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Prognostic Value of Coronary CT Angiography and Calcium Score for Major Adverse Cardiac Events in Outpatients

Zhi-hui Hou, MD,* Bin Lu, MD,* Yang Gao, MD,* Shi-liang Jiang, MD,*
Yang Wang, MD,† Wei Li, MD,† Matthew J. Budoff, MD‡
Beijing, China; and Torrance, California

OBJECTIVES This study sought to evaluate the prognostic value of coronary artery calcium score (CACS) and coronary computed tomography angiography (CTA) for major adverse cardiac events (MACE).

BACKGROUND The prognostic value of CACS has been well described. Few studies use the rich information of coronary CTA to predict future clinical outcomes and compare CACS with coronary CTA.

METHODS We followed up 5,007 outpatients who were suspected of having coronary artery disease (CAD) and who underwent cardiac CTA. Cardiac CT was assessed for CACS and the extent, the location, the stenosis severity, and the composition of the plaque in coronary CTA. The endpoint was MACE, defined as composite cardiac death, nonfatal myocardial infarction, or coronary revascularization.

RESULTS Follow-up was completed in 4,425 patients (88.4%), with a median follow-up period of 1,081 days. At the end of the follow-up period, 363 (8.2%) patients had experienced MACE. Cumulative probability of 3-year MACE increased across CT strata for CACS (CACS 0, 2.1%; CACS 1 to 100, 12.9%; CACS 101 to 400, 16.3%; and CACS >400, 33.8%; log-rank $p < 0.001$); for coronary CTA (no plaque 0.8%, nonobstructive disease 3.7%, 1-vessel disease 27.6%, 2-vessel disease 35.5%, and 3-vessel disease 57.7%; log-rank $p < 0.001$); and for characteristics of the plaques (5.5% for calcified plaque, 22.7% for noncalcified plaque, and 37.7% for mixed plaque; log-rank $p < 0.001$). The area under the receiver-operating characteristic curves showed the incremental value of CACS and coronary CTA for predicting MACE: 0.71 for clinical risk factors, which improved to 0.82 by adding CACS and further improved to 0.93 by adding coronary CTA (both $p < 0.001$).

CONCLUSIONS The CACS and coronary CTA findings have prognostic value and have incremental value over routine risk factors for MACE, and coronary CTA is superior to CACS. Cardiac CT seems to be a promising noninvasive modality with significant prognostic value. (J Am Coll Cardiol Img 2012;5: 990–9) © 2012 by the American College of Cardiology Foundation

From the *Department of Radiology, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; †Department of Medical Statistics Center, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; and the ‡Department of Internal Medicine, Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California. This study was granted by the Ministry of Science and Technology of China (2007BAI05B02). All authors have reported they have no relationships relevant to the contents of this paper to disclose.

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The multivariable statistical models of traditional coronary heart disease risk factors, such as Framingham risk score, are widely recommended for coronary risk stratification among individual patients (1,2). But the models have limitations in their ability to discriminate persons who will or will not experience coronary artery disease (CAD) (3). Since the first report of the use of contrast-enhanced computed tomography (CT)

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to obtain noninvasive coronary angiograms in 1995 (4), cardiac CT has evolved to become a highly accurate method in the diagnosis of CAD, comparable to conventional invasive coronary angiography (5). Given the uncertainty of current risk factors predictive models, a recommended approach to improve risk prediction over the traditional risk factors is coronary artery calcium score (CACS), and the prognostic value of CACS has been well described (6,7). The CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) study showed that nonobstructive and obstructive CAD by coronary computed tomography angiography (CTA) are associated with higher rates of mortality, whereas absence of CAD is associated with a very favorable prognosis (8). Although coronary CTA can give us rich information regarding plaque burden, few studies have evaluated that information to predict future clinical outcomes and compare with the prognostic power of CACS.

METHODS

Patient selection. We evaluated 6,477 consecutive patients between January 2007 and August 2008 in Fu Wai Hospital who underwent cardiac CT using a 64-slice multidetector CT scanner. All of these patients were referred for cardiac CT studies by their cardiologists. The coronary CTA was performed because of symptoms of chest pain, to exclude coronary disease in patients carrying 1 or more risk factors or electrocardiographic abnormalities, or to evaluate prior revascularization. For the present study, we excluded subjects with a history of coronary revascularization (percutaneous coronary intervention [PCI], n = 991), coronary artery bypass graft surgery (CABG) (n = 263), history of acute myocardial infarction (MI) (n = 54), inadequate image quality because of motion artifacts or inadequate contrast concentration (n = 49), or having other heart diseases (cardiomyopathy n = 55, valvular heart disease n = 15, congenital heart disease n = 43). In total, 5,007 patients were enrolled (Fig. 1).

Data acquisition. Scans were performed using a 64-row spiral CT scanner (Light Speed VCT, GE Healthcare, Milwaukee, Wisconsin). Patients with a pre-scan heart rate of 70 beats/min or higher were given 25 mg to 50 mg of metoprolol (Selokeen, AstraZeneca, Zoetermeer, the Netherlands) orally 1 h before scanning. First, patients underwent nonenhanced prospective electrocardiography (ECG)-gated sequential scan to measure CACS. Thereafter, coronary CTA was performed using retrospective ECG gating with ECG-based tube current modulation. A double-head power injector (Stellant, Medrad, Pittsburgh, Pennsylvania) was used to inject contrast media through a 20G trocar in an antecubital vein. A test bolus (10 ml contrast agent followed by a 20-ml saline flush) with injection rate of 5 ml was used to determine the timing of scan delay and image acquisition time. Depending on patient weight, iohexol 350 mgI/ml (Omnipaque 350, GE Healthcare) or iopromide 370 mgI/ml (Ultravist 370, Bayer-Schering Pharma, Berlin, Germany) was injected at a speed of 4 to 5.5 ml/s. The main scanning parameters were as follows: 64 detectors; 0.625 mm individual detector width; 350 ms gantry rotation time; 120 kV tube voltage; ECG-modulated tube current ranged from 200 to 550 mA (the tube current was 550 mA during 40% to 80% RR interval when diagnostic image quality was required, and remained at 200 mA during the other phases of the RR interval); 0.16 to 0.22 pitch; 400 mm table feed/rotation; 200 to 250 mm field of view.

Image analysis. All the scans were retrospectively analyzed on the workstation (Deep Blue, ADW4.3, GE Healthcare). 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 by the scoring algorithm proposed by Agatston et al. (9), and predefined calcium score categories (0, 1 to 100, 101 to 400, and >400) were used (10). The coronary artery tree was segmented according to the modified American Heart Association classification, and these segments were subsequently investigated for the presence and characteristics of coronary plaques. The degree of stenosis was classified as significant

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft surgery
CACS = coronary artery calcium score
CAD = coronary artery disease
CI = confidence interval
CT = computed tomography
CTA = computed tomography angiography
ECG = electrocardiography
HR = hazard ratio
LM = left main
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
ROC = receiver-operating characteristic

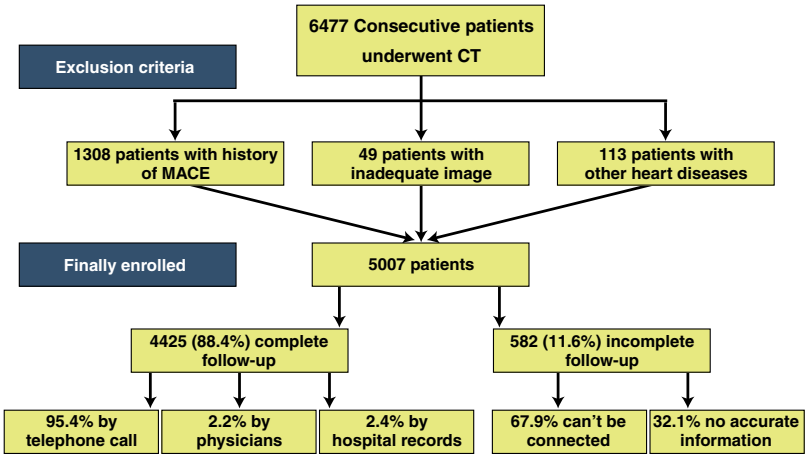

Figure 1. Flow Chart of the Follow-Up

In all, 6,477 consecutive patients who underwent cardiac computed tomography between January 2007 and August 2008 in Fu Wai Hospital were evaluated. For the present study, 5,007 patients were finally enrolled, and 4,425 patients were finally analyzed. CT = computed tomography; MACE = major adverse cardiac events.

if the patient had >50% diameter stenosis on the longitudinal images. We evaluated the plaque extent and stenosis rate by summing the number of epicardial vessels with significant stenosis (no plaque, no obstructive, 1-vessel disease, 2-vessel disease, 3-vessel disease). Coronary plaques were classified as calcified (composed exclusively of high-density material >130 HU), noncalcified (composed exclusively of material having density ≤130 HU), and mixed (having components of both calcified and noncalcified plaques) (11). At patient-level analysis, if >1 type of plaque was present, the characteristic of the most stenotic plaque was recorded for statistical analysis.

CAD risk factors assessment. The conventional coronary risk factors such as obesity, cigarette smoking, hypertension, hypercholesterolemia, diabetes mellitus, and family history were assessed. Obesity was defined as body mass index ≥30 kg/m^2. Smoking was defined as any cigarette smoking within 1 year of the cardiac CT. Hypertension was defined as a previously established diagnosis, systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use. Hypercholesterolemia was defined according to the National Cholesterol Education Panel guidelines or by the current use of lipid-lowering medication (12). Diabetes mellitus was defined as a previously established diagnosis, insulin or oral hypoglycemic therapy, fasting glucose of ≥126 mg/dl, or nonfasting glucose of ≥200 mg/dl. Family history of CAD was defined as MI, coronary revascularization, or sudden cardiac death for father <55 years-of-age or mother <65 years-of-age. Typical angina was defined as a combination of: 1) discomfort in the anterior chest, neck, shoulders, jaw, or arms; 2) precipitated by physical exertion or emotional stress; and 3) relieved by rest or nitroglycerin within minutes. Atypical angina was defined as chest pain with 2 of these 3 factors, and nonanginal chest pain was defined as chest pain with <2 of these 3 factors (13).

Follow-up. Risk factors and MACE information was obtained from patient telephone interviews, contact with the patients' physicians, and hospital records. A standard questionnaire was used during the telephone interview. MACE included any of the following: 1) cardiac death; 2) new acute MI; or 3) coronary revascularization (PCI and CABG). Hard MACE included: 1) cardiac death or 2) new acute MI. Cardiac death was defined as death due to acute MI, ventricular arrhythmias, refractory heart failure, or cardiogenic shock. We reviewed all available data to determine whether a cardiac etiology was the immediate cause of death. New acute MI was defined based on the criteria of typical chest pain, elevated cardiac enzyme levels, and typical alterations of ECG. We contacted patients' physicians and hospital records (including ECG, cardiac enzyme levels, and other available data) to adjudicate all events.

The decisions to submit patients to revascularization were made by referring physicians, taking into account all available information and patient preferences. Revascularization procedures within 60 days after cardiac CT were considered to be trig-

gered by the scan and were not considered events. Using this 60-day landmark for analysis, early coronary CTA-driven events (referring physicians were likely to include coronary CTA findings in management decisions) were excluded. Because most patients were symptomatic and undergoing evaluation for suspected CAD, it was considered ethical and necessary to make CT findings known to referring physicians. When a patient experienced >1 MACE, the first event was chosen. When 2 MACE occurred simultaneously, the worse event was chosen (death worse than MI, MI worse than revascularization). An adjudication outcome panel of 2 physicians reviewed the patient data forms and verified by review of medical records to determine whether a patient had MACE during the follow-up period. The outcome panel was blinded to the findings of the cardiac CT. Disagreement was resolved by consensus, which included an additional senior cardiologist. If a patient could not be contacted, that patient was considered lost to follow-up. Three attempts were made using the patient's direct phone number in 1 week. If we were unsuccessful or if the patient could not provide accurate information, that patient was tabulated as lost to follow-up.

Statistical methods. All the statistical analyses were conducted by a specialist of medical statistics and performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois). For descriptive analysis, continuous variables were represented as the mean ± SD, and categorical variables were represented as percentages. Variables were compared with chi-square statistic for categorical variables and by *t* test for continuous variables. Cumulative event rates as stratified by CT features were estimated using the product-limit (Kaplan-Meier) methods and log-rank test. We fitted Cox proportional hazards models to estimate the unadjusted hazard ratio (HR) of all variables and evaluate the prognostic value of risk factors, risk factors plus CACS, and risk factors plus CACS plus coronary CTA for predicting MACE. The area under the receiver-operating characteristic (ROC) curve was determined to evaluate the prognostic discriminatory capacity for predicting MACE for each Cox model. The incremental prognostic value of adding CACS and coronary CTA beyond that of risk factors was determined by comparing the global chi-square value of the models. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

In all, 582 (11.6%) patients were lost follow-up (395 patients could not be contacted, and 187 patients could not provide accurate information). The remaining 4,425 patients (mean age 59.6 ± 11.3 years; 62.1% men) were finally analyzed. The cohort was followed up for a median of 1,081 days (quartile 1 = 960 days, quartile 3 = 1,192 days). The majority of the patients (n = 4,223, 95.4%) were followed up by a standardized telephone call. Others (n = 202, 4.6%) were followed up by contact with the patients' physicians (n = 98, 2.2%) or hospital records (n = 104, 2.4%). Patients presented with nonanginal chest pain (n = 2,079, 47.0%), atypical angina (n = 708, 16.0%), and typical angina (n = 266, 6.0%). Patients with MACE had more coronary risk factors (Table 1).

Table 1. Baseline Characteristics for All Patients

	Overall (N = 4,425)	MACE (n = 363)	No MACE (n = 4,062)	p Value
Age, yrs	59.6 ± 11.3	63.6 ± 10.8	59.0 ± 11.2	<0.001
Male	2,748 (62.1)	258 (71.1)	2,490 (61.3)	<0.001
Obesity	1,065 (24.1)	90 (24.8)	975 (24.0)	0.736
Hypertension	2,538 (57.4)	261 (71.9)	2,277 (56.1)	<0.001
Diabetes mellitus	640 (14.5)	91 (25.1)	549 (13.5)	<0.001
Dyslipidemia	1,220 (27.6)	102 (28.0)	1,118 (26.5)	0.814
Family history of CAD	1,554 (35.1)	141 (38.8)	1,413 (34.8)	0.071
Smoking	1,367 (30.9)	131 (36.1)	1,236 (30.4)	0.007
Chest pain				
Typical angina	266 (6.0)	30 (8.3)	236 (5.8)	0.059
Atypical angina	708 (16.0)	62 (17.1)	646 (16.0)	0.558
Nonanginal chest pain	2,079 (47.0)	178 (49.0)	1,901 (46.8)	0.413

Values are mean ± SD or n (%).
CAD = coronary artery disease; MACE = major adverse cardiac event.

Table 2. Baseline Characteristics and Rates of Obstructive Coronary Segments for Each Segment in Follow-Up Subjects and Lost to Follow-Up Subjects

	Follow-Up (n = 4,425)	Lost to Follow-Up (n = 582)	p Value
Age, yrs	59.6 ± 11.3	58.9 ± 10.9	0.698
Male	2,748 (62.1)	367 (63.1)	0.655
Obesity	1,065 (24.1)	132 (22.7)	0.461
Hypertension	2,538 (57.4)	312 (53.6)	0.086
Diabetes mellitus	640 (14.5)	76 (13.1)	0.363
Dyslipidemia	1,220 (27.6)	175 (30.1)	0.206
Family history of CAD	1,554 (35.1)	186 (32.0)	0.132
Smoking	1,367 (30.9)	198 (34.0)	0.126
Chest pain			
Typical angina	266 (6.0)	30 (5.5)	0.410
Atypical angina	708 (16.0)	105 (18.0)	0.209
Nonanginal chest pain	2,079 (47.0)	250 (43.0)	0.067
LM	391 (8.8)	48 (8.2)	0.637
LAD	724 (16.4)	108 (18.6)	0.181
Proximal	442 (11.1)	70 (12.0)	0.127
Mid or distal	212 (5.2)	32 (5.5)	0.456
Diagonal	70 (1.6)	6 (1.0)	0.307
LCX	334 (7.5)	43 (7.4)	0.891
Proximal	121 (2.7)	15 (2.6)	0.826
Mid or distal	63 (1.4)	7 (1.2)	0.669
OM	150 (3.4)	21 (3.6)	0.785
RCA	434 (9.8)	55 (9.5)	0.785
Proximal	231 (5.2)	26 (4.5)	0.439
Mid or distal	203 (4.6)	29 (5.0)	0.670

Values are mean ± SD or n (%).
CAD = coronary artery disease; LAD = left anterior descending; LCX = left circumflex artery; LM = left main; OM = obtuse marginal; RCA = right coronary artery.

Cardiac CT findings. In all, 2,536 (57.3%) subjects were noted to have no plaque within the coronary arteries. Additionally, only nonobstructive plaque was noted in 1,021 (23.1%) subjects. Among 868 (19.6%) patients with significant stenosis, 1-vessel disease, 2-vessel disease, and 3-vessel disease were noted in 438 (9.9%), 233 (5.3%), and 197 (4.5%), respectively. Three hundred ninety-one (8.8%) patients had left main (LM) disease, and 78 (1.8%) had occlusion disease. Calcified plaque, noncalcified plaque, and mixed plaque were noted in 1,021 (23.1%), 183 (4.1%), and 685 (15.5%) subjects, respectively. CACS = 0 was noted in 2,785 (62.9%) subjects; CACS 1 to 100, CACS 101 to 400, and CACS >400 were noted in 813 (18.4%), 483 (10.9%), and 344 (7.8%) subjects, respectively. There were no significant differences in the rates of obstructive disease per segment and baseline characteristics between the follow-up group and lost to follow-up group (Table 2).

Table 3. Prevalence of Coronary Artery Disease and MACE in Men and Women

	Total (N = 4,425)	Men (n = 2,748)	Women (n = 1,677)	p Value
Any plaque	1,889 (42.7)	1,235 (44.9)	654 (39.0)	<0.001
Significant stenosis	868 (19.6)	580 (21.1)	288 (17.2)	0.001
MACE	363 (8.2)	258 (9.4)	105 (6.3)	<0.001

Values are n (%).
MACE = major adverse cardiac events.

Follow-up. At the end of the study, 40 cardiac deaths, 87 new acute MI, and 371 coronary revascularizations (319 PCI and 52 CABG) were found. During the first 60 days, MACE developed in 156 patients (1 cardiac death, 20 new acute MI, 122 PCI, and 13 CABG). After eliminating revascularizations within 60 days, 363 (8.2%) patients had experienced MACE. The prevalence of any plaque, significant stenosis, and MACE was significantly higher among men than among women (Table 3).

Figure 2 depicts the Kaplan-Meier estimates of the cumulative probability of MACE as stratified by CT findings; Table 4 provides the probability of events at various time points. The probability of 3-year MACE increased significantly across the strata of CACS categories (2.1% for patients with CACS = 0, 12.9% for patients with CACS 1 to 100, 16.3% for patients with CACS 101 to 400, and 33.8% for patients with CACS >400; log-rank $p < 0.001$), coronary CTA categories (0.8% for no-plaque patients, 3.7% for patients with only nonobstructive plaque, 27.6% for 1-vessel disease patients, 35.5% for 2-vessel disease patients, and 57.7% for 3-vessels patients; log-rank $p < 0.001$), and the characteristics of the plaques (5.5% for calcified plaque, 22.7% for noncalcified plaque, and 37.7% for mixed plaque; log-rank $p < 0.001$).We also found the probability of MACE increased significantly across patients with LM disease and occlusive disease.

Figure 3 depicts CACS and several coronary CTA findings that demonstrated significant associations with MACE. An unadjusted analysis of MACE is presented in Table 5. Table 6 gives the incremental value of adding cardiac CT beyond that of the risk factors for predicting MACE. The discriminatory capacity for predicting MACE improved from an area under the ROC curve of 0.71 with the risk factors alone to 0.82 when CACS was added ($p < 0.001$), which further improved to 0.93 with the addition of coronary CTA ($p < 0.001$) (Fig. 4).

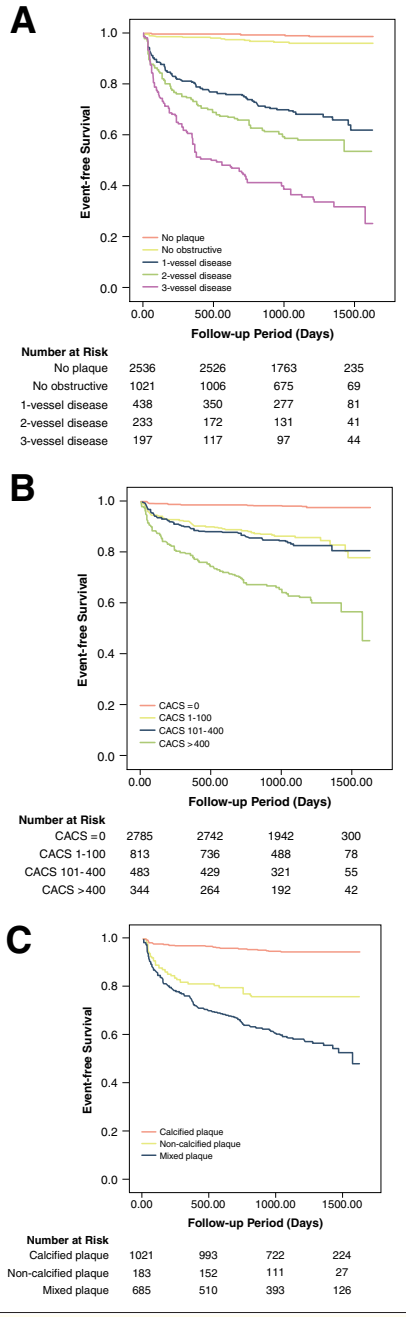

Figure 2. Kaplan-Meier Curves of MACE as Stratified by Coronary CTA Features

(A) Coronary computed tomography angiography (CTA) categories stratified into no plaque **(red line)**, no obstructive **(yellow line)**, 1-vessel disease **(blue line)**, 2-vessel disease **(green line)**, and 3-vessel disease **(purple line)**. **(B)** Coronary artery calcium score (CACS) categories stratified into CACS = 0 **(red line)**, CACS 1 to 100 **(yellow line)**, CACS 101 to 400 **(blue line)**, and CACS >400 **(green line)**. **(C)** The characteristics of the plaques categories stratified into calcified plaque **(red line)**, noncalcified plaque **(yellow line)**, and mixed plaque **(blue line)**. The cohort was followed up for a median of 1,081 days (quartile 1 = 960 days, quartile 3 = 1,192 days). MACE = major adverse cardiac events.

DISCUSSION

The strength of our study is that it provides prognostic data from a large cohort, as stratified by cardiac CT findings for MACE. We also recognize that incomplete follow-up may result in underreporting of MACE. However, no significant difference was found between subjects with follow-up and those lost to follow-up ($p > 0.05$ for all measures). Women in our study had lower rates of both obstructive CAD and MACE in contrast to their male counterparts.

Prognostic value of CACS. The prognostic value of CACS over clinical and laboratory data has been previously demonstrated in a large cohort of patients (14,15). As previous studies have shown, no or very few patients with CACS = 0 had events at follow-up, whereas patients with CACS >400 largely had significant CAD with a very high incidence of events. Michael et al. (16) noted that CACS = 0 predicts excellent survival, with 10-year event rates of approximately 1% (<0.1% per year), and the HR for all-cause mortality among patients with CACS of 101 to 400 and >400 compared with CACS = 0 was 5.56 (95% confidence interval [CI]: 4.27 to 7.21) and 9.65 (95% CI: 7.46 to 12.5), respectively. We similarly found the probability of 3-year MACE was 33.8% for CACS >400 and only 2.1% for CACS = 0 (<1% per year). The HR for patients with CACS of 101 to 400 and >400 compared with patients with CACS = 0 were 9.21 (95% CI: 6.50 to 13.05) and 22.22 (95% CI: 16.08 to 30.71), respectively, modestly higher than the prior study, which only evaluated mortality (16). Previous studies have demonstrated that CACS assessment combined with risk factors among asymptomatic adults provides prognostic information superior to either method alone, and the combined approach can more accurately guide primary preventive strategies for patients with CAD risk factors (17). We found with the addition of CACS to risk factors, the area under the ROC curves improved from 0.71 to 0.82 ($p < 0.001$), indicating the incremental prognostic value of CACS over clinical risk factors in this population.

Prognostic value of coronary CTA. Several groups examined the prognostic value of coronary CTA and showed that normal coronary CTA findings confer an excellent prognosis and abnormal coronary CTA findings are associated with adverse events (18–20). The CONFIRM study confirmed nonobstructive and obstructive CAD by coronary CTA are associated with higher rates of mortality

Table 4. Kaplan-Meier Cumulative Probability of MACE at 60 Days, 1 Year, and 3 Years as Stratified by Computed Tomography Findings

		MACE (Probability)		
	N = 4,425	60 Days	1 Year	3 Years
CACS = 0	2,785 (62.9)	3 (0.1)	37 (1.4)	56 (2.1)
CACS 1–100	813 (18.4)	10 (1.5)	67 (8.6)	103 (12.9)
CACS 101–400	483 (10.9)	1 (0.2)	47 (9.9)	74 (16.3)
CACS >400	344 (7.8)	7 (2.2)	65 (18.9)	113 (33.8)
No plaque	2,536 (57.3)	0 (0)	8 (0.4)	14 (0.8)
No obstructive	1,021 (23.1)	1 (0)	14 (1.6)	33 (3.7)
1-vessel disease	438 (9.9)	8 (1.9)	75 (17.7)	119 (27.6)
2-vessel disease	233 (5.3)	6 (2.7)	53 (22.9)	82 (35.5)
3-vessel disease	197 (4.5)	6 (3.3)	66 (33.7)	98 (57.7)
No LM disease	4,034 (91.2)	13 (0.4)	110 (2.9)	181 (4.9)
LM disease	391 (8.8)	8 (2.1)	106 (27.5)	165 (42.5)
No occlusion disease	4,347 (98.2)	17 (0.5)	195 (4.5)	307 (7.3)
Occlusion	78 (1.8)	4 (5.1)	21 (26.9)	39 (50.1)
Calcified plaque	1,021 (23.1)	4 (0.4)	29 (2.9)	54 (5.5)
Noncalcified plaque	183 (4.1)	0 (0)	31 (16.9)	40 (22.7)
Mixed plaque	685 (15.5)	14 (2.0)	148 (22.6)	238 (37.7)

Values are n (%).
CACS = coronary artery calcium score; other abbreviations as in Tables 1 and 2.

(8). In those studies, CAD severity and coronary atherosclerosis predicted all-cause mortality. However, those studies were not able to stratify according to cause of death nor did they track other MACE such as cardiac death and new acute MI. Further, few studies have used plaque information from coronary CTA to predict future clinical outcomes. Our results expand on previous literature by using 64-slice coronary CTA, capturing MACE, highlighting the incremental value of coronary CTA findings, such as the extent (the number of obstructive major epicardial coronary arteries), the location (LM disease), occlusive disease, and the composition of the plaque (calcified, noncalcified,

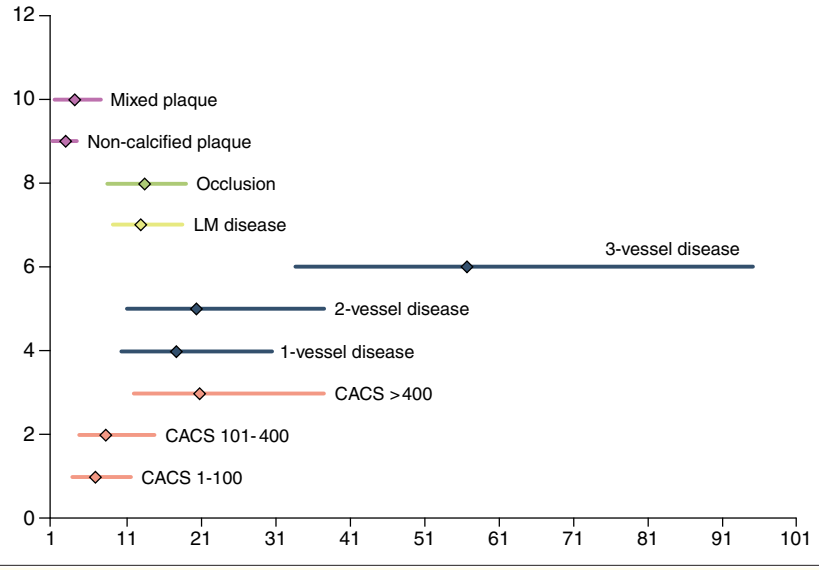

Figure 3. Unadjusted Cardiac CT Findings for Predicting MACE

Computed tomography (CT) strata for coronary artery calcium score (CACS) and several coronary computed tomography angiography (CTA) findings demonstrated significant associations with major adverse cardiac events (MACE). LM = left main.

Table 5. Unadjusted Risk Factors and Cardiac Computed Tomography Findings for Predicting All MACE and Hard MACE

Risk Factors	All MACE HR (95% CI)	p Value	Hard MACE HR (95% CI)	p Value
Age	1.04 (1.03–1.06)	<0.001	1.01 (1.00–1.04)	0.042
Male	2.06 (1.62–2.62)	<0.001	2.00 (1.23–2.34)	<0.001
Diabetes mellitus	1.56 (1.20–2.03)	0.001	1.21 (1.07–1.92)	0.003
Hypertension	1.60 (1.221–2.09)	0.001	1.42 (1.12–2.00)	0.012
Dyslipidemia	1.01 (0.82–1.22)	0.621	1.01 (0.73–1.12)	0.745
Smoking	1.62 (1.21–2.12)	<0.001	1.22 (1.14–2.02)	<0.001
Obesity	1.10 (0.79–1.35)	0.349	1.02 (0.71–1.22)	0.547
Family history	1.27 (1.01–1.61)	0.044	1.21 (1.00–1.44)	0.048
CACS = 0 (reference)	1.00	NA	1.00	NA
CACS 1–100	7.18 (5.16–10.00)	<0.001	6.90 (3.97–12.00)	<0.001
CACS 101–400	9.21 (6.50–13.05)	<0.001	8.33 (4.62–15.00)	<0.001
CACS >400	22.22 (16.08–30.71)	<0.001	20.97(12.22–37.31)	<0.001
No CAD* (reference)	1.00	NA	1.00	NA
One-vessel disease	28.99 (20.86–40.38)	<0.001	17.83 (10.43–30.46)	<0.001
Two-vessel disease	40.86 (28.69–58.19)	<0.001	20.59 (11.32–37.45)	<0.001
Three-vessel disease	75.20 (53.53–105.64)	<0.001	56.81 (33.95–95.06)	<0.001
No LM disease (reference)	1.00	NA	1.00	NA
LM disease	15.64 (12.60–19.42)	<0.001	13.13 (9.22–18.69)	<0.001
No occlusion (reference)	1.00	NA	1.00	NA
Occlusion	15.56 (10.89–22.22)	<0.001	13.55 (8.68–19.21)	<0.001
Calcified plaque (reference)	1.00	NA	1.00	NA
Noncalcified plaque	5.30 (3.67–7.65)	<0.001	3.01 (1.34–4.24)	<0.001
Mixed plaque	9.54 (7.21–12.64)	<0.001	4.23 (1.58–7.57)	<0.001

*No coronary artery disease (CAD) means no plaque plus no obstructive.
CI = confidence interval; HR = hazard ratio; NA = not applicable; other abbreviations as in Tables 1, 2, and 4.

or mixed). We found the probability of 3-year MACE increased significantly across all of the strata of coronary CTA categories, especially for the extent of obstructive disease (the probability of 3-year MACE was 57.7% for 3-vessel disease but only 0.8% for patients with no plaque). Nonobstructive lesions are frequently the culprits in acute coronary syndromes and sudden cardiac death (21). We found the probability of 3-year MACE was 3.7% for patients with nonobstructive lesions, similar to, but a little higher than found by a previous study (2.1%) (22). Most likely, that represents the use of different endpoints, as the prior study only evaluated cardiac death. A meta-analysis showed coronary CTA has excellent sensitivity (99%) and negative likelihood ratio (0.008) to exclude future coronary clinical events when pooled across the 9,592 patients with symptoms of possible angina in 17 studies over a median 20-month follow-up duration (23). The negative predictive value of our study was 99.4%, and the negative likelihood ratio was 0.006, similar to the results of a prior meta-analysis (23). Coronary CTA could evaluate the characteristics of the plaques, which add strength to coronary CTA compared with invasive coronary arteriography. We found the probability of 3-year MACE was significantly higher for noncalcified and mixed plaque than for calcified plaque. The current concept is that soft, lipid-filled plaques are most vulnerable, leading to subsequent clinical events (24). Acknowledging the potential value of plaque location and total occlusion, we also examined LM disease and

Table 6. Incremental Predictive Value of Cardiac Computed Tomography Findings Beyond That of Risk Factors

	AUC	95% CI	p Value	Global Chi-Square Value	Model Comparisons p Value
Risk factors	0.71	0.68–0.74	<0.001	172.07	N/A
Risk factors + CACS	0.82	0.80–0.85	<0.001	636.26	<0.001
Risk factors + CACS + coronary CTA	0.93	0.92–0.95	<0.001	2090.26	<0.001

AUC = area under the curve; CI = confidence interval; CTA = computed tomography angiography; other abbreviations as in Tables 4 and 5.

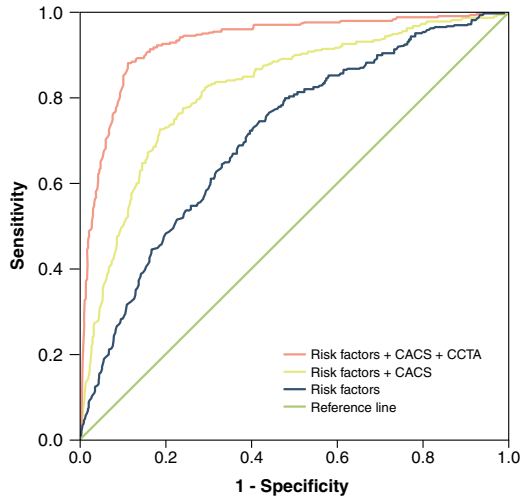

Figure 4. ROC Curves of 3 Models

Receiver-operating characteristic (ROC) curves show the incremental value of coronary artery calcium score (CACS) and coronary computed tomography angiography (CTA): risk factors only (area under the curve [AUC] 0.71; 95% confidence interval [CI]: 0.68 to 0.74, $p < 0.001$ **[blue line]**). Risk factors plus CACS (AUC 0.82; 95% CI: 0.80 to 0.85, $p < 0.001$ **[yellow line]**), and risk factors plus CACS plus coronary CTA (AUC 0.93; 95% CI: 0.92 to 0.95, $p < 0.001$ **[red line]**). **Green line** indicates reference line.

occlusive disease; the unadjusted HRs for predicting MACE were 15.64 and 15.56, respectively. We found that the addition of plaque characterization with coronary CTA to risk factors and CACS led to significant improvement of the area under the ROC curves, from 0.82 to 0.93 ($p < 0.001$).

Comparing prognostic value of CACS and coronary CTA. In the study by Kwon et al. (25), the event-free survival was excellent for patients with CACS = 0. Thus, despite the incremental prognostic value of coronary CTA in the overall patient population, for the subset of patients with a calcium score of 0, longer and higher radiation dose protocols seems inappropriate. However, Henneman et al. (26) noted a 30% prevalence of obstructive CAD as seen by coronary CTA in patients with CACS = 0 presenting to the emergency department with highly suspected acute coronary syndrome. The value of CACS = 0 depends upon the pre-test likelihood of patients. For our outpatients, we found 56 patients with CACS = 0 had events in 3 years, whereas only 14 patients with normal coronary CTA had events in 3 years. Thus, among outpatients, coronary CTA seems appropriate for those with CACS = 0. Michael et al. (16) noted that it is important to keep in mind that even in the absence of coronary artery calcification, relatively more events occur among patients with higher risk, especially persons with diabetes mellitus and smoking history. The positive predictive value of our study for CACS >400 was 32.8%, which was better than 1-vessel disease (27.1%), similar to 2-vessel disease (35.2%), and lower than 3-vessel disease (49.7%). Few patients with heavy coronary artery calcifications had no noncalcified plaque. Although heavy coronary artery calcifications limits the accurate evaluation of the segment, for the vessel level or patient level evaluation, the limitations were fewer (27). Furthermore, we found the probability of 3-year MACE was significantly higher for noncalcified and mixed plaque than for calcified plaque. The discriminatory capacity for predicting MACE further improved when coronary CTA was added beyond risk factors and CACS, indicating that coronary CTA has incremental value over routine risk factors and CACS.

Study limitations. This is a study from a single center, and most of our patients were symptomatic, which may limit the generalizability of our results to similar care settings and the general population. Bias is inevitable, for blinding of CT results may not be realistic because of the advanced use of cardiac CT in clinical practice, and because of the clinical nature of the study, in which cardiac CT was ordered to assist with management.

Another potential weakness is the self-reporting of risk factors. Data gathered by self-report is limited by patient recall, and thus subject to recall bias. The lack of a continuous risk variable may decrease the precision of point estimates of risk, but the use of categorical risk factor data has been validated as an approach to clinical risk stratification (28).

CONCLUSIONS

The CACS and coronary CTA findings have prognostic value and have incremental value over routine risk factors for MACE. In this outpatient population, coronary CTA is superior to CACS and traditional risk factors. Cardiac CT seems to be a promising noninvasive modality with significant prognostic value.

Reprint requests and correspondence: Dr. Bin Lu, Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 167 Bei Li Shi Street, Xi-Cheng District, Beijing 100037, China. *E-mail: blu@vip.sina.com.*

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Key Words: coronary artery calcium score ■ coronary computed tomography angiography ■ major adverse cardiac events ■ outpatients ■ risk factors.