	10 (83)

ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; LV: left ventricular; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention.

Table 2 Characteristics of the lesions treated.

Target vessel n (%)	
Anterior descending	4 (33)
Circumflex	2 (17)
Right coronary	6 (50)
Type of stent (total 20), n (%)	
ACS MULTI-LINK™ TETRA (Guidant/Advanced Cardiovascular Systems)	8 (40)
Bx Velocity™ (Cordis, Johnson & Johnson)	7 (35)
AVE GFX-2™ (Arterial Vascular Engineering)	2 (10)
AVE S670™ (Arterial Vascular Engineering)	1 (5)
NIROYAL™ (Medinol/Scimed Life Systems)	1 (5)
Bx Velocity™ heparin-coated stent (Cordis, Johnson & Johnson)	1 (5)
Quantitative analysis	
Mean reference vessel diameter (mm)	2.56±0.58
Mean minimal luminal diameter (mm)	1.0±0.12
Mean degree of stenosis (%)	64.4±16.9
Mean lesion length (mm)	55.9±19.5 (40–90 mm)

Patients' initial medication was continued, and dual antiplatelet therapy with aspirin and clopidogrel or ticlopidine was added. All patients have been followed regularly up to the present or until death, and control angiography was scheduled in all patients nine months after the intervention.

Following the recommendations of the Academic Research Consortium (ARC),[21] clinical follow-up considered cardiovascular and all-cause mortality, any MI, any new revascularization, angiographic restenosis, and stent thrombosis according to the ARC's new definition.[21] The incidence of major adverse cardiac events (MACE), defined as the combined incidence of cardiac death, MI and urgent target vessel revascularization (TVR), was also assessed.

Statistical analysis

Patients were analyzed according to continuous and categorical variables. Categorical variables were characterized in terms of absolute and relative frequencies. The central tendency and distribution of continuous variables were estimated by sample mean and standard deviation. Event-free survival was analyzed using Kaplan-Meier curves.

The statistical analysis was performed using SPSS version 19.0.0.2.

Results

In all cases there was both clinical and angiographic success. The degree of stenosis decreased from 64.4±16.9 to 25.9±10.3% and minimal luminal diameter increased from 1.0±0.12 to 2.18±0.32 mm. No clinical events were recorded during hospital stay.

At nine-month follow-up, only one patient still had angina; restenosis was detected and the patient subsequently underwent CABG.

Follow-up was achieved in all patients, for a mean of 10.9±2.5 years. During this period, 19 events occurred in seven patients (Tables 3 and 4). Three patients (25%) died, one from cancer at 90 months after the intervention, one at 132 months of sepsis (neither having suffered any cardiac event after brachytherapy), and one (8.3%) from sudden cardiac death at 43 months, a few days after undergoing PCI and implantation of two DES in a different vessel from that treated by brachytherapy.

Table 3 Outcomes.

Mean follow-up (years)	10.9±2.5
Patients with events	n (%)
MACE	2 (16.6)
Cardiac death	1 (8.3)
MI	1 (8.3)
Urgent TVR	0
All-cause death	3 (25)
TVR	5 (41.6)
Any revascularization	5 (41.6)
Definite stent thrombosis	1 (8.3)
Probable stent thrombosis	1 (8.3)
Possible stent thrombosis	0
Events related to the vessel treated by brachytherapy (n)	
Cardiac death	1
Angiographic restenosis at nine months[a]	3
Total TVR	10
Patients with at least one TVR	5
Total TVR by CABG	4

[a] Of the 12 patients treated, only 11 underwent scheduled nine-month control angiography. CABG: coronary artery bypass grafting; MACE: major adverse cardiac events; MI: myocardial infarction; TVR: target vessel revascularization.

At 120 months after brachytherapy, one patient (8.3%) suffered ST-segment elevation myocardial infarction (STEMI) due to stent thrombosis in a non-target vessel and underwent successful primary PCI.

Five patients (42%) underwent 15 revascularizations, at least one of the target vessel (a total of nine), mainly in the first two years, including four patients (33.3%) who underwent CABG.

Table 4 Description of events.

Patient no.	Clinical status at nine months	ISR	Revasc	Event Months FUP	Event Months FUP	Event Months FUP	Event Months FUP	Clinical status Months FUP
2	Asymptomatic	No						Died (cancer) 90 months
3	Asymptomatic	Yes (occlusion)		TVR (CABG) 23 months				Asymptomatic 149 months
5	Asymptomatic	No	NTVR	NTVR	TVR (CABG) 21 months	NTVR	NTVR	STEMI ST NTVR 120 months	Asymptomatic 145 months
7	Asymptomatic	Yes (occlusion)	TVR 9 months	TVR (DES) 13 months	TVR (DES) 19 months	TVR (CABG) 35 months			Asymptomatic 140 months
8	Asymptomatic	No	TVR 9 months	TVR (DES) 30 months	NTVR	MSC 43 months			Sudden cardiac death 43 months
9	Asymptomatic	Angiography not performed							Died (sepsis) 132 months
12	Angina	Yes		TVR (CABG) 14 months					Asymptomatic

CABG: coronary artery bypass grafting; DES: drug-eluting stent; FUP: follow-up; ISR: in-stent restenosis at nine months; NTVR: non-target vessel revascularization; Revasc: revascularization at nine months; ST: stent thrombosis; STEMI: ST-segment elevation myocardial infarction; TVR: target vessel revascularization.

The first TVR occurred on average 12±4.5 months after brachytherapy (9–21 months). Of the five patients who underwent TVR, in three cases this followed scheduled elective angiography that revealed restenosis of the target vessel, two of the patients being asymptomatic.

There was one definite stent thrombosis, in a non-target vessel (8.3%), 120 months after brachytherapy, in an individual who three months previously had undergone drug-eluting balloon angioplasty of a previously implanted DES. One patient (8.3%) had a probable stent thrombosis, identified after sudden cardiac death following revascularization of a non-target vessel 45 months after brachytherapy. No cases of possible stent thrombosis, or of definite or probable stent thrombosis in vessels treated by brachytherapy, were identified.

At 10-year follow-up, the incidence of MACE was 16.6% (two patients): one sudden cardiac death and one non-fatal STEMI. No patient required urgent TVR.

Control coronary angiography to screen for restenosis was performed on average 271.6±50.6 days after brachytherapy in the 11 patients who agreed to undergo the exam. The rate of angiographic restenosis in these patients was 27% (three patients); asymptomatic occlusion was detected in two cases (18%).

Cardiovascular event-free survival at 10 years was 42% (five patients) (Figure 1).

Discussion

This article presents the initial and long-term results of the single and limited experience of intracoronary brachytherapy for the treatment of diffuse BMS ISR in Portugal.

The small number of patients means that conclusions cannot be drawn concerning the value of brachytherapy compared to other techniques used at the time to treat ISR. However, the long follow-up affords an opportunity to increase our knowledge of the late effects of intracoronary radiation.

When brachytherapy was introduced in Portugal, the technique was the best option for treating ISR, which had been shown to be the main obstacle to wider use of BMS in certain situations, such as long lesions, recurrent restenosis and in diabetic patients. Various studies demonstrated its short-term safety and efficacy and advantages over pharmacological therapy, balloon dilatation, cutting balloon, rotational atherectomy, laser coronary angioplasty, and stent-in-stent.[2–11,22] Concerns about the technique focused on three problems: (1) 'geographic miss', by which radiation does not cover the distal and proximal ends of the stent, leading to restenosis; (2) stent thrombosis; and (3) late restenosis of the target vessel treated by brachytherapy, known as 'late catch-up'. In our experience, the first two problems were solved by using a 40-mm delivery catheter with a pullback technique, and by prescribing dual antiplatelet therapy (thienopyridines and aspirin) for all patients at least until the control angiogram. The long follow-up period may clarify the risk and extent of late restenosis and stent thrombosis in treated segments.

There were no immediate complications, either clinical or vessel-related, in any of the patients, and quantitative angiography showed excellent early results.

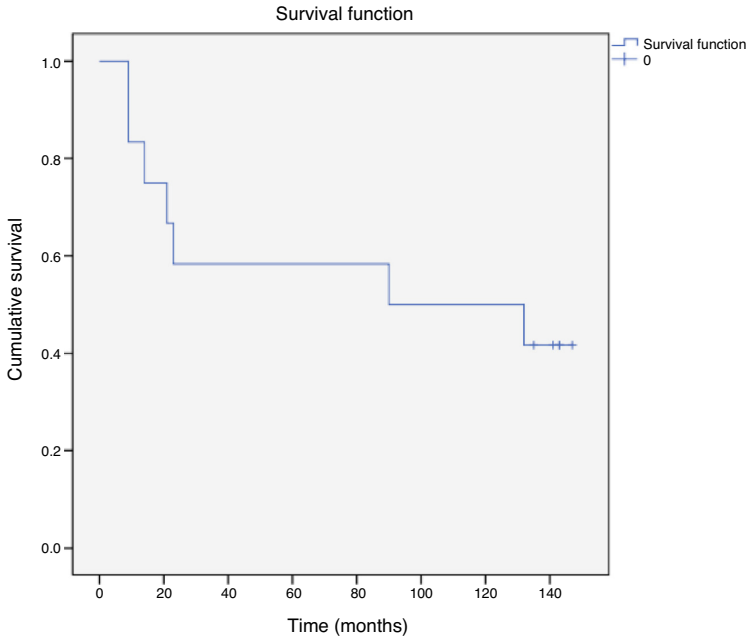


Figure 1 Survival free of first cardiovascular event (cardiac death, myocardial infarction or target vessel revascularization) (Kaplan-Meier curve).

The rate of restenosis on control angiography at nine months (27%) in our study is similar to that reported in the literature. In randomized trials of beta radiation for ISR, the mean restenosis rate at 6–9 months was 30% (26%–34%).[9–11] A surprising finding was two cases (18%) of occlusive target vessel restenosis, despite dual antiplatelet therapy, in patients who did not suffer acute coronary syndrome, and were in fact asymptomatic. In a review by Waksman et al.[23] of 473 patients treated by beta and gamma brachytherapy and who received only one month of dual antiplatelet therapy, late occlusion occurred in 9.1%, and only 7% of these were asymptomatic, while 43% had MI and 50% presented unstable angina. The possibility of late restenosis after brachytherapy for ISR has been demonstrated in studies with longer follow-up (up to five years), frequently necessitating late TVR.[16,17]

In our study, with a mean 10-year follow-up, the incidence of MACE was 16.6%. This figure is low considering the severity of the patients treated and the long follow-up period. In studies with follow-up of up to one year, the mean rate of MACE was 23% (15%–34%).[9–11] In the only published study with a 10-year follow-up (by the Thoraxcenter, Rotterdam[20]), in 124 patients treated by brachytherapy for ISR, death from any cause was 16% and death or non-fatal MI was 25%. The combination of all-cause death, any MI and any revascularization was observed in 70% of these patients, mainly new TVR (47%) between five months and two years of follow-up. Late catch-up following beta brachytherapy was mainly seen in unstented (de novo) lesions.

Despite concerns regarding increased incidence of acute coronary events following brachytherapy, only one patient (8.3%) in this long follow-up suffered acute coronary syndrome, a complication of previous PCI in another vessel. The only cardiac death was late, and occurred almost immediately after complex PCI in a non-target vessel. It can be fairly confidently assumed that these events cannot be attributed to brachytherapy.

In our center, 42% of the patients (n=5) required multiple (n=9) revascularizations of vessels treated by brachytherapy. This is a high proportion compared to the current efficacy of DES, as demonstrated by trials comparing the two approaches.[24–28] However, the complexity of our study population should be borne in mind: 50% with more than one previous restenosis of the treated segment, 67% with multivessel disease, 42% with diabetes and 50% with peripheral arterial disease.

The fact that control angiography was scheduled for nine months may have affected the rate of new TVR observed in our study. The phenomenon of 'oculostenotic reflex' has been recognized since the Benestent II study.[29] Of the five patients who underwent TVR, four had restenosis on angiography but no angina or positive ischemia test and thus the procedure was not ischemia-driven.

The demonstrated efficacy of DES in treating ISR has reduced the use of brachytherapy for this purpose. In a meta-analysis of randomized studies comparing first-generation DES (sirolimus and paclitaxel) with balloon angioplasty or brachytherapy for treatment of ISR, there was a 65% reduction in TVR and 64% reduction in angiographic restenosis with DES compared to balloon angioplasty or brachytherapy, with no difference in the incidence of death or MI, in a follow-up of 9–12 months.[24] In the TAXUS V ISR trial,[25] placlitaxel-eluting stents significantly reduced the need for ischemia-driven TVR compared to beta

brachytherapy (18.1% vs. 27.5%, p=0.03) in a two-year follow-up. The SISR trial[26] compared sirolimus-eluting stents and beta or gamma brachytherapy; at three years, the incidence of TVR was not significantly lower with DES (20.8% vs. 29.6%, p=0.073). At the five-year follow-up of the same study, TVR rates remained similar (24.7% with sirolimus-eluting stents vs. 31.2% with brachytherapy, p=0.179).[27] A more recent trial by Wiemer et al.[28] comparing beta brachytherapy and sirolimus-eluting stents in a three-year follow-up showed that the TVR rate with brachytherapy at six months (10.4%) (vs. 2.3% with stents, p=0.25) increased to 46.7% (vs. 11.6% with stents, p<0.0001) at three years.

One important point is that of the five patients who underwent TVR, this was by CABG in three, and these patients had no further target vessel-related events in the rest of follow-up. By contrast, the two patients implanted with DES both suffered clinical restenosis, one of whom underwent CABG and the other suffered sudden death following PCI of a non-target vessel. It should however be pointed out that there was no significant occlusive disease in the anterior descending artery in these two patients.

Brachytherapy has recently resurfaced as an option for the treatment of restenosis of DES, but it is rarely used.[30]

In conclusion, in our limited experience, intracoronary brachytherapy to treat diffuse restenosis of BMS is safe, with acceptable rates of angiographic restenosis at nine months and MACE at 10 years, bearing in mind the characteristics of the population treated. Although the number of TVRs was high, they were required in only five patients, while 41% of patients were event-free at the end of the follow-up period, confirming the long-term safety of the procedure.

Limitations

The authors acknowledge the following limitations to the present study:

(1) It was a retrospective, observational study in a single center, with a small patient sample.
(2) There was no control group, the results being interpreted by comparison with those in the literature.
(3) The patients included were a highly selected subgroup of considerable clinical and angiographic complexity followed over the course of 10 years, which should be borne in mind when interpreting the rate of clinical events recorded during follow-up.
(4) Since this was our center's initial experience with this technique, the results inevitably reflect the learning curve associated with any new procedure.
(5) Procedures performed 10 years ago may not reflect current practice, which will have been influenced by changes in therapeutic strategies, available devices, and the evidence base.
(6) The control angiography scheduled for all patients, irrespective of evidence of ischemia, may have overestimated the need for TVR.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Aortic valve replacement for severe aortic stenosis in octogenarians: Patient outcomes and comparison of operative risk scores

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KEYWORDS
Aortic valve surgery;
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Abstract
Introduction and Aim: Isolated aortic valve replacement (AVR) in octogenarians is associated with increased operative risk, due to higher prevalence of associated risk factors and other comorbidities, making outcome prediction essential. We sought to analyze operative mortality and morbidity and to compare the predictive accuracy of the logistic European System for Cardiac Operative Risk Evaluation score (EuroSCORE) I, EuroSCORE II and Society of Thoracic Surgeons (STS) score in this population.
Methods: We retrospectively enrolled 106 consecutive octogenarians with symptomatic severe aortic stenosis undergoing isolated AVR in a large-volume single center between January 2003 and December 2010 and calculated surgical risk scores.
Results: Mean logistic EuroSCORE I, EuroSCORE II and STS score were 14.6±11, 4.4±3.1 and 4.0±2.4%, respectively. Mean operative mortality was 5.7% (six patients). Two (1.9%) patients suffered an ischemic stroke, three (2.8%) required temporary hemodialysis and five (4.7%) had a permanent pacemaker implanted. Five (4.7%) required rethoracotomy. No myocardial infarction or sternal wound infection was observed. Calibration-in-the-large showed overestimation of operative mortality with logistic EuroSCORE I (p=0.036), whereas EuroSCORE II (p=1.0) and STS (p=1.0) showed good calibration. C-statistic values were 0.877 (95% CI 0.800–0.933) for logistic EuroSCORE I, 0.792 (95% CI 0.702–0.864) for EuroSCORE II and 0.702 (95% CI 0.605–0.787) for STS, without statistically significant differences.

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Conclusions: These results suggest that AVR can be performed safely in selected octogenarians. EuroSCORE II and STS demonstrated superior calibration and should be the preferred tools for risk assessment, at least for this population.
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PALAVRAS-CHAVE
Cirurgia valvular aórtica;
Estenose aórtica;
Octogenários;
Avaliação do risco;
EuroSCORE;
STS score

Cirurgia valvular aórtica em octogenários com estenose aórtica grave: resultados operatórios e comparação de *scores* de risco

Resumo
Introdução e objetivos: A cirurgia de substituição valvular aórtica (SVA) envolve um risco acrescido em octogenários, pela elevada prevalência de fatores de risco e comorbilidades, tornando essencial a predição de resultados. Pretendemos analisar a mortalidade operatória e comparar as capacidades preditivas do *European System for Cardiac Operative Mortality* (EuroSCORE) I, EuroSCORE II e o Society of Thoracic Surgeons (STS) *score* nesta população.
Métodos: Analisámos retrospetivamente 106 octogenários com estenose aórtica grave sintomática, submetidos a SVA isolada num centro terciário, entre janeiro de 2003 e dezembro de 2010.
Resultados: O EuroSCORE I logístico, o EuroSCORE II e o STS score médios foram 14,6±11, 4,4±3,1 e 4,0±2,4%, respetivamente. A mortalidade operatória foi 5,7% (seis doentes). Registámos como complicações dois (1,9%) acidentes vasculares cerebrais isquémicos, hemodiálise transitória em três doentes (2,8%) e cinco (4,7%) implantes de *pacemaker* definitivo. Cinco doentes (4,7%) requereram revisão da hemostase. Não se verificaram enfarte agudo do miocárdio ou infeção do esterno. O EuroSCORE I logístico sobreestimou a mortalidade (p=0,036), enquanto o EuroSCORE II (p=1,0) e o STS (p=1,0) *score* mostraram boa calibração. A area sob a curva foi de 0,877 (CI 95% 0,800-0,933) para o EuroSCORE I logístico, 0,792 (CI 95% 0,702-0,864) para o EuroSCORE II e 0,702 (CI 95% 0,605-0,787) para o STS score (p=ns para comparações).
Conclusões: Estes resultados sugerem que a SVA pode ser realizada com morbi-mortalidade aceitável em octogenários selecionados. O EuroSCORE II e o STS *score* demonstraram melhor calibração e devem ser as métricas preferidas na avaliação do risco operatório desta população.
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Introduction

Degenerative calcific aortic valve stenosis (AS) is the second most common valvular lesion in western countries, accounting for almost a third of native valve disease.[1,2] Due to its degenerative etiology, the number of affected individuals rises sharply with age, reaching around 8.1% at the age of 85.[3] The burden of AS is further heightened by increased longevity, meaning more elderly patients are expected to require therapeutic intervention in the future.[4,5] Once severe AS becomes symptomatic, the natural course of the disease leads to a poor short-term prognosis, with only 25% survival at three years if left untreated.[3,4] In the light of these findings, aortic valve replacement (AVR) is currently the recommended treatment (class I, level of evidence B) for severe symptomatic AS, in both European and American guidelines.[6,7]

Currently, surgical AVR and, more recently, transcatheter aortic valve implantation (TAVI) are the only treatment options that have an impact on survival.[6,8] A larger body of experience supports AVR as the reference treatment, with TAVI being reserved for patients unsuitable for AVR due to a high risk profile or inoperability.[8] However, the precise operative risk cutoff figure above which AVR surgery should be withheld in a particular patient (for which age is often used as a surrogate) remains a matter of ongoing debate. Hence, there is a need to describe contemporary outcomes of conventional AVR as the population ages and transcatheter options become available. In recent decades, cardiac surgery has been performed with increased safety. Several series have consistently reported progressively lower operative mortality, ranging from 3.9% to 9%, in octogenarians undergoing AVR.[9–16] Medium- and long-term survival after AVR surgery has also improved, paralleling age-matched healthy individuals.[9,17]

In this regard, operative mortality scores can play a role in improving the identification of the subset of elderly patients who could be candidates for conventional surgery. The 2003 logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I has gained widespread popularity as a screening tool.[18] However, it has shown a tendency to overestimate mortality in contemporary surgical series

of elective AVR patients.[19] To overcome this limitation, an updated version (EuroSCORE II) was built that further refined the model variables, which could ultimately translate into better calibration and discriminative power.[20] Overseas, the American counterpart of EuroSCORE II, the Society of Thoracic Surgeons (STS) score, has also been validated in a large cohort of patients and may be used as an alternative.[21] However, controversy remains about the predictive accuracy of these scores in the elderly and their relative performance. We sought to assess the operative mortality of octogenarians undergoing isolated AVR and to compare the performance of the new EuroSCORE II against logistic EuroSCORE I and the STS score in predicting mortality outcomes in this population.

Methods

Between June 2003 and November 2010, 106 consecutive octogenarians with symptomatic severe AS underwent isolated AVR as their first surgical cardiac intervention in a high-volume center and were included in this study. Aortic valve disease severity was graded according to the European Society of Cardiology (ESC) guidelines on valvular heart disease.[6] All patients underwent comprehensive transthoracic Doppler echocardiographic assessment at the institution's core laboratory.

Significant obstructive coronary artery disease requiring concomitant coronary artery bypass grafting (CABG) was excluded by coronary angiography. Patients with associated valvular lesions requiring intervention were also excluded from the study. All operations were performed using a standard approach, with a median sternotomy, the application of extracorporeal circulation and cold blood cardioplegia. Choice of type and size of valve prosthesis was left to the surgeon's discretion.

Operative mortality was defined as death occurring within 30 days of surgery or during the index admission. Logistic EuroSCORE I, II and STS score were computed using the respective online calculators, from data retrospectively retrieved from patients' medical records. Since data on 'poor mobility' were missing for a substantial proportion of patients, EuroSCORE II was calculated without this variable; an analysis by Barili et al. showed that omitting this variable did not reduce the discriminative accuracy of EuroSCORE II.[18] Post-operative complications were defined as myocardial infarction (MI), stroke, need for hemodialysis, atrioventricular block requiring permanent pacemaker implantation, sternal wound infection and redo thoracotomy for bleeding. Variable and outcome data were collected retrospectively from patients' medical records.

Continuous variables are reported as mean ± standard deviation or median (interquartile range [IQR]). Categorical variables are reported as proportions (%). Due to the small population size, calibration-in-the-large was performed using the chi-square test (two-sided), with a significant p-value indicating reduced calibration. The discriminative power of each score was assessed using receiver operating characteristic (ROC) curve analysis and C-statistics for a 95% confidence level. A value of 0.5 signifies absence of discriminative power, while a value of 1 signifies a perfect result. ROC curves were compared using the method proposed by DeLong et al., in which a non-significant p means equal discriminative power (95% confidence level).[22] Statistical Package for the Social Sciences™ version 21.0 (IBM SPSS Modeler, Chicago, IL) and Medcalc™ version 6.0 (MedCalc Software, Ostend, Belgium) were used for data processing and statistical analysis.

Results

Preoperative variables

Patients' mean age was 83.0±2.1 years and 39 (36.8%) were male (Table 1). The surgical procedure was performed electively in 96 patients (90.1%) and as an urgent intervention in the other 10 (9.9%). Twenty-four patients (22.6%) had left ventricular ejection fraction (LVEF) <50%, 37 (34.9%) were in NYHA class III or IV, 39 (36.8%) had angina, 16 (15.1%) had extracardiac arteriopathy and 18 (17.0%) presented creatinine clearance <30 ml/min/m^2.

Perioperative variables

A bioprosthetic valve was implanted in all patients (Table 2); Mitroflow™ was the most widely used model (66%). The most used ring size was 21 mm, with a median of 21 (19 mm: 14 cases; 21 mm: 49 cases; 23 mm: 40 cases; 25 mm: 3 cases).

Median mechanical ventilation time was 10 h (IQR 8–14 h), median intensive care unit stay was 24 h (IQR 14–60 h) and median hospital stay was 9 days (IQR 9–12 days).

Operative mortality, surgical risk scores and post-operative complications

Operative mortality occurred in six patients (5.7%). Causes of death were heart failure in three cases (pump failure in two patients, patient-prosthesis mismatch in one), suspected aortic rupture in one, sepsis in one and pneumonia in one.

Mean logistic EuroSCORE I, EuroSCORE II and STS score were 14.6±11%, 4.4±3.1% and 4.0±2.4%, respectively (Table 3 and Figure 1). Calibration-in-the-large showed

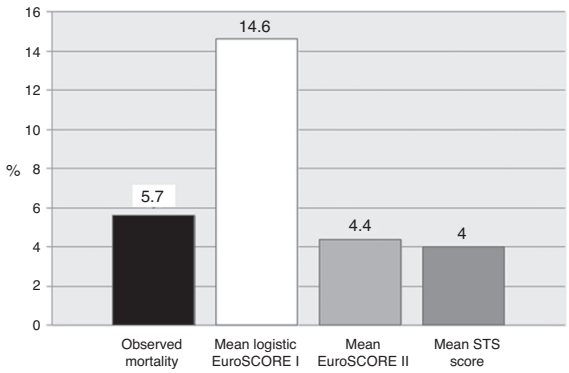


Figure 1 Operative risk score calibration-in-the-large.

Table 1 Pre-operative variables.

Age (years)	83.1±2.2
Male (%)	39
Height (m)	1.59±0.1
Weight (kg)	67.4±13
BMI (kg/m²)	26.5±4.4
Smoking (current or past) (%)	11
Hypertension (%)	81
Diabetes (%)	20
Dyslipidemia	68
Previous MI	10
Previous PCI	8
Previous cardiac surgery	2
Creatinine clearance (ml/min/m²)	
≥60	28
30–59	60
<30	18
LVEF	
Normal	86
30–45%	18
<30%	3
PASP ≥55 mmHg	6
NYHA class	
I	27
II	43
III	31
IV	6
Angina	39
CCS class IV angina	0
Chronic pulmonary disease	8
Extracardiac arteriopathy	16
Neurological dysfunction	4
AVR timing	
Elective	96
Urgent	10
Emergent or salvage	0
Active endocarditis	1
Cardiogenic shock	0
Intra-aortic balloon pump	0

AVR: aortic valve replacement; BMI: body mass index; CCS: Canadian Cardiovascular Society; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PASP: pulmonary artery systolic pressure; PCI: percutaneous coronary intervention.

overestimation of operative mortality with logistic EuroSCORE I (14.6 vs. 5.6%, p=0.036), whereas EuroSCORE II (4.4 vs. 5.6%, p=1.0) and STS score (4.0 vs. 5.7%, p=1.0) exhibited similar mean values, closer to the observed mortality.

ROC curve analysis (Figure 2) yielded significant C-statistic values of 0.877 (95% CI 0.800–0.933) for logistic EuroSCORE I, 0.792 (95% CI 0.702–0.864) for EuroSCORE II and 0.702 (95% CI 0.605–0.787) for STS score. Comparison of ROC curves using the DeLong method was not significant for differences in discriminative power (Table 3).

Table 2 Operative variables.

Type of prosthetic valve implanted	
Biologic	106
Carpentier-Edwards Perimount™ (%)	9
Carpentier-Edwards Perimount Magna™ (%)	2
Mitroflow™ (%)	70
Mosaic Ultra™ (%)	9
St. Jude Epic™ (%)	14
St. Jude Trifecta™ (%)	2
Prosthesis ring size (median, mm)	21
Duration of ICU stay (median, h)	24
Hospital stay (median, days)	9

ICU: intensive care unit.

Non-fatal complications occurred in fifteen patients (14.2%). Two (1.9%) suffered an ischemic stroke (one with full recovery, one with mild residual hemiparesis), three (2.8%) required temporary hemodialysis and five (4.7%) had a permanent pacemaker implanted due to complete atrioventricular block. No MI or sternal wound infection was observed. Five (4.7%) patients required repeat thoracotomy due to hemodynamic instability or suspected ongoing blood loss.

Discussion

The present study aimed to assess up-to-date figures concerning operative mortality for isolated AVR in the geriatric population and to compare the performance of three commonly used risk calculation tools to predict operative outcomes.

Operative results

In this series of octogenarians undergoing isolated AVR for severe symptomatic AS in a single center, operative mortality was 5.6%. In a population generally regarded as high-risk, we consider this figure acceptable.

Elayda et al. published one of the first surgical series, reporting a mortality of 5.3% in 77 patients aged 80 or over undergoing AVR, between 1975 and 1991.[23] The authors found LVEF <45% to be an independent predictor of mortality, together with hypertension and associated CABG. Since then, the number of published surgical series and observational studies has increased modestly, but not without some discrepancies (Table 4). Gehlot et al. described an operative mortality of 13% in 322 octogenarians, of whom 43% had concomitant CABG and 56% were urgent or emergent procedures, both of them independent predictors of operative mortality.[14] The presence of coronary artery disease requiring CABG and clinical instability are two recognized factors that can contribute to increased operative mortality, by 2- and 4–13-fold, respectively.[24] Taken together, these two studies seem to suggest a lower risk associated with isolated elective AVR surgery in octogenarians. However, two other surgical series show higher than average mortality rates. Bloomstein et al. reported mortality of 16.7% in 180 septuagenarians and octogenarians undergoing isolated AVR surgery. In this series, a valve size of 19 mm

Table 3 Operative risk score analysis.

	Mean ± SD	Minimum	Maximum	Calibration-in-the-large	C-statistic	p
Logistic EuroSCORE I	14.6 ± 11	5.8	64.3	p=0.036	0.877 (95% CI: 0.800–0.933)	0.001
EuroSCORE II	4.4 ± 3.1	1.5	17.0	p=1.0	0.792 (95% CI: 0.702–0.864)	0.009
STS score	4.0 ± 2.4	2.3	17.6	p=1.0	0.702 (95% CI: 0.605–0.787)	0.090

CI: confidence interval; SD: standard deviation; STS: Society of Thoracic Surgeons.

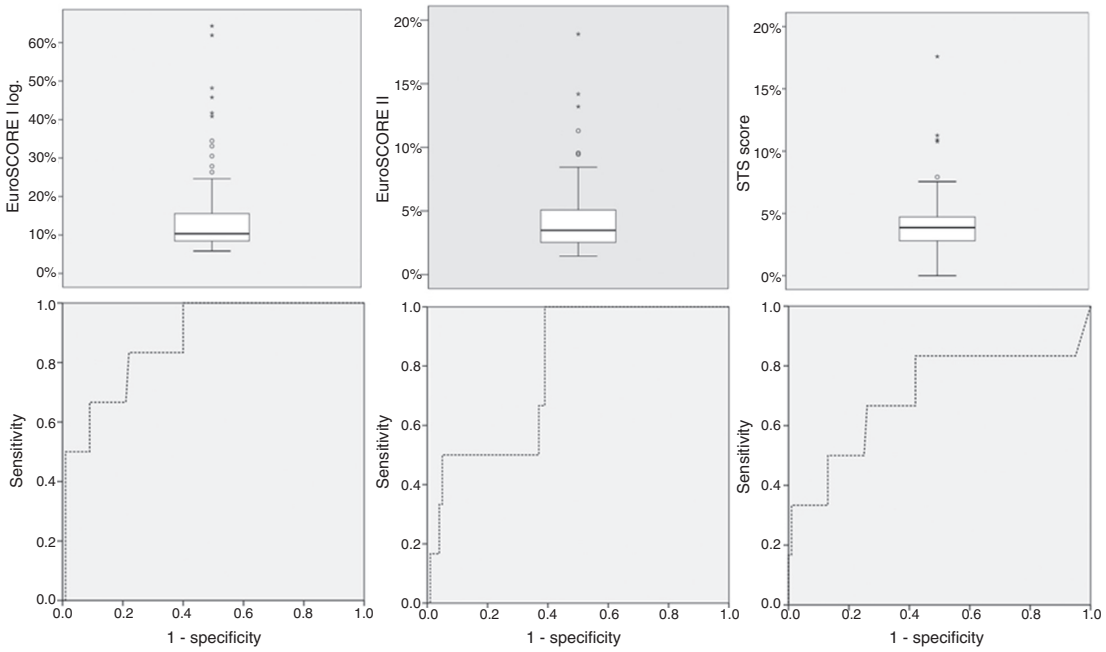


Figure 2 Distribution and receiver operating characteristic curves for logistic EuroSCORE I (a), EuroSCORE II (b) and STS score (c).

Table 4 Examples of literature series of surgical AVR in elderly patients.

Author	Year	Mean age	No. of patients	Operative mortality (%)	Comments
Elayda et al.[23]	1993	82.6	77	5.7	27% mortality with additional surgical procedures
Gehlot et al.[14]	1996	82.7	322	13.0	56% urgent or emergent procedures, 43% concomitant CABG
Bloomstein et al.[25]	2001	76	180	16.7	23.8% mortality with body surface area <1.8 m^2
Mistiaen et al.[35]	2001	73	400	3.8	Previous CABG did not influence mortality
Kohl et al.[9]	2007	82.8	162	9.0	32% mortality for urgent procedures
Leontyev et al.[26]	2009	82.7	282	10.8	EuroSCORE I imprecise for perioperative mortality discrimination
Ferrari et al.[36]	2010	82.2	124	5.6	Very similar results to present study
Litmathe et al.[10]	2011	82.7	304	5.8	50% mechanical valves
Dell'Amore et al.[11]	2012	82.0	188	4.3	No mortality difference between AVR and AVR+CABG patients
Di Eusanio et al.[12]	2012	82.1	638	4.5	One of the largest literature series
Saxena et al.[15]	2012	83.4	531	4.0	One of the lowest mortality results
Total		81.1[a]	3208	6.8[a]	

AVR: aortic valve replacement; CABG: coronary artery bypass grafting.
[a] Mean value.

was associated with significantly increased mortality (26.1% in 66 patients with 19 mm valve vs. 20% in 55 patients with 21 mm valve vs. 23% in 64 patients with 23–29 mm valve, p=0.017). Moreover, there was a strong correlation between small body surface area, small valve size, and female gender.[25] In a series by Leontyev et al., operative mortality was also distinctly higher (10.8%) than in other studies. These authors included patients with low (logistic EuroSCORE I $\leq$10%), intermediate (10–20%) and high ($\geq$20%) operative risk. However, in the 102 low-risk patients, operative mortality was 7.2%.[26] More recently, Di Eusanio et al. reported 4.5% operative mortality in a large regional series of 638 octogenarians undergoing isolated AVR surgery, with a mean logistic EuroSCORE I of 13.0%$\pm$7.9, very similar to our results.[12] In another large series, Saxena et al. reported a 4.0% 30-day mortality rate in 531 octogenarians undergoing isolated AVR surgery. Although no formal surgical risk score calculation was mentioned, precluding a more accurate comparison, these results are also in agreement with the present series.[15]

Understandably, naturally diminished global physiological and organ reserve makes this population more vulnerable to operative complications. Nevertheless, in the present series we observed a low rate of complications in isolated AVR, similar to those reported in the recent series by Di Eusanio et al. (1.3% for stroke, 0.3% for MI, 4.4% for complete atrioventricular block and 3.7% for redo thoracotomy).[12]

Comparison of operative risk scores

All scores showed good discriminative power in our series, but the logistic EuroSCORE I overestimated mortality by almost three times the observed value. Previous studies have demonstrated a systematic exaggeration of operative mortality by a factor of two to three.[19,20,27–30] As EuroSCORE was originally devised in 1995, a large part of this discrepancy can probably be attributed to natural improvements in surgical techniques and post-operative patient management, and changes in population case mix and outcomes in recent years.[12,31] By contrast, both EuroSCORE II and STS score showed excellent calibration.

Nevertheless, the logistic EuroSCORE I showed good discriminative power, which was not statistically different from EuroSCORE II or STS score, so ultimately no particular score was favored. Barili et al. also found this lack of added value when using ROC curves to compare the two versions of EuroSCORE in general cardiac surgery.[18] In another study by the same authors, the STS score showed a slightly higher C-statistic, but again without statistically significant difference.[29]

Still, theoretical and methodological concerns have been voiced regarding calibration of EuroSCORE II, particularly regarding the validity of the Hosmer-Lemeshow test for this purpose. Barili et al. set out to answer such concerns in a recent study including more than 12 000 patients undergoing cardiac surgery.[18] The authors employed four different methods to assess calibration (including the use of calibration curves) and demonstrated that EuroSCORE II has an optimal calibration performance until 30% actual mortality, beyond which it progressively overestimates mortality. On the basis of these findings, EuroSCORE II could be considered an appropriate tool to assess operative risk in the general octogenarian population, including our study cohort. However, in a truly high-risk population, such lack of calibration can be crucial, particularly when considering transcatheter therapy.

Our findings appear to suggest that EuroSCORE II should be the preferred tool for estimation of operative risk mortality in octogenarians undergoing isolated AVR surgery. The STS score, although equally well calibrated, has the potential disadvantages of being derived from an American cohort and being more cumbersome and time-consuming due to a larger set of variables.

More than a decade after the introduction of TAVI for the treatment of severe AS, should age be a decisive factor in the decision whether to deny AVR surgery? Naturally, age per se, or as a surrogate of an increased prevalence of operative risk factors, is always present in all risk scores. An analysis by Iung et al. showed that low LVEF and greater age were significantly associated with the decision to deny surgery to 72 out of 216 patients with severe AS aged $\geq$75.[32] Neurological dysfunction was the only comorbidity significantly linked with the decision not to operate, which seems to suggest that age itself, rather than associated comorbidities, is used as a true criterion more than a surrogate marker to assess a patient's pre-operative physiological status. Still, issues related to quality of life in the very old, which are inherently subjective and difficult to evaluate, should also be considered when deciding on the potential benefit of AVR.

Our patient cohort, although limited in size and inevitably suffering the limitations and biases of a single-center analysis, contributes to the growing evidence that isolated AVR surgery can indeed be performed with acceptable results in selected octogenarians. Furthermore, current age boundaries are progressively being challenged. Yerebakan et al. reported 7.6% overall operative mortality in a cohort of 119 nonagenarian patients, of whom 66 underwent isolated AVR.[33]

Proper patient selection has a decisive role in achieving good operative results. A number of conditions such as LVEF <30%, severe renal failure, severe lung disease, emergent surgery and simultaneous CABG have been identified as markers of poor outcome. Each of these variables, when added to age as the sole variable contributing to increased operative risk, may advise against AVR, not only because of the expected high operative mortality but also due to the reduced long-term benefit of the intervention.[6,24]

In an increasingly aging population, the number of patients who need a therapeutic intervention will continue to grow. From these results, and given the advent of TAVI and the data from the PARTNER trial, the question arises of what is the best treatment option.[8,34] The answer can be found by an objective assessment of each case, and for the most difficult and doubtful cases, a multidisciplinary evaluation by the ''heart team'' would be desirable to find the best option for the patient. In this regard, the development of a new, integrated score, perhaps including variables such as frailty, could help to define the best treatment strategy for each individual case, similar to what the SYNTAX II score did for revascularization in coronary artery disease. Further studies are needed to confirm the feasibility of this strategy.

Conclusions

This study adds to the evidence gathered so far on the safety of isolated AVR in elderly patients, in both morbidity and mortality outcomes. However, further studies are needed to better assess the applicability of these results to patients at increased risk.

EuroSCORE II and the STS score should be the preferred operative risk assessment instruments, offering an important contribution to contemporary clinical decision-making in selected octogenarians with severe symptomatic AS.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ARTIGO ORIGINAL

Evolução da intervenção coronária percutânea entre 2004-2013. Atividade em Portugal segundo o Registo Nacional de Cardiologia de Intervenção

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PALAVRAS-CHAVE
Registo;
Cardiologia de intervenção;
Coronariografia;
Angioplastia coronária;
Stent;
Radial

Resumo
Introdução e objetivos: Foi nosso objetivo estudar as tendências da intervenção coronária percutânea entre 2004-2013 e comparar Portugal com outros países europeus.
Métodos: Análise dos procedimentos coronários efetuados entre 2004-2013 com base num registo prospetivo, multicêntrico, voluntário, doente a doente – Registo Nacional de Cardiologia de Intervenção (RNCI) da Associação Portuguesa de Intervenção Cardiovascular da Sociedade Portuguesa de Cardiologia (APIC-SPC) – e dos dados oficiais publicados pela Direção Geral de Saúde (DGS).
Resultados: Em 2013 realizaram-se 36 810 cateterismos diagnósticos (3529 coronariografias por milhão de habitantes), representando um aumento significativo de 34% relativamente ao ano de 2007 ($p < 0,001$). As intervenções coronárias percutâneas (ICP) cresceram 64% desde 2004, atingindo um total de 13 897 procedimentos e uma taxa de 1333 por milhão de habitantes no ano de 2013 ($p < 0,001$). A angioplastia primária (ICP-P) cresceu 265% (1328 *versus* 3524) atingindo uma taxa de 338/milhão, o que representou 25% do total de angioplastias efectuadas em 2013. Os *stents* foram o dispositivo intracoronário mais utilizado, com uma taxa de *stents* eluidores de fármaco de 73% em 2013. O acesso radial passou de 4,1% em 2004 para 57,9% em 2013 ($p < 0,001$).
Conclusões: A cardiologia de intervenção mantém uma tendência de crescimento desde 2004 a 2013. Neste ano, a totalidade dos centros de cardiologia de intervenção portugueses estavam a exportar os dados para o RNCI, destacando-se o aumento relativo da angioplastia primária e o incremento do acesso radial.
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KEYWORDS
Registry;
Interventional cardiology;
Coronary angiography;
Angioplasty;
Stent;
Radial

Trends in percutaneous coronary intervention from 2004 to 2013 according to the Portuguese National Registry of Interventional Cardiology

Abstract
Introduction and Objectives: The aim of the present paper is to report trends in Portuguese interventional cardiology from 2004 to 2013 and to compare them with other European countries.
Methods: Based on the Portuguese National Registry of Interventional Cardiology and on official data from the Directorate-General of Health, we give an overview of developments in coronary interventions from 2004 to 2013.
Results: In 2013, 36 810 diagnostic catheterization procedures were performed, representing an increase of 34% compared to 2007 and a rate of 3529 coronary angiograms per million population. Coronary interventions increased by 65% in the decade from 2004 to 2013, with a total of 13 897 procedures and a rate of 1333 coronary interventions per million population in 2013. Primary percutaneous coronary intervention (PCI) increased by 265% from 2004 to 2013 (1328 vs. 3524), an adjusted rate of 338 primary PCIs per million, representing 25% of total angioplasties. Stents were the most frequently used devices, drug-eluting stents being used in 73% in 2013. Radial access increased from 4.1% in 2004 to 57.9% in 2013.
Conclusion: Interventional cardiology in Portugal has been expanding since 2004. We would emphasize the fact that in 2013 all Portuguese interventional cardiology centers were participating in the National Registry of Interventional Cardiology, as well as the growth in primary PCI and increased use of radial access.
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Introdução

A Sociedade Portuguesa de Cardiologia (SPC) implementou em 2002 um Registo Nacional de Cardiologia de Intervenção (RNCI), que tem por objetivo documentar de forma prospetiva e contínua as características dos doentes e dos procedimentos percutâneos realizados em Portugal[1]. Paralelamente, a Direção Geral de Saúde (DGS) tem publicado os dados de atividade oficiais, baseados em inquéritos dirigidos aos centros com cardiologia de intervenção[2].

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Abreviaturas

APIC	Associação Portuguesa de Intervenção Cardiovascular
CNCDC	Centro Nacional de Coleção de Dados em Cardiologia
DES	*stent* eluidor de fármaco
DGS	Direção Geral de Saúde
FFR	reserva de fluxo fractional
ICP	Intervenção Coronária Percutânea
ICP-P	angioplastia primária
iFR	instant wave-Free Ratio
IVUS	ecografia intravascular
OCT	tomografia de coerência óptica
RNCI	Registo Nacional de Cardiologia de Intervenção
STEMI	enfarte agudo do miocárdio com supradesnivelamento do segmento ST

Anteriormente, reportámos a evolução da cardiologia de intervenção em Portugal referente à atividade entre 1992-2003[3]. Vimos agora complementar esse registo com a publicação dos dados entre 2004-2013. Esta complementaridade permite avaliar as tendências da cardiologia de intervenção portuguesa durante as últimas duas décadas (1992-2013).

Na análise de atividade é importante o exercício de *benchmark* com outros países, em particular os europeus. Durante vários anos, Bernhard Meier publicou os dados europeus[4,5], embora nos últimos anos essa publicação não tenha existido, pelo que optamos por nos comparar com Espanha e Suíça. A Espanha publica, desde 1990, a sua atividade anual e, além de ser um país europeu e vizinho, será possivelmente aquele que, pelas suas características económicas e culturais, mais se aproxima de Portugal[6,7]. A comparação com a Suíça, que também tem vindo a publicar regularmente os seus dados de atividade, permite uma comparação com outras realidades, nomeadamente mais representativas da Europa do norte e central[8,9].

Métodos

O RNCI é um registo multicêntrico, voluntário, prospetivo, doente a doente, que tem como base o *European data standards for clinical cardiology practice* (CARDS)[10] e está sediado no Centro Nacional de Coleção de Dados (CNCDC), sob a responsabilidade da Associação Portuguesa de Intervenção Cardiovascular (APIC) da SPC. No período compreendido entre 2003-2013 foram incluídas 113 971 intervenções coronárias percutâneas (ICP). Os dados enviados para o RNCI vieram a incluir progressivamente a totalidade dos procedimentos efetuados durante os anos em análise. Os registos oficiais publicados pela DGS, no que se refere ao número total de coronariografias e angioplastias, são complementares do RNCI, sendo coligidos por inquéritos anuais dirigidos aos centros com cardiologia de intervenção. Assim, os dados de atividade, expressos em [illegible] baseados ao RNCI.

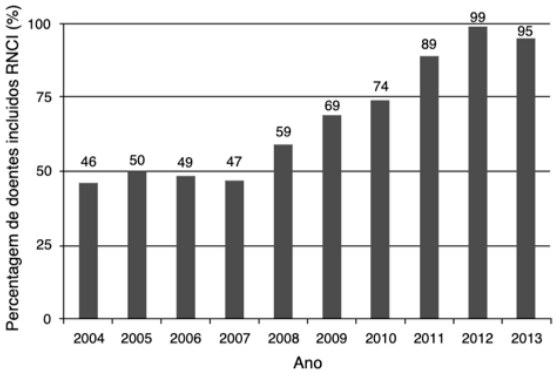


Figura 1 Percentagem de doentes incluídos no RNCI.

Para a comparação com a experiência espanhola, fizemos uso do relatório anual da *Sección de Hemodinámica y Cardiología Intervencionista de la Sociedad Española de Cardiología (1990-2013)*[7]. Para a comparação com a experiência suíça, considerámos os dados da publicação *Interventional Cardiology in Switzerland during the year 2010*[8] e, para o ano de 2013, os dados apresentados pelo *Swiss Working Group of Interventional Cardiology and Acute Coronary Syndrome* relatados por Gregor Fahrni e gentilmente cedidos por Bernhard Meier[9].

A inclusão de doentes no RNCI tem sido progressiva. Para o ano inicial deste registo de atividade (2004), a amostra representa 46% do total de procedimentos efetuados nesse ano. Nos últimos dois anos, praticamente todos os doentes tratados em Portugal foram incluídos no registo (Figura 1), com um decréscimo em 2013.

Resultados

Angiografia coronária

Não estão publicados os números oficiais de coronariografias entre 2004-2006[2]. Em 2007, o número total de coronariografias foi de 27 746 e, em 2013, foi 36 810, verificando-se um aumento percentual de 33% (Figura 2). Neste último ano, realizaram-se 3539 coronariografias/milhão de habitantes.

Angioplastia coronária

Em 2004, foram efetuadas em Portugal 8437 ICP, crescendo sustentada e significativamente para 13 897 ICP em 2013 ($p < 0{,}001$, Figura 3), correspondendo a um incremento de 65%. Neste último ano, realizaram-se 1333 ICP/milhão de habitantes. As Figuras 3 e 4 resumem a evolução entre 2004-2013.

Na Figura 5 apresenta-se a evolução da relação ICP face ao número de coronariografias. Em 2013, esta percentagem foi de 38%.

No que respeita à intervenção em anatomias mais complexas, observou-se que a intervenção multivaso tem mantido uma taxa relativamente estável, embora com

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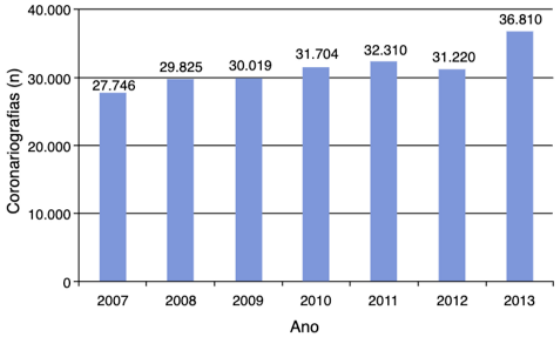


Figura 2 Coronariografias em Portugal entre 2007-2013.

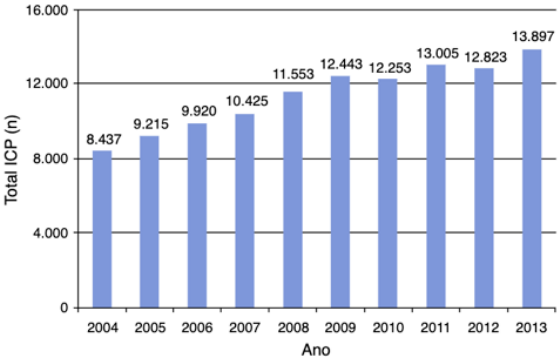
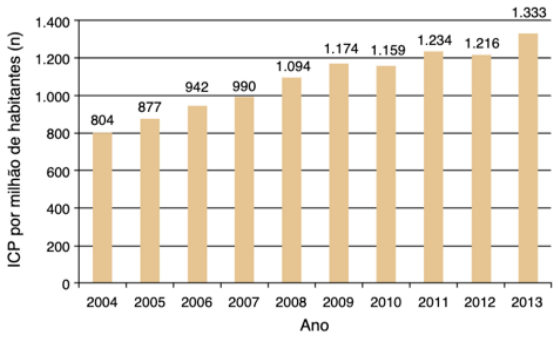


Figura 3 Angioplastias coronárias (ICP) em Portugal entre 2004-2013.

flutuações desde o início do registo: 18% em 1992, pico de 24% em 2004 e, novamente, 18% em 2013 (Figura 6)[3]. A intervenção no tronco comum não protegido tem uma expressão que oscilou entre em máximo de 2,8% e um mínimo de 1,9%, designadamente em 2013 (Figura 7).

A intervenção no enfarte agudo do miocárdio com supradesnivelamento do segmento ST apresentou um incremento progressivo da angioplastia primária (ICP-P) entre 2004 (1328 procedimentos) e 2013 (3524 procedimentos) (Figura 8). Em Portugal, realizaram-se 338 ICP-P/milhão de habitantes em 2013 (Figura 9). Observou-se paralelamente



ão de habitantes entre 2004-2013.

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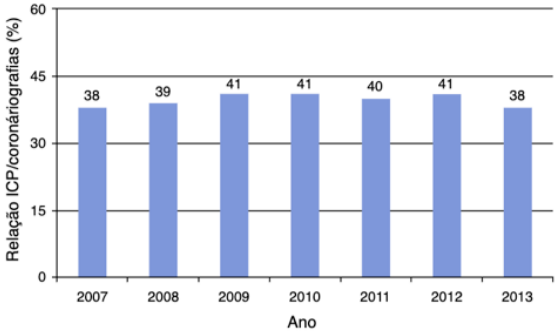


Figura 5 Relação ICP/coronariografias em Portugal.

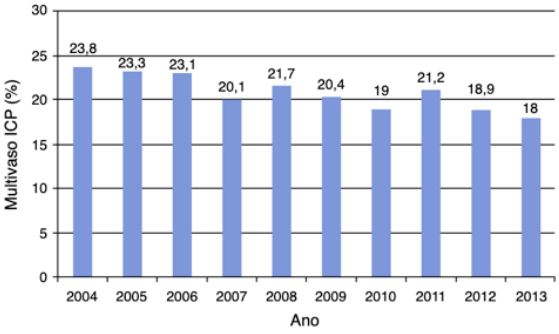


Figura 6 ICP multivaso em Portugal.

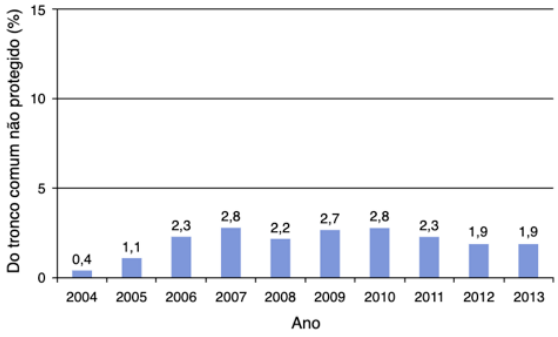


Figura 7 ICP do tronco comum não protegido.

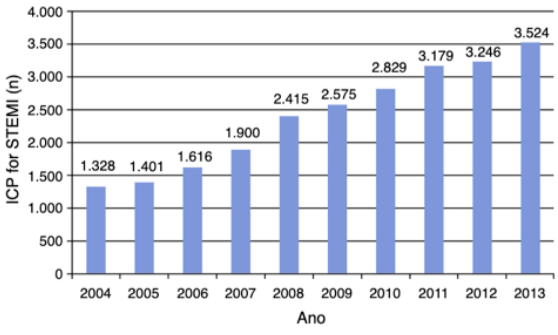


Figura 8 ICP no enfarte agudo do miocárdio (STEMI).

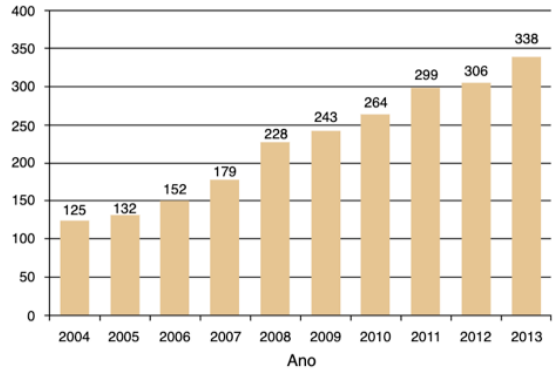


Figura 9 Evolução da ICP-P por milhão de habitantes.

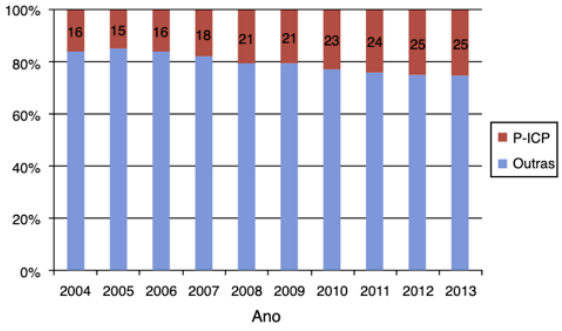


Figura 10 ICP primária *versus* outras ICP.

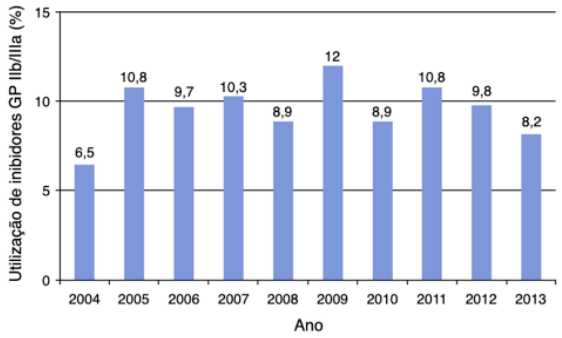


Figura 11 Utilização de inibidores GP IIb/IIIa.

um aumento relativo da ICP-P no contexto da atividade global dos centros de cardiologia de intervenção, atingindo 25% em 2013 (Figura 10).

Durante a década em análise, a utilização de inibidores das glicoproteínas IIb/IIIa, variou entre 6,5-12,0% (Figura 11), com percentagens aproximadas às espanholas (8,2% em Portugal e 10% em Espanha no ano de 2013 [Figura 12]).

Stents

A Figura 13 evidencia que a taxa de implantação de [illegible] em análise se manteve muito

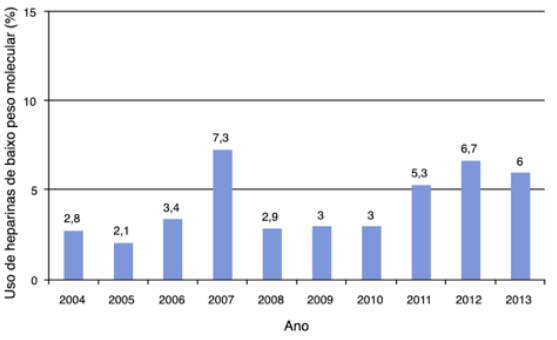


Figura 12 Uso de heparinas de baixo peso molecular.

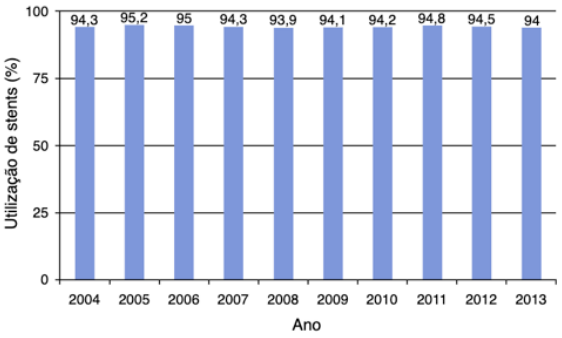


Figura 13 Utilização de *stents* em Portugal.

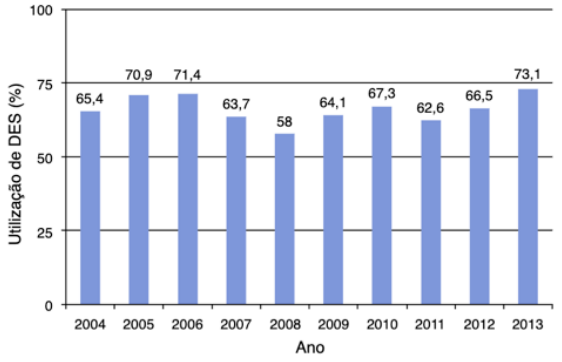


Figura 14 Utilização de DES.

estável entre 94-95%. A taxa de penetração dos *stents* eluidores de fármacos (DES) apresentou flutuações no RNCI, entre um mínimo de 58 em 2008 e um máximo de 73,1% em 2013 (Figura 14).

A Figura 15 resume a taxa de implantação do *stent* direto, mostrando os valores mais elevados entre os anos de 2008-2010.

Outros dispositivos de intervenção coronária

A aspiração/remoção de trombo, no contexto de enfarte do miocárdio com supradesnivelemento do segmento ST, mostrou um franco incremento a partir de 2008, atingindo 46,7%

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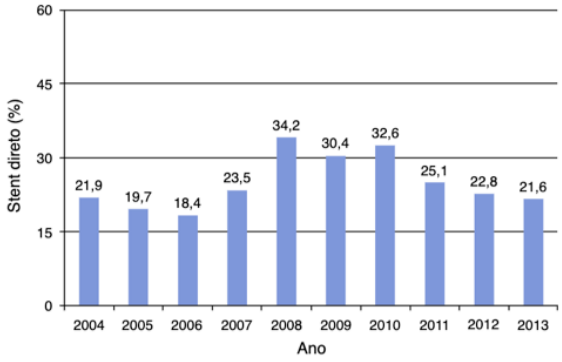


Figura 15 *Stent* direto.

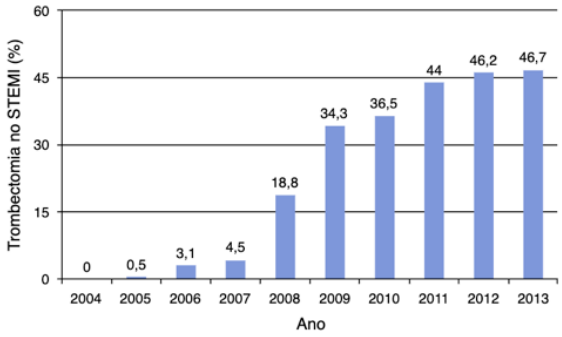


Figura 16 Trombectomia no STEMI.

em 2013 (Figura 16). A utilização dos sistemas de proteção distal na angioplastia das pontagens aortocoronárias oscilou ao longo dos anos, situando-se nos 12% no último biénio (Figura 17).

A taxa de utilização de aterectomia rotacional com Rotablator situa-se abaixo dos 2% (Figura 18). Não há registos de laser, braquiterapia nem aterectomia direcional neste período.

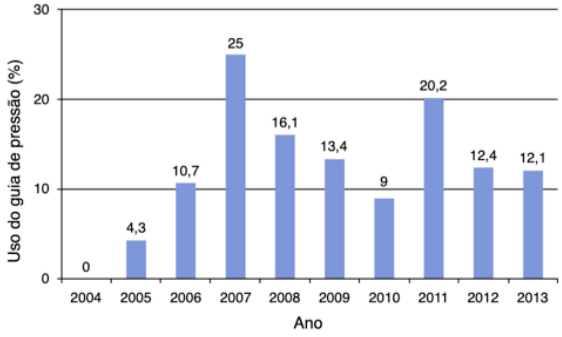


Figura 17 Uso do sistemas de proteção distal nos *bypass* veno-

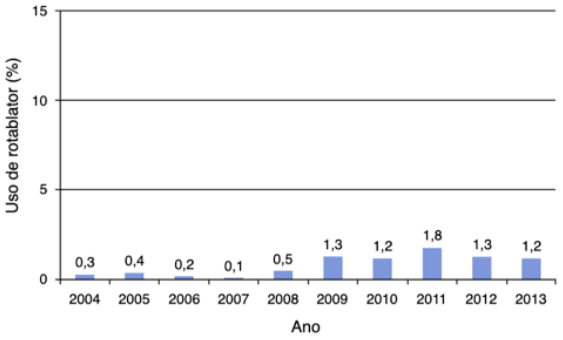


Figura 18 Uso de Rotablator.

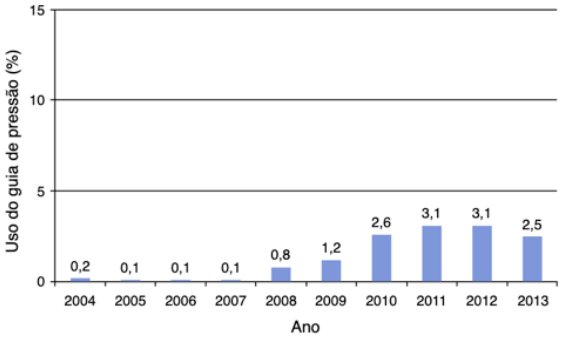


Figura 19 Uso do guia de pressão.

Dispositivos de diagnóstico intracoronário

A avaliação fisiológica com guia de pressão (FFR) teve um incremento a partir de 2008, atingindo o pico em 2011-2012 (3,1% dos procedimentos; Figura 19).

Durante o período em análise, a ecografia intracoronária (IVUS) registou um incremento até 2009, quando atingiu 3,1% dos procedimentos e, posteriormente, iniciou um decréscimo, atingindo 1,5% das intervenções em 2013 (Figura 20).

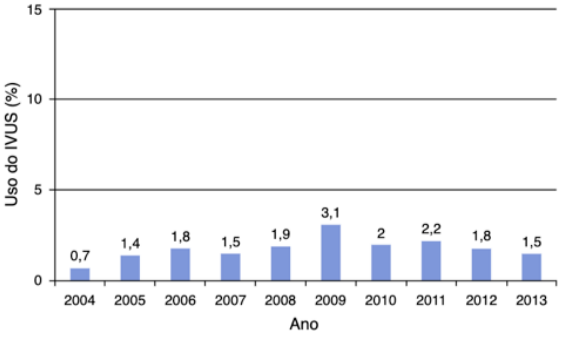


Figura 20 Uso do IVUS.

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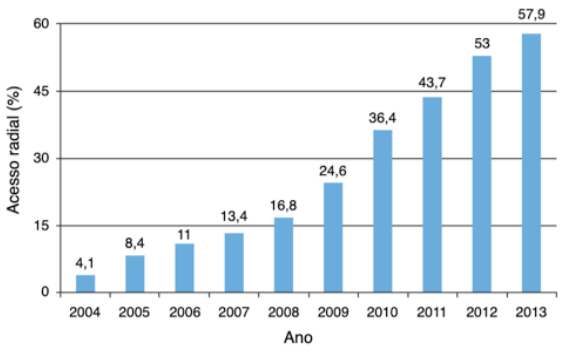


Figura 21 Acesso radial.

Vias acesso e encerramento vascular

A via radial (Figura 21) cresceu progressivamente e, em 2013, atingiu os 57,9%, altura em que também foi a via mais frequentemente utilizada na ICP-P (54,6%). Quando o acesso foi femoral, ao longo da década, a utilização de sistemas de encerramento foi sempre superior a 80%, sendo de 84,8% em 2013.

Discussão

A ICP, como já havíamos assinalado anteriormente, teve uma fase de franco crescimento a partir de 1994 e até 2008[3], fase a partir da qual as taxas de crescimento anuais passaram a ser mais tímidas. Entre 2004-2008, o crescimento foi de 37% e, nos cinco anos seguintes, entre 2009-2013, foi de 20%. A atividade diagnóstica, após um período de estabilização, entre 2010-2012, voltou a crescer em 2013. Este crescimento não foi acompanhado por crescimento igual da angioplastia, tendo resultado numa diminuição da relação angioplastia/coronariografia, que foi de 38% em 2013. Desde 2007, Espanha tem mostrado uma tendência para estabilidade do diagnóstico e da intervenção e revela em 2013 uma relação angiografia/coronariografia mais elevada: 55%. Desta relação resulta um perfil aparentemente distinto entre os dois países, apresentando Portugal maior atividade diagnóstica (3539 procedimentos/milhão de habitantes em 2013, *versus* 2592 em Espanha) e uma menor atividade intervencionista (1333 ICP/milhão de habitantes em 2013 *versus* 1419 em Espanha). Contudo, o registo espanhol não é doente a doente e tal poderá enviesar a comparação. No registo suíço[9], também referente a 2013, a relação angioplastias/coronariografias foi de 48%, superior à portuguesa mas inferior à espanhola. Interessa salientar que a publicação, em 2007, do estudo COURAGE[11] não parece ter afetado a indicação para exames da cardiologia de intervenção, na medida em que não baixou nem o número total de coronariografias, nem a relação angioplastias/coronariografias.

O enquadramento da atividade nacional no contexto europeu é da maior importância, não só para os profissionais de saúde diretamente implicados no estudo e tratamento dos doentes, mas também para os decisores. Durante vários [illegible]tou e publicou a atividade da cardiologia de intervenção europeia[4,5]. Com exceção da ICP-P[12], os últimos números europeus reportam a 2005[5]. O RNCI, que atualmente já recebe dados de todos os centros de cardiologia de intervenção, destaca-se em termos europeus por congregar a atividade total de um mesmo país e pela maioria dos sistemas instalados permitir o envio de dados *online* doente a doente, possibilitando a avaliação conjunta e o *benchmark* via *web* quase instantâneo. Um RNCI robusto e de qualidade constitui uma segurança na publicação de dados fiáveis e pode evitar a publicação de resultados, como os divulgados pela *European Heart Network AISBL*[13], que distorcem a nossa realidade. Nesta publicação, para o ano de 2009 é referida uma taxa de 229 angioplastias por milhão de habitantes, quando na realidade se realizaram 1163/milhão[2].

Na evolução da angioplastia multivaso tem-se observado uma estagnação ao longo dos anos. Em 2013 a nossa taxa foi de 18%, quando 30% dos procedimentos em Espanha[7] foram multivaso. Na base deste perfil, poderá estar o facto de os estudos terem vindo a mostrar que na doença difusa multivaso, em particular nos doentes diabéticos, a intervenção percutânea poder não ser a melhor opção[14–16]. Possivelmente, poderá também não ser alheio o facto de progressivamente estarmos a tratar doentes mais idosos, com várias comorbilidades, em particular a insuficiência renal, que recomenda uma atitude menos agressiva e levar a fasear os procedimentos. Por outro lado, do ponto de vista dos contratos programa dos hospitais em Portugal, também se mostra mais vantajoso realizar o tratamento multivaso em sessões múltiplas. Os bons resultados alcançados com os DES da nova geração[17,18] conduziram a que, pela primeira vez, a intervenção percutânea, quer em doença multivaso quer no tratamento do tronco comum não protegido, para pontuações SYNTAX *scores* baixas ou intermédias, surgisse em pé de igualdade com as recomendações de revascularização cirúrgica da ESC-EACTS de 2014[19].

O tratamento do tronco comum não protegido atingiu 1,9% do total de procedimentos em 2013, e tem-se mantido relativamente estável ao longo da década, sendo a percentagem menor que em Espanha (3,3%)[7]. Será previsível que os bons resultados apurados na avaliação a longo prazo do SINTAX[14,15,20] possam vir a ter impacto nacional no tratamento do tronco comum não protegido.

Desde a sua introdução em 2002, Portugal foi um dos países com maior penetração de DES. Observou-se, em 2007 um decréscimo na utilização de DES (71,4% em 2006 para 58,0% em 2008), possivelmente resultado das suspeitas de aumento da trombose de *stents*[21]. Esta situação rapidamente se reverteu, atingindo a taxa de 67,3% em 2010, para novamente diminuir em 2011, o que se atribui às limitações acrescidas que a crise económica induziu, favorecendo então a utilização de *stents* metálicos cujo custo era inferior. Esta taxa voltou a crescer em 2012 e, em 2013, situava-se em 73,1%, maior do que a espanhola (62%) e bastante menor que a suíça (92%)[9]. Entre outras, uma das explicações para esta diferença na utilização, poderá resultar do custo dos *stents*, que em Portugal e na Suíça é significativamente mais baixo que em Espanha, o que o torna a sua utilização mais custo-efetiva.

O recurso a *stent* direto decresceu sustentadamente a partir de 2010. Dado que complexidade anatómica na ICP

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não aumentou, tal reflete, possivelmente, uma técnica distinta de preparação das lesões, não se podendo excluir o recurso a dispositivos com menos capacidade de entrega por condicionantes económicas.

A ICP-P tem sido objeto de especial atenção no seio da *European Association of Percutaneous Cardiovascular Interventions* (EAPCI), especialmente através da iniciativa *Stent for Life*[22]. A EAPCI considera que no espaço europeu se deverá atingir o valor de 600 ICP-P/milhão/ano[22–24]. Em 2013, a razão ICP-P/milhão foi de 338 em Portugal e 395 em Espanha[7]. Em 2014, Steen Kristensen[12] publicou os números referentes a 2010/2011 de 37 países europeus. Apenas Áustria (769), Bulgária (694), República Checa (596), Alemanha (638), Hungria (553), Holanda (884), San Marino (640) e Suíça (506) estão acima das 500 ICP-P/milhão/ano. Portugal surge num grupo intermédio com 303/milhão/ano, relativamente próximo de outros países europeus: Bélgica (297), Finlândia (265), Grécia (346), Gronelândia (396), Espanha (225) e Inglaterra/País de Gales (286). Este posicionamento contrasta com o anterior relatório europeu, referente a 2007-2008, publicado por Petr Widimsky[25], em que Portugal surgia como um dos países com mais fraca *performance* em ICP-P. O peso da ICP-P tem vindo a aumentar progressivamente nos laboratórios de hemodinâmica e, no último ano, já representou 25% da atividade global. A angioplastia no contexto de enfarte representou 26% da atividade global dos centros espanhóis em 2013[7].

A utilização mais alargada de trombectomia aspirativa teve lugar em 2008, coincidindo com a publicação do estudo TAPAS[26]. A sua utilização nos últimos três anos, agora em análise, aproximou-se dos 50%, sendo de aguardar o impacto que os resultados do estudo TASTE irão ter na sua utilização futura[27]. Em 2013, ano em que a Espanha registou 67% de aspiração[7], salienta-se uma avaliação retrospetiva do RNCI, na qual a aspiração de trombo não teve impacto na mortalidade hospitalar dos doentes com STEMI[28].

A utilização do guia de pressão (FFR) registou a partir de 2008 (0,8%) um franco incremento, coincidindo com a publicação do estudo FAME[29]. Em 2013, Portugal registou uma contração ligeira com uma taxa de 2,5% de FFR e Espanha apresentou 6,2%[7], evidenciando que a nossa experiência deve crescer nesta técnica.

A utilização dos dispositivos de diagnóstico intracoronário tem permanecido baixa. A taxa mais elevada de utilização do IVUS ocorreu em 2009 (3,1%), mas progressivamente decresceu, tendo sido de 1,5% em 2013, valor bastante inferior ao espanhol do mesmo ano, que foi de 6,7%[7]. A utilização de *optical coherence tomography* (OCT) não constava do RNCI, admitindo-se que, no seu conjunto, as técnicas de imagiologia intracoronária permaneçam estáveis.

Finalmente, o acesso radial tem vindo a crescer, tendo-se atingido em 2012 o ponto de viragem, pois as intervenções por via radial ultrapassaram as realizadas por via femoral (53%). Em 2013, atingimos os 58%, estando alinhados com a taxa espanhola de 64%[7].

Limitações

Na avaliação da atividade, além da análise das tendências no uso das várias técnicas, interessa também conhecer [illegible] farmacológica, dos dispositivos, e o resultado, com particular enfâse nas complicações. O RNCI veio a englobar progressivamente a totalidade dos doentes tratados em Portugal durante o período em avaliação, e apresenta um preenchimento dos seguimentos clínicos que é heterogéneo e deve ser alvo de uma análise dedicada, pelo que não estudámos a taxa de complicações. Estas dificuldades são transversais a registos que incluem todos os doentes. Por outro lado, há informações que devem vir a ser colecionadas no futuro, especialmente a classificação da ICP em *ad-hoc*, os fármacos, as características angiográficas, o tratamento de oclusões crónicas totais, a especificidade dos DES (tipo, tamanho e geração) e métodos diagnósticos mais recentes (o OCT e o iFFR).

A cardiologia de intervenção deixou de ser uma especialidade centrada exclusivamente no tratamento da doença coronária, sendo que o seu principal desenvolvimento atual se situa no tratamento da doença estrutural. É fundamental saber as tendências atuais no âmbito do tratamento percutâneo da estenose aórtica, da estenose e insuficiência mitral, do encerramento de *shunts*, da miocardiopatia hipertrófica, da prevenção e tratamento do AVC isquémico, da hipertensão arterial e da doença vascular periférica. Os grupos de trabalho da APIC têm vindo a organizar registos próprios, designadamente no âmbito do implante de válvulas aórticas percutâneas, desnervação renal e encerramento de apêndices auriculares, que posteriormente deverão ser objeto de publicação.

Conclusão

A atividade da cardiologia de intervenção portuguesa, avaliada pelas coronariografias e ICP, revelou crescimento, desde 2004 a 2013. Neste ano, a totalidade dos centros de cardiologia de intervenção nacionais contribuiu com a exportação doente a doente para o RNCI da APIC-SPC.

Globalmente, observou-se o aumento relativo da ICP-P, o crescimento na utilização dos DES e o enorme incremento do acesso radial. A utilização da imagiologia intracoronária e da avaliação invasiva funcional apresenta uma margem de progressão, tendo sido possível identificar variáveis que devem ser incluídas futuramente no RNCI.

Responsabilidades éticas

Proteção de pessoas e animais. Os autores declaram que para esta investigação não se realizaram experiências em seres humanos e/ou animais.

Confidencialidade dos dados. Os autores declaram que não aparecem dados de pacientes neste artigo.

Direito à privacidade e consentimento escrito. Os autores declaram que não aparecem dados de pacientes neste artigo.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

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Agradecimentos

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EDITORIAL COMMENT

Risk assessment in percutaneous coronary intervention and appropriate use criteria: Manual or automatic?☆

Avaliação do risco e uso apropriado da intervenção coronária percutânea. Portagem manual ou via verde eletrónica automática?

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Coronary artery disease is the leading cause of death in developed countries. Percutaneous coronary intervention (PCI) alleviates patients' symptoms and in many cases reduces mortality in settings of cardiac decompensation, particularly acute coronary syndromes (ACS).[1]

In the thirty years since PCI was introduced in Portugal, its indications have widened following improvement in techniques and results, and now include more complex and higher-risk situations. Advances have been seen in drug-eluting stents, adjuvant therapy, arterial access, imaging and understanding of the underlying physiology.[2]

The benefits of PCI must be weighed against the risk associated with intervention, which depends on clinical and angiographic variables. The ability to predict the outcome for a patient before and after PCI is extremely useful, in order to assess individual risk, to counsel patients and their families, and to plan revascularization strategies.[3–5] It also helps in identifying opportunities to improve quality and in comparing results between centers and operators.

The main requirements for cardiovascular risk scores are accessibility, ease and speed of use, ability to integrate with the institution's computer systems, and low cost. Risk scores must be validated, ideally for both short-term and long-term application (up to five years).

Most existing risk scores for PCI have significant limitations. The most widely used in interventional cardiology is the SYNTAX score, both the original and the updated clinical SYNTAX score, which are referred to in the European guidelines but can be complex and laborious to calculate, while the EuroSCORE II uses clinical variables and is easy to calculate. Both have been the subject of extensive external validation.[6–11] A variety of other interesting risk scores have been developed, but with limited applicability and external validation (especially in European populations), and with outcome restricted to in-hospital adverse events.[12]

The article by Timóteo et al. in this issue of the *Journal* is timely, specifically addressing these limitations and analyzing the role of risk scores derived from populations with ACS.[13] It concludes that the Global Registry of Acute Coronary Events (GRACE) score is to be preferred to the Mayo Clinic risk score (MCRS) and the National Cardiovascular Data Registry (NCDR) risk score for predicting in-hospital mortality in Portuguese patients undergoing PCI, mainly for ST-elevation myocardial infarction (STEMI).

The study population was large, reflecting the experience of a reference center between January 2005 and October 2013.

The proportion of STEMI was high (70.9%), which explains the demographic and clinical differences between this population and others, both Portuguese and non-Portuguese, used to derive risk scores, which had a lower prevalence of comorbidities that are generally associated with greater clinical complexity.[14–16]

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This prospective observational registry was notable for the robustness of the statistical methods used to compare the different risk scores, which were calculated retrospectively.

The merit of the study lies in its comparison of the three scores in a Portuguese population, showing that they fulfill some of the main requirements of a risk score: they are freely accessible, easy to apply and free of charge. Ease of calculation was not evaluated, presumably because the GRACE score is available via computers and mobile devices, and although its calculation based on eight variables is manual, it is fast.[17] Calculation of the MCRS is also manual, but is more complex and therefore more time-consuming and less practical.[18] With regard to the NCDR score, presumably the simplified version 3, with eight variables, was used in the study; the simplified version 4 is now available, which uses 13 clinical variables, but only the full version includes significant angiographic predictors such as treated chronic total occlusions and stent thrombosis.[19]

The study focuses on in-hospital mortality, which was 4.5%. On the basis of the inclusion criteria, borderline cases, such as patients who did not undergo angiography or who had mild disease on angiography, were excluded, as were those who needed surgery or did not survive to be treated by PCI. Validation of the scores for events at 30 days and in the longer term would be valuable, since it is over this time-scale that there are the most gaps in our knowledge and the most interest for patients. From this standpoint, the inclusion of biomarkers could be particularly useful.[20,21]

In my opinion, the central question is the implementation and usefulness of risk assessment. First of all, risk scores should be available automatically at the patient's bedside, preferably via the institution's computer systems, in order to facilitate decisions regarding catheterization and treatment strategy. This is especially important given that, for long-term prognosis, the more complex and comprehensive scores are clearly more accurate and sensitive than simplified ones. Secondly, in this study in which two-thirds of the patients had STEMI and were revascularized, it would be of considerable interest to analyze what could have been done to reduce in-hospital mortality. The complications reported (stroke, major bleeding and mechanical complications) are of course associated with mortality, which leads to the question of the appropriate use of PCI, adjuvant therapy and arterial access according to the risk score.

In conclusion, the study by Timóteo et al. is original and significant, validating three risk scores for PCI in Portuguese patients with ACS. Physicians should be able to calculate risk automatically at the patient's bedside, but cannot as yet always do so. Prognostic risk assessment is included in most guidelines and is a valuable aid in counseling, planning, improving quality and assessing outcomes.

Conflicts of interest

The author has no conflicts of interest to declare.

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CASE REPORT

Sequential transcatheter aortic valve implantation due to valve dislodgement - a Portico valve implanted over a CoreValve bioprosthesis

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KEYWORDS
Severe aortic stenosis;
Transcatheter aortic valve implantation complications;
Valve dislocation

Abstract Transcatheter aortic valve implantation (TAVI) has become an important treatment in high surgical risk patients with severe aortic stenosis (AS), whose complications need to be managed promptly.

The authors report the case of an 86-year-old woman presenting with severe symptomatic AS, rejected for surgery due to advanced age and comorbidities. The patient underwent a first TAVI, with implantation of a Medtronic CoreValve®, which became dislodged and migrated to the ascending aorta. Due to the previous balloon valvuloplasty, the patient's AS became moderate, and her symptoms improved. After several months, she required another intervention, performed with a St. Jude Portico® repositionable self-expanding transcatheter aortic valve. There was a good clinical response that was maintained at one-year follow-up.

The use of a self-expanding transcatheter bioprosthesis with repositioning features is a solution in cases of valve dislocation to avoid suboptimal positioning of a second implant, especially when the two valves have to be positioned overlapping or partially overlapping each other.
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PALAVRAS-CHAVE
Estenose aórtica grave;
Complicações da válvula aórtica percutânea;
Deslocamento da válvula

Implantação sequencial de válvula aórtica percutânea por deslocamento da válvula – uma válvula Portico implantada sobre uma CoreValve

Resumo A implantação de válvula aórtica percutânea (VAP) tornou-se um procedimento importante no tratamento de doentes com estenose aórtica grave com elevado risco cirúrgico, cujas complicações devem ser avaliadas e tratadas de forma adequada.

Os autores relatam o caso de uma doente de 86 anos, com estenose aórtica grave sintomática, recusada para intervenção cirúrgica dada a idade avançada e comorbilidades. A doente foi submetida a uma primeira implantação de VAP com uma válvula *Medtronic CoreValve*®, a qual sofreu um deslocamento para a aorta ascendente durante o procedimento. Devido à angioplastia de balão previamente efetuada, a estenose aórtica tornou-se moderada, com melhoria da sintomatologia da doente. Vários meses depois, por agravamento clínico, houve necessidade de reintervenção, a qual foi realizada com um sistema reposicionável *Portico*®. Verificou-se um segundo posicionamento valvular adequado, com boa resposta clínica da doente, que persiste após um ano de *follow-up*.

A utilização de sistemas reposicionáveis de implantação de VAP constitui, atualmente, uma solução em casos de deslocamento da válvula, de forma a evitar uma segunda implantação subótima, sobretudo quando as duas válvulas têm de ficar em sobreposição.
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Introduction

Transcatheter aortic valve implantation (TAVI) has become an alternative to surgical aortic valve replacement (SAVR) in high-risk patients with severe aortic stenosis (AS).[1,2] The complications associated with this procedure are different from those related to SAVR. This article describes the case of a patient who suffered dislocation of a Medtronic CoreValve® during initial TAVI treatment. Eventually, after several months of moderate improvement, she needed another intervention, which was performed with a St. Jude Portico® repositionable self-expanding transcatheter aortic valve.

Case report

The authors report a case of an 86-year-old woman presenting with New York Heart Association (NYHA) class II symptoms and severe AS (maximum and mean transvalvular gradients of 199 and 75 mmHg, respectively; aortic valve area 0.7 cm^2). She had preserved left ventricular systolic function and non-significant coronary artery disease, and was rejected for SAVR due to advanced age, low weight and extreme frailty (logistic EuroSCORE I and II 19.79% and 4.22%, respectively; Society of Thoracic Surgeons score 3.7%).

The patient underwent a first TAVI in 2012, through angiography-guided femoral access. Valvuloplasty was performed with a 20 mm NuMED Nucleus balloon followed by implantation of a 26 mm CoreValve®. During this procedure, the valve became dislodged and migrated to the ascending aorta due to excessive tension on the first-generation delivery catheter making it uncontrollable during fine manipulation of the valve release. A snare technique was used to reposition the prosthesis upward, without affecting the coronaries. Given the fact that valvuloplasty had been performed and the percutaneous aortic valve was of the first generation and not repositionable, it was decided to suspend the procedure and postpone any possible second intervention. The patient's AS became moderate, with maximum and mean gradients decreasing to 67 and 35 mmHg, respectively, and she improved to NYHA class I. No neurologic, aortic or peripheral vascular complications occurred.

One year later her AS worsened (maximum and mean transvalvular gradients of 101 and 61 mmHg, respectively; aortic valve area 0.8 cm^2) and, in 2014, she was hospitalized for congestive heart failure. The heart team decided on a new TAVI with a repositionable system as the first-line approach, and a balloon-expandable TAVI as a second-line solution. Percutaneous coronary intervention (due to progression of coronary artery disease) was followed by transfemoral TAVI (valve-in-valve) under three-dimensional transesophageal echocardiographic guidance (Figure 1). The CoreValve® was immobilized with a 15 mm snare loop by a radial approach. After valvuloplasty with a 20 mm Nucleus balloon, a 25 mm Portico® valve was implanted. Post-dilation was performed for underexpansion. The patient was prescribed dual antiplatelet therapy with aspirin and clopidogrel until six months after the second procedure.

At one-year follow-up the patient remains in NHYA class II, with NT-proBNP level of 510 pg/ml. Transthoracic echocardiography revealed the two bioprostheses overlapping with appropriate transprosthetic gradients and associated mild to moderate leak (Figure 2).

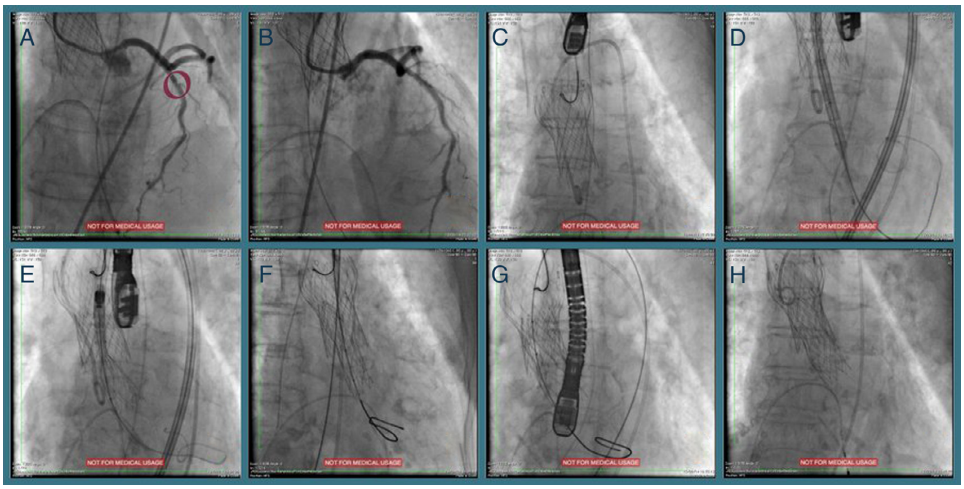


Figure 1 Sequential procedures during the second intervention. (A and B) Percutaneous coronary intervention of the mid left anterior descending artery with a drug-eluting stent; (C) transfemoral transcatheter aortic valve implantation (valve-in-valve) under three-dimensional transesophageal echocardiographic guidance, the Medtronic CoreValve® being immobilized with a 15 mm snare loop by a radial approach; (D) aortic valve balloon valvuloplasty performed with a 20 mm NuMED Nucleus balloon, followed by (E and F) implantation of a 25 mm St. Jude Portico® valve; (G) this valve was underexpanded and post-dilation was performed after changing the Amplatz super stiff wire for a backup Meier wire in order to advance the Nucleus balloon; (H) final result.

Discussion

Malpositioning of the bioprosthesis during TAVI is a serious procedural complication which needs to be managed promptly to avoid vascular and other systemic complications. Two prospective studies conducted in patients undergoing TAVI using the CoreValve® revealed a prevalence of valve dislocation after deployment of 3.2-3.9%, with no long-term vascular or neurological complications.[1,3] Another study observed this complication in about 10% of patients, associated with lower survival rates and higher frequency of coronary ischemia, stroke, and renal failure.[2]

Possible causes of malpositioning are mismatch of the annulus and valve size, which can be solved by precise annulus measurements with echocardiographic and computed tomography imaging; arrhythmias, which hinder stabilization of the valve during deployment (higher ventricular rate pacing is used to stabilize the valve); and by accident, after successful deployment during retraction of the delivery system, if the anchors are not fully released from the deployment catheter or if the tip of the deployment catheter becomes caught at the proximal end of the prosthesis.[2]

Besides morphological or patient-related factors, operator experience appears to be crucial to the prevalence of valve dislocation.[1,2] This was confirmed in a reference center, in which the incidence of CoreValve® dislocation decreased constantly with increasing experience over a period of almost three years.[2]

Valve dislocation after complete deployment often results in the need to implant a second prosthesis, which is a feasible and effective interventional option that appears to be safer than retrieving the first prosthesis.[1] The decision whether to insert a new valve inside the previous one, or to pull the first one to another location in the aorta and implant a second valve sequentially, depends on various factors, including operator preferences and procedural circumstances.[3] When the two valves are positioned overlapping or partially overlapping each other, there are various disadvantages: duplication of the amount of metal residing against the native aortic wall increases the risk of covering the native coronary ostia and requires more time for endothelialization.[3] Emergent surgery may be necessary in some cases.[2]

New transcatheter heart valves have been created in order to overcome some of the limitations of previous systems.[4] The Portico® is a self-expanding transcatheter aortic bioprosthesis with novel capabilities.[4] Its ability to be repositioned, recaptured, and redeployed is a desirable feature, especially when the initial implant positioning is suboptimal. However, only small series with limited follow-up have been published.[4] Only one case of successful Portico® transcatheter aortic valve-in-valve implantation, in a patient with a degenerated bioprosthesis (placed surgically), has been described to our knowledge.[5] This is the first reported case of TAVI valve-in-valve with this type of bioprosthesis, with good results at 12 months. A valve-in-valve procedure with a self-expanding transcatheter bioprosthesis with repositioning features is presently the first-line solution in cases of degenerated biological prostheses or prosthesis displacement during TAVI. However, assessment of more patients in medium- and long-term follow-up is required.

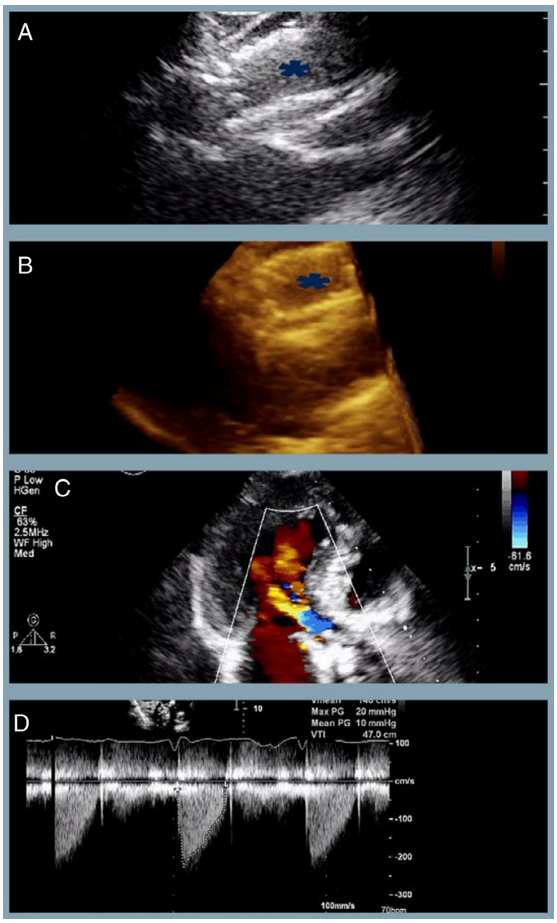


Figure 2 The last transthoracic echocardiography (at one-year follow-up) revealing (A and B) partial overlapping of the two bioprostheses (blue asterisk) (two- and three-dimensional respectively); (C) mild to moderate associated periprosthetic leak; (D) appropriate transprosthetic gradients (maximum and mean of 20 mmHg and 10 mmHg, respectively).

Conclusions

Dislocation of the bioprosthesis during TAVI is a serious procedural complication which needs to be managed promptly to avoid vascular and other systemic complications. This report describes a successful valve-in-valve procedure after valve dislodgement, with implantation of a self-expanding transcatheter bioprosthesis with repositioning capabilities.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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COMENTÁRIO EDITORIAL

Valvuloplastia aórtica de balão na era das válvulas aórticas percutâneas. Um desafio à dimensão organizativa dos programas multidisciplinares

Balloon aortic valvuloplasty in the transcatheter aortic valve replacement era: A challenge to organization of the heart team

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A intervenção por valvuloplastia aórtica de balão (VAoB) foi introduzida por Cribier em 1986 e sofreu um recrudescimento na era das válvulas aórticas percutâneas (VAP)[1,2]. Devido ao treino e evolução técnica do procedimento, a VAoB é hoje em dia mais segura, com uma mortalidade peri-procedimento de 2,2%, uma mortalidade hospitalar de 7,1% e taxas de acidentes cerebrovasculares de 1,1%, de insuficiência aórtica *major* de 1,1% e de complicações vasculares *major* de 7,0%. Isto apesar dos doentes atuais serem mais complexos e dos resultados hemodinâmicos permanecerem modestos[3,4].

Perante a alternativa da VAP, o principal desafio contemporâneo da VAoB prende-se com a dimensão organizativa dos programas multidisciplinares para a estenose aórtica, que constitui a principal doença valvular nos países desenvolvidos. Atualmente, existem em Portugal cerca de um milhão de indivíduos com mais de 75 anos, apresentando cerca de 3,4% uma estenose aórtica grave, sendo sintomáticos cerca de 75%[5]. Destes 25 000 portugueses, cerca de 4500 terão indicação para implantação de uma VAP por alto risco ou inoperabilidade, segundo as recomendações sobre a doença valvular[6–8]. O registo nacional de VAP apresenta, desde 2007 a 2015, cerca de 850 implantes, tendo sido realizados 300 no último ano. Embora não haja registo nacional de cirúrgica cardíaca, estima-se que em 2015 tenham sido realizadas cerca de 2000 cirurgias valvulares aórticas, simples ou com pontagem (CVAo). Como tal, o *ratio* VAP/CVAo é de 1:6, enquanto muitos países da Europa estão no 1:1[5,9].

A pressão assistencial tem subido e os programas multidisciplinares de válvulas percutâneas (VaP) têm que se adaptar ao enorme acréscimo de volume e aos doentes que não são primordialmente para VAP. Assim, as grandes questões atuais são:

1. **A avaliação *fasttrack***: a capacidade de se organizar a avaliação clínica e complementar principal em apenas duas ou três sessões (consulta de cardiologia e cirurgia, análises, angio CT, ecocardiograma com eventual transesofágico, cateterismo com eventual angioplastia);
2. **As indicações para VAoB em 2017**: as recomendações atuais nos adultos (classe IIb, da *European Society of Cardiology* e do *American College of Cardiology/American Heart Association*) não refletem a evolução dos resultados na era das VAP[8,10]. Dado que potencialmente muitas das complicações se replicam quando se faz inicialmente a VAoB e mais tarde a VAP, há que refletir em que condições é aceitável sujeitar o doente ao risco acrescido:
   a. Uma VAoB será apenas aceitável em caso de paleação de sintomas graves (uso por compaixão); ou como ponte paliativa devida a uma comorbilidade grave, seja temporária ou tenha ela um prognóstico indefinido e/ou uma expetativa de longevidade

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inferior a um ano (tipicamente uma neoplasia, uma intervenção urgente que não admita dupla antiagregação ou um caso se pretenda dar o benefício do ambulatório em muito idosos com outras patologias relevantes e irreversíveis).

b. Todas as outras indicações para VAoB devem ser abertamente questionadas. Principalmente aquelas que se relacionam com o acesso à terapêutica em tempo útil (pois temos a obrigação de o proporcionar); ou quando há dúvidas no benefício da eventual VAP, porquanto há métodos não invasivos que têm tal finalidade (o mais comum é a presença de disfunção ventricular esquerda e/ou insuficiência mitral grave).

3. **O tratamento *fasttrack* e a atuação expedita e orientada nas complicações:** colocada a indicação sabemos que, em doentes sintomáticos, a sobrevida se situa entre 1-3 anos[2,11,12]. Seja qual for a opção terapêutica, embora arbitrário, deve ser proporcionado um tratamento entre duas semanas até dois meses, consoante a gravidade. No caso da VAoB, sendo um procedimento paliativo, temos que equacionar a possibilidade de instabilidade ou de complicações tratáveis por VAP – tipicamente uma insuficiência aórtica *major* ou acidente cerebrovascular – estando preparado com um dispositivo VAP na prateleira e/ou cirurgia de prevenção, tal como nas VAP, aliás.

O artigo de Francisco et al.[13] proporciona informação valiosa, que permite aquilatar a importância da VAoB à luz destas considerações. Analisa retrospetivamente a experiência de um centro de alto volume de VAP numa população nacional de doentes que realizaram VAoB e conclui que a técnica melhora significativamente a maioria dos doentes.

O estudo apresentado é meritório porque analisa originalmente uma experiência portuguesa na era das VAP. Trata-se de um registo observacional de centro único incluindo 23 doentes desde janeiro de 2005 até outubro de 2013, comparando-se com séries maiores e mais antigas que compreendem entre 45-473 doentes. Os doentes foram seguidos cerca de nove meses e os resultados analisados retrospetivamente.

A predominância da indicação de ponte para a terapêutica definitiva, presente em 43% dos casos, contrasta com a maioria das séries onde predominam as indicações paliativas e a ponte se situa apenas nos 18%. Por este motivo, exceto pela prevalência maior de diabetes, esta coorte é globalmente menos complexa relativamente a outras, demográfica e clinicamente[3].

Tecnicamente, desconhecemos como se escolheu exatamente a dimensão do balão e como se realizou o *pacing* rápido, designadamente qual a via e a frequência alcançada pela estimulação. A queda de pressões sustentada é crucial para reduzir o movimento do balão e o subdimensionamento do mesmo em 1-2 mm permite uma técnica menos agressiva que, a par dos introdutores menores e sistemas de encerramento arterial, parecem ser responsáveis pela diminuição das complicações na era atual[2,3].

Não ocorreu mortalidade periprocedimento nem insuficiência aórtica *major*. Observou-se uma morte intra-hospitalar por acidente vascular cerebral (4,3%) e a taxa de complicações vasculares *major* foi de 8,6%, o que deve ser relativizado pelo facto de se ter alcançado a extubação em três doentes refratários que estavam ventilados. O prognóstico favorável aos nove meses dos doentes tratados definitivamente com VAP atesta a estratificação realizada e os resultados razoáveis contemporâneos da técnica.

Em conclusão, o estudo de Francisco et al.[13] é significativo porque estuda o risco da VAoB contemporânea em doentes portugueses na era das VAP. A predição do risco do procedimento paliativo é pertinente e os programas multidisciplinares devem ser estruturados, de molde a dar resposta expedita aos doentes com indicação para VAP, evitando a VAoB como procedimento paliativo em doentes que aguardam tratamento definitivo por VAP ou CVAo, dado que algumas complicações permanecem importantes apesar da experiência adquirida.

Conflito de interesses

O autor declara não haver conflito de interesses.

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ORIGINAL ARTICLE

Advantages of a prospective multidisciplinary approach in transcatheter aortic valve implantation: Eight years of experience

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KEYWORDS
Severe aortic stenosis;
Transcatheter aortic valve implantation;
Surgical aortic valve replacement;
Heart team;
Standardization

Abstract
Introduction: Aortic stenosis is the most prevalent type of valvular disease in Europe. Surgical aortic valve replacement (SAVR) is the standard therapy, while transcatheter aortic valve implantation (TAVI) is an alternative in patients at unacceptably high surgical risk. Assessment by a heart team is recommended by the guidelines but there is little published evidence on this subject. The purpose of this paper is to describe the experience of a multidisciplinary TAVI program that began in 2008.
Methods: The heart team prospectively assessed 473 patients using a standardized approach. A total of 214 patients were selected for TAVI and 80 for SAVR. Demographic, clinical and procedural characteristics and long-term success rates were compared between the groups.
Results: TAVI patients were older than the SAVR group (median 83 vs. 81 years), and had higher surgical risk scores (median EuroSCORE II 5.3 vs. 3.6% and Society of Thoracic Surgeons score 5.1 vs. 3.1%), as did the patients under medical treatment only. These scores were unable to assess multiple comorbidities. Patients' outcomes were different between the three groups (mortality with SAVR 25% vs. TAVI 37.6% vs. conservative therapy 57.6%, p=0.001).

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Conclusions: The heart team program was able to select candidates appropriately for TAVI, SAVR and conservative treatment, taking into account the risk of both invasive treatments. The use of a prospective standardized heart team approach is recommended, but requires continuous monitoring to ensure effectiveness in a timely manner.
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PALAVRAS-CHAVE
Estenose aórtica grave;
Válvula aórtica percutânea;
Substituição valvular aórtica cirúrgica;
Heart Team;
Standardização

Vantagens de uma abordagem multidisciplinar na avaliação de doentes em programa VAP: oito anos de experiência

Resumo
Introdução: A estenose aórtica é atualmente a doença valvular mais prevalente na Europa. A substituição valvular aórtica cirúrgica (SVAC) é atualmente considerada a terapêutica de primeira linha, a implantação de válvula aórtica percutânea (VAP) é considerada uma opção em doentes com elevado risco cirúrgico. A avaliação dos doentes pelo *Heart Team* encontra-se preconizada pelas recentes *guidelines* publicadas de doenças valvulares, contudo existem poucas publicações acerca dessa temática. O objetivo deste manuscrito é descrever a experiência de um programa multidisciplinar VAP, iniciado em 2008.
Métodos: O *Heart Team* avaliou de forma prospetiva e padronizada 473 doentes. Desses, 214 foram selecionados para VAP e 80 para SVAC. Os grupos foram comparados no que respeita às suas características demográficas, clínicas, de procedimento e quanto à sua evolução (mortalidade).
Resultados: O grupo VAP apresentou maior idade do que o grupo SVAC (mediana 83 *versus* 81 anos) e apresentou *scores* de risco cirúrgico mais elevados (mediana Euroscore II 5,3 *versus* 3,6% e STS 5,1 *versus* 3,1%), tal como o grupo de doentes apenas sob terapêutica médica. Esses *scores* não foram capazes de avaliar múltiplas comorbilidades. A mortalidade entre os três grupos apresentou diferenças com significado estatístico (SVAC 25% *versus* VAP 37,6% *versus* terapêutica conservadora 57,6%, p=0,001).
Conclusões: O programa *Heart Team* foi capaz de selecionar de forma adequada os doentes para as diversas estratégias terapêuticas tendo em conta o risco de ambos os procedimentos invasivos. Uma abordagem eficiente e standardizada pela *Heart Team* deve ser estimulada, necessitando de reavaliação continua.
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Introduction

Degenerative aortic stenosis (AS) is the most prevalent type of valvular disease in Europe, due to aging populations and increased survival.[1,2] When it develops, there is a long asymptomatic period.[1,2] Once symptoms occur, the prognosis of severe AS is dire; sudden death is frequent and survival rates are only 15-50% at five years.[1,3]

Surgical aortic valve replacement (SAVR) is the standard therapy for severe AS,[1,2,4] increasing survival and improving quality of life.[1] In patients at high surgical risk, transcatheter aortic valve implantation (TAVI) is a good alternative, with procedural success rates of over 90%.[1,4–8]

Assessment by a heart team is currently considered essential in the selection of patients, based on their risk profile and the technical suitability of TAVI.[1,5,6,9] Despite its importance, there is a lack of published evidence on this subject. In addition, considering the complexity and high costs involved in TAVI, the resources involved need to be rationalized.[10]

The aim of this paper was to assess a prospective standardized decision process by a heart team regarding patient selection and performance and results of the procedure, from the beginning of the program in 2008 until 2015.

Methods

From its beginning in 2008 up to 2015, the Hospital Santa Cruz TAVI program assessed 473 patients with severe symptomatic AS. A total of 383 patients completed the assessment process. Of these, 80 (20.9%) were selected for SAVR, 214 (55.9%) for TAVI and 89 (23.2%) for conservative treatment alone.

All patients are included in a prospective program that scrutinizes proposed candidates referred by their attending physicians. Briefly, the patient pathway starts with a clinical appointment that is followed by non-invasive and invasive tests and, finally, a multidisciplinary discussion (Figure 1). Candidate assessment is thorough, including

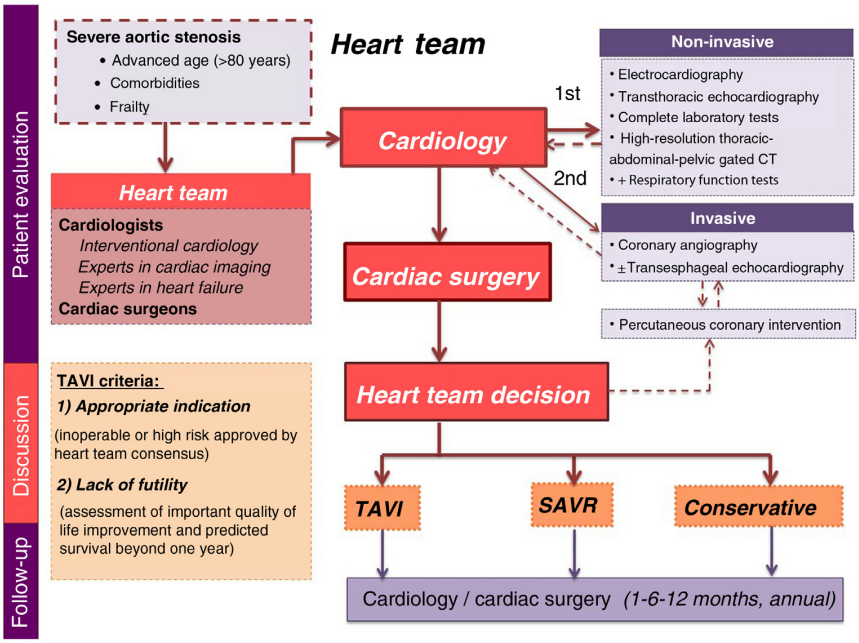


Figure 1 Schematic representation of heart team assessment of patients with severe aortic stenosis. CT: computed tomography; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

the presence of symptoms, comorbidities and functional capacity. If needed, additional exams are requested: transthoracic echocardiography, complete laboratory tests including blood count, coagulation, N-terminal pro-B-type natriuretic peptide (NT-proBNP), kidney and liver function tests, and a high-resolution thoracic-abdominal-pelvic gated computed tomography (CT) scan. After complete assessment, the data are gathered and the patient is discussed at a dedicated heart team meeting to select the most appropriate therapeutic strategy. The team is composed of cardiologists – including clinical cardiologists, interventional cardiologists, and experts in cardiac imaging and heart failure – and cardiac surgeons, who meet fortnightly to discuss clinical cases. Results are continuously monitored for quality assessment.

The TAVI heart team criteria are based on two factors: indication (inoperable or high surgical risk, as approved by heart team consensus) and lack of futility (subjective assessment of significant improvement in quality of life and predicted survival beyond one year).

The possible access routes are determined and the final route is selected according to the first implantation date available in order to intervene as early as possible. Thus, an arterial approach is only considered when there is clinical or anatomical contraindication for any other route.

If the patient is approved for either of the invasive strategies (SAVR or TAVI), he or she goes on a waiting list for the procedure. Patients refused for any invasive intervention return to their referring physician to continue on optimal medical therapy. Those selected for SAVR or TAVI are followed at 30 days, six months and one year after the procedure, and then annually.

Statistical analysis

All clinical and procedural data are collected in a dedicated database (Cardiobase™) and a continuous ongoing registry, the Valve Catheter Restorative Operation on Santa Cruz Hospital (VCROSS). Anonymous data is exported for statistical analysis, performed with SPSS version 20.0 (IBM SPSS, Chicago, IL, USA).

Continuous variables are expressed as median (interquartile range [IQR]). Categorical variables are expressed as absolute value and respective percentages. Differences in means between groups were assessed by the Kruskal-Wallis test and differences between categorical variables were assessed by the chi-square test. A p-value of 0.05 or less was considered significant. Mortality during follow-up was analyzed by Kaplan-Meier survival curves.

Results

Patient selection

From 2008 up to 2015, 473 patients with severe symptomatic AS were assessed in the TAVI program at Hospital Santa Cruz (Figure 2).

As at April 2015, the assessment was not completed in 33 patients (7.0%) and 45 died during the initial assessment (9.5%). An additional 12 (3.0%) patients returned to their physicians because severe AS was not confirmed.

A total of 383 patients with severe AS completed the heart team assessment process. Of these, 80 (20.9%) were selected for SAVR, 214 (55.9%) for TAVI and 89 (23.2%) for medical treatment alone.

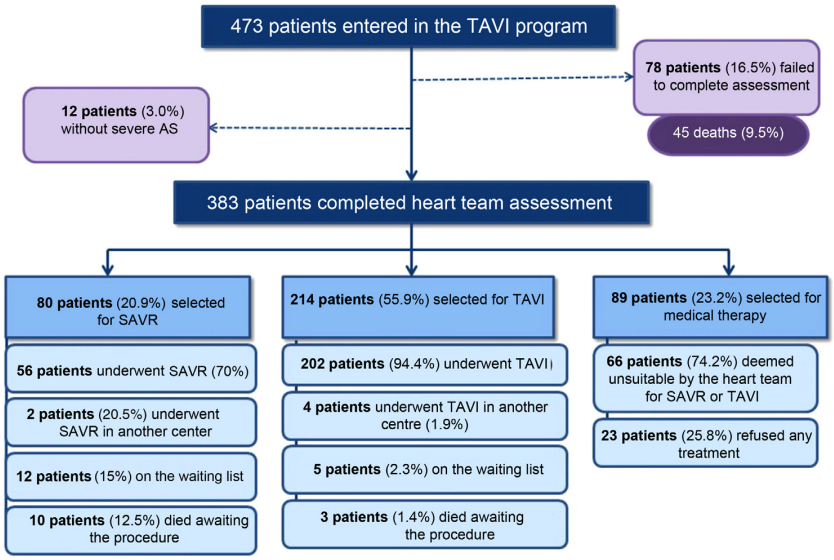


Figure 2 Schematic representation of patient assessment in the TAVI program at Hospital Santa Cruz. AS: aortic stenosis; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Table 1 Characterization of patients treated by the different strategies.

Variables, n (%)	SAVR (n=56)	TAVI (n=202)	Medical therapy (n=66)	p
Demographic characteristics				
Age in years, median (IQR)	81 (76-84)	83 (78-87)	84 (80-88)	0.023[a]
Male gender	26 (46.4%)	89 (44.1%)	28 (42.4%)	0.906[b]
Anthropometric data				
BMI in kg/m^2, median (IQR)	25.4 (22.9-29.3)	25.8 (23.4-28.7)	24.6 (23.3-27.7)	0.435[a]
Comorbidities				
Hypertension	40 (71.4%)	157 (77.7%)	51 (77.3%)	0.609[b]
Diabetes	13 (23.2%)	71 (35.1%)	19 (28.8%)	0.199[b]
Coronary artery disease	26 (46.4%)	116 (57.4%)	35 (53.0%)	0.329[b]
Previous PCI	14 (25%)	86 (42.6%)	16 (24.2%)	0.005[b]
Previous CABG	6 (10.7%)	43 (21.3%)	12 (18.2%)	0.199[b]
Lung disease	8 (14.3%)	35 (17.3%)	19 (28.9%)	0.072[b]
PAD	2 (3.6%)	45 (22.3%)	11 (16.7%)	0.005[b]
Stroke	1 (1.8%)	33 (16.3%)	16 (24.2%)	0.002[b]
Porcelain aorta	0 (0%)	34 (16.8%)	2 (3%)	0.000[b]
Liver cirrhosis	0 (0%)	1 (0.5%)	2 (3%)	0.128[b]
Prior thoracic radiotherapy	0 (0%)	4 (2.0%)	0 (0%)	0.294[b]
CrCl ($\leq$30 ml/min)	7 (12.5%)	46 (22.8%)	17 (25.8%)	0.167[b]
Left ventricular function				
Ejection fraction $\leq$40%	4 (7.1%)	36 (17.8%)	18 (27.3%)	0.015[b]
Surgical risk scores				
EuroSCORE I, median (IQR)	9.8 (8.1-16.9)	16.8 (11.4-25.7)	18.4 (12.8-31.1)	0.000[a]
EuroSCORE II, median (IQR)	3.6 (2.5-5.5)	5.3 (3.6-8.7)	4.8 (3.8-7.6)	0.005[a]
STS mortality, median (IQR)	3.1 (1.8-5.2)	5.1 (3.5-7.0)	4.6 (2.8-6.4)	0.000[a]

BMI: body mass index; CABG: coronary artery bypass surgery; CrCl: creatinine clearance; IQR: interquartile range; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons score.
[a] Kruskal-Wallis test.
[b] Chi-square test.

Table 2 Success of TAVI procedure and causes of reintervention.

Variable, n (%)	
Procedural success (n=202)	197 (97.5%)
Causes of reintervention (n=5)	
Prosthesis migration to LVOT	1 (20%)
Prosthesis embolization to aorta	2 (40%)
Access failure[a]	2 (40%)

LVOT: left ventricular outflow tract.
[a] In two patients the first approach via a transapical route was unsuccessful, so they were later reintervened by another route.

Population characteristics

The characteristics of patients in the different treatment groups are shown in Table 1.

In all groups patients were mostly female. The medical therapy group had a higher median age than the other groups and patients undergoing SAVR were younger overall (p=0.023).

The most prevalent comorbidities were hypertension, diabetes and coronary artery disease. The TAVI group included a significantly higher number of patients previously treated by coronary angioplasty (p=0.005). The medical therapy group showed a higher prevalence of comorbidities such as lung disease, history of stroke and chronic kidney disease (stages 4 and 5). This group also presented a higher incidence of left ventricular dysfunction, followed by the TAVI group (p=0.015). Comorbidities such as porcelain aorta, liver cirrhosis and prior thoracic radiotherapy were only found in the TAVI and medical therapy groups, since these patients were considered inoperable.

Comparing the most used surgical risk scores, the medical therapy group had a higher median logistic EuroSCORE I (18.4%), followed by the TAVI group (16.8%) ($p \leq 0.001$), but the median values of both groups were below 20%. Mortality predicted by the EuroSCORE II and Society of Thoracic Surgeons (STS) scores was higher in the TAVI group, followed by the medical therapy group (p=0.005 and p<0.001, respectively). The SAVR group presented the lowest risk scores.

Patient selection for different treatments

In the eight years of the program, 207 TAVI procedures were performed in 202 patients. The procedure was successful in 97.6% of cases (Table 2). A total of five cases needed reintervention, mostly (n=3) due to prosthesis migration.

The median time between the heart team's decision and bioprosthesis implantation was 70 days (IQR 34-129).

The most frequent implantation route was transfemoral (64.3%), followed by transapical (30.9%) (Table 3). The CoreValve® system was the most used device (58.0%), followed by the Edwards Sapiens® (39.1%). Table 4 describes the main characteristics of the percutaneous aortic valve implantation.

Most of the patients selected for SAVR underwent isolated valvular intervention (85.7%). Only a minority also underwent associated coronary artery bypass surgery (14.3%).

Table 3 Implantation route and type of valve implanted in transcatheter aortic valve implantation procedures.

Variable, n (%)	n=202 patients, 207 procedures
Implantation route	
Transfemoral	133 (64.3%)
Transapical	64 (30.9%)
Subclavian	6 (2.9%)
Transaortic	4 (1.9%)
Type of valve implanted	
Medtronic CoreValve®	113 (54.6%)
Edwards Sapien XT®	78 (37.7%)
St. Jude Portico®	4 (1.9%)
Boston Lotus Valve®	2 (1%)
Medtronic CoreValve Evolut®	7 (3.4%)
Edwards Sapien 3®	3 (1.4%)

This table includes the first intervention and the five cases of reintervention.

Patients were refused for any kind of invasive intervention for a variety of reasons (Table 5). The most frequent reason was predicted lack of improvement of quality of life after the procedure due to comorbidities (39.4%), which included several patients with severe chronic lung disease. The second most frequent cause was life expectancy of less than a year (18.2%), in most cases due to diagnosed cancer at the time of TAVI assessment. The third most frequent reason was frailty (12.2%), an extreme vulnerability to adverse events as determined by the heart team, usually based on very low gait speed, severely decreased muscle mass and/or malnutrition. The fourth was the presence of associated severe disease of other valves making a major contribution to the patient's symptoms (all patients with concomitant severe mitral disease). Although patients were refused predominantly for clinical reasons, some were also rejected for technical reasons, including inadequate annulus size (3.0%) or the absence of a route for a TAVI procedure (1.5%).

Note that a substantial proportion (25.8%) of all patients included in the medical therapy group (89 patients) refused any invasive therapy, either TAVI or SAVR (Figure 2).

Long-term follow-up

Over a median follow-up of 49 months (95% confidence interval 43-55), comparison of the different therapeutic strategies revealed higher mortality in the medical therapy group (57.6%) followed by the TAVI group (37.6%) (Table 6). Mortality at 30 days post-procedure (SAVR vs. TAVI) was almost the same in both groups, slightly higher in the SAVR group.

Analysis of the Kaplan-Meier curves for the different therapeutic strategies shows that after an initial stage in which the surgical procedure and TAVI had higher periprocedural mortality, both subsequently depart from the medical therapy survival curve (Figure 3). Although SAVR appears to present a more favorable survival curve, there was no statistically significant difference in comparison with TAVI (p=0.130). Survival curves for both TAVI and SAVR were significantly different from that of the medical strategy.

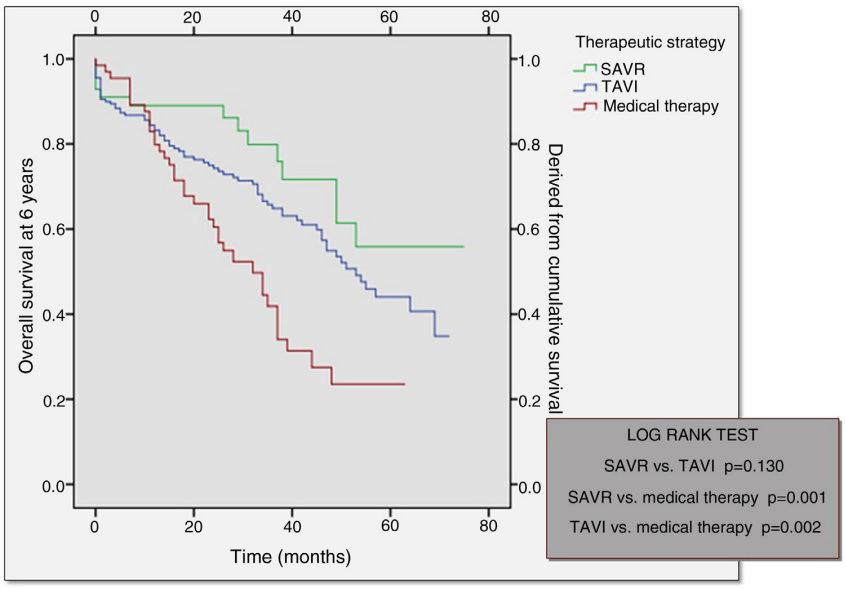


Figure 3 Kaplan-Meier curves of the different therapeutic strategies. SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

Discussion

The main contribution of this study is to provide evidence that implementation of a heart team, as recommended by the guidelines for treatment of severe aortic stenosis, should be performed prospectively under a well-defined, ongoing and carefully staged protocol that enables the activation of a multidisciplinary team that can provide all available therapies (TAVI, SAVR and conservative treatment).

Our group foresaw that patient selection would have a crucial role in the success of transcatheter aortic valve implantation, and thus a visionary multidisciplinary program was set in place. The heart team has become fundamental in the assessment of patients based on their risk profile and the technical suitability of TAVI.[1,4–6,8,9,11–16] In the current context of an increasing elderly population, the availability of new treatments for severe aortic stenosis requires multidisciplinary clinical expertise for the accurate diagnosis of heart valve disease and assessment of comorbidities and risks of intervention, in addition to the rationalization of resources, considering the complexity and high costs of TAVI.[10] The technique should be performed in centers of excellence with a trained multidisciplinary heart team treating a minimum of 50 cases per year, appropriate technical facilities and a prospective registry for monitoring purposes.[14]

A broad group of specialists is required to assess these patients and to provide a rapid selection process, since short-term mortality in these patients is significant.[2,14,15] Our experience reports 45 deaths during the assessment phase (9.5%) and 15 deaths in patients after complete assessment awaiting SAVR or TAVI (3.2%). This highlights the severity of the disease and shows the need for a faster assessment process and treatment. Our median time of 70 days between the decision to perform TAVI and implantation of the bioprosthesis seems excessive, and this recently prompted our center to expand its multislice CT scan facility, which hopefully will reduce this delay.

Multidisciplinary interaction between physicians is needed, enabling all the patient's biopsychosocial characteristics to be considered.[10] The clinical cardiologist is responsible for patient selection and indication and for pre- and post-procedure follow-up.[10] The interventional cardiologist is responsible for organizing the heart team and monitoring procedural performance,[10] while the cardiovascular surgeon is responsible for performing transaortic and transapical procedures, assisting with the transfemoral approach, and treating possible complications.[10] The echocardiographer is responsible for anatomical and functional characterization of the diseased valve, intraoperative assessment of correct positioning of the prosthesis, and monitoring of post-procedural complications.[10] The heart team also includes other professionals such as anesthetists, nurses and physical therapists. The consensus nowadays is not to perform a TAVI procedure in sites lacking a heart team.[10]

TAVI is currently recommended in symptomatic patients with severe AS who are at high surgical risk or are considered ineligible for SAVR.[1,6,8,13,14] Surgical risk has been traditionally assessed using scores such as EuroSCORE and STS. A logistic EuroSCORE I of over 20% and a STS mortality score of more than 10% have been proposed as indicators of high surgical risk (in combination with clinical judgment).[17] A EuroSCORE II cut-off of 7% appears to be equivalent to a Logistic EuroSCORE of 20% or an STS score of 10%.[11] In our center, both the TAVI and medical therapy groups presented lower values than these. This variability of calculated scores has been described in other TAVI populations.[9,11,18,19]

Table 4 Main characteristics of prosthetic aortic valves used in transcatheter aortic valve implantation procedures.

Features	Sapiens XT Ascendra	Sapiens Certitude	Engager	Symetis Acurate	Sapiens XT Novoflex+	Sapiens Commander	CoreValve	CoreValve Evolut R	Portico	Lotus
Implantation route	TA/TAo	TA/TAo	TA	TA	TF	TF	TF/TAo/Sc	TF/TAo/Sc	TF/Sc	TF
Time of preparation	Medium	Medium	Medium	Medium	Medium	Medium	Slow	Slow	Medium	Fast
Profile	24-26F	18F	29F	28F	16-20F	14-16F	18F	14F	18F	18F
Repositioning	No	No	Yes	No	No	No	No	Yes	Yes	Yes
Recapture	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Release	Balloon	Balloon	SE	SE	Balloon	Balloon	SE	SE	SE	Mechanical
Pericardial tissue	Bovine	Bovine	Bovine	Porcine	Bovine	Bovine	Porcine	Porcine	Porcine + bovine	Bovine
Radiopaque marker	No	No	No	Yes	No	No	No	No	Yes	Yes

Sc: subclavian; SE: self-expandable; TA: transapical; TAo: transaortic; TF: transfemoral.

Table 5 Reasons given by the heart team for rejecting patients for surgical aortic valve replacement or transcatheter aortic valve implantation.

Variable, n (%)	n=66
Improvement of quality of life by TAVI unlikely because of comorbidities	26 (39.4%)
Life expectancy <1 year	12 (18.2%)
Frailty	8 (12.2%)
Associated severe primary disease of other valves making a major contribution to the patient's symptoms	6 (9.1%)
Significant clinical improvement after medical therapy or angioplasty	4 (6.1%)
Severe left ventricular dysfunction, without contractile reserve	3 (4.5%)
Inadequate annulus size (<18 mm)	2 (3.0%)
Severe anemia, unable to receive blood transfusions if needed or contraindication to APT	2 (3.0%)
Extreme left ventricular hypertrophy	1 (1.5%)
No access for valve implantation	1 (1.5%)
Active endocarditis	1 (1.5%)

APT: antiplatelet therapy; TAVI: transcatheter aortic valve implantation.

A French center reported only half of patients reaching these threshold values.[11] This is explained by the fact that these scoring systems were created on the basis of standard cardiac surgery databases and are thus unable to assess serious conditions that many of these patients suffer from.[1,5,18,20,21] Comparison between the scores shows no significant differences in discriminatory power, and correlation between them appears to be at best modest.[11,20] In the real world, the available surgical risk scores do not accurately predict mortality after TAVI.[21] New promising and more accurate scores are emerging to replace the currently used surgical risk scores, including variables such as porcelain thoracic aorta, anemia, left ventricular dysfunction, recent myocardial infarction and critical aortic valve stenosis.[22] For this reason, a heart team composed of individuals trained in systematic patient assessment enables better selection of individuals who may benefit from the various treatment strategies until more reliable risk scores become available.

In this cohort the main causes for patients being refused any kind of invasive procedure were low life expectancy and the presence of severe comorbidities which made TAVI unlikely to improve quality of life.[1] One of these comorbidities is chronic obstructive pulmonary disease, which is associated with higher mortality at mid-term follow-up in patients undergoing TAVI.[23] One study has revealed that TAVI was futile in more than one third of these patients and that a shorter distance in the six-minute walk test was a predictor of lack of benefit.[23]

Frailty was the third most common reason for patients being refused for TAVI in our center. Frailty syndrome is characterized by decreased muscle mass and energy expenditure and malnutrition, leading to extreme vulnerability to adverse events.[6,24] A study assessing the frailty status of 159 patients through assessment of gait speed, grip

Table 6 Mortality in the different treatment groups.

	SAVR (n=56)	TAVI (n=202)	Conservative therapy (n=66)	p
Total mortality	14 (25%)	76 (37.6%)	38 (57.6%)	0.001
Mortality 30 days	4 (7.1%)	9 (4.4%)	-	-
Mortality 30 days-1 year	2 (3.6%)	23 (11.4%)	13 (19.7%)	-
Mortality 1-3 years	3 (5.4%)	26 (12.9%)	19 (28.8%)	<0.00111
Mortality 3-5 years	5 (8.9%)	16 (7.9%)	6 (9.1%)	0.001
Mortality >5 years	-	2 (1%)	-	-

SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation.

strength, serum albumin and degree of independence in daily activities determined that frailty was not associated with increased periprocedural complications in patients selected for TAVI, but was associated with increased one-year mortality after the procedure.[24] Our assessment of patients' frailty was mostly subjective. This is a limitation, and the use of objective measurements and questionnaires has since been implemented.

Other comorbidities not included in current scores are liver cirrhosis, porcelain aorta and prior radiotherapy.[1,4–6] Furthermore, assessment of neurocognitive function, functional status, mobility, and supports is increasingly being recognized as important in patient selection.[8] The heart team is thus crucial in individualized patient assessment.[1,5,6] This is particularly important in the current environment of limited resources.[6] In the future a validated risk score for TAVI will probably be created, similar to the logistic EuroSCORE, EuroSCORE II and STS mortality score for surgical procedures, taking into account many variables already considered in the assessment process.[5,6,18,22]

Another important heart team decision is that of revascularization of coronary artery disease, which is often found coexisting with valvular disease, since they share the same risk factors.[5,7] Up to three-quarters of patients undergoing TAVI have coronary artery disease.[5] The optimal management of these patients is not well defined. Some authors argue that a staged approach (percutaneous coronary intervention followed by TAVI) is prudent in patients with lesions in the left main or proximal arteries (especially if dominant in the case of the right coronary artery or circumflex artery).[5] Although this reduces procedure time, radiation and contrast exposure, it requires arterial access twice, with inherent risk for vascular and bleeding complications and additional hospitalization costs.[7] In the elderly population with severe AS who undergo TAVI, coronary revascularization is usually incomplete.[7] Judicious decisions concerning revascularization (not always deciding on complete revascularization) are more likely to achieve favorable mid-term outcomes.[7]

Anatomical assessment of patients is also essential, including arterial vasculature and the aortic valve apparatus (including the left ventricular outflow tract, aortic annulus diameter, sinus of Valsalva, sinotubular junction, ascending aorta and degree of calcification), to choose the most appropriate access route and transcatheter valve size.[4–6,8,15] Which approach is used (transfemoral vs. transapical) has no prognostic value in acute and late outcomes.[16] Usually the transfemoral approach is preferred, and an alternative route is only selected if there is a prohibitively small or diseased iliofemoral arterial system, mobile plaque, excessive calcification, or extreme tortuosity of the descending thoracic aorta.[4,6,8,15] The fact that the most frequent implantation route was transfemoral (64.3%) reflects our strategy of implanting on the first available date without selecting a route if individually possible. This enabled the earliest treatment for each patient to be chosen.

The choice of prosthetic aortic valve is another important issue. As pointed out above, several devices are currently available with different characteristics that confer benefits in different clinical settings. For example, repositioning features are required for cases of extreme aortic calcification, potential coronary obstruction, bicuspid aortic valve, aortic regurgitation, valve-in-valve technique or left ventricular septal hypertrophy. Radiopaque markers are particularly useful in chronic kidney disease patients. The self-expandable feature is important when there is significant concomitant aortic regurgitation.

TAVI has been shown to be a feasible procedure.[1,4–6,8] One-year survival rates of 60-80% are reported, depending on the severity of comorbidities.[1,8] In our population the survival rate of TAVI patients at one-year follow-up was 84.1%. Mortality at 30 days was 4.4%, lower than the 9-10% usually described in other series.[18]

The literature on TAVI vs. SAVR for patients at high surgical risk shows that major adverse outcomes are similar between the two treatment modalities.[3] However, the results are limited by inconsistent patient selection criteria, heterogeneous definitions of clinical endpoints and relatively short follow-up periods.[3]

As in our population, other studies show that after an initial stage in which the surgical procedure and TAVI had higher periprocedural mortality, both subsequently depart from the conservative therapy survival curve, showing a better outcome.[19] Although SAVR appeared to present a more favorable survival curve, this was not statistically significant difference from that of TAVI, both having comparable survival curves at one year. SAVR performed in centers with a TAVI program is associated with significantly lower mortality and complication rates than that performed in centers without a TAVI program.[25]

A heart team approach is essential for TAVI in the current management of patients with severe aortic stenosis. This applies at each step of the procedure: patient selection, performance of the procedure, post-procedural care and evaluation of the results.[26]

Conclusions

A prospective multidisciplinary heart team program was able to appropriately select candidates for transcatheter aortic valve implantation, surgical aortic valve replacement and conservative treatment, matching the risk of both invasive treatments. The study is unique because it demonstrates the success of a standardized approach that requires continuous monitoring to be efficient in a timely manner.

Key points

What is known about the topic?

- The literature available on TAVI vs. SAVR for patients at high surgical risk shows that major adverse outcomes are similar between the two treatment modalities. However, the results are limited by inconsistent patient selection criteria, heterogeneous definitions of clinical endpoints and relatively short follow-up periods.
- A heart team assessment is considered central to the selection of patients with severe AS. This applies at each step of the procedure: patient selection, performance of the procedure, post-procedural care and evaluation of the results.
- Despite its importance, there is a marked lack of publications in this area.

What does this study add?

- The heart team is crucial for individualized assessment of patients. This is particularly important in the current environment of limited resources.
- The main contribution of this study is to provide evidence that implementation of a heart team, as recommended by the guidelines for treatment of severe aortic stenosis, must be performed prospectively under a well-defined, ongoing and carefully staged protocol that enables the activation of a multidisciplinary team that can provide all available therapies (TAVI, SAVR and conservative treatment).
- This standardized approach requires continuous monitoring to be efficient in a timely manner.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Post-procedural N-terminal pro-brain natriuretic peptide predicts one-year mortality after transcatheter aortic valve implantation

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KEYWORDS
Transcatheter aortic valve replacement;
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Prognosis

Abstract
Introduction: Natriuretic peptides are ubiquitously used for diagnosis, follow-up and prognostic assessment in various heart conditions. N-terminal pro-brain natriuretic peptide (NT-proBNP) correlates with aortic stenosis severity, however its significance after transcatheter aortic valve implantation (TAVI) is not well established.
Aim: We aimed to assess the prognostic value of NT-proBNP at one year in patients undergoing TAVI.
Methods: This single-center retrospective analysis included 151 patients in whom both baseline and one-month post-procedure NT-proBNP were measured, from 206 consecutive patients undergoing TAVI between November 2008 and December 2014. The best cut-off values of both baseline and one-month post-TAVI NT-proBNP for one-year mortality were determined by receiver operating characteristic curve analysis. Independent predictors of one-year mortality were assessed by Cox regression.
Results: The areas under the curve of baseline and post-procedural NT-proBNP for one-year mortality were 0.60 and 0.72, with the best cut-off values of 1350 and 2500 pg/ml, respectively. Atrial fibrillation, procedure-related major bleeding, baseline NT-proBNP higher than 1350 pg/ml, post-procedural NT-proBNP higher than 2500 pg/ml, higher creatinine and Society of Thoracic Surgeons score, and lower left ventricular ejection fraction were associated with one-year mortality. Only post-procedural NT-proBNP was independently and negatively associated with one-year survival (HR 5.9, 95% CI 1.6-21.7, p=0.008).

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Conclusions: Baseline NT-proBNP did not predict one-year mortality; on the other hand one-month post-procedural NT-proBNP higher than 2500 pg/ml may identify a high-risk subset of patients, allowing better management, care and hypothetically outcome.
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PALAVRAS-CHAVE
Válvula aórtica percutânea;
Estenose aórtica;
N-terminal pro-BNP;
Prognóstico

O peptídeo natriurético cerebral N-terminal prediz a mortalidade a um ano após implantação de válvula aórtica percutânea

Resumo
Introdução: Os peptídeos natriuréticos são usados de forma ubíqua para o diagnóstico, seguimento e avaliação prognóstica em cardiologia. O NT-ProBNP correlaciona-se com a gravidade da estenose aórtica, porém o seu significado após VAP não está bem estabelecido.
Objetivo: Avaliar o valor prognóstico do NT-ProBNP nos doentes submetidos a VAP.
Métodos: Análise retrospetiva de 151 doentes, de um registo de 206 doentes consecutivos de novembro de 2008 a dezembro de 2014, com doseamentos de NT-ProBNP basal e após um mês da implantação de VAP. Os preditores independentes de mortalidade a um ano foram avaliados por regressão Cox.
Resultados: Os melhores valores discriminativos de NT-ProBNP basal e pós-procedimento foram 1.350 e 2.500, respetivamente. Somente um valor de NT-ProBNP pós-procedimento superior a 2.500pg/ml foi preditor independente e negativamente associado à sobrevida a um ano (HR 5,9; 95% IC 1,6-21,7; p = 0,008).
Conclusões: O NT-ProBNP basal não previu a mortalidade a um ano. Por outro lado, o NT-ProBNP superior a 2.500pg/ml após o procedimento identificou um subgrupo de doentes de alto risco, permitiu um melhor manejo, seguimento e possíveis resultados.
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Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a safe and effective alternative to surgical aortic valve replacement (SAVR) in high-risk or inoperable patients with severe aortic stenosis.[1] Refinement in patient selection has prompted the use of multiple risk scores and analytical parameters to help predict outcomes. Most have been ineffective in that regard, with limited performance in this population with numerous comorbidities.[2]

Patients with severe aortic valve stenosis have elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, due to increased myocardial wall stress and pressure overload.[3] Increased concentrations of this peptide have prognostic value in multiple heart conditions, and can be used for risk stratification.[4,5] There is a correlation between NT-proBNP levels and severity of aortic stenosis.[4] The post-procedural impact of NT-proBNP has been studied,[6–9] and found to predict one-year mortality.[10] However there is no established threshold beyond which outcomes worsen.

We sought to analyze the one-year prognostic value of NT-proBNP levels before and at one month after TAVI.

Methods

Patient population and data collection

The Valve Catheter Restorative Operation on Santa cruz hoSpital (VCROSS) registry is an all-comer prospective single-center observational study that includes all consecutive patients with symptomatic aortic stenosis undergoing TAVI. Between November 2008 and December 2014 a total of 206 patients were treated, of whom 55 were excluded from this analysis (Figure 1): 46 patients deviated from the protocol for baseline or post-procedural NT-proBNP collection (five patients died before the 30-day assessment) and nine had follow-up in different institutions. A total of 151 patients thus entered the final analysis.

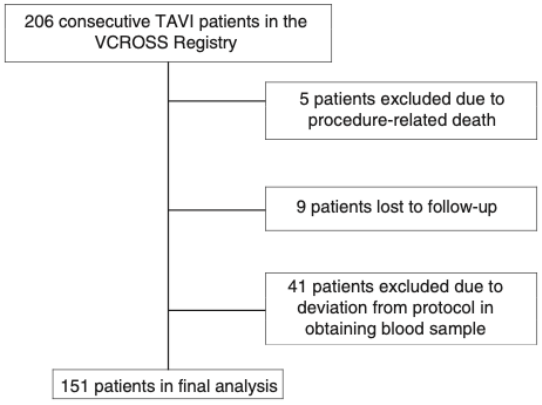


Figure 1 Study population. TAVI: transcatheter aortic valve implantation.

All data concerning demographic, clinical, laboratory and procedural characteristics were prospectively entered in our dedicated institutional database (Cardiobase™, Infor-TUCANO). Post-discharge clinical follow-up was performed during scheduled outpatient visits or telephone interviews. NT-proBNP (chemiluminescence immunoassay, Roche, Minneapolis, MN; normal reference value <125 pg/ml) and other routine blood test parameters were measured in all analyzed patients in the week before and one month after the TAVI procedure. We calculated the difference and the ratio between pre- and post-procedural NT-proBNP and used them as independent variables.

A multidisciplinary heart team discussed and determined the implantation approach based on individual patient characteristics.[11] Complications were reported according to the Valve Academic Research Consortium-2 classification.[12]

Statistical analysis

Continuous variables were expressed as means and standard deviation when normally distributed and as medians and interquartile range (IQR) when not normally distributed. Normality was tested with the Kolmogorov-Smirnov test and/or visual assessment of Q-Q plots. Discrete variables were expressed as frequencies and percentages.

Baseline characteristics and outcomes were compared using the chi-square test or Fisher's exact test, when appropriate, for categorical variables, and the Student's t test or the Mann-Whitney U test for continuous variables, according to normality. Related non-normally distributed variables were compared by the Wilcoxon signed test.

The discriminative ability of baseline and post-procedural NT-proBNP was assessed by receiver operating characteristic (ROC) curve analysis. Areas under the curve (AUC) were compared by the method of DeLong et al. The best cut-off value of baseline and post-procedural NT-proBNP for one-year mortality determined by C-statistics was used to dichotomize the population, converting NT-proBNP into a categorical variable.

The ability of baseline and post-procedural NT-proBNP to predict one-year mortality above the best cut-off value was assessed by Cox regression including clinically significant variables shown to be associated with one-year mortality in univariate analysis.

Event-free survival was computed using Kaplan-Meier estimates and the log-rank test was used for comparison.

All tests were two-sided and differences were considered statistically significant at a p-value of 0.05. The statistical analysis was performed with SPSS 20.0 software (IBM SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The overall baseline clinical characteristics of the study population are shown in Table 1.

Procedure-related characteristics and outcomes

One hundred and twenty procedures (79%) were performed by a transfemoral approach. The devices implanted were

Table 1 Baseline characteristics of the study population.

	Total (n=151)	Alive at 1 year (n=132)	Dead at 1 year (n=19)	p
Age, years	81.5±7.6	81.2±7.7	82.9 (±6.3)	0.29
Female, n	94 (62%)	85 (63.9%)	9 (47.4%)	0.21
BMI, kg/m^2	26.2±4.6	26.2±4.5	26.1±5.6	0.24
Diabetes, n	46 (30.3)	37 (27.8%)	9 (47.4%)	0.109
CAD, n	74 (48.7%)	65 (48.9%)	9 (47.4%)	1.00
AF, n	34 (22.4%)	26 (19.5%)	8 (42.1%)	0.039
CRD, n	47 (31%)	38 (28.8%)	9 (47.4%)	0.11
PAD, n	24 (15.8%)	20(15%)	4 (21%)	0.50
Previous stroke or TIA, n	20 (13.2%)	17 (12.8%)	3 (15.8%)	0.72
Liver failure, n	2 (1.3%)	2 (1.5%)	0 (0%)	1.00
Pulmonary disease, n	20 (13.2%)	17 (12.8%)	3 (15.8%)	0.72
Previous MI, n	17 (11.2%)	15 (11.3%)	2 (10.5%)	1.00
Previous cardiac surgery, n	41 (27%)	34 (25.6%)	7 (36.8%)	0.40
LVEF, % [IQR]	55 [46-67]	55 [50-68]	55 [40-57]	0.034
LVEF <35%, n	14 (9.2%)	10 (7.5%)	4 (21.1%)	0.077
NYHA class III/IV, n	110 (72.4%)	97 (73%)	13 (68.4%)	0.78
EuroSCORE II [IQR]	5.4 [3.4-8.8]	5.5 [3.5-8.8]	4.6 [2.3-6.6]	0.24
STS mortality score [IQR]	5.3 [3.6-7.5]	5.1 [3.5-7.2]	6.3 [4.8-10.3]	0.028
Hemoglobin, g/dl	11.7±1.5	11.7±1.5	11.5±1.6	0.61
Creatinine, mg/ml [IQR]	0.9 [0.63-1.2]	0.88 [0.59-1.17]	1.15 [0.86-1.48]	0.034
TF access	120 (78.9%)	106 (79.7%)	14 (73.7%)	0.55

AF: atrial fibrillation; BMI: body mass index; CAD: coronary artery disease; CRD: chronic renal disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PAD: peripheral arterial disease; STS: Society of Thoracic Surgeons; TF: transfemoral; TIA: transient ischemic attack.

Table 2 Complications according to the Valve Academic Research Consortium-2 classification.

	Total	Alive at 1 year (n=132)	Dead at 1 year (n=19)	p
1-year mortality	19 (12.5%)	–	–	–
MI	22 (14.5%)	18 (13.5%)	4 (21.1)	0.482
Stroke	6 (3.9%)	6 (4.5%)	0 (0.0%)	1.0
AKIN 2/3	5 (3.3%)	3 (2.3%)	2 (10.5%)	0.12
Major bleeding	12 (7.9%)	7 (5.3%)	5 (26.3%)	0.008
Moderate to severe leak	23 (15.1%)	18 (13.5%)	5 (26.3%)	0.17
Pacemaker implantation	32 (21.1%)	27 (20.3%)	5 (26.3%)	0.55

AKIN: Acute Kidney Injury Network classification; MI: myocardial infarction.

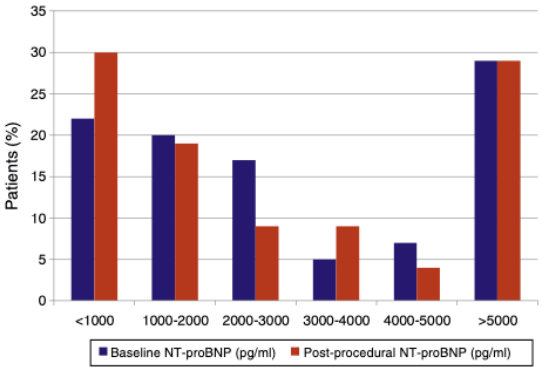


Figure 2 Distribution of baseline and post-procedural N-terminal pro-brain natriuretic peptide levels. NT-proBNP: N-terminal pro-brain natriuretic peptide.

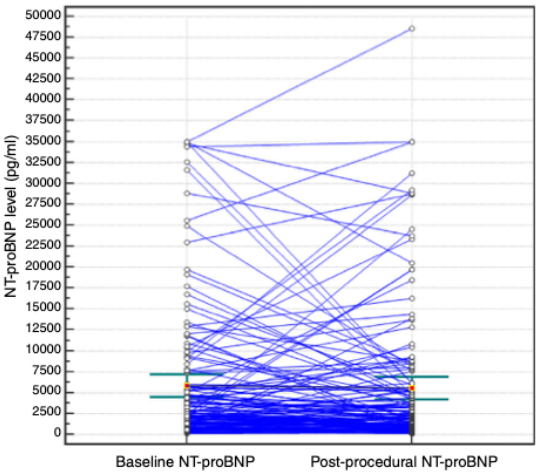


Figure 3 Periprocedural variations in NT-proBNP levels by patient. NT-proBNP: N-terminal pro-brain natriuretic peptide.

102 self-expandable valves (102 CoreValve™, Medtronic®), 43 balloon-expandable valves (Sapiens™, Edwards®) and two Lotus™, Boston Scientific®, mechanical expandable and four Portico™, St Jude®. Procedural outcomes and complications are depicted in Table 2.

N-terminal pro-brain natriuretic peptide levels before and after the procedure

The median NT-proBNP levels pre- and post-procedure were 2335 pg/ml (IQR 1200-5787) and 2175 pg/ml (IQR 795-5589), respectively, and did not differ significantly (p=0.118). The median difference was 316 pg/ml (IQR [-125]-1708). The median of the ratio between NT-proBNP levels pre- and post-procedure was 1.2 (IQR 0.66-2.4). Ninety-six patients (63%) experienced a decrease in NT-proBNP after the procedure; the median decrease was 1110 pg/ml (IQR 349-3411). In patients with increased NT-proBNP (n=56, 37%), the median change was 1895 pg/ml (IQR 737-6240). NT-proBNP distribution and variation are shown in Figures 2 and 3.

One-year mortality

Overall one-year all-cause mortality was 12.6% (19/151). Patients who died had significantly higher Society of Thoracic Surgeons (STS) mortality scores, with more comorbidities including chronic renal disease and atrial fibrillation, and lower left ventricular ejection fraction and glomerular filtration rate (GFR) (Table 1). Periprocedural major bleeding was also associated with higher one-year mortality (Table 2). As for NT-proBNP as a continuous variable, only post-procedural values were shown to be associated with one-year mortality. We dichotomized both baseline and post-procedural NT-proBNP by the best cut-off value for one-year mortality determined by ROC curve analysis. The best cut-off values of baseline and post-procedural NT-proBNP were 1350 and 2500 pg/ml, respectively. Values above both thresholds were associated with one-year mortality (Table 3).

Of the 19 patients who died within a year of the procedure, 18 (95%) had baseline NT-proBNP higher than 1350 pg/ml and 16 (84%) had post-procedural NT-proBNP above 2500 pg/ml (Table 3). The median baseline and post-procedural NT-proBNP of these patients were 2860 (IQR 2000-9190) and 3840 (IQR 2650-19700) pg/ml and did not differ significantly (p=0.227 for comparison).

Discriminative ability

Post-procedural NT-proBNP discriminated one-year mortality numerically, but not significantly better than baseline NT-proBNP (AUC=0.72 for post-procedural NT-proBNP vs. AUC=0.60 for baseline NT-proBNP, p=0.12) (Figure 4).

Table 3 Association of N-terminal pro-brain natriuretic peptide levels with one-year survival.

	Total (n=151)	Alive at 1 year (n=132)	Dead at 1 year (n=19)	p
Pre, pg/ml [IQR]	2335 [1200-5787]	2290 [1130-5550]	2860 [2000-9190]	0.155
Post, pg/ml [IQR]	2175 [795-5589]	1840 [702-5160]	3840 (2650-19700)	0.02
Difference [IQR]	316 [(-125)-1708]	349 [(-748)-1714]	-640 [-2300-660]	0.52
Ratio	1.2 [0.66-2.4]	1.3 [0.69-2.6]	0.85 [0.5-1.2]	<0.001
Pre >1350 pg/ml	110 (72.4%)	92 (69.2%)	18 (94.7%)	<0.025

IQR: interquartile range; Pre: pre-procedural NT-proBNP level; Post: post-procedural NT-proBNP level.

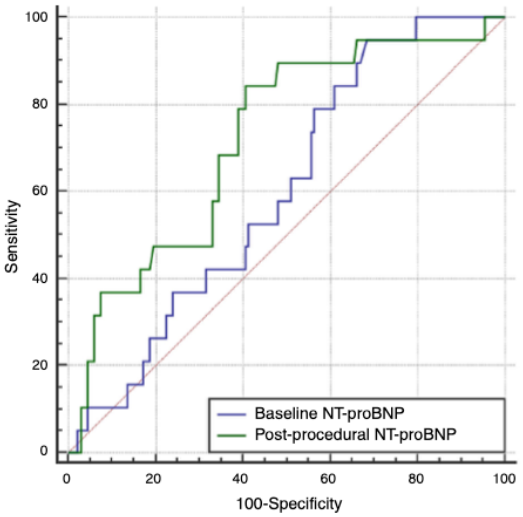


Figure 4 Area under the receiver operating characteristic curve for baseline and post-procedural NT-proBNP (0.60 and 0.72, respectively). NT-proBNP: N-terminal pro-brain natriuretic peptide.

Predictive ability

Multivariate Cox regression showed that only NT-proBNP higher than 2500 pg/ml (hazard ratio [HR] 5.9, 95% confidence interval 1.6-21.7, p=0.008) remained independently and negatively associated with one-year survival (Figures 5 and 6).

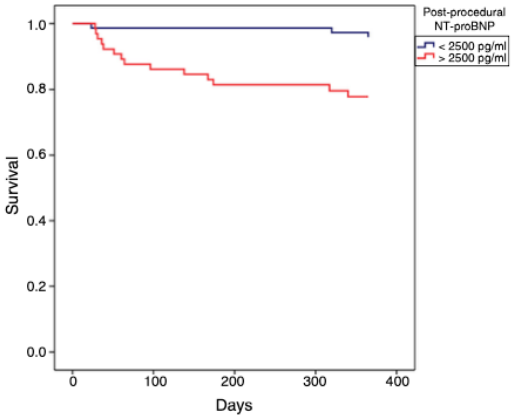


Figure 6 Kaplan-Meier graph of all-cause mortality in patients with NT-proBNP above and below 2500 pg/ml after transcatheter aortic valve implantation. NT-proBNP: N-terminal pro-brain natriuretic peptide.

Discussion

The main findings of the present study were: (1) early variation in NT-proBNP levels (during the first month after TAVI) was highly heterogeneous and the absolute value did not differ significantly from baseline; (2) baseline and post-procedural NT-proBNP above 1350 and 2500 pg/ml, respectively, were both associated with one-year mortality; (3) post-procedural NT-proBNP over 2500 pg/ml was the only independent predictor of one-year mortality on multivariate analysis.

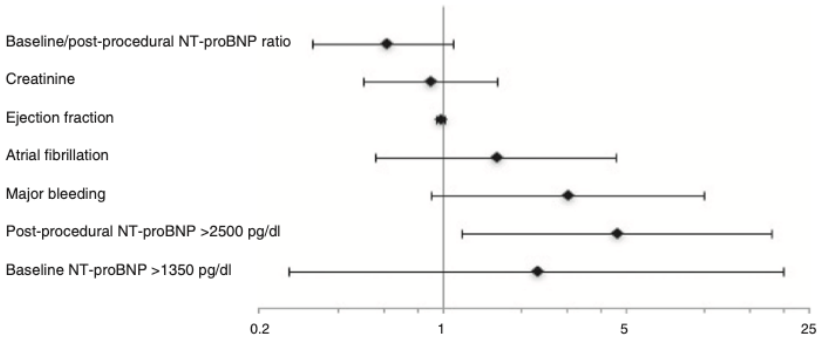


Figure 5 Hazard ratios for one-year mortality. NT-proBNP: N-terminal pro-brain natriuretic peptide.

In our population the variation between pre-procedural and one-month post-procedural NT-proBNP, although not significantly different, was highly heterogeneous (Figure 3). Only 63% of patients had lower NT-proBNP levels at 30 days, a smaller proportion than expected. As with SAVR,[13] an immediate increase is often observed shortly after TAVI,[14] due to hemodynamic fluctuations, fluid shifts and transient increases in wall tension during the procedure. Though a steady decrease is expected thereafter,[7] it is not clear when this happens, as it may be affected by baseline clinical characteristics such as GFR, obesity, gender, other cardiac comorbidities and procedure-related features including access route, acute kidney injury and post-procedural bleeding. Improvement in afterload after TAVI is similar to that of SAVR patients,[14] however baseline NT-proBNP is usually higher in the former as a result of TAVI being performed in older patients with more comorbidities, therefore the absolute reduction may be similar but the relative change is smaller. Notwithstanding, the lack of difference between baseline and post-procedural NT-proBNP in our cohort may be because patients in whom NT-proBNP increased (37%) had a higher absolute change in NT-proBNP values.

After dichotomization by the best cut-off value determined by ROC curve analysis, patients with NT-proBNP levels above these thresholds had higher mortality. However, after adjustment for other variables, only post-procedural NT-proBNP was independently associated with mortality (HR 5.9). Discrimination of patients who died from those who survived was numerically but not significantly better for post-procedural NT-proBNP. These findings suggest that post-procedural NT-proBNP has overall better predictive ability for one-year mortality.

The clinical significance of pre-procedural NT-proBNP regarding prediction of mortality remains controversial. One report showed that baseline NT-proBNP could predict mortality at two years,[7] however in other studies, including a subgroup analysis of the Placement of AoRTic TraNscathetER Valve (PARTNER) I trial,[15] baseline BNP levels did not predict one-year mortality. In our cohort we had similar findings to those of PARTNER I. These later results, along with the fact that the absolute difference and the ratio between baseline and one-month post-procedural NT-proBNP did not predict one-year mortality either, suggest that pre-procedural NT-proBNP is a good marker of cardiac overload but may not reflect the stage of myocardial disease and certainly not the overall mortality risk conferred by other comorbidities. On the other hand, one-month post-procedural NT-proBNP was associated with one-year mortality. Konstantinos et al. had previously reported that post-procedural NT-proBNP outperformed all other single measurements as a predictor of all-cause mortality at two years.[7] Notwithstanding this known relationship, there is no established threshold at which outcomes worsen. In our population, one-month post-procedural NT-proBNP above 2500 pg/ml was the best cut-off value for one-year mortality and was shown to be a strong predictor (HR 5.9) of this endpoint in multivariate analysis. Thus post-procedural NT-proBNP might identify patients with advanced irreversible heart disease in whom overload reduction by aortic valve replacement does not change the natural history of the disease.

Predicted life expectancy is crucial in selecting patients for TAVI to minimize the futility of this procedure in very ill patients. We did not find a role for baseline NT-proBNP in predicting mortality, as it appeared to be ineffective in patient selection. Nevertheless, NT-proBNP shortly after a TAVI procedure can identify high-risk patients and help clinicians to predict outcomes and to optimize follow-up and management of heart failure and other comorbidities. Appropriate management may improve the overall prognosis.

Limitations

Some important limitations should be pointed out in our study. First, it has the inherent limitations of a single-center observational study. Second, the excluded patients may have limited the power of the statistical analysis. Third, the study time frame meant that only two types of valves were implanted in our center, using large sheaths for vascular access. This goes against contemporary practice, in which the trend is to use smaller sheaths. Fourth, both transapical and transfemoral access were used, introducing heterogeneity in the analysis, since the effect of apical scarring and remodeling on NT-proBNP levels in patients undergoing transapical TAVI is unknown. Fifth, it is not possible to ascertain the extent to which confounders intrinsic to specific selection criteria for TAVI influenced one-year mortality rates and thus the predictive ability of NT-proBNP. Sixth, patients who died before collection of post-procedural NT-proBNP were not assessed in our analysis, therefore we cannot exclude a possible association with baseline NT-proBNP.

Conclusions

In a TAVI population that survived the early post-procedure period, baseline NT-proBNP did not predict one-year mortality, possibly making it less attractive for patient selection. Importantly, one-month post-procedural NT-proBNP higher than 2500 pg/ml identifies a high-risk subset of patients, allowing better management, care and hypothetically outcome.

Conflicts of interest

The authors have no conflicts of interest to declare

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ORIGINAL ARTICLE

Comparison of multiparametric risk scores for predicting early mortality after transcatheter aortic valve implantation

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KEYWORDS
Aortic stenosis;
Transcatheter aortic valve implantation;
Risk scores;
Early mortality

Abstract
Introduction: Surgical risk scores are widely used to identify patients at high surgical risk who may benefit from transcatheter aortic valve implantation (TAVI). A multiparametric TAVI mortality risk score based on a French registry (FRANCE-2) has recently been developed. The aim of our study was to compare the 30-day mortality prediction performance of the FRANCE-2, EuroSCORE II and STS scores.
Methods: We retrospectively studied 240 patients from a single-center prospective registry who underwent TAVI between January 2008 and December 2015. All scores were assessed for calibration and discrimination using calibration-in-the-large and ROC curve analysis, respectively.
Results: The observed mortality was 5.8% (n=14). The median EuroSCORE II, STS and FRANCE-2 scores were 5.0 (IQR 3.2-8.3), 5.1 (IQR 3.6-7.1) and 2.0 (IQR 1.0-3.0), respectively. Discriminative power was greater for EuroSCORE II (C-statistic 0.67) and STS (C-statistic 0.67) than for FRANCE-2 (C-statistic 0.53), but this was not statistically significant (p=0.26). All scores showed adequate calibration.
Conclusions: All scores showed modest performance in early mortality prediction after TAVI. Despite being derived from a TAVI population, FRANCE-2 was no better than surgical risk scores in our population.
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PALAVRAS-CHAVE
Estenose aórtica;
TAVI;
Scores de risco;
Mortalidade precoce

Comparação do desempenho de *scores* de risco multiparamétricos na predição de mortalidade precoce em doentes submetidos a TAVI

Resumo
Introdução: Os *scores* de risco cirúrgico têm sido amplamente usados para identificar doentes com alto risco cirúrgico que podem beneficiar da implantação de válvula aórtica por via percutânea (TAVI). Foi recentemente apresentado um «*score* de risco» multiparamétrico de mortalidade por TAVI com base num registo francês – FRANCE 2. O objetivo do nosso estudo foi comparar o desempenho do FRANCE 2, EuroSCORE II (ES II) e STS-Prom (STS) em prever a mortalidade a 30 dias nos doentes submetidos a TAVI.
Métodos: Foram estudados retrospetivamente 240 doentes de um registo prospetivo de centro único que foram submetidos a TAVI entre janeiro de 2008 e dezembro de 2015. Todos os *scores* foram avaliados para discriminação e calibração, com o uso da análise de curvas ROC e da análise de *calibration-in-the-large*, respetivamente.
Resultados: A mortalidade observada foi de 5,8% (n = 14). A mediana do ES II, STS II e FRANCE II foi de 5,0 (IQR 3,2-8,3), 5,1 (IQR 3,6-7,1) e 2,0 (IQR 1,0-3,0), respetivamente. O poder discriminatório foi maior para ES II (C-*statistic* 0,67) e STS (C-*statistic* 0,67) quando comparado com o FRANCE 2 (C-*statistic* 0,53), embora não fosse estatisticamente significativo (p = 0,26). Todos os *scores* apresentaram calibração adequada.
Conclusões: Todos os *scores* apresentaram um desempenho modesto em prever a mortalidade precoce após TAVI. Apesar de ser derivado de uma população de doentes submetidos a TAVI, o FRANCE-2 não mostrou ser melhor do que os *scores* de risco cirúrgicos na nossa população.
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Introduction

Transcatheter aortic valve implantation (TAVI) has emerged as a less invasive treatment alternative for patients with severe symptomatic aortic stenosis at high or very high surgical risk.[1,2] Surgical risk scores are established tools for assisting in the decision-making process for these patients. The Society of Thoracic Surgeons Predicted Risk of Mortality[3] (STS) score and the European System for Cardiac Operative Risk Evaluation[4] (EuroSCORE II) are the most commonly used.

A multiparametric risk score for early mortality prediction has recently been derived based on a TAVI population from a French registry (FRANCE-2).[5] In this registry, early mortality after TAVI was mainly related to age, severity of symptoms, comorbidities and access (transapical or other). The FRANCE-2 score is a simple additive score (ranging from 0 to 21) that can be used to predict early mortality after TAVI. In the internal validation, it showed only moderate discriminative ability,[5] reflecting limited accuracy in the identification of high-risk patients.

In this study, we sought to externally validate the STS, EuroSCORE II and FRANCE II scores and to compare their performance in a TAVI population.

Methods

Patient population and data collection

The Valve Catheter Restorative Operation on Santa cruz hoSpital (VCROSS) was a single-center, prospective, observational study that included 240 consecutive patients who underwent TAVI between January 2008 and December 2015. The interventional strategy was decided after multidisciplinary discussion. Acceptance of a patient for TAVI required consensus of the heart team. All data on demographic, clinical, and procedural characteristics were prospectively entered in our institutional cathlab-based dedicated database. Outcome data during hospital admission and during the first 30 days were entered in the same database. The EuroSCORE II and STS scores were calculated using the online calculators. The FRANCE-2 score was calculated manually in each patient by matching the sum of points of the variables with the corresponding prediction, using the published nomogram.[5] The study was approved by the local ethics committee and informed consent was obtained from all patients.

Statistical analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test and/or visual assessment of Q-Q plots. Continuous variables were expressed as median and interquartile range (IQR) and categorical variables were expressed as percentages. Statistical analyses of categorical and continuous variables were performed using chi-square statistics and Fisher's exact test and the Mann-Whitney test, respectively.

The performance of the three models was analyzed focusing on discriminative power and calibration. Discrimination indicates the extent to which the model distinguishes between patients who will or will not die within the first 30 days. It was assessed by constructing receiver operating characteristic (ROC) curves for each model. Comparison

Table 1 Baseline characteristics of the study population.

Characteristic	n=240	Alive at 30 days (n=226)	Dead at 30 days (n=14)	p
Age, years	83 (78-87)	83 (78-87)	82 (74-87)	0.875
Female	57%	57%	43%	0.298
BMI, kg/m^2	26.1 (23.4-28.8)	26.1 (23.6-29.1)	26.6 (25.9-26.9)	0.641
Diabetes	31%	30%	43%	0.327
Coronary artery disease	46%	45%	71%	0.051
Previous cardiac surgery	27%	25%	43%	0.140
Atrial fibrillation	23%	23%	21%	0.914
Cerebrovascular disease	11%	11%	14%	0.721
Respiratory insufficiency[a]	17%	17%	7.1	0.319
Moderate to severe RF	24%	24%	29%	0.683
NYHA III or IV	73%	72%	79%	0.600
LVEF<40%	22%	19%	73%	<0.001
LVEF, %	55 (44-68)	59 (45-68)	37 (30-44)	<0.001
Transfemoral access	66%	66%	71%	0.673
EuroSCORE II	5.0 (3.2-8.3)	5.0 (3.4-7.5)	9.7 (5.6-21.6)	0.027
STS	5.1 (3.6-7.1)	4.9 (3.4-6.8)	5.8 (5.1-7.8)	0.033
FRANCE-2	2.0 (1.0-3.0)	2.0 (1.5-3.0)	2.5 (1.0-3.0)	0.701
Aortic valve area, cm^2	0.70 (0.50-0.80)	0.70 (0.60-0.80)	0.55 (0.50-0.75)	0.390
Mean gradient, mmHg	50 (41-60)	50 (41-60)	34 (32-38)	<0.001

Values are median (interquartile range) unless stated otherwise.
[a] Obstructive or non-obstructive symptomatic respiratory disease.
BMI: body mass index; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RF: renal failure; STS: Society of Thoracic Surgeons.

between curves was assessed with the method described by DeLong et al.[6] Calibration refers to the agreement between observed outcomes and predictions, and was assessed by calibration-in-the-large (which compares the mean observed frequency of 30-day death with the mean predicted probability) and percent discordance ([expected percentage-observed percentage]/observed percentage). Calibration-in-the-large refers to the difference between mean observed frequency and mean predicted probability. A statistically significant result indicates significant miscalibration, whereas a non-significant result supports the validity of the prediction model.

All tests were two-sided and differences were considered statistically significant at a p-value of 0.05. Statistical analysis was performed with IBM SPSS 21.0 software (IBM SPSS Inc., Chicago, IL, USA) and MedCalc version 9.3.8.0 (MedCalc Software, Acacialaan, Ostend, Belgium).

Results

The mean age of the study population was 81±7 years, 57% were female and 72% presented with New York Heart Association class III or IV. Mean aortic gradient and valve area were 51.3 ± 15.7mmHg and 0.68±0.18cm^2, respectively, 53 patients (22%) had reduced left ventricular ejection fraction (LVEF) (<40%), 65 (27%) had previous cardiac surgery and 58 (24%) had moderate to severe renal failure (six were on dialysis). The baseline characteristics are shown in Table 1. Transfemoral access was chosen in two-thirds of patients; alternative approaches were transapical, and less commonly transaortic and subclavian. Four types of devices were implanted: the balloon-expandable Sapien (Edwards Lifesciences®), the first-generation self-expandable CoreValve (Medtronic®), Portico (St. Jude Medical®), and Lotus (Boston Scientific®).

Mortality

There were 14 deaths in the first 30 days (5.8%). Patients who died more frequently had lower LVEF and mean transaortic gradient. There was a trend for higher mortality in patients with coronary artery disease (Table 1).

Performance of mortality prediction scores

Discriminative power

The median EuroSCORE II, STS and FRANCE-2 scores were 5.0 (IQR 3.2-8.3), 5.1 (IQR 3.6-7.1) and 2.0 (IQR 1.0-3.0), respectively, with a corresponding 30-day mortality prediction of 8%.

EuroSCORE II and STS discriminated patients who died from those who did not numerically but not statistically better than FRANCE-2 (C-statistic for EuroSCORE II: 0.67, p=0.029; C-statistic for STS: 0.67, p=0.029, C-statistic for FRANCE-2: 0.53, p=0.724; p=0.26 for the comparison between areas under the curve using the DeLong method) (Figure 1).

Calibration

Overall, EuroSCORE II, STS and FRANCE-2 overestimated early mortality ([expected percentage-observed percentage]/observed percentage) by 11.2%, 7.2% and 38.8%, respectively. The calibration plots for EuroSCORE II, STS and FRANCE-2 in quartiles are shown in Figure 2. Despite the higher discordance for FRANCE-2, all scores showed

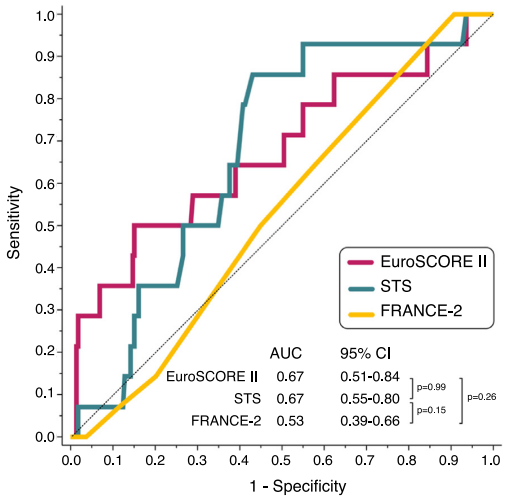


Figure 1 Receiver operating characteristic curves of the three models for the prediction of 30-day mortality. AUC: area under the curve; CI: confidence interval; STS: Society of Thoracic Surgeons.

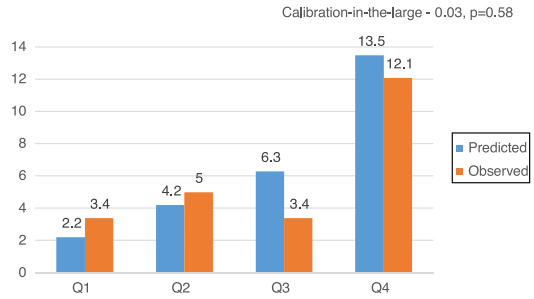


Figure 3 Predicted and observed 30-day mortality (%) for EuroSCORE II in quartiles. Q: quartile.

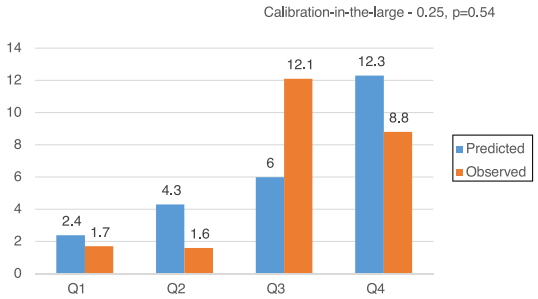


Figure 4 Predicted and observed 30-day mortality (%) for Society of Thoracic Surgeons score in quartiles. Q: quartile.

adequate calibration (calibration-in-the-large for EuroSCORE II -0.03, p=0.51; STS -0.25, p=0.54; and FRANCE-2 -0.38, p=0.29) (Figures 3-5).

Discussion

In our study, all scores showed low discriminative power for prediction of early mortality, though with adequate calibration.

The early mortality rate of our population (5.8%) is within the range of other contemporary multicenter registries and one recent meta-analysis of more than 16 000 procedures (5.4-12.4%).[7-11]

There are conflicting data regarding the role of surgical risk scores for early mortality prediction in TAVI patients. In a Swiss study,[12] EuroSCORE II performed better in predicting short- and long-term mortality compared with STS and logistic EuroSCORE. A French study showed that EuroSCORE II had moderate discrimination for 30-day mortality after TAVI.[13] Watanabe et al.,[14] in another French study, demonstrated that EuroSCORE II had low accuracy in predicting 30-day mortality in 435 patients undergoing TAVI.

The low accuracy of the STS score in predicting short-term mortality after TAVI was also demonstrated in a Canadian study involving 399 patients[15] and in an Italian study that assessed 663 patients.[16] The STS score was an independent predictor of mortality after surgical aortic valve replacement but not after TAVI in the PARTNER trial.[17] In addition, in a real-world Brazilian registry, the surgical

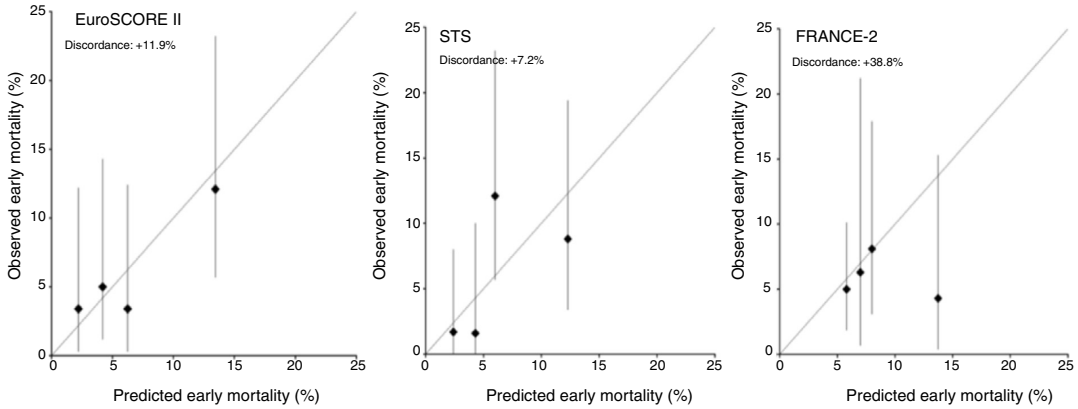


Figure 2 Calibration plots for EuroSCORE II, STS and FRANCE-2 (in quartiles). STS: Society of Thoracic Surgeons.

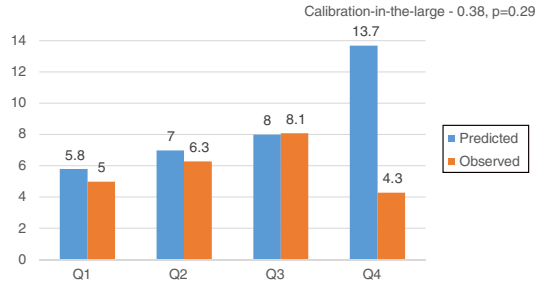


Figure 5 Predicted and observed 30-day mortality (%) for FRANCE-2 in quartiles. Q: quartile.

risk scores were also inaccurate in predicting mortality after TAVI.[18] However, in a German registry[19] including 36% transapical procedures, the STS score proved to be a good predictor of 30-day mortality after TAVI.

Major differences between the FRANCE-2, EuroSCORE and STS scores in terms of included comorbidities are shown in Table 2. New prediction scores aim to improve their accuracy by including features specific to TAVI, as in the FRANCE-2 score, which was derived from a large TAVI population and is designed to predict 30-day mortality by combining nine variables (age, body mass index, functional class, previous pulmonary edema, pulmonary hypertension, respiratory insufficiency, critical hemodynamic state, dialysis and approach). Nevertheless, FRANCE-2 had the worst performance of the three scores in our population. This may be because, being derived from a registry, it does not take in account prognostically important variables like LVEF, mitral regurgitation, obstructive pulmonary disease, cerebrovascular disease, chronic kidney failure, pulmonary hypertension, coronary artery disease or frailty.[20–23] Additionally, procedural success indicators that influence prognosis, particularly perivalvular regurgitation and thrombotic and bleeding events, are not included, which limits its predictive ability. In our population, left ventricular function and mean gradient were independent predictors of death at 30 days (odds ratio [OR] 0.95, 95% CI 0.90-1.00; p=0.039 and OR 0.89, 95% CI 0.83-0.96; p=0.001). These variables are directly or indirectly included in the EuroSCORE II and STS scores.

Table 2 Main comorbidities included in each of the three models.

	STS	EuroSCORE II	FRANCE-2
Peripheral vascular disease	yes	yes	no
Renal failure	yes	yes	no
Dialysis	yes	no	yes
Pulmonary hypertension	no	yes	yes
Neurological dysfunction	yes	yes	no
Redo cardiac surgery	yes	yes	no
Diabetes	yes	no	no
Atrial fibrillation	yes	no	no
COPD	yes	yes	yes
NYHA class	yes	yes	yes
LVEF	yes	yes	no
Coronary artery disease	yes	no	no

COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons.

These results suggest that risk prediction tools should not be used in isolation, although they can help in deciding on the best therapeutic options for the individual patient, as procedural success still has a major role in this complex, albeit increasingly simple, technique. The role of heart teams is crucial, as they offer a better kind of collaboration between cardiologists and cardiac surgeons in many centers, from screening to procedural planning and success.[24]

To our knowledge, this is the first study to compare the performance of the FRANCE-2, EuroSCORE II and STS risk scores in predicting 30-day mortality after TAVI. It is also one of the first external validations of the FRANCE-2 score.

Limitations

Some limitations in our study should be pointed out. First is the inherent limitations of a single-center retrospective study. Secondly, the small number of subjects may have limited the power of the statistical analysis and the ability to find statistical significance for many of the comparisons. Thirdly, the time span of the registry renders the group highly heterogeneous, especially considering that it included the first part of the learning curve of the TAVI program (from patient selection to valve implantation and postprocedural care) in our center. Fourthly, it is not possible to ascertain the extent to which confounders inherent to specific selection criteria for TAVI may have influenced mortality rates and thus the predictive ability of the scores. Finally, full validation of FRANCE-2 score would require random assignment to either surgical valve replacement or TAVI in a prospective study.

Conclusions

A score derived from a TAVI registry, FRANCE-2, did not improve early mortality prediction after TAVI in comparison to the EuroSCORE II and STS surgical scores. Prospective studies are needed for further validation.

Conflicts of interest

The authors have no conflicts of interest to declare.

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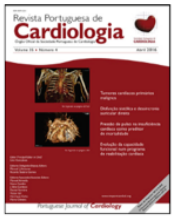
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ARTIGO ORIGINAL

Quinze anos de ecografia intravascular coronária em intervenção coronária percutânea em Portugal

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PALAVRAS-CHAVE
Ecografia intravascular;
Intervenção coronária percutânea;
Doença coronária;
Cardiologia

Resumo:
Introdução: A ecografia intravascular coronária tem ganhado importância nos laboratórios de hemodinâmica pela evidência de impacto prognóstico positivo para os doentes. Este trabalho tem como objetivo caraterizar a utilização de ecografia intravascular em intervenções coronárias percutâneas em Portugal.
Métodos: Estudo observacional retrospetivo com base no Registo Nacional de Cardiologia de Intervenção da Sociedade Portuguesa de Cardiologia. De 2002 a 2016 caraterizou-se o perfil clínico e angiográfico dos doentes submetidos a intervenção coronária percutânea, a percentagem de utilização de ecografia intravascular e as artérias coronárias avaliadas.
Resultados: Foram incluídas 118 706 intervenções coronárias percutâneas, com utilização de ecografia intravascular em 2266 (1,9%). A evolução temporal caraterizou-se por ausência em 2002 e uma utilização maioritariamente crescente de 2003 (0,1%) a 2016 (2,4%). O grupo de doentes com utilização de ecografia intravascular coronária tinha idade semelhante ao grupo de doentes sem utilização de ecografia intravascular coronária, com uma menor prevalência de doentes do sexo masculino e uma maior prevalência de fatores de risco cardiovasculares (hipertensão arterial, hipercolesterolemia, diabetes), enfarte agudo do miocárdio prévio, intervenção coronária percutânea prévia, doença coronária multivaso, lesões coronárias do tipo c ou em bifurcação e reestenose intra-*stent*. A ecografia intravascular foi utilizada em 54,8% das intervenções coronárias percutâneas eletivas e em 19,15% das intervenções coronárias percutâneas do tronco comum.
Conclusão: A ecografia intravascular coronária teve uma utilização crescente em Portugal desde 2003, ocorre preferencialmente em intervenções coronárias percutâneas eletivas, de doentes com maior risco cardiovascular, com lesões coronárias mais complexas e lesões do tronco comum.
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KEYWORDS
Intravascular ultrasound;
Percutaneous coronary intervention;
Coronary disease;
Cardiology

Fifteen years of coronary intravascular ultrasound in percutaneous coronary intervention in Portugal

Abstract
Introduction: Coronary intravascular ultrasound (IVUS) is increasingly important in catheterization laboratories due to its positive prognostic impact. This study aims to characterize the use of IVUS in percutaneous coronary intervention (PCI) in Portugal.
Methods: A retrospective observational study was performed based on the Portuguese Registry on Interventional Cardiology of the Portuguese Society of Cardiology. The clinical and angiographic profiles of patients who underwent PCI between 2002 and 2016, the percentage of IVUS use, and the coronary arteries assessed were characterized.
Results: A total of 118 706 PCIs were included, in which IVUS was used in 2266 (1.9%). Over time, use of IVUS changed from none in 2002 to generally increasing use from 2003 (0.1%) to 2016 (2.4%). The age of patients in whom coronary IVUS was used was similar to that of patients in whom IVUS was not used, but in the former group there were fewer male patients, and a higher prevalence of cardiovascular risk factors (hypertension, hypercholesterolemia and diabetes), previous myocardial infarction, previous PCI, multivessel coronary disease, C-type or bifurcated coronary lesions, and in-stent

restenosis. IVUS was used in 54.8% of elective PCIs and in 19.15% of PCIs of the left main coronary artery.
Conclusion: Coronary IVUS has been increasingly used in Portugal since 2003. It is used preferentially in elective PCIs, and in patients with higher cardiovascular risk, with more complex coronary lesions and lesions of the left main coronary artery.
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Introdução

A ecografia intravascular coronária (IVUS) é utilizada mundialmente em procedimentos de intervenção coronária percutânea (ICP) há mais de 20 anos[1]. A IVUS, através da utilização de ultrassons, permite obter imagens de corte transversal das artérias coronárias com uma resolução de 100-150 μm[2]. A sua utilização em ICP permite complementar a informação obtida pela angiografia coronária por fluoroscopia e saber o grau de estenose luminal da artéria coronária, identificar a presença e caraterizar a morfologia de placas ateroscleróticas, otimizar a escolha do diâmetro e comprimento do *stent* a implantar, confirmar a correta aposição dos *struts* do *stent* implantado, avaliar possíveis complicações pós-angioplastia, bem como perceber os mecanismos implicados na reestenose de *stents*[1].

A utilização de IVUS é segura, com uma taxa de complicações inferior a 1%[3]. Como limitações, a IVUS apenas pode ser utilizada com segurança em artérias coronárias com diâmetro superior a 1,5 mm, pelo risco de oclusão do lúmen da artéria pelo dispositivo de IVUS em artérias de menor calibre, e apresenta resolução de imagem inferior a outras técnicas de imagiologia coronária, com a tomografia de coerência ótima (OCT)[2]. Comparativamente à IVUS, a OCT, ao utilizar radiação eletromagnética infravermelha em vez de ultrassons, tem a vantagem de possuir uma resolução 10 vezes superior, na ordem dos 10-20 μm, mas à custa de uma menor capacidade de penetração (1-2 mm em vez de 4-8 mm) [4].

Existe evidência científica de que a utilização de IVUS durante a ICP tem implicações na estratégia de revascularização[5,6]. A utilização de IVUS previamente à implantação de *stent* permite uma escolha mais adequada do diâmetro e comprimento de balões e *stents*, usualmente recaindo na escolha de balões e *stents* de maior diâmetro do que quando não é utilizada IVUS[5]. A utilização de IVUS pós-implantação de *stent* permite avaliar a correta aposição do *stent* à parede do vaso, traduzindo-se na prática numa mais frequente realização de pós-dilatação com balão[5,6]. Essas alterações na estratégia de revascularização foram associadas a um maior lúmen mínimo pós-intervenção e a uma menor incidência de reestenose e trombose de *stent*[5,6].

Diversos estudos, incluindo estudos observacionais, ensaios clínicos aleatorizados e meta-análises, comparando a implantação de *stents* revestidos com fármaco (DES) guiada por angiografia coronária por fluoroscopia ou guiada por IVUS, concluíram existir benefício na implantação de DES guiada por IVUS, com redução na incidência de trombose de *stent*, enfarte agudo do miocárdio, eventos adversos cardiovasculares *major* (MACE) e mesmo mortalidade[7–13].

Além dos benefícios clínicos demonstrados, existem igualmente estudos a comprovar a custo-efetividade da ICP com DES guiada por IVUS, principalmente em doentes com comorbilidades que acarretem um risco acrescido de eventos cardiovasculares, nomeadamente diabetes, doença renal crónica e síndrome coronária aguda[12,14].

A evidência científica disponível levou a Sociedade Europeia de Cardiologia (ESC), nas suas recomendações sobre revascularização miocárdica atualizadas em 2018, a recomendar a utilização de IVUS para: avaliar a gravidade das lesões do tronco comum desprotegido (classe de recomendação IIa, nível de evidência B); otimizar a implantação de *stent* em doentes selecionados (classe de recomendação IIa, nível de evidência B); detetar problemas mecânicos relacionados com o *stent* que possam levar a reestenose (classe de recomendação IIa, nível de evidência C)[15].

No Japão, a IVUS é utilizada em mais de 80% das ICPs[16]. Em Portugal, a IVUS tem tido uma importância e utilização crescente nos laboratórios de hemodinâmica, mas os autores desconhecem a real percentagem de utilização desta técnica. Os autores pretendem com este trabalho caraterizar a utilização de IVUS em ICPs em Portugal nos últimos 15 anos no que diz respeito à percentagem de utilização, ao perfil clínico e angiográfico dos doentes e à localização das lesões coronárias avaliadas.

Métodos

População de estudo

Estudo observacional retrospetivo com base no Registo Nacional de Cardiologia de Intervenção (RNCI), registo este voluntário, prospetivo e contínuo de 23 centros de Cardiologia de Intervenção portugueses, sob a responsabilidade da Associação Portuguesa de Intervenção Cardiovascular da Sociedade Portuguesa de Cardiologia, cumprindo os requisitos do *European data standards for clinical cardiology practice* (CARDS) definidos pela ESC.[17]

Grupos de estudo

Foram analisadas as ICPs inseridas no RNCI durante 15 anos, ou seja, desde a sua criação em 2002 até 2016. Excluíram-se as ICPs sem informação relativa à utilização ou não de IVUS. As restantes constituíram a amostra deste estudo. As ICPs foram divididas em dois grupos: ICPs sem utilização de IVUS e ICPs com utilização de IVUS. Calculou-se a percentagem de ICPs em que foi utilizada IVUS e a evolução temporal

dessa percentagem de 2002 a 2016. Verificou-se o contexto clínico da ICP e calculou-se a percentagem de cada contexto no grupo das ICPs com utilização de IVUS. Realizaram-se a caraterização do perfil clínico e angiográfico de cada grupo de doentes e a comparação desse perfil entre os dois grupos. Apuraram-se igualmente quais as artérias coronárias mais avaliadas por IVUS e a sua percentagem de utilização.

Análise estatística

Variáveis contínuas são apresentadas como média e desvio-padrão e variáveis categóricas como número e percentagem.

A análise estatística comparativa entre grupos foi realizada utilizando teste *t* de Student e teste $\chi 2$ para variáveis contínuas ou categóricas, respetivamente.

A análise estatística foi realizada utilizando STATA v14 (College Station, Texas, EUA). Um valor $p < 0,05$ foi considerado estatisticamente significativo.

Resultados

Foram realizadas em Portugal entre 2002 e 2016 e incluídas no registo 131.109 ICPs, das quais 118.706 (90,5%) tinham informação referente à utilização ou não de IVUS e constituíram a amostra deste estudo. Das 118 706 ICPs analisadas, em 116.440 (98,1%) ICPs não foi utilizada IVUS e em 2266 (1,9%) ICPs foi utilizada IVUS. A evolução temporal da utilização de IVUS caraterizou-se por: ausência em 2002, utilização crescente de 2003 (0,1%) a 2009 (3,6%), diminuição entre 2009 e 2014 (1,5%) e novo incremento até 2016 (2,4%). (Figura 1)

Em contagem relativa e absoluta, os anos com maior número de ICPs com utilização de IVUS foram, respetivamente, 2009 com 3,6% e 2016 com 273 ICPs. (Figura 2).

A IVUS foi utilizada em 40% das vezes em contexto de angina estável e/ou isquémia miocárdica documentada, em 16% em contexto de enfarte agudo do miocárdio sem supradesnivelamento do segmento ST (EAMSSST), em 15,2% em contexto emergente de angioplastia primária por enfarte

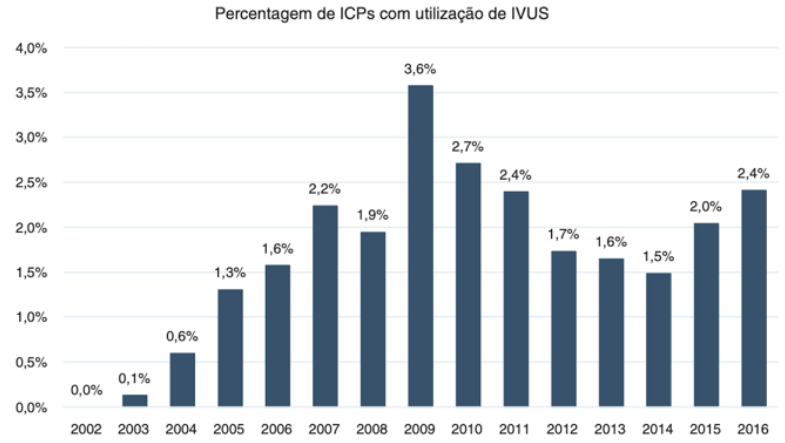


Figura 1 Evolução temporal de 2002 a 2016 da percentagem de ICPs com utilização de IVUS.

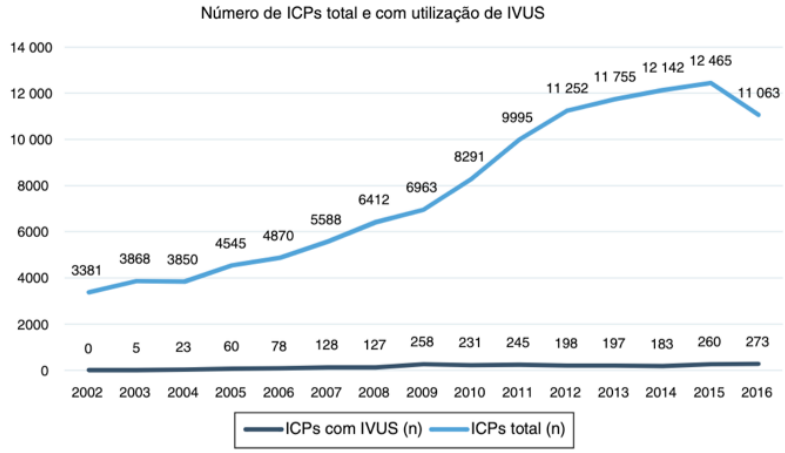


Figura 2 Evolução temporal de 2002 a 2016 do número de ICPs total e com utilização de IVUS.

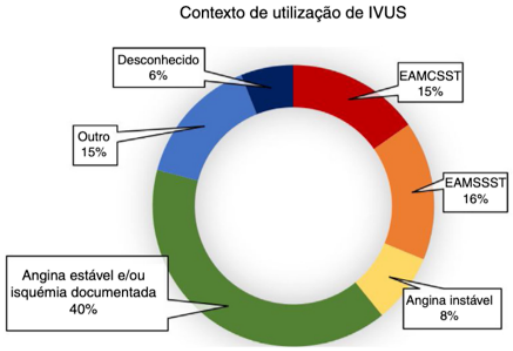


Figura 3 Contexto de utilização de IVUS em ICPs. EAMCSST: Enfarte agudo do miocárdio com supradesnivelamento do segmento ST; EAMSSST: Enfarte agudo do miocárdio sem supradesnivelamento do segmento ST.

agudo do miocárdio com supradesnivelamento do segmento ST (EAMCST), em 8% em contexto de angina instável e em 14,8% em contextos diversos, categorizados no RNCI como «Outros», incluindo doentes com insuficiência cardíaca, miocardiopatia, doença valvular, arritmias. (Figura 3) Considerando as ICPs em contexto de angina estável e/ou isquémia miocárdica documentada e os «Outros» como procedimentos eletivos, estes totalizam 54,8% da utilização de IVUS.

Comparando o perfil clínico dos doentes do grupo ICP sem utilização de IVUS com o grupo ICP com utilização de IVUS, os grupos tinham idade semelhante (63,9 *versus* 64,8 anos, p > 0,5), e o grupo ICP com utilização de IVUS apresentou uma menor prevalência de doentes do sexo masculino (72,2% *versus* 74,2%, p = 0,028), e uma maior prevalência de fatores de risco cardiovasculares [hipertensão arterial (74% *versus* 65%, p < 0,001), hipercolesterolemia (66,5% *versus* 54%, p < 0,001), diabetes (32,6% *versus* 28,3%, p < 0,001)], enfarte agudo do miocárdio prévio (29,9% *versus* 20,1%, p < 0,001) e ICP prévia (40,7% *versus* 23,8%, p < 0,001). (tabela 1)

Em termos angiográficos, os doentes submetidos a ICP com utilização de IVUS tinham mais frequentemente doença coronária multivaso (58,6% *versus* 50,9%, p < 0,001), lesões coronárias do tipo C segundo a classificação da *American College of Cardiology/American Heart Association* (ACC/AHA)[18] (43,5% *versus* 35,2%, p < 0,001), lesões coronárias em bifurcações (13,3% *versus* 8,2%, p < 0,001) e reestenose intra-*stent* (11,2% *versus* 4,9%, p < 0,001). (tabela 2)

A IVUS foi utilizada em 1171 (2,55%) ICPs da artéria coronária descendente anterior e em 383 (19,15%) ICPs do tronco comum. (tabela 3)

De 5.043 ICPs que visaram ao tratamento de reestenose intra-*stent*, em 237 (4,7%) ICPs foi utilizada IVUS.

Discussão

A utilização de IVUS em 1,9% das ICPs realizadas em Portugal nos últimos 15 anos demonstra a baixa penetração desta técnica de imagiologia intracoronária no nosso país.

Um dos motivos para a baixa utilização de IVUS pode ser a noção de aparente falta de benefício por o operador considerar que a angiografia coronária por fluoroscopia é suficiente para avaliar as lesões coronárias. No entanto, diversos estudos comprovam que a avaliação do grau de estenose e do diâmetro do vaso por angiografia é variável, subjetiva e com fraca correlação com o grau de isquemia miocárdica[19,20]. Diversos estudos concluíram existir benefício na implantação de DES guiada por IVUS, com redução na incidência de trombose de *stent*, enfarte agudo do miocárdio, MACE e mesmo mortalidade. Das várias meta-análises realizadas destacamos: uma meta-análise de Jang et al., 2014[10], incluindo três estudos aleatorizados e 12 estudos observacionais com 24 849 doentes, que concluiu que a ICP guiada por IVUS estava associada a uma redução do risco relativo de mortalidade por todas as causas de 36% (2,3% *versus* 3,3%, p < 0,001); uma meta-análise de Elgendy et al., 2016[11], incluindo sete estudos aleatorizados com 3192 doentes, que concluiu que a ICP guiada por IVUS estava associada a uma redução relativa de 40% nos MACE a 15 meses (6,5% *versus* 10,3%, p < 0,001).

Outro possível motivo para a baixa utilização de IVUS poderá estar relacionado com o custo acrescido do dispositivo de IVUS e falta de comparticipação das entidades competentes, principalmente quando os anos em análise no presente estudo, 2002 a 2016, coincidiram em grande parte com anos de crise económica em Portugal. Contudo, existe evidência científica a suportar a custo-efetividade da IVUS, sendo até possível reduzir custos em doentes selecionados com a utilização de IVUS[12,14].

A ESC, nas suas recomendações sobre revascularização miocárdica atualizadas em 2018, defende, com classe de recomendação IIa, a utilização de IVUS para avaliar a gravidade das lesões do tronco comum desprotegido, otimizar

Tabela 1 Caraterísticas clínicas dos doentes submetidos a ICP sem e com utilização de IVUS

	ICP sem IVUS	ICP com IVUS	p
Número	116.440	2.266	-
Idade	64,8 ± 11,86	63,88 ± 11,28	> 0,5
Sexo masculino	74,2%	72,2%	0,028
Hipertensão arterial	65,0%	74,0%	< 0,001
Dislipidemia	54,0%	66,5%	< 0,001
Diabetes	28,3%	32,6%	< 0,001
Enfarte agudo do miocárdio prévio	20,1%	29,9%	< 0,001
ICP prévia	23,8%	40,7%	< 0,001

Tabela 2 Caraterísticas angiográficas dos doentes submetidos a ICP sem e com utilização de IVUS

	ICP sem IVUS	ICP com IVUS	p
Número	116.440	2.266	-
Doença coronária multivaso	50,9%	58,6%	< 0,001
Lesão coronária tipo C	35,2%	43,5%	< 0,001
Lesão coronária em bifurcação	8,2%	13,3%	< 0,001
Reestenose intra-*stent*	4,9%	11,2%	< 0,001

Tabela 3 Percentagem da utilização de IVUS em ICPs dos diferentes vasos

Vasos submetidos a ICP	ICP sem IVUS	ICP com IVUS	Utilização de IVUS
Tronco comum	2.000	383	19,15%
Descendente anterior	45.999	1.171	2,55%
Circunflexa	29.237	537	1,84%
Coronária direita	38.592	632	1,64%
Pontagem	1.270	11	0,87%

a implantação de *stent* em doentes selecionados e detetar problemas mecânicos relacionados com o *stent* que possam levar a reestenose[15]. Assim, seria de esperar um valor bastante superior ao 1,9% de utilização de IVUS encontrado no presente estudo.

Embora em número absoluto o vaso mais frequente avaliado por IVUS seja a artéria coronária descendente anterior, em termos relativos é em ICPs do tronco comum que a IVUS é mais utilizada. Face à já referida recomendação da ESC de utilizar IVUS especificamente no tronco comum não protegido para avaliar a gravidade e otimizar o tratamento de lesões coronárias[15], acreditamos que a utilização de IVUS em 19,15% das ICPs do tronco comum é claramente insuficiente.

Igualmente, face à recomendação da ESC de utilizar IVUS na reestenose intra-*stent* para detetar possíveis problemas mecânicos, consideramos que a utilização de IVUS em 4,7% das ICPs que trataram reestenose intra-*stent* é inferior ao desejável.

Em Portugal, a decisão de utilização de IVUS parece ter como base variáveis clínicas, como, por exemplo, a presença de fatores de risco cardiovasculares (hipertensão arterial, hipercolesterolemia, diabetes) e história de enfarte agudo do miocárdio ou ICP prévia, bem como variáveis angiográficas, como a complexidade da lesão coronária (tipo C e em bifurcações) e a artéria coronária a ser tratada.

Ou seja, a IVUS parece ser uma técnica de imagem reservada para um nicho de doentes de maior risco cardiovascular e para tratar lesões coronárias mais complexas e do tronco comum. Ainda que estes pareçam ser os doentes que mais benefício possam ter da utilização de IVUS, cremos que o benefício é igualmente considerável e não desprezível em doentes de menor risco que estão correntemente a ser privados desta técnica.

Sendo o objetivo do estudo a caraterização da utilização da IVUS, esta pode ter sido influenciada pelo desenvolvimento recente de outras técnicas de imagiologia coronária além da IVUS, nomeadamente a OCT, não tida em conta no presente estudo. Embora o surgimento da OCT possa ser um dos fatores responsáveis pelas flutuações na frequência de utilização de IVUS encontradas, nomeadamente a sua redução relativa entre 2009 e 2014, é nossa convicção que tal não justifica a baixa utilização global de IVUS. Em Espanha em 2016, a IVUS foi utilizada em 3672 (2,4%) ICPs (curiosamente a mesma percentagem que em Portugal), mas com utilização superior à OCT que foi utilizada em 2678 (1,7%) ICPs, pelo que não é de esperar que em Portugal a OCT tenha uma percentagem de utilização muito superior à IVUS que justifique a sua baixa utilização.[21]

Pelo exposto, nomeadamente o demonstrado impacto prognóstico positivo da realização de ICP guiada por IVUS e à custo-efetividade da utilização da IVUS, face aos resultados encontrados, os autores consideram que a utilização de IVUS deve ser fomentada em Portugal.

Limitações

Este estudo apresenta as limitações inerentes ao facto de se tratar de um estudo observacional retrospetivo baseado num registo. Contudo, ressalvamos que o RNCI cumpre os requisitos do CARDS definidos pela ESC e apresenta um elevado número de centros incluídos (23 centros de Cardiologia de Intervenção portugueses), sendo por isso representativo da realidade Portuguesa.

Conclusões

A IVUS foi utilizada em 1,9% das ICPs em Portugal nos últimos 15 anos, com uma utilização maioritariamente crescente desde 2003 e máximo em número absoluto em 2016.

A utilização de IVUS ocorre preferencialmente em contexto eletivo, em doentes com maior risco cardiovascular, para tratar lesões coronárias mais complexas e do tronco comum.

Conflitos de interesse

Os autores declaram que não têm conflitos de interesse.

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CASE REPORT

Innovative transapical-transfemoral loop approach: First case of CoreValve implantation in a 19-mm Mitroflow during double valve-in-valve procedure

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KEYWORDS
Aortic valve;
Mitral valve;
Bioprosthesis;
Valve-in-valve;
Heart failure;
Structural heart intervention

Abstract An 80-year-old woman with rheumatic valve disease and two previous cardiac surgeries was admitted for heart failure exacerbation. The patient presented stenotic aortic 19-mm Mitroflow and mitral 31-mm Carpentier-Edwards bioprostheses, and was deemed inoperable due to frailty and prohibitive surgical risk. The heart team decided on a compassionate double valve-in-valve procedure, with transfemoral implantation of a 23-mm aortic CoreValve Evolut R and transapical implantation of a 29-mm mitral Edwards SAPIEN 3. During the procedure, after extreme difficulty in retrograde crossing of the aortic valve, a transapical-transfemoral loop was successfully performed. The procedure was without complications and the patient was discharged in NYHA class II with normally functioning valves.
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PALAVRAS-CHAVE
Válvula aórtica;
Válvula mitral;
Bioprótese;
Válvula-em-válvula;
Insuficiência cardíaca;
Intervenção estrutural cardíaca

Abordagem inovadora por ansa transapical-femoral: primeiro caso de implantação de Corevalve em Mitroflow 19 durante procedimento *valve-in-valve*

Resumo Uma mulher de 80 anos com valvulopatia reumática e duas cirurgias cardíacas prévias foi internada por insuficiência cardíaca agudizada. A doente apresentava estenose de biopróteses Mitroflow 19 em posição aórtica e Carpentier-Edwards 31 em posição mitral, sendo considerada inoperável devido a fragilidade e a risco cirúrgico proibitivo. A *Heart Team* decidiu por um duplo procedimento *valve-in-valve compassionate*: implantação de Corevalve Evolut R 23 em posição aórtica via transfemoral e de Edwards Sapiens 3 29 em posição mitral

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por via apical. Durante o procedimento e após dificuldades extremas na progressão por via retrógrada aórtica, uma ansa transapical-femoral foi bem-sucedida. O procedimento correu sem complicações. A doente teve alta em classe NYHA II com biopróteses normofuncionantes.
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Introduction

Although surgical valve replacement has been the standard of care for several decades, transcatheter aortic valve implantation (TAVI) is currently a viable option for patients with severe aortic stenosis at intermediate and high surgical risk.[1,2] Experience with TAVI in valve-in-valve procedures due to degenerated surgical bioprostheses is also increasing in patients deemed inoperable.[2] Mitroflow surgical bioprostheses (Sorin S.p.A., Milan, Italy) present an increased incidence of coronary obstruction due to the shorter distance from the leaflets to the coronary ostia.[3]

Case report

An 80-year-old woman with rheumatic valve disease and two previous cardiac surgeries was admitted for exacerbation of chronic heart failure. The patient's first cardiac surgery was in 1974 (mitral valvuloplasty) followed in 2006 by implantation of a 19-mm Mitroflow bioprosthesis in aortic position,

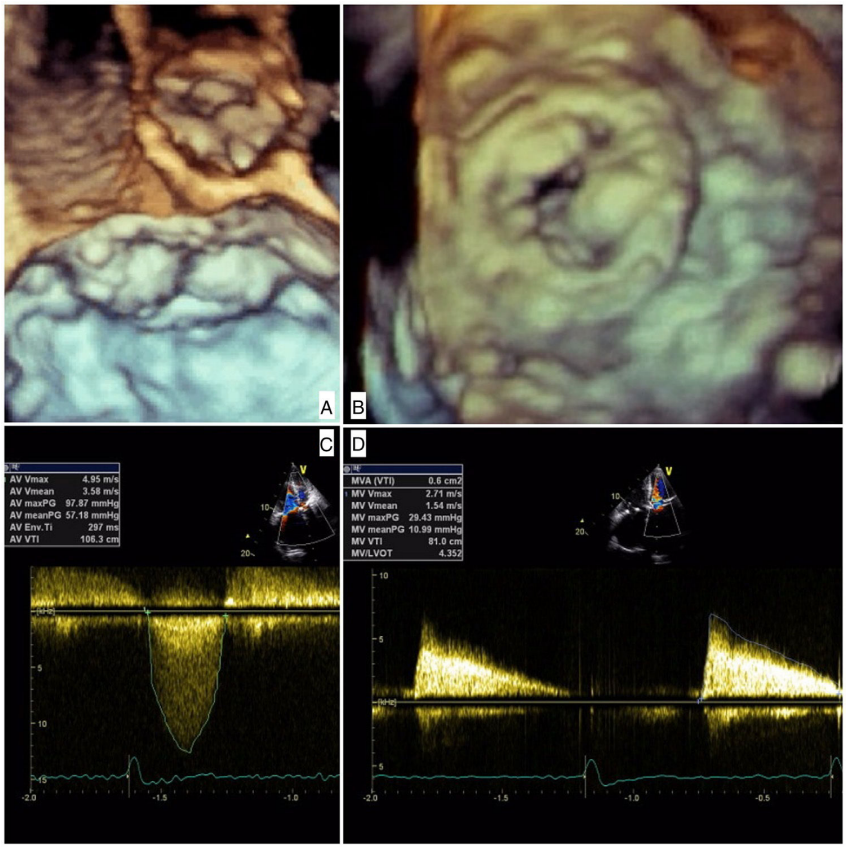


Figure 1 Degenerated aortic (A) and mitral (B) bioprotheses on three-dimensional echocardiography pre-procedure; increased aortic (C) and mitral (D) gradients measured during transesophageal echocardiography.

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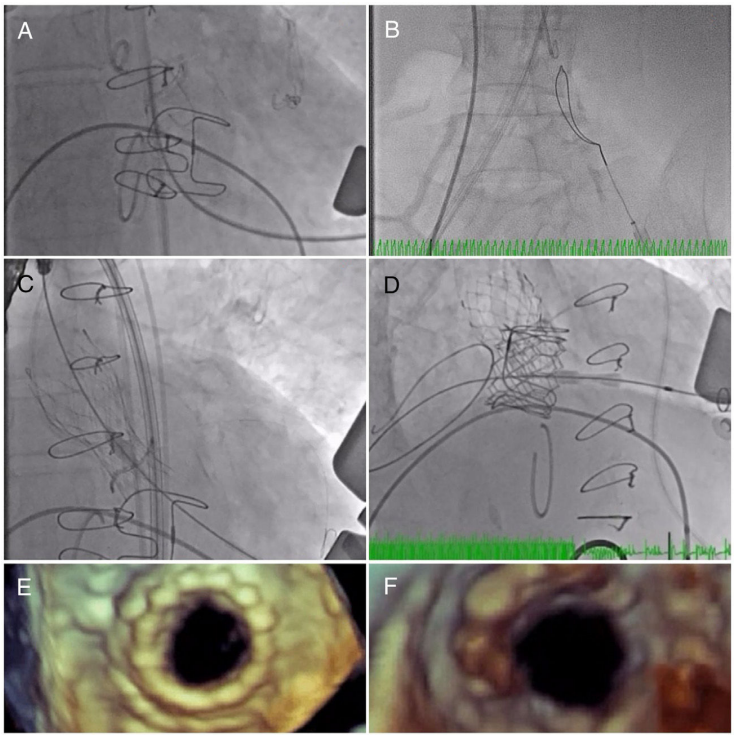


Figure 2 (A) A long Emerald J wire passes through the stenotic Mitroflow, in which it is captured with an Amplatz Goose Neck snare (B); valve-in-valve implantation of a 23-mm CoreValve Evolut R in aortic position by the transfemoral route (C); implantation of a 29-mm Edwards SAPIEN 3 in mitral position by the transapical route (D); new aortic (E) and mitral (F) bioprosthetic valves visualized by transesophageal echocardiography during the procedure following implantation.

a 31-mm Carpentier-Edwards (Edwards Lifesciences, Irvine, CA) bioprosthesis in mitral position, and a 31-mm Edwards annuloplasty ring (Edwards Lifesciences, Irvine, CA) in tricuspid position.

The patient was admitted with dyspnea and marked limitation of physical activity. Baseline serum creatinine was 0.7 mg/dl (estimated glomerular filtration rate [eGFR] 43 ml/min/1.73 m^2 by the Cockcroft-Gault equation) and N-terminal pro-brain natriuretic peptide 18 432 pg/ml. The electrocardiogram showed atrial fibrillation at 90 bpm. Transthoracic echocardiography (TTE) showed severe stenosis of the Mitroflow (maximum gradient 98 mmHg, mean gradient 57 mmHg, aortic valve area 0.4 cm^2) and severe stenosis of the Carpentier-Edwards (maximum gradient 29 mmHg, mean gradient 11 mmHg, mitral valve area 0.6 cm^2) due to thick, almost immobile leaflets (Figure 1 and Video 1]. Coronary angiography showed anomalous left coronary origin of the right coronary artery and no significant lesions. The patient was deemed inoperable due to frailty (height 150 cm, weight 42 kg) and prohibitive surgical risk (Society of Thoracic Surgeons mortality risk score 22%). To further assess prosthesis sizes and vascular anatomy, multislice computed tomography angiography was performed, which revealed a moderate risk of occlusion of the left main with a distance of 7.7 mm from the valve apparatus to the ostium origin. The aortic annulus was small and non-circular (16 mm×18 mm, area 2.0 cm^2) and the iliac and femoral arteries showed a minimal luminal diameter of 6.9 mm. The heart team decided on a compassionate double valve-in-valve procedure as the best therapeutic option for this patient, who consented to the intervention.

Double valve-in-valve transfemoral and transapical procedure

The initial plan was to implant a 23-mm CoreValve Evolut R (Medtronic, Irvine, CA) in aortic position (transfemoral approach) and a 29-mm Edwards SAPIEN 3 in mitral position (transapical approach). The procedure began with a successful left transfemoral approach with a 14-F Fast-Cath sheath, and the left coronary artery was protected with an angioplasty guidewire. Due to extreme difficulty in retrograde crossing of the aorta, a transapical-transfemoral loop approach was considered. The loop was created after gaining transapical access (Figure 2A), through which an INFINITI MPA 2 catheter (5.0 Fr×125 cm, Cordis) was used to advance an Emerald J wire (0.035″×260 cm) anterogradely until it reached the left common iliac artery, where it was captured with a 25-mm Amplatz Goose Neck snare (Figure 2B). After wire externalization at the left groin, the MPA 2 catheter was removed from the apical access and inserted via the groin, enabling the Emerald J wire to be exchanged for an Amplatz Extra Stiff guidewire (0.035″×260 cm) via a left transfemoral route (Video 2). The CoreValve was then

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successfully advanced into the aortic root and implanted in a suprannular aortic position under rapid pacing (Figure 2C and Video 3), 7 mm below the radiopaque Mitroflow ring. The left coronary ostium was unobstructed. Subsequently, the mitral valve-in-valve Edwards was successfully implanted transapically, without complications (Figure 2D and Video 4). Intraprocedural transesophageal echocardiography showed normal gradients (mean aortic gradient 11 mmHg, mean mitral gradient 3 mmHg) (Figure 2E and F) and a mild aortic perivalvular leak (Video 5). There were no immediate procedural complications. Due to contrast nephropathy and development of anuria (serum creatinine increased to 5.1 g/dl), the patient needed temporary renal replacement therapy, which was discontinued after two and a half weeks due to resumed diuresis. Before discharge, TTE revealed a small paravalvular aortic leak and normally functioning prosthetic valves. The patient was discharged in New York Heart Association (NYHA) functional class II on the 67th day with mild anemia (hemoglobin 11.5 g/dl), creatinine 1.0 mg/dl and eGFR 30 ml/min/1.73 m^2.

At 12 months of follow-up the patient was still in NYHA class II, with mean aortic gradient of 25 mmHg but a velocity time integral ratio of 0.53 and mean mitral gradient of 7 mmHg, probably due to mild anemia (hemoglobin 10 g/dl), without morphologic anomalies or new leaks.

Discussion

Reports of valve-in-valve interventions are increasing in both number and complexity in the literature, with apparently favorable outcomes, supporting this approach as a viable option for selected patients.[4,5] Our case depicts a new solution to cross the aortic valve and establish a stable transapical-transfemoral loop. This is an alternative in very small and severely degenerated bioprosthetic valves for which a retrograde approach may be difficult due to severe calcification and configuration, especially in the context of double valve-in-valve interventions. We also showed that while clinically challenging, the CoreValve Evolut is a good option for valve-in-valve implantation in the small diameter 19-mm Mitroflow valve in aortic position.

Conclusion

We report the first use of a transapical-transfemoral wire loop as part of a double valve-in-valve intervention. We believe that this technique may be a viable approach for TAVI procedures in very small stenotic bioprostheses. To our knowledge, this is the first reported case of a CoreValve Evolut implanted in a 19-mm Mitroflow aortic valve.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2017.10.019.

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LETTER TO THE EDITOR

Caring for cardiac patients amidst the SARS-CoV-2 pandemic: The scrambled pieces of the puzzle

O doente cardiovascular durante a pandemia SARS-CoV2: As peças separadas do puzzle

The SARS-CoV-2 (COVID-19) pandemic is disrupting modern societies. By April 12, 2020, more than 1.5 million people had been infected and 114 197 had died worldwide as a result of SARS-CoV-2 infection.[1] The first case in Portugal was reported on March 2. National authorities then established and upgraded contingency measures culminating with the declaration of a state of emergency, for only the second time in almost 50 years of Portuguese democracy. By April 12, a total of 16 585 cases had been confirmed in Portugal; 504 individuals (3.0% of those confirmed as infected) had succumbed to COVID-19 and 228 (1.4%) were in the intensive care unit (ICU).[2]

Portuguese health system workers have been preparing for the expected rise in demand for emergency room (ER) visits and admissions to wards and the ICU. Medical departments and equipment have been adapted and

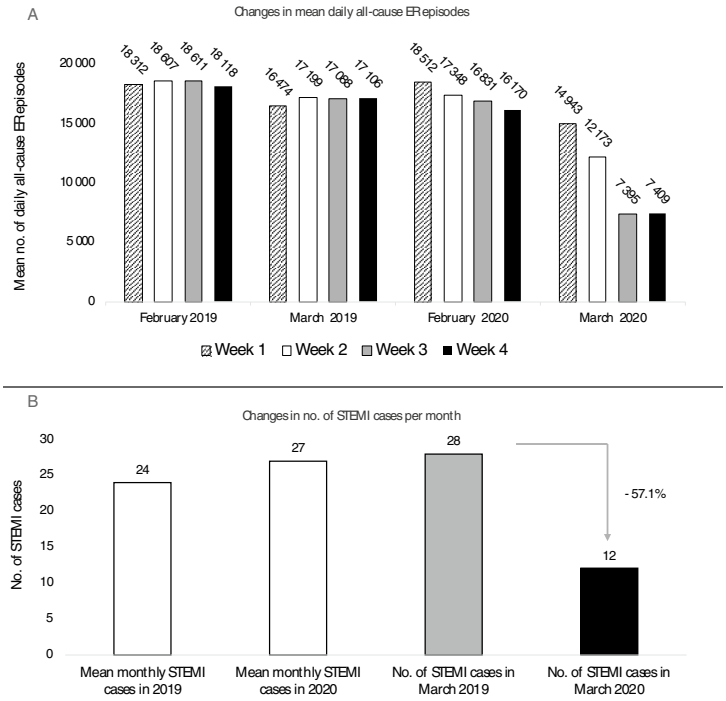


Figure 1 (A) Mean number of daily all-cause emergency room (ER) episodes in Portugal according to week number in February 2019, March 2019, February 2020, and March 2020; (B) number of admissions for ST-elevation myocardial infarction (STEMI) in a public sector tertiary hospital in Portugal, showing mean monthly STEMI admissions for all of 2019 and for January and February 2020 and total STEMI admissions in March 2019 and March 2020.

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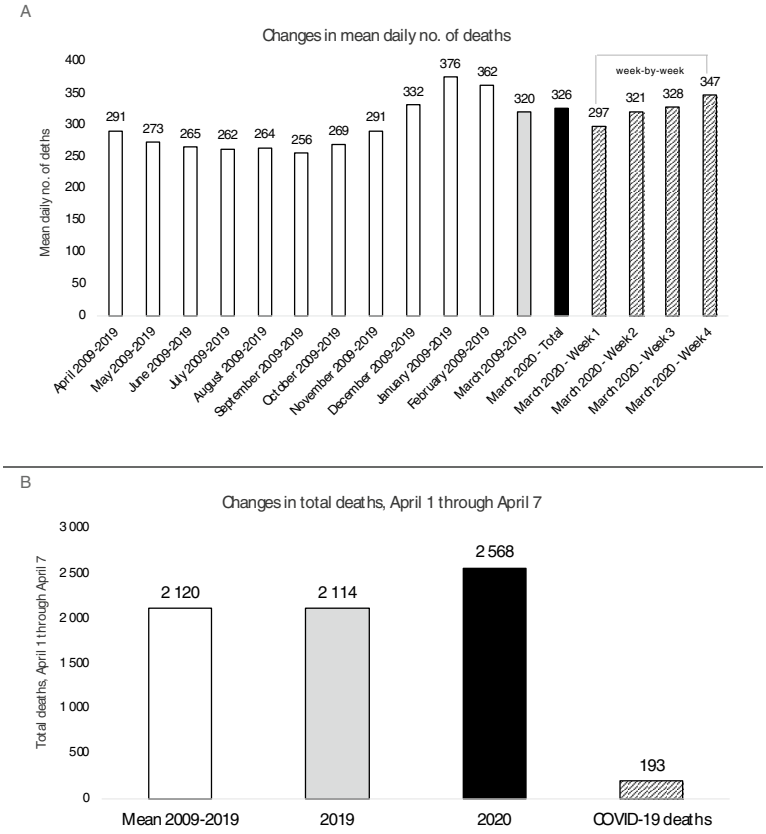


Figure 2 (A) Mean daily number of deaths in Portugal in different time periods. White bars: historical data from 2009 to 2019 by month; gray bar: historical data from March between 2009-2019; black bar: data from March 2020; hatched bars: data from March 2020 by week; (B) total deaths, April 1 through April 7. White bar: mean 2009-2019; gray bar: in 2019; black bar: in 2020; hatched bar: number of deaths attributed to COVID-19. Source: https://evm.min-saude.pt; Relatório de Situação Epidemiológica da Direção-Geral de Saúde.

elective procedures postponed. Meanwhile, patients are being offered telephone appointments to mitigate the impact of such changes. Nevertheless, potentially severe conditions are being denied timely treatment. Although the anticipated bottleneck in the care of COVID-19 patients was ICU beds and ventilators, healthcare workers, including cardiology professionals, are being assigned to tasks unrelated to their specialized training in order to compensate for the structural shortage of human resources in healthcare. This situation poses unique challenges for the care of non-COVID-19 patients, with unpredictable short- and long-term consequences, and a concerted strategy to mitigate these effects must be put in place.

Established cardiovascular disease is a risk factor for worse outcomes of COVID-19.[3] However, acute coronary syndromes and heart failure decompensation are themselves associated with significant morbidity and mortality and are usually among the most frequent diagnoses in the ER. Furthermore, respiratory infections are known to be triggers for these conditions.[4,5] These patients have been strongly advised to stay at home and self-isolate to avoid being infected, in an effort to mitigate the COVID-19 pandemic.

Analysis of overall ER admission data from Portuguese public hospitals shows that all-cause ER episodes have plummeted since the beginning of March – down 39.3% on average compared to March 2019 and down 40.2% compared to February 2019 (Figure 1A).[6] Similar figures are reported in the UK's National Health Service.[7]

Initial data from our center shows that admissions for ST-elevation myocardial infarction (STEMI) have fallen by 57.1% during March, 2020 (Figure 1B). Our findings are similar to those described in other countries. As an example, a nationwide survey in Spain reported a 40% decrease in STEMI admissions in a pre-/post-COVID-19 week-by-week comparison.[8] Preliminary data reported by the Portuguese Association of Cardiovascular Intervention (APIC) on a webinar from the Portuguese Society of Cardiology are in line with these observations.

Nationwide all-cause mortality is continuously updated online.[9] The mean daily number of deaths in March 2020 was 326, slightly above the daily mean recorded in March during the last decade (320). Of note, on a week-by-week analysis, there was a trend for increasing number of deaths during March 2020, anticipating the expected rise in

mortality in the following weeks (Figure 2A). In fact, between April 1 and April 7, 2020, a total of 2568 people died in Portugal, compared to 2114 during the same period in April 2019 (+21.5%), of whom 193 died due to COVID-19 (7.5%) and 2375 from other causes (Figure 2B).[2,9]

Cardiovascular-related symptoms are usually among the most frequent in the ER, and cardiovascular mortality is the leading cause of death in Portugal. It is therefore legitimate to ask whether cardiology patients are refraining from pursuing appropriate care, or alternatively, whether COVID-19 presentation is overlaying cardiovascular disease, leaving non-respiratory disease in the background. Data for the upcoming months will be decisive in solving this puzzle.

As a country, we have anticipated the worst while hoping for the best. It is of paramount importance that patients remain alert to cardiovascular symptoms that need urgent assessment and have severe consequences if left unattended. Therefore, non-COVID-19 hospital circuits must be standing in readiness to provide the necessary care.

Conflicts of interest

The authors have no conflicts of interest to declare.

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EDITORIAL COMMENT

''A momentary lapse of opinion'': The reader should be aware of the iatrogenic potential of this publication

«Um lapso de opinião momentâneo»: O leitor deve estar consciente do potencial iatrogénico desta publicação

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Aortic stenosis is the most frequent native valve disease in Europe, and as the elderly population increases, together with the high prevalence of comorbidities and the extension of indications to low-risk patients, the number of individuals requiring transcatheter aortic valve replacement (TAVR) is likely to increase substantially.[1–3]

Frailty, dependence and comorbidities affect the lives of some of these patients, raising the question whether the intervention justifies the economic cost. High-quality American and European analyses of TAVR have shown generally acceptable cost-effectiveness, with the higher cost of the procedure being offset by the considerable benefits in quality of life and survival. It is, however, important to examine the specifics at a national level, since large differences have been observed between countries.[4–8]

The article by Fontes-Carvalho et al. of the Centro Hospitalar de Vila Nova de Gaia in this issue of the *Journal*[9] points to the need to assess the cost-effectiveness and economic impact of the adoption of new technologies before their dissemination in clinical practice. In this case the time for this objective has passed, which since these authors are well respected I would suggest should be put down to a momentary lapse of opinion. In fact it is now 18 years since the first TAVR procedure was performed, and it was the Gaia Hospital group that introduced it to the Iberian peninsula in 2007.

The article is of interest because it assesses health technology in structural interventional cardiology from a national viewpoint. On the basis of detailed data from 2017 from a single center, it sets out to estimate the potential impact of expanding the indications for TAVR in three hypothetical scenarios, concluding that public expenditure on this treatment is likely to grow considerably. The authors suggest a centralized approach to the management of the required economic and clinical resources, as well as optimization of the procedure itself.

There are two questions that this study raises in 2020.

The first question is whether economic considerations are paramount for a technique that is considered the first-line treatment for high-risk patients and for which good evidence is emerging for low-risk individuals. The answer is no, for the following reasons:

a) Firstly, since 2017, not only has there been an increase of 33% in the number of TAVR procedures, but in line with

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recommendations there have been improvements in the technique, with simplified protocols for arterial access and sedation. These have led to reductions in costs, complications (stroke, vascular complications, bleeding and valvular regurgitation) and rehospitalizations.[5,10–12] As Fontes-Carvalho et al. point out in their article, cost-effectiveness studies such as theirs are most valuable before the technique enters clinical practice, which has already happened.

b) Secondly, in Portugal the laboratories and technicians required to perform TAVR are often unavailable. The European Society of Cardiology (ESC) Atlas[13] shows that Portugal is lagging in 23rd and 34th place, respectively, among ESC member countries for these two parameters.
c) Thirdly, there is no sound economic justification for centralization of material acquisition, which was proposed without success some years ago in the area of coronary intervention. The empirical data are inconclusive concerning the advantages and disadvantages of the mixed funding model of a fixed budget and diagnostic-related groups used by the Portuguese national health system (NHS), but this alone does not justify such a change.[14] There are no reports of such attempts in other areas of medicine in Portugal, and the studies referred to are from the UK and the American PARTNER trial, which are of doubtful applicability to Portugal, unlike studies on measures to increase the efficiency of hospital protocols, which are reproducible in any center.[12,15,16]
d) Fourthly, times have changed, and it is important to overcome inequalities in regional access to cutting-edge technology, without compromising clinical excellence. In an era of rapidly increasing and improving professional mentoring and interchange, a move toward greater concentration would go against current practice and could hamper the ability of several catheterization laboratories to offer techniques that are becoming simpler and easier. This risks losing one of the main strengths of interventional cardiology, that of universality, the clearest example of which is the coronary fast-track system.
e) Finally, the true value of a theoretical cost-effectiveness analysis would be seen if it were directed at areas that really are emerging, such as coronary lithoplasty, coronary sinus narrowing, or intervention for structural mitral regurgitation.

The second question is whether the study's methodological limitations are important. I would like to say they are not, but in fact they are, for the following reasons:

a) The fact that only two of the six devices available nationally are analyzed introduces a selection bias, ignoring around a quarter of the TAVR procedures reported in the Portuguese Registry on Interventional Cardiology (RNCI) run by the Portuguese Association of Cardiovascular Intervention (APIC).
b) A cautious estimate would have been preferable to the approach of Fontes-Carvalho et al.'s study and its three scenarios, since the difference between their projections and the reality is over three-fold. The RNCI recorded 746 TAVR procedures in 2019, in contrast to the 2516 in the meta-analysis by Durko et al.[17] and the 2488 in Fontes-Carvalho et al.'s scenario 2. It is clear that in this country the recommended criteria for TAVR in higher-risk patients aged over 65 years are often not followed; the study by Fontes-Carvalho et al. assumes that in such cases patients undergo surgical aortic valve replacement (SAVR). The number of individuals treated by SAVR in Portugal is not known, to the shame of all the country's cardiac surgery departments, but not even the highest estimates could explain the difference of around 1700 cases, which is probably due to patients being neither diagnosed nor referred. Durko et al. include among the limitations of their study the fact that their estimates are based on a model that contains multiple steps, and that it did not consider all local differences in health care systems among individual countries in Europe.[9,10,17]
c) The costs of the artificial valves, which are central to the analysis, were based on figures from a single center in 2017, and are now lower. It should also be noted that estimates of in-hospital costs (human resources and facilities) are complicated by the unreliability of any nationwide analysis, which would be of necessity based on official reports, given the systematic lack of credible analytical data derived from cost-based management, which is commonplace in private practice but practically unheard of in the NHS.[14]
d) Finally, the opinions expressed in the article are not shared by those working in this area in other centers, which significantly limits their validity, especially when the authors were unable to include data from even a second hospital.[18]

To conclude, this article seemed promising, but has unfortunately become obsolete. Percutaneous aortic valve implantation is now an established technique, due to its clinical benefit and ever-improving patient selection processes.

The study by Fontes-Carvalho et al. has the merits of originality, of developing credible economic studies in the field of interventional cardiology, and of challenging medical societies to adopt a national strategy.

If the methodology behind their estimates had been solid, I would still disagree with their proposed concentration of resources, due to the 'iatrogenic' impact of blocking the expansion of access to TAVR with no guarantee of adding value to what is most important – clinical outcomes and knowledge of the cost-effectiveness of the technique at national level.

Even so, I remain an optimist.

Conflicts of interest

The author has no conflicts of interest to declare.

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ORIGINAL ARTICLE

Ten-year survival of patients undergoing coronary angioplasty with first-generation sirolimus-eluting stents and bare-metal stents

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KEYWORDS
Sirolimus-eluting stent;
Bare-metal stent;
Coronary intervention;
Coronary disease

Abstract
Introduction: Compared to bare-metal stents (BMS), drug-eluting stents reduce stent restenosis and improve subsequent revascularization rates. The impact on patients' survival has been the subject of debate.
Objective: To assess the long-term (10-year) survival of patients undergoing percutaneous coronary intervention (PCI) with first-generation sirolimus-eluting stents (SES) in comparison with BMS.
Methods: In a single-center registry, 600 consecutive patients who underwent successful PCI with SES between April 2002 and February 2003 were compared to 594 patients who underwent PCI with BMS between January 2002 and April 2002, just before the introduction of SES. Clinical and procedural data were collected at the time of intervention and 10-year survival status was assessed via the national life status database.
Results: All baseline characteristics were similar between groups except for smaller stent diameter (2.84±0.38 vs. 3.19±0.49 mm; p<0.001), greater stent length (18.50±8.2 vs. 15.96±6.10 mm; p<0.001) and higher number of stents per patient (1.95 vs. 1.46, p<0.001) in the SES group. Overall five- and 10-year all-cause mortality was 9.6% (n=110) and 22.7% (n=272), respectively. The adjusted HR for 10-year mortality in patients undergoing PCI with SES was 0.74 (95% CI 0.58-0.94; p=0.013), corresponding to a relative risk reduction of 19.8%. Other than PCI with BMS, older age, chronic kidney disease, chronic obstructive pulmonary disease and lower ejection fraction were independent predictors of 10-year mortality.

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Conclusion: To date, this is the longest follow-up study ever showing a potential survival benefit of first-generation sirolimus-eluting stents versus bare-metal stents, supporting prior observations on their sustained efficacy and safety relative to contemporary BMS.
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PALAVRAS-CHAVE
Stent sirolimus-eluting;
Stent de metal nu;
Intervenção coronária;
Doença coronária

Sobrevida aos dez anos de pacientes submetidos a angioplastia coronária com *stents* sirolimus de primeira geração e *stents* metálicos

Resumo
Introdução: Em comparação com os *stents* de metal nulo (BMS), os *stents* com efeito de droga reduzem a restenose do *stent* e melhoram as taxas de revascularização subsequente. O impacto na sobrevivência dos pacientes tem sido objecto de debate.
Objectivo: Avaliar a sobrevivência a longo prazo (10 anos) de pacientes submetidos a intervenção coronária percutânea (ICP) com *stents* sirolimus-eluting de primeira geração (SES) em comparação com a BMS.
Métodos: Num registo de um único centro, 600 pacientes consecutivos submetidos a ICP com SES entre Abril de 2002 e Fevereiro de 2003 foram comparados com 594 pacientes submetidos a ICP com BMS entre Janeiro de 2002 e Abril de 2002, imediatamente antes da introdução da SES. Os dados clínicos e processuais foram recolhidos no momento da intervenção e o estado de sobrevivência de 10 anos foi avaliado através da base de dados nacional do estado de vida.
Resultados: Todas as características de linha de base foram semelhantes entre os grupos, excepto para *stents* de menor diâmetro (2,84±0,38 vs. 3,19±0,49 mm; p<0,001), maior comprimento do *stent* (18,50±8,2 vs. 15,96±6,10 mm; p<0,001) e maior número de *stents* por paciente (1,95 vs. 1,46, p<0,001) no grupo SES. A mortalidade global de cinco e 10 anos por todas as causas foi de 9,6% (n=110) e 22,7% (n=272), respectivamente. A FC ajustada para mortalidade de 10 anos em pacientes submetidos a ICP com SES foi de 0,74 (95% CI 0,58-0,94; p=0,013), correspondendo a uma redução relativa do risco de 19,8%. Para além da ICP com SES, a idade avançada, doença renal crónica, doença pulmonar obstrutiva crónica e a fracção de ejecção inferior foram preditores independentes da mortalidade de 10 anos.
Conclusão: Até à data, este é o estudo de seguimento mais longo a demonstrar um potencial benefício de sobrevida dos *stents* farmacológicos de primeira geração versus *stents* metálicos, em linha com estudos prévios que demonstram a sua eficácia e segurança quando comparados com SC contemporâneos.
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Introduction

Drug-eluting stents (DES) are currently the mainstay of revascularization by percutaneous coronary intervention (PCI) for most patients and clinical settings. It is generally considered that DES reduce stent restenosis and improve subsequent revascularization rates, at the cost of increased risk of stent thrombosis compared with bare-metal stents (BMS), at least for first-generation DES.[1] New-generation DES have been shown to be associated with lower rates of stent thrombosis than older DES and even contemporary BMS.[2–4] Constant improvements in stent technology and optimized implantation techniques may be expected to translate into superior efficacy and safety and even reduced rates of death and myocardial infarction (MI).[5–7]

The first DES available for clinical use in Europe (2002) and shortly after in the US (2003) was the sirolimus-eluting Cypher™ stent (Cordis/Johnson & Johnson). Two large randomized clinical trials (RCTs), Randomized Comparison of a Sirolimus-eluting Stent With a Standard stent for Coronary Revascularization (RAVEL)[8] and Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery (SIRIUS),[9] showed an unequivocal benefit in stent restenosis with the Cypher™ stent. The superior efficacy of the new SES, and the growing enthusiasm around it, led to its being used increasingly in multiple clinical settings, sometimes even without supporting evidence (off-label use). However, based on observational data, concerns about the risk of late and very late stent thrombosis with SES and related mortality were steadily growing among interventional cardiologists. The controversy reached its peak at the 2006 European Society of Cardiology congress when two independent meta-analyses suggested that first-generation DES, particularly SES, were associated with

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increased mortality.[10] This was known as 'the ESC firestorm', sowing deep suspicions concerning the safety of SES and leading to a halt in their widespread use.[11] In the heat of the controversy, one of the first reactions was to prolong dual antiplatelet therapy for 12 months as standard treatment after PCI with SES, even though there was no reliable evidence to support such a measure at that time. Subsequently evidence from RCTs and meta-analyses have shown improvement in quality of life without greater mortality, despite a slight increase in very late stent thrombosis.[10,12]

The Cypher™ stent has been extensively studied in more than 20 RCTs comparing it with BMS in different clinical scenarios and lesion subsets. Despite extensive use (both within and outside clinical trials), very long-term clinical outcome data on this first-generation DES are still scarce. The five-year follow-up analysis of the SIRIUS trial showed a sustained benefit in clinical restenosis without significant differences in MI or death.[13] All-cause mortality at 10 years associated with SES has recently been reported to be 20-24%.[1,14] However, no comparison with BMS has been performed with such a long follow-up. With this analysis, we aimed to help clarify the effect of first-generation SES implantation on very late overall survival, in comparison with contemporary older BMS.

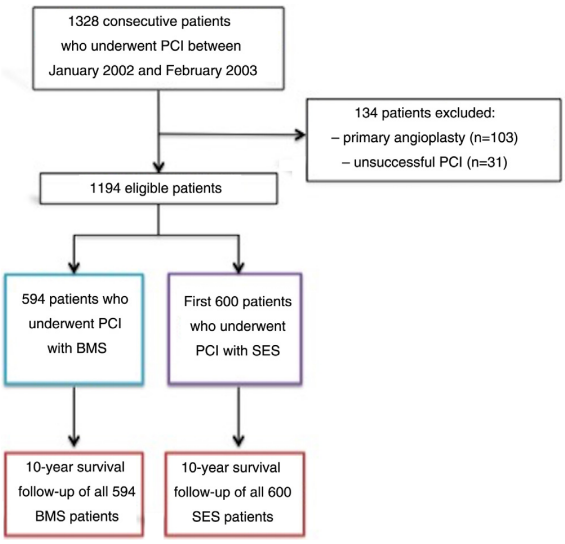


Figure 1 Study design. BMS: bare-metal stents; PCI: percutaneous coronary intervention; SES: sirolimus-eluting stents.

Methods

Patient selection and data collection

This was a prospective registry,[15] from a single tertiary center, of the first 600 patients who underwent successful PCI with SES between April 2002 and February 2003, who were compared to the previous 594 patients who underwent successful PCI with a BMS between January 2002 and April 2002, just before the introduction of SES into clinical practice. Exclusion criteria were as follows: primary PCI in the setting of ST-elevation myocardial infarction (STEMI), because this was considered an off-label indication for DES at that time; and an unsuccessful procedure, defined as greater than 30% residual stenosis, in-hospital clinical complications, such as periprocedural MI, need for urgent coronary artery bypass grafting (CABG), or death (Figure 1). At that time, for patients undergoing PCI with SES, dual antiplatelet therapy with aspirin and clopidogrel was used for eight weeks, in accordance with the protocol used in the RAVEL randomized trial.[8]

All data on demographic, clinical and interventional characteristics were prospectively entered in a study-specific database (Table 1). Follow-up data was limited to all-cause mortality. Information was collected from a nationwide life status database that records all mortality reports. Collection of other significant clinical events was not attempted due to complex challenges hampering all efforts to obtain accurate data.

Table 1 Baseline clinical characteristics of the study population.

	SES (n=600)	BMS (n=594)	p
Age, years	62.6±11.3	63.2±11.0	0.3662
Male	77%	78%	0.7102
Hypertension	75%	73%	0.4072
Dyslipidemia	73%	70%	0.2648
Diabetes	29%	22%	0.0226
Current smoker	24%	24%	0.9753
Previous PCI	29%	27%	0.4390
Previous CABG	15%	14%	0.9907
PAD	13%	13%	0.9368
CKD	4%	5%	0.7005
Previous stroke	6%	5%	0.7880
COPD	5%	4%	0.4970
Stable angina	51%	48%	0.3221
UA/NSTEMI	24%	31%	0.0052
Prognostic indication	12%	12%	0.8686
Preserved LVEF	73%	72%	0.5914
Severely reduced LVEF	4%	2%	0.2456
Aspirin	87%	84%	0.1968
Beta-blocker	68%	64%	0.1486
Statin	67%	62%	0.0505
ACEi	47%	45%	0.6487

ACEi: angiotensin-converting enzyme inhibitor; BMS: bare-metal stents; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; UA: unstable angina.

Statistical analysis

Continuous variables were expressed as means and standard deviation when normally distributed and as medians and interquartile range when not normally distributed. Normality was tested with the Kolmogorov-Smirnov test and/or visual assessment of Q-Q plots. Categorical variables were expressed as frequencies and percentages.

Baseline characteristics and outcomes were compared using the chi-square test or Fisher's exact test, as

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Table 2 Baseline lesion characteristics.

	SES	BMS	p
Multivessel disease	39%	32%	0.0384
1 vessel	39%	42%	0.2989
2 vessels	29%	31%	0.4264
3 vessels	18%	12%	0.0159
Complete revascularization	51.7%	48.3%	0.21
Left main (isolated or in association)	7%	6%	0.6979
Bypass (isolated or in association)	7%	9%	0.2491
GP IIb/IIIa inhibitor	43%	46%	0.3578
No. of stents	1225	725	<0.001
No. of stents/patient	1.95	1.46	0.023
Diameter, mm	2.84±0.38	3.19±0.49	<0.001
Length, mm	18.50±8.2	15.96±6.10	<0.001

BMS: bare-metal stents; SES: sirolimus-eluting stents.

appropriate, for categorical variables and the Student's t test for continuous variables.

Baseline characteristics according to vital status at five and 10 years were compared using the beginning of follow-up as reference. No landmark analysis was performed.

Independent predictors of all-cause mortality at five and 10 years were determined by Cox regression. Event-free survival was computed using Kaplan-Meier analysis and the log-rank test was used for comparison.

All tests were two-sided and differences were considered statistically significant at a p-value of 0.05. The statistical analysis was performed with IBM SPSS 20.0 software (IBM SPSS Inc., Chicago, IL, USA).

Results

The baseline clinical, angiographic and procedural characteristics of the study population are shown in Tables 1 and 2.

Between January 2002 and February 2003, 1328 consecutive patients underwent coronary stenting at our center. Patients who had emergent (n=103) and unsuccessful (n=31) angioplasty (according to study criteria) were excluded. The remaining 1194 patients were included in the follow-up analysis.

Clinical characteristics were similar (Tables 1 and 2), except for a greater prevalence of diabetes and multivessel disease among patients who received SES and a higher rate of patients presenting with non-ST-elevation acute coronary syndromes (ACS) in the BMS group.

There was some heterogeneity in coronary anatomy and interventional characteristics between groups. Patients treated with SES had a higher incidence of multivessel disease (39% vs. 32%; p=0.0384) and a higher number of stents per patient (1.95 vs. 1.46; p<0.0001), and the implanted stents were both narrower (2.84±0.38 vs. 3.19±0.49 mm, p<0.0001) and longer (18.50±8.2 vs. 15.96±6.1 mm; p<0.0001) (Table 2). Despite these differences, the rates of complete revascularization were similar between the groups (51.7% in SES vs. 48.3% in BMS; p=0.21).

Predictors of all-cause mortality

Vital status at 10 years was known for all patients included in the analysis.

All-cause mortality at five years

Five-year mortality was 9.2% in the overall patient cohort. Patients who died were older, had more comorbidities (including peripheral arterial disease [PAD], chronic kidney disease [CKD] and chronic obstructive pulmonary disease [COPD]), and were more likely to be diabetic and have a previous history of stroke. They also had more complex coronary artery disease – reflected by higher rates of previous CABG, multivessel and left main disease – and a lower ejection fraction at baseline (Table 3). After adjustment for confounders, increasing age, CKD and COPD were independent predictors of five-year mortality (Table 4). There was no statistically significant difference in five-year mortality between patients who received DES or BMS (47.3 vs. 52.7%; hazard ratio [HR] 0.86; 95% confidence interval [CI] 0.59-1.26; p=0.432).

All-cause mortality at 10 years

The cumulative rate of all-cause death at 10 years for the overall patient population was 22.7%. Mortality was associated with greater prevalence of hypertension, PAD, CKD, COPD, previous stroke, previous CABG, multivessel disease, left main disease, left ventricular ejection fraction (LVEF) <50%, incomplete revascularization and BMS use.

Crude all-cause mortality rates at the end of the 10-year follow-up were 25.4% in BMS-treated patients and 20.1% in the SES group (absolute difference -5.3% in favor of SES-treated patients) (Table 3). After adjustment for baseline differences, the use of first-generation SES was independently associated with a 26% reduction in the risk of all-cause death at 10 years (HR 0.74; 95% CI 0.58-0.94; p=0.015) (Table 5), which translates into a relative risk reduction of 19.8%, taking BMS as the reference group (Figure 2). Age, CKD and COPD persisted as independent predictors of all-cause death (Table 5).

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Table 3 Patient characteristics according to survival status at five and 10 years.

	Total (1194)	Five years			10 years		p
		Alive (n=1084, 90.8%)	Dead (n=110, 9.2%)	p	Alive (n=922, 77.3%)	Dead (n=272, 22.7%)	
Age, years	62±12.4%	61.5±12.2%	66±13.4%	<0.001	60.76±12.3%	66.2±11.9%	0.561
Male	927 (77.6%)	845 (78.6%)	82 (74.5%)	0.40	720 (78.1%)	207 (76.1%)	0.5
SES	600 (50.3%)	548 (50.6%)	52 (47.3%)	0.55	479 (52%)	121 (44.5%)	0.03
Previous PCI	306 (25.9%)	280 (25.8%)	26 (24.3%)	0.73	227 (24.9%)	79 (29.6%)	0.132
Previous CABG	157 (13.1%)	133 (12.3%)	24 (21.8%)	0.007	111 (12%)	46 (16.9%)	0.04
Hypertension	866 (72.5%)	778 (71.8%)	88 (80%)	0.07	653 (70.8%)	213 (78.3%)	0.02
Dyslipidemia	852 (71.4%)	773 (71.3%)	79 (71.8%)	1.0	668 (72.8%)	184 (67.6%)	0.13
Diabetes	292 (24.5%)	256 (23.6%)	36 (32.7%)	0.037	225 (24.4%)	67 (24.6%)	0.936
PAD	141 (11.8%)	119 (11%)	22 (20%)	0.008	99 (10.7%)	42 (19.9%)	0.04
CKD	50 (4.2%)	36 (3.3%)	14 (12.7%)	<0.001	28 (3.0%)	22 (8.1%)	0.001
COPD	48 (4%)	36 (3.3%)	12 (10.9%)	0.001	29 (3.1%)	19 (7.0%)	0.008
Previous stroke	63 (5.3%)	50 (4.6%)	13 (11.8%)	0.005	40 (4.3%)	23 (8.9%)	0.013
NSTEMI/UA	245 (20.5%)	216 (19.9%)	29 (26.4%)	0.136	183 (19.8%)	62 (22.8%)	0.305
Treated LM	31 (2.6%)	25 (2.3%)	6 (5.5%)	0.05	21 (2.3%)	10 (3.7%)	0.19
Treated LAD	629 (52.7%)	577 (53.2%)	52 (47.3%)	0.27	484 (52.5%)	145 (53.3%)	0.836
Treated LCx	375 (31.4%)	339 (31.3)	36 (32.7%)	0.79	294 (31.9%)	81 (29.8%)	0.552
Treated RCA	463 (38.8%)	418 (38.6%)	49 (40.9%)	0.68	350 (30%)	113 (41.3%)	0.289
Treated bypass	21 (2.6%)	26 (2.4%)	5 (4.5%)	0.19	25 (2.7%)	6 (2.2%)	0.83
1-vessel disease	493 (41.3%)	460 (42.4%)	33 (30%)	0.01	399 (43.3%)	94 (34.6%)	0.01
3-vessel disease	328 (27.5%)	282 (26%)	46 (41.8%)	0.001	238 (25.8%)	90 (33.1%)	0.02
LVEF<50%	345 (28.9%)	299 (27.6%)	46 (41.8%)	0.003	252 (27.3%)	93 (34.2%)	0.03
Complete revascularization	751 (62.9%)	696 (64.2%)	551 (50%)	0.005	597 (64.8%)	154 (56.6%)	0.015

BMS: bare-metal stents; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; LAD: left anterior descending artery; LCx: circumflex artery; LM: left main; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; RCA: right coronary artery; SES: sirolimus-eluting stents; UA: unstable angina.

Table 4 Independent predictors of all-cause mortality at five years (multivariate analysis).

	HR	CI	p
Age	1.035	1.016-1.054	<0.001
Diabetes	1.281	0.85-1.92	0.23
PAD	1.15	0.69-1.93	0.60
CKD	2.66	1.43-4.95	0.002
COPD	2.56	1.39-4.72	0.002
Stroke	1.48	0.79-2.77	0.22
Previous CABG	1.1	0.62-1.97	0.737
3-vessel disease	1.47	0.86-2.504	0.158
LVEF <50%	1.47	0.989-2.19	0.059
SES	0.858	0.588-1.256	0.432
Complete revascularization	0.992	0.615-1.600	0.973

CABG: coronary artery bypass grafting; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; LVEF: left ventricular ejection fraction; PAD: peripheral arterial disease; SES: sirolimus-eluting stent.

Discussion

The main findings of our study were that (1) SES use was independently associated with better long-term survival; (2) the benefit of SES was more pronounced in the elderly, in female patients, in patients with LVEF <50% and in those with incomplete revascularization (Figure 3); and (3) CKD, COPD, depressed LVEF and age at the time of the procedure were the main determinants of poor prognosis after PCI.

Although no longer in use, first-generation SES have been implanted in millions of patients worldwide in different clinical scenarios. Knowledge of their impact on patient survival is therefore of paramount importance.

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Table 5 Independent predictors of all-cause mortality at 10 years (multivariate analysis).

	HR	CI	p
Age	1.036	1.024-1.048	<0.001
Diabetes	1.111	0.83-1.507	0.46
PAD	1.005	0.70-1.43	0.979
CKD	2.39	1.49-3.8	<0.001
COPD	1.95	1.221-3.12	0.005
Stroke	1.3	0.83-2.05	0.251
Previous CABG	1.07	0.71-1.61	0.74
3-vessel disease	1.16	0.818-1.65	0.40
LVEF <50%	1.25	0.96-1.62	0.096
SES	0.74	0.58-0.94	0.016
Complete revascularization	0.97	0.72-1.31	0.86

CABG: coronary artery bypass grafting; CI: confidence interval; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; LVEF: left ventricular ejection fraction; PAD: peripheral arterial disease; SES: sirolimus-eluting stent.

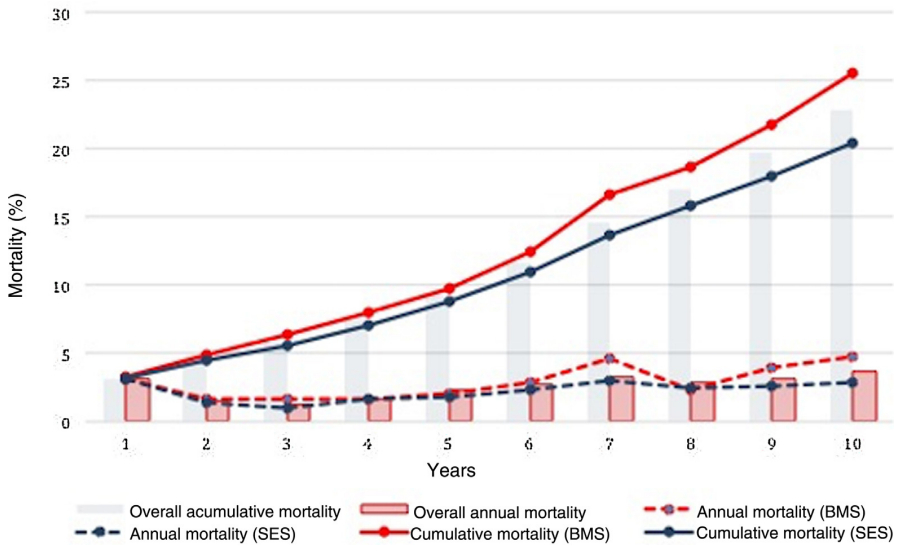


Figure 2 All-cause mortality by year of follow-up and stent type. BMS: bare-metal stents; SES: sirolimus-eluting stents.

After the 'ESC firestorm', the safety and efficacy of first-generation DES were widely studied in observational registries, RCTs and meta-analyses. In general, the available evidence shows that patients treated with SES have better survival free of cardiovascular events, without a negative impact on all-cause and cardiovascular mortality.[9,13,16] Although most studies have a relatively short follow-up, crude mortality rates in our cohort are within the range of prior studies in the literature.[13,17,18] Five-year all-cause mortality was remarkably similar to that reported for both the SIRIUS randomized trial[13] and the SCAAR registry,[19] but was much lower than in the SCORPIUS trial.[18] This may be due to the fact that in the latter, all patients were diabetic, which is known to correlate with adverse outcomes. As stated above, only one study has reported on the 10-year outcome of patients treated with first-generation SES.[14] In the SIRTAX VERY LATE study (which originally compared SES with paclitaxel-eluting stents (PES) in 1012 patients,[1] the cumulative incidence of all-cause death in SES-treated patients was 25%, comparable to the 20.1% reported in our similarly sized population. To our knowledge, no other study has ever reported on the very long-term outcome of first-generation SES as compared to BMS.

The reasons for the observed lower mortality associated with SES (Figure 3) and for it to become significant only over a relatively long time frame are not straightforward (Figure 4). Stent-related mortality can only be explained by (1) a device-related change in the rate of ischemic events; (2) coadjuvant medical therapy associated with that particular device (for example, the benefits of cardiovascular protective drugs); or (3) unmeasured comorbidity in the study population leading to bias. The fact that information was not collected on major clinical events other than mortality (including ACS and repeat revascularizations during

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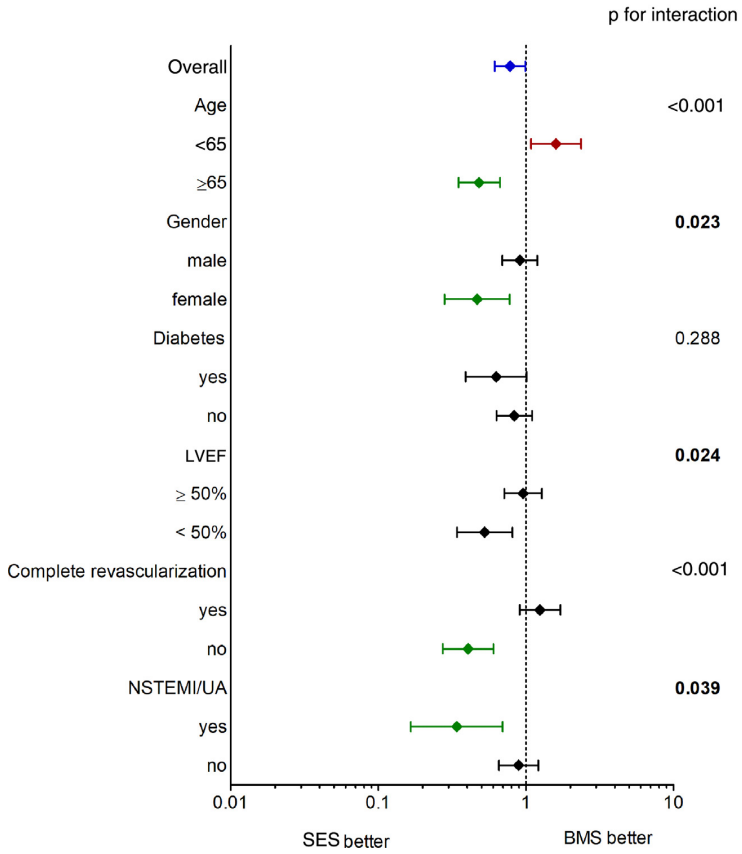


Figure 3 Subgroup analysis of all-cause mortality at 10 years. BMS: bare-metal stents; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; SES: sirolimus-eluting stents; UA: unstable angina.

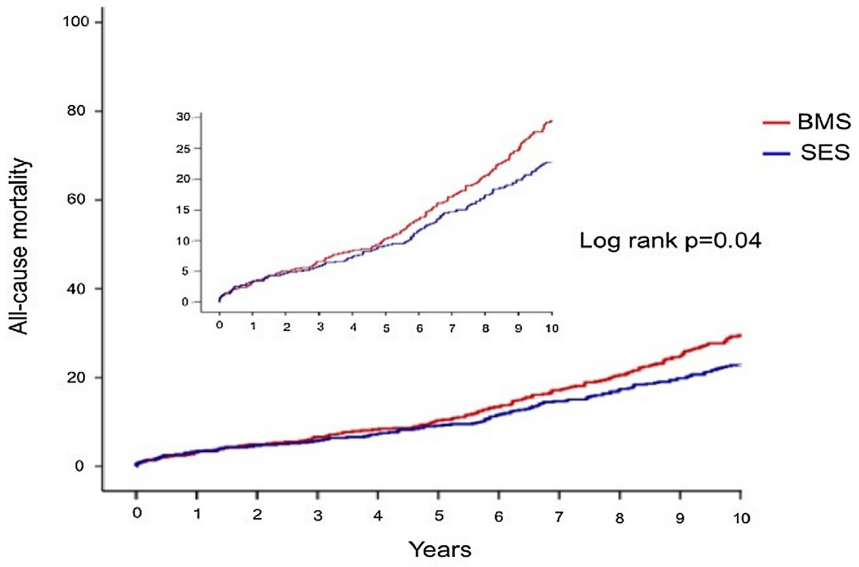


Figure 4 Ten-year all-cause mortality. BMS: bare-metal stents; SES: sirolimus-eluting stents.

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follow-up) precludes any attempts to establish a reliable link between stent-related outcomes and total mortality in our study. Despite the known reduction in target lesion revascularization (TLR)[8,13] associated with first-generation DES, a late catch-up phenomenon regarding late and very late ischemic events due to continuous neointimal growth, late-acquired malapposition, neoatherosclerosis and stent thrombosis[2,5,6,20] has been described and raised concerns. However, this issue has recently been demystified by Yamaji et al.,[1] who reported a significant annual reduction in risk of TLR and stent thrombosis reduction after five years in both first-generation SES and PES. This effect may have contributed to the late survival benefit. Moreover, in our population, SES-treated patients were slightly more likely to be medicated with statins, angiotensin-converting enzyme inhibitor inhibitors and beta-blockers at baseline (Table 1), although the differences were not statistically significant relative to the BMS group and we had no way of assessing therapy prescription and adherence over the entire follow-up period. Finally, a selection bias favoring SES patients cannot be definitively ruled out. Still, patients treated with SES had a higher prevalence of diabetes and multivessel disease, smaller vessels and longer lesions, all of which are surrogates of a greater disease burden and, if anything, would tend to worsen the clinical outcome of the SES group. Nevertheless, they experienced better long-term survival in comparison with those who received BMS. On the other hand, BMS were more often implanted in patients with ACS (excluding primary PCI in STEMI), which could in part contribute to the observed differences in mortality in the long run. However, ACS was not an independent predictor of mortality.

As in other non-cardiac and cardiac clinical settings, age, CKD and COPD[21] were independent predictors of mortality in our cohort. These comorbidities and age reflect increasing patient frailty and overall decreased functional reserve to cope with any pathological insult. LVEF is a fundamental parameter in the clinical management of heart disease, and is one of the strongest prognostic determinants in heart disease, particularly in ischemic heart disease.[22] These predictors are included and used in many predictive risk scores validated in several heart conditions.[23–25]

Subgroup analysis (Figure 3) revealed a greater and significant benefit of SES in older and female patients, which could be expected taking into account that these characteristics are classical predictors of BMS failure.[26] Depressed LVEF and incomplete revascularization, as well as insulin-treated diabetes, also showed a potential survival benefit when treated with SES compared to BMS.

Limitations

Our study has some important limitations that should be considered when interpreting the results, some of which have already been addressed. The inherent limitations of a single-center study with an observational design make it prone to bias. Although the SES-treated patients were consecutive (except for those with exclusion criteria), there is no information on why BMS were still implanted in the remaining patients during that period. Some knowledge on the characteristics of this group, as well as additional information on their long-term outcome, could help clarify the true role of SES in the observed survival benefit.

Finally, long-term follow-up was not prespecified when data were collected at baseline and relevant information on adverse events and cardiac death were not reported, precluding the analysis of other major cardiovascular events.

Conclusions

To date, this is the longest study ever showing a survival benefit of first-generation SMS versus BMS. Although they are no longer in clinical use, our findings are reassuring and build on the perceived efficacy and long-term safety of first-generation SES.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Short and long-term clinical impact of transcatheter aortic valve implantation in Portugal according to different access routes: Data from the Portuguese National Registry of TAVI

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KEYWORDS
Severe aortic valvular disease;
TAVI;
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Abstract
Introduction: The Portuguese National Registry of Transcatheter Aortic Valve Implantation records prospectively the characteristics and outcomes of transcatheter aortic valve implantation (TAVI) procedures in Portugal.
Objectives: To assess the 30-day and one-year outcomes of TAVI procedures in Portugal.
Methods: We compared TAVI results according to the principal access used (transfemoral (TF) vs. non-transfemoral (non-TF)). Cumulative survival curves according to access route, other procedural and clinical variables were obtained. The Valve Academic Research Consortium-2 (VARC-2) composite endpoint of early (30-days) safety was assessed. VARC-2 predictors of 30-days and 1-year all-cause mortality were identified.

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Results: Between January 2007 and December 2018, 2346 consecutive patients underwent TAVI (2242 native, 104 valve-in-valve; mean age 81±7 years, 53.2% female, EuroSCORE-II - EuroS-II, 4.3%). Device success was 90.1% and numerically lower for non-TF (87.0%). Thirty-day all-cause mortality was 4.8%, with the TF route rendering a lower mortality rate (4.3% vs. 10.1%, p=0.001) and higher safety endpoint (86.4% vs. 72.6%, p<0.001). The one-year all-cause mortality rate was 11.4%, and was significantly lower for TF patients (10.5% vs. 19.4%, p<0.002). After multivariate analysis, peripheral artery disease, previous percutaneous coronary intervention, left ventricular dysfunction and NYHA class III-IV were independent predictors of 30-day all-cause mortality. At one-year follow-up, NYHA class III-IV, non-TF route and occurrence of life-threatening bleeding predicted mortality. Kaplan-Meier survival analysis of the first year of follow-up shows decreased survival for patients with an EuroS-II>5% (p<0.001) and who underwent non-TF TAVI (p<0.001).
Conclusion: Data from our national real-world registry showed that TAVI was safe and effective. The use of a non-transfemoral approach demonstrated safety in the short term. Long-term prognosis was, however, adversely associated with this route, with comorbidities and the baseline clinical status.
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PALAVRAS-CHAVE
Doença valvular aórtica grave;
VAP;
Insuficiência cardíaca

Impacto clínico em curto e longo prazo da Válvula Aórtica Percutânea (VAP) em Portugal de acordo com diferentes acessos – Dados do Registo Nacional de Cardiologia de Intervenção de VAP

Resumo
Introdução: O Registo Nacional de Cardiologia de Intervenção de Válvulas Aórticas Percutâneas (RNCI-VaP) documenta prospetivamente as características e resultados da VAP em Portugal.
Objetivos: Avaliar os resultados a 30 dias e um ano da VAP em Portugal.
Métodos: Comparação dos resultados da VAP de acordo com o acesso (transfemoral – TF *versus* não transfemoral – não TF). Obtiveram-se curvas de sobrevivência cumulativa de acordo com o acesso, variáveis do procedimento e clínicas. Avaliou-se a segurança precoce (30 dias) do procedimento, de acordo com os critérios *Valve Academic Research Consortium-2* (VARC-2). Identificaram-se preditores de mortalidade a 30 dias e um ano.
Resultados: Entre janeiro 2007 e dezembro 2018, realizaram-se 2346 VAP (2242 nativas, 104 *Valve-in-Valve* [VIV]; idade média 81±7 anos, 53,2% mulheres, EuroSCORE-II [EuroS-II] 4,3%). Sucesso do dispositivo foi obtido em 90,1%, inferior para o não TF (87,0%). Aos 30 dias, a mortalidade global foi de 4,8%, apresentando o TF menor mortalidade (4,3% *versus* 10,1%, p=0,001) e maior segurança (86,4% *versus* 72,6%, p<0,001). A mortalidade a um ano foi 11,4%, significativamente menor para o TF (10,5% *versus* 19,4%, p<0,002). Após análise multivariável, identificaram-se como preditores de mortalidade a 30 dias doença arterial periférica, angioplastia prévia, disfunção ventricular esquerda e classe NYHA III-IV. A um ano, NYHA III-IV, o acesso não TF e a hemorragia com risco de vida foram preditores de mortalidade. A análise de sobrevivência a um ano evidenciou menor sobrevivência para EuroS-II>5% (p<0,001) e VAP não TF (p<0,001).
Conclusões: Dados do RNCI-VaP mostram que a VAP foi segura e eficaz. O acesso não TF mostrou segurança em curto prazo. O prognóstico em longo prazo foi influenciado negativamente por este acesso, assim como comorbilidades e o estado clínico de base do doente.
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Introduction

Severe aortic stenosis (AS) is the most prevalent type of valvular heart disease in the western world,[1] with particular high prevalence in older patients.[2] Global demography shows a pattern of an aging population and since 1960 life expectancy at birth in Portugal has increased from 64 to 82 years. This will increase the burden of AS and the need to treat it.[3,4] Surgical aortic valve (SAV) replacement is an established treatment for symptomatic severe AS.[5] However,

in the last decade, transcatheter aortic valve implantation (TAVI) has emerged as a minimally invasive treatment for AS, initially for inoperable and high risk patients[6] but increasingly, as evidence grows, it is used in lower risk patients.[7,8] Evidence is building on the durability of transcatheter aortic valves, with over 90% of patients remaining free of structural valve dysfunction between five and 10 years post-implantation.[9] This may encourage increased use of this technology in younger and lower risk patients. Growing experience, solid evidence, refined pre-procedural assessment with multi-slice computed-tomography (MSCT) and new generation transcatheter devices are causing a shift toward new indications, including lower-surgical risk patients.[10,11]

Transfemoral (TF) access is the preferred route, since it is less invasive, and patient recovery is faster, involving shorter hospital stays.[12] Nevertheless, up to one third of eligible patients may not be appropriate candidates for a TF approach because of major peripheral artery disease (PAD). Other routes have emerged as alternatives, but are associated with worse outcomes, particularly when considering the transapical (TA) route.[13]

Another field of increasing importance in TAVI is prosthetic valve dysfunction (PVD). Currently, patients with previously implanted biological SAV can be treated with a valve-in-valve (ViV) procedure for PVD, which has been associated with good one-year outcomes.[14]

Registries have reported the results of TAVI in several countries, showing consistently high implantation success rates; a recent meta-analysis reported an overall European 30-day mortality of 8%, however with substantial differences among registries.[15,16] Mid- and long-term follow-up results show survival rates over 80% at one year, with persistent improvement of clinical status.[17]

The Portuguese National Registry of Transcatheter Aortic Valve Implantation (RNCI-VaP) is a national registry conducted with the main purpose of assessing all comers with aortic valve disease or aortic valve prosthesis dysfunction that undergo TAVI in Portugal, ensuring comprehensive coverage in Portugal.[18] The main goals of the registry are to document in a prospective and consecutive fashion the characteristics of patients who undergo TAVI, ascertain the results of these treatments in Portugal, develop scientific work based on data included in the registry, establish treatment recommendations regarding TAVI procedures and collaborate with other similar international registries. A position paper statement from the Portuguese Association of Cardiovascular Intervention (APIC) has already underlined the importance of a systematic assessment and report of patients who undergo TAVI in Portugal.[19] The members of this committee are all interventional cardiologists. It is divided into an executive board of three members which includes the Registry Coordinator and the scientific board. There is no specific funding for this registry which has been completely developed, maintained and sponsored by APIC.

This article is the first report of real-world clinical data from the RNCI-VaP registry. It aims to identify patient and procedure characteristics and evaluate 30-day and one-year outcomes of TAVI in Portugal.

Methods

Patient selection

The RNCI-VaP is a continuous, observational and prospective registry, which began in 2007. A total of 14 exclusively Portuguese private and public centers participated in the registry on a voluntary basis. Registry data inclusion and analysis are the exclusive responsibility of the members of the RNCI-VaP, which is free from industry body influence. The registry complies with Portuguese data protection laws and was approved by a central ethics board. All patients gave written informed consent.

Selection of symptomatic patients with severe AS or PVD for TAVI followed a multidisciplinary approach in which all individual cases were discussed within a heart team and the procedures performed in hospitals with on-site cardiac surgery.[20] Patients were included if considered high risk for traditional aortic valve replacement (AVR) surgery or deemed inoperable. Patients were excluded if their life expectancy with TAVI was $\leq$1 year or the patient's quality of life was unlikely to improve with TAVI. MSCT was routinely performed to select the access route, and aspects such as size, tortuosity and calcification were assessed. If a femoral approach was not possible, an alternative access was planned (transcarotid, transaortic, transubclavian or transapical). MSCT data also enabled characterization of the aortic annulus and valve, sinus of Valsalva, coronary ostia and ascending aorta. The decision regarding the access route, the prosthesis type and size were made according to each center's routine, taking into consideration the clinical and morphological assessment. At all TAVI centers, the procedure was performed with the support of at least one anesthesiologist.

Data acquisition and quality control

Data were entered into a dedicated database and sent to the National Cardiology Data Collection Center of the Portuguese Society of Cardiology. Events and values collected are site reported, and there are no core laboratories. Data were examined and validated, and the participating centers contacted in the event of any queries or discrepancies. Supervision of the RNCI-VaP is the responsibility of the principal investigators (A.L., A.F., B.S., E.I.O., E.J., F.S., J.S., J.S.M., L.R., R.C., S.B.) and the registry coordinator (R.C.T.).

Study variables and outcomes

Study variables were based on the recommendations of the updated VARC-2 consensus document.[21] They included the following in-hospital and 30-days outcomes: i) immediate procedural mortality (up to 72 hours post-procedure); ii) procedural mortality (all-cause mortality within 30 days or during index procedure hospitalization if the postoperative length of stay was longer than 30 days); iii) early (30 days) safety (defined as freedom from all-cause mortality, all

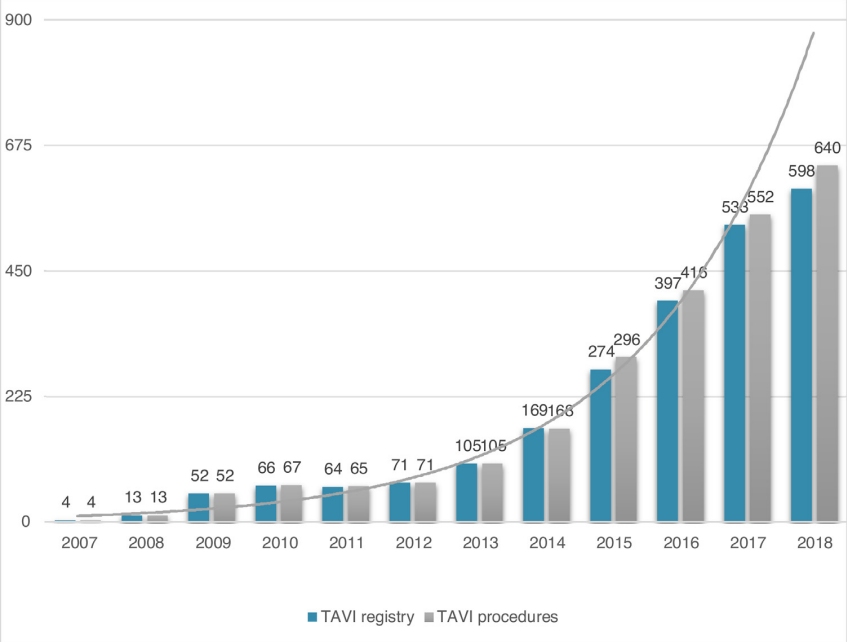


Figure 1 Evolution in the number of transcatheter aortic valve implantation (TAVI) procedures in Portugal since the beginning of the Portuguese Registry of TAVI in 2007 until the end of 2018 (data presented in number of procedures per year; n=2380 global TAVI procedures; n=2346 TAVI procedures in the registry).

stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication and valve-related dysfunction requiring a repeat procedure); iv) myocardial infarction; v) stroke and transient ischemic attack (TIA); vi) bleeding complications (defined by the Bleeding Academic Research Consortium criteria); vii) acute kidney injury (acute kidney injury network classification); viii) vascular complications; ix) other TAVI-related complications. All-cause mortality was assessed at 30 days and at one-year follow-up. Prospective follow-up of adverse events was reported by the investigators. At 30-days and one-year, 48 (2%) and 530 (22%) patients, respectively, were lost to follow-up.

Device description

The national registry is open to any type of commercial device. To date, 12 different valves and their iterations have been used including: Medtronic CoreValve™, Edwards Sapien™, Abbott Portico™, Boston Scientific Acurate neo™ and Lotus Edge™, Direct Flow Medical™, NVT Allegra TAVI System TF™, and Medtronic Engager™. The technical specifications of these devices have been described elsewhere.[22]

Statistical analysis

Distribution of continuous variables was determined using the Shapiro-Wilk test and they are expressed as mean ± SD or as median ± IQR, where appropriate. Categorical variables are reported as frequencies and percentages. Continuous variables were compared using the unpaired Student's t test or the Wilcoxon rank-sum test, as appropriate. Chi-square test or Fisher exact test was used to compare categorical variables.

Multivariate analysis for the prediction of all-cause mortality during 30-days and one-year follow-up was performed using Cox regression, by including all statistically significant variables in the univariate analysis and those considered clinically relevant. The results are expressed as hazard ratios (HR) and 95% confidence intervals (CI 95%). Survival curves were obtained with the Kaplan-Meier method. A log-rank test was used to compare survival between groups during follow-up.

A p value <0.05 was considered statistically significant. All analyses were performed using SPSS statistics software (version 23.0, SPSS, Inc., Chicago, IL).

Results

Study population

Patient population and procedural characteristics. From January 2007 to December 2018, a total of 2346 consecutive patients were included in the Portuguese National Registry of TAVI, with no exclusion criteria. In the last 10 years, there has been an exponential increase in the number of procedures performed, with a slight deceleration in 2018, as illustrated in Figure 1. The baseline characteristics of the population are shown in Table 1. The mean age of our global cohort was 81±7 years with the youngest and oldest patients

Table 1 Baseline characteristics of the study population and according to the transcatheter aortic valve implantation access route.[a]

Variable	All (n=2346)	TF (n=2131)	Non-TF (n=214)	p value (TF vs. non-TF)
Age, years	81.1±7.1 (20-96)	81.3±7.1	79.2±7.0	<0.001
Female	53.2 (1246/2341)	54.5 (1159/2127)	40.6 (87/214)	0.001
Risk factors				
Diabetes	33.1 (683/2062)	32.7 (608/1858)	36.8 (75/204)	0.241
Previous history				
Stroke	12.0 (246/2055)	11.6 (216/1855)	15.0 (30/200)	0.169
PAD	16.1 (323/2012)	13.5 (245/1813)	39.2 (78/199)	<0.001
CAD	43.8 (900/2054)	42.3 (783/1852)	57.9 (117/202)	<0.001
PCI	23.1 (472/2047)	22.7 (419/1845)	26.2 (53/202)	0.254
CABG	17.7 (367/2070)	16.5 (307/1866)	29.4 (60/204)	<0.001
CKD	37.5 (767/2043)	36.9 (679/1842)	43.8 (88/201)	0.056
COPD	22.0 (454/2065)	21.7 (404/1862)	24.6 (50/203)	0.328
Previous ECG				
Atrial fibrillation	25.4 (512/2013)	25.3 (460/1817)	26.5 (52/196)	0.928
Pacemaker/CRT	7.1 (142/2013)	7.0 (128/1817)	7.1 (14/196)	
Clinical status				
Class I-II	31.9 (631/1981)	32.7 (581/1778)	24.6 (50/203)	0.043
Class III-IV	68.1 (1350/1981)	67.3 (1197/1778)	75.4 (153/203)	
EuroS-II	4.3 (2.5-7.1)	4.3 (2.5-7.0)	4.8 (2.9-7.9)	0.058
STS mortality	4.7 (3.0-7.1)	4.7 (3.0-7.1)	4.4 (2.9-6.9)	0.475
Baseline echocardiography				
LVEF<50%	27.8 (538/1934)	27.3 (474/1736)	32.3 (64/198)	0.154
Mean baseline gradient, mmHg	49.4±16.1	49.6±16.3	48.6±14.8	0.461
Aortic valve area, cm^2	0.64±.0.20	0.64±0.21	0.66±0.21	0.101
TAVI indication				
AS	93.2 (2190/2347)	93.5 (1993/2131)	91.6 (196/214)	0.133
Aortic disease	2.3 (53/2347)	2.1 (44/2131)	4.2 (9/214)	
Prosthesis dysfunction	4.4 (104/2347)	4.4 (94/2131)	4.2 (9/214)	
Surgical risk				
High risk	49.7 (1167/2346)	50.3 (1072/2131)	44.4 (95/214)	<0.001
Surgical contraindication[b]	22.0 (517/2346)	20.6 (439/2131)	36.4 (78/214)	
Other non-specified	28.3 (664/2346)	29.1 (620/2131)	19.1 (41/214)	
Bridge balloon aortic valvuloplasty	2.9 (57/1946)	2.7 (48/1749)	4.6 (9/196)	0.174

CABG: coronary artery bypass graft; CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive lung disease; CRT: cardiac resynchronization therapy; EuroS-II: EuroScore II; LVEF: left ventricular ejection fraction; non-TF: non- transfemoral; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; TAVI: transcatheter aortic valve implantation; STS: Society of Thoracic Surgery; TF: transfemoral; TA: transapical.

[a] CKD, defined as glomerular filtration rate <60 mL/min/m^2.

[b] Surgical contraindication, including porcelain aorta, prohibitive respiratory function tests, liver cirrhosis, previous coronary artery bypass surgery with patent thoracic artery, as per heart team discussion.

Note: Data are presented as mean ± standard deviation or n (%).

aged 20 and 96, respectively. The median EuroS-II was 4.3% (IQR 2.5-7.1) and the STS score mortality risk was 4.7% (IQR 3.0-7.1). The majority of patients were in NYHA functional class III or IV (68.1%). The predominant route was transfemoral (90.9%). Self-expandable valves (SEV), particularly Medtronic CoreValve, were used more frequently (69.1%), while the remaining 30.9% were balloon-expandable (BEV) Edwards Valves. Procedural characteristics are presented in Table 2.

Transapical access was the most used non-transfemoral (non-TF) route (64%, 137/214). Patients who were underwent to non-TF prosthesis implantation (9.1%) were significantly younger (non-TF 79±7 vs. TF 81±7 years, p<0.001), had a lower prevalence of females (non-TF 40.6% vs. TF 54.5%, p=0.001) and showed a higher prevalence of PAD and coronary artery disease (CAD), including more patients that had previously undergone surgical coronary revascularization. As expected, this group tended to have a higher surgical risk profile, with an EuroS-II of 4.8% (IQR 2.9-7.9) (vs. TF 4.3 [IQR 3.2-8.6], p=0.058), which was clearly significant when considering only transapical access route patients (TA 5.2% [3.2-8.6], p=0.012). Half of the global

Table 2 Procedural characteristics of the study population and according to the access route.

Variable	All (n=2346)	TF (n=2131)	Non-TF (n=214)	p value (TF vs. non-TF)
TAVI route		-	-	na
Transfemoral	90.9 (2131/2345)			
Transapical	5.8 (137/2345)			
Transaortic	2.0 (48/2345)			
Transubclavian	0.9 (20/2345)			
Transcaval	0.4 (9/2345)			
Valve type				<0.001
CoreValve	52.0 (1217/2341)	54.3 (1153/2125)	29.0 (62/214)	
Edwards valve	30.9 (723/2341)	27.7 (588/2125)	63.1 (135/214)	
Other	17.1 (401/2341)	18.1 (384/2125)	7.9 (17/214)	
SEV	69.1 (1618/2341)	72.3 (1537/2125)	36.9 (79/214)	<0.001
BEV	30.9 (723/2341)	27.7 (588/2125)	63.1 (135/214)	
Post-dilatation	20.5 (408/1986)	21.4 (383/1789)	12.8 (25/195)	0.001
Second prosthesis	2.2 (44/1986)	2.5 (44/1789)	0	0.001
Repeat procedure	1.3 (26/2056)	1.2 (23/1849)	1.5 (3/205)	0.739

BEV: balloon-expandable valve; SEV: self-expandable valve; TAVI: transcatheter aortic valve implantation; TF: transfemoral.
Note: Data are presented as mean ± standard deviation or n (%).

cohort was considered by the heart team as presenting high surgical risk (49.7%). In the non-TF group, when compared with the TF group, a significantly higher proportion presented a surgical contraindication supporting the decision (non-TF 36.4% vs. TF 20.6%, p<0.001). In this particular group, as expected, BEVs were more frequently implanted (BEV 63.1% vs. SEV 36.9%), and less post-dilatation was used (non-TF 12.8% vs. TF 21.4%, p=0.001). There was also less of a need for a second prosthesis during an index procedure (non-TF 0 vs. TF 2.5%, p=0.001).

In-hospital and 30-days results

In-hospital results are shown in Table 3. The median duration of hospitalization decreased over the years (2007-2014 median 9 [IQR 7-14] vs. 2015-2018 median 7 days [IQR 5-11], p<0.001); Figure 2), without significant differences according to the selected route.

Based on the VARC-2 criteria, the immediate implant success was globally high (90.1%), with numerically better results for TF compared to a non-TF approach, although the difference was not significant (TF 90.4% vs. non-TF 87.0%, p=0.174). There was a low rate of procedure-related complications in both access route approaches. TF patients had a lower prevalence of cardiac tamponade (TF 0.5% vs. non-TF 2.2%, p<0.001), perioperative myocardial infarction (TF 4.4% vs. non-TF 40.9%, p<0.001) and Acute Kidney Injury Network stage 2 or 3 (TF 3.9% vs. non-TF 6.9% vs. p<0.001). A non-TF approach, particularly transapical and transaortic, was associated with a higher occurrence of life-threatening and major bleeding, and also major vascular complications (non-TF 7.3% vs. TF 6.3%, p=0.001). Stroke occurred in 4.6% of our cohort, mainly non-disabling (55%, 48/88), and the prevalence of TIA was very low (1.8%).

Globally, moderate or severe aortic valve regurgitation occurred in 7.4% of patients, without significant differences between both approaches. Overall, 19.0% of patients

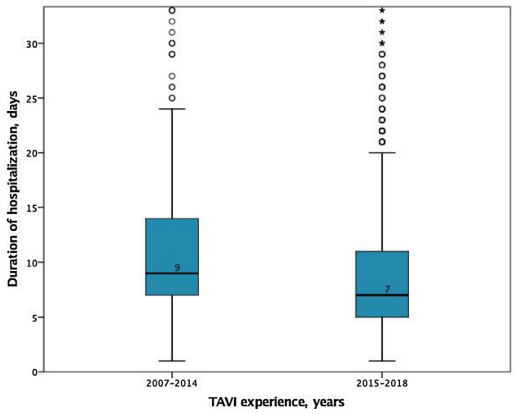


Figure 2 Median duration of hospitalization for the global cohort according to the year strata 2007-2014 and 2015-2018 (p<0.001 for comparison).

required a definitive pacemaker during follow-up, with a numerically lower rate in the non-TF group (non-TF 15.0% vs. TF 19.5%, p=0.153).

Overall, 30-day mortality was 4.8%, and the combined safety endpoint occurred in 85.0% of patients. Both endpoints were significantly better for the TF group, with a lower 30-day mortality rate (TF 4.3% vs. non-TF 10.1%, p=0.001) and higher 30-day safety endpoint (TF 86.4% vs. non-TF 72.6%, p<0.001). It is interesting to note the timeline stratification curve effect in Figure 3, showing the evolution of 30-day mortality incidence, with a significant reduction since 2011, from 14.1% to less than 4% in more recent years.

Follow-up and mortality

The median clinical follow-up duration was 259 (IQR 96-616) days, with an accumulated mortality rate of 14.0%.

Table 3 In-hospital and follow-up results of the study population and according to the access route.

Variable	All (n=2346)	TF (n=2131)	Non-TF (n=214)	p value (TF vs. non-TF)
In-hospital days	8 (6-12)	8 (6-12)	8 (6-11)	0.425
Immediate implant success	90.1 (1545/1714)	90.4 (1395/1543)	87.0 (147/169)	0.174
30-day safety	85.0 (1468/1727)	86.4 (1339/1550)	72.6 (127/175)	<0.001
30-day mortality	4.8 (110/2297)	4.3 (89/2087)	10.1 (21/208)	0.001
Procedure-related complications				
Coronary obstruction	1.8 (14/772)	1.9 (14/738)	0	1.0
ECC support	1.3 (12/954)	1.2 (11/909)	0.5 (1/177)	0.442
Tamponade	1.0 (8/775)	0.5 (4/740)	2.2 (4/177)	<0.001
ViV	1.1 (8/725)	1.2 (8/690)	0	1.0
Conversion to surgery	0.4 (4/954)	0.3 (3/909)	0.5 (1/177)	0.176
In-hospital complications				
Stroke	4.6 (88/1893)	4.7 (81/1714)	4.0 (7/177)	0.916
Disabling	2.1 (40/1893)	2.1 (36/1714)	2.3 (4/177)	0.777
Non disabling	2.5 (48/1893)	2.6 (45/1714)	1.7 (3/177)	
TIA	1.8 (35/1937)	1.8 (32/1757)	1.7 (3/178)	0.916
AKIN				
AKIN stage 2	2.1 (40/1892)	2.0 (35/1717)	2.9 (5/173)	<0.001
AKIN stage 3	2.1 (39/1892)	1.9 (32/1717)	4.0 (7/173)	
Pacemaker requirement	19.0 (374/1964)	19.5 (343/1762)	15.0 (30/200)	0.153
Vascular complication				
Major	6.8 (120/1766)	6.3 (110/1741)	7.3 (13/177)	0.001
Minor	16.5 (291/1766)	18.1 (315/1741)	6.2 (11/177)	
Bleeding				
Life-threatening	4.6 (94/2054)	4.1 (77/1861)	8.9 (17/191)	<0.001
Major	8.7 (179/2054)	7.4 (138/1861)	21.5 (41/191)	
Minor	13.6 (279/2054)	14.0 (261/1861)	9.4 (18/191)	
AMI				
Perioperative	7.5 (145/1945)	4.4 (78/1779)	40.9 (67/164)	<0.001
NYHA on follow-up				
Class I-II	94.3 (1201/1274)	94.3 (1074/1139)	93.9 (125/133)	0.133
Class III-IV	5.7 (73/1274)	5.7 (65/1139)	6.1 (8/133)	
Moderate-severe AR	7.4 (82/1114)	8.6 (77/897)	6.9 (9/131)	0.347
Prosthesis dysfunction	10.1(112/1114)	9.8 (88/897)	7.2 (10/137)	0.508
1-year rehospitalization	9.6 (98/1017)	9.0 (81/898)	14.3 (17/119)	0.071
1-year mortality	11.4 (194/1706)	10.5 (162/1541)	19.4 (32/165)	0.002
Overall mortality	14.0 (321/2300)	12.5 (261/2090)	28.8 (60/208)	<0.001

AKIN: acute kidney injury; AMI: acute myocardial infarction; AR: aortic regurgitation; ECC: extracorporeal circulation; NYHA: New York Heart Association; TIA: transient ischemic attack; ViV: valve-in-valve.
Note: Data are presented as mean ± standard deviation or n (%).

During the first year of follow-up, all-cause mortality rate was 11.4%, and was significantly lower for TF patients (TF 10.5% vs. non-TF 19.4%, p=0.002). Clinically, the majority of patients improved their functional capacity, with a reduction in the percentage of patients in NYHA class III and IV of 59.4% and 8.8% at baseline to 4.5% and 1.3% at follow-up, respectively (p<0.05) (Figure 4).

Thirty-day and one-year predictors of mortality

Following adjustments for gender, age, previous medical history, surgical risk scores and type of valve, the independent predictors of 30-day all-cause mortality were PAD (HR 2.24, CI 95% 1.41-3.53, p<0.001), previous PCI (HR 1.68, CI 95% 1.07-2.63, p=0.024), LV dysfunction (LVEF<50%: HR 1.67, CI 95% 1.07-2.63, p=0.021) and a worse functional status at baseline (NYHA class III-IV: HR 1.98, 95% CI 1.13-3.47, p=0.017) (Table 4). At one-year follow-up, as shown in Table 5, predictors of mortality were NYHA class III-IV (HR 2.11, 95% CI 1.06-4.16), non-transfemoral route (HR 1.76, 95% CI 1.01-3.09, p=0.046), occurrence of life-threatening bleeding (HR 2.44, 95% CI 1.09-5.47, p=0.030). There was also a trend with regard to chronic obstructive pulmonary disease (HR 1.68, 95% CI 0.97-2.93, p=0.063). Valve type did not influence mortality.

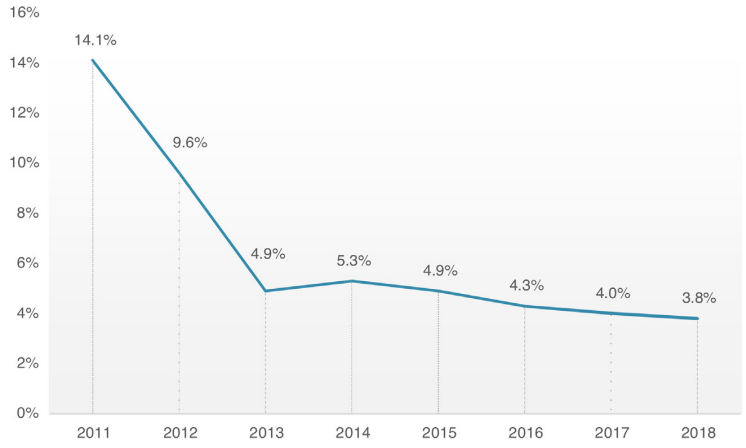


Figure 3 Evolution in 30-day mortality from 2011 to the end of 2018 (data presented in mortality rate per year).

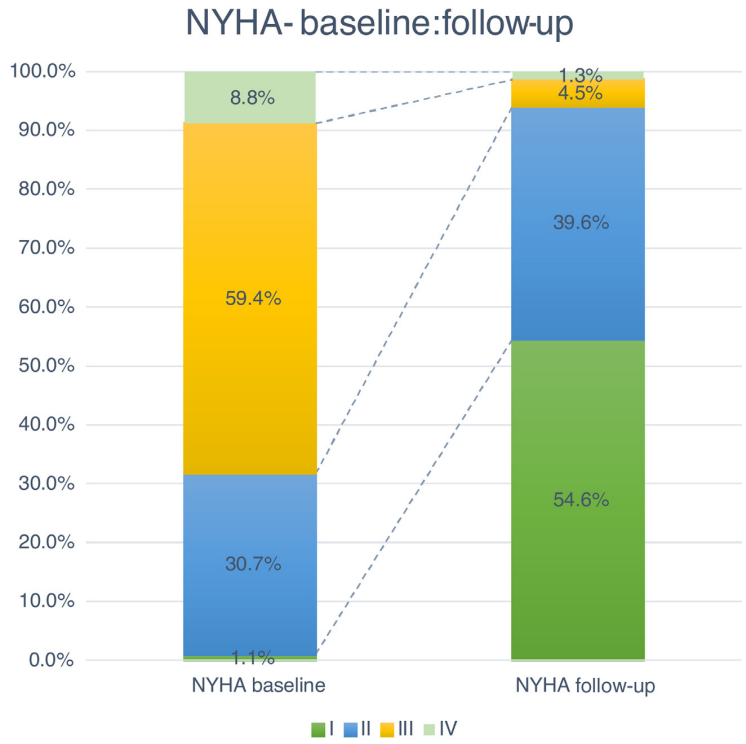


Figure 4 Comparison between New York Heart Association functional class at baseline and follow-up (p<0.05 for comparison).

Kaplan-Meier survival analysis of the first year of follow-up also shows decreased survival of patients who underwent non-transfemoral TAVI (log-rank p<0.001) and those with higher surgical risk (EuroS-II>5%) (log-rank p<0.001). There was also a trend of decreased survival in older patients (log-rank p=0.053) (Figure 5, A-E).

Discussion

Since its introduction in Portugal in 2007, the number of TAVI procedures has grown exponentially,[18] similar to the pattern seen following the adoption of this technology in Western countries.[23]

Table 4 Predictors of 30-day mortality.

Variable	Univariate, HR (CI 95%)	p value	Multivariate analysis, HR (CI 95%)	p value
PAD	2.447 (1.584-3.780)	<0.001	2.235 (1.414-3.534)	<0.001
Non transfemoral route	2.178 (1.338-3.546)	0.002		
PCI	1.957 (1.291-2.965)	0.002	1.677 (1.070-2.629)	0.024
LVEF<50%	1.881 (1.238-2.858)	0.003	1.667 (1.079-2.578)	0.021
NYHA III-IV pre procedure	1.851 (1.132-3.026)	0.014	1.982 (1.131-3.474)	0.017
CAD	1.500 (1.000-2.249)	0.050		
Atrial fibrillation	1.237 (0.794-1.927)	0.346		
Age	1.023 (0.994-1.054)	0.118		
ViV	0.372 (0.092-1.506)	0.166		

Other adjusted variables: Aortic valve area, mean gradient, coronary artery bypass graft, chronic obstructive lung disease, chronic kidney disease, EuroS-II, Society of Thoracic Surgery mortality risk score, type of valve (self-expandable valve and balloon-expandable valve), size of prosthesis, permanent pacemaker need, moderate or severe paravalvular aortic leak.
Abbreviations: CAD: coronary artery disease; CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; ViV: valve-in-valve.

Table 5 Predictors of 1-year mortality.

Variable	Univariate, HR (CI 95%)	p value	Multivariate analysis, HR (CI 95%)	p value
Age	1.021 (1.000-1.043)	0.05		
Non-TF route	1.675 (1.143-2.453)	0.008	1.769 (1.011-3.096)	0.046
NYHA III-IV pre procedure	2.051 (1.397-3.011)	<0.001	2.110 (1.068-4.169)	0.032
Atrial fibrillation	1.839 (1.344-2.516)	<0.001		
ViV	0.734 (0.345-1.563)	0.423		
LVEF<50%	1.208 (0.972-1.673)	0.255		
CAD	1.005 (0.748-1.350)	0.976		
COPD	1.665 (1.213-2.286)	0.002	1.688 (0.971-2.933)	0.063
PAD	1.387 (0.961-2.001)	0.081		
EuroS-II	1.016 (0.992-1.039)	0.187		
STS risk score mortality	1.041 (1.020-1.060)	<0.001		
Permanent pacemaker	1.147 (0.800-1.644)	0.454		
Life-threatening bleeding	2.848 (1.514-5.355)	0.001	2.443 (1.091-5.472)	0.030
AKIN>=stage 2	3.149 (1.746-5.681)	<0.001		
Vascular major complication	2.083 (1.242-3.495)	0.005		
Moderate-severe AR	2.376 (1.312-4.301)	0.004		

Other adjusted variables: Aortic valve area, mean gradient, coronary artery bypass graft, chronic obstructive lung disease, chronic kidney disease, EuroS-II, Society of Thoracic Surgery mortality risk score, type of valve (self-expandable valve and balloon-expandable valve), size of prosthesis, permanent pacemaker need, moderate or severe paravalvular aortic leak.
Abbreviations: AKIN: Acute Kidney Injury Network; AR: aortic regurgitation; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; EuroS-II: EuroScore II; HR: hazard ratio; LVEF: left ventricular ejection fraction; Non-TF: non-transfemoral; NYHA: New York Heart Association; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; STS: Society of Thoracic Surgeons.

Improved survival rates after TAVI, with a significant decrease in periprocedural mortality, reflect innovative device technology, but also the increased use of transfemoral TAVI, learning curves and optimized patient selection.[24] The increasing availability of smaller delivery systems and operator experience have brought about an increase in the number of patients treated with a TF approach, and approximately 90% of our patients were effectively treated using TF access, a percentage slightly above the 80% reported in FRANCE TAVI, with a corresponding decline in transapical access.[25] The predominant use of SEV in our registry may have, on the one hand, been influenced by the steady rise in TF TAVI, and on the other according to their availability in Portugal. As expected, balloon-expandable valves (BEV) were the main valve system used in TA TAVI. Nevertheless, it is noteworthy to mention that currently there is not enough evidence to claim the superiority of one device over the other.[26] Valve selection should be tailored according to the patient's clinical and anatomical characteristics, which is standard of practice at the different Portuguese TAVI centers.

Evidence showing that ViV procedures for prosthesis dysfunction have favorable outcomes[14] also contributed to the increasing number of these procedures in Portugal.

Approximately 50% of patients were considered high risk for surgery following a heart team assessment. This was not exclusively defined according to conventional surgical risk scores, in fact, in our cohort the mean EuroS-II was in the intermediate strata. Other factors, such as advanced age,

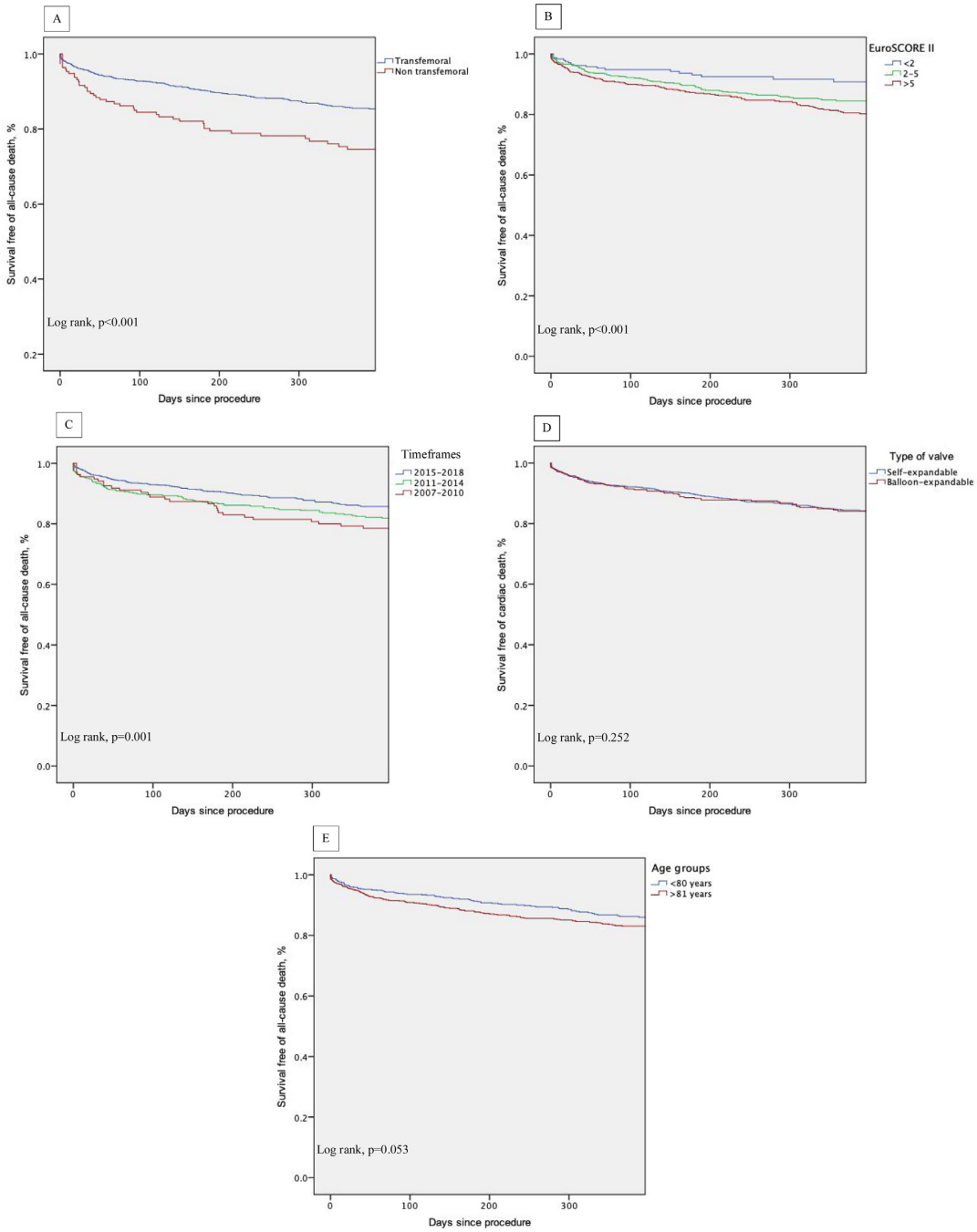


Figure 5 Cumulative survival curves according to access route (A), EuroS-II strata (B), timeframes in years of national experience (C), type of valve (D), age strata (E). *p<0.05.

associated comorbidities and frailty were determining factors, although the latter has not yet been fully reflected in the registry. Evidence shows that decision making in valvular heart disease involves a complex algorithm to define the risk-benefit ratio. Currently there is no single validated specific TAVI risk score, suggesting that the best approach should be based on the combination of the existing surgical scores together with frailty parameters and the presence of specific organ failure. The main goal should be to avoid TAVI futility.[21,22]

Our analysis revealed an incidence of stroke after TAVI of 4.6%, of which almost half were disabling. Although this result is below the incidence of stroke reported in the PARTNER cohorts A and B (5.5 and 6.7% respectively),[27,28] and similar to the incidence of peri-operative stroke following surgical AVR in elderly patients, which ranges from 3 to 7%,[29] this is still a matter of concern and an area of improvement that needs to be addressed. Embolic protection devices (EPD) are not used by default at Portuguese TAVI centers, however, so far, although published results show that EPD may help reduce the volume and size of periprocedural silent ischemic brain lesions identified on MRI, it did not reduce the incidence of new lesions and clinically significant neurological events.[30,31]The clinical impact of EPD needs further investigation in randomized trials prior to its widespread use.

The pacemaker implantation rate in our registry was 19% in the overall cohort, with a significant difference between TF 19,5% and TA 10.7% approach. This attributed to the differences between the predominant prosthesis type used in each of the access routes cohorts, SEV and BEV, respectively. A recent meta-analysis of different registries showed pacemakers were a requirement in 8% of Sapien TFs and 22% for CoreValve,[15] in line with our data, but higher than those reported in the PARTNER trials, probably because of the higher anatomic complexity of real-world patients.

Our registry reported an overall 7.4% incidence of moderate paravalvular leak (>=2), which is similar to other European registries and explained by the operator learning curves, standardization of techniques and new generation devices with extended sealing skirts.[32]

Concerning hard outcomes, in the PARTNER study, mortality was 3.4 and 5% in cohorts A and B, respectively.[6,33] Different registries present wide variability in mortality ranging from 5.4 to 12.4%, however, they compare different patients risk profiles, types of prosthesis and access routes.[29,34–36] In our global cohort, 30-day mortality has been decreasing since the beginning of the TAVI program, from 14.1% in 2011 to approximately 4% in the last 3 years, which is in line or slightly below other reported registries.[14,25] It is probably attributable to the fact that although our cohort had an advanced mean age of 81 years, the mean risk profile was intermediate. There is, in fact, a growing body of evidence that supports the extension of TAVI to increasingly lower risk patients, consistently demonstrating its noninferiority in comparison with conventional surgery.[8,11] It is also important to highlight that the low mortality of our cohort evidences that most of the fatalities were unrelated to periprocedural complications, which had low prevalence. A major conclusion from these data is that our focus should be on better prediction of risks and benefits of the procedure and appropriate patient selection.

Regarding the non-TF approach, and particularly the TA, when comparing with TF route, the former was associated with a lower 30-day safety composite outcome and higher mortality in our registry, similar to what has been reported in other studies.[33,37–39] The explanation is multifactorial, but clearly TA patients had increased prevalence of significant co-morbidities and a higher risk profile. A significant contribution might be derived from the increased rate of procedural complications, such as life-threatening and major bleeding, perioperative myocardial infarction and cardiac tamponade.

Based on VARC 2 criteria, the predictors for 30-day all-cause mortality were PAD, significant CAD with previous PCI, depressed left ventricular ejection fraction (LVEF) and an advanced heart failure (HF) clinical status. Buellesfeld et al. showed the patient's baseline functional state to be an independent predictor of hospital mortality[40] and the Italian registry indicated that an ejection fraction under 40%, diabetes, prior valvuloplasty and procedure-related complications were associated with worse short term prognosis.[29] The Ibero-American registry also underlined the importance of post-TAVI complications and logistic EuroS-II as predictors of mortality at 30 days.[16] Also, in a recent meta-analysis stage>=2 AKI was a strong predictor for 30-day mortality, although interestingly many patients saw an improvement in renal function after TAVI rather than kidney injury due to renal decongestion and increased perfusion. Preprocedural pro-brain natriuretic peptide levels were also a strong predictor of 30-day and midterm mortality. This is believed to be related to advanced HF with systolic and diastolic dysfunction. Likewise, baseline clinical status, represented by prior hospitalizations and preprocedural LVEF<=30%, had a significant impact on short term mortality.[41]

As independent predictors of one-year all-cause mortality we identified patient characteristics before the procedure, such as pre-procedural NYHA class III/IV and chronic obstructive pulmonary disease, and procedural factors such as the non-NF access route, which may be a surrogate for significant PAD. These results are corroborated by other registries and trials, showing also that some comorbidities are related to worse long-term prognosis, such as advanced age,[17] frailty,[35] male gender, end-stage renal disease,[34] porcelain aorta,[35] low gradient aortic stenosis,[42] reduced LVEF,[17] NYHA class,[36] mitral insufficiency grade>=2+,[42] residual postintervention aortic regurgitation,[6] intraprocedural conversion to surgery, peri-intervention stroke,[39] or postintervention pulmonary embolism.[42]

In our registry there was a sub-optimal percentage of patients lost to follow-up at one-year (22%), although acceptable when compared to other observational studies.[43,44,45] This can be explained by the nature of this prospective nationwide real-world registry that involves participating centers with various differences relating to the volume of procedures, follow-up approach and data registration. Also, compared to other European countries, the small number of 0.3[46] to 0.7 TAVI centers per million inhabitants in the registry history, can limit patient accessibility to those hospital centers because of distance, which is a known predictor of loss to follow-up.[47] It is worth mentioning that an automatic registration of a patient's vital status in the RNCI-VaP could be an effective way of strengthening the quality and completeness of data in the future.

Despite the acknowledged potential bias, the findings from this landmark study should help us to select appropriate candidates for TAVI accurately, with the main goal of referring patients in whom treatment benefit outweighs the risk, thus improving clinical benefit and avoiding futility. Nevertheless, a balance needs to be achieved because even

in high risk patients with several comorbidities, health- related improvements in quality of life and reduced congestive HF hospitalizations should be taken in account.

Study limitations

The data from the RNCI-VaP registry is self-reported and consequently subject to inclusion bias. Nevertheless, this registry is representative of the current standards of practice in Portugal, because it obtained data on 96.5% of the total number of implanted valves.

For some relevant variables we could not obtain data from all patients, which is a limitation inherent to the characteristics of a national registry that depends on the voluntary participation of the investigators, potentially causing selection bias. Events were reported by the investigators and were not independently reviewed, so we cannot rule out the possibility of under or over reporting of events. Also, the RNCI-VaP does not currently have either internal or external auditing. As such, definitive conclusions regarding cause and effect cannot be drawn from this study.

Although we acknowledge these limitations, the investigators of the RNCI-VaP consider this registry to be essential to ensure the safe and successful clinical applicability of the constantly evolving transcatheter aortic valve technology in Portugal. This paper includes the first published data on patients treated with TAVI in Portugal. It is noteworthy that the success and complication rates were similar to those reported by other European countries' registries.[32]

Conclusions

The RNCI-VaP shows that TAVI has been implemented with great success in Portugal. In this real-world all-comers all-centers registry of patients who underwent TAVI (both conventional and ViV), the procedure was safe and effective. Characteristics related to the access route, patient comorbidities and baseline clinical status adversely affected long-term prognosis and should therefore be taken in consideration when selecting patients for the procedure.

The systematic assessment and reporting of patients who underwent TAVI in Portugal is of paramount importance, eliciting a pragmatic assessment of TAVI results in the different centers and stimulating scientific multicentric production.

Author contributions

CG, PCF and RCT: study concept, design and drafting of the manuscript; CG, PCF, SM, RCT: analysis and interpretation of data; PB, PCS, LP, JCS, JB, MA, VGR, BS, JB, EIO, DC, JS: critical revision of the manuscript for important intellectual content.

Disclosure statement

The authors report no financial relationships or conflicts of interest regarding the content herein.

Conflicts of interest

The authors have no conflicts of interest to declare.

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EDITORIAL COMMENT

My patient cannot or will not comply with oral anticoagulation. Do I cross my fingers or cross the septum?☆

O meu doente não pode, não quer ou não cumpre a anti-coagulação oral. Cruzo os dedos ou cruzo o septo?

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Atrial fibrillation (AF) is a prevalent disease that affects up to 3% of the population and accounts for 1–3% of health care costs due to stroke, sudden death, heart failure, unplanned hospitalizations and other complications.[1–3]

Once non-valvular AF is diagnosed, a multidisciplinary and multifaceted approach is required, including acute management, treatment of underlying and concomitant conditions, rate and rhythm control, and prevention of the most feared complication, stroke. The tendency for blood pooling in the left atrium and left atrial appendage (LAA) due to AF was first reported in 1996, and although oral anticoagulation with vitamin K antagonists and direct oral anticoagulants (DOACs) has significantly reduced stroke risk, up to 40% of patients with AF are untreated, due to intolerance, bleeding, or other contraindications.[1,4,5]

Left atrial appendage occlusion (LAAO) aims to perform complete mechanical blockage of the LAA, which is the anatomical origin of around 90% of the thrombi that cause stroke. The two main trials comparing LAAO with warfarin, PROTECT AF and PREVAIL, demonstrated that closure is non-inferior for the prevention of ischemic stroke and is superior for the prevention of cardiovascular and all-cause mortality.[2,5,6] However, the randomized clinical trials were restricted to a single device and did not include patients who were intolerant to anticoagulation. Percutaneous LAAO, like AF ablation, has not been properly assessed in randomized trials with the standard current comparator, DOACs, in terms of major cardiovascular events. There have, of course, been large observational studies that suggest a reduction in stroke risk compared with risk estimates such as the CHA_2DS_2-VASc score. These studies often included patients who were only prescribed antiplatelet agents or took no antiplatelet or anticoagulant agents at all following the implantation procedure.[6] Furthermore, there is no evidence that the presence of peri-device leak is associated with subsequent thromboembolic events, although these

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studies had short follow-up periods and varying antithrombotic regimens (antiplatelet, anticoagulant or both). In the largest randomized trial, PROTECT AF (455 participants), and in 339 patients from the multicenter Amplatzer Cardiac Plug study, the number of ischemic events was low (16 and seven, respectively).[5,7]

The study by Paiva et al. published in this issue of the *Journal*[8] is highly relevant to this question. They set out to determine whether the risk-benefit ratio of LAAO for cerebrovascular prevention is superior to that of DOACs over a mean follow-up of 17 months. This prospective observational study assessed 302 patients (62 of whom were excluded) with non-valvular AF at high risk for stroke admitted to a single reference center between 2015 and 2017. The authors concluded that LAAO (n = 91) was not inferior to long-term treatment with NOAC (n = 149) for preventing the composite endpoint of death, stroke and major bleeding. This result differs from those of previous large observational studies, in which the reduction in stroke risk was similar in patients who received only antiplatelets, or neither antiplatelets nor anticoagulants, after the procedure.

The study has several merits. It provides a clear picture of the skill and expertise of a highly-regarded Portuguese group with extensive experience in this procedure, whose success rate is 96.3%, and who make use of guidance by intracardiac echocardiography (ICE) and transesophageal echocardiography.[9] It is unusual in bringing together two different high stroke risk case mixes: primary and secondary prevention by LAAO and secondary prevention with DOACs in the Neurology AF registry. This naturally reflects the different profiles of these two patient groups but does not consistently favor the LAAO group. Three devices used in real-world practice, selected by individual operators, are analyzed: the AMPLATZER Cardiac Plug™ or Amulet™ (St. Jude Medical) and the WATCHMAN™ (Boston Scientific). The study portrays real-world contemporary anticoagulant and antiplatelet regimens following LAAO, including the fact that a fifth of these patients stopped antiplatelet treatment six months after device implantation, and observes that mortality in the DOACs group was initially higher, while in the LAAO group it was distributed more evenly over the follow-up period. Finally, it reports a very real risk of fatal bleeding, with two deaths due to severe bleeding.

The authors point out certain methodological limitations. Besides the biases inherent to the study design, its statistical power (approximate and not always consensual) was estimated at 51%, indicating a 49% probability of not finding a statistically significant difference and a 5% probability of finding a difference that does not exist (type 1 error). However, this does not invalidate the conclusions.

It is important to bear in mind that despite progress, stroke prevention, by LAAO and generally in the context of non-valvular AF, still faces several challenges. The CHA_2DS_2-VASc and HAS-BLED risk scores, which are recommended in the guidelines, are useful tools but have their limitations. Even in the best circumstances, they are not particularly robust for predicting individual stroke and bleeding risk.[3]

Individuals who stand to derive greater benefit from LAAO – those who are intolerant of chronic anticoagulation – are excluded from studies of the procedure, despite its growing use in these cases. For example, a recent meta-analysis of 12 observational studies (seven retrospective and five prospective) in patients with a history of intracranial bleeding concluded that LAAO can potentially be an effective and relatively safe treatment option after shared decision-making with individual patients.[5,6]

The presence on screening exams of thrombi in the LAA that do not respond to anticoagulation is another exclusion criterion in the major studies, due to concerns that they increase the risk of complications. The impact of embolic protection devices in such cases is not known, but there have been reports of successful implantation using appropriate techniques and selected devices.[10]

The LAA's considerable anatomical variability in shape, volume, length and width requires a variety of devices to be available. In addition, fibrosis of this structure may have prognostic impact.[5]

Increasing access to three-dimensional ICE may help to widen the use of LAAO.[5,11]

In conclusion, the study by Paiva et al. is original and has the merit of describing the profile of a real-world population of Portuguese patients with non-valvular AF at high stroke risk. It indicates that percutaneous LAAO is safe and effective compared to DOAC therapy in the medium term. The use of LAAO is supported by the pressing need for therapeutic alternatives to chronic OAC, but assessment of the prognostic value of the procedure requires further validation in randomized trials, led by individual researchers or by medical societies. That is our present challenge.

Conflicts of interest

The author has no conflicts of interest to declare.

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ORIGINAL ARTICLE

Adoption and patterns of use of invasive physiological assessment of coronary artery disease in a large cohort of 40 821 real-world procedures over a 12-year period

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KEYWORDS
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Adoption

Abstract
Introduction and Objectives: Use of invasive physiological assessment in patients with coronary artery disease varies widely and is perceived to be low. We aimed to examine adoption rates as well as patterns and determinants of use in an unselected population undergoing invasive coronary angiography over a long time frame.
Methods: We retrospectively determined the per-procedure prevalence of physiological assessment in 40 821 coronary cases performed between 2007 and 2018 in two large-volume centers. Adoption was examined according to procedure type and patient- and operator-related variables. Its association with relevant scientific landmarks, such as the release of clinical trial results and practice guidelines, was also assessed.
Results: Overall adoption was low, ranging from 0.6% in patients undergoing invasive coronary angiography due to underlying valve disease, to 6% in the setting of stable coronary artery disease (CAD); it was 3.1% in patients sustaining an acute coronary syndrome. Of scientific landmarks, FAME 1, the long-term results of FAME 2 and the 2014 European myocardial revascularization guidelines were associated with changes in practice. Publication of instantaneous wave-free ratio (iFR) trials had no influence on adoption rates, except for a higher proportion of iFR use. In 42.9% of stable CAD patients undergoing percutaneous coronary intervention

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there was no objective non-invasive evidence of ischemia, nor was physiological assessment performed. Younger operator age (4.5% vs. 4.0% vs. 0.9% for ages <40, 40-55 and >55 years, respectively; p<0.001) and later time of procedure during the day (2.9% between 6 and 8 p.m. vs. 4.4% at other times) were independent correlates of use of invasive physiology.
Conclusions: Our study confirms the low use of invasive physiology in routine practice. The availability of resting indices did not increase adoption. Strategies are warranted to promote guideline implementation and to improve patient care and clinical outcomes.
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PALAVRAS-CHAVE
Fisiologia coronária;
FFR;
iFR;
Doença coronária;
Adoção

Prevalência e determinantes da utilização da avaliação funcional invasiva da doença coronária em 40 821 procedimentos consecutivos ao longo de 12 anos

Resumo
Introdução e objetivos: A avaliação funcional invasiva da doença coronária varia significativamente na prática clínica e em geral parece ser subutilizada. O objetivo deste estudo foi determinar a sua adoção no mundo real, assim como estudar os padrões e os principais determinantes da sua utilização, numa população não selecionada de doentes submetidos a coronariografia invasiva, ao longo de um período alargado.
Métodos: A prevalência da avaliação funcional invasiva foi determinada retrospetivamente, por procedimento, em 40 821 casos realizados entre 2007 e 2018, em dois centros de grande volume. As taxas de adoção foram avaliadas de acordo com variáveis relacionadas com o procedimento, com o doente e com o operador, assim como em relação com marcos científicos relevantes, como a publicação de resultados de ensaios clínicos e de recomendações internacionais.
Resultados: De acordo com o contexto clinico, a utilização variou entre 0,6% em doentes submetidos a coronariografia no contexto de patologia valvular e 6% em doentes com doença coronária estável (DAC) e foi 3,1% em doentes com síndroma coronária aguda. Dos marcos científicos estudados, a publicação dos resultados do estudo FAME 1, dos resultados a longo prazo do FAME 2 e das Recomendações para a Revascularização da ESC de 2014 associaram-se às taxas de adoção. Para além de um aumento da utilização do iFR, a publicação dos ensaios clínicos consubstanciando clinicamente o seu uso não influenciou a utilização global de fisiologia invasiva. Em 42,9% dos doentes com DAC estável submetidos a angioplastia, não havia referência a isquémia objetivável nem foi utilizada fisiologia invasiva. A idade dos operadores (4,5% *versus* 4,0% *versus* 0,9% para idades < 40, 40-55 e > 55 anos, respetivamente; p < 0,001) e a hora de realização do procedimento (2,9% entre as 6-8PM *versus* 4,4% durante o restante dia) relacionaram-se inversamente com a utilização de fisiologia durante os procedimentos.
Conclusões: Esta análise confirma a baixa de utilização da avaliação funcional invasiva na prática clínica. A disponibilidade de evidência sobre o uso de índices não hiperémicos não aumentou a adoção. São necessárias estratégias dirigidas que potenciem a implantação das recomendações, de forma que o manejo dos doentes com doença coronária e os benefícios clínicos da estratificação invasiva possam ser aprimorados.
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Introduction

Fractional flow reserve (FFR)-guided revascularization has been widely validated and is associated with added net benefits in patient-oriented health outcomes, as compared to angiography alone.[1,2] The instantaneous wave free ratio (iFR) has proved to be similar to FFR concerning clinical outcomes,[3,4] and additional evidence suggests that other diastolic pressure indices are numerically similar to iFR and may be used interchangeably.[5,6] The reasons for the underuse of invasive physiology during diagnostic and interventional procedures in daily practice are not fully clear, despite extensive validation[7] and guideline recommendations,[8,9] and may also be subject to geographical variations. In addition, there is no consensus on how actual adoption should be calculated. In most reports, the number of percutaneous coronary interventions (PCI) is used as the denominator, which may result in underestimation, as it does not account for procedures in which revascularization may not have been performed consequently to a negative functional interrogation.

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The aim of the present study was to describe the prevalence of physiological assessment in a large unselected population undergoing invasive coronary angiography (ICA) in an unbiased setting over a long 12-year time span, and to elucidate its patterns and determinants of use.

Methods

Study definitions and design and data collection

Data on all ICA exams performed for any clinical indication in two large-volume centers in Portugal between January 2007 and December 2018 were analyzed retrospectively. Patient-, angiographic- and procedure-related data were recorded in a dedicated electronic database (Cardiobase®, Infortucano™) at the time of the index procedure by the attending team. Information was extracted separately from each center's database and then merged into a single dataset. To ensure consistency, similar queries were used for data retrieval. All patients provided written informed consent for the procedure and data collection in accordance with local institutional review board guidelines.

Use of invasive functional assessment was assessed per procedure. Diagnostic procedures in which PCI was deferred based on invasive physiology were also considered when determining adoption rates. Functional studies included FFR, resting full-cycle distal-to-aortic pressure ratio (Pd/Pa) and iFR. Attempted percutaneous coronary intervention included all cases in which PCI was decided and attempted, regardless of procedural success.

The adoption of physiological assessment was analyzed over the study period according to scientific landmarks, which included the publication of relevant clinical trials and the European guidelines on the management of stable coronary artery disease (CAD) and myocardial revascularization,[9–11] and also according to operator experience, time of the procedure during the workday, availability and type of baseline non-invasive testing prior to ICA, CAD extent and whether or not PCI was subsequently performed.

Study population and definition of the clinical indication for coronary angiography

All patients undergoing ICA for any clinical indication were included. Indications were classified as stable CAD, ongoing acute coronary syndrome (ACS), recent ACS, valve disease, or miscellaneous indications. Uniform definitions of each clinical indication are provided in the online Supplementary Material.

Statistical analysis

Continuous variables are expressed as means and standard deviations and were compared using the unpaired t test or the Mann-Whitney U test, as appropriate. Categorical variables are expressed as proportions and were compared using the chi-square test. Normality was tested with the Kolmogorov-Smirnov test and by visual inspection of Q-Q plots.

Independent predictors of the use of invasive physiology were assessed using binary logistic regression models. To examine the impact of time-varying scientific landmarks, the variable was entered in the model as categorical. Use of a repeated contrast method means that estimations represent the odds between contiguous categories, rather a comparison with any given reference category. Model calibration and discriminative power were assessed with the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve, respectively. A two-sided p-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with IBM® SPSS® Statistics version 23.

Results

Population baseline characteristics

Between January 2007 and December 2018, 40 821 procedures were performed, in which PCI was attempted in 42.1% of cases (n=17 183). ACS was the most common indication for ICA (35.5% ongoing ACS and 8% recent ACS cases). Patients' baseline characteristics and clinical indications for ICA are further detailed in Table 1.

Overall adoption of invasive physiology according to indications for invasive coronary angiography

Over the study period, physiology assessment was used in 1631 procedures (4%). Regarding the main clinical indications, adoption was 6.0% in stable CAD, 2.7% in patients suffering ongoing non-ST elevation ACS, 5.4% in patients with recent ACS (mostly for assessment of residual non-culprit lesions after primary PCI), 0.6% in patients undergoing ICA due to underlying valve disease, and 2.0% in other miscellaneous indications. Adoption was 4.1% considering all attempted PCI procedures as the denominator (n=17 183) and 6.4% in stable CAD patients undergoing PCI (Supplementary Figure S10).

Adoption of invasive physiology according to scientific landmarks

Rates of invasive physiology over time, as well as their relationship with relevant landmarks, both overall and within the main clinical settings, are represented in Figure 1 and in Supplementary Figure S1A. Adoption increased significantly from 0.9% to 4.0% after the publication of FAME 1[1] in 2009 and remained stable thereafter, as no major changes were associated with the release of early results from FAME 2.[12] Although the absolute annualized adoption rate was higher after 2015 (5% vs. 4% in the previous period; p=0.01), closer analysis demonstrates that it actually started rising in late 2014, temporally coinciding with the publication of the two-year results of the FAME 2 study (Supplementary Figure S1).[13] Finally, following the publication of the two iFR outcome trials[3,4] in early 2017, no increase was noted in the use of invasive physiology (either overall or in stable CAD), although the proportion of cases using iFR rather than FFR

Table 1 Baseline patient and procedural characteristics in the overall cohort and according to use of invasive physiology in invasive coronary angiography.

Variable	Overall population (n=40 821)	Angiography group (n=39 190)	Physiology group (n=1631)	p
Demographic				
Age, years, mean ± SD	66.2±12	66.2±12.1	65.1±10.9	<0.001
Male gender	27 239 (66.7%)	26 073 (66.5%)	1166 (71.5%)	<0.001
Previous clinical history				
Diabetes	12 686 (31.1%)	12 088 (30.8%)	598 (36.7%)	<0.001
Hypercholesterolemia	23 483 (57.5%)	22 417 (57.3%)	1066 (65.5%)	<0.001
Hypertension	30 108 (73.8%)	28 845 (73.7%)	1263 (77.5%)	0.001
Smoking history	15 671 (38.4%)	14 989 (38.3%)	682 (41.8%)	0.004
Family history of CVD	3477 (8.5%)	3308 (8.5%)	169 (10.4%)	0.006
Peripheral arterial disease	2407 (5.9%)	2311 (5.9%)	96 (5.9%)	0.987
Stroke	3161 (7.7%)	3049 (7.8%)	112 (6.9%)	0.346
Previous myocardial infarction	9251 (22.7%)	8430 (21.5%)	438 (26.9%)	<0.001
Previous PCI	9733 (23.8%)	9109 (23.2%)	558 (34.2%)	<0.001
Previous CABG	3053 (7.5%)	2973 (7.6%)	80 (4.9%)	<0.001
Cardiomyopathy	144 (0.36%)	134 (0.3%)	10 (0.6%)	0.082
Valve disease (moderate or severe)	5896 (14%)	5824 (14.9%)	72 (4.4%)	<0.001
Heart transplantation	35 (0.1%)	35 (0.1%)	0	–
Clinical setting				<0.001
Stable disease	16 223 (39.7%)	15 251 (39.1%)	972 (59.6%)	
Ongoing ACS	16 109 (39.5%)	15 676 (40.2%)	433 (26.5%)	
Recent ACS	3234 (7.9%)	3060 (7.8%)	174 (10.7%)	
Valvular heart disease	4017 (9.8%)	3993 (10.2%)	24 (1.5%)	
Miscellaneous	1075 (2.6%)	1054 (2.7%)	21 (1.3%)	
Not reported	163 (0.4%)	156 (0.4%)	7 (0.4%)	
Angiographic findings				<0.001
All <50% lesions	15 324 (37.5%)	14 978 (38.2%)	346 (21.2%)	
1-vessel disease	9627 (23.6%)	9107 (23.2%)	520 (31.9%)	
2-vessel disease	8315 (20.4%)	7862 (20.1%)	453 (27.8%)	
3-vessel disease	7555 (18.5%)	7243 (18.5%)	312 (19.1%)	
Coronary intervention				
PCI performed/attempted	17 183 (42.1%)	16 477 (42%)	706 (43.3%)	0.319

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CVD: cardiovascular disease; PCI: percutaneous coronary intervention; SD: standard deviation.

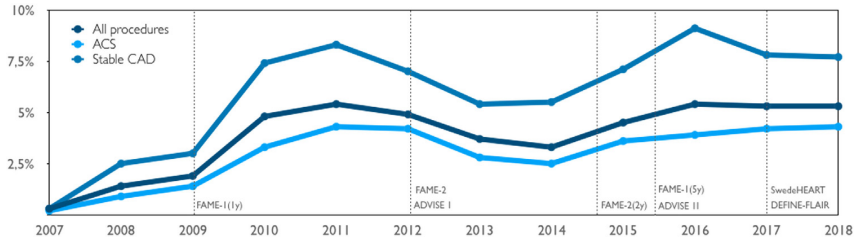


Figure 1 Use of physiological assessment between 2007 and 2018 and trends according to scientific landmarks in the overall population and in the main clinical settings. ACS: acute coronary syndrome; CAD: coronary artery disease.

increased (Figure 2). These trends were consistent across the stable CAD and ACS clinical settings, which comprised more than 80% of all procedures.

European guidelines on myocardial revascularization were issued in August 2013,[11] September 2014[10] and August 2018.[9] In an analysis restricted to the population undergoing ICA in the setting of stable CAD, a significant 1.67-fold increase (95% confidence interval [CI] 1.28-2.19; p<0.001) in adoption rates (from 4.7% to 8%) was seen in the period following the release of the 2014 guidelines, which also coincided with the publication of the long-term (two-year) results of the FAME 2 study (Supplementary Figure S1B).

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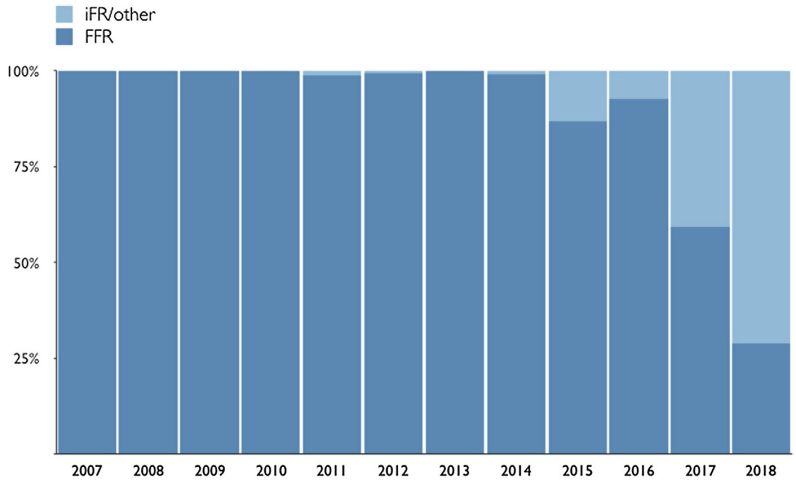


Figure 2 Relative use of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) over time.

Relationship between physiological assessment and operator experience

There was a statistically significant and independent association between operator experience and use of invasive physiology. Procedures performed by younger physicians were significantly more likely to include physiological assessment, both overall – 4.5% vs. 4.0% vs. 0.9% (p<0.001) – and in stable CAD – 7.4% vs. 5.1% vs. 1.5% (p<0.001) – for ages <40, 40-55 and >55 years, respectively (Figure 3 and Table 2).

Trends in the use of physiological assessment in high- versus low-adoption operators

For the purpose of this analysis, considering the average overall prevalence, the threshold for high versus low adoption was set at 5% or more of use of physiological assessment, including all procedures. All operators <40 years-old were classified as high adopters (according to the study criteria), versus none in the age group >55 years. Temporal trends diverged in high versus low adopters. While in the former adoption followed the previously described general pattern, in the latter it was mostly insensitive to scientific landmarks (Supplementary Figure S2). In the low-adopter group, only the FAME 1 landmark was associated with an increase in adoption (adjusted odds ratio [OR] 7.0, relative to the prior time period; 95% CI 2.4-19.9; p<0.001), but still, overall penetration remained less than 3%.

Adoption of physiological assessment according to time of the procedure during the workday

The proportion of procedures in which physiological assessment was used decreased progressively during the day, from

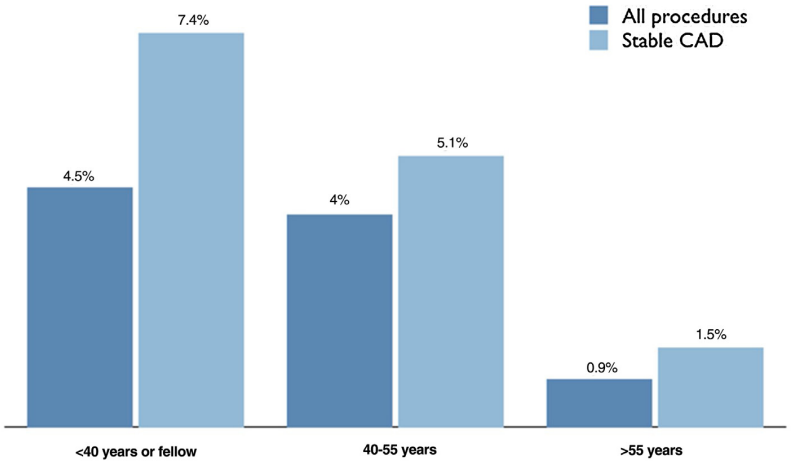


Figure 3 Adoption of physiological assessment according to operator experience. Operator age groups are shown on the horizontal axis as a surrogate of operator experience. CAD: coronary artery disease.

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Table 2 Multivariate predictors of physiological assessment during invasive coronary angiography (n=1631).

Variable	OR	95% CI	p
Clinical setting (stable CAD vs. other settings)	2.09	1.84-2.37	<0.001
Patient age (per 1-year increase)	0.98	0.98-0.99	<0.001
Previous PCI	1.51	1.36-1.69	0.03
Previous CABG	0.39	0.30-0.49	0.034
Diabetes	1.12	1.01-1.25	0.03
Baseline stress test performed	1.15	1.01-1.30	0.025
Operator experience (reference category >55 years old)			
Fellow or <40 years old	5.1	3.69-7.24	<0.001
40-55 years old	4.45	3.16-3.27	<0.001
CAD extent			
Overall	1.27	1.21-1-33	<0.001
3-vessel disease	0.82	0.70-0.95	0.012
2-vessel disease	1.03	0.90-1.18	0.582
1-vessel disease	2.5	2.2-2.9	<0.001
All <50% lesions	–	–	–
Time of procedure during the day[a]	0.93	0.90-0.96	<0.001
Relevant scientific landmarks[b]			
DEFINE-FLAIR and iFR-SwedeHEART	1.01	0.87-1.18	0.813
FAME 2 (long-term results)	1.29	1.11-1.49	0.001
FAME 2 (initial results)	0.91	0.79-1.05	0.217
FAME 1	4.16	3.08-5.6	<0.001

CABG: coronary artery bypass grafting; CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PCI: percutaneous coronary intervention.
Hosmer-Lemeshow goodness-of-fit test: chi-square=13.2; p=0.13. Area under the curve=0.72 (95% CI 0.71-0.74).
[a] Per each two-hour increase during the regular workday (from 8 a.m. to 8 p.m.).
[b] ORs are for comparisons between contiguous categories. There is no statistic for 'All lesions <50%' as it is the last category.

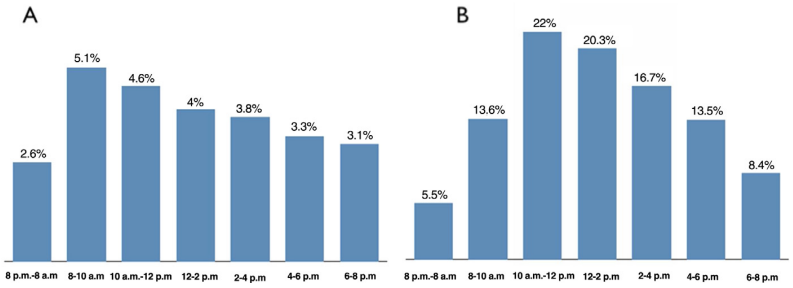


Figure 4 Proportion (A) and distribution (B) of invasive coronary angiography cases including physiological assessment according to time of the procedure during the regular workday.

5.1% during the first two hours (8-10 a.m.) to 3.1% between 6 and 8 p.m. (Figure 4). The majority of cases with invasive measurements (61%) were performed between 10 a.m. and 4 p.m. (Figure 4B).

Association between physiological assessment and baseline non-invasive testing, coronary disease burden and percutaneous coronary intervention

The overall prevalence of non-invasive stress tests was 25.7%, varying widely between clinical settings (from 2% to 53.9%; Supplementary Figure S3). The association between baseline non-invasive tests and use of invasive physiology was highly inconsistent. In stable CAD and recent ACS patients, the availability of functional information prior to ICA was not associated with the use of invasive physiology (5.9% vs. 6.1% for stable CAD and 3.6% vs. 5.6% for recent ACS, in procedures with and without baseline testing, respectively (p=NS; Supplementary Figure S4). However, in ongoing ACS adoption was higher in cases in which a baseline stress test was available (6.7% vs. 2.4%; p<0.001). Among stable CAD cases (n=16 223), the prevalence of physiological assessment was highest in multislice computed tomography (MSCT)-based referrals and in those with a negative non-invasive test at baseline (11% and 9.6% respectively; Supplementary Figure S5). In patients undergoing PCI who had no baseline non-invasive test available

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(either anatomical or functional), physiological assessment was used in only 6% of cases. Adoption was similar in procedures with non-specific positive ECG stress tests and imaging tests (6.8% and 6.3%, respectively), but was almost twice as high (11.9%) in patients in whom a baseline stress test had been performed but without evidence of ischemia (Supplementary Figures S6 and S7). Moreover, in 42.9% of stable CAD patients undergoing PCI, there was no record of inducible ischemia on non-invasive testing (including stress ECG), nor was physiological assessment performed.

On univariate analysis, there was no consistent association between CAD extent and the pattern of invasive physiology (Figure 5). When all cases are taken together, physiological assessment was more frequently performed in patients with one- or two-vessel disease (5.4% in both) than in three-vessel disease (4.1%) or in cases with less severe disease (2.3%). In stable CAD, adoption actually decreased through the spectrum of increasing CAD severity (9.1% vs. 8.3% vs. 5.8% for one-, two- and three-vessel disease, respectively) and in ongoing ACS it was numerically similar from mild to three-vessel disease (2.3% vs. 2.9% vs. 3.3% vs. 2.5%).

Considering only interventional procedures, cases in which physiological assessment was used had a higher disease burden (1.8±0.9 vs. 1.6±0.9 vessels with >50% stenosis; p<0.001). Overall prevalence of PCI was similar in cases with and without physiological assessment (42% vs. 43.3%; p=0.30; Supplementary Figure S8); however, the ratio of vessels treated by PCI to the number of diseased vessels was marginally lower in invasive physiology-guided cases, suggesting less extensive intervention (Supplementary Figure S9).

Independent predictors of use of coronary physiological assessment

In a multivariate binary regression model, the stable CAD clinical setting (versus other indications), diabetes, prior PCI and the availability of baseline stress tests were positive independent predictors of the use of invasive physiology. Prior CABG, time of the procedure during the workday and increasing patient age were inversely associated with the likelihood of use of invasive physiology in the index procedure. Also, younger operators – less than 40 and 40-55 years old – were four to five times more likely to use invasive physiology than older interventionists (>55 years old). As pointed out above, the overall association between CAD extent and use of physiology was inconsistent. In the multivariate model, increasing CAD extent (per diseased vessel) was associated with a significant 1.2-fold average greater likelihood of operators performing physiological assessment. However, this was driven by a higher OR in patients with one- and two-vessel disease compared both to milder cases and to three-vessel disease. Adjusted ORs of the independent predictors as well as model characteristics are summarized in Table 2.

Discussion

Our findings, which refer to a large cohort of patients undergoing ICA over a long time frame and encompassing a wide range of clinical scenarios, underscore (1) the low use of invasive physiological assessment of CAD in daily practice, regardless of the clinical setting; (2) that factors unrelated to procedural and patient characteristics significantly influenced penetration; and (3) that the clinical evidence sustaining the use of adenosine-free indices (mainly iFR) did not result in a significant increase in adoption.

Low adoption rates

Despite mounting evidence from randomized trials and large registries[14,15] and also strong guideline recommendations,[8,9,16] it is known that the use of invasive physiology varies widely and is generally perceived to be lower than expected.[17–20] Our results are in line with these observations.

Although trends may be changing worldwide,[21] partly due to more effective reimbursement policies, the underuse of invasive physiology-guided management is due to different reasons, ranging from technical and operator-related issues to site-specific and regional determinants. In some settings, factors such as unavailability or lack of funding have been pinpointed as the main reasons for the low uptake.[18] Nevertheless, there is evidence that even when all potential external constraints are overcome, visual estimation continues to dominate treatment decisions for intermediate

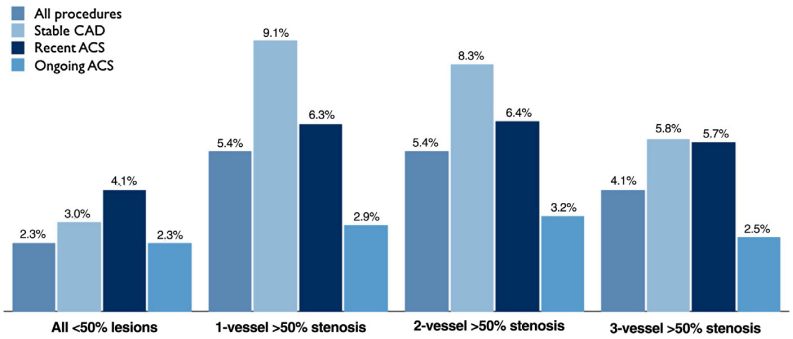


Figure 5 Use of physiological assessment according to coronary artery disease extent in the main clinical settings. ACS: acute coronary syndrome; CAD: coronary artery disease. *p<0.001; § p=0.089; † p=0.039.

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stenoses.[22] The extent to which similar factors apply to our sample cannot be accurately quantified. However, considering the wide availability of the technology in Portugal and the virtually unrestricted reimbursement policies, it is unlikely that financial issues have played a significant role.

Clinical correlates of use of invasive physiology

Despite overall low adoption rates, the stable CAD clinical setting was an independent predictor of use of physiological assessment. This may be influenced by current recommendations, which are mostly applicable to stable CAD. Diabetes and previous PCI were also associated with higher adoption. Both subgroups had more extensive CAD, which was itself an independent predictor. The use of FFR and iFR in patients with diabetes has recently been analyzed in large cohorts and both indices have been shown to retain diagnostic and prognostic reliability.[23,24] Conversely, prior CABG and increasing patient age were both inversely associated with the use of invasive physiology. It is conceivable that factors such as CAD complexity and comorbidity may have rendered operators less likely to consider additional diagnostic techniques. Also, concerns about microvascular dysfunction and adenosine hyporesponsiveness in elderly patients have been noted, compared to younger patients.[13,25]

Relationship with non-invasive functional tests, coronary artery disease extent and use of percutaneous coronary intervention

Our findings underscore important complexities of patient workup, for which straightforward explanations may not be attainable based on available data alone. Considering the main clinical settings (stable CAD and ACS), no consistent pattern could be detected regarding the association between the availability of stress tests at baseline (including stress ECG) and the use of invasive physiology. Operators could have been expected to perform invasive physiology mostly in the absence of prior non-invasive tests for the detection and/or localization of ischemia. However, this was not the case, except in the subgroup with recent ACS, at least in part because many of these cases were patients with ST-elevation myocardial infarction and bystander disease, in whom the prevalence of stress tests was low (Supplementary Figure S4). Another possible explanation relies on the observation that most functional tests were treadmill ECG stress tests and single-photon emission computed tomography myocardial perfusion imaging, which may lack accuracy in a real-world environment,[26,27] leading operators to use invasive physiology to clarify non-invasive findings, as in MSCT, in which no functional information is available at all. Nevertheless, the overall low penetration of physiological assessment renders further conclusions elusive.

The benefits of PCI in stable patients are thought to be linked to the severity of inducible ischemia,[28,29] although recent evidence from randomized trials has questioned this approach.[30,31] Even if this cannot be extended to other clinical settings, particularly ongoing ACS and valve disease, it is noteworthy that in our large cohort a high proportion of stable patients undergoing PCI had no demonstration of inducible ischemia, nor were invasive measurements performed. Although the ultimate reasons driving PCI in these cases – such as symptom severity, specific angiographic findings or information from intravascular imaging – cannot be definitively ascertained, this suggests that inappropriate revascularization potentially remains a significant problem.[21] The perceived safety of current revascularization techniques (notably PCI) may be driving a persistent unwillingness to adopt coadjuvant technologies such as invasive physiological assessment. However, our findings reinforce the need for the implementation of strategies aiming at a wider adoption of physiological assessment, if clinical benefits are to be optimized.[32,33]

The routine integration of physiological measurements in the management of patients with CAD has moved pressure indices to the center of the diagnostic workflow and risk stratification of patients undergoing ICA.[24] The more extensive the assessment and the greater the extent of CAD, the more likely are changes in the patient's management to occur, particularly when lesions are in fact intermediate.[14,15] Significant heterogeneity was found in our study concerning the use of invasive physiology according to the extent of CAD (as measured by the number of diseased vessels). Although CAD extent was an overall predictor of adoption across all main clinical settings, lesion assessment was always lower in three-vessel CAD. A higher prevalence of chronic total occlusions and other features of anatomical and clinical complexity may have rendered these patients worse candidates for assessment with pressure wires, which on their own may lack important mechanical characteristics as compared to regular workhorse guidewires. Our data support this observation, as three-vessel CAD patients were older, had lower creatinine clearance, and were more likely to have multiple risk factors, previous CABG and clinically overt vascular disease elsewhere (analysis not shown). Finally, it should be noted that the proportion of patients undergoing PCI was no lower in cases that included physiological assessment than in those that did not. This is in line with prior observations from the POST-IT registry and goes against the common belief that the routine use of physiological assessment will reduce PCI rates, as reclassification between management strategies ultimately allows patients who would not otherwise have been treated to undergo PCI.[14]

Patient-independent determinants of adoption: impact of operator experience and scientific evidence

For decades angiography has been the gold standard for guiding revascularization, and studies providing evidence for myocardial revascularization have been mostly based on angiography alone. It may thus not be surprising that older operators, who have been trained for many years in this technique, are less likely to use and rely on pressure gradients to decide on management of obstructive CAD. Unlike in previous reports, in which no difference in FFR use by operator age, practice setting, or case volume was observed,[18] in our large dataset we demonstrate that younger interventionists were significantly more likely to use physiological assessment than older operators, regardless of any other

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significant determinants. This may be due to a variety of reasons, such as increased awareness of the limitations of angiography as a surrogate of lesion severity,[34] changes in training patterns, and easier adoption of new technologies. For similar reasons, the penetration of physiological assessment could be expected to be related to the available clinical evidence. To assess this, we assessed its temporal relationship with scientific landmarks. All cases considered, there was a significant association with the publication of FAME 1[1] and the near-simultaneous release of the two-year results of FAME 2[13] and the 2014 European myocardial revascularization guidelines[10] (Supplementary Figure S1B). Overall adoption appears to have been insensitive to the initial results of the FAME 2 study[1] as well as to the publication of the two main randomized trials comparing iFR and FFR in clinical outcomes.[3,4] Importantly, trends were similar across the main clinical settings, despite higher absolute penetration in stable CAD. Also, high adopters (all of whom belonged to younger age groups) followed (and possibly were the drivers of) the general trend (Figure 1 and Supplementary Figure S2).

The fact that adoption did not increase with the advent of adenosine-free and non-hyperemic indices (such as contrast FFR and iFR) deserves consideration. Additional reasons that have been implicated in the low use of FFR are adverse effects of hyperemic agents, the costs associated with adenosine, contraindications and patient-related discomfort,[20] all of which have contributed to the pursuit of more patient-friendly techniques. In both DEFINE-FLAIR[3] and iFR-SWEDEHEART[4] the duration of the procedure was shorter and the percentage of patients who developed adverse procedure-related symptoms was lower than with FFR, potentially providing a solution for some of the previously reported barriers. Also, contrast-induced hyperemia has been shown to be an adequate surrogate of standard adenosine for FFR determination.[35,36] Still, we provide clear evidence that these well-publicized improvements appeared to have had little, if any, impact on the adoption of invasive physiology. As overall rates remained stable, there was simply a larger proportion of cases using iFR, progressively driving FFR use down to less than 30% of invasive physiology cases toward the end of the study period (Figure 2). Whether or not this observation extends to other countries and practice environments, particularly in Europe, remains to be determined.

Finally, it is noteworthy that the time of day the procedure was performed during the regular workday independently affected the likelihood of pressure indices being incorporated in patient assessment, as it decreased by a significant 7% for every two hours throughout the day (Figure 4). This can be explained mainly by logistical factors, mostly in the cath lab setup and workflow, as well as by the team's own perceptions of potential unwarranted delays and added complexity to the procedures, despite improvements in the technique. Inherent limitations can and should be progressively overcome by increasing operator experience and improving cath labs' routines and logistics, given that such measures are justified by important factors such as reduced need for further testing[14] and possibly unnecessary coronary interventions. Also, it is reasonable to expect that technical improvements in pressure sensor-tipped guidewires, continuous education in coronary physiology, and successful implementation of emerging technologies, such as real-time angiography and non-invasive CCTA-derived FFR and virtual PCI planning, may overcome some of these hurdles and help to change the scenario in the near future.

Strengths and limitations

Despite the high number of procedures, encompassing a wide range of clinical indications, our data were obtained from only two large-volume centers, and it could be argued that these may not be representative of the situation in the entire country. However, based on the Portuguese Registry on Interventional Cardiology, the rate of FFR-guided PCI was in the range of 0.2-0.8% before 2009, rising to 2.6-3.1% in 2010-2012.[37] These estimates mirror our results in that same period, which is a reassuring confirmation of the external validity of our data.

The full spectrum of reasons underlying the low adoption of invasive physiology is difficult to ascertain and there is no bullet-proof methodology that could provide unequivocal answers. A prospective inquiry on why invasive physiology may or may not have been used in any given case could induce observation bias and unwarranted changes in usual practice. On the other hand, a retrospective approach, such as the one used in our study, necessarily relies on the quality of registry data, a limitation that is inherent to all observational studies. However, we provide an unbiased analysis based on variables that are easy to collect and report and thus potentially less prone to uncertainty. Accurate identification of the original reasons underlying low adoption rates should prompt the implementation of dedicated strategies, in each specific setting.

Conclusion

This study builds on the evidence concerning the suboptimal use of invasive physiological assessment in routine practice, which is due in part to issues unrelated to patient and procedural characteristics. The availability of adenosine-free pressure indices has not increased adoption. In order to improve patient outcomes, dedicated strategies are needed both to motivate adherence to current guidelines and to increase awareness of the advantages of integrating invasive functional information into management algorithms.

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Conflicts of interest

Dr. Raposo has received grants from Abbott, Volcano, and HeartFlow, has served as a member of advisory boards for Abbott and Boston Scientific, and has received personal fees from Abbott, Boston Scientific, and HeartFlow outside the submitted work.

Dr. Baptista has received grants from Abbott, Volcano, and HeartFlow, has served as a member of advisory boards for Abbott, Boston Scientific and Opsens Medical, and has

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received personal fees from Abbott, Boston Scientific, and HeartFlow outside the submitted work.

Dr. Teles has received grants from Abbott, and has served as a member of advisory boards for Abbott, Medtronic and Boston Scientific.

The other authors have no conflict of interests to declare.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2021.01.010.

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ARTIGO DE REVISÃO

Tratamento não farmacológico da angina refratária. Dispositivo de redução do seio coronário, uma nova alternativa terapêutica

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PALAVRAS-CHAVE
Dispositivo de redução do seio coronário;
Terapia antianginosa não farmacológica;
Angina refratária;
Doença coronária

Resumo A angina refratária define-se como a persistência de sintomas superior a três meses apesar da terapêutica médica otimizada e revascularização. É uma entidade em crescimento, resultado da melhoria do prognóstico da doença coronária com a terapêutica farmacológica e com as técnicas de revascularização contemporâneas. A mortalidade a longo prazo enquadra-se no espetro prognóstico da doença estável assintomática, contudo interfere com a qualidade de vida do doente e tem um impacto significativo nos sistemas de saúde.

Múltiplos alvos terapêuticos têm sido investigados, contudo, a maioria com resultados dececionantes. Muitas das técnicas foram abandonadas por ausência de eficácia, problemas de segurança e limitações tanto logísticas como económicas à sua implantação.

Esta revisão incide essencialmente sobre o dispositivo de redução do seio coronário, cuja evidência, embora ainda escassa, é promissora relativamente à segurança e eficácia na redução dos sintomas anginosos e na melhoria da qualidade de vida. Para além do seu efeito terapêutico, é uma opção virtualmente acessível a todos os serviços de cardiologia de intervenção.
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KEYWORDS
Coronary sinus reducer device;
Non-pharmacological antianginal therapy;

Non-pharmacological treatment of refractory angina: The coronary sinus reducer, the new kid on the block

Abstract Refractory angina is defined as persistent angina (≥3 months) despite optimal medical and interventional therapies. It is increasing in frequency, due to the success of current medical and interventional therapies in improving the prognosis of coronary artery disease.

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Refractory angina;
Coronary artery disease.

Long-term mortality is similar to that of patients with asymptomatic stable disease, but it affects patients' quality of life, and has a significant impact on health care resources.

Several therapeutic targets have been investigated, most with disappointing results. Many of the techniques have been abandoned because of lack of efficacy, safety issues, or economic and logistic limitations to wider applicability.

The primary focus of this review is the coronary sinus Reducer, supporting evidence for which, although scarce, is promising regarding safety and efficacy in improving anginal symptoms and quality of life. It is also accessible to virtually all interventional cardiology departments.
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Definição, epidemiologia e impacto na sociedade da angina refratária

A angina refratária é definida nas recomendações para o tratamento das síndromes coronárias crónicas da Sociedade Europeia de Cardiologia como a persistência de sintomas superior a três meses, na presença de isquemia e doença coronária obstrutiva, que não é controlável por terapêutica médica com fármacos antianginosos de segunda e terceira linha, cirurgia de revascularização ou intervenção percutânea, incluindo angioplastia de oclusões crónicas.[1] Não obstante, esta classificação exclui os doentes com sintomas de longa duração e isquemia, sem doença obstrutiva, pelo que muitos investigadores adotam uma definição mais abrangente, baseada no conceito de insuficiência coronária, permitindo deste modo a inclusão dos doentes com angina microvascular.[2,3]

Pensa-se que a incidência esteja a aumentar, em virtude do envelhecimento da população, aumento da complexidade da doença coronária e da convivência com múltiplas comorbilidades, que limitam as opções terapêuticas.[1] Contudo, devido à grande variabilidade na definição, heterogeneidade clínica dos doentes afetados e constante evolução terapêutica, não existem estimativas contemporâneas exatas acerca da prevalência da angina refratária. A evidência existente deriva principalmente de registos de laboratórios de hemodinâmica do fim do século XX e início do século XXI, tendo-se estimado uma prevalência entre 9,3% e 15% entre os doentes referenciados para angiografia,[4–9] levando a que o grupo de estudo de estudo e tratamento da angina refratária da Sociedade Europeia de Cardiologia tenha estimado uma incidência de 30.000 a 50.000 novos casos por ano, na Europa.[3]

A mortalidade anual dos doentes com angina refratária num registro de consulta dedicada foi inferior a 4% ano, sendo 3,9% no primeiro ano e 17,5% aos 5 anos.[10] Num registro francês de mundo real incluindo 4.184 doentes com doença coronária estável, observou-se uma mortalidade aos cinco anos de aproximadamente 16%, o risco de morte variava entre menos de 2% em doentes com idade inferior a 65 anos sem história de insuficiência cardíaca e com fração de ejeção preservada para mais de 50% em doentes com mais de 65 anos, insuficiência cardíaca e fração de ejeção menor que 40%.[11] Por sua vez, em estudos aleatorizados com populações altamente selecionadas de comparação de estratégias terapêuticas em contexto de doença coronária estável, a mortalidade foi de aproximadamente 7,9% aos 4,6 anos no estudo COURAGE;[12] 11,4% *versus* 13,9% aos cinco anos no grupo de revascularização cirúrgica *versus* grupo de revascularização percutânea no estudo SYNTAX;[13] e 9% *versus* 8,3% aos cinco anos no estudo ISCHEMIA para estratégia invasiva e conservativa, respetivamente.[14]

A comparação entre o prognóstico da angina refratária com o da doença coronária estável assintomática está limitada pelas diferenças existentes nas características demográficas, no contexto clínico e nas comorbilidades das populações avaliadas.[7] É expectável que o prognóstico dos doentes com angina refratária se enquadre no espetro prognóstico da doença estável, quando ajustado para outros fatores clinicamente relevantes.[10] Por outro lado, estes doentes têm maior grau de incapacidade, pior qualidade de vida e maior consumo de recursos (internamentos, polimedicação, exames complementares de diagnóstico).[15]

Assim, a angina refratária configura-se como um problema emergente que carece de terapêuticas eficazes para mitigar os sintomas, melhorar a qualidade de vida dos indivíduos e otimizar a utilização de recursos e dos custos associados para a sociedade.

Fenótipos dos doentes com angina refratária

A angina é um diagnóstico clínico, tendo a investigação adicional o objetivo de confirmar a presença de doença coronária obstrutiva significativa ou de isquemia, não sendo a presença de ambas uma condição *sine qua non*.[1]

A doença coronária obstrutiva tem sido o alvo terapêutico mais reconhecido. Contudo, existem outros mecanismos potencialmente responsáveis, como a disfunção microvascular, o vasoespasmo e a componente neuro/psicogênica, que podem justificar os sintomas na ausência de doença obstrutiva ou após revascularização.

Atualmente a terapêutica médica e a revascularização aliviam os sintomas em cerca de 80% dos doentes, permanecendo ainda um grupo heterogéneo de doentes com queixas persistentes.[16] Estes doentes devem ser categorizados como tendo síndrome de dor torácica crónica, que engloba um espectro que vai desde a dor torácica não

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Tabela 1 Probabilidade clínica de angina refratária. Probabilidade de angina refratária de acordo com variáveis clínicas, anatómicas e funcionais.[17]

	Angina típica	Angina atípica	Doença epicárdica presente (+) ou ausente (-)	Documentação de isquemia	Etiologia provável
Alta	+	-	+	+	Doença epicárdica ± Doença microvascular
	+	-	-	+	Doença microvascular
Intermédia	+	-	+	-	Doença epicárdica ± doença microvascular
	-	+	+	+	
	-	+	-	+	Doença epicárdica ± doença microvascular
					Doença microvascular
Baixa	+	-	-	-	Provavelmente dor não cardíaca
	-	+	+	-	
	-	+	-	-	Provavelmente dor não cardíaca
					Provavelmente dor não cardíaca

cardíaca à angina refratária. A integração de dados clínicos (tipicidade das queixas), anatómicos (presença de doença obstrutiva) e funcionais (presença de isquemia) é fundamental para estabelecer a probabilidade de angina refratária[17] (Tabela 1).

Assim, a angina refratária é a manifestação clínica de uma variedade de entidades, incluindo doença coronária obstrutiva, doença microvascular, vasoespasmo, doenças do miocárdio e disfunção diastólica.[17,18]

Estão descritos quatro fenótipos angiográficos em doentes com angina refratária;[2] 1) ausência de doença coronária obstrutiva (síndrome X); 2) território circunscrito em risco; 3) aterosclerose coronária difusa filiforme; e 4) doença coronária obstrutiva terminal (Tabela 2).

Opções terapêuticas não farmacológicas

O paradigma do tratamento da angina baseia-se no restabelecimento do equilíbrio entre oferta e a demanda de oxigénio.[19] No entanto, nos doentes com angina refratária, os sintomas resultam da interação de múltiplos mecanismos, pelo que a abordagem deverá ser holística (Figura 1).

A primeira linha de intervenção em todos os doentes deverá ser a reabilitação pragmática com desmistificação dos receios do doente, estímulo de autoconfiança e ensino de métodos para controlo dos sintomas. A intervenção subsequente deverá ser individualizada de acordo com o principal mecanismo para as queixas e os recursos locais.

A segunda linha de intervenção consiste na redução de isquemia. Foram desenvolvidas técnicas não invasivas e invasivas. As técnicas não invasivas incluem contrapulsação externa[20] e a terapia de onda de choque extracorporal.[21] As técnicas invasivas dividem-se em mecânicas, como a intervenção coronária percutânea de oclusões crónicas,[22,23] a revascularização transmiocárdica com laser[24,25] e a redução do seio coronário,[26–32] e em biológicas, com terapia génica e celular.[33,34]

A terceira linha de intervenção passa pela modulação da dor, que pode ser não invasiva com estimulação nervosa elétrica subcutânea e invasiva com bloqueio do gânglio estrelado e modulação da medula espinhal.[17,35–37] A Tabela 3 resume as principais características, os resultados e as limitações dos estudos das terapêuticas não farmacológicas para angina, apenas a terapia celular, a intervenção percutânea de oclusões crónicas e a redução do seio coronário apresentam evidência sugestiva de eficácia e segurança na redução da angina.

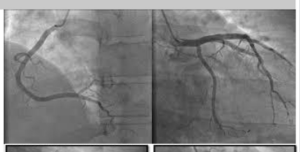
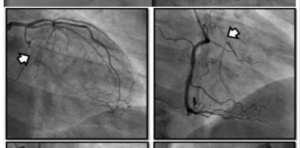
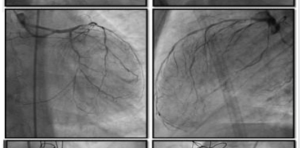
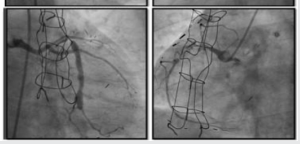
A terapia com dispositivo de redução do seio coronário apresenta-se, assim, como uma intervenção segura, potencialmente eficaz e implantável em qualquer laboratório de hemodinâmica.

Efeito antianginoso da redução do calibre do seio coronário

Conceito de redução do seio coronário

Na década de 50 do século XX, numa era pré angiografia coronária,[38] altura em que o tratamento não ia além do alívio empírico dos sintomas com nitratos, atropina, fenobarbital e narcóticos,[39] Claude Beck investigava intensamente diferentes intervenções cirúrgicas para o tratamento da angina, categorizadas como: 1) intervenções de revascularização indireta, com intuito de estimular a neoangiogénese e a colateralidade, através de insultos mecânicos ao pericárdio e miocárdio e 2) pela redução cirúrgica do calibre do seio coronário.[40] Destas, apenas a ligação do seio coronário com o intuito de reduzir o lúmen 60-70% para aproximadamente 3 mm revelou utilidade clínica. Um estudo comparativo incluindo 185 doentes demonstrou redução de mortalidade aos cinco anos (13% no grupo tratado *versus* 30% no grupo não tratado) e eficácia no alívio da angina, com 90% dos doentes tratados reportando alívio completo ou significativo da angina.[41] Contudo, o interesse nesta intervenção veio a diminuir com os avanços e o sucesso tanto da

Tabela 2 Fenótipos angiográficos da angina refratária[2]

Fenótipo	Características	
Síndrome X	1.Angiografia sem doença obstrutiva - Evidência de isquemia sem doença obstrutiva - Resulta de disfunção microvascular, doenças metabólicas, doenças infiltrativas do miocárdio 2. Após revascularização - Evidência de isquemia apesar de revascularização completa com patência de pontagens e sem reestenose de stent - Provavelmente resulta de disfunção microvascular	
Território em risco circunscrito	1. Território em risco sem CABG prévia -Estenose epicárdica significativa não passível de angioplastia, mas suficiente para causar angina e sem características de alto risco na estratificação não invasiva - Pode resultar de oclusão crónica de vaso único (excluindo descendente anterior), ou de doença em ramos secundários finos ou no segmento distal 2. Território em risco após CABG - Estenose epicárdica significativa não passível de angioplastia, mas não suficiente grave que justifique repetição de CABG - Pode resultar de oclusão de pontagens venosas ou revascularização incompleta inicial	
Aterosclerose difusa filiforme	Infiltração ateromatosa difusa filiforme dos segmento proximais aos distais com leito distal fino (< 1 mm) Tipicamente afeta os três território vasculares, pode coexistir doença focal, mas de baixo potencial de revascularização eficaz. Frequente nos diabéticos.	
Doença coronária terminal	Estado de falência coronária que combina a presença de doença significativa proximal com doença difusa distal. Associa-se frequentemente a colateralidade acentuada nos territórios viáveis. Encontra-se geralmente em doentes com CABG prévia degenerada.	

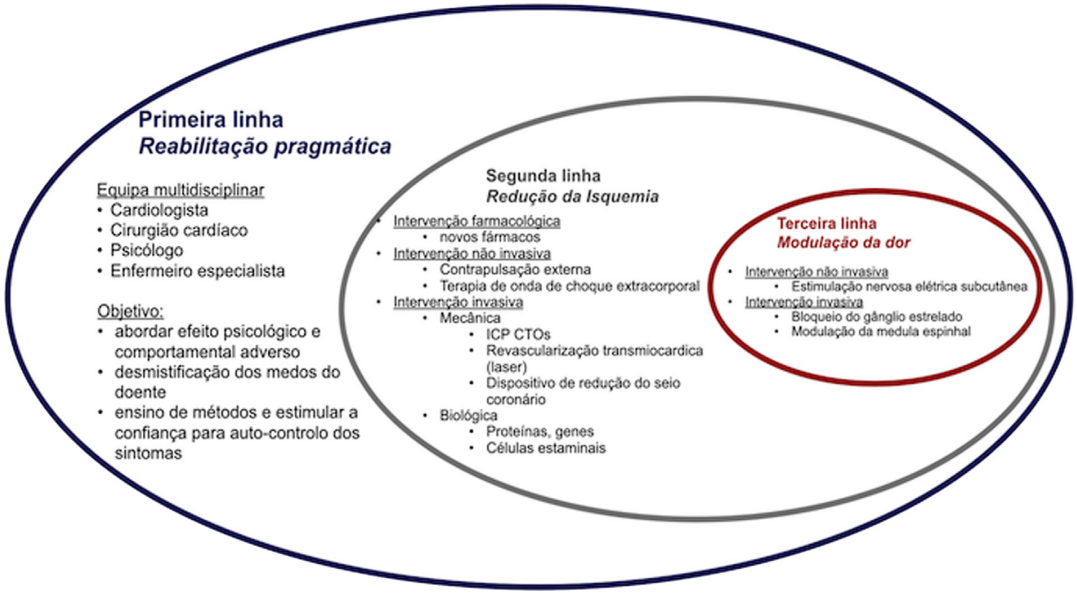


Figura 1 Abordagem e opções terapêuticas para a angina refratária (CTO - oclusão crónica, ICP - intervenção coronária percutânea).

terapêutica médica como da revascularização cirúrgica direta no tratamento da doença coronária estável.

Na década de 80, ressurgiu o interesse na utilidade da redução/oclusão percutânea intermitente do seio coronário em contexto de síndrome coronária aguda[42] e cirurgia de revascularização miocárdica.[43] Esta técnica foi progressivamente refinada e investigada no início do século XXI. Contudo, a pesar do benefício demonstrado na redução da extensão de enfarte e na recuperação funcional miocárdica,[44] nunca se firmou na prática clínica quotidiana.

Mais recentemente, como consequência da população crescente de doentes com angina refratária; dos resultados

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Tabela 3 Terapias não farmacológicas para angina. ICP-CTO, intervenção coronária percutânea de oclusão crónica; Cosira, *COronary SInus Reducer for treatment of Refractory Angina*; Decision-CTO, *Drug-Eluting Stent Implantation versus Optimal Medical Treatment in Patients with Chronic Total Occlusion*; Direct, *Direct myocardial laser revascularization in Regeneration of Endomyocardial Channels Trial*; Euro-CTO, *European Study on the Utilization of Revascularization vs. Optimal Medical Therapy for the Treatment of Chronic Total Coronary Occlusions*; Mace, evento cardiovascular major; Rascal, *Effectiveness and Cost--Effectiveness of Spinal Cord Stimulation for Refractory Angina*; Renew, *Efficacy and Safety of Intramyocardial Autologous CD34+ Cell Administration inPatients With Refractory Angina*; Startstim, *Stimulation Therapy for Angina RefracTory to Standard Treatments, Interventions, and Medications*

	População testada	Evidência	Redução de angina	Redução de MACE	Mortalidade	Limitações
Intervenção coronária de oclusões crónicas	Angina>angina refratária	Aleatorizada (ICP-CTO *vs.* TMO) — Euro-CTO (22), Decision-CTO (23)	+	-	-	• Taxa de sucesso < angioplastia convencional, sem excesso de risco
Contrapulsação externa	Angina >angina refratária	Aleatorizada (MUST-EECP - contrapulsação ativa *vs.* contrapulsação inativa) (20)	+	-	-	• Tratamento proposto de 35h ao longo de várias sessões durante 4 a 7 semanas, • Necessidade de infraestrutura física e profissionais habilitados • Desconhecimento de duração de eficácia e protocolo ideal de tratamento
Terapia de onda de choque extracorporal	Angina >angina refratária	Aleatorizada (vários pequenos estudos sem grupo *sham* adequado) (21)	+	-	-	• Necessidade de estudos aleatorizados adequadamente dimensionados e com grupo *sham* bem definido • Necessidade de infraestrutura física e profissionais habilitados • Desconhecimento de duração de eficácia e protocolo ideal de tratamento
Estimulação nervosa elétrica subcutânea	Angina	Estudos observacionais de pequena dimensão	+/-	-	-	• Necessidade de estudos aleatorizados • Evidência para angina refratária escassa • Efeito temporário
Estimulação da medula espinhal	Angina refratária > angina	Estudos aleatorizados de pequenas dimensões (maior estudo EARL) e meta-análise destes estudos (35-37)	+	-	-	• Estudos aleatorizados Rascal e Starstim (17) terminados precocemente • Ausência de *sham*
Revascularização Transmiocardica com laser (cirúrgica e percutânea)	Angina > angina refratária	Ensaios aleatorizados de pequena dimensão e meta-análise (27-29)	+ cirúrgica +/- percutânea	-	↑	• Aumento de mortalidade com procedimento cirúrgico (19) • Estudo de fase II negativo (DIRECT (20)) para a técnica percutânea

Tabela 3 (*Continued*)

	População testada	Evidência	Redução de angina	Redução de MACE	Mortalidade	Limitações
Terapia celular	Angina refratária	Meta-análises e estudos aleatorizados pequenos (33,34)	+	+/-	+/-	• Elevada heterogeneidade (tipo celular, protocolo de processamento celular, modo de entrega) • Ausência de *sham* Único estudo de fase III (RENEW (34)) terminado precocemente • Necessidade de equipa multidisciplinar diferenciada e de infraestrutura necessárias para o processamento celular • Necessidade de estudo aleatorizado com poder adequado para confirmar os resultados favoráveis de estudos mais pequenos e meta-análises
Redução do seio coronário	Angina refratária	Múltiplos estudos observacionais e um estudo aleatorizado com *sham procedure* (26-32)	+	-	-	• Evidência aleatorizada escassa (1 estudo fase II - Cosira (24) incluindo 104 doentes) • Ausência de efeito em casos de isquemia confinada ao território da coronária direita

subótimos das opções terapêuticas alternativas contemporâneas; e dos resultados positivos dos estudos pioneiros, renovou-se o interesse neste potencial alvo terapêutico. Foi desenvolvido e investigado um dispositivo de implantação percutânea intraluminal para redução persistente do seio coronário à semelhança da ligação externa cirúrgica realizada por Beck.

Possíveis mecanismos de ação

No coração sem patologia, durante o exercício ocorre uma vasoconstrição simpático-mediada dos vasos subepicárdicos, que favorece um fluxo preferencial para a camada subendocárdica.[45–47] Na presença de doença obstrutiva epicárdica ou de doença microvascular, os mecanismos reguladores estão desajustados. A distribuição da perfusão não favorece a camada subendocárdica, promovendo isquemia desta região, diminuindo a contractilidade, que por sua vez contribui para o aumento das pressões de enchimento do ventrículo esquerdo e desequilíbrio adicional da razão entre a perfusão subendocárdica e a perfusão subepicárdica, sendo responsável pelos sintomas de angor e dispneia de esforço.[45,46] Embora o mecanismo de ação do dispositivo de redução do seio coronário não esteja inequivocamente definido, especula-se que uma elevação da pressão no nível da extremidade venosa da circulação coronária poderá resultar numa dilatação ligeira das arteríolas, que consequentemente leva a aumento significativo da área de secção deste leito vascular e, assim, a uma diminuição significativa da resistência ao nível da camada subendocárdica. Deste modo há uma redistribuição do fluxo das regiões subepicárdicas para as regiões isquemicas subendocárdicas, equilibrando a razão entre a perfusão subendocárdica e perfusão subepicárdica que contribuirá para o alívio dos sintomas[48] (Figura 2).

Outros autores sugerem que o aumento de pressão ao nível do sistema venoso coronário promove a neoangiogénese e que este fenómeno é o responsável pela melhoria da perfusão subendocárdica e dos sintomas.[49]

Dispositivo

O único dispositivo de redução do seio coronário disponível e aprovado para uso clínico

é o Reducer® (Neovasc, Richmond, Canada). O dispositivo consiste numa malha de aço inoxidável, montada num balão em forma de ampulheta, que após insuflação configura a malha metálica na forma de um tubo com as extremidades proximal e distal de diferentes dimensões de modo a se adaptarem ao calibre crescente do seio coronário em direção ao óstio e com um estreitamento central que após endotelização (processo que cursa ao longo de quatro a seis semanas) é responsável por criar um gradiente de pressão

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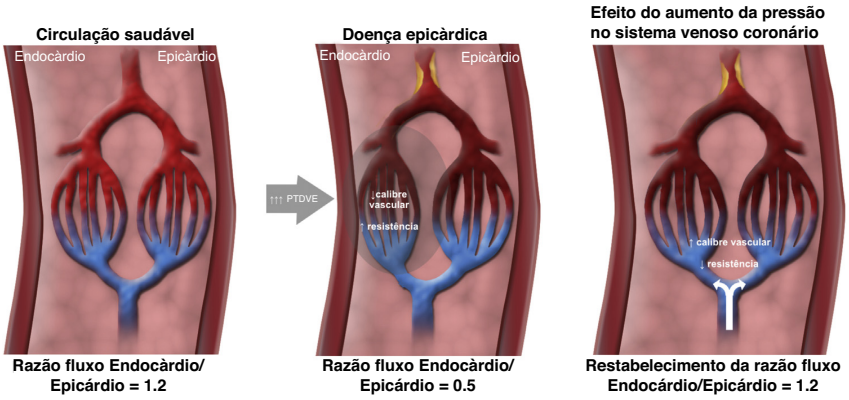


Figura 2 Mecanismo de ação da redução do seio coronário (PTDVE - pressão telediastólica do ventrículo esquerdo)[46].

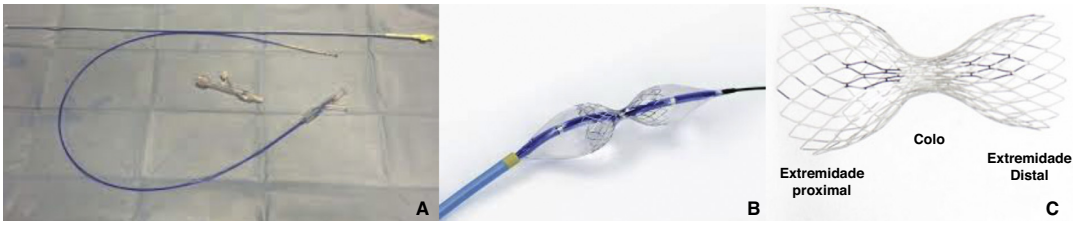


Figura 3 Bainha de entrega e cateter com balão e dispositivo de redução do seio coronário A) conjunto dispositivo montado no balão do sistema de entrada; B) balão insuflado; C) dispositivo na conformação assumida após insuflação e remoção do balão.

entre a circulação venosa correspondente ao território da artéria coronária esquerda e a aurícula direita. O balão é semicomplacente e está apenas disponível em tamanho único, estando os calibres finais das extremidades dependentes da pressão de insuflação, permitindo adaptar-se à anatomia do seio coronário da maioria dos doentes (calibres a variar 9-14 mm) mantendo sempre o diâmetro de 3 mm ao nível do estreitamento central (Figura 3).

A implantação é realizada com uma sobre-expansão intencional de 10-20% relativamente ao calibre do seio coronário em ambas a extremidades, de modo a ancorar adequadamente o dispositivo e promover lesão vascular indutora de regeneração tecidular e endotelização.

O dispositivo *in-situ* poderá ser sempre expandido com balão, não obviando intervenções adicionais através do seio coronário, caso necessário.

Evidência

Nos últimos 15 anos, desde o início da sua utilização em humanos, mais de 1000 dispositivos de redução do seio coronário foram implantados mundialmente, sem que tenham sido relatadas complicações a longo prazo.

O desempenho do dispositivo foi inicialmente testado em modelos animais e posteriormente passou para a avaliação clínica em pequenos estudos de prova de conceito, registos e um estudo aleatorizado. Todos os estudos em humanos incluíram exclusivamente doentes com angina refratária sob terapêutica médica otimizada, não candidatos a revascularização.

Estudos pré-clínicos

A exequibilidade, eficácia e segurança foram inicialmente testadas em modelos suínos.[50] Foram criados dois braços, um de avaliação de exequibilidade/segurança e outro de eficácia. No global, o sucesso de implantação foi 100% em 32 animais, sem complicações imediatas associadas ao procedimento. No braço de segurança (n = 26), o exame histológico dos dispositivos recolhidos entre o 1.° e o 6.° mês após implantação demonstrou reparação tecidular favorável. A porção central demonstrou ao longo do tempo endotelização progressiva e em continuidade com o restante lúmen do vaso. Não se observaram complicações (migração, trombose, estenose, oclusão e erosão) associadas ao dispositivo, à data do sacrifício dos animais. No braço de avaliação de eficácia, 22 animais foram submetidos a constrição artificial da circunflexa proximal, oito destes apresentaram alterações segmentares deste território em ecocardiografia com *stress* farmacológico com dobutamina e alterações de perfusão por ecocardiografia com ecocontraste. Posteriormente, quatro implantaram Reducer e outros quatro não, no grupo de implantação verificou-se redução de 50% da isquemia aos seis meses em comparação com ausência de melhoria no grupo não tratado. No grupo não tratado, três dos quatro animais morreram prematuramente comparativamente com nenhuma morte no grupo tratado.

Estudos clínicos

O primeiro estudo de exequibilidade e segurança em humanos, incluiu 15 doentes com angina refratária e evidência de isquemia por cintigrafia de perfusão miocárdica ou ecocardiografia de stress.[26] A implantação foi bem-sucedida em todos os doentes. Aos seis meses: todos os dispositivos estavam patentes por angiotomografia computadorizada, a classe de angina pela *Canadian Cardiovascular Society* (CCS) melhorou em 12 doentes, de 3 (valor médio) pré-implantação para 1,6 aos seis meses, documentou-se redução da extensão e gravidade de isquemia por cintigrafia de perfusão miocárdica e ecocardiografia de *stress*. A patência e localização do dispositivo foi reavaliada por angiotomografia computadorizada ao três anos, sem registo de nenhuma oclusão ou migração.[51] Tabela 4.

Para destrinçar o efeito mecanicista antianginoso do efeito placebo habitualmente atribuído às intervenções na angina,[52,53] os mesmos investigadores desenharam um estudo aleatorizado, multicêntrico, de dupla ocultação e com grupo controlo submetido a *sham-procedure* – o ensaio COSIRA.[28] Cento e quatro doentes com angina refratária (CCS III-IV) e evidência de isquemia foram incluídos ao longo de 38 meses, refletindo em parte a baixa prevalência relativa da angina refratária no universo da doença coronária estável e o carácter restritivo dos critérios de inclusão. Observou-se uma melhoria de pelo menos uma classe CCS em 42% dos doentes do grupo submetido a *sham-procedure* e de 71% no grupo que recebeu dispositivo (p = 0,003). O *endpoint* primário (redução de dois valores da classe CCS) foi atingido em 35% dos doentes que receberam dispositivo *versus* 15% grupo controlo (p = 0,024). A qualidade de vida avaliada pelo *Seattle Angina Questionnaire* (SAQ) apresentou uma melhoria significativamente superior no grupo tratado *versus* grupo controlo (17,6 *versus* 7,6 pontos, p = 0,03). Não se observaram diferenças estatisticamente significativas entre os grupos no tempo de exercício e na extensão da isquemia determinada pelo *wall-motion index* (WMI). No entanto, a duração média do exercício melhorou 59 segundos (13%) no grupo de tratamento e apenas um segundo (1%) no grupo controlo (p = 0,07), que do ponto de vista clínico pode traduzir um benefício significativo. Relativamente à extensão e gravidade da isquemia, na análise incluindo apenas os 11 segmentos dependentes da coronária esquerda (WMI modificado), verificou-se uma melhoria em 13% no grupo tratado *versus* 3% no grupo controlo (p = 0,06), que, apesar de não ser estatisticamente significativa, demonstra uma clara tendência para redução da isquemia. Não houve diferença entre os grupos, na taxa de efeitos adversos associados ao procedimento ou durante o primeiro ano de seguimento.

Múltiplos estudos observacionais e registos pós-entrada no mercado demonstram consistentemente uma melhoria de pelo menos uma classe CCS em 70-80% dos doentes com uma percentagem de não respondedores constante à volta de 20-30%.[29,31,32,54] Figura 4.

Apesar da maioria dos doentes incluídos nos estudos e registos apresentar doença coronária obstrutiva e de os doentes com doença microvascular estarem sub-representados, não se tem observado diferença do efeito terapêutico entre estes fenótipos de doentes com angina refratária. Um pequeno estudo de dois centros italianos selecionou (de um pool de doentes referenciados para coronariografia) oito doentes com angina refratária (CCS III e IV), evidência não invasiva de isquemia e ausência de doença obstrutiva, para implantação *compassionate* de Reducer. O valor médio da classe CCS diminuiu de 3 para 1,5 (p = 0,014), os índices do SAQ melhoraram, 40% dos doentes descontinuaram pelo menos um fármaco antianginoso e a distância percorrida no teste de marcha dos seis minutos aumentou. Três dos doentes realizaram ressonância cardíaca pré e pós-implantação de Reducer, o índice de reserva de perfusão miocárdica aumentou em todos.[55] Estes resultados sugerem um beneficio da redução do seio coronário potencialmente extensível aos doentes com doença microvascular.

Não obstante a redução de sintomas e melhoria da qualidade de vida observada nos estudos observacionais estar em linha com os resultados do braço de tratamento do estudo COSIRA, a interpretação destes resultados têm que ter em linha de conta o enorme peso do efeito placebo nos doentes submetidos a esta intervenção. Estudos aleatorizados com dupla-ocultação controlados com *sham procedure* devidamente potenciados para identificar diferenças em medidas objetivas de isquemia poderão permitir esclarecer em que medida a melhoria sintomática se correlaciona com a diminuição da isquemia.

Com base na evidência apresentada, que embora consistente é ainda escassa (apenas um ensaio aleatorizado de pequenas dimensões e evidência não aleatorizada limitada pela reconhecida amplificação do efeito placebo associada a intervenções para o tratamento de angina[24,53]), a Sociedade Europeia de Cardiologia atribuiu pela primeira vez uma indicação II b para o uso do dispositivo de redução do seio coronário no tratamento da angina refratária.[1]

Para reforçar a evidência existente sobre o potencial beneficio terapêutico do Reducer, está planeada a realização de um segundo estudo aleatorizado – COSIRA II – que apresenta um desenho idêntico ao Cosira I, visando incluir 380 doentes em 35 centros dos Estados Unidos da América e do Canadá.

Não respondedores

Cerca de 20 a 25% dos doentes não apresentam melhoria sintomática, a razão para tal não está completamente esclarecida. Poderá estar relacionada com a natureza heterogénea da circulação venosa cardíaca, em que a presença de sistemas de drenagem venosa alternativos ao seio coronário diminuiria hipoteticamente o benefício da redução do seio coronário. Outros fatores potencialmente associados à ausência de resposta são a isquemia proveniente do território da coronária direita, cardiopatias concomitantes que elevem a pressão da aurícula direita (> 15 mmHg), pressões de enchimento do ventrículo esquerdo muito elevadas em doentes com insuficiência cardíaca, endotelização incompleta da malha metálica com gradiente de pressão inadequado e a possibilidade da dor não ser anginosa.[56,57]

Custo-eficácia

Um estudo de coorte retrospetivo, multicêntrico, incluindo 215 doentes com angina refratária que implantaram dispositivo de redução do seio coronário na Bélgica, Holanda e

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Tabela 4 Estudos clínicos de avaliação do dispositivo de redução do seio coronário em doentes com angina refratária

Estudo	Ano	N	Desenho do estudo	Critérios de inclusão	Endpoints	Resultados
Banai S. et al (26)	2007	15	Prospetivo, multicêntrico, sem ocultação, primeiro estudo de exequibilidade e segurança em humanos	Doença epicárdica não passível de CABG ou ICP, angina refratária (CCS II-IV) sob TMO	Primário (segurança): ausência de complicações associadas ao procedimento. Secundário (sucesso técnico): entrada e implantação bem-sucedida no seio coronário	Segurança: sem eventos adversos reportados; melhoria da angina em 12 dos 14 doentes, redução média CCS de 3,07 basal para 1,64 ($p < 0,0001$) Redução da depressão do segmento ST induzido por esforço em 6 de 9 doentes Redução da extensão e gravidade da isquemia por ecocardiografia com dobutamina ($p = 0,004$) e por cintigrafia de perfusão miocárdica ($p = 0.042$)
Konigstein M., et al. (27)	2014	23	Multicêntrico, observacional	Doentes com angina refratária (CCS II-IV) sob TMO não passível de CABG ou ICP, evidência objetiva de isquemia e Fej > 25%	Avaliação objetiva de isquemia aos 6 meses	A implantação foi bem-sucedida em 21 doentes (2 falências por anatomia do seio coronário desfavorável), sem efeitos adversos. 80% dos doentes tiveram uma redução de pelos menos 1 classe CCS e 45% 2 classes CCS. Redução CCS basal de $3,3 \pm 0,6$ para $2,0 \pm 1,0$ ($p < 0.001$). Aumento do tempo de exercício $3:16 \pm 1:48$ *vs.*. $5:16 \pm 1:14$ min ($p = 0,17$) e do tempo até depressão de ST ($1:47 \pm 1:12$ *vs.*. $3:57 \pm 2$ min, $p = 0,17$). Melhoria do WMSI durante ecocardiografia de stress ($1,9 \pm 0,4$ *vs.* $1,4 \pm 0,4$, $p = 0,046$).
Verheye S., et al. Cosira Trial (28)	2015	104	Multicêntrico, aleatorizado, dupla ocultação comparando procedimento terapêutico com *sham procedure*	Doentes com angina refratária (CCS III-IV) sob TMO não passível de CABG ou ICP, evidência objetiva de isquemia e Fej > 25%	Primário: redução de pelo menos 2 classes CCS aos 6 meses Secundário: redução de pelo menos 1 classe CCS aos 6 meses	Melhoria de pelo menos duas classes ocorreu em 35% dos doentes do grupo de tratamento *vs.* 15% dos doentes do grupo controlo ($p = 0,02$) Melhoria de 1 classe funcional em 71% dos doentes do grupo tratado *vs.* 42% do grupo controlo ($p = 0,003$) A classificação do SAQ QoL melhorou (numa escala de 100) no grupo tratado comparativamente ao controlo 17,6 pontos *vs.* 7,6 pontos ($p = 0.001$)

Tabela 4 (*Continued*)

Estudo	Ano	N	Desenho do estudo	Critérios de inclusão	Endpoints	Resultados
Abawi M., et al. (29)	2016	23	Registo retrospetivo de centro-único	Doentes com angina refratária (CCS II-IV) sob TMO não passível de CABG ou ICP, evidência objetiva de isquemia	Segurança: ausência de complicações associadas ao procedimento. Eficácia: qualquer redução na classe CCS, sobrevivência livre de revascularização	Sem eventos adversos reportados Redução da classe CCS de $3,4 \pm 0,6$ basal para $2,1 \pm 1,0$, co redução de pelo menos 1 classe CCS em 74% dos doentes ($p = 0,001$) e 2 classes 30% ($p = 0,001$)
Giannini, F., et al. (31)	2018	141	Prospetivo, observacional, multicêntrico	Doentes com angina refratária (CCS II-IV) sob TMO não passível de CABG ou ICP, evidência objetiva de isquemia e Fej > 35%	Segurança: sucesso do procedimento e ausência de complicações associadas ao procedimento. Eficácia: redução da classe CCS, melhoria da qualidade de vida pelo SAQ	Sucesso de implantação 98,6% (2 falências por anatomia do seio coronário desfavorável), sem efeitos adversos associados. 81% dos doentes tiveram uma redução de pelos menos 1 classe CCS e 45% 2 classes CCS, com uma redução de $3,05 \pm 0,53$ para $1,63 \pm 0,98$ ($p < 0,001$) Todos os items do SAQ melhoraram ($p < 0,001$) Redução significativa do número médio de fármacos antianginosos prescritos $2,37 \pm 0,97$ *vs.* $2,17 \pm 0,9$
Giannini, F., et al. (32)	2018	50	Prospetivo, observacional, centro único	Doentes com angina refratária (CCS II-IV) sob TMO não passível de CABG ou ICP, evidência objetiva de isquemia e Fej > 35%	Segurança: sucesso do procedimento e ausência de complicações associadas ao procedimento. Eficácia: redução da classe CCS, melhoria da qualidade de vida pelo SAQ, tolerância ao exercício (teste da marcha 6 minutos) e redução de fármacos antianginosos aos 4 e 12 meses	Sucesso de implantação 100%, sem efeitos adversos associados. 80% dos doentes tiveram uma redução de pelos menos 1 classe CCS e 20% 2 classes CCS, com uma redução de $2,98 \pm 0,5$ para $1,67 \pm 0,8$ ($p < 0,001$) Todos os items do SAQ melhoraram ($p < 0,001$) Aumento da distância percorrida em 6 minutos de 287 ± 139 para 389 ± 120 m ($p = 0,004$) 32% reduziram pelo menos 1 fármaco antianginoso

Itália, avaliou os custos associados do ponto de vista do sistema de saúde de cada país.[58] Compararam o período pré-implantação de Reducer (como *standard of care*) com período o pós-implantação (seguimento um ano) e verificaram uma redução significativa dos internamentos motivados por angina, consultas, coronariografias e intervenções coronárias percutâneas por doente-ano, o que se traduziu em rácios de custo-efetividade incremental (ICER) 55.356 €/QALY, 34.948 €/QALY e 63.146 €/QALY para a Bélgica, Holanda e Itália, respetivamente, abaixo dos limiares de custo-efetividade definidos pela OMS (ICER menor três vezes o produto interno bruto *per capita* do respetivo país)[59] em 99,9%, 100% e 93,3% dos doentes de cada país, respetivamente.

A interpretação deste estudo está condicionada pela ausência de um grupo controlo formal, curto período de seguimento e não contabilização dos custos associados à terapêutica farmacológica e custos indiretos. Contudo, atendendo ao cariz crónico dos sintomas, à história natural progressiva da doença coronária e ao benefício clínico

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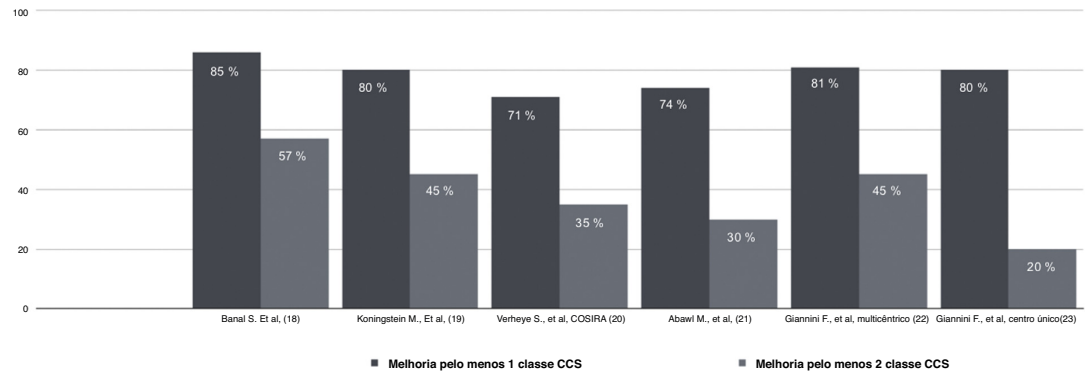


Figura 4 Variação de classe CCS após implantação de dispositivo de redução do seio coronário.

do dispositivo de redução do seio coronário, os resultados são sugestivos de custo efetividade nestes países. O limiar de custo efetividade em Portugal de acordo com os últimos dados do produto interno bruto *per capita* disponíveis,[60] pela definição da OMS, é de 65.040 € /QALY, acima dos ICERs determinados para as realidades belga, holandesa e italiana, sendo previsível que na realidade portuguesa o dispositivo de redução do seio coronário seja custo efetivo.

Conclusão

O dispositivo de redução do seio coronário é uma alternativa terapêutica promissora na redução dos sintomas e na melhoria da qualidade de vida, em doentes selecionados com angina refratária. Carece ainda de validação adicional por ensaios clínicos devidamente desenhados e dimensionados.

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APPENDICES

12. Appendices

NOVA MEDICAL SCHOOL

DECISÃO FINAL SOBRE O PROJETO

"Transcatheter aortic valve implantation (TAVI). A reference model in percutaneous cardiovascular interventions"

A Comissão de Ética da NMS|FCM-UNL (CEFCM) decidiu aprovar por unanimidade, do ponto de vista ético, o projeto de investigação intitulado "Transcatheter aortic valve implantation (TAVI). A reference model in percutaneous cardiovascular interventions" (nº 32/2022/CEFCM), submetido pelo Doutorando Rui Campante Teles, no âmbito do Doutoramento em Medicina da NOVA Medical School | Faculdade de Ciências Médicas.

Lisboa, 11 de agosto de 2022

O Presidente da Comissão de Ética,

(Professor Doutor Diogo Pais)

TO WHOM IT MAY CONCERN

The Ethics Research Committee of NMS|FCM-UNL (CEFCM) has unanimously approved the project entitled "Transcatheter aortic valve implantation (TAVI). A reference model in percutaneous cardiovascular interventions" (No. 32/2022/CEFCM), submitted by the PhD student Rui Campante Teles, in the scope of the Doctoral Programme in Medicine at the NOVA Medical School.

Lisbon, August 11th 2022

The Chairman of the Ethics Research Committee,

(Diogo Pais, MD, PhD)

Campo Mártires da Pátria, 130
1169-056 Lisboa · Portugal

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Ministério da Saúde

CES
COMISSÃO DE ÉTICA PARA A SAÚDE
Centro Hospitalar de Lisboa Ocidental

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE

Tese de Doutoramento,

"The role of aging, atherosclerosis and calcification in interventional cardiology"

Após reunião de 19 de outubro de 2015 e no seguimento da receção do modelo de Consentimento Informado retificado, estando atualmente o projeto de acordo com as normas de submissão impostas por esta CES, deliberou-se emitir **parecer favorável** à realização do mesmo.

A Comissão de Ética para a Saúde solicita ao Investigador Principal que, quando da conclusão deste projeto, lhe seja enviada uma síntese dos resultados e conclusões do mesmo.

Nota
O Dr. Rui Campante Teles esteve ausente na votação uma vez que é o Investigador Principal do projeto supramencionado.

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética para a Saúde do Centro Hospitalar de Lisboa Ocidental presentes em reunião de 19 de outubro de 2015:

Presidente: Prof.ª Doutora Maria Teresa Marques

Dr. Carlos Costa, Enf.ª Clara Carvalho, Dra. Helena Farinha,
Dr. José Santana Carlos, Dra. Paula Peixe e Padre João Valente

Pelo exposto, emitiu-se a 04 de novembro de 2015, **parecer favorável**.

Presidente da Comissão de Ética para a Saúde

Prof.ª Doutora Maria Teresa Marques

MARIA TERESA MARQUES
Presidente da Comissão
de Ética para a Saúde

Hospital de Egas Moniz
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CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.
HOSPITAL DE SANTA CRUZ

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE PARA PARTICIPAÇÃO EM ESTUDOS DE INVESTIGAÇÃO

(DE ACORDO COM A DECLARAÇÃO DE HELSÍNQUIA E A CONVENÇÃO DE OVIEDO)

Consentimento livre, esclarecido e livre para a realização do estudo ***O papel da idade, da aterosclerose e da calcificação na intervenção endovascular***.

Por favor leia cuidadosamente a seguinte informação e discuta com o(a) seu(sua) médico(a) antes de concordar em fazer parte do estudo. O(a) seu(sua) médico(a) responderá a qualquer questão que possa ter acerca da sua participação

Enquadramento:
A idade é um factor de risco para doença cardiovascular e a calcificação tem sido relacionada com ambos. A compreensão da calcificação aterosclerótica permanece limitada, apesar da extensa investigação. As implicações da distribuição e gravidade da calcificação na doença vascular e valvular permanecem um desafio e podem afectar a tolerância aos tratamentos. A avaliação geriártrica global compreende o estudo das comorbidades, da dependência e da fragilidade associadas ao passar dos anos.
O objectivo desta investigação é propor alterações na nossa abordagem clínica de acordo com a idade, a calcificação e a fragilidade individuais. Iremos medir a resistência à adversidade de cada um, diferenciar padrões de calcificação cardiovascular e contribuir para o esclarecimento das suas causas.
Este estudo decorre no Serviço de Cardiologia do Hospital de Santa Cruz (Centro Hospitalar de Lisboa Ocidental) no âmbito de uma tese de Doutoramento do Centro de Estudos de Doenças Crónicas da Faculdade de Ciências Médicas de Lisboa (CEDOC-FCM), orientada pela Profª Ana Aleixo. Caso tenha alguma questão sobre a investigação pode contactar o doutorando e investigador responsável, o Dr. Rui Campante Teles pelo telefone 2142413080.
Explicação do estudo: *Esta investigação é observacional e portanto não interfere com a prática clínica de rotina. Assim, não se antecipa um aumento dos possíveis riscos, desvantagens ou vantagens associadas com a investigação.*
Consiste na recolha dos dados médicos e clínicos com o objectivo de estudar a condição em que se encontra e que levou a que propusessem realizar um cateterismo. Por isso, caso nos autorize, iremos recolher os seus dados clínicos, tais como os seus sintomas, o motivo da sua angiografia (cateterismo), a sua medicação atual, os exames laboratoriais e as imagens angiográficas. Complementarmente, vamos avaliar a sua forma física e bem estar geral, avaliando a sua capacidade de deslocação, de fazer força e utilizar questionários para preencher que estudam a sua qualidade de vida.
Caso realize alguma intervenção, estas provas poderão ser repetidos quando for reavaliado na sua consulta de rotina.
A duração total da sua participação no estudo será de 12 meses.
Condições e financiamento:
A sua participação no estudo é voluntária e benevolente, não havendo pagamento de deslocações ou contrapartidas. Se não quiser participar a sua decisão não irá afectar a qualidade do seu tratamento médico ou a sua relação com o(a) seu(sua) médico(a). Se decidir fazer parte do estudo, ser-lhe-á dada qualquer nova informação, que surja durante o estudo,

relacionada consigo ou que possa alterar o seu consentimento. Da mesma forma, o(a) seu(sua) médico(a), que é responsável pelo seu seguimento, poderá retirá-lo(a) do estudo a qualquer altura, se considerar necessário..

O estudo mereceu parecer favorável da Comissão de Ética para a Saúde do Centro Hospitalar de Lisboa Ocidental.

Confidencialidade e anonimato:

Todos os dados serão processados garantindo a sua confidencialidade. O investigador irá realizar, posteriormente, uma análise estatística baseada em todos os dados recolhidos, mantendo o anonimato. Poderá perguntar ao seu médico pelos resultados deste estudo. Após terminar a sua participação no estudo, irá continuar a ser seguido(a) tal como todos os doentes conforme a sua patologia.

As informações identificativas, tal como o seu nome, irão ser removidas das cópias dos registos quando não forem absolutamente necessárias.

De acordo com as leis relativas à proteção de dados, ser-lhe-á possível exercer os seus direitos de aceder e rectificar estes dados a qualquer altura. Os formulários de recolha de dados, os formulários de clarificação de dados e outros documentos, irão ser preenchidos e arquivados nas instalações do investigador e do hospital. O(a) seu(sua) médico(a) de medicina geral e familiar poderá ser informado(a) da sua participação neste estudo. Se desejar que ele(a) não seja informado(a), por favor diga ao(à) seu(sua) cardiologista.

Contato Institucional do Médico: +351 21 4241380 ou unicarv@chlo.min-saude.pt

CENTRO HOSPITALAR DE LISBOA OCIDENTAL, E.P.E.
HOSPITAL DE SANTA CRUZ

CONSENTIMENTO INFORMADO, ESCLARECIDO E LIVRE PARA PARTICIPAÇÃO EM ESTUDOS DE INVESTIGAÇÃO

(DE ACORDO COM A DECLARAÇÃO DE HELSÍNQUIA E A CONVENÇÃO DE OVIEDO)

A preencher pelo MÉDICO:

- No âmbito do estudo ***O papel da idade, da aterosclerose e da calcificação na intervenção endovascular*** confirmo que expliquei à pessoa abaixo indicada, de forma adequada e inteligível, os diagnósticos, as avaliações, os questionários e as intervenções ou os tratamentos referidos, o tipo de anestesia no caso de ser proposta, assim como os riscos e complicações, e as alternativas possíveis à situação clínica:
  - cateterismo cardíaco e/ou angiografia aorto-coronária com ou sem angioplastia coronária associada; e/ou
  - angiografia aorto-ilíaca e valvuloplastia aórtica ou mitral, com ou sem Implantação percutânea de prótese valvular; e/ou
  - cateterismo e angiografia periférica e/ou carotídea com ou sem angioplastia periférica e/ou carotídea associada
- Respondi a todas as questões que me foram colocadas e assegurei-me de que houve um período de reflexão suficiente para a tomada da decisão.
- Também garanti que, em caso de recusa, serão assegurados os melhores cuidados possíveis nesse contexto, no respeito pelos seus direitos.

Nome do Médico: Cédula Profissional nº:

Assinatura: Data:

A preencher pelo **DOENTE** / **Representante Legal / Procurador de Cuidados de Saúde**

Por favor, leia com atenção a seguinte informação. Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações. Se concorda com a proposta que lhe foi feita, queira assinar este documento.

- Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela/s pessoa/s que acima assina/m.
- Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelo/a investigador/a.

Nome:		
Assinatura:		
CC/BI. nº	Validade:	Grau de parentesco ou tipo de representação:
Este documento é feito em duas vias – uma para o processo e outra para ficar na posse de quem consente.		

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