Capítulo 4.

Doença coronária não obstrutiva – identificação por angio TC cardíaca

RESUMO:

Neste capitulo é descrita a capacidade da angio TC cardíaca identificar a presença da doença coronária não obstrutiva, característica impar entre os vários exames de diagnóstico não invasivos em cardiologia. O desempenho da angio TC na identificação da placa aterosclerótica é comparado com o dos métodos de imagem intracoronária.

Neste capítulo é feita ainda uma revisão dos diferentes marcadores de aterosclerose subclínica e das actuais limitações ao uso da angio TC com este objectivo.

Foram incluídos neste capítulo dois artigos: O **artigo 11** discute, a propósito de um caso clínico, o contraste entre a carga aterosclerótica documentada por angio TC e o risco cardiovascular; o **artigo 12** é um artigo original em que foi avaliada a prevalência e os preditores de doença coronária na ausência de calcificação coronária.

ABSTRACT:

In this chapter, the evaluation of nonobstructive coronary artery disease by cardiac CT is described, a unique feature among noninvasive diagnostic tests in cardiology. The performance of cardiac CT is compared to other invasive imaging modalities used for the identification of the atherosclerotic plaque. It is also provided in this chapter a review on the subclinical atherosclerosis markers and the present limitation on the use of cardiac CT for this indication.

Included in this chapter are two manuscripts: **Manuscript 11** is a case report related to which the contrast between cardiovascular risk and coronary atherosclerotic burden in discussed; **manuscript 12** is an original paper describing the prevalence and predictors of coronary artery disease in patients with a calcium score of zero.

ARTIGO 11/ MANUSCRIPT 11:

DOENÇA CORONÁRIA NAO OBSTRUTIVA DOCUMENTADA POR ANGIOTC CARDÍACA: CONTRASTE ENTRE A CARGA ATEROSCLERÓTICA E O RISCO CARDIOVASCULAR.

H. Dores, P. Araújo Gonçalves, M.S. Carvalho, P. Jeronimo Sousa, H. Marques, N. Cardim, A. Aleixo, M. Mota Carmo, F. P. Machado, J. Roquette.

Rev Port Cardiol. 2013 Jun 28. doi: 10.1016/j.repc.2012.10.013. [Epub ahead of print]

ARTIGO 12/ MANUSCRIPT 12:

PREVALENCE AND PREDICTORS OF CORONARY ARTERY DISEASE IN PATIENTS WITH A CALCIUM SCORE OF ZERO.

Carvalho MS, de Araújo Gonçalves P, Garcia-Garcia HM, Jerónimo Sousa P, Dores H, Ferreira A, Cardim N, Mota Carmo M, Aleixo A, Mendes M, Pereira Machado F, Roquette J, Marques H.

Int J Cardiovasc Imaging. 2013; *submetido para publicação*

SUMÁRIO DO CAPÍTULO 4:

4.1 INTRODUÇÃO

Existem importantes limitações à capacidade de identificar clinicamente os indivíduos em risco de eventos cardíacos e, em números absolutos, a grande maioria dos indivíduos que sofrem um EAM seriam considerados previamente de baixo risco (1, 2). Este dado epidemiológico espelha a discrepância entre o risco relativo (ou seja, indivíduos com scores de risco mais altos tem taxas de eventos mais altas) e os números em absoluto (na população geral existem muito mais indivíduos em patamares de risco mais baixos) justificando assim que a grande maioria dos eventos ocorram em indivíduos que não se qualificariam previamente para medidas de prevenção mais agressivas (3). Esta discrepância entre o risco individual e o risco populacional, por um lado, e a ausência prévia de sintomas e a dramática forma de apresentação clínica inaugural da DC - EAM e morte súbita numa larga fatia de doentes - por outro, fornecem o racional para o uso de marcadores de aterosclerose subclínica.

Por outro lado, muitas das lesões que estão na origem de eventos coronários agudos não condicionam estenoses significativas (4-9), tornando difícil a sua identificação com os habituais métodos de diagnóstico baseados na detecção de isquémia. O facto de lesões não obstrutivas estarem frequentemente na origem de SCA resulta do facto de estas serem muito mais prevalentes, apesar de se reconhecer que o risco individual por placa ser superior para as lesões obstrutivas (4, 10) . Assim, as modalidades de imagem não invasivas que forneçam informação acerca da totalidade da carga aterosclerótica (obstrutiva e não obstrutiva) têm um elevado potencial na estratificação do risco de eventos cardíacos.

4.2 MARCADORES DE ATEROSCLEROSE SUBCLÍNICA.

Os marcadores de aterosclerose subclínica ao permitirem identificar a presença de doença numa fase precoce, poderão categorizar um indivíduo em particular num patamar de risco mais elevado. Os dois principais marcadores de aterosclerose subclínica são a espessura intima-média carotídea e o score de cálcio das coronárias, apresentando este último uma clara superioridade em nível de evidencia científica gerada nos últimos anos (11-13), que é mais modesta para a espessura intima-média carotidea (14-16).

Uma vez que a calcificação coronária ocorre quase em exclusividade em placas ateroscleróticas, a quantificação do cálcio nas artérias coronárias fornece uma estimativa da carga aterosclerótica global (17, 18) tendo sido já demonstrado em vários estudos clínicos que o score de cálcio é um bom preditor de eventos CV (19). Por outro lado, a ausência de cálcio nas coronárias, embora não exclua totalmente a presença de DC (podem existir placas ateroscleróticas não calcificadas), associa-se a um excelente prognóstico CV a longo prazo e tem uma elevada sensibilidade e especificidade para excluir a presença de DC obstrutiva (20, 21). Numa análise de 3012 doentes

que realizaram score de cálcio seguido de angioTC cardíaca, a ausência de cálcio nas artérias coronárias (n=864 doentes) associou-se a uma taxa de placas na árvore coronária na angioTC de apenas 12,4%, das quais apenas uma minoria condicionava estenose significativa (estenoses ≥50% em 1,6% dos doentes com CaSc=0) (21).

Recentemente, foi comparado o poder discriminativo do score de cálcio com o de outros marcadores de aterosclerose subclínica numa larga população de doentes incluídos no estudo MESA (*Multi-Ethnic Study of Atherosclerosis*)(13) . Quando comparado com outros marcadores de risco (como a proteina C-reactiva ou o índice calcanhar-braço) e mesmo com a espessura íntima-média carotídea, o score de cálcio demonstrou ter o maior poder discriminativo um desempenho superior na reclassificação do risco CV de indivíduos que estariam à partida num grupo de risco intermediário.

Um aspecto importante nos marcadores de aterosclerose é o facto de eles não serem apenas bons preditores para a ocorrência do evento CV do seu território mais especifico, tendo sido já demonstrado que a espessura intima-media carótidea é um bom preditor do risco de EAM (22), assim como o score de cálcio é um bom preditor do risco de acidente vascular cerebral (23). Isto não é de estranhar uma vez que o processo arteriosclerótico é sistémico, partilha os mesmo factores de risco e com frequência coexistem no mesmo indivíduos manifestações em vários territórios vasculares, como aliás ficou elegantemente documentado pelo estudo REACH *(Reduction of Atherothrombosis for Continued Health)* (24).

No entanto o score de cálcio apresenta também algumas limitações, nomeadamente a ausência de informação relativamente ao grau de estenose e assim acerca do potencial impacto funcional das placas e não detectar a presença de placas não calcificadas, subvalorizando assim a real extensão da aterosclerose coronária.

Assim, no futuro, outros marcadores de aterosclerose subclínica poderão vir a entrar na prática clinica, um dos quais é a angio TC cardíaca, técnica que tem vindo a ganhar uma robustez na avaliação da DC, com a evolução técnica na tecnologia multidetectores, conduzindo a melhorias da resolução espacial, temporal, bem como uma progressiva redução da dose de radiação.

Uma das vantagens da angio TC neste campo reside na sua capacidade de identificar não só as lesões calcificadas mas também as placas não calcificadas, dando assim uma informação mais completa da carga aterosclerótica coronária total pela informação acerca do tipo de placa (calcificada, mista ou não calcificada), localização precisa na árvore vascular e grau de estenose (obstrutiva e não obstrutiva), informação esta que pode ser reunida e quantificada em scores de carga aterosclerótica (ver ***Capítulo 8***).

Tem-se tornado evidente que a DC não obstrutiva identificada pela angio TC cardíaca tem um impacto prognóstico adverso e claramente diferente da ausência de placas na árvore coronária. Esta evidência tem sido consolidada com o resultado de estudos multicêntricos (25, 26) e também em estudos do valor prognóstico da angio TC cardíaca a longo prazo (27) (ver ***Capítulo 9***).

Num estudo realizado em doentes com EAM sem supradesnivelamento do segmento ST, foi avaliado o valor prognóstico das lesões não obstrutivas, avaliada por angioTC cardíaca (28). Neste trabalho, a carga de placa não calcificada correlacionou-se com a taxa de eventos CV no seguimento, não se tendo verificado o mesmo para a carga de placa calcificada. Este facto demonstra que mesmo num contexto que não o da DC estável, a identificação da DC não obstrutiva poderá fornecer informação prognóstica adicional na estratificação de risco deste grupo heterogéneo de doentes (29). Numa meta-análise englobando vários estudos que avaliaram o valor prognóstico da angio TC cardíaca, a presença de DC (independente de condicionar ou não estenose significativa) aumentava o risco de eventos CV em 4,5 vezes. Nesse trabalho, foi ainda feita a estimativa de risco de eventos CV por cada segmento da árvore coronária com placa, sendo o HR estimado em 1,23 por cada segmento com doença, o que significa um aumento de risco de 23% por cada segmento envolvido. Esta avaliação foi independente da presença de calcificação coronária e o risco relativo até foi ligeiramente superior (HR 1,29) para os segmentos com placa não calcificada (30).

4.3 IDENTIFICAÇÃO DA PLACA ATEROSCLERÓTICA POR ANGIO TC E CORRELAÇÃO COM MÉTODOS DE IMAGEM INTRAVASCULAR

A identificação e caracterização da placa aterosclerótica têm sido o alvo de extensa investigação de diferentes modalidades de imagem coronária invasiva, nomeadamente da ecografia intravascular (intravascular ultrasound - IVUS), da histologia virtual (IVUS-VH) e da tomografia de coerência óptica (optical coherence tomography - OCT). Estas modalidades têm uma elevada resolução espacial, possibilitando a avaliação detalhada das placas ateroscleróticas, permitindo assim identificar características associadas à sua potencial vulnerabilidade.

No entanto, embora sejam úteis para estudar a fisiopatologia da DC, a sua aplicabilidade está limitada por se tratarem de modalidades diagnósticas invasivas. Por outro lado, dado serem realizadas em doentes referenciados para coronariografia por suspeita de DC e frequentemente após um SCA, muitos destes doentes já se qualificam para medidas de prevenção secundária que alteram a história natural da doença e reduzem o risco de eventos CV no seguimento (31, 32). No estudo multicêntrico PROSPECT, foi feita a avaliação por IVUS complementada por histologia virtual, com o objectivo de estudar a história natural das lesões não intervencionadas (não *culprit*). Neste estudo, uma elevada carga de placa (≥70%), uma baixa área luminal mínima (≤4mm2) e a presença de um fibroateroma com cápsula fibrosa fina (Thin-cap fibroatheroma - TCFA) foram preditores independentes de eventos cardíacos adversos no seguimento. Por outro lado, as lesões que estiveram na origem de eventos no seguimento, tinham uma estenose angiograficamente não significativa (estenose média de 32%) na coronariografia basal (32).

O estudo PROSPECT foi um marco na investigação da história natural da DC, mas a sua aplicabilidade fica limitada pelo tipo de população estudada, que foi incluída na sequência de um SCA e assim já se qualificaria (independentemente do resultado na avaliação por imagem intravascular) para medidas de prevenção secundária. Este facto poderá explicar a baixa taxa de eventos major (morte e EAM) verificados no seguimento e o baixo poder preditivo destas variáveis mesmo quando associadas, uma vez que mesmo na presença dos 3 preditores independentes, a probabilidade de um evento foi de apenas 18,2%, sendo na sua grande maioria novas revascularizações e reinternamentos por angina instável.

A possibilidade de identificar e caracterizar placas ateroscleróticas na árvore coronária por angio TC cardíaca foi já avaliada em vários estudos, por comparação com modalidades de imagem intravascular (IVUS, IVUS-VH e OCT). Existem habitualmente pequenas diferenças na avaliação da área e volume da placa entre a angio TC e a IVUS, bem como do grau de estenose, com uma tendência para sobrevalorização da área lúminal por angio TC. Numa meta-análise recente, foi demonstrada uma boa acuidade diagnóstica da angio TC cardíaca para a detecção da presença de placas, por comparação com a IVUS, com uma área abaixo da curva ROC de 0,94, uma sensibilidade de 90% e uma especificidade de 92%. (33).

Mais importante ainda é o potencial que a angio TC tem de poder identificar características nas placas ateroscleróticas associadas à sua vulnerabilidade. Num estudo de Hoffman e col, as lesões *culprit* de doentes com SCA tinham mais frequentemente *remodeling* positivo e uma área de placa superior, por comparação com indivíduos com DC estável (34).

Num trabalho de Motoyama e col, as lesões culprit de doentes com SCA tinham com maior frequência *remodeling* positivo, placas com baixa atenuação (<30 HU) e calcificação *spotty* (35). Posteriormente, estes mesmos autores, foram avaliar prospectivamente a associação destas características identificadas na angio TC, com o desenvolvimento futuro de SCA num estudo que envolveu 1059 doentes com um seguimento médio de 27 meses. Foi possível demonstrar que o *remodeling* positivo e a presença de placas com baixa atenuação se associavam ao desenvolvimento subsequente de SCA, que ocorreram em 22,2% dos doentes que apresentavam simultaneamente estas 2 características. Em contrapartida, nos doentes em que apenas se documentou uma destas características, a taxa de SCA foi de 3,7% e nos doentes sem *remodeling* positivo nem placas com baixa atenuação a incidência de SCA foi de apenas 0,5%, validando assim prospectivamente o conceito de placa vulnerável por angio TC.

A angio TC foi também validada por comparação com a tomografia de coerência óptica (OCT) (36) e a histologia virtual (IVUS-VH) (37), sendo consistente nos vários trabalhos que as características que marcam as placas potencialmente vulneráveis na angio TC são o *remodeling* positivo e a baixa atenuação.

Mais recentemente foi descrito um sinal de atenuação em anel da porção não calcificada das placas, tendo sido designado como "*napkin ring sign*" , tendo esta característica por angio TC sido associada a placas de maior risco de instabilidade (36, 38, 39).

No entanto, apesar do elevado potencial da angio TC na caracterização das placas ateroscleróticas existem presentemente importantes limitações à capacidade da angio TC identificar as placas potencialmente vulneráveis, nomeadamente por limitações de resolução espacial dos actuais aparelhos, pela influência de diferentes protocolos de aquisição na valorização dos valores medidos de atenuação nas placas (40, 41) (tornando assim difícil padronizar um valor para definição de placa de baixa densidade, como marcador de vulnerabilidade) e por fim pela baixa reprodutibilidade inter-observador desta avaliação (42, 43).
No futuro, melhorias na resolução espacial, maior padronização dos protocolos de aquisição e adopção de softwares de quantificação da carga aterosclerótica poderão contribuir para melhorar o desempenho da angio TC cardíaca na identificação das placas potencialmente vulneráveis.

4.4 LIMITAÇÕES DA ANGIO TC CARDÍACA NA AVALIAÇÃO DA ATEROSCLEROSE SUBCLÍNICA

Existem actualmente importantes limitações à utilização da angio TC cardíaca em indivíduos assintomáticos com o objectivo de identificar a aterosclerose subclínica, nomeadamente:

1. Trata-se de uma exame actualmente ainda pouco disponível. Apesar de se ter assistido nos últimos anos a uma adopção crescente da angio TC cardíaca na pratica clínica, esta tem sido essencialmente empregue para exclusão de DC obstrutiva. A avaliação e quantificação das placas não obstrutivas requer uma elevada qualidade de imagem, que é mais consistente nos aparelhos de ultima geração, com melhor resolução espacial, temporal e de cobertura volumétrica, não estando estes aparelhos ainda amplamente difundidos.

2. Emprega radiação ionizante, com os associados potenciais riscos estocásticos. Nos últimos anos tem-se assistido a uma impressionante redução na dose de radiação, mas esta permanece ainda como uma importante limitação, sobretudo ao se considerar a sua utilização em indivíduos mais jovens.

3. Em face da elevada prevalência da DC não obstrutiva na população em geral, torna-se necessário desenvolver métodos para quantificar a carga aterosclerótica coronária global (scores – um dos objectivos desta tese e desenvolvido no ***Capítulo 8***)

4. Ausência de normogramas que permitam enquadrar a carga aterosclerótica documentada pela angio TC cardíaca de acordo com o esperado para a idade e o sexo (à semelhança do que já foi

feito para outros marcadores de aterosclerose subclínica como é o caso do score de cálcio) e assim sejam identificados os indivíduos cuja carga aterosclerótica seja acima do esperado e possa beneficiar de medidas mais intensivas de prevenção primária.

5. Ainda não existe evidência de que a utilização da angio TC com este objectivo possa modificar favoravelmente o manejo dos doentes e em última análise conduzir a uma redução dos eventos CV.

Assim, até à presente data, ao contrário do score de cálcio, a angio TC cardíaca não está indicada para a detecção de DC subclínica como método para estimar o risco CV (44, 45). No entanto, a capacidade que a angio TC cardíaca tem de documentar a presença de DC não obstrutiva, mesmo na ausência de calcificação, a par da impressionante redução da dose de radiação já possível com os aparelhos de ultima geração (46-48), fazem dela um método de elevado potencial para avaliação da carga aterosclerótica coronária global, podendo vir a ter um papel no futuro como método de avaliação da aterosclerose subclínica.

4.5 BIBLIOGRAFIA

1. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? J Am Coll Cardiol. 2003 May 7;41(9):1475-9.
2. Moscoso Costa F AGP, Campante Teles R, Ferreira J, Carvalho MS, Dores H, Sousa PJ, Raposo L, Sousa Almeida M, Mesquita Gabriel H, Mendes M. Baixo risco cardiovascular prévio numa população de EAM inaugural estimado pelo Heartscore. Rev Port Cardiol. 2012;31(Espec Congr):189.
3. Braunwald E. Epilogue: what do clinicians expect from imagers? J Am Coll Cardiol. 2006 Apr 18;47(8 Suppl):C101-3.
4. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003 Oct 7;108(14):1664-72.
5. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation. 1988 Nov;78(5 Pt 1):1157-66.
6. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005 Jun 28;111(25):3481-8.
7. Braunwald E. Noninvasive detection of vulnerable coronary plaques: Locking the barn door before the horse is stolen. J Am Coll Cardiol. 2009 Jun 30;54(1):58-9.
8. Falk E. Morphologic features of unstable atherothrombotic plaques underlying acute coronary syndromes. Am J Cardiol. 1989 Mar 7;63(10):114E-20E.
9. De Araujo Goncalves P, Brito J, Sousa PJ, Carvalho MS, Dores H, Teles RC, et al. Nonobstructive coronary disease leading to STEMI: assessment of residual stenosis after thrombus aspiration. Coron Artery Dis. 2013 Mar;24(2):154-9.
10. Achenbach S. Anatomy meets function. Modeling coronary flow reserve on the basis of coronary computed tomography angiography. J Am Coll Cardiol. 2011 Nov 1;58(19):1998-2000.
11. Erbel R, Mohlenkamp S, Kerkhoff G, Budde T, Schmermund A. Non-invasive screening for coronary artery disease: calcium scoring. Heart. 2007 Dec;93(12):1620-9.
12. Ardehali R, Nasir K, Kolandaivelu A, Budoff MJ, Blumenthal RS. Screening patients for subclinical atherosclerosis with non-contrast cardiac CT. Atherosclerosis. 2007 Jun;192(2):235-42.
13. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012 Aug 22;308(8):788-95.
14. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010 Apr 13;55(15):1600-7.
15. Elias-Smale SE, Kavousi M, Verwoert GC, Koller MT, Steyerberg EW, Mattace-Raso FU, et al. Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study. Eur J Prev Cardiol. 2012 Aug;19(4):698-705.
16. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008 Apr 3;358(14):1431-43.
17. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Jr., et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. Arterioscler Thromb Vasc Biol. 1995 Sep;15(9):1512-31.
18. Budoff MJ, Jollis JG, Dowe D, Min J, for the VCTSG. Diagnostic accuracy of coronary artery calcium for obstructive disease: Results from the ACCURACY trial. Int J Cardiol. 2011 Dec 26.
19. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008 Mar 27;358(13):1336-45.

20. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging. 2009 Jun;2(6):675-88.
21. Carvalho MS dAGP, Garcia-Garcia HM, Jerónimo Sousa P, Dores H, Ferreira A, Cardim N, Mota Carmo M, Aleixo A, Mendes M, Pereira Machado F, Roquette J, Marques H. Prevalence and predictors of coronary artery disease in patients with a calcium score of zero. . Int J Cardiovasc Imaging. 2013;(submitted to publication).
22. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999 Jan 7;340(1):14-22.
23. Vliegenthart R, Hollander M, Breteler MM, van der Kuip DA, Hofman A, Oudkerk M, et al. Stroke is associated with coronary calcification as detected by electron-beam CT: the Rotterdam Coronary Calcification Study. Stroke. 2002 Feb;33(2):462-5.
24. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006 Jan 11;295(2):180-9.
25. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011 Aug 16;58(8):849-60.
26. Lin FY, Shaw LJ, Dunning AM, Labounty TM, Choi JH, Weinsaft JW, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. J Am Coll Cardiol. 2011 Jul 26;58(5):510-9.
27. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging. 2012 Jul;5(7):690-701.
28. Kristensen TS, Kofoed KF, Kuhl JT, Nielsen WB, Nielsen MB, Kelbaek H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. J Am Coll Cardiol. 2011 Jul 26;58(5):502-9.
29. Wijns W, Schuijf JD. Nonobstructive coronary plaque matters. J Am Coll Cardiol. 2011 Jul 26;58(5):520-1.
30. Bamberg F, Sommer WH, Hoffmann V, Achenbach S, Nikolaou K, Conen D, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011 Jun 14;57(24):2426-36.
31. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504.
32. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35.
33. Voros S, Rinehart S, Qian Z, Joshi P, Vazquez G, Fischer C, et al. Coronary atherosclerosis imaging by coronary CT angiography: current status, correlation with intravascular interrogation and meta-analysis. JACC Cardiovasc Imaging. 2011 May;4(5):537-48.
34. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol. 2006 Apr 18;47(8):1655-62.
35. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol. 2007 Jul 24;50(4):319-26.
36. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovasc Imaging. 2009 Dec;2(12):1412-9.

37. Papadopoulou SL, Brugaletta S, Garcia-Garcia HM, Rossi A, Girasis C, Dharampal AS, et al. Assessment of atherosclerotic plaques at coronary bifurcations with multidetector computed tomography angiography and intravascular ultrasound-virtual histology. Eur Heart J Cardiovasc Imaging. 2012 Aug;13(8):635-42.
38. Maurovich-Horvat P, Hoffmann U, Vorpahl M, Nakano M, Virmani R, Alkadhi H. The napkin-ring sign: CT signature of high-risk coronary plaques? JACC Cardiovasc Imaging. 2010 Apr;3(4):440-4.
39. Maurovich-Horvat P, Schlett CL, Alkadhi H, Nakano M, Otsuka F, Stolzmann P, et al. The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. JACC Cardiovasc Imaging. 2012 Dec;5(12):1243-52.
40. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using multislice computed tomography: observations in an ex vivo model of coronary computed tomography angiography. Eur Radiol. 2005 Jul;15(7):1426-31.
41. Cademartiri F, Runza G, Palumbo A, Maffei E, Martini C, McFadden E, et al. Lumen enhancement influences absolute noncalcific plaque density on multislice computed tomography coronary angiography: ex-vivo validation and in-vivo demonstration. J Cardiovasc Med (Hagerstown). 2010 May;11(5):337-44.
42. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. J Am Coll Cardiol. 2006 Feb 7;47(3):672-7.
43. Boogers MJ, Broersen A, van Velzen JE, de Graaf FR, El-Naggar HM, Kitslaar PH, et al. Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. Eur Heart J. 2012 Apr;33(8):1007-16.
44. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.
45. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2012 Jul;33(13):1635-701.
46. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.
47. Schuhbaeck A, Achenbach S, Layritz C, Eisentopf J, Hecker F, Pflederer T, et al. Image quality of ultra-low radiation exposure coronary CT angiography with an effective dose <0.1 mSv using high-pitch spiral acquisition and raw data-based iterative reconstruction. Eur Radiol. 2013 Mar;23(3):597-606.
48. Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dubel HP, Schlattmann P, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. Circulation. 2009 Sep 8;120(10):867-75.

4.6 ARTIGO 11/ MANUSCRIPT 11:

+Model
REPC-257; No. of Pages 6
ARTICLE IN PRESS

Rev Port Cardiol. 2013;xxx(xx):xxx–xxx

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

CASO CLÍNICO

Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular

Hélder Dores[a,*], Pedro de Araújo Gonçalves[a,b,c], Maria Salomé Carvalho[a], Pedro Jerónimo Sousa[a], Hugo Marques[d], Nuno Cardim[b], Ana Aleixo[a,c], Miguel Mota Carmo[c], Francisco Pereira Machado[b], José Roquette[b]

[a] *Serviço de Cardiologia, Centro Hospitalar Lisboa Ocidental, Lisboa, Portugal*
[b] *Centro Cardiovascular, Hospital da Luz, Lisboa, Portugal*
[c] *Centro de Estudos de Doenças Crónicas, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal*
[d] *Centro de Imagiologia, Hospital da Luz, Lisboa, Portugal*

Recebido a 19 de maio de 2012; aceite a 31 de outubro de 2012

PALAVRAS-CHAVE
Tomografia computorizada cardíaca;
Doença coronária não obstrutiva;
Exercício físico

Resumo A tomografia computorizada cardíaca (angioTC cardíaca) permite documentar a presença de doença coronária, independentemente do seu grau de estenose. Recentemente, foi validado o valor prognóstico da doença coronária não obstrutiva documentada por angioTC cardíaca. No entanto, não existem ainda recomendações claras acerca da abordagem destes doentes, nomeadamente sobre o início de medidas farmacológicas mais agressivas em prevenção primária. A abordagem destes doentes permanece controversa, sobretudo nos casos em que existe uma discrepância entre o risco cardiovascular e a carga aterosclerótica objetivada na angioTC.

Os autores descrevem o caso de um doente com discrepância entre a extensão da aterosclerose coronária objetivada e a sua estimativa de acordo com os *scores* de probabilidade pré-teste e de eventos cardiovasculares. Tratando-se de um indivíduo com documentação de aterosclerose coronária acima do esperado - *score* de cálcio superior ao percentil 90 e doença coronária não obstrutiva na angioTC cardíaca, mas por outro lado, assintomático e sem fatores de risco nem antecedentes cardiovasculares, com uma estimativa de risco cardiovascular muito baixa e atleta de competição, torna-se difícil decidir acerca do risco/benefício de medidas farmacológicas de prevenção primária.

* Autor para correspondência.
Correio eletrónico: heldores@hotmail.com (H. Dores).

0870-2551/$ – see front matter © 2012 Sociedade Portuguesa de Cardiologia. Publicado por Elsevier España, S.L. Todos os direitos reservados.
http://dx.doi.org/10.1016/j.repc.2012.10.013

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

+Model
REPC-257; No. of Pages 6
ARTICLE IN PRESS

KEYWORDS
Cardiac computed tomography;
Non-obstructive coronary artery disease;
Physical exercise

Non-obstructive coronary artery disease documented by cardiac computed tomography: Discrepancy between atherosclerotic burden and cardiovascular risk

Abstract Cardiac computed tomography (CT) documents the presence of coronary artery disease, regardless of the degree of stenosis. The prognostic value of non-obstructive coronary artery disease documented by cardiac CT has recently been validated. However, there are still no clear guidelines on the management of such patients, particularly concerning initiation of more aggressive pharmacological measures for primary prevention. The approach to these patients remains controversial, especially in cases in which there is a discrepancy between cardiovascular risk and the atherosclerotic burden as documented by cardiac CT.

The authors describe the case of a patient with a discrepancy between the extent of documented coronary atherosclerosis and that estimated according to pretest probability and cardiovascular risk scores. As this individual had more severe coronary atherosclerosis than expected (calcium score above the 90th percentile and non-obstructive coronary artery disease on cardiac CT) but was a competitive athlete and otherwise asymptomatic and without risk factors or cardiovascular history, with a very low estimated cardiovascular risk, it was difficult to decide on the risks and benefits of pharmacological primary prevention.

Caso clínico

Descreve-se o caso de um homem de 47 anos, sem fatores de risco cardiovascular ou antecedentes pessoais/familiares relevantes, desportista de alta competição, praticante de *Ironman* – triatlo de longas distâncias composto por natação (3 800 m), ciclismo (180 km) e corrida (42,2 km). O doente negava a toma de medicação regular e o abuso de substâncias aditivas como tabaco, álcool ou estimulantes como sendo esteroides anabolizantes. Na sequência de um quadro de infeção respiratória e a pedido do seu médico assistente (Medicina Geral e Familiar), realizou uma tomografia computorizada (TC) torácica, em que foi relatada como achado extrapulmonar a presença de «calcificação das artérias coronárias». Por este motivo, realizou uma angioTC cardíaca para quantificação da calcificação coronária e exclusão da presença de doença coronária obstrutiva. O *score* de cálcio foi de 226, distribuído por todas as artérias coronárias epicárdicas, com predomínio na artéria descendente anterior proximal (Figura 1). De acordo com os normogramas publicados[1], este valor estava muito acima do esperado para o sexo masculino nesta faixa etária (superior ao percentil 90). Este valor seria o expectável (percentil 50) para um indivíduo na sexta década de vida.

Na aquisição com contraste foi possível excluir doença coronária obstrutiva. Documentou-se a presença de placas mistas, mas predominantemente calcificadas, dispersas por toda a árvore coronária, sobretudo no tronco comum e no segmento proximal da artéria descendente anterior. Foram evidentes placas com remodelagem positiva (Figuras 2 e 3).

Com o resultado deste exame, o doente recorreu a consulta de cardiologia. Encontrava-se assintomático e, ao exame objetivo, não apresentava alterações relevantes: TA 140/80 mmHg, FC 60 bpm, IMC 23,7 kg/m^2; auscultação cardíaca com S1S2 rítmicos, sem sopros e auscultação pulmonar com murmúrio vesicular mantido, simétrico e sem ruídos adventícios audíveis; membros sem edemas periféricos, pulsos distais palpáveis, amplos e simétricos.

O doente tinha realizado recentemente (há menos de 6 meses) exames laboratoriais, prova de esforço e ecocardiograma, pedidos no âmbito de avaliação em medicina do trabalho. Nos *exames laboratoriais* havia a destacar: hemoglobina 14,0 g/dl, glicemia em jejum 84 mg/dl, colesterol total 217 mg/dl, colesterol LDL 116 mg/dl, colesterol HDL 116 mg/dl e triglicéridos 70 mg/dl. A *prova de esforço* foi efetuada segundo o protocolo Bruce, teve a duração de 21 min, atingiu 19,3 MET, normal evolução cronotrópica (101% da FC máxima prevista) e normal evolução tensional (TA basal 130/80 mmHg e 200/80 mmHg no pico de esforço). Não apresentou queixas durante a realização da prova, nomeadamente angor, nem ocorreram alterações electrocardiográficas sugestivas de isquemia nem disritmias. O *ecocardiograma* revelou alterações típicas de coração de atleta – hipertrofia ventricular esquerda excêntrica ligeira, sem dilatação ventricular, com fração de ejeção e função diastólica normais, assim como dilatação auricular esquerda ligeira (Figura 4).

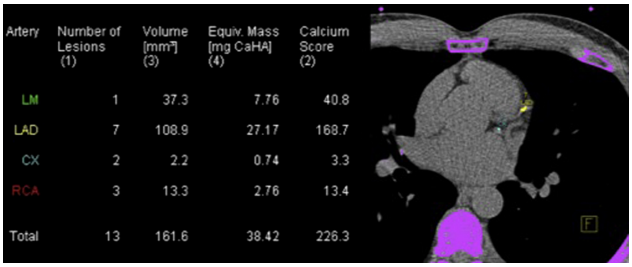
Pelo cálculo de *scores* de probabilidade de doença coronária, o doente encontra-se numa categoria de baixa probabilidade, sobretudo atendendo à idade e à ausência de sintomas: *Score* de *Diamond-Forrester* – baixa probabilidade; *Score* de *Morise* – *score* 6 (baixa probabilidade se < 8).

O risco de eventos cardiovasculares estimado foi igualmente baixo: *HeartScore* – 1%; *Framingham* – 4%, nomeadamente atendendo à idade, à ausência de fatores de risco e a um perfil lipídico favorável.

Apesar de se tratar de um indivíduo assintomático e com baixo risco cardiovascular, pela presença de doença aterosclerótica coronária na angioTC cardíaca com um *score* de cálcio elevado, além da manutenção de medidas preventivas para o controlo dos fatores de risco cardiovascular, optou-se por iniciar terapêutica farmacológica com estatina (rosuvastatina 5 mg/d). Foi também recomendada a redução da intensidade da prática desportiva, nomeadamente em contexto de alta competição.

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

+Model
REPC-257; No. of Pages 6
ARTICLE IN PRESS



Artery	Number of Lesions (1)	Volume [mm³] (3)	Equiv. Mass [mg CaHA] (4)	Calcium Score (2)
LM	1	37.3	7.76	40.8
LAD	7	108.9	27.17	168.7
CX	2	2.2	0.74	3.3
RCA	3	13.3	2.76	13.4
Total	13	161.6	38.42	226.3

Figura 1 *Score* de cálcio – distribuição pelas artérias coronárias epicárdicas. Cx: circunflexa; LAD: descendente anterior; LM: tronco comum; RCA: coronária direita.

Discussão

O caso apresentado descreve um quadro clínico com uma importante discrepância entre a carga aterosclerótica coronária objetivada na angioTC cardíaca e o baixo risco cardiovascular estimado. Este caso levanta várias questões controversas e com resposta ainda inconclusiva, nomeadamente em relação à indicação para realização de angioTC cardíaca e à abordagem de doentes em que se documenta doença coronária não obstrutiva, sendo representativo de um subgrupo de doentes com que cada vez mais somos confrontados e para os quais ainda não existem recomendações claras.

O primeiro passo a adotar na avaliação de um doente com suspeita de doença coronária deve ser a avaliação clínica exaustiva com o cálculo da probabilidade pré-teste para a presença de doença coronária e a estimativa da ocorrência de eventos cardiovasculares. Existem inúmeros *scores* que permitem fazer esta estratificação de risco, sendo os mais usados na determinação da probabilidade pré-teste para a presença de doença coronária o *Diamond-Forrester* e o *Morise* e na estimativa da probabilidade para a ocorrência

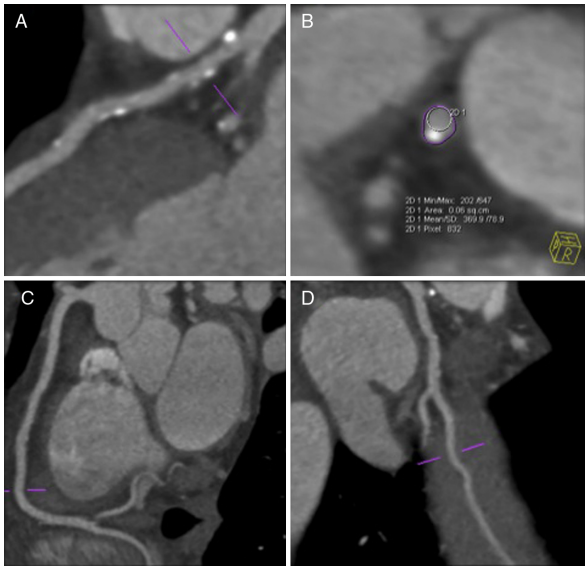


Figura 2 AngioTC cardíaca: A – placas predominantemente calcificadas dispersas no segmento proximal da artéria descendente anterior, sem condicionar estenose significativa; B – placa mista, excêntrica, com remodelagem positiva; C e D – artérias circunflexa e coronária direita (vaso dominante) com placas mistas *minor*, sem estenoses significativas.

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

+Model
REPC-257; No. of Pages 6
ARTICLE IN PRESS

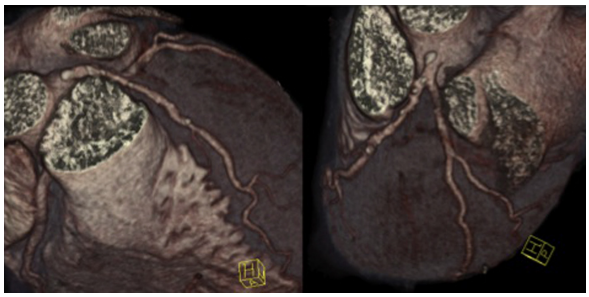


Figura 3 Imagens de reconstrução volumétrica da árvore coronária demonstrando placas ateroscleróticas dispersas na coronária esquerda, não condicionando estenoses significativas.

de eventos cardiovasculares o *HeartScore* e o *Framingham*. O doente em causa, de acordo com todos estes *scores*, encontra-se na categoria de baixa probabilidade de doença coronária e de baixo risco para eventos cardiovasculares.

No caso descrito, o primeiro ponto que importa analisar e discutir é a indicação deste doente para o cálculo do *score* de cálcio e a realização de angioTC cardíaca. Nos doentes assintomáticos e com baixo risco cardiovascular não está indicada a avaliação do *score* de cálcio nem a realização de angioTC cardíaca. Nas recomendações para a avaliação do risco cardiovascular em adultos assintomáticos da *American Heart Association*, neste contexto, ambos os exames têm classe de recomendação III, não devendo, portanto, ser realizados[2]. A maior acessibilidade existente atualmente para o pedido e a realização de exames complementares de diagnóstico leva a que, por vezes, estes sejam realizados de forma indiscriminada e sem indicação, sendo difícil a interpretação dos seus resultados. No caso descrito, após a realização destes exames, o doente passou para um patamar de risco superior ao indicado pelos *scores* de avaliação e de predição de risco cardiovascular. Por um lado, o valor do *score* de cálcio associa-se diretamente a maior mortalidade a longo prazo[3]. Por outro lado, além do pior prognóstico comprovado pela presença de doença coronária obstrutiva determinada

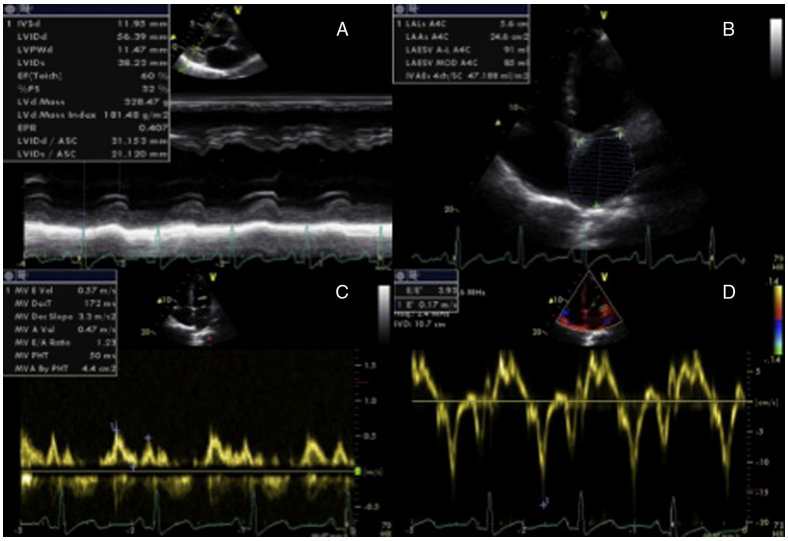


Figura 4 Ecocardiograma transtorácico revelando hipertrofia ventricular esquerda excêntrica (A), dilatação auricular esquerda (B), fluxo Doppler transmitral e padrão de enchimento normais (C e D).

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

+Model
REPC-257; No. of Pages 6
ARTICLE IN PRESS

pela angioTC cardíaca, também a presença de doença não obstrutiva se associa a maior mortalidade, comparativamente aos doentes sem estenoses coronárias. Estes dados foram comprovados pelo registo multicêntrico CONFIRM, recentemente publicado, após a análise de 23 854 doentes[4]. Portanto, as alterações encontradas neste doente, *score* de cálcio elevado e placas não obstrutivas, terão impacto negativo no seu prognóstico.

Com estes dados, surge também a questão sobre quais deverão ser as medidas preventivas a implementar. A presença de doença aterosclerótica representa uma manifestação subclínica de doença coronária e pode ser considerada como um *qualifier*, colocando o doente num patamar de risco superior, com indicação para estratégias preventivas diferentes dos doentes com o mesmo perfil de risco, mas sem estas alterações[5]. Independentemente do perfil lipídico, que neste caso é normal, salientando-se mesmo o elevado valor do colesterol HDL, comum em atletas, poderá estar indicado o início de terapêutica farmacológica com estatina, além das medidas preventivas comuns de controlo dos fatores de risco cardiovascular[6,7]. Assim, além do controlo destes fatores de risco através da manutenção de hábitos de vida saudáveis, a estratégia adotada incluiu o início de terapêutica com estatina. Esta atitude advém da comprovada redução do grau de estenose e do volume da placa aterosclerótica nos doentes medicados com estatina[8]. Outra classe farmacológica com benefício comprovado em doentes com doença coronária conhecida são os antiagregantes plaquetários. No entanto, segundo as recomendações da Sociedade Europeia de Cardiologia para a prevenção da doença cardiovascular, deverão ser apenas prescritos aos doentes com doença coronária estabelecida ou risco cardiovascular elevado (*HeartScore* > 10%)[5]. Neste sentido e adicionalmente aos efeitos adversos não desprezíveis destes fármacos, sobretudo num doente potencialmente exposto a eventuais complicações hemorrágicas pelo tipo de desporto que pratica, optou-se pela sua não prescrição.

Outro ponto importante é avaliar a indicação para a suspensão ou redução do exercício físico, nomeadamente em contexto de alta competição. O triatlo, segundo a 36.ª Conferência de *Bethesda*, é um desporto caracterizado tanto por uma elevada intensidade dinâmica como estática[9]. Por outro lado, o *Ironman* (triatlo levado ao extremo) corresponderá a cargas de intensidade ainda mais elevadas. Segundo esta conferência, os atletas de baixo risco cardiovascular com doença coronária, como o caso do doente apresentado, podem realizar desporto competitivo de baixa intensidade dinâmica e de baixa/moderada intensidade estática, mas deverão evitar provas com intensidade competitiva elevada. Nas mesmas recomendações releva-se também o papel do *score* de cálcio na avaliação dos atletas, devendo os cuidados ser acrescidos quando os valores são superiores a 100[9]. Assim, o doente foi aconselhado a suspender provas de alta competição e a reduzir a intensidade do exercício efetuado.

Conclusão

A determinação do risco cardiovascular e da probabilidade pré-teste constituem o primeiro passo na avaliação dos doentes com suspeita de doença coronária. A presença de doença coronária não obstrutiva tem impacto prognóstico, devendo estes doentes, mesmo com risco cardiovascular baixo, ser alvo de medidas preventivas mais intensas. Contudo, a melhor abordagem a adotar, especialmente iniciar terapêutica farmacológica, permanece mal definida. Adicionalmente, na presença de doentes que praticam desporto de alta competição, a controvérsia estende-se ao tipo de recomendação relativamente à redução da sua prática. Provavelmente, a melhor atitude deverá ser a avaliação de cada doente caso a caso, de acordo com o tipo de desporto efetuado e a intensidade do mesmo.

Responsabilidades éticas

Proteção dos seres humanos e animais. Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com os da Associação Médica Mundial e da Declaração de Helsínquia.

Confidencialidade dos dados. Os autores declaram ter seguido os protocolos de seu centro de trabalho acerca da publicação dos dados de pacientes e que todos os pacientes incluídos no estudo receberam informações suficientes e deram o seu consentimento informado por escrito para participar nesse estudo.

Direito à privacidade e consentimento escrito. Os autores declaram ter recebido consentimento escrito dos pacientes e/ou sujeitos mencionados no artigo. O autor para correspondência deve estar na posse deste documento.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

Bibliografia

1. Hoff JA, Chomka EV, Krainik AJ, et al. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol. 2001;87:1335–9.
2. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010;122:e584–636.
3. Budoff MJ, Shaw LJ, Liu ST, et al. Long-Term prognosis associated with coronary calcification: Observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007;49:1860–70.
4. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011;58:849–60.
5. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth Joint Task Force of the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representative of nine societies and by invited experts). Eur Heart J. 2007;28:2375–414.

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

6. Reiner Z, Catapano AL, de Backer G, et al., European Association for Cardiovascular Prevention & Rehabilitation. ESC/EAS Guidelines for the management of dyslipidemias: The Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–818.
7. Banfi G, Colombini A, Lombardi G, et al. Metabolic markers in sports medicine. Adv Clin Chem. 2012;56:1–54.
8. Ballantyne CM, Raichlen JS, Nicholls SJ, et al. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: A study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. Circulation. 2008;117:2458–66.
9. Vogel R, Abrams J, Anderson J, et al. 36th Bethesda conference: Eligibility recommendations for competitive athletes with cardiovascular abnormalities. J Am Coll Cardiol. 2005;45:1313–5.

Como citar este artigo: Dores H, et al. Doença coronária não obstrutiva documentada por tomografia computorizada cardíaca: contraste entre a carga aterosclerótica e o risco cardiovascular. Rev Port Cardiol. 2013. http://dx.doi.org/10.1016/j.repc.2012.10.013

ARTIGO 12 *(submetido para publicação)/* **MANUSCRIPT 12** *(submitted for publication):*

International Journal of Cardiovascular Imaging

Prevalence and predictors of coronary artery disease in patients with a calcium score of zero

--Manuscript Draft--

Manuscript Number:	
Full Title:	Prevalence and predictors of coronary artery disease in patients with a calcium score of zero
Article Type:	Original Article
Keywords:	Zero calcium score; coronary artery disease; noncalcified plaque
Corresponding Author:	Maria Salomé Leal de Carvalho Lisboa, PORTUGAL
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	
Corresponding Author's Secondary Institution:	
First Author:	Maria Salomé Leal de Carvalho
First Author Secondary Information:	
Order of Authors:	Maria Salomé Leal de Carvalho
	Pedro de Araújo Gonçalves
	Hector Garcia-Garcia
	Pedro Jerónimo de Sousa
	Helder Dores
	António Ferreira
	Nuno Cardim
	Miguel Mota Carmo
	Ana Aleixo
	Miguel Mendes
	Francisco Pereira Machado
	José Roquette
	Hugo Marques
Order of Authors Secondary Information:	
Abstract:	Aims: The absence of coronary calcification is associated with an excellent prognosis. However, a calcium score of zero does not exclude the presence of coronary artery disease (CAD) or the possibility of future cardiovascular events. Our aim was to study the prevalence and predictors of coronary artery disease in patients with a calcium score of zero. Methods and Results: Prospective registry of 3012 consecutive patients that performed Cardiac CT (Dual source CT). Stable patients referred for evaluation of possible CAD that had a calcium score of zero (n=864) were selected for this analysis. The variables that were statistically significant were included in a multivariable logistic regression model. From 864 patients with a calcium score of zero, 107 (12.4%) had coronary plaques on

	the contrast CT (10.8%, n=93 with nonobstructive CAD and 1.6%, n=14 with obstructive CAD). By logistic regression analysis, the independent predictors of CAD in this population were age >55 years [OR:1.63 (1.05-2.52)], hypertension [OR:1.64 (1.05-2.56)] and dyslipidemia [OR:1.54 (1.00-2.36)]. In the presence of these 3 variables, the probability of having coronary plaques was 21%. Conclusions: The absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low. In this population, the independent predictors of CAD in the setting of a calcium score of zero were hypertension, dyslipidemia, and age above 55 years. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population.

ABSTRACT

Aims:

The absence of coronary calcification is associated with an excellent prognosis. However, a calcium score of zero does not exclude the presence of coronary artery disease (CAD) or the possibility of future cardiovascular events. Our aim was to study the prevalence and predictors of coronary artery disease in patients with a calcium score of zero.

Methods and Results:

Prospective registry of 3012 consecutive patients that performed Cardiac CT (Dual source CT). Stable patients referred for evaluation of possible CAD that had a calcium score of zero (n=864) were selected for this analysis. The variables that were statistically significant were included in a multivariable logistic regression model.

From 864 patients with a calcium score of zero, 107 (12.4%) had coronary plaques on the contrast CT (10.8%, n=93 with nonobstructive CAD and 1.6%, n=14 with obstructive CAD). By logistic regression analysis, the independent predictors of CAD in this population were age >55 years [OR:1.63 (1.05-2.52)], hypertension [OR:1.64 (1.05-2.56)] and dyslipidemia [OR:1.54 (1.00-2.36)]. In the presence of these 3 variables, the probability of having coronary plaques was 21%.

Conclusions:

The absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low. In this population, the independent predictors of CAD in the setting of a calcium score of zero were hypertension, dyslipidemia, and age above 55 years. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population.

KEYWORDS

Zero calcium score; coronary artery disease; noncalcified plaque.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of death in developed countries and it is expected to remain the most important disease in the upcoming years [1].

Quantification of coronary artery calcium (*Calcium scoring – CaSc*) can provide a measure of the atherosclerotic plaque burden, since coronary arterial calcification occurs almost exclusively in atherosclerotic plaques [2,3]. Also, it has been demonstrated in many large clinical trials, that CaSc is a strong predictor of cardiovascular events [4,5].

On the other hand, the absence of calcium in the coronary arteries, although it does not rule out atherosclerotic disease, is consistent with an excellent long-term prognosis [6] and has a high sensitivity and negative predictive value for excluding obstructive CAD. This fact prompted some recent guidelines to suggest that a calcium score of zero might exclude the need for coronary angiography in symptomatic patients [7]. Nevertheless, in previous studies, a high variation was reported in the incidence of obstructive CAD in patients with a CaSc of zero, raging from 3.5 to 32% [8,9,10,11]. For instance, in the recent CONFIRM registry, it was shown that in patients with a CaSc of zero, obstructive CAD is possible and is associated with increased cardiovascular events [12]. The aim of this study was to assess the prevalence and predictors of coronary artery disease in a population of stable patients referred for evaluation of possible CAD who had a calcium score of zero.

METHODS

Study design and patient population

Single center prospective registry including 3012 consecutive patients undergoing Dual Source Cardiac CT angiography (CCTA) from February 2007 to March 2012. For this analysis, 864 stable patients (with symptoms and/or positive or inconclusive stress tests) referred for evaluation of possible CAD that had a calcium score of zero were included.

Exclusion criteria included: 1) preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n=51); 2) evaluation of possible CAD in cardiomyopathies (dilated cardiomyopathy or hypertrophic cardiomyopathy) (n=162); 3) cardiac CT for atrial fibrillation ablation (n=330); 4) previous myocardial infarction and/or revascularization procedures (n=257); 5) suspected ACS (n=70); 6) other indications (n=102). Patients with atrial fibrillation or other significant arrhythmias during scan acquisition or artifacts that significantly compromised image quality were also excluded, as every patient with a CaSc>0 (Figure 1).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history with a risk factors questionnaire was obtained from the patients to assess for the presence of: 1) Diabetes mellitus (defined as a fasting glucose level of ≥126 mg/dL or the need for insulin or oral hypoglycemic agents) [13]; 2) Dyslipidemia (defined as a total cholesterol level ≥200 mg/dL or treatment with lipid-lowering drugs) [14]; 3) Hypertension

(defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medication) [15]; 4) Obesity (body mass index ≥30 kg/m^2); 5) positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 [male] or 65 [female] years of age) [16]; 6) smoking (defined as previous [less<1year] or current smoker.

Pre-test probability of CAD was determined using both the modified Diamond and Forrester [17] and the Morise score [18]. The cardiovascular risk was assessed with the HeartScore [19]. In the modified Diamond-Forrester, patients were classified into very low (<5%), low (<10%), intermediate (10-90%) and high probability (>90%). For the Morise score, patients were classified into low (scores 0-8), intermediate (scores 9-15) and high probability (scores ≥16). For the HeartScore, the cut-off of ≥5% (high-risk) was used.

Scan protocol and image reconstruction

All scans were performed with a first generation dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold.

The calcium score acquisition consisted of step and shoot – prospective ECG gating technique with ECG triggering at 70% of the R-R interval if the heart rate was below 80bpm or at 40% of the R-R interval if the heart rate was higher. From the topogram, a cranio-caudal scan was obtained from the carina to the plane just below the heart *silhouette*, with 120kV and 128mAs/rot tube current, with CAREDose 4D mAs modulation. The value of the calcium score was obtained with the analysis of consecutive non-contrast 3 mm slices,

with a reconstruction b35f Kernel and a small (cardiac) FOV, with a dedicated software (CaScoring- Siemens), where every area at least with 3mm^2 within a coronary vessel with a density above 130HU (Hounsfield Units) was selected.

For CCTA, sublingual nitroglycerin was administered to all patients, except when contraindicated, and intravenous metoprolol (5mg, with a titration dose up to 20 mg) was administered in patients with heart rate >70 beats/min.

During the scan acquisition, a bolus of iodinated contrast was injected at a 6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time + 6 s delay) x flow (6 ml/s). A ROI was defined in the ascending aorta for the bolus trigger technique, set at 120 HU.

Dose reduction strategies - including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering - were used whenever feasible.

Mean estimated radiation dose was 0.8 ± 0.5 mSv for CaSc and 4.6 ± 3.8 mSv for CT scan. Mean contrast dose was 96.2 ± 13.6 ml and heart rate was 67.8 ± 12.9 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique. All scans were analysed in the same session by both a cardiologist and a radiologist with Level III– equivalent experience. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that

could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [20]. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. Obstructive CAD was defined by presence of at least one plaque with ≥ 50% stenosis.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± one standard deviation. Categorical variables were expressed as percentages and their frequencies were compared with the chi-square test.

Binary logistic regression models were built to elucidate independent predictors of CAD without coronary calcification.

The objective of this model was the assessment of clinical variables that aid to predict the presence of CAD in patients with a calcium score of zero. All the demographic, risk factors and clinical variables present in table 2 that had a $p<0.1$ in univariate analysis were included in a multivariate logistic regression model (Enter method).

Statistical analysis was performed with SPSS 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline and Procedural Characteristics

In the final study population of 864 patients, most of the patients were female (55%) and mean age was 53.8 ± 11.0. The prevalence of traditional risk factors was low, with only 9.0% of patients with diabetes. This was predominantly a low risk population with few high risk patients (only 9.0% with the Morise score and 3.1% with the modified Diamond-Forrester had a high CAD probability). Likewise, most of the patients were not considered as high cardiovascular risk, as assessed by the HeartScore (only 11.9% had a Heart Score≥5%) - table 1.

Coronary plaques were detected on CCTA in 107 patients (12.4%): 10.8% (n=93) with nonobstructive CAD and 1.6% (n=14) with obstructive CAD – figure 2. Considering the degree of stenosis of the obstructive CAD group, 64% (n=9) had a 50 to 70% stenosis and 36% (n=5) a >70% stenosis. Considering the extent of disease, all these patients had obstructive CAD in only 1 vessel and 93% had a single lesion. Regarding the distribution, most of the obstructive CAD lesions were found in proximal or mid segment locations (87%).

Univariate analysis

Patients with CAD were older (prevalence of age≥55 years 64% vs 47%, p=0.001) than patients without CAD and had a higher prevalence of dyslipidemia (65% vs 51%, p=0.010) and hypertension (67% vs 51%,

p=0.002).

The pre-test CAD probability assessed both by the Morise score and the modified diamond-Forrester was higher in the CAD group and these patients had a 2 to 4 times higher probability of being of a high CAD probability group. Cardiovascular risk, estimated by the HeartScore, was also significantly higher in patients with CAD. Although there was a trend in this group towards a higher prevalence of diabetes and male gender, these differences were not statistically significant – table 2.

Multivariate analysis

By multivariate analysis, the independent predictors of CAD in patients with a calcium score of zero were age≥55 (odds ratio=1.631, confidence interval 95% 1.054-2.524, p=0.028), hypertension (odds ratio=1.641, confidence interval 95% 1.051-2.560, p=0.029) and dyslipidemia (odds ratio=1.538, confidence interval 95% 1.002-2.361, p=0.049) (table 3 and figure 3). In the presence of these 3 variables (n=176 patients, 20.4% of the population), the probability of having coronary plaques was 21% (versus 12.4% in the total studied population).

DISCUSSION

In this single center cohort of stable patients without known CAD, referred for cardiac CT angiography, we found a very low prevalence of obstructive CAD (1,6%) in the subset with a CaSc of zero. When considering the degree of stenosis, only 0,6% had a stenosis >70%.

The prevalence and clinical significance of obstructive CAD on coronary CT angiography among patients with a calcium score of zero has been evaluated in several cohorts, but with conflicting results, depending on the population included. Data from the CONFIRM registry [12], Rubinshtein et al [11] and Akram et al [9], are in line with our results, with a low prevalence of obstructive CAD (3.5%, 7.2% and 8.2%, respectively). Our prevalence was even lower, and this might be explained by a high prevalence of patients with a low pretest probability of CAD.

In contrast, in the work of Harberl et al [8] and Gottlieb et al [10], there was a high prevalence of CAD (32% and 19.4%, respectively), which can be related to the fact that these studies included patients referred for conventional angiography, including patients with possible acute coronary syndromes.

Calcium scoring enables a noninvasive quantification of the total coronary atherosclerotic burden, although it underestimates the burden of disease, by not measuring noncalcified plaque [21]. Nevertheless, it has been shown to outperform traditional risk stratification tools, such as clinical risk factor assessment, ankle-brachial index, carotid intima-media thickness and high-

sensitivity C-reactive protein, as a predictor of cardiovascular events [**Error! Bookmark not defined.**,5].

Our data suggests that, although the absence of calcium does not exclude the presence of CAD, it was associated with a very low probability of obstructive lesions, when the pretest CAD probability is low. This is in line with the excellent prognosis that has been demonstrated for patients with a calcium score of zero [6].

In our population, older age (≥55 years), hypertension and dyslipidemia were independent predictors of CAD in this subset of patients without calcium, and in the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the general population. Nevertheless, the odds ratios for the independent predictors were rather modest and other traditional CAD risk factors were not found to be independent predictors. This way, we could hypothesize that coronary plaques without calcium could be a different phenotypical subset of CAD. Another possibility could be that these patients with coronary plaques in the absence of calcium represent CAD at earlier stages, since calcium is considered to be associated with more advanced forms of atherosclerotic lesions [**Error! Bookmark not defined.**]. In fact, in our population, all the patients with obstructive CAD had only 1 vessel disease, most (93%) with a single lesion, and only a minority (36%) had >70% stenosis.

One last hypothesis could be that these plaques can have microcalcifications below the threshold of cardiac CT spacial resolution, as in the case example

(figure 4), in which small spots of calcium were only detected by intravascular ultrasound (IVUS) virtual histology.

LIMITATIONS

There are a number of limitations related to this report: 1) this is a single center retrospective study with medium size cohort; 2) our population in mainly of low CAD probability and CV risk; the very low percentage of obstructive CAD found can not be extrapolated to cohorts with more patients with higher CAD probability and CV risk 3) the definition of CAD was made using CCTA and not invasive angiography, which may lead to false-positive findings, although this is unlikely in the absence of calcium; 4) lack of prognostic information, since we did not evaluate the prognostic importance of obstructive CAD in patients with a CaSc of zero.

CONCLUSIONS

In this population of stable patients referred for evaluation of possible CAD that had a calcium score of zero, 12.4% had coronary plaques and 1.6% had obstructive (≥ 50%) CAD.

Therefore, and despite the known high negative predictive value of CaSc for coronary events, the absence of coronary artery calcification does not exclude the presence of coronary artery disease, but the prevalence of obstructive disease is very low.

In this population, we found that age≥55, hypertension, dyslipidemia were independent predictors of CAD in the setting of a calcium score of zero. In the presence of these 3 predictors, the probability of having CAD was almost 2 times higher than in the total studied population.

All the authors declare that they have no conflict of interest.

REFERENCES

[1] Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee (2009) Circulation. Jan 27;119(3):480-6.

[2] Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W Jr, et al.: A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association (1995) Arterioscler Thromb Vasc Biol, 15:1512–1531.

[3] Budoff M, Jollis JG, Dowe D, Min J for the VCT study group. Diagnostic accuracy of coronary artery calcium for obstructive disease: results from the ACCURACY trial (2011) Int J Cardiol; (Epub ahead of print).

[4] Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR et al.: Coronary calcium as a predictor of coronary events in four racial or ethnic groups (2008) N Engl J Med, 358:1336–1345.

[5] Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals (2012) JAMA; 308:788-795.

[6] Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification (2009) J Am Coll Cardiol Img; 2:675– 88.

[7] National Institute for Health and Clinical Excellence. Chest pain of recent onset. Assessment and diagnosis of recent onset chest pain or discomfort of

suspected cardiac origin. London: NICE (2010) Available from: http://www.nice.org.uk/guidance/CG95

[8] Haberl R, Tittus J, Böhme E, Czernik A, Richartz BM, Buck J, et al. Multislice spiral computed tomographic angiography of coronary arteries in patients with suspected coronary artery disease: an effective filter before catheter angiography? (2005) Am Heart J. 149: 1112-1119.

[9] Akram K, O'Donnell RE, King S, Superko HR, Agatston A, Voros S. Influence of symptomatic status on the prevalence of obstructive coronary artery disease in patients with zero calcium score (2009) Atherosclerosis. 203:533–7.

[10] Gottlieb I, Miller JM, Arbab-Zadeh A, Dewey M, Clouse ME, Sara L, et al. The absence of coronary calcification does not exclude obstructive coronary artery disease or the need for revascularization in patients referred for conventional coronary angiography (2009) J Am Coll Cardiol. 44:627-634.

[11] Rubinshtein R, Gaspar T, Halon DA, Goldstein J, Peled N, Lewis BS. Prevalence and extent of obstructive coronary artery disease in patients with zero or low calcium score undergoing 64-slice cardiac multidetector computed tomography for evaluation of a chest pain syndrome (2007) Am J Cardiol; 99:472–5.

[12] Vilines TC, Hulten EA, Shaw LJ, Goyal M, Dunning A, Achenbach S et al. Prevalence and Severity of Coronary Artery Disease and Adverse Events Among Symptomatic Patients With Coronary Artery Calcification Scores of Zero Undergoing Coronary Computed Tomography Angiography: results from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter) registry (2011) J Am Coll Cardiol. 58:2533-2540.

[13] Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) Diabetes Care. Jul;20(7):1183-97.

[14] Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III) (2001) JAMA. May 16;285(19):2486-97.

[15] European Society of Hypertension-European Society of Cardiology Guidelines C. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension (2003) J Hypertens. 21(6):1011-53

[16] Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in 18 the Prospective Army Coronary Calcium (PACC) project (2005) J Am Coll Cardiol. Sep 6;46(5):807-14

[17] Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. American College of Cardiology/ American Heart association task force on practice guidelines (Committee to update the 1997 exercise testing guidelines). ACC/AHA 2002 Guideline update for exercise testing: summary article: a report of the American College of Cardiology/ American Heart Association task force on practice guidelines (2002) Circulation. 106 (14): 1883-92.

[18] Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and

women presenting with suspected coronary disease (1997) Am J Med. Apr;102(4):350-6.

[19] Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR) (2012) Eur Heart J. Jul;33(13):1635-701.

[20] Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality (2007) J Am Coll Cardiol. Sep 18;50(12):1161-70.

[21] Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary Artery Calcium Area by Electron-Beam Computed Tomography and Coronary Atherosclerotic Plaque Area (1995) Circulation. 92:2157-2162.

Table 1: Demographic, clinical and CCTA characteristics of the study population

	All patients (n=864)
Demographic	
Age	53.8 ± 11.0
Male sex	389 (45.0)
Risk factors	
Obesity (BMI ≥30)	160 (18.5)
Diabetes	78 (9.0)
Hypertension	459 (53.1)
Dyslipidemia	454 (52.5)
Smoking	206 (23.8)
Family history of premature CAD	284 (32.9)
Chest pain	
Asymptomatic	441 (51.0)
Noncardiac	194 (22.5)
Atypical	182 (21.1)
Typical	47 (5.4)
CAD probability - Morise	
Score ≥ 16	78 (9.0)
Score 9-15	446 (51.6)
Score 0-8	340 (39.4)
CAD probability - modified Diamond Forrester	
Very Low	188 (21.8)
Low	391 (45.3)
Intermediate	257 (29.7)
High	27 (3.1)
CV risk	
HeartScore ≥5%	103 (11.9)
CCTA	
Normal / no plaque	737 (87.3)
Non obstructive CAD	93 (10.8)
Obstructive CAD	14 (1.6)
Technical data	
Heart rate (bpm)	67.8 ± 12.9
Contrast dose (ml)	96.2 ± 13.6
Radiation dose – CTA (mSv)	4.6 ± 3.8
Radiation dose – CaSc (mSv)	0.8 ± 0.5

Values are mean ± SD or n (%);BMI – body mass index; CAD – coronary artery disease; CV – cardiovascular; CCTA – Coronary Computed

Table 2: Univariate analysis.

	No CAD (n=757)	CAD (n=107)	p
Demographic			
Age ≥55 years	355 (47.0)	68 (63.6)	**0.001**
Male gender	335 (44.3)	54 (50.5)	0.254
Risk factors			
Diabetes	64 (8.5)	14 (13.1)	0.147
Obesity (BMI ≥30)	139 (18.4)	21 (19.6)	0.790
Hypertension	387 (51.1)	72 (67.3)	**0.002**
Dyslipidemia	385 (50.9)	69 (64.5)	**0.010**
Smoking	184 (24.3)	22 (20.6)	0.467
Family history of premature CAD	248 (32.8)	36 (33.6)	0.913
Symptoms			
Chest pain	371 (49.0)	52 (48.6)	1.000
CAD probability - Morise			
Score ≥ 16	62 (8.2)	16 (15.0)	**0.002**
Score 9-15	382 (50.5)	64 (59.8)	
Score 0-8	313 (41.3)	27 (25.2)	
CAD probability - modified Diamond Forrester			
Very Low	171 (22.6%)	17 (15.9)	**0.005**
Low	342 (45.2)	49 (45.8)	
Intermediate	225 (29.8)	32 (29.9)	
High	18 (2.4)	9 (8.4)	
CV risk			
Heart Score ≥ 5	79 (10.4)	24 (22.4)	**0.001**

Values are mean ± SD or n (%); CAD – coronary artery disease; BMI – body mass index; CV – cardiovascular

Table 3: Multivariate analysis.

Independent predictors of CAD			
	OR	**CI (95%)**	**p**
Age ≥55	**1.631**	**1.054-2.524**	**0.028**
Hypertension	**1.641**	**1.051-2.560**	**0.029**
Dyslipidemia	**1.538**	**1.002-2.361**	**0.049**

OR – odds ratio; CI – confidence interval

21

FIGURE LEGENDS

Figure 1: Patient selection and study design

Figure 2: Distribution of CT angiographic findings

Figure 3: Independent predictors of CAD in patients with a CaSc of zero

Figure 4: Non-calcified plaque on cardiac CT (on the right) in a patient with a CaSc of zero; the angiography (on the left) confirmed the presence of a 50-70% stenosis in the mid-RCA; intravascular ultrasound with virtual histology (in the middle) suggests the presence of microcalcifications.

Figure 1
Click here to download Figure: figure1.ppt

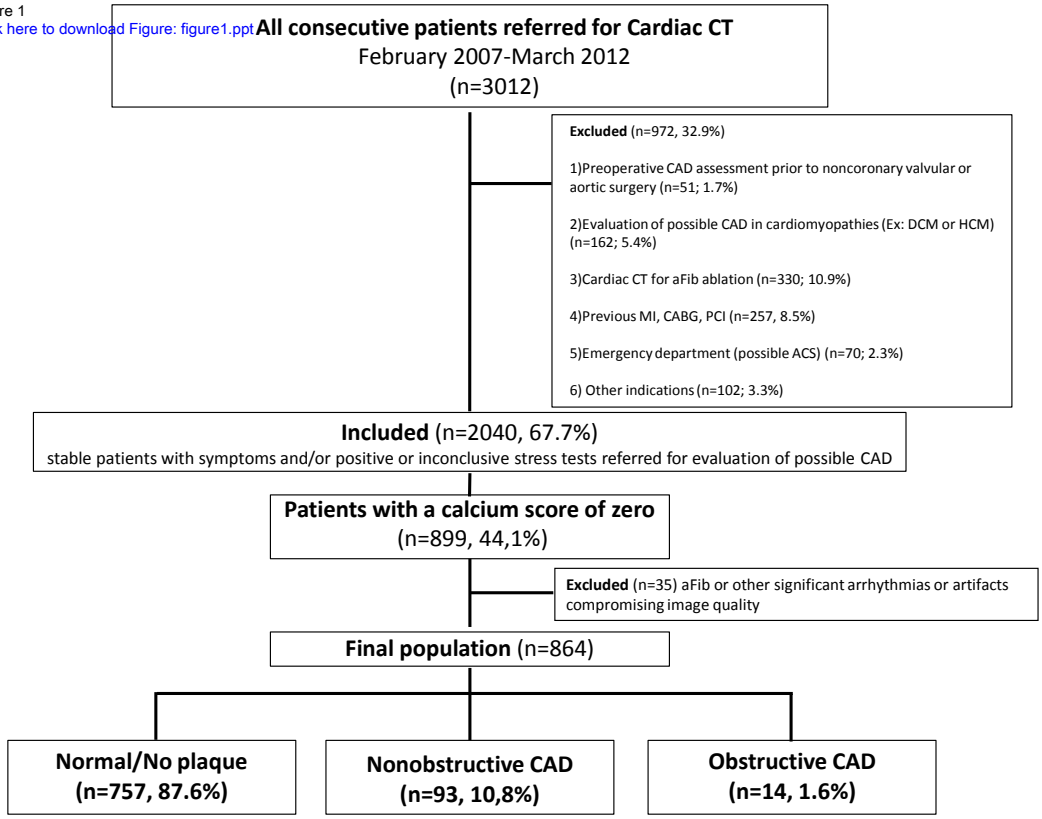


Figure 2
Click here to download Figure: Figure2.ppt

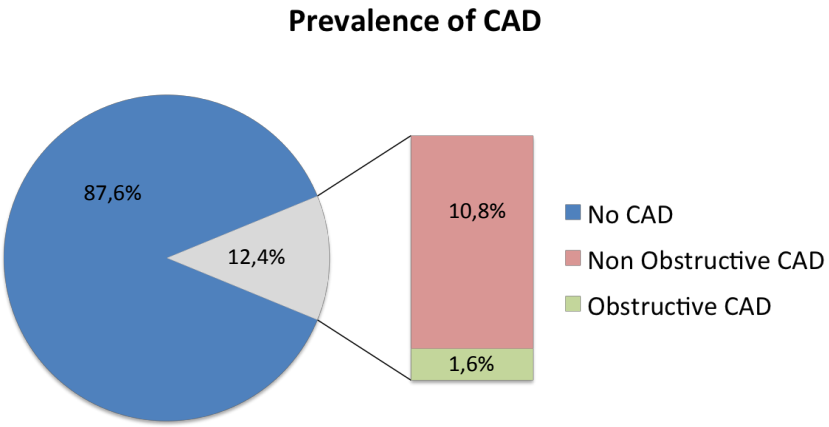


Figure 3
Click here to download Figure: figure3.ppt

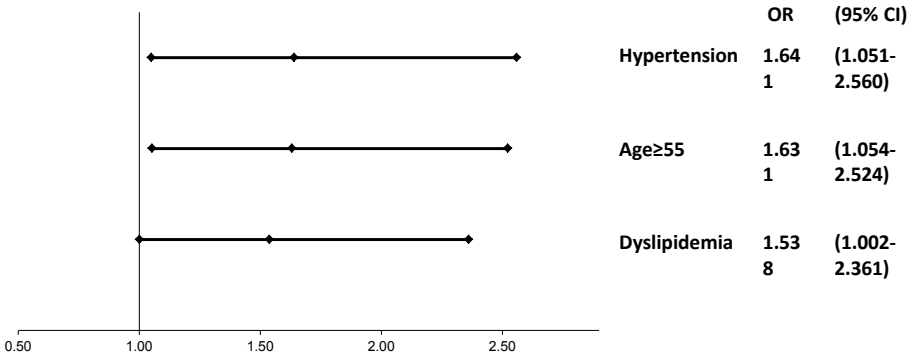
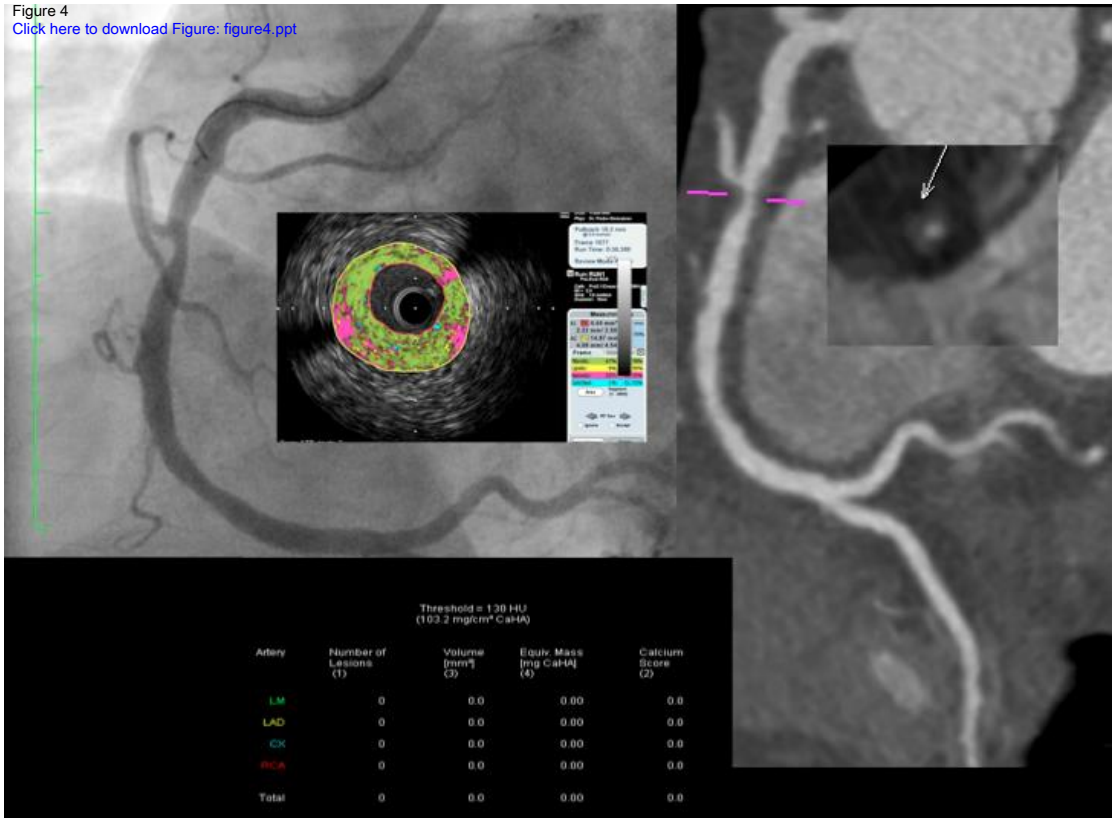


Figure 4
Click here to download Figure: figure4.ppt



Capitulo 5.

Angio TC cardíaca – aspectos técnicos

RESUMO:

Neste capitulo é feita uma revisão de alguns aspectos técnicos da angio TC, nomeadamente da resolução espacial e temporal, da cobertura craneo-caudal e da dose de radiação, cuja evolução nos últimos anos tem contribuído para uma melhoria significativa da qualidade dos exames. É dado particular destaque à dose de radiação empregue e às diferentes estratégias e protocolos desenvolvidos para a reduzir, aspecto essencial para a sua adopção na prática clínica e influenciando o seu posicionamento no algoritmo de avaliação da doença coronária.

Estão incluídos neste capitulo dois artigos que abordam a questão da radiação em angio TC. No **artigo 13** é feita uma avaliação dos preditores de maior dose utilizada e a sua progressiva redução ao longo do tempo, dependente em larga medida da implementação de novos protocolos de aquisição. No **artigo 14**, a dose de radiação da angio TC é comparada com a dos outros exames usados para estudo da doença coronária que usam radiação ionizante. Neste estudo que incluíu mais de 6000 exames, a angio TC cardíaca foi o exame com a dose média mais baixa, seguida da coronariografia invasiva, que por sua vez foi mais baixa que a da cintigrafia de perfusão miocárdica.

ABSTRACT:

In this chapter, some technical issues related to cardiac CT are described, like spatial and temporal resolution, volume coverage and radiation dose, whose recent advancements have lead to significant improvements in image quality. The issue of radiation dose and the different available strategies to reduce it are discussed in more detail, since this influences its clinical use and the positioning of cardiac CT in the coronary artery disease evaluation algorithm.

Two manuscripts are included in this chapter, both related to the issue of cardiac CT radiation dose. In **manuscript 13**, the predictors of higher dose are described, as well as its reduction over time, largely dependent of the adoption of new acquisition protocols. In **manuscript 14**, a comparison of the radiation dose of three diagnostic tests is provided. In this study, including more than 6000 exams, cardiac CT was associated with a mean lower dose than invasive coronary angiography, which, in turn, was lower than that of single-photon emission computed tomography.

ARTIGO 13/ MANUSCRIPT 13:

RADIAÇÃO NA ANGIOTC CARDÍACA: PREDITORES DE MAIOR DOSE UTILIZADA E SUA REDUÇÃO AO LONGO DO TEMPO.

P. Sousa, P. Araújo Gonçalves, H. Marques, L. Raposo, R. Cale, J. Brito, A. Gaspar, F. Machado, J. Roquette.

Rev Port Cardiol. 2010, 29 (11): 1655-65.

ARTIGO 14/ MANUSCRIPT 14:

RADIATION DOSE OF 3 DIAGNOSTIC TESTS: SINGLE-PHOTON EMISSION COMPUTED TOMOGRAPHY, INVASIVE CORONARY ANGIOGRAPHY AND CARDIAC COMPUTED TOMOGRAPHY

Araújo Gonçalves P, Jerónimo Sousa P, Cale R, Marques H, Santos MB, Dias A, Dores H, Carvalho MS, Ventosa A, Martins T, Teles R, Almeida M, Mendes M.

Rev Port Cardiol 2013; aceite para publicação (REPC-D-13-00036).

SUMÁRIO DO CAPÍTULO 5:

5.1 Introdução

Nos últimos anos, tem-se assistido a impressionante evolução na tecnologia da TC multidetectores com progressivas melhorias na resolução espacial, temporal e de cobertura craneo-caudal que vieram permitir a avaliação não invasiva das artérias coronárias e tornar a angio TC cardíaca uma ferramenta importante na prática clínica diária.
De seguida são revistos alguns aspectos técnicos da angio TC cardíaca, com especial ênfase na dose de radiação e nas estratégias desenvolvidas para a sua redução.

5.2 Resolução espacial, temporal e cobertura craneo-caudal

A primeira geração de aparelhos de TC multidetectores que possibilitava a avaliação das artérias coronárias foi introduzida no ano 2000 e eram aparelhos de 4-cortes (1). Estes aparelhos, apesar de inaugurarem uma nova era de avaliação coronária não invasiva, apresentavam ainda marcadas limitações de resolução temporal e espacial, que vieram a ser posteriormente minimizadas com o desenvolvimento de aparelhos de 16 e 64 cortes, sendo estes últimos considerados actualmente como o requisito ideal mínimo para a realização de exames de angio TC cardíaca (2).

A ***resolução espacial*** dos primeiros aparelhos, intimamente relacionada com a colimação dos cortes, variava entre 1 a 4mm, tendo melhorado para 0.5 a 0.75mm com a introdução dos aparelhos de 16 e 64 detectores. Desde essa altura, não tem havido melhoria significativa neste parâmetro, sendo uma das importantes limitações desta técnica, dificultando a avaliação de segmentos de pequeno calibre, bem como a avaliação na presença de importante calcificação e de artefactos metálicos, como os provocados na presença de stents.
A resolução actualmente possível impõe igualmente limitações à avaliação detalhada das placas ateroscleróticas, nomeadamente quando comparada com a resolução das modalidades de imagem intracoronária – 200 a 250 μm para a IVUS e 10-15 μm para a OCT (3). Este é um aspecto técnica a ter em consideração no que diz respeito à possibilidade de avaliação das características de potencial instabilidade das placas por TC, em face das limitações já apresentadas pelas técnicas intracoronárias de muito mais elevada resolução espacial (4).

A ***resolução temporal*** é igualmente um aspecto técnico importante na TC multidetectores quando aplicada a estruturas em movimento como é o caso do coração. Esta é função do tempo que demora a adquirir uma imagem, que por sua vez é função da velocidade de rotação da gantry. Para formação de uma imagem de TC, torna-se necessária a aquisição de raios-X em 180 graus, ou seja, em meia rotação da *gantry*. Assim, nos aparelhos de 1ª geração com 4 cortes, como a

gantry demorava 500 ms a dar uma volta completa, a resolução temporal era de 250 ms (meia volta para aquisição de 1 imagem). O desenvolvimento dos aparelhos de 16 e mais tarde de 64 cortes acompanhou-se de uma redução do tempo de rotação e assim uma melhoria da resolução temporal. Para um aparelho de 64 cortes com um tempo de rotação de 330 ms, a resolução temporal correspondente é de 165ms.

A resolução temporal tem importantes implicações na qualidade dos exames, uma vez que quanto mais rápida for a aquisição menor é o tempo necessário de apneia e assim minimiza o risco de artefactos relacionados com a respiração. Por outro lado, a melhoria da resolução temporal permitiu aumentar o ritmo de administração do contraste sem aumentar muito a dose total (a aquisição dura menos ciclos cardíacos) e assim melhorar a qualidade do exame (melhor contraste entre o lúmen e a parede do vaso e restantes tecidos.

A resolução temporal tem ainda importantes implicações na dependência de uma frequência cardíaca baixa durante a aquisição e assim da necessidade de administração de beta-bloquentes previa à realização do exame. Nos actuais aparelhos de 64 cortes, o número de batimentos cardíacos necessário para completar a aquisição cardíaca baixou dos iniciais 20 a 30m batimentos (com os aparelhos de 4 cortes) para 4 a 8 batimentos. Com o desenvolvimento mais recente de ***aparelhos de dupla ampola***, associados a uma rotação da *gantry* de 330 ms foi possível reduzir a resolução temporal para 82,5ms, uma vez que as imagens são obtidas por integração da informação obtida das 2 ampola (separadas 90º) bastando assim apenas ¼ de rotação para se obter uma imagem (330ms/4) elevando a uma menor dependência da frequência cardíaca na qualidade dos exames e permitindo inclusive a avaliação de doentes com arritmias (5).

Mais recentemente, os aparelhos de dupla ampola que na 1ª geração tinham 2 conjuntos de 64 detectores (2x 64) evoluíram na 2ª geração para 2x128 cortes e com ainda menor tempo de rotação da *gantry* (280ms) melhorando a resolução temporal para 75 ms (280ms/4). Com estes aparelhos de ultima geração foi possível desenvolver protocolos de aquisição de *pitch* elevado e assim aquisição simultânea de todo o exame num único ciclo cardíaco e com uma impressionante redução na dose de radiação (6-8).

Outro aspecto técnico importante na angio TC prende-se com a ***cobertura craneo-caudal,*** que depende directamente do número de detectores. A largura de um detector varia entre 0,5 a 0,6mm e assim os aparelhos de 64 cortes adquirem em cada rotação 3,2cm do volume total. Com o desenvolvimento de aparelhos de 320 cortes, foi possível uma cobertura craneo-caudal de 16cm (0,5mm x 320=160mm) e assim possibilitar a aquisição cardíaca total numa única rotação da ampola e num único ciclo cardíaco. Estes aparelhos eliminaram os artefactos de escada e levaram a importantes reduções na dose de contraste, pelo menor tempo de aquisição, e de radiação, uma vez que deixa de haver sobreposição de detectores (9, 10). Mais importante ainda, uma vez que a distribuição do contraste é uniforme na totalidade do volume cardíaco adquirido,

estes aparelhos vieram abrir um novo campo de possibilidades na avaliação da perfusão do miocárdio e na realização de protocolos de isquémia (11).

5.3 Dose de radiação e estratégias para sua redução

Uma das limitações da angio TC cardíaca está relacionada com o uso de radiação ionizante e o seu risco para a saúde resultante dos seus efeitos determinísticos e estocásticos. Os efeitos determinísticos resultam da exposição a doses elevadas e num curto período de tempo, originando lesão celular directa, sendo incomuns verificar-se no contexto de imagem médica. Os efeitos estocásticos são neste contexto mais importantes, pelo potencial de indução de mutações no DNA e consequentemente do desenvolvimento posterior de neoplasias. A relação entre a radiação ionizante e o risco de desenvolvimento de neoplasias foi bem documentada nos acidentes nucleares, tendo sido depois feita uma extrapolação linear das doses elevadas registadas nesses acidentes para as doses habitualmente empregues nos exames médicos. A proporção estimada é de que o risco de morte por neoplasia aumenta 0,5% por uma exposição a 100mSv (12). Não havendo dados observacionais com doses inferiores a 100mSv tem sido assumida a teoria "*linear no threshold*", que é deliberadamente conservadora e defende que não havendo prova em contrario, qualquer exposição a radiação ionizante aumenta o risco de desenvolvimento de uma neoplasia mantendo a mesma proporção nas doses baixas. Este é o modelo sobre o qual é defendido o principio de ALARA – "*As low as reasonably achievable*" que deve orientar o uso de radiação ionizante em medicina (13, 14).

A melhoria na qualidade dos exames com o desenvolvimento dos aparelho de 16 e 64 cortes foi acompanhada de uma aumento significativo na dose de radiação empregue pela angio TC cardíaca que chegou a 20 mSv. Varias estratégias foram desenvolvidas para redução da dose de radiação na angio TC cardíaca, nomeadamente a correcta limitação da janela de aquisição, a modulação da dose pelo ECG e o uso de uma reduzida kilovoltagem (100Kv) em indivíduos não obesos, aspectos que levaram a uma redução significativa da dose empregue neste exames (15).

Em 2009 foram publicados os resultados do registo multinacional e multicêntrico PROTECTION I (*Prospective Multicenter Study On Radiation Dose Estimates Of Cardiac CT Angiography in Daily Practice*) no qual a dose média de radiação foi de 12 mSv, reflexo já da implementação de algumas destas estratégias de redução da dose (16).

Em 2010 publicamos um trabalho em que foi avaliada a evolução temporal da dose de radiação, tendo sido possível demonstrar uma redução significativa da dose ao longo do tempo com a progressiva implementação de novos protocolos, nomeadamente com o uso de uma reduzida kilovoltagem da ampola (17). Nesta trabalho, a dose média foi de 6,6 mSv e foi possível identificar os preditores associados a uma elevada dose de radiação que foram: um IMC>32 kg/m2, o uso de 120 Kv (pela impossibilidade de se adquirir o exame com 100 Kv nos indivíduos obesos); antecedentes de cirurgia cardíaca (pela necessidade de irradiar todo o tórax para

inclusão das pontagens); presença de ritmo de fibrilhação auricular (uma vez que impossibilita o correcto *gating* cardíaco).

Mais recentemente foram desenvolvidas estratégias adicionais que contribuíram para reduzir ainda mais a dose de radiação, sendo um exemplo disto a aquisição prospectiva ou adaptativa, conduzindo a doses médias de 2-3 mSv (18) e a aquisição com *high-pitch* nos aparelhos topo de gama de dupla ampola (128x2) com doses inferiores a 1mSv (6), sem que estas redução da dose leve a uma compromisso da qualidade da imagem.

Actualmente, as doses médias empregues pela angio TC cardíaca são inferiores às dos outros exames em cardiologia que empregam radiação ionizante, nomeadamente a cintigrafia de perfusão miocárdica (dose 10-15 mSv) e a coronariografia por cateterismo cardíaco (dose 7 mSv) (12, 19, 20).

Num outro trabalho em que comparamos a dose de radiação deste 3 exames numa população de 6196 doentes consecutivos avaliados durante 2 anos, a dose mais baixa foi a da angio TC cardíaca (5,4 mSv), seguida da coronariografia por cateterismo cardíaco (8,1 mSv), que por sua vez foi mais baixa do que a da cintigrafia de perfusão miocárdio (10,7 mSv) (21). Neste trabalho, foi ainda possível verificar uma redução na dose de radiação ao longo do tempo (resultado da adopção de novos protocolos) e uma subida da dose da coronariografia (resultante sobretudo do uso crescente do acesso radial), não havendo modificação significativa nos exames de cintigrafia ao longo do tempo. Em todos os exames, a obesidade associou-se a uma dose de radiação significativamente mais alta em todos os exames, sendo a subida mais evidente na angio TC cardíaca.

Por fim, os softwares de reconstrução iterativa recentemente desenvolvidos poderão ainda levar a uma redução adicional da dose, tendo muito recentemente sido descritos protocolos com doses mesmo inferiores a 0,1mSv (22). Caso se venha a confirmar ser possível a aplicação clínica destes protocolos com doses que se aproximam das usadas num simples RX de tórax, sem compromisso da qualidade dos exames, poderá ter implicações no posicionamento da angio TC cardíaca na avaliação da DC, nomeadamente na estratificação do risco CV em doentes assintomáticos.

5.4 BIBLIOGRAFIA

1. Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Giesler T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. Circulation. 2000 Dec 5;102(23):2823-8.

2. Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2009 May-Jun;3(3):190-204.

3. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J. 2012 Oct;33(20):2513-20.

4. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35.

5. Flohr TG, McCollough CH, Bruder H, Petersilka M, Gruber K, Suss C, et al. First performance evaluation of a dual-source CT (DSCT) system. Eur Radiol. 2006 Feb;16(2):256-68.

6. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.

7. Alkadhi H, Stolzmann P, Desbiolles L, Baumueller S, Goetti R, Plass A, et al. Low-dose, 128-slice, dual-source CT coronary angiography: accuracy and radiation dose of the high-pitch and the step-and-shoot mode. Heart. 2010 Jun;96(12):933-8.

8. Achenbach S, Goroll T, Seltmann M, Pflederer T, Anders K, Ropers D, et al. Detection of coronary artery stenoses by low-dose, prospectively ECG-triggered, high-pitch spiral coronary CT angiography. JACC Cardiovasc Imaging. 2011 Apr;4(4):328-37.

9. Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dubel HP, Schlattmann P, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. Circulation. 2009 Sep 8;120(10):867-75.

10. de Graaf FR, Schuijf JD, van Velzen JE, Kroft LJ, de Roos A, Reiber JH, et al. Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease. Eur Heart J. 2010 Aug;31(15):1908-15.

11. George RT, Arbab-Zadeh A, Cerci RJ, Vavere AL, Kitagawa K, Dewey M, et al. Diagnostic performance of combined noninvasive coronary angiography and myocardial perfusion imaging using 320-MDCT: the CT angiography and perfusion methods of the CORE320 multicenter multinational diagnostic study. AJR Am J Roentgenol. 2011 Oct;197(4):829-37.

12. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation. 2009 Feb 24;119(7):1056-65.

13. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23.

14. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol. 2012 Feb 7;59(6):553-65.

15. Hausleiter J, Meyer T, Hadamitzky M, Huber E, Zankl M, Martinoff S, et al. Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. Circulation. 2006 Mar 14;113(10):1305-10.

16. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA. 2009 Feb 4;301(5):500-7.

17. Sousa PJ, Goncalves PA, Marques H, Raposo L, Cale R, Brito J, et al. Radiation in cardiac CT: predictors of higher dose and its reduction over time. Rev Port Cardiol. 2010 Nov;29(11):1655-65.

18. Hausleiter J, Meyer TS, Martuscelli E, Spagnolo P, Yamamoto H, Carrascosa P, et al. Image quality and radiation exposure with prospectively ECG-triggered axial scanning for coronary CT angiography: the multicenter, multivendor, randomized PROTECTION-III study. JACC Cardiovasc Imaging. 2012 May;5(5):484-93.
19. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med. 2009 Aug 27;361(9):849-57.
20. Kaufmann PA, Knuuti J. Ionizing radiation risks of cardiac imaging: estimates of the immeasurable. Eur Heart J. 2011 Feb;32(3):269-71.
21. de Araújo Gonçalves P, Jerónimo Sousa P, Calé R, Marques H, Dias A, Dores H, et al. Radiation effective dose of three diagnostic tests in Cardiology: Single-Photon Emission Computed Tomography, Invasive Coronary Angiography and Cardiac Computed Tomography Angiography. Rev Port Cardiol. 2013.
22. Schuhbaeck A, Achenbach S, Layritz C, Eisentopf J, Hecker F, Pflederer T, et al. Image quality of ultra-low radiation exposure coronary CT angiography with an effective dose <0.1 mSv using high-pitch spiral acquisition and raw data-based iterative reconstruction. Eur Radiol. 2013 Mar;23(3):597-606.

5.5 ARTIGO 13/ MANUSCRIPT 13:

ARTIGOS ORIGINAIS

Radiação na AngioTC cardíaca: preditores de maior dose utilizada e sua redução ao longo do tempo [115]

PEDRO JERÓNIMO SOUSA[1], PEDRO ARAÚJO GONÇALVES[1], HUGO MARQUES[2], LUÍS RAPOSO[1], RITA CALÉ[1], JOÃO BRITO[1], AUGUSTO GASPAR[2], FRANCISCO PEREIRA MACHADO[11], JOSÉ ROQUETTE[1]

[1] Centro Cardiovascular, Hospital da Luz, Lisboa, Portugal
[2] Centro de Imagiologia, Hospital da Luz, Lisboa, Portugal

Rev Port Cardiol 2010; 29 (11): 1655-1665

RESUMO

A tomografia computorizada cardíaca é um método não invasivo de obter informação da anatomia cardíaca, permitindo avaliar a doença coronária. No entanto, uma das limitações que tem vindo a ser apontada a este exame é a utilização de radiação. O objectivo deste trabalho foi avaliar a variação da dose de radiação ao longo do tempo e identificar variáveis que se associassem ao seu aumento.

Foi analisado um registo prospectivo de 643 doentes submetidos a TC cardíaca com 64 cortes e dupla ampola (Dual source CT - Somaton Definition®, Siemens-medical) durante os anos de 2007 e 2008.

A amostra foi dividida em quartis, segundo a ordem cronológica de realização dos exames. Verificou-se uma redução progressiva da mediana da dose de radiação ao longo dos quartis analisados [Q1: 8,9 (5,9-14,1), Q2: 6,6 (5,5-10,7), Q3: 6,4 (5,3-8,7), Q4: 6,1 (5,2-7,9)], significativa quando o primeiro quartil foi comparado com os restantes (p<0,05). Paralelamente a este decréscimo, verificou-se uma utilização progressivamente maior de uma voltagem da ampola de 100Kv (p<0,001). Os predictores

Radiation in cardiac CT: predictors of higher dose and its reduction over time

ABSTRACT

Introduction: Cardiac CT provides noninvasive information on cardiac anatomy, particularly in coronary artery disease. However, exposure to radiation has been identified as a limitation of this exam. The aim of this study was to evaluate variations in radiation dose over time and to identify variables associated with use of higher radiation doses.

Methods: A prospective registry of 643 patients who underwent 64-slice dual source cardiac CT scan (Dual souce CT - Somaton Definition®, Siemens-Medical) during 2007 and 2008 was analyzed.

Results: The sample was divided into quartiles according to the chronological order of the exams. There was a progressive reduction in median radiation dose in the quartiles analyzed (Q1: 8.9 [5.9-14.1], Q2: 6.6 [5.5-10.7], Q3: 6.4 [5.3-8.7], Q4: 6.1 [5.2-7.9] mSv), significant when the first quartile was compared with the others

Recebido para publicação: Março de 2010 • Aceite para publicação: Julho de 2010
Received for publication: March 2010 • Accepted for publication: July 2010

Rev Port Cardiol
Vol. 29 Novembro 10 / November 10

de uma dose de radiação alta foram: IMC>32, cirurgia cardíaca prévia, presença de fibrilhação auricular na aquisição, maior tempo de aquisição e o uso 120 kV como voltagem da ampola. Quando pelo menos uma destas características estava presente (um terço da população), a dose de radiação foi significativamente superior [12,1 (9,5-14,8) *versus* 5,7 (5,0-6,7) mSv. p<0,001].

Palavras Chave:
AngioTC Cardíaco; Radiação

(p<0.05). Along with this reduction, there was a progressive increase in the use of a tube voltage of 100 kV (p<0.001). Predictors of a higher radiation dose were higher body mass index, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV. When one or more of these variables were present (one third of the population), the radiation dose was significant higher (12.1 [9.5-14.8] vs. 5.7 [5.0-6.7] mSv, p<0.001).

Key words
Cardiac CT; Radiation

INTRODUÇÃO

A coronariografia invasiva é considerada o *gold standard* para o diagnóstico de doença coronária. Contudo, exames não invasivos, tais como a prova de esforço, a cintigrafia de perfusão miocárdica, o ecocardiograma de sobrecarga, a tomografia computorizada e a ressonância magnética nuclear cardíaca são uma alternativa na avaliação da anatomia e fisiologia cardíacas.

Nas três últimas décadas, a tomografia computorizada (TC) tem demonstrado um papel importante na avaliação diagnóstica. A era moderna da angiotomografia computorizada cardíaca (AngioTC cardíaca) iniciou-se aproximadamente em 1997, com a introdução na prática clínica dos sistemas helicoidais de corte único[1]. Com as gerações sucessivas de aparelhos de TC, até aos sistemas de 64 cortes, verificou-se uma melhoria progressiva da resolução espacial e temporal, bem como uma diminuição importante do tempo de aquisição. Assim, desde 2004, com a introdução da TC de 64 cortes na prática clínica, a coronariografia não invasiva por TC cardíaca tem despertado interesse particular, nomeadamente pela sua utilidade na exclusão da presença de doença coronária, fruto do seu elevado valor preditivo negativo[2] (*Figura 1*).

INTRODUCTION

Invasive coronary angiography is considered the gold standard for diagnosis of coronary artery disease. However, noninvasive exams such as exercise testing, myocardial perfusion scintigraphy, stress echocardiography, computed tomography (CT) and cardiac magnetic resonance imaging are alternative methods of assessing cardiac anatomy and physiology.

Over the last thirty years, CT has come to play an important role in diagnostic evaluation. The modern era of CT angiography began around 1997 with the introduction into clinical practice of single-slice spiral systems[1]. The development of new generations of CT scanners led to progressive improvements in spatial and temporal resolution and significant reductions in acquisition time. Since the introduction of 64-slice systems in 2004, noninvasive coronary CT angiography has aroused particular interest for its ability to exclude the presence of coronary artery disease due to its high negative predictive value[2] (*Figure 1*).

In parallel with these technological advances, the radiation doses used to acquire CT images has increased in the most recent systems, with exposure rising from 5-8 mSv (four-slice) to 15-20 mSv (64-slice)[3]. However, it is hoped that the better image quality of the

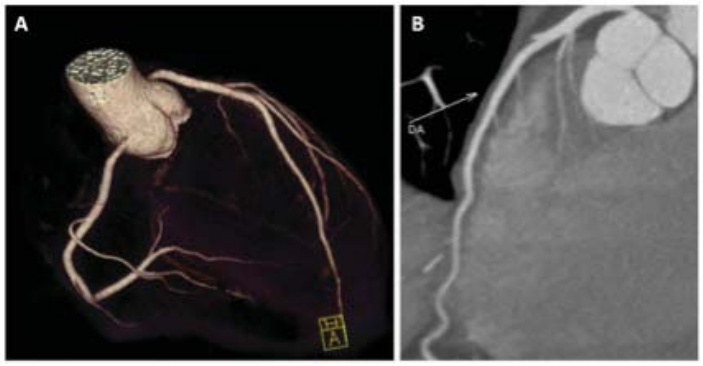


Figura 1. Coronariografia virtual (A) e reconstrução multiplantar (B) em exame com boa qualidade de imagem documentando coronárias sem placas significativas

Figure 1. Virtual coronary angiography (A) and multiplane reconstruction (B) in good-quality cardiac CT images showing coronaries without significant plaques

Paralelamente a esta evolução tecnológica, a dose de radiação utilizada na aquisição de imagens de TC tem vindo a aumentar com os aparelhos mais recentes. A exposição estimada aumentou de 5-8 mSv (TC de quatro cortes) para 15-20 mSv (TC de 64 cortes)[3]. Com os sistemas de última geração, em particular com os aparelhos de dupla ampola e os de 320 cortes, espera-se que a melhoria da qualidade de imagem seja acompanhada por uma redução da dose de radiação.

Existe igualmente uma grande variabilidade nesta dose entre os vários centros e os vários aparelhos, com medianas de doses de radiação que variam entre 4,9 e 29,1 mSv[4].

No entanto, esta dose de radiação elevada, apontada como uma limitação para esta técnica, pode ser eficazmente reduzida tanto pela optimização dos protocolos de aquisição existentes, como pelo desenvolvimento de novos *softwares* e protocolos.

O objectivo deste trabalho foi avaliar a evolução temporal da dose de radiação na TC cardíaca e identificar variáveis associadas a doses mais elevadas de radiação.

MÉTODOS

Todos os doentes submetidos a TC cardíaca

latest generation scanners, particularly dual-source and 320-slice machines, will be accompanied by a reduction in radiation dose.

There are also considerable variations between different centers and systems, with median radiation doses ranging between 4.9 and 29.1 mSv[4].

This high radiation dose has been identified as a limitation of the technique, but it can be significantly reduced by optimization of existing acquisition protocols and by the development of new software and protocols.

The aim of this study was to evaluate variations in radiation dose in cardiac CT over time and to identify variables associated with use of higher radiation doses.

METHODS

All patients who underwent cardiac CT with a dual-source 64-slice scanner (Somatom Definition® - Siemens Medical Systems) during 2007 and 2008 were enrolled in a prospective single-center registry. This population of 643 patients was divided into quartiles (Q1-Q4) according to the chronological order of the exams, in order to analyze radiation dose over time.

Demographic (age and gender) and clinical

Rev Port Cardiol
Vol. 29 Novembro 10 / November 10

de 64 cortes de dupla ampola (*Somaton Definition® - Siemens Medical*) de 2007 e 2008 foram incluídos num registo prospectivo de centro único. Esta população (643 doentes) foi dividida em quartis, de acordo com a ordem cronológica dos exames, para estudar a dose de radiação ao longo do tempo.

Variáveis demográficas (idade, sexo), clínicas [presença de factores de risco cardiovascular, índice de massa corporal (IMC), cirurgia cardíaca prévia, enfarte de miocárdio prévio e presença de fibrilhação auricular] e de protocolo (tempo de aquisição, dose de contraste, frequência cardíaca e uso de voltagem da ampola de 120 kVs) foram avaliadas de modo a identificar os preditores de uma dose de radiação mais elevada (definida como presente quando superior à mediana da população). As variáveis identificadas como preditores por análise univariada foram combinadas num modelo de regressão logística para apurar os preditores independentes da utilização de elevada dose de radiação.

Procotocolo de aquisição e reconstrução de imagens

Todas as TC cardíacas foram efectuadas com um aparelho de 64 cortes com dupla ampola (*Somatom Definition, Siemens Medical®, Forchheim, Germany*), com o doente em decúbito dorsal e em apneia após inspiração profunda. Foi administrada nitroglicerina sublingual em todos os doentes (salvo contra-indicações). Não foi administrado beta-bloqueante especificamente para a realização do exame.

A voltagem da ampola foi definida para 100 ou 120 kVs, de acordo com o IMC. Utilizou-se modulação por ECG da corrente da ampola, reduzindo-a a 20% nas fases do ciclo cardíaco não utilizadas para avaliação das coronárias. Esta modulação não foi utilizada nos doentes em fibrilhação auricular. O *pitch* – velocidade de movimento da mesa – foi variável com a frequência cardíaca, aspecto regulado automaticamente pelo equipamento dependendo da frequência cardíaca, sendo este ajuste feito automaticamente. Foram reconstruídas imagens transaxiais, sendo a resolução

variables (cardiovascular risk factors, body mass index [BMI], previous cardiac surgery, previous myocardial infarction [MI] and atrial fibrillation) and protocol parameters (acquisition time, contrast dose, heart rate and use of 120-kV tube voltage), were analyzed in order to identify predictors of a higher radiation dose (defined as higher than the median in the population). Variables identified as predictors on univariate analysis were combined in a logistic regression model to determine independent predictors of use of higher radiation doses.

Acquisition protocol and image reconstruction

All scans were performed with a dual-source 64-slice scanner (Somatom Definition, Siemens Medical Systems, Forchheim, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated. No beta-blockers were administered specifically for the exam.

Tube voltage was 100 or 120 kV, depending on BMI. ECG-gated tube current, which reduces current by 20% in phases of the cardiac cycle that are not used for assessment of the coronary arteries, was used except for patients in atrial fibrillation. Pitch was varied according to heart rate, this adjustment being carried out automatically by the equipment. Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplane reconstructions, maximum intensity projection and volume rendering technique.

The contrast medium used was intravenous iodixanol (320 mg/ml – Visipaque®) in a 6 ml/s infusion. The quantity of contrast was calculated according to the following formula: (acquisition time + 6 s delay) x flow (6 ml/s).

Contrast administration was followed by flushing with 50 ml saline (6 ml/s).

Statistical analysis

SPSS version 17.0 was used for the statistical analysis. Continuous variables are pre-

temporal de 83ms, a espessura dos cortes de 0,75mm, com incrementos de 0,4mm. Foi feito o pós-processamento numa consola com o *software Circulation*, sendo utilizadas reconstruções multiplanares (MPR), de projecção de intensidade máxima (MIP) e de volume (VRT).

Foi utilizado meio de contrastre (Iodixanol 320 mg/mL – Visipaque®) endovenoso, a uma infusão de 6 ml/seg. A quantidade de contraste dependeu da duração da aquisição e foi calculada pela seguinte fórmula: (duração da aquisição + *delay* 6 seg) x fluxo (6ml/seg) .

A injecção de contraste foi seguida de um *flush* de 50 mL de soro fisiológico (6 mL/seg).

ANÁLISE ESTATÍSTICA

A análise estatística foi efectuada utilizando a aplicação SPSS Statistics 17,0 para Windows. As variáveis contínuas apresentam-se como mediana (intervalo interquartil) e as categóricas como número (n) ou frequência (%).

Para comparar diferenças entre variáveis contínuas, utilizaram-se os testes não paramétricos de Mann-Whitney ou Kruskal-Wallis e o Chi quadrado foi aplicado para testar diferenças em frequências. A análise multivariada foi efectuada através de um modelo de regressão logística.

Aceitou-se existir diferença significativa quando p<0,05 (duas caudas).

RESULTADOS

Os resultados apresentam-se na Tabela I.

A mediana da idade foi de 59 (52-66) anos, 60% dos indivíduos eram do sexo masculino e o IMC foi de 26 (24-29) kg/m^2. O tempo de aquisição foi de 8 (7-10) segundos, foi administrado 84 (78-96) mL de contraste e a dose de radiação foi de 6,6 (5,4-10,7) mSv. A frequência cardíaca durante a aquisição foi 65 (56-75) bpm, não tendo sido efectuada redução adicional da frequência cardíaca para a aquisição. Não se verificaram diferenças entre os quartis analisados relativamente a estas variáveis.

A mediana da dose de radiação foi de 6,6

sented as medians (interquartile range) and categorical variables as frequencies (n) or percentages (%).

The non-parametric Mann-Whitney or Kruskal-Wallis tests were used to compare continuous variables, and the chi-square test to test differences in frequencies. Multivariate analysis was performed using a logistic regression model.

Differences were taken to be significant when p<0.05 (two-tailed).

RESULTS

The results are presented in Table I.

The patients' median age was 59 (52-66) years, 60% were male and BMI was 26 (24-29) kg/m^2. Acquisition time was 8 (7-10) s, 84 (78-96) ml of contrast was administered and the radiation dose was 6.6 (5.4-10.7) mSv. Heart rate during acquisition was 65 (56-75) bpm, with no additional heart rate lowering being carried out. No differences were observed between quartiles in terms of these variables.

There was a progressive reduction in the median radiation dose over time (Q1: 8.9 [5.9-14.1], Q2: 6.6 [5.5-10.7], Q3: 6.4 [5.3-8.7], Q4: 6.1 [5.2-7.9] mSv). This difference was significant when the first quartile was compared with the others (*Figure 2*).

A tube voltage of 100 kV was used in 78% of the exams. There was a progressive increase in the use of this voltage over time (Q1: 54%, Q2: 79%, Q3: 87%, Q4: 91%; p<0.001) (*Figure 2*).

On univariate analysis, predictors of a higher radiation dose (above the median) were male gender, higher BMI, previous cardiac surgery, previous MI, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV (*Table II*).

On multivariate analysis, predictors of a higher radiation dose were higher BMI, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV (*Table III*).

Patients with one or more of the following:

Rev Port Cardiol
Vol. 29 Novembro 10 / November 10

Tabela I. Resultados da população total e após divisão em quartis das variáveis estudadas

	Total	Q1	Q2	Q3	Q4	p
n	643	161	161	161	160	NS
Idade (anos)	59 (52-66)	58 (52-64)	59 (51-68)	61 (51-67)	59 (52-67)	NS
% sexo masculino	60	69	53	63	56	NS
IMC (kg/m^2)	26 (24-29)	27 (24-29)	26 (24-29)	26 (24-28)	27 (24-29)	NS
FRCV (n)	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	2 (1-3)	0,01
Dose de contraste (mL)	84 (78-96)	84 (78-96)	84 (78-90)	84 (78-96)	84,0 (72-90)	NS
Duração aquisição (seg)	8 (7-10)	8 (7-10)	8 (7-9)	8 (7-10)	8 (6-10)	NS
FC média (bpm)	65 (56-75)	65 (56-75)	64 (54-72)	65 (57-76)	66 (57-76)	NS
Dose de radiação (mSv)	6,6 (5,4-10,7)	8,9 (5.9-14,1)	6,6 (5.5-10,7)	6,4 (5.3-8,7)	6,1 (5,2-7,9)	<0,05
% 100 Kv	78	54	79	87	91	<0,01

FC: frequência cardíaca; FRCV: índice de RFCV; IMC: Índice de massa corporal

Table I. Variables studied for the total study population and divided into quartiles

	Total	Q1	Q2	Q3	Q4	p
n	643	161	161	161	160	NS
Age (years)	59 (52-66)	58 (52-64)	59 (51-68)	61 (51-67)	59 (52-67)	NS
% male	60	69	53	63	56	NS
BMI (kg/m^2)	26 (24-29)	27 (24-29)	26 (24-29)	26 (24-28)	27 (24-29)	NS
CVRF (n)	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)	2 (1-3)	0.01
Contrast dose (ml)	84 (78-96)	84 (78-96)	84 (78-90)	84 (78-96)	84,0 (72-90)	NS
Acquisition time (s)	8 (7-10)	8 (7-10)	8 (7-9)	8 (7-10)	8 (6-10)	NS
Mean HR (bpm)	65 (56-75)	65 (56-75)	64 (54-72)	65 (57-76)	66 (57-76)	NS
Radiation dose (mSv)	6.6 (5.4-10.7)	8,9 (5.9-14.1)	6.6 (5.5-10.7)	6.4 (5.3-8.7)	6.1 (5.2-7.9)	<0.05
% 100 kV tube voltage	78	54	79	87	91	<0.01

BMI: body mass index; CVRF: cardiovascular risk factors; HR: heart rate

(5,4-10,7) mSv e verificou-se uma redução progressiva ao longo do tempo [Q1: 8,9 (5,9-14,1), Q2: 6,6 (5,5-10,7), Q3: 6,4 (5,3-8,7), Q4: 6,1 (5,2-7,9)]. Esta diferença foi significativa quando o primeiro quartil foi comparado com os restantes (*Figura 2*).

Em 78% dos exames utilizou-se uma voltagem da ampola de 100 kVs. Houve um aumento progressivo da selecção desta voltagem com o tempo (Q1: 54%, Q2: 79%, Q3: 87%, Q4: 91%; p<0,001 – *Figura 2*).

Por análise univariada, os preditores de uma dose de radiação alta (acima da mediana) foram: sexo masculino, maior IMC, cirurgia cardíaca prévia, enfarte de miocárdio prévio, ritmo de fibrilhação auricular na aquisição, maior tempo de aquisição ou dose de contraste administrada, menor frequência cardíaca e utilização de uma voltagem da ampola de 120 kV (*Tabela II*).

Por análise multivariada, os preditores de uma dose de radiação alta foram: maior IMC, cirurgia cardíaca prévia, presença de fibrilhação auricular na aquisição, maior tempo de

BMI >32.4 kg/m^2 (the best cutoff to predict high radiation dose), previous cardiac surgery, atrial fibrillation during acquisition or acquisition time >10 s (the best cutoff to predict high radiation dose) made up 38% of the population. Radiation dose was higher in this subgroup than in patients without any of these characteristics (12.1 [9.5-14.8] vs. 5.7 [5.0-6.7] mSv, p<0.001).

DISCUSSION

In this study we set out to identify the factors associated with a higher radiation dose in cardiac CT angiography. The use of a 120-kV tube voltage was a predictor of a higher radiation dose, as was higher BMI, since this meant the voltage could not be reduced. Longer acquisition time and higher contrast dose (which, as it depends on the former, lost its predictive value on multivariate analysis) were also associated with higher radiation dose.

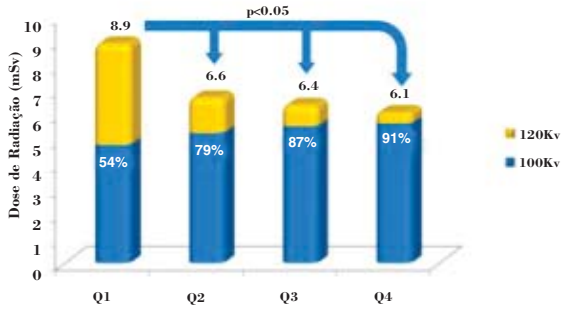


Figura 2. Representação gráfica da evolução da dose de radiação de acordo com os quartis de tempo. A percentagem incluída nas colunas representa a proporção de utilização de 100 kV como voltagem da ampola (*versus* 120 kV)

Figure 2. Chart showing changes in radiation dose by quartiles of time. The percentages in the columns represent the proportion of use 100 kV tube voltage (vs. 120 kV)

Tabela II. Variáveis testadas para preditores de dose de radiação elevada por análise univariada

	Dose de radiação		
	Abaixo da mediana (6,6mSv)	Acima da mediana (6,6mSv)	p
Variáveis demográficas			
Idade (anos)	58 (52-65)	60 (51-68)	0,202
Sexo masculino (%)	50	68	<0,001
Variáveis clínicas			
≥ 1 FRCV (%)	83%	87%	0,
IMC (k²/m²)	26 (24-28)	27 (25-30)	<0,001
Cirurgía cardiaca prévia (%)	1%	11%	<0,001
Enfarte de miocárdio prévio (%)	5%	10%	0,010
FA (%)	0%	11%	<0,001
Variáveis do protocolo			
Tempo de aquisição (seg)	7 (6-8)	9 (7-11)	<0,001
Dose de contraste	78 (72-84)	90 78-102)	<0,001
Frequência cardíaca	68 (60-77)	63 (54-73)	<0,001
Voltagem da ampola120 kV	2%	41%	<0,001

FA: Fibrilhação auricular; FRCV: Factores de Risco Cardiovasculars; IMC: Índice de Massa Corporal;

Table II. Variables tested to identify predictors of higher radiation dose on univariate analysis.

	Radiation dose		
	Below median (6.6mSv)	Above median (6.6mSv)	p
Demographic variables			
Age (years)	58 (52-65)	60 (51-68)	0,202
% male	50	68	<0.001
Clinical variables			
≥ 1 CVRF (%)	83%	87%	0.170
BMI (kg/m²)	26 (24-28)	27 (25-30)	<0.001
Previous cardiac surgery (%)	1%	11%	<0.001
Previous MI (%)	5%	10%	0.010
AF (%)	0%	11%	<0.001
Protocol parameters			
Acquisition time (s)	7 (6-8)	9 (7-11)	<0.001
Contrast dose	78 (72-84)	90 78-102)	<0.001
Heart rate	68 (60-77)	63 (54-73)	<0.001
120 kV tube voltage	2%	41%	<0.001

AF: atrial fibrillation; BMI: body mass index; CVRF: cardiovascular risk factor; MI: myocardial infarction

Rev Port Cardiol
Vol. 29 Novembro 10 / November 10

aquisição e o uso 120 kV como voltagem da ampola (*Tabela III*).

Doentes com pelo menos uma das seguintes variáveis de: IMC >32,4 kg/m² (melhor limiar para discriminar radiação alta), cirurgia cardíaca prévia, aquisição em fibrilhação auricular ou duração da aquisição >10s (melhor limiar para discriminar radiação alta) constituíram 38% da população. Neste subgrupo, a dose de radiação foi superior, quando comparados com a ausência de todas estas características [12,1 (9,5-14,8) *versus* 5,7 (5,0-6,7), p<0,001].

DISCUSSÃO

Neste trabalho procurámos identificar os factores associados a uma dose de radiação superior, na AngioTC cardíaca. A utilização de uma voltagem da ampola de 120 kV foi um preditor de maior dose de radiação. Em concordância com este achado, um elevado IMC, pela impossibilidade de se reduzir a voltagem da ampola, associou-se a uma maior dose de radiação. Um maior tempo de aquisição e maior dose de contraste (que, dependendo da anterior, perdeu o valor preditor por análise multivariada) associaram-se igualmente a uma dose de radiação superior.

O tempo de aquisição maior aumenta a dose de radiação, por traduzir uma maior área corporal adquirida ou por estarmos na presença de frequências cardíacas mais lentas, aumentando o tempo de diástole e a duração da aquisição nesta fase do ciclo cardíaco. A frequência cardíaca baixa, quando analisada isoladamente, também foi um preditor de maior dose de radiação. Igualmente, a presença de cirurgia cardíaca prévia, associou-se a uma maior dose de radiação. Isto resulta de uma maior prevalência de doentes com revascularização miocárdica cirúrgica, o que aumenta a janela de aquisição, para incluir as pontagens. Já a presença de enfarte de miocárdio prévio, que também foi preditor de maior dose de radiação, perdeu este valor na análise multivariada, possivelmente pelo efeito de incluir neste grupo doentes com

Longer acquisition time increases radiation dose and may reflect a larger body surface area scanned or lower heart rate causing prolonged diastole and hence acquisition time. Low heart rate, when analyzed in isolation, also predicted higher radiation dose, as did previous cardiac surgery (due to the high proportion of patients with previous CABG who required a longer acquisition window in order to include the grafts). Previous MI, which was a predictor of higher radiation dose on univariate analysis, lost its predictive value on multivariate analysis, possibly because this group included patients with previous CABG. Finally, atrial fibrillation during acquisition was associated with higher radiation dose, since it prevented ECG pulsing (see below).

Other studies have likewise found that greater body weight and absence of a stable sinus rhythm are associated with higher radiation doses [4].

After excluding the main predictors of higher radiation dose (BMI >32.4 kg/m2, previous cardiac surgery, atrial fibrillation during acquisition, and acquisition time >10 s), a subgroup of two-thirds of the population was identified in whom the radiation dose was significantly lower (5.7 mSv), a reduction of 53%.

As well as identifying the variables associated with higher radiation dose, we found that there was a progressive reduction in radiation dose over time, due to the increasing availability of low-radiation protocols, such as limiting tube voltage to 100 kV, which did not exist when our center began operating. There has also been progressive optimization of acquisition protocols to individual patient characteristics, which also helps reduce radiation dose.

There have been few studies analyzing changes in radiation dose over time. A study by Hausleiter et al. showed that a 12-month increase in experience in cardiac CT angiography was associated with a reduction of 1% in radiation dose [4]. Another, presented by Bettencourt de Sousa et al. at the 2008 Congress of the European Society of Cardiac Radiology, demonstrated an inverse relation-

Tabela III. Preditores independentes de dose de radiação elevada por análise multivariada

Variável	HR	IC (95%)	p
IMC	1,129	1,038-1,229	0,045
Cirurgia cardíaca prévia	5,776	1,042-32,28	0,003
FA	30,874	3,247-293,617	<0,001
Duração da aquisição	1,975	1,672-2,334	<0,001
120 kV	71,394	23,363-218,170	<0,001

FA: Fibrilhação Auricular; HR: *Hazard Ratio*; IC: Intervalos de Confiança; K: Índice de Massa Corporal

Table III. Independent predictors of higher radiation dose on multivariate analysis.

Variable	HR	CI (95%)	p
BMI	1.129	1.038-1.229	0.045
Previous cardiac surgery	5.776	1.042-32.28	0.003
AF	30,874	3.247-293.617	<0.001
Acquisition time	1.975	1.672-2.334	<0.001
120 kV tube voltage	71.394	23.363-218.170	<0.001

AF: atrial fibrillation; BMI: body mass index; CI: confidence interval; HR: hazard ratio

revascularização miocárdica cirúrgica prévia. Finalmente, a presença de fibrilhação auricular na aquisição associou-se a maior dose de radiação administrada por prejudicar a aquisição com "ECG *gating*" (descrito abaixo).

Em concordância com o encontrado, outros estudos verificaram que maior peso e a ausência de um ritmo sinusal estável, se associava a uma maior dose de radiação utilizada[4].

Após exclusão dos principais preditores de elevada dose de radiação (IMC>32,4 kG/m², cirurgia cardíaca prévia, aquisição em fibrilhação auricular, duração da aquisição >10seg), foi identificado um subgrupo, correspondente a 2/3 da população, em que a dose de radiação foi significativamente menor (5,7 mSv, redução de 53%).

Além de apurarmos as variáveis que se associaram a uma dose superior de radiação, verificámos que esta foi sendo progressivamente menor ao longo do tempo. Contribuíu para este efeito o facto de terem surgido uma maior disponibilidade de protocolos de baixa radiação, como a limitação da voltagem da ampola a 100 kV, que não estava presente no início do funcionamento deste centro. Por outro lado, houve uma progressiva optimização dos protocolos de aquisição às características dos doentes, com consequente redução da dose de radiação.

A informação disponível no que respeita à

ship between a center's experience and radiation dose, with a 22% reduction after 1000 exams[5].

Reductions can be achieved by tailoring the acquisition protocol to individual patient characteristics[6]. Firstly, instead of rigidly scanning from carina to diaphragm, the scan range can be adjusted to the patient's anatomy, according to a prior low-dose scan for calcium scoring [4]. This is a simple way to reduce the radiation used, since each 1 cm increase in scan range is associated with an increase of 5% in radiation dose[4]. Secondly, the tube voltage should be reduced to the lowest value that will allow image quality to be maintained for a given patient's anatomic shape and for the equipment used[4]. Reducing tube voltage from 120 to 100 kV considerably reduces radiation dose, since this varies with the square of the tube voltage[7]. In suitable patients (nonobese), this measure can lead to a reduction of 40-46% in radiation dose without compromising image quality[4, 8]. Finally, since cardiac motion is least during diastole, diastolic image reconstructions are most likely to be free of motion artifacts, and so restricting maximum tube current to a predefined time window during diastole and decreasing it during the rest of the cycle (ECG pulsing) can reduce total radiation while maintaining image quality [4, 9, 10]. In the extreme form of this

Rev Port Cardiol
Vol. 29 Novembro 10 / November 10

análise da variação da dose de radiação com a evolução temporal é escassa. Um trabalho de Hausleiter demonstrou que um aumento de 12 meses de experiência na realização de AngioTC cardíaca se associou a uma diminuição da dose de radiação de 1%[4]. Um outro trabalho, apresentado por Bettencourt de Sousa no Congresso da Sociedade Europeia de Radiologia Cardíaca 2008, demonstrou a presença de uma relação inversa entre a experiência do centro e a dose de radiação utilizada (redução de 22% após 1000 exames)[5].

Esta redução na dose de radiação pode conseguir-se ajustando os parâmetros do protocolo de aquisição às características individuais dos doentes[6]. Em primeiro lugar, em vez da aquisição de imagens se estender sistematicamente da carina ao diafragma, esta deve ser ajustada de acordo com a anatomia de cada doente, de acordo com uma primeira passagem com baixa dose de radiação para *score* de cálcio[4]. Esta é uma técnica fácil para reduzir a radiação utilizada, já que por cada centímetro a mais na extensão de aquisição de imagens há um aumento de 5% na dose de radiação[4]. Em segundo lugar, a corrente da ampola deve ser reduzida para o valor mais baixo que se espere manter uma boa qualidade de imagem para determinado biótipo de doente e aparelho de AngioTC. Uma redução da voltagem da ampola de 120 kV para 100 kV diminui consideravelmente a dose de radiação, já que esta varia com o quadrado da voltagem[7]. Em doentes apropriados (IMC não elevado) esta medida pode levar a uma redução de 40-46% da dose de radiação sem comprometer a qualidade da imagem[4,8]. Finalmente, tendo em conta que o movimento cardíaco é menor durante a diástole, as reconstruções de imagem efectuadas nesta fase serão, com maior probabilidade, livres de artefactos de movimento. Assim, limitando a corrente máxima da ampola a uma porção pré-definida da diástole e diminuindo-a no restante ciclo cardíaco, pode diminuir-se a radiação total utilizada, mantendo a possibilidade de obter imagens de qualidade (técnica denominada "ECG *pulsing*")[4, 9, 10]. Levando este protocolo ao extremo, pode ligar-se ape-

protocol, prospective gating, the X-ray tube is only switched on during part of diastole and is switched off for the rest of the cardiac cycle, resulting in sequential rather than spiral scanning. This protocol requires a stable heart rate below 65 bpm and hence intravenous beta-blockers are often needed [8]. Although it results in a substantial reduction in radiation dose, this technique does not provide functional information such as ventricular or valve function [8, 9]. A combination of 100 kV tube voltage and prospective gating can achieve an impressive reduction of 90% [8].

Although the debate on the use of radiation in imaging studies has focused on cardiac CT angiography, it should be remembered that other common techniques use radiation. In 2006, cardiac CT angiography accounted for only 3% of the collective radiation exposure resulting from medical exams in the US [11]. Considering only cardiological exams, the mean radiation dose in coronary angiography is 7 mSv, while for myocardial perfusion scintigraphy it is 15.7 mSv. The latter exam accounted for 22.1% of radiation exposure resulting from diagnostic exams (cardiac or non-cardiac) in the US [12].

CONCLUSION

In this study of consecutive patients undergoing cardiac CT angiography, independent predictors of higher radiation dose were higher body mass index, previous cardiac surgery, atrial fibrillation during acquisition, longer acquisition time and use of a tube voltage of 120 kV. In two-thirds of the study population, none of these characteristics was present and radiation dose was significantly lower (5.7 mSv). Over time, it has been possible to reduce the radiation dose used in these exams, as a result of the development of new protocols and progressive optimization of existing protocols and by adapting them to individual patient characteristics.

nas a ampola durante parte da diástole e desligá-la no restante ciclo cardíaco com aquisição não helicoidal ("*gating* prospectivo"). Este protocolo requer uma frequência cardíaca estável e inferior a 65 batimentos por minuto, com necessidade frequente da utilização de betabloqueantes endovenosos[9]. Apesar de diminuir bastante a dose de radiação utilizada, não permite obter informação funcional (ex: função ventricular ou valvular)[8, 9]. A combinação da utilização de uma voltagem da ampola de 100 kV e a aquisição prospectiva podem conseguir uma impressionante redução de 90%[8].

Embora o debate sobre o uso de radiação em exames de imagem se tenha centrado na AngioTC cardíaca, deve referir-se que outras técnicas frequentemente utilizadas usam radiação. Em 2006, a AngioTC cardíaca correspondeu apenas a cerca de 3% da dose colectiva de radiação recebida em consequência de exames médicos[11]. Considerando apenas os exames na área da cardiologia, referimos que a dose de radiação usada numa coronariografia 7 mSv e de uma cintigrafia de perfusão miocárdica é de 15,6 mSv. Este último exame foi responsável por 22,1% da exposição de radiação em consequência da realização de exames complementares de diagnóstico (cardíacos ou não cardíacos)[12].

CONCLUSÃO

Nesta análise de doentes consecutivos submetidos a AngioTC cardíaco, foram preditores independentes de maior dose de radiação um elevado índice de massa corporal, antecedentes de cirurgia cardíaca, presença de fibrilhação auricular na aquisição, maior tempo de aquisição e o uso 120 kV como voltagem da ampola. Em 2/3 da nossa população, nenhuma destas características está presente e a dose de radiação é significativamente mais baixa (5,7mSv). Ao longo do tempo tem sido possível diminuir a dose de radiação utilizada nestes exames, resultante do aparecimento de novos protocolos e por uma progressiva optimização dos já disponíveis, adaptando-os às características individuais de cada doente.

Pedido de Separatas para:
Address for Reprints:

Pedro Jerónimo Sousa
Centro Cardiovascular
Hospital da Luz
Av. Lusíada
1500-650 Lisboa
e-mail: p965675551@gmail.com

BIBLIOGRAFIA / REFERENCES

1. Hurlock GS, Higashino H, Mochizuki T. History of cardiac computed tomography: single to 320-detector row multislice computed tomography. Int J Cardiovasc Imaging 2009;25 Suppl 1:31-42

2. Schroeder S., Achenbach S., Bengel F et al. Cardiac computed tomography: indications, applications, limitations, and training requirements. Eur Heart J 2008;29(4), 531-56.

3. Pugliese F, Mollet NR, Hunink MG et al. Diagnostic performance of coronary CT angiography by using different generations of multisection scanners: single-center experience. Radiology 2008;246(2):384-93.

4. Hausleiter J, Meyer T, Hermann F et al. Estimated radiation dose associated with cardiac CT angiography. JAMA 2009;301(5):500-7

5. Bettencourt de Sousa N, Sampaio F, Mateus P et al. Multislice computed tomography coronary angiography – radiation dose is inversely related to experience. European Radiology 2008;18(S3):C74

6. Alkadhi H, Stolzmann P, Scheffel H et al. Radiation dose of cardiac dual-source CT: the effect of tailoring the protocol to patient-specific parameters. Eur J Radiol 2008;68(3):385-91.

7. Hausleiter J, Meyer T, Hadamitzky M et al. Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. Circulation 2006;113(10):1305-10

8. Gopal A, Mao SS, Karlsberg D et al. Radiation reduction with prospective ECG-triggering acquisition using 64-multidetector Computed Tomographic angiography. Int J Cardiovasc Imaging 2009;25(4):405-16

9. Alkadhi H. Radiation dose of cardiac CT - what is the evidence? Eur Radiol 2009;19(6):1311-5.

10. Jakobs TF, Becker CR, Ohnesorge B et al. Multislice helical CT of the heart with retrospective ECG gating: reduction of radiation exposure by ECG-controlled tube current modulation. Eur Radiol 2002;12(5):1081-6.

11. Mettler FA Jr, Thomadsen BR, Bhargavan M et al. Medical radiation exposure in the U.S. in 2006: preliminary results. Health Phys 2008;95(5):502-7.

12. Fazel R, Krumholz HM, Wang Y et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med 2009;361(9):849-57.

ARTIGO 14 *(aceite para publicação)/* **MANUSCRIPT 14** *(accepted for publication)*:

Elsevier Editorial System(tm) for Revista Portuguesa de Cardiologia
Manuscript Draft

Manuscript Number: REPC-D-13-00036R1

Title: Radiation effective dose of three diagnostic tests in Cardiology: Single-Photon Emission Computed Tomography, Invasive Coronary Angiography and Cardiac Computed Tomography Angiography

Article Type: Artigo Original

Keywords: Radiação ionizante; Cintigrafia de perfusão miocárdica; Coronariografia invasiva; Tomografia computorizada cardíaca; Obesidade

Ionizing radiation, Single Photon Emission Computerized Tomography, Invasive Coronary Angiography, and Cardiac Computed Tomography; Obesity

Corresponding Author: Dr. Pedro de Araújo Gonçalves,

Corresponding Author's Institution:

First Author: Pedro de Araújo Gonçalves

Order of Authors: Pedro de Araújo Gonçalves; Pedro Jerónimo Sousa, MD; Rita Calé, MD; Hugo Marques, MD; André Dias, MD; Helder Dores, MD; Maria Salomé Carvalho, MD; Miguel Borges Santos, MD; António Ventosa, MD; Teresa Martins, MD; Rui Campante Teles, MD; Manuel Sousa Almeida, MD; Miguel Mendes, MD

Abstract: Introdução
Os exames diagnósticos que usam radiação ionizante têm um papel central na Cardiologia e a par do seu uso crescente, tem aumentado a preocupação pelos seus potenciais efeitos estocásticos.
Os objectivos deste estudo foram: 1) Comparar a dose de radiação de três exames: Cintigrafia de perfusão miocárdica (SPECT), coronariografia invasiva (CAT) e tomografia computorizada cardíaca (AngioTC) e a sua evolução temporal. 2) Avaliar o impacto do índice de massa corporal na dose de radiação.

Métodos
Doentes consecutivos incluídos em três registos prospectivos (SPECT, CAT e AngioTC) durante 2 anos. A dose de radiação foi convertida a mSv e comparada entre os três registos. A evolução temporal foi avaliada por comparação do primeiro e quarto semestres.

Resultados
Foram avaliados 6196 exames: 35% SPECT, 53% CAT e 22% AngioTC. A dose de radiação foi: 10.7±1.2 mSv para o SPECT; 8.1±6.4 mSv para o CAT; 5.4±3.8 mSv para a AngioTC ($p<0.001$ todas comparações). Evolução temporal da dose de radiação: redução muito ligeira no SPECT (10.7 para 10.5 mSv; $p=0.004$); aumento significativo (25%) no CAT (7.0 para 8.8 mSv; $p<0.001$); redução significativa (29%) na AngioTC (6.5 para 4.6 mSv; $p<0.001$). A obesidade associou-se a níveis de radiação significativamente mais elevados nos 3 exames.

Conclusão
O exame associado a uma menor dose de radiação foi a AngioTC, seguida do CAT que, por sua vez, foi menor que a do SPECT. Houve um aumento significativo da dose de radiação no registo CAT e uma redução significativa no registo da AngioTC ao longo do tempo.

Background
Diagnostic tests that use ionizing radiation play a central role in cardiology and their use has grown in the last years, leading to an increasing concern because of their potential stochastic effects.
The aims of this study were: 1) To compare the radiation dose of three diagnostic tests: Single-Photon Emission Computed Tomography (SPECT), Invasive Coronary Angiography (ICA) and Cardiac Computed Tomography (Cardiac CT) and their time trends. 2) To evaluate the impact of body mass index in the radiation dose.

Methods
Consecutive patients included in three prospective registries (SPECT, ICA and Cardiac CT) during 2 years.
Radiation dose was converted to mSv and compared between the 3 registries.
Differences over time were evaluated by comparing the first with the forth semesters.
Results
6196 exams were evaluated: 35% were SPECT, 53% ICA and 22% Cardiac CT. Mean radiation dose was: 10.7±1.2 mSv for SPECT; 8.1±6.4 mSv for ICA; 5.4±3.8 mSv for Cardiac CT ($p<0.001$ for all).
Radiation dose over time: Very small reduction in SPECT´s (10.7 to 10.5 mSv, $p=0.004$); significant increase (25%) in ICA (7.0 to 8.8 mSv; $p<0.001$); significant reduction (29%) in Cardiac CT (6.5 to 4.6 mSv, $p<0.001$). Obesity was associated with a significantly higher radiation dose, across the different exams.

Conclusions
Cardiac CT had a mean radiation effective dose lower than Invasive Coronary Angiography, which, in turn, had a mean radiation effective dose lower than SPECT.
There was a significantly increase in the ICA registry and a significantly decrease in Cardiac CT registry radiation dose over time.

***Documento com corpo do artigo**

TITLE: Radiation effective dose of three diagnostic tests in Cardiology: Single-Photon Emission Computed Tomography, Invasive Coronary Angiography and Cardiac Computed Tomography Angiography

TITULO: Dose efectiva de radiação de três exames de diagnóstico em Cardiologia: Cintigrafia de perfusão miocárdica, Coronariografia invasiva e Tomografia computorizada cardíaca

AUTORES:

Pedro de Araújo Gonçalves (1,2,3), Pedro Jerónimo Sousa (1,3), Rita Calé (4), Hugo Marques (5), Miguel Borges dos Santos (1), André Dias (6), Hélder Dores (1), Maria Salomé Carvalho (1), António Ventosa (1), Teresa Martins (6), Rui Campante Teles (1), Manuel Almeida (1), Miguel Mendes (1)

(1) Serviço de Cardiologia, Hospital de Santa Cruz – Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal
(2) CEDOC – Chronic Diseases Research Center – Faculdade de Ciências Médicas-UNL, Lisboa, Portugal
(3) Centro Cardiovascular, Hospital da Luz, Lisboa, Portugal
(4) Serviço de Cardiologia, Hospital Garcia de Orta, Almada, Portugal
(5) Centro de Imagiologia, Hospital da Luz, Lisboa, Portugal
(6) Serviço de Medicina Nuclear, Hospital de Santa Cruz – Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

Autor para correspondência

Pedro de Araújo Gonçalves,

Instituições: (1) Serviço de Cardiologia, Hospital de Santa Cruz – Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal; (2) CEDOC – Chronic Diseases Research Center – Faculdade de Ciências Médicas-UNL, Lisboa, Portugal; (3) Centro Cardiovascular, Hospital da Luz, Lisboa, Portugal;
Telefone: +351966866455 ; Fax: +351214241388; Email: paraujogoncalves@yahoo.co.uk; Morada: Hospital de Santa Cruz, Avenida Prof. Dr. Reinaldo dos Santos, 2790-134 Carnaxide

Palavras chave: Radiação, Cintigrafia de Perfusão Miocárdica, Coronariografia invasiva; Tomografia Computorizada Cardíaca, Obesidade.

Key words: Ionizing radiation, Single Photon Emission Computerized Tomography, Invasive Coronary Angiography, and Cardiac Computed Tomography; Obesity

RESUMO

Introdução

Os exames diagnósticos que usam radiação ionizante têm um papel central na Cardiologia e a par do seu uso crescente, tem aumentado a preocupação pelos seus potenciais efeitos estocásticos.

Os objectivos deste estudo foram: 1) Comparar a dose de radiação de três exames: Cintigrafia de perfusão miocárdica (SPECT), coronariografia invasiva (CAT) e tomografia computorizada cardíaca (AngioTC) e a sua evolução temporal. 2) Avaliar o impacto do índice de massa corporal na dose de radiação.

Métodos

Doentes consecutivos incluídos em três registos prospectivos (SPECT, CAT e AngioTC) durante 2 anos. A dose de radiação foi convertida a mSv e comparada entre os três registos. A evolução temporal foi avaliada por comparação do 1º e 4º semestres.

Resultados

Foram avaliados 6196 exames: 35% SPECT, 53% CAT e 22% AngioTC. A dose de radiação foi: 10.7±1.2 mSv para o SPECT; 8.1±6.4 mSv para o CAT; 5.4±3.8 mSv para a AngioTC ($p<0.001$ todas comparações).

Evolução temporal da dose de radiação: redução muito ligeira no SPECT (10.7 para 10.5 mSv; $p=0.004$); aumento significativo (25%) no CAT (7.0 para 8.8 mSv; $p<0.001$); redução significativa (29%) na AngioTC (6.5 para 4.6 mSv; $p<0.001$). A obesidade

associou-se a níveis de radiação significativamente mais elevados nos 3 exames.

Conclusão

O exame associado a uma menor dose de radiação foi a AngioTC, seguida do CAT que, por sua vez, foi menor que a do SPECT. Houve um aumento significativo da dose de radiação no registo CAT e uma redução significativa no registo da AngioTC ao longo do tempo.

4

ABBREVIATIONS

Cardiac CT: Cardiac Computed Tomography

ICA: Invasive Coronary Angiography

SPECT: Single-Photon Emission Computed Tomography

BMI: Body mass index

INTRODUCTION

In recent years, the development of imaging techniques using ionizing radiation has resulted in considerable progress in the diagnosis and treatment of heart diseases. For the evaluation of patients with possible coronary artery disease, three commonly used diagnostic modalities use ionizing radiation: Single Photon Emission Computerized Tomography (SPECT), Cardiac Computed Tomography (Cardiac CT) and Invasive Coronary Angiography (ICA), the later being considered the gold standard for coronary artery disease diagnosis. (1)

Different dosages of radiation have been reported for each of these exams, ranging from 5 to 10 mSv for ICA, 6 to 15 mSv for SPECT, and 4 to 21 mSv for Cardiac CT. (2-5)

With the more frequent use of these exams, there have been growing concerns about radiation's potential secondary effects, especially the stochastic effects related to the high cumulative doses over time (6, 7).

We have previously reported on the radiation effective dose associated with cardiac CT in a single center registry, documented a significantly decrease in dose over time, and were able to identify the predictors of higher dose. (8)

Recently, new scanners and acquisition protocols were developed which lead to significant reductions in radiation dose associated with cardiac CT (9, 10).

The aims of this study were: 1) To evaluate and compare the radiation effective dose used in three diagnostic tests: SPECT, ICA and Cardiac CT, as well as their time trends. 2) To evaluate the impact of body mass index (BMI) in the radiation dose.

METHODS

From three prospective registries of SPECT, ICA and Cardiac CT, we selected for this analysis the exams performed during two consecutive years (01/October/2008 to 30/September/2010) and in which the indication was the evaluation of possible coronary artery disease.

The exams were performed with: Gamma-camera SMV DST-SX using 99mTc-tetrofosmin with stress / rest protocol (SPECT registry); Siemens Coroscop top / ARTIS dFC (ICA registry) and Siemens Dual Source Somaton definition CT (Cardiac CT registry). Radiation effective dose was converted to mSv (according with current literature references and manufacturer information) and compared between the registries. Briefly, for the conversion of cardiac CT dose length product (DLP) a conversion factor of 0.014 mSv Gy^{-1} cm^{-1} was used (9, 11); for the conversion of the ICA dose area product (DAP), a conversion factor of 0.183 mSv Gy^{-1} cm^{-1} was used (12, 13) ; for the conversion of the SPECT injected activity the conversion factors of 0.0060 mSv MBq^{-1} (after exercise) and 0.0071 mSv MBq^{-1} (at rest) were used (14-16).

To evaluate the time trend in radiation doses, the population was divided in 4 semesters according to the date of the exam and radiation effective dose was compared between the first and the last semester in each registry. All prospectively collected variables in the respective registries were analyzed looking for predictors of dose change over time.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation (otherwise specified),

and categorical variables as number (n) or frequency of patients (%).

Continuous variables were analyzed using Mann-Whitney or the Kruskal-Wallis nonparametric tests. Chi squared was used to test for differences in the frequencies.

Statistical significance was accepted for 2-sided P values <0.05.

Statistical analysis was performed using SPSS Statistics 17.0 for Windows.

RESULTS

During the 2 years included in this analysis, 6196 exams were performed: 3267 (52.7%) were ICAs, 1585 (25.6%) were SPECTs and 1344 (21.7%) were Cardiac CTs. Population demographic and clinical characteristics are presented in Table 1.

Mean radiation effective dose was 8.2±5.6 mSv for the whole population. Mean radiation effective dose was 10.7±1.2 mSv for SPECT, 8.1±6.4 mSv for ICA and 5.4±3.8 mSv for Cardiac CT (p<0.001 for all comparisons, Figure 1).

After the population was divided in semesters, the temporal analysis showed that there was a very small but significant reduction in SPECT´s mean radiation effective dose (10.7 to 10.5 mSv; p<0.01). In Cardiac CT there was a significant 29% decrease (6.5 to 4.6 mSv, p<0.001) and in the ICA registry a significant 25% increase in mean radiation effective dose with time (7.0 to 8.8 mSv; p<0.001) (table 2 and figure 2).

Considering the 25% increase in ICA's mean radiation effective dose from the first to the forth semester, the variables associated with this increase were: higher proportion of positive exams, of radial vascular access and of exams performed by fellows in training

(Table 3). In the first semester 39% of the ICAs progressed to percutaneous coronary intervention, while in the fourth semester this proportion increased to 42% (p<0.001). Regarding vascular access, in the first semester only 1% of the ICAs were performed by radial access, while in the fourth semester this proportion increased to 46%. In our population, the use of a radial vascular access was associated with a mean increase in 15% of the radiation effective dose (from 7.8 mSv with femoral to 9.0 with radial access, p<0.001). Finally, the proportion of exams performed by fellows in training increased from 26% in the first semester to 52% in the fourth. In this registry, when the exam was performed by a fellow in training there was a mean increase in 29% of the radiation effective dose (from 7.3 mSv with a senior operator to 9.4 mSv with a fellow operator, p<0.001).

Considering the decrease in Cardiac CT radiation effective dose, the only variable associated with this decrease was the use of the prospective ("step-and-shoot") acquisition. The use of prospective acquisition protocol was associated with a decrease of 60% in radiation effective dose. In the first semester there were no exams performed with this acquisition protocol while in the fourth semester 45% were acquired prospectively (Table 3).

The influence of body mass index in mean radiation effective doses was also evaluated. There was a significantly higher dose in obese patients (BMI ≥30 kg/m^2) as compared to overweight patients which in turn was higher that that of patients with normal weight (BMI <25kg/m^2) – figure 3.

DISCUSSION

In this analysis, we found significantly different radiation effective doses associated with common diagnostic tests used in Cardiology. The dose was higher for SPECT, followed by ICA and lower for Cardiac CT. Furthermore, in the present registry we found some time trends in the mean radiation effective dose associated with ICA and Cardiac CT, related to different clinical and procedural methodologies.

The biologic effects of ionizing radiation are related with the cumulative effective doses, and doses above 100 mSv have been linked to stochastic effects like the development of cancer, while the effects of lower levels of radiation, common in diagnostic X-ray imaging, are much less clear (4, 17). Although some theoretical models like the dose threshold and the hormetic models have been proposed, the more conservative linear no-threshold model is widely accepted and in this regard it is assumed that no level of radiation is without risk (4, 17).

This is the reason that procedures that use ionizing radiation should be performed in accordance with the As Low As Reasonably Achievable (ALARA) philosophy and physicians ordering and performing cardiac imaging should be very familiar with the dosage of radiation from cardiac diagnostic tests and ways in which dose can be minimized.

The mean radiation effective dose we found for each exam is in line with previously published data (3, 4, 6, 18). Furthermore, we confirmed that there are variables that influence the radiation effective dose delivered by these exams. For ICA, the radiation

effective dose increased with the use of radial access and when operators had less experience, which is in line with data previously published (13, 19). The higher radiation dose in the ICA registry over time was also associated with a higher proportion of positive exams. Although we did not quantify the radiation effective dose difference between positive and negative ICAs, we could assume that positive tests needed more cine angiograms of the coronary arteries with a consequent increase in radiation effective dose used.

For Cardiac CT, the introduction and progressively more frequent use of the prospective protocol during the study period was associated in our experience with a significant decrease in the radiation effective dose in this exam, as was demonstrated by other authors (20-22). Finally, for SPECT, the dose change over time was very small, and this was expected since there were no protocol changes during the study period.

Mean radiation effective doses were significantly higher for obese patients in all the evaluated exams. This was especially true for cardiac CT and ICA, with an almost two fold difference in radiation dose between them and their normal weight counterparts. In the SPECT registry, the effect of BMI was less pronounced. This should be taken in consideration when selecting the appropriate diagnostic exam, especially for those at higher risk from radiation exposure, like women and younger patients (23). In line with this, special consideration should be taken regarding cardiac CT dose, since patients in our registry undergoing cardiac CT were significantly younger than patients in the ICA or the SPECT registries.

Although the present manuscript is focused on the comparison of the radiation dose between 3 different diagnostic exams, other features should be regarded when

comparing different imaging modalities. As cardiac CT and ICA require the administration of iodinated contrast, some attention should be directed to the presence of an impaired renal function and history of allergies; likewise, the probability of coronary artery disease is considered to be also an important factor, as SPECT and ICA are more adequate for patients at higher CAD probability (24, 25). This way, all these features (dose of radiation, need for iodinated contrast and CAD probability) should be taken into consideration when selecting the most appropriate exam for each patient.

CONCLUSIONS

In these registries of diagnostic tests commonly used in cardiology, the radiation effective dose used in Cardiac CT was lower than the one used in Invasive Coronary Angiography, which, in turn, was lower than the effective dose used in SPECT. There was a significant increase over time in the mean radiation effective dose associated with Invasive Coronary Angiography, mainly related to the increase use of radial access, and a decrease in Cardiac CT effective dose as a consequence of the implementation of the prospective protocol. Obesity was associated with a significantly higher radiation dose, across the different exams.

FIGURE LEGENDS:

Figure 1. Mean radiation effective dose used in each exam studied.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography

Figure 2. Time trends in mean radiation effective dose used in each exam.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography

Figure 3: Mean radiation effective doses for each exam across different BMI classes.

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography; Body mass index

REFERENCES:

1. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010 Oct;31(20):2501-55.
2. Hirshfeld JW, Jr., Balter S, Brinker JA, Kern MJ, Klein LW, Lindsay BD, et al. ACCF/AHA/HRS/SCAI clinical competence statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures: a report of the American College of Cardiology Foundation/American Heart Association/American College of Physicians Task Force on Clinical Competence and Training. Circulation. 2005 Feb 1;111(4):511-32.
3. Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation. 2007 Sep 11;116(11):1290-305.
4. Gerber TC, Carr JJ, Arai AE, Dixon RL, Ferrari VA, Gomes AS, et al. Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. Circulation. 2009 Feb 24;119(7):1056-65.
5. Fazel R, Shaw LJ. Radiation exposure from radionuclide myocardial perfusion imaging: concerns and solutions. J Nucl Cardiol. 2011 Aug;18(4):562-5.
6. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med. 2009 Aug 27;361(9):849-57.
7. Almeida AG. Cardiac computed tomography and radiation: balancing benefit and risk. Rev Port Cardiol. 2010 Nov;29(11):1677-82.
8. Sousa PJ, Goncalves PA, Marques H, Raposo L, Cale R, Brito J, et al. Radiation in cardiac CT: predictors of higher dose and its reduction over time. Rev Port Cardiol. 2010 Nov;29(11):1655-65.
9. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.
10. Duarte R, Bettencourt N, Costa JC, Fernandez G. Coronary computed tomography angiography in a single cardiac cycle with a mean radiation dose of approximately 1 mSv: initial experience. Rev Port Cardiol. 2010 Nov;29(11):1667-76.
11. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. JAMA. 2009 Feb 4;301(5):500-7.
12. Betsou S, Efstathopoulos EP, Katritsis D, Faulkner K, Panayiotakis G. Patient radiation doses during cardiac catheterization procedures. Br J Radiol. 1998 Jun;71(846):634-9.

13. Neill J, Douglas H, Richardson G, Chew EW, Walsh S, Hanratty C, et al. Comparison of radiation dose and the effect of operator experience in femoral and radial arterial access for coronary procedures. Am J Cardiol. 2010 Oct 1;106(7):936-40.
14. Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC, et al. Recommendations for reducing radiation exposure in myocardial perfusion imaging. J Nucl Cardiol. 2010 Aug;17(4):709-18.
15. Hesse B, Tagil K, Cuocolo A, Anagnostopoulos C, Bardies M, Bax J, et al. EANM/ESC procedural guidelines for myocardial perfusion imaging in nuclear cardiology. Eur J Nucl Med Mol Imaging. 2005 Jul;32(7):855-97.
16. Myoview package insert. European Prescribing Information. Available at http://www.gehealthcare.com/euen/molecular-imaging/congress/pdf/myoview-pi.pdf.
17. Einstein AJ. Effects of radiation exposure from cardiac imaging: how good are the data? J Am Coll Cardiol. 2012 Feb 7;59(6):553-65.
18. Kaufmann PA, Knuuti J. Ionizing radiation risks of cardiac imaging: estimates of the immeasurable. Eur Heart J. 2011 Feb;32(3):269-71.
19. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet. 2011 Apr 23;377(9775):1409-20.
20. Gopal A, Mao SS, Karlsberg D, Young E, Waggoner J, Ahmadi N, et al. Radiation reduction with prospective ECG-triggering acquisition using 64-multidetector Computed Tomographic angiography. Int J Cardiovasc Imaging. 2009 Apr;25(4):405-16.
21. Stolzmann P, Leschka S, Scheffel H, Krauss T, Desbiolles L, Plass A, et al. Dual-source CT in step-and-shoot mode: noninvasive coronary angiography with low radiation dose. Radiology. 2008 Oct;249(1):71-80.
22. Ferreira AM, Lopes R, Correia Mda G, Gil V. Low-dose cardiac CT. Rev Port Cardiol. 2010 Mar;29(3):459-62.
23. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA. 2007 Jul 18;298(3):317-23.
24. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.
25. NICE clinical guideline 95. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.; Available from: http://www.nice.org.uk/guidance/CG95.

Tabelas 1-3

Table 1. Population demographic and clinical characteristics

	Cardiac CT (n=1344)	**ICA** (n=3267)	**SPECT** (n=1585)
Age (years, mean± SD)	59 ± 12	66 ± 12	64 ± 9
Male gender (%)	60%	61%	63%
BMI (Kg/m^2)	27.3 ± 4.3	27.3 ± 4.2	27.5 ± 4.4
Diabetes (%)	16%	29%	N/A
Hypertension (%)	57%	72%	N/A
Dyslipidemia (%)	54%	57%	N/A
Smoking Habits (%)	27%	31%	N/A
Previous MI (%)	3%	17%	N/A
Previous PCI (%)	7%	18%	N/A
Previous CABG (%)	3%	7%	N/A

Values are mean SD or percentages.
N/A: Not available

Table 2. Mean radiation effective dose for each exam across the 4 semesters.

	1st semester	2nd semester	3rd semester	4th semester	p (1st vs 4th)
SPECT	10.7±1.1	10.7±1.4	10.7±1.3	10.5±0.9	0.004
ICA	7.0±6.0	7.6±5.6	9.0±6.9	8.7±6.9	<0.001
Cardiac CT	6.5±3.7	6.2±4.2	5.0±4.1	4.6±3.0	<0.001

SPECT: Single Photon Emission Computerized Tomography; Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography;

Table 3. Variables associated with the increase of ICA radiation dose and decrease in cardiac CT radiation dose

		Δ mSv	1st Semester	4th Semester
ICA	Proportion of patients that performed PCI	N.D.	39%	42%
	Exams performed by fellows in training	↑29%	26%	52%
	Proportion of radial vascular access	↑15%	1%	46%
Cardiac CT	Prospective acquisition	↓60%	0%	45%

Cardiac CT: Cardiac Computed Tomography; ICA: Invasive Coronary Angiography;

Figura 1
Click here to download high resolution image

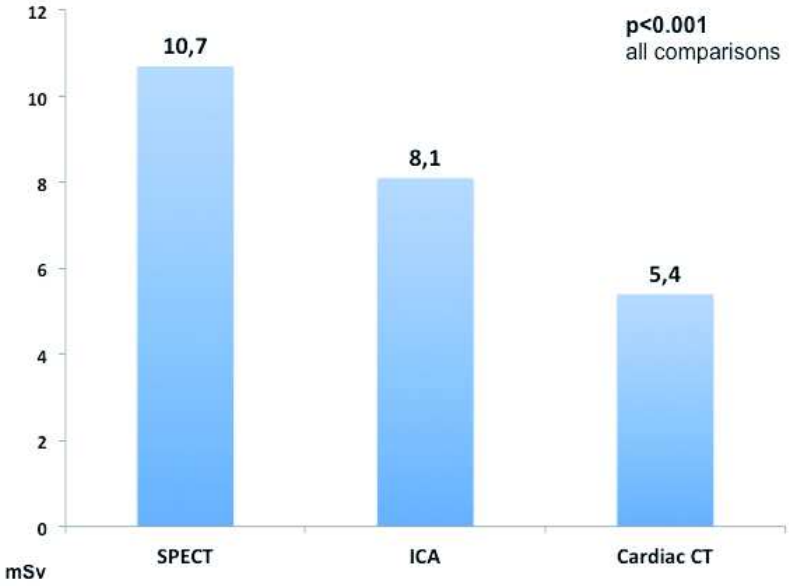


Figura 2
Click here to download high resolution image

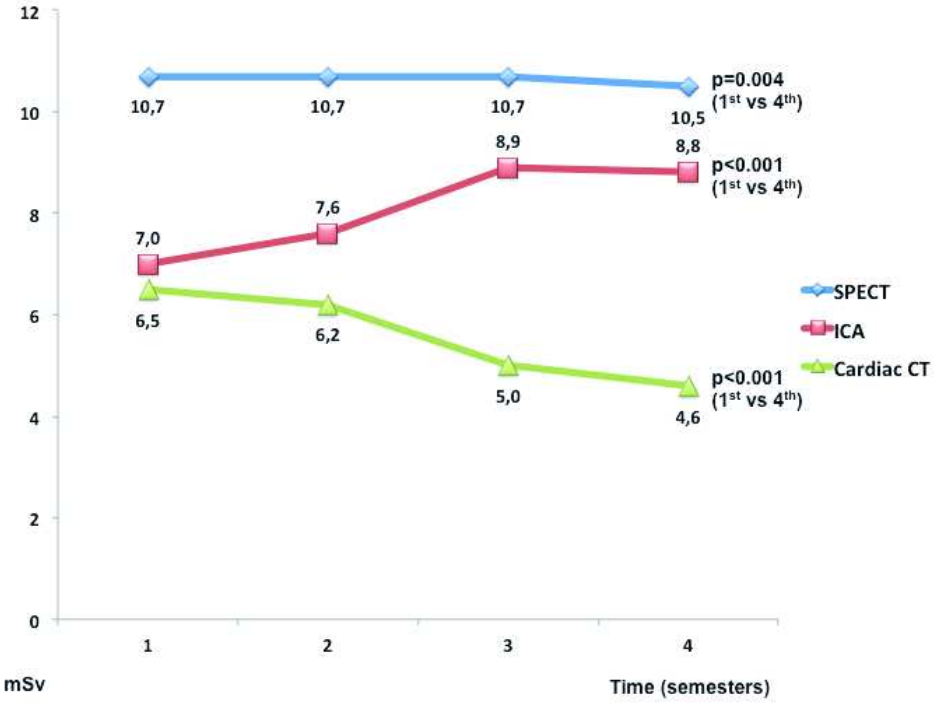
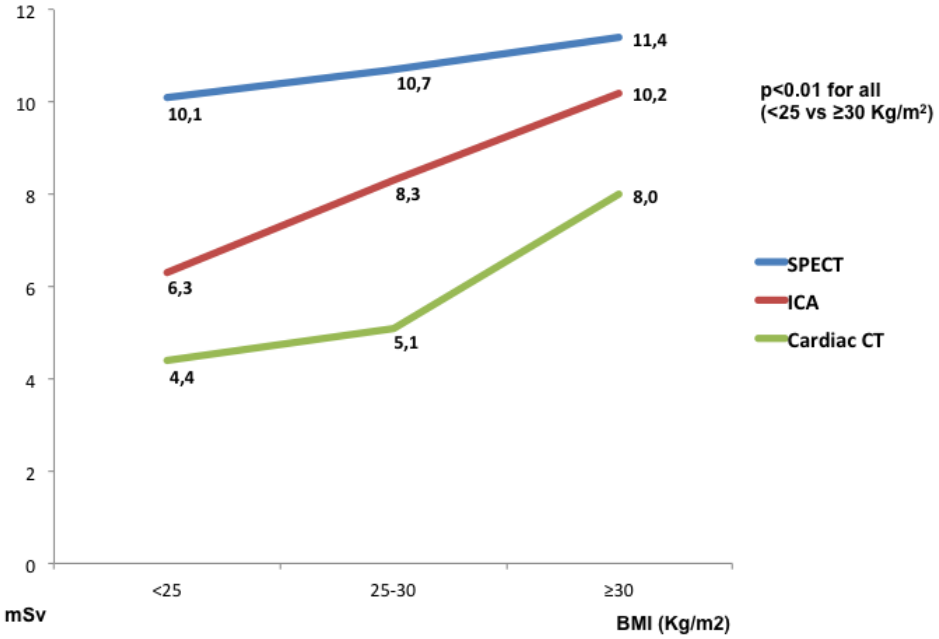


Figura 3
Click here to download high resolution image



Capítulo 6.
Desempenho dos scores de risco clínicos

RESUMO:

Este capítulo aborda um dos objectivos desta tese: a avaliação do desempenho dos scores de risco clínicos na identificação da presença e da gravidade da doença coronária documentada por angio TC cardíaca. São descritos os scores de probabilidade de DC (Diamond-Forrester e Morise) e de risco CV (HeartScore) usados e os resultados modestos na identificação dos doentes com elevada carga aterosclerótica. Uma importante percentagem dos doentes estudados considerados de baixa probabilidade de DC ou de baixo risco CV apresentavam doença, com predomínio de DC não obstrutiva. Por outro lado, um subgrupo de doentes considerados pelos scores clínicos como de elevada probabilidade e/ou risco CV, não tinha qualquer placa identificável na sua árvore coronária.

Foi incluído neste capitulo um artigo original (**artigo 15**) que aborda a questão do paradoxo da obesidade revisitado pela angio TC cardíaca e ilustra as limitações da estimativa clínica da carga aterosclerótica coronária.

ABSTRACT:

This chapter describes one of the objectives of the present thesis: to evaluate the performance of clinical scores to identify the presence and severity of coronary artery disease documented by cardiac CT. The pre-test coronary disease probability (Diamond-Forrester and Morise) and the CV risk (HeartScore) scores are described, as well as their modest results in the identification of patients with a high disease burden. A significant percentage of the studied population considered as low probability or CV risk had coronary disease, predominantly nonobstructive. On the other hand, a subset of patients considered by the risk scores as high probability or CV risk had no atherosclerotic plaques in the coronary tree.

Included in this chapter is an original manuscript (**manuscript 15**) on the obesity paradox revisited by cardiac CT, as it illustrates well the limitations to clinically estimate the coronary atherosclerotic burden.

ARTIGO 15/ MANUSCRIPT 15:

BODY MASS INDEX AS A PREDICTOR OF THE PRESENCE BUT NOT THE SEVERITY OF CORONARY ARTERY DISEASE EVALUATED BY CARDIAC-CT

Dores H, de Araújo Gonçalves P, Carvalho MS, Jerónimo Sousa P, Ferreira A, Cardim N, Mota Carmo M, Aleixo A, Mendes M, Pereira Machado F, Roquette J, Marques H.

Eur J Prev Cardiol. 2013 Jun 17. [Epub ahead of print] DOI:10.1177/2047487313494291.

SUMÁRIO DO CAPÍTULO 6:

6.1. INTRODUÇÃO

Os doentes que já sofreram uma manifestação clínica do processo aterosclerótico, qualificam-se automaticamente para um patamar de risco mais elevado e, após esta etapa, existem linhas claras acerca da sua orientação e seguimento, na chamada prevenção *secundária*. O desafio mais importante, tanto na Cardiologia como em outras áreas da Medicina, consiste na correcta identificação dos indivíduos que estão em risco de eventos CV, identificando assim a doença numa fase precoce e iniciando medidas de prevenção *primária* com o objectivo de alterar a sua história natural.

Os factores de risco modificáveis (tabagismo, diabetes, dislipidémia, hipertensão arterial, obesidade) e não modificáveis (idade, sexo e história familiar) permitem estimar o risco CV e o seu desempenho melhora quando agrupados em scores. O uso dos scores de risco CV é recomendados nas varias *guidelines* uma vez que permitem através da conjugação dos diferentes factores de risco, fornecer uma estimativa do risco de eventos CV, sendo assim útil para decidir o nível de agressividade nas medidas de prevenção primaria.

Para alem dos scores de risco CV, existem scores que permitem estimar a probabilidade de DC, os chamados scores de probabilidade pré-teste, úteis sobretudo na selecção do melhor exame a usar na investigação da DC.

6.2 SCORES DE RISCO CARDIOVASCULAR

Um dos exemplos de score de risco CV é o **score de Framingham** (1), amplamente divulgado na recomendações do "*National Cholesterol Educational Program-Adult Treatment Panel III*" (NCEP-ATPIII) para decisão no manejo do doente com dislipidémia (2). A variáveis incluídas no score de Framingham são a idade, o sexo, tabagismo, diabetes, colesterol total, colesterol HDL e a tensão arterial sistólica. De acordo com o resultado, os doentes são classificados em baixo risco de eventos coronários (EAM e morte) a 10 anos se <10%; em risco intermédio se entre 10 e 20%; em risco elevado se >20%. O score de Framingam tem sido usado em varias recomendações de prevenção primária (3, 4), sendo também referido como ferramenta para selecção dos doentes para angio TC cardíaca (5).

Mais recentemente, foi desenvolvido o **HeartScore** (ou SCORE), que acompanhou as *guidelines* de prevenção primária da sociedade europeia de cardiologia em 2003(6), actualizadas em 2012 (7) e que foi construído a partir da dados epidemiológicos de vários países da Europa. Na sua constituição, e à semelhança do score de Framingham, entram as variáveis idade, sexo, colesterol total, tabagismo e tensão arterial sistólica – **figura 1**. Os intervalos de risco do HeartScore são inferiores aos do score de Framingham porque este foi desenvolvido para prever apenas morte

CV. Os seus patamares para morte CV a 10 anos são os seguintes: Baixo risco de <1%; risco moderado de 1-5%; ≥5% risco elevado; ≥10% risco muito elevado.

Assim, quer o score de Framingham quer o HeartScore são ferramentas úteis para estimar o risco CV, etapa fundamental para adequar as medidas de prevenção primária. No entanto, apesar de esta estimativa resultar em termos populacionais, torna-se difícil por vezes perante um individuo em particular estimar o seu risco, que frequentemente vem subvalorizado, nomeadamente nos indivíduos mais novos ou com história familiar de doença CV prematura. Por outro lado, apesar de em *termos relativos* os indivíduos de patamares de risco superiores terem maior probabilidade de virem a sofrer um evento CV, em *termos absolutos*, como a maior parte da população está em patamares de risco mais baixos, a grande maioria dos indivíduos que vem a sofrer um acidente CV estaria previamente classificados em patamares de risco não elevados (8).

6.3 SCORES DE PROBABILIDADE PRÉ-TESTE DE DOENÇA CORONÁRIA

A selecção de determinado tipo de exame, bem como a valorização do seu resultado está na dependência não só da acuidade diagnóstica do exame mas também da probabilidade pré-teste de doença, de acordo com o teorema de *Bayes*. No caso concreto da DC, existem varias ferramentas que permitem, a partir da dados demográficos e clínicos, fazer esta estimativa.

Um destes exemplo é o ***score de Diamond-Forrester***, desenvolvido como um método para estimar a probabilidade de DC obstrutiva a partir de 3 variáveis facilmente colhidas: idade, sexo e características da dor torácica (9) – **figura 2**. Apesar das suas limitações, nomeadamente por não entrar em linha de conta com os habituais factores de risco CV e a larga dependência nas características da dor torácica, este score tem resistido à passagem do tempo e o seu uso ainda é actualmente recomendado em varias guidelines (10, 11). O score de Diamond e Forrester espelha algo que é transversal a todos os scores: o balanço entre a sua complexidade (para ter poder discriminativo) e simplicidade (influenciada pelo número e operacionalização das variáveis) é crucial para a adopção na prática clínica (12) – aspecto discutido no ***capítulo 2***.

Recentemente, foi feita uma actualização deste score a partir de dados de coortes mais recentes de doentes incluídos em bases de dados de coronariografia convencional, tendo sido demonstrado que o score original sobrestimava a probabilidade real de DC nesta população mais recente (13). Esta calibração, publicada pelo **CAD consortium**, entra com as mesmas variáveis embora usando a idade como variável continua. As categorias de probabilidade são as seguintes:

-<30%, baixa probabilidade

-≥30-70%, probabilidade intermédia

-≥70% - probabilidade alta

Esta disponível *online* uma calculadora para este efeito (14) – **figura 3**.

Um outro score validado para estimar a probabilidade de DC obstrutiva é o ***score de Morise***, que entra em linha de conta com os mesmas 3 variáveis do score de Diamond-Forrester e adicionalmente com factores de risco CV, nomeadamente a diabetes, dislipidémia, hipertensão arterial, obesidade, status estrogénico e tabagismo (15) – **figura 4**.

Este score demonstrou ser útil não só para prever a presença de DC, mas também a sua gravidade e posteriormente foi também avaliado o seu desempenho como score prognóstico (16). Neste score , as categorias de probabilidade são as seguintes:

-scores de 0 a 8, probabilidade baixa

-scores de 9 a 15, probabilidade intermédia

-scores ≥16 , probabilidade alta.

FIGURA 1: Tabela do HeartScore para países de baixo risco cardiovascular

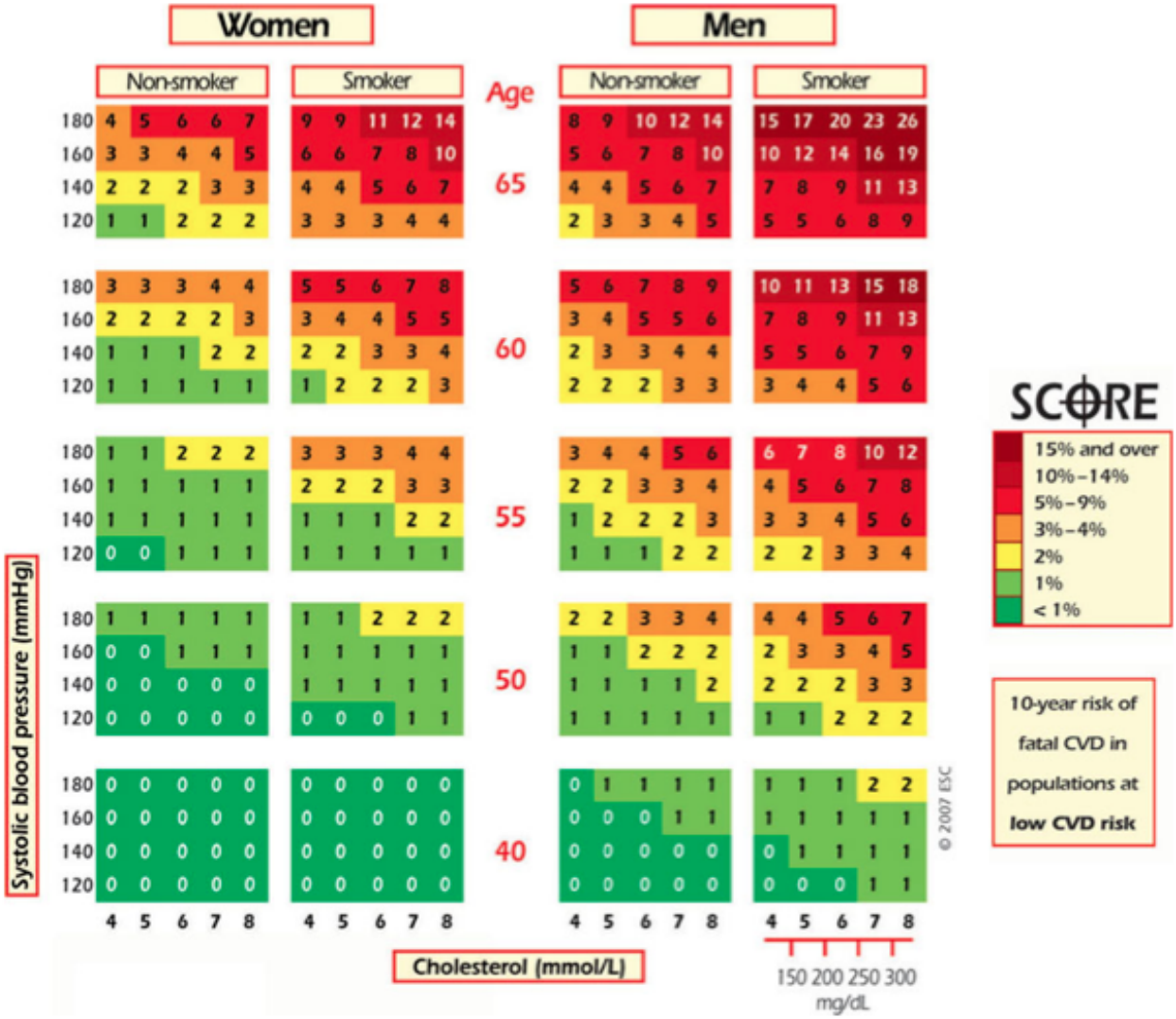


FIGURA 2: Score de Diamond-Forrester

(adaptação das Guidelines "Exercice testing ACC/AHA 2002")

Table 4. Pretest Probability of Coronary Artery Disease by Age, Gender, and Symptoms*

Age (y)	Gender	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

FIGURA 3: Score de Diamond-Forrester – CAD consortium

(calculadora disponível no site:

http://rcc.simpal.com/RCEval.cgi?Owner=tgenders&RCName=CAD%20consortium)

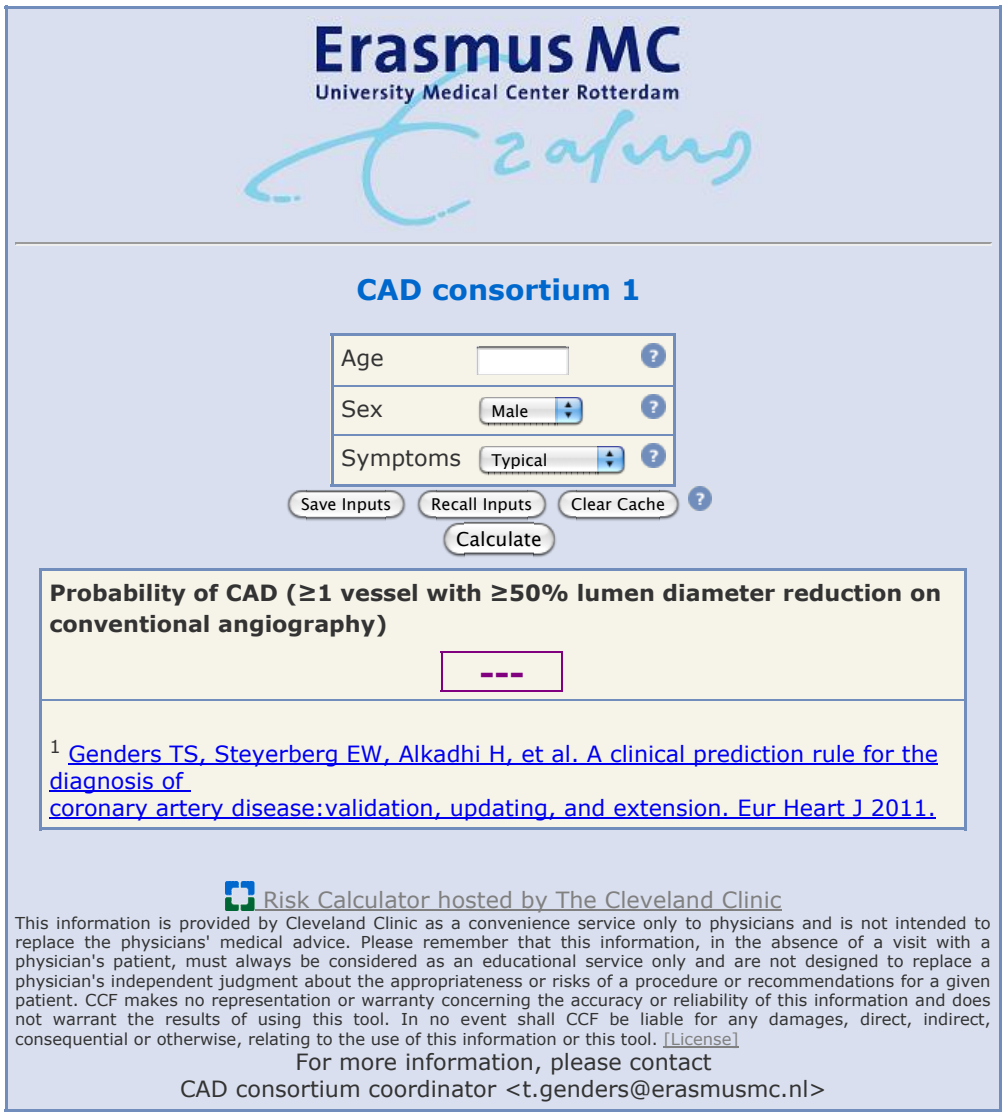


FIGURA 4: **Score de Morise**

A

Pretest

Variable	*Choose response*	*Sum*
Age Men Women		
<40 <50	3	
40-54 50-64	6	
≥55 ≥65	9	
Estrogen Status	Positive = -3	
Women only	Negative = +3	
Angina History	Typical = 5	
Diamond Method	Atypical = 3	
	Non-anginal = 1	
Diabetes?	2	
Hyperlipidemia?	1	
Hypertension?	1	
Smoking? (Any)	1	
Family Hx CAD? 1°	1	
Obesity? BMI>27	1	
	Total Score:	

6.4 DESEMPENHO DOS SCORES CLÍNICOS NA IDENTIFICAÇÃO DE PRESENÇA E GRAVIDADE DA DOENÇA CORONÁRIA DOCUMENTADA POR ANGIO TC CARDÍACA.

Um dos objectivos da tese foi avaliar o desempenho dos scores clínicos na identificação da presença e da gravidade da DC (obstrutiva e não obstrutiva) documentada por angio TC cardíaca.
Para esta análise, foi feita a distribuição da população previamente descrita (***capitulo 1***) pelos diferentes scores clínicos: HeartScore, Morise e Diamond-Forrester.

Foi possível documentar um razoável desempenho dos scores clínicos, mas uma importante percentagem dos doentes estudados considerados de baixa probabilidade de DC ou de baixo risco CV apresentavam doença, com predomínio de DC não obstrutiva. Por outro lado, um subgrupo de doentes considerados pelos scores clínicos como de elevada probabilidade e/ou risco CV, não tinha qualquer placa identificável na sua árvore coronária (***Figuras 5, 6 e 7 e tabela 1)***.

Na ***Figuras 5*** é apresentada a distribuição da presença e gravidade de DC de acordo com o risco CV classificado pelo **HeartScore**. A percentagem de doentes com DC (obstrutiva e não obstrutiva) foi significativamente mais alta na população de elevado risco CV (HeartScore ≥5%). No entanto, em quase metade (48,7%) da população considerada como de baixo risco CV, foram documentadas placas na árvore coronária e em 8,5% dos casos a doença era obstrutiva.
Foi interessante verificar que o HeartScore, ferramenta útil para estimar o risco CV, foi também um bom preditor da presença de DC, tendo inclusive sido o score com melhor desempenho a este nível. Na nossa população, os doentes com um HeartScore ≥5 tinham uma probabilidade cerca de 4 vezes superior de ter DC (qualquer placa na arvore coronária) e quase 3 vezes superior de ter DC obstrutiva (***Tabela 1***).

Nas ***Figuras 6 e 7*** está representada a análise da distribuição da população em função da presença e gravidade da DC nos vários patamares de probabilidade pré-teste de DC, estimada pelo score de **Diamond-Forrester** e de **Morise** respectivamente. À semelhança da distribuição encontrada para o score de risco CV, apesar da percentagem de DC (quer obstrutiva quer não obstrutiva) acompanhar o aumento da probabilidade de DC, uma percentagem significativa dos doentes com baixa probabilidade (45,2% com o Diamond-Forrester e 25% com o Morise) tinham placas ateroscleróticas na árvore coronária.

Os scores de probabilidade pré-teste de DC estão muito na dependência da presença de sintomas. Estes, sobretudo no caso da angina típica, dão um contributo muito importante para a probabilidade de DC, uma vez que estes scores foram desenvolvidos para prever a presença de DC obstrutiva identificada na coronariografia invasiva. Isto é sobretudo verdade para o score de Diamond-Forrester, uma vez que para além dos sintomas entra apenas em linha de conta com a idade e o sexo. No caso do score de Morise, para além dos sintomas, sexo e idade, estão incluídos os habituais factores de risco CV, sendo inclusive dado um valor ponderal superior à diabetes em relação aos restantes factores de risco. Esta maior robustez do score faria prever um melhor desempenho em relação ao score de Diamond-Forrester, mas na nossa análise o desempenho para prever a presença de DC, quer obstrutiva quer não obstrutiva foi muito semelhante para estes dois scores. Isto pode ter sido o resultado de nesta análise se ter usado a nova calibração do Diamond-Forrester (CAD consortium), que foi validada recentemente com bases de dados contemporâneas, tendo-se percebido que o score original sobrestimava a probabilidade, sobretudo nas mulheres (13).

FIGURA 5: Desempenho do HeartScore na identificação da presença e gravidade da doença coronária

HeartScore (n=581)	Sem placas (n=240)	DC não obstrutiva (n=263)	DC obstrutiva (n=78)
HeartScore <5% (n=433, 74,5%)	222 (51,3%)	174 (40,2%)	37 (8,5%)
HeartScore ≥5% (n=148, 25.5%)	18 (12,2%)	89 (60,1%)	41 (27,7%)
AUC (IC 95%)	0,757 (0,718-0,797)	0,663 (0,619-0,706)	0,691 (0,627-0,754)

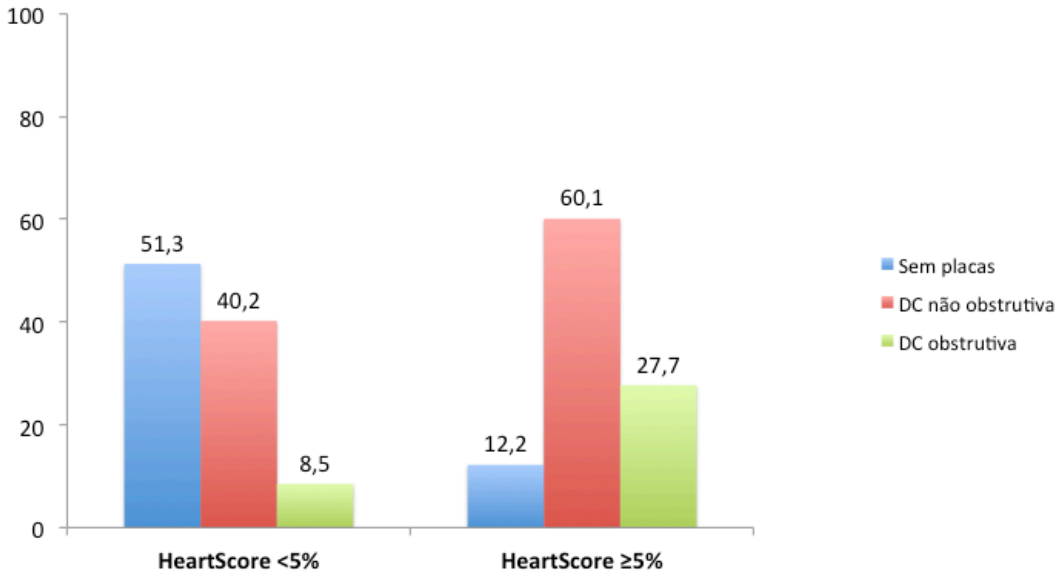


FIGURA 6: Desempenho do score de Diamond-Forrester (calibração CAD consortium) na identificação da presença e gravidade da doença coronária.

Diamond-Forrester (n=581)	Sem placas (n=240)	DC não obstrutiva (n=263)	DC obstrutiva (n=78)
DF <30% (n=349, 60.1%)	191 (54,7%)	131 (37,5%)	27 (7,7%)
DF ≥30% (n=232, 39.9%)	49 (21,1%)	132 (56,9%)	51 (22,0%)
AUC (IC 95%)	0,713 (0,670-0,756)	0,620 (0,575-0,666)	0,688 (0,627-0,748)

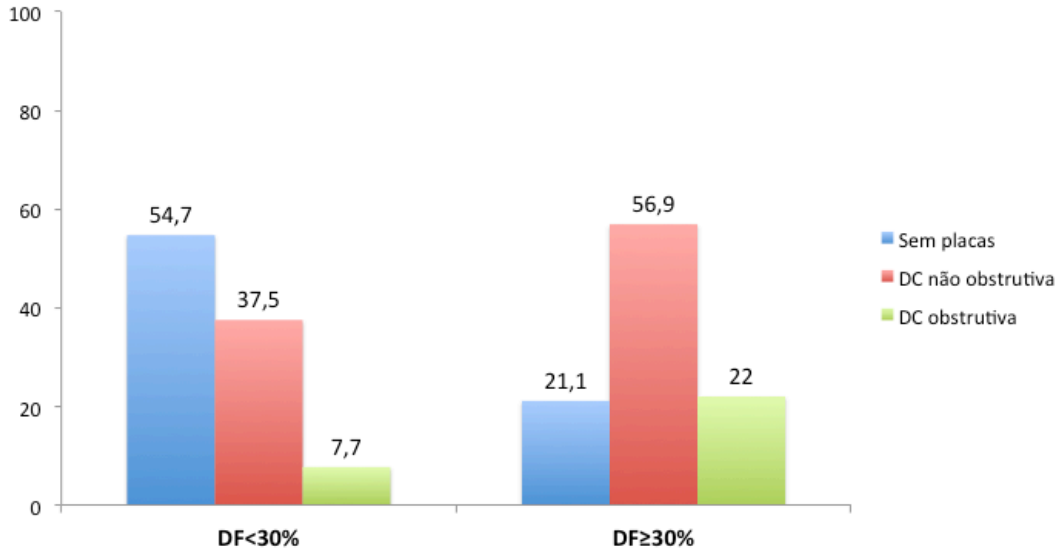


FIGURA 7: Desempenho do score de Morise na identificação da presença e gravidade da doença coronária.

Morise score (n=581)	Sem placas (n=240)	DC não obstrutiva (n=263)	DC obstrutiva (n=78)
Low (0-8) (n=140, 24.1%)	105 (75,0%)	32 (22,9%)	3 (2,1%)
Intermediate (9-15) (n=369, 63.5%)	116 (31,4%)	193 (52,3%)	60 (16,3%)
High (≥16) (n=72, 12.4%)	19 (26,4%)	38 (52,8%)	15 (20,8%)
AUC (IC 95%)	0,698 (0,653-0,742)	0,619 (0,573-0,664)	0,660 (0,605-0,715)

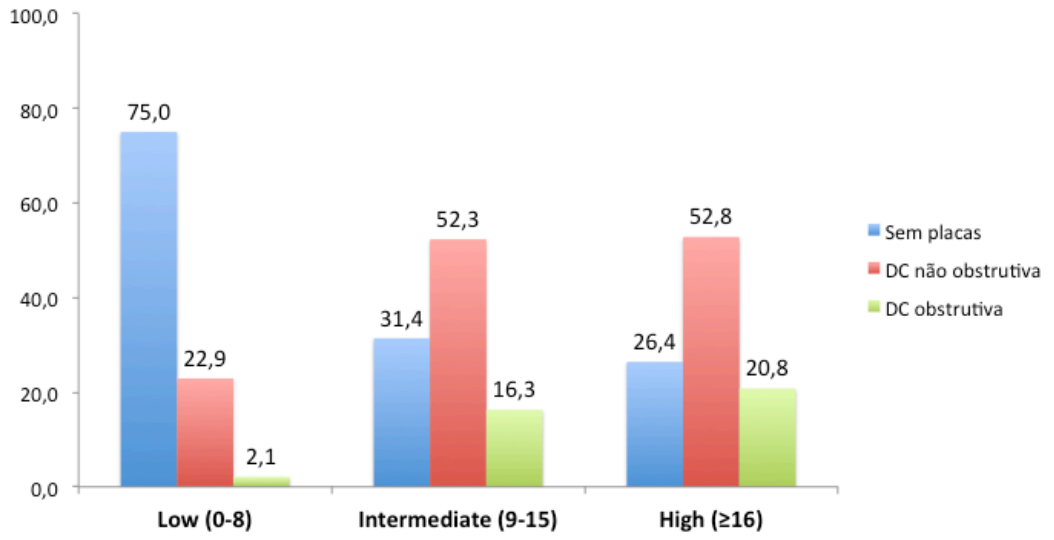


TABELA 1: Análise multivariável dos scores clínicos como preditores independentes da presença e gravidade da doença coronária.

Presença de doença coronária (qualquer placa)

	OR	(IC 95%)	p
HeartScore≥5	3,896	2,189-6,935	<0,001
DF-CAD consortium ≥30%	2,623	1,697-4,052	<0,001
Morise ≥16	2,549	1,568-4,144	<0,001

Doença coronária obstrutiva (estenose ≥50%)

	OR	(95% CI)	p
HeartScore≥5	2,709	1,503-4,880	0,001
DF-CAD consortium ≥30%	1,884	1,036-3,424	0,038
Morise ≥16	1,838	1,057-3,197	0,031

6.5 OBESIDADE E DOENÇA CORONÁRIA – IMPLICAÇÕES PARA OS SCORES

Nos últimos anos tem-se assistido a um aumento da prevalência da obesidade, sendo considerado um importante factor de risco CV, sobretudo pela sua associação com a síndrome metabólica e o desenvolvimento de diabetes tipo 2 (17, 18).

No entanto, a sua associação com a DC tem sido controversa, tendo sido descrito por alguns autores um paradoxo, com menor carga aterosclerótica e prevalência mais baixa de uma anatomia coronária de elevado risco nos doentes obesos, quando corrigido para os restantes factores de risco (19-21).

Um dos scores de probabilidade pré-teste usados, o score de Morise, incluí a obesidade (com o limiar discriminativo >27 kg/m2) como um dos factores que aumenta a probabilidade de DC, com o mesmo valor que os restantes factores de risco (tabagismo, hipertensão arterial, dislipidémia) à excepção da diabetes ao qual é atribuído um valor ponderal superior (15). Na nossa análise o score de Morise, apesar de incluir estas variáveis adicionais, não demonstrou ter uma acuidade diagnóstica superior ao score de Diamond-Forrester, podendo em certa medida ter sido influenciado também pelo paradoxo da obesidade.

A avaliação detalhada da carga aterosclerótica coronária possível com a angio TC cardíaca, com identificação não só de DC obstrutiva mas também de placas não obstrutivas, poderá contribuir para esclarecer melhor este paradoxo.

Com o objectivo de esclarecer a relação entre o índice de massa corporal e a presença e extensão da DC, fizemos uma análise envolvendo um elevado número de doentes (n=1706), estáveis e sem antecedentes de DC conhecida, referenciados para avaliação de eventual DC por angio TC (22). Neste trabalho, foi possível identificar que a obesidade (BMI ≥30Kg/m2; presente em 21,9% dos doentes) na análise multivariável, era um preditor independente da presença de DC (qualquer placa na arvore coronária), embora com um *OR* muito modesto. No entanto, o IMC não foi significativamente diferente quando comparados os doentes com ou sem DC obstrutiva (IMC médio 27.7 vs 27.2 kg/m2) e na distribuição dos doentes com DC obstrutiva pela diferentes classes de IMC não houve diferenças estatisticamente significativas.

Por outro lado, na avaliação detalhada da carga aterosclerótica, a percentagem de doentes com pelo menos 5 segmentos da arvore coronária com placa (SIS >5) também não foi diferentes entre os grupos de doentes com peso normal, excesso de peso e obesidade . Assim, na nossa população de doentes estáveis, sem antecedentes de DC conhecida, a obesidade não foi um preditor da gravidade da DC, avaliada quer pela prevalência de DC obstrutiva, quer pelo número de segmentos da árvore coronária com placas, marcadores da carga aterosclerótica com reconhecido impacto prognóstico.

5.6 BIBLIOGRAFIA

1. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12;97(18):1837-47.
2. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.
3. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation. 2002 Jul 16;106(3):388-91.
4. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010 Dec 21;122(25):2748-64.
5. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.
6. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J. 2003 Sep;24(17):1601-10.
7. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2012 Jul;33(13):1635-701.
8. Braunwald E. Epilogue: what do clinicians expect from imagers? J Am Coll Cardiol. 2006 Apr 18;47(8 Suppl):C101-3.
9. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979 Jun 14;300(24):1350-8.
10. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002 Oct 1;106(14):1883-92.
11. Hendel RC, Patel MR, Kramer CM, Poon M, Carr JC, Gerstad NA, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. J Am Coll Cardiol. 2006 Oct 3;48(7):1475-97.
12. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005 May;26(9):865-72.

13. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K, et al. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J. 2011 Jun;32(11):1316-30.
14. CAD consortium online calculator. http://rccsimpalcom/RCEvalcgi?Owner=tgenders&RCName=CAD%20consortium.
15. Morise AP, Haddad WJ, Beckner D. Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med. 1997 Apr;102(4):350-6.
16. Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. J Am Coll Cardiol. 2003 Sep 3;42(5):842-50.
17. Haslam DW, James WP. Obesity. Lancet. 2005 Oct 1;366(9492):1197-209.
18. Berrington de Gonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ, et al. Body-mass index and mortality among 1.46 million white adults. N Engl J Med. 2010 Dec 2;363(23):2211-9.
19. Rubinshtein R, Halon DA, Jaffe R, Shahla J, Lewis BS. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol. 2006 May 1;97(9):1277-80.
20. Niraj A, Pradhan J, Fakhry H, Veeranna V, Afonso L. Severity of coronary artery disease in obese patients undergoing coronary angiography: "obesity paradox" revisited. Clin Cardiol. 2007 Aug;30(8):391-6.
21. Hastie CE, Padmanabhan S, Slack R, Pell AC, Oldroyd KG, Flapan AD, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous coronary intervention. Eur Heart J. 2010 Jan;31(2):222-6.
22. Dores H, de Araújo Gonçalves P, Carvalho M, Jerónimo Sousa P, Ferreira A, Cardim N, et al. Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac computed tomography. Eur J Prev Cardiol. 2013.

6.7 ARTIGO 15

XML Template (2013) [5.6.2013–2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

European Journal of Preventive Cardiology
EUROPEAN SOCIETY OF CARDIOLOGY®

Original Scientific Paper

European Journal of Preventive Cardiology
0(00) 1–7

DOI: 10.1177/2047487313494291
ejpc.sagepub.com
SAGE

Body mass index as a predictor of the presence but not the severity of coronary artery disease evaluated by cardiac computed tomography

Helder Dores[1], Pedro de Araújo Gonçalves[1,2,3], Maria S Carvalho[1], Pedro J Sousa[1], António Ferreira[4], Nuno Cardim[2], Miguel M Carmo[3], Ana Aleixo[1,3], Miguel Mendes[1], Francisco P Machado[2], José Roquette[2] and Hugo Marques[4]

Abstract

Background: The relation between body mass index (BMI) and coronary artery disease (CAD) extension remains controversial. The aim of this study was to evaluate the correlation between BMI and CAD extension documented by coronary computed tomography angiography (CCTA).

Methods and results: Prospective registry including 1706 consecutive stable patients that performed CCTA (dual source scanner) for the evaluation of CAD. The population was stratified by BMI: normal 530 (31.1%), overweight 802 (47.0%) and obesity 374 (21.9%). BMI was significantly higher in patients with CAD (27.7 ± 4.3 vs $26.8 \pm 4.3\,kg/m^2$, $p < 0.001$); these patients were also older, more often male and had higher prevalence of diabetes, hypertension and dyslipidemia. By multivariate analysis (logistic regression) BMI remains an independent predictor of CAD (odds ratio (OR) 1.03, 95% confidence interval (CI) 1.01–1.06; $p = 0.012$). Regarding the severity of CAD, BMI was not significantly different among patients with and without obstructive CAD (27.7 ± 4.3 vs $27.2 \pm 4.3\,kg/m^2$, $p = 0.120$). In 319 patients (4516 segments; 4077 evaluable), a detailed atherosclerotic burden was evaluated and compared among BMI classes, defined according to the presence of plaque and the degree of stenosis. Obstructive CAD was identified in 16.9% of the patients and 45.1% had non-obstructive CAD. The discriminative threshold for high burden, established by the segment involvement score (SIS), was >5 segments with plaque (15.4% patients). The prevalence of SIS >5 among the BMI classes was: 18.7%, 13.7% and 13.6% for normal, overweight and obesity respectively (*p* values for the specific classes versus all other patients: 0.241, 0.450 and 0.663).

Conclusions: In this population of stable patients undergoing CCTA for suspected CAD, BMI was an independent predictor of its presence, but was not correlated with the coronary disease severity.

Keywords

Cardiac computed tomography, body mass index, coronary artery disease

Received 7 January 2013; accepted 29 May 2013

Introduction

In recent years, obesity has reached epidemic proportions, and is currently a highly prevalent chronic condition associated with significant morbidity and mortality.[1] In the general population, overweight and obesity are associated with an increased risk of cardiovascular disease and all-cause mortality.[2,3] However, among patients with known coronary artery disease

[1]Cardiology Department, Centro Hospitalar Lisboa Ocidental, Portugal
[2]Cardiovascular Centre, Hospital da Luz, Portugal
[3]Chronic Diseases Research Centre (CEDOC), Universidade Nova de Lisboa, Portugal
[4]Imaging Centre, Hospital da Luz, Portugal

Corresponding author:
Hélder Dores, Av. Prof. Reinaldo dos Santos, 2799-523 Carnaxide, Lisbon, Portugal.
Email: heldores@hotmail.com

XML Template (2013) [5.6.2013–2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

(CAD), the evidence is contradictory. Several studies have suggested an 'obesity paradox' due to a protective effect of obesity against adverse outcomes, and the correlation between body mass index (BMI) and survival has been described as having a U-shaped curve.[4,5] Additionally, the relationship between obesity and CAD extension remains controversial. Several authors suggest that, paradoxically, obese patients have a lower CAD burden (Duke myocardial jeopardy scores) and lower prevalence of high-risk coronary anatomy (significant left main or triple vessel disease) compared to non-obese patients.[6,7]

Recently, coronary computed tomography angiography (CCTA) has become widely available and adopted in the clinical practice, mainly due to the high negative predictive value to rule out obstructive CAD.[8,9] In addition, CCTA allows also the identification of non-obstructive CAD, providing in this way a noninvasive quantification of the total coronary atherosclerotic burden. As showed in the large CONFIRM Registry,[10] both non-obstructive and obstructive CAD, identified by CCTA, were associated with worse cardiovascular outcomes, while the absence of CAD was associated with a favorable prognosis. To the best of our knowledge, there are no previous published studies evaluating the relationship of BMI with both the presence and extension of CAD, documented by CCTA, and this was the aim of the present study.

Methods

Population

From February 2007 to October 2011 all consecutive stable patients undergoing CCTA (dual source scanner) for the evaluation of possible CAD were included in a single centre prospective registry. Figure 1 shows patient selection and study design. Patients referred from the emergency department (possible acute coronary syndrome) or indications other than evaluation for possible CAD were excluded from this analysis. For the purpose of this study, 1706 patients were included in the context of: previous equivocal or inconclusive stress tests or discordant with the clinical evaluation ($n=1253$; 73.5%), CCTA as first line investigation of possible CAD ($n=294$; 17.2%), preoperative CAD assessment prior to non-coronary valvular or aortic surgery ($n=34$, 2.0%), evaluation of possible CAD in cardiomyopathies ($n=125$, 7.3%).

A detailed medical history with a risk factors questionnaire was obtained from the patients to assess for the presence of: (a) diabetes mellitus (defined as a fasting glucose level of $\geq$7.0 mmol/l or the need for insulin or oral hypoglycemic agents); (b) dyslipidemia (defined as a total cholesterol level $\geq$5 mmol/l or treatment with lipid-lowering drugs); (c) hypertension (defined as blood pressure $\geq$140/90 mm Hg or the use of antihypertensive medication); (d) Positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years old); (e) smoking (defined as previous (less <1 year) or current smoker). Weight and height were self-reported by the patients in the questionnaire. The overall population was stratified by the BMI value, according to the World Health Association classification:[11] underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obesity (IMC$\geq$30.0 kg/m^2). Underweight patients were excluded from the present analysis. In a cohort of patients, the detailed atherosclerotic burden was evaluated and compared among the BMI classes. The local ethics committee approved the study and all patients gave written informed consent.

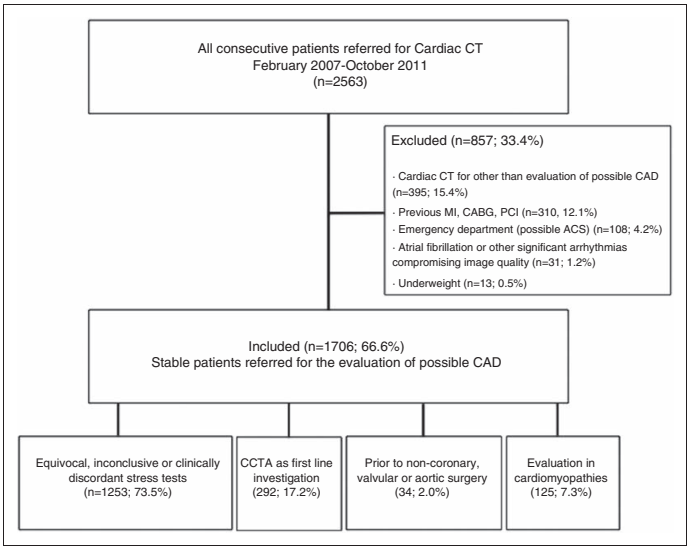
Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition®, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and beta-blockers were administered to lower the heart rate when indicated. During the scan acquisition, a bolus of iodinated contrast (Visipaque®, GE Healthcare, USA) was injected at a 6 ml/s infusion rate, followed by a 50 ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time-+6 s delay) x flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries. Dose reduction strategies-including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering-were used whenever feasible. Mean estimated radiation dose was 5.3 $\pm$ 3.7 mSv, contrast dose was 97.1 $\pm$ 14.4 ml and heart rate was 67.8 $\pm$ 13.3 bpm. Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments. Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III-equivalent experience. The Society of Cardiovascular Computed Tomography (SCCT) recommended classification[12] was used regarding segmentation (16 segments), stenosis severity (<25%; 25–49%; 50–69%; 70–99%;

XML Template (2013) [5.6.2013-2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]



8 **Figure 1.** Patient selection and study design.
CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CT: computed tomography; PCI: percutaneous coronary intervention.

100%) and plaque composition (calcified, non-calcified or mixed). CAD was defined as the presence of any coronary plaque identified in CCTA (both obstructive and non-obstructive lesions; including non-calcified plaque). Obstructive CAD was defined as the presence of plaque with ≥50% stenosis. The discriminative threshold for high coronary atherosclerotic burden was established as the SIS with the previously tested prognostic threshold of >5 segments with plaque.[13] In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat or the vessel lumen itself. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. The value of the Agatston calcium score was obtained with the analysis of consecutive non-contrast 3 mm slices, with a reconstruction b35f Kernel and a small (cardiac) FOV, with a dedicated software (CaScoring- Siemens™), where every area at least with 1 mm^2 within a coronary vessel with a density above 130 HU (Hounsfield Units) was selected.[14]

Statistical analysis

Continuous variables with normal distribution were expressed as means and standard deviation (SD), those with non-normal distribution as medians and interquartile range (IQR). Normality was tested with the Kolmogorov-Sminorv test. Categorical 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 Mann-Whitney or Kruskal-Wallis test for continuous variables. Multivariate analyze (binary logistic regression model - enter method) was performed to identify independent predictors of CAD and independent predictors of obstructive CAD. In this model all the statistically significant variables in the univariate analysis were included. Two-tailed tests of

XML Template (2013) [5.6.2013–2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

significance are reported. For all comparisons, a p value of <0.05 was considered statistically significant. When appropriate, a 95% confidence interval (CI) was calculated. Statistical analysis was performed with SPSS version 19.0 (SPSS® Inc., Chicago, Illinois, USA).

Results

Study population

Of the 1706 patients included in the final analysis, the median age was 59.0 (51.0–66.0) years and the majority (57.2%) were male. Demographic and clinical characteristics are depicted in the Table 1. The percentage of patients with diabetes was 15.0% and there was a high prevalence of both hypertension and dyslipidemia (60.5% and 59.8% respectively). The median HeartScore was 2(1–4)%, and 17.2% patients had high cardiovascular risk (HeartScore ≥5%). The median BMI was 26.7 (24.4–29.4) kg/m^2 and the stratification according to the BMI classes was: normal (n = 530, 31.1%), overweight (n = 802, 47.0%) and obesity (n = 374, 21.9%).

CAD burden

In the overall population, the median calcium score was 4(0-100), 58.9% patients had CAD and 19.1% patients had obstructive CAD. By univariate analysis, BMI was significantly higher in patients with CAD (27.7 ± 4.3 vs 26.8 ± 4.3 kg/m^2, $p < 0.001$); these patients were also older, more often male and had higher prevalence of diabetes, hypertension and dyslipidemia. Regarding the presence of obstructive CAD, this was more prevalent in the older patients, in males and in patients with hypertension, diabetes, dyslipidemia and smoking. However, BMI was not significantly different among patients with and without obstructive CAD (27.7 ± 4.3 vs 27.2 ± 4.3 kg/m^2, p = 0.120) (Table 2). By multivariate analysis (adjusted for age, male gender, BMI, dyslipidemia, diabetes and hypertension), BMI remain an independent predictor of CAD (OR 1.03, 95% CI 1.01–1.06, p = 0.012) (Figure 2).

In a cohort of 319 patients in whom the detailed atherosclerotic burden evaluation was performed (4516 segments; 4077 evaluable), the distribution according BMI classes was: normal (n = 107, 33.5%), overweight (n = 146, 45.8%) and obesity (n = 66, 20.7%). Obstructive CAD was identified in 16.9% of the patients and 45.1% had non-obstructive CAD. The median number of coronary segments with lesions was 1.0 (0.0–4.0) and 15.4% patients had SIS >5. The distribution of the variable SIS >5 among the BMI classes was: 18.7%, 13.7% and 13.6% for normal, overweight and obesity respectively (p values for the specific classes versus all other patients: 0.241, 0.450 and 0.663 respectively).

Table 1. Demographic and clinical characteristics

Variables	All patients (n = 1706)
Demographic	
Age, median (IQR) years	59.0 (51.0–66.0)
Male gender, n (%)	976 (57.2)
Cardiovascular risk factors, n (%)	
Diabetes mellitus	256 (15.0)
Hypertension	1032 (60.5)
Smoking	459 (26.9)
Dyslipidemia	1021 (59.8)
Family history of premature CAD	606 (35.5)
Cardiovascular risk	
HeartScore, median (IQR)	2.0 (1.0–4.0)
HeartScore ≥5%, n (%)	293 (17.2)
Chest pain, n (%)	
Asymptomatic	836 (49.0)
Non-cardiac	369 (21.6)
Atypical	363 (21.3)
Typical	138 (8.1)
BMI (kg/m^2)	
Median (IQR)	26.7 (24.4–29.4)
Normal, n (%)	530 (31.1)
Overweight, n (%)	802 (47.0)
Obesity, n (%)	374 (21.9)

BMI: body mass index; CAD: coronary artery disease; IQR: interquartile range.

Discussion

Our findings suggest that in this population of stable patients with low to intermediate cardiovascular risk referred for CCTA for suspected CAD, BMI was an independent predictor of CAD presence, but was not correlated with CAD severity. There were no significant differences across different BMI classes in the percentage of patients with obstructive CAD or in the overall coronary atherosclerotic burden, as evaluated by the segment involvement score.

In the general population, obesity is a well-known risk factor for CAD, being associated with poor clinical outcomes. In patients with documented CAD this relationship remains controversial, but the prevalence of obesity is patients with CAD is still increasing and the current management of obesity seems inadequate.[15] Some previous studies described an 'obesity paradox' with better outcomes of obese patients when compared with non-obese, frequently with an U-shaped relationship. This paradoxical association between BMI and

XML Template (2013) [5.6.2013-2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

Table 2. Characteristics distribution according to the presence of coronary artery disease and obstructive stenosis

Variables	CAD ($n=1005$)	Non-CAD ($n=701$)	*p* value	Obstructive ($n=326$)	Non-obstructive ($n=1380$)	*p* value
Age (years) (mean ± SD)	61.5 ± 9.9	53.5 ± 11.9	<0.001	62.1 ± 9.9	57.3 ± 11.6	<0.001
Male gender, *n* (%)	648 (64.5)	328 (46.8)	<0.001	239 (73.3)	737 (53.4)	<0.001
Diabetes mellitus, *n* (%)	191 (19.0)	65 (9.3)	<0.001	84 (25.8)	172 (12.5)	<0.001
Hypertension, *n* (%)	669 (66.6)	363 (51.8)	<0.001	226 (69.3)	806 (58.4)	<0.001
Dyslipidemia, *n* (%)	664 (66.1)	357 (50.9)	<0.001	222 (68.1)	799 (57.9)	0.001
Smoking, *n* (%)	287 (28.6)	172 (24.5)	0.065	111 (34.0)	348 (25.2)	0.001
Familiar history of CAD, *n* (%)	362 (36.0)	244 (34.8)	0.607	113 (34.7)	493 (35.7)	0.719
BMI (kg/m^2) (mean ± SD)	27.7 ± 4.3	26.8 ± 4.3	<0.001	27.7 ± 4.3	27.2 ± 4.3	0.120

BMI: body mass index; CAD: coronary artery disease; SD: standard deviation.

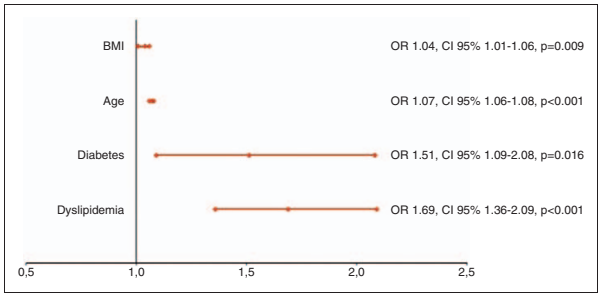


Figure 2. Independent predictors of coronary artery disease (CAD) presence (multivariate analysis).
BMI: body mass index; CI: confidence interval; OR: odds ratio.

survival in patients with CAD occurs irrespectively of the treatment strategy and, in fact, among patients undergoing percutaneous coronary intervention (PCI) an increased BMI was associated with improved survival[4] and a meta-analysis of patients undergoing PCI showed a lower risk of death in patients with higher BMI.[5] Several explanations are frequently given for this paradox. Adipose tissue is a recognized major endocrine organ and obesity is associated with high serum levels of low-density lipoproteins that have anti-inflammatory effect.[4,16] As an example, in patients with heart failure, it has been demonstrated that obese individuals have lower levels of tumor necrosis factor and other inflammatory cytokines.[16] On the other hand, poor clinical outcomes in patients with lower weight can be related to malnutrition or cachexia and prevalence of comorbid conditions, such as occult malignancy and heart failure.[4]

The controversy is not limited to the association between obesity and clinical outcomes, but also occurs with the relationship between obesity and atherosclerotic CAD extension. Studies from Israel performed by Rubinshtein et al.[6] and from the USA by Niraj et al.[7] showed that obesity was associated with less severe CAD among patients undergoing coronary angiography. The better prognosis of obese patients in these studies could be explained by the investigation and treatment at earlier stages in the disease course. Patients with higher BMI are also more frequently submitted to standard medical therapies, diagnostic coronary angiography and revascularization procedures.[17] Among patients undergoing coronary invasive angiography, obese patients are younger and also have a lower prevalence of other cardiovascular risk factors. This evidence contributes to the lower prevalence of high-risk coronary anatomy in patients with higher BMI in some of the previous reports. The Duke jeopardy score was frequently used in these studies, as an estimate of the amount of myocardium at risk according to the coronary artery stenosis location, and provided

XML Template (2013) [5.6.2013–2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

independent prognostic information.[18] The association between BMI and CAD assessed by CCTA to our knowledge was not previously reported. CCTA is a noninvasive and accurate method to evaluate CAD, with a good correlation with invasive angiography (QCA) and intravascular ultrasound.[12]

6

In our study, after adjusting for traditional cardiovascular risk factors including age, gender, hypertension, diabetes, smoking, familiar history of CAD and dyslipidemia, BMI as a continuous variable remained an independent predictor for CAD presence but was not a predictor of CAD severity. One possible explanation for these findings could be related to the baseline characteristics of the population: stable patients (most of them without typical chest pain) and only a minority with high cardiovascular risk, probably representing early stages in the coronary disease evolution. This population is significantly different from those referred for invasive angiography who were included in the previous studies. On the other hand, BMI does not differentiate central and peripheral adiposity. Measurements of abdominal obesity and waist-hip ratio could be more discriminant, as abdominal obesity has been more closely associated with cardiovascular events.[19] In this regard, computed tomography has been recognized as a highly effective, accurate, and reproducible technique for measuring visceral adiposity,[20] and it has been documented by previous authors that there is a correlation between abdominal adiposity and the extent of coronary atherosclerosis.[21]

Limitations

There are some limitations related to this report: (a) single centre data with medium size cohort; (b) use of BMI as the only marker of adiposity, instead of the more specific markers of abdominal obesity that could have a better correlation with CAD severity; (c) studied population predominantly with low-intermediate cardiovascular risk which could have underestimated the coronary disease burden of patients with high BMI; (d) referral bias, since the presence of obesity itself could have played a role in the decision to refer for evaluation, as obese patients are generally considered to be at higher risk of CAD; (e) the risk factors dyslipidemia and hypertension were included in the analysis as categorical variables which could have resulted in some underestimation of their predictive power; (f) lack of follow-up data to evaluate the prognostic impact of BMI in clinical outcomes.

Conclusions

In this population of stable patients undergoing CCTA for suspected CAD, BMI was an independent predictor of the presence of CAD, but was not correlated with severity. There were no significant differences in the percentage of obstructive CAD or in the overall coronary atherosclerotic burden, evaluated by the number of segments with plaque, across the different BMI classes.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None declared.

7

References

1. Haslam DW and James WP. Obesity. *Lancet* 2005; 366: 1197–1209.
2. Gonzalez A, Hartge P, Cerhan J, et al. Body-mass index and mortality among 1.46 million white adults. *N Engl J Med* 2010; 363: 2211–2219.
3. Dudina A, Cooney MT, Bacquer DD, et al. SCORE investigators. Relationships between body mass index, cardiovascular mortality, and risk factors: A report from the SCORE investigators. *Eur J Cardiovasc Prev Rehabil* 2011; 18: 731–742.
4. Hastie C, Padmanabhan S, Slack R, et al. Obesity paradox in a cohort of 4880 consecutive patients undergoing percutaneous-coronary intervention. *Eur Heart J* 2010; 31: 222–226.
5. Oreopoulos A, Padwal R, Norris CM, et al. Effect of obesity on short- and long-term mortality post coronary revascularization: A meta-analysis. *Obesity* 2008; 16: 442–450.
6. Rubinshtein R, Halon DA, Jaffe R, et al. Relation between obesity and severity of coronary artery disease in patients undergoing coronary angiography. *Am J Cardiol* 2006; 97: 1277–1280.
7. Niraj A, Pradahan J, Fakhry H, et al. Severity of coronary artery disease in obese patients undergoing coronary angiography: 'Obesity paradox' revisited. *Clin Cardiol* 2007; 30: 391–396.
8. Meijboom WB, van Mieghem CA, Mollet NR, et al. 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. *J Am Coll Cardiol* 2007; 50: 1469–1475.
9. Weustink AC, Mollet NR, Neefjes LA, et al. Preserved diagnostic performance of dual-source CT coronary angiography with reduced radiation exposure and cancer risk. *Radiology* 2009; 252: 53–60.
10. Min JK, Dunning A, Lin FY, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011; 58: 849–860.

XML Template (2013) [5.8.2013-2:38pm] [1–8]
//blmas3/cenpro/ApplicationFiles/Journals/SAGE/3B2/CPRJ/Vol00000/130237/APPFile/SG-CPRJ130237.3d (CPR) [PREPRINTER stage]

11. World Health Organization. *Physical status: The use and interpretation of anthropometry. Report of a WHO Expert Committee*. WHO Technical Report Series 854. Geneva, World Health Organization 1995.
12. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009; 3: 122–136.
13. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007; 50: 1161–1170.
14. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15: 827–832.
15. De Bacquer D, Dallongeville J, Heidrich J, et al. EUROASPIRE III Study Group. Management of overweight and obese patients with coronary heart disease across Europe. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 4474–4454.
16. Feldman AM, Combes A, Wagner D, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. [Review]. *J Am Coll Cardiol* 2000; 35: 537–544.
17. Steinberg BA, Cannon CP, Hernandez AF, et al. Medical therapies and invasive treatments for coronary artery disease by body mass: The 'obesity paradox' in the Get With The Guidelines database. *Am J Cardiol* 2007; 100: 1331–1335.
18. Graham MM, Faris PD, Ghali WA, et al. Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. *Am Heart J* 2001; 142: 254–261.
19. Wajchenberg BL. Subcutaneous and visceral adipose tissue: Their relation to the metabolic syndrome. *Endocr Rev* 2000; 21: 697–738.
20. Yoshizumi T, Nakamura T, Yamane M, et al. Abdominal fat: Standardized technique for measurement at CT. *Radiology* 1999; 211: 283–286.
21. Ohashi N, Yamamoto H, Horiguchi J, et al. Association between visceral adipose tissue area and coronary plaque morphology assessed by CT angiography. *J Am Coll Cardiol Img* 2010; 3: 908–917.

Capítulo 7.

Diabetes mellitus - subgrupo modelo de elevada carga aterosclerótica

RESUMO:

Este capítulo é dedicado à diabetes mellitus, como modelo de DC mais avançada, tendo sido o preditor clínico mais importante da presença e da gravidade da DC. Deste modo a diabetes mereceu uma análise detalhada, servindo como subgrupo modelo para a avaliação do desempenho de diferentes scores de carga aterosclerótica.

Foi incluído neste capítulo o **artigo 16**, que resulta da análise dos diferentes índices de carga aterosclerótica na população incluída na tese e no qual é discutida a questão da diabetes como equivalente de risco de DC.

O padrão de DC na diabetes, mais extensa e difusa, justifica as dificuldades impostas à revascularização, tema ilustrado pelo **artigo 17** e discutido numa secção específica deste capítulo.

ABSTRACT:

This chapter is dedicated to diabetes mellitus, as a model for more advanced coronary disease, since it was identified as the single most important predictor of the presence and severity of coronary disease. In this regard, the subgroup of diabetic patients was the subject of an individual detailed analysis, useful as a model to evaluate the performance of different atherosclerotic burden scores.

Manuscript 16 was included in this chapter, since it was the result of the analysis of the different atherosclerotic burden scores and includes a discussion on the issue of diabetes as a coronary artery disease equivalent.

The coronary disease pattern in diabetes, more diffuse and severe, explains the difficulties posed to revascularization, and this issue is illustrated by **manuscript 17** and also discussed in a specific section in this chapter.

ARTIGO 16/ MANUSCRIPT 16:

DIABETES AS AN INDEPENDENT PREDICTOR OF HIGH ATHEROSCLEROTIC BURDEN ASSESSED BY CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY: THE CORONARY ARTERY DISEASE EQUIVALENT REVISITED.

De Araújo Gonçalves P, Garcia-Garcia HM, Carvalho MS, Dores H, Jerónimo Sousa P, Marques H, Ferreira A, Cardim N, Teles R, Raposo L, Mesquita-Gabriel H, Almeida M, Aleixo A, Mota Carmo M, Pereira Machado F, Mendes M.

Int J Cardiovasc Imaging. 2013; 29:1105–1114

ARTIGO 17/ MANUSCRIPT 17:

COMPLEMENTARY EFFECTS OF SIROLIMUS-ELUTING STENTS AND GLYCOPROTEIN IIB/IIIA INHIBITORS FOR PERCUTANEOUS CORONARY INTERVENTION IN DIABETIC PATIENTS: 1-YEAR FOLLOW-UP OF A SINGLE CENTER REGISTRY.

De Araújo Gonçalves P, Seabra-Gomes R, Teles R, Almeida M, Aguiar C, Raposo L, Ferreira J, Pereira Machado F.

Heart 2006, 92; 1155-56.

SUMÁRIO DO CAPÍTULO 7:

7.1 INTRODUÇÃO

A diabetes mellitus é um distúrbio metabólico complexo, caracterizado por um estado de hiperglicémia crónico, resultante da interacção de diferentes factores genéticos e ambientais e culminando na lesão de vários órgãos alvo. É um importante factor de risco CV, não só pela sua estreita associação fisiopatológica, mas também pela elevada prevalência, o que a torna um importante problema de saúde pública (1).

No estudo PREVDIAB, a prevalência de diabetes tipo 2 em 2009, na população portuguesa (amostra de 5167 indivíduos entre os 20 e os 79 anos) era de 11,7%, dos quais 43,6% não tinham sido previamente diagnosticados. Esta prevalência era mais elevada nos homens e na faixa etária entre os 60 e os 79 anos, onde atingia cerca de 1 em cada 4 indivíduos (26,3%) (2).

De acordo com os últimos números do relatório anual do observatório nacional da diabetes, em 2011 esta prevalência aumentou para 12,7%, correspondendo em números absolutos a cerca de 1 milhão de doentes com diabetes em Portugal (3).

Os doentes com diabetes representam um subgrupo com elevado risco de eventos CV, estando recomendado, de acordo com as varias linhas de orientação, um manejo mais agressivo destes doentes (4-6).

No entanto este trata-se também de um subgrupo muito heterogéneo de doentes e para o qual não está actualmente indicada antiagregação em prevenção primária, reforçando o potencial papel de métodos de estratificação de risco que possam identificar os doentes antes das manifestações clínicas da aterosclerose.

7.2 DIABETES COMO EQUIVALENTE DE RISCO DE DOENÇA CORONÁRIA

Num estudo clássico publicado em 1998 no *New England Journal of Medicine*, que ficou conhecido como o estudo *Haffner*, foi avaliada a taxa de EAM numa população com e sem diabetes, para responder à questão se os doentes com diabetes deveriam ser alvo de uma terapêutica agressiva semelhante à que se fazia para os doentes com antecedentes de EAM. Neste trabalho, a taxa de enfarte verificada ao longo dos 7 anos de seguimento nos doentes com diabetes, foi sobreponível à dos doentes já com antecedentes de EAM (7). Este foi um dos trabalhos que levou ao conceito da diabetes como equivalente de risco de doença coronária, justificado por se antecipar uma taxa de eventos semelhante ao de uma população de prevenção secundária pós-enfarte.

Nas recomendações do NCEP-ATP3 publicadas em 2001 a diabetes vem considerada no patamar de risco mais elevado, a par de outros equivalentes como a doença vascular periférica, o aneurisma da aorta abdominal, a doença carotídea sintomática ou uma conjugação de diferentes factores de risco que confiram um risco de morte ou EAM superior a 20% aos 10 anos (6).

Nas recomendações europeias é feita a mesma equivalência, sendo um doente com diabetes considerado pelo menos de elevado risco CV, com risco ≥5% de morte CV a 10 anos ou até de muito alto risco (≥10% morte CV a 10 anos) se tiver associado outros factores de risco e/ou lesões de órgão alvo como microalbuminúria (5).

No entanto, a diabetes representa um grupo bastante heterogéneo de doentes e trabalhos mais recentes colocaram em questão se o risco desta população estaria ao nível de um patamar de prevenção secundaria.

Num estudo que desafiou o conceito de diabetes como equivalente de doença coronária, foi feita a comparação da taxa de eventos vasculares de acordo com a presença de diabetes ou de doença coronária (estenose ≥50% na coronariografia invasiva), tendo sido concluído que a diabetes por si só não deveria ser considerado como equivalente de risco de doença coronária, uma vez que a taxa de eventos verificada aos 4 anos de seguimento nos doentes com diabetes mas sem doença coronária era significativamente inferior à dos doentes com antecedentes de doença coronária e sem diabetes (8).

Num outro trabalho recentemente publicado que envolveu 1,2 milhões de doentes da base de dados do "*Alberta Kidney Disease Network* (AKDN) e o *National Health and Nutrition Examination Survey* (NHANES)", seguidos durante 4 anos, a taxa de EAM no subgrupo de doentes com diabetes (5,4 EAM por 1000 doentes/ano) foi claramente inferior à dos doentes com EAM prévio. (18,5 EAM por 1000 doentes/ano) (9). Neste registo de larga dimensão, esta taxa de EAM verificada nos doentes com diabetes foi ainda inferior à verificada nos doentes com insuficiência renal crónica (6,9 EAM por 1000 doentes/ano), definida neste estudo como uma taxa de filtração glomerular estimada <60ml/min/1.73m2.

Por outro lado, embora o benefício dos antiagregantes plaquetares seja indiscutível nos doentes com diabetes e doença CV estabelecida (10), a sua indicação em prevenção primária é mais duvidosa e actualmente não recomendada na ausência de manifestações clínicas de aterosclerose (5).

Numa meta-análise de 6 estudos randomizados de aspirina vs placebo, envolvendo mais de 10.000 indivíduos em prevenção primária, não foi possível documentar redução significativa da taxa de eventos CV na população global, embora tenha ocorrido uma redução significativa na taxa de EAM no sexo masculino (11).

Este achado é aparentemente paradoxal, uma vez que nos doentes com diabetes existe um estado de maior activação plaquetar e endotelial que contribuem para a criação de um meio pró-trombótico (12). No entanto, a ausência de um benefício claro da antiagregação em prevenção primária poderá ser reflexo de uma maior taxa de resistência ao acido acetilsalicílico nestes doentes (13). Por outro lado, esta ausência de benefício do uso indiscriminado de antiagregação nos doentes com diabetes pode colocar em evidência a heterogeneidade desta população, sendo que em vários casos a baixa taxa de eventos CV pode não ser suficiente para contrabalançar o

aumento das complicações hemorrágicas associadas ao uso destes fármacos. Torna-se assim necessário em prevenção primária estratificar o risco destes doentes, para melhor decidir quais beneficiam destas medidas farmacológicas mais agressivas.

7.3 A DIABETES MELLITUS COMO SUBGRUPO MODELO DE ELEVADA CARGA ATEROSCLERÓTICA CORONÁRIA

A doença coronária é a causa de morte mais comum nos doentes com diabetes (14) e em termos epidemiológicos, o risco de EAM destes doentes é cerca de 2 vezes superior ao da população não diabética, de acordo com os resultados do estudo INTERHEART ((15).

Independentemente de se considerar ou não a diabetes como equivalente de risco de doença coronária e assim alvo de prevenção secundária, nos doentes que têm doença coronária estabelecida existem alguns aspectos particulares, nomeadamente em relação à extensão e distribuição da doença, que a tornam um ***subgrupo modelo*** de elevada carga aterosclerótica coronária. Na presença de diabetes, a doença coronária é frequentemente mais extensa, com maior número de lesões e vasos envolvidos. Por outro lado, a distribuição anatómica das placas na árvore coronária pode ser diferente, favorecendo uma localização mais distal nos doentes com diabetes. De acordo com a análise da distribuição dos diferentes índices de carga aterosclerótica dos doentes incluídos na tese, todos os índices estudados eram significativamente mais prevalentes nos doentes com diabetes, que tinham um número superior de placas em todos os vasos – **artigo 16** (16). Neste trabalho foi feita a análise detalhada por segmento da árvore coronária (mais de 8000 segmentos avaliados), incluindo as lesões não obstrutivas, o que permitiu estudar a distribuição anatómica na árvore coronária, tendo-se verificado uma distribuição preferencial das lesões pelos segmentos mais distais (rácio proximal/distal 0,75), por comparação com os doentes sem diabetes (rácio proximal/distal 1,04). Esta mais elevada carga aterosclerótica e diferente distribuição na árvore coronária poderá ter implicações para a eficácia das estratégias de revascularização miocárdica nestes doentes.

Por outro lado, a inflamação desempenha um papel central na aterosclerose e pode ser um factor unificador da fisiopatologia da diabetes e da doença coronária, de acordo com a hipótese *"common soil"* que sugere que um estado de inflamação de baixo grau poderia ser o meio propicio ao desenvolvimento da resistência à insulina e à formação e desenvolvimento das placas ateroscleróticas na árvore vascular (17). Esta hipótese vem reforçada não só pela associação epidemiológica, mas sobretudo por trabalhos que demonstraram o papel da inflamação no

desenvolvimento do processo aterosclerótico (18) e a associação entre níveis elevados de factores inflamatórios e pró-tromboticos e o desenvolvimento subsequente de diabetes (19).
De qualquer modo, em última análise, o aparecimento dos eventos CV nestes doentes é o resultado de complexas interacções entre as lesões ateroscleróticas vulneráveis, do meio pró-trombótico ou sangue vulnerável e também da vulnerabilidade do miocárdio, no conceito actual que ultrapassa a visão mais simplificada da placa, passando para o conceito do doente vulnerável (20, 21).

7.4 IMPLICAÇÕES PARA A DECISÃO DA ESTRATÉGIA DE REVASCULARIZAÇÃO.

A escolha da estratégia de revascularização, deve ter em conta estes aspectos particulares da DC na diabetes. Vários estudos demonstraram que quanto mais extensa e complexa é a doença coronária maior é o beneficio da revascularização cirúrgica em relação à angioplastia, motivo pelo qual na doença do tronco comum, na doença de 3 vasos e na doença de 2 vasos com envolvimento da descendente anterior proximal a recomendação é mais forte para a cirurgia vs angioplastia (22), sobretudo em scores de Syntax elevados (23, 24).
Por outro lado, os doentes com diabetes representam um subgrupo com maior mortalidade e morbilidade após revascularização, seja ela cirurgia ou percutânea (4, 22). Após a angioplastia em particular, os doentes com diabetes tem maior risco de reestenose e de trombose, sendo justificado o uso de stents "*drug-eluting*" e medidas farmacológicas mais agressivas (25-27).

No estudo BARI-2D, doentes com diabetes e doença coronária estável foram randomizados para terapêutica medica optimizada isolada ou em associação à revascularização, tendo havido um beneficio desta ultima, mas apenas no subgrupo cirúrgico (28).
No recentemente publicado ensaio randomizado FREEDOM, ficou demonstrada mais uma vez a superioridade da revascularização cirúrgica em relação à angioplastia com stents "*drug-eluting*" nos doentes com diabetes e envolvimento multivaso, com menor taxa de morte e EAM, embora à custa e uma maior incidência de acidentes vasculares cerebrais (29).
Na análise dos doentes com diabetes ou síndrome metabólico incluídos no estudo SYNTAX, foi igualmente demonstrada superioridade da revascularização cirúrgica, embora apenas nos doentes com anatomia coronária mais complexa, no último tercil de score de Syntax (30).

No registo multicêntrico PORTO, que avaliou a eficácia da angioplastia com stents "drug-eluting" em vasos de pequeno calibre, a taxa de eventos cardíacos foi significativamente superior no subgrupo de doentes com diabetes (que representaram 44% dos doentes incluídos, nomeadamente a taxa de reestenose. No entanto, a grande maioria das novas revascularizações verificadas no seguimento a 1 ano deste registo resultaram de progressão da doença noutros

segmentos da árvore coronária, com revascularizações do mesmo vaso não resultantes de restenose e bem como de outros vasos (31).

O principal motivo para a consistente superioridade da cirurgia em relação à angioplastia nos doentes com diabetes está relacionado com a necessidade de novos procedimentos de revascularização no seguimento, por progressão de lesões anteriormente não obstrutivas. Esta variável é mais importante para um tratamento mais focal, como é o caso da angioplastia, embora também possa interferir com o resultado da cirurgia, se houver progressão de doença nos segmentos da árvore coronária distais às anastomoses. Deste modo, a carga aterosclerótica coronária parece ser determinante para a manutenção a longo prazo de um bom resultado do procedimento de revascularização, pelo que a sua avaliação poderá ser útil no manejo destes doentes.

7.5 BIBLIOGRAFIA

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004 May;27(5):1047-53.
2. Gardete-Correia L, Boavida JM, Raposo JF, Mesquita AC, Fona C, Carvalho R, et al. First diabetes prevalence study in Portugal: PREVADIAB study. Diabet Med. 2010 Aug;27(8):879-81.
3. Gardete Correia L BJ, Fragoso de Almeida, JP, Massano Cardoso S, Dores J, Sequeira Duarte J, Duarte R, Ferreira H, Guerra F, Medina JL, Nunes JS, Pereira M, Raposo J. . Diabetes: Factos e números 2012 - relatório anual do Observatório Nacional da Diabetes.ISBN: 978-989-96663-1-3. http://www.spd.pt/images/ond2013.pdf. 2012.
4. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J. 2007 Jan;28(1):88-136.
5. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2012 Jul;33(13):1635-701.
6. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.
7. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998 Jul 23;339(4):229-34.
8. Saely CH, Aczel S, Koch L, Schmid F, Marte T, Huber K, et al. Diabetes as a coronary artery disease risk equivalent: before a change of paradigm? Eur J Cardiovasc Prev Rehabil. 2010 Feb;17(1):94-9.
9. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012 Sep 1;380(9844):807-14.
10. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8;308(6921):81-106.
11. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009;339:b4531.
12. Ferroni P, Basili S, Falco A, Davi G. Platelet activation in type 2 diabetes mellitus. J Thromb Haemost. 2004 Aug;2(8):1282-91.
13. Evangelista V, Totani L, Rotondo S, Lorenzet R, Tognoni G, De Berardis G, et al. Prevention of cardiovascular disease in type-2 diabetes: how to improve the clinical efficacy of aspirin. Thromb Haemost. 2005 Jan;93(1):8-16.
14. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. Diabetologia. 2001 Sep;44 Suppl 2:S14-21.
15. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):937-52.
16. de Araujo Goncalves P, Garcia-Garcia HM, Carvalho MS, Dores H, Sousa PJ, Marques H, et al. Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited. Int J Cardiovasc Imaging. 2012 Dec 13.
17. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. Diabetes. 1995 Apr;44(4):369-74.

18. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes. 2003 Jul;52(7):1799-805.
19. Festa A, D'Agostino R, Jr., Tracy RP, Haffner SM, Insulin Resistance Atherosclerosis S. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. Diabetes. 2002 Apr;51(4):1131-7.
20. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003 Oct 7;108(14):1664-72.
21. Hess K, Marx N, Lehrke M. Cardiovascular disease and diabetes: the vulnerable patient. Eur Heart J Suppl. 2012;14 (suppl B):B4-B13.
22. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010 Oct;31(20):2501-55.
23. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72.
24. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet. 2013 Feb 23;381(9867):629-38.
25. Bhatt DL, Marso SP, Lincoff AM, Wolski KE, Ellis SG, Topol EJ. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. J Am Coll Cardiol. 2000 Mar 15;35(4):922-8.
26. de Araujo Goncalves P, Seabra-Gomes R, Teles R, Almeida M, Aguiar C, Raposo L, et al. Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow up of a single-centre registry. Heart. 2006 Aug;92(8):1155-6.
27. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schomig A, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ. 2008;337:a1331.
28. Group BDS, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009 Jun 11;360(24):2503-15.
29. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012 Dec 20;367(25):2375-84.
30. Mack MJ, Banning AP, Serruys PW, Morice MC, Taeymans Y, Van Nooten G, et al. Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or metabolic syndrome. Ann Thorac Surg. 2011 Dec;92(6):2140-6.
31. Seabra-Gomes R, Sousa JE, Sousa A, Teles R, Pereira H, Farto Abreu P, et al. Small coronary arteries treated with sirolimus-eluting stents: one-year results of the PORTO multicentre registry. EuroIntervention. 2007 Aug;3(2):197-205.

7.6 ARTIGO 16 / MANUSCRIPT 16:

Int J Cardiovasc Imaging (2013) 29:1105–1114
DOI 10.1007/s10554-012-0168-4

ORIGINAL PAPER

Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited

Pedro de Araújo Gonçalves · Hector M. Garcia-Garcia · Maria Salomé Carvalho · Helder Dores · Pedro Jeronimo Sousa · Hugo Marques · Antonio Ferreira · Nuno Cardim · Rui Campante Teles · Luís Raposo · Henrique Mesquita Gabriel · Manuel Almeida · Ana Aleixo · Miguel Mota Carmo · Francisco Pereira Machado · Miguel Mendes

Received: 10 October 2012 / Accepted: 5 December 2012 / Published online: 13 December 2012

Abstract (1) To study the prevalence and severity of coronary artery disease (CAD) in diabetic patients. (2) To provide a detailed characterization of the coronary atherosclerotic burden, including the localization, degree of stenosis and plaque composition by coronary computed tomography angiography (CCTA). Single center prospective registry including a total of 581 consecutive stable patients (April 2011–March 2012) undergoing CCTA (Dual-source CT) for the evaluation of suspected CAD without previous myocardial infarction or revascularization procedures. Different coronary plaque burden indexes and plaque type and distribution patterns were compared between patients with (n = 85) and without diabetes (n = 496). The prevalence of CAD (any plaque; 74.1 vs. 56 %; $p = 0.002$) and obstructive CAD (≥50 % stenosis; 31.8 vs. 10.3 %; $p < 0.001$) were significantly higher in diabetic patients. The remaining coronary atherosclerotic burden indexes evaluated (plaque in LM-3v-2v with prox. LAD; SIS; SSS; CT-LeSc) were also significantly higher in diabetic patients. In the *per segment* analysis, diabetics had a higher percentage of segments with plaque in every vessel (2.6/13.1/7.5/10.5 % for diabetics vs. 1.4/7.1/3.3/4.4 % for nondiabetics for LM, LAD, LCx, RCA respectively; $p < 0.001$ for all) and of both calcified (19.3 vs. 9.2 %, $p < 0.001$) and noncalcified or mixed types (14.4 vs. 7.0 %; $p < 0.001$); the ratio of proximal-to-distal relative plaque distribution (calculated as LM/proximal vs. mid/distal/branches) was lower for diabetics (0.75 vs. 1.04; $p = 0.009$). Diabetes was an independent predictor of CAD and was also associated with more advanced CAD, evaluated by indexes of coronary atherosclerotic burden. Diabetics had a significantly higher prevalence of plaques in every anatomical subset and for the different plaque composition. In this report, the relative geographic distribution of the plaques within each subgroup, favored a more mid-to-distal localization in the diabetic patients.

Keywords Diabetes · Coronary artery disease · Atherosclerotic burden · Coronary CT angiography

P. de Araújo Gonçalves (✉) · M. S. Carvalho · H. Dores · P. J. Sousa · A. Ferreira · R. C. Teles · L. Raposo · H. M. Gabriel · M. Almeida · A. Aleixo · M. Mendes
Cardiology Department, Centro Hospitalar Lisboa Ocidental, Av. Prof. Reinaldo dos Santos, 2790-134 Carnaxide, Lisbon, Portugal
e-mail: paraujogoncalves@yahoo.co.uk

P. de Araújo Gonçalves · H. Marques · A. Ferreira · N. Cardim · F. P. Machado
Hospital da Luz, Lisbon, Portugal

P. de Araújo Gonçalves · A. Aleixo · M. M. Carmo
CEDOC—Chronic Diseases Research Center—FCM-NOVA, Lisbon, Portugal

H. M. Garcia-Garcia
Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

Introduction

Patients with diabetes are considered to be at an increased risk of cardiovascular events and therefore it has been recommended by many guidelines a more aggressive management of this subset of patients, especially for those with established cardiovascular disease [1, 2].

By contrast, on a primary prevention unselected population level, some of the preventive measures for diabetic patients, like the use of antiplatelets, have failed to demonstrate a clear clinical benefit [3] and are no longer recommended in the absence of clinical evidence of atherosclerotic disease [4]. The reason for the lack of

benefit of aspirin in diabetic patients is likely related to the fact that diabetic patients represents an heterogeneous subset in what concerns the prevalence and severity of atherosclerotic coronary burden.

This illustrates the need for risk stratification of diabetic patients to identify the ones that can benefit from a more aggressive management at earlier stages. This is an opportunity for noninvasive imaging modalities, such as coronary computed tomography angiography (CCTA), which provides a detailed and comprehensive evaluation of the presence and extent of coronary artery disease (CAD), and can play an important role identifying the diabetic patients that could benefit from a more aggressive prevention of cardiovascular events.

Since CCTA is used mainly as a gatekeeper for the exclusion of significant CAD [5], most of the referred patients are at low to intermediate risk, this provides a good setting to study atherosclerotic disease at an earlier stage.

Therefore the aim of this study is two-folded:

1. To study the prevalence and severity of CAD in diabetic patients at earlier stages of CAD, to further evaluate the concept of CAD equivalent.
2. To provide a detailed characterization of the coronary atherosclerotic burden in diabetic patients, using the comprehensive information derived from CCTA on the localization, degree of stenosis and plaque composition.

Methods

Population

Single center prospective registry, including a total of 772 consecutive patients undergoing CCTA (with Dual source CT), from April 2011 to March 2012.

Patients were excluded if: (1) previous history of myocardial infarction and/or revascularization procedures (n = 70); (2) referred for Cardiac CT for other indications than the evaluation of possible CAD (cardiac CT for atrial fibrillation ablation or transcatheter aortic valve implantation procedures; n = 88); (3) referred for suspected acute coronary syndromes (n = 24); (4) with atrial fibrillation or other significant arrhythmias during scan acquisition that compromised image quality (n = 9). This resulted in a 24.7 % of the total population being excluded.

For the purpose of this study, 581 stable patients referred for suspected CAD were included in the context of: (1) Previous equivocal or inconclusive stress tests or discordant with the clinical evaluation (n = 417, 71.8 %); (2) Cardiac CT as 1st line investigation of possible CAD (n = 136, 23.4; %); 3) Preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 17; 2.9 %); (4) Evaluation of possible CAD in cardiomyopathies (Dilated or Hypertrophic) (n = 11; 1.9 %) (Fig. 1: Patient selection and study design).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history by means of a risk factors questionnaire was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents) [6]; (2) Dyslipidemia (defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) [7]; (3) Hypertension (defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medication) [8]; (4) Obesity (body mass index ≥30 kg/m^2); (5) positive family history of premature CAD [defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years of age] [9]; (6) smoking (defined as previous <1 year) or current smoker.

Pre-test probability of CAD was determined using both the Diamond and Forrester extended CAD consortium method (DF–CAD consortium model) [10] and the Morise score [11]. The cardiovascular risk was assessed with the HeartScore [4]. For the DF–CAD consortium probability model, as the CAD probability and CV risk of our population was shifted to lower probability (less that 2 % had a ≥70 % DF probability), the DF–CAD consortium model categories ≥30–70 % and ≥70 % were gathered in a intermediate to high (≥30 %) probability group. For the Morise, the original described cut-off points (for low, intermediate and high probability) were used, and for the HeartScore the established high risk cut-off of ≥5 % was used.

Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >65 beats/min.

During the scan acquisition, a bolus of iodinated contrast (Visipaque, GE Healthcare, USA) was injected at a 6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time + 6 s delay) x flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever

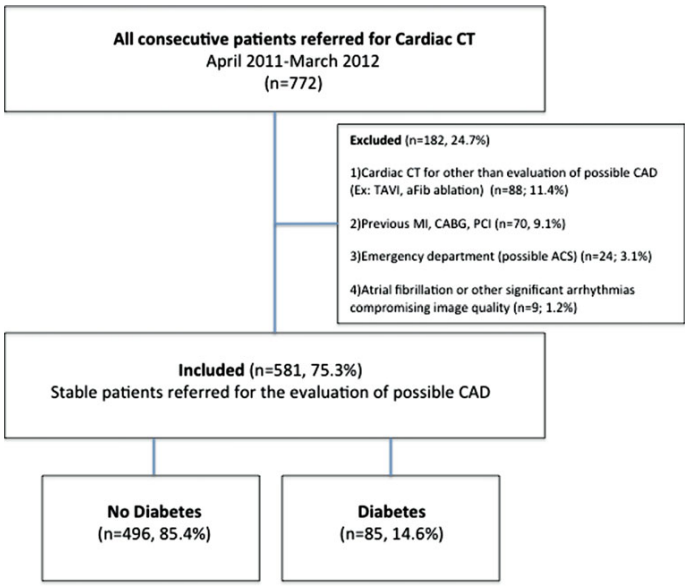


Fig. 1 Patient selection and study design. *CAD* coronary artery disease, *TAVI* transcatheter aortic valve implantation, *aFib* atrial fibrillation, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *ACS* acute coronary syndromes

feasible. Mean estimated radiation dose was 4.6 ± 3.7 mSv, contrast dose was 98.9 ± 14.4 ml and heart rate was 65.6 ± 10.6 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments.

Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III—equivalent experience. The Society of Cardiovascular Computed Tomography (SCCT) recommended classification was used regarding segmentation (16 segments), stenosis severity (<25; 25–49; 50–69; 70–99; 100 %) and plaque composition (calcified, noncalcified, mixed plaque) [12]. In each coronary artery segment, coronary atherosclerosis was defined as tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. [13] Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque.

In the detailed *per segment* analysis, for the distribution of plaque on the 3 main coronary vessels, this rules were applied: plaques in the diagonal branches were counted as belonging to the left anterior descending (LAD); plaques in the obtuse marginal an intermediate branch were counted as belonging to the LCx; plaques in the posterior descending and right postero-lateral were counted as belonging to the right coronary artery (RCA). For the last two, coronary dominance was taking into account. The ratio of "proximal-to-distal relative plaque distribution" was calculated as the proportion of plaques between these two subgroups: (1) Left main and proximal segments of the LAD, LCx and RCA; (2) Mid and distal segments of LAD and RCA, distal LCx and all evaluable coronary branches.

Definition of the coronary atherosclerotic burden indexes

The following coronary atherosclerotic burden indexes were evaluated and compared between patients with and

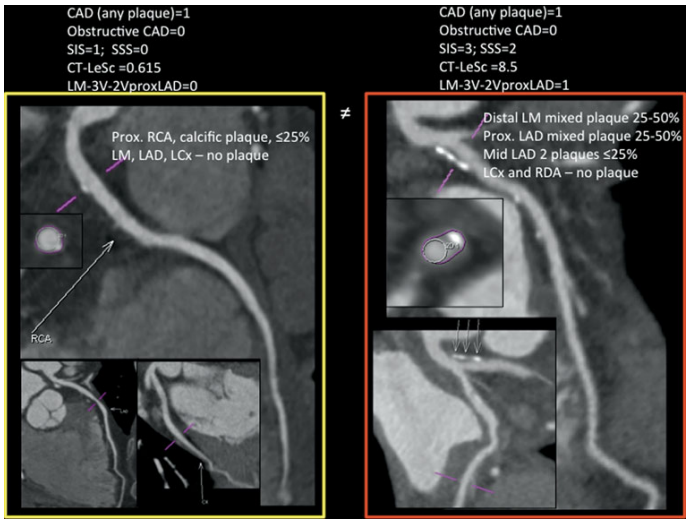


Fig. 2 Two case examples of diabetic patients with nonobstructive CAD. The different plaque burden indexes are shown. *CAD* coronary artery disease, *SIS* segment involvement score, *SSS* segment stenosis score, *CT-LeSc* CT Leaman score, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery, *LM-3 V-2VproxLAD* plaque in left main or 3 vessels or 2 vessels with proximal LAD

without diabetes: (1) Coronary artery disease (CAD)—presence of any plaque in the coronary tree; (2) "Obstructive CAD"—presence of at least one plaque with ≥50 % stenosis; (3) "LM-3v-2v with proximal LAD"—Plaque in the left main or in the 3 main epicardial vessels or in 2 main epicardial vessels including the proximal left anterior descending (LAD); (4) "SIS"—segment involvement score, obtained as the total number of segments with plaque; (5) "SSS"—segment stenosis score, obtained by grading the stenosis severity of each segment with plaque, as was previously described [13]. For these last two, the prognostically validated cut-offs (>5) were used [13]

(6) "Calcium score (CaSc) ≥100"; (7) "CaSc ≥75th percentile" (according to published nomograms [14]; (8) CCTA-adapted Leaman score (CT-LeSc)—this score was calculated taking in account 3 weighting factors (localization, plaque composition and stenosis severity) according to previously described methodology and the same cut-off for high plaque burden (≥8.3) was used (provided as additional information to the reviewers, since the manuscript, where it is originally described, is under consideration elsewhere). In Fig. 2, two case examples of diabetic patients with nonobstructive CAD are shown, with the different plaque burden indexes.

Statistical analysis

Continuous variables are presented as mean ± SD or medians (interquartile range) and categorical variables as frequencies with percentages.

The non-parametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables. Chi square test was used to evaluate differences in frequencies. Differences were regarded significant when $p < 0.05$ (two-tailed).

Multivariate analyses (binary logistic regression model—enter method) were performed to identify independent predictors of CAD (any plaque and obstructive) using the demographic and clinical variables presented in Table 1, that were significant in univariate analysis ($p < 0.05$). A second multivariable analyses was performed to identify independent predictors among the clinical scores of CAD probability (Diamond-Forrester CAD consortium model and Morise score) and the CV risk score HeartScore. For the detailed *per segment* analysis, the unit of measure was each segment and there were no adjustments or corrections made for the serial correlation between segments.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Study population

In the final study population (n = 581), 85 patients were diabetics (14.6 %).

Regarding the demographic and clinical variables, diabetic patients were older (mean age 61.4 ± 8.7 vs. 56.9 ± 11.3) and had a higher prevalence of obesity (28.6 % vs. 17.4 %) and hypertension (84.7 vs. 58.9 %). This was predominantly a population with low to intermediate CAD probability, more so in the nondiabetic population since 61.7 % had a DF–CAD consortium <30 and 90.7 % had a Morise score <16. The cardiovascular risk, as estimated with the HeartScore (≥5 %), was significantly higher in the patients with diabetes (42.4 vs. 22.6 %) (Table 1).

Independent predictors of CAD

Diabetes was an independent predictor of both the presence of plaque (OR 1.81; 95 % CI 1.02–3.21; $p = 0.041$) and of obstructive CAD (OR 3.69; 95 % CI 2.08–6.53; $p < 0.001$). The other independent predictors of the *presence of plaque* were age ≥65 years (OR 3.42; 95 % CI 2.15–5.45; $p < 0.001$), male sex (OR 2.72; 95 % CI 1.85–4.01; $p < 0.001$), hypertension (OR 1.82; 95 % CI 1.23–2.67; $p = 0.002$), dyslipidemia (OR 1.89; 95 % CI 1.29–2.77; $p = 0.001$), chest pain (OR 0.62; 95 % CI 0.42–0.91; $p = 0.014$) an DF–CAD consortium ≥30 % (OR 2.62; 95 % CI 1.70–4.05; $p < 0.001$), a Morise score ≥16 (OR 2.55; 95 % CI 1.57–4.14; $p < 0.001$), and an HeartScore ≥5 % (OR 3.90; 95 % CI 2.19–6.94; $p < 0.001$). The other independent predictors of *obstructive CAD* were age ≥65 years (OR 1.98; 95 % CI 1.16–3.37; $p = 0.012$), male sex (OR 2.94; 95 % CI 1.68–5.15; $p < 0.001$), an DF–CAD consortium ≥30 % (OR 1.88; 95 % CI 1.04–3.42; $p = 0.038$), a Morise score ≥16 (OR 1.84; 95 % CI 1.06–3.20; $p = 0.031$), and an HeartScore ≥5 % (OR 2.71; 95 % CI 1.50–4.88; $p = 0.001$).

Coronary artery disease prevalence, severity and coronary atherosclerotic burden indexes—*per patient* analysis

The prevalence of plaques in the coronary arteries was high in the overall study population, but this was significantly higher for diabetic patients, as almost 3 out of 4 diabetic patients (74.1 %) had plaques in the coronary arteries.

Table 1 Demographic and clinical characteristics of the study population

	No diabetes (n = 496)	Diabetes (n = 85)	*p*
Demographic			
Age	56.9 ± 11.3	61.4 ± 8.7	<0.001
Male sex	277 (55.8)	47 (55.3)	1.000
Risk factors			
Obesity (BMI ≥30)	85 (17.4)	24 (28.6)	0.023
Hypertension	292 (58.9)	72 (84.7)	<0.001
Dyslipidemia	301 (60.7)	59 (69.4)	0.147
Smoking	118 (23.8)	20 (23.5)	1.000
Family history of premature CAD	168 (33.9)	26 (30.6)	0.619
Chest pain	265 (54.3)	46 (54.1)	1.000
CAD probability			
DF–CAD consortium ≥30 %	189 (38.1)	42 (49.4)	0.049
DF–CAD consortium <30 %	307 (61.9)	43 (50.6)	
Morise score ≥16	46 (9.3)	26 (30.6)	<0.001
Morise score 9–15	316 (63.7)	53 (62.4)	
Morise score 0–8	134 (27.0)	6 (7.1)	
CV risk			
HeartScore ≥5 %	112 (22.6)	36 (42.4)	<0.001

Values are mean ± SD or n (%)

CAD coronary artery disease, *BMI* body mass index, *DF–CAD* consortium diamond-forrester CAD consortium model, *CV* cardiovascular

Table 2 Calcium score and CCTA characteristics of the study population

	No diabetes (n = 496)	Diabetes (n = 85)	*p*
Calcium score			
Median	0 (0-67)	68 (0-311)	<0.001
CaSc ≥100	96 (19.4)	40 (47.1)	<0.001
CaSc ≥75th percentile	60 (12.1)	23 (27.1)	0.001
CCTA			
Normal/No plaque	217 (43.8)	22 (25.9)	<0.001
Nonobstructive CAD	228 (46.0)	36 (42.4)	
Obstructive CAD	51 (10.3)	27 (31.8)	
Coronary atherosclerotic burden indexes			
Plaque in LM-3v-2v with prox. LAD	178 (35.9)	53 (62.4)	<0.001
Segment involvement score >5	66 (13.3)	31 (36.5)	<0.001
Segment stenosis score >5	25 (5.0)	21 (24.7)	<0.001
CT-Leaman Score ≥8.3	79 (15.9)	35 (41.2)	<0.001
Technical data			
Heart rate (bpm)	65.3 ± 10.6	67.0 ± 10.2	0.172
Contrast dose (ml)	99.3 ± 14.7	96.7 ± 12.3	0.119
Radiation dose (mSv)	4.7 ± 4.9	5.7 ± 3.8	0.069

Values are mean ± SD, median (IQR) or n (%)

CaSc calcium score, *CCTA* coronary computed tomography angiography, *CAD* coronary artery disease, *LM-3v-2v* left main, 3 vessel, 2 vessel, *LAD* left anterior descending, *bpm* beats per minute, *mSv* milisievert

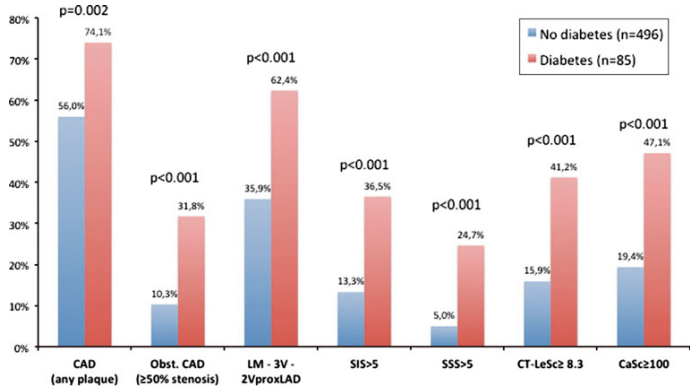


Fig. 3 Diabetes and indexes of coronary atherosclerotic burden. *CAD* coronary artery disease, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *LM-3 V-2VproxLAD* plaque in left main or 3 vessels or 2 vessels with proximal LAD, *SIS* segment involvement score, *SSS* segment stenosis score, *CT-LeSc* CT Leaman score

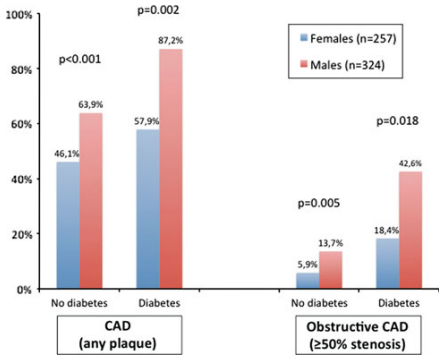


Fig. 4 Prevalence of coronary artery disease (any plaque and obstructive) across the different diabetes and sex subgroups. *CAD* coronary artery disease

All the indexes of coronary atherosclerotic burden were significantly higher in diabetics as compared to nondiabetics (Table 2; Fig. 3).

For some of these indexes, like the presence of obstructive disease, and the SSS, the prevalence was 3–5 times higher in diabetics.

By gender, male diabetics had more often coronary artery disease (any plaque and obstructive), as compared to their counterparts (Fig. 4).

Prevalence, localization and type of plaques—*per segment* analysis

For the analysis of the atherosclerotic burden indexes, 8,136 coronary segments were evaluated for the presence of plaque, degree of stenosis and type of plaque. Because of small size (<2 mm) or insufficient image quality related to artifacts or severe calcification, 866 (10.6 %) segments were excluded (n = 723–10.4 % in nondiabetics; n = 143–12.0 % in diabetics).

On a *"per evaluable segment"* analysis, diabetics had significantly more segments with plaque and this was observed in the left main as well as in the other 3 coronary territories and in both more proximal and more distal locations (Table 3; Fig. 5). The prevalence of obstructive plaque was also significantly higher in patients with, as compared to patients without diabetes (11.6 vs. 6.9 %, $p < 0.001$).

On a *"per segment with plaque"* analysis, nondiabetics had an almost equal distribution of plaques between more proximal (LM/proximal segments) and more mid-to-distal (Mid/distal/branches) localization (ratio of 1.04), but the opposite was seen in patients with diabetes, in whom more plaques were found in the more mid-to-distal segments, as reflected by a ratio of "proximal-to-distal relative plaque distribution" of 0.75 (Table 3).

Regarding plaque composition, diabetics had also a higher percentage of all types of plaques (both calcified and noncalcified or mixed plaques) per evaluable segment (Table 4).

Discussion

The main findings of this study are:

1. Although diabetic patients had a higher prevalence of coronary artery disease, coronary atherosclerotic plaques were commonly observed in both patients with and without diabetes.

Table 3 Prevalence, and localization of plaques—*per segment* analysis

	No diabetes (n = 496; 6,957 segments)	Diabetes (n = 85; 1,187 segments)	*p*
All evaluable segments	6,234 (89.6)	1,044 (88.0)	0.093
Segments with any plaque	1,008 (16.2)	352 (33.7)	<0.001
Coronary artery distribution			
Any plaque in the LM	87 (1.4)	27 (2.6)	0.007
Any plaque in the RCA	276 (4.4)	110 (10.5)	<0.001
Any plaque in the LAD	441 (7.1)	137 (13.1)	<0.001
Any plaque in the LCx/Ramus	204 (3.3)	78 (7.5)	<0.001
Proximal versus distal distribution			
Any plaque in LM/Proximal	514 (8.2)	151 (14.5)	<0.001
Any plaque in Mid/Distal/Branches	494 (7.9)	201 (19.3)	<0.001
"Ratio of proximal-to-distal relative plaque distribution"	1.04 (514/494)	0.75 (151/201)	0.009

"Ratio of proximal-to-distal relative plaque distribution"—proportion of plaques in the "LM/Proximal" versus "Mid/Distal/branches"

LM left main, *RCA* right coronary artery, *LAD* left anterior descending, *LCx* left circunflex, *Ramus* intermediate branch, "*LM/Prox*" left main or proximal segments of the LAD, LCx or RCA, "*Mid/Distal/Branches*" mid or distal segments of the LAD and RCA, distal segment of the LCx, and branches

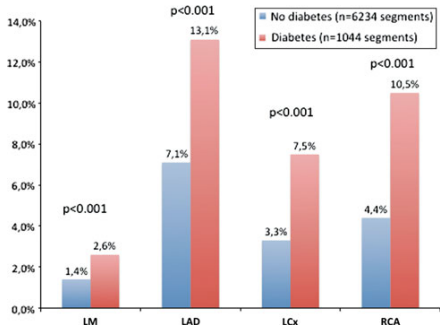


Fig. 5 Prevalence and localization of plaques (any plaque) on a *per segment* analysis. *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery

2. Several different coronary atherosclerotic burden indexes were more prevalent in diabetics, indicating more diffuse and severe CAD, and this was especially true for males.
3. In the detailed per segment analysis, diabetics had a higher percentage of segments with plaque in every vessel and of both calcified and noncalcified or mixed types; ratio of proximal-to-distal relative plaque distribution suggested an anatomical gradient in the geographic distribution, with higher proportion of disease involvement in the mid/distal/branches segments in diabetic patients.

Diabetes as an heterogeneous group—not all diabetics have the same CV risk

For many years, diabetic patients have been considered as a subset at higher risk of cardiovascular events. Nevertheless,

Table 4 Type of plaques—*per segment* analysis

	No diabetes (n = 496; 6,957 segments)	Diabetes (n = 85; 1,187 segments)	*p*
All evaluable segments	6,234 (89.6)	1,044 (88.0)	0.093
Segments with any plaque	1,008 (16.2)	352 (33.7)	<0.001
Calcified plaque			
All segments	571 (9.2)	202 (19.3)	<0.001
LM/Proximal	291 (4.7)	83 (8.0)	<0.001
Mid/Distal/Branches	280 (4.5)	119 (11.4)	<0.001
Noncalcified or mixed plaques			
All segments	437 (7.0)	150 (14.4)	<0.001
LM/Proximal	223 (3.6)	68 (6.5)	<0.001
Mid/Distal/Branches	214 (3.4)	82 (7.9)	<0.001

LM left main, *RCA* right coronary artery, *LAD* left anterior descending, *LCx* left circunflex, *Ramus* intermediate branch, "*LM/Proximal*" left main or proximal segments of the LAD, LCx or RCA, "*Mid/Distal/Branches*" Mid or distal segments of the LAD and RCA, distal segment of the LCx, and branches

it has been difficult to prove a clear benefit of some primary prevention measures, like is the case of aspirin in the primary prevention of cardiovascular events. This inconsistent benefit of aspirin in the absence of clinical manifestations of cardiovascular disease, can be related to the fact that it is less effective in these patients [15] or more likely that diabetic patients are an heterogeneous group in terms of cardiovascular disease presence and extent. This way, without risk stratification, we could be overtreating some low risk diabetic patients, exposing them to the risk of side effects that could offset the reduction in expected atherothrombotic events rate.

Of note, there has been a more consistent beneficial effect of aspirin as primary preventive measure in males, for reducing the risk of myocardial infarction [3] and this is in line with our findings of higher prevalence of coronary plaques and obstructive CAD in this subgroup, as compared to females.

Recently, Saely et al. [16] revisited the concept of diabetes as a CAD equivalent in a study comparing the vascular event rate of patients according to the presence of diabetes and/or CAD. In this study, diabetes was not per se a CAD risk equivalent, since diabetic patients without significant CAD had a lower event rate than nondiabetic patients with significant CAD.

CCTA derived coronary atherosclerotic burden indexes

Scores derived from invasive angiography have previously demonstrated to further stratify diabetic patients with more advanced CAD [17]. We hypothesized that this could also be the case for diabetics with less severe CAD, using the comprehensive information derived from CCTA on the presence, localization, degree of stenosis and plaque composition.

Several different aspects of coronary disease are reflected in these scores: prevalence and severity (*any plaque and obstructive CAD*), number of plaques (*SIS*), number and distribution (*plaque in LM-3v-2v with prox. LAD*), number and stenosis severity (*SSS*), absolute and relative amount of calcified plaque (CaSc ≥100 and ≥75th percentile) and localization, stenosis severity and type of plaque (CT-Le score). All the coronary atherosclerotic burden indexes were significantly higher in diabetics as compared to nondiabetics, reflecting the higher prevalence as well as the more severe coronary disease of this subset of patients and they can be useful as noninvasive imaging tools for risk stratification. Some of these indexes have already been prognostically validated and demonstrated a good correlation with major cardiovascular events [13, 18, 19]. In our view, since the prevalence of plaque is very high, even in this predominantly low-to-intermediate CAD probability population, these coronary atherosclerotic burden indexes can help risk stratify patients and should ideally be included in the CCTA report. However, since they convey information on different aspects of CAD, with some overlap in the information they provide and, in clinical practice, reporting on all of them is not suitable, ideally we should be able to decide in the future which one(s) should be routinely used, based on their prognostic performance.

Anatomical distribution and plaque composition

In this report, the higher prevalence of plaques in diabetic patients was seen in the left main as well as in the other 3 coronary territories and in both proximal and distal locations. Regarding the left main and the other proximal locations, we observed a higher percentage of plaques in diabetics as compared to nondiabetics. This is in line with previous studies linking the geographic distribution of myocardial infarction culprit lesions to more proximal locations in the coronary tree [20] and could explain the higher incidence of coronary events experienced by diabetic patients.

One interesting finding in our study is related to the relative geographic localization of plaques in diabetics as compared to patients without diabetes.

Although in prevalence of evaluable segments, diabetics had more plaques in every location (both proximal and distal) compared to nondiabetics, the relative geographic plaque distribution was different in the two subgroups of patients, since diabetics had a ratio of "proximal-to-distal relative plaque distribution" of 0.75 (vs. 1.04 for nondiabetics), suggesting a higher predisposition to disease involvement of the more distal segments. This finding, on a *per segment* analysis, together with the higher prevalence of a SIS >5 on the *per patient* analysis reflects the more diffuse nature of coronary atherosclerotic burden of diabetic patients.

As diabetic patients are considered to be a model of more advanced CAD, this could suggest that as the coronary atherosclerosis progresses, distal segments become more involved by disease, although serial measurements in time would be the ideal setting to evaluate this hypothesis.

The *per segment* analysis allowed also the evaluation of the plaque composition. Diabetic patients had a significantly higher prevalence of segments with both calcified and noncalcified or mixed plaques, in both more proximal or more distal locations. The proportion of calcified to noncalcified or mixed plaques was the same for both subgroups of patients.

Limitations

There are a number of limitations related to this report:

1. This is a single center data with medium size cohort;

2. The population included in our study was mainly composed of patients with low to intermediate CAD probability and CV risk, as this reflects daily practice of CCTA being used as a gatekeeper to exclude obstructive CAD and are in line with the recommendations. Since coronary plaques were present in nearly 60 % of the patients, this was an opportunity to evaluate the coronary atherosclerotic burden pattern of DM patients at earlier stages.
3. There were some differences in the baseline characteristics of the two subgroups of patients, that could have contributed to the higher disease extent observed in diabetic patients. Nevertheless, after adjusting for those differences, diabetes remained an independent predictor of both the presence and severity of CAD.
4. Since patients were referred for CCTA because of symptoms and/or the results of stress tests, some referral bias has to be acknowledged.

Conclusions

Diabetes was an independent predictor of CAD and was also associated with more advanced CAD, evaluated by indexes of coronary atherosclerotic burden.

The comprehensive information regarding the presence, severity and type of plaque noninvasively provided by CCTA, has made possible a detailed characterization of the coronary disease pattern of diabetic patients at an earlier stage of disease.

Diabetics had a significantly higher prevalence of plaques in every anatomical subset (type of vessel and both proximal or distal localizations) and for the different plaque composition (both calcified and noncalcified or mixed). In this report, the relative geographic distribution of the plaques within each subgroup, favored a more mid-to-distal localization in the diabetic patients.

Conflict of interest None.

References

1. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R et al (2007) Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 115(1):114–126
2. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ et al (2007) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The task force on diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). Eur Heart J 28(1):88–136
3. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G et al (2009) Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 339:b4531
4. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M et al (2012) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 33(13):1635–1701
5. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P et al (2010) ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 56(22):1864–1894
6. (1997) Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 20(7): 1183–1197
7. Expert Panel on Detection E (2001) Treatment of high blood cholesterol in A. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285(19):2486–2497
8. European Society of Hypertension-European Society of Cardiology Guidelines C (2003) European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 21(6):1011–1053
9. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG (2005) Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the prospective army coronary calcium (PACC) project. J Am Coll Cardiol 46(5):807–814
10. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 32(11):1316–1330
11. Morise AP, Haddad WJ, Beckner D (1997) Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med 102(4):350–356
12. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ et al (2009) SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 3(2):122–136
13. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ et al (2007) Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 50(12):1161–1170
14. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT (2001) Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 87(12):1335–1339
15. Evangelista V, Totani L, Rotondo S, Lorenzet R, Tognoni G, De Berardis G et al (2005) Prevention of cardiovascular disease in

type-2 diabetes: how to improve the clinical efficacy of aspirin. Thromb Haemost 93(1):8–16
16. Saely CH, Aczel S, Koch L, Schmid F, Marte T, Huber K et al (2010) Diabetes as a coronary artery disease risk equivalent: before a change of paradigm? Eur J Cardiovasc Prev Rehabil 17(1):94–99
17. Mack MJ, Banning AP, Serruys PW, Morice MC, Taeymans Y, Van Nooten G et al (2011) Bypass versus drug-eluting stents at three years in SYNTAX patients with diabetes mellitus or metabolic syndrome. Ann Thorac Surg 92(6):2140–2146
18. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L et al (2012) A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging 5(7):690–701
19. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ et al (2011) Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the international multicenter CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol 58(8):849–860
20. Wang JC, Normand SL, Mauri L, Kuntz RE (2004) Coronary artery spatial distribution of acute myocardial infarction occlusions. Circulation 110(3):278–284

ARTIGO 17/ MANUSCRIPT 17:

SCIENTIFIC LETTER

Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow up of a single-centre registry

P de Araujo Goncalves, R Seabra-Gomes, R Teles, M Almeida, C Aguiar, L Raposo, J Ferreira, F Pereira Machado

Heart 2006;**92**:1155–1156. doi: 10.1136/hrt.2005.079780

Patients with diabetes mellitus have an increased risk of cardiac events after percutaneous coronary intervention (PCI). As drug-eluting stents (DES) reduce restenosis and glycoprotein (Gp) IIb/IIIa inhibitors reduce the risk of death and myocardial infarction, the use of both treatments may be complementary and be a powerful tool for reducing cardiac events after PCI in diabetic patients. On the other hand, there are some concerns about the rate of stent thrombosis with DES, and some recent reports have pointed to diabetes as one of the risk factors.[1]

We therefore tested the hypothesis that Gp IIb/IIIa inhibitors may reduce the rate of major cardiac events after PCI with sirolimus-eluting stents (SES) in patients with diabetes mellitus.

METHODS

This was a prospective non-randomised single-centre registry, including all consecutive patients with diabetes undergoing PCI with at least one SES at our institution from April 2002 to April 2003.

One-year clinical follow up was assessed in all patients. Patients were divided into two subgroups according to the periprocedural use of Gp IIb/IIIa inhibitors (99 patients in the group with Gp IIb/IIIa inhibitors and 104 in the group without).

The intervention strategy was entirely dependent on the operator and was performed according to standard guidelines. Patients were given a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter, for at least three months.

We evaluated a clinical end point defined as the combined incidence of the major adverse cardiac events (MACE) death, non-fatal myocardial infarction and target vessel revascularisation (TVR) at the one-year follow up.

Data were statistically analysed with SPSS V.11.0 software (SPSS Inc, Chicago, Illinois, USA) by χ^2 test, Student's unpaired t test, log rank test and Cox proportional hazards models as appropriate.

RESULTS

Of 1310 patients undergoing PCI at our institution from April 2002 to April 2003, 203 (15.5%) had diabetes and were treated with at least one SES. The Gp IIb/IIIa inhibitor used most often was abciximab (83%). Patients with acute coronary syndromes were given eptifibatide (13%) and tirofiban (4%) upstream before going to the cath lab.

The two groups of patients did not differ significantly in the baseline characteristics. However, more of the patients treated with Gp IIb/IIIa inhibitors were current smokers (20.4% *v* 12.1%, p = 0.16) and had PCI in the setting of an acute coronary syndrome (40.8% *v* 28.3%, p = 0.08), and fewer of them had peripheral arterial disease (9.7% *v* 18.2%, p = 0.12) or a previous stroke (2.9% *v* 10.1%, p = 0.07).

Regarding the angiographic characteristics, patients treated with Gp IIb/IIIa inhibitors had a higher rate of PCI on a total occlusion (16.3% *v* 4.0%, p = 0.008), a higher mean total stent length (42.6 *v* 29.3 mm, p = 0.002) and more stents ⩾ 33 mm implanted (41.3% *v* 24.2%, p = 0.015). Other important differences between the two groups of patients were the higher numbers of implanted stents (2.5 *v* 1.9, p = 0.021) and SES (2.1 *v* 1.6, p = 0.028) per patient in the group treated with Gp IIb/IIIa inhibitors.

Complete one-year follow-up information was available for all patients. The cumulative incidence of MACE at one year was significantly lower in the patients treated with Gp IIb/IIIa inhibitors (8.7% *v* 23.2%; hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.16 to 0.74, p = 0.006). There was a trend for a lower combined incidence of death and non-fatal myocardial infarction (4.8% *v* 12.1%; HR 0.38, 95% CI 0.14 to 1.09, p = 0.072) and for a lower target lesion revascularisation rate (1.9% *v* 7.1%; HR 0.26, 95% CI 0.05 to 1.23, p = 0.089) in the Gp IIb/IIIa inhibitor treated group. The rate of TVR, which includes lower target lesion revascularisation, was significantly lower in the Gp IIb/IIIa inhibitor group (4.8% *v* 13.1%; HR 0.34, 95% CI 0.12 to 0.95, p = 0.040). Two insulin-requiring patients in the group not treated with Gp IIb/IIIa inhibitors presented with subacute stent thrombosis (2.02%), on day 6 and day 8 after the procedure. Both patients had a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter. No further thrombotic stent occlusion or unexplained sudden cardiac deaths were observed in the late follow up.

Multivariable Cox proportional hazards analysis identified Gp IIb/IIIa inhibitor use to be independently associated with a reduced risk of MACE (adjusted HR 0.30, 95% CI 0.13 to 0.67, p = 0.003) (fig 1) and of death and myocardial infarction (adjusted HR 0.34, 95% CI 0.12 to 0.99, p = 0.048).

The incidence of death, non-fatal myocardial infarction and TVR was consistently lower in patients treated with Gp

Abbreviations: CARDia, Coronary Artery Revascularization in Diabetes; DES, drug-eluting stents; Gp, glycoprotein; HR, hazard ratio; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; SES, sirolimus-eluting stents; TVR, target vessel revascularisation

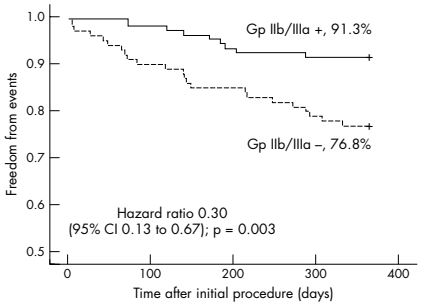


Figure 1 Major adverse cardiac event-free survival at one year. CI, confidence interval; Gp, glycoprotein.

IIb/IIIa inhibitors across the different subgroups analysed. The benefit was higher in insulin-treated patients.

DISCUSSION

This was a clinical study with consecutive patients in routine daily practice that evaluated the benefit of Gp IIb/IIIa inhibition in the context of SES in patients with diabetes mellitus. The use of Gp IIb/IIIa inhibitors was associated with a reduction in the combined incidence of death and myocardial infarction and the overall combined MACE. To the best of our knowledge, no other data have been published on this issue.

Although DES are a powerful tool against restenosis, they are not expected to have a significant impact on the rate of death and myocardial infarction after PCI.[2] Gp IIb/IIIa inhibitors, by having a favourable effect on these major events, can therefore exert an important complementary effect, especially in high-risk patients with diabetes. In the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry, there was a 16% rate of Gp IIb/IIIa inhibitor administration. Diabetes mellitus was an independent predictor of both MACE and TVR, and patients with diabetes were one of the subgroups in which the benefit of SES did not reach significance.[3] In the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) study, which found no benefit of abciximab in low- to intermediate-risk patients undergoing elective PCI after pretreatment with 600 mg of clopidogrel, patients with diabetes under medical treatment were excluded from enrolment.[4]

Insulin-treated patients with diabetes have been one of the most difficult groups of patients to treat with DES. In our registry, the benefit of the Gp IIb/IIIa inhibitor was higher in the insulin-treated patients and in other high-risk subgroups such as patients with multivessel disease or acute coronary syndromes and patients receiving 33 mm or longer stents. Insulin-requiring patients mainly have type 2 diabetes who became insulin dependent in a later stage of disease progression. This is a particularly diseased subgroup of patients, with a more extensive burden of atherothrombotic disease. In these patients, the high incidence of death, myocardial infarction and repeat PCI at different sites may offset the benefit of local interventions, even with very effective DES that, at best, reduce restenosis.

Although in randomised clinical trials the reported rate of DES thrombosis has been within the expected range, a substantially higher incidence was recently reported in registries of real-world patients, and diabetes was identified as one of the independent predictors.[1] In our registry, the two cases of stent thrombosis were observed in the group undergoing PCI without a Gp IIb/IIIa inhibitor, and the patients were treated with insulin. Although this study is underpowered to look for differences in this infrequent event, the lack of a single case of SES thrombosis in the high-risk group of patients with diabetes taking Gp IIb/IIIa inhibitors underscores the potential benefit of these agents in this context.

In the CARDia (Coronary Artery Revascularization in Diabetes) trial, up-to-date coronary artery bypass grafting is being compared with optimal PCI, in which the use of abciximab was recommended.[5] This is one of the ongoing randomised trials designed to evaluate the best revascularisation strategy in patients diabetes that are expected to consider these issues in a more definite manner.

This was a single-centre registry and not a randomised study with a 2 × 2 factorial design, which would have been better suited for evaluating the complementary effects of two different interventions. The baseline characteristics of the two groups were well matched but there were some differences in the angiographic and procedural characteristics. Nevertheless, these differences were in favour of the group not receiving a Gp IIb/IIIa inhibitor, and this could have underestimated the benefit of these agents.

The use of Gp IIb/IIIa inhibitors in the context of SES in patients with diabetes gave superior clinical results, due to a significant reduction in the combined incidence of death, myocardial infarction and TVR. This benefit was greater in insulin-treated patients with diabetes. This, and the lack of a single case of SES thrombosis in this high-risk group of patients who were given a Gp IIb/IIIa inhibitor during stenting, seems to warrant a randomised controlled trial to examine this issue.

Authors' affiliations
P de Araujo Goncalves, R Seabra-Gomes, R Teles, M Almeida, C Aguiar, L Raposo, J Ferreira, F Pereira Machado, Hospital de Santa Cruz, Carnaxide, Portugal

Correspondence to: Dr Pedro de Araujo Goncalves, Urb Quinta de Sao Goncalo, lote 56, 4 E, Carcavelos, 2775-629, Portugal; paraujogoncalves@yahoo.co.uk

Accepted 3 March 2006
Competing interests: None declared.

REFERENCES

1 **Iakovou I**, Schmidt T, Bonizzoni E, *et al*. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–30.
2 **Babapulle MN**, Joseph L, Bélisle P, *et al*. A hierarchical Bayesian meta-analysis of randomized clinical trials of drug-eluting stents. *Lancet* 2004;**364**:583–91.
3 **Lemos PA**, Serruys PW, van Domburg RT, *et al*. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004;**109**:190–5.
4 **Kastrati A**, Mehilli J, Schuhlen H, *et al*. Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment Study Investigators. A clinical trial of abciximab in elective percutaneous coronary intervention after pre-treatment with clopidogrel. *N Engl J Med* 2004;**350**:232–8.
5 **Smith D**. The CARDia trial protocol. *Heart* 2003;**89**:1125–6.

Editorial do **ARTIGO 17/** Editorial of **MANUSCRIPT 17:**

EDITORIAL

Darwin and the survival of the fittest in modern interventional cardiology

V K Bhatia, C Di Mario

Heart 2006;**92**:1017–1018. doi: 10.1136/hrt.2005.083923

The diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome

The use and disuse of new drugs, devices and treatments follows a frantic pace in interventional cardiology. A taste for innovation is probably a necessary inborn trait that may "naturally select" individuals who successfully pursue a career in interventional cardiology. In a healthcare environment with limited resources the competition between new and old treatments resembles the Darwinian "struggle for survival". However, the dark side of this Darwinian marker of success is the attitude of the interventionalist to forget too hastily the proven benefits of established treatments when their attention is distracted by newly emerging therapies.

DIABETES CONFERS HIGHER RISK FOR PCI

Diabetes mellitus portends a worse prognosis in patients with coronary artery disease who undergo either percutaneous coronary intervention (PCI) or surgical revascularisation.[1 2] The pathophysiology for the higher complication rate found in diabetic patients may involve an enhanced platelet activation state[3] and proliferative response[4] resulting in an elevated risk of thrombosis, embolisation and re-stenosis.[2 5]

Platelet glycoprotein (Gp) IIb/IIIa inhibitors are potent antiplatelet agents and pooled analysis of earlier studies have shown they confer sustained mortality benefit in diabetic patients undergoing plain balloon angioplasty or percutaneous bare metal stent implantation (PCI).[6]

The recent trials of drug eluting stents (DES) have shown a significant fall in target vessel revascularisation rates, but they have failed thus far to show any clear mortality benefit in diabetic patients.[7 8] One may argue that the characteristics of the population treated in these initial trials, including mainly patients with single vessel disease and a good ejection fraction, may have undermined the potential benefit of DES. Restenosis may conceivably have deadly consequences in patients with multivessel or left main stem disease who have silent ischaemia and accelerated disease progression in untreated segments.

BENEFITS OF GLYCOPROTEIN IIB/IIIA INHIBITORS IN DIABETIC PATIENTS RECEIVING DES

In this issue of Heart, Goncalves *et al*[9] remind us of an obvious truth: the benefit conferred by a new treatment does not cancel the effectiveness of a pre-existing proven therapy if the two treatments have completely different operative mechanisms. In a relatively large cohort of 203 patients receiving sirolimus eluting stents, the use of Gp IIb/IIIa inhibitors led to a reduction of death and non-fatal myocardial infarction (MI) (from 12.1 to 4.8 at one year) that was greater than that observed with Gp IIb/IIIa inhibitors in the seminal trials of plain balloon angioplasty and bare metal stents.[6] In a real world population with complex coronary disease (average stent length of 42.6 mm in the treated group) it may be hypothesised that prompt inhibition of platelet function reduces platelet plugging at the ostia of multiple side branches covered by stents and prevents distal embolisation, these being the main causes of periprocedural damage during stent implantation. As the use of longer stents is a consequence of the strategy of full plaque coverage adopted with DES, one may postulate that the advantages of Gp IIb/IIIa inhibitors are likely to be greater now than before.

LIMITATIONS OF THE STUDY

It is more difficult to explain another striking result from this study—the finding that at one year the curves of the two randomisation arms for major adverse cardiac events (MACE)-free and death or MI-free survival continue to separate. Although one can foresee a reduced late mortality rate from the initial fall of non-Q wave infarction, it would be difficult to understand why the effect on MI would continue long term. Since this is a non-randomised study, any difference in the observed outcome can be significantly influenced by differences in the baseline clinical, angiographic and procedural characteristics driven by the selection process of candidates for Gp IIb/IIIa inhibitors. Although not reaching statistical significance, there was a noticeable trend of greater unfavourable variables stacked against the group not receiving the Gp IIb/IIIa inhibitors (for example, greater percentage of patients with previous MI, coronary artery bypass surgery and peripheral arterial disease).

See end of article for authors' affiliations

Correspondence to: Professor Carlo Di Mario, Department of Interventional Cardiology, The Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; c.dimario@rbh.nthames.nhs.uk

Published Online First 31 January 2006

Abbreviations: DES, drug eluting stents; Gp, glycoprotein; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularisation

Various mechanism(s) have been proposed to explain the reduced target lesion revascularisation (TLR) rates observed with Gp IIb/IIIa inhibitors in some of the aforementioned studies. These include cross-reaction with the leucocyte integrin Mac-1[10] and also blocking vitronectin ($\alpha_v\beta_3$) receptors on platelets and smooth muscle cells,[11] thereby limiting neointimal hyperplasia.[12] However, no randomised comparisons have confirmed these observations, and the results of this study suggest that such effects of Gp IIb/IIIa inhibitors persist and cause an additional positive response even in the presence of high local concentrations of an antiproliferative agent (sirolimus) in the stent.

Another limitation of the study by Goncalves *et al*[9] involved the timing and dose of clopidogrel in relation to the procedure. Recent studies have demonstrated that an aggressive pre-PCI regimen of aspirin and 600 mg clopidogrel leads to no significant additional benefit of Gp IIb/IIIa inhibitor on risk of death or MI in diabetic patients receiving mainly bare metal stents.[13 14] This issue becomes all the more pertinent when it was subsequently disclosed that the two insulin-requiring diabetics who suffered thrombotic complications had an insufficient loading regimen of 300 mg clopidogrel apparently given immediately after the procedure.

FUTURE DIRECTIONS

Clopidogrel with a high loading dose of 600 mg is now being tested by the Munich group in a new randomised trial of unstable patients, but this drug, unlike Gp IIb/IIIa inhibitors, induces no more than 80% inhibition of platelet aggregation with a slow onset of action and a large variability in response. As developments in peri-PCI adjuvant drug treatment evolve, newer safer agents may threaten to supersede the use of Gp IIb/IIIa inhibitors. Another drug which may reduce the need for Gp IIb/IIIa inhibitors is the direct anti-thrombin bivalirudin which, unlike heparin, does not induce platelet activation. In a recent study with stable or mildly unstable patients undergoing PCI, bivalirudin was as effective as heparin and Gp IIb/IIIa inhibitors with lower bleeding, vascular complication rates and shorter intensive therapy unit stay.[15] Bivalirudin is now under evaluation in a trial of highly unstable patients with a complex randomisation scheme.[16]

While awaiting the results of such trials, this study reminds us all that the diabetic patient requires a full armamentarium of proven and developing treatments in order to minimise periprocedural risk as well as improve long term outcome.

Authors' affiliations
V K Bhatia, C D Mario, Department of Interventional Cardiology, The Royal Brompton Hospital, London, UK

Conflict of interest: none.

REFERENCES

1 **Barsness GW**, Peterson ED, Ohman EM, *et al*. Relationship between diabetes mellitus and long-term survival after coronary bypass and angioplasty. *Circulation* 1997;**96**:2551–6.
2 **Stein B**, Weintraub WS, Gebhart SP, *et al*. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. *Circulation* 1995;**91**:979–89.
3 **Ferroni P**, Basili S, Falco A, *et al*. Platelet activation in type 2 diabetes mellitus. *J Thromb Haemost* 2004;**2**:1282–91.
4 **Aronson D**, Bloomgarden Z, Rayfield EJ. Potential mechanisms promoting restenosis in diabetic patients. *J Am Coll Cardiol* 1996;**27**:528–35.
5 **Tang WH**, Lincoff AM. Diabetes, coronary intervention, and platelet glycoprotein IIb/IIIa blockade: the triad revisited. *Circulation* 2004;**110**:3618–20.
6 **Bhatt DL**, Marso SP, Lincoff AM, *et al*. Abciximab reduces mortality in diabetics following percutaneous coronary intervention. *J Am Coll Cardiol* 2000;**35**:922–8.
7 **Hermiller JB**, Raizner A, Cannon L, *et al*. Outcomes with the polymer-based paclitaxel-eluting TAXUS stent in patients with diabetes mellitus: the TAXUS-IV trial. *J Am Coll Cardiol* 2005;**19**:1172–9.
8 **Moussa I**, Leon MB, Baim DS, *et al*. Impact of sirolimus-eluting stents on outcome in diabetic patients: a SIRIUS (sirolimus-coated Bx velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) substudy. *Circulation* 2004;**109**:2273–8.
9 **de Araujo Goncalves P**, Seabra-Gomes R, Teles R, *et al*. Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow-up of a single-centre registry. *Heart* 2006;**92**:1155–6.
10 **Simon DI**, Xu H, Ortlepp S, *et al*. 7E3 monoclonal antibody directed against the platelet glycoprotein IIb/IIIa cross-reacts with the leukocyte integrin Mac-1 and blocks adhesion to fibrinogen and ICAM-1. *Arterioscler Thromb Vasc Biol* 1997;**17**:528–35.
11 **Tam SH**, Sassoli PM, Jordan RE, *et al*. Abciximab (ReoPro, chimeric 7E3 Fab) demonstrates equivalent affinity and functional blockade of glycoprotein IIb/IIIa and alpha(v)beta3 integrins. *Circulation* 1998;**98**:1085–91.
12 **Srivatsa SS**, Fitzpatrick LA, Tsao PW, *et al*. Selective alpha v beta 3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury: evidence for the functional importance of integrin alpha v beta 3 and osteopontin expression during neointima formation. *Cardiovasc Res* 1997;**36**:408–28.
13 **Mehilli J**, Kastrati A, Schuhlen H, *et al*. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. *Circulation* 2004;**110**:3627–35.
14 **Kastrati A**, Mehilli J, Schuhlen H, *et al*. A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004;**350**:232–8.
15 **Rha SW**, Kuchulakanti PK, Pakala R, *et al*. Bivalirudin versus heparin as an antithrombotic agent in patients treated with a sirolimus-eluting stent. *Am J Cardiol* 2004;**94**:1047–50.
16 **Stone GW**, Bertrand M, Colombo A, *et al*. Acute catheterization and urgent intervention triage strategy (ACUITY) trial: study design and rationale. *Am Heart J* 2004;**148**:764–75.

Capítulo 8.

Desenvolvimento do CT-LeSc

RESUMO:

Neste capítulo é descrito o CT-LeSc,, uma ferramenta para quantificação da carga aterosclerótica coronária, cujo desenvolvimento foi um dos objectivos centrais desta tese. O CT-LeSc engloba informação acerca da localização, grau de estenose e tipo de placa, traduzindo assim a carga aterosclerótica coronária global (obstrutiva e não obstrutiva) obtida de modo não invasivo pela angio TC cardíaca.

O **artigo 18** incluído neste capítulo descreve a sua metodologia e os seus preditores clínicos.

ABSTRACT:

The development of the CT-LeSc, as a tool to quantify coronary atherosclerotic burden, was one of the main objectives of the Thesis, and is described in this chapter. The CT-LeSc reflects the comprehensive information about localization, degree of stenosis and type of plaque, reflecting total (obstructive and nonobstructive) coronary atherosclerotic burden, noninvasively provided by cardiac CT.

The methodology is described in **manuscript 18**, as well as the analysis on its clinical predictors.

ARTIGO 18/ MANUSCRIPT 18:

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY-ADAPTED LEAMAN SCORE AS A TOOL TO NONINVASIVELY QUANTIFY TOTAL CORONARY ATHEROSCLEROTIC BURDEN.

Araújo Gonçalves P, Garcia-Garcia HM, Dores H, Carvalho MS, Jeronimo Sousa P, Marques H, Ferreira A, Cardim N, Teles R, Raposo L, Mesquita-Gabriel H, Almeida M, Aleixo A, Mota Carmo M, Pereira Machado F, Mendes M.

Int J Cardiovasc Imaging 2013; [Epub ahead of print] DOI:10.1007/s10554-013-0232-8

SUMÁRIO DO CAPÍTULO 8:

8.1 - INTRODUÇÃO

O desenvolvimento e implementação da coronariografia por cateterismo cardíaco veio permitir documentar a presença e extensão da DC, tendo sido desenvolvidos desde cedo vários **scores angiográficos** para quantificação da carga aterosclerótica coronária. Estes scores, usaram diferentes combinações e ponderações acerca da localização e do grau de estenose, tendo sido possível demonstrar que a carga aterosclerótica coronária tinha um forte valor prognóstico (1-4). Um dos scores angiográficos mais recentemente desenvolvidos foi o score de Syntax, reunindo informação detalhada acerca da localização, grau de estenose, presença e tipo de bifurcação, presença e tipo de oclusão, tortuosidade, calcificação, presença de trombo e comprimento das lesões (5). Este score foi desenvolvido para permitir quantificar a extensão e a gravidade da DC num estudo que comparou a revascularização percutânea com stents "*drug-eluting*" com a revascularização cirúrgica. Grande parte das variáveis incluídas neste score estão relacionadas com a complexidade da DC e a dificuldade imposta ao tratamento por angioplastia, que foi menos eficaz nos doentes com scores de Syntax mais elevados (6, 7). No entanto, foi interessante verificar que este score, apesar de ter apenas variáveis angiográficas na sua composição, leva consigo importante informação prognóstica, o que demonstra o importante valor da carga aterosclerótica coronária global para prever a ocorrência de eventos coronários adversos (8, 9) .

Mais recentemente, com o desenvolvimento tecnológico que permitiu o uso de **técnicas de imagem intracoronária**, foi possível quantificar a carga aterosclerótica coronária de um modo mais preciso, tirando proveito da sua elevada resolução espacial (10-12). No entanto, estas técnicas tem a sua aplicação inerentemente limitada pelo facto de serem invasivas e assim só empregues em populações seleccionadas referenciadas para coronariografia invasiva. Esta população geralmente já está em prevenção secundária e assim sob o efeito de múltiplos fármacos que provaram alterar a historia natural da DC e diminuir a taxa de eventos CV (13-16).

Nos últimos anos, assistimos a uma crescente adopção da **angioTC cardíaca** na prática clínica, resultante essencialmente do seu elevado valor preditor negativo, o que a torna uma técnica ideal para exclusão de DC e assim um bom *gatekeeper* para a coronariografia invasiva (17) (ver ***Capítulo 3***).

A angio TC permite também a identificação de lesões coronárias não obstrutivas e assim poderá ser uma ferramenta útil na quantificação da carga aterosclerótica coronária global. No entanto, dada a elevada prevalência de placas na árvore coronária (18-21), torna-se necessário desenvolver ferramentas que permitam quantificar a carga aterosclerótica e assim o risco de eventos coronários. A angio TC cardíaca permite avaliar não só a presença, mas também a localização das lesões, o grau de estenose e o tipo de placa, fornecendo assim uma avaliação detalhada da carga aterosclerótica coronária global.

Alguns scores foram já desenvolvidos, reflectindo algumas destas características e demonstraram ter valor prognóstico (22-24).

8.2 – DESENVOLVIMENTO DE UM SCORE DE CARGA ATEROSCLERÓTICA QUANTIFICADA POR ANGIO TC CARDÍACA – CT-LeSc

O CT-LeSc foi desenvolvido com o objectivo de permitir quantificar a carga aterosclerótica coronária, englobando três aspectos avaliáveis por angio TC, nomeadamente acerca da localização das lesões na árvore coronária, do grau de estenose e do tipo de placa aterosclerótica. Neste score foi feita a adaptação do score angiografico de Leaman, desenvolvido para quantificar a gravidade da DC obstrutiva, de acordo com a sua localização documentada na coronariografia invasiva (1).

No CT-LeSc foi feita a ponderação para 3 variáveis identificadas na angio TC (***tabela 1***):

1. Localização das lesões: Foram atribuídos pesos diferentes às lesões de acordo com a sua localização mais proximal na árvore coronária, reflectindo a massa de miocárdio em risco dependente dessa lesão. Na adaptação do score de Leaman angiográfico original, fizemos uma modificação na ponderação por segmento compatível com anatomia balanceada, usando valores intermédios entre e dominância direita e esquerda, de acordo com metodologia já empregue em numa tese de doutoramento prévia realizada na nossa instituição (25). Esta adaptação teve implicações nos valores atribuídos aos segmentos da CD (proximal, médio, distal) à descendente posterior, ao TC e à CX (segmentos proximal e distal),

1. Tipo de placa: No CT-LeSc foi introduzida uma ponderação para o tipo de placa, explorando a acuidade diagnostica da angio TC na identificação e classificação dos diferentes tipo de placas (26). Para efeito do CT-LeSc as placas não calcificadas e mistas foram agrupadas na mesma categoria, à qual foi atribuído o valor ponderal de 1,5. O valor ponderal atribuído às placas calcificadas foi deliberadamente inferior (1,0), tentando reflectir o maior potencial de instabilização das placas mistas e não calcificadas (12, 23, 27, 28).

3. Grau de estenose: Foi ainda feita uma última ponderação para o grau de estenose, sendo que na presença de uma lesão obstrutiva (estenose ≥50%) o valor era multiplicado por 1; no caso das lesões não obstrutiva, o score dessa placa era multiplicado por 0,615. Este factor foi obtido a partir da proporção dos *hazard ratios* para mortalidade associados à DC obstrutiva e não obstrutiva (2,6 e 1,6 respectivamente) obtidos no largo registo CONFIRM (24). Assim, tentou-se que esta proporção reflectisse o menor risco por placa das lesões não obstrutiva vs obstrutivas,

mas mantendo uma contribuição destas para o score global, explorando assim a mais valia do angio TC em identificar lesões mesmo na ausência de estenoses significativas.

Por fim, o valor do CT-LeSc para cada doente é obtido pelo somatório dos valores parciais de cada lesão identificada na árvore coronária.

TABELA 1: CT-LeSc: Factores de ponderação para localização, grau de estenose e tipo de placa

Localização			
Segmento	**Dominância direita**	**Dominância esquerda**	**Dominância balanceada**
CD proximal	1	0	0.5
CD média	1	0	0.5
CD distal	1	0	0.5
Descendente Posterior	1	na	0.5
Tronco comum	5	6	5.5
DA proximal	3.5	3.5	3.5
DA media	2.5	2.5	2.5
DA distal	1	1	1
1ª Diagonal	1	1	1
2ª Diagonal	0.5	0.5	0.5
Cx proximal	1.5	2.5	2.0
1ª Obtusa marginal	1	1	1
Cx distal	0.5	1.5	1
2ª Obtusa marginal	1	1	1
DP esquerda	na	1	na
Postero-lateral esquerda	na	0.5	0.5
Postero-lateral direita	0.5	na	na
Ramo intermediário	1	1	1
Grau de estenose			
DC obstrutiva (≥50%)	1		
DC não obstrutiva	0.615		
Tipo de placa			
Não calcificada ou mista	1.5		
Calcificada	1		

8. 3 – RESULTADOS DO CT-LeSc NA POPULAÇÃO DA TESE

Na população total estudada (n=581), a mediana do CT-LeSc foi de 2.2 (IQR 0-6.8). Na população com DC (n=341), a mediana do CT-LeSc foi de 5.8 (IQR 3.2-9.6), sendo de 4.6 (IQR 2.9-7.7) na DC não obstrutiva (n=263) e 11.7 (IQR 8.7-14.4) nos doentes com DC obstrutiva (n=78).
A população com DC foi dividida em tercis de acordo com o valor do CT-LeSc e o valor do 3º tercil foi considerado o limiar discriminativo para identificar um subgrupo de elevada carga aterosclerótica.
Os tercis do CT-LeSc foram: T1 ≤3.7 (0.3-3.7); T2 (3.8-8.3); T3 ≥ 8.3(8.3-24.1).
O CT-LeSc foi significativamente mais elevado nos homens, nos doentes com diabetes, com HTA bem como nos doentes considerados como de elevado risco CV (HeartScore ≥5%) (***figura 1***).

Na **análise univariada**, um CT-LeSc elevado associou-se a uma idade mais avançada (≥60 anos), à presença de diabetes e de HTA. O sexo masculino e a dislipidémia também foram percentualmente mais frequentes nos doentes com elevado CT-LeSc, embora esta diferença não tenha atingido significado estatístico. Os doentes com elevado CT-LeSc eram com maior frequência doentes com probabilidade de pré-teste mais elevada (com um Diamond-Forrester-CAD consortium ≥30% e um score de Morise≥ 16) e com maior risco cardiovascular (reflectida na maior percentagem de doentes com um HeartScore≥5%). Alguns dos tradicionais factores de risco CV como a obesidade e o tabagismo, não tiveram uma distribuição preferencial pelo grupo de elevado CT-LeSc, o que foi igualmente verificado com a presença de dor torácica (***tabela 2***).

Na **análise multivariada**, os preditores independentes de um CT-LeSc elevado (≥ 8.3) foram: sexo masculino, diabetes, HTA, score Morise ≥16 e HeartScore≥ 5 (**figura 2**). No que diz respeito aos factores de risco modificáveis, a diabetes associou-se a um risco 3x superior e a HTA a um risco 2,5x superior de um elevado CT-LeSc. Um HeartScore ≥5% (elevado risco CV) e um score de Morise ≥16 (elevada probabilidade de DAC) associaram-se a um risco 2,5x e 2x superior de ter uma elevada carga aterosclerótica, avaliada pelo CT-LeSc (***tabela 3***).

FIGURA 1: Mediana do CT-LeSc em diferentes subgrupos de doentes.

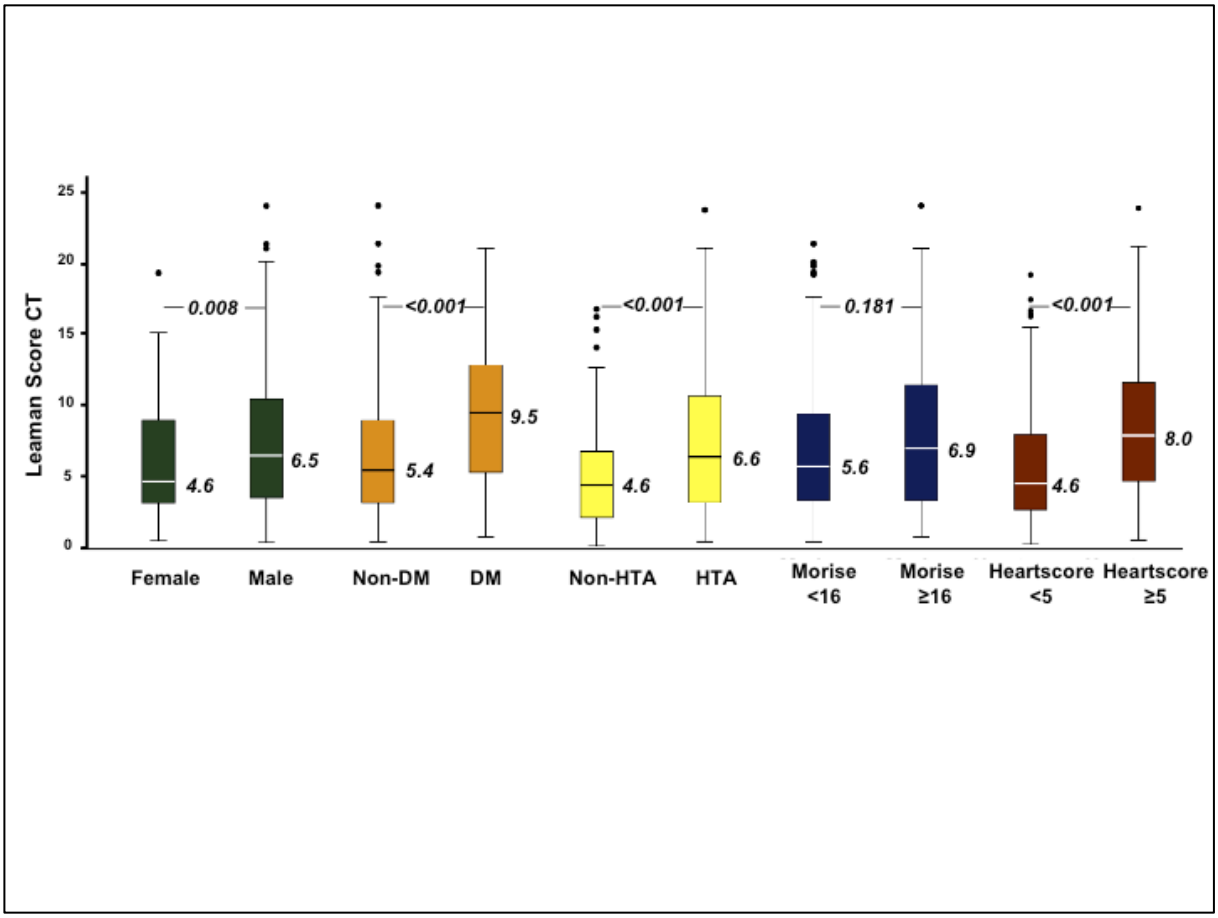


TABELA 2: Preditores de um CT-LeSc elevado (≥ T3) - Análise univariada.

	CT LeSc T1+2 (<8.3)	CT LeSc ≥ T3 (≥8.3)	p
Idade≥60 anos	126 (56.0)	79 (68.1)	0.031
Sexo masculino	138 (61.3)	81 (69.8)	0.121
IMC ≥30 kg/m2	41 (18.3)	25 (22.1)	0.404
Diabetes	26 (11.6)	36 (31.0)	<0.001
Hipertensão arterial	144 (64.0)	98 (84.5)	<0.001
Dislipidémia	146 (64.9)	87 (75.0)	0.057
Tabagismo	53 (23.6)	31 (26.7)	0.520
História familiar de DC prematura	77 (34.2)	37 (31.9)	0.666
Dor torácica	106 (47.3)	59 (51.3)	0.487
DF-CAD consortium ≥30%	66 (29.3)	64 (55.2)	<0.001
Score de Morise ≥ 16	105 (46.7)	78 (67.2)	<0.001
HeartScore ≥5	29 (12.9)	24 (20.7)	0.060

Valores apresentados em média ± desvio padrão

TABELA 3: Preditores independentes de um CT-LeSc elevado (≥ T3) - Análise multivariada.

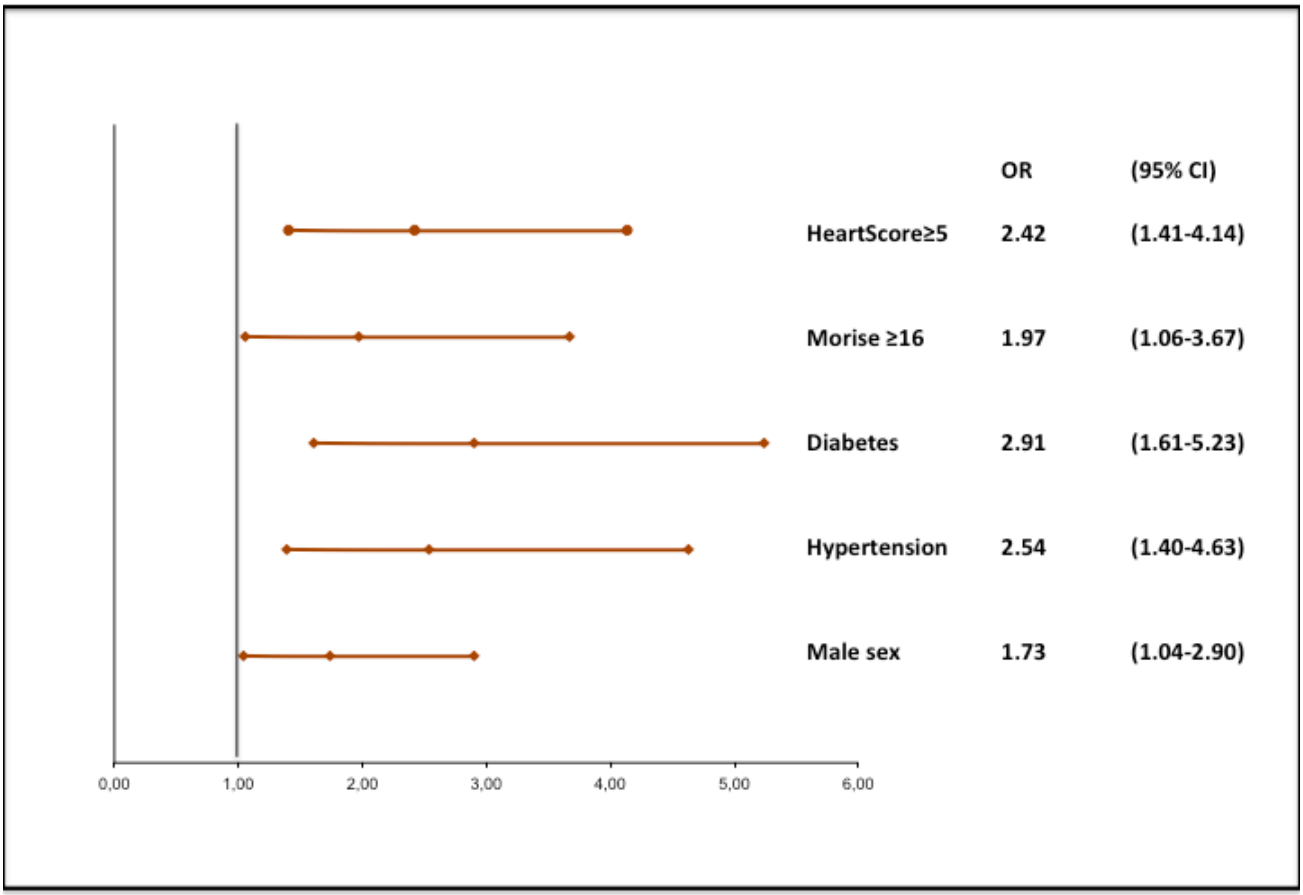
VARIÁVEIS DEMOGRÁFICAS E CLÍNICAS

	OR	(IC 95%)	p
Idade≥60 anos	1.370	0.819-2.291	0.230
Sexo masculino	**1.732**	**1.035-2.901**	**0.037**
Diabetes	**2.905**	**1.612-5.234**	**<0.001**
Hipertensão arterial	**2.543**	**1.395-4.634**	**0.002**
Dislipidémia	1.563	0.919-2.660	0.099

SCORES CLÍNICOS

	OR	(IC 95%)	p
HeartScore≥5	**2.416**	**1.411-4.135**	**0.001**
DF-CAD consortium ≥30%	1.590	0.918-2.754	0.098
Morise ≥16	**1.971**	**1.060-3.666**	**0.032**

FIGURA 2: Preditores independentes de um elevado CT-LeSc (>8,3).



8.5 BIBLIOGRAFIA

1. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation. 1981 Feb;63(2):285-99.
2. Califf RM, Phillips HR, 3rd, Hindman MC, Mark DB, Lee KL, Behar VS, et al. Prognostic value of a coronary artery jeopardy score. J Am Coll Cardiol. 1985 May;5(5):1055-63.
3. Alderman EL SM. The angiographic definitions of the Bypass Angioplasty Revascularization Investigation. Coronary Artery Disease. 1992(3):1189–207.
4. Graham MM, Faris PD, Ghali WA, Galbraith PD, Norris CM, Badry JT, et al. Validation of three myocardial jeopardy scores in a population-based cardiac catheterization cohort. Am Heart J. 2001 Aug;142(2):254-61.
5. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005 Aug;1(2):219-27.
6. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. Circulation. 2010 Jun 22;121(24):2645-53.
7. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009 Mar 5;360(10):961-72.
8. Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Swart M, et al. A patient-level pooled analysis assessing the impact of the SYNTAX (synergy between percutaneous coronary intervention with taxus and cardiac surgery) score on 1-year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. JACC Cardiovasc Interv. 2011 Jun;4(6):645-53.
9. Brito J, Teles R, Almeida M, de Araujo Goncalves P, Raposo L, Sousa P, et al. Predictive value of SYNTAX score in risk stratification of patients undergoing unprotected left main coronary artery angioplasty. J Invasive Cardiol. 2011 Dec;23(12):494-9.
10. Valgimigli M, Rodriguez-Granillo GA, Garcia-Garcia HM, Malagutti P, Regar E, de Jaegere P, et al. Distance from the ostium as an independent determinant of coronary plaque composition in vivo: an intravascular ultrasound study based radiofrequency data analysis in humans. Eur Heart J. 2006 Mar;27(6):655-63.
11. Brugaletta S, Garcia-Garcia HM, Serruys PW, Gomez-Lara J, de Boer S, Ligthart J, et al. Distance of lipid core-rich plaques from the ostium by NIRS in nonculprit coronary arteries. JACC Cardiovasc Imaging. 2012 Mar;5(3):297-9.
12. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35.
13. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006 Apr 5;295(13):1556-65.
14. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207.
15. Antithrombotic Trialists C, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.
16. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 Jan 20;342(3):145-53.
17. Shaw LJ, Hausleiter J, Achenbach S, Al-Mallah M, Berman DS, Budoff MJ, et al. Coronary computed tomographic angiography as a gatekeeper to invasive diagnostic and surgical procedures: results from the multicenter CONFIRM (Coronary CT Angiography Evaluation for

Clinical Outcomes: an International Multicenter) registry. J Am Coll Cardiol. 2012 Nov 13;60(20):2103-14.
18. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. Circ Cardiovasc Imaging. 2011 Sep;4(5):463-72.
19. Lin FY, Shaw LJ, Dunning AM, Labounty TM, Choi JH, Weinsaft JW, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. J Am Coll Cardiol. 2011 Jul 26;58(5):510-9.
20. Pen A, Yam Y, Chen L, Dennie C, McPherson R, Chow BJ. Discordance between Framingham Risk Score and atherosclerotic plaque burden. Eur Heart J. 2013 Jan 9.
21. de Araujo Goncalves P, Garcia-Garcia HM, Carvalho MS, Dores H, Sousa PJ, Marques H, et al. Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited. Int J Cardiovasc Imaging. 2012 Dec 13.
22. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007 Sep 18;50(12):1161-70.
23. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging. 2012 Jul;5(7):690-701.
24. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011 Aug 16;58(8):849-60.
25. Machado Macedo M. Revascularização do miocárdio. A primeira experiencia como cirurgia electiva e de rotina no Hospital de Santa Cruz. Dissertação de Doutoramento apresentada à Faculdade de Ciências Médicas, Universidade Nova de Lisboa 1986.
26. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr. 2009 Mar-Apr;3(2):122-36.
27. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol. 2007 Jul 24;50(4):319-26.
28. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009 Jun 30;54(1):49-57.

8.4 ARTIGO 18/ MANUSCRIPT 18:

Int J Cardiovasc Imaging
DOI 10.1007/s10554-013-0232-8

ORIGINAL PAPER

Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden

Pedro de Araújo Gonçalves · Hector M. Garcia-Garcia · Helder Dores · Maria Salomé Carvalho · Pedro Jerónimo Sousa · Hugo Marques · Antonio Ferreira · Nuno Cardim · Rui Campante Teles · Luís Raposo · Henrique Mesquita Gabriel · Manuel Sousa Almeida · Ana Aleixo · Miguel Mota Carmo · Francisco Pereira Machado · Miguel Mendes

Received: 19 April 2013 / Accepted: 24 April 2013

Abstract To describe a coronary computed tomography angiography (CCTA)-adapted Leaman score (CT-LeSc) as a tool to quantify total coronary atherosclerotic burden with information regarding localization, type of plaque and degree of stenosis and to identify clinical predictors of a high coronary atherosclerotic burden as assessed by the CT-LeSc. Single center prospective registry including a total of 772 consecutive patients undergoing CCTA (Dual-source CT) from April 2011 to March 2012. For the purpose of this study, 581 stable patients referred for suspected coronary artery disease (CAD) without previous myocardial infarction or revascularization procedures were included. Pre-test CAD probability was determined using both the Diamond–Forrester extended CAD consortium method (DF-CAD consortium model) and the Morise score. Cardiovascular risk was assessed with the HeartScore. The cut-off for the 3rd tercile (CT-LeSc $\geq$8.3) was used to define a population with a high coronary atherosclerotic burden. The median CT-LeSc in this population (n = 581, 8,136 coronary segments evaluated; mean age 57.6 $\pm$ 11.1; 55.8 % males; 14.6 % with diabetes) was 2.2 (IQR 0–6.8). In patients with CAD (n = 341), the median CT-LeSc was 5.8 (IQR 3.2–9.6). Among patients with nonobstructive CAD, most were classified in the lowest terciles (T1, 43.0 %; T2, 36.1 %), but 20.9 % were in the highest tercile (T3). The majority of the patients with obstructive CAD were classified in T3 (78.2 %), but 21.8 % had a CT-LeSc in lower terciles (T1 or T2). The independent predictors of a high CT-LeSc were: Male sex (OR 1.73; 95 % CI 1.04–2.90) diabetes (OR 2.91; 95 % CI 1.61–5.23), hypertension (OR 2.54; 95 % CI 1.40–4.63), Morise score $\geq$16 (OR 1.97; 95 % CI 1.06–3.67) and HeartScore $\geq$5 (OR 2.42; 95 % CI 1.41–4.14). We described a cardiac CT adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA. Male sex, hypertension, diabetes, a HeartScore $\geq$5 % and a Morise score $\geq$16 were associated with a high coronary atherosclerotic burden, as assessed by the CT-LeSc. About one fifth of the patients with nonobstructive CAD had a CT-LeSc in the highest tercile, and this could potentially lead to a reclassification of the risk profile of this subset of patients identified by CCTA, once the prognostic value of the CT-LeSc is validated.

Keywords CCTA · Coronary artery disease · Atherosclerotic burden · Risk scores

P. de Araújo Gonçalves (✉) · H. Dores · M. S. Carvalho · P. Jerónimo Sousa · A. Ferreira · R. Campante Teles · L. Raposo · H. Mesquita Gabriel · M. Sousa Almeida · A. Aleixo · M. Mendes
Cardiology Department, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
e-mail: paraujogoncalves@yahoo.co.uk

P. de Araújo Gonçalves · H. Marques · A. Ferreira · N. Cardim · F. Pereira Machado
Hospital da Luz, Lisbon, Portugal

P. de Araújo Gonçalves · A. Aleixo · M. Mota Carmo
CEDOC, Chronic Diseases Research Center, FCM-NOVA, Lisbon, Portugal

H. M. Garcia-Garcia
Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

Published online: 01 May 2013

Introduction

Coronary atherosclerosis is the leading cause of mortality and it is expected to remain the most important disease in the upcoming years [1]. Frequently, the first manifestation of coronary disease is an acute coronary syndrome (ACS), and many patients were previously asymptomatic [2]. An early detection of coronary disease is of utmost relevance and a non-invasive diagnostic test is desirable.

In the recent years, coronary computed tomography angiography (CCTA) has become widely available and adopted. The main reason for this is the high predictive accuracy of detection of obstructive coronary artery disease (CAD) compared to conventional invasive coronary angiography [3, 4]. In addition, CCTA allows also the identification of nonobstructive CAD and in this way it can provide a noninvasive quantification of the total coronary atherosclerotic burden. Since the percentage of patients with nonobstructive CAD is very high, there is a need for tools to stratify cardiovascular risk by the degree of plaque burden [5]. The information regarding the localization, severity and composition of coronary plaques identified with CCTA can be collected in scores to reflect the total coronary plaque burden, and some have been already developed and validated [6].

Conventional cardiovascular (CV) risk factors relate to the risk of subsequent CV events and they can be combined in tools as it has been done in the Heart Score [7]. Notwithstanding these observations, accurate prediction of major coronary events on the individual patient level, as opposed to population based studies, remains challenging.

Therefore the aim of this study is two folded: (1) To describe a CCTA-adapted Leaman score (CT-LeSc) as a tool to quantify total coronary atherosclerotic burden including information regarding localization, type of plaque and degree of stenosis and; (2) To identify clinical predictors of a high coronary atherosclerotic burden as assessed by CT-LeSc in a population of stable patients referred for CCTA for suspected CAD.

Methods

Population

Single center prospective registry including a total of 772 consecutive patients undergoing CCTA (with Dual source CT) from April 2011 to March 2012. Patients were excluded if: (1) previous myocardial infarction and/or revascularization procedures (n = 70); (2) referred for Cardiac CT for other indications than the evaluation of possible CAD (cardiac CT for atrial fibrillation ablation or transcatheter aortic valvular implantation procedures; n = 88); (3) referred for suspected ACS (n = 24); (4) with atrial fibrillation or other significant arrhythmias during scan acquisition that compromised image quality (n = 9). This resulted in a 24.7 % of the total population being excluded.

For the purpose of this study, 581 stable patients referred for suspected CAD were included in the context of: (1) Previous equivocal or inconclusive stress tests or discordant with the clinical evaluation (n = 417; 71.8 %); (2) Cardiac CT as 1st line investigation of possible CAD (n = 136; 23.4 %); (3) Preoperative CAD assessment prior to noncoronary valvular or aortic surgery (n = 17; 2.9 %); (4) Evaluation of possible CAD in cardiomyopathies (DCM or HCM; n = 11; 1.9 %; Fig. 1: Patient selection and study design).

The study was approved by the local ethics committee and all patients gave a written informed consent.

A detailed medical history with a risk factors questionnaire was obtained from the patients to assess for the presence of: (1) Diabetes mellitus (defined as a fasting glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents) [8]; (2) Dyslipidemia (defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) [9]; (3) Hypertension (defined as blood pressure ≥140/90 mm Hg or the use of antihypertensive medication) [10]; (4) Obesity (body mass index ≥30 kg/m^2); (5) positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 [male] or 65 [female] years of age) [11]; (6) smoking (defined as previous [less <1 year] or current smoker.

Pre-test probability of CAD was determined using both the Diamond and Forrester extended CAD consortium method (DF-CAD consortium model) [12] and the Morise score [13]. The cardiovascular risk was assessed with the HeartScore [7]. As the CAD probability and CV risk of our population was shifted to lower probability and risk, the cut-offs used were: (1) for DF-CAD consortium model categories ≥30–70 and ≥70 % were gathered in a Intermediate to High (≥30 %) probability group.

For the Morise, the population was divided in terciles, and for the HeartScore the established high risk cut-off of ≥5 % was used.

Scan protocol and image reconstruction

All scans were performed with a dual-source scanner (Somatom Definition, Siemens Medical, Germany), with the patient in dorsal decubitus and in deep inspiration breath-hold. Sublingual nitroglycerin was administered to all patients except when contraindicated and intravenous metoprolol (5 mg, with a titration dose up to 20 mg) was administered in patients with heart rate >65 beats/min.

During the scan acquisition, a bolus of iodinated contrast (Visipaque, GE Healthcare, USA) was injected at a

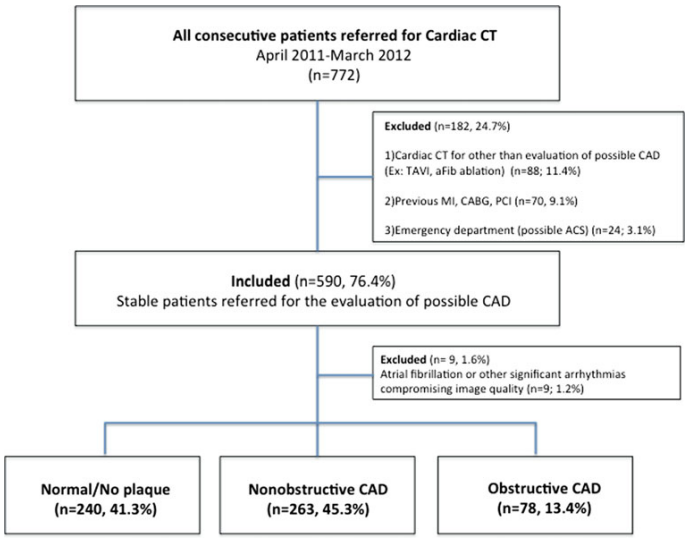


Fig. 1 Patient selection and study design. *CAD* coronary artery disease, *TAVI* transcatheter aortic valve implantation, *aFib* atrial fibrillation, *MI* myocardial infarction, *CABG* coronary artery bypass grafting, *PCI* percutaneous coronary intervention, *ACS* acute coronary syndromes

6 ml/s infusion rate, followed by a 50-ml saline flush. The dose of contrast was calculated according to the following formula: (acquisition time +6 s delay) × flow (6 ml/s). Contrast timing was performed to optimize uniform contrast enhancement of the coronary arteries.

Dose reduction strategies—including electrocardiogram-gated tube current modulation, reduced tube voltage, and prospective axial triggering—were used whenever feasible. Mean estimated radiation dose was 4.6 ± 3.7 mSv, contrast dose was 98.9 ± 14.4 ml and heart rate was 65.6 ± 10.6 bpm.

Transaxial images were reconstructed with a temporal resolution of 83 ms and slice thickness of 0.75 mm with 0.4 mm increments.

Post-processing was carried out using Circulation® software, with multiplanar reconstructions, maximum intensity projection and volume rendering technique.

Coronary artery analysis

All scans were analyzed in the same session by both a cardiologist and a radiologist with Level III-equivalent experience. The Society of Cardiovascular Computed Tomography recommended classification was used regarding segmentation (16 segments), stenosis severity (<25, 25–49, 50–69, 70–99, 100 %) and plaque composition (calcified, non calcified, mixed plaque) [14].

In each coronary artery segment, coronary atherosclerosis was defined as a tissue structure >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself [6]. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percent obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque.

CCTA adapted Leaman score (CT-LeSc)

For the CT adaptation of the LeSc, we used three sets of weighting factors, all noninvasively provided by CCTA: (1) *localization* of the coronary plaques as originally described [15]. In this study, a modification was made to account for balanced dominance. In cases of balanced dominance, not taken in account in the original Leaman or in the Syntax scores, we assumed an intermediate value between right and left dominance which changed the values for the posterior descending and the proximal, mid and

distal RCA segments as well as for the left main and proximal and distal segments of the circumflex; (2) *type of plaque* (i.e. noncalcified, calcified or mixed plaques). To take in account the cardiac CT added information related to plaque composition, an additional weighting factor of 1.5 was added to predominantly noncalcified of mixed plaques and a factor of 1 to predominantly calcified plaques, reflecting the assumption of less plaque vulnerability of the later ones [16, 17]; (3) *degree of stenosis* (<50 ≥% stenosis). In the presence of obstructive CAD (≥50 % stenosis), the score in each segment was multiplied by 1 and for nonobstructive CAD it was multiplied by a factor of 0.615. This factor reflects the relative proportion in the published hazard ratios for mortality in the large CONFIRM registry [5] for obstructive versus nonobstructive CAD (2.6 vs 1.6 respectively) and it was assumed to reflect the relative prognostic impact of nonobstructive CAD (Table 1).

Table 1 CT-adapted Leaman Score (CT-LeSc) weighting factors

Segment	Right dominance	Left dominance	Balanced
Coronary segments			
RCA proximal	1	0	0.5
RCA mid	1	0	0.5
RCA distal	1	0	0.5
PDA	1	na	0.5
Left main	5	6	5.5
LAD proximal	3.5	3.5	3.5
LAD mid	2.5	2.5	2.5
LAD distal	1	1	1
1st diagonal	1	1	1
2nd diagonal	0.5	0.5	0.5
LCx proximal	1.5	2.5	2.0
1st obtuse marginal	1	1	1
LCx distal	0.5	1.5	1
2nd obtuse marginal	1	1	1
PDA from LCA	na	1	na
PL branch from LCA	na	0.5	0.5
PL branch from RCA	0.5	na	na
Intermediate branch	1	1	1
Stenosis severity			
Obstructive CAD	1		
Nonobstructive CAD	0.615		
Plaque composition			
Non-calcified or mixed	1.5		
Calcified	1		

RCA right coronary artery, *PDA* posterior descending artery, *LAD* left anterior descending, *LCx* left circumflex, *PL* postero-lateral, *CAD* coronary artery disease

The CT-LeSc on a patient level was calculated as the sum of the partial CT-LeSc of all evaluable coronary segments. Two cases examples are shown in Fig. 2.

Statistical analysis

Continuous variables are presented as mean ± SD or medians (interquartile range) and categorical variables as frequencies with percentages.

The non-parametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables, and the Chi square test to evaluate differences in frequencies. Differences were regarded significant when $p < 0.05$ (two-tailed).

Since there are no previous validated cut-offs for the presently described CCTA score, the population with CAD was divided in terciles. A high CT-LeSc was defined with the cut-off for the 3rd tercile (a score ≥8.3, n = 116; 34.8 % of the CAD population) and patients in this group were compared with the remaining population.

Multivariate analyses (binary logistic regression model—enter method) were performed to identify independent predictors of a high CT-LeSc using the demographic and clinical variables presented in Table 2 that had a *p* value <0.2 at univariate analyses. A second multivariable analyses was performed to identify independent predictors among the clinical scores of CAD probability (Diamond–Forrester CAD consortium model and Morise score) and the CV risk score HeartScore.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

In the final study population of 581 patients, 8,136 coronary segments were evaluated. Segments <2 mm (n = 742; 9.1 %) or with suboptimal image quality related to artefacts or severe calcification (n = 120; 1.5 %) were excluded.

Most of patients were male (55.8 %) and mean age was 57.6 ± 11.1, and 14.6 % were diabetics. This was predominantly a population with low to intermediate CAD probability since 60.1 % had a DF-CAD consortium <30 and 87.6 % had a Morise score <16. A high cardiovascular risk, as assessed by an HeartScore ≥5 %, was present in 25.5 % of the patients. In this population, the median calcium score was 1 (IQR 0–93), 23.4 % had a calcium score (CaSc) ≥100 and 14.3 % had a CaSc ≥75th percentile. In the population with CAD, the median CaSc was 64 (IQR 8–200; Table 2).

CT-LeSc

Overall (n = 581), the median CT-LeSc in this population was 2.2 (IQR 0–6.8). In patients with CAD (n = 341), the

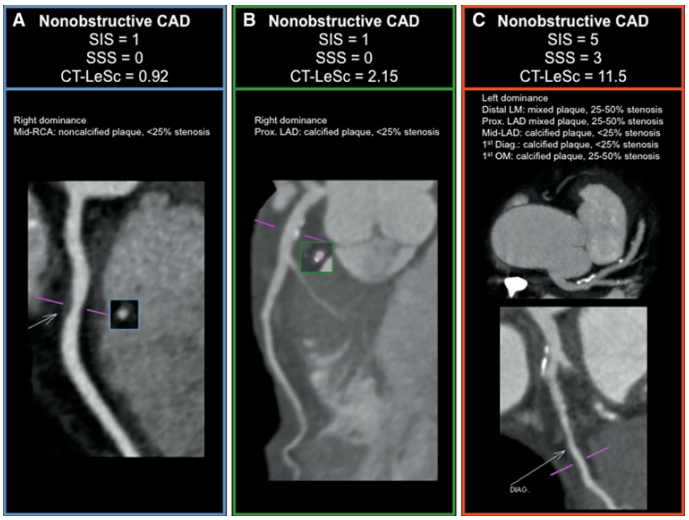


Fig. 2 Three cases examples of patients with nonobstructive CAD stratified by different coronary atherosclerotic burden scores. In panel *A*, a patient with a single lesion in the mid-RCA (weighting for localization × type of plaque × stenosis severity = 1 × 1.5 × 0.615 = 0.92); In panel *B*, a patient with a single proximal LAD lesion (CT-LeSc = 3.5 × 1 × 0.615 = 2.15). In panel *C*, a patient with left dominance and 5 nonobstructive lesions with a total CT-LeSc = LM (6 × 1.5 × 0.615) + prox. LAD (3.5 × 1.5 × 0.615) + mid-LAD (2.5 × 1 × 0.615) + 1st Diag. (1 × 1 × 0.615) + 1st OM (1 × 1 × 0.615) = 11.5. *CAD* coronary artery disease, *CT-LeSc* CT Leaman score, *SIS* segment involvement score, *SSS* segment stenosis score, *LM* left main, *LAD* left anterior descending, *LCx* left circunflex, *RCA* right coronary artery, *1st Diag.* first diagonal branch, *1st OM* first obtuse marginal branch

median CT-LeSc was 5.8 (IQR 3.2–9.6). Within this population the median CT-LeSc in patients with non-obstructive disease (n = 263) was 4.6 (IQR 2.9–7.7) and in patients with obstructive disease (n = 78) it was 11.7 (IQR 8.7–14.4). The terciles in population with CAD were: *T1* ≤*3.7 (0.3–3.7)*; *T2 (3.8–8.3)*; *T3* ≥8.3 (8.3–24.1).

Regarding the distribution of patients with nonobstructive versus obstructive CAD across the CT-LeSc terciles, most of the patients with nonobstructive CAD were in T1 (n = 113, 43.0 %) or T2 (n = 95, 36.1 %), but about one fifth (n = 55, 20.9 %) were in the highest tercile (T3, CT-LeSc ≥8.3). On the other hand, although most of the patients with obstructive CAD were classified in T3, 21.8 % had a CT-LeSc in lower terciles (T1, 2.6 %; T2, 19.2 %; Fig. 3).

The median CT-LeSc was significantly higher in males and in the presence of diabetes and hypertension, as well as in patients with a high cardiovascular risk assessed by an HeartScore ≥5 %. The median CT-LeSc was also significantly higher in patients with a CaSc ≥100 and CaSc ≥75th percentile (Fig. 4: Median CT-LeSc in different patient subgroups).

Univariate predictors

In the univariate analysis, a high CT-LeSc was associated with older age (≥60 years), diabetes and hypertension. The percentage of male patients and patients with dyslipidemia was also higher in the high CT-LeSc group, but not statistically significant. Patients in the high CT group had also a higher pre-test CAD probability (DF-CAD consortium ≥30 % and Morise score ≥16) as well as higher CV risk, reflected in the significantly higher percentage of patients with a HeartScore ≥5 %. Of note, some traditional risk factor as obesity, smoking status and family history of premature CAD were not differently distributed in the two groups, and this was also the case for chest pain (Table 3).

Multivariate predictors

By multivariate analysis, the independent predictors of a high CT-LeSc were: male sex; diabetes, hypertension, Morise score ≥16 and HeartScore ≥5 (Table 4; Fig. 5). Of note, regarding the modifiable risk factors, patients with

Table 2 Demographic, clinical and CCTA characteristics of the study population

	All patients (n = 581)
Demographic	
Age	57.6 ± 11.1
Male sex	324 (55.8)
Risk factors	
Obesity (BMI ≥30)	109 (18.8)
Diabetes	85 (14.6)
Hypertension	364 (62.7)
Dyslipidemia	360 (62.0)
Smoking	138 (23.8)
Family history of premature CAD	194 (33.4)
Chest pain	
Asymptomatic	270 (46.5)
Noncardiac	169 (29.1)
Atypical	109 (18.8)
Typical	33 (5.7)
CAD probability	
DF-CAD consortium ≥70 %	11 (1.9)
DF-CAD consortium 30–70 %	221 (38.0)
DF-CAD consortium <30 %	349 (60.1)
Morise score ≥16	72 (12.4)
Morise score 9–15	369 (63.5)
Morise score 0–8	140 (24.1)
CV risk	
Heart score ≥5 %	148 (25.5)
Calcium score	
Median	1 (0–93)
Median in patients with CAD	64 (8–200)
CaSc ≥100	136 (23.4)
CaSc ≥75th percentile	83 (14.3)
CCTA	
Normal/no plaque	240 (41.3)
Nonobstructive CAD	263 (45.3)
Obstructive CAD	78 (13.4)
Technical data	
Heart rate (bpm)	65.6 ± 10.6
Contrast dose (ml)	98.9 ± 14.4
Radiation dose (mSv)	4.6 ± 3.7

Values are mean ± SD, median (IQR) or n (%)

CAD coronary artery disease, *BMI* body mass index, *DF-CAD consortium* Diamond–Forrester CAD consortium model, *CV* cardiovascular, *CCTA* coronary computed tomography angiography, *CaSc* calcium score, *bpm* beats per minute, *mSv* milisievert

diabetes had a threefold and patients with hypertension a 2.5-fold higher probability of having a high CT-LeSc.

A high HeartScore (≥5 %) and a high Morise score (≥16) were associated respectively with a 2.5 and twofold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc.

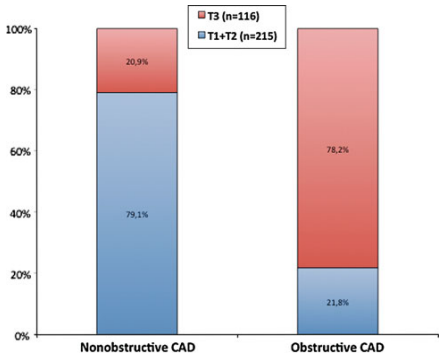


Fig. 3 Distribution of the two subgroups of patients (nonobstructive and obstructive CAD), according to CT-LeSc terciles (T1 + T2 vs T3). *CAD* coronary artery disease, *T1* 1st tercile, *T2* 2nd tercile, *T3* 3rd tercile

Discussion

The main findings of this study are: (1) Calculation of a cardiac CT adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA is feasible; (2) There was a significant association between the CT-LeSc and diabetes, a well recognized subset of advanced coronary atherosclerotic burden. A high CV risk (HeartScore) and a high CAD probability (Morise score) were also both associated with nearly a 2–2.5 fold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc.

Although the exclusion of obstructive CAD remains presently the main indication to refer a patient for CCTA, this noninvasive diagnostic tool can also provide information regarding the presence of nonobstructive plaques, detecting CAD at earlier disease stages. Although on a *per lesion* basis, vulnerability is positively associated with the degree of stenosis, on a *per patient* level most of the acute events come from nonobstructive lesions [18–20]. It is also recognized that many of the nonstenotic lesions can have a high plaque burden, underestimated by luminal angiograms, since they undergo expansive or positive outward enlargement, and such remodeling is a potential surrogate marker of plaque vulnerability [21]. In the multicenter virtual histology intravascular ultrasound (VH-IVUS) PROSPECT study [22], a large plaque burden, a small lumen area and the presence of a thin cap fibroatheroma were independent predictors of future nonculprit lesion major adverse cardiac events (MACE). In this study, lesions that led to MACE had a high plaque burden by

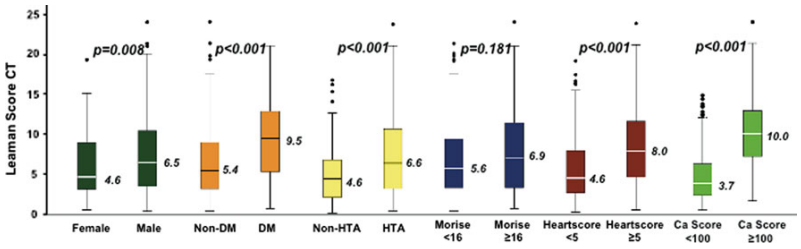


Fig. 4 Median CT-LeSc in different patient subgroups. *DM* diabetes mellitus, *HTA* hypertension, *CA score* calcium score, *CT-LeSc* CT Leaman score

Table 3 Univariate analysis

	CT LeSc T1 + 2 (<8.3)	CT LeSc ≥ T3 (≥8.3)	*p*
Age ≥60	126 (56.0)	79 (68.1)	0.031
Male sex	138 (61.3)	81 (69.8)	0.121
BMI ≥30	41 (18.3)	25 (22.1)	0.404
Diabetes	26 (11.6)	36 (31.0)	<0.001
Hypertension	144 (64.0)	98 (84.5)	<0.001
Dyslipidemia	146 (64.9)	87 (75.0)	0.057
Smoking	53 (23.6)	31 (26.7)	0.520
Family history of premature CAD	77 (34.2)	37 (31.9)	0.666
Chest pain	106 (47.3)	59 (51.3)	0.487
DF-CAD consortium ≥30 %	66 (29.3)	64 (55.2)	<0.001
Morise score ≥16	105 (46.7)	78 (67.2)	<0.001
Heart score ≥5	29 (12.9)	24 (20.7)	0.060

Values are n (%); *CAD* coronary artery disease, *BMI* body mass index, *DF-CAD* consortium-diamond–Forrester CAD consortium model

Table 4 Multivariate analysis—independent predictors of a high CT-LeSc (3rd tercile, score ≥8.3)

	OR	(95 % CI)	*p*
Demographic and clinical variables			
Age ≥60	1.370	0.819–2.291	0.230
Male sex	1.732	1.035–2.901	0.037
Diabetes	2.905	1.612–5.234	<0.001
Hypertension	2.543	1.395–4.634	0.002
Dyslipidemia	1.563	0.919–2.660	0.099
Clinical scores			
Heart score ≥5	2.416	1.411–4.135	0.001
DF-CAD consortium ≥30 %	1.590	0.918–2.754	0.098
Morise ≥16	1.971	1.060–3.666	0.032

OR odds ratio, *DF-CAD consortium* Diamond–Forrester CAD consortium model

IVUS, but were mild by baseline angiography (mean diameter stenosis 32 %). The prognostic value of nonobstructive CAD has also been recently reinforced from large cardiac CT registries (CONFIRM) and meta-analysis [23].

In the large international multicenter CONFIRM registry, all-cause mortality was significantly higher for patients with nonobstructive CAD, as compared with patients without coronary atherosclerosis. One notable finding in this registry is the superimposed survival curves of nonobstructive and 1 vessel obstructive CAD, reinforcing the prognostic impact of nonobstructive coronary lesions [6].

Why a plaque burden CT score?

The main reason is because CAD represents a very heterogeneous condition and there is a need to structure the quantification of the plaque burden and to integrate the most important information collected by CT and finally to homogenize the reporting of CT findings.

There are already some CT scores developed and prognostically validated namely the segment involvement score (SIS) and the segment stenosis score (SSS), but they only reflect some aspects of the coronary atherosclerotic burden, the former only takes into account the number of segments with plaque and the latter the degree of stenosis [6]. The CT-LeSc reflects some of the aspects that are partially included in the SIS (number of segments with plaque) and the SSS (degree of stenosis), and combines these two aspects, and also the localization, on a more comprehensive score.

Why these three components?

Individually, *localization* of the plaque within the coronary tree, *the type of plaques* and *degree of stenosis* are strong predictors of future coronary events.

Since CCTA is able to reliably collect information on these three aspects, a comprehensive score should be able to integrate these components.

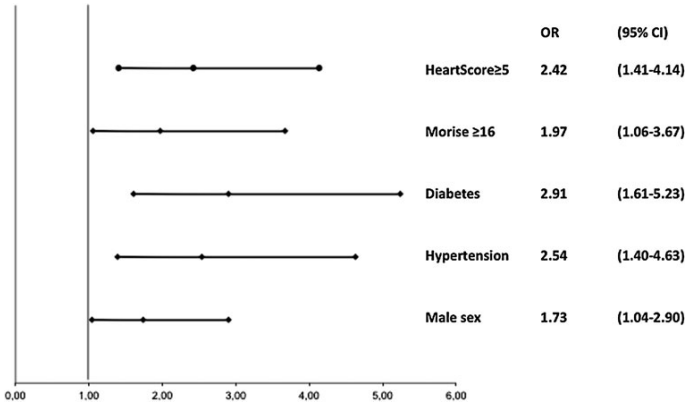


Fig. 5 Independent predictors of a high CT-LeSc (score ≥8.3). *CT-LeSc* CT Leaman score

Regarding *localization*, the original Leaman score was developed as a score to quantify obstructive coronary disease identified with invasive angiography [15]. In this score, with the rational of relative blood supply to the left ventricle, all coronary segments were given a weighting factor, reflecting the relative contribution of blood flow to the left ventricle of each vessel segment, taking also in account the specific right or left dominance systems. Recently, this score was used as the segment weighting factor for the development of the syntax score [24] which has been proven to have a strong prognostic value in different clinical scenarios [25, 26]. In our score, values were also provided for balanced dominance, reflecting more adequately the anatomical variants of the coronary tree.

Plaque composition has been found in both pathological and clinical studies associated with cardiac events [22, 27]. CCTA has shown to be able to characterize plaque composition [28]. Thin cap fibroatheroma is the most common pathological substrate of ACS and in CCTA these plaques appear as noncalcified or mixed plaques [16]. In a recent study by Maurovich-Horvat et al. [16], the frequency of a napkin-ting sign, a CCTA feature of advanced lesions by histology, was similar between noncalcified and mixed plaques, which also reinforces our weighting factor in the CT-LeSc for plaque composition that was the same between these two types (a factor of 1.5), and different from predominantly calcified plaques (a factor of 1).

Regarding the *degree of stenosis*, we assumed in our scoring system a factor reflecting the proportion of the hazard ratios for obstructive versus nonobstructive observed in the recently large scale CONFIRM registry. By gathering all the nonobstructive (<25, 25–49 %) and obstructive (50–69, 70–99, 100 %) in the same risk categories, this scoring system is expected to have a good intra and inter-observer correlation, since the other two weighting factors (localization and plaque calcification) have also an excellent reproducibility and are usually described in CCTA reporting.

Clinical implications

Many tools are already available to help stratifying patients at risk of a CV event and some scores have been already developed gathering the information provided by the different traditional risk factors, like the Framingham score or the HeartScore. Notwithstanding these observations, accurate prediction of major coronary events on the individual patient level, as opposed to population based studies, remains challenging.

The clinical implications of a score that reflect the extent of coronary atherosclerotic burden is related to the fact that this way we can have a tool to quantify and compare this burden, which is particularly useful when reporting a CCTA of a patient without obstructive CAD, but in whom the extent of nonobstructive CAD could lead to a reclassification of his risk profile and thereby his cardiovascular treatment.

Of note in our study is the fact that although the CT-LeSc, by having the degree of stenosis in its composition, tends to favour patients with obstructive CAD, we were able to demonstrate that a significant percentage (20.9 %) of patients with nonobstructive CAD had in fact a CT-LeSc in the highest tercile (T3). Conversely, among patients with obstructive CAD, about one fifth had a coronary

atherosclerotic burden, as assessed by the CT-LeSc, in lower terciles.

The CT-LeSc, by having a weight related to the localization, it reflects not only the extent of CAD but also the expected clinical consequences in case that the more proximal lesions evolve to a significant stenosis or become unstable and trigger a coronary event.

In our study, a high HeartScore and a high Morise score were both associated with nearly a 2–2.5 fold higher probability of having a high coronary atherosclerotic burden, as assessed by the CT-LeSc. This could be expected for the HeartScore, as it was develop as a tool to predict cardiovascular risk. In the case of the Morise score, is was developed and validated as a clinical tool to estimate the probability of CAD, but it has also been linked to cardiovascular outcomes [29]. The Diamond–Forrester was not an independent predictor of a high CT-LeSc and although we used the recently calibrated CAD consortium model [12], is has been developed and calibrated for obstructive CAD identified with invasive angiography and doesn't take in account the cardiovascular risk factors in its composition.

Limitations

There are a number of limitations related to this report: (1) This is a single center data with medium size cohort; (2) High prevalence of low CAD probability/CV risk patients. The population included in our study was mainly composed of patients with low to intermediate CAD probability and CV risk. Nevertheless, CAD was present in nearly 60 % of the patients and this reflects the daily practice and the recommendations that high CAD probability patients have not an appropriate indication for CCTA [30]; (3) For the weighting factor of plaque composition, we used a multiplication factor of 1.5 for mixed and noncalcified plaques. Although this was an arbitrary factor, this is in line with several CCTA prognostic studies that demonstrated lower hazard ratios for calcified plaques and reflects an assumption of less plaque vulnerability of calcified plaques. (4) Lack of prognostic validation: the aim of this study was to describe a CCTA score to quantify total coronary atherosclerotic burden and to identify its clinical predictors. Future studies will be needed to provide a prognostic validation of this described CT-LeSc.

Conclusions

The calculation of the CCTA-adapted Leaman score as a tool to quantify total (obstructive and nonobstructive) coronary atherosclerotic burden, reflecting the comprehensive information about localization, degree of stenosis and type of plaque provided by CCTA is feasible. There was a significant association between the CT-LeSc and some traditional demographic and clinical risk factors. In face of this association, we expect this score to be a useful tool to quantify the coronary atherosclerotic burden evaluated by CCTA and it is expected to convey prognostic information, and this should be evaluated in future studies.

About one fifth of the patients with nonobstructive CAD had a CT-LeSc in the highest tercile, which could potentially lead to a reclassification of the risk profile of these subset of patients identified by CCTA, once the prognostic value of the CT-LeSc is validated.

Conflict of interest There were no sources of funding and the authors have no conflicts of interest related to this manuscript.

References

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K et al (2009) Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 119(3):480–486
2. Braunwald E (2006) Epilogue: what do clinicians expect from imagers? J Am Coll Cardiol 47(8 Suppl):C101–C103
3. Meijboom WB, van Mieghem CA, Mollet NR, Pugliese F, Weustink AC, van Pelt N et al (2007) 64-slice computed tomography coronary angiography in patients with high, intermediate, or low pretest probability of significant coronary artery disease. J Am Coll Cardiol 50(15):1469–1475
4. Weustink AC, Mollet NR, Neefjes LA, van Straten M, Neoh E, Kyrzopoulos S et al (2009) Preserved diagnostic performance of dual-source CT coronary angiography with reduced radiation exposure and cancer risk. Radiology 252(1):53–60
5. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M et al (2011) Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COro-Nary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. Circ Cardiovasc Imaging 4(5):463–472
6. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ et al (2007) Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol 50(12):1161–1170
7. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M et al (2012) European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 33(13):1635–1701
8. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997) Diabetes Care 20(7):1183–1197
9. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 285(19):2486–2497
10. European Society of Hypertension-European Society of Cardiology Guidelines C (2003) 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 21(6):1011–1053

11. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG (2005) Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. J Am Coll Cardiol 46(5):807–814
12. Genders TS, Steyerberg EW, Alkadhi H, Leschka S, Desbiolles L, Nieman K et al (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 32(11):1316–1330
13. Morise AP, Haddad WJ, Beckner D (1997) Development and validation of a clinical score to estimate the probability of coronary artery disease in men and women presenting with suspected coronary disease. Am J Med 102(4):350–356
14. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ et al (2009) SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. J Cardiovasc Comput Tomogr 3(2):122–136
15. Leaman DM, Brower RW, Meester GT, Serruys P, van den Brand M (1981) Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 63(2):285–299
16. Maurovich-Horvat P, Schlett CL, Alkadhi H, Nakano M, Otsuka F, Stolzmann P et al (2012) The napkin-ring sign indicates advanced atherosclerotic lesions in coronary CT angiography. JACC Cardiovasc Imaging 5(12):1243–1252
17. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L et al (2012) A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging 5(7):690–701
18. Little WC, Downes TR, Applegate RJ (1991) The underlying coronary lesion in myocardial infarction: implications for coronary angiography. Clin Cardiol 14(11):868–874
19. Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. Circulation 92(3):657–671
20. Libby P, Theroux P (2005) Pathophysiology of coronary artery disease. Circulation 111(25):3481–3488
21. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J et al (2003) From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: part I. Circulation 108(14):1664–1672
22. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS et al (2011) A prospective natural-history study of coronary atherosclerosis. N Engl J Med 364(3):226–235
23. Bamberg F, Sommer WH, Hoffmann V, Achenbach S, Nikolaou K, Conen D et al (2011) Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol 57(24):2426–2436
24. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K et al (2005) The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 1(2):219–227
25. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ et al (2009) Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 360(10):961–972
26. Brito J, Teles R, Almeida M, de Araujo Goncalves P, Raposo L, Sousa P et al (2011) Predictive value of SYNTAX score in risk stratification of patients undergoing unprotected left main coronary artery angioplasty. J Invasive Cardiol 23(12):494–499
27. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM (2000) Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arterioscler Thromb Vasc Biol 20(5):1262–1275
28. Pundziute G, Schuijf JD, Jukema JW, Decramer I, Sarno G, Vanhoenacker PK et al (2008) Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. JACC Cardiovasc Interv 1(2):176–182
29. Morise AP, Jalisi F (2003) Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. J Am Coll Cardiol 42(5):842–850
30. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P et al (2010) ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 56(22):1864–1894

CAPÍTULO 9.
VALOR PROGNÓSTICO DA ANGIOTC CARDÍACA

RESUMO:

Neste capítulo é revisto o valor prognóstico da angio TC cardíaca nas suas várias etapas, desde os pequenos estudos iniciais, passando pelas meta-análises e até aos grandes registos multicêntricos e à validação a longo prazo.

O **artigo 19** incluído neste capítulo é uma carta ao editor, comentando alguns aspectos de um trabalho publicado acerca do valor prognóstico da angio TC cardíaca a longo prazo..

Foi ainda incluído um **capítulo de um livro de texto** onde são revistos alguns aspectos da angio TC cardíaca, com particular ênfase na sua validação prognóstica.

ABSTRACT:

The prognostic value of cardiac CT is reviewed in this chapter, from the initial small studies and the subsequent meta-analysis, leading to the large multicenter registries and long-term validation.

Included in the chapter is manuscript 19, a letter to the editor commenting on a work addressing the long-term prognostic value of cardiac CT.

It was also included a textbook chapter in which several aspects of cardiac CT are reviewed, with a particular emphasis of the prognostic validation.

ARTIGO 19/ MANUSCRIPT 19:

PROGNOSTIC VALUE OF CORONARY CT ANGIOGRAPHY

Araújo Gonçalves P, Garcia-Garcia HM.

JACC Cardiovasc Imaging. 2013; 6(1):127-128.

CAPÍTULO EM LIVRO DE TEXTO/ TEXTBOOK CHAPTER:

ANGIO TC CARDÍACA II. CARACTERIZACIÓN DE PLACA POR TC. CORRELACIÓN CON LA CINECORONARIOGRAFÍA Y EL ULTRASONIDO INTRAVASCULAR. VALOR PRONÓSTICO.

de Araújo Gonçalves P, Garcia-Garcia HM

Em: Rodriguez-Granillo G, Gómez E, Bastarrika G, Cademartiri F, editores. TC y RM Cardiovascular: Fundamentos Clínicos. Editora Ediciones Journal 2013.

SUMÁRIO DO CAPÍTULO 9:

9.1 INTRODUÇÃO

Uma importante limitação apontada à angioTC cardíaca era, até muito recentemente, a ausência de validação prognóstica, o que não seria de estranhar dado tratar-se da técnica mais recente no campo da avaliação não invasiva da DC. No entanto, nos últimos anos, assistiu-se a uma adopção crescente da angio TC cardíaca na prática clínica, nomeadamente na sua indicação mais comum de exclusão de DC em doentes de probabilidade e risco CV intermédio a baixo (1). À melhoria da qualidade e do número de exames realizados, seguiu-se a evidência científica que permitiu validar o valor prognóstico da angio TC cardíaca na avaliação de doentes com suspeita de DC (2-7).

9.2 ESTUDOS INICIAIS DE VALIDAÇÃO PROGNÓSTICA

Um dos primeiros estudos que avaliou esta temática foi publicado por Pundziute e col (2) num pequeno grupo de doentes (n=100) referenciados para a realização de angio TC cardíaca por suspeita DC ou para avaliação de DC prévia. No seguimento médio de 16 meses, não ocorreram eventos cardíacos major nos indivíduos em que a angio TC excluiu a presença de doença, em claro contraste com uma taxa de eventos de 30% nos doentes em que foi identificada DC. Um dos aspectos mais interessantes deste estudo pioneiro, foi ter sido possível demonstrar que a taxa de eventos cumulativa no subgrupo com DC não obstrutiva era significativamente mais elevada do que a dos indivíduos sem placas identificadas na angio TC cardíaca, cujo prognóstico foi excelente. Este estudo inicial teve algumas limitações, nomeadamente a reduzida dimensão da amostra e a inclusão das revascularizações no seguimento e os internamentos por AI como eventos. Este último aspecto é importante, uma vez que estes eventos "não-major" podem ser influenciados pelo resultado da angio TC cardíaca, o que pode ter exagerado o impacto prognóstico desta técnica nesta pequena coorte de doentes.

Num outro trabalho inicial em que foi avaliado o valor prognóstico da angio TC, Min e col (3) avaliaram 1127 doentes sintomáticos com suspeita de DC. Neste estudo foi demonstrado o excelente prognóstico dos indivíduos com uma angio TC negativa (sem quaisquer placas ateroscleróticas na árvore coronária) com uma taxa de mortalidade de 0.3% nos 15 meses subsequentes. O aspecto mais importante deste estudo foi o desenvolvimento e validação prognóstica de vários índices de carga aterosclerótica. Para alguns destes índices o resultado não foi surpreendente, uma vez que já tinham sido avaliados com a coronariografia invasiva e reflectem apenas o que já era sabido sobre a fisiopatologia da DC, nomeadamente que o prognóstico se agrava com a extensão da doença (nº de vasos envolvidos), grau de estenose e localização mais proximal da árvore coronária (nomeadamente no TC e DA proximal). No

entanto, alguns índices foram especificamente desenvolvidos com a informação obtida pela angio TC e entrando em linha de conta com a presença de placas não obstrutivas (<50% de estenose), como foi o caso dos índices "segment involvement score" e "segment stenosis score" (estes índices são descritos em mais detalhe nos ***capítulos 1 e 8***).

9.3 META-ANÁLISES E ESTUDOS MULTICÊNTRICOS

Mais recentemente, em 2011, foram publicadas 2 meta-análises que avaliaram o impacto prognóstico da DC documentada por angioTC (4, 5) chegando a conclusões semelhantes:

1)A presença e extensão da DC avaliada na angio TC cardíaca são importantes preditores de eventos CV futuros.

2) A ausência de DC na angio TC associa-se a um excelente prognóstico CV.

É de realçar o facto de em ambas as meta-análises ter sido possível isolar o impacto prognóstico da DC não obstrutiva, com um comportamento nas curvas de sobrevivência para eventos CV claramente diferente do dos indivíduos sem placas identificadas na angio TC cardíaca.

Mais recentemente foram publicados do dados do registo CONFIRM (*Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry*) (6) onde também foi avaliado o impacto prognóstico da DC avaliada por angio TC. Neste registo multinacional e multicêntrico que incluiu nesta análise dados de mais de 20.000 doentes que realizaram uma angio TC cardíaca, a ausência de DC associou-se a um prognóstico excelente (taxa de morte anual de 0,28%). Neste registo, aos 2,3 anos de seguimento, o risco de mortalidade conferido pela DC foi 2,6 vezes superior para a DC obstrutiva e 1,6 vezes superior para a DC não obstrutiva (valor dos *HR*, por comparação com a ausência de doença). Numa outra análise do registo CONFIRM, Chow e col (7) demonstraram que o valor prognóstico das variáveis relacionadas com a presença e gravidade da DC era independente e incremental ao fornecido pela fracção de ejecção ventricular esquerda e pelos habituais factores de risco, mesmo agrupados no scores clínicos. Neste trabalho, a mortalidade total foi de 0,65% nos indivíduos sem DC, de 1,99% na presença de DC não obstrutiva, de 2,9% na DC obstrutiva e de 4,95% na DC obstrutiva com critérios de gravidade (definida neste estudo como doença do TC com estenose ≥50% ou doença de 3 vasos com estenoses ≥70% ou doença de 2 vasos com envolvimento da DA proximal).

9.4 VALIDAÇÃO PROGNÓSTICA A LONGO PRAZO

Sendo uma técnica de implementação relativamente recente na prática clínica, são ainda poucos os estudos que evidenciem o valor prognóstico da angio TC cardíaca a longo prazo. Recentemente, foi publicado um trabalho por Andreini e col (8) no qual foi avaliada a taxa de

eventos CV a 4 anos de seguimento numa coorte de 1304 doentes referenciados para angio TC cardíaca por suspeita de DC. Neste estudo, embora os autores tenham excluídos doentes com DC prévia, a probabilidade pré-teste da população incluída foi bastante elevada (42,5%), sendo que ¼ dos doentes era de elevada probabilidade e foram igualmente incluídos doentes com SCA. A taxa de eventos registada (54% de eventos major no subgrupo com DC obstrutiva) foi muito acima do esperado para uma população de DC estável e assim o desenho deste estudo poderá ter exagerado o valor prognóstico da angio TC cardíaca (9).

9.5 VALOR INCREMENTAL E COMPARAÇÃO COM OUTRAS TÉCNICAS DE IMAGEM

No que diz respeito ao valor prognóstico incremental da angio TC cardíaca ao de outras técnicas de imagem, van Werkhoven e col (10) demonstraram o potencial efeito sinergistico da angio TC cardíaca, como exame anatómico, com o de um exame funcional, neste caso e cintigrafia de perfusão miocárdica.

No entanto, esta combinação de diferentes técnicas de imagem, apesar de ser apelativa e interessante do ponto de vista investigacional, quer para efeitos de diagnóstico quer prognóstico, esse conceito pode ser difícil de implementar na prática clínica, sendo necessário avaliar também qual o seu incremento numa abordagem de custo-eficácia. Mais importante ainda é a posição relativa das diferentes técnicas de imagem disponíveis num algoritmo de avaliação do doentes com suspeita de DC. Uma das abordagens recomendadas consiste na selecção do tipo de exame em função da probabilidade pré-teste de doença, estratégia que favorece a escolha de exames funcionais nos doentes de probabilidade intermédia e da angio TC cardíaca nos doentes de baixa probabilidade, explorando assim o seu elevado valor preditor negativo (11) (aspectos discutidos no ***capítulo 3***).

A validação prognóstica da informação obtida na angio TC cardíaca está em larga medida na dependência do risco basal na população incluída, como é aliás verdade para as varias modalidade de imagem disponíveis para estratificação da DC. Assim, estudos que incluam uma elevada percentagem de doentes com probabilidade pré-teste e/ou risco CV intermédio a elevado ou até mesmo com DC já conhecida podem mais facilmente atestar o valor prognóstico da angio TC. Do mesmo modo, estudos que incluam eventos CV não major, como é o caso das hospitalizações e das revascularizações subsequentes, mais facilmente demonstram o desempenho prognóstico, uma vez que o resultado da angio TC poderá influenciar a taxa de revascularizações subsequente, como já foi demonstrado em vários estudos (12). Por este motivo, vários estudos mais recentes que avaliaram esta temática excluíram as revascularizações realizadas após a angioTC (geralmente nos 3 a 6 meses subsequentes) da análise de impacto prognóstico (4, 8).

Por fim, é importante enquadrar a informação prognóstica da angio TC cardíaca com a que é fornecida pelas outras modalidade de imagem não invasiva como é o caso da cintigrafia de perfusão miocárdica e o ecocardiograma de sobrecarga, já avaliadas em estudos prévios (13, 14). Nesta comparação, é de destacar que o prognóstico de uma angioTC cardíaca normal (ausência de placas identificáveis na árvore coronária) – taxa de eventos anual de 0,17% numa meta-análise (4) é ainda melhor que o previamente demonstrado nas respectivas meta-análises para um ecocardiograma de sobrecarga normal (sem alterações segmentares; taxa de eventos anual de 1%) e até mesmo que o de uma cintigrafia normal (perfusão normal; taxa de eventos anual de 0,6%) (15).

Esta diferença poderá ser explicada pelo facto de a angio TC cardíaca identificar a doença coronária não obstrutiva, que geralmente é negativa nos exames de imagem baseados na detecção de isquémia, e deste modo pode fornecer uma informação mais completa da carga aterosclerótica coronária total, que parece ser o factor de prognóstico mais forte para prever a ocorrência de eventos CV.

9.6 BIBLIOGRAFIA

1. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.
2. Pundziute G, Schuijf JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007 Jan 2;49(1):62-70.
3. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007 Sep 18;50(12):1161-70.
4. Bamberg F, Sommer WH, Hoffmann V, Achenbach S, Nikolaou K, Conen D, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011 Jun 14;57(24):2426-36.
5. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol. 2011 Mar 8;57(10):1237-47.
6. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011 Aug 16;58(8):849-60.
7. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. Circ Cardiovasc Imaging. 2011 Sep;4(5):463-72.
8. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging. 2012 Jul;5(7):690-701.
9. Goncalves Pde A, Garcia-Garcia HM. Prognostic value of coronary CT angiography. JACC Cardiovasc Imaging. 2013 Jan;6(1):127-8.
10. van Werkhoven JM, Schuijf JD, Gaemperli O, Jukema JW, Boersma E, Wijns W, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol. 2009 Feb 17;53(7):623-32.
11. NICE clinical guideline 95. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.; Available from: http://www.nice.org.uk/guidance/CG95.
12. Hulten E, Pickett C, Bittencourt MS, Villines TC, Petrillo S, Di Carli MF, et al. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. J Am Coll Cardiol. 2013 Feb 26;61(8):880-92.
13. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol. 2004 Mar-Apr;11(2):171-85.
14. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol. 2007 Jan 16;49(2):227-37.
15. Shaw L, Narula J. Bridging the detection gap chasm of risk: where can computed tomography angiography take us? JACC Cardiovasc Imaging. 2009 Apr;2(4):524-6.

9.7 ARTIGO 19/ MANUSCRIPT 19:

JACC: CARDIOVASCULAR IMAGING, VOL. 6, NO. 1, 2013
JANUARY 2013:124–30

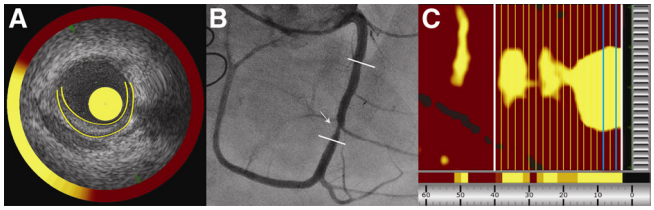


Figure 2. Lipid-Rich Cardiac Allograft Vasculopathy

IVUS **(A)**, angiography **(B)**, and NIRS **(C)** scans of the medial right coronary artery (RCA) in a 24-year-old male patient. The **white arrow (B)** indicates the location of the presented IVUS cross-sectional image. **White lines (B and C)** represent a region of the angiogram corresponding to the NIRS scan. **Yellow lines (C)** represent 2-mm blocks. The patient underwent heart transplantation 19 years earlier after aortic root wrapping surgery for an aortic root aneurysm that resulted in severe left ventricular dysfunction. His medical regimen (tacrolimus, sirolimus, nifedipine, losartan, and aspirin) did not include any lipid-lowering therapy. Coronary angiography revealed a focal 80% lesion in the mid RCA, IVUS minimal lumen area = 3.5 cm^2, and a lipid core burden index in a 4-mm segment = 524 (**blue lines**). Abbreviations as in Figure 1.

yellow). Chemogram analysis enables one to divide the scan into 2-mm blocks and quantify the amount of lipid on a scale of 0 to 1,000, termed the lipid core burden index (LCBI).

Similar to Hou et al., we captured 2 distinct patterns of CAV by NIRS during the routine hemodynamic and angiographic assessment in long-term survivors after heart transplantation. Simultaneous gray-scale IVUS and NIRS scans in the 2 allograft recipients 11 and 19 years after the transplantation demonstrated fibrotic (Fig. 1) and lipid-rich plaques (Fig. 2), respectively. Interestingly, the NIRS chemogram showed lipid-rich regions, even for the angiographically normal-appearing vessel in the latter patient who did not receive statin therapy.

The 2 different NIRS scans of CAV in transplant recipients may correspond to the difference in elapsed survival time from transplantation and use of medical therapy. Autopsy studies have confirmed that in the first 5 years after transplantation, CAV plaques are mostly composed of fibrotic tissue, whereas lipid accumulation is seen later. Gray-scale IVUS studies have provided some insight into the etiology of CAV in survivors 1 to 9 years post-transplantation (4). They have revealed diffuse and circumferential lesions in mid and distal coronary segments, suggestive of the fibrotic tissue. Focal and noncircumferential lesions observed in the proximal segment of the vessel early after transplantation indicated pre-existing atherosclerotic lesions. Radiofrequency (RF) analysis by IVUS (virtual histology) suggested that lipid-rich regions in neointima increased and fibrosis decreased with time over 1 to 20 years after the heart transplantation (5). However, the accuracy of RF-IVUS in lipid-rich plaque determination has been questioned, and characterization of the IH by other imaging modalities should be confirmatory. Interestingly, the accelerated lipid-rich atherosclerotic process in CAV seems to be slower compared with vein coronary graft plaques and in-stent restenosis development. This insidious process is often a result of younger vasculature of the allografts, which is likely to be devoid of pre-existing disease. The immunosuppressive therapy could also contribute to the delay in the process; statin supplementation further enhances the immunosuppressive efficacy of calcineurin inhibitors.

New intravascular imaging modalities may improve CAV screening in allograft recipients. They would contribute to the understanding of the disease process and help to better define management strategies. Allograft vasculopathy is not unique to heart transplantation and may occur similarly in all transplanted organs, and the knowledge gained from coronary screening may have wider implications.

Raman Sharma, MD, Tomasz Roleder, MD, PhD, Ziad Ali, MD, PhD, Bary A. Love, MD, Annapoorna S. Kini, MD*

*The Mount Sinai Hospital, Interventional Cardiology, One Gustave L. Levy Place, Box 1030, New York, New York 10029.
E-mail: annapoorna.kini@mountsinai.org.

http:dx.doi.org/10.1016/j.jcmg.2012.09.009

Please note: Drs. Sharma and Roleder contributed equally to this paper.

REFERENCES

1. Hou J, Lv H, Jia H, et al. OCT assessment of allograft vasculopathy in heart transplant recipients. J Am Coll Cardiol Img 2012;5:662–3.
2. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621–7.
3. Tuzcu EM, Kapadia SR, Sachar R, et al. Intravascular ultrasound evidence of angiographically silent progression in coronary atherosclerosis predicts long-term morbidity and mortality after cardiac transplantation. J Am Coll Cardiol 2005;45:1538–42.
4. Tuzcu EM, De Franco AC, Goormastic M, et al. Dichotomous pattern of coronary atherosclerosis 1 to 9 years after transplantation: insights from systematic intravascular ultrasound imaging. J Am Coll Cardiol 1996;27:839–46.
5. Hernandez JM, de Prada JA, Burgos V, et al. Virtual histology intravascular ultrasound assessment of cardiac allograft vasculopathy from 1 to 20 years after heart transplantation. J Heart Lung Transpl 2009;28:156–62.

Prognostic Value of Coronary CT Angiography

We read with interest the paper from Andreini et al. (1) that provided more evidence on the prognostic value of cardiac computed tomography angiography (CTA) in patients referred for evaluation of possible coronary

artery disease (CAD), an area of research in need of long term follow up studies like this one (mean follow-up >4 years).

However, we noticed that the mean pre-test probability of CAD in the study population was 42.5%, with one-quarter of the patients having a high CAD probability, which is not in line with the most favored low-to-intermediate probability population referred for CTA for the exclusion of possible CAD (2), and that could explain the higher-than-expected hard event rate for a stable CAD population (almost 1 out of 2 patients with obstructive CAD dying or having a nonfatal myocardial infarction [MI]) in the follow-up (3). This could have been the result of having included patients admitted to the hospital because of new-onset chest pain (43%), a subset that could be considered as possible acute coronary syndrome (ACS) unstable angina/non–ST-segment elevation MI) and can explain the higher than expected rate of major (death/MI) events in the follow-up (event-free survival of 54%). In how many cases was an ACS diagnosis confirmed? If any, the authors should have excluded these patients from the study. We fully agree that CTA can provide useful prognostic information beyond the exclusion of obstructive CAD, but the inclusion of patients with possible ACS and high CAD probability could have lead to an overestimation of the prognostic power of CTA.

Another striking point was the fact that 45% of patients had hypercholesterolemia but only 26% were treated with statins. Further, statins turned out in multivariable analysis to be independent predictors for hard events. Likewise, 26% of the population (with suspected CAD) was taking aspirin, which is not generally recommended as primary prevention. Use of aspirin was also an independent predictor of all cardiac events. It would have been interesting to know if the use of these drug groups is allocated to a more severe subset of patients (more frequently used in obstructive vs. nonobstructive vs. normal patients) and in this way are just a surrogate marker of higher disease burden. Likewise, it would be of interest to know if patients were already taking these drugs before the CTA or if they were just started after significant disease was identified and, in this way, they could not have had enough time to come out with its protective effects in a more severe CAD subgroup of patients.

The Framingham risk score (FRS) was used to estimate the cardiovascular risk of this Italian cohort of patients; it could have been more accurately estimated with the European-based HeartScore (4). This could have also influenced the results, as the multivariable analysis models were adjusted for the FRS.

It is not mentioned that the events were independently adjudicated and that the adjudication event committee is an experienced one with acceptable intra-committee reproducibility for the adjudication of events. This point is of utmost relevance in a report of this nature. In addition, regarding *revascularizations*, we agree that early revascularizations should be excluded to avoid the influence of CTA results in patient management but most of the previous studies considered early as 30 days (5) and not 6 months like in the paper from Andreini et al. (1). This could have also influenced the results, as revascularizations in obstructive CAD group are likely to have happened sooner after the CTA and in this regard could have underestimated the prognostic value of obstructive versus nonobstructive CAD. Further, it is not mentioned whether the revascularizations were ischemia-driven (i.e., only for obstructive lesions) or not.

Despite the fact that authors have scored hierarchically the plaque type per segment (i.e., in case of presence of 2 plaques, calcified and noncalcified, only one was scored and labeled as calcified) which underestimates the frequency of noncalcified plaques, in the univariate analysis, these were found to be independent predictors of hard events. This methodology seems to us to be counterintuitive, since it has been reported many times that high-risk plaques (i.e., plaques prone to rupture and associated with an event) are those noncalcified or mixed, which could have come out as strong predictors also in the multivariate analysis if the authors had not underscored them.

Undoubtedly, this is a report with an important message, but we feel that the above-mentioned points should be further explained to strengthen the conclusions.

Pedro de Araujo Goncalves, MD,
Hector M. Garcia-Garcia, MD, PhD*

*Thoraxcenter, Erasmus Medical Center, Interventional Cardiology, Z120, 's-Gravendijkwal 230, Rotterdam, Zuid Holland 3015 CE, the Netherlands. *E-mail: hgarcia@cardialysis.nl* OR *h.garciagarcia@erasmusmc.nl*

http:dx.doi.org/10.1016/j.jcmg.2012.10.005

REFERENCES

1. Andreini D, Pontone G, Mushtaq S, et al. A long-term prognostic value of coronary ct angiography in suspected coronary artery disease. J Am Coll Cardiol Img 2012;5:690–701.
2. Taylor AJ, Cerqueira M, Hodgson JM, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2010;56:1864–94.
3. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503–16.
4. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts): developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33:1635–701.
5. Bamberg F, Sommer WH, Hoffmann V, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol 2011;57:2426–36.

REPLY

The comments of Garcia-Garcia and Goncalves are relevant and allow us to expand on some results of our study (1). First, we found

JACC: CARDIOVASCULAR IMAGING, VOL. 6, NO. 1, 2013
JANUARY 2013:124–30

a relatively high cumulative event rate at follow-up in multidetector computed tomography coronary angiographic (MDCT-CA) obstructive coronary artery disease compared with other studies, which may be due to characteristics of patients who had chest pain and positive stress tests in 43% and 29% of cases, respectively. However, the CONFIRM registry demonstrated that MDCT-CA has the best prognostic value in this patient subset, whereas its value in asymptomatic patients is quite limited (2). We agree that including patients with acute coronary syndromes (ACS) may lead to an overestimation of MDCT-CA prognostic capability. Accordingly, we excluded patients in whom ACS was confirmed by cardiac enzyme or electrocardiographic changes. The discrepancy between hypercholesterolemia rate and statin use in our patients is in agreement with the suboptimal therapy adherence reported in a substantial proportion of European patients (3). Medical therapy reported in our patients was administered before MDCT-CA. Indeed, 26% of them were taking aspirin, not for CAD but for other indications. We agree that the European Heart Score would have been more appropriate than Framingham cardiovascular risk estimation. However, the former has been challenged because it is not mathematically consistent and unfit to estimate cardiovascular mortality (4). In the first version of our paper, revascularizations were defined "early" if performed within 2 months after MDCT-CA. However, a reviewer criticized this definition. Indeed, using a 2-month cutoff, only 6 patients were excluded despite 295 patients having MDCT-CA stenosis ≥70%. This indicates that many revascularizations occurring later than 60 days were probably driven by MDCT-CA. We agree that the 6-month cutoff may have led to an underestimation of obstructive CAD prognostic value. However, this limitation did not affect hard cardiac events survival analysis. Finally, we believe that assigning 1 coronary plaque per coronary segment and classifying a plaque as calcific in cases in which a coronary segment contained calcific and noncalcific plaques was correct, as previously reported (5). Indeed, in the presence of small plaques, those calcific plaques are the easiest to detect with MDCT-CA, and most prognostic data are based on simple coronary plaque scores, regardless of plaque composition (3).

***Daniele Andreini, MD, Gianluca Pontone, MD, Saima Mushtaq, MD, Antonio L. Bartorelli, MD, Mauro Pepi, MD**

*Centro Cardiologico Monzino, Via Parea 4, 20138 Milan, Italy. *E-mail: daniele.andreini@ccfm.it*

http:dx.doi.org/10.1016/j.jcmg.2012.10.011

REFERENCES

1. Andreini D, Pontone G, Mushtaq S, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. J Am Coll Cardiol Img 2012;5:690–701.
2. Cho I, Chang HJ, Sung JM, et al. Coronary computed tomographic angiography and risk of all-cause mortality and nonfatal myocardial infarction in subjects without chest pain syndrome from the CONFIRM Registry. Circulation 2012;126:304–13.
3. Degli Esposti L, Saragoni S, Batacchi P, et al. Adherence to statin treatment and health outcomes in an Italian cohort of newly treated patients. Clin Ther 2012;34:190–9.
4. Støvring H, Harmsen CG, Wisløff T, et al. A competing risk approach for the European Heart SCORE model based on cause-specific and all-cause mortality. Eur J Prev Cardiol 2012 Apr 12 [Epub ahead of print].
5. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. Eur Heart J 2009;30:362–71.

Ultrasonographic Measure of Carotid Plaque Burden

In their excellent paper, Sillesen et al. (1) omitted mention of the original work on measurement of carotid plaque burden. Spence et al. (2) first measured carotid total plaque area (TPA) in 1990, and developed it for patient management and genetic research, and 3-dimensional methods for evaluation of new therapies. They showed that TPA and progression of TPA strongly predicted the 5-year risk of stroke, death, or myocardial infarction after adjusting for coronary risk factors.

Sillesen et al. (1) stated that the prevalence of plaque they observed (78%) was 2-fold higher than previously reported. However, in the NOMAS (Northern Manhattan Study) study, a population-based study of individuals free of stroke at similar ages, plaque prevalence was 58% on 2-dimensional ultrasound imaging and it was greater by age and among certain race-ethnic groups (3). Prevalence of plaque depends on age and how it is defined. If defined as a focal thickening >1 mm, in vascular patients it increases from 75% of patients at age 35 to 45 years to 99% by age 65 to 75 years, and 100% over age 75 years (2).

Besides plaque burden, other ultrasonographic characteristics of plaque morphology such as plaque surface irregularity, ulceration, texture, and plaque density may be even more important predictors of stroke and cardiovascular disease.

The Tromsø study showed that TPA was a stronger predictor of myocardial infarction and stroke (4) than intima-media thickness, and this was confirmed in a meta-analysis (5). Three-dimensional plaque volume is highly correlated with TPA, and is much more sensitive to change with therapy than intima-media thickness or TPA, so it is the best way to assess effects of new therapies (2). There is little doubt that carotid plaque burden will be a stronger predictor of cardiovascular events in the High Risk Plaque Bioimaging Study than any of the other imaging modalities measured, with the possible exception of coronary calcium.

Tatjana Rundek, MD, PhD,* J. David Spence, MD

*Department of Neurology, Miller School of Medicine, University of Miami, Clinical Research Building, Suite #1348, 1120 Northwest 14th Street, Miami, Florida 33136. *E-mail: trundek@med.miami.edu*

http:dx.doi.org/10.1016/j.jcmg.2012.08.015

Please note: Dr. Spence holds an interest in Vascularis.com.

REFERENCES

1. Sillesen H, Muntendam P, Adourian A, et al. Carotid plaque burden as a measure of subclinical atherosclerosis: comparison with other tests for subclinical arterial disease in the High Risk Plaque BioImage Study. J Am Coll Cardiol Img 2012;5:681–9.

9.8 CAPÍTULO EM LIVRO DE TEXTO / TEXTBOOK CHAPTER:

Libro: TC y RM Cardiovascular: Fundamentos Clínicos

Capítulo número 9

TÍTULO:

ANGIO TC CARDÍACA II. CARACTERIZACIÓN DE PLACA POR TC. CORRELACIÓN CON LA CINECORONARIOGRAFÍA Y EL ULTRASONIDO INTRAVASCULAR. VALOR PRONÓSTICO

AUTHORS:

Pedro de Araújo Gonçalves, MD
Hospital de Santa Cruz, CHLO, Lisbon, Portugal
Hospital da Luz, Lisbon, Portugal

Hector M Garcia-Garcia, MD, PhD
Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands
Cardialysis, Rotterdam, The Netherlands

INDEX:

9.1 INTRODUCTION

Advances in the field of Computed Tomography (CT) have made possible to noninvasively evaluate the presence of coronary artery disease (CAD) and in recent years Coronary CT angiography (CCTA) has become a widely adopted technique. This was due not only to its high diagnostic accuracy, but also to the fact that CCTA provides a comprehensive evaluation of both obstructive and nonobstructive CAD and, more recently, its prognostic information has been validated.

The initial studies of CCTA addressed mainly its diagnostic accuracy. This was done both by comparison with the gold standard invasive coronary angiography (ICA) and with intravascular ultrasound (IVUS) (both described in more detail in sections 9.2 and 9.3 of this chapter).

From the beginning it was also evident that this technique allowed not only the exclusion of obstructive CAD but also provided information regarding the presence of nonobstructive lesions, and this was a unique feature in the field of noninvasive CAD evaluation.

As the technique became more robust and widely adopted in clinical practice, data was gathered regarding cardiovascular outcomes and this opened a 2nd phase of studies addressing its prognostic value (described in more detail in section 9.4 of this chapter).

The latest technological advances have significantly improved CCTA temporal resolution and volume coverage, leading to a decrease in radiation and contrast dose, and improvements in image quality, that will further reinforce the role of CCTA for the evaluation of patients with possible CAD.

9.2 CORRELATION WITH INVASIVE CORONARY ANGIOGRAPHY – *Cardiac CT diagnostic accuracy*

Many studies have been published evaluating the diagnostic accuracy of CCTA, by comparing with the gold standard invasive coronary angiography. These were initially done with 4-slices (1-4), followed by 16-slices scanners (5-9), but by that time significant limitations existed related to the dose of contrast, long breath-hold times and high percentage of segments excluded from analysis due to insufficient image quality. In a meta-analysis of 27 studies comparing CCTA (with scanners of at least 16 slices) with invasive coronary angiography, the per-patient sensitivity was very high (96%) but the specificity was only modest (74%), leading to a positive predictive value of 68% (10).

With the development of 64-slices scanners, now considered to be the minimum requirement for CCTA (11), significant technological advances were incorporated, which have been translated to improvements in diagnostic performance and lead to the widely adoption of CCTA in clinical practice. In a more recent meta-analysis, including only studies with 64 slices scanners, the reported per-patient sensitivity was 99%, specificity 89%, positive predictive value (PPV) was 93% and negative predictive value (NPV) was 100% (12).

Nevertheless, even with 64 scanner slices, some multicenter trials, have reported low specificity when evaluating consecutive nonselected patients. In the ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial, a prospective multicenter evaluating stable patients without known CAD who underwent CCTA before clinically indicated ICA, CCTA had a diagnostic sensitivity, specificity,
PPV, and NPV of 94%, 83%, 48%, and 99%, respectively. (13). The low specificity reported in this trial could be related to the fact that patients were consecutively included irrespective of baseline coronary calcium score, body mass index or heart rate, variables that are well known to influence image quality.

In another multicenter study, Meijboom and coll (14) evaluated the diagnostic performance of CCTA in a population including both stable and acute chest pain patients without known CAD referred for invasive coronary angiography. No

patients or segments were excluded because of impaired image quality attributable to either coronary motion or calcifications and the prevalence of obstructive CAD was 68%, factors that could explain the low per-patient specificity of 64% for CCTA found in this study, leading to a positive predictive value of 86%. Once again, the per-patient sensitivity was 99% and the negative predictive value was 97%.

Improvements in spatial and temporal resolution and volume coverage with the newest generation scanners lead to further improvements in image quality, and significant reductions on radiation and contrast dose, all factors expected to further reinforce the role of CCTA in the evaluation of patients with suspected CAD.

With the development of dual source scanners, there was a significant increase in temporal resolution, leading to a less dependence on heart rate control (15) and a significant reduction in radiation dose with high-pitch spiral acquisitions, without compromising diagnostic accuracy (16, 17) – figure 1.

Likewise, 320-rows scanners also lead to significant improvements, reducing the radiation dose and amount of contrast while maintaining high diagnostic accuracy (18, 19)

Summing up the different multicenter trials and meta-analysis addressing this issue, it has become clear now that this noninvasive imaging technique has a very high sensitivity for detecting patients with significant CAD, leading to a very high (virtually 100%) negative predictive value, which makes CCTA a perfect gatekeeper for invasive angiography.

Regarding the still limited specificity, this has to be taken in consideration, especially when evaluating patients with severe calcification, since CCTA often overestimates the degree of coronary stenosis in this setting (blooming effect).

In conclusion, when evaluating the diagnostic accuracy of CCTA, some factors have to be considered, that could influence the performance of the exam, and could explain the differences between different studies:

-type of scanner technology (64 slices is now considered to be the typical minimum standard)
-population studied, regarding expected prevalence of obstructive CAD (can be calculated with pre-test CAD probability scores – CCTA is indicated in low to intermediate CAD probability)
-inclusion of nonevaluable segments in the analysis (considering nonevaluable segments as positive improves sensitivity but reduces specificity)
-inclusion of patients with high body mass index, high calcium score or high heart rates, factors known to negatively affect image quality.

9.3 PLAQUE CARACTERIZATION AND CORRELATION WITH INTRAVASCULAR ULTRASOUND – *pushing the limits of spatial resolution*

Relevance of plaque characterization and limitations of the presently available imaging modalities (both invasive and ischemia based)

Since many myocardial infarctions present in previously asymptomatic patients and not infrequently the first manifestation of CAD is sudden cardiac death, the main challenge that we face today is to identify patients at risk before those events occur. In this regard, clinical evaluation alone might be insufficient, as many patients don't have previous symptoms and it has also been demonstrated that only a minority of patients experiencing and acute myocardial infarction would have been identified as high risk by the available risk-factors based scores, prior to the event (20).

Coronary plaque characterization, namely the identifications of features of vulnerability, has been the focus of extensive research by different coronary imaging modalities like intravascular ultrasound (IVUS), IVUS-virtual histology (IVUS-VH) and optical coherence tomography (OCT). These imaging modalities, although providing the highest possible spatial resolution, have there applicability limited by their invasive nature, and are usually employed in patients already referred for invasive angiography because of suspected CAD or with acute coronary syndromes (ACS). Many of these patients will be (independent of the result of the imaging modality) under secondary prevention of CAD, which changes natural history and reduces the risk of subsequent cardiovascular events (21, 22).

In the multicenter PROSPECT study (22), a large plaque burden, a small lumen area and the presence of a thin cap fibroatheroma assessed by IVUS-VH in nonculprit lesions, were independent predictors of future major adverse cardiac events. In this study, lesions that led to major adverse cardiac event had a high plaque burden by IVUS, but were mild by baseline angiography, with a mean diameter stenosis of only 32%. Although the Prospect trial was a landmark study of CAD natural-history, its applicability is limited by the fact that patients were evaluated in the setting of an acute coronary syndrome, for whom aggressive

secondary prevention is, in any case, recommended, independent of the imaging evaluation. This is important since medication changes natural history and can explain why the prediction power of the identified variables is rather weak. In fact, even in the presence of these 3 features, only 18,2% of the patients really experienced an event in the subsequent 3.4 years of follow-up, and many of those events were rehospitalization for unstable or progressive angina, a rather soft event.

On the other hand, *ischemia based imaging modalities* have also some limitation in this regard, especially related to the fact that nonobstructive lesions are not associated with ischemia, but can also be the culprit of coronary events (22-25) – (figure 2).

This is of utmost importance since it has been demonstrated that nonobstructive lesions can lead to myocardial infarctions (25-27). On the other hand, it is now recognized that although obstructive plaques can be more prone to rupture than their nonobstructive conterparts, these nonobstructive lesions are much more prevalent with makes them, on absolute numbers, frequently the culprit of acute coronary syndromes (28). Therefore, the importance of nonobstructive disease should not be underestimated and imaging techniques that convey information about the whole (obstructive + nonobstructive) coronary atherosclerotic burden have a great potential for risk stratification (29) (figure 3)

In this regard, *CCTA* might qualify as a possible useful tool, in face of its noninvasive nature, widespread adoptance in clinical practice and the impressive reductions in radiation dose made possible with the new generation scanners (figure 4).

Correlation with invasive imaging modalities

Several studies have reported on the correlation between CCTA plaque features with invasive coronary imaging modalities like IVUS, IVUS-VH and OCT. In a recent meta-analysis, CCTA had a good diagnostic accuracy to detect coronary plaques compared with the gold standard IVUS, with an area under the curve for the receiver operating characteristics analysis of 0.94, a sensitivity of 90%, and a

specificity of 92%, with small differences in the assessment of plaque area and volume, percent area stenosis, and a slight overestimation of lumen area (30).
Several CCTA plaque characteristics have now been show to be more prevalent in culprit lesions in the setting of acute coronary syndromes. In a study done by Hoffman and coll, a significantly larger plaque area and positive remodelling were found in culprit lesions of ACS patients, compared with patients with stable CAD (31). Positive remodelling has been considered for many years a surrogate marker of plaque vulnerability, and many of these lesions have a high plaque burden that is underestimated by luminal angiograms because they undergo expansive or positive outward enlargement and are frequently nonstenotic (24). Figure 6.
In another small study, Motoyama and coll found that culprit lesions of patients with ACS had more frequently positive remodelling, low-density plaque [<30 Hounsfield units (HU)] and spotty calcifications (32).
Extending on these results, the same authors conducted a large prospective trial including 1059 patients who underwent CCTA, and demonstrated that positive remodelling and low attenuation plaques were associated with the subsequent development of acute coronary syndromes (23). In this study, the percentage of patients with these 2 features that subsequently developed and ACS was 22,2%, compared with only 3,7% for patients with only one feature and 0,5% for patients with neither positive remodelling or low-attenuation plaques.

In a study by Kashiwagi and col, evaluating 105 patients with coronary artery disease, CCTA findings have been also validated against OCT (33). In this study, thin cap fibroatheromas (TCFAs) had higher remodelling indexes, lower CT attenuation values and more often "ring-like" enhancement by CCTA (44% in the TCFA group vs 4% for the non-TCFA group).

In a recent study, Papadopoulou and coll evaluated the distribution and composition of coronary plaques at bifurcations with both CCTA and IVUS-VH (34). They found that plaques with high-risk phenotype as assessed by IVUS-VH were more commonly found in segments proximal to the bifurcation, rather than in the bifurcation or distal to the bifurcation. Interestingly, by evaluating the

geometry of the bifurcation, a feature easily assessed with CCTA, they found that a wide angle was more often associated with high-risk plaques.
As a group, these studies provide evidence on how CCTA can noninvasively provide information on several plaque characteristics - like plaque volume, remodelling, plaque composition, distribution and geometry of the coronary tree – that can be associated with the development of future coronary events (Figure 6).

Limitations of CCTA for plaque characterization:

In recent years, several technical developments were possible in the field of cardiac CT, leading to significant improvements in temporal resolution (with increased gantry rotation speed and dual source scanners) and high volume coverage (with scanners up to 320 rows). It has become possible to scan patients in one heart cycle leading to very low breath-hold times, impressive reductions in contrast and radiation doses and significant improvements in image quality.
Nevertheless, spatial resolution has not seen significant improvements and remains presently one of the major technical limitations of CCTA. In what concerns plaque characterization, the spatial resolution of current available scanners (in the range of 400-600 μm) prevent the detailed assessment of several features associated with vulnerable plaques, as is the case of the evaluation of a thin fibrous cap. This spatial resolution is significantly lower than that of IVUS (200-250 μm) or OCT (10-15 μm) (35) and this has to be taken in consideration and should temper our expectations regarding the potential of CCTA for plaque assessment in face of the limitations already faced by other invasive imaging modalities regarding the identification of the vulnerable plaque.

Another limitation faced by CCTA plaque characterization is related to the fact that coronary plaque attenuation values are significantly modified by differences in lumen contrast densities, as has been demonstrated both ex vivo and in vivo

(36, 37). This is important because lumen attenuation can be influenced by different contrast and scanning protocols and therefore makes it difficult to establish thresholds for the definition low attenuation plaque as a surrogate of vulnerable plaque, that can be widely adopted.

One last important limitation in this regard is related to the reproducibility of CCTA plaque measurements, as many previous studies have reported significant interobserver variability in the assessment of several CCTA plaque characteristics (38, 39). This is dependent on image quality, vessel size and degree of calcification, features that are dependent again on spatial resolution. In the future, improvements in spatial resolution and the development of robust dedicated automated quantification software could contribute to overcome these difficulties.

9.4 PROGNOSTIC VALUE – *Cardiac CT reaching adulthood*

The lack of prognostic validation was, until recently, one of the major limitations of cardiac CT. This was expected as cardiac CT was the new player in the field of noninvasive imaging of coronary artery disease. Nevertheless, this "new player" has now become widely adopted in clinical practice, being commonly used in low-to intermediate risk patients to exclude the presence of obstructive CAD (11). As the technique became more robust and more data become available, cardiac CT proved also to be a strong prognostic tool for the evaluation of patients with suspected CAD (40-45).

One of the first studies addressing this issue was done by Pundziute and col (40) in a small subset of 100 patients with known or suspected CAD. During a mean follow-up of 16 months, there were no major cardiac events on the subset of patients without CAD, contrasting with the 30% event rate of patients with CCTA documented CAD. More importantly, the cumulative event rate of patients with nonobstructive CAD was higher and different from the excellent prognosis of patients without plaques on CCTA. This earlier study had some limitations, both related to the small sample size and the fact that some of the included cardiovascular events (revascularization and unstable angina requiring hospitalization) are not "hard" endpoints and could be influenced by the CCTA result.

In another important work addressing this issue, Min and coll (41) evaluated the prognostic value of identifying CAD with CCTA in a single-center cohort of 1127 patients with stable chest symptoms. In this initial study, a negative CCTA was associated with an excellent prognosis and some CCTA derived CAD indexes were developed and prognostically validated. Some of those indexes were expected to convey prognostic information, as these observations extend on what was previously documented for invasive coronary angiography, as was the case of number of diseased vessels, degree of stenosis and more proximal location. More importantly was the fact that they were able to demonstrate the prognostic value of more CCTA specific indexes derived from the comprehensive

information of both obstructive and nonobstructive plaque. The authors developed 2 indexes that reflect some aspects of the coronary atherosclerotic burden and could be used as CCTA prognostic tools: The Segment involvement score (SIS), obtained as the total number of segments with plaque (1 point for each segment with plaque, irrespective of the degree of luminal stenosis) and the Segment stenosis score (SSS), obtained by grading the stenosis severity of each segment with plaque (segments graded from 0 to 3 according to the degree of stenosis). For both SIS and SSS, a value of 5 was identified as the best cut-off to predict all cause mortality.

In 2011, 2 meta-analysis were published (42, 43) evaluating the prognostic value of CCTA and (not surprisingly) had the same 2 main conclusions: 1) that the presence and extent of coronary artery disease on CCTA are strong and independent predictors of future cardiovascular events; 2) the absence of CAD on CCTA is associated with an excellent prognosis.

Of note, in both meta-analysis, it was possible to distinguish between the excellent prognosis of patients in the absence of CAD from that of patients with nonobstructive CAD, as documented by CCTA.

More recently, data from the CCTA registry CONFIRM (Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (44) was published and examined once again the prognostic power of CCTA. In this large (>20.000 patients) multicenter and multinational registry of patients evaluated by CCTA, absence of CAD was associated with an excellent prognosis (annualized death rate of 0.28%). At 2.3 years follow-up, both obstructive and nonobstructive CAD conferred an increased mortality risk with hazard ratios of 2.6 and 1.6 respectively.

In another report of the CONFIRM database, it was demonstrated that CCTA measures of CAD severity yield independent and incremental prognostic value to that of left ventricle ejection fraction (LVEF) and routine clinical predictors (45). In this report, all-cause mortality occurred in 0.65% of patients without CAD, in 1.99% of patients with nonobstructive CAD, 2.90% of patients with non–high-risk CAD, and 4.95% with high-risk CAD.

In what concerns the incremental prognostic value of CCTA over other CAD imaging modalities, Werkhoven JM and coll (46) have evaluated the potential

synergistic effect of a functional test (single-positron emission CT – SPECT) and CCTA (as an anatomical test). They found CCTA to be an independent predictor of cardiovascular events and its prognostic information was incremental to that of SPECT. Nevertheless, although the potential synergistic role of both anatomical and functional imaging modalities can be appealing, for both diagnostic and prognostic purposes, this concept might can be difficult to prove as a cost effective strategy and probably not desirable to perform both exams in the same patient. This way, more research is needed to further evaluate the role and relative position of the different imaging modalities in the algorithm for the evaluation of patients presenting with possible CAD. One proposed approach is to select the type of exam according to the patient CAD probability, favoring functional exams in the intermediate probability and CCTA for the lower probability patient, as recommended by the National Institutes of Clinical Excelence – NICE - clinical guidelines on "Chest pain of recent onset" (47).

The prognostic evaluation of CCTA data (as is the case for other CAD imaging modalities) is dependent on the baseline risk of the population included and the outcomes evaluated. Studies including higher percentage of patients with intermediate to high CAD probability and/or risk, or even with known CAD, can more easily document the prognostic power of CCTA. This is also the case for studies evaluating the impact on total cardiovascular events (instead of only "hard" CV events). This is especially true regarding the inclusion of revascularizations after CCTA, as the result of this anatomical test could influence and increase subsequent procedures. For this reason, many study's addressing this issue have now excluded earlier revascularizations from the outcome analyses (42, 48).

In another recently published study, Andreini and coll evaluated the long term (>4 years follow-up) prognostic value of CCTA in a cohort of 1304 patients with suspected CAD (48). Although the authors excluded patients with known CAD, the mean pre-test probability of CAD in the study population was high (42.5%, with one-quarter of the patients having a high CAD probability) and they also included patients with possible acute coronary syndromes. This led to a higher-than-expected hard event rate for a stable CAD population (event-free survival of

54% for patients with obstructive CAD). Therefore, the design of studies to address the prognostic value of CCTA can be influenced by these 2 important aspects: inclusion of many high risk/high CAD probability patients and of revascularization as a cardiovascular event can lead to an overestimation of the prognostic power of CTA.

When comparing the prognostic prognostic information conveyed by CCTA with that of other noninvasive imaging modalities like SPECT or stress echo, it is remarkable that the excellent prognosis of a normal CCTA – no plaque - (0.17.% annual event rate in a CCTA meta-analysis (43) is even lower than what was previously demonstrated for patients with normal perfusion on SPECT (0.6% annual event rate) or normal wall motion on stress echo (1.0% annual event rate) in previous meta-analysis (49, 50).
This difference could be explained by the fact that CCTA identifies nonobstructive CAD (usually negative of stress based exams) and in this way provides a more comprehensive evaluation of the total coronary atherosclerotic burden that has a stronger prognostic meaning.

Figure 1: CCTA performed on a dual-source scanner (B) and corresponding invasive coronary angiography (A) at a low radiation dose of 3mSv (212 DLP, conversion factor of 0.014) depicting a noncalcified plaque (C) with 50-70% stenosis in the mid-segment of the right coronary artery.

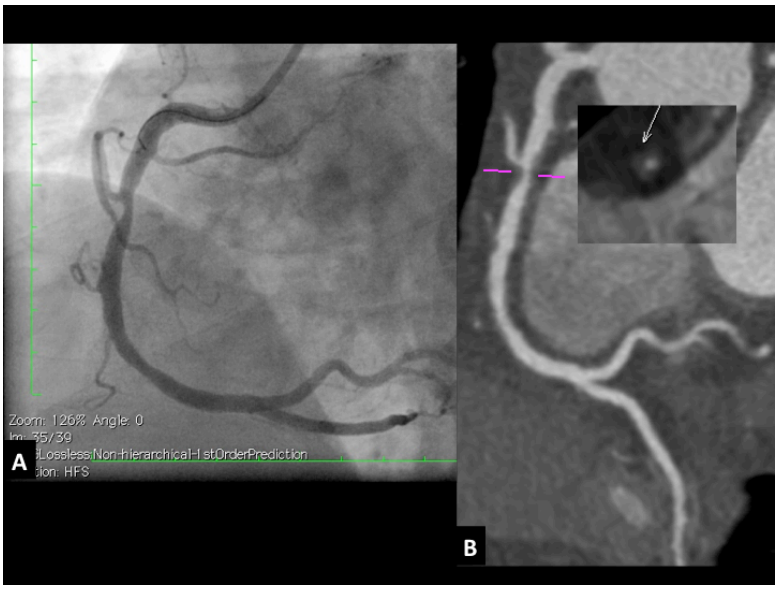


Figure 2: Identification of nonobstructive CAD as a unique feature of CCTA as a noninvasive CAD imaging modality.

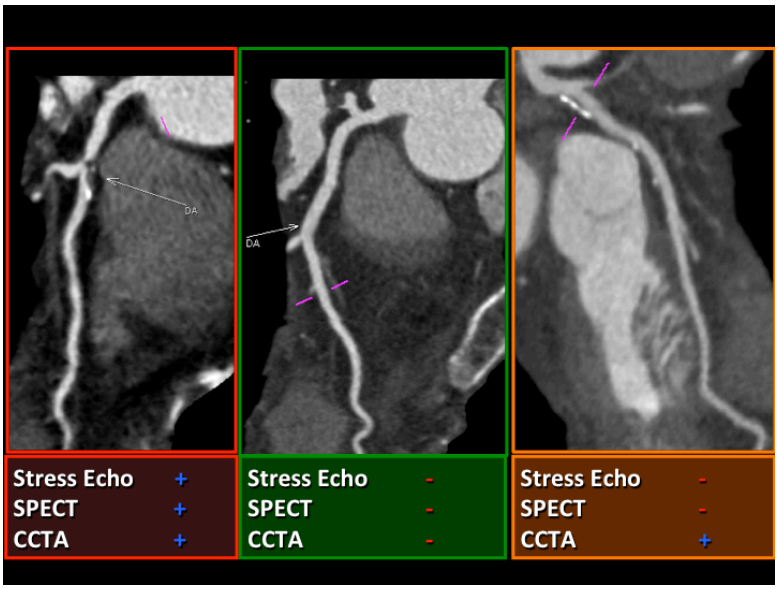


Figure 3: Contrast between CV risk, as assessed by the HeartScore, and the presence of nonobstructive (but probably not innocent!) mixed plaque in the left main in a 51 years-old male with hypertension, dyslipidemia and an HeartScore <5%.

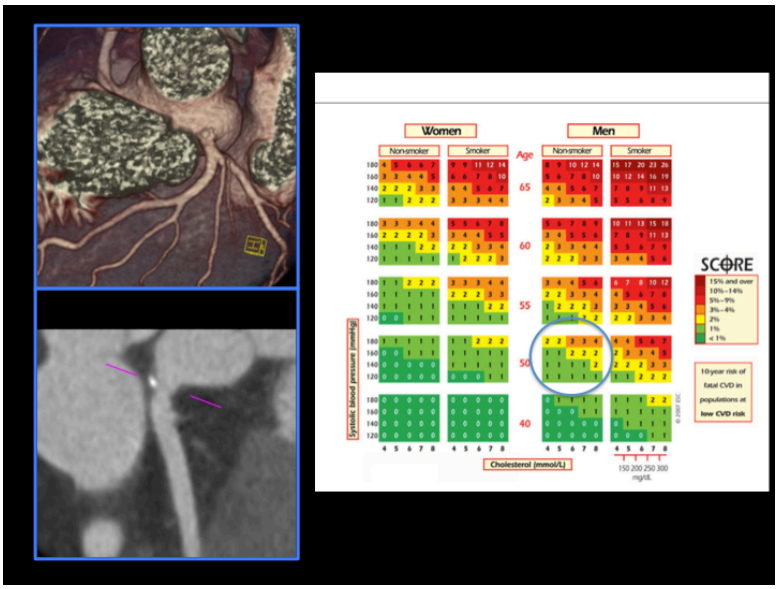


Figure 4: CCTA with prospective triggering with an estimated radiation dose of 1.1mSv (79DLP, conversion factor of 0.014), in a patient with normal coronary arteries.

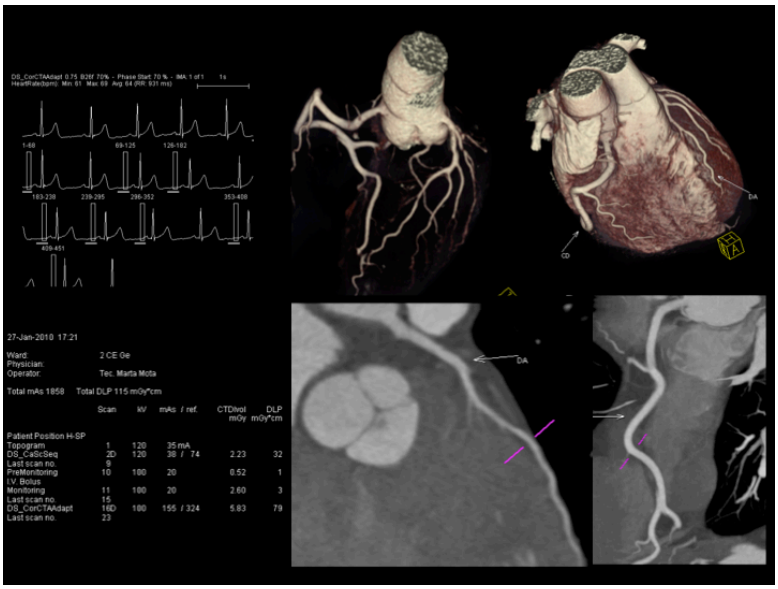


Figure 5: CCTA depicting a noncalcified plaque in the proximal left anterior descending artery without significant stenosis (A). In invasive angiography (B) this lesion was not apparent but was confirmed with IVUS (C).

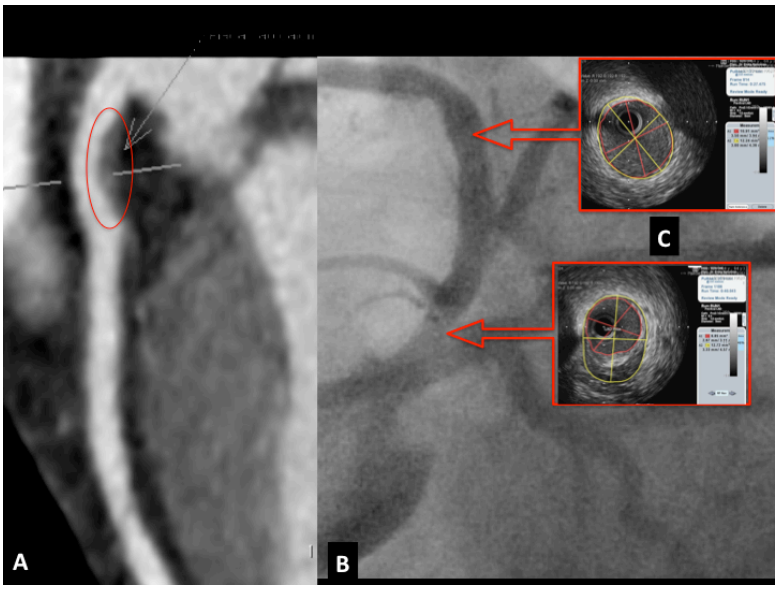
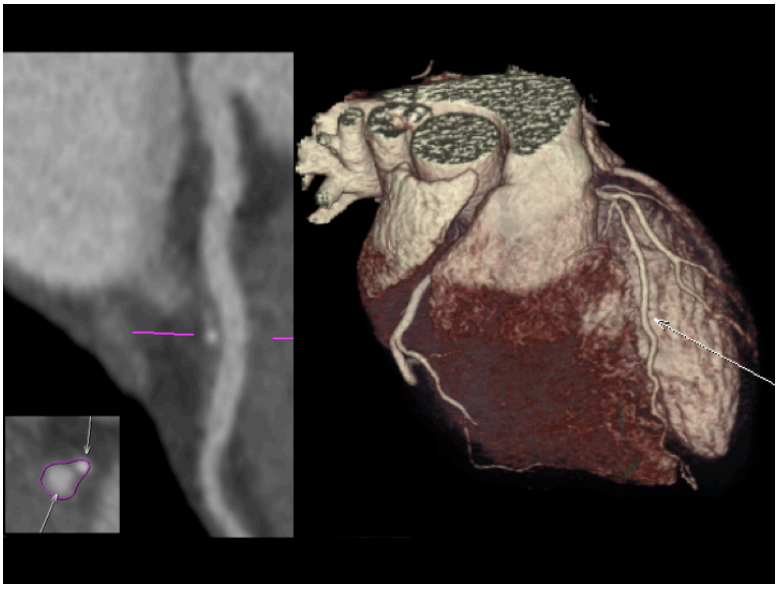


Figure 6: Mixed plaque in the proximal left anterior descending artery with positive remodeling and without significant stenosis (<25% by visual estimation). This was a 31 year old male patient with a family history of premature coronary artery disease.



REFERENCES

1. Becker CR, Knez A, Leber A, Hong C, Treede H, Wildhirt S, et al. [Initial experiences with multi-slice detector spiral CT in diagnosis of arteriosclerosis of coronary vessels]. Radiologe. 2000 Feb;40(2):118-22.
2. Ohnesorge B, Flohr T, Becker C, Kopp AF, Schoepf UJ, Baum U, et al. Cardiac imaging by means of electrocardiographically gated multisection spiral CT: initial experience. Radiology. 2000 Nov;217(2):564-71.
3. Achenbach S, Ulzheimer S, Baum U, Kachelriess M, Ropers D, Giesler T, et al. Noninvasive coronary angiography by retrospectively ECG-gated multislice spiral CT. Circulation. 2000 Dec 5;102(23):2823-8.
4. Nieman K, Oudkerk M, Rensing BJ, van Ooijen P, Munne A, van Geuns RJ, et al. Coronary angiography with multi-slice computed tomography. Lancet. 2001 Feb 24;357(9256):599-603.
5. Ropers D, Baum U, Pohle K, Anders K, Ulzheimer S, Ohnesorge B, et al. Detection of coronary artery stenoses with thin-slice multi-detector row spiral computed tomography and multiplanar reconstruction. Circulation. 2003 Feb 11;107(5):664-6.
6. Kuettner A, Trabold T, Schroeder S, Feyer A, Beck T, Brueckner A, et al. Noninvasive detection of coronary lesions using 16-detector multislice spiral computed tomography technology: initial clinical results. J Am Coll Cardiol. 2004 Sep 15;44(6):1230-7.
7. Mollet NR, Cademartiri F, Nieman K, Saia F, Lemos PA, McFadden EP, et al. Multislice spiral computed tomography coronary angiography in patients with stable angina pectoris. J Am Coll Cardiol. 2004 Jun 16;43(12):2265-70.
8. Hoffmann U, Moselewski F, Cury RC, Ferencik M, Jang IK, Diaz LJ, et al. Predictive value of 16-slice multidetector spiral computed tomography to detect significant obstructive coronary artery disease in patients at high risk for coronary artery disease: patient-versus segment-based analysis. Circulation. 2004 Oct 26;110(17):2638-43.
9. Mollet NR, Cademartiri F, Krestin GP, McFadden EP, Arampatzis CA, Serruys PW, et al. Improved diagnostic accuracy with 16-row multi-slice computed tomography coronary angiography. J Am Coll Cardiol. 2005 Jan 4;45(1):128-32.
10. Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morello R, Valgimigli M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. J Am Coll Cardiol. 2006 Nov 7;48(9):1896-910.
11. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and

Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.
12. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart. 2008 Nov;94(11):1386-93.
13. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008 Nov 18;52(21):1724-32.
14. Meijboom WB, Meijs MF, Schuijf JD, Cramer MJ, Mollet NR, van Mieghem CA, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. J Am Coll Cardiol. 2008 Dec 16;52(25):2135-44.
15. Achenbach S, Ropers U, Kuettner A, Anders K, Pflederer T, Komatsu S, et al. Randomized comparison of 64-slice single- and dual-source computed tomography coronary angiography for the detection of coronary artery disease. JACC Cardiovasc Imaging. 2008 Mar;1(2):177-86.
16. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.
17. Schuhbaeck A, Achenbach S, Layritz C, Eisentopf J, Hecker F, Pflederer T, et al. Image quality of ultra-low radiation exposure coronary CT angiography with an effective dose <0.1 mSv using high-pitch spiral acquisition and raw data-based iterative reconstruction. Eur Radiol. 2013 Mar;23(3):597-606.
18. Dewey M, Zimmermann E, Deissenrieder F, Laule M, Dubel HP, Schlattmann P, et al. Noninvasive coronary angiography by 320-row computed tomography with lower radiation exposure and maintained diagnostic accuracy: comparison of results with cardiac catheterization in a head-to-head pilot investigation. Circulation. 2009 Sep 8;120(10):867-75.
19. Khan A, Khosa F, Nasir K, Yassin A, Clouse ME. Comparison of radiation dose and image quality: 320-MDCT versus 64-MDCT coronary angiography. AJR Am J Roentgenol. 2011 Jul;197(1):163-8.
20. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? J Am Coll Cardiol. 2003 May 7;41(9):1475-9.
21. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504.
22. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35.
23. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques

subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009 Jun 30;54(1):49-57.
24. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003 Oct 7;108(14):1664-72.
25. De Araujo Goncalves P, Brito J, Sousa PJ, Carvalho MS, Dores H, Teles RC, et al. Nonobstructive coronary disease leading to STEMI: assessment of residual stenosis after thrombus aspiration. Coron Artery Dis. 2013 Mar;24(2):154-9.
26. Giroud D, Li JM, Urban P, Meier B, Rutishauer W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. Am J Cardiol. 1992 Mar 15;69(8):729-32.
27. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation. 1988 Nov;78(5 Pt 1):1157-66.
28. Achenbach S. Anatomy meets function. Modeling coronary flow reserve on the basis of coronary computed tomography angiography. J Am Coll Cardiol. 2011 Nov 1;58(19):1998-2000.
29. de Araujo Goncalves P, Garcia-Garcia HM, Carvalho MS, Dores H, Sousa PJ, Marques H, et al. Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited. Int J Cardiovasc Imaging. 2012 Dec 13.
30. Voros S, Rinehart S, Qian Z, Joshi P, Vazquez G, Fischer C, et al. Coronary atherosclerosis imaging by coronary CT angiography: current status, correlation with intravascular interrogation and meta-analysis. JACC Cardiovasc Imaging. 2011 May;4(5):537-48.
31. Hoffmann U, Moselewski F, Nieman K, Jang IK, Ferencik M, Rahman AM, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol. 2006 Apr 18;47(8):1655-62.
32. Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, et al. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol. 2007 Jul 24;50(4):319-26.
33. Kashiwagi M, Tanaka A, Kitabata H, Tsujioka H, Kataiwa H, Komukai K, et al. Feasibility of noninvasive assessment of thin-cap fibroatheroma by multidetector computed tomography. JACC Cardiovasc Imaging. 2009 Dec;2(12):1412-9.
34. Papadopoulou SL, Brugaletta S, Garcia-Garcia HM, Rossi A, Girasis C, Dharampal AS, et al. Assessment of atherosclerotic plaques at coronary bifurcations with multidetector computed tomography angiography and intravascular ultrasound-virtual histology. Eur Heart J Cardiovasc Imaging. 2012 Aug;13(8):635-42.
35. Prati F, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, et al. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. Eur Heart J. 2012 Oct;33(20):2513-20.
36. Cademartiri F, Mollet NR, Runza G, Bruining N, Hamers R, Somers P, et al. Influence of intracoronary attenuation on coronary plaque measurements using

multislice computed tomography: observations in an ex vivo model of coronary computed tomography angiography. Eur Radiol. 2005 Jul;15(7):1426-31.
37. Cademartiri F, Runza G, Palumbo A, Maffei E, Martini C, McFadden E, et al. Lumen enhancement influences absolute noncalcific plaque density on multislice computed tomography coronary angiography: ex-vivo validation and in-vivo demonstration. J Cardiovasc Med (Hagerstown). 2010 May;11(5):337-44.
38. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, et al. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. J Am Coll Cardiol. 2006 Feb 7;47(3):672-7.
39. Boogers MJ, Broersen A, van Velzen JE, de Graaf FR, El-Naggar HM, Kitslaar PH, et al. Automated quantification of coronary plaque with computed tomography: comparison with intravascular ultrasound using a dedicated registration algorithm for fusion-based quantification. Eur Heart J. 2012 Apr;33(8):1007-16.
40. Pundziute G, Schuijf JD, Jukema JW, Boersma E, de Roos A, van der Wall EE, et al. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. J Am Coll Cardiol. 2007 Jan 2;49(1):62-70.
41. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. J Am Coll Cardiol. 2007 Sep 18;50(12):1161-70.
42. Bamberg F, Sommer WH, Hoffmann V, Achenbach S, Nikolaou K, Conen D, et al. Meta-analysis and systematic review of the long-term predictive value of assessment of coronary atherosclerosis by contrast-enhanced coronary computed tomography angiography. J Am Coll Cardiol. 2011 Jun 14;57(24):2426-36.
43. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol. 2011 Mar 8;57(10):1237-47.
44. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011 Aug 16;58(8):849-60.
45. Chow BJ, Small G, Yam Y, Chen L, Achenbach S, Al-Mallah M, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. Circ Cardiovasc Imaging. 2011 Sep;4(5):463-72.
46. van Werkhoven JM, Schuijf JD, Gaemperli O, Jukema JW, Boersma E, Wijns W, et al. Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. J Am Coll Cardiol. 2009 Feb 17;53(7):623-32.
47. NICE clinical guideline 95. Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin.; Available from: http://www.nice.org.uk/guidance/CG95.

48. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L, et al. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. JACC Cardiovasc Imaging. 2012 Jul;5(7):690-701.
49. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. J Nucl Cardiol. 2004 Mar-Apr;11(2):171-85.
50. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol. 2007 Jan 16;49(2):227-37.

Capítulo 10.
Discussão, conclusões e direcções para trabalhos futuros

SUMÁRIO DO CAPÍTULO 10:

Capítulo 10: Discussão, conclusões e direcções para trabalhos futuros

10.1 DISCUSSÃO GLOBAL

O trabalho que foi desenvolvido no âmbito desta tese esteve assente em vários pressupostos de **epidemiologia e fisiopatologia da DC** e do relativo contributo e respectivas limitações das **diferentes modalidades de diagnóstico por imagem** no estudo da DC, nomeadamente na identificações dos doentes em risco de eventos coronários:

1) Apesar de toda a evolução farmacológica e de meios complementares de diagnóstico possível nos últimos anos, ***o EAM e a morte súbita continuam a ser a primeira manifestação da aterosclerose coronária*** para muitos doentes. Muitos destes doentes não tinham sintomas previamente ao evento e o seu risco CV era baixo, sendo difíceis de identificar clinicamente (1-3). A justificação para esta discrepância entre o risco por doente e o risco populacional resulta do facto de a população de risco CV moderado ou baixo ser muito superior à de risco elevado e assim uma importante fatia dos eventos CV ocorre em indivíduos de menor risco relativo (4).

2) Os exames complementares de diagnóstico tradicionalmente usados para avaliar a DC, baseiam-se na ***documentação de isquémia***, sendo esta a sua maior limitação, uma vez que a sua positividade exige a presença de lesões coronárias obstrutivas. Assim, estes exames não permitem a avaliação da carga aterosclerótica coronária global e a detecção de lesões coronária não obstrutivas, que se sabe estarem também implicadas na etiologia de eventos coronários (5-7).

3) Estudos de placa vulnerável com ***imagiologia intracoronária*** avançada, de elevada resolução espacial e suplementada por caracterização tecidular - IVUS-VH - forneceram resultados desapontadores acerca da possibilidade de identificação das placas vulneráveis. No estudo PROSPECT (8), com esta avaliação invasiva e numa população que já tinha sofrido um SCA, foi possível identificar 3 características de risco nas placas associadas ao desenvolvimento subsequente de eventos coronários. No entanto, mesmo pela conjugação dessas 3 variáveis, a probabilidade de um evento coronário no seguimento médio de 3,4 anos foi de apenas 18,2%, ou seja, cerca de 4 em cada 5 doentes que tem placas que reúnem simultaneamente estas 3 características de risco não vieram a sofrer qualquer evento. Neste trabalho considerado um marco no estudo da história natural da DC, mesmo a identificação de um TCFA teve uma baixa especificidade para prever a ocorrência de eventos, uma vez que apenas 26 das 595 placas identificadas como de risco estiveram na origem de eventos. Por outro lado, a grande maioria dos eventos verificados foram rehospitalizações por AI e novas revascularizações e não os eventos major que verdadeiramente gostaríamos de poder prevenir, a morte e o EAM. Este último aspecto pode ter sido igualmente influenciado pelo facto de estes doentes estarem já em prevenção secundária, com medicação que reconhecidamente reduz o seu risco (nomeadamente antiagregação plaquetar e estatina) e com a habitual vigilância apertada dos ensaios clínicos, o

que pode ter contribuído para reduzir a taxa de eventos. De qualquer modo, este trabalho está em linha com o conceito de que apesar de o risco por placa poder ser superior para determinadas lesões que reúnem estas características de instabilidade, o risco final para o doente resulta da probabilidade somada de todas as suas lesões, sendo que quanto maior for a carga aterosclerótica maior será o risco, conceito bem alicerçado por toda a evidência reunida ao longo de vários anos sobre o valor prognóstico do score de cálcio (9-11).

4) Existe um ***contraste entre o risco absoluto por placa e a prevalência dos diferentes tipos de placas***. Apesar de o risco absoluto de instabilização por placa ser superior para placas mais volumosas e obstrutivas (assumindo o mesmo nível das restantes características de risco, nomeadamente o grau de inflamação e a espessura da cápsula fibrosa), estas são menos prevalentes do que as placas não obstrutivas e assim, por questões probabilísticas, os eventos coronários resultam com frequência de instabilização destas lesões não obstrutivas (12, 13).

A ***angio TC cardíaca*** é a mais recente técnica não invasiva para o estudo da DC, tendo surgiu nos últimos anos fruto de importantes avanços tecnológicos na tecnologia de TC multidetectores. Desde o seu aparecimento, tem-se assistido a uma progressiva melhoria da resolução espacial e temporal, contribuindo para uma evolução favorável da qualidade dos exames, bem como uma significativa redução da dose de radiação (14-16). A par desta ***evolução tecnológica***, foi aumentando a experiência e gerada mais evidencia clínica, tornando a angio TC cardíaca numa técnica cada vez mais robusta na avaliação da DC, sendo já considerada o exame de eleição em varias indicações e tendo vindo a aumentar progressivamente a sua ***aplicabilidade clínica*** e o numero de indicações para a qual é considerada como apropriada (17, 18).

Para além de permitir excluir a presença de DC e de identificar a presença de estenoses significativas, a angio TC cardíaca permite identificar ainda um 3º grupo de doentes com ***lesões coronárias não obstrutivas***, característica impar desta técnica como modalidade de imagem não invasiva. Ao permitir identificar a totalidade das lesões ateroscleróticas (obstrutivas e não obstrutivas), a angio TC cardíaca poderá fornecer uma quantificação da carga aterosclerótica coronária total, podendo essa identificação ser útil na estratificação dos indivíduos em risco de eventos coronários. No entanto, dada a elevada prevalência de placas ateroscleróticas identificáveis na árvore coronária por angio TC, que na maioria dos estudos corresponde a mais de metade dos doentes (19, 20), torna-se importante desenvolver ferramentas que permitam quantificar a carga aterosclerótica coronária e assim identificar os indivíduos com maior carga aterosclerótica que poderão eventualmente beneficiar de medidas de prevenção mais agressivas (21).

Capítulo 10: Discussão, conclusões e direcções para trabalhos futuros

A angio TC cardíaca, como modalidade não invasiva, tem ainda importantes limitações de resolução espacial para a avaliação detalhada das características de potencial instabilidade de uma placa em particular, nomeadamente não permitindo avaliar a espessura da cápsula fibrosa nem o grau de inflamação, mas permite avaliar de modo não invasivo a carga aterosclerótica coronária global, incluindo as lesões não obstrutivas. Esta identificação e quantificação da ***carga aterosclerótica*** poderá ser mais importante para o desenvolvimento futuro de eventos do que as potenciais características de instabilidade de uma placa em particular.

A angio TC cardíaca, ao fornecer uma avaliação detalhada da árvore coronária, no que diz respeito à presença, localização, grau de estenose e tipo de placa, poderá dar informação acerca do risco não apenas resultante de uma placa em particular, mas da totalidade da carga aterosclerótica da árvore coronária.
Assim, torna-se fundamental desenvolver e validar prospectivamente scores que integrem toda esta informação e permitam quantificar a carga aterosclerótica coronária global que terão provavelmente uma boa correlação com o risco de eventos coronários futuros. Este foi o objectivo do desenvolvimento do ***CT-LeSc*** (22).

Por fim, o conceito de ***árvore coronária vulnerável*** poderá ser mais importante do que o da placa vulnerável e a sua identificação pela angio TC cardíaca poderá ser importante numa estratégia de prevenção mais avançada. Esta poderá permitir ***personalizar as medidas de prevenção primária***, doseando melhor a sua intensidade em função da carga aterosclerótica, podendo esta vir a constituir uma das mais importantes indicações da angio TC cardíaca no futuro.

10.2 CONCLUSÕES

1. Foram identificados preditores demográficos e clínicos para uma elevada carga aterosclerótica, avaliada pela angio TC cardíaca. A diabetes mellitus em particular foi um dos preditores clínicos mais importantes, funcionando como modelo de DC mais avançada, útil para avaliar o desempenho dos diferentes índices de carga aterosclerótica (***artigo 16***).

2. O desempenho destas variáveis demográficas e clínicas, mesmo quando agrupadas em scores clínicos para prever a presença e da gravidade da DC (obstrutiva e não obstrutiva) documentada por angioTC cardíaca foi modesta. Entre os vários scores, o desempenho foi um pouco melhor para o score de risco cardiovascular HeartScore. Estas limitações espelham a dificuldade de prever apenas com base em variáveis clínicas, mesmo quando agrupadas em scores, a presença e extensão da DC. Um dos factores de risco clássicos, a obesidade, parece ter uma relação paradoxal com a carga aterosclerótica, o que pode justificar algumas limitações da estimativa com base em scores clínicos (***artigo 15***).

3. Foi desenvolvido um índice de carga aterosclerótica que reúne a informação global acerca da localização, do grau de estenose e do tipo de placa, obtida não invasivamente pela angio TC cardíaca (***artigo 18***). Este score poderá vir a ser uma ferramenta útil para quantificação da carga aterosclerótica coronária sendo de esperar que possa traduzir a informação prognóstica da angio TC cardíaca, uma vez que a DC pode manifestar-se clinicamente mesmo na ausência de lesões obstrutivas (***artigo 1***), numa fase em que não é expectável que cause sintomas e em que é silenciosa nos habituais exames de documentação de isquémia.

10.3 DIRECÇÕES PARA TRABALHOS FUTUROS

1. Um dos objectivos centrais desta tese foi o desenvolvimento de um score que reflecte a carga aterosclerotica coronária global, o CT-LeSc. Na nossa população foi possível demonstrar uma associação significativa entre o CT-LeSc e reconhecidos factores de risco cardiovasculares como a diabetes, cuja presença de associou a uma probabilidade quase 3 vezes superior de um elevado CT-LeSc. Por outro lado, também um elevado risco cardiovascular (estimado pelo Heartscore) associou-se a uma probabilidade 2,5 vezes superior de se encontrar uma elevada carga aterosclerotica traduzida por este índice.

No entanto, o CT-LeSc carece ainda de validação prognóstica, antes da sua adopção na prática clínica. A sua validação como ferramenta para identificar os doentes em maior risco de eventos, mesmo no subgrupo sem doença coronária obstrutiva, deverá idealmente ser feito numa população com um tempo de seguimento não muito curto e/ou com maior risco cardiovascular, dada a baixa taxa de eventos observada nas populações de risco intermédio a baixo, tipicamente referenciadas para angio TC cardíaca para exclusão de doença coronária. Este será o próximo passo, tendo já sido desenvolvido algum trabalho nesta área por ligação a grupos internacionais que fazem investigação nesta área .

2. Por fim, a identificação por angio TC cardíaca dos doentes com elevada carga aterosclerótica em maior risco de eventos coronários e que assim poderão beneficiar de uma prevenção primária mais agressiva, irá levar ao desafio de se desenvolver estratégias de prevenção mais avançadas.

Estas poderão no futuro passar pela adopção de medidas já empregues em prevenção secundária, nomeadamente pelo uso de dupla antiagregação plaquetar ou dos novos antiagregantes mais potentes, já validados no contexto de síndromes coronários agudos (23, 24), embora estas medidas tenham sempre de ser contrabalançadas pelo esperado aumento do risco de complicações hemorrágicas. Um abordagem alternativa e possivelmente mais segura poderá passar por uma terapêutica mais direccionada aos mecanismos do desenvolvimento da aterosclerose. À medida que se conhece cada vez melhor a fisiopatologia da aterosclerose e o papel central da inflamação (5, 6, 25, 26), não só na progressão destas lesões mas sobretudo no seu risco de instabilização, novas estratégias direccionadas para estes mecanismos poderão vir a ser empregues, estando já alguns fármacos em fase de ensaios clínicos (27) .

Por outro lado, o paradigma de intervenção na doença coronária poderá vir a mudar. Actualmente a angioplastia no contexto de doença coronária estável está sobretudo indicada para melhoria dos sintomas, podendo ter impacto prognostico favorável quando realizada em lesões obstrutivas responsáveis por extensas áreas de isquémia (28). A intervenção percutânea em lesões não obstrutivas mas que apresentam outras características de potencial instabilidade é para já uma hipótese teórica, tendo duas limitações importantes: Em primeiro lugar, está limitada pela actual baixa especificidade na identificação não invasiva (29) e mesmo invasiva (8),

das placas vulneráveis. Em segundo lugar, a intervenção nesta lesões tem que partir do pressuposto de que a historia natural destas placas vulneráveis se associa a um risco de eventos superior ao risco relacionados com a própria intervenção, estando assim intimamente ligada à eficácia e segurança da própria angioplastia. Nos últimos anos tem-se assistido a avanços tecnológicos impressionantes na área da cardiologia de intervenção, com reduções muito significativas da taxa de restenose e mais recentemente também da taxa de trombose. O desenvolvimento recente de stents absorvíveis veio abrir um novo campo de possibilidades à intervenção percutânea e os impressionantes resultados experimentais e clínicos obtidos poderão levar a reequacionar as indicações clínicas e contribuir para esta mudança de paradigma.

10.4 BIBLIOGRAFIA

1. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation. 2012 Jan 31;125(4):620-37.
2. Akosah KO, Schaper A, Cogbill C, Schoenfeld P. Preventing myocardial infarction in the young adult in the first place: how do the National Cholesterol Education Panel III guidelines perform? J Am Coll Cardiol. 2003 May 7;41(9):1475-9.
3. Moscoso Costa F AGP, Campante Teles R, Ferreira J, Carvalho MS, Dores H, Sousa PJ, Raposo L, Sousa Almeida M, Mesquita Gabriel H, Mendes M. Baixo risco cardiovascular prévio numa população de EAM inaugural estimado pelo Heartscore. Rev Port Cardiol. 2012;31(Espec Congr):189.
4. Braunwald E. Epilogue: what do clinicians expect from imagers? J Am Coll Cardiol. 2006 Apr 18;47(8 Suppl):C101-3.
5. Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. Acute coronary events. Circulation. 2012 Mar 6;125(9):1147-56.
6. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013 May 23;368(21):2004-13.
7. De Araujo Goncalves P, Brito J, Sousa PJ, Carvalho MS, Dores H, Teles RC, et al. Nonobstructive coronary disease leading to STEMI: assessment of residual stenosis after thrombus aspiration. Coron Artery Dis. 2013 Mar;24(2):154-9.
8. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011 Jan 20;364(3):226-35.
9. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008 Mar 27;358(13):1336-45.
10. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation. 2007 Jan 23;115(3):402-26.
11. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012 Aug 22;308(8):788-95.
12. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation. 2003 Oct 7;108(14):1664-72.
13. Achenbach S. Anatomy meets function. Modeling coronary flow reserve on the basis of coronary computed tomography angiography. J Am Coll Cardiol. 2011 Nov 1;58(19):1998-2000.
14. Sousa PJ, Goncalves PA, Marques H, Raposo L, Cale R, Brito J, et al. Radiation in cardiac CT: predictors of higher dose and its reduction over time. Rev Port Cardiol. 2010 Nov;29(11):1655-65.
15. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J. 2010 Feb;31(3):340-6.
16. Schuhbaeck A, Achenbach S, Layritz C, Eisentopf J, Hecker F, Pflederer T, et al. Image quality of ultra-low radiation exposure coronary CT angiography with an effective dose <0.1 mSv using high-pitch spiral acquisition and raw data-based iterative reconstruction. Eur Radiol. 2013 Mar;23(3):597-606.
17. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2010 Nov 23;56(22):1864-94.

18. Goncalves Pde A, Marques H. Cardiac CT: the end of invasive coronary angiography as a diagnostic procedure? Rev Port Cardiol. 2009 Jul-Aug;28(7-8):825-42.
19. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011 Aug 16;58(8):849-60.
20. Pen A, Yam Y, Chen L, Dennie C, McPherson R, Chow BJ. Discordance between Framingham Risk Score and atherosclerotic plaque burden. Eur Heart J. 2013 Apr;34(14):1075-82.
21. de Araujo Goncalves P, Garcia-Garcia HM, Carvalho MS, Dores H, Sousa PJ, Marques H, et al. Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited. Int J Cardiovasc Imaging. 2012 Dec 13.
22. de Araujo Goncalves P, Garcia-Garcia HM, Dores H, Carvalho MS, Jeronimo Sousa P, Marques H, et al. Coronary computed tomography angiography-adapted Leaman score as a tool to noninvasively quantify total coronary atherosclerotic burden. Int J Cardiovasc Imaging. 2013 May 1.
23. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001-15.
24. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045-57.
25. Collaboration IRGCERF, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, et al. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet. 2012 Mar 31;379(9822):1205-13.
26. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005 Apr 21;352(16):1685-95.
27. van Diepen JA, Berbee JF, Havekes LM, Rensen PC. Interactions between inflammation and lipid metabolism: Relevance for efficacy of anti-inflammatory drugs in the treatment of atherosclerosis. Atherosclerosis. 2013 Jun;228(2):306-15.
28. Task Force on Myocardial Revascularization of the European Society of C, the European Association for Cardio-Thoracic S, European Association for Percutaneous Cardiovascular I, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010 Oct;31(20):2501-55.
29. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009 Jun 30;54(1):49-57.

All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as being self-evident.

Arthur Schopenhauer