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Coronary 64-slice CT angiography predicts outcome in patients with known or suspected coronary artery disease

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Abstract The aim of this study was to assess the prognostic value of 64-slice CT angiography (CTA) in patients with known or suspected coronary artery disease (CAD). Sixty-four-slice coronary CTA was performed in 220 patients [mean age 63±11 years, 77 (35%) female] with known or suspected CAD. CTA images were analyzed with regard to the presence and number of coronary lesions. Patients were followed-up for the occurrence of the following clinical endpoints: death, nonfatal myocardial infarction, unstable angina, and coronary revascularization. During a mean follow-up of 14±4 months, 59 patients (27%) reached at least one of the predefined clinical endpoints. Patients with abnormal coronary arteries on CTA (i.e., presence of coronary plaques) had a 1st-year event rate of 34%, whereas in patients with normal coronary arteries no events occurred (event rate, 0%, $p<0.001$). Similarly, obstructive lesions (≥50% luminal narrowing) on CTA were associated with a high first-year event rate (59%) compared to patients without stenoses (3%, $p<0.001$). The presence of obstructive lesions was a significant independent predictor of an adverse cardiac outcome. Sixty-four-slice CTA predicts cardiac events in patients with known or suspected CAD. Conversely, patients with normal coronary arteries on CTA have an excellent mid-term prognosis.

Keywords Sixty-four-slice CT angiography · Coronary artery disease · Prognosis

Abbreviations CT: computed tomography · CTA: CT angiography · CA: coronary angiography · CAD: coronary artery disease · SPECT: single photon emission computed tomography · CCS: coronary calcium score

Introduction

The advent of multislice computed tomography (CT) technology, including short gantry rotation times and submillimeter spatial resolution, has provided clinicians with a new promising tool for the noninvasive coronary artery assessment. Several reports have documented the excellent diagnostic accuracy of multislice CT angiography (CTA) compared to conventional coronary angiography (CA) in multiple populations [1–4], suggesting a potential role of CTA as an alternative first-line imaging modality in the diagnosis of patients with suspected coronary artery disease (CAD) [5, 6].

However, as with most emerging techniques, the prognostic value of CTA has not been elucidated yet. Nevertheless, in patients with known or suspected CAD, assessment of prognosis is crucial, and a considerable part of therapeutic decisions is based upon this knowledge. In CAD assessment, a large number of diagnostic tools, particularly imaging techniques, has proved to provide prognostic information that may aid to stratify patients into high-risk or low-risk categories. For example, coronary

artery calcium assessed with electron beam or multislice CT is known to provide an estimate of coronary atherosclerosis and has proven to correlate closely with the occurrence of long-term coronary events and cardiac death [7–10]. Similarly, a normal myocardial perfusion single photon emission computed tomography (SPECT) is associated with a low risk of cardiac events (<1% per year) even when angiographic CAD is present, whereas the risk in patients with abnormal SPECT is significantly higher [11]. Conventional CA provides a variety of information used for risk stratification of stable patients. Patients with three-vessel disease on CA have an approximately twofold higher 12-year mortality than patients with one-vessel disease, and the presence of left main disease is an important negative predictor [12]. Additionally, left ventricular angiography provides an estimate of systolic function and helps to determine which patients are at higher risk and should receive more aggressive treatment [12, 13].

Intuitively, it seems that conventional CA and CTA may deliver similar prognostic information, both being angiographic techniques. However, in addition to assessing coronary luminology, CTA has the potential of visualizing coronary artery wall morphology, thereby identifying and characterizing non-stenotic plaques that may often remain undetected by routine angiographic procedures. Previous reports have suggested that assessment of non-stenotic coronary plaques may allow for improved cardiovascular risk stratification [14, 15], but the prognostic value of these findings has not been sufficiently investigated yet [16]. Therefore, the aim of the present study was to assess the prognostic value of 64-slice CTA in a population with known or suspected CAD.

Materials and methods

Study population

The study population consisted of consecutive patients with known or suspected CAD undergoing further testing in our institution as part of their diagnostic workup (conventional CA, myocardial perfusion imaging, stress electrocardiography). Reasons for patient's referral to further testing were typical or atypical chest pain, pathological exercise test, dyspnea, unexplained syncope, or preoperative cardiac risk evaluation. Patients were eligible for CTA if they were in stable clinical condition, i.e., if they were in Canadian Cardiac Society class I to III, and in New York Heart Association functional class I to III, had normal renal function, regular sinus rhythm, and no contraindications to iodinated contrast agents. Patients with coronary artery bypass grafts were excluded. The study protocol was approved by the local institutional review board, and written informed consent was obtained from all subjects before enrollment.

After enrollment and prior to CT image acquisition, patients were questioned by a physician regarding their cardiac history, symptoms, cardiovascular risk factors, and current medication. Preexisting CAD was defined by previous angiographical evidence (on conventional CA) of coronary stenoses >50%. A history of myocardial infarction was defined on the basis of typical chest pain symptoms, typical electrocardiographic changes and/or elevated cardiac enzyme levels as recommended by the European Society of Cardiology [17]. Anginal pain was defined as dull, strangling or constricting retrosternal pain with irradiation to neck, left arm, or abdomen provoked by exertion and relieved by rest or nitrates (typical) or occurring regardless of physical activity (atypical). Non-anginal chest pain lacked the characteristic qualities described above [13]. Obesity was defined as a body mass index >30 kg/m^2; diabetes mellitus as a fasting glucose level ≥7.0 mmol/l (126 mg/dl) or the need for insulin treatment or oral antidiabetic agents; hypercholesterolemia as a total cholesterol level ≥5.0 mmol/l (195 mg/dl) or current treatment with lipid-lowering drugs; arterial hypertension as a blood pressure ≥140/90 mm Hg or current treatment with antihypertensive medication.

CTA image acquisition

Electrocardiographically (ECG) gated CTA was performed using 64-slice CT systems (GE Lightspeed VCT, GE Healthcare, Milwaukee, WI, or Siemens Somatom Sensation 64, Siemens Medical Solutions, Forchheim, Germany). The CT scans were performed according to standard scanning parameters provided by either type of scanner and recommended by the manufacturer and have been described in detail elsewhere [18–20]. First, a prospectively gated low-dose sequential CT scan of the heart was run for coronary artery calcium detection and quantification [19]. Thereafter, a contrast-enhanced retrospectively gated spiral CT scan was performed covering the distance from the tracheal bifurcation to the diaphragm during a single inspiratory breath hold (6 to 10 s) using prespecified scan parameters [1, 18–21]. The arrival of contrast material in the coronary arteries was timed using either an automated bolus tracking approach or an additional timing bolus sequence as previously reported [1, 18, 19, 21]. Depending on the total scan time, 80 to 135 ml nonionic iodinated contrast material (Visipaque 320, 320 mg/ml; GE Healthcare, Buckinghamshire, UK, or Ultravist 370, 370 mg/ml, Schering AG, Berlin, Germany) was injected into an antecubital vein with a flow rate of 5 ml/s followed by a saline chaser bolus. Patients with prescan heart rates above 70 beats per minute (bpm) received intravenous beta-blocker therapy (5 to 15 mg metoprolol tartrate, Lopresor, Daiichi Sankyo, Switzerland) immediately prior to the CT scan if no contraindications were present. Additionally, sublingual isosorbiddinitrate 2.5 mg

(Isoket, Schwarz Pharma AG, Munchenstein, Switzerland) for coronary dilatation was administered to every patient prior to the scan.

ECG-pulsing for radiation dose reduction was used in all patients. Synchronized to ECG, CT data sets were retrospectively reconstructed in mid- to end-diastolic phases and additional phases if needed for optimal coronary artery visualization. The reconstruction parameters for slice thickness, field of view, and convolution kernel have been described previously and are in keeping with standard clinical practice [18, 19, 21]. For post-processing and image interpretation, the images were then transferred to an external designated workstation (Advantage Workstation, GE, or Leonardo, Siemens).

Coronary calcium score

The coronary calcium score (CCS) was determined using the SmartScore software package (GE Healthcare, Milwaukee, WI). Coronary artery lesions were manually planimetered by a single experienced observer. The total calcium burden in the coronary arteries was quantified based on the scoring algorithm of Agatston et al. [22], where coronary calcifications were defined as a lesion with an area greater than 1 mm^2 and a peak intensity greater than 130 Hounsfield units (HU). CCS was determined for the four main coronary arteries in all slices and summed to generate the total score.

CTA image interpretation

CTA image interpretation was performed on axial source images, multiplanar and curved reformations, and thin-slab maximum intensity projections. First, coronary arteries were subdivided into 17-segments according to a modified model proposed by the American Heart Association [23]. Each coronary segment was visually evaluated by two independent experienced readers with regard to the presence of coronary plaques, plaque morphology and constitution, and coronary stenoses. In cases of disagreement between both readers, a joint reading was performed and consensus reached. CTA findings were not made available to clinicians and, therefore, not implemented in decision making.

Initially, image quality and interpretability were assessed, and each coronary segment was rated evaluable or nonevaluable. Segments were rated non-evaluable if severe motion artifacts prevented reliable evaluation of the vessel wall and lumen or if intracoronary stents were present as the stent strut artifacts prevent assessment of plaque morphology. Patients were excluded if one or more proximal segments or more than three segments overall were nonevaluable. Only segments with a diameter >1.5 mm were included in the analysis.

Assessment of CT coronary plaques

Both readers independently evaluated every segment with regard to the presence of coronary plaques. For plaque analysis and tissue differentiation, the optimal image display setting was chosen on an individual basis, in general at a window between 600 and 900 HU and at a level between 40 and 250 HU [14, 24]. Plaque analysis was performed on longitudinal sections of straight multiplanar reconstructions (along the vessel center-line) and axial cross-sections (perpendicular to the vessel center-line) with a thickness of 1 mm using the Coronary Vessel Analysis protocol of the CardIQ Xpress software on a Advantage Workstation 4.3 (GE Healthcare, Milwaukee, WI) (Fig. 1). Coronary plaques were defined as structures ≥1 mm^2 (visible in at least one of the cross-sections) within and/or adjacent to the coronary artery lumen, which can be clearly distinguished from the vessel lumen and the surrounding tissue. The composition of the plaque was characterized based on the presence of calcified (structures with densities above the adjacent vessel lumen) and non-calcified elements (structures with densities below the adjacent vessel lumen) as follows [3, 24]: (1) non-calcified plaques (lower CT density than the contrast-enhanced vessel-lumen and/or no coronary calcium on CCS scan, (2) mixed plaques (noncalcified and calcified elements within the plaque, calcified elements occupying <50% of the total plaque), and (3) calcified plaques (calcified elements occupying ≥50% of the total plaque). For each patient, the number of affected segments and the location and composition of coronary plaques were recorded. Patients without coronary calcium on CCS scans and without evidence of coronary plaques on CTA were considered to have normal coronary arteries.

Assessment of CT coronary stenoses

For assessment of obstructive lesions, all the segments with plaques were visually evaluated on at least two image planes, one parallel (longitudinal sections) and one perpendicular (axial sections) to the vessel center-line as described above. The axial cross-sections were reconstructed with a thickness of 3 mm using the Coronary Vessel Analysis protocol of the CardIQ Xpress software on a Advantage Workstation 4.3 (GE Healthcare, Milwaukee, WI) [24]. For coronary stenoses analysis, the minimal luminal diameter of the stenotic segment was visually compared to the adjacent proximal and distal nonstenotic reference segment with regard to coronary luminal narrowing. A coronary plaque was considered to be obstructive if the minimal luminal diameter was less than 50% of the adjacent reference diameter in either the longitudinal section or one of the cross-sections (Fig. 1). For every patient, the number and location of obstructive lesions was recorded.

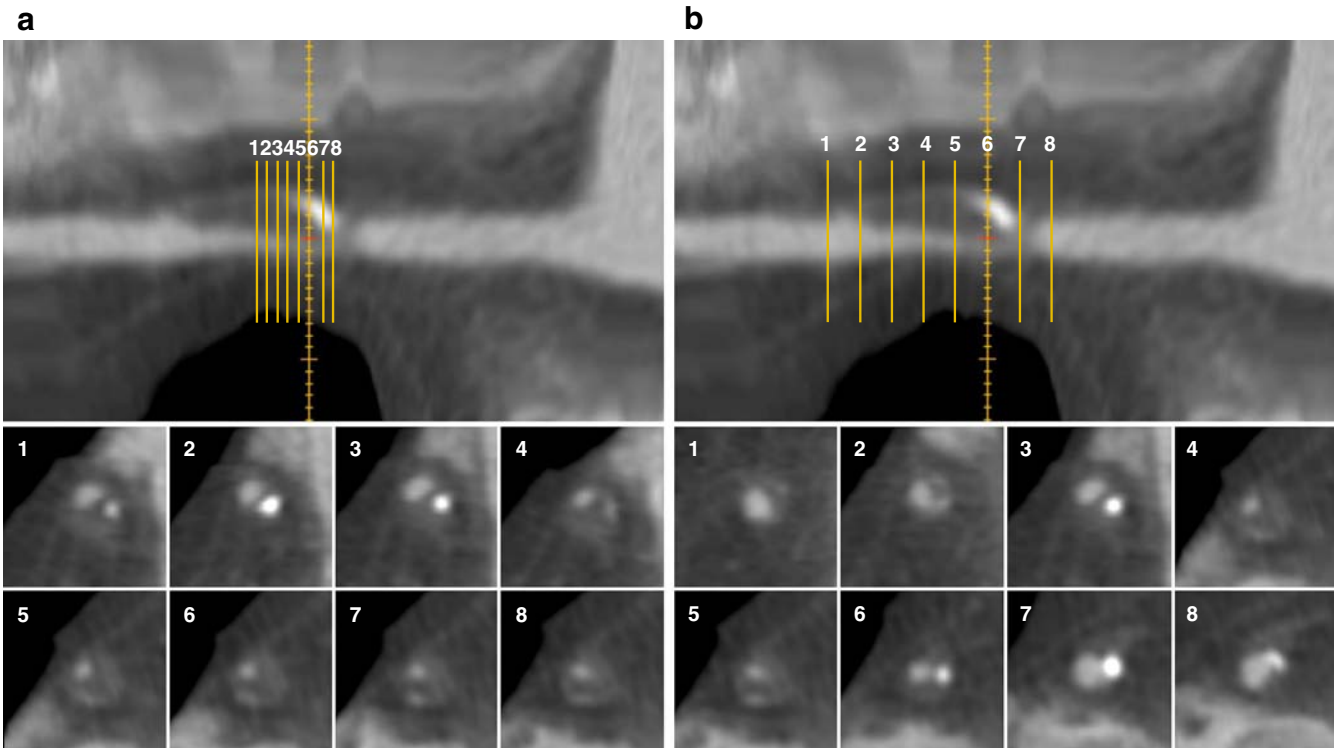

Fig. 1 Visual assessment of a right coronary artery plaque with regard to coronary plaques (**a**) and coronary stenoses (**b**) on multiplanar reformations. For coronary plaque analysis (**a**) cross-sections (**1–8**) were reconstructed with a thickness of 1 mm. The longitudinal vessel section and the corresponding cross-section show a mixed plaque with calcified and non-calcified elements. For coronary stenosis analysis (**b**), cross-sections were reconstructed with a thickness of 3 mm. Comparison of the minimal luminal diameter with adjacent vessel segments yields a high-grade (≥50%) stenosis

Follow-up data

Follow-up data were obtained from clinical visits and/or telephone calls to patients and their physicians. Clinical endpoints were (1) death from any cause, (2) cardiac death, (3) non-fatal myocardial infarction, (4) unstable angina requiring hospitalization, and (5) coronary revascularization [percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG)]. Cardiac death was defined as death from myocardial infarction, cardiac arrhythmia, refractory heart failure, or cardiogenic shock. Nonfatal myocardial infarction was defined as described above [17].

Data interpretation and statistical analysis

Follow-up data were analyzed by obtaining cumulative event rates using the Kaplan-Meier function. Event-free survival curves were plotted for a composite endpoint of death, myocardial infarction, unstable angina, and coronary revascularization and compared using the log-rank test. To assess the influence of CTA findings on clinical endpoints, univariate Cox regression analysis was used. Additionally, multivariate Cox regression was applied to identify independent predictors by including all factors with $p<0.05$ and correction for the baseline characteristics with $p<0.1$ on univariate analysis. The regression results are presented as hazard ratios (HR) and their respective confidence intervals (CI). Receiver-operating characteristics (ROC) analysis was applied to determine the optimal cut-off for the number of coronary plaques, and stenoses that predicted cardiac events and sensitivity, specificity, positive (PPV) and negative predictive value (NPV) were subsequently calculated based upon that cut-off.

Statistical analysis was performed using the SPSS software package (SPSS 12.0.1 for Windows, SPPS Corp., Chicago, IL) and the MedCalc statistical software (MedCalc 9.0.1.1 for Windows, Medcalc Software, Mariakerke, Belgium). Quantitative data are expressed as means±SD and compared using a two-tailed unpaired Student's t test. Categorical data are given in proportions or percentages and compared by a chi-squared test. A p-value <0.05 was considered statistically significant for all tests.

Results

From February 2005 until June 2006, a total of 223 patients who met the inclusion criteria gave written informed consent. Three patients (1%) had to be excluded due to

insufficient CTA image quality. In the remaining 220 patients follow-up data were recorded, and none of the patients was lost to follow-up.

The mean age of the study population was 63±11 years (range, 38 to 89 years), and 77 patients (35%) were female. Thirty-seven patients (17%) had known CAD at the time of CTA, and 24 patients (11%) had a history of myocardial infarction. The complete clinical characteristics are given in Table 1.

CT findings

In 220 patients a total of 3,031 coronary segments was evaluated. After excluding 53 (1.7%) segments due to insufficient image quality or intracoronary stents, plaque burden and composition were assessed in 2,978 segments. Coronary plaques were found in 839 segments (28%) corresponding to 177 patients (80%). Of these plaques, 28 (3%) were noncalcified, 223 (27%) mixed and 588 (70%) calcified. Obstructive lesions were identified in 251 segments (8%) corresponding to 95 patients (43%). The mean Agatston score was 507±833 (range, 0 to 6,690). According to the CT findings, 40 patients (18%) had coronary one-vessel disease, 39 patients (18%) two-vessel disease, and 16 patients (7%) three-vessel disease. In 43 patients (20%), normal coronary arteries without radiological evidence for coronary plaques were found. All coronary segments in patients with normal coronary arteries were evaluable. A left dominant coronary distribution type was found in 20 patients (9%). The exact distribution and properties of coronary plaques among patients with or without cardiac events on follow-up are shown in Table 2.

Table 1 Clinical characteristics of the study population

	All patients (n=220)	Patients with events (n=59)	Patients without events (n=161)	p
Age (years)	63±11	65±8	62±11	0.02
Gender (female)	77 (35%)	17 (29%)	60 (37%)	0.24
BMI (kg/m^2)	27±4	27±5	26±4	0.15
Cardiac history (n)				
Known CAD	37 (17%)	18 (31%)	19 (12%)	0.001
Previous MI	24 (11%)	13 (22%)	11 (7%)	0.001
Previous PCI	33 (15%)	17 (29%)	16 (10%)	<0.001
Symptoms (n)				
No complaints	78 (35%)	11 (17%)	67 (42%)	0.002
Non-anginal chest pain	18 (8%)	2 (3%)	16 (10%)	0.12
Atypical angina	48 (22%)	16 (27%)	32 (20%)	0.25
Typical angina	42 (19%)	22 (37%)	20 (12%)	<0.001
Dyspnea	34 (15%)	8 (14%)	26 (16%)	0.64
Cardiovascular risk factors (n)				
Obesity	37 (17%)	13 (22%)	24 (15%)	0.21
Diabetes mellitus	34 (15%)	15 (25%)	19 (12%)	0.01
Hypercholesterolemia	106 (48%)	36 (61%)	70 (43%)	0.02
Arterial hypertension	138 (63%)	45 (76%)	93 (58%)	0.009
Current smoking	82 (37%)	31 (53%)	51 (32%)	0.005
Current medication (n)				
ACEI/ARB	98 (45%)	34 (58%)	64 (40%)	0.02
Nitrates	9 (4%)	2 (3%)	7 (4%)	0.75
Beta-receptor antagonists	107 (49%)	42 (71%)	65 (40%)	<0.001
Aspirin	145 (66%)	52 (88%)	93 (58%)	<0.001
Statins	78 (35%)	28 (47%)	50 (31%)	0.02

Data not shown as n (%) are mean±SD. BMI, body mass index; CAD, coronary artery disease; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers. p-value is given for comparison of patients with events versus patients without events

Table 2 CT findings

	All patients (n=220)	Patients with events (n=59)	Patients without events (n=161)	p
Total calcium score*	507±833	886±900	376±769	<0.001
Coronary plaques	177 (80%)	59 (100%)	118 (73%)	<0.001
Plaques in LMA/LAD	163 (74%)	57 (97%)	106 (66%)	<0.001
Plaques in LMA	65 (30%)	24 (41%)	41 (25%)	0.03
Plaques in LAD	160 (73%)	57 (97%)	103 (64%)	<0.001
Plaques in LCX	121 (55%)	51 (86%)	70 (43%)	<0.001
Plaques in RCA	116 (53%)	48 (81%)	68 (42%)	<0.001
Plaques in proximal segments†	163 (74%)	56 (95%)	107 (66%)	<0.001
Distal plaques only‡	14 (6%)	3 (5%)	11 (7%)	0.64
Segments with plaques	3.8±3.3	6.3±2.8	2.9±2.9	<0.001
Noncalcified plaques	0.1±0.4	0.3±0.5	0.1±0.4	0.006
Mixed plaques	1.0±1.5	2.2±1.9	0.6±1.1	<0.001
Calcified plaques	2.7±2.6	3.9±2.7	2.2±2.4	<0.001
Nonobstructive plaques only	82 (37%)	3 (5%)	79 (49%)	<0.001
Coronary stenoses	95 (43%)	56 (95%)	39 (24%)	<0.001
Stenoses in LMA/LAD	76 (35%)	47 (80%)	29 (18%)	<0.001
Stenoses in LMA	5 (2%)	3 (5%)	2 (1%)	0.09
Stenoses in LAD	73 (33%)	46 (78%)	27 (17%)	<0.001
Stenoses in LCX	41 (19%)	27 (49%)	14 (9%)	<0.001
Stenoses in RCA	44 (20%)	28 (47%)	16 (19%)	<0.001
Stenoses in proximal segments†	75 (34%)	41 (69%)	34 (21%)	<0.001
Distal stenoses only‡	20 (9%)	15 (25%)	5 (3%)	<0.001
Segments with stenoses	1.1±1.7	2.7±1.9	0.6±1.3	<0.001
One-vessel disease	40 (18%)	20 (34%)	20 (12%)	<0.001
Two-vessel disease	39 (18%)	24 (41%)	15 (9%)	<0.001
Three-vessel disease	16 (7%)	12 (20%)	4 (2%)	<0.001
Left dominance	20 (9%)	8 (14%)	12 (7%)	0.16

Data not shown as n (%) are mean±SD. *Calcium score is given as Agatston score. †Proximal segments include the LMA and the proximal segments of LAD, LCX, and RCA. ‡Distal segments comprise all segments not included as proximal segments. LMA, left main artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; p-value is given for comparison of patients with events versus patients without events

Results of follow-up

During a mean follow-up of 14±4 months (range, 3 to 24 months), 59 patients (27%) reached at least one of the predefined endpoints. Four deaths (2%) occurred during follow-up, none of which was cardiac [septicemia (n=1), aspiration pneumonia (n=1), graft infection (n=1), and hematologic neoplasia (n=1)]. Three patients (1%) suffered myocardial infarction, and two patients (1%) unstable angina requiring hospitalization. In 58 patients (26%) a revascularization procedure was performed [CABG (n=16), PCI (n=43)]. Table 3 summarizes the results of follow-up in the study population. If revascularizations were excluded, patients with abnormal CTA had more hard cardiac events (myocardial infarction, unstable angina) [5 (3%)] compared to patients with normal CTA [0 (0%); p=0.30].

Survival analysis

Figures 2 to 4 show the Kaplan-Meier event-free survival curves. Patients with normal coronary arteries on CT (no coronary plaques or stenoses present) had an excellent event-free survival compared to those with abnormal coronary arteries (Fig. 2). None of the patients with normal coronary arteries on CTA suffered a cardiac event during follow-up. First-year event rates were 34% and 0% for patients with abnormal and normal coronary arteries, respectively.

Patients with obstructive lesions had significantly more cardiac events during follow-up compared to patients without obstructive lesions (Fig. 3). First-year event rates were 59% and 3% for patients with and without obstructive lesions on CTA, respectively.

Table 3 Follow-up results

	All patients (n=220)	Patients with plaques (n=177)	Patients without plaques (n=43)	p	Patients with stenoses (n=95)	Patients without stenoses (n=125)	p
Any cardiac event	59 (27%)	59 (33%)	0 (0%)	<0.001	56 (59%)	3 (2%)	<0.001
All-cause mortality	4 (2%)	3 (2%)	1 (2%)	0.78	1 (1%)	3 (2%)	0.46
Myocardial infarction	3 (1%)	3 (2%)	0 (0%)	0.39	2 (2%)	1 (1%)	0.41
Unstable angina requiring hospitalization	2 (1%)	2 (1%)	0 (0%)	0.48	2 (2%)	0 (0%)	0.10
Revascularization	58 (26%)	58 (33%)	0 (0%)	<0.001	55 (58%)	3 (2%)	<0.001
CABG	16 (7%)	16 (9%)	0 (0%)	0.04	16 (17%)	0 (0%)	<0.001
PCI	43 (20%)	43 (24%)	0 (0%)	<0.001	40 (42%)	3 (2%)	<0.001

Data are shown as n (%). CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention

When comparing patients with normal coronary arteries, non-obstructive plaques and obstructive lesions on CTA, the highest event rates were noted in the latter group, while event rates were lower yet slightly elevated in patients with non-obstructive plaques (Fig. 4).

Predictors of outcome

The results of univariate Cox regression analysis applied for clinical characteristics, symptoms, cardiovascular risk factors, and CT findings are shown in Table 4. Advanced age, history of CAD, and history of MI were associated with an increased incidence of cardiac events. The patient's symptoms were not found to predict cardiac events during follow-up except for typical angina (p<0.001). Furthermore, the traditional cardiovascular risk factors showed a weak, but significant association with a worse outcome except for obesity, which was not a significant predictor of events.

Conversely, the presence of coronary atherosclerosis as evidenced by coronary plaques on CT was a strong predictor of cardiac events [HR, 30.05 (95% CI, 2.15–420.07); p=0.011]. Other significant predictors were the presence of plaques in the LMA or LAD, the presence of plaques in any of the proximal segments of the three main coronary arteries, and the number of segments with plaques. Patients with coronary stenoses on CTA were at significantly higher risk for cardiac events on follow-up [HR, 35.22 (95% CI, 11.00–112.81); p<0.001], particularly if stenoses were located in the LMA or in the LAD. Further univariate predictors for cardiac events were the number of segments with stenoses and the number of vessels with stenoses (p<0.001). Multivariate Cox regression analysis identified the presence of obstructive coronary plaques on CTA as an independent predictor of cardiac events [HR, 12.65 (95% CI, 2.59–61.72); p=0.002].

ROC curves plotted for the number of coronary plaques and the number of coronary stenoses on CTA revealed an optimal cut-off at ≥3 coronary plaques and ≥1 coronary

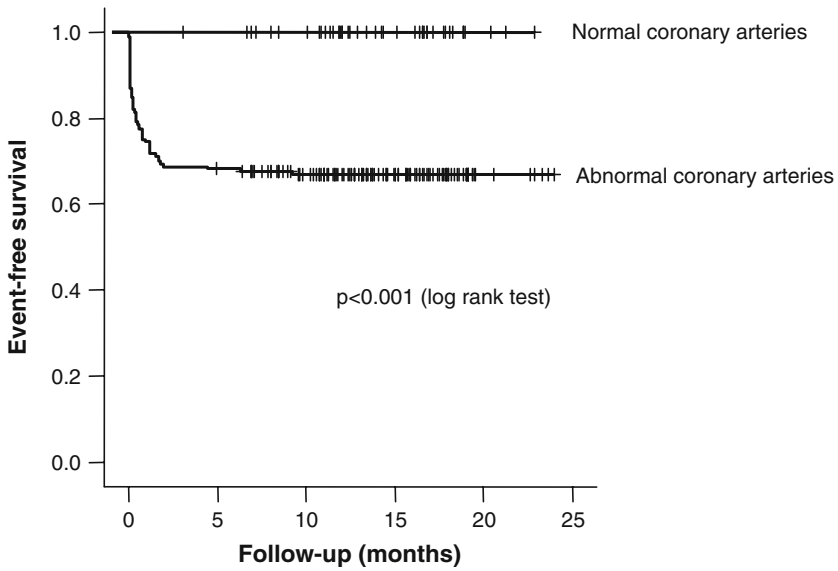

Fig. 2 Kaplan-Meier analysis for event-free survival in patients with normal or abnormal coronaries on CTA

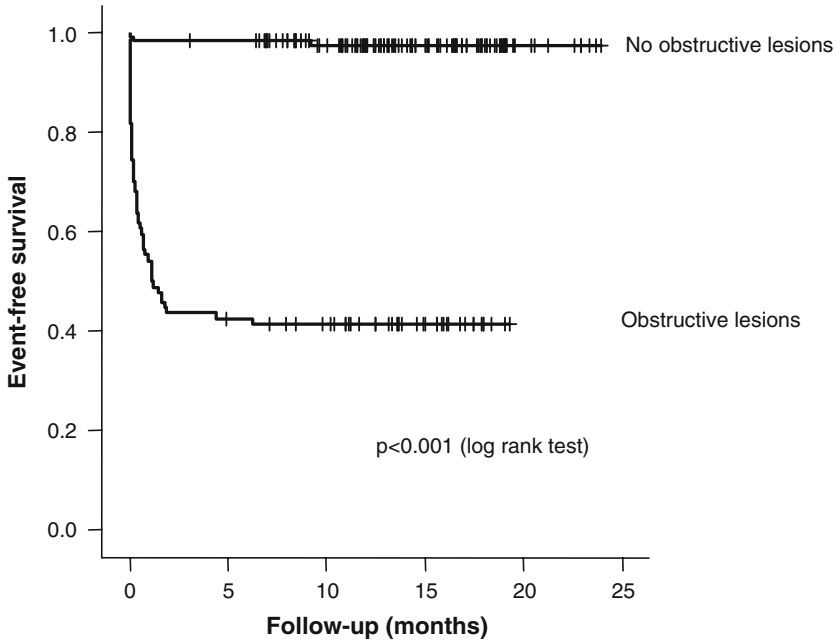

Fig. 3 Kaplan-Meier curves for event-free survival in patients with or without obstructive lesions on CTA

stenoses providing the highest diagnostic accuracy for the prediction of cardiac events on follow-up (for ≥3 coronary plaques: sensitivity 93%, specificity 57%, PPV 38%, NPV 99%; for ≥1 coronary stenosis: sensitivity 90%, specificity 76%, PPV 51%, NPV 96%) (Fig. 5).

Discussion

In the present study, CTA provided prognostic information in patients with known or suspected CAD. Patients with no evidence of coronary atherosclerosis on CTA had an excellent mid-term prognosis, and no cardiac events occurred in this group. The risk for cardiac events, however, increased significantly if coronary plaques or obstructive coronary lesions were present (1st-year event rates, 34% and 59%, respectively). There was a strong positive correlation between the extent of coronary atherosclerosis (i.e., the number of segments with coronary plaques) and an adverse cardiac outcome. Interestingly, the strongest association was found for coronary lesions in the LMA or LAD or in proximal segments of any of the three

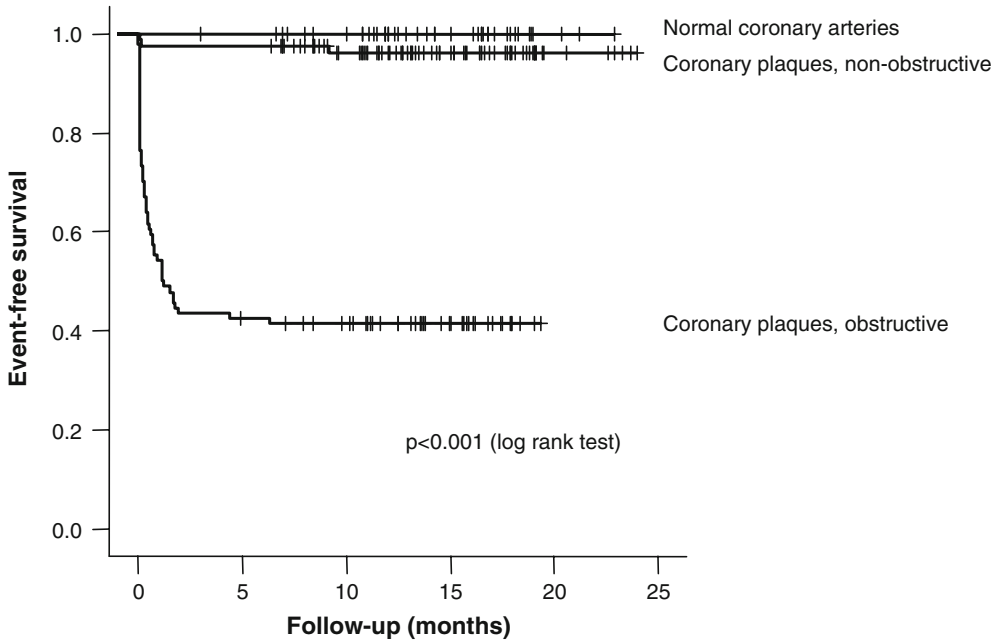

Fig. 4 Kaplan-Meier analysis for event-free survival in patients with normal coronaries, non-obstructive and obstructive coronary lesions on CTA

Table 4 Univariate predictors of cardiac events

	HR (95% CI)	p
Clinical characteristics		
Age, years	1.03 (1.00–1.05)	0.02
Female gender	1.36 (0.78–2.40)	0.28
History of CAD	2.71 (1.55–4.73)	<0.001
Previous MI	3.07 (1.65–5.70)	<0.001
Symptoms		
No complaints	0.37 (0.19–0.72)	0.003
Non-anginal chest pain	0.37 (0.09–1.52)	0.17
Atypical angina	1.46 (0.82–2.59)	0.20
Typical angina	3.10 (1.82–5.27)	<0.001
Dyspnea	0.75 (0.34–1.65)	0.47
Cardiovascular risk profile		
Obesity	1.50 (0.81–2.79)	0.20
Diabetes mellitus	2.11 (1.17–3.79)	0.013
Hypercholesterolemia	1.76 (1.04–2.98)	0.036
Arterial hypertension	2.22 (1.20–4.11)	0.011
Current smoking	2.17 (1.30–3.64)	0.003
CT findings		
Calcium score	1.00 (1.00–1.01)	<0.001
Presence of coronary plaques	30.05 (2.15–420.07)	0.011
Plaques in LMA/LAD	11.55 (2.82–47.34)	0.001
Plaques in proximal segments	7.50 (2.34–23.97)	0.001
Plaques in distal segments only	0.80 (0.25–2.54)	0.70
Segments with plaques	1.28 (1.19–1.37)	<0.001
Segments with noncalcified plaques	1.71 (1.14–2.56)	0.009
Segments with mixed plaques	1.57 (1.38–1.79)	<0.001
Segments with calcified plaques	1.21 (1.11–1.32)	<0.001
Presence of coronary stenoses	35.22 (11.00–112.81)	<0.001
Stenoses in LMA/LAD	10.45 (5.52–19.80)	<0.001
Segments with stenoses	1.41 (1.29–1.54)	<0.001
Number of vessels with stenoses	2.57 (2.05–3.22)	<0.001

HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; LMA, left main artery; LAD, left anterior descending artery

main vessels. The presence of three or more coronary plaques was the cut-off providing the highest accuracy to predict future cardiac events.

Our results are well in line with previously published data by Pundziute and coworkers [16] analyzing 100 patients with 16- and 64-slice CT. In this population the 1st-year event rate for patients with abnormal coronary arteries was 30% compared to 0% in patients with normal coronary arteries. These results support the notion, that not only obstructive lesions, but also non-obstructive plaques may play an important role in cardiac risk calculations and emphasize the importance of noninvasive tools for the evaluation of coronary plaque burden.

It is well established that coronary stenoses as evidenced by angiographic techniques are associated with an adverse outcome depending on their location and amount [12, 13], even more so if stenoses are associated with myocardial underperfusion as assessed by myocardial perfusion imaging [11]. However, fatal cardiac events may arise from rupture of vulnerable non-stenotic plaques that remain undetected by clinical evaluation or routine angiographic procedures [25, 26]. To date, visualization of non-stenotic plaques is cumbersome, and the existing technology, among others intravascular ultrasound [27], plaque thermography [28], optical coherence tomography [29], and angioscopy [30], is invasive and not suitable for routine clinical use. Multislice high-resolution CTA has been introduced as a rapid noninvasive tool for the assessment of coronary arteries, evaluating both the coronary lumen and vessel wall and providing information not only on coronary stenoses, but also on non-stenotic plaques.

The present study showed a high cardiac event rate in patients with obstructive lesions. Nevertheless, an elevated event rate was also observed in patients with coronary

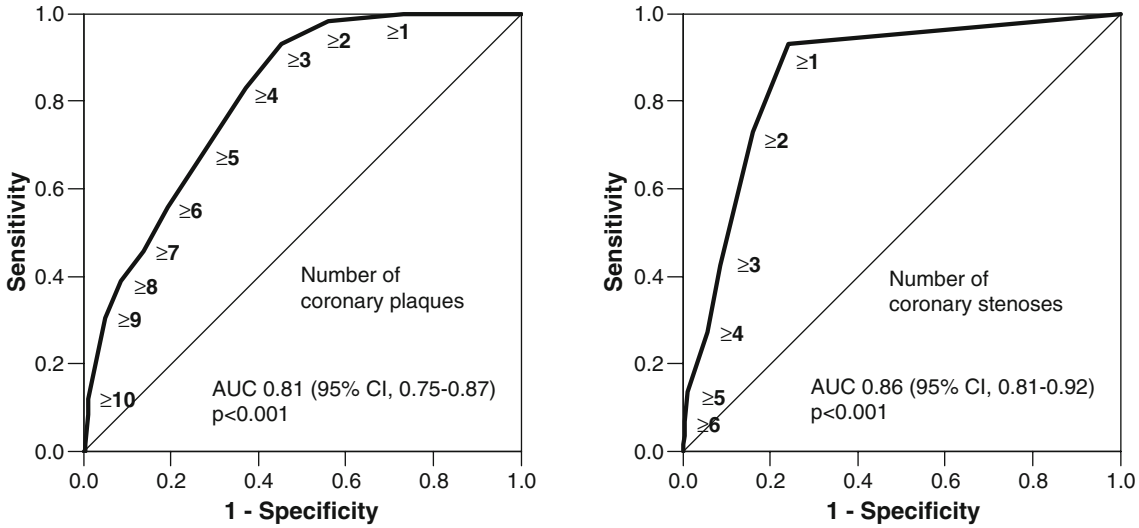

Fig. 5 Receiver-operating characteristics (ROC) curves. ROC curve analysis yields a cut-off of ≥3 coronary plaques and ≥1 coronary stenoses as the optimal cut-off providing the highest accuracy for the prediction of a high risk of cardiac events on follow-up. AUC=area under the curve. CI=confidence interval

plaques regardless whether obstructive or non-obstructive. This observation may provide a rationale for a more aggressive risk modification in patients with non-stenotic coronary plaques. However, further studies are needed to investigate a potential benefit of aggressive risk modification in patients with non-stenotic coronary plaques as evidenced by CTA.

The management of patients with suspected or known CAD is largely based on initial clinical evaluation, with the low-risk patients being reassured and the high-risk patients referred for invasive CA. Unfortunately, a significant number of patients belong to an intermediate risk category where prognosis and management are less well defined. In these patients further diagnostic workup with noninvasive techniques is needed to narrow down each patient's individual risk profile and guide further management decisions. The detection of considerable myocardial ischemia by stress echocardiography or myocardial perfusion imaging is associated with a high short- to mid-term cardiovascular risk and warrants aggressive treatment and coronary revascularization [31]. On the other hand, the presence of atherosclerotic coronary plaques as assessed with calcium scoring by electron-beam or multislice CT is an important predictor of long-term cardiovascular events. Similarly, in our study, the presence of obstructive coronary lesions was associated with the highest risk for cardiac events. Nevertheless, the risk was also slightly elevated for non-obstructive coronary plaques, and the presence of three or more coronary plaques appears to represent the best cut-off above which the mid-term risk of cardiac events is increased. In the future, this cut-off may provide a simple tool for clinicians to stratify patients to low- or high-risk categories and guide further risk management decisions. Most importantly, however, a 100% event-free survival was noted in patients with normal coronary arteries on CTA. This finding is clinically relevant since patients with normal coronary arteries can be safely reassured of a good prognosis.

Study limitations

An important drawback of the present study was the relatively short follow-up interval and the limited number of patients. As a result, the higher incidence of cardiac events in the group with abnormal coronary arteries on CTA was largely driven by a high amount of revascularization procedures. It seems that the follow-up time was too short for enough hard cardiac events, such as myocardial infarction and cardiac death, to happen. Nonetheless, more hard cardiac events occurred in the group with abnormal coronary arteries compared to those with normal CT findings (3% versus 0%), and larger studies are needed to confirm these results.

The study population was heterogeneous and consisted of patients with suspected and known CAD, including patients with a history of myocardial infarction and previous PCI. Accordingly, treatment strategies may have varied considerably across the study population depending on the patients' clinical characteristics. Further studies must be conducted to evaluate the prognostic role of CTA in more homogeneous populations.

Conclusion

Our study results demonstrate that 64-slice CTA provides prognostic information in patients with suspected or known

CAD. The highest rate of cardiac events was noted in patients with obstructive coronary lesions. Nevertheless, patients with coronary plaques on CTA were also associated with an elevated risk for future cardiac events. Most importantly, however, a 100% event-free survival was present in patients with normal coronary arteries, thus reassuring these patients and avoiding further testing.

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