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Millie Gomez, MD; James K. Min, MD; on behalf of the CONFIRM Investigators

Background—The predictive value of coronary computed tomographic angiography (cCTA) in subjects without chest pain syndrome (CPS) has not been established. We investigated the prognostic value of coronary artery disease detection by cCTA and determined the incremental risk stratification benefit of cCTA findings compared with clinical risk factor scoring and coronary artery calcium scoring (CACS) for individuals without CPS.

Methods and Results—An open-label, 12-center, 6-country observational registry of 27 125 consecutive patients undergoing cCTA and CACS was queried, and 7590 individuals without CPS or history of coronary artery disease met the inclusion criteria. All-cause mortality and the composite of all-cause mortality and nonfatal myocardial infarction were measured. During a median follow-up of 24 months (interquartile range, 18–35 months), all-cause mortality occurred in 136 individuals. After risk adjustment, compared with individuals without evidence of coronary artery disease by cCTA, individuals with obstructive 2- and 3-vessel disease or left main coronary artery disease experienced higher rates of death and composite outcome ($P<0.05$ for both). Both CACS and cCTA significantly improved the performance of standard risk factor prediction models for all-cause mortality and the composite outcome (likelihood ratio $P<0.05$ for all), but the incremental discriminatory value associated with their inclusion was more pronounced for the composite outcome and for CACS (C statistic for model with risk factors only was 0.71; for risk factors plus CACS, 0.75; for risk factors plus CACS plus cCTA, 0.77). The net reclassification improvement resulting from the addition of cCTA to a model based on standard risk factors and CACS was negligible.

Conclusions—Although the prognosis for individuals without CPS is stratified by cCTA, the additional risk-predictive advantage by cCTA is not clinically meaningful compared with a risk model based on CACS. Therefore, at present, the application of cCTA for risk assessment of individuals without CPS should not be justified. (*Circulation*. 2012;126: 304-313.)

Key Words: asymptomatic ■ coronary artery calcium ■ coronary CT angiography ■ prognosis

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in developed countries.[1] Coronary atherosclerosis involves a prolonged asymptomatic developmental phase, with its first manifestations often resulting in sudden cardiac death or nonfatal myocardial infarction (MI).[2,3] Given the importance of identification of subjects at risk of CHD events, atherosclerosis imaging such as coronary artery calcium scoring (CACS) or carotid intimal-medial thickness for individuals without chest pain syndrome has been advocated recently for use by professional consensus guidelines.[4] Among the available modalities, CACS, as an atherosclerotic disease surrogate, has been studied the most extensively, with population-based studies demonstrating the ability of CACS findings to improve prognostic risk stratification over clinical risk factor–based scoring in asymptomatic individuals for both sexes and across age groups and ethnicities.[5–9] Furthermore, CACS has been demonstrated to improve risk restratification above and beyond global risk scores that combine traditional coronary artery disease (CAD) risk factors.[10]

Clinical Perspective on p 313

Recently, coronary computed tomographic angiography (cCTA) has been introduced as a novel noninvasive atherosclerosis imaging test that may permit diagnostically accurate and prognostically robust assessment of the presence of CAD and risk of CHD events across categories of pretest CAD risk.[11,12] Although the majority of data to date has focused on symptomatic patients with suspected CAD, cCTA has also been evaluated for use in individuals without chest pain syndrome for an array of potential indications, including equivocal stress test results, preoperative surgical evaluation, assessment of congenital heart disease, and prediction of CAD events in pretest high-risk patients. However, in these groups without chest pain syndrome, limited data exist to substantiate the prognostic value and clinical usefulness of cCTA over traditional strategies of CAD evaluation.[13–17]

We therefore evaluated in a large international multicenter registry whether CAD assessment by cCTA improved the stratification of risk in individuals without chest pain syndrome, and we examined the incremental value of cCTA findings to clinical risk factor scoring and CACS.

Methods

Design Overview, Setting, and Participants

The overall study design of the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry has been described previously.[18] Briefly, the CONFIRM registry is an open-label, international, multicenter observational registry intended to evaluate associations between cCTA findings and their ability to predict mortality and major adverse cardiac events. Strong

prognostic value of cCTA in the overall CONFIRM registry has been demonstrated recently.[19]

Between February 2003 and December 2009, 27 125 consecutive patients underwent cCTA at 12 centers in 6 countries (United States, Canada, Germany, Switzerland, Italy, and South Korea). Inclusion criteria included the following: (1) age ≥18 years; (2) evaluation by cCTA by CT scanners of ≥64 detector rows; (3) clinical indication for CAD evaluation; (4) interpretable cCTA; and (5) prospective data collection for CAD risk factors. Clinical indications for CONFIRM included evaluation of angina-equivalent symptoms (dyspnea and angina equivalents including pain, tightness, and pressure), dyspnea, preoperative evaluation, and electrophysiological indications (eg, pulmonary vein mapping, left atrial appendage evaluation), as well as evaluation of individuals without chest pain syndrome for assessment of CAD in individuals with congenital heart disease and risk assessment of CAD in individuals with history of peripheral arterial disease, cerebrovascular disease, or multiple CAD risk factors. For the present analysis, we excluded the following: (1) individuals with chest pain (14 063 patients); (2) individuals with unknown symptom status (4685 patients); (3) individuals with a history of prior MI, coronary revascularization, or cardiac transplantation (752 patients); and (4) individuals without follow-up data of mortality or cCTA findings (35 patients). Therefore, 7590 individuals without chest pain syndrome were included for the final primary efficacy analyses. For analyses of the composite end point of death and nonfatal MI, we included only the 4870 individuals at 7 centers that performed comprehensive ascertainment of nonfatal MI. The study protocol was approved by the institutional review boards of all centers, and, when required, all patients provided written informed consent.

Data Acquisition and Image Analysis

All testing, data acquisition, and image postprocessing for cCTA and CACS in the CONFIRM cohort were in accordance with the Society of Cardiovascular Computed Tomography guidelines on cCTA acquisition.[20,21] CACS studies and cCTAs were uniformly acquired by multi–detector row CT scanners of ≥64 rows. Radiation dose reduction strategies, including prospective ECG-gated axial acquisition or ECG-gated tube-current modulation, and tube voltage reduction were employed by the decision of the performing providers when clinically feasible. CACS was measured with the use of the scoring system described previously by Agatston et al.[22] On the basis of the CACS, participants were categorized in the following manner; 0, 1 to 100, 101 to 400, and >400.

In each coronary segment, coronary atherosclerosis was defined as any tissue structures >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Each identified lesion was examined with the use of maximum intensity projection and multiplanar reconstruction techniques along multiple longitudinal axes and in the transverse plane. Each site interpreted cCTA in accordance with Society of Cardiovascular Computed Tomography guidelines.[20,21] A 16-segment coronary artery tree model was employed (left main; proximal, mid, and distal left anterior descending artery; first and second diagonal branches of the left anterior descending coronary artery; proximal and distal left circumflex artery; first and second obtuse marginal branches of the left circumflex artery; proximal, mid, and distal right coronary artery; posterior descending artery; and posterolateral branch [left or right]). CAD was defined as the presence of any plaque. CAD extent and severity were graded by various methods: First, obstructive CAD was defined when coronary

Table 1.   Baseline Characteristics of the Study Population According to the Existence of Obstructive CAD Evidenced by cCTA

| Variable | Total (n=7590) | Obstructive CAD* on cCTA | | P |
		Absent (n=5674)	Present (n=1916)	
Mean age, y	58±12	57±12	64±10	<0.001
Sex (male)	4623 (60.9)	3343 (58.9)	1280 (66.8)	<0.001
Hypertension	3572 (47.5)	2459 (43.9)	1113 (58.5)	<0.001
Diabetes mellitus	1103 (14.6)	669 (11.9)	434 (22.7)	<0.001
Current smoking	1247 (16.5)	841 (14.9)	406 (21.3)	<0.001
Body mass index, kg/m^2	27±5	27±5	27±5	0.289
Dyslipidemia	4721 (62.7)	3372 (60.1)	1349 (70.7)	<0.001
Total cholesterol, md/dL	200±53	194±48	190±50	0.057
HDL cholesterol, mg/dL	53±17	54±17	49±16	<0.001
LDL cholesterol, mg/dL	118±39	119±38	115±42	0.048
Family history of premature CHD	2592 (34.9)	1848 (33.3)	744 (39.3)	<0.001
FRS 10-y risk categories†				<0.001
Low (<10)	3235 (48.2)	2797 (55.6)	438 (26.2)	
Low-intermediate (10–15)	1585 (23.6)	1171 (23.3)	414 (24.8)	
High-intermediate (16–20)	622 (9.3)	420 (8.3)	202 (12.1)	
High (>20)	1264 (18.8)	647 (12.9)	617 (36.9)	
CACS‡				<0.001
0	1971 (44.9)	1,875 (52.2)	96 (12.0)	
1–100	1119 (25.5)	964 (26.8)	155 (19.4)	
101–400	732 (16.7)	499 (13.9)	233 (29.2)	
>400	568 (12.9)	255 (7.1)	313 (39.3)	

Continuous values are mean±SD; categorical values are number (%). CAD indicates coronary artery disease; cCTA, coronary computed tomographic angiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CHD, coronary heart disease; FRS, Framingham Risk Score; and CACS, coronary artery calcium score.

*Obstructive CAD was defined when coronary artery segments exhibited plaque with a luminal diameter stenosis ≥50%.

†FRS 10-y risk was available in 6706 patients.

‡CACS was available in 4390 patients.

artery segments exhibited plaque with a luminal diameter stenosis ≥50%, and nonobstructive CAD was defined when coronary artery segments exhibited plaque with a luminal diameter stenosis >0%<50%. Individuals manifesting obstructive CAD were further categorized as having 1-, 2-, and 3-vessel disease or left main disease. In addition, coronary artery plaque scores were calculated for overall plaque burden by extent and severity of CAD with the use of a modified Duke prognostic score, segment stenosis score (SSS), and segment involvement score (SIS), as we have described previously.[23] Detailed methods for calculating modified Duke prognostic CAD score, SSS, and SIS are described in Methods in the online-only Data Supplement.

Patient Follow-Up

Follow-up for all-cause mortality and nonfatal MI was performed by each local institution by a dedicated physician and/or research nurse blinded to the cCTA results. At US sites, ascertainment of death was determined by query of the National Death Index. In non-US sites, ascertainment of death was determined by direct interview and/or telephone contact and/or review of medical records. Additional event ascertainment, including MI, was performed at certain sites by direct interview, telephone contact, or review of medical records.

Statistical Analysis

Continuous variables are expressed as mean±SD, and categorical variables are presented as absolute counts and percentages. Differences between continuous variables were analyzed by Student t test, and those between categorical variables were analyzed by the χ^2 test

or Fisher exact test, as appropriate. We considered 2 end points: all-cause mortality and a composite of all-cause mortality and nonfatal MI. Cumulative event rates as a function of time and cCTA-diagnosed CAD were calculated with the Kaplan-Meier estimator and compared with the log-rank statistic. The hazards for the association of the various measures of cCTA-diagnosed CAD with the outcomes were calculated with the use of Cox proportional hazards models, first unadjusted and then adjusted for Framingham Risk Score (FRS) risk factors, as follows: age, sex, current smoking, hypertension, dyslipidemia, and diabetes mellitus. For assessment of the added value of CACS and cCTA in risk prediction, we considered the following models. Model I was based on risk factors only. To allow for different strengths of adjustment, we used 2 forms of risk factors: The first one included categories of the published FRS (low [<10%], low-intermediate [10–15%], high-intermediate [16–20%], high [>20%]), and the second incorporated the aforementioned individual risk factors. In model II, we added CACS expressed as 4 categories (0, 1–100, 101–400, >400) to the models containing Framingham risk factors. Model III added cCTA-diagnosed number of involved vessels (NIV) (none, nonobstructive CAD, obstructive 1-vessel disease, 2-vessel disease, or 3-vessel disease or left main CAD) to model II. Model IV added the Duke CAD prognostic index to model II. Model V added cCTA-diagnosed SSS, and model VI added cCTA-diagnosed SIS to model II. From the Cox models, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

The statistical significance of the contribution of the added variable was assessed with the likelihood ratio test, following recent

Table 2.   Risk of All-Cause Mortality According to FRS, CACS, and cCTA

Variable	Unadjusted				Adjusted for Individual Framingham Risk Factors*			
	n†	HR	95% CI	P	n	HR	95% CI	P
FRS	6706			<0.001‡				
Low (<10)	3235	1.0						
Low-intermediate (10–15)	1585	1.32	0.81–2.15	0.262		NA		
High-intermediate (16–20)	622	1.86	1.03–3.36	0.040				
High (>20)	1264	2.57	1.67–3.95	<0.001				
CACS	4390			<0.001‡	3900			<0.001‡
0	1971	1.0			1765	1.0		
1–100	1119	1.66	0.85–3.25	0.142	987	1.05	0.52–2.12	0.895
101–400	732	2.43	1.23–4.83	0.011	644	1.44	0.70–2.95	0.321
>400	568	4.97	2.68–9.21	<0.001	504	2.38	1.19–4.74	0.014
cCTA								
Presence of obstructive CAD	7590				6706			
None or nonobstructive CAD	5674	1.0			5035	1.0		
Obstructive CAD	1916	2.72	1.94–3.80	<0.001	1671	1.70	1.20–2.41	0.003
No. of involved vessels	7590			<0.001‡	6706			<0.001‡
None	2844	1.0			2551	1.0		
Nonobstructive CAD	2830	2.04	1.25–3.35	0.002	2484	1.19	0.71–1.98	0.511
1-vessel disease	1109	2.77	1.59–4.83	<0.001	953	1.42	0.80–2.53	0.232
2-vessel disease	494	4.61	2.53–8.42	<0.001	435	2.20	1.19–4.16	0.013
3-vessel disease or left main CAD	313	7.91	4.41–14.21	<0.001	283	2.91	1.55–5.47	0.001
Duke index (per score increased)	7590	1.36	1.26–1.47	<0.001‡	6706	1.20	1.10–1.31	<0.001‡
SSS (per segment severity)	7590	1.11	1.07–1.13	<0.001‡	6706	1.06	1.02–1.09	0.001‡
SIS (per segment involved)	7590	1.15	1.10–1.21	<0.001‡	6706	1.06	0.99–1.12	0.058

FRS indicates Framingham Risk Score; CACS, coronary artery calcium score; cCTA, coronary computed tomographic angiography; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; Duke index, Duke CAD prognostic index; SSS, segment stenosis score; SIS, segment involvement score; and NA, not applicable.

*Individual Framingham risk factors included age, sex, hypertension, diabetes mellitus, current smoking, and dyslipidemia.

†Among the study cohort with cCTA data, FRS was available in 6706 patients; CACS in 4390; and both FRS and CACS in 3900.

‡P value for trend.

recommendations.[24] To evaluate model discrimination, we calculated the C statistics for the aforementioned models.[25,26] We used a 2.5-year horizon for the analyses, but not all subjects had follow-up completed until 2.5 years. To address the issue of censored data, the prospective form of net reclassification improvement (NRI) proposed by Pencina et al[27,28] was employed. Detailed methods to calculate NRI are described in Methods in the online-only Data Supplement. We defined 2.5-year risk categories as follows: (1) 0% to <1.5%; (2) 1.5% to <5%; and (3) ≥5%; these categories were derived from Framingham 10-year risk of CHD categories (0% to <6%; 6% to <20%; ≥20%). A standard bootstrap method was used to generate the corresponding CIs for this estimate. P<.05 was considered statistically significant. The CIs of Cox regression, C statistics, and NRI are 95% throughout this article. All analyses were performed with SAS (version 9.1.3; SAS Institute Inc, Cary, NC).

Results

Clinical Characteristics and Outcomes

Overall, the study population consisted of 7590 individuals without chest pain syndrome; 61% were male, and the mean age was 58±12 years. Among the study cohort, 2830 had nonobstructive CAD, and 1916 (25.2%) had obstructive CAD: 1-vessel disease, 1109 (14.6%); 2-vessel disease, 494

(6.5%); 3-vessel disease or left main disease, 313 (4.1%). Patients with obstructive CAD were generally older, were male, and had a higher prevalence of hypertension, diabetes mellitus, and dyslipidemia (all P<0.001) (Table 1). FRS was available in 6706 patients, and CACS was available in 4390 patients. Among them, patients with obstructive CAD had higher FRS and CACS (P<0.001 for both).

During the median follow-up duration of 24 months (25th to 75th percentile, 18–35 months), there were 136 deaths by any cause among 7590 individuals. The overall cumulative 2.5-year mortality rate was 2.3% (CI, 1.9–2.7%). The 2.5-year mortality rate of individuals with obstructive CAD (4.1%; CI, 3.2–5.2%) was higher than that of those without obstructive CAD (1.7%; CI, 1.3–2.1%) (log-rank P<0.001). Among individuals who had follow-up data of both nonfatal MI and all-cause mortality (n=4870), 74 events (14 nonfatal MIs and 60 deaths) were reported. The overall cumulative 2.5-year composite outcome rate was 2.2% (CI, 1.7–2.7%). The cumulative 2.5-year composite outcome rate of individuals with obstructive CAD (4.6%; CI, 3.2–6.6%) was higher than that of those without obstructive CAD (1.6%; CI, 1.2–2.2%) (log-rank P<0.001).
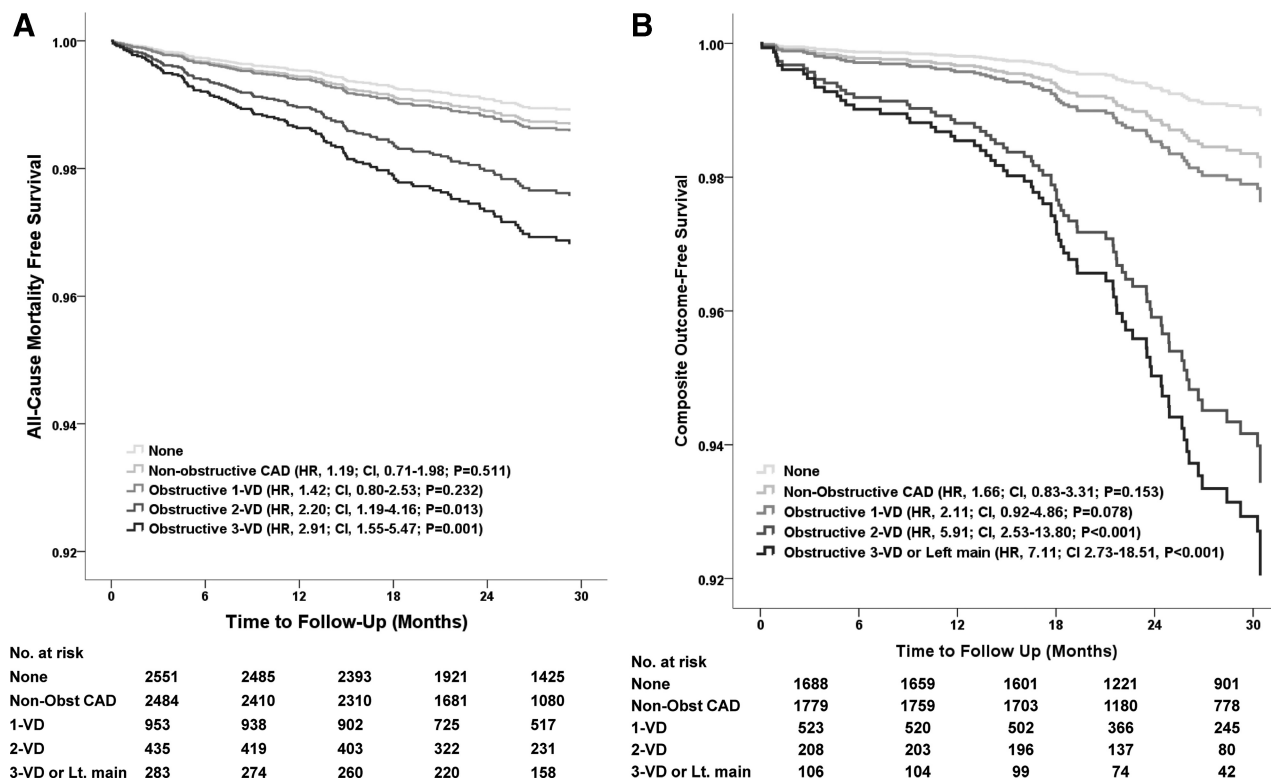
Figure. A, Adjusted (by Framingham risk factors including age, sex, hypertension, diabetes mellitus, current smoking, and dyslipidemia) all-cause mortality–free survival by number of involved vessels detected by coronary computed tomographic angiography in individuals without chest pain syndrome. **B**, Adjusted (by Framingham risk factors including age, sex, hypertension, diabetes mellitus, current smoking, and dyslipidemia) composite outcome of all-cause mortality– and nonfatal myocardial infarction–free survival by number of involved vessels detected by coronary computed tomographic angiography in individuals without chest pain syndrome. CAD indicates coronary artery disease; HR, hazard ratio; CI, 95% confidence interval; Non-Obst, nonobstructive; VD, vessel disease; and Lt, left.

Univariable Cox Models of FRS, CACS, and cCTA

Compared with individuals with low FRS, increasing hazards for all-cause mortality were observed in relation to increasing FRS ($P<0.001$ for trend), in particular for those with high FRS (HR, 2.57; CI, 1.67–3.95; $P<0.001$) (Table 2). Increasing CACS was also associated with increased risk for death ($P<0.001$ for trend), principally for those with CACS 101 to 400 (HR, 2.43; CI, 1.23–4.83; $P=0.011$) and CACS >400 (HR, 4.97; CI, 2.68–9.21; $P<0.001$). By cCTA, compared with those without CAD, the relative hazards for death increased proportionally to CAD extent for nonobstructive CAD (HR, 2.04; CI, 1.25–3.35; $P=0.002$), obstructive 1-vessel disease (HR, 2.77; CI, 1.59–4.83; $P<0.001$), obstructive 2-vessel disease (HR, 4.61; CI, 2.53–8.42; $P<0.001$), and obstructive 3-vessel disease or left main CAD (HR, 7.91; CI, 4.41–14.21; $P<0.001$). Similarly, cCTA scores measuring CAD plaque burden, including the Duke CAD prognostic index, SSS, and SIS, were uniformly predictive of incident death ($P<0.001$ for trend, for all).

Multivariable Cox Models of CACS and cCTA

In multivariable models accounting for individual Framingham risk factors, CACS >400 (HR, 2.38; CI, 1.19–4.74; $P=0.014$) was significantly associated with future death. Similarly, cCTA-based CAD was independently predictive of mortality ($P<0.001$ for trend; Table 2), with individual

significant effects observed for obstructive 2-vessel disease (HR, 2.20; CI, 1.19–4.16; $P=0.013$) and obstructive 3-vessel disease or left main CAD (HR, 2.91; CI, 1.55–5.47; $P=0.001$), as depicted in the Figure, panel A. cCTA CAD plaque burden scores were also independently associated with future death, as measured by the Duke CAD prognostic index and SSS ($P\leq0.001$ for trend, for both), as described in Table 2.

For the composite outcome, cCTA was independently predictive of future death and nonfatal MI for measures of obstructive 2-vessel disease (HR, 5.91; CI, 2.53–13.80; $P<0.001$) and obstructive 3-vessel disease or left main CAD (HR, 7.11; CI, 2.73–18.51; $P<0.001$), as shown in the Figure, panel B. cCTA CAD plaque burden scores including Duke CAD prognostic index, SSS, and SIS showed an independent association with the composite outcome as well ($P<0.001$ for all) (Table I in the online-only Data Supplement).

Incremental Value of CACS and cCTA for Prediction of Future Mortality and Composite Outcome

Inclusion of CACS significantly improved the model based on risk factors only; the mortality model likelihood ratio test P value for adding CACS to FRS was <0.001 and for adding it to individual risk factors was <0.001; the composite outcome model likelihood ratio test P value for adding CACS to FRS was <0.001 and for adding it to individual risk factors was <0.001 (Table II in the online-only Data Supplement).

Table 3. C Statistics for Prediction of 2.5-Year Risk of All-Cause Mortality and Composite Outcome of All-Cause Mortality and Nonfatal MI Using Combined Models of Framingham Risk Factors Plus CACS or cCTA

	C Statistics*	
Model	FRS*	Individual Risk Factors*
All-cause mortality (n=3900)		
Model I: RFs only	0.62 (0.55–0.69)	0.76 (0.70–0.83)
Model II: RFs+CACS	0.71 (0.65–0.77)	0.78 (0.65–0.84)
Model III: RFs+CACS+NIV	0.73 (0.67–0.78)	0.78 (0.67–0.84)
Model IV: RFs+CACS+Duke	0.72 (0.66–0.78)	0.78 (0.66–0.84)
Model V: RFs+CACS+SSS	0.72 (0.66–0.78)	0.78 (0.66–0.84)
Model VI: RFs+CACS+SIS	0.72 (0.66–0.78)	0.78 (0.66–0.84)
Composite outcome of all-cause mortality and nonfatal MI (n=3217)		
Model I: RFs only	0.59 (0.52–0.67)	0.71 (0.63–0.78)
Model II: RFs+CACS	0.71 (0.64–0.78)	0.75 (0.68–0.81)
Model III: RFs+CACS+NIV	0.74 (0.66–0.81)	0.77 (0.70–0.84)
Model IV: RFs+CACS+Duke	0.74 (0.67–0.81)	0.76 (0.69–0.83)
Model V: RFs+CACS+SSS	0.74 (0.67–0.81)	0.76 (0.69–0.83)
Model VI: RFs+CACS+SIS	0.74 (0.68–0.81)	0.76 (0.69–0.83)

Values in parentheses are 95% confidence intervals. MI indicates myocardial infarction; CACS, coronary artery calcium score; cCTA, coronary computed tomographic angiography; FRS, Framingham Risk Score; RFs, risk factors; NIV, number of involved vessels (categorized as none, nonobstructive coronary artery disease, obstructive 1-, 2-, 3-vessel disease or left main coronary artery disease); Duke, Duke coronary artery disease prognostic index; SSS, segment stenosis score; and SIS, segment involvement score.

*Baseline risk factors were entered as a combined score in the FRS column and as individual Framingham risk variables (age, sex, hypertension, diabetes mellitus, current smoking, and dyslipidemia) in the Individual Risk Factors column.

This translated into appreciable increases in model discrimination compared with the model with categorical FRS (from 0.62 to 0.71 for all-cause mortality and from 0.59 to 0.71 for the composite outcome; Table 3), which were attenuated when compared with the model with individual risk factors (from 0.76 to 0.78 for all-cause mortality and from 0.71 to 0.75 for the composite outcome; Table 3).

However, the addition of cCTA to a model with Framingham risk factors and CACS did not lead to a significant improvement for all-cause mortality; the likelihood ratio test *P* value for adding cCTA to FRS plus CACS was 0.423 and for adding it to individual risk factors plus CACS was 0.469 (Table II in the online-only Data Supplement). This translated into modest improvements in discrimination as measured by the change in the C statistics (at best, this was 0.02 compared with the FRS plus CACS model and <0.01 compared with the model with individual risk factors plus CACS; Table 3). For the composite outcome, the addition of cCTA to a model with Framingham risk factors and CACS led to a significant improvement (the likelihood ratio test *P* value for adding cCTA to FRS plus CACS was <0.001 and for adding it to individual risk factors plus CACS was 0.003). The increments of C statistics were also more promising (0.03 compared with the FRS plus CACS model and from 0.01 to 0.02 compared with the model with individual risk factors plus CACS; Table 3). However, the increments of C statistics were minor compared with those for adding CACS to FRS and individual risk factors (0.12 and 0.04, respectively).

As demonstrated in Table 4, the ability of CACS to correctly reclassify individuals from FRS was significant for all-cause mortality and the composite outcome (NRI for adding CACS to FRS was 0.43 and 0.53, respectively); these values were attenuated when individual risk factors were entered as the baseline model (0.04 and 0.14, respectively). However, the ability of cCTA to correctly reclassify individuals from model II, with a priori established risk categories based on the model with Framingham risk factors plus CACS, was limited. The claim of no effect could not be ruled out on the basis of the 95% CIs. The NRI was particularly weak numerically for all-cause mortality, at ≤0.05, and was modestly better for the composite outcome (maximum 0.09; Table 4).

Discussion

Principal Findings

In this international multicenter study of individuals without chest pain syndrome, increasing extent and severity of CAD, as measured by CACS and cCTA, independently and proportionately stratify risk of future death and a composite outcome of death and nonfatal MI. Importantly, the added risk-predictive advantage by cCTA measures of CAD is imperceptible compared with Framingham risk factors plus CACS. These present data have major implications for the decision to perform cCTA in subjects without chest pain syndrome and suggest that use of CACS may be sufficient for risk stratification of this population.

The Role of CACS for Risk Stratification

CACS has been known to provide powerful prognostic information in multiple population-based studies for both sexes and multiple ethnic groups.[5–8] The Multi-Ethnic Study of Atherosclerosis (MESA), conducted in 6722 asymptomatic subjects as a representative multiethnic US population, demonstrated an incremental prognostic value of CACS over traditional risk factors by comparison of the areas under the receiver operating characteristic curves.[8] More recently, Polonsky et al[10] showed that addition of CACS to a prediction model based on traditional risk factors significantly improved the stratification of future risk of CHD in the same cohort by using NRIs (0.25; CI, 0.16–0.34; *P*<0.001) and integrated discrimination improvement (0.026; *P*<0.001). Similarly, the Heinz Nixdorf Recall Study showed that CACS successfully reclassified and improved risk prediction of "hard" CHD events including nonfatal MI and coronary death over traditional risk factors.[9] Given these findings, the use of CACS for risk stratification of an asymptomatic population has been advocated by numerous professional guidelines.[4,29,30]

Previous cCTA Registry Data

Recently, the use of cCTA has been advocated as a potentially valuable atherosclerosis imaging tool for risk stratification.[12,31] Several studies have explored the prognostic value of cCTA, primarily limited to symptomatic populations.[23,32]

Table 4. Reclassification of 2.5-Year Risk of All-Cause Mortality and Composite Outcome Using Multivariate Risk Prediction Model With and Without Inclusion of cCTA

Model	FRS*			Individual Risk Factors*		
	NRI† (95% CI)	Proportion of Events Correctly Reclassified	Proportion of Nonevents Correctly Reclassified	NRI† (95% CI)	Proportion of Events Correctly Reclassified	Proportion of Nonevents Correctly Reclassified
All-cause mortality (n=3900)						
Compared with model I (baseline RFs)						
Model II: RFs+CACS	0.43 (0.25 to 0.64)	0.00	0.43	0.04 (−0.08 to 0.16)	0.08	−0.04
Model III: RFs+CACS+NIV	0.45 (0.26 to 0.64)	0.05	0.40	0.06 (−0.08 to 0.22)	0.10	−0.04
Model IV: RFs+CACS+Duke	0.47 (0.27 to 0.67)	0.04	0.42	0.00 (−0.10 to 0.12)	0.04	−0.04
Model V: RFs+CACS+SSS	0.48 (0.27 to 0.68)	0.03	0.44	0.03 (−0.09 to 0.16)	0.08	−0.05
Model VI: RFs+CACS+SIS	0.49 (0.28 to 0.70)	0.05	0.44	0.04 (−0.08 to 0.17)	0.08	−0.04
Compared with model II (RFs+CACS)						
Model III: RFs+CACS+NIV	0.01 (−0.04 to 0.07)	0.05	−0.04	0.03 (−0.06 to 0.17)	0.03	0.01
Model IV: RFs+CACS+ Duke	0.03 (−0.02 to 0.10)	0.05	−0.02	−0.03 (−0.10 to 0.05)	−0.03	0.00
Model V: RFs+CACS+SSS	0.04 (−0.01 to 0.09)	0.03	0.01	−0.01 (−0.06 to 0.04)	−0.01	0.00
Model VI: RFs+CACS+SIS	0.05 (0.01 to 0.09)	0.05	0.00	0.00 (0.00 to 0.00)	0.00	0.00
Composite outcome of all-cause mortality and nonfatal MI (n=3217)						
Compared with model I (baseline RFs)						
Model II: RFs+CACS	0.53 (0.29 to 0.77)	0.12	0.42	0.14 (−0.03 to 0.33)	0.17	−0.03
Model III: RFs+CACS+NIV	0.51 (0.32 to 0.71)	0.16	0.34	0.19 (0.03 to 0.37)	0.17	0.03
Model IV: RFs+CACS+Duke	0.58 (0.35 to 0.81)	0.20	0.37	0.21 (0.03 to 0.39)	0.21	0.00
Model V: RFs+CACS+SSS	0.62 (0.39 to 0.86)	0.18	0.45	0.19 (0.01 to 0.38)	0.20	−0.01
Model VI: RFs+CACS+SIS	0.56 (0.33 to 0.80)	0.15	0.41	0.14 (−0.04 to 0.34)	0.16	−0.02
Compared with model II (RFs+CACS)						
Model III: RFs+CACS+NIV	−0.01 (−0.16 to 0.15)	0.07	−0.07	0.07 (−0.06 to 0.21)	0.02	0.05
Model IV: RFs+CACS+Duke	0.06 (−0.07 to 0.18)	0.10	−0.04	0.06 (−0.04 to 0.14)	0.04	0.02
Model V: RFs+CACS+SSS	0.09 (−0.02 to 0.21)	0.06	0.03	0.03 (−0.07 to 0.12)	0.01	0.02
Model VI: RFs+CACS+SIS	0.02 (−0.07 to 0.13)	0.03	−0.01	−0.02 (−0.11 to 0.06)	−0.02	0.01

cCTA indicates coronary computed tomographic angiography; FRS, Framingham Risk Score; NRI, net reclassification index; CI, confidence interval; RFs, risk factors; CACS, coronary artery calcium score; Duke, Duke coronary artery disease prognostic index; NIV, number of involved vessels (categorized as none, nonobstructive coronary artery disease, obstructive 1-, 2-, 3-vessel disease or left main coronary artery disease); SSS, segment stenosis score; and SIS, segment involvement score.

*Framingham score risk factors were entered as a combined score in the FRS column and as individual variables in the Individual Risk Factors column.

†NRI was calculated with 2.5-y risk categories: (1) 0% to <1.5%; (2) 1.5% to <5%; and (3) ≥5%.

Although not recommended by current guidelines,[21,29] a few early reports have emerged evaluating the use of cCTA for risk stratification in asymptomatic high-risk individuals.[13–17] However, the prognostic implication of occult CAD was not addressed adequately because of a very low rate of hard events (death or nonfatal MI).[33] In addition, the value of cCTA to predict mortality could not be evaluated because of small study samples, and evaluation of cCTA compared with CACS for the prediction of cardiac events was not performed.[34]

Prognostic Value of cCTA in Asymptomatic Individuals

To our knowledge, this is the first registry analysis that evaluates the additive contribution of cCTA-defined CAD compared with risk factors and CACS in a large cohort without chest pain syndrome. Although the overall prevalence of obstructive CAD was generally low, our prognostic models nevertheless revealed an independent prediction of cCTA-defined CAD for incident mortality and composite outcome. However, the ability of these findings to improve risk stratification for the prediction of all-cause mortality beyond information derived from CACS was not observed. Although the cCTA showed a statistically significant likelihood ratio test when it was added to CACS plus risk factors for the composite outcome, the increments of C statistics and NRI of cCTA were modest (at best, they were 0.03 and 0.09, respectively), whereas the increments of C statistics and NRI were obvious when CACS was added to Framingham risk factors alone (at best, they were 0.12 and 0.62, respectively). When the potential population-based radiation burden, use of iodinated contrast, and greater cost of cCTA over CACS are considered, the evidence that cCTA offered in this study is not enough to justify the use of cCTA for risk stratification in a population without chest pain syndrome.

The underlying reasons that cCTA demonstrates low incremental prognostic value over models incorporating CACS and Framingham risk factors necessitate discussion. Our present study evaluated stenosis severity as well as overall coronary artery plaque burden, accounting for location and extent of subtended myocardium. Although the ability of these findings to improve risk stratification for the prediction of all-cause mortality beyond information derived from CACS was not observed, cCTA offered minimal statistical improvement in risk prediction for a composite end point of death and MI. It appears that the added risk prediction of cCTA is driven largely by the risk of future MI. cCTA offers a potential diagnostic advantage over CACS, given the contrast enhancement and ensuing ability to identify atherosclerotic plaque components beyond calcified plaque, including fibrous, fibrolipoid, and lipoid plaque.[35,36] These plaque characteristics have been related to myocardial ischemia and incident MI for symptomatic patients with suspected CAD.[37–39] In this regard, the added benefit of cCTA over CACS for the prediction of MI may be related to the detection of noncalcified plaque by cCTA in current analyses. Therefore, future studies evaluating the totality of plaque characteristics may be useful for determining the role of noncalcified plaque for risk stratification in individuals without chest pain syndrome.

Furthermore, the calcified atherosclerotic plaque burden indicated by CACS may have an intrinsically greater prognostic value in a population without chest pain syndrome than in symptomatic patients. In symptomatic patients, identification of "lesions of interest" (ie, high-grade stenoses responsible for symptoms of CHD) is a major goal, and identification of these lesions is important for prognosticating future events. Conversely, in a population without chest pain, atherosclerosis evaluation may be more useful to identify "patients of interest" or individuals with coronary plaque that increases the likelihood of incident CHD events. Although CACS is incapable of imaging the severity of luminal stenoses, it is nevertheless an excellent surrogate marker for total plaque burden of individuals and unstable plaques.[40,41] Therefore, despite its inability to directly visualize the coronary artery, CACS provides robust prognostic information within a population without chest pain for which the visualization of coronary artery luminal stenosis is not additive.

Study Limitations

This study is not without limitations. First, the study population was a subset of the CONFIRM registry with the potential for selection and individual site-related biases potentially operating herein. However, we attempted to minimize these potential biases by using standardized data definitions and inclusion of sites only where cCTA has been incorporated into general clinical care and where performance and interpretation of cCTA are led by individuals with adequate proficiency. Additionally, the primary outcome of our study was all-cause mortality, with the specific cause of death unavailable. The lack of cardiac-specific causes may result in variable prediction models. However, the use of all-cause mortality has the advantage of minimizing misclassification of causality.[42] Furthermore, given the relatively low

rate of adverse events, it remains possible that larger studies with longer follow-up may identify a potential value of cCTA for risk prediction in this low-risk cohort without chest pain syndrome.

Conclusions

In a large international multicenter study of individuals without chest pain syndrome, the additional risk-predictive advantage by cCTA is not clinically meaningful compared with a risk model based on CACS. Therefore, at present, the application of cCTA for risk assessment of individuals without chest pain syndrome should not be justified.

Disclosures

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CLINICAL PERSPECTIVE

This is the first registry analysis to evaluate the additive contribution of coronary computed tomographic angiography (cCTA)–defined coronary artery disease compared with clinical risk factors and coronary artery calcium score in a large international multicenter cohort of individuals without chest pain syndrome. Although the overall prevalence of obstructive coronary artery disease was generally low, our prognostic models revealed an independent prediction of cCTA-defined coronary artery disease for incident mortality and the composite outcome of all-cause mortality and nonfatal myocardial infarction. However, the ability of these findings to improve risk stratification for the prediction of all-cause mortality beyond information derived from coronary artery calcium score was not observed. cCTA offered minimal statistical improvement in risk prediction and reclassification for a composite end point of death and myocardial infarction. Given the ability of cCTA to identify atherosclerotic plaque components beyond calcified plaque, including fibrous, fibrolipoid, and lipoid plaque, future studies examining these plaque characteristics in asymptomatic individuals undergoing cCTA and coronary artery calcium score may be useful to further investigate the present study findings. At present, however, the application of cCTA for risk assessment of individuals without chest pain syndrome beyond coronary artery calcium score does not appear justified.

<u>**SUPPLEMENTAL MATERIAL**</u>

<u>**Supplemental Methods**</u>

1. Coronary Artery Plaque Scores

Coronary artery plaque scores were calculated for overall plaque burden by extent and severity of CAD using a modified Duke prognostic CAD score, segment stenosis score (SSS) and segment-involvement score (SIS), as we have previously described. .[1]

Modified Duke prognostic CAD score

Modified Duke prognostic CAD index was used to assess prognosis in patients with <50% stenosis. Individuals were assigned to the highest disease category, and categorized as following subsets: 1) <50% stenosis; 2) ≥2 stenoses 30% to 49% (including 1 artery with proximal disease or 1 vessel with 50% to 69% stenosis; 3) 2 stenoses 50% to 69% or 1 vessel with ≥70% stenosis; 4) 3 stenoses 50% to 69% or 2 vessels with ≥70% stenosis or proximal left anterior descending stenosis ≥70%; 5) 3 vessels ≥70% stenoses or 2 vessels ≥70% stenosis with proximal left anterior descending; and 6) left main stenosis ≥50%.

Segment stenosis score (SSS)

The SSS was employed as a measure of overall coronary artery plaque extent. Each individual coronary segment of patient was graded as no plaque to severe plaque (scores from 0 to 3) based on extent of obstruction of coronary luminal diameter. After that, the extent scores of all 16 segments were summed to yield a total score ranging from 0 to 48.

Segment involvement score (SIS)

The SIS was calculated as a measure of overall coronary artery plaque distribution. The SIS was calculated by summation of the absolute number of coronary artery segments with plaque, irrespective of the degree of luminal stenosis within each segment (scores from 0 to 16).

2. Prospective form net reclassification improvement (NRI)[2]

The NRI measures the degree of correct movement in categories or probability values between subjects who experienced and did not experience events. Consider a situation in which predicted probabilities of a given event of interest come from two different risk prediction algorithms denoted here as 'new' (ex. FRS+CACS) and 'old' (ex. FRS alone). Divide the predicted probabilities based on two algorithms (ex. FRS alone vs FRS+CACS) into a set of clinically meaningful ordinal categories of absolute risk and then cross-tabulate these two classifications. Define upward movement (*up*) as a change into higher category based on the new algorithm (ex. FRS+CACS) and downward movement (*down*) as a change in the opposite direction. The NRI is defined as:

$$\text{NRI}= P(\text{up}|\text{event})-P(\text{down}|\text{event})+P(\text{down}|\text{non-event})-P(\text{up}|\text{non-event}) \qquad (1)$$

Using the Bayes rule we rewrite formula (1) in a different but equivalent form:

$$\text{NRI}= \frac{(P(\text{event}|\text{up})-P(\text{event}))\cdot P(\text{up})+(P(\text{event})-P(\text{event}|\text{down}))\cdot P(\text{down})}{P(\text{event})\cdot(1-P(\text{event}))} \qquad (2)$$

The latter form gives a prospective interpretation and allows the substitution of relevant Kaplan-Meier rates in place of simple proportions and thus accounts for premature discontinuations.

Supplemental Tables

Supplement Table1. Risk of Composite Outcome of Non-fatal Myocardial Infarction and All-Cause Mortality According to FRS, CACS, and cCTA Models

Variable	Unadjusted Model				Adjusted for Individual Framingham RFs*			
	No	HR	95% CI	P Value	No	HR	95% CI	P Value
FRS model	4,304			0.019[†]				
Low(<10)	2,200	1.00						
Low intermediate(10-15)	1,004	1.38	0.75-2.54	0.294		NA		
High intermediate(16-20)	407	1.63	0.74-3.58	0.228				
High(>20)	693	2.01	1.10-3.69	0.024				
CACS model	3,640			<0.001[†]	3,217			<0.001[†]
0	1,773	1.00			1,581	1.00		
1-100	920	1.55	0.73-3.28	0.252	811	1.10	0.50-2.41	0.809
101-400	546	3.14	1.53-6.44	0.002	472	2.16	1.02-4.58	0.045
>400	401	6.18	3.20-11.94	<0.001	353	3.82	1.85-7.88	<0.001
cCTA models								
Presence of obstructive CAD	4,870				4,304			
None or non-obstructive CAD	3,912	1.00			3,467	1.00		
Obstructive CAD	958			<0.001	837	2.48	1.52-4.05	<.0001
No of involved vessels	4,870			<0.001[†]	4,304			<0.001[†]
None	1,881	1.00			1,688	1.0		
Non-obstructive CAD	2,031	2.23	1.16-4.28	0.017	1,779	1.66	0.83-3.31	0.153
1-VD	605	2.99	1.67-6.56	0.006	523	2.11	0.92-4.86	0.078
2-VD	236	8.35	3.80-18.31	<0.001	208	5.91	2.53-13.80	<0.001
3-VD or left main CAD	117	11.27	4.67-27.20	<0.001	106	7.11	2.73-18.51	<0.001
Duke index (per score increased)	4,870	1.41	1.27-1.57	<0.001[†]	4,304	1.33	1.17-1.50	<0.001[†]
SSS (per segment severity)	4,870	1.11	1.08-1.15	<0.001[†]	4,304	1.09	1.05-1.13	<0.001[†]
SIS (per segement involved)	4,870	1.18	1.11-1.26	<0.001[†]	4,304	1.14	1.06-1.22	<0.001[†]

FRS indicates Framingham risk score; CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval; CACS, coronary artery calcium score;

cCTA, coronary computed tomographic angiography; VD, vessel disease; No, number; Duke score, Duke CAD prognostic index; SSS, segment stenosis score; SIS, segment involvement score; NA, not applicable

[*] Individual Framingham risk factors included age, gender, hypertension, diabetes, current smoking, and dyslipidemia.

[†] *P* Value for trend

Supplement Table 2. Comparison of performance of CACS and cCTA in predicting 2.5-Year Risk of All-Cause Mortality and Composite Outcome of All-Cause Mortality and Non-Fatal MI using Likelihood Ratio Tests.

Model	FRS*		Individual Risk Factors*	
	Likelihood Ratio	P-Value	Likelihood Ratio	P-Value
All-cause mortality (N=3,900)				
Compared with Model I (RFs only)				
Model II: RFs + CACS	1128.35	<0.001	1146.02	<0.001
Model III: RFs + CACS+NIV	1132.23	<0.001	1149.58	<0.001
Model IV: RFs + CACS+ Duke	1131.37	<0.001	1149.58	<0.001
Model V: RFs + CACS+ SSS	1131.37	<0.001	1149.58	<0.001
Model VI: RFs + CACS+ SIS	1128.84	<0.001	1146.02	<0.001
Compared with Model II (FRS+CACS)				
Model III: RFs + CACS+ NIV	3.88	0.423	3.557	0.469
Model IV: RFs + CACS+ Duke	3.02	0.082	3.557	0.059
Model V: RFs + CACS+ SSS	1.64	0.200	3.557	0.059
Model VI: RFs + CACS+ SIS	0.49	0.482	0.001	0.975
Composite Outcome of All-Cause Mortality and Non-Fatal MI (N=3,217)				
Compared with Model I (RF only)				
Model II: RFs + CACS	240.16	<0.001	247.25	<.0001
Model III: RFs + CACS+NIV	258.81	<0.001	263.26	<.0001
Model IV: RFs + CACS+ Duke	250.80	<0.001	254.24	<.0001
Model V: RFs + CACS+ SSS	250.58	<0.001	254.17	<.0001
Model VI: RFs + CACS+ SIS	246.86	<0.001	250.60	<.0001
Compared with Model II (FRS+CACS)				
Model III: RFs + CACS+NIV	18.65	<0.001	16.02	0.003
Model IV: RFs + CACS+ Duke	10.65	0.001	7.00	0.008
Model V: RFs + CACS+ SSS	10.42	0.001	6.92	0.009
Model VI: RFs + CACS+ SIS	6.70	0.010	3.36	0.067

* Baseline risk factors were entered as a combined score in the FRS (Framingham Risk Score) column and as individual Framingham risk variables (age, gender, hypertension, diabetes, current smoking, and dyslipidemia) in the Individual Risk Factors column

CACS indicates coronary artery calcium score; CAD, coronary artery disease; cCTA, coronary computed tomographic angiography; CI, confidence interval;

Duke, Duke CAD prognostic index; FRS, Framingham risk score; N, number of patients; NIV, number of involved vessels (categorized as none, non-

obstructive CAD, obstructive 1-VD, 2-VD, 3-VD or left main CAD); RFs, Framingham risk factors; SIS, segment involvement score; SSS, segment stenosis

score ;VD, vessel disease

Reference

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