Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

Werkhoven, J.M. van

Chapter 12

Incremental prognostic value of multi-slice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease

JM van Werkhoven, JD Schuijf, O Gaemperli, JW Jukema,
LJ Kroft, E Boersma, A Pazhenkottil, I Valenta, G Pundziute, A de Roos,
EE van der Wall, PA Kaufmann, JJ Bax

Abstract

The purpose of this study was to assess the relationship between calcium scoring (CS) and multi-slice computed tomography coronary angiography (MSCTA) and to determine if MSCTA has an incremental prognostic value to CS. In 432 patients (59% male, age 58±11 years) referred for cardiac evaluation due to suspected coronary artery disease (CAD), CS and 64-slice MSCTA were performed. The following events were combined in a composite endpoint: all cause mortality, non-fatal infarction, and unstable angina requiring revascularization. CS was 0 in 147 (34%) patients, CS 1-99 was present in 122 (28%), CS 100-399 in 75 (17%), CS 400-999 in 56 (13%), and CS≥1000 in 32 (7%). MSCTA was normal in 133 (31%) patients, MSCTA 30-50% stenosis was observed in 190 (44%), and MSCTA ≥50% stenosis in 109 (25%). During follow-up (median 670 days (25-75th percentile:418-895), an event occurred in 21 patients (4.9%) patients. After multivariate correction for CS, MSCTA≥50% stenosis, the number of diseased segments, obstructive segments, and non-calcified plaques were independent predictors with an incremental prognostic value to CS. In conclusion, MSCTA provides additional information to CS regarding stenosis severity and plaque composition. This additional information was shown to translate into incremental prognostic value over CS.

Introduction

Non-invasive imaging plays an important role in the diagnosis and prognosis of coronary artery disease (CAD). The development of non-invasive anatomic imaging techniques such as coronary calcium scoring (CS) and multi-slice computed tomography coronary angiography (MSCTA) have resulted in substantially increased interest in non-invasive imaging of atherosclerosis.

Extensive data are available supporting the value of CS in risk stratification and patients with increased CS are generally considered to have a higher likelihood of future cardiac events. The majority of data however have been obtained in asymptomatic patients at low to intermediate risk although the technique may also be useful in symptomatic patients.[1-4]

Direct non-invasive detection of luminal narrowing has become possible with the introduction of MSCTA. Preliminary studies addressing the prognostic value of MSCTA have demonstrated a low risk for events in case of a normal MSCTA study compared to a higher risk in the presence of significant CAD on MSCTA.[5-8] Importantly, MSCTA is not restricted to luminography and the technique allows simultaneous visualization of the vessel wall. As a result, also non-stenotic lesions can be identified and even some information on plaque composition can be derived.[9] This may be an important feature of the technique as several plaque characteristics observed on MSCTA have been linked to acute coronary syndromes in retrospective studies.[10, 11] Nevertheless, only limited prospective data are currently available supporting this notion.

Accordingly, both CS and MSCTA may be useful for risk stratification in patients with suspected CAD, it is unclear however if the information regarding stenosis severity and plaque composition on MSCTA may provide additional prognostic information to CS. To answer this clinical question amongst others we have started a prospective registry that addresses the prognostic value of MSCTA in relation to baseline characteristics as well as other imaging techniques.[12] The purpose of the present study was to assess the relationship between observations on CS and MSCTA and to determine whether the information regarding stenosis severity and plaque composition on MSCTA translates into incremental prognostic value over CS alone.

Methods

Patient selection

The study population consisted of patients with suspected coronary artery disease (CAD) who were clinically referred for further cardiac assessment because of chest pain, a positive exercise ECG test, or a high risk profile for cardiovascular disease as part of an ongoing study protocol addressing the prognostic value of MSCTA in relation to other imaging techniques. From this prospective registry, results addressing the incremental prognostic value of MSCTA over myocardial perfusion imaging have been recently published.[12] Patients were enrolled at the University Hospital in Zurich, Switzerland, and at the Leiden University Medical Center, The Netherlands. The included patients prospectively underwent a CS scan followed by MSCTA. Exclusion criteria were: cardiac arrhythmias, renal insufficiency (defined as a glomerular filtration rate <30 ml/min), known hypersensitivity to iodine contrast media, and pregnancy. In addition, patients with an uninterpretable MSCTA examination were excluded. The pre-test likelihood of CAD was determined using the Diamond and Forrester method, with a risk threshold of <13.4% for low risk, >87.2% for high risk, and between 13.4 and 87.2% for intermediate risk, as previously described.[13] The study was approved by the local ethics committee in both participating centers.

CS and MSCTA protocol

Patients were scanned using a 64-slice CT scanner (Aquillion64, Toshiba Medical Systems, Tokyo, Japan; or General Electrics LightSpeed VCT, Milwaukee, WI, US). Before CS and MSCTA examinations, the patient's heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding the threshold of 65 beats per minute were administered beta-blocking medication (50-100 mg metoprolol, oral or 5-10 mg metoprolol, intravenous). Before the helical scan, a non-enhanced low dose ECG-gated scan was performed to measure CS. The CS scan was prospectively triggered at 70% or 75% of the R-R interval and performed using the following scan parameters: 4x3.0 mm or 2.5 mm; gantry rotation time, 350-500 milliseconds; tube voltage, 120 kV; and tube current, 200-250 mA.

The CS scan was used to determine the start and end positions of the MSCTA examination. The helical scan was performed using a collimation of 64 x 0.5 mm or 64x0.625 mm. All scan parameters have been previously published.[14, 15]

Datasets were reconstructed from the retrospectively gated raw data. Images were reconstructed with an effective slice thickness of 0.3 or 0.5. Coronary arteries were evaluated using the reconstruction dataset with the least motion artifacts, typically an end-diastolic phase.

The effective dose of the CS and MSCTA scans was estimated from the product of the dose-length product and an organ weighing factor [k=0.014 mSv x (mGy x cm)-1) for the chest as the investigated anatomical region.[16]

Data Analysis

Post-processing of the CS and MSCTA examinations was performed on dedicated workstations (Vitrea2, Vital Images, USA and Advantage, GE healthcare, USA). The CS was calculated using the Agatston method.[17] MSCTA angiograms were examined using the axial slices, curved multiplanar reconstructions (MPR), and maximum intensity projections (MIP). Coronary anatomy was assessed in a standardized manner by dividing the coronary artery tree into 17 segments according to the modified American Heart Association classification. First segments were classified based on the maximum luminal diameter stenosis. Normal MSCTA was defined as completely normal anatomy or minimal wall irregularities <30%, non-significant CAD was defined as the presence of luminal narrowing with a maximal luminal diameter stenosis <50%, and significant CAD was defined as the presence of an atherosclerotic lesion exceeding the threshold of 50% maximal luminal diameter stenosis. After assessment of stenosis severity, plaque composition was determined in all diseased segments (non-significant or significant CAD on MSCTA). Plaque composition was graded as non-calcified plaque (plaques having lower density compared with the contrast-enhanced lumen), calcified plaque (plaques with high density), and mixed plaque (containing elements of both non-calcified and calcified plaque).

Follow-up

Patient follow-up data were gathered using clinical visits or standardized telephone interviews. A composite endpoint was construed using the following events: all cause mortality, non-fatal myocardial infarction, and unstable angina requiring revascularization. Non-fatal infarction was defined based on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the ECG. Unstable angina was defined according to the European Society of Cardiology guidelines as acute chest pain with or without the presence of ECG abnormalities, and negative cardiac enzyme levels.[18] Patients with stable complaints undergoing an early elective revascularization within 60 days after imaging with CS and MSCTA were excluded from the survival analysis.

Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical baseline data were expressed in numbers and percentages. Cox regression analysis was used to determine the prognostic value of CS, and MSCTA variables. First univariate analysis of baseline CS and MSCTA variables was performed using the composite endpoint of all cause mortality, non-fatal infarction, and unstable angina requiring revascularization. For

each variable a hazard ratio with a 95%-confidence interval (95%-CI) was calculated. The predictive value of CS was assessed using binary cutoff values (CS >0, CS ≥100, CS ≥ 400, and CS ≥ 1000). For the survival analysis of MSCTA, plaque burden (number of (non) significantly diseased segments) and plaque composition (number of segments with non-calcified, mixed or calcified plaque) were analyzed as continuous variables. Finally, multivariate models were created to assess the independent predictive value of MSCTA corrected for CS and baseline clinical variables. The incremental value of MSCTA over CS and baseline clinical variables was assessed by calculating the global chi-square. Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Results

The current study population, derived from our prospective registry, [12] consisted of 533 patients presenting with suspected CAD at the University Hospital Zurich (n=270) and at the Leiden University Medical Center (n=263). The demographics in the two populations were similar. In 24 (4.5%) of these patients the MSCTA examination was uninterpretable due to the presence of motion artifacts, increased noise due to a high body mass index, and breathing. In addition, 35 patients (6.9%) were lost to follow-up, and an early revascularization occurred in 42 (8.3%) patients. After exclusion of these patients, a total of 432 remained for further analysis. The baseline characteristics of the patient population are presented in Table 1. In summary, the average age of the study cohort was 58±11 years and 58% of patients were men. A low or intermediate pre-test likelihood was observed in respectively 24% and 65% of patients. A high pre-test likelihood was observed in 11%.

Table 1. Patient characteristics

Gender (male)	59%
Age (yrs)	58±11
Risk Factors	
Diabetes	121 (28%)
Hypertension	244 (57%)
Hypercholesterolemia	170 (39%)
Family history CAD	157 (36%)
Current Smoking	119 (28%)
Obesity (BMI ≥ 30)	92 (21%)
Pre-test likelihood of CAD	
Low	102 (24%)
Intermediate	281 (65%)
High	49 (11%)

CS and MSCTA results

The average CS of the cohort was 290±730. Calcium was absent in 117 (34%) patients, a CS of 1-99 was observed in 122 (28%), a CS between 100 and 399 in 75 (17%), a CS between 400 and 999 in 56 (13%), and a CS ≥ 1000 was present in 32 (7%) patients. MSCTA was normal in 133 (31%) patients, and atherosclerosis (non-significant or significant CAD) was present in the remaining 299 (69%) patients. Within the patients with atherosclerosis, non-significant CAD was observed in 190 (44%), and significant CAD was present in 109 (25%) patients. For the GE scanner the estimated average radiation dose for the MSCTA protocol was 18.3±5.9 mSv, and the average radiation dose for the CS protocol was 1.2±0.6 mSv. For the Toshiba scanner the estimated average radiation dose for the coronary angiography protocol was 17.6±5.6 mSv and the estimated radiation dose for the CS protocol was 1.5±0.7 mSv.

Relationship between CS and stenosis severity and plaque composition assessed on MSCTA

Stenosis severity

Figure 1 illustrates the MSCTA findings in patients with increasing CS values. In patients without any coronary calcium, MSCTA was normal in 80%. Non-calcified plaque was observed in the remaining 20% of patients (7% of the total study population). Importantly, significant CAD was observed in 4% of patients with a CS of 0. An example of a patient with a CS of 0 and a large non-calcified plaque on MSCTA, confirmed on conventional coronary

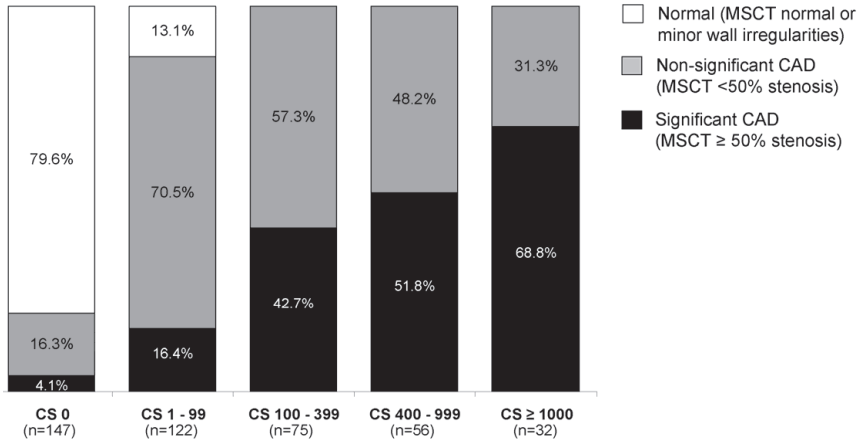

Figure 1. The relationship between increasingly higher CS categories and the prevalence of normal coronary anatomy (completely normal or minor wall irregularities), non-significant CAD (MSCTA < 50% stenosis) and significant CAD (MSCTA ≥ 50% stenosis) on MSCTA.

angiography is shown in Figure 2. In patients with coronary calcifications non-significant and significant lesions were present in all but a few patients. However the relationship between CS and significant CAD on MSCTA was less evident. Particularly in patients with an intermediate CS between 100 and 1000, significant CAD was observed in approximately 50% of patients. In patients with a high CS ≥ 1000, non-significant CAD was observed in 30% of patients.

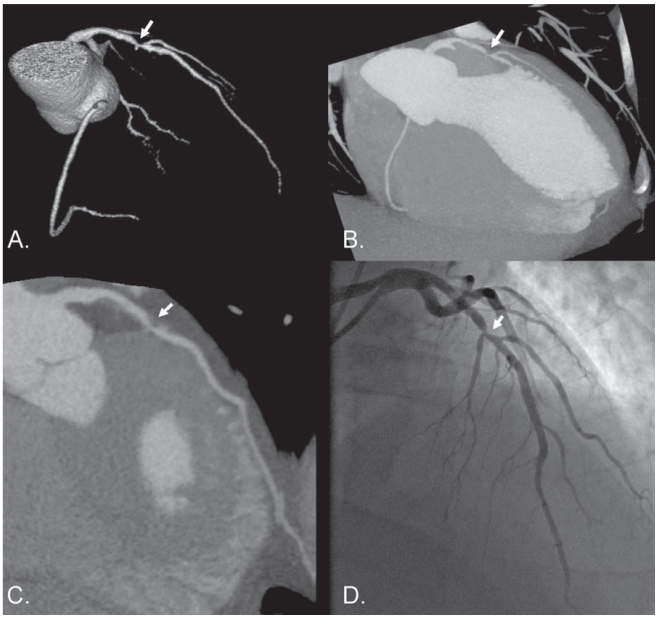

Figure 2. Case example of a 54-year old male patient presenting with atypical complaints. On CS no coronary calcifications were observed. However a large significant non-calcified plaque was detected in the left anterior descending artery on MSCTA (Panels A-C), which was confirmed on conventional coronary angiography (Panel D).

Plaque composition

MSCTA enables assessment of plaque composition in addition to stenosis severity. Figure 3 shows the distribution of segments with non-calcified plaque, mixed plaque and calcified plaque in each CS category as a percentage of the total diseased segments. In patients with CS of 0 all 76 diseased segments showed non-calcified plaque. With increasing CS categories the percentage of segments with calcified plaque contributing to the total of diseased segments increased. MSCTA was however able to identify a large proportion of diseased segments with elements of non-calcified plaque (either mixed plaque or non-calcified plaque) in each category.

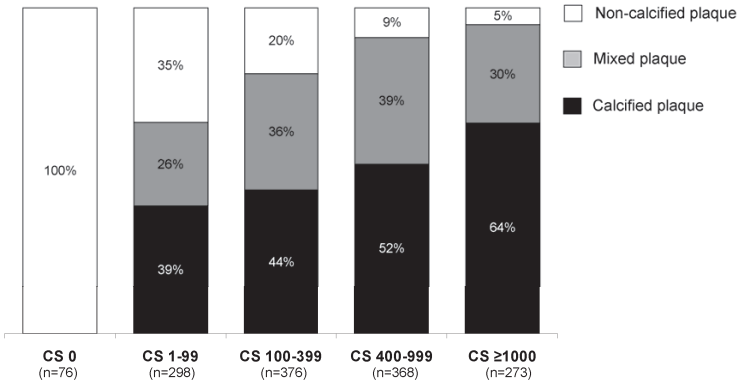

Figure 3. The distribution of segments with non-calcified plaque, mixed plaque and calcified plaque as a percentage of the total diseased segments on MSCTA per CS category. In patients with a CS 0, all 76 diseased segments showed non-calcified plaque. With increasing CS categories the percentage of diseased segments with calcified plaque increased. Nevertheless, non-calcified plaque and mixed plaque were still observed in a large proportion of diseased segments in each CS category.

Follow-up results

A median follow-up time of 670 days (25-75th percentile: 418-895) was obtained, during which the composite endpoint occurred in 21 patients (4.9%). All cause death was reported in 6 patients (1.4%), whereas non-fatal myocardial infarction occurred in 8 patients (1.8%) and 7 patients (1.6%) were revascularized due to unstable angina pectoris.

Survival analysis

Univariate analysis of CS and MSCTA categories is shown in Table 2. Within the CS cutoff categories CS ≥ 100, CS ≥ 400 and CS ≥ 1000 were significant predictors of events. The

Table 2. Univariate CS and MSCTA predictors of coronary events

	HR (95%-CI)	p-value
CS		
Calcium score (per unit increase in CS score)	1.00 (1.00-1.01)	0.019
Any calcium	3.2 (0.9-10.9)	0.062
Calcium score ≥100	3.9 (1.5-10.2)	0.005
Calcium score ≥400	3.5 (1.5-8.3)	0.004
Calcium score ≥1000	4.1 (1.5-11.3)	0.006
MSCTA		
Atherosclerosis	4.3 (1.0-18.6)	0.048
Significant CAD	3.9 (1.7-9.3)	0.002
Nr. of Diseased segments	1.2 (1.08-1.3)	<0.001
Nr. Segments with significant CAD	1.4 (1.2-1.6)	<0.001
Nr. Segments with non-calcified plaque	1.2 (1.07-1.4)	0.003
Nr. Segments with mixed plaque	1.3 (1.07-1.5)	0.005
Nr. Segments with calcified plaque	1.09 (0.9-1.3)	0.254

highest hazard ratio was observed when using a cutoff of 1000. On MSCTA several variables reached statistical significance. The presence of any stenosis (non-significant (30-50% stenosis) or significant (≥50% stenosis) as well as the presence of significant CAD (≥50% stenosis) both were strong significant predictors. When regarding plaque burden, both the number of diseased segments as well as the number of segments with significant CAD were significant univariate predictors. When regarding plaque composition, the number of segments with non-calcified plaque and the number segments with mixed plaque were also significant predictors of events. The number of segments with calcified plaque was not a significant predictor of events.

Event rates

The annualized event rate in patients without any coronary calcium was 1.1%. Increasingly higher CS was associated with increasingly higher annualized event rates, the annualized event rate was 1.4% in patients with a CS 1-99, 3.7% in patients with a CS 100-399, and 4.8% in patients with a CS 400-999. The highest annualized event rate of 8.5% was observed in patients with a CS ≥ 1000.

When regarding MSCTA, an event rate of 0.8% was observed in patients with a normal MSCTA (completely normal or minor wall irregularities); while in patients with atherosclerosis (non-significant and/or significant CAD) the annualized event rate was 3.5%. In patients with non-significant CAD the annualized event rate was 2.1%, versus 5.9% in patients with significant CAD.

Independent and incremental prognostic value of MSCTA over CS

To determine the independent prognostic value of MSCTA, multivariate models were created including all MSCTA variables corrected for age, gender and CS ≥ 1000. Table 3 shows that the presence of significant CAD, the number of diseased segments, obstructive segments, segments with non-calcified plaque, and the number of segments with mixed plaque remained independent predictors. Furthermore plaque burden and plaque composition provided incremental prognostic value over clinical variables and MSCTA as shown in Figures 4 and 5. These results suggest that MSCTA may provide additional prognostic information. In particular, the number of segments with significant CAD and and the number of segments with non-calcified plaque provided significant incremental prognostic value over CS. The number of mixed plaques provided borderline significant (p=0.058) incremental prognostic value to CS.

Table 3. Multivariate models for the prediction of coronary events

		HR (95%-CI)	p-value
Model 1	Atherosclerosis	4.5 (0.9-21.3)	0.056
	Calcium score ≥1000	4.0 (1.3-12.4)	0.016
Model 2	Significant CAD	3.6 (1.4-9.4)	0.009
	Calcium score ≥1000	2.9 (0.9-9.3)	0.064
Model 3	Nr. Diseased segments	1.2 (1.1-1.3)	0.006
	Calcium score ≥1000	2.0 (0.6-6.9)	0.268
Model 4	Nr. Segments with significant CAD	1.3 (1.1-1.5)	0.003
	Calcium score ≥1000	2.6 (0.7-9.3)	0.148
Model 5	Nr. Segments with non-calcified plaque	1.3 (1.1-1.4)	0.001
	Calcium score ≥1000	5.8 (1.9-18.2)	0.003
Model 6	Nr. Segments with mixed plaque	1.2 (1.0-1.4)	0.039
	Calcium score ≥1000	3.6 (1.1-11.6)	0.029

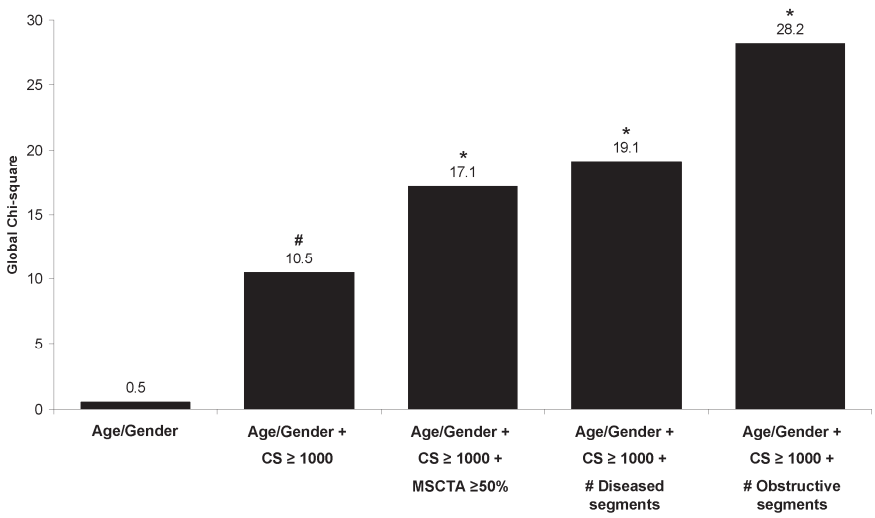

Figure 4. Bar graphs illustrating the incremental prognostic value (depicted by chi-square value on the y-axis) of significant CAD (≥50% stenosis) on MSCTA and plaque burden (defined as the number of diseased or segments with significant CAD on MSCTA) over age, gender and CS. CS has a significant incremental prognostic value over age and gender (#). A further incremental prognostic value over age, gender and CS was observed with the addition of MSCTA (*).

Discussion

The main finding of the current study was that MSCTA may provide additional anatomic information regarding stenosis severity and plaque composition compared to CS. Furthermore this information offers important prognostic information which is incremental to CS for risk stratification.

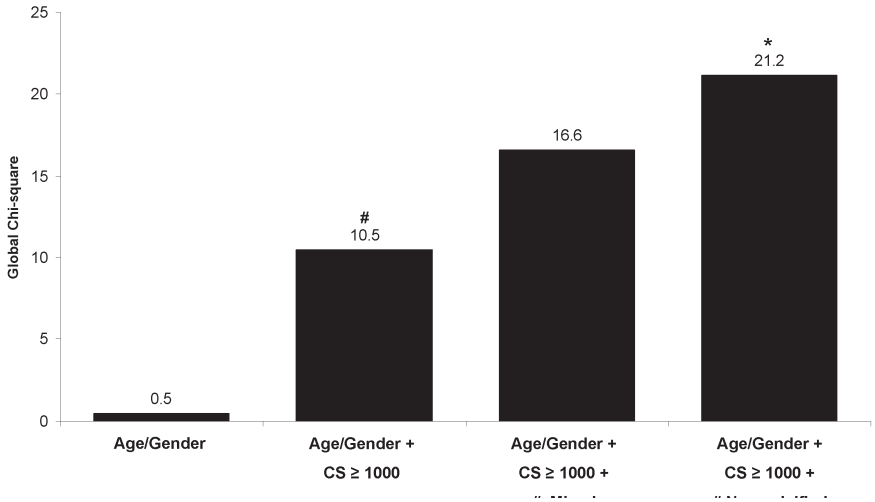

Figure 5. Bar graphs illustrating the incremental prognostic value (depicted by chi-square value on the y-axis) of MSCTA plaque composition variables over age, gender and CS. CS has a significant incremental prognostic value over age and gender (#). A further incremental prognostic value over age, gender and CS was observed with the addition of MSCTA (*).

CS and MSCTA for atherosclerosis detection

In asymptomatic patients, CS may be useful to identify the presence of atherosclerosis and thus identify patients that may be at higher risk than recognized based on traditional risk assessment.[19] Vice versa, absence of calcium on the other hand in general implies a low likelihood of events.[20] However in a small proportion of patients with a negative CS, non-calcified plaque has been observed.[21, 22] Indeed, in certain subpopulations, such as those at higher risk or in symptomatic patients the prevalence of non-calcified plaque may be higher.[23-25] Akram et al. specifically studied the relationship between symptomatic status and the prevalence of non-significant and significant CAD in patients with a CS of 0 and observed 22% non-significant and significant CAD and 8% significant CAD in symptomatic patients.[23] In the current study non-significant or significant CAD was identified on MSCTA in 20% of patients with a CS of 0, whereas significant CAD was observed in 4%. Accordingly, particularly in symptomatic populations a small proportion of patients with atherosclerosis may not be recognized by CS.

Considering patients with evidence of coronary calcifications, a positive association has been observed between CS and the presence of significant CAD on MSCTA and conventional coronary angiography.[26, 27] Indeed in the current study the prevalence of significant CAD paralleled increasing CS categories. Nevertheless, in a substantial proportion of patients with extensive calcifications, significant CAD was absent on MSCT, indicating somewhat lower specificity of CS to diagnose significant CAD in line with previous investigations.[28, 29] Since

particularly in symptomatic patients identification of significant CAD is of importance for guiding clinical management (including decisions for potential revascularization), MSCTA may provide incremental diagnostic information to CS in this regard.

Prognostic value of CS and MSCTA

A considerable amount of evidence regarding risk stratification is available with CS in asymptomatic patients.[19, 20, 30-33] Although less frequently studied, also in symptomatic patients CS has been shown to provide important prognostic information ([1-4] In the study by Detrano et al. a 6 times higher event rate was observed in patients with a CS above the median compared to those with a CS below the median.[1]

The prognostic value of MSCTA has been studied less extensively.[5-8] In the largest study thus far by Min et al, a cohort of 1,127 patients undergoing 16-slice MSCT was evaluated.[6] The prognostic value of the Duke Prognostic Coronary Artery Disease Index was assessed and event rates for all cause mortality ranging between 0.3% for none or mild atherosclerosis (stenosis <50%) to 15% for mild to moderate left main disease were observed in a period of 2 years. Similar findings were reported in smaller studies by Gilard et al and Pundziute et al.[5, 7] Furthermore, recently published results from our current prospective registry have demonstrated an incremental prognostic value of MSCTA over myocardial perfusion imaging using single photon emission computed tomography.[12]

To our knowledge the current study is the first study assessing the incremental prognostic value of both stenosis severity and plaque composition on MSCTA over CS. In a previous study however, the incremental value of plaque burden, derived by non-invasive coronary angiography with electron beam computed tomography, over CS was assessed by Ostrom and colleagues.[34] The authors showed that plaque burden, defined as the number of non-significantly or significantly diseased vessels, had independent and incremental value in predicting all-cause mortality independent of age, gender, conventional risk factors, and CS. Similar findings were recently reported by Rubinshtein et al.[8] Accordingly, in combination with our own observations, it appears that non-invasive measures of the extent and severity of stenosis provide incremental prognostic information over CS.

Importantly, assessment of plaque composition may further enhance risk stratification. However, only limited prospective data are available addressing the potential relationship between plaque composition on MSCTA and outcome. When exploring plaque composition in the current study, the number of segments with non-calcified plaque as well as the number of segments with mixed plaque was shown to be independently associated with increased risk for events. Interestingly, no such relation was observed for the number of segments with calcified plaque. An explanation may be that CS is more accurate at quantifying

calcium burden. Furthermore when regarding only the number of calcified plaques on MSCT the calcium in mixed plaques is disregarded. Secondly, another explanation may be that non-calcified plaque is more important from a prognostic standpoint. Currently two previous studies have addressed the prognostic value of plaque composition assessed by MSCTA.[7, 12] Pundziute et al observed that the number of mixed plaques was a significant predictor when corrected for baseline clinical variables.[7] In addition, we recently showed that plaque composition on MSCTA provides incremental prognostic value over myocardial perfusion imaging.[12]

Limitations

Even though the diagnostic accuracy of MSCTA is high, uninterpretable images are still encountered in a small percentage of patients due to motion because of high or irregular heart rates or breathing during the examination. It is however anticipated that the number of uninterpretable studies will continue to decrease with newer generation scanners. Another potential limitation of MSCTA is the use of iodinated contrast media. As a result MSCTA is contraindicated in patients with renal insufficiency or known hypersensitivity to iodine contrast media. Currently 64-slice MSCTA is still associated with a significantly higher radiation exposure than CS, although the radiation dose of MSCTA will decrease with the use of dedicated dose reduction techniques that have recently become available.[35-38]

Conclusion

Non-invasive anatomic imaging using CS and MSCTA is useful for the detection of atherosclerosis; MSCTA however provides additional information to CS regarding stenosis severity and plaque composition. This additional information was shown to translate into incremental value for risk stratification.

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