Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

Schuijf, J.D.

Chapter 20

Prognostic Value of Multi-Slice Computed Tomography Coronary Angiography in Patients with Known or Suspected CAD

Joanne D. Schuijf, Gabija Pundziute, J. Wouter Jukema, Eric Boersma, Albert de Roos, Ernst E. van der Wall, Jeroen J. Bax

J Am Coll Cardiol 2007; 49: 62-70

Abstract

Background

It is expected that multi-slice computed tomography (MSCT) will be increasingly used as an alternative imaging modality in the diagnosis of patients with suspected CAD. Data on prognostic value of MSCT however are currently not available. The purpose of the study was to determine the prognostic value of MSCT coronary angiography in patients with known or suspected coronary artery disease (CAD).

Methods

A total of 100 patients (73 men, age 59±12 years), who were referred for further cardiac evaluation due to suspicion of significant CAD, underwent additional MSCT coronary angiography to evaluate the presence and severity of CAD. Patients were followed for the occurrence of: 1. cardiac death, 2. non-fatal myocardial infarction, 3. unstable angina requiring hospitalization, 4. revascularization.

Results

Coronary plaques were detected in 80 (80%) patients. During a mean follow-up of 16 months, 33 events occurred in 26 patients. In patients with normal coronary arteries on MSCT, first year event rate was 0% versus 30% in patients with any evidence of CAD on MSCT. Observed event rate was highest in the presence of obstructive lesions (63%) and when obstructive lesions were located in the left main (LM) /left anterior descending (LAD) coronary arteries (77%). Nonetheless elevated event rate was also observed in patients with non-obstructive CAD (8%). In multivariate analysis, significant predictors of events included the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, and number of segments with obstructive plaques.

Conclusions

MSCT coronary angiography provides independent prognostic information over baseline clinical risk factors in patients with known and suspected CAD. Excellent prognosis was noted in patients with a normal MSCT.

Introduction

In patients presenting with suspected or known coronary artery disease (CAD), assessment of prognosis is essential in selecting appropriate patient management. Currently, extensive data are available on the prognostic value of myocardial perfusion imaging with single photon emission computed tomography (SPECT). A normal SPECT study has been shown to indicate a good clinical outcome with an annual death or infarct rate of < 1% per year, whereas the likelihood to develop cardiac events is significantly increased when perfusion abnormalities are detected [1;2]. Similarly, coronary artery calcium score assessed by electron beam computed tomography (EBCT) or, less frequently, by multi-slice computed tomography (MSCT) has been used for risk stratification in patients with known or suspected CAD, and a calcium score < 100 has been associated with excellent outcome, with an increase in event rate paralleling the increase in calcium score [3;4].

More recently non-invasive coronary angiography techniques (magnetic resonance imaging, EBCT and MSCT) have been introduced which allow direct visualization of coronary artery lesions. At present, MSCT appears to be to most robust technique for this purpose and it is expected that this technique will be increasingly used as an alternative first-line imaging modality in the diagnosis of patients presenting with chest pain suspect for CAD. MSCT allows detection of both obstructive as well as non-obstructive lesions, while also non-calcified lesions are visualized. Although the diagnostic accuracy of MSCT has been demonstrated, data on the prognostic value of MSCT are not available. Accordingly, the aim of the study was to determine the prognostic value of MSCT in patients with known or suspected CAD.

Methods

Patients and study protocol

The study population consisted of consecutive patients who presented to the outpatient clinic and were referred for further evaluation (using exercise-ECG, perfusion imaging or invasive coronary angiography) of suspected CAD (chest pain complaints, elevated risk profile or abnormal test results). In all patients, MSCT coronary angiography was performed in addition to the standard clinical work-up. Subsequent clinical management was based on the latter; MSCT findings were not included in the diagnostic/therapeutic work-up.

Only patients without previous coronary bypass grafting who were in sinus rhythm and without contraindications to iodinated contrast media were included. As a result of these inclusion criteria, 5 potentially eligible patients were not enrolled in the study due to potential contrast allergy (n=3) and atrial fibrillation (n=2), respectively. All patients gave written informed consent to the study protocol, which was approved by the local ethics committee.

A structured interview and clinical history were acquired and the following cardiac risk factors were assessed before the MSCT examination.

1. Diabetes mellitus (defined as a fasting glucose level of ≥ 7 mmol/L or the need for insulin or oral hypoglycaemic agents) [5]. 2. Hypercholesterolemia (defined as a total cholesterol level ≥ 5 mmol/L or treatment with lipid lowering drugs) [6]. 3. Hypertension (defined as blood pressure was ≥ 140/90 mmHg or by the use of antihypertensive medication) [7]. 4. Obesity (body mass index ≥30kg/m^2) [8]. 5. Positive family history of CAD (defined as the presence of CAD in first degree relatives younger than 55 (males) or 65 (females) years of age) [9] and 6. Smoking (defined as previous or current smoking).

MSCT data acquisition

All examinations were performed using Toshiba Multi-slice Aquilion systems (Toshiba Medical Systems, Tokyo, Japan). If the heart rate was ≥65 beats/min additional oral beta-blockers (metoprolol, 50 mg, single dose, 1 hour prior to scan) were provided if tolerated. First, a prospectively triggered coronary calcium scan was performed prior to MSCT angiography with identical parameters for 16- and 64-slice MSCT systems: collimation 4 x 3.0 mm, gantry rotation time 500 ms, the tube voltage and tube current 120 kV and 200 mA, respectively. The temporal window was set at 75% after the R-wave for electrocardiographically triggered prospective reconstruction.

Sixteen-slice MSCT coronary angiography was performed according to the protocol described elsewhere [10]. The following parameters were applied for 64-slice MSCT CA: collimation of 64 x 0.5 mm, tube rotation time of 400, 450 or 500 ms, depending on the heart rate, tube current 300 mA at 120 kV. Non-ionic contrast material was administered in the antecubital vein with an amount of 80 to 105 ml, depending on the total scan time, and a flow rate of 5 ml/sec (Iomeron 400 ®, Bracco Altana Pharma, Konstanz, Germany). Automated detection of peak enhancement in the aortic root was used for timing of the scan. All images were acquired during an inspiratory breath hold of approximately 10 s, with simultaneous registration of the patient's electrocardiogram. With the aid of a segmental reconstruction algorithm, data of one, two or three consecutive heartbeats were used to generate a single image.

To evaluate the presence of coronary artery plaques, reconstructions in diastole (typically 75% of the cardiac cycle) were generated with a slice thickness of 0.5 mm at an increment of 0.3 mm. If motion artefacts were present, additional reconstructions were made in different time points of the R-R interval. Axial data sets were transferred to a remote workstation (Vitrea2, Vital Images, Plymouth, Minn. USA) for post-processing and subsequent evaluation.

MSCT data analysis

Coronary artery calcium score

The coronary artery calcium score was assessed with the application of dedicated software (Vitrea2, Vital Images, Plymouth, Minn. USA). Coronary artery calcium was identified as a dense area in the coronary artery exceeding the threshold of 130 HU. An overall Agatston score was recorded for each patient.

Coronary plaque assessment

For the current study, all MSCT angiograms were evaluated within a time-frame of 2 weeks by 2 experienced observers unaware of the clinical history of the patients, using a standard analysis (see below). In case of disagreement, a joint reading was performed and a consensus decision was reached. Coronary arteries were divided into 17 segments according to the modified American Heart Association classification [11]. Only segments with a diameter >1.5 mm (as measured on the MSCT coronary angiogram) were included. First, each segment was classified as interpretable or not. Predefined, patients were excluded from the analysis in case of 1. an uninterpretable proximal or mid segment or 2. more than 3 uninterpretable segments in general.

Then, the interpretable segments were evaluated for the presence of any atherosclerotic plaque using axial images and curved multiplanar reconstructions. Coronary plaques were defined as structures >1 mm^2 within and/or adjacent to the coronary artery lumen, which could be clearly distinguished from the vessel lumen and the surrounding pericardial tissue, as previously described [12]. Subsequently, the type of plaque was determined per segment using the following classification: 1. non-calcified = plaque having lower density compared with the contrast-enhanced vessel lumen present without any calcification discernible, 2. calcified plaque = only plaque with high density present and 3. mixed plaque = plaque with non-calcified and calcified elements present. Finally, it was determined for each segment whether obstructive luminal narrowing, using a threshold of 50% luminal narrowing, was present or not. For each patient, the number of diseased coronary segments, number of segments with obstructive lesions as well as number of each type of plaques was calculated. Patients without coronary artery calcium or coronary plaques on MSCT were considered normal; an abnormal MSCT was defined in the presence of ≥1 coronary plaque. Abnormal patients were further classified as having obstructive coronary plaques (≥50% luminal narrowing) in one ore more coronary arteries, as well as having obstructive coronary lesions in the left main (LM) and/or left anterior descending (LAD) coronary arteries.

Follow-up

Follow-up information was obtained by either clinical visits or telephone interviews. Hospital records of all patients were screened for the occurrence of clinical events to confirm the obtained information. Clinical endpoints were the occurrence of 1. cardiac death, 2. non-fatal infarction, 3. unstable angina requiring hospitalization, 4. revascularization. Cardiac death was defined as death caused by acute myocardial infarction, ventricular arrhythmias, or refractory heart failure. Nonfatal myocardial infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG [13].

Statistical analysis

Categorical baseline characteristics are expressed as numbers and percentages, and compared between 2 groups with the Chi-square test. Continuous variables are expressed as mean (standard deviation) and compared with the two-tailed t-test for independent samples. When not normally

distributed, continuous variables are expressed as medians (25^{th} - 75^{th} percentile range) and compared using non-parametric Mann-Whitney test.

To identify the association between MSCT variables and outcomes, Cox regression analysis was used. A composite endpoint of cardiac death, non-fatal infarction, unstable angina requiring hospitalization, and revascularization was used. First, univariate analysis of baseline clinical characteristics and MSCT variables was performed to identify potential predictors. Hazard ratios were calculated with 95% confidence intervals as an estimate of the risk associated with a particular variable. To determine independent predictors of the composite endpoint, multivariate analysis of MSCT variables with $p \leq 0.05$ in the univariate analysis was performed, which was corrected for scanner type, age, EuroSCORE and baseline characteristics with $p \leq 0.5$ in the univariate analysis.

Cumulative event rates as a function over time were obtained by the Kaplan-Meier method. Event curves of the composite endpoint (cardiac death, non-fatal infarction, unstable angina requiring hospitalization, revascularization) and hard cardiac events (cardiac death, non-fatal infarction and unstable angina requiring hospitalization) were compared using the log-rank test.

Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.). P-values < 0.05 were considered as statistically significant.

Results

Patient characteristics

In total, 104 consecutive patients were enrolled in the present study and underwent MSCT coronary angiography. In 4 patients, an elevated and/or irregular heart rate during MSCT data acquisition rendered the MSCT data set uninterpretable, and these patients were excluded from the analysis. As a result, 100 patients (73 men, mean age 59±12 years) were included in the analysis (15 patients were included in a previous study on the diagnostic accuracy of MSCT in direct comparison with invasive angiography [10]). Baseline characteristics are provided in Table 1. Briefly, 65 patients (65%) presented with suspected CAD at the time of MSCT, whereas CAD was known in the remaining 35 patients (35%) (33 patients had previous myocardial infarction, 31 patients had previous percutaneous coronary intervention). In total, 55 patients underwent 16-slice MSCT and 45 underwent 64-slice MSCT.

Multi-Slice Computed Tomography

MSCT characteristics are provided in Table 2. Only coronary segments with sufficient lumen diameter for evaluation of presence of plaques were included in the analysis. After exclusion of 33 (2%) coronary segments with stents and 19 (1%) non-evaluable segments due to motion artefacts, plaque burden was evaluated in 1298 segments. CAD was completely absent in 20 patients. In the remaining 80 patients, 345 coronary segments with plaques were observed, of which 47 (14%) contained non-calcified plaques, 109

Table 1. Characteristics of the study population and comparison between patients with and without events (data are expressed as number (%)).

	All patients (n=100)	Patients with events (n=26)	Patients without events (n=74)
Clinical characteristics			
Age (yrs)* (mean ± SD)	59±12	63±10	58±12
Male gender	73 (73%)	20 (77%)	53 (72%)
Obesity	20 (20%)	4 (18%)	16 (22%)
Diabetes	21 (21%)	5 (19%)	16 (22%)
Hypercholesterolemia	50 (50%)	15 (58%)	35 (47%)
Hypertension	44 (44%)	9 (35%)	35 (47%)
Family history of CAD	42 (42%)	12 (46%)	30 (41%)
Smoking	39 (39%)	13 (50%)	26 (35%)
EuroSCORE value* (mean ± SD)	2.4±2.2	3.4±2.5	2.1±2
Cardiac history			
Suspected CAD	65 (65%)	14 (54%)	51 (65%)
Previous MI	33 (33%)	11 (42%)	22 (30%)
Previous revascularization	31 (31%)	10 (39%)	21 (28%)?
Medical therapy			
ACE inhibitors	37 (37%)	7 (27%)	30 (41%)
Nitrates	14 (14%)	4 (15%)	10 (14%)
Beta-blockers	56 (56%)	16 (62%)	40 (54%)
Aspirin	54 (54%)	17 (65%)	37 (50%)
Statins	50 (50%)	12 (46%)	38 (51%)

* $p < 0.05$ between patients with and without events.
ACE: angiotensin converting enzyme; CAD: coronary artery disease; MI: myocardial infarction.

(31%) mixed plaques and 189 (55%) calcified plaques. In 71 (21%) segments of 32 (32%) patients, plaques were regarded as obstructive (≥ 50% luminal narrowing). Thirty-two (9%) segments with obstructive lesions in 23 (23%) patients were located in the LM and/or LAD coronary artery. In Figure 1, examples of different MSCT observations, including normal coronary arteries, non-obstructive CAD and obstructive CAD in the LM, are illustrated.

Follow-up results

During a mean follow-up of 16 ± 8 months (median 12 months, range 5 – 39 months), 33 events occurred in 26 patients (with 7 events occurring repeatedly). One patient (1%) died of acute myocardial infarction. Non-fatal myocardial infarction occurred in 3 patients (3%), unstable angina requiring hospitalization occurred in 4 patients (4%, with 1 also undergoing revascularization). A total of 24 patients (24%) underwent coronary revascularization; percutaneous coronary intervention was performed in 17 patients, whereas the remaining 7 patients underwent coronary artery bypass grafting. The decision for revascularization was based on worsening angina and/or the presence of ischemia on non-invasive testing.

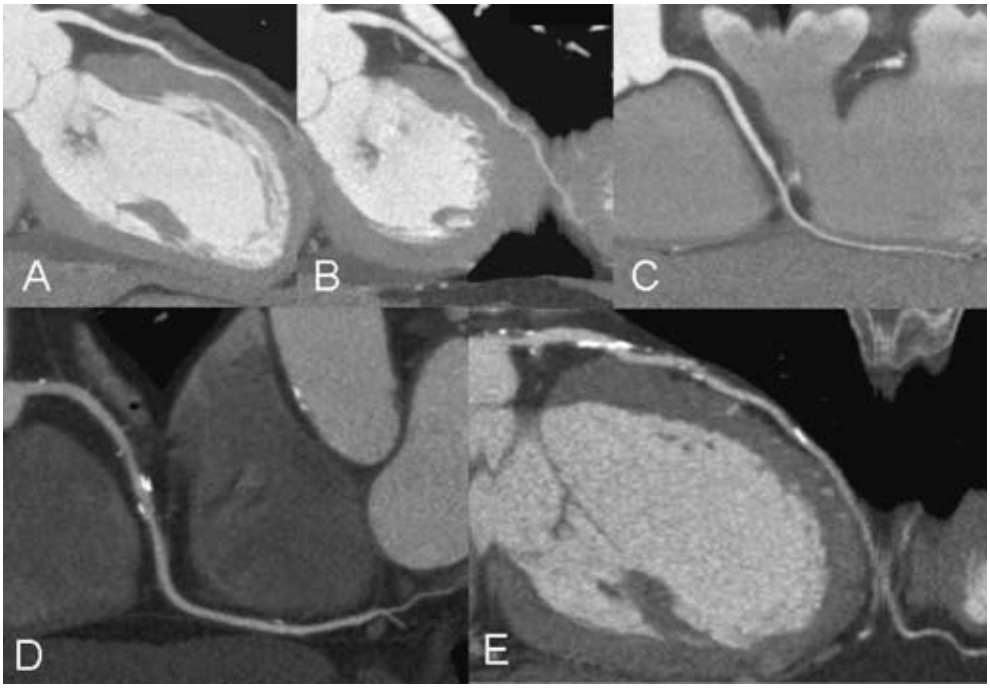

Figure 1. Examples of different MSCT observations. In Panels A, B, and C, curved multi-planar reconstructions of respectively the LAD, LCx and RCA of a patient with normal coronary arteries are provided. In Panel D, a curved multi-planar reconstruction of the RCA is provided revealing diffuse CAD without obstructive lesions. In Panel E, stenosis of the LM as well as proximal LAD can be observed.

Table 2. MSCT Characteristics of the study population and comparison between patients with and without events

	All patients (n=100)	Patients with events (n=26)	Patients without events (n=74)
Total Agatston score* (median, 25th-75th percentile)	147 (0-383)	311 (122-552)	62 (0-309)
Coronary plaques on MSCT* (number (%))	80 (80%)	26 (100%)	54 (73%)
Obstructive CAD* (number (%))	32 (32%)	20 (77%)	12 (16%)
Obstructive CAD in LM/LAD* (number (%))	23 (23%)	18 (69%)	5 (7%)
Nr of segments with plaques* (median, 25th-75th percentile)	3 (1-5)	5 (4-7)	2 (0-5)
Nr of segments with obstructive plaques* (median, 25th-75th percentile)	0 (0-1)	1.5 (0.8-3)	0
Nr of segments with non-calcified plaques (median, 25th-75th percentile)	0 (0-1)	0 (0-1)	0 (0-1)
Nr of segments with mixed plaques* (median, 25th-75th percentile)	0 (0-2)	2 (0.8-3.3)	0 (0-2)
Nr of segments with calcified plaques* (median, 25th-75th percentile)	1 (0-3)	2.5 (1-4)	1 (0-3)

* $p < 0.05$ between patients with and without events.

CAD: coronary artery disease; LAD: left anterior descending coronary artery; LM: left main coronary artery; MSCT: multi-slice computed tomography.

Predictors of events

Baseline and clinical characteristics of patients with and without events are described in Table 1. Patients presenting with events during follow-up were significantly older (p = 0.03) and had worse clinical condition, as indicated by an elevated EuroSCORE value (p = 0.01). No significant differences in risk factors for CAD and use of medication were observed.

Differences in MSCT characteristics of patients with and without events are summarized in Table 2. Patients with events had more extensive atherosclerosis on MSCT as reflected by a higher coronary calcium score, and a higher number of segments showing (obstructive) plaques. Also, relatively more mixed and calcified plaques were observed as compared to patients without events.

In Table 3, the univariate analysis of both clinical and MSCT characteristics to predict events is summarized. In the multivariate analysis (Table 4), MSCT characteristics that were significant during

Table 3. Univariate predictors of events

	HR (95% CI)	p-value
Clinical characteristics		
Age (yrs)	1.0 (0.99 -1.0)	0.12
Male gender	0.86 (0.34-2.2)	0.75
Obesity	0.71 (0.24-2.0)	0.52
Diabetes	0.85 (0.32-2.3)	0.74
Hypercholesterolemia	1.4 (0.62-3.0)	0.45
Hypertension	0.62 (0.28-1.3)	0.24
Family history of CAD	1.3 (0.61-2.9)	0.47
Smoking	1.7 (0.77-3.6)	0.19
Previous revascularization	1.4 (0.62-3.1)	0.63
Previous infarction	1.5 (0.67-3.2)	0.92
EuroSCORE value	1.1 (0.99-1.3)	0.08
Medical therapy		
ACE inhibitors	0.65 (0.28-1.6)	0.34
Nitrates	1.0 (0.36-3.0)	0.94
Beta-blockers	1.4 (0.61-3.0)	0.46
Aspirin	1.8 (0.80-4.0)	0.15
Statins	0.86 (0.40-1.9)	0.70
MSCT characteristics		
Total Agatston score	1.1 (1.0-1.1)	0.06
Presence of coronary plaques on MSCT	8.0 (1.1-59)	0.04
Abnormal coronary arteries, non-obstructive CAD (as compared to no CAD)	2.7 (0.32-22)	0.36
Abnormal coronary arteries, obstructive CAD (as compared to no CAD)	22 (2.9-166)	0.003
Abnormal coronary arteries, non-obstructive CAD in LM/LAD	3.1 (0.39-25)	0.29
Abnormal coronary arteries, obstructive CAD in LM/LAD	36 (4.7-276)	0.0006
Nr of segments with plaques*	1.3 (1.1-1.4)	0.0005
Nr of segments with obstructive plaques*	1.8 (1.5-2.1)	<0.0001
Nr of segments with non-calcified plaques*	1.1 (0.78-1.6)	0.43
Nr of segments with mixed plaques*	1.5 (1.3-1.9)	0.0002
Nr of segments with calcified plaques*	1.1 (0.98-1.3)	0.1

* Ratio per segment

ACE: angiotensin converting enzyme; CAD: coronary artery disease; CI: confidence interval; HR: hazard ratio; LAD: left anterior descending coronary artery; LM: left main coronary artery; MI: myocardial infarction; MSCT: multi-slice computed tomography.

Table 4. Multivariate predictors of events, corrected for baseline variables

MSCT characteristics	Multivariate	p-value
Presence of coronary plaques on MSCT	8.8 (1.1-70)	0.04
Obstructive CAD	28 (3.3-239)	0.002
Obstructive CAD in LM/LAD	35 (4.3-288)	0.0009
Nr of segments with plaques*	1.3 (1.1-1.6)	0.0009
Nr of segments with obstructive plaques*	1.8 (1.5-2.2)	<0.0001
Nr of segments with mixed plaques*	1.6 (1.2-2.0)	0.0003

* Ratio per segment
Data are Cox's proportional hazard ratios (95% confidence intervals).
MSCT: multi-slice computed tomography.

univariate analysis were corrected for age and EuroSCORE as well baseline characteristics with $p \leq 0.5$ during univariate analysis to ensure absence of potential confounders. Also, the type of scanner (16- versus 64-slice MSCT) used was included in the multivariate analysis. As indicated in Table 4, the remaining significant independent predictors of cardiac events in the multivariate analysis were the presence of coronary plaques, obstructive CAD, LM/LAD disease, number of coronary segments with plaques, number of coronary segments with obstructive plaques and number of coronary segments with mixed plaques.

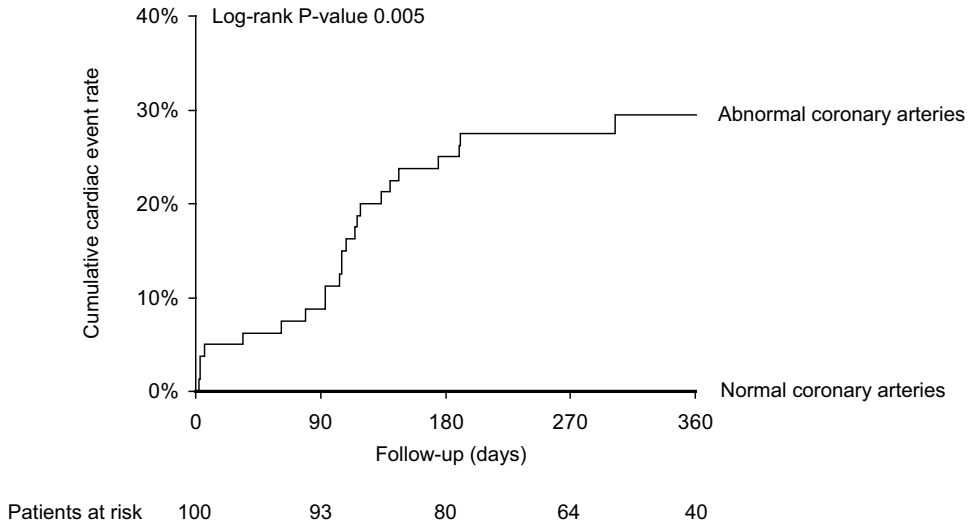

Figure 2. Kaplan-Meier curves for all events (cardiac death, non-fatal infarction, unstable angina requiring hospitalization, revascularization) in patients with normal and abnormal coronary arteries on MSCT.
Abbreviations: MSCT: multi-slice computed tomography.

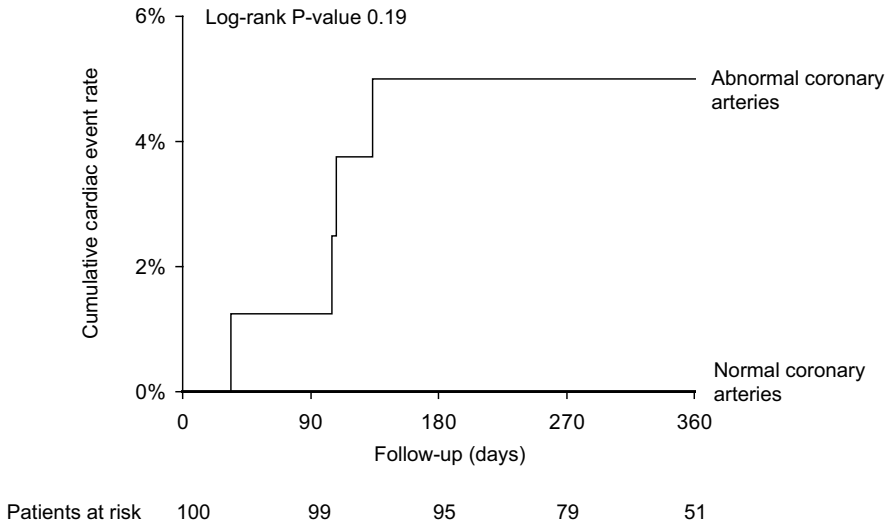

Figure 3. Kaplan-Meier curves for hard cardiac events (cardiac death, non-fatal infarction and unstable angina requiring hospitalization) in patients with normal and abnormal coronary arteries on MSCT.
MSCT: multi-slice computed tomography.

Survival analysis

Kaplan-Meier survival curves are provided in Figures 2 to 5. As can be derived from Figure 2, no events occurred in patients with normal coronary arteries on MSCT, whereas a first year event rate (including all events) of 30% was observed in patients with any CAD on MSCT (log-rank p-value = 0.005). Excluding revascularizations resulted in a first year hard cardiac event rate of 5% in patients with CAD on MSCT, as compared to 0% in patients with completely absent CAD on MSCT (log-rank p-value = 0.19) (Figure 3).

In Figure 4, the relation between the severity of CAD and the occurrence of events was further explored, showing an increased event rate in patients with obstructive CAD (63%) as compared to patients without CAD (0%) or non-obstructive CAD (8%) (log-rank p-value < 0.001). Finally, LM/LAD disease was found to be associated with the highest event rate (77%) as shown in Figure 5 (log-rank p-value < 0.001).

Discussion

In the present study MSCT coronary angiography provided independent prognostic information for predicting cardiac events. Patients with completely absent CAD on MSCT coronary angiography had excellent prognosis (0% event rate), whereas an increased event rate (30%) was observed in patients with CAD on MSCT. Furthermore, the risk of cardiac events increased with the extent of CAD as observed on MSCT, and patients with obstructive lesions (particularly in the LM and LAD) were shown

to be at the greatest risk for cardiac events. Even after correction for baseline clinical variables such as age and risk factors, MSCT variables reflecting coronary plaque burden, including the severity, extent and location of atherosclerosis, remained independent predictors of cardiac events.

The prognostication and subsequent management of patients with known or suspected CAD in current practice relies on initial clinical evaluation, with the low-risk patients being reassured and the high-risk patients being referred for invasive angiography [14]. However, the majority of these patients are in the intermediate risk group, in whom prognosis and subsequent management is less well-defined. Accordingly, these patients need additional testing with one or more of the established non-invasive modalities, which include exercise electrocardiography, stress SPECT imaging or stress echocardiography [14]. All these techniques aim at detecting ischemia. Exercise electrocardiography is not an ideal modality due to the suboptimal accuracy, and imaging of stress-induced perfusion abnormalities or systolic wall motion abnormalities may be preferred; indeed average sensitivity and specificity of 87% and 73% to detect CAD have been reported for SPECT versus 82% and 84% for stress echocardiography [15;16]. In addition, these tests proved to be predictive of future cardiac events when abnormalities were found and were associated with a low risk for events when the test results were normal [17-19].

MSCT coronary angiography is a highly accurate, non-invasive imaging technique for the diagnosis of CAD; in particular, the negative predictive value of MSCT approaches 100%, allowing rule out of CAD [20;21].

The current study explored the prognostic value of MSCT in a symptomatic patient population with known or suspected CAD and a high prevalence of conventional risk factors. Consequently, the pre-test likelihood of CAD was high in this population, and even in patients without known

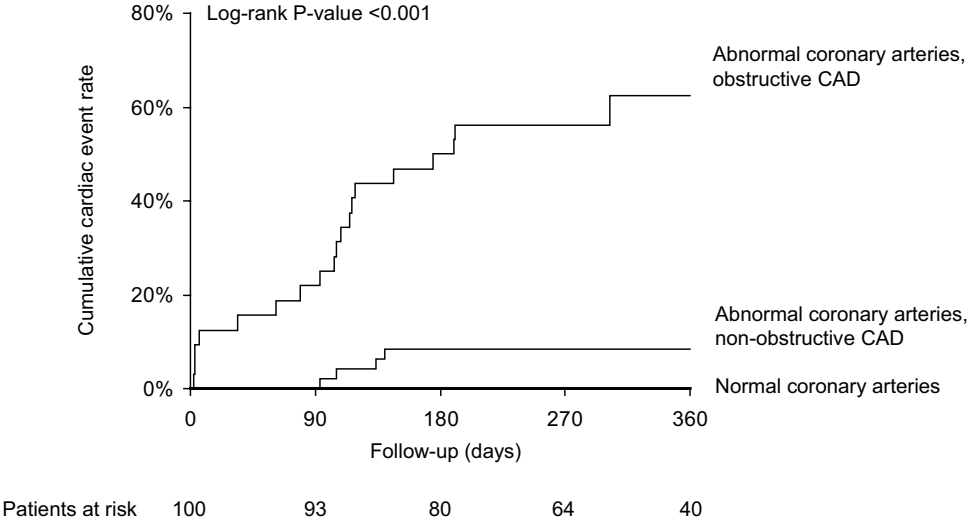

Figure 4. Kaplan-Meier curves for all events (cardiac death, non-fatal infarction, unstable angina requiring hospitalization, revascularization) in patients with normal coronary arteries, non-obstructive CAD and obstructive CAD on MSCT.

CAD: coronary artery disease; MSCT: multi-slice computed tomography.

disease, CAD was present on MSCT in 69%. Not surprisingly therefore, high cardiac event rates were observed. Most importantly however, a 100% event free survival was noted in patients without any abnormalities on MSCT, highlighting an excellent negative predictive value of a normal MSCT. This finding is of major clinical relevance, since these patients may indeed be safely reassured without need for further testing. Patients with coronary atherosclerosis identified on MSCT were shown to have worse prognosis. More detailed analysis revealed that although the risk of events was considerably higher in patients with obstructive CAD, patients with non-obstructive CAD still were at elevated risk as compared to patients without CAD. Indeed, previous studies support the notion that plaque composition (in addition to stenosis severity) is predictive of events. Moreover, Mann et al demonstrated in a post-mortem study that lipid core size and minimal cap thickness, 2 major determinants of plaque vulnerability, were not related to absolute plaque size or degree of stenosis [22]. Accordingly, vulnerable plaques may occur across the full spectrum of severity of stenosis, underlining that also non-obstructive lesions may contribute to coronary events [23;24]. Since less-obstructive plaques are more frequent than severely obstructive plaques, coronary occlusion and myocardial infarction may in fact most frequently arise from mild to moderate stenoses [23;25-28]. Pooling of these angiographical studies showed that 68% of myocardial infarctions were attributable to so-called "angiographically silent" lesions (luminal narrowing < 50%), whereas the culprit in only 14% could be assigned to a severe stenotic lesion (> 70%) [29]. In line with these observations, multivariate analysis of the possible predictors of cardiac events in the present study demonstrated that non-obstructive CAD was indeed an independent predictor of future cardiac events. Of interest, the presence of mixed plaques, which may represent less advanced and possibly less stabilized

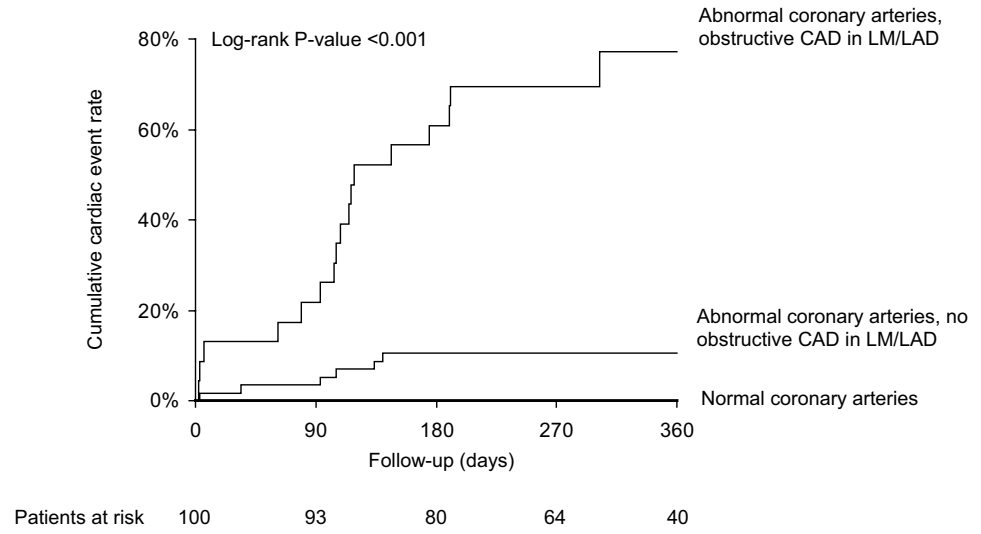

Figure 5. Kaplan-Meier curves for all events (cardiac death, non-fatal infarction, unstable angina requiring hospitalization, revascularization) in patients with normal coronary arteries, patients without obstructive CAD in LM/LAD and patients with obstructive CAD in LM and/or LAD on MSCT.
CAD: coronary artery disease; LAD: left anterior descending coronary artery; LM: left main coronary artery; MSCT: multi-slice computed tomography.

atherosclerosis as compared to dense calcified lesions [30], was shown to be an independent predictor as well. However, further investigations are clearly needed to support these observations.
Nonetheless, considering individual lesions, the likelihood of progression to coronary occlusion (and subsequent myocardial infarction) remains highest for severe obstructive lesions [23;25;26]. Indeed, prospective evaluation of non-bypassed coronary segments, as was performed in the Coronary Artery Surgery Study (CASS), showed that during a 5 year follow-up only 0.7% and 2.3% of segments with narrowing of respectively <5% and 5% to 49% resulted in coronary occlusion [25]. In contrast, occlusion occurred in 10.1% and even 23.6% of lesions with narrowing 50% to 80% and 81% to 95%, respectively. In agreement, high event rates were observed for patients with obstructive CAD in the present study. More detailed analysis showed that hazard ratios were highest for patients with obstructive CAD in either the LM or LAD coronary arteries. Indeed previous studies demonstrated that patients with severe proximal LAD disease are at high risk [31-33]; for example Califf et al reported a 59% event free survival at 5 years in patients with 3-vessel disease and proximal LAD disease [34]. Accordingly, early identification of these patients with MSCT will be crucial to optimize therapy.

Study limitations

The prognostic value of MSCT in the present study was evaluated in patients presenting with a wide spectrum of different conditions, including patients with no previous history of CAD as well as patients with previous myocardial infarction and revascularization. Accordingly, treatment strategies may have differed substantially within the studied population and future studies will need to address the prognostic role of MSCT coronary angiography in more homogeneous patient populations. Also, the study population was small and some clinically relevant predictors may not have reached statistical significance. Studies in larger cohorts (with longer follow-up) are clearly warranted to confirm these initial results.

Conclusion

This is the first study to demonstrate the independent prognostic value of MSCT coronary angiography over baseline clinical risk factors in patients presenting with chest pain. An excellent prognosis (0% event rate) was noted in patients with a normal MSCT. The presence of CAD (either non-obstructive or obstructive atherosclerotic lesions) was associated with an event rate of 30%. The event rate was highest in the presence of obstructive lesions and when lesions were located in the LM/LAD coronary arteries. Future studies are needed to further define the prognostic value of MSCT.

References

1. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, Kelion AD, Al Mohammad A, Prvulovich EM, Shaw LJ, Tweddel AC. Myocardial perfusion scintigraphy: the evidence. *Eur J Nucl Med Mol Imaging*. 2004;31:261-291.
2. Shaw LJ, Iskandrian AE. Prognostic value of gated myocardial perfusion SPECT. *J Nucl Cardiol*. 2004;11:171-185.
3. O'Rourke RA, Brundage BH, Froelicher VF, Greenland P, Grundy SM, Hachamovitch R, Pohost GM, Shaw LJ, Weintraub WS, Winters WL, Jr. American College of Cardiology/American Heart Association Expert Consensus Document on electron-beam computed tomography for the diagnosis and prognosis of coronary artery disease. *J Am Coll Cardiol*. 2000;36:326-340.
4. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology*. 2003;228:826-833.
5. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183-1197.
6. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
7. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011-1053.
8. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. *Obes Res*. 1998;6 Suppl 2:51S-209S.
9. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol*. 2005;46:807-814.
10. Schuijf JD, Bax JJ, Salm LP, Jukema JW, Lamb HJ, van der Wall EE, de Roos A. Noninvasive coronary imaging and assessment of left ventricular function using 16-slice computed tomography. *Am J Cardiol*. 2005;95:571-574.
11. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5-40.
12. Leber AW, Knez A, Becker A, Becker C, von Ziegler F, Nikolaou K, Rist C, Reiser M, White C, Steinbeck G, Boekstegers P. Accuracy of multidetector spiral computed tomography in identifying and differentiating the composition of coronary atherosclerotic plaques: a comparative study with intracoronary ultrasound. *J Am Coll Cardiol*. 2004;43:1241-1247.
13. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J*. 2000;21:1502-1513.
14. Management of stable angina pectoris. Recommendations of the Task Force of the European Society of Cardiology. *Eur Heart J*. 1997;18:394-413.
15. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC, Jr., Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J Am Soc Echocardiogr*. 2003;16:1091-1110.
16. Klocke FJ, Baird MG, Lorell BH, Bateman TM, Messer JV, Berman DS, O'Gara PT, Carabello BA, Russell RO, Jr., Cerqueira MD, John Sutton MG, DeMaria AN, Udelson JE, Kennedy JW, Verani MS, Williams KA, Antman EM, Smith SC, Jr., Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol*. 2003;42:1318-1333.

17. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol*. 2002;40:1531-1540.
18. Sozzi FB, Elhendy A, Roelandt JR, Van Domburg RT, Schinkel AF, Vourvouri EC, Bax JJ, Rizzello V, Poldermans D. Long-term prognosis after normal dobutamine stress echocardiography. *Am J Cardiol*. 2003;92:1267-1270.
19. Yao SS, Qureshi E, Sherrid MV, Chaudhry FA. Practical applications in stress echocardiography: risk stratification and prognosis in patients with known or suspected ischemic heart disease. *J Am Coll Cardiol*. 2003;42:1084-1090.
20. Schuijf JD, Bax JJ, Shaw LJ, de Roos A, Lamb HJ, van der Wall EE, Wijns W. Meta-analysis of comparative diagnostic performance of magnetic resonance imaging and multislice computed tomography for noninvasive coronary angiography. *Am Heart J*. 2006;151:404-411.
21. Mollet NR, Cademartiri F, van Mieghem CA, Runza G, McFadden EP, Baks T, Serruys PW, Krestin GP, de Feyter PJ. High-resolution spiral computed tomography coronary angiography in patients referred for diagnostic conventional coronary angiography. *Circulation*. 2005;112:2318-2323.
22. Mann JM, Davies MJ. Vulnerable plaque. Relation of characteristics to degree of stenosis in human coronary arteries. *Circulation*. 1996;94:928-931.
23. Giroud D, Li JM, Urban P, Meier B, Rutishauer W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol*. 1992;69:729-732.
24. Davies MJ, Thomas AC. Plaque fissuring--the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J*. 1985;53:363-373.
25. Alderman EL, Corley SD, Fisher LD, Chaitman BR, Faxon DP, Foster ED, Killip T, Sosa JA, Bourassa MG. Five-year angiographic follow-up of factors associated with progression of coronary artery disease in the Coronary Artery Surgery Study (CASS). CASS Participating Investigators and Staff. *J Am Coll Cardiol*. 1993;22:1141-1154.
26. Nobuyoshi M, Tanaka M, Nosaka H, Kimura T, Yokoi H, Hamasaki N, Kim K, Shindo T, Kimura K. Progression of coronary atherosclerosis: is coronary spasm related to progression? *J Am Coll Cardiol*. 1991;18:904-910.
27. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borrico S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12:56-62.
28. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988;78:1157-1166.
29. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657-671.
30. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Jr., Rosenfeld ME, Schwartz CJ, Wagner WD, Wissler RW. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol*. 1995;15:1512-1531.
31. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, . Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563-570.
32. Nwasokwa ON, Koss JH, Friedman GH, Grunwald AM, Bodenheimer MM. Bypass surgery for chronic stable angina: predictors of survival benefit and strategy for patient selection. *Ann Intern Med*. 1991;114:1035-1049.
33. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. *N Engl J Med*. 1988;319:332-337.
34. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:1007-1019.