



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

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## 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 ( $27.7 \pm 4.3$  vs  $26.8 \pm 4.3$  kg/m<sup>2</sup>,  $p < 0.001$ ); 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 ( $27.7 \pm 4.3$  vs  $27.2 \pm 4.3$  kg/m<sup>2</sup>,  $p = 0.120$ ). 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

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## Introduction

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

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(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.<sup>4,5</sup> 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.<sup>6,7</sup>

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.<sup>8,9</sup> 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,<sup>10</sup> 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

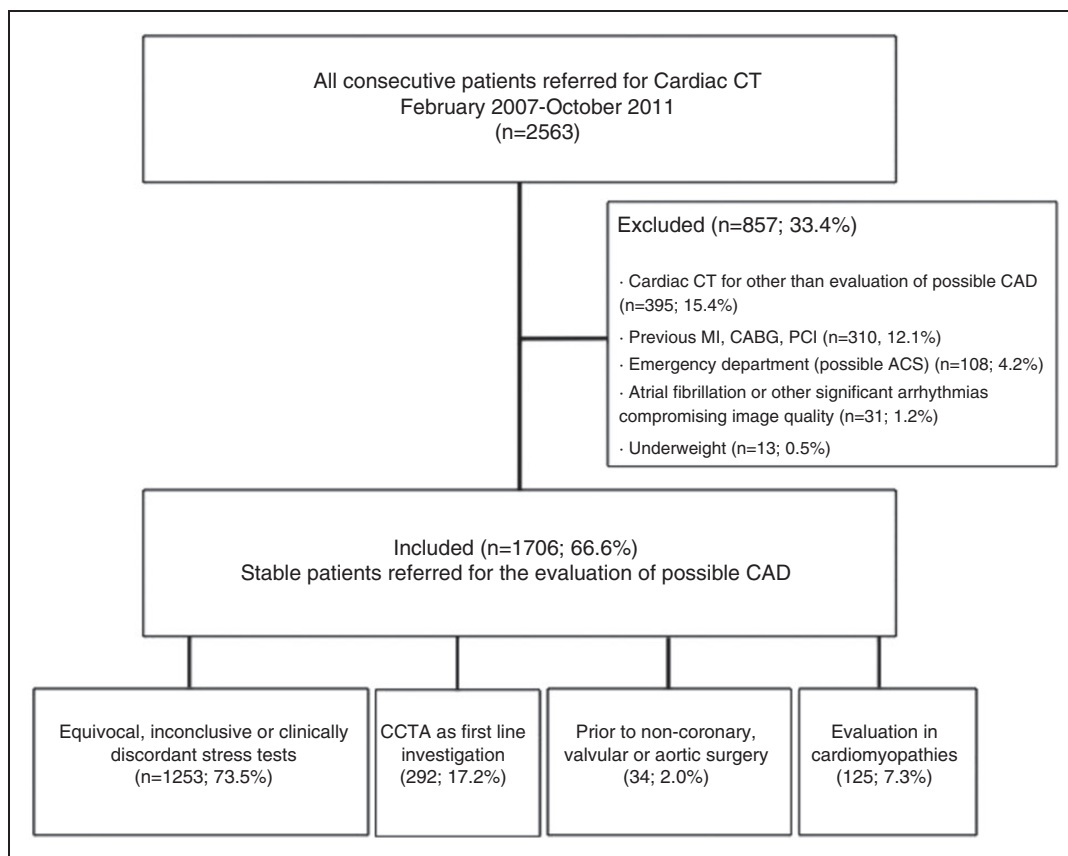
lipid-lowering drugs); (c) hypertension (defined as blood pressure  $\geq 140/90$  mm Hg or the use of antihypertensive medication); (d) Positive family history of premature CAD (defined as the presence of CAD in first-degree relatives younger than 55 (male) or 65 (female) years old); (e) smoking (defined 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:<sup>11</sup> underweight ( $<18.5$  kg/m<sup>2</sup>), normal (18.5–24.9 kg/m<sup>2</sup>), overweight (25.0–29.9 kg/m<sup>2</sup>) and obesity ( $\text{IMC} \geq 30.0$  kg/m<sup>2</sup>). 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<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup> 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<sup>12</sup> was used regarding segmentation (16 segments), stenosis severity ( $<25\%$ ; 25–49%; 50–69%; 70–99%;



**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  $\geq 50\%$  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.<sup>13</sup> In each coronary artery segment, coronary atherosclerosis was defined as tissue structures  $>1\text{ mm}^2$  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<sup>TM</sup>), where every area at least with  $1\text{ mm}^2$  within a coronary vessel with a density above 130 HU (Hounsfield Units) was selected.<sup>14</sup>

### 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

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  $\geq 5\%$ ). The median BMI was 26.7 (24.4–29.4) kg/m<sup>2</sup> 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 ( $27.7 \pm 4.3$  vs  $26.8 \pm 4.3$  kg/m<sup>2</sup>,  $p < 0.001$ ); 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 ( $27.7 \pm 4.3$  vs  $27.2 \pm 4.3$  kg/m<sup>2</sup>,  $p = 0.120$ ) (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

**Table 1.** Demographic and clinical characteristics

Variables	All patients ( $n = 1706$ )
<b>Demographic</b>	
Age, median (IQR) years	59.0 (51.0–66.0)
Male gender, $n$ (%)	976 (57.2)
<b>Cardiovascular risk factors, <math>n</math> (%)</b>	
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)
<b>Cardiovascular risk</b>	
HeartScore, median (IQR)	2.0 (1.0–4.0)
HeartScore $\geq 5\%$ , $n$ (%)	293 (17.2)
<b>Chest pain, <math>n</math> (%)</b>	
Asymptomatic	836 (49.0)
Non-cardiac	369 (21.6)
Atypical	363 (21.3)
Typical	138 (8.1)
<b>BMI (kg/m<sup>2</sup>)</b>	
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.

versus all other patients: 0.241, 0.450 and 0.663 respectively).

## Discussion

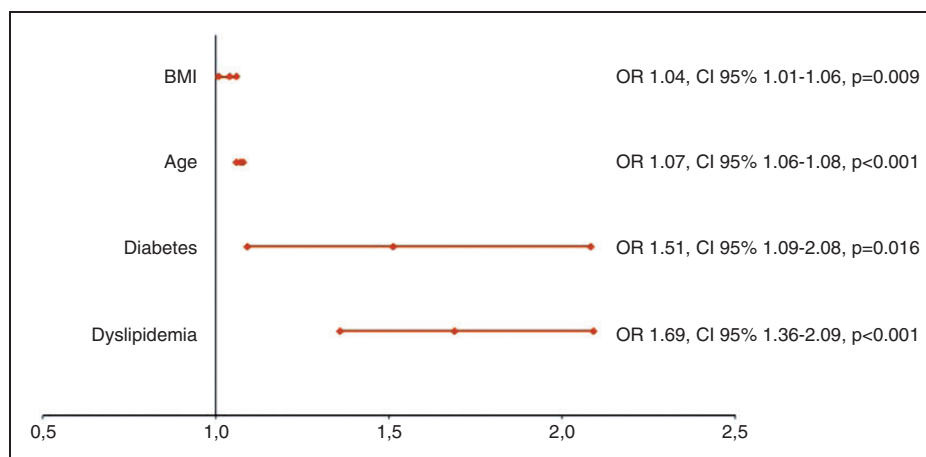
Our findings suggest that in this population of stable patients with low to intermediate cardiovascular risk referred for CCTA for suspected CAD, BMI was an independent predictor of CAD presence, but was not correlated with CAD severity. There were no significant differences across different BMI classes 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 in patients with CAD is still increasing and the current management of obesity seems inadequate.<sup>15</sup> 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

**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 <sup>2</sup> ) (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<sup>4</sup> and a meta-analysis of patients undergoing PCI showed a lower risk of death in patients with higher BMI.<sup>5</sup> 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.<sup>4,16</sup> 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.<sup>16</sup> 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.<sup>4</sup>

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.<sup>6</sup> and from the USA by Niraj et al.<sup>7</sup> 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.<sup>17</sup> 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

independent prognostic information.<sup>18</sup> 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.<sup>12</sup>

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.<sup>19</sup> In this regard, computed tomography has been recognized as a highly effective, accurate, and reproducible technique for measuring visceral adiposity,<sup>20</sup> and it has been documented by previous authors that there is a correlation between abdominal adiposity and the extent of coronary atherosclerosis.<sup>21</sup>

### 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.

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### Conflict of interest

None declared.

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