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

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Chapter 14

Multi-slice computed tomography coronary angiography for risk stratification in patients with an intermediate pre-test likelihood

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Abstract

The purpose of this study was to assess whether MSCTA may be useful for risk stratification of patients with suspected CAD at intermediate pre-test likelihood according to Diamond and Forrester. MSCTA images were evaluated for the presence of significant CAD in 316 included patients (60% male, average age 57±11 years) with suspected CAD and an intermediate pre-test likelihood according to Diamond and Forrester. Patients were followed in time for the occurrence of an event. A combined endpoint of all cause mortality, non-fatal infarction, and unstable angina requiring revascularization. Significant CAD was observed in 89 patients (28%), whereas normal MSCTA or non-significant CAD was observed in the remaining 227 (72%) patients. During follow-up (median 621 days (95%-confidence interval: 408-835) an event occurred in 13 patients (4.8%). The annualized event rate was 0.8% in patients with normal MSCT, 2.2% in patients with non-significant CAD and 6.5% in patients with significant CAD. Moreover, MSCTA remained a significant predictor ($p<0.05$) of events after multivariate correction. In conclusion, our results suggest that in an intermediate pre-test likelihood population, MSCTA is highly effective in re-stratifying patients into either a low or high post-test risk group. These results further emphasize the usefulness of non-invasive imaging with MSCTA in this patient population.

Introduction

Coronary artery disease (CAD) is a leading cause of mortality and morbidity worldwide. The diagnosis and management of this disease is increasingly dependent on non-invasive imaging strategies. With the introduction of multi-slice computed tomography coronary angiography (MSCTA) non-invasive assessment of coronary anatomy has become possible, allowing early identification of atherosclerosis. MSCTA has a high diagnostic accuracy for the detection of significant CAD (≥50% luminal narrowing) on conventional coronary angiography, [1-7] and may be particularly useful for diagnosis in patients with an intermediate pre-test likelihood for significant CAD.[8] Although the prognostic value of MSCTA has been evaluated in previous studies ([7, 9-16] , no studies have specifically addressed the target population for MSCTA. The purpose of this study therefore was to assess if MSCTA may be useful for risk stratification in patients with suspected CAD and an intermediate pre-test likelihood.

Methods

The study population consisted of 331 patients with suspected CAD and an intermediate pre-test likelihood. Patients were clinically referred for further cardiac assessment as part of an ongoing study protocol addressing the prognostic value of MSCTA. From this prospective registry, results addressing the incremental prognostic value of MSCTA over myocardial perfusion imaging have been recently published.[13]

Baseline clinical demographic values were recorded from the electronic patient file based on physician documented history. Symptoms were classified as typical angina, atypical angina, non-anginal chest pain and asymptomatic. Typical anginal chest pain was defined as combination of: 1) discomfort in the anterior chest, neck, shoulders, jaw, or arms; 2) precipated by phycial exertion or psychic stress; and 3) relieved by rest or nitroglycerin within minutes. Atypical chest pain was defined as chest pain with two 2 of these 3 factors and non-anginal chest pain was defined as chest pain with less than 2 of these 3 factors.[17] Pre-test likelihood was defined according to Diamond and Forrester criteria which are based on age, gender and symptomatic status.[18] Intermediate likelihood was defined as a pre-test likelihood between 13.4 and 87.2%. In addition, asymptomatic diabetic patients were also classified as having an intermediate pre-test likelihood according to the increased prevalence of CAD and increased risk of events in this population.[19-21] 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 from further analysis. The study was approved by the local ethics committee in both participating centers.

Patients were scanned using a 64-slice CT scanner (Aquillion64, Toshiba Medical Systems, Tokyo, Japan; General Electrics LightSpeed VCT, Milwaukee, WI, US; or Sensation64, Siemens, Forchheim, Germany). For each patient, the heart rate and blood pressure were monitored before the scan. 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). The contrast enhanced helical scan was performed using 80-140 ml of non-ionic contrast agent (Xenetix 300; Iomeron 400; or Iodixanol 370) administered at a flow rate of 3.5-5 ml/s followed by a bolus of saline flush (30-50 ml at 3.5-5 ml/s). All scan parameters have been previously published.[22-24]

Datasets were reconstructed from the retrospectively gated raw data. Images were reconstructed with an effective slice thickness of 0.3, 0.5 or 0.625 mm with the Toshiba, Siemens, and GE systems respectively. Coronary arteries were evaluated using the reconstruction dataset with the least motion artifacts, typically an end-diastolic phase. Post-processing was performed on dedicated workstations (Vitrea2, Vital Images, USA , Advantage, GE healthcare, USA, Leonardo, Siemens, Germany). The interpretation of MSCTA angiograms was performed in a standardized manner using the axial slices, curved multiplanar reconstructions (MPR), and maximum intensity projections (MIP). MSCTA examinations were scored on a patient basis by two experienced observers in each center, based on the maximum luminal diameter stenosis. Discrepancies in interpretation were resolved by consensus. Normal MSCTA was defined as completely normal anatomy, non-significant stenosis was defined as the presence of luminal narrowing with a maximal luminal diameter stenosis <50%, and significant stenosis was defined as the presence of an atherosclerotic lesion exceeding the threshold of ≥50% luminal narrowing. 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.[25]

Patient follow-up data were gathered using clinical visits or standardized telephone interviews. The following events were regarded as clinical endpoints: all cause mortality, non-fatal myocardial infarction, and unstable angina requiring revascularization. Two combined endpoints were used: a combined endpoint of all events; and a combined hard endpoint including only all cause mortality and non-fatal myocardial infarction. 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.[26] Patients with stable complaints undergoing an early elective revascularization within 60 days after MSCTA were excluded from the survival 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 MSCTA. First univariate analysis of baseline clinical variables and MSCTA variables was performed using a 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. Finally a multivariate model was created using backward stepwise selection to assess the independent predictive value of MSCTA corrected for baseline clinical variables. At each step, the least significant variable was discarded from the model, until all variables in the model reached a p-value <0.25.

Cumulative event rates for MSCTA were obtained by the Kaplan-Meier method, and the survival curves were compared using the log-rank test. 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

Patient characteristics

The study population, derived from our prospective registry, [27] consisted of 331 patients with suspected CAD and an intermediate pre-test likelihood. The MSCTA examination was uninterpretable in 15 patients (4.5%). Reasons for uninterpretability were the presence of motion artifacts, increased noise due to high body mass index, and breathing. After exclusion of these patients, a total of 316 patients remained for analysis. The average age of the study cohort was 57±11 years and 60% of patients were men. Patients presented with asymptomatic diabetes (25%) non-anginal chest pain (22%), atypical chest pain (48%), and typical chest pain (5%). A complete overview of the baseline characteristics of the study population is presented in Table 1.

MSCT results

During MSCTA image acquisition, an average heart rate of 63±10 beats per minute was recorded. MSCTA was classified as normal in 85 (27%) of patients. Atherosclerosis was detected in the remaining 231 (73%) patients, classified as non-significant CAD (<50% luminal narrowing) in 142 (45%) and significant CAD (≥50% luminal narrowing) in 89 (28%) patients.(Figure 1) The estimated average radiation dose for the coronary angiography protocol was 18.1±5.9 mSv and the estimated radiation dose for the CS protocol was 1.4±0.6 mSv.

Table 1. Patient characteristics.

Gender (male)	190 (60.1%)
Age (yrs)	57±11
Risk Factors	
Diabetes	127 (40.2%)
Hypertension	174 (55.1%)
Hypercholesterolemia	125 (39.6%)
Family history CAD	123 (38.9%)
Current Smoking	102 (32.3%)
Obesity (BMI ≥ 30)	71 (22.5%)
Symptoms	
Asymptomatic	78 (24.7%)
Dyspnoea	34 (10.8%)
Non-anginal chest pain	36 (11.4%)
Atypical chest pain	151 (47.8%)
Typical chest pain	17 (5.4%)

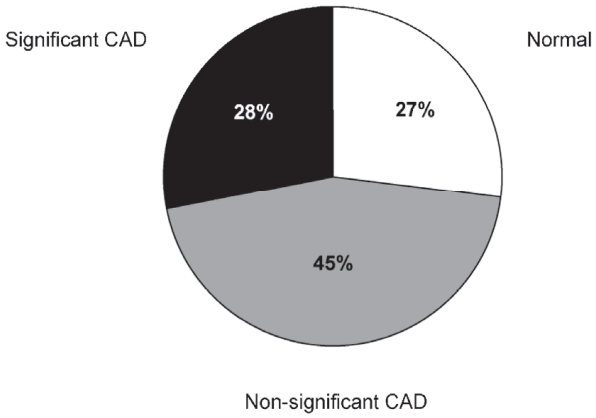

Figure 1. Pie chart illustrating the distribution of MSCTA findings.

Follow-up results

In total, 26 (8%) patients were lost to follow-up and 21 (7%) patients underwent early revascularization. In the remaining 269 patients the median follow-up time achieved was 621 days (25-75th percentile: 408-835). During the follow-up period an event occurred in 13 patients (5%). All cause mortality was reported in 5 patients (2%), whereas non-fatal myocardial infarction occurred in 3 patients (1%) and 5 patients (2%) were revascularized due to unstable angina pectoris. In the excluded patients with an early revascularization myocardial infarction occurred in 1 of 21 patients.

Event rates

In patients with a normal MSCTA an annualized event rate (annualized event rate for hard events between parentheses) of 0.8% (0%) was observed, while in patients with atherosclerosis (non-significant and/or significant CAD) the annualized event rate was 3.5% (2.6%). Significant CAD (≥50% luminal narrowing) on MSCTA resulted in an event rate of 6.5% (4.6%). The total event rates (all cause mortality, non-fatal myocardial infarction and unstable angina requiring revascularization) and the hard event rates (all cause mortality and non-fatal myocardial infarction) in all patients and stratified according to MSCTA are shown in Figure 2.

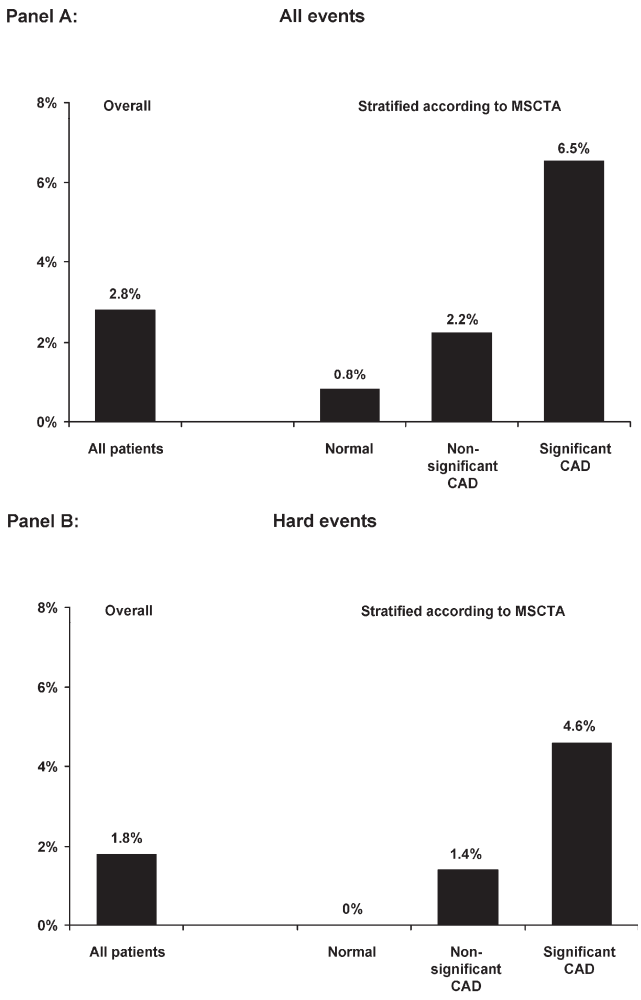

Figure 2. The annualized event rate in all patients and stratified according to MSCTA results. Panel A: Bar graph for all events (all cause mortality, non-fatal myocardial infarction, and unstable angina requiring revascularization); Panel B: Bar graph for hard events (all cause mortality, and non-fatal myocardial infarction).

Survival analysis

Baseline univariate predictors of events are listed in Table 2. Significant CAD (≥50% luminal narrowing) was the best univariate predictor of events with a hazard ratio of 3.9 (95%-confidence interval: 1.3-11.7). After correcting for smoking in a multivariate model this variable remained an independent predictor of events.Table 2) The Kaplan-Meier survival analysis in Figure 3 further illustrates the usefulness of ≥50% luminal narrowing on MSCTA as a cutoff for risk stratification. A significant difference (Logrank P-value 0.008) in survival was observed between patients with normal or non-significant CAD and patients with significant CAD (≥50% luminal narrowing) on MSCTA. Similar results were obtained when using a combined hard endpoint of all cause mortality and non-fatal myocardial infarction (Logrank P-value 0.0077).(Figure 3)

Table 2. Univariate and Multivariate predictors of events.

	Univariate analysis		Multivariate analysis	
	HR (95%-CI)	p-value	HR (95%-CI)	p-value
Risk factors				
Gender (male)	0.84 (0.28-2.50)	0.754		
Age (yrs)	1.00 (0.95-1.05)	0.814		
Diabetes	0.98 (0.32-3.01)	0.981		
Hypertension	0.85 (0.28-2.55)	0.781		
Hypercholesterolemia	1.25 (0.42-3.72)	0.685		
Family history CAD	0.96 (0.31-2.95)	0.951		
Current Smoking	2.54 (0.85-7.57)	0.093		
Obesity (BMI ≥ 30)	1.27 (0.34-4.65)	0.714		
MSCTA				
Atherosclerosis	4.71 (0.61-36.30)	0.136		
Significant CAD	3.92 (1.31-11.68)	0.014	3.46 (1.14-10.48)	0.028

Discussion

The main finding of the current study is that in an intermediate pre-test likelihood population, MSCTA has a good prognostic value and may effectively identify patients at higher or lower risk for coronary events. These results further emphasize the usefulness of non-invasive imaging with MSCTA in this patient population.

MSCTA is increasingly used in the diagnosis of CAD, and may be specifically useful for the rule out of CAD. The diagnostic accuracy of MSCTA has been studied extensively, and in early single center studies an average weighted sensitivity of 97.5 (95%-confidence interval 96-99) and specificity of 91 (95%-confidence interval 87.5-95) has been observed.[5] More recently several prospective multi-center studies have been published showing similar

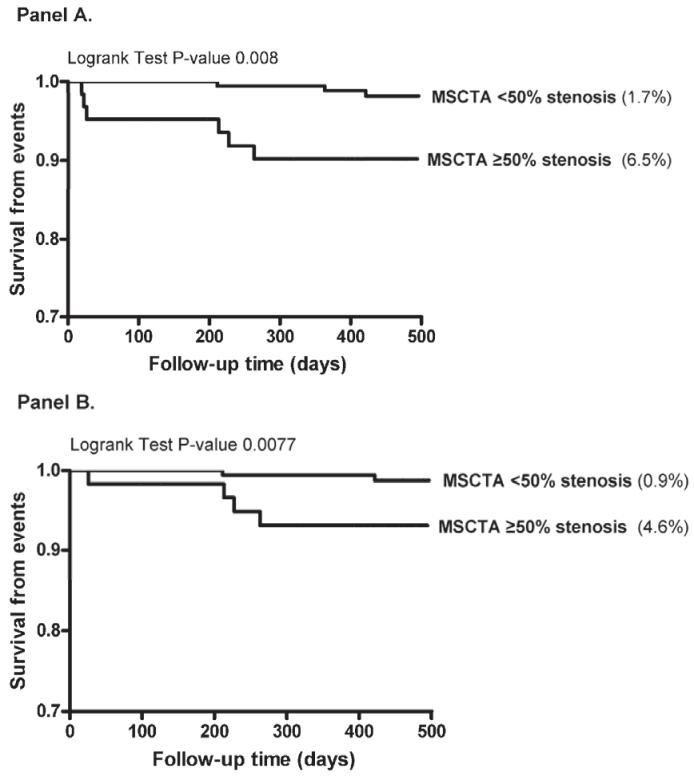

Figure 3. Kaplan-Meier survival curves in patients with normal or non-significant CAD (<50% luminal narrowing) compared to patients with significant CAD (≥50% luminal narrowing). Panel A: Kaplan-Meier curves for all events (all cause mortality, non-fatal myocardial infarction, and unstable angina requiring revascularization); Panel B: Kaplan-Meier curves for hard events (all cause mortality, and non-fatal myocardial infarction).

sensitivities and specificities.[1, 3, 4] Importantly however, in the majority of these diagnostic accuracy studies patients were included who were referred for conventional diagnostic coronary angiography and thus with high pre-test probability. Accordingly, when interpreting these observations, it is important to take into account the pre-test probability, as according to Bayes theorem, pre-test probability may have a major influence on the positive and negative predictive value. With increasingly higher pre-test probability, the prevalence of disease is higher and as a consequence the positive predictive value will increase, with a subsequent decrease in negative predictive value. Conversely, in lower pre-test probability populations, with lower disease prevalence, positive predictive value will decrease, but negative predictive value will improve.

The relationship between pre-test probability and the diagnostic accuracy of MSCTA was recently studied by Meijboom et al. among patients with a high, intermediate, or low pre-test likelihood. In patients with a high pre-test likelihood for CAD, the post-test probability

for significant CAD after MSCT was not substantially different from the pre-test probability. As a result, a normal examination did not result in sufficient reduction of post-test probability to reliably rule out the presence of significant CAD. These observations indicate that the clinical value of MSCTA is limited in this patient group. In contrast, in patients with a low and intermediate pre-test likelihood, a negative MSCTA scan was able to reduce the post test probability of CAD to 0%.[28] The effectiveness of MSCTA in patients with an intermediate pre-test likelihood was also confirmed by Henneman et al.[29] The authors assessed the prevalence of completely normal MSCTA, and thus the efficacy to rule out CAD, in patients with suspected CAD and related these observations to the pre-test likelihood of CAD. The authors showed that normal MSCTA was observed in only 17% of patients with a high pre-test likelihood further underlining the limited clinical value in those patients. Conversely, MSCTA was able to rule out the presence of atherosclerosis in 33% of patients with an intermediate pre-test likelihood.

However, in addition to diagnosis, prognostification is an important component of imaging tests and determines subsequent management. Thus far, several prognostic studies have addressed the potential prognostic value of MSCTA. ([7, 9-11, 13] However, most of these observations have been derived from heterogeneous patient populations including patients with known CAD. In several more recent publications the prognostic value of MSCT has been determined specifically in patients with suspected CAD.[14-16] In the study by Carrigan et al. 227 patients without documented CAD were included.[16] The absence of obstructive CAD was associated with a 99% freedom from cardiac death, myocardial infarction and revascularization during an average of 2.3 years of follow-up. In patients with one or more vessels with obstructive CAD a significantly increased event rate was observed (Log rank p-value 0.01). Similar findings were recently reported by Hadamitzky et al.[14]

Although these observations underline the usefulness of MSCT for prognosis in patients with suspected CAD, dedicated data in the target population for MSCT, patients with an intermediate pre-test likelihood, are lacking. Importantly, the results of the current study confirm the prognostic value of MSCT in this particular patient population as MSCTA was shown to be highly effective for risk stratification. Indeed, hard event rates were <1% for patients without significant stenosis on MSCTA, indicating that these patients may be safely reassured. In contrast, the presence of a significant stenosis implied a substantially increased risk approaching 5% of coronary events.

Limitations

Several limitations need to be acknowledged. Even though the diagnostic accuracy of MSCTA is high, uninterpretable images are still being 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. Currently 64-slice MSCTA is still associated with a high radiation exposure, although the radiation dose of MSCTA will decrease with the use of dedicated dose reduction techniques that have recently become available.[30-33] Importantly, low-dose computed tomography with prospective ECG-triggering has recently been shown to reduce radiation burden while maintaining diagnostic image quality and a high diagnostic accuracy.[34, 35]

Conclusion

These results suggest that in an intermediate pre-test likelihood population, MSCTA is highly effective in re-stratifying patients into either a low or high post-test risk group. These results further emphasize the usefulness of non-invasive imaging with MSCTA in this patient population.

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