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Baseline Subclinical Atherosclerosis Burden and Distribution Are Associated With Frequency and Mode of Future Coronary Revascularization

Multi-Ethnic Study of Atherosclerosis

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OBJECTIVES The aim of this study was to evaluate the impact of coronary artery calcium (CAC) burden and regional distribution on the need for and type of future coronary revascularization—percutaneous versus surgical (coronary artery bypass graft [CABG])—among asymptomatic subjects.

BACKGROUND The need for coronary revascularization and the chosen mode of revascularization are thought to be functions of disease burden and anatomic distribution. The association between the baseline burden and regional distribution of CAC and the risk and type of future coronary revascularization remains unknown.

METHODS A total of 6,540 participants in the MESA (Multi-Ethnic Study of Atherosclerosis) (subjects aged 45 to 84 years, free of known baseline cardiovascular disease) with vessel-specific CAC measurements were followed for a median of 8.5 years (interquartile range: 7.7 to 8.6 years). Annualized rates and multivariate-adjusted hazard ratios for revascularization and revascularization type were analyzed according to CAC score category, number of vessels with CAC (0 to 4, including the left main coronary artery), and involvement of individual coronary arteries.

RESULTS A total of 265 revascularizations (4.2%) occurred during follow-up, and 206 (78% of the total) were preceded by adjudicated symptoms. Revascularization was uncommon when CAC score was 0.0 (0.6%), with a graded increase over both rising CAC burden and increasingly diffuse CAC distribution. The revascularization rates per 1,000 person-years for CAC scores of 1 to 100, 101 to 400, and >400 were 4.9, 11.7, and 25.4, respectively; for 1, 2, 3, and 4 vessels with CAC, the rates were 3.0, 8.0, 16.1, and 24.8, respectively. In multivariate models adjusting for CAC score, the number of vessels with CAC remained predictive of revascularization and mode of revascularization. Independent predictors of CABG versus percutaneous coronary intervention included 3- or 4-vessel CAC, higher CAC burden, and involvement of the left main coronary artery. Risk for CABG was extremely low with <3-vessel baseline CAC. Results were similar when considering only symptom-driven revascularizations.

CONCLUSIONS In this multiethnic cohort of asymptomatic subjects, baseline CAC was highly predictive of future coronary revascularization procedures, with measures of CAC burden and distribution each independently predicting need for percutaneous coronary intervention versus CABG over an 8.5-year follow-up. (J Am Coll Cardiol Img 2014;7:476–86) © 2014 by the American College of Cardiology Foundation

Measurement of the total coronary artery calcium (CAC) score (Agatston score) using noncontrast cardiac gated computed tomography provides an excellent estimation of cardiovascular risk through its strong correlation with total coronary atherosclerotic burden. Moderate to high CAC is a strong independent predictor of hard cardiovascular events, including myocardial infarction and death (1–4). In contrast, absence of CAC among asymptomatic patients identifies a low-risk population with <1% estimated 10-year risk for cardiovascular mortality (5–7) and a low probability of significant coronary artery disease on invasive coronary angiography (5). When added to traditional risk prediction scores, CAC scoring provides significant improvement in risk discrimination and risk reclassification across sex and ethnic groups (2,8–10).

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Although CAC is a strong marker of future cardiovascular risk, the extent to which regional distribution of CAC provides additional risk information beyond the Agatston score has not been fully explored. A prior analysis from a registry of more than 25,000 subjects suggested that left main or multivessel CAC may identify a higher risk group independent of the overall CAC score (11). Further supporting the potential importance of CAC distribution, there is a significant association between the burden of CAC within an individual coronary artery and the severity of angiographic stenosis within the same artery (12).

Revascularization remains an important clinical endpoint, and the need for and chosen method of revascularization are directly influenced by the overall burden and distribution of angiographic coronary artery disease. For example, coronary artery bypass graft (CABG) is commonly associated with more diffusely distributed angiographic coronary atherosclerosis compared with percutaneous coronary intervention (PCI). Thus, mode of revascularization provides an excellent opportunity to test the importance of the anatomic information inherent in measures of regional CAC distribution that is not accounted for in the traditional Agatston score.

We first sought to evaluate whether the distribution of subclinical atherosclerosis, as measured by CAC, was independently and incrementally associated with risk for future revascularization. We then sought to evaluate whether the overall burden and distribution of CAC was associated with a specific mode of revascularization (percutaneous vs. surgical), hypothesizing that increasingly diffuse CAC would be preferentially associated with future surgical revascularization.

METHODS

Study population. Full details of the MESA (Multi-Ethnic Study of Atherosclerosis) study design have been published previously (13). In brief, MESA is a prospective observational cohort of 6,814 men and women aged 45 to 84 years from different ethnic origins (white, black, Hispanic, and Chinese), with no known baseline clinical cardiovascular disease who were asymptomatic at the time or enrollment. Subjects were enrolled between July 2000 and September 2002 at 6 field centers across the United States (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York City; and St. Paul, Minnesota). The study protocol was approved by the institutional review board at each site, and all participants provided written informed consent.

Risk factor measurement. As part of the baseline examination, staff members at each of the 6 centers collected information about cardiovascular risk factors, including medical history, smoking history, blood pressure measurement, anthropometric measurements, and laboratory data, as previously described (13). A central laboratory (University of Vermont, Burlington, Vermont)

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CAC = coronary artery calcium

IQR = interquartile range

PCI = percutaneous coronary intervention

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measured levels of total and high-density lipoprotein cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein after a 12-h fast.

CAC measurement. As previously described by Carr et al. (14), all MESA study participants underwent measurement of CAC by cardiac computed tomography. Participants were scanned twice, and CAC was reported as the average CAC (Agatston) (15) score. Vessel-specific CAC measurements were performed in 6,540 MESA participants (96%). Subjects were told after the baseline visit (2000 to 2002) whether they had no, less than average, average, or greater than average CAC and were encouraged to discuss the results with their physicians.

Regional CAC was analyzed according to: 1) the number of vessels with CAC, defined as the number of main coronary arteries (left main, left anterior descending, left circumflex, and right) with calcification (values ranging from 0 to 4); and 2) involvement of individual coronary arteries. Three-vessel CAC was defined as involvement of either the left main or left anterior descending coronary artery in addition to CAC in the left circumflex and the right coronary arteries.

Follow-up. Participants were followed for a median of 8.5 years (interquartile range [IQR]: 7.7 to 8.6 years). At intervals of 9 to 12 months, an interviewer contacted each participant or family member by telephone to inquire about interim revascularization, hospital admission, or death. To verify self-reported diagnoses, MESA obtained medical records for approximately 98% of hospital events and 95% of outpatient diagnoses. Two physicians from the MESA mortality and morbidity review committee independently classified events. In the event of disagreement, the full committee made the final classification.

The primary endpoints for this study were time to first revascularization, time to first CABG, and time to first PCI. In analyses of mode of revascularization, all CABG events were considered. For these analyses, we excluded PCIs that followed CABG procedures.

At the time of hospitalization, before the revascularization procedure, individuals were classified as having preceding adjudicated myocardial infarctions, angina, or neither. The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. A classification of angina required symptoms of chest pain (or other related symptoms), a physician diagnosis of angina, and medical treatment for the symptoms. Revascularization or a physician diagnosis of angina or coronary heart disease without documented symptoms was not considered angina.

For sensitivity analyses, "symptom-driven revascularization" was defined as having adjudicated

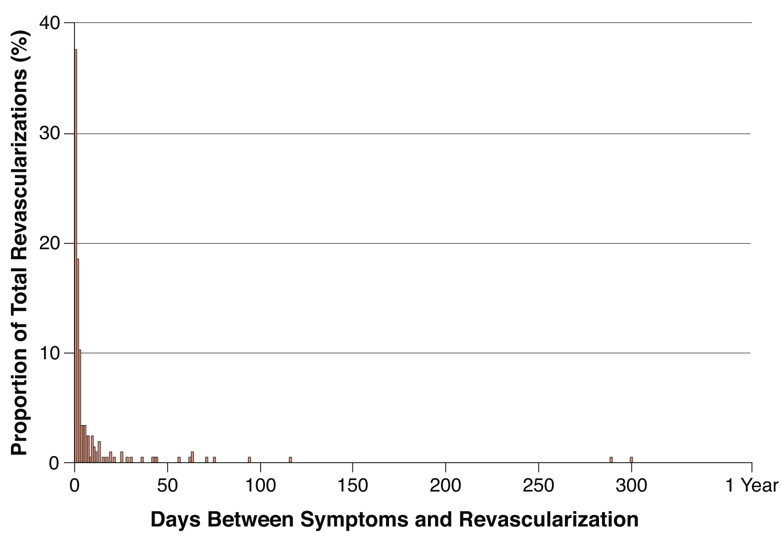

Figure 1. Time Elapsed Between MESA Adjudicated MI or Angina and Revascularization

A majority of all revascularizations occurred within 10 days after adjudicated symptoms. MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction.

myocardial infarction or angina within 365 days before revascularization.

Statistical analysis. The baseline characteristics of the study population were analyzed according to revascularization status. Frequencies and proportions were calculated for categorical variables, and either means with standard deviations or medians with IQRs were calculated for continuous variables. Differences between the 2 groups were calculated using chi-square tests, Student *t* tests, or nonparametric testing as appropriate.

Kaplan-Meier curves were constructed expressing time to revascularization as a function of number of vessels with CAC (0, 1, 2, 3, or 4) and CAC score groups (0, 1 to 100, 101 to 400, and >400).

To evaluate the predictive value of CAC score and CAC distribution on the need for subsequent revascularization and revascularization type, annualized absolute event rates (number of events divided by number of person-years at risk) were calculated after stratification by CAC distribution (0, 1, 2, 3, or 4 vessels with CAC) and CAC score category (0, 1 to 100, 101 to 400, or >400). Multivariate-adjusted Cox proportional-hazards models were used to calculate hazard ratios and 95% confidence intervals, with a CAC score of 0 as the reference group. Models were adjusted for age, sex, race or ethnicity, smoking, diabetes mellitus, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, family history of coronary heart disease, antihypertensive medication use, lipid-lowering medication use, education level, and MESA study site. To test for an additive value of regional measures of CAC beyond traditional CAC scoring, additional models were constructed in the subgroup of participants with CAC scores >0, further adjusting for the CAC score group.

We then compared specific CAC characteristics among those who underwent revascularization, according to the chosen mode of revascularization (PCI vs. CABG). Among the few participants with baseline CAC scores of 0 who ultimately underwent revascularization, we produced a descriptive analysis summarizing the data on demographics, risk factors, serial CAC scanning, adjudicated symptomatology, and mode of revascularization.

Sensitivity analyses. Sensitivity analyses were performed excluding subjects who underwent early revascularization within 90 days of CAC scanning (n = 2). Among subjects who underwent revascularization, there was a small number (22% of revascularizations) without MESA-adjudicated angina or myocardial infarction within 365 days revascularization. To confirm that the inclusion of these subjects did not cause biased results that could be directly attributable to CAC testing, sensitivity analyses were performed among only those subjects with MESA-adjudicated diagnoses of angina or myocardial infarction at hospitalization before revascularization.

Additionally, to evaluate whether change in medication use had an impact on revascularization rates, sensitivity analysis was performed adjusting for change in medication (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,

Table 1. Baseline Characteristics by Coronary Revascularization Status

	No Revascularization (n = 6,275 [95.9%])	Revascularization (n = 265 [4.1%])	p Value
Age, yrs	62 ± 10	66 ± 9	<0.001
Women	54	24	<0.001
Race/ethnicity			<0.001
White	38	52	
Black	28	20	
Hispanic	23	20	
Chinese	12	8	
Smoking (current)	13	15	0.004
Pack-years	11 ± 22	17 ± 28	<0.001
Hypertension	44	62	<0.001
Systolic blood pressure, mm Hg	126 ± 21	132 ± 22	<0.001
Diastolic blood pressure, mm Hg	72 ± 10	73 ± 11	0.05
Antihypertensive medication	37	54	<0.001
Diabetes	12	24	<0.001
LDL, mg/dl	117 ± 31	123 ± 35	<0.001
HDL, mg/dl	51 ± 15	45 ± 14	<0.001
Triglycerides, mg/dl	111 (77–159)	123 (90–189)	0.001
Lipid-lowering medication	16	25	<0.001
hsCRP, mg/dl	1.9 (0.8–4.2)	2.0 (1.0–4.7)	0.08
Family history of CHD	42	59	<0.001
Education			0.22
Bachelor's degree	35	41	
No bachelor's degree	65	59	
CAC presence	48	93	<0.001
CAC score, % of total			<0.001
0	52	7	
1–100	27	24	
101–400	13	29	
>400	9	40	
Agatston score	0 (0–70)	254 (66–741)	<0.001
No. of vessels with CAC	1.03 ± 1.3	2.7 ± 1.2	<0.001

Values are mean ± SD, %, or median (interquartile range).
CAC = coronary artery calcium; CHD = coronary heart disease; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

amlodipine, thiazide diuretics, beta-blockers, fibrates, niacin, statins, and aspirin) before revascularization. This analysis required the exclusion of individuals who underwent revascularization before examination 2 (in whom change in medications was likely a result of revascularization).

RESULTS

Clinical characteristics of the study cohort. The mean age of the study cohort was 62.2 ± 10.2 years, with slightly more than half women (52.8%). A total of 265 participants (4.1%) underwent revascularization, including 206 symptom-driven revascularizations (78%), with the majority occurring shortly after the diagnosis of myocardial infarction or angina (Fig. 1). Subjects who underwent revascularization were more likely to be male and Caucasian. As expected, the cardiovascular risk profile was less favorable for those requiring revascularization compared with those without revascularization (Table 1). Participants treated with revascularization had a significantly higher median CAC score (254 [IQR: 66 to 741] vs. 0 [IQR: 0 to 70], $p < 0.001$) and mean number of vessels with CAC (2.7 ± 1.2 vs. 1.0 ± 1.3, $p < 0.001$) than those not requiring revascularization.

CAC and revascularization. The frequency of revascularization increased with increasing CAC score (CAC score 0, 19 events [0.6%]; CAC score 1 to 100, 64 events [3.8%]; CAC score 101 to 400, 76 events [9.4%]; CAC score >400, 106 events [19.8%]) and with the total number of vessels with CAC (0 vessels, 19 [0.6%]; 1 vessel, 25 events [2.4%]; 2 vessels, 49 events [6.3%]; 3 vessels, 110 events [12.7%]; 4 vessels, 62 events [19.4%]). The annualized revascularization rates increased according to CAC score category from 0.7 events per 1,000 person-years for a CAC score of 0 to 25.4 events per 1,000 person-years for a CAC score >400 (Fig. 2A). Similarly, the rate of revascularization increased proportionally to the number of vessels with CAC

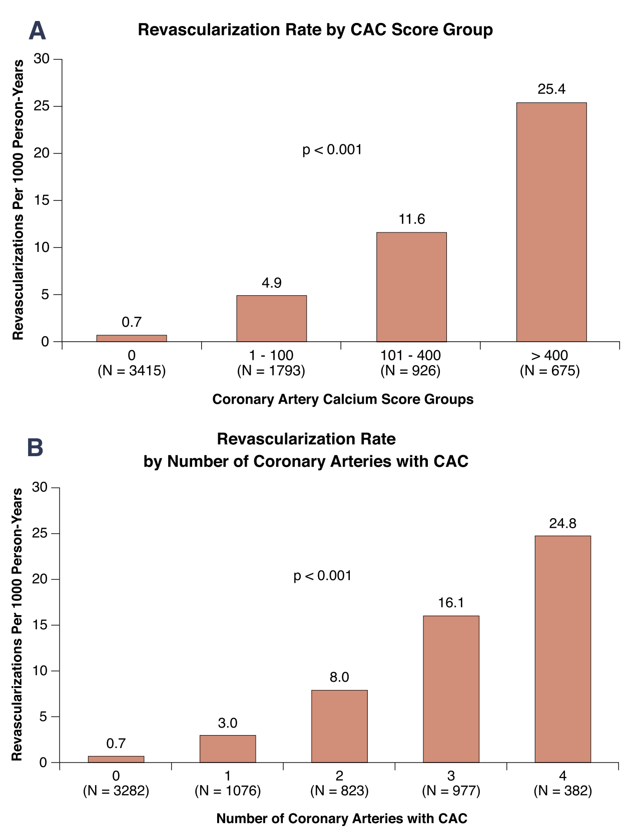

Figure 2. Revascularization Rate by CAC Score Group and Number of Coronary Arteries With CAC

There was a strong, statistically significant increase in revascularization with both increasing coronary artery calcium (CAC) score group **(A)** and increasingly diffuse CAC **(B)**.

Table 2. Multivariate-Adjusted HRs for Incident Coronary Revascularization

	HR	95% CI	p Value
All subjects (n = 6,540)*			
CAC group			
0	1.0		
1–100	4.4	2.6–7.5	<0.001
101–400	9.8	5.8–16.8	<0.001
>400	17.5	10.1–30.3	<0.001
No. of vessels with CAC			
0	1.0		
1	2.6	1.4–4.8	0.004
2	7.0	4.0–12.3	<0.001
3	12.2	7.2–20.7	<0.001
4	16.8	9.6–29.6	<0.001
Subjects with CAC scores >0 (n = 3,259)†			
No. of vessels with CAC			
1	1.0		
2	2.5	1.5–4.4	0.001
3	3.4	1.9–6.0	<0.001
4	4.1	2.2–7.7	<0.001

*Model adjusted for age, sex, race or ethnicity, diabetes, smoking, hypertension, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, family history, antihypertensive medication use, lipid-lowering medication use, education level, and Multi-Ethnic Study of Atherosclerosis study site. †Model additionally adjusted for CAC group (1 to 100, 101 to 400, or >400).
CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio.

from an annualized event rate of 0.7 events per 1,000 person-years to 24.8 events per 1,000 person-years when 4 vessels were involved (Fig. 2B). Kaplan-Meier estimates of revascularization-free survival according to CAC score and number of vessels with CAC are shown in Figures 3A and 3B, respectively.

Table 2 shows the risk for revascularization associated with CAC score and number of vessels with CAC after comprehensive adjustment for cardiovascular risk factors. The hazard ratio increased stepwise to >16-fold risk for both CAC score >400 and 4-vessel CAC compared with a CAC score of 0. CAC distribution remained a significant predictor even after concomitant adjustment for CAC score. Among those subjects with CAC scores >0, the number of coronary vessels with CAC remained a strong, independent predictor of revascularization, with a more than 4-fold increased risk associated with 4-vessel CAC compared with CAC in 1 vessel. Online Tables 1A and 1B repeat these analyses for individual revascularization types (PCI and CABG), with similar results for each revascularization type.

Mode of revascularization according to CAC distribution. Among subjects who underwent revascularization, PCI was more common than CABG (n = 154 vs. n = 111). Figures 4A and 4B compare the absolute annualized event rates of PCI and CABG by CAC score category and number of vessels, respectively. Rates for both PCI and CABG increased with higher CAC scores; however, for all CAC score categories, PCI was more common. In contrast, when the population was stratified by number of vessels with CAC, rates of CABG were higher than those of PCI among subjects with baseline 4-vessel CAC.

Figure 5 demonstrates the impact of CAC distribution on types of revascularization across CAC score categories (1 to 100, 101 to 400, and >400). Within all CAC score categories, more diffuse CAC was associated with an increased proportion of CABG revascularizations. Among subjects with CAC scores >400, 4-vessel CAC was associated with a greater proportion of subjects undergoing CABG than PCI.

Table 3 demonstrates the specific characteristics of CAC distribution according to mode of revascularization. Individuals who underwent CABG in general had significantly higher CAC scores in the left main, left anterior descending, left circumflex, and right coronary arteries ($p < 0.01$). Among participants who underwent CABG, 42% had left main coronary artery involvement, compared with 22% of participants who underwent PCI ($p = 0.001$). A total of 74% of subjects who underwent CABG had 3-vessel CAC, compared with only 51% of those who underwent PCI ($p < 0.001$). Just 8% of all CABG procedures occurred in participants with no CAC or 1-vessel CAC, whereas these subjects accounted for 23% of all those treated with PCI ($p < 0.001$).

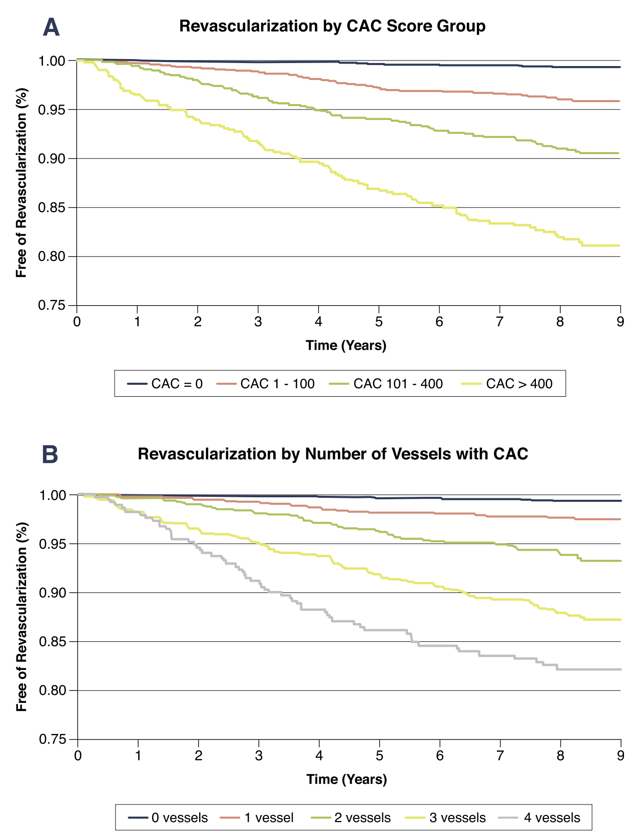

Figure 3. Kaplan-Meier Estimates of Revascularization-Free Survival

Kaplan-Meier estimates of revascularization-free survival by CAC burden **(A)** and distribution **(B)**. Log-rank $p < 0.001$ for both models. CAC = coronary artery calcium.

Revascularization among subjects with baseline CAC scores of 0. Revascularization during a median 8.5 years of follow-up was extremely rare among participants with baseline CAC scores of 0 (19 of 3,281 [0.6%]). The median time to revascularization for this group was 4.6 years (IQR: 1.7 to 6.0 years). Table 4 shows person-level characteristics of subjects with baseline CAC scores of 0 who ultimately required revascularization. Fifteen of the 19 participants were classified as having either angina or a myocardial infarction within 365 days of revascularization. Of the 12 participants with baseline CAC scores of 0 who had repeat MESA protocol–driven CAC measurements before revascularization, 6 (50%) had developed interim CAC scores >0.

Sensitivity analyses. The results of the sensitivity analysis excluding the 2 subjects who underwent early revascularization within 90 days of CAC scanning were identical to those of the main analysis and thus are not shown.

A total of 206 of 265 individuals undergoing revascularization (78%) were classified as having symptom-driven revascularization. Within this subset, revascularization rates and multivariate-adjusted risks of revascularization associated with increasing CAC score and number of vessels with CAC were similar to the trends noted for the overall population (Online Figs. 1 and 2, Online Table 2).

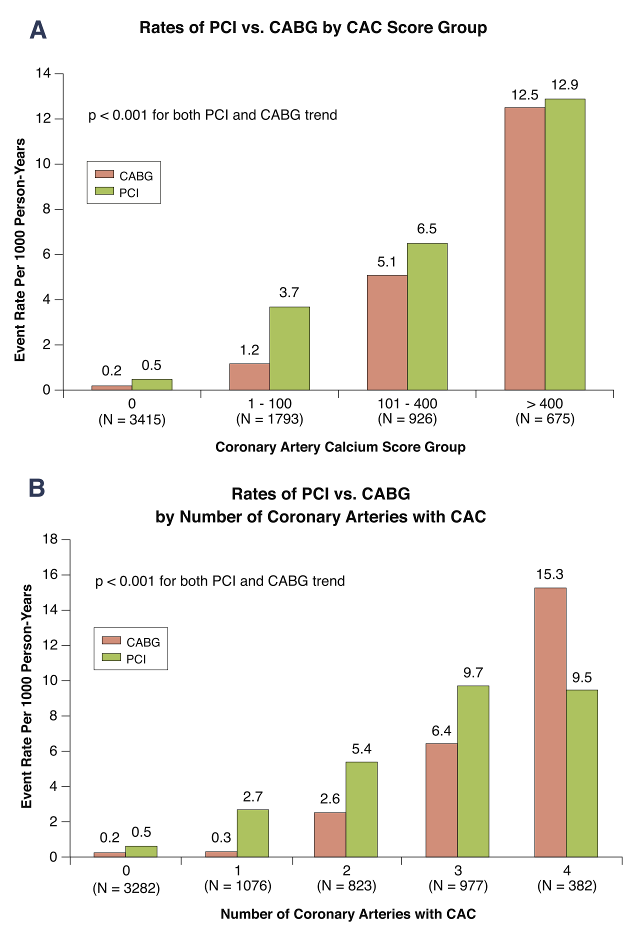

Figure 4. Rates of CABG and PCI by CAC Burden and Distribution

There was a strong, statistically significant increase in both percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) with both increasing coronary artery calcium (CAC) score group **(A)** and increasing number of coronary arteries with CAC **(B)**.

The risk for revascularization associated with increasing CAC score and number of vessels with CAC was similar to the primary analysis after adjustment for change in medication use between MESA visits 1 and 2 (Online Table 3).

DISCUSSION

In this multiethnic cohort of asymptomatic individuals, we demonstrate that the distribution of CAC on baseline scans provides incremental risk information to the Agatston score for predicting need for future coronary revascularization over 9-year follow-up. Individuals with baseline CAC scores >400 or CAC in all 4 coronary vessels had an approximately 25% risk for revascularization at 8.5-year follow-up, compared with a rate of <1% among those with zero CAC. Importantly, we also found that both the total burden and the distribution of CAC were predictive of the mode of revascularization. A higher CAC burden, more diffuse distribution of CAC, and left main involvement were all strongly associated with need for CABG versus PCI. CABG was particularly uncommon among participants with zero CAC or 1-vessel CAC (8%), whereas 74% of 111 total CABG procedures occurred in subjects with at least 3-vessel CAC at baseline. To our knowledge, this is the first study evaluating the relationship between CAC distribution and subsequent need for surgical versus percutaneous revascularization.

Predictors of revascularization. Since Agatston et al. (15) first demonstrated the utility of computed tomography in detecting and quantifying CAC, multiple studies have established the value of CAC in asymptomatic subjects in predicting cardiovascular events, including myocardial infarction and death (1–4). The utility of CAC has been shown to extend across sex and ethnic groups and adds significant improvement in risk reclassification when added to standard risk factors or risk factor scores (2,8,9). Recently, CAC has been shown to provide superior discrimination and risk reclassification compared with other common markers of cardiovascular risk when added to the Framingham risk score or the Reynolds score (16).

Some prior analyses have included revascularization as part of a combined composite cardiovascular endpoint, but the relationship between CAC and revascularization has not been independently evaluated. Although revascularization is often considered a "soft" endpoint, it accounts for large health care expenditures, exceeding $28 billion annually in the United States (17,18), and remains an important outcome for both patients and physicians. Furthermore, there is increasing interest in exploring the additional prognostic utility of measuring regional or vessel-specific CAC above and beyond the total burden of CAC.

Regional measures of CAC distribution and coronary stenosis. CAC has been shown to correlate with myocardial perfusion defects (5,19–21), a marker of ischemia and a surrogate for anatomic stenosis that is a common indication for revascularization. Schuijf et al. (21) performed a comparative regional analysis of CAC scores versus vessel-specific myocardial perfusion imaging in 140 patients with clinically suspected coronary artery disease. The mean calcium score in coronary arteries with normal myocardial perfusion on single-photon emission computed tomography was 69 ± 167, whereas a significantly higher calcium score of 272 ± 646 was noted for coronary arteries with abnormal myocardial perfusion ($p < 0.001$).

Furthermore, previous studies have evaluated the relationship between CAC and angiographic coronary artery stenosis (12,21). Budoff et al. (22) previously reported in symptomatic patients that both increasing CAC burden and number of vessels with CAC are independently associated with increased likelihood of angiographically significant disease. The reported sensitivity of CAC to detect significant angiographic disease (>50% stenosis) was 95%, with a specificity of 44%. Notably, the specificity of CAC increased substantially with increasing number of vessels with CAC (22).

In addition to total CAC score and number of vessels with CAC, vessel-specific CAC score has been shown to be a robust predictor of angiographic coronary stenosis (12,23). Qian et al. (23) showed that lesion-specific and vessel-specific CAC scoring is superior to total Agatston score for the prediction of obstructive coronary artery disease.

In our study, although we did not directly evaluate the relationship between CAC and myocardial perfusion defects or angiographic stenosis, we did evaluate the association between CAC and revascularization, which is often driven by anatomic stenosis or ischemia.

Zero CAC score. There has been a tremendous amount of interest in the potential clinical utility of a CAC score of 0 (5–7). Blaha et al. (6) studied more than 44,000 asymptomatic patients referred for CAC scoring. More than 19,000 had CAC scores of 0 and had an excellent prognosis, with estimated 10-year mortality of approximately 1%. In addition, subjects with CAC scores >10 had

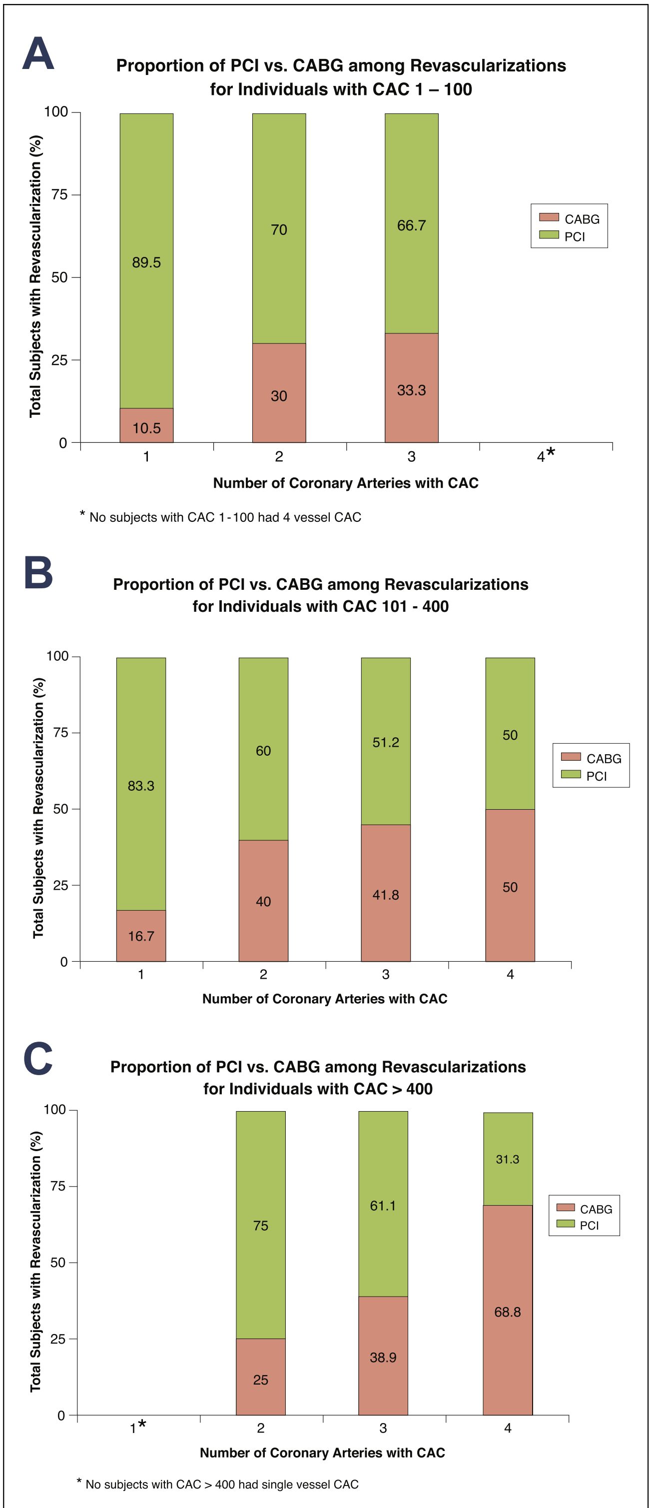

Figure 5. Proportion of Revascularizations Comparing PCI Versus CABG by CAC Burden and Distribution

Coronary artery bypass graft (CABG) was more frequent with increasing coronary artery calcium (CAC) score group **(A)** and with more diffusely distributed CAC **(B,C)**. CABG became the predominant mode of revascularization when all coronary arteries were diseased at baseline.

Table 3. CAC Characteristics of Participants Who Underwent Incident Coronary Revascularization Stratified by Mode of Revascularization

CAC Distribution	PCI (n = 154)	CABG (n = 111)	p Value
Time from CAC measurement to revascularization, yrs	3.6 ± 2.3	4.0 ± 2.4	0.19
By vessel, CAC prevalence and score			
LM	22	42	<0.001
LM CAC score	17.0 ± 63.8	26.8 ± 72.8	0.008*
LAD	86	92	0.12
LAD CAC score	159 ± 210	298 ± 300	<0.001*
LCx	66	86	<0.001
LCx CAC score	95 ± 166	244 ± 382	<0.001*
RCA	66	80	0.009
RCA CAC score	125 ± 300	333 ± 592	<0.001*
Total CAC score, all vessels	396 ± 550	901 ± 1,131	<0.001
Number of vessels	2.4 ± 1.2	3.0 ± 1.1	<0.001
≥3-vessel CAC	51	74	<0.001

Values are mean ± SD or %. *p values were calculated using nonparametric Kruskal-Wallis tests.
CABG = coronary artery bypass grafting; CAC = coronary artery calcium; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main coronary artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

a 4-fold to 8-fold increased risk for dying over 10 years compared with those with CAC scores of 0. The excellent prognosis of a CAC score of 0 in asymptomatic subjects persists among the elderly, women, and patients with diabetes and across ethnic groups (24).

In our present analysis of subjects who were asymptomatic and free of known cardiovascular disease at enrollment, we found that the rate of revascularization during 8.5 years of follow-up was extraordinarily low among subjects with baseline CAC scores of 0 (0.7%). Interestingly, 50% of subjects with baseline CAC scores of 0 who were rescanned before revascularization had incident CAC on subsequent protocol-driven CAC scans, suggesting that measurable interval progression of coronary atherosclerosis occurred. Progression of coronary artery calcium has been shown to be associated with diabetes, metabolic syndrome, and other traditional risk factors (25,26) and has been shown to predict total and hard coronary heart disease events in asymptomatic subjects both with and without baseline CAC scores > 0 (27).

Study limitations. MESA participants received limited information about their baseline CAC scans

Table 4. Description of Participants With Baseline CAC Scores of 0 Who Subsequently Required Coronary Revascularization

Age (yrs)	Sex	Race/ Ethnicity	Smoking	Diabetes	HTN	Family History of CHD	Time (yrs) From Baseline to Most Proximal CAC Scan	CAC on Repeat Scan?	Time of Revascularization (yrs) From Baseline	Revascularization Type	MI or Angina Before Revascularization?
63	Male	White	Former	No	Yes	Yes	3.5	No	4.6	PCI	No
67	Male	White	Yes	No	No	Yes	—	—	1.0	PCI	Yes
48	Male	Black	No	No	Yes	No	4.3	No	5.1	PCI	Yes
57	Male	Hispanic	Former	Yes	Yes	No	1.8	No	7.4	PCI	No
52	Female	White	Former	No	No	Yes	2.8	Yes	4.9	PCI	Yes
78	Male	Black	No	Yes	Yes	No	—	—	3.0	PCI	No
46	Male	Hispanic	Yes	No	No	No	4.8	Yes	6.0	PCI	Yes
56	Female	White	No	No	No	Yes	—	—	0.4	PCI	Yes
59	Female	Black	Former	Yes	No	No	—	—	0.3	PCI	Yes
68	Female	Hispanic	No	Yes	Yes	Yes	—	—	1.7	PCI	Yes
55	Male	White	Former	No	No	Yes	—	—	3.0	PCI	Yes
65	Male	White	Former	No	Yes	No	4.3	Yes	4.8	PCI	Yes
59	Male	White	Former	No	Yes	Yes	3.3	No	7.5	PCI	Yes
59	Female	White	Yes	No	No	Yes	1.2	Yes	7.3	CABG	Yes
71	Female	White	Former	No	No	Yes	3.3	Yes	4.3	CABG	Yes
54	Female	Black	Former	No	Yes	Yes	1.7	No	5.8	CABG	Yes
51	Male	Hispanic	Yes	Yes	Yes	Yes	1.5	No	4.0	CABG	Yes
70	Female	Black	Former	No	No	No	—	—	1.5	CABG	Yes
65	Male	Hispanic	No	Yes	Yes	No	4.6	Yes	7.9	CABG	No

HTN = hypertension; MI = myocardial infarction; other abbreviations as in Tables 1 and 3.

and were instructed to share these limited results with their physicians. It is possible that this knowledge may have influenced the clinical evaluation, thus potentially biasing the results toward a stronger relationship between CAC and revascularization. However, in our sensitivity analysis excluding revascularizations performed within 90 days of CAC scoring, we observed an equally significant relationship between CAC and revascularization. Furthermore the Kaplan-Meier estimates show that the majority of revascularization events occurred proportionally and remotely. This suggests that the limited communication of CAC scores in MESA had little impact on revascularization.

Alternatively, as a result of the limited knowledge of the CAC scan results, subjects with elevated CAC may have had more aggressive risk factor modification, thereby reducing revascularizations and possibly weakening the relationship between CAC and revascularization. However, there was no significant difference in the change in use of aspirin or statins by CAC score groups. Furthermore, when adjusted for change in medication use, the risk for revascularization was similar to that in the primary analysis.

Additionally, revascularization as an outcome is subject to differences in physician preference and regional practice and in some cases may have been done in the absence of symptoms. Furthermore, there was likely a significant temporal shift in the application of PCI during the time of the study, whereas the indications for CABG remained largely constant. Despite these concerns, rates of both PCI and CABG were proportional during the course of the study and remain increasingly important outcomes for patients and physicians.

CONCLUSIONS

In a multiethnic cohort of subjects free of baseline cardiovascular disease, the overall burden and distribution of CAC are highly predictive of future coronary revascularization, including both PCI and CABG. Among subjects undergoing revascularization, more diffuse CAC was predictive of CABG compared with PCI. Additional research is necessary to further define whether the anatomic distribution of CAC can add to the risk stratification of other cardiovascular endpoints.

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REFERENCES

1. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
2. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210–5.
3. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. J Am Coll Cardiol 2005;46:158–65.
4. LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol 2005;162:421–9.
5. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Hoffman U, et al. Diagnostic and prognostic value of absence of coronary artery calcification. J Am Coll Cardiol Img 2009;2:675–88.
6. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. J Am Coll Cardiol Img 2009;2:692–700.
7. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2009; 158:554–61.
8. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610–6.
9. Erbel R, Möhlenkamp S, Moebus S, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397–406.
10. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010;56:2182–99.
11. Budoff MJ, Shaw LJ, Liu ST, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
12. Rosen BD, Fernandes V, McClelland RL, et al. Relationship between baseline coronary calcium score and demonstration of coronary artery stenoses during follow-up MESA (Multi-Ethnic Study of

Atherosclerosis). J Am Coll Cardiol Img 2009;2:1175–83.

13. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
14. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology 2005;234:35–43.
15. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
16. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012;308:788–95.
17. Nagal PC, Smith AW. Review of recent US cost estimates of revascularization. Am J Manag Care 2004;10:S370–6.
18. Shaw LJ, Min JK, Budoff M, et al. Induced cardiovascular procedural costs and resource consumption patterns after coronary artery calcium screening: results from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study. J Am Coll Cardiol 2009;54:1258–67.
19. He ZX, Hedrick TD, Pratt CM, et al. Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. Circulation 2000;101:244–51.
20. Berman DS, Wong ND, Gransar H, et al. Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. J Am Coll Cardiol 2004;44:923–30.
21. Schuijf JD, Wijns W, Jukema JW, Decramer I, Atsma DE, de Roos A, et al. A comparative regional analysis of coronary atherosclerosis and calcium score on multislice CT versus myocardial perfusion on SPECT. J Nucl Med 2006;47:1749–55.
22. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. Circulation 1996;93:898–904.
23. Qian Z, Anderson H, Marvasty I, et al. Lesion- and vessel-specific coronary artery calcium scores are superior to whole-heart Agatston and volume scores in the diagnosis of obstructive coronary artery disease. J Cardiovasc Comput Tomogr 2010;4:391–9.
24. Blaha MJ, Blumenthal RS, Budoff MJ, Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. Circ Cardiovasc Qual Outcomes 2011;4:253–6.
25. DeFilippis A, Blaha MJ, Ndumele CE, et al. The association of Framingham and Reynolds risk scores with incidence and progression of coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2011;58:2076–83.
26. Okwuosa TM, Greenland P, Burke GL, et al. Prediction of coronary artery calcium progression in individuals with low Framingham Risk Score: the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol Img 2012;5:144–53.
27. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: the Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol 2013;61:1231–9.

Key Words: cardiac CT ▪ coronary artery calcium ▪ coronary artery disease ▪ revascularization.

▶ APPENDIX

For supplemental tables and figures and their legends, please see the online version of this article.