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Implications of Coronary Artery Calcium Testing Among Statin Candidates According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines

MESA (Multi-Ethnic Study of Atherosclerosis)

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ABSTRACT

BACKGROUND The American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol management guidelines have significantly broadened the scope of candidates eligible for statin therapy.

OBJECTIVES This study evaluated the implications of the absence of coronary artery calcium (CAC) in reclassifying patients from a risk stratum in which statins are recommended to one in which they are not.

METHODS MESA (Multi-Ethnic Study of Atherosclerosis) is a longitudinal study of 6,814 men and women 45 to 84 years of age without clinical atherosclerotic cardiovascular disease (ASCVD) risk at enrollment. We excluded 1,100 participants (16%) on lipid-lowering medication, 87 (1.3%) without low-density lipoprotein levels, 26 (0.4%) with missing risk factors for calculation of 10-year risk of ASCVD, 633 (9%) >75 years of age, and 209 (3%) with low-density lipoprotein <70 mg/dl from the analysis.

RESULTS The study population consisted of 4,758 participants (age 59 ± 9 years; 47% males). A total of 247 (5.2%) ASCVD and 155 (3.3%) hard coronary heart disease events occurred over a median (interquartile range) follow-up of 10.3 (9.7 to 10.8) years. The new ACC/AHA guidelines recommended 2,377 (50%) MESA participants for moderate- to high-intensity statins; the majority (77%) was eligible because of a 10-year estimated ASCVD risk ≥7.5%. Of those recommended statins, 41% had CAC = 0 and had 5.2 ASCVD events/1,000 person-years. Among 589 participants (12%) considered for moderate-intensity statin, 338 (57%) had a CAC = 0, with an ASCVD event rate of 1.5 per 1,000 person-years. Of participants eligible (recommended or considered) for statins, 44% (1,316 of 2,966) had CAC = 0 at baseline and an observed 10-year ASCVD event rate of 4.2 per 1,000 person-years.

CONCLUSIONS Significant ASCVD risk heterogeneity exists among those eligible for statins according to the new guidelines. The absence of CAC reclassifies approximately one-half of candidates as not eligible for statin therapy. (J Am Coll Cardiol 2015;66:1657–68) © 2015 by the American College of Cardiology Foundation.

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In 2014, the American College of Cardiology (ACC) and the American Heart Association (AHA) accentuated the importance of atherosclerotic cardiovascular disease (ASCVD) risk derived from the Pooled Cohort Equations in determining candidates for statin therapy [1,2]. It is estimated that 45 million middle-aged adults in the United States free of established cardiovascular disease (CVD) are now recommended or considered for statins on the basis of their estimated 10-year ASCVD risks of ≥7.5% and 5% to 7.5%, respectively [1]. The implication for widening the scope of those eligible for statins has been widely debated [3-5]. Because the net benefit from treatment is directly proportional to the absolute risk [1], many of those newly eligible for statins will likely not accrue a large absolute reduction in risk from treatment. With a significant increase in the population eligible for treatment, accurate identification of low-risk statin candidates who are less likely to yield meaningful benefits is critical to facilitate appropriate resource allocation and shared decision-making processes.

<div align="center">SEE PAGES 1654 AND 1669</div>

Coronary artery calcium (CAC), detected by low radiation, noncontrast cardiac computed tomography testing, estimates the burden of coronary atherosclerosis and is a method for further risk stratification in the primary prevention setting [6,7]. Increased CAC is associated with almost a 10-fold higher risk of adverse ASCVD events, independent of the baseline traditional risk profile [6,7]. More importantly, the absence of CAC in an asymptomatic adult confers a very low risk for future cardiac events [8-11]. This can potentially allow patient choices to focus on low-cost lifestyle modifications and the pursuit of flexible treatment goals.

In this study, we specifically aimed to determine the implications of the absence of CAC in reclassifying ASCVD risk such that many participants currently eligible for statin therapy move to a category in which the guideline no longer recommends treatment. These results can have important implications for public health discussions aimed at improving the efficiency and cost-effectiveness of statin use in primary prevention settings.
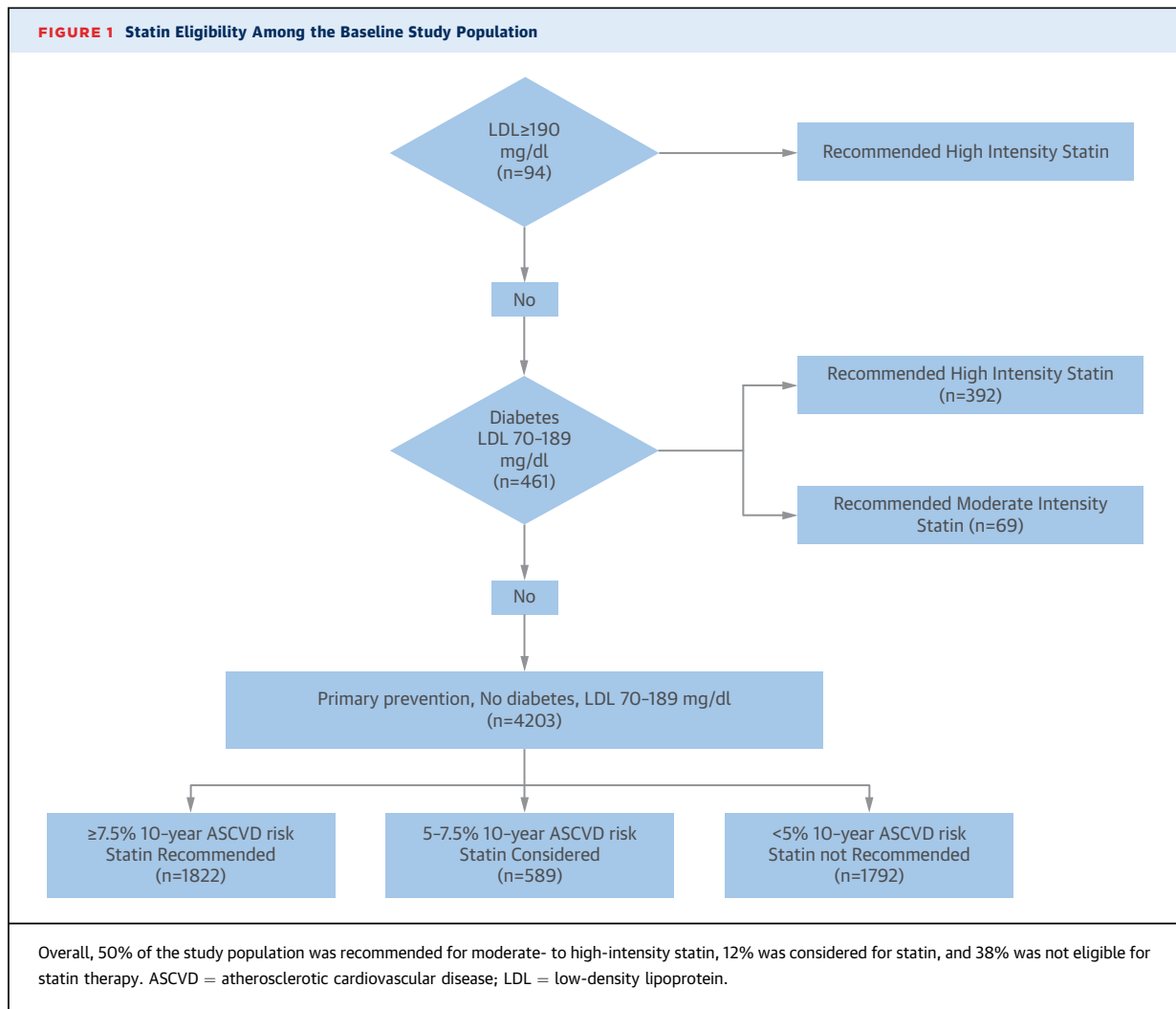
METHODS

STUDY PARTICIPANTS. Full details of the MESA (Multi-Ethnic Study of Atherosclerosis) study design have been published previously [12]. MESA is a prospective observational cohort of 6,814 men and women, 45 to 84 years of age, without known CVD at enrollment. Participants were enrolled from July 2000 through September 2002 at 6 different field centers in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Participants identified themselves as white, black, Chinese, or Hispanic at the time of enrollment. All participants gave written informed consent.

RISK FACTORS. As part of the baseline examination, staff at each of the 6 centers collected information about cardiovascular risk factors. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride measurements were performed at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota) in blood samples obtained after a 12-h fast. Diabetes was defined as fasting blood glucose ≥7.0 mmol/l (126 mg/dl), self-reported diabetes, or use of hypoglycemic drugs. Hypertension was defined as untreated diastolic blood pressure ≥90 mm Hg, systolic blood pressure ≥140 mm Hg, or use of antihypertensive medication. Smoking was defined as current use of cigarettes.

The 10-year risk of hard ASCVD events for MESA participants was calculated on the basis of age, total cholesterol and high-density lipoprotein cholesterol levels, systolic blood pressure, treatment of

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FIGURE 1　Statin Eligibility Among the Baseline Study Population

LDL≥190 mg/dl (n=94) → Recommended High Intensity Statin

No

Diabetes LDL 70–189 mg/dl (n=461) → Recommended High Intensity Statin (n=392)
→ Recommended Moderate Intensity Statin (n=69)

No

Primary prevention, No diabetes, LDL 70–189 mg/dl (n=4203)

≥7.5% 10-year ASCVD risk Statin Recommended (n=1822)

5–7.5% 10-year ASCVD risk Statin Considered (n=589)

<5% 10-year ASCVD risk Statin not Recommended (n=1792)

Overall, 50% of the study population was recommended for moderate- to high-intensity statin, 12% was considered for statin, and 38% was not eligible for statin therapy. ASCVD = atherosclerotic cardiovascular disease; LDL = low-density lipoprotein.

hypertension, current smoking, and history of diabetes mellitus, using the race-/sex-specific parameters from the ACC/AHA Pooled Cohort Equations with Hispanics/Chinese calculated as white (2).

STATIN ELIGIBILITY. On the basis of the ACC/AHA guidelines, MESA participants were classified into the following groups for statin eligibility (1).

1. **Statin recommended:** In accordance with strong evidence from randomized controlled trials suggesting that the reduction in ASCVD events from statin therapy exceeds adverse events when used in primary prevention.
   a. Low-density lipoprotein cholesterol (LDL-C) levels ≥190 mg/dl
   b. Diabetes and LDL-C levels between 70 and 189 mg/dl
   c. Without diabetes and with a 10-year ASCVD risk ≥7.5% and LDL-C levels between 70 and 189 mg/dl

2. **Statin considered:** Moderate evidence supports consideration of statin therapy for primary prevention in participants with a 10-year ASCVD risk of 5% to <7.5% (1).

CAC SCORE MEASUREMENTS. The MESA methods for computed tomography scanning and interpretation were published previously (13). All participants were scanned twice, with mean CAC (Agatston) score used for all analyses (14). Estimates of radiation dose determined according to the MESA protocol for a single scan obtained through the heart with the Imatron C150, Volume Zoom, and LightSpeed Pro 16 scanners were as follows: 0.6 and 0.7, 0.9 and 1.1, and 0.9 and 1.1 mSv for men and women, respectively (15). Participants were told that they had no CAC or that it was less than average, average, or greater than average, and that they should discuss the results with their physicians.

ASCERTAINMENT OF ASCVD EVENTS. At intervals of 9 to 12 months, an interviewer contacted each

TABLE 1	Baseline Characteristics of Study Population			
	Statin Recommended (n = 2,377)	Statin Considered (n = 589)	Statin Not Recommended (n = 1,792)	p Value
Age, yrs	64.7 ± 7.3	58.4 ± 6.5	52.4 ± 5.6	<0.001
Male	1,434 (60)	299 (51)	506 (28)	<0.001
Race				<0.001
White	795 (33)	220 (37)	772 (43)	
Black	791 (33)	180 (31)	326 (18)	
Hispanic	534 (23)	124 (21)	437 (25)	
Asian	257 (11)	65 (11)	257 (14)	
Diabetes	472 (20)	0 (0)	0 (0)	<0.001
Hypertension	1,439 (61)	194 (33)	317 (18)	<0.001
Smoking				<0.001
Never	1,023 (43)	280 (47)	1,079 (60)	
Former	918 (39)	211 (36)	569 (32)	
Current	436 (18)	98 (17)	144 (8)	
Education				<0.001
<High school	1,306 (56)	290 (50)	758 (43)	
College	291 (12)	71 (12)	256 (14)	
Bachelor or above	753 (32)	224 (38)	764 (43)	
Family history of CHD	948 (43)	237 (43)	652 (38)	0.002
BMI, kg/m^2	28.7 ± 5.3	28.5 ± 5.4	27.8 ± 5.8	<0.001
Total cholesterol, mg/dl	201.5 ± 34.8	199.8 ± 30.6	195.1 ± 29.4	<0.001
LDL-C, mg/dl	126.4 ± 31.2	124.6 ± 26.4	117.7 ± 25.5	<0.001
HDL-C, mg/dl	48.5 ± 13.8	49.9 ± 13.9	54.5 ± 15.2	<0.001
Triglycerides, mg/dl	132.8 ± 67.0	126.4 ± 64.4	114.5 ± 59.1	<0.001

Values are mean ± SD or n (%).

BMI = body mass index; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

participant or family member by telephone to inquire about interim hospital admissions, outpatient diagnoses of coronary heart disease (CHD) and CVD, and deaths. A MESA study committee of cardiologists, physician epidemiologists, and neurologists adjudicated ASCVD events. In the event of disagreement, the full committee made the final classification. MESA was successful in obtaining medical records for approximately 98% of reported hospitalized CHD and CVD events and information on 95% of reported outpatient cardiovascular diagnostic encounters. Follow-up telephone interviews were completed in 92% of living participants.

For the purpose of this study, CHD events were classified as myocardial infarction, resuscitated cardiac arrest, or CHD death. ASCVD events included CHD events plus nonfatal and fatal strokes. Transient ischemic attacks were not included. The diagnosis of myocardial infarction was on the basis of a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. We used hospital records and family interviews to determine whether deaths were related to CHD. A death was considered related to CHD if it occurred within 28 days after a myocardial infarction, if the participant had chest pain within 72 h before death, or if the participant had a history of CHD and there was no known non-atherosclerotic, noncardiac cause of death. Stroke was on the basis of rapid onset of a documented focal neurological deficit lasting 24 h or until death or, if <24 h, with accompanying evidence of a clinically relevant lesion on brain imaging. Study participants with focal neurological deficits secondary to brain trauma, tumor, infection, or other nonvascular cause were excluded. A more detailed description of the MESA follow-up methods is available at the MESA website (16).

STATISTICAL ANALYSIS. Baseline characteristics of the study participants were analyzed according to statin eligibility criteria. Frequencies and proportions were calculated for categorical variables, and either means with standard deviations or medians with interquartile ranges were calculated for continuous variables. Chi-square tests and 1-way analysis of variance were used for comparison of variables between groups. We used Kaplan-Meier estimates of cumulative event-free survival to describe the occurrence of ASCVD and CHD events over time. To determine if CAC can further stratify risk in statin eligibility groups, we compared ASCVD and CHD event rates, as well as Cox multivariable-adjusted hazard ratios, after stratifying by the CAC categories listed previously. Models were adjusted for age, sex, race/ethnicity, education level, and MESA site. A 10-year number needed to treat (NNT_{10}) for LDL-C lowering by statins was estimated for both ASCVD and CHD by applying the hazard ratio associated with the expected relative event reduction of 30% with a 1.0 mmol/l reduction in LDL-C on the basis of a Cochrane meta-analysis (17) of statin therapy in primary prevention. The NNT_{10} was calculated directly as the reciprocal of the absolute risk difference at the median follow-up of the cohort on the basis of Kaplan-Meier estimates and was subsequently adjusted to a NNT_{10} according to the Altman-Anderson method (18).

RESULTS

Of 6,814 participants at baseline, participants were excluded from the analysis as follows: 1,100 (16%) on lipid-lowering medication; 87 (1.3%) with absent LDL levels; 27 (0.4%) with missing risk factors for calculation of the 10-year risk of ASCVD using the new Pooled Cohort Equations; 633 (9%) age >75 years; and 209 (3%) with LDL <70 mg/dl.
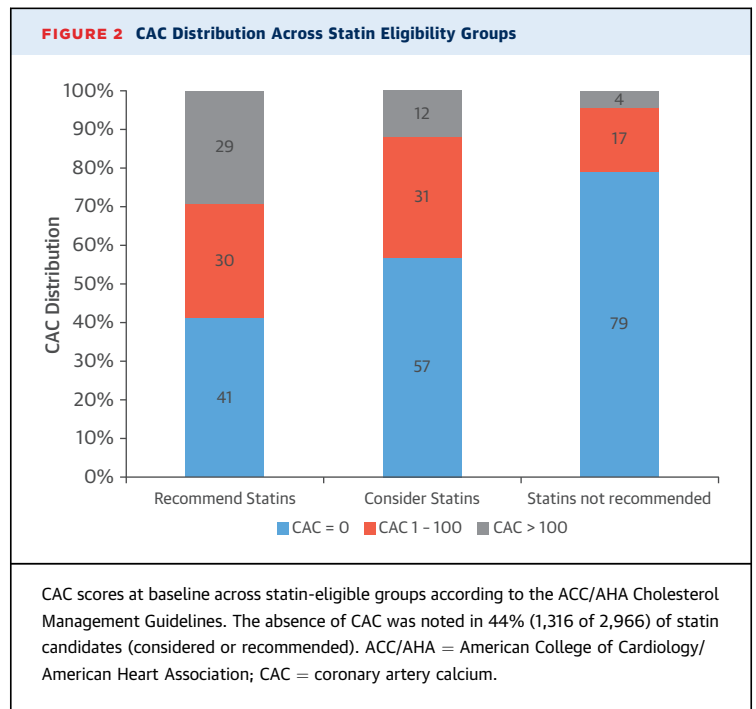
STATIN ELIGIBILITY ACCORDING TO ACC/AHA CHOLESTEROL MANAGEMENT GUIDELINES. The final study population consisted of 4,758 participants (59 ± 9 years, 47% males), among whom 2% (n = 94)

had LDL-C ≥190 mg/dl and 10% (n = 461) had diabetes with LDL-C 70 to 189 mg/dl and were eligible for moderate- to high-intensity statins (**Figure 1**). According to the ACC/AHA guidelines, 38% (n = 1,822) nondiabetic patients with LDL-C 70 to 189 mg/dl were eligible for moderate- to high-intensity statins because of their 10-year estimated ASCVD risk ≥7.5% (**Figure 1**). As a result, in total, 50% (n = 2,377) of the study participants were recommended statins. In addition, 589 (12%) were considered for moderate-intensity statins (nondiabetic patients, LDL-C 70 to 189 mg/dl and 10-year ASCVD risk 5% to 7.5%). Baseline characteristics of the study population according to statin eligibility are shown in **Table 1**.

DISTRIBUTION OF CAC ACCORDING TO STATIN ELIGIBILITY CRITERIA. Of the participants included in the analysis, 2,733 (58%) had CAC = 0, whereas 1,196 (25%) had CAC between 1 and 100 and 829 (17%) had CAC ≥100. The distribution of CAC according to statin-eligible groups is shown in **Figure 2**. Overall, 41% of MESA participants recommended for moderate- to high-intensity statins by ACC/AHA guidelines had CAC = 0. More than one-half (57%) of MESA participants considered for moderate-intensity statins (n = 338) had no detectable CAC. Conversely, only 21% (n = 375) who were not candidates for statins had CAC >0, with 4% demonstrating elevated CAC >100 (**Figure 2**).
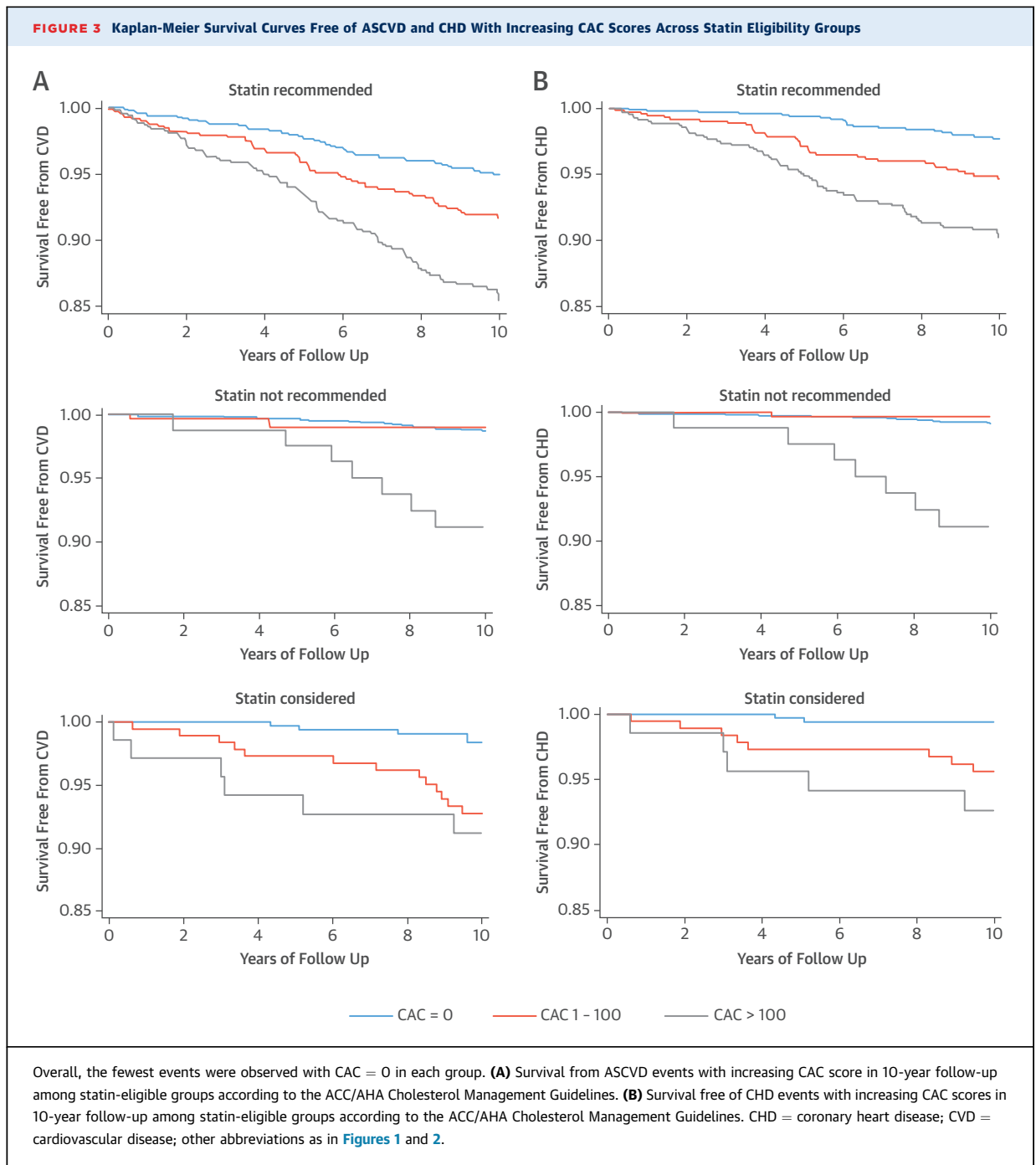
STATIN ELIGIBILITY AND INCIDENT CARDIOVASCULAR EVENTS. Over a median (interquartile range) follow-up of 10.3 (9.7 to 10.8) years, 247 (5.2%) ASCVD and 155 (3.3%) hard CHD events were observed. The ASCVD rate was 9.1 per 1,000 person-years (95% confidence interval [CI]: 7.9 to 10.5) for those recommended statins as compared with 4.00 (95% CI: 2.6 to 6.0) among those considered for statins and 1.62 (95% CI: 1.2 to 2.3) per 1,000 person-years among those who were not statin candidates. The respective CHD event rates in these groups were 5.5 (95% CI: 4.6 to 6.6), 2.4 (95% CI: 1.4 to 4.1), and 1.2 (95% CI: 0.8 to 1.8).

INCIDENT CARDIOVASCULAR EVENTS ACCORDING TO CAC SCORES ACROSS STATIN-ELIGIBLE GROUPS. Figure 3 shows Kaplan-Meier estimates of event-free survival for ASCVD and CHD among the population by CAC burden among groups according to statin eligibility criteria. The frequency of observed ASCVD and CHD events, the corresponding event rates per 1,000 person-years, and the multivariable-adjusted HRs associated with the prevalence and burden of CAC in MESA participants across statin eligibility criteria are detailed in **Table 2**. Among the 41% of participants

FIGURE 2 CAC Distribution Across Statin Eligibility Groups

CAC scores at baseline across statin-eligible groups according to the ACC/AHA Cholesterol Management Guidelines. The absence of CAC was noted in 44% (1,316 of 2,966) of statin candidates (considered or recommended). ACC/AHA = American College of Cardiology/American Heart Association; CAC = coronary artery calcium.

recommended for statins with CAC = 0, ASCVD events in 4.9% were noted as corresponding to 5.2 events per 1,000 person-years of follow-up. The respective ASCVD event rate among study participants considered for statins with CAC = 0 was 1.5 person-years. Overall, 44% (1,316 of 2,966) of statin-eligible (recommended or considered) candidates had CAC = 0 at baseline, with a subsequent ASCVD event rate of 4.2 per 1,000 person-years. In contrast, the presence of any CAC (56%) was associated with an ASCVD event rate of 11.2 per 1,000 person-years. In comparison, among participants not eligible for statins, the ASCVD event rates with any CAC present (21%) or CAC >100 (4%) were 2.7 per 1,000 person-years and 9.6 per 1,000 person-years, respectively (**Table 2**).

Figure 4 highlights the distribution of CAC burden across increasing 10-year ASCVD risk-score cutoffs among nondiabetic participants with LDL-C 70 to 189 mg/dl recommended for statins on the basis of their 10-year ASCVD risk ≥7.5% (n = 1,822). **Figures 5A and 5B** show that the lowest event rates were noted in those with CAC = 0 across increasing 10-year ASCVD risk estimates. Overall, 45% (618 of 1,381) of participants with 10-year ASCVD risks of 7.5% to 20% had CAC = 0, and corresponding observed 10-year ASCVD event rates of 4.6 per 1,000 person-years (**Central Illustration**). The respective ASCVD event rate with the presence of CAC in this group was 10.4 per 1,000 person-years. Conversely, among participants with estimated risk >20% (n = 441), absence of CAC was

FIGURE 3 Kaplan-Meier Survival Curves Free of ASCVD and CHD With Increasing CAC Scores Across Statin Eligibility Groups

Overall, the fewest events were observed with CAC = 0 in each group. **(A)** Survival from ASCVD events with increasing CAC score in 10-year follow-up among statin-eligible groups according to the ACC/AHA Cholesterol Management Guidelines. **(B)** Survival free of CHD events with increasing CAC scores in 10-year follow-up among statin-eligible groups according to the ACC/AHA Cholesterol Management Guidelines. CHD = coronary heart disease; CVD = cardiovascular disease; other abbreviations as in **Figures 1** and **2**.

noted in 26% (**Figure 4**), and the observed ASCVD risk was above the threshold recommended for treatment (11.7 per 1,000 person-years).

ESTIMATED NUMBER NEEDED TO TREAT TO PREVENT 1 CARDIOVASCULAR EVENT. As shown in **Table 3**, applying a 30% relative risk reduction associated with statin therapy, the NNT_{10} to prevent an ASCVD in

participants recommended for statins was 64 for those with CAC = 0 and 28 for those with CAC >100. The corresponding NNT_{10} in those considered for statins was 223 for those with CAC = 0 and 46 for those with CAC >100. When considering prevention of CHD, NNT_{10} in the absence of CAC was 139 among candidates recommended for statins and 556 for those considered for statins. Similar results were noted

TABLE 2 ASCVD and CHD Outcomes With CAC Across Statin Eligibility Groups

		ASCVD			CHD		
	N	**Events (%)**	**Event Rate Per 1,000 Person-Years (95% CI)**	**HR (95% CI)**	**Events (%)**	**Event Rate Per 1,000 Person-Years (95% CI)**	**HR (95% CI)**
Statin recommended	2,377						
CAC = 0	978	48 (4.9)	5.2 (4.0–7.0)	Reference group	22 (2.3)	2.4 (1.6–3.6)	Reference group
CAC 1–100	714	56 (7.9)	8.8 (6.8–11.4)	1.64 (1.11–2.43)	37 (5.2)	5.7 (4.1–7.9)	2.2 (1.3–3.8)
CAC >100	685	91 (13.3)	15.4 (12.5–18.9)	2.88 (1.97–4.21)	61 (8.9)	10.0 (7.8–12.8)	3.7 (2.2–6.3)
Any CAC present	1,399	147 (10.5)	12.0 (10.2–14.1)	2.15 (1.53–3.04)	98 (7.0)	7.8 (6.4–9.5)	2.9 (1.8–4.6)
Statin considered	589						
CAC = 0	338	5 (1.5)	1.5 (0.6–3.6)	Reference group	2 (0.6)	0.6 (0.2–2.4)	Reference group
CAC 1–100	184	14 (7.6)	7.8 (4.6–13.2)	5.45 (1.90–15.6)	9 (4.9)	5.0 (2.6–9.6)	7.5 (1.5–36.6)
CAC>100	67	4 (6.0)	6.3 (2.4–16.8)	4.23 (1.10–16.2)	3 (4.5)	4.7 (1.5–14.4)	8.2 (1.3–51.5)
Any CAC present	251	18 (7.2)	7.4 (4.7–11.8)	5.11 (1.8–14.1)	12 (4.8)	4.9 (2.8–8.6)	7.7 (1.7–35.9)
Statin not recommended	1,792						
CAC = 0	1,417	19 (1.3)	1.3 (0.9–2.1)	Reference group	13 (0.9)	0.9 (0.5–1.6)	Reference group
CAC 1–100	298	3 (1.0)	1.0 (0.3–3.1)	0.7 (0.2–2.3)	1 (0.3)	0.3 (0.1–2.3)	0.3 (0.4–2.5)
CAC >100	77	7 (9.1)	9.6 (4.6–20.2)	6.1 (2.4–15.6)	7 (9.1)	9.6 (4.6–20.1)	8.9 (3.2–24.4)
Any CAC present	375	10 (2.7)	2.7 (1.4–5.0)	1.7 (0.7–3.9)	8 (2.1)	2.1 (1.0–4.3)	1.8 (0.78–4.9)

Adjusted for age, sex, race, MESA site, and education status (CAC = 0 was the reference group). Statin recommended: patients 45 to 75 years of age with primary elevations of LDL-C ≥190 mg/dl, or diabetes and LDL-C 70 to 189 mg/dl, or nondiabetic patient with LDL-C 70 to 189 mg/dl and an estimated 10-year ASCVD risk of 7.5% or higher. Statin considered: 10-year ASCVD risk 5% to <7.5%, Statin not recommended: 10-year ASCVD risk <5%.

ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MESA = Multiethnic Study of Atherosclerosis.

across increasing risk categories among those with ASCVD risk >7.5% (Online Table 1). Online Tables 2 and 3 highlight the results of the sensitivity analyses for the estimated NNT_{10} among statin-eligible groups as well as increased ASCVD risk estimates.

INCIDENT CARDIOVASCULAR EVENTS ACCORDING TO CAC SCORES AMONG PATIENTS WITH DIABETES. Among patients with diabetes with LDL-C 70 to 189 mg/dl, the absence of CAC was associated with an ASCVD event rate of 4.9 per 1,000 person-years and a corresponding NNT_{10} of 69 to prevent 1 event. The respective ASCVD event rate and NNT_{10} among those with CAC >0 was 14.7 per 1,000 person-years and 23 (Online Table 4).

INCIDENT CARDIOVASCULAR EVENTS ACCORDING TO CAC SCORES AMONG THE ELDERLY (>75 YEARS) AND THOSE WITH LOW LDL-C (<70 mg/dl). In our study, among 633 participants >75 years of age who were excluded from analysis, almost all (99%) were recommended for statins, as per ACC/AHA cholesterol management guidelines. Overall, 18% of these elderly participants had CAC = 0, whereas 30% and 52% had CAC between 1 and 100 and CAC >100, respectively. The respective 10-year event rates across these CAC categories were 6.7 per 1,000, 18.0 per 1,000, and 26.8 per 1,000 person-years.
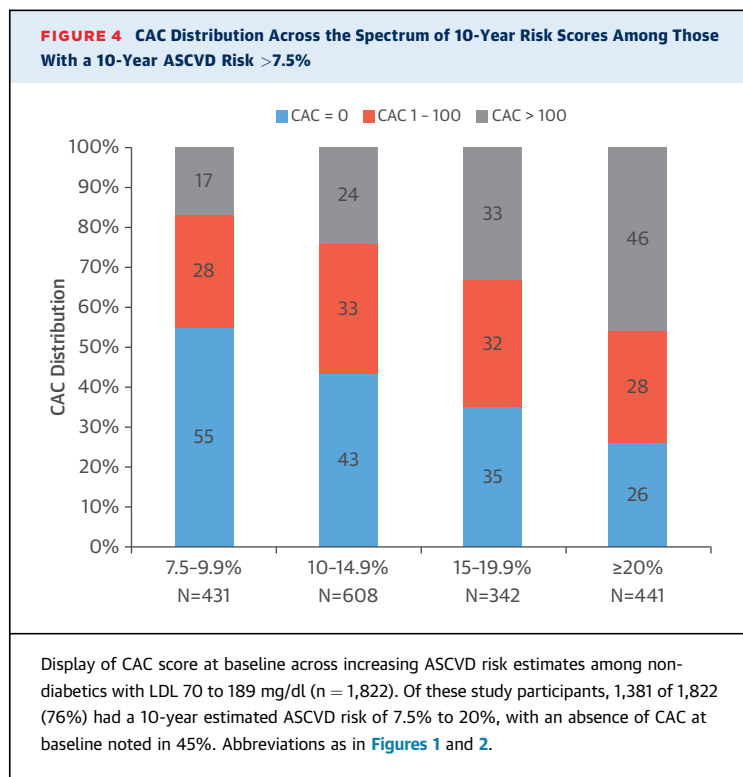
Among study participants with LDL-C <70 mg/dl who were excluded from the primary analysis, the majority (67%) had CAC = 0, whereas 21% had CAC 1 to 100 and 12% had CAC >100. Overall, the revised risk above the threshold for considering statins was only noted in those with CAC >100 (10-year observed ASCVD event rates for CAC = 0: 2.9 per 1,000 person-years; CAC 1 to 100: 2.6 per 1,000 person-years; and CAC >100: 9.5 per 1,000 person-years).

DISCUSSION

When applying the 2013 ACC/AHA cholesterol treatment guidelines (1), we noted that nearly two-thirds of MESA participants 45 to 75 years of age without known CVD are potentially eligible for statins (recommended or considered). Approximately one-half of these statin-eligible candidates had CAC = 0 and, as a group, had a lower 10-year observed ASCVD risk than the threshold recommended for treatment. The majority of ASCVD events occurred among those with detectable CAC, consistent with 10-year risk levels suggested by ACC/AHA cholesterol management guidelines for statin therapy.

Since the release of the ACC/AHA cholesterol management guidelines in 2013, the central role of 10-year ASCVD risk estimation in guiding statin eligibility has received considerable attention (3–5). Recent studies have demonstrated that the impact of the updated recommendations will be higher treatment rates among those expected to have future cardiovascular

FIGURE 4 CAC Distribution Across the Spectrum of 10-Year Risk Scores Among Those With a 10-Year ASCVD Risk >7.5%

Display of CAC score at baseline across increasing ASCVD risk estimates among non-diabetics with LDL 70 to 189 mg/dl (n = 1,822). Of these study participants, 1,381 of 1,822 (76%) had a 10-year estimated ASCVD risk of 7.5% to 20%, with an absence of CAC at baseline noted in 45%. Abbreviations as in **Figures 1** and **2**.

events (19), such as those with increased atherosclerotic burden, as compared with prior guidelines (20). However, we are also challenged to treat a significant proportion of patients in low-risk groups, who may derive minimal benefit from these therapies. Accurate risk assessment that can identify these lower-risk subjects can potentially have a profound impact in facilitating appropriate resource allocation and shared decision-making to allow flexible treatment choices.

Our study results suggest that the absence of CAC can potentially overcome these challenges by providing incremental information that may move many people from risk levels that are recommended for treatment to risk levels that are not. This observation is consistent with prior reports highlighting the value of the absence of CAC (power of zero). In a pooled analysis of more than 71,000 patients with CAC = 0, only 0.5% of participants suffered an adverse event in a 4.2-year follow-up (8). In the prospective MESA and Heinz Nixdorf Recall cohorts, only 1% of participants had a hard CHD event during 5 years of follow-up (6,7). Furthermore, CAC = 0 has also been associated with a much more favorable prognosis, even among groups traditionally considered at higher risk (9-11,21). Our current study adds to the literature by demonstrating that the absence of CAC is associated with a meaningfully lower ASCVD risk among those deemed as statin candidates in a

follow-up extending to 10 years. Among 41% who were recommended moderate- to high-intensity statins and who had no detectable CAC, only 4.9% experienced an ASCVD event. Furthermore, in those considered for statins (10-year risk of 5% to 7.5%), the absence of CAC was noted in a much larger proportion (57%), with an extremely low 10-year ASCVD risk of 1.5%.

These findings may have important implications. The patient-centered emphasis within the guidelines recognizes that thresholds identified for treatment do not mandate a statin prescription, but rather call for a discussion between providers and patients to foster informed decisions regarding initiation of statin therapy (1). The process by which individual patients reach an informed choice when considering a statin medication for the next 10 years, in which they balance concerns of side effects, costs, and burden of use, is also influenced by the estimate of the absolute risk reduction likely to be achieved (1,22-24). As the absolute ASCVD risk decreases, so does the net benefit of any intervention with a relative risk reduction that does not increase with lower patient risk. In these circumstances, the absence of CAC can afford significant value in promoting shared decision-making and better informing patients, who may consider avoiding statins to focus on prudent lifestyle changes, of their choices.

Our study findings also suggest that CAC testing may have limited impact on decisions regarding statin utilization in a meaningful manner at the extremes of calculated 10-year ASCVD risk. For example, among MESA participants with a 10-year ASCVD risk <5%, we noted an extremely low 10-year event rate of 1.6%. The majority (79%) of these participants have CAC = 0. The presence of mild CAC (1 to 100) did not result in reclassifying ASCVD risk above 5%, with only 4% of participants with CAC >100 having an observed ASCVD risk above the threshold for statin eligibility. Although the current guidelines suggest that CAC testing can be considered in selected patients among those with ASCVD risk <5% to inform treatment decision-making, because 25 patients will need to be scanned to influence the treatment decision, its utility in this group is likely to be limited. At the other end of the risk spectrum (estimated 10-year risk >20%), although the presence of CAC = 0 is associated with a much lower observed event rate of 11% than predicted, it may not impact the decision to avoid statins because the risk still remains above the threshold suggested by the guidelines for treatment (1). By avoiding testing at the extremes of risk (<5% and >20%), 49% of study participants with 10-year ASVCD risk estimates of 5% to 20% can be reclassified by the absence of CAC to a risk threshold below that

FIGURE 5 ASCVD and CHD Rates Among Nondiabetics With LDL-C From 70 to 189 mg/dl Across the Spectrum of CAC Burden and Increasing 10-Year ASCVD Risk >7.5% Categories
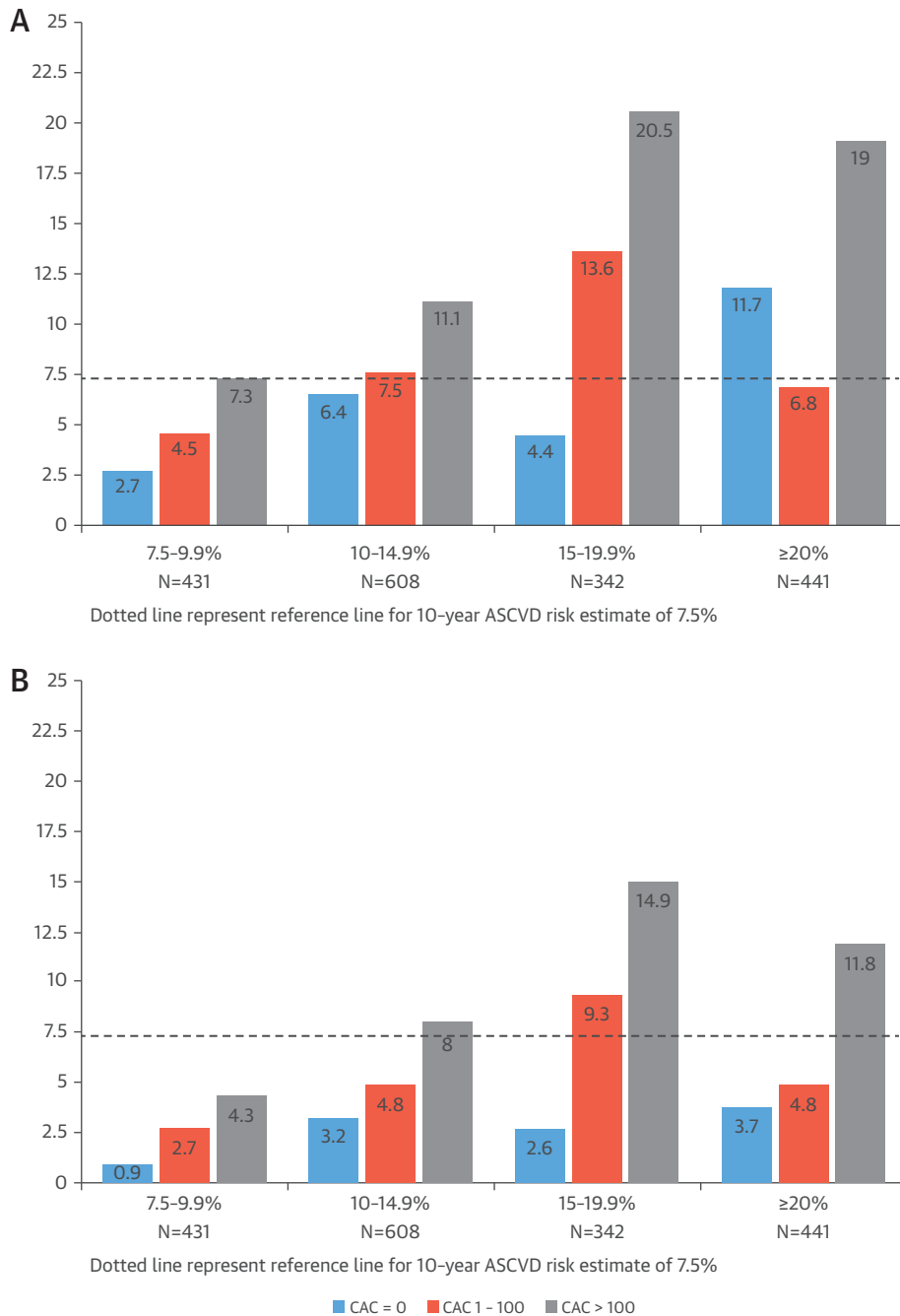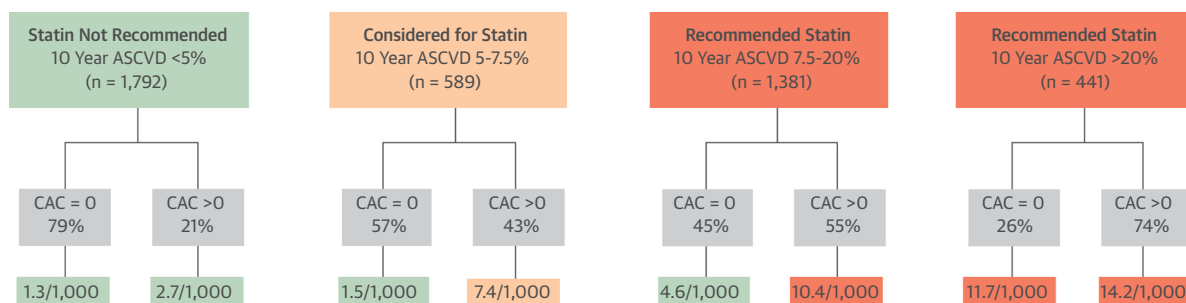

The lowest event rates were noted in those with CAC = 0 across increasing 10-year risk estimates among nondiabetics with LDL 70 to 189 mg/dl (n = 1,822). **(A)** ASCVD event rate per 1,000 persons. **(B)** CHD event rate per 1,000 persons. LDL-C = low-density lipoprotein cholesterol; other abbreviations as in **Figures 1**, **2**, and **3**.

suggested for statin therapy (**Central Illustration**). In addition, among participants not considered for statins by current guidelines, such as those >75 years of age and with LDL-C <70 mg/dl, CAC testing may have limited impact because it provided meaningful risk reclassification in approximately 10% of study participants to influence the decision regarding statin use.

CENTRAL ILLUSTRATION Impact of the Absence of CAC in Reclassifying Risk Below the Threshold for Statin Consideration Suggested by ACC/AHA Cholesterol Management Guidelines Across the Spectrum of Estimated 10-Year ASCVD Risk Score (Nondiabetic Patients With LDL-C of 70 to 189 mg/dl)

Statin Not Recommended 10 Year ASCVD <5% (n = 1,792)		Considered for Statin 10 Year ASCVD 5-7.5% (n = 589)		Recommended Statin 10 Year ASCVD 7.5-20% (n = 1,381)		Recommended Statin 10 Year ASCVD >20% (n = 441)	
CAC = 0 79%	CAC >0 21%	CAC = 0 57%	CAC >0 43%	CAC = 0 45%	CAC >0 55%	CAC = 0 26%	CAC >0 74%
1.3/1,000	2.7/1,000	1.5/1,000	7.4/1,000	4.6/1,000	10.4/1,000	11.7/1,000	14.2/1,000

Nasir, K. et al. J Am Coll Cardiol. 2015; 66(15):1657–68.

The absence of CAC reclassifies risk below the threshold for statin consideration in 40% (956 of 2,411) of statin candidates (>5% ASCVD estimate), and in 49% (956 of 1,970) of those with ASCVD risk between 5% and 20%. ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; LDL-C = low-density lipoprotein cholesterol.

Consideration of CAC testing for identifying appropriate candidates for statin therapy is not a straightforward decision; the pros and cons of this strategy deserve further discussion. First, with current guidelines, nearly two-thirds of U.S. adults are already candidates (recommended or considered) for statins. In this setting, screening with CAC testing to identify additional candidates for preventive treatments is questionable. We believe that the value of CAC testing in the current era may be in limiting the scope of statin therapy to more selective use, rather than in expanding it. Wijns et al. termed this risk-reduction approach "interventional prevention" (25). Second, it is important to realize that CAC testing adds to health care costs. The average national cost for CAC testing is around $100, which may be equivalent to 18 months of a generic statin priced at $5 per month. Noncardiac findings on CAC testing, such as nodules, can generate recommendations for follow-up imaging in approximately 5% of adults without a history of smoking. However, a recent study from MESA has demonstrated that even accounting for this, it may still be cost-effective to treat only those with CAC >0, compared with strategies from established risk-assessment guidelines (26). There are also concerns that CAC scoring may lead to additional cardiac testing and interventions, although a recent report from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study showed no such trends, with fewer downstream tests noted among those with CAC = 0 (27). In addition, the literature supports significant lifestyle optimization as well as improved preventive medication adherence among those with increasing CAC burden (28). Third, CAC testing is associated with an average radiation dose of 0.89 mSv compared with background radiation of 3 mSv per year, which should be

TABLE 3 Estimated 10-Year NNT for an ASCVD and CHD Event by CAC Burden Across Statin-Eligible Groups

	N	ASCVD *10-Year NNT (30% RRR)	CHD *10-Year NNT (30% RRR)
Statin recommended	2,377		
CAC = 0	978	64	139
CAC 1-100	714	38	59
CAC >100	685	22	34
Any CAC present	1,399	28	43
Statin considered	589		
CAC = 0	338	223	556
CAC 1-100	184	43	67
CAC >100	67	53	71
Any CAC present	251	46	69
Statin not recommended	1,792		
CAC = 0	1,417	257	371
CAC 1-100	298	334	1,112
CAC >100	77	35	35
Any CAC present	375	124	159

*30% relative risk reduction from a Cochrane meta-analysis of statin therapy in primary prevention. Statin recommended: patients aged 45 to 75 years of age with primary elevations of LDL-C ≥190 mg/dl, diabetes with LDL-C 70-189 mg/dl, nondiabetic with LDL-C 70-189 mg/dl, and an estimated 10-year ASCVD risk of 7.5% or higher. Statin considered: 10-year ASCVD risk 5% to <7.5%. Statin not recommended: 10-year ASCVD <5%.

NNT = number needed to treat; RRR = relative risk reduction; other abbreviations as in **Tables 1** and **2**.

discussed with the patient to allow informed decision-making. Finally, it is also important to note that our study does not address the issue of whether a CAC-based strategy versus guideline-based recommendations for statin selection is better or will have a favorable impact on outcomes; this vital question needs to be critically tested by well-designed comparative-effectiveness clinical studies.

STUDY LIMITATIONS. Subjects enrolling in research studies such as MESA may be more health-conscious, with better general risk profiles, and, as a result, have a lower risk for cardiovascular events. However, on the basis of risk factor clustering, a similar proportion of MESA participants were candidates for statin therapy compared with national estimates. In MESA, CAC scores were reported to participants and their physicians, which may have led to extensive risk modification that influenced ASCVD events. In spite of these potential early interventions, the 10-year observed ASCVD risk was consistently above the threshold for statin recommendation in the presence of a higher CAC burden.

CONCLUSIONS

Significant heterogeneity exists among those eligible for statins according to the ACC/AHA cholesterol management guidelines. Approximately one-half of these candidates have no detectable CAC, and, as a result, they have a much lower observed 10-year ASCVD risk and a higher estimated NNT to prevent 1

event. These findings should stimulate discussions among key stakeholders on the potential role of CAC = 0 to facilitate shared decision-making processes for flexible treatment goals in patients deemed eligible for lifelong statins.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Nearly one-half of patients without established atherosclerosis, who are classified as eligible for statin therapy according to the 2013 ACC/AHA blood cholesterol guidelines, have no detectable CAC, suggesting that their 10-year risk of clinical events may be lower than those for whom statin use is generally recommended.

TRANSLATIONAL OUTLOOK: Among candidates for statin therapy, clinicians should consider the role of CAC testing in shared decision-making processes to facilitate informed choices for flexible treatment goals.

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KEY WORDS atherosclerosis, cholesterol, hydroxymethylglutaryl-CoA reductase inhibitors, risk assessment

APPENDIX For a full list of participating MESA investigators and institutions as well as supplemental tables, please see the online version of this article.