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Authors
Criqui, Michael H
Denenberg, Julie O
Ix, Joachim H
et al.

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Calcium Density of Coronary Artery Plaque and Risk of Incident Cardiovascular Events

Michael H. Criqui, MD, MPH,
Department of Family and Preventive Medicine, University of California, San Diego, La Jolla; Department of Medicine, University of California, San Diego, La Jolla

Julie O. Denenberg, MA,
Department of Family and Preventive Medicine, University of California, San Diego, La Jolla

Joachim H. Ix, MD, MAS,
Department of Medicine, University of California, San Diego, La Jolla

Robyn L. McClelland, PhD,
Department of Biostatistics, University of Washington, Seattle

Christina L. Wassel, PhD,
Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

Dena E. Rifkin, MD, MS,
Department of Medicine, University of California, San Diego, La Jolla

Jeffrey J. Carr, MD, MS,
Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee

Corresponding Author: Michael H. Criqui, MD, MPH, Department of Family and Preventive Medicine, University of California, San Diego, 9500 Gilman Dr, MC 0607, La Jolla, CA 92093-0607 (mcriqui@ucsd.edu).

Author Contributions: Dr Criqui had full access to all of thedata in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Criqui, Denenberg, Allison, Wassel, Ix.
Acquisition of data: Criqui, Carr, Budoff.
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Matthew J. Budoff, MD, and
Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles

Matthew A. Allison, MD, MPH
Department of Family and Preventive Medicine, University of California, San Diego, La Jolla

Abstract

Importance—Coronary artery calcium (CAC), measured by computed tomography (CT), has strong predictive value for incident cardiovascular disease (CVD) events. The standard CAC score is the Agatston, which is weighted upward for greater calcium density. However, some data suggest increased plaque calcium density may be protective for CVD.

Objective—To determine the independent associations of CAC volume and CAC density with incident CVD events.

Design, Setting, and Participants—Multicenter, prospective observational MESA study (Multi-Ethnic Study of Atherosclerosis), conducted at 6 US field centers of 3398 men and women from 4 race/ethnicity groups; non-Hispanic white, African American, Hispanic, and Chinese. Participants were aged 45-84 years, free of known CVD at baseline, had CAC greater than 0 on their baseline CT, and were followed up through October 2010.

Main Outcomes and Measures—Incident coronary heart disease (CHD) and all CVD events

Results—During a median of 7.6 years of follow-up, there were 175 CHD events and an additional 90 other CVD events for a total of 265 CVD events. With both *ln*CAC volume and CAC density scores in the same multivariable model, the *ln*CAC volume score showed an independent association with incident CHD, with a hazard ratio (HR) of 1.81 (95% CI, 1.47-2.23) per standard deviation (SD = 1.6) increase, absolute risk increase 6.1 per 1000 person-years, and for CVD an HR of 1.68 (95% CI, 1.42-1.98) per SD increase, absolute risk increase 7.9 per 1000 person-years. Conversely, the CAC density score showed an independent inverse association, with an HR of 0.73 (95% CI, 0.58-0.91) per SD (SD = 0.7) increase for CHD, absolute risk decrease 5.5 per 1000 person-years, and an HR of 0.71 (95% CI, 0.60-0.85) per SD increase for CVD, absolute risk decrease 8.2 per 1000 person years. Area under the receiver operating characteristic curve analyses showed significantly improved risk prediction with the addition of the density score to a model containing the volume score for both CHD and CVD. In the intermediate CVD risk group, the area under the curve for CVD increased from 0.53 (95% CI, 0.48-0.59) to 0.59 (95% CI, 0.54-0.64), $P = .02$.

Conclusions and Relevance—CAC volume was positively and independently associated with CHD and CVD risk. At any level of CAC volume, CAC density was inversely and significantly associated with CHD and CVD risk. The role of CAC density should be considered when evaluating current CAC scoring systems.

The standard methodology for scoring the amount of coronary artery calcium (CAC) from computed tomography (CT) scans is the Agatston method,[1] and software that applies this semiautomated scoring system is widely used. The Agatston score is the product of the within-slice CAC plaque area and a plaque-specific density factor of 1, 2, 3, or 4, summed

for all cardiac CT slices. The density factor reflects increasing categories of Hounsfield units (Hu). Thus, the Agatston score is weighted upward for greater CAC density.

Despite the strong predictive value of CAC for cardiovascular disease (CVD),[2] there has been little rigorous comparison of what specific measure of CAC is most predictive, or whether upweighting a CAC score for greater density is appropriate.

An increasing body of evidence suggests that greater calcium density in plaques is associated with decreased CVD risk. Several studies comparing acute heart disease with stable coronary heart disease (CHD) have shown denser calcified plaque in stable CHD.[3-7] A recent study of CT angiography showed that the majority of individuals with CAC had calcified plaques, and that the CHD risk in this group was markedly lower than in patients with some or all plaques uncalcified.[8] Randomized trials of statin therapy have reported a consistent tendency for the statin group to have more CAC progression,[9,10] consistent with stabilizing plaque.[11]

To test the role of CAC density in CVD risk prediction, we used data from the MESA trial (Multi-Ethnic Study of Atherosclerosis) and derived a formula using the individual Agatston scores and the volume scores to create a per-participant CAC density score. We then evaluated the independent associations of the volume and density scores with risk of incident CVD events. We hypothesized that at any given volume of CAC plaque burden, greater CAC density would be inversely related to incident CVD events.

Methods

Study Participants

MESA is a prospective cohort study of individuals aged 45 to 84 years, who were free of known clinical CVD at baseline. First examinations were conducted from 2000 to 2002 at 6 field centers: Baltimore, MD; Chicago, IL; Los Angeles, CA; New York, NY; St Paul, MN; and Winston-Salem, NC. The study design, recruitment methods, examination components, and data collection have been described[12] and are available at http://www.mesa-nhlbi.org. MESA was approved by each of the institutional review boards at the participating centers, and all participants provided written informed consent.

Risk Factor Assessment

Standardized questionnaires were used to obtain information about participant demographics, medical history, and medication usage including current blood pressure and cholesterol-lowering medications. Resting blood pressure was measured in a standardized manner. Blood measures obtained after a 12-hour fast included glucose, total cholesterol, and high-density lipoprotein cholesterol (HDL-C). Diabetes was defined as a fasting blood glucose level greater than 125 mg/dL or use of hypoglycemic medications. Smoking status was classified as never, former, or current use of cigarettes. The variables of age, sex, total cholesterol, HDL-C, systolic blood pressure, antihypertensive medication use, current smoking, and diabetes status were used to calculate the general Framingham Risk Score (FRS), which is a validated score for predicting CHD and other CVD events.[13]

CAC Measurement

The methodology for acquisition and interpretation of the CAC scans, as well as the reproducibility of the readings, has been reported previously.[14] Scanning centers assessed CAC using either an electron-beam CT scanner (Chicago, Los Angeles, and New York) or a multidetector CT system (Baltimore, St Paul, and Winston-Salem). All scanners were cardiac gated. Slice thickness was 3mm using the electron-beam CT scanners and 2.5 mm using the multidetector CT scanners. Each participant was scanned twice for CAC, which was measured during the same examination using the same site-specific scanners. CAC scans were read centrally at the MESA CT Reading Center and were brightness adjusted using a standard phantom to control for any scanner differences.[15] In addition to the Agatston score, a volume score was also calculated.[16] To qualify as a calcified plaque using CAC scoring, the plaque calcium density, measured in Hounsfield units, must be 130 Hu or higher. The Agatston scoring method for CAC measures each such discrete plaque area in square millimeters. Each discrete plaque area is then multiplied by 1, 2, 3, or 4, depending on the highest density measurement in Hu anywhere in the plaque. Plaques with a maximum density of 130 to 199 Hu are multiplied by 1, those with 200 to 299 Hu by 2, those with 300 to 399 by 3, and those with 400 Hu or greater by 4. These plaque-specific scores are then summed for all slices of the heart to give the Agatston score, which is thus an area score upweighted for increased plaque density. The participants received their Agatston score, were told that the presence of CAC represented hardening of the coronary arteries, and told of their amount of CAC (less than average, average, or greater than average).

The MESA database does not contain the individual area score for each participant. Thus, to calculate the individual area scores, the volume scores in cubic millimeters were divided by the appropriate slice thickness, 2.5 mm or 3 mm, resulting in the area score in square millimeters. The Agatston score was then divided by the area score and the quotient was the average CAC density score for each participant. The formula was: Agatston score/area score = density score. The density score thus ranged from 1 to 4 and reflected the average plaque density for all CT slices from that participant.

CVD and Mortality Follow-up

Follow-up began at the time of the baseline examination and continued until the first CVD event, death, loss to follow-up, or the ninth follow-up call, which took place between May 2008 and October 2010. Details of CVD event ascertainment have been published.[17] For this report, we analyzed 2 separate end points: (1) hard CHD, defined as myocardial infarction, resuscitated cardiac arrest, or CHD death; and (2) hard CVD, defined as hard CHD, stroke, or stroke death. Softer end points such as angina and revascularization were not included in these analyses since such outcomes could have been biased by participants' knowledge of their CAC scores at baseline.

Statistical Analysis

Spearman correlation coefficients were used to evaluate the degree of association between the Agatston, volume, area, and density scores. Cox proportional hazard regression was used to estimate hazard ratios (HRs) for time to CHD and CVD events for both the volume score and the density score, adjusting for covariates. Cox models were run adjusting initially for

age, sex, and ethnicity, and then additionally for the general FRS, which includes age, HDL-C, total cholesterol, systolic blood pressure stratified by treatment, smoking, and diabetes. In addition, we included a term for statin use at baseline. We included race/ethnicity in the model since MESA had a diverse cohort. We defined statistical significance as a 2-tailed α of less than 0.05. We performed tests for nonproportional hazards using Schoenfeld residuals. All results were nonsignificant.[18]

The incremental value of the CAC density score for the prediction of CVD events was evaluated by the increase in the area under the receiver operating characteristic curve (AUC [area under the curve]).[19] Analyses were performed using STATA version 10.1 (StataCorp, LP) statistical software and SAS version 9.2 (SAS Institute, Inc). The natural logarithm (*ln*) of the Agatston, area, and volume scores were used since previous analyses in MESA have shown log linear relationships between CAC and CVD risk.[20]

Results

Because this analysis was focused on the predictive value of different components of calcified plaques, of necessity we restricted analyses to the 3398 MESA participants (1964 [58%] men and 1434 [42%] women) with a CAC score greater than zero at baseline. The MESA has previously reported that individuals without detectable CAC had very low rates of incident CHD.[21] The race/ethnicity distribution was 44% non-Hispanic white, 24% African American, 20% Hispanic, and 12% Chinese. We excluded 4 individuals who were lost to follow-up, leaving 3394 for analysis. The median follow-up was 7.6 years with a mean of 7.0 years. There were a total of 23 204 person-years of follow-up.

Table 1 shows CVD risk factors, CAC scores, and CHD and CVD out comes in the study cohort by quartile of volume score. The mean age was 66 years. Age, proportion of men, and proportion of non-Hispanic white participants increased across volume scores, as did blood pressure treatment, systolic blood pressure, diabetes, statin use, and the general FRS. The volume score, by definition, is between 2.5 and 3 times the area score, since it is the area score multiplied by the CT slice thickness. The density score was lower in the first quartile of volume but similar in the upper 3 quartiles. During follow-up, there were 175 CHD events and 90 other CVD events totalling 265 CVD events. CHD and CVD rates increased monotonically across the 4 quartiles of volume score.

Table 2 shows the same data by quartile of density score. The density score can theoretically range between 1 and 4. The actual range was quite close, 0.83 to 4.00, varying slightly from expected due to minor software differences for measuring the Agatston and volume scores. The fourth quartile of density showed the lowest proportion of non-Hispanic white participants and the highest percentage of Chinese. Age and the general FRS were lower in the first quartile of density, but similar across quartiles 2, 3, and 4. Agatston, area, and volume scores increased across quartiles 1 2, and 3 of density, but were slightly lower in the fourth quartile compared with the third. CHD and CVD rates increased across the first 3 quartiles of density but were much lower in quartile 4.

Table 3 shows a Spearman correlation matrix for the various CAC scores. The Agatston, volume, and area scores were all highly correlated (coefficient for bivariate analysis, r >0.99). The density score was positively correlated with the other 3 scores, but only moderately, with correlations of 0.623, 0.560, and 0.539 for the Agatston, volume, and area scores respectively. The somewhat higher correlation of the density score with the Agatston score reflects the density upweighting of the Agatston score.

Table 4 shows the associations of the 4 CAC scores individually (*ln*Agatston, *ln*volume, *ln*area, and density) for both CHD and CVD, using Cox proportional hazard models with the hazard ratios (HRs) reflecting 1 standard deviation of the independent variable. The standard deviations for *ln*Agatston, *ln*volume, *ln*area, and density were 1.8, 1.6, 1.6, and 0.7 respectively. *P* values and 95% CIs are shown. The values at the top of the table are adjusted for age, sex, and race/ethnicity, and at the bottom of the table are fully adjusted for race/ethnicity, the general FRS, and statin use. One person was missing data on statin use, leaving 3393 for these analyses. In the age, sex, and ethnicity-adjusted models, the Agatston, volume, and area scores all showed similar and significant associations for both outcomes. The similarity for the associations reflects the high correlation (r >0.99) of these 3 CAC scores. The associations were somewhat stronger for CHD than for CVD. The density score showed no association for CHD or for CVD. When additionally adjusted for the general FRS and statin use, associations were modestly attenuated for the Agatston, volume, and area scores. The associations for the density score were essentially unchanged.

Table 5 shows the results for fully adjusted Cox models with the volume score and density score placed in the same models, and with the HRs again reflecting a 1 standard deviation difference. With the density score included in the models, the HRs for the volume score increased for both end points from 1.52 (95% CI, 1.29-1.80) to 1.81 (95% CI, 1.47-2.23), absolute risk increase 6.1 per 1000 person-years for CHD and from 1.38 (95% CI, 1.21-1.58) to 1.68 (95% CI, 1.42-1.98), absolute risk increase 7.9 per 1000 person-years, for CVD, and remained significant. The density score became significantly and inversely associated with CHD (HR, 0.73; 95% CI, 0.58-0.91), absolute risk decrease 5.5 per 1000 person-years, and with CVD (HR, 0.71; 95% CI, 0.60-0.85), absolute risk decrease 8.2 per 1000 person-years. Thus, the strength of the volume score was increased when accounting for the density score in the model, and at any given CAC volume score, a 1 standard deviation higher CAC density score was associated with a significantly lower risk for CHD and CVD. Additional models including interaction terms for the density score with sex and race/ethnicity revealed no significant interactions. The *P* values for interaction for CHD and CVD respectively were 0.50 and 0.55 for sex and 0.71 and 0.59 for race/ethnicity. Additional stratified analyses showed an inverse density association at both high and low CAC volume levels, although somewhat more so at lower volume levels. However, CAC volume × CAC density interaction terms were not significant for either CHD (P = .80) or CVD (P = .95). The general FRS was independently associated with both CHD and CVD. Statin use was inversely but nonsignificantly associated with both CHD and CVD. None of the race/ethnicity associations were significant.

The Figure shows the associations of volume score and density score in quartiles with CHD (panel A) and CVD (panel B). Data are adjusted for the general FRS, race/ethnicity, and

statin use. Volume score quartiles are adjusted for the density score and the density score quartiles for the *ln*(volume score). The cut points for the volume score quartiles were 24.5, 85.2 and 273.4 mm^3, and the cut points for the density score quartiles were 2.23, 2.80, and 3.18 Hu category units. HRs with 95% CIs are shown, plotted on a log scale. There was a stepwise increase in CHD risk by quartile of volume score, with HRs of 1.99 (95% CI, 1.08-3.67), 3.10 (95% CI, 1.68-5.73), and 4.50 (95% CI, 2.35-8.61) compared with the first quartile. There was a stepwise decrease in risk across the density score quartiles, with HRs of 0.89 (95% CI, 0.53-1.47), 0.79 (95% CI, 0.45-1.37), and 0.50 (95% CI, 0.27-0.90). For CVD, the left side of panel B shows a similar stepwise increase in CVD risk by volume score quartiles, with HRs of 1.51 (95% CI, 0.95-2.39), 2.27 (95% CI, 1.43-3.62), and 3.36 (95% CI, 2.05-5.51). For the density score quartiles, a similar stepwise decrease is shown with HRs of 0.76 (95% CI, 0.51-1.13), 0.66 (95% CI, 0.43-1.02), and 0.47 (95% CI, 0.30-0.75).

Table 6 shows the AUC analyses. The base model contained the general FRS, race/ethnicity, and statin use. For CHD, the AUC for the base model was 0.668 (95% CI, 0.629-0.726), which increased to 0.700 (95% CI, 0.664-0.735; $P = .01$) by adding the volume score, and to 0.711 (95% CI, 0.675-0.746; $P = .05$) with further addition of the density score. For CVD, the AUC for the base model was 0.669 (95% CI, 0.637-0.700), which increased to 0.691 (95% CI, 0.661-0.721; $P = .01$) by adding the volume score, and to 0.704 (95% CI, 0.675-0.734; $P = .02$) by further addition of the density score. In comparison, addition of the Agatston score to the base model improved the AUC to only 0.696 (95% CI, 0.660-0.732; $P = .02$) for CHD and only 0.688 for CVD (95% CI, 0.658-0.718; $P = .02$). Additional AUC analyses were performed separately in annual CVD risk groups: low (0%-0.99%,), medium (1.0%-1.99%), and high (≥2.0%). For CHD, numbers were insufficient for these analyses. For CVD, the AUC increase with the density score added did not provide significant additional discrimination in either the low ($P = .41$; n = 1859) or high ($P = .74$; n = 501) risk groups. For the intermediate-risk group (n = 1021), where incremental risk prediction may be most clinically relevant, the AUC for CVD increased from 0.532 (95% CI, 0.477-0.587) to 0.590 (95% CI, 0.538-0.642; $P = .017$), with addition of the density score. In the intermediate-risk group 908 participants did not have CVD events and 113 participants did. In those with events, addition of the density score correctly reclassified 179 individuals to the low-risk group and incorrectly classified 85 individuals to the high-risk group, for a net correct reclassification of 94 individuals (10.4%). In participants who had CVD events, addition of the density score correctly classified 14 to the high-risk group and incorrectly classified 10 of them to the low-risk group, for a net correct reclassification of 4 individuals (3.5%).

Discussion

Measurement of CAC has consistently proven to be the best subclinical CVD measure in terms of improving CHD risk prediction.[2,] Table 4 shows that there are only minor differences in CHD and CVD risk prediction with different CAC scoring algorithms due to the very high correlation of the Agatston score with other CAC scores (Table 3). However, the data here suggest that the Agatston area or volume scores alone are not optimal measures

to use in CVD risk prediction since the demonstrated inverse association with density also needs consideration.

Measurement of CAC appears particularly useful in individuals at intermediate CVD risk, generally considered to be in the range of 1.0% to 2.0% per year, in whom treatment decisions may be influenced by improved CVD risk prediction based on measuring CAC.[2] In these data, stratified analysis by CVD risk group showed that the largest improvement in the AUC with the addition of the density score was in the intermediate-risk group.

The data presented here—that CAC density was inversely related to CVD events at a given CAC volume and that CAC volume was more predictive when adjusted for CAC density—are novel observations. Our data are consistent with numerous prior observations including the modest correlation between CAC and coronary stenoses,[1,22] autopsy data showing that although there was a good correlation between calcium area (not weighted for density) and plaque area, there was a poor correlation between residual histologic lumen area and calcium area,[23] and studies showing that patients with stable angina were more likely to have calcified and less likely to have echolucent plaques than patients with unstable angina.[3-7] Also consistent with our data are clinical trials of statin therapy vs placebo reporting that CAC progression using the Agatston score was greater in the statin group than in the placebo group.[9,10] Statins appear to have their salutary effects on CVD risk by reducing the lipid core in unstable plaque,[11] and statin therapy may increase calcium density in such plaques, along with a more favorable prognosis. Similarly, a recent report from MESA showed that favorable changes in LDL-C were correlated with a significant increase in CAC progression.[24] A recent report of 4425 referred patients evaluated with both CT for CAC and CT angiography showed that 1021 had only calcified plaque, 183 had only noncalcified plaque, and 685 had both calcified and noncalcified plaque. The incidence of CVD events after a median follow-up of 3 years in these 3 groups was 5.5%, 22.7%, and 37.7%, respectively.[8] These results suggest that higher calcium density of plaques may be protective.

Results of other CAC scoring systems have been reported, showing predictive capability similar to or slightly better than the Agatston score.[25-28] Importantly and to our knowledge, no CAC score has previously evaluated the relationship of plaque calcium density with CVD risk.

CAC is present in more than half of middle-aged US residents and by age 70, the probability of CAC exceeds 90%.[29-31] Many patients have had serial CAC scans to evaluate progression. The use of the Agatston score in assessing CAC progression is problematic since an increase in CAC could be due to an increase in volume, an increase in density, or both.

Our study has limitations. Although the data suggest that CAC density at a given CAC volume is independently and inversely associated with risk, and thus should to be assessed along with plaque volume, the assessment of density was crude, using an arbitrary 4-point scale rather than a continuous Hu scale. The highest score (4) was for densities of 400 Hu or greater when in fact, CAC density can be greater than 3000 Hu. In addition, for each plaque,

the maximum density noted (in Hounsfield units) was used to define the multiple, and thus some plaques that were primarily low density, and possibly at increased risk, were rated as maximum density. However, such misclassification would have produced an underestimate of the inverse association with denser CAC and so this association is likely underestimated in our data. Participants were told their CAC scores at baseline, which could have led to increased intervention in those with high CAC scores. However, we minimized any ascertainment bias by using hard CHD and hard CVD as end points for analysis. The AUC values observed for CAC in this study are modestly lower than previous reports because of the population considered here, namely participants with CAC greater than 0. The distinction between individuals with and without CAC is a large component of the predictive ability of CAC and thus, exclusion of individuals with CAC equal to 0 results in lower predictive measures. However, the importance of plaque density is clearly only a relevant concept for individuals with some measured plaque and thus, our analysis was restricted to this population.

Conclusions

In conclusion, CAC volume was positively and independently associated with CHD and CVD risk. At any level of CAC volume, CAC density was inversely and significantly associated with CHD and CVD risk. The role of CAC density should be considered when evaluating current CAC scoring systems.

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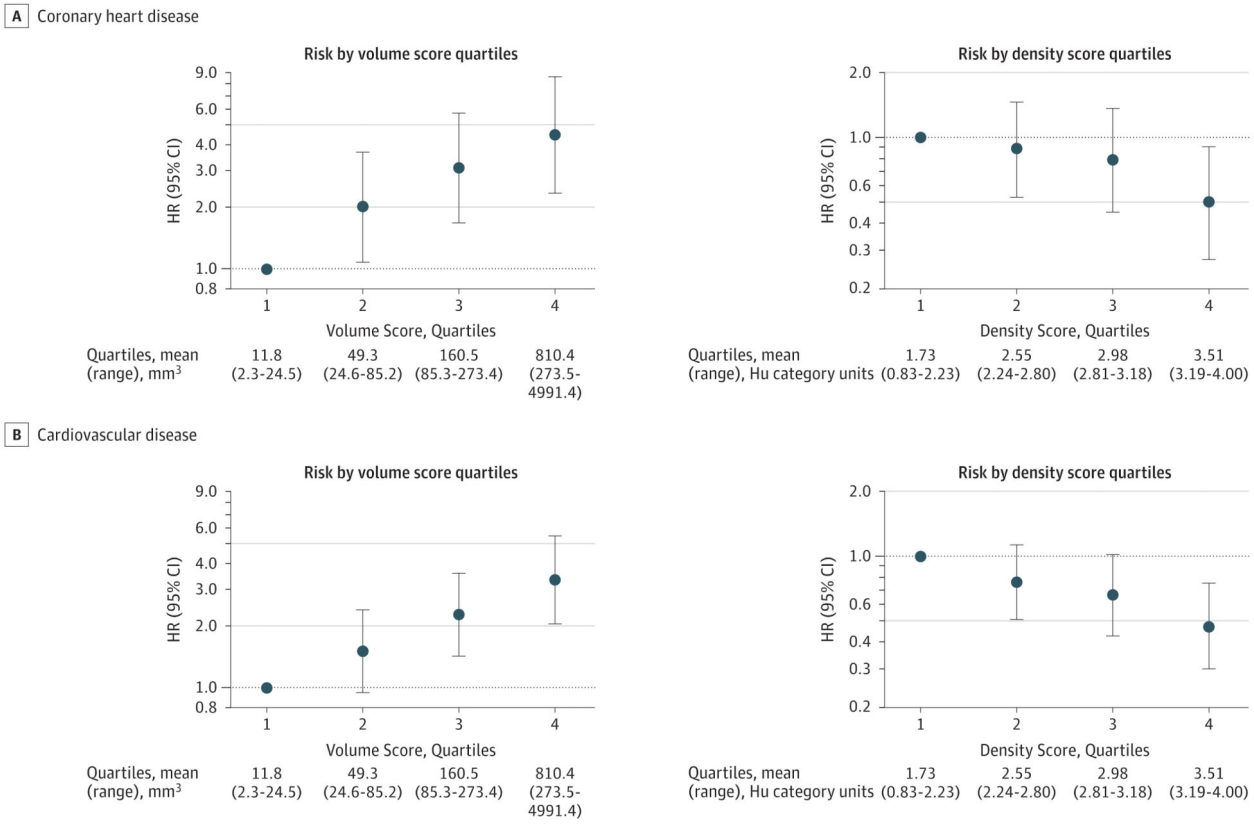

Figure. Adjusted Hazard Ratios of Volume and Density Score Quartiles for Coronary Heart Disease and Cardiovascular Disease

Hazard ratios (HRs) for volume score quartiles are adjusted for density score, race/ethnicity, statin use, and general Framingham Risk Score (FRS). HRs for density score quartiles are adjusted for natural logarithm volume score, race/ethnicity, statin use, and general FRS. Error bars indicate 95% CIs. Hu indicates Hounsfield unit.

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Table 1

CVD Risk Factors, CAC Measurements, and CVD Outcomes in Men and Women in MESA With Nonzero CAC Scores, by Quartile of CAC Volume Score

	Volume Score, Quartile				
	1 (n=852)	2 (n=847)	3 (n=850)	4 (n=849)	All Participants (N=3398)
Volume range, mm^3	2.3-24.5	24.6-85.2	85.3-273.4	273.5-4491.4	2.3-4491.4
Age, mean (SD), y	62.4 (9.8)	65.3 (9.3)	67.4 (9.1)	70.2 (8.1)	66.4 (9.5)
Men, No. (%)	420 (49.3)	454 (53.6)	511 (60.1)	579 (68.2)	1964 (57.8)
Race/ethnicity, No. (%)					
Non-Hispanic white	340 (39.9)	320 (37.8)	391 (46.0)	446 (52.5)	1497 (44.1)
Chinese	105 (12.3)	124 (14.6)	107 (12.6)	68 (8.0)	404 (11.9)
African American	224 (26.3)	221 (26.1)	187 (22.0)	189 (22.3)	821 (24.2)
Hispanic	183 (21.5)	182 (21.5)	165 (19.4)	146 (17.2)	676 (19.9)
Clinical characteristics					
Total cholesterol, mean (SD), mg/dL	196.9 (35.2)	193.5 (36.9)	194.8 (35.6)	193.2 (38.0)	194.6 (36.5)
HDL-C, mean (SD), mg/dL	49.8 (13.9)	49.7 (14.7)	49.2 (14.8)	48.9 (14.5)	49.4 (14.5)
Systolic BP, mean (SD), mm Hg	126.5 (20.6)	130.5 (21.7)	131.7 (21.6)	134.5 (22.0)	130.8 (21.7)
BP treatment, No. (%)	308 (36.2)	363 (42.9)	409 (48.1)	472 (55.6)	1552 (45.7)
Current smoking, No. (%)	120 (14.1)	105 (12.4)	105 (12.4)	106 (12.5)	436 (12.8)
Diabetes, No. (%)	117 (13.8)	129 (15.3)	158 (18.7)	203 (24.1)	607 (17.9)
Statin use, No. (%)	138 (16.2)	159 (18.8)	176 (20.7)	208 (24.5)	681 (20.1)
Scores, mean (SD)					
General FRS, 10-y % CVD risk	14.5 (9.0)	17.2 (9.2)	19.3 (8.8)	22.4 (8.3)	18.3 (9.3)
Agatston	9.6 (7.0)	48.8 (21.5)	170.9 (64.3)	943.0 (802.0)	292.9 (553.2)[a]
Area	4.3 (2.3)	18.0 (6.5)	58.9 (20.7)	300.7 (245.9)	95.4 (172.2)[a]
Volume	11.8 (6.4)	49.3 (17.2)	160.5 (54.1)	810.4 (652.9)	257.9 (460.4)[a]
Density	2.1 (0.7)	2.7 (0.6)	2.9 (0.5)	3.1 (0.4)	2.7 (0.7)
CHD per 1000 patient-years, (No.)[b]	3.0 (18)	5.4 (32)	8.7 (51)	13.4 (74)	7.5 (175)
CVD per 1000 patient-years, (No.)[b]	6.3 (37)	8.2 (48)	12.7 (73)	19.8 (107)	11.6 (265)

Abbreviations: BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

[a] Median (25%-75% range) is 88.0 (21.8-298.8) for the Agatston score, 30.8 (8.9-103.0) for the area score, and 85.2 (24.5-273.4) for the volume score.

[b] There were 4 participants lost to follow-up and excluded.

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Table 2

CVD Risk Factors, CAC Measurements, and CVD Outcomes in Men and Women in MESA With Nonzero CAC Scores, by Quartile of CAC Density Score

	Density Score, Quartile				
	1 (n=850)	2 (n=849)	3 (n=850)	4 (n=849)	All Participants (N=3398)
Density range, Hu category units	0.8-2.23	2.24-2.80	2.81-3.18	3.19-4.0	0.8-4.0
Age, mean (SD), y	62.8 (10.0)	66.8 (9.5)	67.7 (8.7)	68.1 (9.0)	66.4 (9.5)
Men, No. (%)	441 (51.9)	498 (58.7)	512 (60.2)	513 (60.4)	1964 (57.8)
Race/ethnicity, No. (%)					
Non-Hispanic white	373 (43.9)	407 (47.9)	437 (51.4)	280 (33.0)	1497 (44.1)
Chinese	88 (10.4)	53 (6.2)	71 (8.4)	192 (22.6)	404 (11.9)
African American	203 (23.9)	232 (27.3)	203 (23.9)	183 (21.6)	821 (24.2)
Hispanic	186 (21.9)	157 (18.5)	139 (16.4)	194 (22.9)	676 (19.9)
Clinical characteristics					
Total cholesterol, mean (SD), mg/dL	195.6 (36.1)	195.7 (36.9)	193.9 (36.1)	193.3 (36.7)	194.6 (36.5)
HDL-C, mean (SD), mg/dL	49.0 (13.9)	49.1 (14.7)	48.7 (14.3)	50.8 (15.0)	49.4 (14.5)
Systolic BP, mean (SD), mm Hg	127.9 (21.3)	131.5 (21.0)	132.9 (21.4)	131.0 (22.6)	130.8 (21.7)
BP treatment, No. (%)	340 (40.0)	399 (47.0)	415 (48.9)	398 (46.7)	1552 (45.7)
Current smoking, No. (%)	125 (14.7)	105 (12.4)	114 (13.4)	92 (10.8)	436 (12.8)
Diabetes, No. (%)	137 (16.1)	163 (19.3)	152 (18.0)	155 (18.3)	607 (17.9)
Statin use, No. (%)	166 (19.5)	149 (17.6)	186 (21.9)	180 (21.2)	681 (20.1)
Scores, mean (SD)					
General FRS, 10-y % CVD risk	15.6 (9.2)	18.9 (9.1)	19.8 (9.0)	19.1 (9.2)	18.3 (9.3)
Agatston[a]	22.5 (39.0)	186.6 (279.6)	498.6 (724.1)	464.1 (681.9)	292.9 (553.2)
Area[b]	11.7 (18.7)	71.7 (104.5)	166.4 (240.5)	131.9 (188.9)	95.4 (172.2)
Volume[c]	30.4 (47.1)	183.2 (261.5)	427.1 (601.9)	390.2 (558.6)	257.9 (460.4)
Density	1.7 (0.4)	2.6 (0.2)	3.0 (0.1)	3.5 (0.2)	2.7 (0.7)
CHD per 1000 patient-years, (No.)[d]	4.7 (28)	8.9 (52)	10.4 (60)	6.1 (35)	7.5 (175)
CVD per 1000 patient-years, (No.)[d]	8.7 (51)	13.3 (76)	14.8 (84)	9.5 (54)	11.6 (265)

Abbreviations: BP, blood pressure; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; Hu, Hounsfield unit; MESA, Multi-Ethnic Study of Atherosclerosis.

[a] Median (25%-75% range) Agatson score for density was 8.9 (3.9-24.2) for quartile 1, 89.2 (32.0-221.8) for quartile 2, 214.4 (73.0-551.6) for quartile 3, 215.7 (80.8-558.4) for quartile 4, and 88.0 (21.8-298.8) for all participants.

[b] Median (25%-75% range) area score for density was 5.1 (2.3-12.6) for quartile 1, 34.6 (12.9-87.4) for quartile 2, 71.7 (25.0-186.5) for quartile 3, 61.7 (23.4-161.0) for quartile 4, and 30.8 (8.9-103.0) for all participants.

[c] Median (25%-75% range) volume score for density was 14.0 (7.0-33.3) for quartile 1, 90.5 (34.9-224.3) for quartile 2, 194.5 (67.8-488.9) for quartile 3, 183.0 (68.7-470.4) for quartile 4, and 85.2 (24.5-273.4) for all participants.

[d] Four participants were lost to follow-up and excluded.

Table 3

Spearman Correlation Coefficients for 4 CAC Scores[a]

	ln(Agatston)	*ln*(Volume)	*ln*(Area)	Density
ln(Agatston)	1.00	0.995	0.994	0.623
ln(Volume)		1.00	0.998	0.560
ln(Area)			1.00	0.539
Density				1.00

Abbreviations: CAC, coronary artery calcium; *ln*, natural logarithm.

[a] All *P* values were less than .001.

Table 4
Adjusted HRs for 4 Separate CAC Scores for Hard CHD and Hard CVD

	CHD		CVD	
CAC Scores	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
Adjusted for age, sex, and race/ethnicity				
ln(Agatston), per SD	1.56 (1.31-1.86)	<.001	1.41 (1.23-1.62)	<.001
ln(Volume), per SD	1.58 (1.33-1.88)	<.001	1.43 (1.25-1.64)	<.001
ln(Area), per SD	1.60 (1.35-1.89)	<.001	1.45 (1.27-1.66)	<.001
Density, per SD	1.05 (0.89-1.23)	.59	0.98 (0.68-1.11)	.75
Adjusted for general FRS, statin use, and race/ethnicity[a]				
ln(Agatston), per SD	1.51 (1.27-1.79)	<.001	1.36 (1.19-1.56)	<.001
ln(Volume), per SD	1.52 (1.29-1.80)	<.001	1.38 (1.21-1.58)	<.001
ln(Area), per SD	1.54 (1.30-1.82)	<.001	1.40 (1.22-1.60)	<.001
Density, per SD	1.06 (0.90-1.25)	.49	0.99 (0.87-1.13)	.89

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HR, hazard ratio; *ln*, natural logarithm.

[a]One participant was missing statin use and was excluded.

Table 5

Multivariable HRs for the *ln*(Volume Score), Density Score, the General FRS, Race/Ethnicity, and Statin Use for CHD and CVD

	CHD			CVD		
	No./Total Events	**HR (95% CI)**	***P* Value**	**No./Total Events**	**HR (95% CI)**	***P* Value**
ln(Volume score), per SD	NA	1.81 (1.47-2.23)	<.001	NA	1.68 (1.42-1.98)	<.001
Density score, per SD	NA	0.73 (0.58-0.91)	.006	NA	0.71 (0.60-0.85)	<.001
General FRS, per SD	NA	1.59 (1.33-1.90)	<.001	NA	1.62 (1.40-1.87)	<.001
Race/ethnicity						
Non-Hispanic white	83/1493	1 [Reference]		124/1493	1. [Reference]	
Chinese	11/404	0.65 (0.34-1.24)	.19	15/404	0.59 (0.34-1.02)	.059
African American	43/821	1.00 (0.69-1.45)	.98	67/821	1.04 (0.77-1.40)	.81
Hispanic	38/675	1.10 (0.74-1.62)	.63	59/675	1.14 (0.83-1.56)	.41
Statins						
No statin use[a]	143/2714	1 [Reference]		216/2714	1 [Reference]	
Statin use[a]	32/679	0.79 (0.54-1.16)	.23	48/679	0.80 (0.58-1.09)	.16

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; FRS, Framingham Risk Score; HR, hazard ratio; NA, not applicable.

[a]One participant was missing statin use and was excluded.

Table 6
Areas Under the ROC Curve for the Base Model and Various CAC Measures

	CHD		CVD	
Model	**AUC (95% CI)**	***P* Value**	**AUC (95% CI)**	***P* Value**
Base[a]	0.668 (0.629-0.706)		0.669 (0.637-0.700)	
Base + *ln*(Agatston)	0.696 (0.660-0.732)	vs Base = *P*.02	0.688 (0.658-0.718)	vs Base = *P*.02
Base + *ln*(volume)	0.700 (0.664-0.735)	vs Base = *P*.01	0.691 (0.661-0.721)	vs Base = *P*.01
Base + *ln*(volume)	0.711 (0.675-0.746)	vs Base = *P*.006	0.704 (0.675-0.734)	vs Base = *P*.<001
+ density		vs Base + volume = *P*.05		vs Base + volume = *P*.02

Abbreviations: AUC, area under the curve; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; ROC, receiver operating characteristic.

[a]General Framingham Risk Score + race/ethnicity + statin use.