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Prognostic Value of Multidetector Computed Tomography Coronary Angiography in Diabetes: Excellent Long-term Prognosis in Patients with Normal Coronary Arteries

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INTRODUCTION

Diabetes mellitus (DM) is associated with premature atherosclerosis (1) and increased risk for coronary artery disease (CAD) and CAD is the most common cause of death in diabetic adults (2). However, CAD diagnosis may be missed or delayed in diabetic patients since the typical symptoms are often masked despite diffuse multi-vessel coronary atherosclerosis is frequently present. Therefore, there is a clear clinical need to detect CAD at an early stage in DM patients who are at risk of both fatal and non fatal cardiac events before the onset of symptoms. Unfortunately, cardiac stress imaging test have a limited negative predictive value in DM patients (3). Multidetector computed tomography coronary angiography (MDCT-CA) is a reliable diagnostic modality for evaluating patients with suspected CAD with high diagnostic performance for the detection of obstructive coronary lesions, particularly in selected subgroups (4,5). Moreover, recent but robust data support the prognostic role of MDCT-CA in patients with suspected CAD, demonstrating that the detection of CAD by MDCT-CA predicts cardiac events (6-9) and the CONFIRM registry, a large, international multicenter study, stated a strong role of MDCT-CA in the prediction of all-cause mortality, with risk profiles differing for age and sex (10,11). However, data supporting the prognostic value of MDCT-CA in diabetics are limited. Two early studies, characterized by a mid-term follow-up (20 and 33 months, respectively) demonstrated that MDCT-CA is a predictor of major adverse cardiac events (12,13). The aim of the present study was the evaluation of the long-term prognostic role of MDCT-CA in a population of DM patients without known cardiac disease and in whom CAD was suspected.

MATERIALS AND METHODS

Patients and study protocol.

Study population consisted of 539 consecutive DM patients who presented to our outpatient clinic or were admitted to our hospital for cardiac evaluation (exercise electrocardiogram, stress echocardiography or invasive coronary angiography [ICA]) between January 2006 and January 2007 because of suspected CAD (new onset chest pain, abnormal stress test, multiple cardiovascular risk factors including DM). In all, MDCT-CA was performed in addition to standard clinical work-up. A total of 90 patients were excluded because of known CAD (42 patients, of whom 27 for previous myocardial infarction and 15 for previous coronary revascularization) or other known cardiovascular diseases (48 patients, of whom 10 for heart failure, 4 for congenital heart disease, 20 for significant valvular disease, 7 for cardiomyopathy, 7 for ascending aorta aneurysm). Other exclusion criteria were contraindications to contrast agents (5 patients), impaired renal function (creatinine clearance <60 ml/min) (8 patients), inability to sustain a 15-second breath hold (2 patients) and cardiac arrhythmias (5 patients). Thus, the analytic study population consisted of 429 subjects. The study was approved by our institution's scientific and ethical committees and all patients gave written informed consent. A structured interview and clinical history were acquired, and the following cardiac risk factors were assessed before MDCT-CA: diabetes mellitus (glucose level of ≥7 mmol/l or the need for medications) (14), hypercholesterolemia (total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) (15), hypertension (blood pressure ≥140/90 mmHg or use of antihypertensive medications) (16), positive family history of CAD (presence of CAD in first-degree relatives younger than 55 years [male] or 65 years [female]) (17) and current smoking. Pre-test probability of CAD was determined using the Diamond and Forrester method (18).

MDCT-CA scan protocol, image reconstruction and patient preparation.

Metoprolol was intravenously administered before MDCT-CA with a titration dose up to 20 mg in patients with heart rate >65 bpm. In all patients, MDCT-CA was performed using a 64-slice scanner (VCT, GE Medical System, Milwaukee, WI, 64x0.625 mm collimation, 330 msec gantry rotation time). Dose modulation was attained with "electrocardiographic gating" for a maximum gantry delivery between 40% and 80% during the R-R interval. A bolus of 80 ml of high concentration contrast (Iomeron 400 mg/ml, Bracco, Milan, Italy) was administered intravenously at 5 ml/sec, followed by 50 ml of saline injected at the same infusion rate. The scan was initiated according to bolus-tracking technique. Image data sets were analyzed using multi-planar reconstruction on post-processing workstations (CardioQ3 package, Advantage Workstation version 4.2, GE Healthcare, Milwaukee, WI).

MDCT-CA data analysis.

All MDCT-CA examinations were evaluated by two expert readers unaware of patient clinical data. In case of disagreement, a joint reading was performed and a consensus decision was reached. Coronary arteries were divided into 16 segments according to the AHA classification (19). Each segment was classified as interpretable or not. Patients were excluded when proximal or mid segment or more than 3 segments were uninterpretable (6). Then, the interpretable segments were evaluated for presence of atherosclerotic plaques. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to artery lumen, clearly distinguishable from vessel lumen and surrounding pericardial tissue (6). One coronary plaque was assigned per coronary segment even in presence of multiple plaques. Plaque type was determined using the following classification: 1) non-calcified (plaques having lower density compared with the contrast-enhanced vessel lumen); 2) calcified (high-density plaques); and 3) mixed (non-calcified and calcified components within a single plaque). In case a segment contained calcified and non-calcified plaques, we classified the

plaque as calcified. The number of segments with non-calcified, calcified, and mixed plaques was recorded. Vessel segments were graded on the basis of visually estimated obstruction of coronary lumen as normal, non-obstructive lesions (<50%) and obstructive lesions (≥50%). The number of segments with any obstructive plaque was also recorded. Patients were divided into 3 groups: normal (no coronary plaques), non-obstructive CAD (lesions <50%) and obstructive CAD (lesions ≥50%). Moreover, coronary arteries were analyzed using 2 evaluation methods: presence of obstructive lesions in major epicardial vessels and coronary plaque scores (6). To this purpose, MDCT-CA scans were firstly analyzed and the number of major epicardial vessels exhibiting ≥50% stenosis was recorded. Patients with obstructive CAD in diagonal or obtuse marginal branches were included in the left anterior descending and left circumflex artery obstructive CAD groups, respectively. In case of obstructive stenosis of the left main coronary artery (LMCA), patients were assigned to this category even if they had other diseased vessels. Second, we analyzed the extent of atherosclerotic burden using 2 coronary artery plaque scores (6): 1) the segment-involvement score (SIS), i.e. the number of segments (minimum=0; maximum=16) with at least one plaque irrespective of the degree of stenosis; and 2) the segment-stenosis score (SSS), i.e. the overall coronary artery plaque extent. With the latter score, each coronary segment was graded as having no to severe plaque (i.e., score from 0 to 3) based on the extent of obstruction of coronary lumen diameter. The SSS of the 16 coronary segments were summed to yield a total score ranging from 0 to 48. For both scores, a cut off of 5 was used to differentiate patients with low or high probability of cardiac events (6).

Follow-up.

Follow-up, either clinical visit or telephone interview, was performed by researchers blinded to MDCT-CA data. Hospital records were screened for clinical events to confirm the obtained information. Outcome measures were a composite of hard cardiac events (cardiac death, non-fatal

myocardial infarction and unstable angina requiring hospitalization) and all cardiac events (cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization and revascularization). All deaths were reviewed and classified as cardiac (death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure) or non-cardiac. All revascularizations were classified in early (patients underwent an early elective revascularization within 60 days after MDCT-CA) and late revascularizations. Only late revascularizations were considered as cardiac events, whereas patients with elective early revascularization were excluded from the analysis. The diagnosis of non-fatal myocardial infarction was based on the presence of typical chest pain, elevated cardiac enzymes, and typical ECG changes (20). Unstable angina was defined as acute chest pain with or without the presence of ECG abnormalities and no cardiac enzyme elevation (21).

Statistical analysis.

Statistical analysis was performed using SAS (version 9.1.3, SAS Institute Inc., Cary, North Carolina) and SPSS 13.0 software (SPSS Inc, Chicago, IL). Statistical significance was defined as $P<0.05$. Continuous variables are presented as mean±SD, and discrete variables as absolute numbers and percentages. To compare patient characteristics and MDCT-CA data, Chi-square or Fisher exact tests were used for categorical variables and Student t-test for continuous variables. When not normally distributed, continuous variables were expressed as median (25^{th} to 75^{th} percentile range) and compared using nonparametric Mann-Whitney test. To identify the association between MDCT-CA variables and outcomes, Cox regression analysis was used. First, univariate analysis of clinical characteristics and MDCT-CA variables was performed to identify potential predictors. Hazard ratios (HR) were calculated with 95% confidence intervals as an estimate of the risk associated with a particular variable. To determine independent predictors of the composite end points, multivariate analysis of MDCT-CA variables with $P\leq0.05$ in univariate analysis was performed, which was

corrected for baseline characteristics (male gender, age, cardiovascular risk factors). Cumulative event-free survival rates as a function over time were obtained by Kaplan-Meier method. Hard and all cardiac event-free survival curves were compared using the log-rank test.

RESULTS

Patient's characteristics.

Of the 429 patients prospectively enrolled, 24 were excluded because MDCT-CA images were uninterpretable. Of the remaining 405 patients, 15 were lost to follow-up, whereas 390 (98%) had a complete follow-up (mean 62±9 months, up to 72 months). In 40 patients, blood glucose levels were controlled by diet, 281 patients took oral antidiabetic medication and 69 patients were using insulin. Patients lost to follow-up had no significant differences in clinical characteristics and MDCT-CA results. 279 events were recorded, whose 117 hard events (9 cardiac death, 66 non-fatal myocardial infarction and 42 unstable angina) and 142 late revascularizations. Twenty patients with early elective revascularizations were excluded from survival analysis. Indications for MDCT-CA were chest pain (35%), multiple cardiac risk factors including DM (38%), and equivocal or abnormal stress test (27%). Mean pre-test probability of CAD was 46±28%. Prevalence of male gender and hypertension was significantly higher in patients with events than in those without events (Table 1).

MDCT-CA results.

Table 2 shows MDCT-CA results and patient outcomes. SIS, SSS, number of segments with obstructive plaques and prevalence of obstructive CAD, 3-vessel disease (VD) and LMCA disease were significantly higher in patients with events than in patients without events.

Univariate predictors of events.

Univariate clinical predictors of events were male gender, hypertension, high pre-test likelihood of CAD and medical therapy with beta-blockers, aspirin and statins (Table 3). Univariate MDCT-CA predictors of events are reported in Table 4. Regarding obstructive CAD, HR was 3.41 for hard events and 7.93 for all events. HRs were particularly increased in patients with 3-VD (5.79 for hard events and 11.62 for all events) and LMCA disease (10.57 for hard events and 22.83 for all events).

Multivariate predictors of events.

Significant independent predictors of hard events were 3-VD, LMCA disease and number of segments with noncalcified, mixed and calcified plaques. Significant independent predictors of all events were multi-VD, LMCA disease and number of segments with mixed and calcified plaques. The HRs were particularly high in patients with 3-VD (5.21 for hard events and 7.93 for all events) and LMCA disease (5.35 for hard events and 7.92 for all events) (Table 5).

Survival analysis.

Kaplan-Meier survival curves are provided in Figures 1 to 3. No events occurred in patients with normal coronary arteries. On the contrary, the 62-month cumulative hard and all event-free survival rates were 78% and 56% in patients with non-obstructive CAD and 60% and 16% in those with obstructive CAD, respectively (log-rank P value=0.0001) (Figure 1). Figure 2 shows the relationship between CAD extension, expressed as number of major epicardial vessels exhibiting ≥50% stenosis, and event-free survival rate. Regarding all events, cumulative event-free survival was 20% with 1-VD, 12% with 2-VD, 18% with 3-VD and 0% with LMCA disease (log-rank P value=0.0001). Excluding revascularization procedures, cumulative event-free survival was 73% with 1-VD, 62% with 2-VD, 50% with 3-VD and 25% with LMCA disease (log-rank P value=0.0001). The relationship between atherosclerotic burden, expressed as SIS and SSS, and event-free survival rate is reported in Figure 3. Regarding all events, cumulative event-free survival was 50% with SIS≤5,

16% with SIS>5, 67% with SSS≤5 and 11% with SSS>5 (log-rank P value=0.0001). Regarding hard events, cumulative event-free survival was 77% with SIS≤5, 54% with SIS>5, 88% with SSS≤5 and 54% with SSS>5 (log-rank P value=0.0001).

DISCUSSION

Management guidelines in Europe and the U.S. consider type 2 diabetes to be a cardiovascular disease equivalent (22) and CAD is the major cause of morbidity, mortality and medical cost of DM (22). Therefore, the early diagnosis of CAD to prevent progression and clinical events has intuitive appeal. Recently, the American Diabetes Association (ADA) convened an expert panel that revisited the issue of screening for CAD in DM patients, motivated by the goal of identifying patients with high risk whose outcomes might be improved through more aggressive risk factor modification, medical surveillance or revascularization of their CAD (22). Unfortunately, the sensitivity of clinical risk assessment is limited in diabetics, mainly because typical symptoms of ischemia are often absent and cardiac stress tests also have limited negative predictive value in these patients (3). Particularly, diagnostic accuracy of exercise ECG is lower in diabetics in comparison with nondiabetic patients (23) but also specificity of stress echocardiography and nuclear perfusion imaging is markedly lower in diabetic patients (24,25). MDCT-CA is currently considered a reliable diagnostic method for the evaluation of patients with suspected CAD, thanks to its high diagnostic performance in the rule-out but also in the detection of obstructive coronary stenosis (4). Many recent studies demonstrated an increased prevalence of obstructive and nonobstructive CAD and fewer normal coronary arteries in diabetic patients in comparison with nondiabetic population (22,26,27). However, only two mid-term follow-up (20 and 33 months, respectively) studies supported the prognostic value of MDCT-CA in DM patients (12,13). As compared to previous

investigations, our study has longer follow-up in a large group of very selected diabetic patients who underwent MDCT-CA for suspected CAD. Indeed, patients with any type of known cardiac disease were excluded. Then, to the best of our knowledge, our study population is the most homogeneous among the body of literature on the prognostic value of MDCT-CA in DM patients. The main finding of our study is that MDCT-CA is able to provide long-term prognostic information in diabetic patients with suspected CAD and may predict hard cardiac events. However, we found that diabetic patients without evidence of CAD at MDCT-CA evaluation had an excellent prognosis at 62 months follow-up, without cardiac events recorded.

Specifically, detection of obstructive CAD at MDCT-CA was a strong predictor of cardiac events in univariate analysis (HR 3.41 and 7.93 for hard and all events, respectively). Kaplan-Meier survival curves confirmed this finding, showing an event-free survival of 60% for hard events and 16% for all events in these patients. Moreover, MDCT-CA allowed a strong prognostic grading based on the classification in 1-VD, 2-VD, 3-VD and LMCA disease. In both univariate and multivariate analysis, HR for hard and all events were significantly increased in patients with 3-vessel CAD and LMCA disease. Accordingly, survival curves free of hard events were progressively reduced, from 73% with 1-VD to 25% with LMCA disease. Another major result of this study with important clinical implications is that found in DM patients with non-obstructive CAD at MDCT-CA. In these patients, all stress tests are usually negative because rarely this type of lesions triggers myocardial ischemia. Although traditional non-invasive testing in this subset of patients suggests a prognosis similar to that found in patients with normal coronary arteries, our data indicate a worse long-term outcome instead. Indeed, Kaplan-Meier survival curves showed an event-free survival of 78% for hard events and of 56% for all events in patients with non-obstructive CAD at 62-month follow-up. Thus, these patients have a cardiac event probability intermediate between that found in patients with normal coronary arteries and obstructive CAD. This finding requires some comments. First of all, a

recent study of van Velzen et al. demonstrated that MDCT-CA has an accuracy of 100% in comparison with intravascular ultrasound (IVUS) in the detection of non-obstructive CAD and coronary atherosclerosis (defined on IVUS as a plaque burden of ≥40% cross-sectional area) (28). On the other hand, previous studies indicated that also plaque composition may be a predictor of adverse events, demonstrated that vulnerable plaques may occur across the full spectrum stenosis severity, suggesting that also non-obstructive lesions may contribute to coronary events (29) and showed that lipid core size and minimal cap thickness, two major determinants of plaque vulnerability, are not related to absolute plaque size or degree of stenosis (30). In our study, the number of non-calcified plaques had HR by univariate and multivariate analysis for hard events higher than the number of calcified and mixed plaques. Because non-obstructive plaques are more frequent than obstructive plaques, it is conceivable that coronary occlusion and myocardial infarction are due more frequently to moderate stenosis (31). Another possible explanation of the high prognostic value of non-obstructive CAD in our study may reside in the long-term follow-up. In fact, we cannot rule out that some moderate stenosis at the time of MDCT-CA examination could have become obstructive over time. Nevertheless, the early identification of non-obstructive CAD with MDCT-CA in diabetics is clinically important because may lead to a more aggressive strategy of cardiovascular risk factor control and modification of clinical follow-up, accordingly with ADA expert panel that recommended a more aggressive risk factor modification and medical surveillance in high cardiac risk diabetic patients (22). Moreover, MDCT-CA also showed the ability to stratify the prognosis of diabetics by means of the atherosclerotic burden evaluation. Indeed, in 2010, Hadamitzky et al. demonstrated that atherosclerotic burden assessed with MDCT-CA was able to stratify cardiac events in diabetics who were followed for 33 months (12). Our study confirms that MDCT-CA is able to predict events on the basis of atherosclerotic burden evaluated with coronary artery plaque scores. Indeed, event-free survival significantly decreased at 62-month follow-up from

67% for SSS ≤5 to 11% for SSS >5 considering revascularizations and from 88% for SSS ≤5 to 54% for SSS >5 excluding revascularizations. Another remarkable finding is that atherosclerotic burden maintains similar prognostic value and event-free survival rate using SIS.

Certainly, one of the main finding of our study regards the clinical scenario represented by diabetic patients with normal coronary arteries at MDCT-CA evaluation. Indeed, in agreement with a previous study that enrolled a smaller number of less homogeneous DM patients with shorter follow-up (13), our study confirmed that the absence of CAD at MDCT-CA (found in 90 patients in our study) is associated with an event-free survival of 100% for both hard and all cardiac events at 62-month follow-up. The excellent outcome in diabetic patients with completely absent CAD is clinically relevant, because it suggests that MDCT-CA, in contrast to other imaging modalities, can help to identify the truly low-risk for cardiovascular events diabetic patients. Indeed, although nuclear stress imaging and stress echocardiography, the 2 most widely used stress imaging test in the clinical practice, demonstrated a good prognostic value in the general population with suspected CAD, as shown by very large meta-analysis of 31 studies and 69.655 patients and 13 studies and 32.739 patients, respectively (32,33), studies dedicated to diabetics not confirmed these results. In fact, 7 studies with >100 patients each specifically addressed the prognostic value of SPECT imaging in diabetics, although confirmed the higher events rate in the presence of an abnormal scan compared with a normal scan, similar to nondiabetic population, demonstrated that the event rate in the presence of a normal scan also appeared higher in comparison with the general population (34). Similarly, five studies >100 patients that studied the prognostic value of stress echocardiography in diabetics using either exercise or pharmacological stress, although confirmed the higher events rate in the presence of an abnormal study compared with a normal study, similar to nondiabetic population, shown that the event rate in the presence of a normal echocardiography also appeared higher in comparison with the general population (35). Specifically, Kamalesh et al., who performed

a follow-up study in 233 patients (144 diabetics) with a negative stress echocardiography, demonstrated that DM patients had a significantly higher incidence of nonfatal infarctions and a higher annual hard event rate in comparison with nondiabetics (36). This issue has been confirmed by Elhendy et al. that evaluated 563 DM patients with normal exercise echocardiography with follow-up of up to 5 years, showing that although the 1-year event rate was 0%, there was a gradual increase up to 7.6% at 5-year follow-up (37). On the contrary, in our study, we recorded an event rate of 0% in patients with normal coronary arteries at 5-years follow-up (mean 62±9 months, up to 72 months). Therefore, this diagnostic modality can be used to reassure regarding their outcome diabetic patients with suspected CAD, with a warranty period of 5 years in the presence of a MDCT-CA completely normal.

Study limitations.

In interpreting these data, some limitations should be considered. First, this is a relatively small, single-center study evaluating mainly caucasian patients and its results may not necessarily reflect the patient population of other centers or countries. Second, we recognize that incomplete follow-up may result in underreporting of cardiac events. However, the percentage of patients with complete follow-up was remarkably high (98%). Third, MDCT-CA allowed the identification of patients with obstructive CAD, likely resulting in an increased revascularization rate, which constituted a large proportion of the composite all cardiac event end point. However, in our study MDCT-CA was performed in addition to the standard diagnostic work-up. Moreover, all decisions regarding revascularization were based on symptoms, presence of ischemia on non-invasive testing and ICA results and patients with early elective revascularizations were excluded from the survival analysis. Finally, the presence of obstructive CAD at MDCT-CA was strongly associated with hard cardiac events not including revascularization procedures.

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Table 1. Clinical characteristics of the study population and patient clinical outcome

Characteristics	All patients (n=390)	Patients with events (n=225)	Patients without events (n=165)	Patients with hard events (n=108)	Patients without hard events (n=282)
Clinical Characteristics					
Age, mean±SD	65±11	67±9	64±13*	65±9	66±12
Male gender, n (%)	270 (69)	171 (76%)	99 (60%) *	84 (78%)	186 (66%) †
BMI, mean±SD	27.2±5.2	28.1±5.6	26.7±5	27.7±5.5	27.1±4.8
Hypercholesterolemia n (%)	210 (54)	126 (56)	84 (51)	57 (53)	153 (54)
Hypertension, n (%)	300 (77)	183 (81)	117 (71) *	96 (89)	204 (72) †
Family history of CAD, n (%)	138 (35)	81 (36)	57 (34)	39 (36)	99 (35)
Smoking, n (%)	96 (25)	45 (20)	51 (31)	12 (11)	84 (30)
Pre-test likelihood of CAD					
Low, n (%)	198 (51)	120 (53)	78 (47)	69 (64)	129 (46)
Moderate, n (%)	63 (16)	21 (9)	42 (25)	9 (8)	54 (19)
High, n (%)	129 (33)	84 (37)	45 (27) *	30 (28)	99 (35)
Indications for MDCT-CA					
Chest pain, n (%)	135 (35)	75 (33)	60 (36)	27 (25)	108 (38)
Risk factors, n (%)	150 (38)	81 (36)	69 (42)	36 (33)	114 (40)
Positive stress test, n (%)	105 (27)	69 (31)	36 (22)	45 (42)	60 (22) †
Medical therapy					
Ace-inhibitors, n (%)	99 (25)	54 (24)	45 (27)	18 (17)	81 (29)
Nitrates, n (%)	42 (11)	18 (8)	24 (14)	12 (11)	30 (11)
Beta-blockers, n (%)	159 (41)	87 (39)	72 (44)	48 (44)	111 (39)
Aspirin, n (%)	195 (50)	132 (59)	63 (38) *	60 (56)	135 (48)
Diuretics, n (%)	138 (35)	105 (47)	33 (20) *	57 (53)	81 (29) †
AT1-blockers, n (%)	63 (16)	51 (23)	12 (7)	42 (39)	21 (7)
Calcium channel blockers, n (%)	114 (29)	72 (32)	42 (25)	36 (33)	78 (28)
Statins, n (%)	138 (35)	87 (39)	51 (31)	51 (47)	87 (31) †

* $p < 0.05$ vs. patients with events; † $p < 0.05$ vs. patients with hard events.
ACE=Angiotensin convering enzyme; AT1=Angiotensin 1; BMI= Body mass index; CAD=Coronary artery disease; MDCT-CA=Multidetector computed tomography coronary angiography.

Table 2. MDCT results and patient clinical outcome

MDCT characteristics	All patients (n=390)	Patients with events (n=225)	Patients without events (n=165)	Patients with hard events (n=108)	Patients without hard events (n=282)
No coronary disease, n (%)	90 (23)	0	90 (54) *	0	90 (32) †
Non-obstructive CAD, n (%)	69 (18)	33 (15)	36 (22)	21 (19)	48 (17)
Obstructive CAD, n (%)	231 (59)	192 (85)	39 (24) *	87 (81)	144 (51) †
≥50% 1-vessel CAD , n (%)	87 (22)	69 (31)	18 (11) *	24 (22)	63 (22)
≥50% 2-vessel CAD , n (%)	60 (15)	54 (24)	6 (4) *	21 (19)	39 (14)
≥50% 3-vessel CAD, n (%)	72 (18)	60 (27)	12 (7) *	36 (33)	36 (13) †
≥50% LMCA CAD, n (%)	12 (3)	12 (5)	0 *	9 (8)	3 (1) †
SIS, median (25^{th}-75^{th} percentile)	1 (0-4)	3 (2-6)	0 (0-4) *	4 (3-7)	1 (0-5) †
SSS, median (25^{th}-75^{th} percentile)	1 (0-7)	6 (3-10)	0 (0-5) *	7 (4-13)	1 (1-6) †
N of segments with OP, median (25^{th}-75^{th} perc.)	0 (0-2)	2 (1-3)	0 (0-0) *	2 (1-3)	0 (0-1) †
N of segments with NP, median (25^{th}-75^{th} perc.)	0 (0-1)	1 (0-2)	0 (0-0)	1 (0-2)	0 (0-1)
N of segments with MP, median (25^{th}-75^{th} perc.)	0 (0-1)	1 (0-2)	0 (0-0)	1 (0-2)	0 (0-1)
N of segments with CP, median (25^{th}-75^{th} perc.)	0 (0-1)	1 (0-3)	0 (0-0)	1 (0-3)	0 (0-1)

* $p < 0.05$ vs. patients with events; † $p < 0.05$ vs. patients with hard events.
CAD= Coronary artery disease; CP=calcified plaques; MP=mixed plaques;
NP= noncalcified plaques; OP=obstructive plaques.

Table 3. Clinical characteristics and univariate predictors of events

Characteristics	HR (95% CI), for all cardiac events	P Value	HR (95% CI), for hard cardiac events	P Value
Clinical Characteristics				
Age	1.01 (0.99-1.03)	0.08	0.99 (0.97-1.01)	0.32
Male gender	1.71 (1.24-2.35)	0.001	1.61 (1.02-2.54)	0.04
BMI	1.02 (1.01-1.03)	0.23	1.05 (1.01-1.08)	0.12
Hyphercholesterolemia	1.11 (0.85-1.44)	0.45	0.93 (0.64-1.36)	0.71
Hypertension	1.41 (1.01-1.97)	0.04	2.76 (0.97-7.81)	0.05
Family history of CAD	0.67 (0.35-1.18)	0.15	0.89 (0.59-1.32)	0.57
Smoking	0.73 (0.53-1.02)	0.06	0.37 (0.2-0.66)	0.001
Pre-test likelihood of CAD				
Moderate	0.51 (0.32-0.82)	0.30	0.47 (0.23-0.95)	0.23
High	1.29 (0.98-1.72)	0.005	0.73 (0.47-1.13)	0.42
Indications for MDCT				
Chest pain	0.88 (0.67-1.15)	0.10	1.37 (0.93-2.01)	0.10
Risk factors	1.12 (0.71-1.78)	0.61	0.69 (0.47-1.02)	0.06
Positive stress test	0.96 (0.56-1.66)	0.89	1.22 (0.57-2.63)	0.60
Medical therapy				
Ace-inhibitors	1.02 (0.76-1.37)	0.95	0.60 (0.38-0.95)	0.03
Nitrates	1.08 (0.79-1.46)	0.61	0.88 (0.48-1.62)	0.69
Beta-blockers	2.15 (1.61-2.9)	<0.0001	2.35 (1.48-3.71)	0.0002
Aspirin	3.46 (2.20-5.43)	<0.0001	2.98 (1.51-5.90)	0.0018
Diuretics	1.19 (0.92-1.55)	0.18	1.86 (1.25-2.77)	0.002
AT1-blockers	1.08 (0.78-1.51)	0.63	1.24 (0.78-1.96)	0.36
Calcium channel blockers	1.05 (0.79-1.38)	0.71	1.23 (0.82-1.85)	0.29
Statins	1.73 (1.32-2.26)	<0.0001	2.43 (1.61-3.67)	<0.0001

ACE= Angiotensin converting enzyme; AT1= Angiotensin 1;
BMI= Body mass index; CAD= Coronary artery disease;
MDCT-CA= Multidetector computed tomography coronary angiography.

Table 4. MDCT-CA results and univariate predictors of events

MDCT-CA results	HR (95% CI), for all cardiac events	P Value	HR (95% CI), for hard cardiac events	P Value
Obstructive CAD	7.93 (4.59-13.68)	0.0001	3.41 (1.78-6.72)	0.001
≥50% 1-vessel CAD	8.94 (5.80-13.79)	<0.0001	2.80 (1.52-5.17)	0.001
≥50% 2-vessel CAD	9.1 (5.83-14.21)	<0.0001	4.36 (2.31-8.25)	<0.0001
≥50% 3-vessel CAD	11.62 (7.34-18.41)	<0.0001	5.79 (3.27-10.25)	<0.0001
≥50% LMA CAD	22.83 (11.49-45.35)	<0.0001	10.57 (4,27-23.62)	<0.0001
SIS >5	2.40 (1.79-3.23)	<0.0001	2.26 (1.50-3.41)	<0.0001
SSS >5	5.31 (3.98-7.08)	<0.0001	3.92 (2.59-5.91)	<0.0001
N of segments with obstructive plaques	1.27 (1.21-1.33)	<0.0001	1.21 (1.13-1.29)	<0.0001
N of segments with noncalcified plaques	1.36 (1.25-1.48)	<0.0001	1.43 (1.28-1.60)	<0.0001
N of segments with mixed plaques	1.46 (1.35-1.58)	<0.0001	1.31 (1.17-1.47)	<0.0001
N of segments with calcified plaques	1.23 (1.15-1.29)	<0.0001	1.19 (1.09-1.29)	<0.0001

CAD= Coronary artery disease; LMCA= Left main coronary artery;
MDCT-CA= Multi detector computed tomography coronary angiography;
SIS= Segment-involvement score; SSS= Segment-stenosis score.

Table 5. Multivariate significant predictors of events, corrected for baseline variables.

MDCT-CA results	HR (95% CI), for all cardiac event	P Value	HR (95% CI), for hard cardiac event	P palue
≥50% 1-vessel CAD	3.94 (1.49-10.45)	0.006	1.91 (0.84-4.3)	0.12
≥50% 2-vessel CAD	4.82 (2.17-10.73)	0.0001	2.61 (0.76-8.93)	0.12
≥50% 3-vessel CAD	7.93 (4.56-13.79)	<0.0001	5.21 (1.33-20.33)	0.01
≥50% LMA CAD	7.92 (2.62-23.88)	0.005	5.35 (1.39-20.52)	0.01
N of segments with noncalcified plaques	1.07 (0.93-1.23)	0.34	1.84 (1.49-2.27)	<0.0001
N of segments with mixed plaques	1.40 (1.22-1.61)	<0.0001	1.39 (1.12-1.72)	0.003
N of segments with calcified plaques	1.18 (1.04-1.35)	0.01	1.62 (1.33-1.96)	<0.0001

CAD= Coronary artery disease; LMCA= Left main coronary artery;
MDCT-CA= Multidetector computed tomography coronary angiography.

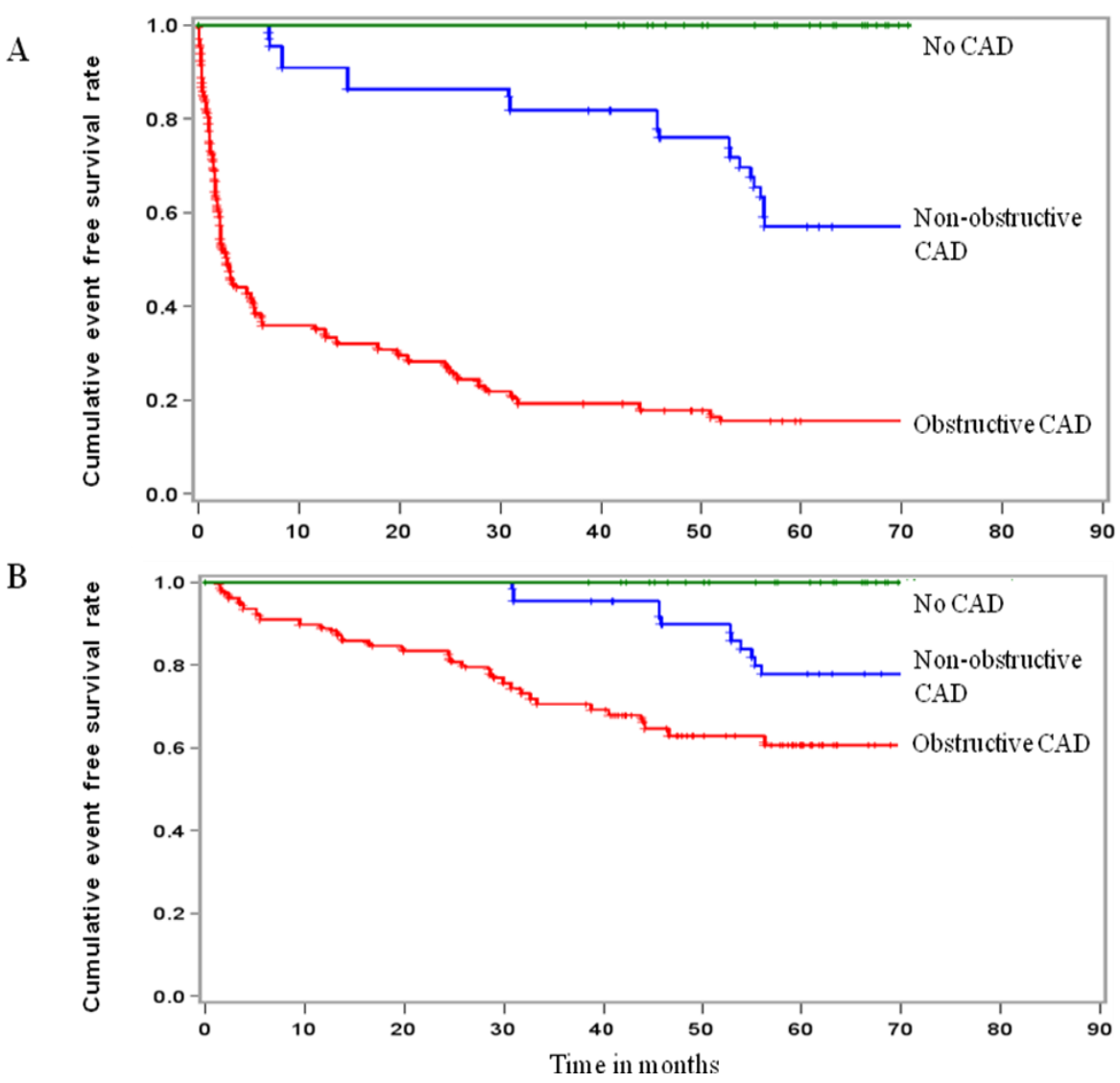

Figure 1. Kaplan-Meier curves for all events (Figure 1A) and for hard events (Figure 1B) in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD.

CAD=coronary artery disease.

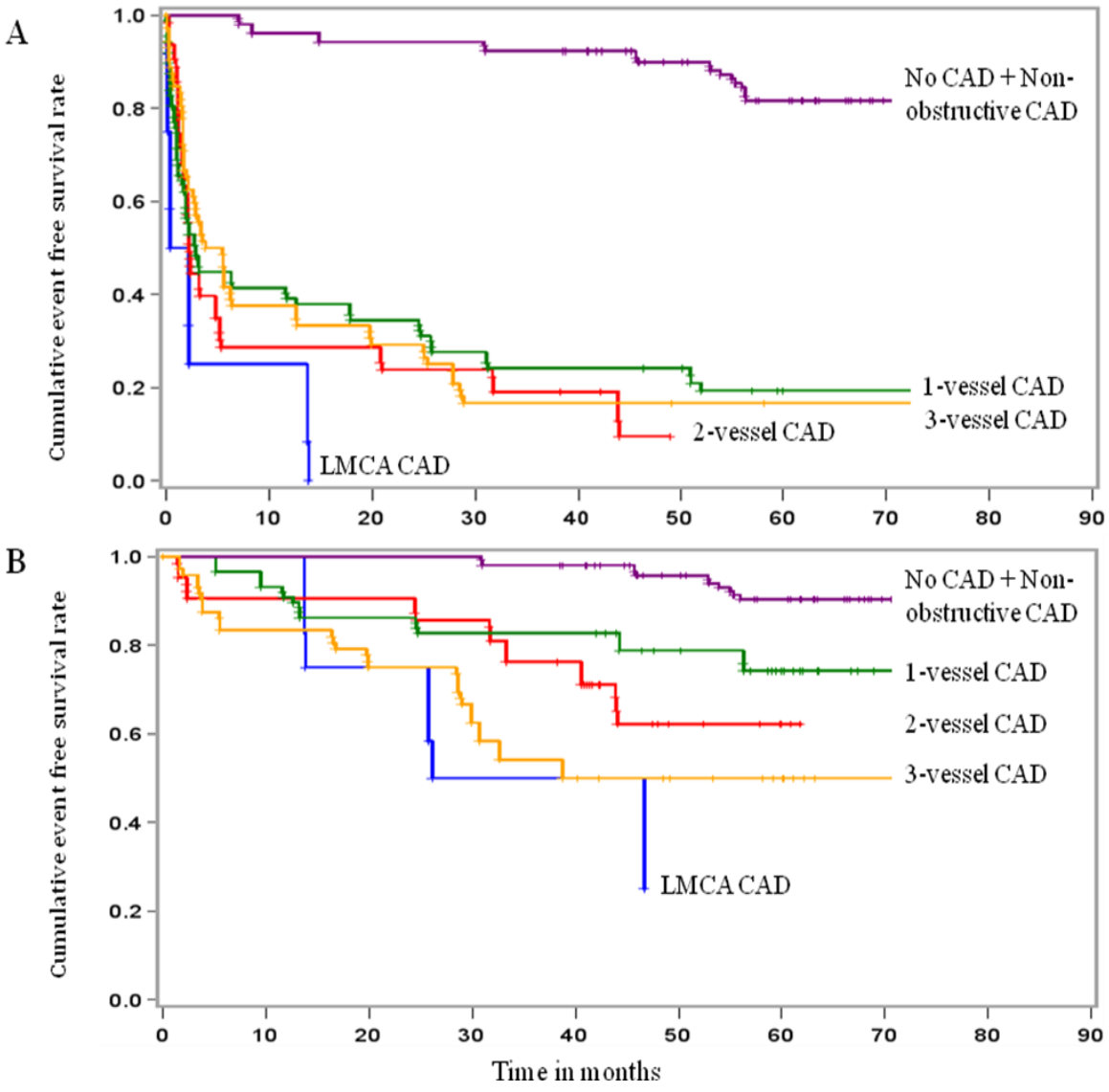

Figure 2. Kaplan-Meier curves for all events (Figure 2A) and for hard events (Figure 2B) in patients with normal coronary arteries and non-obstructive CAD, ≥50% 1-vessel, ≥50% 2-vessel, ≥50% 3-vessel CAD and ≥50% LMCA CAD.

CAD=coronary artery disease; LMCA=left main coronary artery.

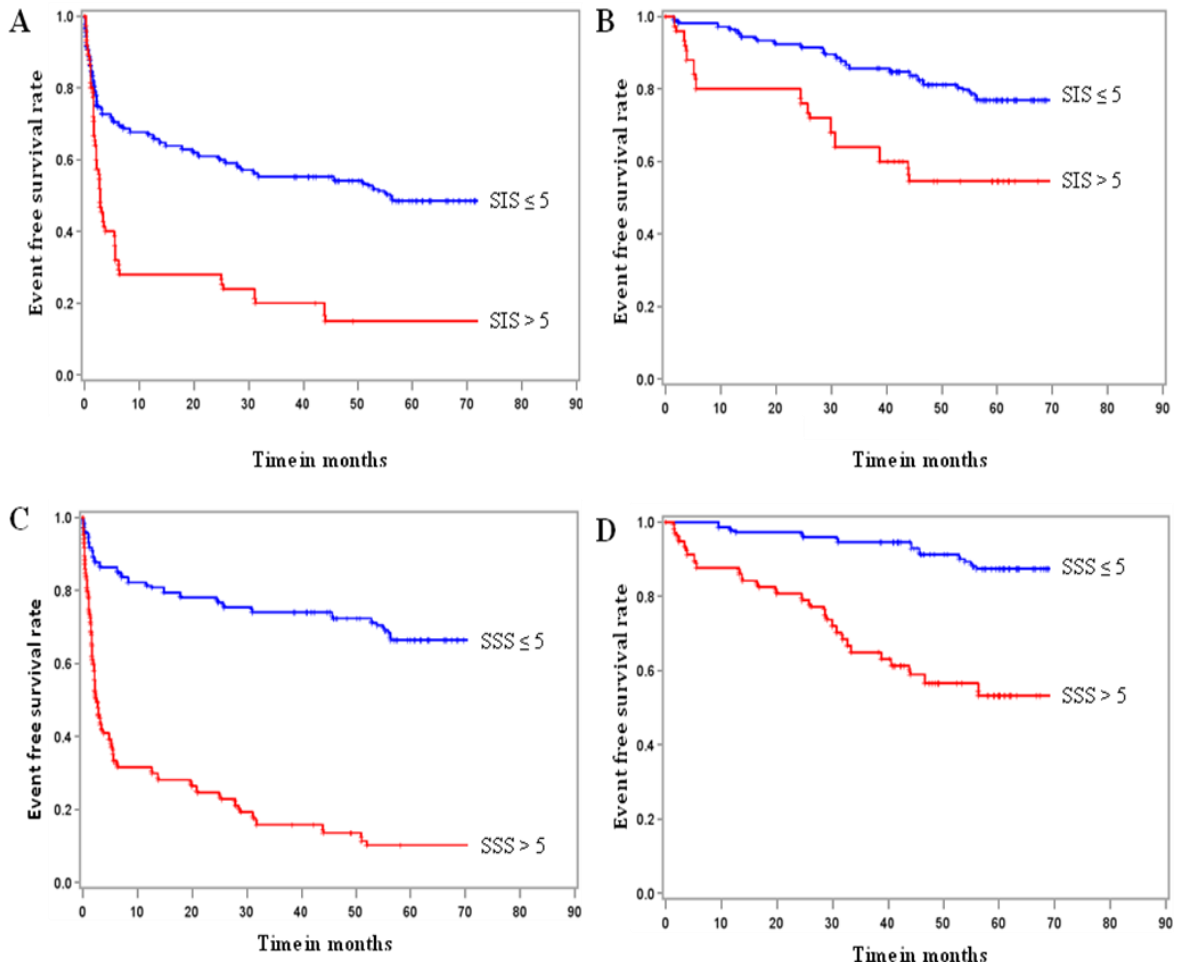

Figure 3. Kaplan-Meier curves for all events (Figure 3A) and for hard events (Figure 3B) in patients with SIS ≤5 and SIS >5. Kaplan-Meier curves for all events (Figure 3C) and for hard events (Figure 3D) in patients with SSS ≤5 and SSS >5.

SIS=segment involvement score; SSS=segment stenosis score.