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Prognostic Value of Multislice Computed Tomography and Gated Single-Photon Emission Computed Tomography in Patients With Suspected Coronary Artery Disease

Jacob M. van Werkhoven, MSc,*§ Joanne D. Schuijf, PhD,* Oliver Gaemperli, MD,‖¶ J. Wouter Jukema, MD, PhD,*§ Eric Boersma, MSc, PhD,** William Wijns, MD, PhD,†† Paul Stolzmann, MD,# Hatem Alkadhi, MD,# Ines Valenta, MD,¶ Marcel P. M. Stokkel, MD, PhD,† Lucia J. Kroft, MD, PhD,‡ Albert de Roos, MD, PhD,‡ Gabija Pundziute, MD,* Arthur Scholte, MD,* Ernst E. van der Wall, MD, PhD,*§ Philipp A. Kaufmann, MD,¶‡‡ Jeroen J. Bax, MD, PhD, FACC*

Leiden, Utrecht, and Rotterdam, the Netherlands; Zurich, Switzerland; and Aalst, Belgium

Objectives This study was designed to determine whether multislice computed tomography (MSCT) coronary angiography has incremental prognostic value over single-photon emission computed tomography myocardial perfusion imaging (MPI) in patients with suspected coronary artery disease (CAD).

Background Although MSCT is used for the detection of CAD in addition to MPI, its incremental prognostic value is unclear.

Methods In 541 patients (59% male, age 59 ± 11 years) referred for further cardiac evaluation, both MSCT and MPI were performed. The following events were recorded: all-cause death, nonfatal infarction, and unstable angina requiring revascularization.

Results In the 517 (96%) patients with an interpretable MSCT, significant CAD (MSCT ≥50% stenosis) was detected in 158 (31%) patients, and abnormal perfusion (summed stress score [SSS]: ≥4) was observed in 168 (33%) patients. During follow-up (median 672 days; 25th, 75th percentile: 420, 896), an event occurred in 23 (5.2%) patients. After correction for baseline characteristics in a multivariate model, MSCT emerged as an independent predictor of events with an incremental prognostic value to MPI. The annualized hard event rate (all-cause mortality and nonfatal infarction) in patients with none or mild CAD (MSCT <50% stenosis) was 1.8% versus 4.8% in patients with significant CAD (MSCT ≥50% stenosis). A normal MPI (SSS <4) and abnormal MPI (SSS ≥4) were associated with an annualized hard event rate of 1.1% and 3.8%, respectively. Both MSCT and MPI were synergistic, and combined use resulted in significantly improved prediction (log-rank test p value <0.005).

Conclusions MSCT is an independent predictor of events and provides incremental prognostic value to MPI. Combined anatomical and functional assessment may allow improved risk stratification. (J Am Coll Cardiol 2009;53:623–32) © 2009 by the American College of Cardiology Foundation

From the Departments of *Cardiology, †Nuclear Medicine, and ‡Radiology, Leiden University Medical Center, Leiden, the Netherlands; §The Interuniversity Cardiology Institute of the Netherlands, Utrecht, the Netherlands; Departments of ‖Cardiology and ¶Nuclear Medicine and #Institute of Diagnostic Radiology, University Hospital Zurich, Zurich, Switzerland; **Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands; ††Cardiovascular Center, Aalst, Belgium; and the ‡‡Zurich Integrative Human Physiology, University of Zurich, Zurich, Switzerland. Dr. van Werkhoven is financially supported by a research grant from the Netherlands Society of Cardiology, Utrecht, the Netherlands. Dr. Jukema is an established investigator of the Netherlands Heart Foundation, The Hague, the Netherlands (grant 2001T032). Dr. Pundziute is financially supported by the training fellowship grant of the European Society of Cardiology, Sophia Antipolis, France, and a Huygens scholarship. Drs. Stolzmann and Alkadhi are supported by the National Center of Competence in Research, Computer Aided and Image Guided Medical Interventions of the Swiss National Science Foundation, Zurich, Switzerland. Dr. Alkadhi has research grants from Siemens Medical Solutions. Dr. Kaufmann is supported by a grant (PPOOA-114706) from the Swiss National Science Foundation, Bern, Switzerland, and has research grants from GE Healthcare. Dr. Bax has research grants from Medtronic, Boston Scientific, Bristol-Myers Squibb Medical Imaging, St. Jude Medical, GE Healthcare, and Edwards Lifesciences. Drs. van Werkhoven and Schuijf contributed equally to this work. Frans J. Th. Wackers, MD, served as Guest Editor for this article.

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Abbreviations and Acronyms

CAD = coronary artery disease

CS = coronary artery calcium score

ECG = electrocardiogram

MPI = myocardial perfusion imaging

MSCT = multislice computed tomography coronary angiography

SPECT = single-photon emission computed tomography

SSS = summed stress score

With the arrival of multislice computed tomography coronary angiography (MSCT), the focus of noninvasive imaging has shifted from functional imaging to a combination of both anatomical and functional imaging. Several studies (1–3) have addressed the association between the anatomical and functional information obtained with MSCT and myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT), respectively. These comparative studies have shown that MSCT may provide complementary rather than overlapping diagnostic information when used in combination with MPI. Whether MSCT provides complementary information to MPI with regard to risk stratification remains to be determined. Interestingly, studies in the past have shown that MPI provides substantial incremental value over anatomical information obtained with invasive coronary angiography. However, no studies have addressed this issue more recently (4,5). Moreover, MSCT may have an important advantage over invasive coronary angiography due to its ability to provide information on plaque composition in addition to stenosis severity (6). Accordingly, the information obtained by MSCT may potentially enhance risk stratification by MPI. The aim of this study was therefore to assess in patients presenting with suspected coronary artery disease (CAD) whether MSCT has incremental prognostic value over MPI.

Methods

Patient selection. The study population consisted of 541 patients who prospectively underwent both MPI and MSCT within 3 months of each other. Enrollment of patients started in June 2003 and continued until December 2007. Follow-up information was obtained from the start of the study until August 2008. Patients were included at the University Hospital in Zurich, Switzerland (n = 269); the Cardiovascular Center in Aalst, Belgium (n = 17); and at the Leiden University Medical Center in Leiden, the Netherlands (n = 255). Patients were referred because of chest pain complaints, a positive exercise electrocardiogram (ECG) test, or a high-risk profile for cardiovascular disease. Exclusion criteria were cardiac arrhythmias, renal insufficiency (serum creatinine >120 mmol/l), known hypersensitivity to iodine contrast media, and pregnancy. In addition, patients with a cardiac event in the period between MSCT and MPI or an uninterpretable MSCT scan were excluded. The pre-test probability of CAD was determined using the Diamond and Forrester method, as previously described (7). The study was approved by the local ethics committees in all 3 participating centers, and informed consent was obtained from all patients.

MPI. MPI was performed using gated SPECT. Two ECG-gated MPI protocols were used. A total of 272 patients underwent a 2-day gated stress-rest MPI using technetium (Tc) 99m tetrofosmin (500 MBq) or Tc 99m sestamibi (500 MBq) with either a symptom-limited bicycle test or pharmacological stress using adenosine (140 μg/kg/min for 6 min) or dobutamine (up to 40 μg/kg/min in 15 min). The remaining 269 patients underwent a 1-day stress-rest protocol with adenosine stress (140 μg/kg/min during 7 min) using Tc 99m tetrofosmin (300 MBq at peak stress and 900 MBq at rest).

The images were acquired on a triple-head SPECT camera (GCA 9300/HG, Toshiba Corp., Tokyo, Japan) or a dual-head detector camera (Millennium VG & Hawkeye, General Electric Medical Systems, Milwaukee, Wisconsin; or Vertex Epic ADAC Pegasus, Philips Medical Systems, Eindhoven, the Netherlands). All cameras were equipped with low-energy high-resolution collimators. A 20% window was used around the 140-keV energy peak of Tc 99m, and data were stored in a 64 × 64 matrix.

Stress and rest SPECT perfusion datasets were quantitatively evaluated using previously validated automated software (8). The myocardium was divided into a 20-segment model, and for each segment, myocardial perfusion was evaluated using a standard 5-point scoring system. The segmental perfusion scores during stress and rest were added together to calculate the summed stress score (SSS) and the summed rest score. The summed difference score was calculated by subtracting the summed rest score from the SSS. Abnormal MPI was defined as SSS ≥4 and severely abnormal MPI was defined as SSS ≥8.

MSCT. In 33 patients, the MSCT examination was performed using a 16-slice scanner (Aquillion16, Toshiba Medical Systems, Tokyo, Japan). The remaining 508 (94%) patients were scanned using a 64-slice MSCT scanner (Aquillion64, Toshiba Medical Systems, Tokyo, Japan; General Electric LightSpeed VCT, Milwaukee, Wisconsin; or Sensation64, Siemens, Forchheim, Germany). The patient's heart rate and blood pressure were monitored before each scan. In the absence of contraindications, patients with a heart rate exceeding the threshold of 65 beats/min were administered beta-blocking medication (50- to 100-mg metoprolol, oral, or 5- to 10-mg metoprolol, intravenous).

Before the helical scan, a nonenhanced low-dose prospective ECG-gated scan, prospectively triggered at 75% of the R-R interval, was performed to measure the coronary artery calcium score (CS). The helical scan parameters have been previously described (3,9).

Post-processing of the MSCT and CS scans was performed on dedicated workstations (Vitrea2, Vital Images, Minneapolis, Minnesota; Advantage, GE Healthcare, St. Giles, United Kingdom; Syngo InSpace4D application, Siemens, Munich, Germany; and Aquarius, TeraRecon,

San Mateo, California). The CS was calculated using the Agatston method. 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. For each segment, both the presence of atherosclerotic plaque as well as its composition was determined. Atherosclerotic lesions were deemed significant if the diameter stenosis was ≥50%. Lesions below this threshold were considered to be nonsignificant or mild. Plaque composition was graded as noncalcified plaque (plaques having lower density than the contrast-enhanced lumen), calcified plaque (plaques with high density), and mixed plaque (containing elements from both noncalcified and calcified plaque).

Follow-up. Patient follow-up data were gathered by 3 observers blinded to the baseline MSCT and MPI results using clinical visits or standardized telephone interviews. The following events were regarded as clinical end points: all-cause mortality, nonfatal myocardial infarction, and unstable angina requiring revascularization. Nonfatal 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 (10). Patients with stable complaints undergoing an early elective revascularization within 60 days after imaging with MSCT or MPI were excluded from the survival analysis. Annualized event rates were calculated based on events per patient year follow-up.

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, MSCT, and MPI variables. First, univariate analysis of baseline characteristics, CS, MSCT, and MPI variables was performed using a composite end point of all-cause mortality, nonfatal infarction, and unstable angina requiring revascularization. For each variable, a hazard ratio (HR) with a 95% confidence interval (CI) was calculated. Using univariate analysis, optimal cutoffs (based on the number of segments affected) were created for plaque composition on MSCT. Finally, multivariate models were created correcting MSCT and MPI for baseline risk factors. The incremental value of MSCT over baseline clinical variables and MPI was assessed by calculating the global chi-square test.

Cumulative event rates for MSCT, MPI, and for MSCT and MPI combined were obtained by the Kaplan-Meier method using a composite end point of all-cause mortality, nonfatal infarction, and unstable angina requiring revascularization, and a hard composite end point of all-cause mortality and nonfatal infarction. Statistical analyses were performed using SPSS software, version 12.0 (SPSS Inc, Chicago, Illinois) and the SAS system 6.12 (SAS Institute Inc., Cary, North Carolina). A p value <0.05 was considered statistically significant.

Results

Patient characteristics. In the study population of 541 patients, an uninterpretable MSCT examination was present in 24 patients (4%). Reasons for uninterpretability were the presence of motion artifacts, increased noise due to high body mass index, and breathing. In patients with an uninterpretable MSCT, MPI was abnormal (SSS ≥4) in 9 (38%) patients and normal (SSS >4) in the remaining 15 (62%) patients. After exclusion of these patients, 517 patients remained for analysis. A complete overview of the baseline characteristics of these patients is presented in Table 1. The average age of the study cohort was 59 ± 11 years, and 59% of patients were men. The majority of patients (65%) presented with an intermediate pre-test probability for CAD, and a low or a high probability was present in, respectively, 22% and 13% of patients.

MSCT and SPECT results. An exercise test was performed in 88 patients (17%), while a pharmacological stress with adenosine was used in 397 patients (77%) and with dobutamine in 30 patients (6%). All MPI results are listed in Table 2. The gated SPECT images during rest and stress were normal (SSS <4) in 349 (67%) patients. An abnormal MPI (SSS ≥4) was present in 192 (33%) patients and severely abnormal MPI (SSS ≥8) was present in 64 (13%) patients. During MSCT image acquisition, an average heart rate of 63 ± 11 beats/min was recorded. The CS and MSCT results are listed in Table 2. The average CS was 325 ± 751 Agatston units. A CS >400 was present in 113 (22%) patients, and CS was normal or ≤400 in 404 patients (78%). A CS >1,000 was observed in 47 (9%) patients, but a CS ≤1,000 was observed in the remaining 470 patients (91%). During the contrast-enhanced helical scan, a completely normal MSCT examination was observed in 155 (30%) of patients. Atherosclerosis, both mild (<50% stenosis) and significant (≥50% stenosis), was observed in 362

Table 1 Patient Characteristics

	Total (n = 517)
Male	303 (59%)
Age, yrs	59 ± 11
Risk factors	
Diabetes	156 (30%)
Hypertension	290 (56%)
Hypercholesterolemia	209 (40%)
Family history of CAD	191 (37%)
Current smoking	154 (30%)
Obesity (BMI ≥30 kg/m^2)	111 (22%)
Pre-test likelihood of CAD	
Low	113 (22%)
Intermediate	336 (65%)
High	68 (13%)

BMI = body mass index; CAD = coronary artery disease.

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Table 2 Imaging Results

	Patients (%)
CS	
>400	113 (22%)
>1,000	47 (9%)
MSCT	
Atherosclerosis	362 (70%)
Significant CAD	158 (31%)
Patients with noncalcified plaques	130 (25%)
Patients with mixed plaques	204 (40%)
Patients with calcified plaques	270 (52%)
MPI	
SSS <4 (normal)	349 (67%)
SSS 4–7	104 (20%)
SSS 8–12	44 (9%)
SSS ≥13	20 (4%)
SDS 0–1	378 (73%)
SDS 2–3	72 (14%)
SDS ≥4	67 (13%)

CAD = coronary artery disease; CS = coronary artery calcium score; MPI = myocardial perfusion imaging; MSCT = multislice computed tomography coronary angiography; SDS = summed difference score; SSS = summed stress score.

(70%). Significant CAD with lesions ≥50% stenosis was observed in 158 (31%) patients. Noncalcified plaques were observed in 130 patients (25%), mixed plaques in 204 patients (40%), and calcified plaques in 270 patients (52%).

The results of MSCT in relation to MPI are illustrated in Figure 1. This figure illustrates the complementary value of MSCT and MPI. Only approximately 50% of patients with a significant lesion (≥50% stenosis) showed a perfusion defect on MPI (SSS ≥4). Importantly, a significant stenosis was observed in 22% of patients with normal perfusion on MPI (SSS <4).

Follow-up results. Of the cohort of 517 patients, 35 (6.8%) were lost to follow-up, and 43 (8.3%) patients underwent early revascularization (within 60 days of MSCT or MPI). In the remaining 439 patients, the median follow-up time achieved was 672 days (25th, 75th percentile: 420, 896). During this period, an event occurred in 23 patients (5.2%). Death by any cause occurred in 8 patients (1.8%); in 2, the cause of death could be ascertained as cardiac. Nonfatal myocardial infarction occurred in 8 patients (1.8%), and 7 patients (1.6%) were hospitalized due to unstable angina pectoris.

Univariate and multivariate analysis. Baseline univariate predictors of events are listed in Table 3. This study found CS, MSCT coronary angiography, and MPI were significant univariate predictors of events. Both CS >400 and CS >1,000 were significant predictors. When regarding the MSCT results on a patient level, the presence of significant CAD (≥50% stenosis) was a strong significant predictor (HR: 3.683, 95% CI: 1.611 to 8.420), whereas the presence of any atherosclerosis was not (HR: 3.087, 95% CI: 0.917 to 10.388). Importantly, plaque composition on MSCT was also identified as a predictor of events. On a patient level, the presence of ≥2 segments with noncalcified plaque (n = 65) (HR: 5.0, 95% CI: 2.2 to 11.7) or ≥3 segments with mixed plaque (n = 68) (HR: 3.5, 95% CI: 1.5 to 8.1) were

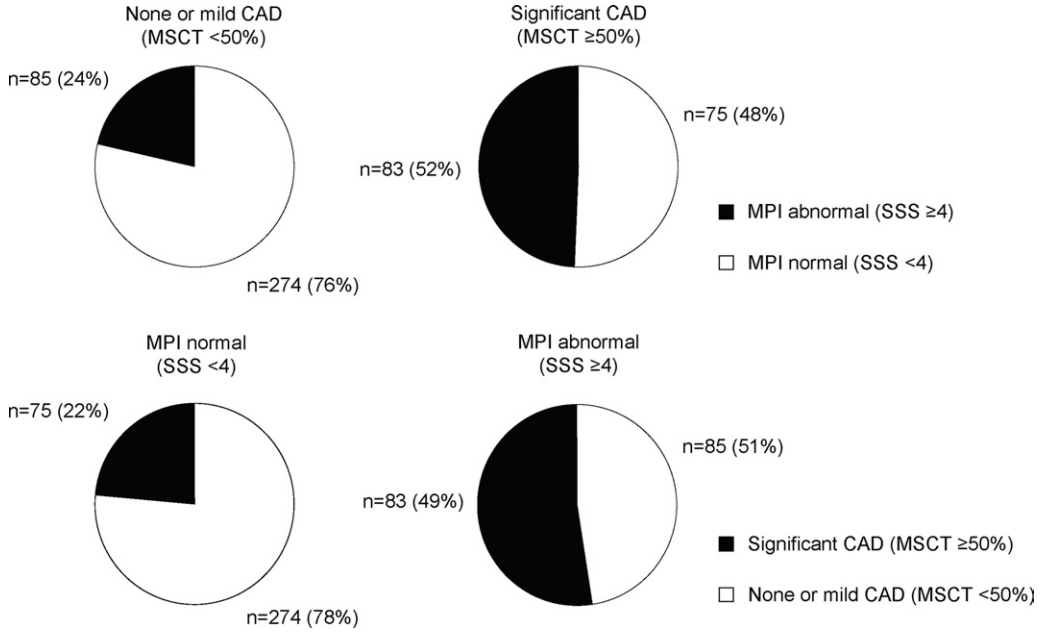

Figure 1 Anatomic Information From MSCT and Functional Information From MPI

Pie charts depicting the relationship between the anatomic information obtained by MSCT and the functional information from MPI.
CAD = coronary artery disease; MPI = myocardial perfusion imaging; MSCT = multislice computed tomography coronary angiography; SSS = summed stress score.

Table 3 Univariate Predictors of Events

	HR (95% CI)	p Value
CS		
>400	3.007 (1.318–6.860)	0.009
>1,000	3.752 (1.392–10.114)	0.009
MSCT		
Atherosclerosis	3.087 (0.917–10.388)	0.069
Significant CAD	3.683 (1.611–8.420)	0.002
≥2 noncalcified plaques	5.0 (2.2–11.7)	<0.001
≥3 mixed plaques	3.5 (1.5–8.1)	<0.005
≥4 calcified plaques	1.5 (0.6–4.1)	0.409
MPI		
SSS ≥2	3.500 (1.513–8.094)	0.003
SSS ≥4	4.029 (1.742–9.319)	0.001
SSS ≥8	1.922 (0.653–5.656)	0.236
SDS ≥2	1.853 (0.783–4.381)	0.160
SDS ≥4	2.142 (0.724–6.336)	0.169

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 2.

both significant predictors of events. Of the MPI variables, the SSS ≥4 was the strongest significant predictor of events (HR: 4.0, 95% CI: 1.7 to 9.3).

After univariate analysis, multivariate models were created for both MSCT and MPI correcting for baseline risk factors. MSCT (≥50% stenosis) remained a significant predictor when corrected for CS >400 or CS >1,000. However, CS >400 and CS >1,000 did not reach statistical significance. Myocardial perfusion imaging also remained a significant predictor when corrected for CS >400 or CS >1,000. In this model, CS >1,000, however, also remained a significant independent predictor of events.

Subsequently, several multivariate models were created to assess the independent predictive value of different MSCT variables, corrected for MPI and baseline risk factors. On a patient level, no independent prognostic value over MPI and baseline risk factors was observed for the presence of any atherosclerosis on MSCT. In contrast, the observation of significant CAD on MSCT was shown to provide independent prognostic value over MPI. When regarding plaque composition, only the presence of 2 or more segments with noncalcified plaque was an independent significant predictor. Importantly, MPI remained an independent significant predictor of events in each multivariate model.

To assess the incremental prognostic value of these MSCT variables over baseline clinical variables and MPI, global chi-square scores were calculated. The results of this analysis are presented in Figure 2. This figure shows that information on the presence of significant stenosis obtained by MSCT has incremental prognostic value to both baseline clinical variables alone and baseline clinical variables and MPI combined. Finally, the addition of noncalcified plaque on a patient basis resulted in further enhancement of risk stratification incremental to the combination of clinical variables, MPI, and significant stenosis on MSCT.

Event rates. The Kaplan-Meier survival curves in Figures 3 and 4 illustrate the different survival rates of the MPI and MSCT test outcomes both for the composite end point of all-cause mortality, nonfatal myocardial infarction, and unstable angina requiring revascularization (log-rank test $p < 0.001$), as well as for the combined hard end point of all-cause mortality and nonfatal myocardial infarction (log-rank test $p < 0.05$). The annualized event rate (annualized

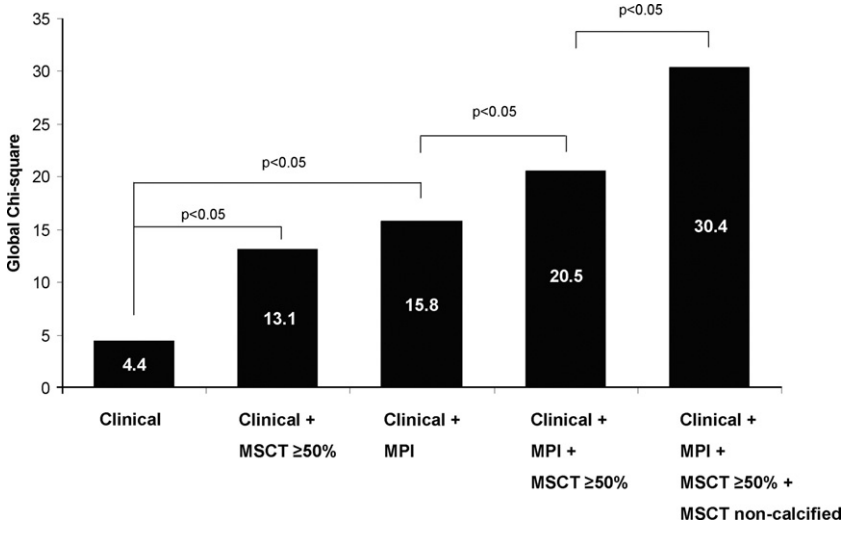

Figure 2 Incremental Prognostic Value of MSCT

Bar graph illustrating the incremental prognostic value (depicted by chi-square value on the y axis) of MSCT. The addition of MSCT provides incremental prognostic information to baseline clinical variables and MPI. Furthermore, the addition of noncalcified plaque on MSCT (≥2 segments with noncalcified plaque) results in further incremental prognostic information over baseline clinical variables, MPI, and significant CAD (≥50% stenosis) on MSCT. Abbreviations as in Figure 1.

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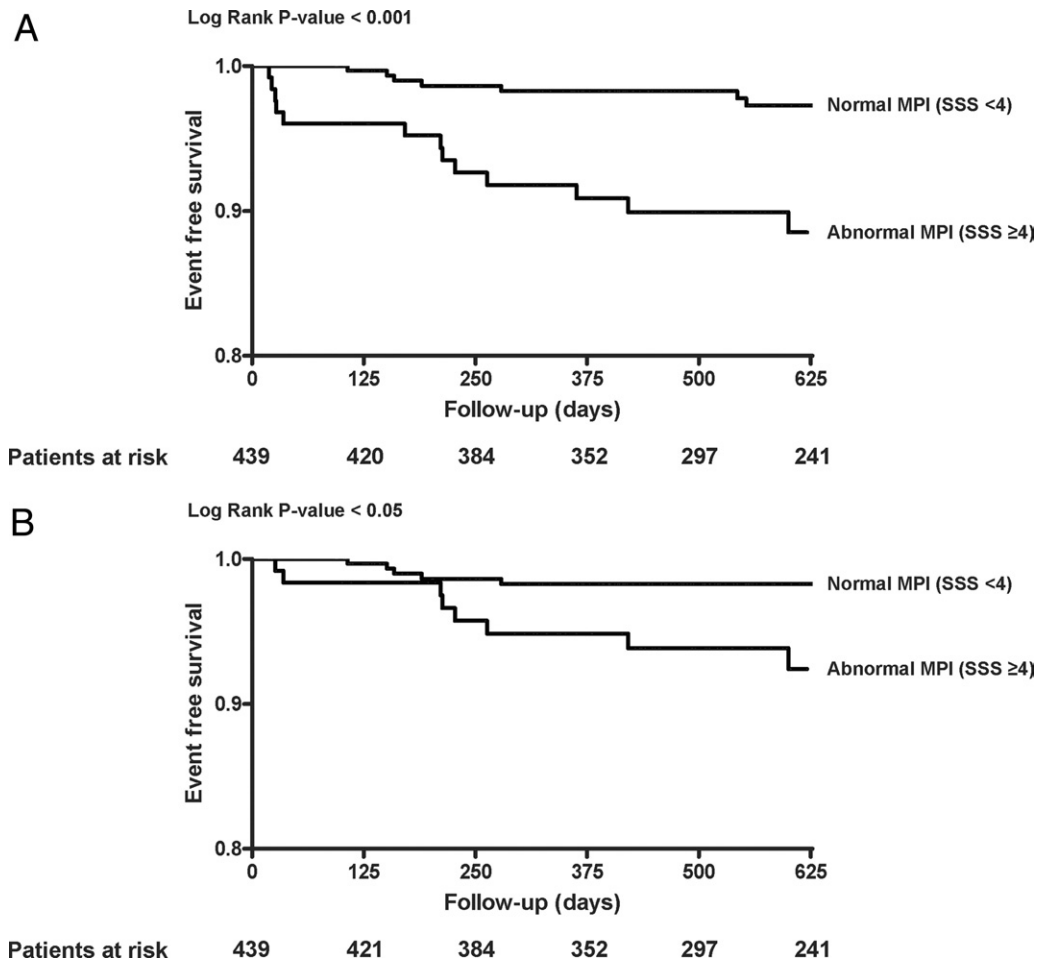

Figure 3 Event-Free Survival in Patients With a Normal MPI (SSS <4) or an Abnormal MPI (SSS ≥4)

(A) Kaplan-Meier curves for all events (all-cause mortality, nonfatal infarction, and unstable angina requiring revascularization) in patients with a normal MPI (SSS <4) or an abnormal MPI (SSS ≥4). **(B)** Kaplan-Meier curves for hard events (all-cause mortality and nonfatal infarction) in patients with a normal MPI (SSS <4) or an abnormal MPI (SSS ≥4). Abbreviations as in Figure 1.

event rate for hard events between parentheses) in patients with a normal MPI examination (SSS <4) was 1.5% (1.1%); the annualized event rate in patients with an abnormal MPI (SSS ≥4) was 6.0% (3.8%). The annualized event rate in patients with none or mild CAD (MSCT <50% stenosis) was 3.0% (1.8%). When these patients were further divided into patients with mild atherosclerosis and patients without any evidence of atherosclerosis, the annualized event rates were 2.0% (1.4%) and 1.1% (0.3%), respectively. The annualized event rate for patients with a significant stenosis (≥50%) on MSCT was 6.3% (4.8%). When regarding plaque composition, the annualized event rate in patients with 2 or more segments with noncalcified plaque was 8.4% (6.7%) compared with 1.9% (1.2%) in patients with no or <2 segments with noncalcified plaque.

Combined use of MSCT and MPI resulted in significantly improved prediction of the composite hard end point of all-cause mortality and nonfatal myocardial infarction (log-rank test $p < 0.005$), as illustrated in the Kaplan-Meier survival curve in Figure 5. In patients with none or mild CAD (MSCT <50% stenosis) and a normal MPI (SSS <4) (n = 256), the annualized event rate (annualized hard event rate in parenthesis) was 1.0% (0.6%). In patients with none or mild CAD (MSCT <50% stenosis) but an abnormal MPI (SSS ≥4) (n = 72), the annualized event rate increased to 3.7% (2.2%), whereas patients with significant CAD (MSCT ≥50% stenosis) and a normal MPI (SSS <4) (n = 57) were associated with an annualized event rate of 3.8% (3.8%). Interestingly, the event rates between patients with none or mild CAD (<50%) stenosis and an abnormal MPI and patients with significant CAD (MSCT ≥50% stenosis) did not differ significantly. In patients with both significant CAD (MSCT ≥50% stenosis) and an abnormal MPI (SSS <4) (n = 54), the annualized event rate was 9.0% (6.0%). In these patients, the addition of plaque composition (the presence of 2 or more segments with

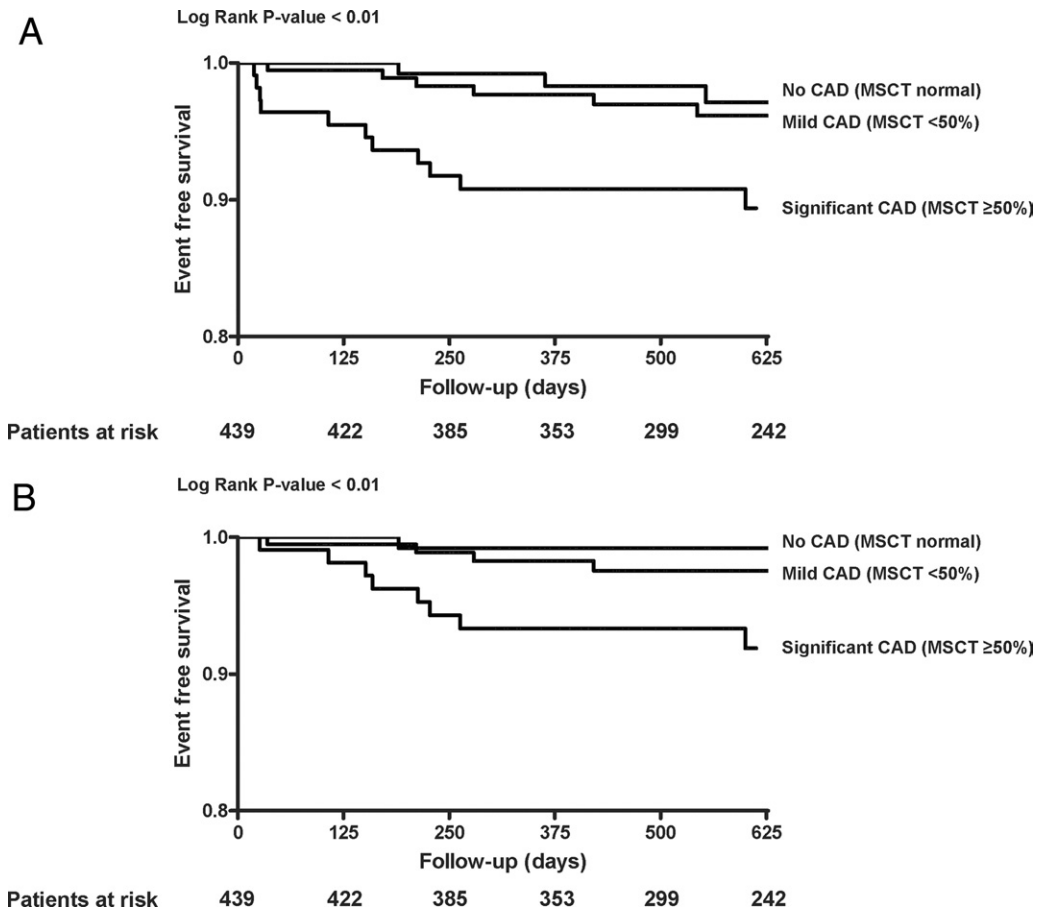

Figure 4 **Event-Free Survival in Patients With No CAD (MSCT Normal), Mild CAD (MSCT <50% Stenosis), or Significant CAD (MSCT ≥50% Stenosis)**

(A) Kaplan-Meier curves for all events (all-cause mortality, nonfatal infarction, and unstable angina requiring revascularization) in patients with no CAD (MSCT normal), mild CAD (MSCT <50% stenosis), or significant CAD (MSCT ≥50% stenosis). **(B)** Kaplan-Meier curves for hard events (all-cause mortality and nonfatal infarction) in patients with no CAD (MSCT normal), mild CAD (MSCT <50% stenosis), or significant CAD (MSCT ≥50% stenosis). Abbreviations as in Figure 1.

noncalcified plaque [n = 20]) resulted in the highest event rate, 10.8% (8.2%).

Discussion

The main finding of the current study is that when used in combination with MPI, MSCT not only provides complementary information about the presence, extent, and composition of atherosclerosis, but importantly, also results in improved risk stratification than the use of MPI alone.

Risk stratification with MPI. A wealth of data has been published on the diagnostic accuracy and prognostic value of MPI (11–16). In an extensive review of the available literature, a low-risk scan was associated with a low annualized hard event rate (cardiac death and nonfatal myocardial infarction) of 0.6% in a population of 69,655 patients (17). In a recent meta-analysis, Metz et al. (18) specifically focused on the prognostic value of a normal MPI. The pooled summary absolute event rate in their study was 1.21 (95% CI: 0.98 to 1.48) for the occurrence of cardiac death and nonfatal myocardial infarction. The slightly higher absolute hard event rate in the current study (2.2%) may have been caused by the inclusion of all-cause mortality and the fact that the majority of patients underwent pharmacological testing (17,19). Importantly, event rates were significantly higher in patients with abnormal MPI (SSS ≥4), which is in line with the previous studies (17).

Risk stratification with MSCT. Although MSCT coronary angiography is a relatively new technique, a considerable amount of evidence is available with calcium scoring (20–27). Moreover, in a systematic review of the available literature (n = 27,622 patients), the presence of any coronary artery calcium was shown to confer a 4-fold increased risk of cardiac death or myocardial infarction ($p < 0.0001$) compared with the absence of coronary artery calcifications (24). In contrast, an extremely low event rate of 0.4% was observed in patients without any coronary artery calcium.

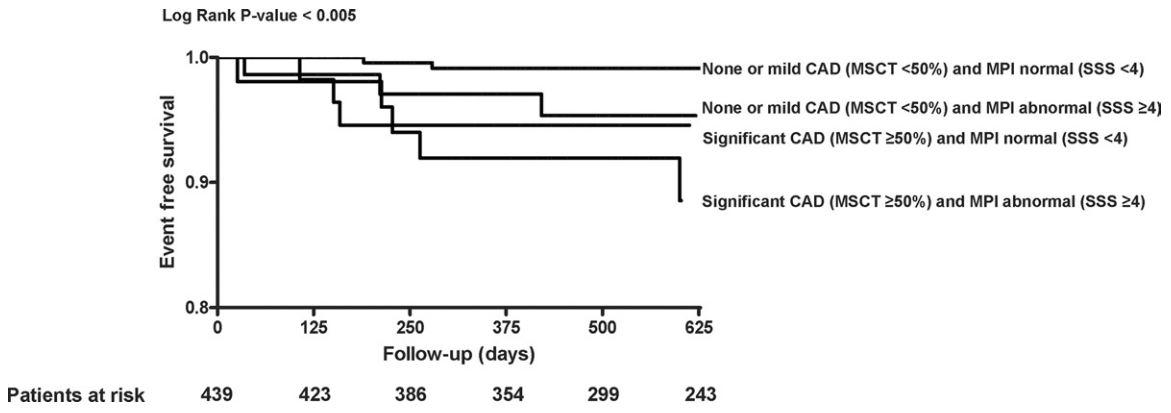

Figure 5 Kaplan-Meier Curves for Hard Events in Patients With a Normal or Abnormal MPI and With or Without CAD

Kaplan-Meier curves for hard events (all-cause mortality and nonfatal infarction) in patients with a normal MPI (SSS <4) and none or mild CAD (<50% stenosis) on MSCT, in patients with an abnormal MPI (SSS ≥4) and with none or mild CAD (<50% stenosis) on MSCT, in patients with a normal MPI (SSS <4) and significant CAD (MSCT ≥50% stenosis), and finally, in patients with an abnormal MPI (SSS ≥4) and significant CAD (MSCT ≥50% stenosis). Abbreviations as in Figure 1.

Only limited data are available on the prognostic value of anatomic imaging with MSCT coronary angiography (28–30). In the present study, annual hard event rates of 0.3%, 2.0%, and 4.8% were observed in patients with completely normal, nonsignificant, and significant CAD on MSCT, respectively. Min et al. (29) evaluated 1,127 patients undergoing 16-slice MSCT with a mean follow-up of 15.3 ± 3.9 months. In line with our study, event rates for all-cause mortality ranging between 0.3% for none or mild atherosclerosis (stenosis <50%) and 15% for mild to moderate left main disease were observed in a period of 2 years.

Currently, 1 previous study by Pundziute et al. (30) has addressed the prognostic value of plaque components assessed by MSCT. The number of mixed plaques was a significant predictor when corrected for baseline clinical variables. In the current study, only noncalcified plaque remained an independent predictor of events. The discrepancy between the current results and the study by Pundziute et al. (30) may be explained by differences in the studied patient populations as well as the use of optimized cutoffs and correction for MPI results in the current study.

Combination of MSCT and MPI. In previous studies, the prognostic value of anatomic imaging using calcium scoring in relation to MPI has been addressed (31–34). Recently, Schenker et al. (34) showed that the risk of all-cause mortality and myocardial infarction increased with increasing CS, both in patients with normal and in patients with abnormal perfusion on MPI. The present study is the first to address the incremental prognostic value of MSCT when used in combination with MPI. Previous studies have shown that MPI provides incremental prognostic information over invasive coronary angiography (4,5). Vice versa, the current study has revealed that the anatomic information on MSCT is not only an independent predictor of events but also provides incremental prognostic information over baseline clinical variables and MPI, particularly in patients with a normal MPI. Although several MSCT variables were able to provide prognostic information, on a patient level the presence of significant CAD (≥50% stenosis) was identified as a robust independent predictor. This is an important finding, as diagnostic MSCT examinations are often graded in this manner. In addition to stenosis severity, plaque composition was also identified to further enhance risk stratification. Indeed, the presence of noncalcified plaques provided incremental prognostic information over baseline clinical variables, MPI, and significant CAD on MSCT. This finding suggests that potentially assessment of plaque composition on MSCT may provide clinically relevant information in addition to stenosis severity.

Study limitations. Even though the diagnostic accuracy of MSCT is high, images are still uninterpretable in a small percentage of patients. It is, however, anticipated that the amount of uninterpretable studies will continue to decrease with newer-generation scanners (35,36). In contrast, none of the SPECT examinations were uninterpretable in this study.

Another potential limitation is that the MSCT studies were evaluated visually; no validated accurate quantitative algorithms are currently available. In the current study, a composite end point including all-cause mortality was used, which is not a direct cardiac end point. An important advantage of all-cause mortality, however, is the fact that it is not affected by verification bias (37). Furthermore, most deaths in adults are linked to cardiovascular disease. All-cause mortality is therefore a commonly used end point allowing comparison of the current results to previous investigations (21,26,29,34). Finally, the radiation burden associated with combined MSCT and MPI imaging is a limitation. However, the radiation dose can decrease significantly when using dedicated dose reduction MSCT acquisition techniques that have recently become available (38–41).

Conclusions

MSCT is an independent predictor of events and provides incremental prognostic value to MPI. Furthermore, addition of plaque composition to stenosis severity was shown to provide incremental prognostic information. The results of this study suggest that combined anatomical and functional assessment may allow improved risk stratification.

Reprint requests and correspondence: Dr. Jeroen J. Bax, Department of Cardiology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, the Netherlands. E-mail: j.j.bax@lumc.nl.

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