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Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease

Martin Hadamitzky[1,2]*, Sebastian Täubert[1], Simon Deseive[3], Robert A. Byrne[2], Stefan Martinoff[1], Albert Schömig[2], and Jörg Hausleiter[3]

[1]Institut für Radiologie und Nuklearmedizin, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany; [2]Klinik für Herz- und Kreislauferkrankungen, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; and [3]Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Munich, Germany

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Aims Coronary computed tomography angiography (CCTA) has a high accuracy for detection of obstructive coronary artery disease (CAD). Several studies also showed a good predictive value for subsequent cardiac events. However, the follow-up period of these studies was limited to ~2 years and long-term follow-up data on prognosis out to 5 years are very limited.

Methods and results This study is based on 1584 patients with suspected CAD undergoing CCTA between December 2003 and November 2006. Among other CCTA parameters, the total plaque score defined as number of abnormal segments (having either a non-obstructive plaque or a stenosis) and the most severe stenosis were recorded. The primary endpoint was a composite of death and non-fatal myocardial infarction. Revascularization procedures later than 90 days after the CT study were assessed as secondary endpoints.

During a median follow-up of 5.6 years (IQR: 5.1–6.3 years) 61 patients suffered death or myocardial infarction and 52 underwent late revascularization. The severity of CAD and the total plaque score were the best predictors of death and non-fatal myocardial infarction, both significantly improving prediction over standard clinical risk scores (multivariate c-index 0.60 and 0.66, respectively, $P = 0.002$ and <0.0001, respectively). The annual event rate ranged from 0.24% for patients with no CAD to 1.1% for patients with obstructive CAD and 1.5% for patients with CAD and extensive plaque load (>5 segments). Both parameters also improved prediction of need for subsequent revascularization (c-index 0.72 and 0.63, respectively, $P < 0.0001$ and $P = 0.0013$, respectively).

Conclusion Data from CCTA predict both death and myocardial infarction as well as need for subsequent revascularizations out to 5 years. CCTA imaging may be a valuable tool in the assessment of long-term prognosis in patients with suspected CAD.

Keywords Coronary CT angiography • Coronary artery disease • Prognosis

Background

During recent years, coronary computed tomography angiography (CCTA) has emerged as an important non-invasive imaging modality for the assessment of coronary artery disease (CAD). Multiple studies demonstrated a high diagnostic accuracy for the detection and the exclusion of coronary stenosis when compared with invasive coronary angiography and established CCTA as a useful alternative to invasive angiography in certain indications. Moreover, due to its ability to delineate non-obstructive plaques, both calcified and non-calcified, CCTA can detect early changes of CAD and, therefore, may serve as a new prognostic tool for assessing subsequent cardiac risk.

* Corresponding author. Tel: +49 8912181586, Fax: +49 8912184513, Email: mhy@dhm.mhn.de

The prognostic value of CCTA for adverse cardiac events over short-to-intermediate follow-up has been shown in several single-centre studies,[1–5] a meta-analysis[6] as well as in a pooled analysis from multiple international centres[7] and follow-up of >25 000 CCTA-imaged patients is currently available. Nevertheless, the average follow-up duration of these studies is roughly 2 years, a time frame too short to adequately address atherosclerosis disease progression in view of the long latency between the onset of CAD and the occurrence of adverse clinical events. If CCTA is to prove useful for guiding preventive measures for CAD, longer follow-up periods are warranted.

As long-term surveillance data after CCTA imaging is very limited, we conducted extended follow-up of patients enrolled in a previously published CCTA study[8] and adjudicated outcomes out to 5 years. The rationale of the study is to assess the long-term predictive value of CCTA for incident major cardiac events as well as to investigate the incremental predictive value and the risk reclassification utility in comparison with standard clinical risk assessment in a population of patients with suspected CAD.

Methods

Study population

We enrolled all consecutive patients undergoing CCTA at our institution from 1 December 2003 to 30 November 2006. Written informed consent was obtained from all the patients before the investigation. Patients were eligible for this study, if CAD was not previously known, but suspected. Exclusion criteria comprised patients investigated in an acute life-threatening condition and patients without stable sinus rhythm during investigation.

A structured interview was performed before the investigation, and information about age, height, and weight of the patient, symptoms, cardiac history, and current medication was collected. The following cardiac risk factors were recorded: (i) presence and degree of hypertension (for binary analysis hypertension was defined as a systolic blood pressure of >140 mmHg or the administration of antihypertensive therapy), (ii) diabetes mellitus (defined as fastening blood glucose level >7 mmol/L or use of oral anti-diabetic therapy or insulin), (iii) smoking (defined as current smoker or previous smoker within the last year) and (iv) a positive family history (defined as presence of CAD in first-degree relatives younger than 55 years in male or 65 years in female). In addition, laboratory tests for total cholesterol, LDL- and HDL-fraction, and triglycerides were performed. From these data, the Morise pre-test score and the CAD-consortium clinical risk for obstructive CAD were calculated. The Morise pre-test score extends the risk stratification by Diamond and Forrester[9] by including both risk factors and current symptoms and is the most recent clinical score validated for cardiac events.[10] Since this score fitted best to our patient population both regarding symptoms and endpoint, it was used to assess the pre-test cardiac risk. The CAD-consortium clinical risk prediction model estimates the presence of obstructive CAD based on clinical risk factors and symptoms.[11] For the subgroup analysis according to symptoms, patients having both chest pain and dyspnoea were only assigned to the dyspnoea group if dyspnoea was the leading symptom. The study design was approved by the local ethics committee.

Computed tomography procedure

The detailed scan protocol is described elsewhere.[12,13] Different CT system configurations were used during the study period: A 16-slice CT system was used from December 2003 to September 2004, a 64-slice single source CT system from October 2004 to September 2006, and a 64-slice dual source CT system from October 2006 to November 2006 (all Siemens Healthcare, Erlangen, Germany).

In patients with a heart rate of >60 b.p.m., up to four doses of 5 mg of metoprolol were administered intravenously to lower heart rate at the beginning of the CT study. All the patients with a systolic blood pressure of at least 100 mmHg received nitroglycerin 0.8 mg sublingually for coronary vasodilatation after the patient was positioned on the scanner table. Images for calcium scoring were acquired by a non-contrast-enhanced sequential scan and analysed with a commercially available software package (Siemens Calcium Score, Siemens, Erlangen, Germany) using the Agatston score with a threshold of 130 HU. Contrast timing was tested by an initial bolus-timing scan using 10–20 ml of contrast (Iomeprol, Imeron 350, Bracco Altana Pharma GmbH, Konstanz, Germany, iodine content 350 mg/ml) followed by a 50 ml saline chaser. The contrast-enhanced scan was obtained using 80–140 ml of contrast individually adapted to the selected table feed and scan range at a rate of 4–6 ml/s followed by a 50 ml saline chaser. Data sets of axial slices, multiplanar reformations, and three perpendicular sets of thin-slab maximum intensity projections orientated along the heart axis (5 mm thickness, 1 mm increment) were reconstructed and investigated for the presence of plaque composition and luminal stenosis.

The coronary artery tree was segmented according to a simplified American Heart Association classification[14] using only the first 15 segments of the original 18. Each vessel segment with a diameter >1.5 mm was evaluated visually by two readers with an experience of having read >400 cardiac CT-studies at the time the scan was read. Any disagreement was settled by consensus. The results are based on clinical reads. The degree of stenosis was rated visually using four groups: no relevant stenosis (<25%), mild (25–49%), moderate (50–74%), and severe (≥75%) stenosis. Segments with artefacts were assigned to the most appropriate group.

In addition, for each segment the presence of calcified and non-calcified plaques were assessed. Calcified plaques were defined as plaques in the coronary wall showing signal intensities well above the contrast of the vessel lumen. Non-calcified plaques were defined as any non-calcified stenosis >25% or any discernible structure in the coronary artery wall with a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue. Plaques meeting these criteria, but additionally showing calcification, were classified as mixed plaques. From the primary analysis the following CCTA scores were calculated:

CAD severity as proposed by Chow *et al.*[5] with the categories 'normal', 'non-obstructive', 'one-vessel obstructive', 'two-vessel obstructive' and 'three-vessel obstructive'.

Total plaque score: number of segments with any stenosis ≥25% or any calcified, mixed or non-calcified plaques, irrespective of the degree of stenosis.[1,5] In addition the non-calcified, mixed, and calcified plaque score, defined as the number of coronary segments with non-calcified, mixed or calcified plaques irrespective of stenosis was calculated.

Derived scores: for comparison, two recently published scores were calculated: The segment stenosis score combining number and degree of stenoses and the modified Duke score combining number, degree and proximal location of stenoses, both proposed by Min *et al.*[1]

Follow-up

Follow-up information was obtained by clinical visits if available (10%), by detailed questionnaires sent by mail (40%), or, if the questionnaire was not returned, by telephone contact (50%, all numbers estimated based on a representative subsample of 261 patients scanned in 6 randomly selected months). All reported events were verified by hospital

records or direct contacts with the attending physician as possible and adjudicated by two cardiologists in consensus.

The primary endpoint of this study was a composite endpoint including death of any cause and non-fatal myocardial infarction. Non-fatal myocardial infarction was defined based on the criteria of typical acute chest pain and persistent ST-segment elevation or positive cardiac enzymes.

Two secondary endpoints were defined: first, cardiac events, defined as a composite of cardiac death and myocardial infarction (with cardiac death defined as any death of clearly cardiac cause and any death of unknown reason), and second, the single endpoint of late revascularization defined as percutaneous coronary intervention or bypass surgery performed later than 90 days after CCTA. Coronary revascularizations within 90 days after CCTA were not counted as events, because they most likely were performed in the context of an invasive angiography that was recommended due to abnormal CCTA findings; to eliminate confounding from restenosis, these patients were censored at the time of the first revascularization.

This study re-analyses patients from a previous study[8] extending the follow-up period from 2.4 to 5.5 years. Follow-up events were defined prospectively; but the performance of this analysis and its point in time was not prospectively specified.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, continuous variables were expressed as means ± standard deviation or as median (inter-quartile range) in time intervals and the Agatston score. All statistical evaluations are based on the event-free survival for

Table 1 Patient characteristics

	Study population, $n = 1584$ (%)	Lost on follow-up, $n = 36$ (%)	*P*-value
Age (years)	58.4 ± 11.1	55.7 ± 12.9	0.21
Male gender	1091 (68.9)	27 (75)	0.47
Body mass index (kg/m^2)	26.3 ± 4.0	28.5 ± 4.9	0.017
Arterial hypertension	934 (59.0)	19 (53)	0.5
Smoking	551 (34.8)	15 (42)	0.38
Diabetes	122 (7.7)	5 (14)	0.2
Hyperlipidaemia	846 (53.4)	17 (47)	0.5
Total cholesterol (mg/dL)	215 ± 43	216 ± 57	0.89
LDL-cholesterol (mg/dL)	129 ± 36	132 ± 53	0.78
HDL-cholesterol (mg/dL)	59 ± 19	56.2 ± 14	0.32
Triglycerides (mg/dL)	148 ± 93	153 ± 69	0.62
Family history of CAD	522 (33.0)	14 (39)	0.48
Atypical chest pain	578 (36.5)	8 (22)	0.21
Typical angina pectoris	97 (6.1)	4 (11)	0.47
Dyspnoea (>NYHA II)	72 (4.5)	2 (6)	0.68
Positive test for ischaemia	174 (11.0)	4 (11)	>0.99
Morise risk score	11.1 ± 3.1	10.7 ± 3.2	0.47
Low	348 (22.0)	9 (25)	
Intermediate	1122 (70.8)	24 (67)	
High	114 (7.2)	3 (8)	
CAD-Consortium risk in %	10 (5, 21)	12 (6, 22)	0.66
Low (<10%)	676 (42.7)	18 (50)	
Intermediate	870 (54.9)	17 (47)	
High (>60%)	38 (2.4)	1 (3)	
Leading indication for CCTA			
Thoracic pain	599 (37.8)	13 (36)	0.98
Dyspnoea	78 (4.9)	3 (8)	0.65
Ischaemia	166 (10.5)	1 (3)	0.32
Arrhythmias	268 (16.9)	2 (6)	0.19
Cardiac risk assessment	419 (26.5)	15 (42)	0.13
Other	54 (3.4)	2 (6)	0.78

Data are given as means ± standard deviation (median and inter-quartile range for CAD-Consortium risk because of marked non-normal distribution) or absolute numbers and percentages, since only one indication is counted for each patient there may be differences to the number of symptoms.

Table 2 Computed tomography results

	Study population, $n = 1584$ (%)	Lost on follow-up, $n = 36$	*P*-value
CAD severity			0.91
Normal coronaries	464 (29.3)	11 (31)	
Non-obstructive	794 (50.1)	19 (53)	
One-vessel disease	232 (14.6)	5 (14)	
Two-vessel disease	66 (4.2)	1 (3)	
Three-vessel disease	28 (1.8)	0	
Plaque scores			
Total plaques	3.03 ± 3.39	3.19 ± 3.55	0.78
Non-calcified plaques	0.86 ± 1.79	1.22 ± 2.90	0.46
Mixed plaques	0.46 ± 1.08	0.25 ± 0.55	0.032
Calcified plaques	1.71 ± 2.38	1.72 ± 2.26	0.97
Calcium (Agatston) score	93 (0, 1252)	88 (0, 1032)	0.71
0	565 (38.1%)	14 (47%)	
0.1–100	185 (12.5%)	1 (3%)	
100.1–400	166 (11.2%)	2 (7%)	
>400	567 (38.2%)	13 (43%)	

The Agatston score is available in 1483 patients only and is given as median (inter-quartile range) due to non-normal distribution. Total plaque score: number of segments with any stenosis ≥25% or any calcified, mixed, or non-calcified plaque. Non-calcified, mixed, and calcified plaque score: number of coronary segments with non-calcified, mixed, or calcified plaques.

the study endpoint using the Kaplan–Meier method; hazard ratios (for difference between 75 and 25th percentile) and multivariable analyses were calculated with the Cox proportional hazard model. Owing to the low number of events, correction for clinical risk was done by using a multivariable model including the Morise risk score. Concordance (C)-indices were calculated from time-to-event data as proposed by Harrell *et al.*,[15] in the multivariable model the incremental C-index for adding the CCTA variable to the Morise score was calculated. In addition the category less net reclassification improvement as proposed by Pencina *et al.*[16] was calculated. Statistical significance was accepted for two-sided *P*-values <0.05. The statistical package R version 2.10.1,[17] including the package rms,[18] was used for statistical analysis.

Results

Study population and clinical characteristics

During the study period 1714 patients with suspected CAD underwent CCTA. In total 94 patients were excluded per protocol, seven patients with acute aortic dissection undergoing pre-operative assessment for CAD, 2 patients because of other life-threatening conditions and 85 patients due to the absence of stable sinus rhythm during the examination. Of the 1620 remaining patients, 1584 (97.8%) were contacted for follow-up at a median of 5.5 years (inter-quartile range 5.1–6.2 years). The mean patient age was 58 ± 11 years and 1091 patients (69%) were male. The pre-test risk assessed by the Morise score was low in 348 patients (22%), intermediate in 1122 patients (71%), and high in 141 patients (7%). In sensitivity analyses, except for a higher body mass index in patients lost on follow-up, there was no significant difference between the overall study population and the population lost on follow-up. Detailed patient baseline characteristics are provided in *Table 1*.

Computed tomography results

The CT scan was performed on a 16-slice scanner in 305 patients (19%), on a 64-slice single source scanner in 1168 patients (74%), and on a 64-slice dual source scanner in 111 patients (7%). No CAD found in 464 patients (30%), 794 patients (50%) had non-obstructive CAD, and 326 patients (20%) had obstructive CAD. On average 3.0 segments demonstrated atherosclerotic plaque, of which 0.9 segments had non-calcified plaque, 0.5 segments had mixed plaque, and 1.7 segments had calcified plaque. Correlation between the total plaque score and the presence of obstructive CAD was moderate (Pearson's *r* 0.67). The fraction of uncertain segments was 399 out of 3453 (11.6%), 640 out of 13 552 (4.7%), and 41 out of 1294 (3.2%) for the 16-slice scanner, the 64-slice single source scanner, and the 64-slice dual source scanner, respectively.

Table 3 Predictive value of coronary computed tomography angiography variables for primary endpoint

CCTA variable	No events, $n = 1523$	Events, $n = 61$	Univariate model			Multivariate model (+Morise)		
			Hazard ratio	C-index	*P*-value	Hazard ratio	C-index	*P*-value
CAD severity				0.632	<0.0001		0.586	0.021
Normal	458 (30.1)	6 (10)	Reference			Reference		
Non-obstructive	759 (49.8)	35 (57)	3.33 (1.40, 7.91)			2.46 (1.02, 5.90)		
One-vessel disease	219 (14.4)	13 (21)	1.46 (0.50, 2.43)			2.60 (0.97, 7.00)		
Two-vessel disease	63 (4.1)	3 (5)	3.85 (0.96, 15.4)			1.95 (0.47, 8.02)		
Three-vessel disease	24 (1.6)	4 (7)	13.0 (3.67, 46.3)			6.66 (1.81, 24.5)		
Segments with stenosis >25%	1.88 ± 2.75	4.15 ± 4.15	1.53 (1.29, 1.81)	0.676	<0.0001	1.42 (1.17, 1.71)	0.634	0.0016
Segments with stenosis >50%	0.98 ± 2.10	2.59 ± 3.85	1.13 (1.06, 1.20)	0.624	0.0013	1.12 (1.04, 1.20)	0.563	0.16
Plaque scores								
Total plaques	2.93 ± 3.32	5.46 ± 4.06	2.06 (1.55, 2.72)	0.700	<0.0001	1.77 (1.30, 2.42)	0.655	0.00011
Non-calcified plaques	0.82 ± 1.70	1.92 ± 3.15	1.11 (1.04, 1.19)	0.625	0.0014	1.12 (1.04, 1.21)	0.581	0.083
Mixed plaques	0.46 ± 1.08	0.51 ± 1.13	1.08 (0.87, 1.34)	0.520	0.51	0.98 (0.78, 1.22)	0.587	0.053
Calcified plaques	1.66 ± 2.34	3.03 ± 2.91	1.70 (1.35, 2.13)	0.668	<0.0001	1.40 (1.09, 1.80)	0.589	0.041
Derived scores								
Segment stenosis score	5.71 ± 7.16	11.5 ± 9.63	1.99 (1.54, 2.59)	0.680	<0.0001	1.68 (1.26, 2.22)	0.636	<0.0001
Modified Duke score				0.601	0.0078		0.529	0.52
0	1069 (70.2)	34 (56)	Reference			Reference		
1	306 (20.1)	15 (25)	1.51 (0.82, 2.77)			1.07 (0.57, 1.98)		
2	85 (5.6)	5 (8)	2.03 (0.79, 5.21)			1.20 (0.46, 3.13)		
≥3	63 (4.1)	7 (12)	3.77 (1.67, 8.53)			2.17 (0.93, 5.04)		

Endpoint all cause death and myocardial infarction, the multivariate model additionally includes the Morise score as clinical predictor. Total plaque score: number of segments with any stenosis ≥25% or any calcified, mixed or non-calcified plaque. Non-calcified, mixed and calcified plaque score: number of coronary segments with non-calcified, mixed or calcified plaques.

Calcium scoring was performed in 1483 patients (94%). The median Agatston score was 93 (IQR 0–1252). A summary of the CT results is shown in *Table 2*.

Follow-up events

During follow-up, the primary endpoint of death or non-fatal myocardial infarction occurred in 61 patients (3.8%). Overall 48 patients (3.0%) died; 12 patients (0.8%) from cardiac causes and 36 patients (2.3%) from non-cardiac causes. In addition 13 patients (0.8%) suffered from non-fatal myocardial infarction. Overall, the annual rate of death or myocardial infarction was 0.7% (95% CI: 0.6–0.9%).

The secondary endpoint of cardiac events occurred in 25 patients (1.6%). During the follow-up 226 patients (14%) underwent coronary revascularization, of which 174 (11%) were performed within 90 days after CCTA and 52 (3.3%) beyond 90 days. There were 48 late percutaneous coronary interventions (3.0%) and 7 late bypass graft surgeries (0.3%), 3 patients had both types of intervention.

Prognostic value of coronary computed tomography angiography

For the primary endpoint, both CAD severity and total plaque score correlated well with outcome. Coronary artery disease severity had a univariate c-index of 0.63 and a multivariate c-index of 0.59. The total plaque score performed slightly better with a univariate and multivariate c-index of 0.70 and 0.66, respectively. The annual event rate for the primary endpoint ranged from 0.2% (95% CI: 0.1–0.5%) for patients without CAD to 0.81% (95% CI: 0.58–1.1%) for patients with non-obstructive CAD to 1.1% (95% CI: 0.7–1.8%) for patients with obstructive CAD; patients with a total plaque score of more than five segments had an annual event rate of 1.5% (95% CI: 1.1–2.2%). Of note is the fact that total plaque score counting segments with any plaque or stenosis performed better than a score counting segments with mild (>25%) obstruction (multivariate c-index 0.63) and a score counting segments with moderate (>50%) obstruction (multivariate c-index 0.56). Plaque classification did not improve prediction, non-calcified, mixed, and calcified plaques scores all had multivariate c-indices between 0.58 and 0.59 at the border of significance. Further details of the prognostic value of CCTA are summarized in *Table 3* and *Figure 1*. Prognostic assessment was similar between 16-slice scanners and later generations with a trend for correlation between CAD severity and primary endpoint (multivariate c-index 0.60, $P = 0.14$ and c-index = 0.57, $P = 0.11$, respectively) and a significant correlation between total plaque score and outcome (multivariate c-index 0.81, $P < 0.001$ and c-index = 0.60, $P = 0.028$, respectively).

For the secondary endpoint of cardiac events, the correlation between CCTA variables and outcome was slightly better. The multivariate c-indices of the total plaque score and the CAD severity score were 0.74 ($P < 0.0001$) and 0.68 ($P = 0.0012$), respectively (see also *Table 4*).

For the secondary endpoint of late revascularization, CAD severity performed best [hazard ratio of 1.7 (95% CI: 1.3–2.2), c-index 0.659, $P < 0.0001$]. The total plaque score performed slightly worse with a hazard ratio of 1.9 (95% CI: 1.3–2.7) and a c-index of 0.636 ($P = 0.0013$, all multivariate). Kaplan–Meier curves are shown in *Figure 2*.

Subgroup analysis according to symptoms

For the primary endpoint, annual event rate was highest in patients with dyspnoea (1.3%, 95% CI: 0.56–2.8%) and lower for patients with chest pain (0.77%, 95% CI: 0.53–1.1%) and other or no symptoms (0.60%, 95% CI: 0.42–0.87%). None of these differences was significant.

Correlation between CCTA parameters and outcome was similar between patients with chest pain and those no or other symptoms. For the total plaque score c-index was 0.64 ($P = 0.0015$) for patients with chest pain and 0.66 ($P = 0.0051$) for those without chest pain and dyspnoea. In the few patients with dyspnoea, no correlation was significant (see also *Table 5*).

Comparison with calcium scoring

Calcium scoring significantly improved prediction beyond the Morise score both for the primary endpoint and the cardiac events. The c-index rose from 0.661 to 0.703 ($P = 0.034$) and from 0.636 to 0.713 ($P = 0.034$), respectively. For the primary endpoint no CCTA variable could further improve prediction (c-index for the total plaque score 0.718, *P* not significant), while for cardiac events the combination of the Morise score, calcium score, and total plaque score had a better predictive value than the Morise and calcium score alone (c-index = 0.745, $P = 0.034$ for difference) (*Figure 3*).

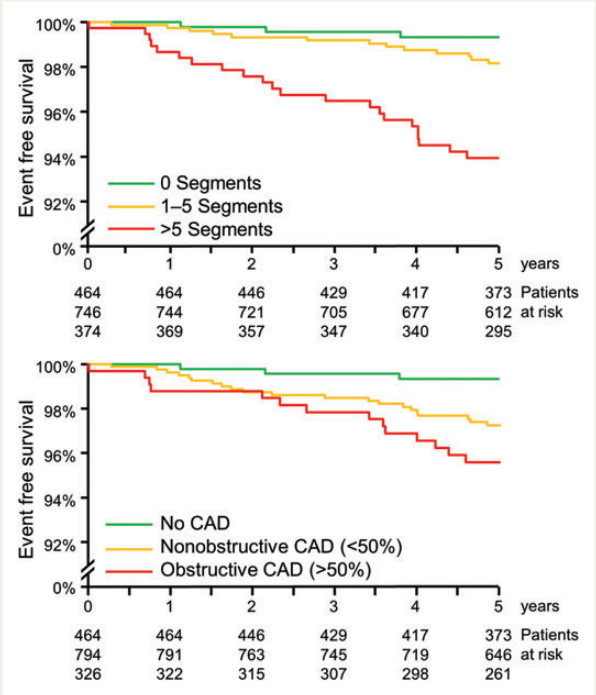

Figure 1 Kaplan–Meier plot for event-free survival stratified for total plaque score (upper plot) and coronary artery disease severity (lower plot).

Table 4 Predictive value of coronary computed tomography angiography variables for cardiac events

CCTA variable	No events, $n = 1559$	Events, $n = 25$	Univariate model			Multivariate model (+Morise)		
			Hazard ratio	C-index	*P*-value	Hazard ratio	C-index	*P*-value
CAD severity				0.699	0.00061		0.681	0.0012
Normal	463 (29.7)	1 (4)	Reference			Reference		
Non-obstructive	780 (50.0)	14 (56)	7.94 (1.04, 60.4)			6.16 (0.80, 47.3)		
One-vessel disease	226 (14.5)	6 (24)	11.9 (1.43, 98.8)			2.07 (1.09, 4.21)		
Two-vessel disease	65 (4.2)	1 (4)	8.04 (0.50, 128)			4.50 (0.27, 75.0)		
Three-vessel disease	25 (1.6)	3 (12)	61.9 (6.62, 617)			38.6 (3.84, 388)		
Segments with stenosis >25%	1.92 ± 2.80	5.00 ± 4.38	1.65 (1.03, 2.10)	0.738	0.00061	1.59 (1.22, 2.08)	0.727	0.00037
Segments with stenosis >50%	1.00 ± 2.15	3.36 ± 4.13	1.16 (1.06, 1.26)	0.677	0.01	1.15 (1.05, 1.26)	0.662	0.017
Plaque scores								
Total plaques	2.98 ± 3.35	6.16 ± 4.14	2.33 (1.53, 3.53)	0.762	<0.0001	2.14 (1.35, 3.38)	0.739	<0.0001
Non-calcified plaques	0.836 ± 1.75	2.2 ± 3.28	1.11 (1.00, 1.23)	0.659	0.012	1.13 (1.01, 1.25)	0.679	0.0032
Mixed plaques	0.461 ± 1.08	0.6 ± 1.29	1.18 (0.87, 1.59)	0.536	0.5	1.07 (0.78, 1.46)	0.579	0.33
Calcified plaques	1.68 ± 2.35	3.36 ± 3.41	1.89 (1.34, 2.67)	0.702	0.0026	1.61 (1.10, 2.34)	0.621	0.1
Derived scores								
Segment stenosis score	4.2 ± 4.8	9.8 ± 6.94	3.06 (1.98, 4.72)	0.735	0.00088	2.69 (1.69, 4.29)	0.719	0.00083
Modified Duke score				0.647	0.023		0.599	0.14
0	1089 (69.9)	14 (56)	Reference			Reference		
1	316 (20.3)	5 (20)	1.22 (0.44, 3.38)			0.89 (0.31, 2.52)		
2	88 (5.6)	2 (8)	2.07 (0.47, 9.14)			1.30 (0.29, 5.91)		
≥3	66 (4.2)	4 (16)	5.61 (1.84, 17.1)			3.39 (1.05, 10.9)		

Endpoint cardiac death and myocardial infarction, the multivariate model additionally includes the Morise score as a clinical predictor.

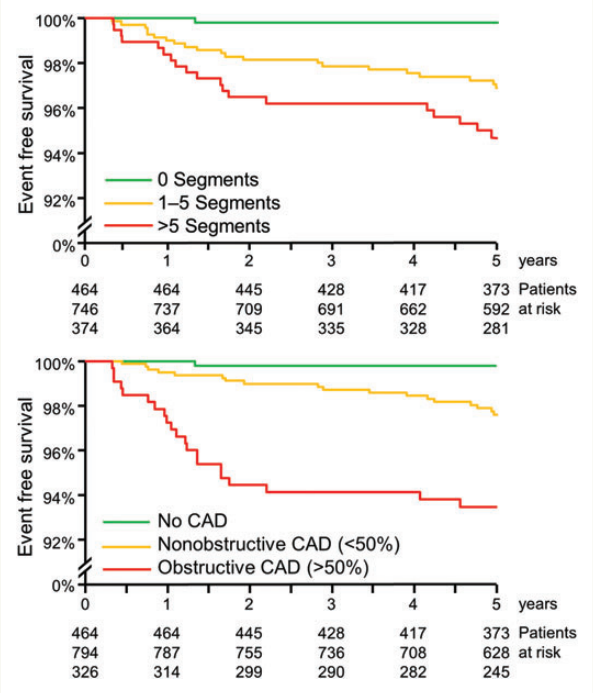

Figure 2 Kaplan–Meier plot for revascularization later than 90 days after investigation stratified for total plaque score (upper plot) and coronary artery disease severity (lower plot).

Reclassification from clinical risk

A substantial number of patients could be reclassified regarding their risk after performance of CCTA. The total plaque score showed an overall net reclassification improvement of 49% ($P = 0.0002$) for the primary endpoint and 54% ($P = 0.0028$) for cardiac events. While all variables showed a highly significant improvement in identifying patients without events (all $P < 0.0001$), no parameter could significantly improve prediction of events (all $P > 0.32$) (*Table 6* and *Figure 4*).

Discussion

For patients with suspected CAD, we could demonstrate that (i) the exclusion of CAD by CCTA is associated with an excellent prognosis over the subsequent five years with an annual rate of major events well <0.5%; (ii) both the severity of CAD and the total plaque score can be used to identify patients at high long-term risk deserving intensified medical therapy; and (iii) about half of all the patients can be reclassified regarding their 5-year cardiac risk.

Coronary obstruction is the hallmark of advanced CAD and although the obstruction itself may be alleviated by revascularization, these patients remain at increased risk. In our study, the conventional classification of CAD severity correlated well with outcome. However, additional analyses including the total plaque score, which also takes into account non-obstructive plaques, carried additional prognostic information. Indeed in our study the total plaque score is one of the best

Table 5 Subgroup analysis according symptoms on presentation

	Chest pain ($n = 644$)		Dyspnoea ($n = 91$)		Other/none ($n = 849$)	
Events	**27**		**6**		**28**	
Annual event rate	**0.77% (0.53 to 1.1%)**		**1.3% (0.56 to 2.8%)**		**0.60% (0.42 to 0.87%)**	
CCTA variable	**C-index**	***P*-value**	**C-index**	***P*-value**	**C-index**	***P*-value**
CAD severity						
Extent of CAD	0.545	0.46	0.589	0.47	0.597	0.036
Segments with stenosis>25%	0.627	0.045	0.541	0.66	0.655	0.013
Segments with stenosis>50%	0.554	0.45	0.563	0.46	0.544	0.54
Plaque scores						
Total plaques	0.639	0.015	0.511	0.88	0.665	0.0051
Non-calcified plaques	0.503	0.97	0.678	0.079	0.743	<0.0001
Mixed plaques	0.638	0.054	0.636	0.23	0.567	0.34
Calcified plaques	0.627	0.043	0.571	0.34	0.53	0.68
Derived scores						
Segment stenosis score	0.618	0.044	0.544	0.73	0.682	0.00016
Modified Duke score	0.548	0.43	0.546	0.74	0.514	0.85

Annual event rate including 95% confidence interval and predictive value of CT-Parameters for primary endpoint, multivariate model including the Morise score as a clinical predictor, patients with both chest pain and dyspnoea were categorized according to the leading indication.

predictors of outcome, surpassing scores that only count segments with mild or moderate obstruction. While these findings already were observed at 2-year follow-up,[8] this study confirms that the prognostic power of CCTA endures over a 5-year period, a time-frame which much better reflects the natural history of evolving CAD and the impact of targeted therapeutic strategies.

The results of our analysis are consistent with other emerging data on long-term follow-up after CCTA imaging. In a small study, Chong *et al.*[19] observed 70 patients without obstructive CAD out of a cohort of 259 patients for the occurrence of major cardiac events during a mean follow-up of 4.6 years, and observed just a single myocardial infarction event, concluding that the negative predictive value of a CCTA without evidence of CAD for long-term major cardiac events is 99% (95% CI: 92–99%). Andreini *et al.*[20] analysed 980 patients with suspected CAD for hard cardiac events (cardiac death or myocardial infarction) and major cardiac events (additionally including late revascularizations) during a follow-up period of 4.3 years. They found a significant improvement of event prediction beyond clinical risk scores both for obstructive CAD and the number of segments with plaque. Annual rates of major cardiac events ranged from 0% for patients without CAD to 19.9% for patients with obstructive CAD. The main limitation of this study was the fact that 22% of the original population was excluded because of inconclusive CCTA findings or early coronary revascularization. Similar results were found by Ostrom *et al.*[21] who assessed the mortality incidence after electron-beam CCTA during a 6.5-year follow-up and describe annual mortality rates between 0.25% for patients without CAD to 1.3% for those with evidence of obstructive CAD.

Hard clinical endpoints, like mortality or myocardial infarction, are of cause the most important parameters for assessing the prognostic value of CCTA. But the risk of other CAD-associated morbidity such as the presence of symptomatic angina pectoris and/or need for subsequent revascularization may influence decisions on the intensity of preventive measures. Our data confirms that CCTA can also predict need for subsequent coronary revascularization and while the correlation between the presence of obstructive CAD and subsequent revascularization is not surprising, the correlation between the total plaque score and the revascularization rate is not self-evident. While this result in part is caused by a moderate correlation between plaque load and coronary obstruction, it may also reflect the higher risk of plaque progression in patients with extensive disease ultimately leading to a higher incidence of obstructive lesions.

For the total plaque score, we found a slight but significant improvement in cardiac event prediction compared with a combined model of Calcium scoring and Morise score. Taking into account the observation by Cho *et al.*,[22] who could not demonstrate an incremental predictive value of CCTA in 7590 asymptomatic individuals, and the non-significant result for prediction of the primary endpoint in our analysis, further evaluation of the use of this parameter for the assessment of cardiac risk is warranted, a task beyond the scope of this study.

An additional analysis looking at the reclassification of patient risk from pre-test clinical risk scores indicated that 49% of the patients could be reclassified regarding their cardiac risk. In particular, the prediction of an event-free follow-up could be improved by all the CCTA variables analysed. Nevertheless, patients with a high pre-test risk and a low risk CCTA had an annual event rate as high as 1%. Although there is an uncertainty in this number due to the small subgroup, the incremental prognostic value of CCTA in high-risk patients may be limited.

The results from this study further support the role of CCTA as an additional means of assessing cardiovascular risk. The use of CCTA may play a role in guiding preventive treatment, but such concepts

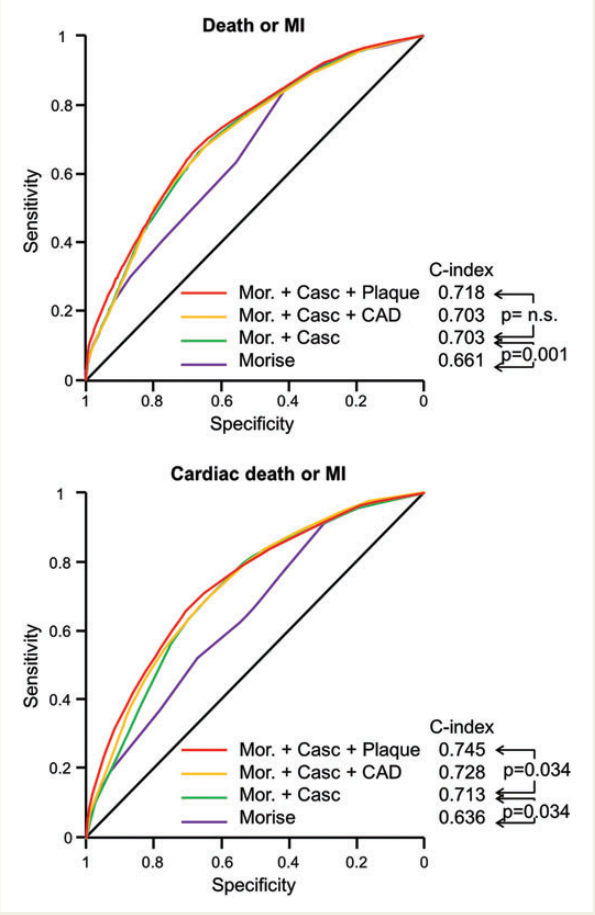

Figure 3 Receiver operator curve for the incremental predictive value of Calcium scoring (Casc) and coronary computed tomography angiography—both total plaque (Plaque) and coronary artery disease severity (coronary artery disease)—beyond the Morise score (Mor.) for primary endpoint (top) and secondary endpoint of cardiac events (bottom).

have first to be validated in prospective outcome studies. In the meantime, CCTA could be used as further guidance for medical therapy if clinical risk assessment is inconclusive or if a patient has a high risk of complications when taking certain preventive medication.

Limitations

This is an observational single-centre study. The results may be affected by characteristics unique to the patients investigated. Furthermore, outcome might be confounded by treatment decisions based on the results of the investigation. In addition, complete information on medication prescription and compliance during the follow-up is not available.

More than 30 patients were lost on follow-up; events in these patients could significantly alter the findings of this study.

Compared with other studies the study population has a higher number of patients without chest pain and ischaemia and a lower rate of obstructive CAD. In addition, the event rate, particularly for cardiac death and myocardial infarction is quite low. Although we found no difference in the predictive value of CCTA between patient with and without chest pain, the results of this study may not be generalizable to other populations.

The results of our study should be validated by a multicentre analysis.

Conclusion

In a large population of >1500 patients with suspected CAD, CCTA proved a useful tool in predicting cardiovascular outcomes over long-term follow-up out to 5 years. While the exclusion of atherosclerotic changes in CCTA is associated with an excellent prognosis, the documentation of both atherosclerotic plaques (CAD without obstruction) and of obstructive CAD in CCTA improve the risk prediction for hard cardiovascular endpoints including death and myocardial infarction over and above the predictive ability of traditional clinical risk scores. In addition, both parameters predicted the risk of need for subsequent coronary

Table 6 Reclassification

	All		Events		No events	
	NRI	*P*-value	NRI	*P*-value	NRI	*P*-value
Primary endpoint (all events)						
CAD severity	10%	0.45	−21%	0.09	31%	<0.0001
Total plaque score	49%	0.0002	11%	0.37	37%	<0.0001
Segment stenosis score	38%	0.0028	11%	0.37	28%	<0.0001
Modified Duke Score	11%	0.42	−27%	0.03	38%	<0.0001
Secondary endpoint (cardiac events)						
CAD severity	21%	0.29	−20%	0.32	41%	<0.0001
Total plaque score	54%	0.0078	12%	0.55	42%	<0.0001
Segment stenosis score	60%	0.0028	30%	0.32	40%	<0.0001
Modified Duke Score	24%	0.24	−20%	0.32	44%	<0.0001

Net reclassification improvement beyond the Morise risk score of different CCTA variables.

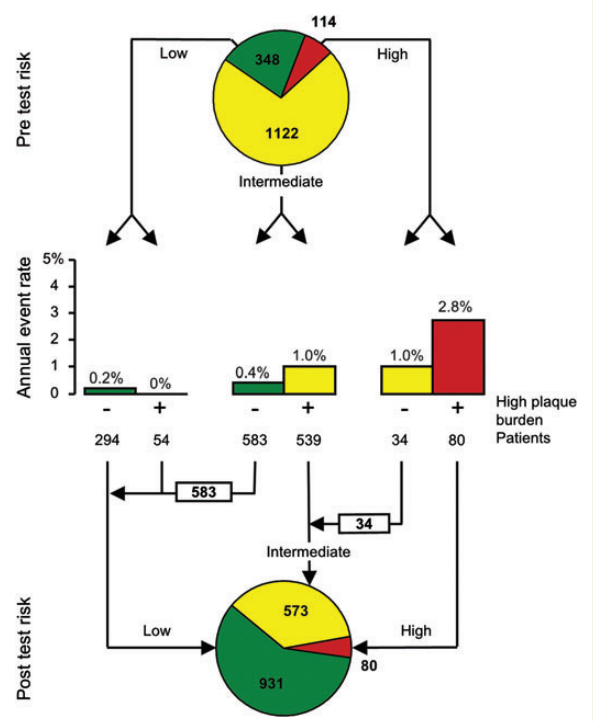

Figure 4 Cardiovascular risk reclassification applying a coronary computed tomography angiography plaque score on top of the clinical risk assessment according to the Morise clinical score.

revascularization. The results of our analysis should be confirmed by larger multicentre studies.

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