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Discordance Between Coronary Artery Calcium Area and Density Predicts Long-Term Atherosclerotic Cardiovascular Disease Risk

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Abstract

BACKGROUND—Coronary artery calcium (CAC) is commonly quantified as the product of 2 generally correlated measures: plaque area and calcium density.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

OBJECTIVES—The authors sought to determine whether discordance between calcium area and density has long-term prognostic importance in atherosclerotic cardiovascular disease (ASCVD) risk.

METHODS—The authors studied 10,373 primary prevention participants from the CAC Consortium with CAC >0. Based on their median values, calcium area and mean calcium density were divided into 4 mutually exclusive concordant/discordant groups. Cox proportional hazards regression assessed the association of calcium area/density groups with ASCVD mortality over a median of 11.7 years, adjusting for traditional risk factors and the Agatston CAC score.

RESULTS—The mean age was 56.7 years, and 24% were female. The prevalence of plaque discordance was 19% (9% low calcium area/high calcium density, 10% high calcium area/low calcium density). Female sex (odds ratio [OR]: 1.48 [95% CI: 1.27–1.74]) and body mass index (OR: 0.81 [95% CI: 0.76–0.87], per 5 kg/m^2 higher) were significantly associated with high calcium density discordance, whereas diabetes (OR: 2.23 [95% CI: 1.85–3.19]) was most strongly associated with discordantly low calcium density. Compared to those with low calcium area/low calcium density, individuals with low calcium area/high calcium density had a 71% lower risk of ASCVD death (HR: 0.29 [95% CI: 0.09–0.95]).

CONCLUSIONS—For a given CAC score, high calcium density relative to plaque area confers lower long-term ASCVD risk, likely serving as an imaging marker of biological resilience for lesion vulnerability. Additional research is needed to define a robust definition of calcium area/density discordance for routine clinical risk prediction.

Keywords

calcium density; cardiovascular diseases; coronary artery calcium; multidetector computed tomography

Coronary artery calcium (CAC) is a specific marker of subclinical coronary atherosclerosis.[1] Current American College of Cardiology/American Heart Association[2] and European Society of Cardiology[3] guidelines recommend noninvasive CAC measurement via cardiac-gated noncontrast computed tomography (CT) as the strongest established imaging modality to help guide atherosclerotic cardiovascular disease (ASCVD) risk assessment and the initiation of preventive pharmacotherapy, particularly among primary prevention patients aged 40 to 79 years who have an intermediate 10-year ASCVD risk. Although CAC is closely associated with ASCVD risk, there may be considerable heterogeneity in plaque morphology among individuals with similar CAC burden, which could differentially influence long-term ASCVD outcomes and thus the approach to risk reduction.[4,5]

The Agatston method is the most widely used CAC scoring algorithm, defined as the product of plaque area and a quantized peak calcium density weighting factor for each lesion, the latter of which is summed across all lesions to provide a total CAC score.[6] However, recent preliminary evidence suggests that mean and peak calcium density display large differences during the initial development of coronary atherosclerosis,[7] and that mean calcium density more precisely reflects early plaque biology, vulnerability, and risk. Likewise, calcium area and density values may themselves have wide interindividual variability within a CAC score category, with implications for the development of coronary

heart disease (CHD) and the probability of culprit lesion events. Despite these important subtleties, no previous studies have assessed the collective relationship of upstream risk factors, calcium area, and calcium density with ASCVD mortality.

Therefore, among primary prevention patients with prevalent CAC, we sought to assess: 1) the proportion with discordant calcium area and density values; 2) the association between traditional ASCVD risk factors with calcium area and density phenotypes; and 3) the prognostic implications of discordant calcium area and density for ASCVD mortality over a follow-up period of 11.7 years.

METHODS

STUDY POPULATION.

The CAC Consortium is a multicenter cohort study that includes 4 high-volume centers in the United States: Cedars-Sinai Medical Center (Los Angeles, California, USA), PrevaHealth Wellness Diagnostic Center (Columbus, Ohio, USA), Harbor-UCLA Medical Center (Torrance, California, USA), and Minneapolis Heart Institute (Minneapolis, Minnesota, USA). The multicenter retrospective cohort study was designed to assess the association of CAC with long-term, disease-specific mortality, and the study design and methods have been previously described in detail elsewhere.[8] In brief, the study included individuals aged 18 years or older who were free of clinical ASCVD or cardiovascular symptoms at the time of CAC scanning. The presence of underlying ASCVD risk factors and uncertainty regarding risk assessment were the major indications for CAC testing among participants. Hyperlipidemia and/or family history of CHD were among the most common risk factors that precipitated CAC scanning. All study participants provided written informed consent at baseline, and study protocols were approved by the Johns Hopkins University School of Medicine.

Findings in the current analysis represent the baseline CAC Consortium data collection, occurring from 1991 to 2010. After excluding participants with CAC = 0, there were 10,373 primary prevention patients with prevalent CAC who had direct measurements of mean calcium density.

MEASUREMENT OF CAC AND MEAN CALCIUM DENSITY.

Noncontrast cardiac-gated CT was used to quantify CAC according to the standard Agatston protocol using measured calcified coronary plaque area (mm^2) and peak calcium density (HU) on a per lesion basis.[8] Both electron beam tomography and multidetector CT were used for imaging, and previous studies have shown no clinically significant differences in CAC measurement between these 2 scanning methods.[9]

Mean per lesion calcium density was directly measured from CT images for each participant who had calcified plaques (3 contiguous voxels of at least 130 HU). Similar to previous studies, mean (composite) calcium density (in HU) across all lesions was then divided by 100 to create a mean calcium weight factor scale that matched the Agatston peak calcium density weighting factor scale.[7]

CALCULATION OF CALCIFIED PLAQUE AREA AND PEAK CALCIUM DENSITY.

Calcified plaque area (mm^2) for each participant was calculated by dividing CAC volume scores by the slice thickness used for each respective CT imaging protocol. As previously described, the average peak calcium density was then back-calculated (Supplemental Figure 1) as the quotient of the Agatston score and total plaque area for each participant (average peak calcium density = Agatston score/total plaque area).[10,11]

According to the Agatston algorithm,[12] a value of 1 to 4 was assigned for peak calcium density based on the measured peak calcium density attenuation value of the lesion (1: 130–199 HU; 2: 200–299 HU; 3: 300–399 HU; 4: >400 HU).

EVALUATION OF ASCVD RISK FACTORS.

ASCVD risk factor status was ascertained at the time of CAC scans. Hypercholesterolemia (low-density lipoprotein cholesterol >160 mg/dL), hypertriglyceridemia (triglycerides >150 mg/dL), and low high-density lipoprotein cholesterol (<40 mg/dL in men, <50 mg/dL in women) were defined by a previous clinical diagnosis or the use of lipid-lowering therapy. Dyslipidemia was defined as the presence of hypercholesterolemia, hypertriglyceridemia, and/or low high-density lipoprotein cholesterol. Diabetes and hypertension were defined by a previous clinical diagnosis or reported antihypertensive or glucose-lowering medication utilization, respectively. Information on smoking and family history of CHD (first-degree relative with history of CHD at any age) was obtained through self-reported data.

ASCVD MORTALITY ASCERTAINMENT.

A previously validated algorithm was used to ascertain mortality in the CAC Consortium and included linking patient records with the Social Security Administration Death Master File.[13] A semiflexible hierarchical matching process is used in the algorithm that leverages unique patient identifiers. Death certificates were acquired from the National Death Index service, and deaths were classified using the International Classification of Diseases, 9th and 10th Revision.[8] There was >90% specificity and 72% to 90% sensitivity for identifying known deaths with respect to the outcome of all-cause mortality.

STATISTICAL ANALYSIS.

For the main analysis, mean calcium density rather than peak calcium density values were used because mean calcium density was directly measured on noncontrast CT scans, whereas peak calcium density values were back-calculated.[7] First, mean calcium density and plaque area were categorized as high (above the median for the study population) or low (below the median for the study population). Next, participants were divided into quartiles of 4 mutually exclusive concordant/discordant groups: low/low (< the median for both mean calcium density and calcified plaque area); high/low ($ the median for mean calcium density and < the median for calcified plaque area); low/high (< the median for mean calcium density and $ the median for calcified plaque area); and high/high ($ the median for both mean calcium density and calcified plaque area). We similarly created 4 mutually exclusive concordant/discordant groups using calculated peak calcium density values. To visualize discordance and to express the relationship between calcium density and area, bivariate

linear regression models were calculated for the expected relationship of mean and peak calcium density and calcium area using log-transformed values.

Study population characteristics were stratified according to calcium area and density phenotypes, using mean calcium density (Table 1) and peak calcium density values (Supplemental Table 1). The Student's *t*-test and Wilcoxon signed rank test were used to assess differences in normally and non-normally distributed continuous variables, respectively. Differences between categorical variables were evaluated through the Pearson chi-square test.

Using individuals with low calcium area and mean calcium density as the reference outcome group, the association of traditional ASCVD risk factors with calcium area and mean calcium density phenotypes (low calcium area/high mean calcium density, high mean calcium area/low mean calcium density, high mean calcium area/high mean calcium density) was assessed using multinomial logistic regression. The multinomial logistic regression model included age, sex, ethnicity, current cigarette smoking, hypertension, hyperlipidemia, diabetes, and a family history of CHD.

To assess long-term ASCVD risk, we compared ASCVD mortality across calcium area and mean calcium density area groups, which were expressed as absolute numbers and proportions. The total number of events was divided by person-years to calculate an ASCVD mortality rate (per 1,000-year follow-up). Kaplan-Meier survival curves were computed for ASCVD mortality in concordant/discordant calcium area and mean calcium density groups. Differences in survival among calcium area and mean calcium density groups were assessed through the log-rank test.

Multivariable Cox proportional hazards regression was used to estimate the hazard of ASCVD mortality associated with calcium area and mean calcium density phenotypes. The proportional hazards assumption was satisfied and was tested by assessing the significance of time-dependent independent variables concurrently. The association of calcium area and mean calcium density phenotypes with ASCVD mortality was assessed in 2 models: model 1, which adjusted for age, sex, ethnicity, current cigarette smoking, hypertension, hyperlipidemia, diabetes, and a family history of CHD; and model 2, which adjusted for model 1 covariables and the Agatston CAC score.

Because previous studies have demonstrated that ASCVD risk may be different according to mean vs peak calcium density,[7] we conducted sensitivity analyses using peak calcium density values to create calcium density and plaque area phenotypes that were used in multinomial logistic regression and multivariable logistic regression models.

Lastly, we performed sensitivity analyses using an alternative definition of area/density discordance leveraging continuous data without dichotomization. Here, calcium area/density discordance was defined as an observed calcium density that deviated >15% (discordantly high) or <15% (discordantly low) from the expected value for a given calcium area. Expected density values for a given area were generated and plotted using linear regression and log-transformed values similar to those described earlier.

RESULTS

Participants were on average 56.7 years of age, 24.4% were women, and 3.3% were of non-White ethnicity (Table 1). There was a higher mean age and higher proportion of females among persons with discordantly high mean calcium density compared to persons with both low calcium area and mean calcium density. A similar pattern was observed across peak calcium density and plaque area phenotypes (Supplemental Table 1).

Median CAC score was 68 (IQR: 16–253), and more than one-half (57.7%) of participants had CAC <100. The average 10-year ASCVD risk was 5.9% among all primary prevention patients with prevalent CAC, and individuals who had low mean and peak calcium density with high calcium area had the highest calculated 10-year risk among discordant groups. Approximately 1 in 5 persons with borderline or intermediate ASCVD risk had discordance between calcium area and mean density values (Figure 1), which was approximately 2-fold higher when using peak calcium density (Supplemental Figure 2).

The distribution of concordant and discordant calcium area/density groups strongly differed when using mean vs peak calcium density values, which was consistent across both the dichotomized (Figure 2) and linear (Supplemental Figure 3) definitions of discordance. Mean and peak calcium density values were modeled as a function of age, sex, and calcium area (Figure 3A). The distribution of concordant and discordant calcium area/density groups strongly differed when using mean vs peak calcium density values (Figures 3B to 3C).

Independent of traditional risk factors, female sex was associated with a 48% higher odds for the high mean calcium density and low calcium area phenotype (Table 2). Higher body mass index (BMI) (odds ratio [OR]: 0.81 [95% CI: 0.76–0.87], per 5 kg/m^2 higher), hypertension (OR: 0.83 [95% CI: 0.70–0.99]), and family history of CHD (OR: 0.81 [95% CI: 0.70–0.94]) were all inversely associated with discordantly high mean calcium and low calcium area. In contrast, the presence of nearly all modifiable traditional risk factors conferred a higher odds for the low mean calcium density and high calcium area group, with diabetes having the strongest magnitude association (OR: 2.23 [95% CI: 1.68–2.95]). Current cigarette smoking was associated with a 59% higher odds of concordantly high mean calcium density and plaque area but was not associated with discordant groups. The associations of BMI with low calcium density and high calcium area, and diabetes with high calcium density and low calcium area remained consistent when using peak calcium density (Supplemental Table 2).

A total of 197 ASCVD deaths occurred over a median follow-up period of 11.7 years (Table 3). The distribution of ASCVD deaths differed among the 4 groups, with similar event rates observed for individuals with high mean calcium density/low calcium area (0.3 per 1,000 person-years) and low mean calcium density/low calcium area (0.8 per 1,000 person-years) vs the ASCVD mortality rates of 2.3 and 2.8 events per 1,000 person-years for the low mean calcium density/high calcium area and high mean calcium density/high calcium area groups, respectively. A similar pattern was observed for peak calcium density and calcium area phenotypes (Supplemental Table 3). Kaplan-Meier curves for calcium density/area groups showed significant divergence ($P < 0.001$) as early as 7.5 years of follow-up

for ASCVD mortality (Figure 4). In contrast, there was overlap between concordant and discordant Kaplan-Meier curves when categorizing participants with peak calcium density values (Supplemental Figure 4).

In multivariable modeling, there were significant differences in ASCVD mortality risk among calcium area and mean calcium density phenotypes (Central Illustration, Table 4). Compared to persons with low calcium area/low mean calcium density, individuals with low calcium area/high mean calcium density had a 71% lower risk (HR: 0.29 [95% CI: 0.09–0.95]) for ASCVD death after adjustment for the Agatston CAC score. In contrast, the concordant high calcium area and mean calcium density phenotype was associated with a 50% (HR: 1.50 [95% CI: 1.01–1.26]) higher ASCVD mortality risk, but this was not significant when considering the Agatston CAC score. No significant differences in risk for ASCVD mortality were observed across peak calcium density and calcium area groups (Supplemental Table 4). Type 3 (overall) *P* values for the 4-level CAC area/density concordance/discordance variables were consistently significant across all models when using mean calcium density but not peak calcium density.

Higher chi-square likelihood ratio statistics were observed when adding CAC area/density concordance/discordance to models that included either continuous or categorical measures of CAC (Table 5, Supplemental Table 5). However, higher magnitude improvements in the likelihood ratio chi-square statistic were observed when using mean calcium density versus peak calcium density in the 4-level definition of density/area discordance. Using the alternate discordance definition, discordantly lower mean calcium density (HR: 2.44 [95% CI: 1.21–4.94]) and peak calcium density (HR: 1.71 [95% CI:1.19–2.46]) relative to calcium area conferred higher risks of ASCVD mortality after adjusting for age, sex, and the Agatston CAC score (Supplemental Table 6).

DISCUSSION

In a sample of physician-referred primary prevention patients who underwent CAC scanning, we defined groups that placed approximately one-fifth of persons with prevalent CAC into phenotypes characterized by calcium area/density discordance. Furthermore, CAC area/density groups were associated with different risk factor burden, with lower BMI, normal blood pressure, and the absence of a family history of CHD conferring a higher likelihood for the low calcium area/high calcium density phenotype, whereas all modifiable risk factors except for cigarette smoking were positively associated with high calcium area and low calcium density. For a given CAC score, high CAC density relative to plaque area confers lower long-term ASCVD risk, likely serving as an imaging marker of biological resilience for lesion vulnerability.

The main clinical implication of our findings relates to the concept of risk refinement among persons with prevalent CAC, which ultimately may relate to the optimal intensity of preventive pharmacotherapies according to calcium density and area groups. The CAC Consortium represents a clinical referral-based sample rather than a population-based sample; therefore, our findings should be generalized to persons who have been referred by physicians to undergo CAC scans because of the presence of 1 or more traditional risk

factors. Independent of traditional risk factors and CAC score, we found that individuals with discordantly high mean calcium density (≥207 HU) and low calcified plaque area (<22 mm^2) had a 71% lower risk of ASCVD death compared to those with concordantly low mean calcium density and calcium area. In contrast, the low mean calcium density and high calcified plaque area group trended toward a 58% higher risk for ASCVD mortality. Thus, in the future, it may be reasonable to leverage and specifically quantify mean calcium density and/or recognize area/density discordance to help further guide precision in ASCVD risk assessment among primary prevention patients with prevalent CAC. This approach may be especially important in younger persons with prevalent CAC[14] to help inform utilization of the most optimal preventive therapies in younger patients who are not included in formal ASCVD risk calculators.[15]

Whereas several mean calcium density phenotypes were significantly associated with ASCVD mortality, peak calcium density phenotypes were not. Peak calcium density currently is used in the Agatston scoring algorithm to quantify CAC, which is expressed as the product of total calcified plaque area (mm^2) and a quantized peak calcium density weighting factor.[6] Although a detection threshold of 130 HU is used for both mean and peak calcium density, mean calcium density is a *composite* measure of low-attenuation lipid-rich and higher-attenuation plaque across all lesions, whereas peak calcium density only captures the highest attenuation value for a single fibrous and/or calcified plaque.[7] Thus, our results suggest that mean calcium density may be a more integrative measure of risk compared to peak calcium density, and that calcified plaque area is a predominant driver of elevated risk in the Agatston CAC score,[16] especially during the early development of atherosclerosis.

Although the presence of all traditional ASCVD risk factors except for current cigarette smoking was associated with high calcium area/low calcium density plaque, diabetes had the strongest association with this high-risk phenotype. In particular, the likelihood of low calcium density discordance was more than 2-fold higher in the presence of diabetes, independent of other risk factors. These results support the concept that diabetes is associated with a higher-risk atherosclerotic milieu and plaque phenotype that ultimately confers a worse mortality prognosis compared to other ASCVD risk factors.[17,18] Our findings build on current guidelines, including those recommended in 2020 by the National Lipid Association, which suggest that it is reasonable to obtain a CAC scan among persons with diabetes aged 30 to 39 years when there is uncertainty regarding the initiation of statin therapy in younger patients.[19]

Between 25% and 40% of persons with an intermediate calculated 10-year ASCVD risk had plaque area/calcium density discordance, which may have important implications for refining clinical risk assessment. Current American College of Cardiology/American Heart Association guidelines recommend CAC scoring for primary prevention patients with intermediate risk when there is uncertainty regarding the initiation of statin therapy.[2] However, it is possible that an individual with a CAC score of 50 that is driven predominantly by high mean calcium density has different short-term and long-term ASCVD risks compared to an individual with a CAC score of 50 that is due to predominantly high calcified plaque area.

The major strength of this study was the assessment of both mean and peak calcium density measures with ASCVD risk factors and mortality among nearly 11,000 primary prevention patients. Few previous studies have described and/or characterized calcium area and calcium density phenotypes; therefore, our study serves as a fundamental analysis in the modern understanding of the ASCVD implications of CAC testing. Likewise, we performed comprehensive and thorough multivariable analyses that controlled for both modifiable and non-modifiable risk factors when assessing the association between calcium area and calcium density groups with ASCVD mortality, which occurred over a median follow-up interval of more than 11 years. Future research work should focus on deriving a reliable and clinically reproducible definition of discordance. We performed sensitivity analyses defining this at a threshold of ±15% of the derived expected calcium density value for the current CAC Consortium sample. This analysis was overall consistent with the main study results and showed a significantly higher ASCVD mortality risk for individuals with discordantly low calcium density relative to area. There was also a trend toward statistical significance for individuals with high calcium density relative to area, suggesting that the general concept of density/area discordance is likely to improve ASCVD risk stratification as subsequent studies continue to refine the exact quantitative definition of calcium discordance.

STUDY LIMITATIONS.

First, our study consisted nearly entirely of participants of Caucasian ethnicity, and a low proportion of women were included; therefore, future studies with more diverse samples are required to understand the relationship between calcium area/density discordance on ASCVD risk. One major driver for the potential sex homogeneity may be that women are more likely to develop thoracic aorta calcium before CAC,[20] so fewer women with prevalent CAC were available for inclusion in the current sample. Implementation and outcomes research is needed to address the more generalized problem of lower CAC scan access and utilization among minority communities and those of lower socioeconomic status.[21] Accordingly, our definition of discordance is purely dependent on our included sample of participants, so area/density thresholds will expectedly be different in samples with more or less coronary artery disease. As such, there was a small number of events in certain calcium area/density groups, such as those with discordantly high mean calcium density. We sought to minimize this limitation by performing sensitivity analyses using an alternative definition of discordance based on expected mean and peak calcium density values. Further work will be needed to define a reproducible general definition of discordance, preferably using coronary CT angiography rather than noncontrast CT, which can be used across cardiology practice. Furthermore, although imprecisions in ASCVD mortality outcome ascertainment are also important to consider, this limitation is universal to all national death statistics in the United States that involve ASCVD death as an outcome. The method of ASCVD death adjudication performed in the CAC Consortium through death certificates was achieved by the Centers for Disease Control and Prevention and their services provided in the United States. Moreover, the measurement of ASCVD risk factors and CAC scoring occurred contemporaneously; therefore, ORs reflect cross-sectional associations, and conclusions regarding temporal relationships may be difficult to ascertain. Although our results adjusted for lipid-lowering therapy, the CAC Consortium did not collect detailed data on the intensity and initiation of adjacent pharmacotherapies, including blood pressure–

and glucose-lowering agents. Lastly, calcium plaque area and peak calcium density values in the current study were back-calculated because raw image files were not available for re-reading.

CONCLUSIONS

Independent of Agatston CAC score, individuals with high mean calcium density and low calcium area have a low long-term ASCVD risk compared to persons with low mean calcium density and low calcium area. In contrast, persons with low mean calcium density and high calcium area have a substantially elevated risk of ASCVD mortality, which is similar and at times higher than in those with concordantly high calcium area and mean calcium density. Overall, these results suggest that the presence of calcium area/density discordance may be important for clinical risk stratification to differentiate lesion vulnerability among primary prevention patients with prevalent CAC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CAC	coronary artery calcium
CHD	coronary heart disease
CT	computed tomography
OR	odds ratio

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Approximately one-fifth of primary prevention patients with prevalence CAC have calcium area/density discordance. Female sex, lower BMI, normal blood pressure, and an absent family history of CHD were significantly associated with high calcium density discordance, whereas diabetes was most strongly associated with high calcium area and low calcium density. For a given CAC score, high calcium density relative to plaque area confers low long-term ASCVD risk, suggesting that the presence of calcium area/density discordance may be important for clinical risk stratification and an imaging marker of biological resilience for lesion vulnerability.

TRANSLATIONAL OUTLOOK:

Future prospective studies in more diverse patient populations are required to comprehensively define the temporal relationship of calcium area/density discordance with upstream risk factors and long-term ASCVD risk.

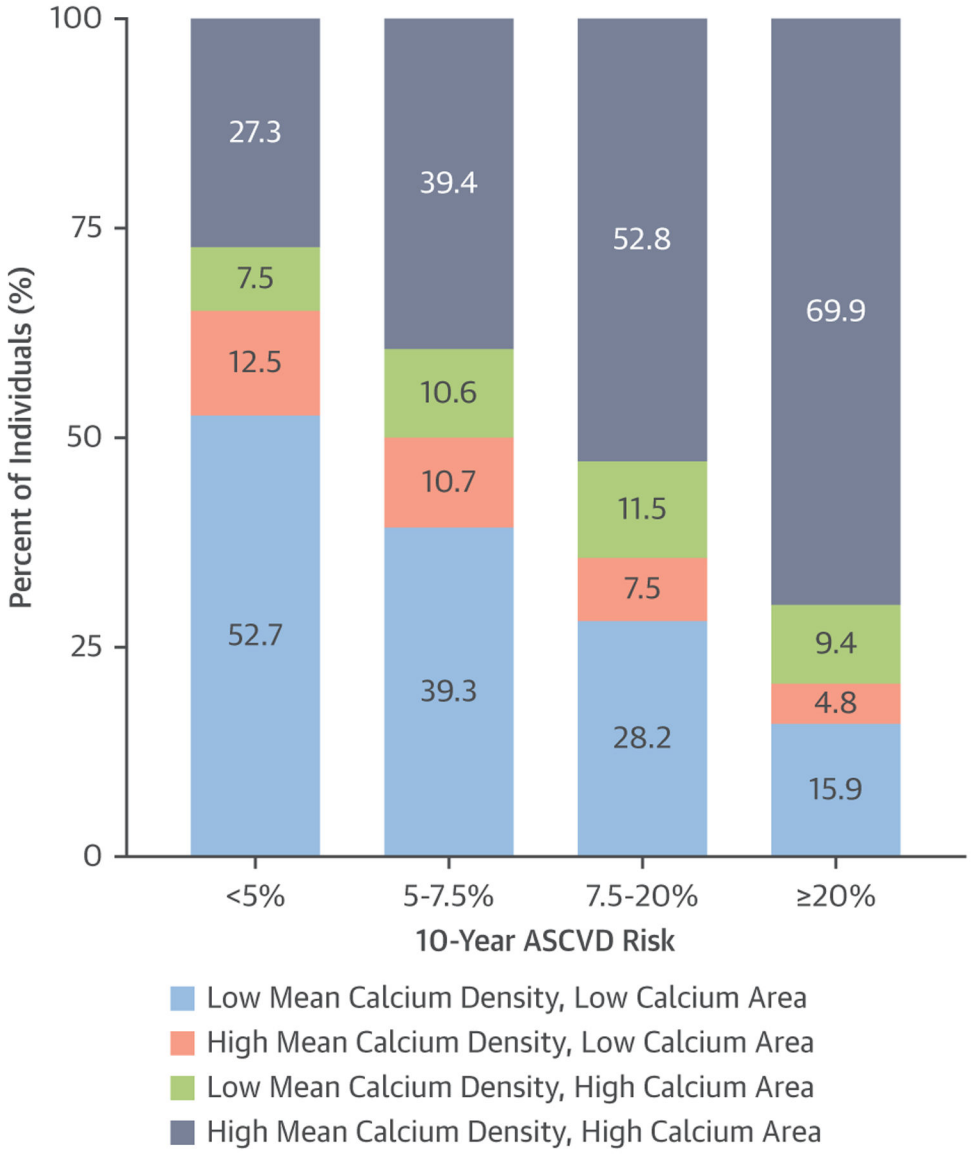


FIGURE 1. Distribution of CAC Scores Among Persons With Incident CAC

The average 10-year atherosclerotic cardiovascular disease (ASCVD) risk was 5.9% among all primary prevention patients with prevalent coronary artery calcium (CAC). Individuals who had low mean and peak calcium density with high calcium area had the highest calculated 10-year risk among discordant groups. Approximately 1 in 5 persons with borderline to intermediate ASCVD risk had discordance between calcium density and plaque area values.

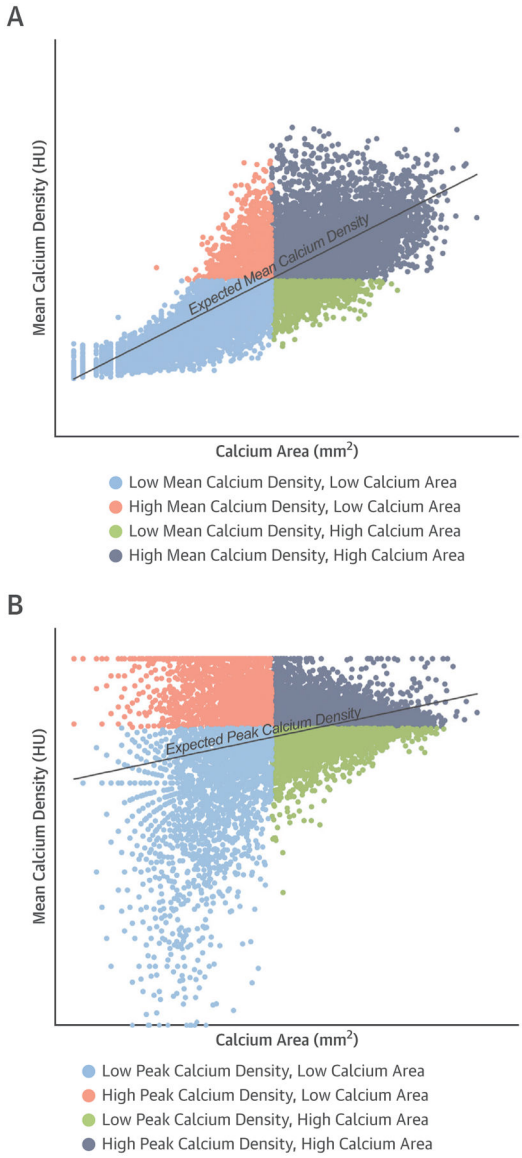


FIGURE 2. Observed vs Expected Mean and Peak Calcium Density Values, Dichotomized by Median Cutpoints for Calcium Area and Density

Distribution of concordant and discordant calcium area-density groups differed when using mean **(A)** versus peak **(B)** calcium density values.

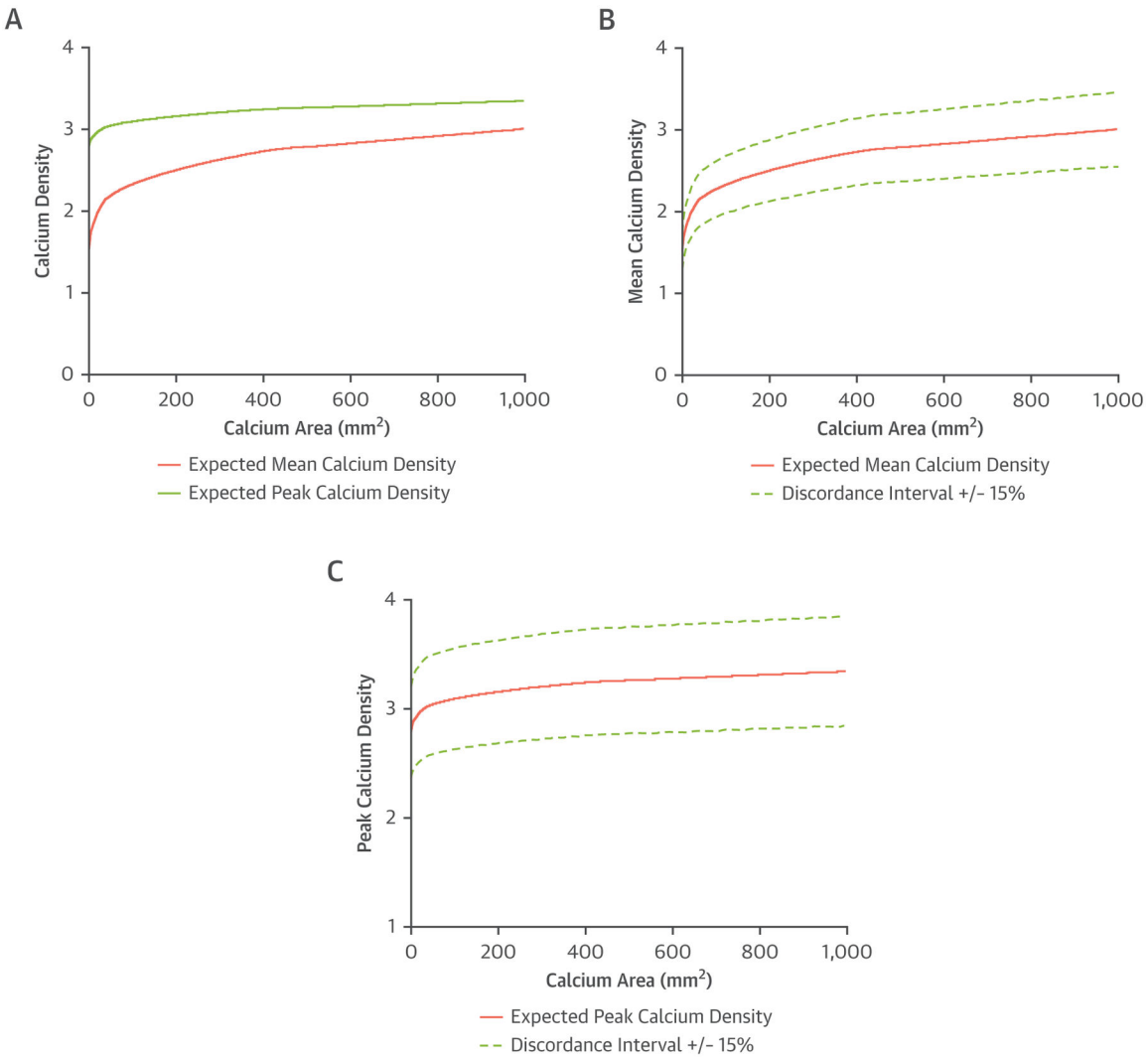


FIGURE 3. Mean and Peak Calcium Density as a Function of Age, Sex, and Calcium Area

Distribution of concordant and discordant calcium area-density **(A)** groups differed when using mean **(B)** vs peak calcium **(C)** density values.

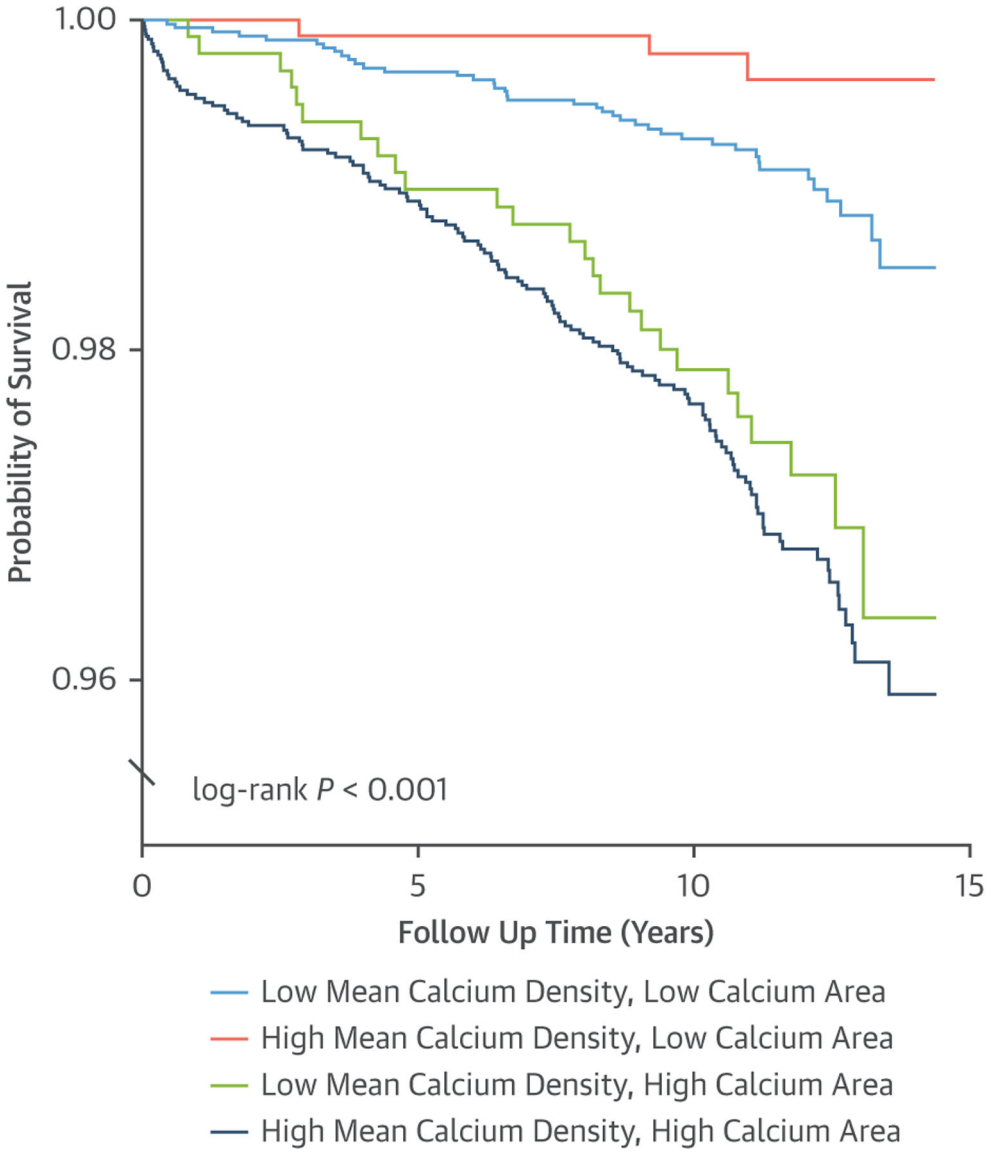
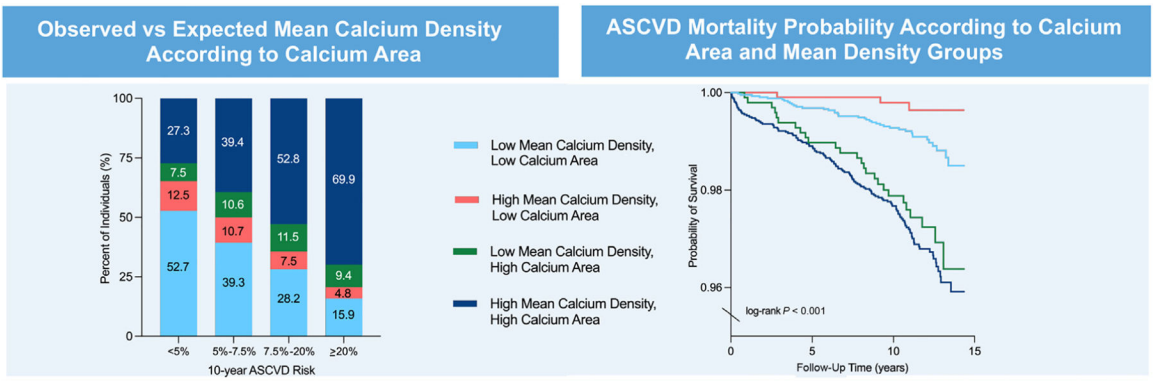


FIGURE 4. Kaplan-Meier Plots for ASCVD Mortality Survival Probability According to Mean Calcium Density and Coronary Plaque Phenotypes

Kaplan-Meier curves showed significant divergence ($P < 0.001$) as early as 2.5 years follow-up for ASCVD mortality, particularly for persons with high mean calcium density/low calcium area and low mean calcium density/low calcium area. Abbreviation as in Figure 1.



Association of Coronary Calcium Area and Mean Calcium Density with ASCVD Mortality

	Model 1*		Model 2**	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Low Mean Calcium Density, Low Calcium Area	Ref.	-	Ref.	-
High Mean Calcium Density, Low Calcium Area	0.30 (0.09-0.97)	0-04	0.29 (0.09-0.95)	0.04
Low Mean Calcium Density, High Calcium Area	1.58 (0.92-2.71)	0-10	1.58 (0.92-2.72)	0.10
High Mean Calcium Density, High Calcium Area	1.53 (1.03-2.26)	0-03	1.21 (0.80-1.83)	0.38

CENTRAL ILLUSTRATION. Discordance in Coronary Calcium Area and Mean Density on Atherosclerotic Cardiovascular Disease Mortality

Compared to persons with low mean calcium density and low calcium area, individuals with discordantly high mean calcium density relative to low calcium area had a 71% lower risk for atherosclerotic cardiovascular disease (ASCVD) death. In contrast, the concordant high mean calcium density and calcium area phenotype was associated with a 1.54-fold higher ASCVD mortality risk. *Adjusted for age, sex, race, cigarette smoking, BMI, hypertension, hyperlipidemia, diabetes, family history of CHD. **Adjusted for age, sex, race, cigarette smoking, BMI, hypertension, hyperlipidemia, diabetes, family history of CHD, and Agatston CAC score. BMI = body mass index; CAC = coronary artery calcium; CHD = coronary heart disease.

TABLE 1

Characteristics of 10,373 Primary Prevention Patients With Prevalent CAC, Stratified by Mean Calcium Density and Coronary Plaque Area

	All Participants (N = 10,373)	Low Mean Calcium Density, Low Calcium Area (n = 4,124)	High Mean Calcium Density, Low Calcium Area (n = 1,024)	Low Mean Calcium Density, High Calcium Area (n = 978)	High Mean Calcium Density, High Calcium Area (n = 4,212)	*P* Value[a]
Demographics						
Age, y	56.7 ± 9.2	53.6 ± 8.7	55.5 ± 8.5	57.2 ± 8.5	59.8 ± 8.9	<0.001
Women	24.4	26.4	36.5	15.6	21.3	<0.001
Ethnicity						0.24
White	96.7	96.5	97.3	96.5	96.8	
Asian	0.7	0.7	0.6	0.6	0.7	
Black	0.4	0.3	0.4	1.0	0.3	
Hispanic	0.3	0.5	0.3	0.1	0.2	
Other	1.9	2.0	1.4	1.8	2.0	
Subclinical atherosclerosis						
CAC, AU						
Median (Q1, Q3)	68 (16, 253)	10 (3, 25)	42 (31, 55)	127 (89, 215)	310 (155, 680)	<0.001
1–99	57.7	99.9	100.0	34.4	11.0	
100–399	25.0	0.1	0.0	58.0	48.1	
>400	17.3	0.0	0.0	7.6	40.9	
Mean calcium density, HU						
Median (Q1, Q3)	2.1 (1.7, 2.4)	1.7 (1.5, 1.8)	2.3 (2.2, 2.5)	1.9 (1.9, 2.0)	2.5 (2.3, 2.7)	<0.001
Mean ± SD	2.1 ± 4.9	1.7 ± 2.0	2.4 ± 2.7	1.9 ± 1.0	2.5 ± 3.6	<0.001
Total coronary calcium area, mm^2						
Median (Q1, Q3)	21.6 (5.3, 80.8)	3.6 (1.2, 8.4)	13.0 (8.8,17.1)	41.7 (29.2, 67.4)	98.4 (50.0, 218.0)	<0.001
Mean ± SD	81.6 ± 165.5	5.6 ± 5.4	13.0 ± 4.9	60.2 ± 51.9	178.2 ± 224.8	<0.001
ASCVD risk factors						
10-y ASCVD risk						
Median (Q1, Q3)	5.9 (3.1, 10.6)	4.2 (2.3, 7.8)	4.6 (2.5, 7.9)	7.1 (4.1, 11.7)	8.3 (4.5, 13.7)	<0.001
<5%	43.4	57.3	54.1	34.3	29.1	
5%−7.5%	16.8	16.6	18.0	18.8	16.3	
7.5%−20%	33.1	23.5	24.8	40.3	43.0	

	All Participants (N = 10,373)	Low Mean Calcium Density, Low Calcium Area (n = 4,124)	High Mean Calcium Density, Low Calcium Area (n = 1,024)	Low Mean Calcium Density, High Calcium Area (n = 978)	High Mean Calcium Density, High Calcium Area (n = 4,212)	*P* Value[a]
≥20%	6.7	2.7	3.2	6.6	11.5	
Body mass index, kg/m^2	28.9 ± 5.5	29.2 ± 5.7	27.8 ± 5.3	30.3 ± 5.8	28.5 ± 5.2	<0.001
Smoking	11.8	10.4	11.5	10.7	13.6	<0.001
Hypertension	28.0	24.0	21.7	34.5	32.1	<0.001
Hyperlipidemia	63.1	61.3	61.3	65.0	64.9	0.002
Lipid-lowering medication	24.8	20.7	19.6	29.0	29.0	<0.001
Diabetes	6.0	4.0	4.0	10.3	7.5	<0.001
Family history of CHD	51.5	52.7	47.2	50.8	51.6	0.02

Values are mean ± SD, %, or median (Q1, Q3), unless otherwise indicated.

[a]Analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, chi-square test for categorical variables.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease.

TABLE 2

Association of ASCVD Risk Factors With Mean Calcium Density and Coronary Plaque Area Phenotypes[a]

	High Mean Calcium Density, Low Calcium Area		Low Mean Calcium Density, High Calcium Area		High Mean Calcium Density, High Calcium Area	
	OR (95% CI)[b]	*P* Value	OR (95% CI)[b]	*P* Value	OR (95% CI)[b]	*P* Value
Age, per 10 y older	1.19 (1.09–1.30)	<0.001	1.85 (1.69–2.03)	<0.001	2.51 (2.36–2.66)	<0.001
Female	1.48 (1.27–1.74)	<0.001	0.35 (0.28–0.43)	<0.001	0.44 (0.39–0.49)	<0.001
Current cigarette smoking	1.13 (0.90–1.41)	0.30	1.14 (0.90–1.45)	0.28	1.59 (1.37–1.84)	<0.001
Body mass index, per 5 kg/m^2 higher	0.81 (0.76–0.87)	<0.001	1.16 (1.09–1.24)	<0.001	0.91 (0.87–0.96)	<0.001
Hypertension	0.83 (0.70–0.99)	0.04	1.38 (1.17–1.63)	<0.001	1.22 (1.10–1.37)	<0.001
Hyperlipidemia	0.99 (0.86–1.15)	0.92	1.26 (1.08–1.47)	0.004	1.25 (1.13–1.37)	<0.001
Diabetes	1.15 (0.80–1.66)	0.44	2.23 (1.68–2.95)	<0.001	1.78 (1.43–2.21)	<0.001
Family history of CHD	0.81 (0.70–0.94)	0.004	1.17 (1.01–1.36)	0.04	1.27 (1.16–1.41)	<0.001

[a]Adjusted for age, sex, race, smoking, body mass index, hypertension, hyperlipidemia, diabetes, and family history of CHD. Odds ratios (ORs) for race are not presented due to cell size limitations and unstable point estimates.

[b]Reference phenotype is low mean calcium density, low coronary calcium area.

Other abbreviations as in Table 1.

TABLE 3

Absolute ASCVD Mortality, Stratified by Mean Calcium Density and Coronary Plaque Area

	ASCVD Deaths	ASCVD Mortality Rate (per 1,000 person-years)
All	197	1.7 (1.4–1.9)
Low mean calcium density, low calcium area	40	0.8 (0.6–1.1)
High mean calcium density, low calcium area	3	0.3 (0.0–0.5)
Low mean calcium density, high calcium area	26	2.3 (1.4–3.2)
High mean calcium density, high calcium area	128	2.7 (2.2–3.2)

Values are n or HR (95% CI).

Abbreviation as in Table 1.

TABLE 4

Association of Mean Calcium Density and Coronary Plaque Area Groups With ASCVD Mortality

	ASCVD Mortality		
	HR (95% CI)	***P* Value**	**Overall *P* Value[a]**
Model 1[b]			
Low mean calcium density, low calcium area	Ref.	–	0.01
High mean calcium density, low calcium area	0.30 (0.09–0.98)	0.04	
Low mean calcium density, high calcium area	1.54 (0.90–2.65)	0.12	
High mean calcium density, high calcium area	1.50 (1.01–2.22)	0.04	
Model 2[c]			
Low mean calcium density, low calcium area	Ref.	–	0.04
High mean calcium density, low calcium area	0.29 (0.09–0.95)	0.04	
Low mean calcium density, high calcium area	1.55 (0.90–2.66)	0.12	
High mean calcium density, high calcium area	1.20 (0.79–1.81)	0.39	

[a]Type 3 *P* value testing the significance of each concordance/discordance phenotype with all other phenotypes in the model.

[b]Adjusted for age, sex, race, cigarette smoking, body mass index, hypertension, hyperlipidemia, diabetes, family history of CHD, and lipid-lowering medications.

[c]Adjusted for age, sex, race, cigarette smoking, body mass index, hypertension, hyperlipidemia, diabetes, family history of CHD, lipid-lowering medications, and Agatston CAC score.

Ref. = reference; other abbreviations as in Table 1.

TABLE 5

Model Performance Utilizing Different CAC Metrics

Model[a]	Likelihood Ratio Chi-Square Statistic	*P* Value
Continuous CAC	268.4	
Continuous CAC + mean density-area concordance/discordance	270.1	<0.001
Categorical CAC	271.1	
Categorical CAC + mean density-area concordance/discordance	280.5	<0.001

[a]All models also include age, sex, race, cigarette smoking, body mass index, hypertension, hyperlipidemia, diabetes, family history of CHD, and lipid-lowering medications.

Abbreviations as in Table 1.