Coronary Artery Calcium Distribution Is an Independent Predictor of Incident Major Coronary Heart Disease Events

Results From the Framingham Heart Study

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Background—The presence and extent of coronary artery calcium (CAC) are associated with increased risk for cardiovascular events. We determined whether information on the distribution of CAC and coronary dominance as detected by cardiac computed tomography were incremental to traditional Agatston score (AS) in predicting incident major coronary heart disease (CHD).

Methods and Results—We assessed total AS and the presence of CAC per coronary artery, per segment, and coronary dominance by computed tomography in participants from the offspring and third-generation cohorts of the Framingham Heart Study. The primary outcome was major CHD (myocardial infarction or CHD death). We performed multivariable Cox proportional hazards analysis and calculated relative integrated discrimination improvement. In 1268 subjects (mean age, 56.2±10.3 years, 63.2% men) with AS >0 and no history of major CHD, a total of 42 major CHD events occurred during median follow-up of 7.4 years. The number of coronary arteries with CAC (hazard ratio, 1.68 per artery; 95% confidence interval, 1.10–2.57; *P*=0.02) and the presence of CAC in the proximal dominant coronary artery (hazard ratio, 2.59; 95% confidence interval, 1.15–5.83; *P*=0.02) were associated with major CHD events after multivariable adjustment for Framingham risk score and categories of AS. In addition, measures of CAC distribution improved discriminatory capacity for major CHD events (relative integrated discrimination improvement, 0.14).

Conclusions—Distribution of coronary atherosclerosis, especially CAC in the proximal dominant coronary artery and an increased number of coronary arteries with CAC, predict major CHD events independently of the traditional AS in community-dwelling men and women. (***Circ Cardiovasc Imaging*. 2017;10:e006592. DOI: 10.1161/CIRCIMAGING.117.006592.)**

Key Words: atherosclerosis ■ coronary angiography ■ coronary artery disease ■ coronary disease ■ epidemiology

Coronary artery calcium (CAC) is a hallmark of atherosclerosis and plays an important role in progression, destabilization, and stabilization of coronary plaques.[1] The presence and amount of CAC are strong predictors of cardiovascular events.[2–4] CAC scoring provides significant improvement over traditional cardiovascular risk scores in risk discrimination and reclassification.[3,4] The amount of CAC is associated with the overall burden of coronary atherosclerosis, including both calcified and noncalcified plaques.[5]

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The extent of CAC is traditionally assessed by total Agatston score.[6] Agatston method uses multiplication of calcified plaque density and area, and results are a strong indicator of extensive disease and significant involvement of vessels with calcification. However, the detailed information on regional CAC distribution is not included in Agatston score. Diffuse coronary artery disease including both calcified and noncalcified plaque as detected by coronary computed tomograpic (CT) angiography was associated with worse cardiovascular outcomes independently of the presence of significant stenosis.[7] Similarly, anatomic coronary plaque burden determined on invasive coronary angiography was a predictor

Received April 20, 2017; accepted July 28, 2017.

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The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

The Data Supplement is available at http://circimaging.ahajournals.org/lookup/suppl/doi:10.1161/CIRCIMAGING.117.006592/-/DC1.

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of death, myocardial infarction, or non–ST-segment–elevation acute coronary syndrome.[8]

These findings underscore the importance of studying CAC distribution and diffuse pattern of coronary atherosclerosis. An early fluoroscopy and electron beam CT studies demonstrated association of diffuse pattern of CAC (measured as number of coronary arteries with CAC) with the presence and extent of obstructive coronary disease.[9,10] However, there are limited data on the predictive value of CAC distribution beyond total CAC score. Williams et al[11] showed that the number of CAC lesions and the high amount of CAC in the left main coronary artery were predictive of subsequent mortality, but these measures were not incremental to total Agatston score. In contrast, in a subanalysis of the MESA (Multi-Ethnic Study of Atherosclerosis), calcium coverage score was a significant predictor of coronary heart disease (CHD) events after including Agatston score in the model.[12] Recently, Blaha et al[13] reported results from the MESA study, in which number of coronary arteries with CAC improved the prediction of CHD and total cardiovascular events when added to Agatston score.

We studied whether the distribution of CAC in individual coronary arteries and segments, as well as CAC in the proximal dominant coronary artery as detected by cardiac CT, predicts incident major CHD events independent of traditional CAC score expressed as Agatston score in asymptomatic community-dwelling men and women without prevalent major CHD.

Methods

Study Population

The selection criteria and design of the Framingham multidetector CT study and the method of CAC quantification have been described previously.[14] Participants for this study were drawn from the offspring and the third-generation cohorts of the community-based Framingham Heart Study. Participants in the analysis attended the offspring seventh examination cycle (1998–2001) and third-generation first examination cycle (2002–2005) and have complete risk factor information. Participating men were at least 33 years of age and women at least 36 years of age. In our analysis, we excluded patients with prevalent major CHD at the time of CT scan (Figure 1). We included all subjects with CAC detected on the scan (CAC score >0). The Institutional Review Boards of the Boston University Medical Center and Massachusetts General Hospital approved the study. All participants provided written informed content.

CT Imaging

Participants were imaged on an 8-slice multidetector row CT scanner (LightSpeed Ultra; General Electric, Milwaukee, WI). A noncontrast prospectively ECG-triggered CT scan for the assessment of CAC was performed during breath hold (tube potential 120 kVp, tube current of 320 mA [weight <220 pounds)] or 400 mA [weight >220 pounds], 2.5-mm-thick slices). The estimated effective radiation dose was 1.0 to 1.25 mSv.

CAC Analysis

All CT scans were evaluated by an experienced reader for the presence and amount of CAC using a workstation (Aquarius; TeraRecon, San Mateo, CA). A calcified lesion was defined as an area >3 connected pixels with a CT number >130 Hounsfield units using 3-dimensional connectivity criteria (6 points). CAC score was calculated using the method described by Agatston et al.[6] CAC score was categorized as low (1–100), intermediate (101–300), and high (>300).[2,3] We also performed a sensitivity analysis and categorized CAC score as low (1–100), intermediate (101–400), and high (>400).

Two independent readers evaluated CT scans with CAC >0 and determined the presence of CAC in each coronary segment. The discrepant results were resolved by a consensus. We used the coronary segment model of the Society of Cardiovascular Computed Tomography.[15] CAC was present in the coronary segment if at least one calcified lesion was present. We recorded the number of coronary segments and number of coronary arteries with CAC. We determined coronary dominance. The coronary system was considered right dominant if both posterior descending artery and posterolateral branch originated from the right coronary artery. The coronary system was considered left dominant if both posterior descending artery and posterolateral branch originated from the left circumflex coronary artery. The coronary system was considered codominant if posterior descending artery originated from the right coronary artery and posterolateral branch originated from the left circumflex coronary artery. The proximal coronary segments for the purpose of this analysis were defined as segment 1 (proximal right coronary artery), segment 2 (mid right coronary artery), segment 5 (left main coronary artery), segment 6 (proximal left anterior descending coronary artery), and segment 11 (proximal left circumflex coronary artery). The presence

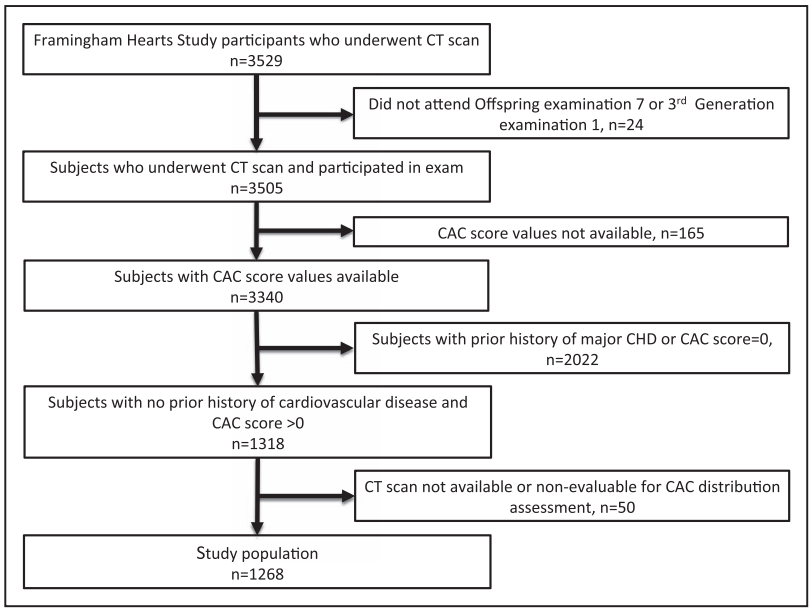

Figure 1. Study population, exclusions and inclusions. CAC indicates coronary artery calcium; CHD, coronary heart disease; and CT, computerized tomography.

of proximal CAC was considered positive if CAC was present in segments 1 or 2 (right dominant); segments 5, 6, or 11 (left dominant); and segments 1, 2, 5, 6, or 11 (codominant).

Cardiovascular Risk Factors and Cardiovascular Disease Outcomes

A standard clinic examination at the offspring seventh cycle or the third-generation first examination cycle was conducted and included an interview with and physical examination by a physician and conduct of laboratory tests.[16,17] Standardized measurements of traditional risk factors were conducted. The cardiovascular outcomes were defined in the Framingham Heart Study previously.[4,18] For the purpose of this study, major CHD events included recognized myocardial infarction and death from CHD. In the Framingham Heart Study, all study participants were under continuous surveillance for the development of outcomes. Information about outcomes on follow-up was obtained with the aid of medical histories, physical examinations at the study clinic, hospitalization records, and communication with personal physicians. A panel of 3 experienced investigators who evaluated all pertinent medical records reviewed all suspected new events.

Statistical Analysis

Continuous data are presented as mean±SD or median (25th–75th percentile). Comparisons between groups were performed with an independent Student *t* test or the Wilcoxon rank-sum test for continuous variables and Fisher exact test for categorical variables. To evaluate the predictive value of CAC distribution measures and CAC score on subsequent major CHD, we calculated numbers of participants with major CHD per 1000 person-years after stratification by number of coronary arteries with CAC, number of coronary segments with CAC, presence of CAC in the proximal dominant coronary artery, and CAC score categories. Kaplan–Meier estimates of major CHD-free survival according to number of coronary arteries and segments with CAC, presence of CAC in the proximal dominant coronary artery, and CAC score categories were calculated. After checking the assumption of proportional hazards between categories of CAC distribution metrics (all $P>0.10$), we used Cox proportional hazards regression models to relate each CAC distribution measures to time-to-event and calculated hazard ratios with 95% confidence intervals. Multivariable models were adjusted for 10-year Framingham risk score,[18] Atherosclerotic Cardiovascular Disease score,[19] and total CAC score categories or log-transformed CAC scores. To assess the ability of the model to discriminate major CHD events after the addition of CAC distribution measures, we calculated area under the receiver-operating characteristics curve and relative integrated discrimination improvement.[20] Analyses were performed with the use of SAS software, version 9.2 (SAS Institute). All hypotheses were tested with 2-sided 0.05 α level.

Results

Baseline Characteristics

We studied 1268 out of 3529 subjects who underwent a CAC scan in the Framingham Heart Study and had a CAC >0 (Figure 1). We excluded subjects with prevalent major CHD. The median follow-up was 7.4 years (6.3–8.3 years). There were 42 major CHD events, 38 myocardial infarctions, and 4 CHD deaths during follow-up (event rate: major CHD 3.3%, myocardial infarction 3.0%, CHD death 0.3%). The baseline characteristics of subjects are summarized in Table 1. Subjects with subsequent major CHD events were older and had higher prevalence of current or former smoking. The mean Framingham Heart Study risk score was higher in subjects with major CHD events.

CAC and Major CHD Events

Cardiac CT characteristics are summarized in Table 2. Subjects with major CHD events had higher CAC score, were classified more often in higher CAC score category, had more coronary arteries and coronary artery segments with CAC, and had more often CAC in the proximal dominant, proximal right, and proximal left coronary segments. There was no difference in coronary artery dominance between those with and without major CHD events. The results categorized with the highest CAC score category of Agatston score >400 are summarized in Table I in the Data Supplement. The prevalence of CAC in the proximal dominant coronary artery increased across CAC categories and also with increasing number of coronary arteries with CAC (Table II in the Data Supplement).

Major CHD event rates increased with increasing CAC score categories (Agatston score 1–100: 1.1%, 8/721; Agatston score 101–300: 3.3%, 9/269; Agatston score >300: 9.0%, 25/278). Similar results were observed with the highest CAC score category of Agatston score >400 (Agatston score 1–100: 1.1%, 8/721; Agatston score 101–400: 3.1%, 10/319; Agatston score >400: 10.5%, 24/228). Major CHD event rates also increased with increasing number of coronary segments with CAC (1–2 segments: 0.5%, 3/650; 3–4 segments: 3.6%, 10/279; 5–8 segments: 8.3%, 22/264; >8 segments: 9.3%, 7/75), number of coronary arteries with CAC involvement (1 vessel: 0.2%, 1/546; 2

Table 1. Baseline Demographic and Cardiovascular Risk Factors of Study Subject Stratified by Major CHD Events

	All (n=1268)	No Major CHD (n=1226)	Major CHD (n=42)	*P* Value
Age, y	56.2±10.3	56.0±10.3	60.4±9.3	0.01
Men, %	801 (63.2)	771 (62.9)	30 (71.4)	0.33
Cardiovascular risk factors, %				
Hypertension	530 (41.8)	510 (41.6)	20 (47.6)	0.43
Dyslipidemia	387 (30.5)	378 (30.8)	9 (21.4)	0.23
Diabetes mellitus	124 (9.8)	116 (9.5)	8 (19.0)	0.06
Current or former smoking	725 (57.8)	694 (57.3)	31 (73.8)	0.04
Obesity (body mass index >30 kg/m^2)	419 (33.0)	403 (32.9)	16 (38.1)	0.51
Framingham risk score, %	14.0±11.4	13.8±11.3	21.5±12.7	<0.001

CHD indicates coronary heart disease.

Table 2. Coronary Artery Calcium Characteristics as Detected by Cardiac CT and Stratified by Major Coronary Heart Disease Events

	All (n=1268)	No major CHD (n=1226)	Major CHD (n=42)	*P* Value
Total CAC score (median, 25th–75th percentile)	71 (15–256)	68 (14–233)	484 (158–730)	<0.001
CAC score categories, %				<0.001
1–100	721 (56.9)	713 (58.2)	8 (19.1)	
101–300	269 (21.2)	260 (21.2)	9 (21.4)	
>300	278 (21.9)	253 (20.6)	25 (59.5)	
No. of segments with CAC (median, 25th–75th percentile)	2 (1–5)	2 (1–5)	4 (6–8)	<0.001
No. of coronary segments with CAC, %				<0.001
1–2 segments	650 (51.3)	647 (52.8)	3 (7.1)	
3–4 segments	279 (22.0)	269 (21.9)	10 (23.8)	
5–8 segments	264 (20.8)	242 (19.7)	22 (52.4)	
>8 segments	75 (5.9)	68 (5.5)	7 (16.7)	
No. of coronary arteries with CAC, %				<0.001
1 vessel	546 (43.1)	545 (44.5)	1 (2.4)	
2 vessels	294 (23.2)	284 (23.2)	10 (23.8)	
3 vessels	239 (18.9)	225 (18.4)	14 (33.3)	
4 vessels	189 (14.9)	172 (14.0)	17 (40.5)	
Coronary dominance, %				
Right	1177 (92.8)	1136 (92.7)	41 (97.6)	0.71
Left	49 (3.9)	48 (3.9)	1 (2.4)	
Codominant	42 (3.3)	42 (3.4)	0 (0)	
Proximal dominant coronary artery CAC, %				<0.001
Yes	442 (34.9)	411 (33.5)	31 (73.8)	
No	826 (65.1)	815 (66.5)	11 (26.2)	
Right proximal segments CAC, %				
Yes	620 (48.9)	585 (47.7)	35 (83.3)	<0.001
No	648 (51.1)	641 (52.3)	7 (16.7)	
Left proximal segments CAC, %				
Yes	1079 (85.1)	1038 (84.7)	41 (97.6)	0.02
No	189 (14.9)	188 (15.3)	1 (2.4)	…

CAC indicates coronary artery calcium; and CHD, coronary heart disease.

vessels: 3.4%, 10/294; 3 vessels: 5.9%, 14/239; 4 vessels: 9.0%, 17/189), and the presence of CAC in the proximal dominant coronary artery (no: 2.4%, 20/846; yes: 5.2%, 22/422).

Numbers of participants with major CHD events per 1000 person-years are summarized in Figure 2. There was gradual increase of the number of participants with major CHD per 1000 person-years among categories of CAC score and measures of CAC distribution ($P<0.001$ for all). Number of participants with major CHD events per 1000 person-years in those with CAC in the proximal coronary artery increased across categories of CAC score (1–100, 101–300, >300) but not in those without CAC in the proximal coronary artery (Figure I in the Data Supplement).

Kaplan–Meier estimates of major CHD-free survival according to CAC score categories, number of coronary segments and arteries with CAC, and the presence of CAC in the proximal dominant coronary artery are shown in Figure 3 (highest CAC score category of Agatston score >400; Figure II in the Data Supplement).

Incremental Value of CAC Distribution for Prediction of Major CHD Events

In the multivariable Cox proportional hazard analysis, number of coronary segments with CAC, number of coronary arteries with CAC, and the presence of CAC in the proximal dominant coronary artery were associated with increased risk of major

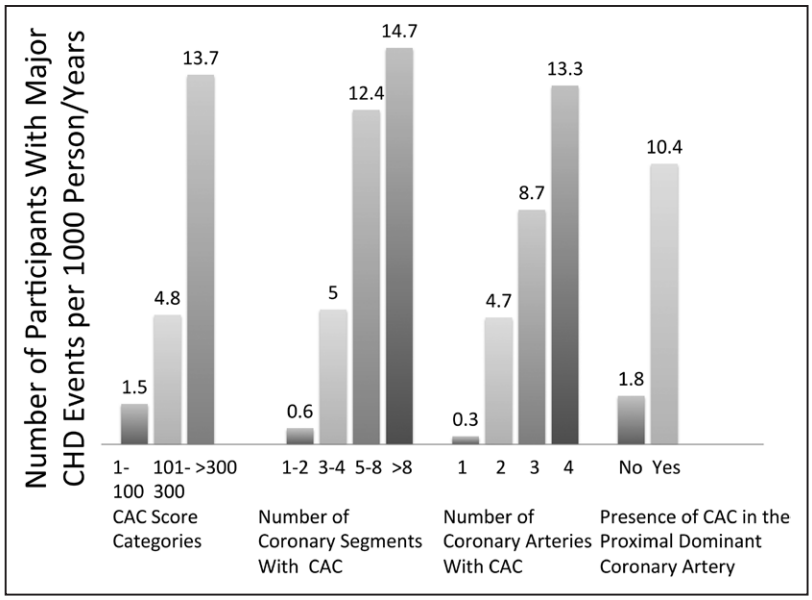

Figure 2. Numbers of participants with major coronary heart disease (CHD) per 1000 person-years stratified by coronary artery calcium (CAC) score categories, number of coronary segments with CAC, number of coronary arteries with CAC, and the presence of CAC in the proximal dominant coronary artery.

CHD after adjustment for age and sex, as well as after adjustment for Framingham risk score (Table 3). The results were similar when individual risk factors were used instead of Framingham risk score (data not shown). After adjustment for both Framingham risk score and CAC score categories, number of coronary arteries was independently associated with major CHD events. The risk of major CHD events increased by ≈70% with each additional coronary artery with CAC. Similarly, the

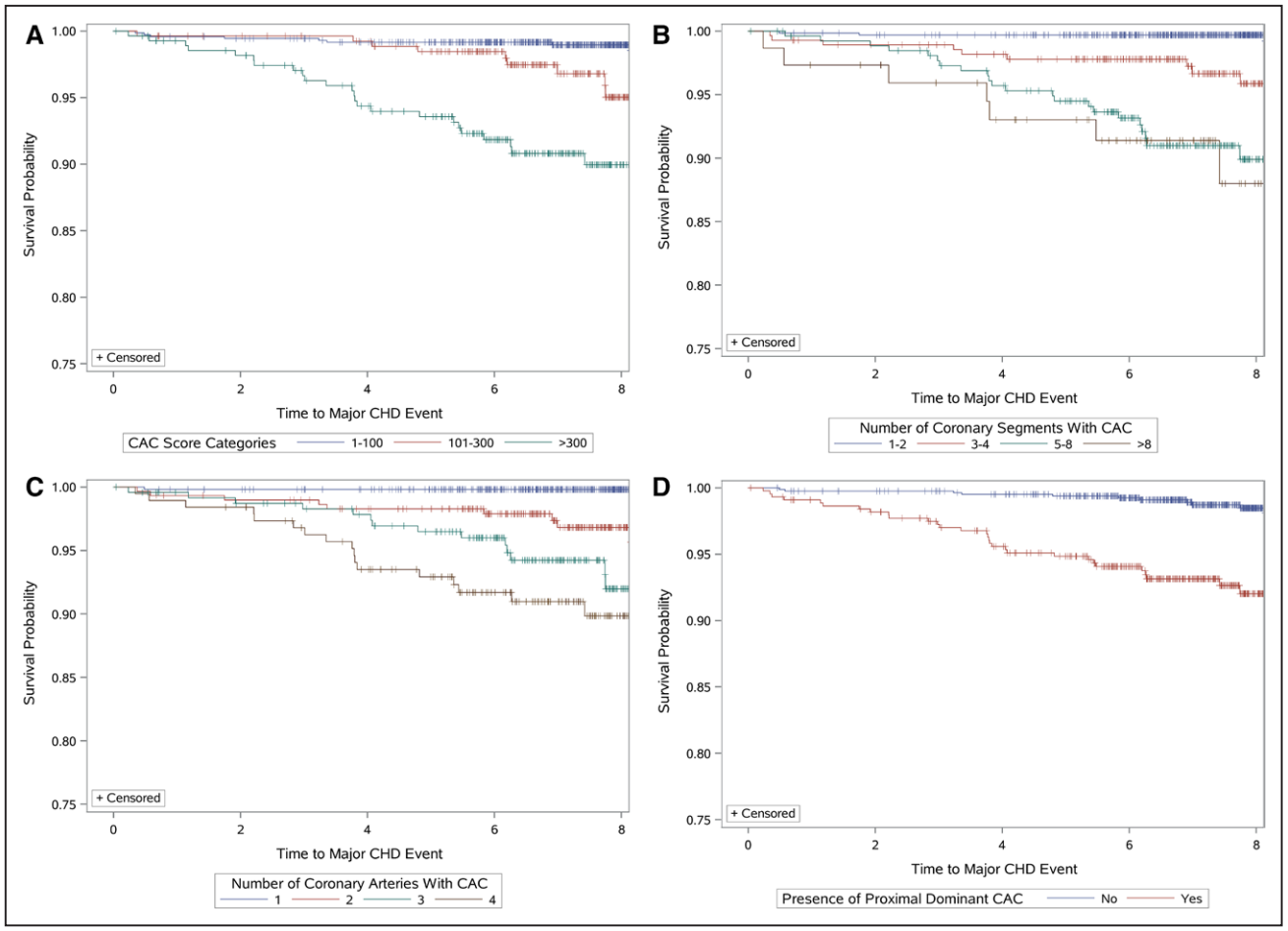

Figure 3. Kaplan–Meier estimates of major coronary heart disease (CHD) events by (**A**) coronary artery calcium (CAC) score categories (Agatston score 1–100, 101–300, and >300), (**B**) number of coronary segments with CAC (1–2, 3–4, 5–8, and >8), (**C**) numbers of coronary arteries with CAC (1, 2, 3, and 4), and (**D**) the presence of CAC in the proximal dominant coronary artery (yes and no) in the Framingham Heart Study population.

Table 3. Results of Multivariable Cox Proportional Hazards Regression Analysis for the Prediction of Major CHD Events During Follow-Up

	Hazard Ratio (95% CI)	*P* Value
Model adjusted for age and sex		
No. of coronary segments with CAC	1.31 (1.18–1.45)	<0.001
No. of coronary arteries with CAC	2.29 (1.66–3.18)	<0.001
Proximal dominant coronary artery CAC	4.83 (2.35–9.91)	<0.001
Model adjusted for Framingham risk score		
No. of coronary segments with CAC	1.28 (1.16–1.42)	<0.001
No. of coronary arteries with CAC	2.20 (1.61–3.02)	<0.001
Proximal dominant coronary artery CAC	4.68 (2.28–9.61)	<0.001
Model adjusted for Framingham risk score and CAC score categories (1–100, 101–300, and >300)		
No. of coronary segments with CAC	1.14 (0.99–1.32)	0.07
No. of coronary arteries with CAC	1.68 (1.10–2.57)	0.02
Proximal dominant coronary artery CAC	2.59 (1.15–5.83)	0.02
Model adjusted for Framingham risk score and log-transformed CAC score		
No. of coronary segments with CAC	1.09 (0.93–1.28)	0.31
No. of coronary arteries with CAC	1.53 (1.00–2.36)	0.05
Proximal dominant coronary artery CAC	2.35 (1.05–5.29)	0.04

CAC indicates coronary artery calcium; CHD, coronary heart disease; and CI, confidence interval.

presence of CAC in the proximal dominant coronary artery was independently associated with ≈2.6-fold increase in the risk of major CHD events. Finally, the number of coronary segments was not significantly associated with major CHD events after adjustment for Framingham risk score and CAC score categories. The results were similar when log-transformed CAC scores were used instead of CAC score categories. The risk of major CHD events increased by ≈50% with each additional coronary artery with CAC. The presence of CAC in the proximal dominant coronary artery increased the risk of major CHD events ≈2.4 times. The number of coronary segments was not significantly associated with major CHD events after adjustment. The results were similar when the highest CAC score category of Agatston score >400 and Atherosclerotic Cardiovascular Disease score was used (Table III in the Data Supplement).

There was good discriminatory capacity of multivariable model including CAC score categories for major CHD events, with area under the receiver-operating characteristics curve of 0.77 (95% confidence interval, 0.69–0.85). The addition of CAC distribution measures improved the discriminatory capacity of the models for major CHD events (area under the receiver-operating characteristics curve between 0.79 and 0.80) with relative integrated discrimination improvement of 0.14 to 0.20, indicating good improvement of model performance (Table 4). These results suggest independent and incremental value of novel CAC distribution measures for major CHD events when added to traditional cardiovascular risk factors (expressed as Framingham risk score) and CAC score. The results were similar when the highest CAC score category of Agatston score >400 or Atherosclerotic Cardiovascular Disease score was used (Tables IV and V in the Data Supplement). The presence of CAC in the proximal right and left coronary segments was not an independent and incremental predictor of major CHD events (Tables VI and VII in the Data Supplement).

Table 4. Measures of Performance Improvement With 95% CIs Adding Novel CAC Distribution Measures to Framingham Risk Score and CAC Score Categories for the Prediction of Major CHD Events

Marker	AUC (C Statistics)*	Relative IDI
No. of coronary segments with CAC	0.79 (0.72–0.86)	0.20 (0.06–0.38)
No. of coronary arteries with CAC	0.80 (0.73–0.87)	0.14 (0.06–0.23)
Proximal dominant coronary artery CAC	0.79 (0.71–0.87)	0.14 (0.09–0.20)

AUC indicates area under the receiver-operating characteristics curve; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; and IDI, relative integrated discrimination improvement.

*AUC (C statistic) for Framingham risk score 0.72 (0.64–0.80) and for multivariable model with CAC categories and Framingham risk score 0.77 (0.69–0.85).

The risk of major CHD events increased with the increasing number of CAC measures in the highest category (CAC score >300, number of arteries with CAC=4, number of coronary segments >8, and presence of CAC in the proximal dominant coronary artery; Figure 4).

Discussion

In a well-characterized population of asymptomatic community-dwelling men and women with no history of CHD, measures of CAC distribution (number of coronary arteries with CAC and the presence of CAC in the proximal dominant coronary artery) were associated with major CHD events. The association persisted after adjustment for traditional measure of CAC extent by Agatston score and cardiovascular risk factors. Our results suggest that a simple measure of CAC distribution—number of coronary arteries with CAC—may serve as an incremental

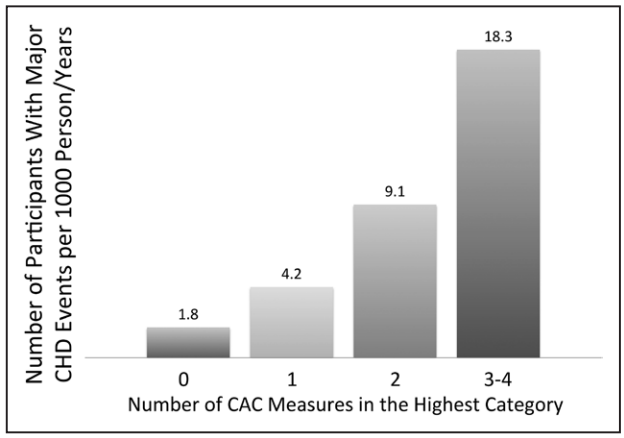

Figure 4. Number of participants with major coronary heart disease (CHD) per 1000 person-years stratified by the number of coronary artery calcium (CAC) measures in the highest category (CAC score >300, number of coronary segments with CAC >8, number of coronary arteries with CAC=4, and the presence of CAC in the proximal dominant coronary artery).

marker of risk for CHD events in persons with CAC. Furthermore, we showed that the presence of CAC in the proximal dominant coronary artery also increases the risk of major CHD events incrementally to CAC score.

Traditional CAC Score Assessment Using Agatston Method

The quantification of CAC using Agatston method has been the cornerstone of cardiovascular risk assessment for >2 decades.[6] Epidemiological studies demonstrated a graded increase in the risk of cardiovascular events across strata of CAC scores.[2–4] However, Agatston score does not account for CAC distribution and does not include information on the involvement of individual coronary arteries and on the involvement of proximal and distal segments. The results of studies using coronary CT angiography showed a strong association of coronary atherosclerosis burden, typically expressed as number of coronary arteries or segments with plaque, with adverse outcomes.[7] Similar association between coronary atherosclerotic burden and cardiovascular events was observed in COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) using invasive coronary angiography.[8]

Distribution of CAC as a Predictor of Cardiovascular Events

Previous studies showed the relationship of CAC distribution and segmental extent of coronary atherosclerosis to the presence of obstructive CAD and ischemia and their additive value to total CAC score.[21,22] Total CAC score was also correlated with total plaque burden as assessed by coronary CT angiography and expressed as segment involvement score.[23] Number of coronary arteries with CAC improved correlation to plaque burden in categories of mild (CAC score 1–100) and moderate (101–400) CAC. Furthermore, higher segment involvement score was associated with more diffuse distribution of CAC. The authors concluded that addition of measures of CAC distribution improved the association of CAC scores with overall coronary plaque burden. However, these studies did not evaluate the relation to cardiovascular outcomes.

In the first outcome study, Williams et al[11] analyzed CAC scores obtained by electron beam CT in 14 759 asymptomatic subjects and found that the total number of CAC lesions and number of calcified lesions in the left main and left anterior descending coronary arteries were associated with increased all-cause mortality. However, number of CAC lesions was closely correlated to total CAC score and was not incremental to CAC score in prediction of mortality.[11] Silverman et al[24] studied 6540 subjects from the MESA study. They found that CAC in 3 or 4 vessels, higher CAC burden, and involvement of the left main coronary artery were independent predictors of coronary artery bypass surgery versus percutaneous coronary intervention in multivariate models adjusting for CAC score. Regional distribution of CAC predicted need for revascularization and mode of revascularization, which was indicative of meaningful communication of clinically important distribution of plaque. In another analysis from the MESA study, Brown et al[12] developed calcium coverage score, which quantified the percentage of the entire length of major epicardial coronary arteries with CAC plaque. Calcium coverage score was an independent, but not an incremental, predictor of CHD events after controlling for total CAC score.[12] In the recently published comprehensive analysis of CAC distribution in 3262 participants from the MESA study, Blaha et al[13] observed that number of vessels with CAC significantly improved capacity to predict CHD and cardiovascular events. Addition of number of vessels with CAC to total CAC score improved discriminatory capacity for CHD and cardiovascular events, especially in intermediate CAC score (1–400) category.

Our study confirms the observations from the MESA study in an independent cohort. The number of coronary arteries with CAC was an independent and incremental predictor of major CHD events after controlling for traditional cardiovascular risk assessment using Framingham risk score and total CAC score. The number of coronary segments was predictive of major CHD events in univariate analysis but lost its significance after adjustment for CAC score. Our results add to the MESA study results by highlighting the importance of proximal CAC, especially when present in multiple coronary arteries and in the proximal dominant coronary artery, and add to the previous observations by Blaha et al,[13] which showed that CAC diffusivity index was not an independent predictor of events. This is in contrast with the observation that increasing number of vessels with plaque and higher CAC scores were associated with higher odds of distal plaque, and distal plaques were associated with significant stenosis.[25,26] Indeed, previous invasive coronary angiographic study found that the majority of culprit lesions of myocardial infarctions are located in the proximal coronary arteries, and our study confirms the importance of proximal coronary atherosclerosis in dominant vessels for major CHD events.[27]

Coronary Dominance as Predictor of Adverse Events

The novel finding of the association of the CAC presence in the proximal dominant coronary artery expands on previous studies exploring the relationship of coronary dominance and cardiovascular events. Parikh et al[28] found higher in-hospital mortality in patients with left dominant and codominant circulation undergoing percutaneous coronary intervention for acute coronary syndrome. In patients with ST-segment–elevation myocardial infarction, left dominant system was associated with increased risk of 30-day mortality and early reinfarction but did not influence long-term outcomes.[29] In a study using coronary CT angiography in 1425 patients, the presence of left coronary dominance was an independent predictor of myocardial infarction and all-cause mortality, especially in patients with obstructive CAD.[30] In contrast, the results from the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) did not show difference in all-cause mortality between patients with right and left coronary dominance in both patients with and without 50% stenosis.[31] Our results emphasize the importance of the presence of atherosclerosis in proximal dominant coronary artery as a predictor of major CHD events.

Study Limitations

The exact determination of coronary segments and thus assignment to appropriate segment may be difficult in noncontrast scans. However, our results for the number of coronary arteries with CAC and proximal dominant coronary artery CAC were not affected by this problem. The number of major CHD events was relatively low. The low number of major CHD events limited our ability to perform multivariable analyses of predictive value of CAC distribution measures in each of the CAC score categories separately.

Conclusions

A greater distribution of coronary atherosclerosis with the presence of CAC in the proximal dominant coronary artery and increased number of coronary arteries with CAC predicts major CHD events and provides improved discrimination and reclassification, independent of total amount of CAC and cardiovascular risk factors in asymptomatic community-dwelling men and women free of major CHD. Our findings support future studies to evaluate these simple measures of regional CAC distribution. The measures of CAC distribution should be considered for the inclusion in standardized reports in addition to the traditional Agatston score.

Sources of Funding

This work was supported by the National Institutes of Health Heart, Lung, and Blood Institute's Framingham Heart Study (contract number N01- HC-25195, HL076784, AG028321, HL070100, HL060040, HL080124, HL071039, HL077447, and HL107385).

Disclosures

Dr Ferencik received support from the American Heart Association (13FTF16450001). Dr Hoffmann received Research Grants from the National Institutes of Health (U01HL092040, U01HL092022), and Siemens Medical Solutions, Heart Flow, Inc and served as a consultant for Heart Flow. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

The presence and extent of coronary artery calcium (CAC) are associated with increased risk for cardiovascular events. The extent of CAC is traditionally assessed by calculating total Agatston score (multiplication of calcium density and calcium area). However, the detailed information on regional CAC distribution is not included in Agatston score. We determined whether information on the distribution of CAC and coronary dominance as detected by cardiac computed tomography were incremental to traditional Agatston score in predicting incident major coronary heart disease. In a well-characterized population of asymptomatic community-dwelling men and women with no history of coronary heart disease from the Framingham Heart Study, measures of CAC distribution (number of coronary arteries with CAC and the presence of CAC in the proximal dominant coronary artery) were associated with major coronary heart disease events. The association persisted after adjustment for traditional measure of CAC extent by Agatston score and cardiovascular risk factors. Our results suggest that simple measures of CAC distribution—number of coronary arteries with CAC and the presence of CAC in the proximal dominant coronary artery—may serve as an incremental marker of risk for coronary heart disease events in people with CAC. Our findings support future studies to evaluate these simple measures of regional CAC distribution. The measures of CAC distribution should be considered for the inclusion in standardized reports in addition to the traditional Agatston score.