

Statin Eligibility, Coronary Artery Calcium, and Subsequent Cardiovascular Events According to the 2016 United States Preventive Services Task Force (USPSTF) Statin Guidelines: MESA (Multi-Ethnic Study of Atherosclerosis)

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Background—The potential impact of the 2016 United States Preventive Services Task Force (USPSTF) guidelines on statins for primary prevention of atherosclerotic cardiovascular disease (ASCVD) warrants further analysis.

Methods and Results—We studied participants from MESA (Multi-Ethnic Study of Atherosclerosis) aged 40 to 75 years and not on statins. We compared statin eligibility at baseline (2000–2002) and over follow-up between USPSTF and the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Coronary artery calcium (CAC) was measured at baseline. Absolute ASCVD event rates were calculated according to eligibility categories for each guideline. Among 4962 MESA participants (aged 59.3 ± 8.8 years, 47.2% female), compared with ACC/AHA guidelines, baseline statin eligibility by USPSTF was significantly lower (34.4% versus 49.1%) and increased less over time (39.1% versus 59.1%) at examination 5 [years 2010–2012]. Compared with ACC/AHA, participants eligible by USPSTF were less likely to have zero CAC at baseline (36.6% versus 41.2%) and had higher rates of hard ASCVD events per 1000 person-years (11.6 [95% confidence interval, 10.2–13.3] versus 10.0 [8.9–11.3]). The hard ASCVD event rate in those eligible by ACC/AHA but not USPSTF was 6.5 (4.9–8.5) events per 1000 person-years, with the rate varying significantly according to baseline CAC (4.2 [2.7–6.7] events in those with CAC=0, 12.8 [8.3–19.9] events in those with CAC >100).

Conclusions—In MESA, compared with ACC/AHA, the USPSTF statin guidelines resulted in a 15% absolute decrease in eligibility. Participants with discordant eligibility had ASCVD rates that varied significantly according to baseline CAC, suggesting CAC could aid clinical decision making for statins in these individuals. (*J Am Heart Assoc.* 2018;7:e008920. DOI: 10.1161/JAHA.118.008920.)

Key Words: guideline • primary prevention • statin therapy

In 2016, the United States Preventive Services Task Force (USPSTF) released guidelines on statin use for the primary prevention of atherosclerotic cardiovascular disease (ASCVD).¹ These guidelines recommended that individuals aged 40 to 75 years with 1 or more major ASCVD risk factors (hypertension, tobacco use, diabetes mellitus, or dyslipidemia) and a 10-year ASCVD risk $\geq 10\%$ initiate statin therapy. Similar to the USPSTF guidelines, the 2013 American College of

Cardiology (ACC)/American Heart Association (AHA) guidelines for the treatment of blood cholesterol recommended a risk-based approach to allocation of statin therapy in primary prevention,² with an important focus on a clinician–patient risk discussion before initiation of statin therapy.³ The ACC/AHA guidelines identified a lower threshold for initiating statin therapy compared with the USPSTF guidelines, recommending statins for individuals with a 10-year ASCVD risk $\geq 7.5\%$.

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Clinical Perspective

What Is New?

- Using data from MESA (Multi-Ethnic Study of Atherosclerosis), we found that application of the United States Preventive Services Task Force statin guidelines resulted in a 15% absolute decrease in statin eligibility compared with the 2013 American College of Cardiology/American Heart Association guidelines.
- MESA participants with discordant statin eligibility according to the 2 guidelines had atherosclerotic cardiovascular disease events rates that varied significantly according to baseline coronary artery calcium.

What Are the Clinical Implications?

- Healthcare providers and organizations should understand that adoption of the USPSTF guidelines, compared to the ACC/AHA guidelines, will lead to a significant decrease in statin eligibility at a population level.
- For individuals with discordant statin recommendations, coronary artery calcium testing may be useful as a tool to guideline clinical decision making regarding statin use.

Importantly, the presence of 1 major ASCVD risk factor is not required by the ACC/AHA guidelines, leading to the observation that individuals may be eligible for statin therapy based on age alone.⁴ Prior studies have demonstrated that age plays a significant role in determining statin eligibility according to the ACC/AHA guidelines.^{5,6}

Recent data from the National Health and Nutrition Examination Survey (NHANES) estimated that \approx 9 million fewer middle-aged US adults are statin eligible using USPSTF criteria compared with ACC/AHA guidelines.⁷ The implications of not recommending statin therapy for this significant portion of the US population are unclear. The goal of this analysis was to compare the prevalence of statin eligibility according to the 2 guidelines in MESA (Multi-Ethnic Study of Atherosclerosis) participants at baseline and over 4 follow-up examinations as well as to analyze the prevalence of coronary artery calcium (CAC) at baseline according to guideline eligibility categories. Additionally, we sought to analyze ASCVD event rates over time according to statin eligibility categories within each guideline as well as in those individuals with discordant recommendations.

Methods

Study Design and Participants

MESA is a community-based prospective cohort study of asymptomatic individuals to determine factors associated with the prevalence, incidence, progression, and implications

of subclinical and clinical ASCVD. Details of the MESA study design and objectives have been previously reported.⁸ Briefly, 6814 participants aged 45 to 84 years old who were free of clinical cardiovascular disease at baseline were enrolled between 2000 and 2002 (baseline visit) at 6 US field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). Four additional follow-up visits (examinations 2–5) were conducted in 2002 to 2004, 2004 to 2006, 2005 to 2007, and 2010 to 2012. This study was approved by the institutional review boards at each center and all participants provided written informed consent. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Use of statin therapy, including frequency and dosage, was evaluated by self-report and also review of pharmacy containers for all medications used during the 2 weeks preceding the MESA visit. Of the 6814 MESA participants at baseline, we excluded 806 participants aged >75 years old (both statin guidelines target individuals aged 40–75 years old), 859 on statin therapy at baseline, 3 participants missing statin use data, and 184 with a low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (both guidelines exclude these individuals because of probable familial hypercholesterolemia), leaving 4962 individuals in the baseline analysis.

Measurement and Definition of CVD Risk Factors

Systolic and diastolic blood pressure were measured 3 times using an automated sphygmomanometer (Dinamap, Critikon, Tampa, FL), with 1-minute intervals, and the mean of the last 2 measurements was used. The Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, MN) measured concentrations of total and high-density lipoprotein cholesterol, triglycerides, and plasma glucose, after a 12-hour fast. LDL-C was calculated using the Friedewald equation.

Traditional ASCVD risk factors were identified based on definitions used by the USPSTF guidelines.¹ Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, or a diastolic blood pressure ≥ 90 mm Hg, or antihypertensive medication use. Diabetes mellitus was defined as a fasting glucose of ≥ 7 mmol/L (126 mg/dL) or use of hypoglycemic medication (oral agents and/or insulin). Dyslipidemia was defined as an LDL-C > 130 mg/dL or a high-density lipoprotein cholesterol < 40 mg/dL. Tobacco use was defined as current tobacco within the last 30 days of the time of the baseline MESA examination.

Measurement of CAC

CAC is not included in the primary eligibility criteria for either guideline. However, MESA includes CAC scores on everyone,

enabling analysis of the burden of subclinical coronary atherosclerosis in different eligibility categories for each guideline. CAC scoring was performed with cardiac-gated chest computed tomography (CT) utilizing either an electron-beam CT scanner (Los Angeles, Baltimore, and New York) or a multidetector CT system (Chicago, St. Paul, and Forsyth County).⁹ All patients were scanned twice and CAC Agatston scores were averaged. A cardiologist or radiologist interpreted all scans at the MESA CT reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center).

Assessing Statin Eligibility Based on the USPSTF and the ACC/AHA Guidelines

As described in the guidelines for both the USPSTF and ACC/AHA, 10-year ASCVD risk was calculated by the Pooled Cohorts Equation (PCE),² using data from the baseline MESA examination on age, sex, race, total cholesterol, high-density lipoprotein cholesterol, history of antihypertensive treatment, and diabetes mellitus. Participants were considered eligible according to the USPSTF guidelines if they had 1 or more major ASCVD risk factors (hypertension, tobacco use, diabetes mellitus, or dyslipidemia) and a 10-year ASCVD risk $\geq 10\%$. Participants with 1 major ASCVD risk factor and a 10-year risk of $\geq 7.5\%$ and $< 10\%$ were considered potentially eligible and participants with ASCVD risk of $< 7.5\%$ were considered not eligible.¹

For primary prevention in individuals with an LDL-C < 190 mg/dL, the ACC/AHA guidelines recommend moderate- to high-intensity statin therapy for patients with diabetes mellitus or individuals with an estimated 10-year ASCVD risk $\geq 7.5\%$. Per ACC/AHA guidelines, individuals with a 10-year ASCVD risk $\geq 5\%$ and $< 7.5\%$ were considered potentially eligible, and individuals with a 10-year ASCVD risk $< 5\%$ were considered not eligible for statin treatment.²

To assess eligibility over time, we reassessed eligibility at each MESA examination based on updated risk factor data and recalculation of 10-year ASCVD risk. Individuals were excluded at each follow-up visit if they had developed ASCVD or started statin therapy. Of the 4962 individuals included in our study at baseline, 1062 were excluded at examination 2, 375 at examination 3, 455 at examination 4, and 1035 at examination 5, leaving 2035 participants who remained free of ASCVD and not on statin therapy at the time of examination 5.

Assessment of CVD Outcomes During Follow-Up

MESA staff contacted each participant or a family member about interim hospital admissions, outpatient diagnoses of ASCVD, and deaths at 9-to-12-month intervals. Follow-up telephone interviews were completed in 92% of living

participants or relatives of deceased individuals. Medical records were successfully obtained for $\approx 98\%$ of hospitalized events and 95% of outpatient cardiovascular diagnoses. Two physicians from the MESA mortality and morbidity review committee independently adjudicated events. In the event of a disagreement, a consensus was made by the full committee.

The PCE used for risk calculation in both guidelines calculates the 10-year risk for hard ASCVD outcomes including nonfatal myocardial infarction, coronary heart disease (CHD) death, and fatal or nonfatal stroke. We therefore used a similar definition for hard ASCVD events. Hard CHD included myocardial infarction, resuscitated cardiac arrest, and CHD death. Hard ASCVD included hard CHD events plus nonfatal and fatal stroke. All CHD included coronary revascularization in addition to hard CHD events. All ASCVD included all CHD plus stroke and transient ischemic attacks. A more detailed description of the follow-up methods and event classification is available on the MESA website.¹⁰

Statistical Analysis

We tabulated baseline characteristics for the total population, across statin-eligibility categories as defined by the USPSTF and ACC/AHA guidelines, and the “discordant” group that was statin eligible by ACC/AHA but not USPSTF criteria. Continuous variables were presented as mean \pm SD for normally distributed data and medians with interquartile ranges for non-normally distributed data. Categorical data were presented as frequencies and proportions. We calculated changes in statin eligibility over time, determining changes in the absolute prevalence of statin eligibility for each guideline at subsequent MESA follow-up visits as well as relative percentage increases in eligibility compared with baseline.

Absolute ASCVD event rates were calculated by dividing the total number of events by total person-years contributed (expressed per 1000 person-years) based on statin eligibility categories at the time of the baseline examination. Events were also presented as total number and proportion of each statin-eligibility category. Kaplan–Meier survival curves were constructed for ASCVD events in each statin-eligibility guideline definition. The log-rank was used to test the equality of survivor functions among statin-eligibility groups.

Using eligibility categories at the time of the baseline examination, Cox proportional hazards regression models were used to model time-to-first event for each ASCVD outcome including hard ASCVD, all ASCVD, hard CHD, all CHD, myocardial infarction, and stroke. Using not statin eligible as the reference group in both guideline definitions, comparisons of event risk were made between the eligibility categories. To control for potential confounding, income, MESA site, and body mass index were included in our adjusted models. All statistical analyses were conducted

using STATA 13 (Stata Corp., College Station, TX). A *P* value of <0.05 was considered statistically significant.

Results

The baseline characteristics of the 4962 MESA participants (mean age 59.3±8.8 years, 47.2% female) included in the study are shown in Table 1, stratified according to statin eligibility by the USPSTF and ACC/AHA guidelines. According to the USPSTF guidelines, 1709 (34.4%) of MESA participants at the time of the baseline examination were eligible for statin therapy, 384 (7.7%) were potentially eligible, and 2869 individuals (57.8%) were not eligible. According to ACC/AHA guidelines, 2436 (49.1%) of MESA participants were statin eligible, 617 (12.4%) were potentially statin eligible, and 1909 (38.5%) were not eligible for statin therapy.

The changes in the prevalence of statin eligibility over time according to both guidelines are shown in Figure A. Statin eligibility increased over the course of the follow-up examinations according to both guidelines, though eligibility according to ACC/AHA guidelines increased more significantly with 59.1% eligible at examination 5 (20.4% increase from baseline) compared with 39.1% (13.7% increase) by USPSTF. At examination 5, only 544 individuals (26.7%) were not statin eligible according to ACC/AHA compared with 1042 individuals (51.2%) not eligible according to USPSTF guidelines.

Participants eligible by USPSTF recommendations compared with ACC/AHA tended to be older and male with a higher prevalence of diabetes mellitus, hypertension, and smoking (Table 1). USPSTF guidelines require at least 1 major ASCVD risk factor and therefore no participants with zero major risk factors qualified for statin therapy compared with 266 (10.9% of ACC/AHA eligible participants) who qualified by ACC/AHA despite having zero major risk factors. Those eligible by USPSTF were more likely to have significant subclinical atherosclerosis, with 32.8% having CAC ≥100 compared with 28.9% in those eligible by ACC/AHA. Additionally, participants eligible by USPSTF were less likely to have zero CAC as 36.6% of those eligible by USPSTF had CAC=0 compared with 41.2% of those eligible by ACC/AHA. The prevalence of CAC=0 and CAC >100 according to eligibility categories for each guideline is shown in Figure B.

The absolute cardiovascular event rates per 1000 person-years by statin eligibility categories at baseline according to the USPSTF and the ACC/AHA guidelines are shown in Table 2 and Figure C. The median follow-up was 12.4 years (interquartile ranges 11.8, 12.8). ASCVD event rates varied significantly according to eligibility categories within either guideline. ASCVD event rates according to USPSTF criteria were higher in all 3 eligibility categories compared with ACC/AHA. Individuals who were eligible for statin therapy by USPSTF experienced 11.6 (95% confidence interval [CI], 10.2–

13.3) hard ASCVD events per 1000 person-years compared with a hard ASCVD event rate of 2.8 (95% CI, 2.8–3.5) in those who were not eligible according to USPSTF. Individuals eligible according to ACC/AHA experienced 10.0 (95% CI, 8.9–11.3) hard ASCVD events per 1000 person-years compared with 1.8 (95% CI, 1.3–2.4) events in those not eligible according to ACC/AHA.

The baseline characteristics of the 727 (14.7%) individuals with “discordant” recommendations who were eligible for statin therapy according to ACC/AHA guidelines but either potentially eligible (n=384) or not statin eligible by USPSTF guidelines (n=343) are also shown in Table 1. Compared with the total sample, individuals in the discordant group were older with lower total and LDL-C levels, a lower prevalence of hypertension and smoking, but a higher prevalence of diabetes mellitus. Of the 727 individuals in the discordant group, 145 (19.9%) had CAC >100 while 379 (52.1%) had CAC=0. The absolute cardiovascular event rates according to baseline CAC for the discordant group are shown in Table 3. Overall, the discordant group had a hard ASCVD event rate of 6.5 (95% CI, 4.9–8.5) per 1000 person-years. However, event rates varied significantly according to baseline CAC, as those with CAC zero had a hard ASCVD rate of 4.2 (95% CI, 2.7–6.7) per 1000 patient-years compared with a rate of 12.8 (95% CI, 8.3–19.9) in those with CAC >100.

Discussion

In MESA, we found that statin eligibility according to the 2016 USPSTF guidelines was significantly lower compared with the 2013 ACC/AHA guidelines, with 34% of MESA participants eligible according to USPSTF guidelines compared with 49% eligible for a risk-based statin discussion according to the ACC/AHA guidelines. Statin eligibility in the MESA cohort increased over time by both guidelines, though the increase was larger for the ACC/AHA guidelines. As would be expected because of a higher risk threshold for eligibility, compared with ACC/AHA, participants eligible by USPSTF had a higher baseline prevalence of CAC and higher ASCVD event rates over time. Importantly, the 15% of MESA participants eligible by ACC/AHA but not USPSTF had modestly elevated ASCVD event rates that varied significantly according to baseline CAC, suggesting CAC could aid clinical decision making for statin therapy in individuals with discordant eligibility.

Applying the USPSTF Guidelines: Implications for the US Population

The recent NHANES data comparing eligibility between USPSTF and ACC/AHA guidelines estimated that 36.3% of the US adult population aged 40 to 75 years without known ASCVD is either already on a statin or eligible for statin therapy according to the

Table 1. Baseline Characteristics of 4692 MESA Participants Based on Statin Eligibility According to the USPSTF and the 2013 ACC/AHA Guidelines

Participants' Characteristics	Total (N=4962)*	Statin Eligible		Potentially Statin Eligible		Not Statin Eligible		Discordant Recommendations for Statin Eligibility† (N=727)
		USPSTF (N=1709)	ACC/AHA (N=2436)	USPSTF (N=384)	ACC/AHA (N=617)	USPSTF (N=2869)	ACC/AHA (N=1909)	
Age, y	59.3±8.8	66.1±6.6	64.9±7.2	59.5±6.3	58.4±5.7	55.3±7.6	52.5±5.7	62.1±7.9
Female (%)	2622 (47.16)	616 (36.0)	943 (38.7)	185 (48.8)	301 (48.8)	1821 (63.5)	1378 (72.2)	327 (45.0)
Race								
White	1862 (37.5)	545 (31.9)	811 (33.3)	119 (31.0)	234 (37.9)	1198 (41.8)	817 (42.8)	266 (36.6)
Black	1381 (27.8)	625 (36.6)	825 (33.9)	135 (35.2)	190 (30.8)	621 (21.7)	366 (19.2)	200 (27.5)
Hispanic	1120 (22.6)	365 (21.4)	539 (22.1)	98 (25.5)	125 (20.3)	657 (22.9)	456 (23.9)	174 (23.9)
Chinese American	599 (12.07)	174 (10.2)	261 (10.7)	32 (8.3)	68 (11.0)	393 (13.7)	270 (14.1)	87 (12.0)
Education (above high school)	3251 (65.8)	983 (57.5)	1461 (60.1)	240 (62.5)	409 (66.3)	2028 (71.2)	1381 (73.0)	478 (66.0)
Income (≥\$40 000)	2520 (52.7)	667 (41.2)	1021 (44.1)	186 (50.1)	363 (59.9)	1667 (59.7)	1136 (61.1)	354 (50.6)
Current smoking	728 (14.7)	371 (21.7)	456 (18.7)	83 (21.6)	105 (17.0)	274 (9.6)	167 (8.8)	85 (11.7)
BMI, kg/m ²	28.4±5.6	28.9±5.3	28.8±5.4	29.0±5.3	28.5±5.4	27.9±5.8	27.8±5.9	28.4±5.6
LDL-C, mg/dL	118.2±28.8	121.3±29.7	119.7±29.2	124.4±29.7	122.3±28.9	115.5±27.8	115.0±28.0	115±27.6
HDL-C, mg/dL	51.0±15.0	47.3±14.0	48.5±14.3	48.7±13.2	49.9±14.1	53.6±15.3	54.7±15.4	51.2±14.5
Total cholesterol, mg/dL	194.3±32.1	196.1±32.9	194.8±32.5	199.4±34.2	197.7±32.6	192.5±31.2	192.5±31.3	191.7±31.5
Hypertension	1927 (38.8)	1195 (69.9)	1420 (68.3)	201 (52.3)	191 (31.0)	531 (18.5)	316 (16.6)	225 (31.0)
Diabetes mellitus	509 (10.3)	398 (23.3)	509 (20.9)	34 (8.9)	0 (0)	77 (2.7)	0 (0)	111 (15.3)
Anti-hypertensive medications	1537 (31.0)	913 (53.4)	1119 (45.9)	147 (38.3)	147 (23.8)	477 (16.6)	271 (14.2)	206 (28.3)
Nonstatin lipid-lowering medications	68 (1.4)	37 (2.2)	48 (2.0)	6 (1.6)	6 (1.0)	25 (0.9)	14 (0.7)	11 (1.5)
Family history of heart attack	1908 (40.8)	692 (43.8)	971 (42.8)	165 (45.0)	245 (42.5)	1051 (38.6)	692 (37.8)	279 (40.6)
ASCVD risk, %	10.1±9.8	20.3±9.5	17.1±9.6	8.7±7.1	6.2±7.2	4.2±3.6	2.4±1.4	9.6±3.8
≥2 risk factors‡	1563 (31.6)	1033 (60.4)	1244 (51.1)	161 (41.9)	153 (24.8)	369 (13.0)	166 (8.8)	211 (29.1)
No risk factors‡	1266 (25.6)	0 (0)	266 (10.9)	0 (0)	144 (23.3)	1296 (44.5)	856 (45.3)	266 (36.7)
CAC=0	2869 (57.8)	625 (36.6)	1004 (41.2)	219 (57.0)	350 (56.7)	2025 (70.6)	1515 (79.4)	379 (52.1)
CAC >100	858 (17.3)	560 (32.8)	705 (28.9)	66 (17.2)	73 (11.8)	232 (8.1)	80 (4.2)	145 (19.9)
CAC >400	326 (6.6)	246 (14.4)	293 (12.0)	23 (6.0)	22 (3.6)	57 (2.0)	11 (0.6)	47 (6.5)

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease⁺; BMI, body mass index; CAC, coronary artery calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; USPSTF, US Preventive Services Task Force.

*Participants who were taking statin, were younger than 40 or older than 75 years old, or had LDL-C >190 were excluded. Numbers may not add up to total or 100% because of missing values or rounding, respectively.

†Considered as participants who were statin-eligible according to the 2013 ACC/AHA guidelines but potentially eligible (n=384) or not eligible (n=343) according to USPSTF guidelines.

‡Major risk factors included dyslipidemia (HDL-C <40 or LDL-C >130), hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg or use of antihypertensive medications), diabetes mellitus (fasting plasma glucose ≥126 mg/dL or use of hypoglycemic medications), and current smoking status.

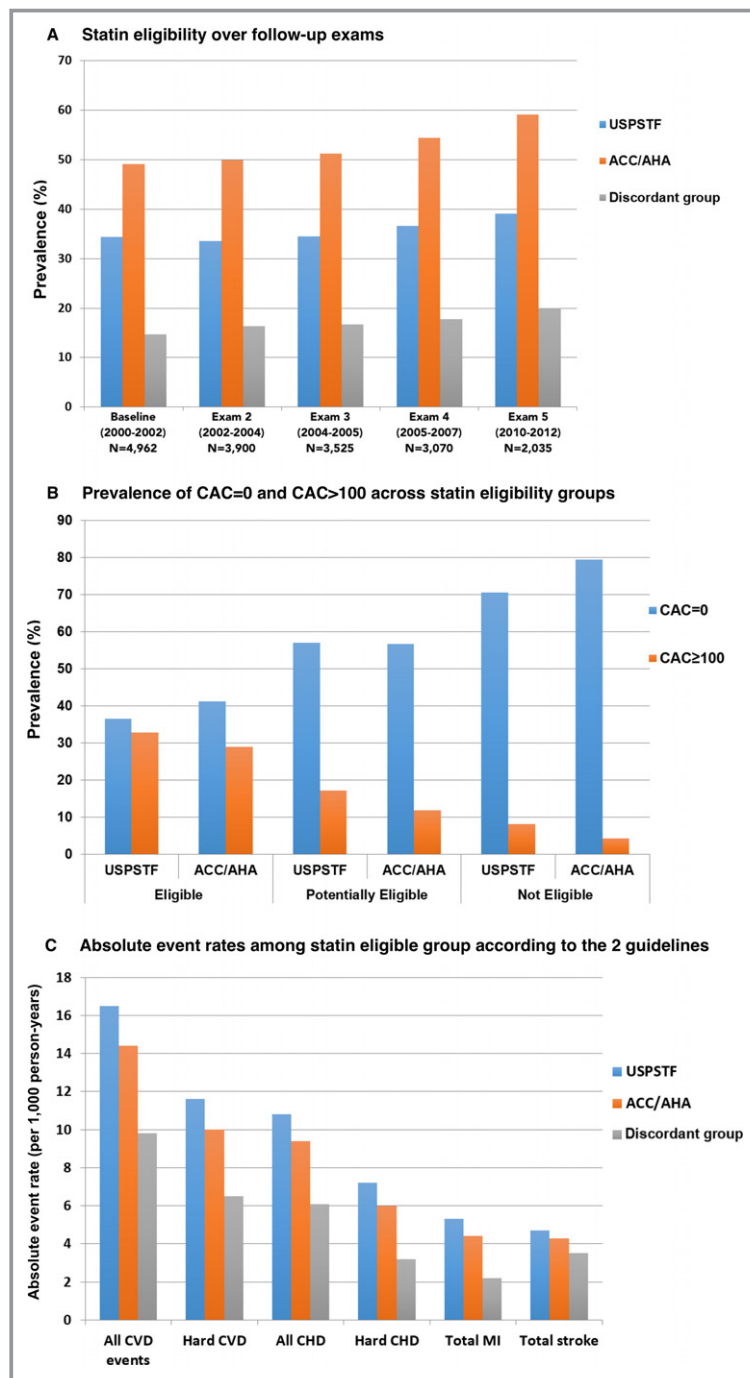


Figure. A, Statin eligibility according to USPSTF and ACC/AHA guidelines in 4962 MESA participants at baseline (2000–2002) and in those who remained free of ASCVD and off of statin therapy during follow-up (through 2012). B, The prevalence of CAC=0 and CAC≥100 across statin eligibility categories according to USPSTF and ACC/AHA guidelines in 4962 MESA participants at baseline. C, Absolute cardiovascular event rates per 1000 patient-years in MESA participants eligible for statin therapy according to USPSTF and ACC/AHA guidelines as well as the discordant group who were eligible by ACC/AHA but not USPSTF guidelines. ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CVD, cardiovascular disease; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; USPSTF, United States Preventive Services Task Force.

Table 2. Absolute Cardiovascular Event Rates Per 1000 Person-Years With 95% CIs by Statin Eligibility According to the USPSTF and the 2013 ACC Guidelines Over 12-Year Follow-Up of 4962 MESA Participants

ASCVD Events	Total (%)	Statin Eligible		Potentially Statin Eligible		Not Statin Eligible	
		USPSTF (N=1709)	ACC/AHA (N=2436)	USPSTF (N=384)	ACC/AHA (N=617)	USPSTF (N=1048)	ACC/AHA (N=1909)
Hard ASCVD	326 (6.6)	11.6 (10.2–13.3)	10.0 (8.9–11.3)	6.1 (4.1–8.9)	4.1 (2.8–5.9)	2.8 (2.3–3.5)	1.8 (1.3–2.4)
All ASCVD	451 (9.0)	16.5 (14.7–18.6)	14.4 (13.0–16.0)	10.3 (7.6–13.9)	5.2 (3.8–7.2)	3.7 (3.1–4.5)	2.4 (1.8–3.1)
Hard CHD	200 (4.0)	7.2 (6.1–8.6)	6.0 (5.1–7.0)	3.5 (2.1–5.8)	2.4 (1.5–3.8)	1.6 (1.3–2.1)	1.2 (0.8–1.7)
All CHD	304 (6.1)	10.8 (9.4–12.5)	9.4 (8.3–10.6)	7.6 (5.4–10.7)	3.5 (2.4–5.2)	2.5 (2.0–3.1)	1.8 (1.3–2.4)
Total MI	150 (3.0)	5.3 (4.4–6.5)	4.4 (3.6–5.2)	2.8 (1.6–4.9)	2.0 (1.2–3.3)	1.3 (0.9–1.7)	1.0 (0.6–1.5)
Total stroke	138 (2.7)	4.7 (3.8–5.8)	4.3 (3.6–5.2)	2.6 (1.4–4.6)	1.7 (0.9–2.9)	1.3 (1.0–1.7)	0.6 (0.4–1.0)

ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CIs, confidence intervals; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; USPSTF, US Preventive Services Task Force.

USPSTF guidelines, compared with 45.8% already on a statin or eligible according to the ACC/AHA guidelines.⁷ This 9.5% absolute increase in statin eligibility for primary prevention equates to an estimated 9 million US adults.

We excluded individuals on statin therapy at baseline but found similar rates of eligibility according to the 2 guidelines (34% and 49%). Our data suggest that the discordance between the 2 guidelines may be higher in older, healthier populations because in MESA we found a 15% absolute increase in statin eligibility according to ACC/AHA compared with USPSTF. This higher prevalence of discordance is likely secondary to the older age of the MESA cohort (mean age 59 years) compared with the NHANES analysis (mean age 53 years), thus increasing the prevalence of those with elevated ASCVD risk regardless of the presence of other major risk factors. More than 10% of MESA participants eligible for statin therapy according to ACC/AHA were eligible despite having no major modifiable ASCVD risk factors. Additionally, the discordance between the 2 guidelines increased during follow-up, with only ≈25% of participants not statin eligible according to ACC/AHA

guidelines at MESA examination 5 compared with ≈50% not eligible according to USPSTF.

What Is the Ideal Risk Threshold: 7.5% Versus 10%?

Although the 2.5% difference in the risk thresholds between the 2 guidelines may appear small, our data, in addition to the prior NHANES data,⁷ demonstrate that even small differences in risk thresholds can have substantial implications at a population level. The USPSTF performed a systematic review and produced an evidence report that was used to determine the 10% risk threshold.¹¹ The authors of the USPSTF guidelines did cite data raising concern that the PCE may overestimate risk in modern populations as one of the rationales for choosing the more conservative 10% risk threshold.^{12,13} The USPSTF decided to require the presence of 1 major risk factor in addition to the 10% risk threshold because no randomized controlled trial has included patients without any major ASCVD risk factors.

Table 3. Absolute Cardiovascular Event Rates Per 1000 Person-Years With 95% CIs Over 12 Years of Follow-Up According to Baseline CAC in 727 MESA Participants Eligible for Statin Therapy by ACC/AHA Guidelines But Not Eligible by USPSTF

Cardiovascular Events		All (N=727)*	CAC 0 (N=379)	CAC 1 to 100 (N=203)	CAC >100 (N=145)
All ASCVD	N, %	77, 10.6%	24, 6.3%	25, 12.3%	28, 19.2%
	Event rate	9.8 (7.8, 12.2)	5.7 (3.8, 8.5)	11.7 (7.9, 17.3)	18.5 (12.8, 26.8)
Hard ASCVD	N, %	52, 7.2%	18, 4.8%	14, 6.9%	20, 13.8%
	Event rate	6.5 (5.0, 8.5)	4.2 (2.7, 6.7)	6.4 (3.8, 10.8)	12.8 (8.3, 19.9)
All CHD	N, %	49, 6.7%	10, 2.6%	18, 8.9%	21, 14.5%
	Event rate	6.2 (4.7, 20.9)	2.3 (1.3, 4.4)	8.4 (5.3, 13.3)	13.6 (8.9, 20.9)
Hard CHD	N, %	26, 3.6%	6, 1.6%	8, 3.9%	12, 8.3%
	Event rate	3.2 (2.2, 4.7)	1.4 (0.63, 3.1)	3.6 (1.8, 7.2)	7.5 (4.3, 13.2)

ACC/AHA indicates American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CIs, confidence intervals; MESA, Multi-Ethnic Study of Atherosclerosis; USPSTF, US Preventive Services Task Force.

*Includes participants who were statin eligible according to the 2013 ACC/AHA guidelines but potentially eligible (n=384) or not eligible (n=343) according to USPSTF guidelines.

A recent analysis from the Jackson Heart Study demonstrated that application of USPSTF to a cohort of blacks resulted in eligibility for 55% of individuals with CAC >0 compared with 69% eligibility in those with CAC >0 according to ACC/AHA guidelines.¹⁴ However, the study also found that blacks with discordant eligibility appeared to be at relatively low risk, with 4.1 ASCVD events per 1000 patient-years. In our multiethnic analysis, we found that individuals with discordant eligibility appeared to be at intermediate risk, because 20% had CAC scores >100 and they experienced 6.5% ASCVD events per 1000 person-years. More than 50% of the discordant group had a CAC score of zero and event rates varied significantly according to baseline CAC. Prior research has hypothesized that CAC could be utilized to more effectively allocate statin therapy to individuals most likely to benefit.¹⁵ The arbitrary nature of risk thresholds and the lack of definitive trial data for the utility of CAC as well as in individuals at elevated ASCVD risk because of age alone highlight the importance of the clinician–patient risk discussion in making the decision to start statin therapy.³

Statin Allocation: The Importance of Absolute Risk

We found that ASCVD event rates during follow-up in MESA varied significantly according to eligibility categories by both guidelines, with individuals who were statin eligible having an ≈5-fold increase in ASCVD events compared with those who were not statin eligible. Both USPSTF and ACC/AHA rely largely on absolute risk to determine statin eligibility, a significant paradigm shift from prior Adult Treatment Panel guidelines (ATP III), which relied more heavily on LDL-C levels to determine statin eligibility.¹⁶

The transition to utilizing absolute risk to determine statin allocation is evidence based because absolute risk has been shown to be a much stronger predictor of ASCVD events compared with LDL-C levels, and the cardiovascular benefit of statin therapy in randomized controlled trials has largely been independent of baseline LDL-C.^{17–21} A recent study from a large Midwestern cohort of patients who experienced ST-segment–elevation myocardial infarction demonstrated further evidence supporting a risk-based approach to statin allocation as application of the ACC/AHA guidelines, compared with ATP III guidelines, doubled the prevalence of pre-ST-segment–elevation myocardial infarction statin eligibility, with 39% of the cohort statin eligible before ST-segment–elevation myocardial infarction by ATP III compared with 79% being statin eligible with application of ACC/AHA guidelines.²²

Potential Opportunities for Improvement

The USPSTF and ACC/AHA guidelines both represent significant progress towards the optimal population-level allocation

of statin therapy. However, these guidelines do have potential limitations. The PCE was modeled using data from an era when the prevalence of ASCVD risk factors and subsequent ASCVD event rates were significantly higher compared with more recent data.²³ New risk equations based on more modern data may allow for more accurate risk assessment. Further risk assessment with CAC testing may provide a more robust method of individualized risk assessment,²⁴ and CAC scoring has been hypothesized to more accurately identify individuals who are likely to benefit from statin therapy.¹⁵ In our study, we found that 37% and 41% of individuals who are statin eligible by USPSTF and ACC/AHA, respectively, had zero CAC, a finding associated with low ASCVD rates even in the presence of traditional ASCVD risk factors.²⁵

Strengths and Limitations

Our analysis has several strengths and limitations. Strengths include a large, multiethnic, geographically diverse, community-representative, sex-balanced cohort with data on baseline ASCVD risk factors and CAC, as well as long-term follow-up with thoroughly adjudicated ASCVD events. Long-term follow-up with good participant retention allowed for assessment of statin eligibility over 10 years of follow-up. Survivor bias and loss to follow-up may have influenced the prevalence of statin eligibility in the MESA cohort over time. As discussed above, the PCE calculator used to determine 10-year ASCVD risk has been shown to overestimate risk when applied to modern cohorts.^{12,13} However, how to best calibrate the PCE to modern populations is still subject to debate and the overestimation of risk was cited by the USPSTF as one of the reasons for choosing a more conservative risk threshold for consideration of statin therapy.¹

Conclusion

In conclusion, using data from MESA, we found that application of the USPSTF statin guidelines led to a 15% absolute decrease in statin eligibility compared with application of the 2013 ACC/AHA guidelines. Compared with ACC/AHA-eligible participants, those eligible by USPSTF had a higher prevalence of CAC and higher ASCVD event rates during follow-up, while those eligible by ACC/AHA but not USPSTF had a modestly elevated ASCVD event rate that varied significantly by baseline CAC. Healthcare providers and organizations should understand that the choice of which guideline to adopt and if and how to integrate CAC scoring may have a substantial impact on statin utilization and subsequent ASCVD outcomes at a population level.

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Disclosures

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