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A Long-Term Prognostic Value of Coronary CT Angiography in Suspected Coronary Artery Disease

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OBJECTIVES The aim of this study was to assess the long-term prognostic role of multidetector computed tomography coronary angiography (CTA) in patients with suspected coronary artery disease (CAD).

BACKGROUND Use of CTA is increasing in patients with suspected CAD. Although there is a large body of data supporting the prognostic role of CTA for major adverse cardiac events in the intermediate term, its long-term prognostic role in patients with suspected CAD is not well studied.

METHODS Between February 2005 and March 2008, 1,304 consecutive patients were prospectively studied with CTA for detecting the presence and assessing extent of CAD (disease extension and coronary plaque scores). Patients were classified according to the presence of normal coronaries and nonobstructive (<50%) and obstructive (>50%) coronary lesions. The composite rates of hard cardiac events (cardiac deaths and nonfatal myocardial infarctions) and all cardiac events (including late revascularization) were the endpoints of the study.

RESULTS Seventy patients were excluded because their CTA data were uninterpretable. Of the remaining 1,234 patients, clinical follow-up (mean 52 ± 22 months) was obtained for 1,196 (97%). A total of 475 events were recorded, with 136 hard events (18 cardiac deaths and 118 nonfatal myocardial infarctions) and 123 late revascularizations. A total of 216 patients with early elective revascularizations were excluded from the survival analysis. Significant independent predictors of events in multivariate analysis were multivessel disease and left main CAD. Cumulative event-free survival was 100% for hard and all events in patients with normal coronary arteries, 88% for hard events and 72% for all events in patients with nonobstructive CAD, and 54% for hard events and 31% for all events in patients with obstructive CAD. Multivessel CAD was associated with a higher rate of hard cardiac events.

CONCLUSIONS CTA provides prognostic information in patients with suspected CAD and unknown cardiac disease, showing excellent long-term prognosis when there is no evidence of atherosclerosis and allowing risk stratification when CAD is present. (J Am Coll Cardiol Img 2012;5: 690–701) © 2012 by the American College of Cardiology Foundation

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Coronary artery disease (CAD) is the leading cause of morbidity and mortality (1). Although there is a large body of data supporting the prognostic role of multidetector computed tomography coronary angiography (CTA) for major adverse cardiac events in the intermediate term, its long-term prognostic role in patients with suspected CAD is not well studied. However, data from electron beam computed tomography (CT) suggest that CT angiography provides an incremental value in long-term prediction of all-cause mortality (2–8). More recently, evidence that CAD severity at CTA evaluation is a predictor of major adverse cardiac events was provided by a single study (9). The main limitations of these studies were the short follow-up (on average 1 year for most of them and no longer than 2 years for all) and the inclusion of heterogeneous patients undergoing CTA because of known or suspected CAD (5,6) or for the workup of other cardiac diseases (3,4,7–9). Thus, the aim of the present study was the evaluation of the long-term prognostic role of CTA in a large group of patients without known cardiac disease and in whom CAD was suspected.

MATERIALS AND METHODS

Patients and study protocol. The study population consisted of 3,421 consecutive patients who presented to our outpatient clinic or were admitted to our hospital for cardiac evaluation (exercise electrocardiogram [ECG], stress echocardiography, or invasive coronary angiography [ICA]) between February 2005 and March 2008 because of suspected CAD (elevated risk profile, new-onset chest pain, abnormal stress test). In all, CTA was performed in addition to standard clinical workup. A total of 1,777 patients were excluded because of known CAD (n = 1,242 [586 with previous myocardial infarction and 656 with previous coronary revascularization]) or other known cardiovascular diseases (n = 535 [181 for heart failure, 45 for congenital heart disease, 120 for significant valvular disease, 97 for cardiomyopathy, 21 for endocarditis, and 71 for ascending aorta aneurysm]). Other exclusion criteria were contraindications to contrast agents (n = 55), impaired renal function (creatinine clearance <60 ml/min) (n = 100), inability to sustain a 15-s breath hold (n = 40), and cardiac arrhythmias (n = 145). Thus, the analytical study population consisted of 1,304 patients. The study was approved by our institution's scientific and ethical committees, and all patients gave written informed consent. A structured interview was conducted and clinical history acquired. The following cardiac risk factors were assessed before CTA: diabetes mellitus (glucose level of ≥7 mmol/l or the need for insulin or oral hypoglycemic agents) (10), hypercholesterolemia (total cholesterol level ≥5 mmol/l or treatment with lipid-lowering drugs) (11), hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medications) (12), positive family history of CAD (presence of CAD in first-degree relatives younger than 55 years [male] or 65 years [female]) (13), and current smoking. Pre-test probability of CAD was determined using the Diamond and Forrester method (14). The Framingham risk score was calculated as previously described (15).

Patient preparation, scan protocol, and image reconstruction. Metoprolol was intravenously administered before CTA with a titration dose up to 20 mg in patients with heart rate >65 beats/min. In all patients, CTA was performed using a 64-slice scanner (64 × 0.625 mm collimation, 330 ms gantry rotation time, VCT, GE Medical Systems, Milwaukee, Wisconsin). 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 Imaging, Milan, Italy) was administered intravenously at 5 ml/s, followed by 50 ml of saline injected at the same infusion rate. The scan was initiated according to the bolus-tracking technique.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CTA = computed tomography coronary angiography
ICA = invasive coronary angiography
LMCA = left main coronary artery
SIS = segment-involvement score
SSS = segment-stenosis score
VD = vessel disease

The coronary calcium score was assessed with dedicated software (CaScore Package, GE Healthcare, Milwaukee, Wisconsin), and Agatston score was recorded. Image datasets were analyzed using volume rendering and multiplanar reconstruction on post-processing workstations (CardioQ3 package, Advantage Workstation version 4.2, GE Healthcare).

CTA data analysis. All CTA examinations were evaluated within 2 weeks by 2 expert readers unaware of patient clinical status. 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 American Heart Association classification (16). 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 the 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 (3). One coronary plaque was assigned per coronary segment even in the presence of multiple plaques. Plaque type was determined using the following classification: 1) noncalcific (plaques with lower density compared with the contrast-enhanced vessel lumen); 2) calcific (high-density plaques); and 3) mixed (noncalcific and calcific components within a single plaque). If a segment contained calcific and noncalcific plaques, we classified the plaque as calcific. The number of segments with noncalcific, calcific, and mixed plaques was recorded. Vessel segments were graded on the basis of visually estimated obstruction of coronary lumen as normal, mildly stenotic (<50%), moderately stenotic (50% to 69%), or severely stenotic (≥70%). Moderate and severe stenoses were considered as obstructive lesions. The number of segments with any obstructive plaque was also recorded. Patients were divided into 3 groups: normal (no coronary plaques), nonobstructive CAD (mild lesions), and obstructive CAD (obstructive lesions). Moreover, coronary arteries were evaluated using 2 methods: presence of obstructive lesions in major epicardial vessels and coronary plaque scores (3). To this end, CTA scans were first analyzed, and then the number of major epicardial vessels exhibiting moderate or severe plaques 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 cases of moderate or severe obstruction of the left main coronary artery (LMCA), patients were assigned to the obstructive CAD group even if they had other diseased vessels.

Table 1. Clinical Characteristics of the Study Population and Patient Clinical Outcome

	All Patients (N = 1,196)	Patients With Events (n = 412)	Patients Without Events (n = 784)	Patients With Hard Events (n = 125)	Patients Without Hard Events (n = 1,071)
Clinical characteristics					
Age, yrs	62 ± 11	65 ± 10	61 ± 11*	66 ± 10	62 ± 11‡
Male	782 (62)	318 (76)	467 (59)*	92 (75)	690 (64)§
BMI	27.2 ± 5.2	28.1 ± 5.6	26.7 ± 5	27.7 ± 5.5	27.1 ± 4.8
Diabetes	131 (11)	67 (17)	64 (8)*	28 (23)	103 (9)‡
Hypercholesterolemia	540 (45)	226 (55)	314 (40)*	70 (56)	470 (44)§
Hypertension	703 (59)	282 (68)	421 (54)*	91 (73)	612 (57)‡
Family history of CAD	393 (33)	143 (35)	250 (32)	42 (34)	351 (33)
Smoking	343 (29)	129 (32)	214 (27)	35 (29)	308 (29)
Pre-test likelihood of CAD					
Low	646 (54)	213 (52)	433 (55)	59 (47)	587 (55)
Moderate	245 (20)	49 (13)	196 (25)*	16 (13)	229 (21)§
High	305 (26)	144 (35)	161 (20)*	48 (40)	257 (24)‡
Indications for CTA					
Chest pain	514 (43)	171 (42)	343 (44)	63 (51)	451 (42)
Risk factors	339 (28)	77 (19)	262 (33)*	25 (20)	314 (29)§
Positive stress test	343 (29)	158 (39)	185 (23)*	35 (29)	308 (29)
Medical therapy					
ACE inhibitors	210 (17)	84 (21)	126 (16)	20 (17)	190 (18)
Nitrates	71 (6)	32 (8)	39 (5)†	10 (9)	61 (6)
Beta-blockers	282 (23)	116 (29)	166 (21)†	27 (22)	255 (24)
Aspirin	298 (25)	150 (39)	148 (18)*	34 (28)	264 (25)
Diuretics	211 (18)	92 (23)	119 (15)†	32 (26)	179 (17)§
AT1-blockers	116 (10)	47 (12)	69 (8)	13 (11)	103 (10)
Calcium-channel blockers	198 (16)	85 (21)	113 (14)†	25 (21)	173 (16)
Statins	311 (26)	162 (40)	149 (19)*	45 (36)	266 (25)§

Values are mean ± SD or n (%). *$p < 0.0001$ versus patients with events. †$p < 0.05$ versus patients with events. ‡$p < 0.0001$ versus patients with hard events. §$p < 0.05$ versus patients with hard events.

ACE = angiotensin-converting enzyme; AT1 = angiotensin 1; BMI = body mass index; CAD = coronary artery disease; CTA = computed tomography coronary angiography.

Second, we analyzed the extent of atherosclerotic burden using 2 coronary artery plaque scores (3): 1) the segment-involvement score (SIS) (i.e., the number of segments [minimum 0; maximum 16] with at least 1 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 having severe plaque (i.e., score from 0 to 3) based on the extent of obstruction of the coronary lumen diameter. The SSS of the 16 coronary segments was summed to yield a total score ranging from 0 to 48. For both scores, a cutoff of 5 was used to differentiate patients with low or high probability of cardiac events (3).

Follow-up. Follow-up, either clinical visit or telephone interview, was performed by trained researchers blinded to the CTA data. Hospital records were screened for clinical events to confirm the obtained information. Outcome measures were a composite of hard cardiac events (cardiac deaths and nonfatal myocardial infarctions) and all cardiac events (cardiac deaths, nonfatal myocardial infarctions, and revascularizations). All deaths were reviewed and classified as cardiac (death caused by acute myocardial infarction, ventricular arrhythmia, or refractory heart failure) or noncardiac. All revascularizations were classified as early (patients underwent an early elective revascularization within 6 months after CTA) or late. Only late revascularizations were considered cardiac events, whereas patients with elective early revascularization were excluded from the analysis. The diagnosis of nonfatal myocardial infarction was based on the presence of typical chest pain, elevated cardiac enzymes, and typical ECG changes (17). Cardiac enzymes used for the diagnosis were troponin I and mass creatine kinase-myocardial band. Nonfatal myocardial infarction associated with revascularization procedures was not included in the analysis.

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, Illinois). 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 CTA 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 (25th to 75th percentile range) and compared using the nonparametric Mann-Whitney test. To identify the association between CTA variables and outcomes, Cox regression analysis was used. First, univariate analysis of clinical characteristics and CTA variables was performed to identify potential

Table 2. CTA Results and Patient Clinical Outcome

	All Patients (N = 1,196)	Patients With Events (n = 412)	Patients Without Events (n = 784)	Patients With Hard Events (n = 125)	Patients Without Hard Events (n = 1,071)
Agatston score	151 (0–380)	274 (112–560)	88 (0–305)*	278 (115–595)	115 (22–378)†
No coronary disease	503 (42)	0	503 (64)*	0	503 (47)†
Nonobstructive CAD	241 (20)	55 (13)	186 (24)*	23 (18)	218 (20)
Obstructive CAD	452 (38)	357 (87)	95 (12)*	102 (82)	350 (33)†
≥50% 1-vessel CAD	202 (17)	136 (33)	66 (7)*	33 (27)	169 (16)‡
≥50% 2-vessel CAD	124 (10)	111 (27)	13 (2)*	30 (24)	94 (9)†
≥50% 3-vessel CAD	103 (9)	90 (22)	13 (2)*	30 (24)	73 (7)†
≥50% LMCA-CAD	23 (2)	20 (5)	3 (0.4)*	9 (7)	14 (1)†
≥70% 1-vessel CAD	153 (13)	131 (32)	22 (3)*	34 (27)	119 (11)†
≥70% 2-vessel CAD	80 (7)	72 (17)	8 (13)*	20 (16)	60 (6)†
≥70% 3-vessel CAD	58 (5)	51 (12)	7 (1)*	16 (13)	42 (4)†
≥70% LMCA-CAD	4 (0.3)	2 (0.5)	2 (0.2)	1 (1)	3 (0.2)
SIS	1 (0–4)	3 (2–6)	0 (0–4)*	4 (3–7)	1 (0–5)†
SSS	1 (0–7)	6 (3–10)	0 (0–5)*	7 (4–13)	1 (1–6)†
No. of segments with plaques	1 (0–4)	3 (2–6)	0 (0–4)*	4 (3–7)	1 (0–5)†
No. of segments with obstructive plaques	0 (0–2)	2 (1–3)	0 (0–0)*	2 (1–3)	0 (0–1)†
No. of segments with noncalcified plaques	0 (0–1)	1 (0–2)	0 (0–0)*	1 (0–2)	0 (0–1)†
No. of segments with mixed plaques	0 (0–1)	1 (0–2)	0 (0–0)*	1 (0–2)	0 (0–1)†
No. of segments with calcified plaques	0 (0–1)	1 (0–3)	0 (0–0)*	1 (0–3)	0 (0–1)†

Values are median (25th to 75th percentile) or n (%). *$p < 0.0001$ versus patients with events. †$p < 0.0001$ versus patients with hard events. ‡$p < 0.05$ versus patients with hard events. LMCA = left main coronary artery; SIS = segment-involvement score; SSS = segment-stenosis score; other abbreviations as in Table 1.

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predictors. Hazard ratios (HRs) were calculated with 95% confidence intervals as an estimate of the risk associated with a particular variable. To determine independent predictors of the composite endpoints, multivariate analysis of variables with $p \leq 0.05$ in univariate analysis was performed, adjusted for variables with $p \leq 0.05$ in univariate analysis, including the Framingham risk score. To avoid overfitting and multicollinearity issues, we developed 4 different models, for both all and hard events. The first model was adjusted for coronary artery classification in 1-vessel disease (VD), 2-VD, 3-VD, and LMCA-CAD ≥50% and for the Framingham risk score; the second model was adjusted for coronary artery classification in 1-VD, 2-VD, and 3-VD plus LMCA-CAD ≥70% and for the Framingham risk score. The third model was adjusted for coronary artery classification in 1-VD, 2-VD, 3-VD, and LMCA-CAD ≥50% and for the clinical baseline characteristics. The fourth model was adjusted for coronary artery classification in 1-VD, 2-VD, and 3-VD plus LMCA-CAD ≥70% and for the clinical baseline characteristics. Cumulative event-free survival rates as a function over time were obtained by the Kaplan-Meier method. Hard and all cardiac event-free survival curves were compared using the log-rank test. Annual event rates were calculated by dividing the Kaplan-Meier event rates by mean number of years of follow-up.

RESULTS

Patient characteristics. Of the 1,304 patients prospectively enrolled, 70 were excluded because the CTA images were uninterpretable. Of the remaining 1,234 patients, 38 were lost to follow-up and 1,196 (97%) had a complete follow-up (mean 52 ± 22 months, up to 76 months). Apart from being older and more hypertensive, patients lost to follow-up had no significant differences in clinical characteristics and CTA results. A total of 475

Table 3. Clinical Characteristics and Univariate Predictors of Events

	HR (95% CI) for All Cardiac Events	p Value	HR (95% CI) for Hard Cardiac Events	p Value
Clinical characteristics				
Age	1.04 (1.03–1.06)	<0.0001	1.04 (1.02–1.05)	<0.0001
Male	1.76 (1.28–2.42)	0.0005	1.63 (1.08–2.44)	0.02
BMI	1.03 (1.01–1.04)	0.14	1.05 (1.03–1.07)	0.09
Diabetes	2.77 (1.94–3.95)	<0.0001	2.68 (1.76–4.07)	<0.0001
Hypercholesterolemia	1.97 (1.46–2.65)	<0.0001	1.76 (1.22–2.53)	0.002
Hypertension	1.99 (1.45–2.72)	<0.0001	2.12 (1.41–3.19)	0.0003
Family history of CAD	0.99 (0.73–1.35)	0.96	0.99 (0.68–1.43)	0.98
Smoking	1.05 (0.76–1.44)	0.79	1.00 (0.68–1.48)	0.98
Framingham risk score	1.04 (1.03–1.05)	<0.0001	1.05 (1.03–1.06)	<0.0001
Pre-test likelihood of CAD				
Low	0.62 (0.40–0.95)	0.38	0.79 (0.55–1.12)	0.18
Moderate	1.05 (1.04–1.06)	0.02	1.01 (1.0–1.03)	0.05
High	1.72 (1.26–2.35)	0.0007	1.84 (1.28–2.65)	0.001
Indications for CT				
Chest pain	1.29 (1.01–1.64)	0.05	1.22 (1.01–1.42)	0.04
Risk factors	1.41 (1.04–1.79)	0.005	1.40 (1.02–1.72)	0.01
Positive stress test	1.62 (1.17–2.27)	0.005	1.54 (1.11–2.13)	0.005
Medical therapy				
ACE inhibitors	1.32 (0.92–1.89)	1.32	0.90 (0.61–1.56)	0.9
Nitrates	1.90 (1.18–3.05)	0.0086	1.52 (0.82–2.82)	0.18
Beta-blockers	1.47 (1.08–2.02)	0.0157	0.92 (0.6–1.40)	0.69
Aspirin	1.98 (1.46–2.69)	<0.0001	1.17 (0.79–1.74)	0.44
Diuretics	1.72 (1.24–2.39)	0.0013	1.69 (1.13–2.53)	0.01
AT1-blockers	1.20 (1.00–1.44)	0.05	1.06 (0.75–1.49)	0.73
Calcium-channel blockers	1.52 (1.08–2.16)	0.018	1.35 (0.87–2.09)	0.17
Statins	2.39 (1.78–3.22)	<0.0001	1.73 (1.19–2.50)	0.004

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

events were recorded, including 136 hard events (18 cardiac deaths and 118 nonfatal myocardial infarctions) and 123 late revascularizations. A total of 216 patients with early elective revascularizations were excluded from the univariate, multivariate, and survival analyses. The mean interval between CTA and revascularizations was 7.3 ± 13 months (range 1 to 60 months). Indications for CTA were chest pain (43%), multiple cardiac risk factors (28%), and equivocal or abnormal stress test (29%). Mean pre-test probability of CAD was 42.5 ± 9.9%. The prevalence of male sex, diabetes, hypercholesterolemia, and hypertension was significantly higher in patients with events than in those without events (Table 1). The prevalence of high pre-test likelihood of CAD was significantly higher in patients with events than in patients without events (Table 1).

CTA results. Table 2 shows CTA results and patient outcomes. Agatston score, SIS, SSS, and number of segments with obstructive plaques were significantly higher in patients with events than in patients without events. The prevalence of obstructive CAD, 1-VD, 2-VD, and 3-VD was significantly higher in patients with events than in patients without events.

Univariate predictors of events. Univariate clinical predictors of events were male sex, diabetes, hypercholesterolemia, hypertension, and high pre-test likelihood of CAD (Table 3). Univariate CTA predictors of events are reported in Table 4. Regarding obstructive CAD, the HR was 5.49 for hard events and 4.84 for all events. The HR was also significantly increased in patients with multi-VD and LMCA-CAD (Table 4).

Multivariate predictors of events. In multivariate analysis, CTA characteristics that were significant by univariate analysis were corrected for baseline characteristics. Significant independent predictors of events in multivariate analysis were multi-VD and LMCA disease. The HRs were particularly high for ≥50% LMCA-CAD in both models (HR: 34.41 for hard events; HR: 34.46 for all events in the model adjusted for Framingham risk score; HR: 39.6 for hard events; HR: 34.66 for all events in the model adjusted for clinical baseline characteristics) (Tables 5 and 6).

Survival analysis. Kaplan-Meier survival curves are provided in Figures 1 to 4. No events occurred in patients with normal coronary arteries. On the contrary, the 52-month cumulative hard- and all-event–free survival rates were 88% and 72% in patients with nonobstructive CAD and 54% and 31% in those with obstructive CAD, respectively (log-rank p = 0.0001) (Fig. 1). The annual hard- and all-event rates were 3.2% and 8% in patients with nonobstructive CAD and 12.3% and 19.9% in those with obstructive CAD, respectively. Figure 2 shows the relationship between CAD extent, expressed as number of major epicardial vessels exhibiting ≥50% stenosis, and event-free survival rate.

Table 4. CTA Results and Univariate Predictors of Events

CTA Results	HR (95% CI) for All Cardiac Events	p Value	HR (95% CI) for Hard Cardiac Events	p Value
Agatston score	1.12 (1.00–1.15)	0.06	1.14 (1.00–1.19)	0.07
Obstructive CAD	4.84 (3.45–6.79)	<0.0001	5.49 (3.46–8.70)	<0.0001
≥50% 1-vessel CAD	3.18 (2.16–4.69)	<0.0001	3.46 (2.28–5.28)	<0.0001
≥50% 2-vessel CAD	6.89 (4.49–10.59)	<0.0001	3.58 (2.73–4.71)	<0.0001
≥50% 3-vessel CAD	7.10 (4.61–10.93)	<0.0001	4.33 (3.06–6.11)	<0.0001
≥50% LMCA-CAD,	9.97 (4.84–20.53)	<0.0001	6.02 (3.02–11.99)	<0.0001
≥70% 1-vessel CAD	3.70 (2.63–5.20)	<0.0001	3.98 (2.59–6.11)	<0.0001
≥70% 2-vessel CAD	3.89 (2.47–6.14)	<0.0001	3.96 (2.51–6.26)	<0.0001
≥70% 3-vessel CAD or ≥70% LMCA-CAD	4.90 (3.09–7.75)	<0.0001	5.51 (3.21–9.47)	<0.0001
SIS	1.49 (1.43–1.56)	<0.0001	1.38 (1.31–1.47)	<0.0001
SSS	1.16 (1.14–1.18)	<0.0001	1.13 (1.10–1.16)	<0.0001
No. of segments with plaques	1.49 (1.43–1.56)	<0.0001	1.36 (1.29–1.44)	<0.0001
No. of segments with obstructive plaques	1.50 (1.43–1.57)	<0.0001	1.38 (1.30–1.47)	<0.0001
No. of segments with noncalcified plaques	1.75 (1.61–1.91)	<0.0001	1.41 (1.28–1.54)	<0.0001
No. of segments with mixed plaques	1.80 (1.64–1.97)	<0.0001	1.48 (1.34–1.64)	<0.0001
No. of segments with calcified plaques	1.49 (1.39–1.59)	<0.0001	1.31 (1.22–1.42)	<0.0001

Abbreviations as in Tables 1, 2, and 3.

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Table 5. Multivariate Significant Predictors of Events, Corrected for Framingham Risk Score

CTA Results	HR (95% CI) for All Cardiac Events	p Value	HR (95% CI) for Hard Cardiac Events	p Value
Model 1: ≥50%				
Framingham risk score	1.01 (1.00–1.02)	0.20	1.02 (1.00–10.3)	0.03
Nitrates	0.56 (0.32–0.98)	0.04	0.60 (0.29–1.23)	0.16
Beta-blockers	1.05 (0.72–1.53)	0.81	0.62 (0.38–1.02)	0.06
Aspirin	0.63 (0.42–0.94)	0.02	0.55 (0.34–0.89)	0.02
Diuretics	1.64 (1.13–2.37)	0.01	1.83 (1.18–2.85)	0.01
AT1-blockers	1.03 (0.83–1.28)	0.81	0.93 (0.63–1.37)	0.71
Calcium-channel blockers	0.99 (0.68–1.44)	0.95	0.95 (0.60–1.52)	0.84
Statins	1.41 (1.00–1.99)	0.05	1.36 (0.90–2.05)	0.15
≥50% 1-vessel CAD	12.41 (7.92–19.43)	<0.0001	8.76 (4.94–15.53)	<0.0001
≥50% 2-vessel CAD	24.00 (14.25–40.41)	<0.0001	18.95 (10.16–35.33)	<0.0001
≥50% 3-vessel CAD	29.60 (17.74–49.40)	<0.0001	23.11 (12.77–41.83)	<0.0001
≥50% LMCA-CAD	34.46 (15.53–76.43)	<0.0001	34.41 (14.34–82.59)	<0.0001
Model 2: ≥70%				
Framingham risk score	1.02 (1.00–1.03)	0.001	1.02 (1.01–1.04)	0.0002
Nitrates	0.70 (0.40–1.22)	0.21	0.85 (0.42–1.72)	0.65
Beta-blockers	0.84 (0.57–1.23)	0.38	0.55 (0.34–0.90)	0.01
Aspirin	0.83 (0.56–1.24)	0.37	0.63 (0.39–1.04)	0.07
Diuretics	1.43 (0.49–2.06)	0.05	1.51 (0.98–2.34)	0.05
AT1-blockers	0.98 (0.78–1.21)	0.85	0.87 (0.58–1.31)	0.52
Calcium-channel blockers	0.97 (0.66–1.42)	0.89	0.88 (0.55–1.41)	0.60
Statins	1.83 (1.30–2.50)	0.0004	1.89 (1.26–2.80)	0.0002
≥70% 1-vessel CAD	6.91 (4.03–11.05)	<0.0001	5.03 (2.64–9.61)	<0.0001
≥70% 2-vessel CAD	9.17 (6.12–13.72)	<0.0001	7.29 (4.54–11.70)	<0.0001
≥70% 3-vessel CAD or ≥70% LMCA-CAD	11.92 (7.04–20.17)	<0.0001	11.04 (6.21–19.62)	<0.0001

Abbreviations as in Tables 1 and 2.

Regarding all events, cumulative event-free survival was 48% with 1-VD, 14% with 2-VD, 16% with 3-VD and 25% with LMCA disease (log-rank p = 0.0001). Excluding revascularization procedures, cumulative event-free survival was 71% with 1-VD, 33% with 2-VD, 41% with 3-VD and 19% with LMCA disease (log-rank p = 0.0001). The annual hard- and all-event rates were 7.7% and 14.9% in patients with 1-VD, 17.7% and 24.8% in those with 2-VD, 15.6% and 24.1% in those with 3-VD, and 21.5% and 21.5% in those with LMCA-CAD, respectively. The relationship between atherosclerotic burden, expressed as SIS and SSS, and event-free survival rate is reported in Figures 3 and 4. Regarding all events, cumulative event-free survival was 77% with SIS ≤5, 25% with SIS >5, 85% with SSS ≤5, and 20% with SSS >5 (log-rank p = 0.0001). Regarding hard events, cumulative event-free survival was 88% with SIS ≤5, 39% with SIS >5, 93% with SSS ≤5, and 43% with SSS >5 (log-rank p = 0.0001). The annual hard- and all-event rates were 3.2% and 6.5% in patients with SIS ≤5 and 16.4% and 20.1% in those with SIS >5, respectively. The annual hard- and all-event rates were 1.9% and 4.4% in patients with SSS ≤5 and 15.3% and 23% in those with SSS >5, respectively.

DISCUSSION

On the basis of high diagnostic performance for ruling out CAD and detecting obstructive coronary stenosis, CTA is considered a reliable method for evaluating patients with suspected CAD (2). However, data supporting a prognostic value of CTA in this subset of patients are limited. Early studies demonstrated that CTA is a predictor of all-cause mortality (3,4) and of a combined endpoint that includes all-cause mortality (5). Particularly, the study of Ostrom et al. (4) demonstrated that cardiac CTA with electron-beam tomography provides an incremental long-term prognostic value in predicting all-cause mortality in symptomatic patients (4). Moreover, small studies have suggested a role of independent predictor of cardiac events (7,8). Recently, Chow et al. (9) showed that CAD severity at

Table 6. Multivariate Significant Predictors of Events, Corrected for Baseline Variables

CTA Results	HR (95% CI) for All Cardiac Events	p Value	HR (95% CI) for Hard Cardiac Events	p Value
Model 1: ≥50%				
Age	1.00 (0.98–1.02)	0.86	1.01 (0.99–1.03)	0.60
Male	1.03 (0.70–1.51)	0.88	1.02 (0.63–1.66)	0.92
Diabetes	1.52 (1.02–2.27)	0.04	1.46 (0.92–2.33)	0.11
Hypercholesterolemia	1.21 (0.84–1.75)	0.30	1.10 (0.70–1.75)	0.68
Hypertension	1.15 (0.79–1.67)	0.46	1.50 (0.94–2.41)	0.09
Nitrates	0.61 (0.34–1.08)	0.09	0.67 (0.32–1.40)	0.28
Beta-blockers	1.01 (0.69–1.49)	0.95	0.59 (0.36–0.96)	0.03
Aspirin	0.63 (0.41–0.96)	0.03	0.60 (0.36–1.00)	0.05
Diuretics	1.50 (1.02–2.21)	0.04	1.63 (1.03–2.59)	0.04
AT1-blockers	1.01 (0.81–1.27)	0.93	0.90 (0.59–1.36)	0.61
Calcium-channel blockers	0.92 (0.62–1.37)	0.69	0.82 (0.50–1.34)	0.42
Statins	1.29 (0.87–1.91)	0.21	1.27 (0.77–2.08)	0.35
≥50% 1-vessel CAD	12.49 (7.98–19.55)	<0.0001	10.62 (5.94–18.96)	<0.0001
≥50% 2-vessel CAD	24.04 (14.27–40.50)	<0.0001	24.92 (13.12–47.33)	<0.0001
≥50% 3-vessel CAD	29.70 (17.80–49.57)	<0.0001	26.05 (14.29–47.47)	<0.0001
≥50% LMCA-CAD	34.66 (15.64–76.81)	<0.0001	39.60 (16.27–96.38)	<0.0001
Model 2: ≥70%				
Age	1.01 (0.99–1.02)	0.49	1.01 (0.99–1.03)	0.20
Male	1.44 (0.98–2.11)	0.06	1.46 (0.90–2.36)	0.13
Diabetes	1.47 (0.99–2.16)	0.05	1.67 (1.04–2.65)	0.03
Hypercholesterolemia	1.36 (0.96–1.93)	0.08	1.19 (0.76–1.85)	0.44
Hypertension	1.37 (0.94–1.99)	0.10	1.65 (1.03–2.64)	0.03
Nitrates	0.78 (0.44–1.35)	0.37	0.98 (0.48–2.00)	0.95
Beta-blockers	0.81 (0.56–1.20)	0.28	0.53 (0.34–0.87)	0.01
Aspirin	0.88 (0.58–1.33)	0.55	0.72 (0.43–1.19)	0.20
Diuretics	1.32 (0.91–1.97)	0.15	1.31 (0.83–2.05)	0.25
AT1-blockers	0.98 (0.77–1.23)	0.85	0.85 (0.55–1.33)	0.48
Calcium-channel blockers	0.90 (0.61–1.33)	0.60	0.78 (0.48–1.27)	0.32
Statins	1.57 (1.07–2.31)	0.02	1.73 (1.07–2.79)	0.02
≥70% 1-vessel CAD	6.95 (4.05–11.91)	<0.0001	6.56 (3.36–12.80)	<0.0001
≥70% 2-vessel CAD	9.07 (6.05–13.59)	<0.0001	8.24 (5.08–13.36)	<0.0001
≥70% 3-vessel CAD or ≥70% LMCA-CAD	11.53 (6.84–19.44)	<0.0001	11.42 (6.37–20.44)	<0.0001

Abbreviations as in Tables 1 and 2.

CTA evaluation is a predictor of major adverse cardiac events at 16-month follow-up in a large patient population. Very recently, the results of the CONFIRM (Coronary CT Angiography Evaluation For Clinical Outcomes: an International Multicenter Registry) registry, a large, international multicenter study, showed a strong role for CTA in the prediction of all-cause mortality, with risk profiles differing for age and sex (18,19). As compared with previous investigations, our study has longer follow-up in a large group of very selected patients who underwent CTA for suspected CAD. Indeed, patients with any type of known cardiac disease were excluded. To the best of our knowledge, our study population is the most homogeneous among the body of literature on the prognostic value of CTA. Our main finding was that CTA was able to provide long-term prognostic information in this type of patient and may predict hard cardiac events. Specifically, we found that patients without evidence of CAD had excellent prognosis at 52 months, without any cardiac events recorded. On the contrary, the cumulative event-free survival rate was significantly lower in patients with CAD, particularly in those with 3-VD or LMCA disease. It is noteworthy that patients with nonobstructive CAD showed a cumulative event-free survival significantly lower than that of patients without CAD. Overall, our study population had an intermediate (42.5%) pre-test CAD probability, and accordingly, the prevalence of obstructive lesions (38%) and number of patients with events at follow-up (39%)

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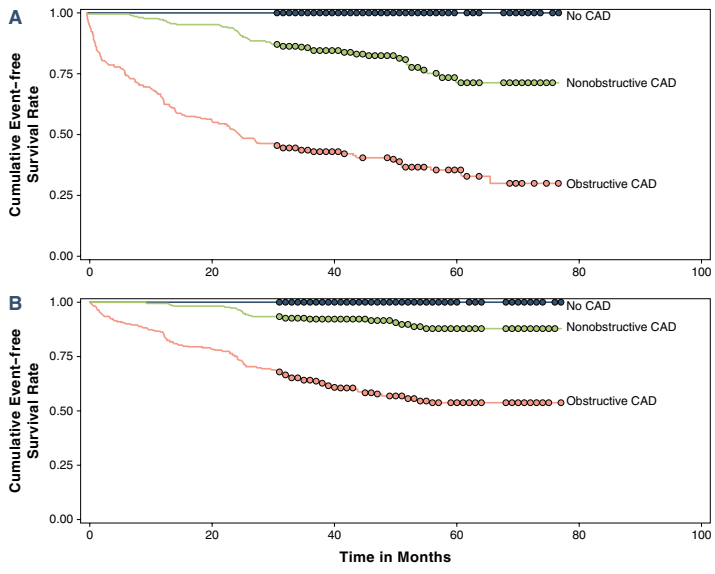

Figure 1. Kaplan-Meier Survival Curves in Patients With Normal and Abnormal Coronary Arteries

Kaplan-Meier curves for **(A)** all events and **(B)** hard events in patients with normal coronary arteries, nonobstructive coronary artery disease (CAD), and obstructive CAD, showing that patients with normal coronary arteries had excellent prognosis. On the contrary, the 52-month cumulative hard and all event-free survival rates were 88% and 72% in patients with nonobstructive CAD and 54% and 31% in those with obstructive CAD, respectively.

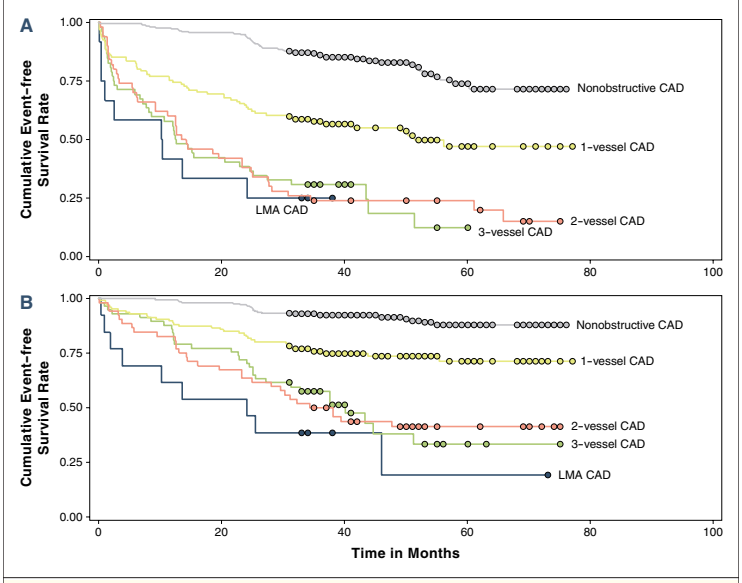

Figure 2. Kaplan-Meier Survival Curves in Patients Classified on the Basis of Number of Major Epicardial Vessels Exhibiting ≥50% Stenosis

Kaplan-Meier curves for **(A)** all events and **(B)** hard events in patients with nonobstructive CAD, ≥50% 1-vessel, ≥50% 2-vessel, ≥50% 3-vessel CAD, and ≥50% left main coronary artery (LMCA) CAD, showing that patients with multivessel and LMCA-CAD had poor prognosis. Abbreviation as in Figure 1.

were relatively low. In this subgroup, CTA demonstrated the best diagnostic accuracy in comparison with ICA, with a negative predictive value close to 100% (2). In agreement with previous studies that enrolled a smaller number of less homogeneous patients with shorter follow-up (6,8), our study confirmed that the absence of CAD at CTA is associated with an event-free survival of 100% for both hard and all cardiac events at the 52-month follow-up. Therefore, this diagnostic modality can be used to reassure patients with suspected CAD who have equivocal results of exercise ECG, stress single-photon emission computed tomography (SPECT) imaging, and stress echocardiography without the need of ICA about their outcome. Of note, despite exercise ECG, stress SPECT imaging, and stress echocardiography having lower diagnostic performance than CTA, their normality has been associated with low event risk (20). A major drawback of CTA in comparison with exercise ECG and stress echocardiography is radiation exposure. However, different strategies such as dual-source CT (21), high-pitch scanning (21), and prospective ECG triggering (22) have been shown to reduce radiation dose.

Detection of obstructive CAD at CTA was a strong predictor of cardiac events in univariate analysis (HR: 5.49 and 4.84 for hard and all events, respectively). Kaplan-Meier survival curves confirmed this finding, showing an event-free survival of 54% for hard events and 31% for all events in these patients. Moreover, CTA allowed prognostic grading based on the classification in 1-VD, 2-VD, 3-VD, and LMCA disease. In both univariate and multivariate analyses, HRs for hard and all events were significantly increased in patients with multivessel CAD and LMCA disease. Accordingly, survival curves free of hard events were progressively reduced, from 71% with 1-VD to 19% with LMCA-CAD. In 2007, Min et al. (3) demonstrated that atherosclerotic burden assessed with CTA was able to stratify all-cause mortality in patients who were followed for 15 months (3). Our study showed that, in addition to having a prognostic role when obstructive CAD was detected, CTA was able to predict events on the basis of atherosclerotic burden evaluated with coronary artery plaque scores. Indeed, event-free survival significantly decreased at the 52-month follow-up from 85% for SSS ≤5 to 20% for SSS >5 considering revascularizations and from 93% for SSS ≤5 to 43% for SSS >5 excluding

revascularizations. Another remarkable finding was that atherosclerotic burden maintained similar prognostic value and event-free survival rate using SIS.

Another major result of this study with important clinical implications was that found in patients with nonobstructive CAD at CTA. In these patients, all stress tests are usually negative because this type of lesion rarely triggers myocardial ischemia. Although traditional noninvasive testing in this subset of patients suggests a prognosis similar to that found in patients with normal coronary arteries, our data indicated a worse long-term outcome instead. Indeed, Kaplan-Meier survival curves showed an event-free survival of 87% for hard events and 69% for all events in patients with nonobstructive CAD at the 52-month follow-up. Thus, these patients had a cardiac event probability intermediate between that found in patients with normal coronary arteries and that in obstructive CAD. This finding requires some comments. Previous studies indicated that plaque composition may be a predictor of adverse events; demonstrated that vulnerable plaques may occur across the full spectrum of stenosis severity, suggesting that nonobstructive lesions may also contribute to coronary events (23); and showed that lipid core size and minimal cap thickness, 2 major determinants of plaque vulnerability, are not related to absolute plaque size or degree of stenosis (24). In our study, the number of noncalcific and mixed plaques had higher HRs by univariate analysis for hard and all events than the number of calcific plaques. Because nonobstructive plaques are more frequent than obstructive plaques, it is conceivable that coronary occlusion and myocardial infarction are due more frequently to moderate stenoses (25). Another possible explanation of the high prognostic value of nonobstructive CAD in our study may reside in the long-term follow-up. In fact, we cannot rule out that some moderate stenoses at the time of CTA examination could have become obstructive over time. Nevertheless, the early identification of nonobstructive CAD with CTA is clinically important because it may lead to a more aggressive strategy of cardiovascular risk factor control and modification of clinical follow-up.

Study limitations. In interpreting these data, some limitations should be considered. First, this was a single-center study, and its results may not necessarily reflect the patient population of other centers. 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 (97%). Third, CTA allowed the identification of patients with obstruc-

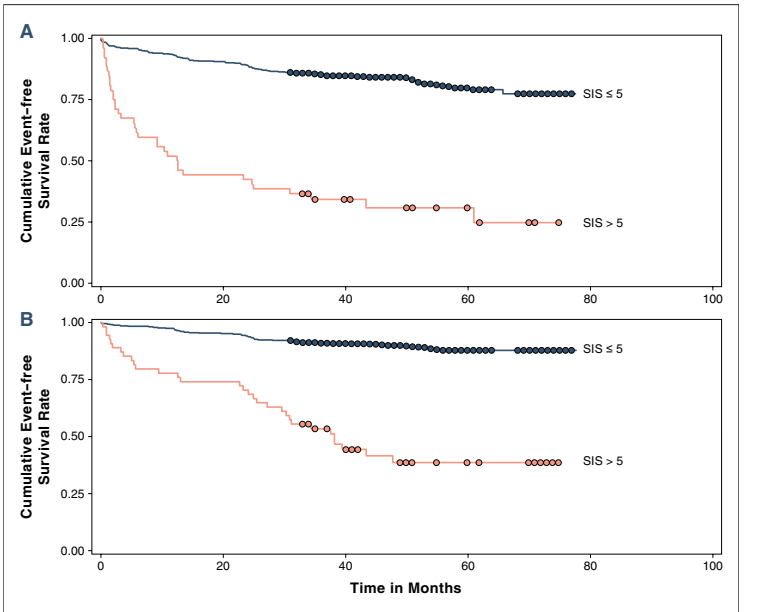

Figure 3. Kaplan-Meier Survival Curves in Patients Classified on the Basis of Segment-Involvement Score

Kaplan-Meier curves for **(A)** all events and **(B)** hard events in patients with segment-involvement score (SIS) ≤5 and SIS >5, showing that patients with SIS >5 had a significant poor prognosis in both analyses.

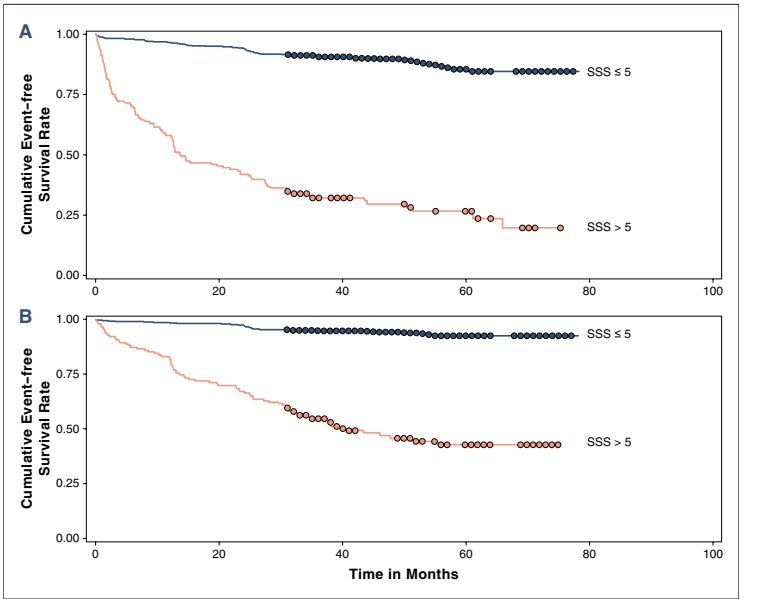

Figure 4. Kaplan-Meier Survival Curves in Patients Classified on the Basis of Segment-Stenosis Score

Kaplan-Meier curves for **(A)** all events and **(B)** hard events in patients with segment-stenosis score (SSS) ≤5 and SSS >5, showing that patients with SSS >5 had a significant poor prognosis in both analyses.

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tive CAD, likely resulting in an increased revascularization rate, which constituted a large proportion of the composite all cardiac event endpoint. However, in our study, CTA was performed in addition to the standard diagnostic workup; all decisions regarding revascularization were based on symptoms, the presence of ischemia on noninvasive testing, and ICA results; and patients with early elective revascularizations were excluded from the survival analysis. Finally, the presence of obstructive CAD at CTA was strongly associated with hard cardiac events not including revascularization procedures. We found a relatively high 52-month cumulative event rate of 46% in obstructive CAD at CTA in comparison with other clinical studies (26). Indeed, although our population is the most homogeneous among the body of literature on the prognostic value of CTA in patients without known CAD, differences in prognosis might be related to clinical characteristics of our patients (symptomatic for chest pain in 43% of cases and with positive stress test in 29% of cases).

CONCLUSIONS

CTA provided prognostic information in patients with unknown cardiac disease, showing excellent long-term prognosis when there was no evidence of atherosclerosis and allowing risk stratification when CAD was present.

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Key Words: coronary artery disease ■ multidetector computed tomography coronary angiography ■ prognosis.