Long-term prognostic value of coronary artery calcium scanning, coronary computed tomographic angiography and stress myocardial perfusion imaging in patients with suspected coronary artery disease

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Background. **We compared the long-term prognostic value of coronary artery calcium (CAC) scanning, coronary computed tomographic angiography (CCTA), and stress single-photon emission computed tomography myocardial perfusion imaging (MPI) in patients with suspected coronary artery disease (CAD).**

Methods and Results. **A total of 164 patients were studied. CAC score was measured according to the Agatston method and patients were categorized into 3 groups (0, 1-300, and >300). The following events were recorded: cardiac death, nonfatal infarction, and unstable angina requiring revascularization. Follow-up was 95% complete during a mean period of 82 ± 34 months. During follow-up, 22 events occurred (14% cumulative event rate). Event-free survival decreased with worsening of CAC score category ($P < .001$) and it was worse ($P < .001$) in patients with significant CAD (≥50% stenosis) and in those with stress-induced ischemia (summed difference score >2). At multivariable analysis, CAC ($P = .001$) and ischemia ($P = .012$) were independent predictors of events. MPI data added prognostic information to a model including clinical variables, CAC and CCTA findings, increasing the global Chi-square from 36.2 to 41.9 ($P = .013$). The decision curve analyses in patients with CAC score >0 indicate that the prognostic model including MPI resulted in a higher net benefit across a wide range of decision threshold probabilities.**

Conclusions. **CAC and MPI, but not CCTA, are independent predictors of cardiac events. Stress MPI appears to improve risk stratification over clinical variables, CAC scanning and CCTA findings. (J Nucl Cardiol 2018;25:833–41.)**

Key Words: Coronary artery calcium • coronary computed tomographic angiography • myocardial perfusion imaging • prognosis • coronary artery disease

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Abbreviations

CAD	Coronary artery disease
CAC	Coronary artery calcium
CCTA	Coronary artery computed tomography angiography
MPI	Myocardial perfusion imaging
ECG	Electrocardiographic
HU	Hounsfield units
SDS	Summed difference score

See related editorial, pp. 842–844

INTRODUCTION

The current approach to coronary artery disease (CAD) is based on anatomic and functional imaging.[1] Coronary artery calcium (CAC) scoring, coronary artery computed tomography angiography (CCTA), and stress myocardial perfusion imaging (MPI) are commonly used for risk stratification and treatment choice in patients with suspected CAD. In particular, measurement of CAC is considered reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk.[2] On the other hand, prior studies evaluating the value of CCTA and MPI in patients with stable CAD found comparable results in terms of long-term outcomes.[3-5] It has also been showed that CAC score and stress MPI provide independent and complementary prediction of cardiac risk.[6,7] However, cardiac CT and MPI provide information regarding different aspects of the disease, atherosclerotic and ischemic changes, respectively. Therefore, these techniques complement each other. Yet, to date there has been no comparison of CAC scanning, CCTA and stress MPI for risk stratification in the same cohort of patients. The purpose of this study was to compare the long-term prognostic value of CAC, CCTA, and stress MPI in patients with suspected CAD. The incremental prognostic value of each technique compared with clinical variables was also evaluated.

METHODS

Patients

From December 2006 to March 2010, we prospectively enrolled 164 consecutive outpatients (mean age 62 ± 12 years, male gender 67%) at low to intermediate pre-test likelihood of CAD undergoing cardiac CT and stress MPI within one month from each other as part of their diagnostic program. The treating physician ordered the two tests based on clinical grounds. For each patient, the presence of coronary risk factors and angina symptoms was noted. Hypertension was defined as a blood pressure ≥140/90 mm Hg or the use of anti-hypertensive medication. Dyslipidemia was defined as total cholesterol level ≥6.2 mmol/L or treatment with cholesterol lowering medication. Patients were classified as having diabetes if they were receiving treatment with oral hypoglycemic drugs or insulin. Pre-test probability of CAD was calculated by extended Diamond-Forrester model.[8] The probability of CAD was analyzed as aggregate descriptors of the following clinical data: age, gender, hypertension, diabetes, dyslipidemia, smoking history, and angina symptoms. Pre-test probability of CAD was considered low when <.15, intermediate between .15 and .85, and high when >.85. Exclusion criteria were documented history of CAD defined as previous percutaneous coronary intervention, coronary artery bypass graft surgery or myocardial infarction, coronary revascularization performed within 2 months after imaging tests. Patients with atrial fibrillation, pacemaker or prosthetic valve, iodine allergy, severe loss of renal function, symptomatic asthma, and pregnancy were also excluded. All patients gave written informed consent to the study protocol.

CT Imaging

All patients were scanned with a 64-slice CT (Lightspeed VCT, GE Healthcare, Milwaukee, WI, USA). Patients with heart rate >65 bpm received intravenous beta-blockers (5-10 mg atenolol). First, patients underwent non-enhanced prospective electrocardiographic (ECG) gated sequential scan to measure the calcium score. Thereafter, patients were injected with 60-80 mL of contrast medium (Iomeron 400, Bracco, Milan, Italy) in an antecubital vein at a high flow rate (5 mL/s) followed by a saline flush and coronary CT angiography was performed by using retrospective ECG gating with ECG-based tube current modulation. The collimation was 64 × 9 × .625 mm; gantry rotation time was 350 ms, tube current was 600-mA, and voltage was 100-120 kV, depending on patient size. Synchronization of the scan with contrast medium arrival was achieved by using the bolus tracking technique (region of interest in ascending aorta) with an increment of 100 Hounsfield units (HU) relative to baseline value.[9] Axial reconstructions were transferred to a dedicated workstation (Advantage Workstation, GE Healthcare, Milwaukee, WI, USA) for post-processing and subsequent analysis. At CAC score analysis calcium was defined as the presence of at least 3 contiguous pixels with a density >130 HU. The total calcium burden in the coronary arteries was quantified based on the scoring algorithm proposed by Agatston et al.[10] and predefined calcium score categories (0, 1-300, and >300) were used.[11] Axial images, multiplanar reconstructions, and curved multi planar reformations were used for coronary evaluation. Two experienced cardiac radiologists who were blinded each other and unaware of the clinical history of the patients independently assessed CTCA images. In the case of disagreement (12% of the scans), a consensus decision was reached after a joint reading session. The coronary arteries were divided into 16 segments according to the modified American Heart Association classification.[12] Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Stenoses were

categorized as non-significant (<50% luminal narrowing) and significant (≥50% luminal narrowing). Modified Duke CAD index, an angiographic score integrating proximal CAD, plaque extent, and left main disease, was also constructed.[13]

MPI

All patients underwent same-day Tc-99 m sestamibi exercise stress and rest MPI according to the recommendations of the European Association of Nuclear Medicine and European Society of Cardiology,[14] as previously described in detail.[15] In all patients, beta-blocking medications and calcium antagonists were withheld for 48 h and long-acting nitrates for 12 h before testing. Imaging was performed using a dual-head rotating gamma camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL, USA) equipped with a low-energy, high-resolution collimator and connected with a dedicated computer system. No attenuation or scatter correction was used. An automated software program (e-soft, 2.5, QGS/QPS, Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate the scores incorporating the extent and severity of perfusion defects, using standardized segmentation of 17 myocardial regions.[16] Briefly, this commercial package determines reconstruction limits for the projection dataset, reconstruct the projection images into transaxial images using standard filtered back projection, and then reorient the transaxial images into short-axis images. LV contours were checked visually and manually adjusted if the computer-generated automatic contours were found to be incorrect. Quantitative defect extent and severity were defined from sex-specific normal limits, and summed stress score was obtained by adding the scores of the 17 segments (0 = normal to 4 = absent perfusion) of the stress images. A similar procedure was applied to the resting images to calculate the summed rest score. The summed difference score (SDS) represents the difference between the stress and rest scores and is used as an index of ischemic burden: SDS < 2, no ischemia; 2-6, mild ischemia; >6, moderate-severe ischemia.[17] CCTA and MPI images were also analyzed combined with regard to morphologically significant lesions (≥50%) and reversible perfusion defects. Patients were assigned to one of the following three categories: (1) matched: reversible MPI defect in a territory subtended by a coronary artery with a significant stenosis at CCTA; (2) unmatched: any unmatched pathological finding from CCTA and/or MPI; and (3) normal: normal CCTA or any luminal narrowing <50% and no defect by MPI.

Follow-up Data

Patient follow-up was obtained by use of a questionnaire that was assessed by a phone call to all patients and general practitioners or cardiologists and by review of hospital or physicians' records by individuals blinded to the patient's test results. The outcome was a composite end point of cardiac death, nonfatal myocardial infarction, or unstable angina requiring coronary revascularization whichever occurred first. The cause of death was confirmed by review of death certificate, hospital chart, or physician's records. Two physicians reviewed each death, rescreened medical records when appropriate, and resolved disparity by consensus. Death was considered to be of cardiac origin if the primary cause was defined as acute myocardial infarction, congestive heart failure, valvular heart disease, sudden cardiac death, cardiac interventional/surgical procedure related. Myocardial infarction was defined when ≥2 of the following 3 criteria were met: chest pain or equivalent symptom complex, positive cardiac biomarkers, or typical electrocardiographic changes.[18] Two patients experiencing noncardiac death and four undergoing late elective revascularization not due to unstable angina were censored at the time of death or at the time of revascularization, respectively. The date of the last examination or consultation was used to determine the length of follow-up.

Statistical Analysis

Continuous data are expressed as mean ± standard deviation and categorical data as percentage. Comparison between groups was performed with unpaired *t* test and Chi-square test as appropriate. A P value $< .05$ was considered statistically significant. The ln(CAC + 1) score transformation was used to adjust for the rightward skew of the data and to reduce heteroscedasticity. Survival analysis was performed by univariable and multivariable Cox proportional hazard regression analysis. Only variables showing a P value $< .01$ at univariable analysis were considered for multivariable analysis. Annualized event rates were expressed as the number of patients having event as a proportion of the number of patients at risk divided by the number of patient-years follow-up. Event-free survival curves were obtained by the Kaplan-Meier method and compared with the log-rank test. The incremental prognostic value of clinical data and imaging findings was assessed considering variables in hierarchical order. The estimation of the potential additive value of SDS over the model including pre-test probability of CAD, ln(CAC + 1) and modified Duke CAD index was also assessed comparing the clinical net benefit curves obtained with decision curve analysis.[19,20] The usefulness of SDS in reducing the number of false positive at the same number of true positive prediction was also evaluated and graphically represented. All the analyses were performed using STATA version 14.0 for Windows (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics and Outcome

Of the 164 patients enrolled, follow-up data were not available for 9 patients (5%). The mean age of patients lost at follow-up was 63 ± 10 years and the prevalence of cardiovascular risk factors comparable to those of the 156 patients with available follow-up data. The median follow-up was 82 ± 34 months. During follow-up, 22 events occurred (14% cumulative event rate). The events were cardiac death in 4 patients, nonfatal myocardial infarction in 2 and unstable angina requiring revascularizations in 16. In the overall study

population, 80 (51%) patients were at low and 76 (49%) at intermediate pre-test likelihood of CAD.

Clinical characteristics and imaging findings of patients with and without events are reported in Table 1. Coronary calcium score, extent and severity of CAD, and SDS were significantly higher in patients with events than in those without. Among patients with events, 15 (68%) had stress-induced ischemia compared with 35 (26%) without events ($P < .001$). In particular, stress-induced ischemia was mild in 13 and moderate-severe in 2 patients with events, and mild in 27 and moderate-severe in 8 patients without events. The prevalence of significant CAD by CCTA and stress-induced ischemia by MPI in each CAC score category is depicted in Figure 1. The event-free survival curves according to calcium score category, CAD severity and stress-induced ischemia are reported in Figure 2. As showed, event-free survival decreased with worsening of CAC score category (P for trend <.001) and it was worse in patients with significant CAD ($P < .001$) and in those with stress-induced ischemia ($P < .001$). Of note, no patients with calcium score of 0 suffered events at follow-up. When these patients were excluded from the analysis, the most favorable event-free survival was found in the normal followed by the unmatched group (unmatched pathological finding from CCTA and/or MPI), whereas the matched group (reversible MPI defect in a territory subtended by a coronary artery with a significant stenosis at CCTA) had the most unfavorable outcome (P for trend <.001) (Figure 3).

Predictors of Events

Significant predictors of events at univariable and multivariable Cox regression analyses are reported in Table 2. To eliminate redundancy and avoid model overfitting, only calcium score, SDS, and Duke CAD index were included in the multivariable model. As shown, calcium score ($P = .001$) and SDS ($P = .012$) were independent predictors of events. The results of incremental analysis are reported in Figure 4. Stress-induced ischemia added prognostic information to a model including in hierarchical order clinical variables, CAC score and CCTA findings, increasing the global Chi-square from 36.2 to 41.9 ($P = .013$). Conversely, CCTA data did not provide incremental prognostic

Table 1. Clinical characteristics and imaging findings of patients with and without events

	All patients ($n = 156$)	Events ($n = 22$)	No events ($n = 134$)	*P* value
Age (years)	63 ±11	65 ±11	62 ±11	.23
Male gender	108 (69%)	20 (91%)	88 (66%)	.017
Diabetes	24 (15%)	5 (23%)	19 (14%)	.30
Hypertension	92 (59%)	9 (41%)	83 (62%)	.06
Dyslipidemia	48 (31%)	8 (36%)	40 (30%)	.54
Smoking	42 (27%)	3 (14%)	39 (29%)	.13
Angina symptoms				.79
Typical	24 (15%)	3 (14%)	21 (16%)	
Atypical	47 (30%)	7 (32%)	44 (33%)	
LV ejection fraction (%)	51 ± 6	49 ± 5	52 ± 6	.42
CAC categories[a]				<.0001
0	42 (27%)	0 (0%)	42 (31%)	
1-300	98 (63%)	14 (64%)	84 (62%)	
>300	16 (10%)	8 (36%)	8 (6%)	
ln(CAC + 1) score	3.2 ± 2.2	5.1 ± .8	2.9 ± 2.2	<.0001
Significant CAD[b]	66 (42%)	18 (82%)	48 (36%)	<.0001
Modified Duke CAD index	1.0 ± 1.1	2.2 ± .8	.8 ± 1.0	<.0001
Summed stress score	2.3 ± 4.0	4.5 ± 4.4	1.9 ± 3.8	.005
Summed rest score	.6 ± 2.8	.7 ± 2.1	.6 ± 2.9	.91
Summed difference score	1.7 ± 2.7	3.8 ± 3.8	1.3 ± 2.4	<.0001

Values are expressed as mean value ± standard deviation or as number (percentage) of subjects
LV, left ventricular; *CAC*, coronary artery calcium; *CAD*, coronary artery disease
[a]Agatston units; [b] by CCTA

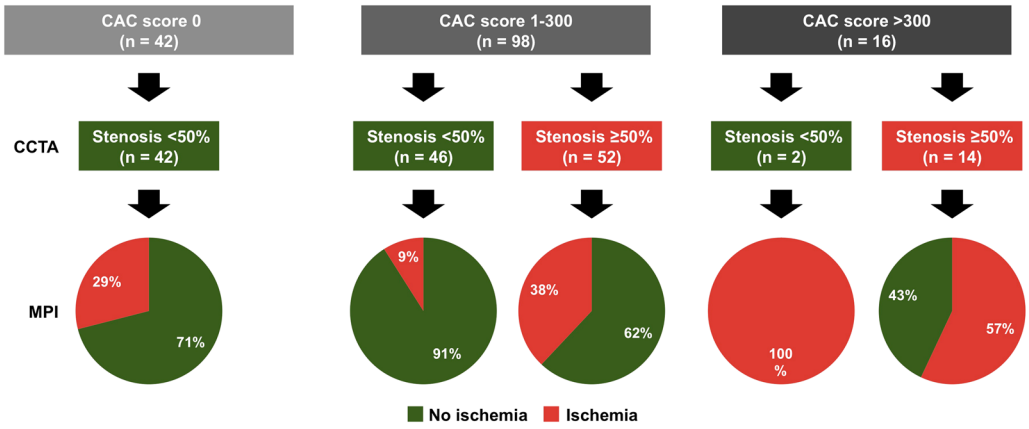

Figure 1. Prevalence of significant CAD by CCTA and stress-induced ischemia by MPI in each of the CAC score category.

information over the model including clinical data, CAC score, and MPI findings (global Chi square from 38.9 to 41.9, $P = .075$).

Clinical Benefit

The decision curve analyses in patients with CAC score >0 indicate that the prognostic model including MPI resulted in a higher net benefit across a wide range of decision threshold probabilities (approximately 25% to 50% risk of cardiac events) (Figure 5). As example, after 60 months of follow-up, using an event-free survival probability of 40% as a threshold, the net benefit of the full model was .05, which is superior to .02 for the model without MPI. The net benefit increase of .03 has a ready clinical interpretation, indicating that including MPI in the model is the equivalent of a strategy that found 3 events per hundred patients after 60 months of follow-up without increasing the number false positive event. Conversely, at the same probability threshold of 40%, the net reduction in false positive is about 63 per 100 patients for the model including MPI compared to 58 per 100 patients for the model without (Figure 4). Thus, at this threshold, including MPI in the model is the equivalent of a strategy that reduced the false positive rate of 5% without missing the prediction of any cardiac events.

DISCUSSION

To the best of our knowledge, this is the first study comparing the long-term prognostic value of CAC scanning, CCTA and stress MPI in the same subjects with suspected CAD. We found that CAC and MPI, but not CCTA, are independent predictors of cardiac events. In addition, functional data by stress MPI improve risk stratification over clinical variables, CAC scanning and CCTA findings.

CAC score provides a quantitative measurement of the overall coronary atherosclerotic burden[21] and is a strong predictor of cardiac events. The prognostic value of the CAC score has been consistently found in several studies. A zero CAC score is a consistent predictor of very low risk for cardiac events[22,23] while event rates increase incrementally according to CAC score among those with abnormal CAC scans.[24,25] Moreover, CAC scanning provides incremental information for predicting outcomes when considering all other available clinical information. In a large study population, CAC scanning has been shown to provide strong net reclassification improvement for the prediction of cardiac events, far outweighing that provided by other potential screening tests for CAD.[26] CCTA and MPI are alternatively used in clinical practice, but the choice of the most appropriate prognostic approach is still debated. The prognostic value of MPI and CCTA for the occurrence of hard events is similar, while CCTA is more associated with events when coronary revascularization is considered.[5] CCTA has a high negative predictive value for suspected CAD and a high prognostic value in patients with low to intermediate probability of CAD while MPI leads the coronary intervention, by detecting ischemia and assessing the severity of CAD.[27-29] The results of the present study indicate that event-free survival decreased with worsening of CAC score category and it was worse in patients with significant CAD and in those with stress-induced ischemia. Noteworthy, no patients with calcium score of 0 suffered events at follow-up. When only patients with CAC > 0 were considered, the most favorable event-free survival was found in the normal followed by the unmatched group, whereas the matched

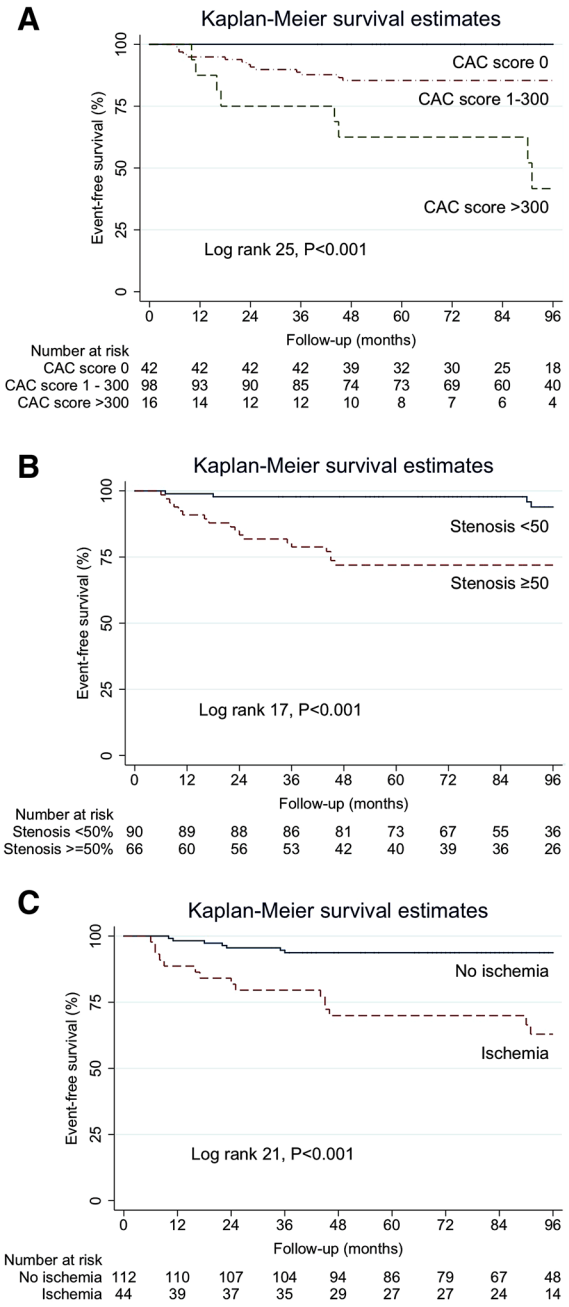

Figure 2. Event-free survival curves by Kaplan-Meier analysis according to CAC score categories (**A**), CCTA (**B**) and MPI (**C**) findings.

group had the most unfavorable outcome. These findings suggest that combined anatomical and functional assessment may allow improved risk stratification in patients with suspected CAD.

The relationship between CAC score and coronary vascular function has not been fully investigated. Recently, Assante et al.[30] in a large cohort of patients with suspected CAD and normal myocardial perfusion

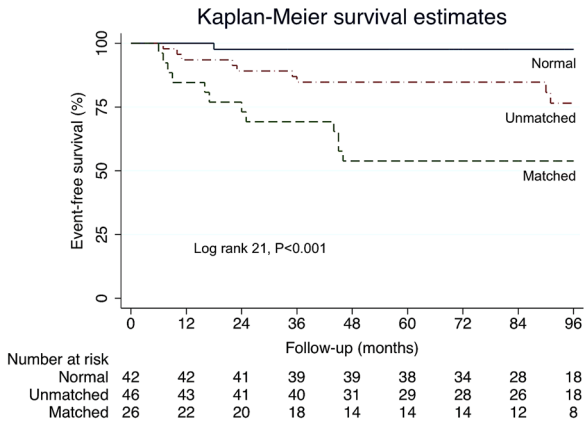

Figure 3. Event-free survival curves by Kaplan-Meier analysis in patients with CAC score >0 assigned to one of the following three categories: (1) matched: reversible MPI defect in a territory subtended by a coronary artery with a significant stenosis at CCTA; (2) unmatched: any unmatched pathological finding from CCTA and/or MPI; and (3) normal: normal CCTA or any luminal narrowing <50% and no defect by MPI.

found that CAC provides incremental information over established CAD risk factors for predicting coronary vascular dysfunction. Chang et al.[6] showed, in a population of 1175 asymptomatic subjects that underwent both CAC determination and stress MPI imaging, that CAC and MPI are independent and complementary in prediction of cardiac events over a follow-up of 7 years. Of note, we found that CAC and stress-induced ischemia were independent predictors of events also including CCTA findings in the multivariable Cox regression analysis. Chang et al.[6] proposed to perform CAC scanning in patients at intermediate or high clinical risk for CAD with normal SPECT result. Our findings show that a CAC of 0 boasts a great value in identification of patients at low probability of cardiac events, suggesting to perform further evaluation only in patients with CAC > 0.

The decision curve analysis indicates that the incremental prognostic value of MPI data over clinical variables, CAC and CCTA findings translates into a clinically relevant benefit that could change clinical decision making. The prognostic model including MPI resulted in a higher net benefit across a wide range of decision threshold probabilities including the range between 25% and 50% risk of cardiac events.

Some limitations of our study should be acknowledged. First, our study was performed at a single center in a small number of patients at low to intermediate pretest likelihood of CAD, which makes it uncertain whether results will be equally applicable to general clinical practice. In addition, according to the average low cardiac risk of the population, the events were

Table 2. Univariable and multivariable predictors of cardiac events

	Univariable analysis		Multivariable analysis	
	Hazard ratio (CI)	***P* value**	**Hazard ratio (CI)**	***P* value**
ln(CAC + 1) score	1.95 (1.43–2.67)	<.0001	1.99 (1.31–3.02)	.001
Significant CAD[a]	7.07 (2.39–16.9)	<.0001		
Modified Duke CAD index	2.57 (1.74–3.78)	<.0001	1.57 (.96–2.59)	.075
Summed stress score	1.10 (1.03–1.18)	.007		
Summed difference score	1.27 (1.26–1.43)	<.0001	1.20 (1.04–1.38)	.012

CAC, coronary artery calcium; *CAD*, coronary artery disease
[a]by CCTA

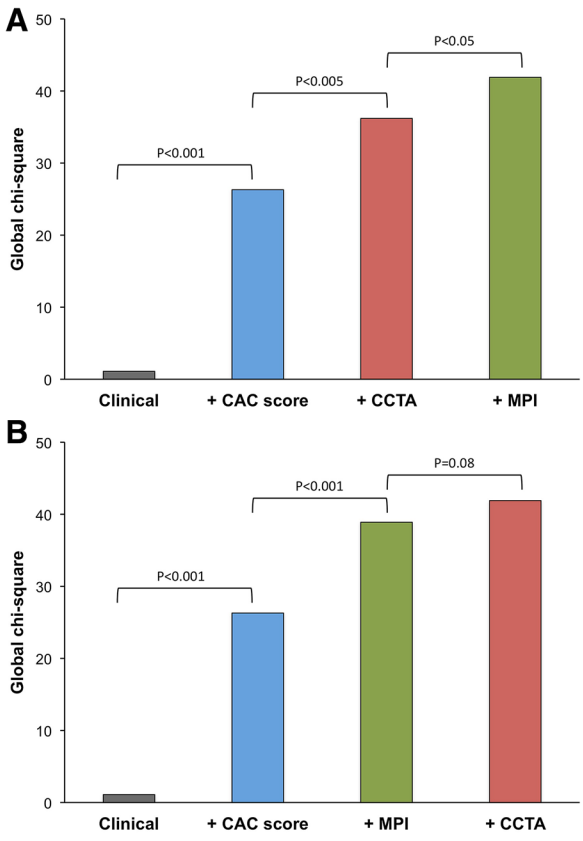

Figure 4. Incremental prognostic value (global Chi-square values on *y*-axis) of clinical data, CAC score, CCTA and MPI results (**A**) and clinical data, CAC score, MPI and CCTA results (**B**).

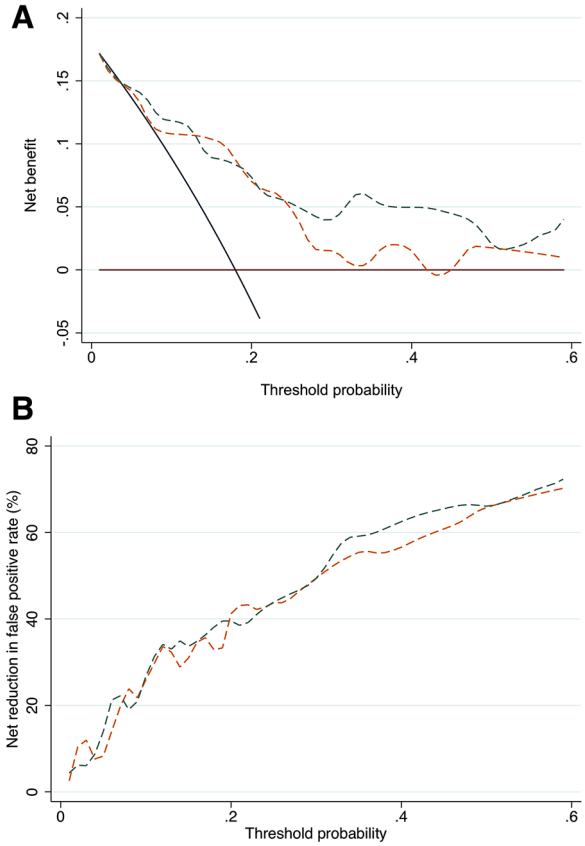

Figure 5. (**A**) Decision curves graphically representing net benefit (*y*-axis) for the model without (*dashed orange line*) and with (*solid green line*) MPI data in a range of decision threshold probabilities (*x*-axis) in patients with CAC score >0. The blue (*treat all*) and purple (*treat none*) solid lines represent making the same decision in all patients. (**B**) Reduction in false positive rate for the model without (*dashed orange line*) and with (*solid green line*) MPI data.

weighted towards the ''soft'' event of unstable angina with revascularization. Studies in larger series are warranted to confirm our results.

NEW KNOWLEDGE GAINED

CAC and MPI, but not CCTA, are independent predictors of cardiac events. The decision curve analyses in patients with CAC score >0 indicate that the prognostic model including MPI resulted in a higher net benefit across a wide range of decision threshold

probabilities. These findings also confirm that the major predictors of events are the extent of atherosclerosis (best assessed with CAC) and extent of myocardial ischemia (as assessed by MPI or other imaging modalities).

CONCLUSION

The results of this study suggest that patients with suspected CAD without CAC do not need further cardiac imaging investigations. Stress MPI appears to improve risk stratification over clinical variables, CAC scanning, and CCTA findings. Combined information from CCTA and MPI might allow risk stratification in patients with suspected CAD and documented coronary calcium.

Disclosure

The authors have indicated that they have no financial conflict of interest.

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