JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 2, 2018

PUBLISHED BY ELSEVIER

Statin Trials, Cardiovascular Events, and Coronary Artery Calcification

Implications for a Trial-Based Approach to Statin Therapy in MESA

Martin Bødtker Mortensen, MD, PhD,[a] Erling Falk, MD, DMSc,[a] Dong Li, MD,[b] Khurram Nasir, MD, MPH,[c,d,e] Michael J. Blaha, MD, MPH,[e] Veit Sandfort, MD,[f] Carlos Jose Rodriguez, MD, MPH,[g] Pamela Ouyang, MD, MBBS,[h] Matthew Budoff, MD[b]

ABSTRACT

OBJECTIVES This study sought to determine whether coronary artery calcium (CAC) could be used to optimize statin allocation among individuals for whom trial-based evidence supports efficacy of statin therapy.

BACKGROUND Recently, allocation of statins was proposed for primary prevention of atherosclerotic cardiovascular disease (ASCVD) based on proven efficacy from randomized controlled trials (RCTs) of statin therapy, a so-called trial-based approach.

METHODS The study used data from MESA (Multi-Ethnic Study of Atherosclerosis) with 5,600 men and women, 45 to 84 years of age, and free of clinical ASCVD, lipid-lowering therapy, or missing information for risk factors at baseline examination.

RESULTS During 10 years' follow-up, 354 ASCVD and 219 hard coronary heart disease (CHD) events occurred. Based on enrollment criteria for 7 RCTs of statin therapy in primary prevention, 73% of MESA participants (91% of those >55 years of age) were eligible for statin therapy according to a trial-based approach. Among those individuals, CAC = 0 was common (44%) and was associated with low rates of ASCVD and CHD (3.9 and 1.7, respectively, per 1,000 person-years). There was a graded increase in event rates with increasing CAC score, and in individuals with CAC >100 (27% of participants) the rates of ASCVD and CHD were 18.9 and 12.7, respectively. Consequently, the estimated number needed to treat (NNT) in 10 years to prevent 1 event varied greatly according to CAC score. For ASCVD events, the NNT was 87 for CAC = 0 and 19 for CAC >100. For CHD events, the NNT was 197 for CAC = 0 and 28 for CAC >100.

CONCLUSIONS Most MESA participants qualified for trial-based primary prevention with statins. Among the individuals for whom trial-based evidence supports efficacy of statin therapy, CAC = 0 and CAC >100 were common and associated with low and high cardiovascular risks, respectively. This information may guide shared decision making aimed at targeting evidence-based statins to those who are likely to benefit the most. (J Am Coll Cardiol Img 2018;11:221–30)

From the [a]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [b]Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, University of California Los Angeles, Torrance, California; [c]Center for Healthcare Advancement and Outcomes, Baptist Health South Florida, Miami, Florida; [d]Department of Epidemiology, Robert Stempel College of Public Health and Department of Medicine, Herbert Wertheim College of Medicine, Florida International University, Florida; [e]The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland; [f]Radiology and Imaging Sciences, National Institutes of Health, Bethesda, Maryland; [g]Division of Public Health Sciences, Department of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, North Carolina; and [h]The John Hopkins University School of Medicine, Baltimore, Maryland. This research was supported by National Heart, Lung, and Blood Institute contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169; and The National Center for Research Resources (NCRR) grants UL1-TR-000040 and UL1-TR-001079. Dr. Nasir is a consultant for Regeneron; a member of the Quest Diagnostic advisory board; and has received honoraria from Regeneron and Quest Diagnostic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 6, 2016; revised manuscript received January 18, 2017, accepted January 25, 2017.

ISSN 1936-878X/$36.00 http://dx.doi.org/10.1016/j.jcmg.2017.01.029

ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

PCE = pooled cohort equation

RCT = randomized controlled trial

Low-density lipoprotein cholesterol lowering by using HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, also known as statins, constitutes the cornerstone of pharmacological prevention of atherosclerotic cardiovascular disease (ASCVD). Although it is widely accepted that statins should be offered to patients with clinical ASCVD (secondary prevention), controversies exist about whom to treat for primary prevention. Leading international guidelines for the use of ASCVD prevention agree on the principle of allocating statin therapy based on absolute 10-year risk estimates of future ASCVD (1–3). This long-held principle, however, was recently questioned by leading cardiovascular investigators who proposed a paradigm shift in ASCVD prevention in which statin eligibility is based on randomized controlled trials (RCT) of statin therapy (4–7). In this alternative proposal, allocation of statins is based strictly on proven trial evidence ("trial-based approach"), that is, on the principle of "what works" and "in whom." The rationale behind such a trial-based approach is clear: no RCTs of statin therapy have ever enrolled participants based on 10-year ASCVD risk assessment (the approach recommended for statin allocation by current guidelines), and abundant data from large-scale RCTs have now proven the efficacy and safety of statin therapy in a wide range of different patient populations. Unfortunately, as recently highlighted (8), most individuals eligible for statin therapy using a trial-based approach are at low absolute risk of ASCVD, in whom the net benefit of treatment may be questioned.

SEE PAGE 231

Nevertheless, accepting the rationale behind a trial-based approach to statin therapy, we sought to determine whether assessment of subclinical atherosclerosis, the root cause of ASCVD, could be used to improve trial-based statin allocation. Specifically, we hypothesized that assessment of coronary artery calcium (CAC) among individuals for whom trial-based evidence supported efficacy of statin therapy could be used to identify subgroups with high and low ASCVD event rates and, thereby, those individuals who could be expected to benefit the most, and least, from trial-based evidence supporting primary prevention with statin therapy.

METHODS

STUDY PARTICIPANTS. MESA (Multi-Ethnic Study of Atherosclerosis) is a National Institutes of Health/National Heart, Lung, and Blood Institute-funded study of the characteristics of subclinical atherosclerosis and is designed to identify risk factors involved in progression of atherosclerosis to clinical ASCVD. A total of 6,814 men and women, 45 to 84 years of age and free of clinical ASCVD at baseline examination, were recruited between July 2000 and September 2002. Subjects were enrolled at 6 sites in the United States (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York City, New York; and St. Paul, Minnesota). Details on the design and organization were published previously (9).

RISK FACTOR DETERMINATION AND ASSESSMENT. The baseline examination in MESA included completion of an interview/questionnaire, a physical examination, and blood sampling for biochemical measurements. In the interview, MESA staff collected information on conventional and nonconventional risk factors. Systolic and diastolic blood pressures were measured at rest by using an automated oscillometric sphygmomanometer (Dinamap Pro 1000, Critikon, Tampa, Florida), using the mean of the previous 2 measurements for analysis. Blood samples were drawn after a 12-h fast and used for the measurement of total cholesterol, LDL-C, and triglycerides at the collaborative Studies Clinical Laboratory (Fairview University Medical Center, Minneapolis, Minnesota). Smoking was defined as current smoking by self-report. Diabetes was defined as self-reported diabetes, a fasting glucose concentration of ≥7.0 mmol/l or use of antidiabetic drugs.

CAC SCORE MEASUREMENTS. All MESA participants underwent noncontrast cardiac-gated computed tomography at baseline examination to determine the Agatston CAC score. Participants were scanned twice, using mean CAC score for analysis. The estimated average radiation dose was 0.89 mSv.

TRIAL-BASED RECOMMENDATIONS FOR STATIN THERAPY. A trial-based approach to statin therapy for primary prevention based on currently available evidence is guided by enrollment criteria in the following 7 large RCTs (named in chronological order by publication year): WOSCOPS (West of Scotland Coronary Prevention Study) (10), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (11), ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) (12), CARDS (Collaborative Atorvastatin Diabetes Study) (13), MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (14), JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (15), and HOPE-3

(Heart Outcomes Prevention Evaluation-3) (16). Characteristics of these 7 RCTs to guide trial-based allocation of statins in primary prevention of ASCVD are shown in **Figure 1**.

CARDIOVASCULAR DISEASE ENDPOINTS. Ascertainment of events has been described previously and is available at the MESA Website (17). Briefly, at intervals of 9 to 12 months, trained MESA personnel contacted participants or family members to inquire about ASCVD diagnosis, including hospital admissions, outpatient diagnoses, and deaths. Follow-up was completed in 92% of living participants. Medical records were obtained for approximately 98% of hospital admissions and 95% of outpatient diagnoses. A MESA study committee, including cardiologists, neurologists, and epidemiologists, adjudicated every event.

For this study, we defined coronary heart disease (CHD) events as myocardial infarction, resuscitated cardiac arrest, and CHD death. ASCVD was defined as CHD plus fatal and nonfatal strokes. Myocardial infarction was diagnosed based on the combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. Hospital records and family interviews were used to determine whether a death was related to CHD. Stroke was diagnosed based on a documented focal neurological deficit lasting 24 h or until death or, if <24 h, with imaging evidence of relevant brain lesions. In this study, participants were followed for 10 years (i.e., data were ended at 10 years).

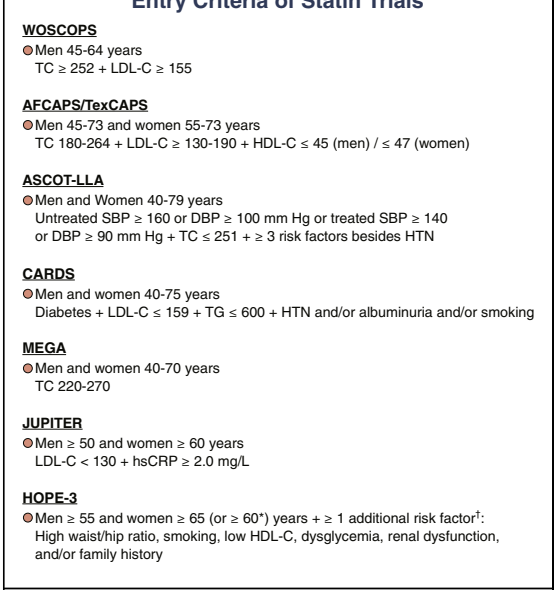
STATISTICAL ANALYSIS. Baseline characteristics are presented as proportions for categorical variables and as median (interquartile range) for continuous variables.

We calculated the number and percentage of participants eligible for statin therapy under the above-described trial-based approach. Among these trial-based eligible individuals, for whom RCT evidence supports efficacy of statin therapy, we assessed the distribution of CAC using 3 well-defined CAC groups: 0, 1 to 100, and >100 (18–21).

To determine whether CAC could be used to risk stratify trial-based eligible individuals, we calculated the 10-year ASCVD and CHD event rates across the 3 CAC groups and used Cox regression modeling (analyzing time to event) to obtain multivariate-adjusted hazard ratios. Analyses were adjusted for race and MESA site. Furthermore, we used Kaplan-Meier estimates to describe the occurrences of ASCVD and CHD events over time, stratified by the CAC groups.

Finally, we calculated a 10-year number needed to treat (NNT_{10}) to prevent 1 ASCVD or CHD event by assuming a 30% relative risk reduction with statin therapy in primary prevention (22,23). The NNT_{10} was calculated for each CAC group as the reciprocal of the absolute risk difference in 10-year event rates. In a sensitivity analysis, we also estimated 5-year NNT (NNT_5), using 5-year Kaplan-Meier estimates (24) to better comply with follow-up length in the RCTs. Furthermore, in a second sensitivity analysis, we recalculated NNT_{10} after assuming a more optimistic benefit of long-term statin therapy for primary

FIGURE 1 Enrollment Criteria for Primary Prevention With Statins Under the Trial-Based Approach



The figure summarizes the criteria for initiation of statin therapy in people free of ASCVD as defined by a trial-based approach to statin therapy. Studies (named in chronological order by publication year): WOSCOPS (West of Scotland Coronary Prevention Study) (10); AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (11); ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) (12); CARDS (Collaborative Atorvastatin Diabetes Study) (13); MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (14); JUPITER (Justification for the Use of Statins in prevention: An Intervention Trial Evaluating Rosuvastatin) (15); HOPE-3 (Heart Outcomes Prevention Evaluation-3) (16). Cholesterol concentrations are shown in mg/dl (to convert to mmol/l, divide by 38.6). *Women 60 to 65 years of age were eligible for statins in the HOPE-3 trial if they had at least 2 additional risk factors. †High waist-to-hip ratio is ≥0.90 in men and ≥0.85 in women; LDL-C is <1.0 mmol/l in men and <1.3 mmol/l in women. Dysglycemia = impaired fasting glucose, impaired glucose tolerance, or uncomplicated diabetes treated with diet only; renal dysfunction = microalbuminuria, eGFR <60 ml/min/1.73 m^2, or creatinine >124 μmol/l. ASCVD = atherosclerotic cardiovascular disease; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; HTN = hypertension; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TC = total cholesterol.

TABLE 1 Baseline Characteristics and Observed Events in MESA Study Population

	All (N = 5,600)	Men (n = 2,635)	Women (n = 2,965)
Age, yrs	61.0 (53.0–70.0)	61.0 (53.0–70.0)	61.0 (53.0–69.0)
Systolic blood pressure, mm Hg	123.0 (111.0–139.0)	122.0 (112.0–138.0)	123.0 (109.0–140.0)
Diastolic blood pressure, mm Hg	72.0 (65.0–79.0)	75.0 (69.0–81.0)	69.0 (63.0–76.0)
Plasma cholesterol concentration, mmol/l			
Total cholesterol	5.0 (4.5–5.6)	4.9 (4.3–5.4)	5.1 (4.6–5.7)
HDL cholesterol	1.2 (1.0–1.5)	1.1 (1.0–1.3)	1.4 (1.2–1.7)
LDL cholesterol	3.1 (2.6–3.6)	3.1 (2.6–3.5)	3.1 (2.6–3.6)
Current smokers, %	13	15	12
C-reactive protein concentration, mg/l	1.9 (0.8–4.3)	1.5 (0.7–3.2)	2.6 (1.0–5.9)
% with diabetes	11	12	9
% with hypertension	44	43	46
10-year ASCVD risk, %*	8.4 (3.6–18.4)	12.0 (6.0–22.0)	5.4 (1.9–13.7)
10-year ASCVD events	354	205	149
10-year CHD events	219	142	77

Values are median (interquartile range) or %. *The 10-year ASCVD risk was calculated using the pooled cohort equations.

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

prevention (40% relative risk reduction). Analyses were performed using Stata version 13.1 SE (Stata Corp., College Station, Texas).

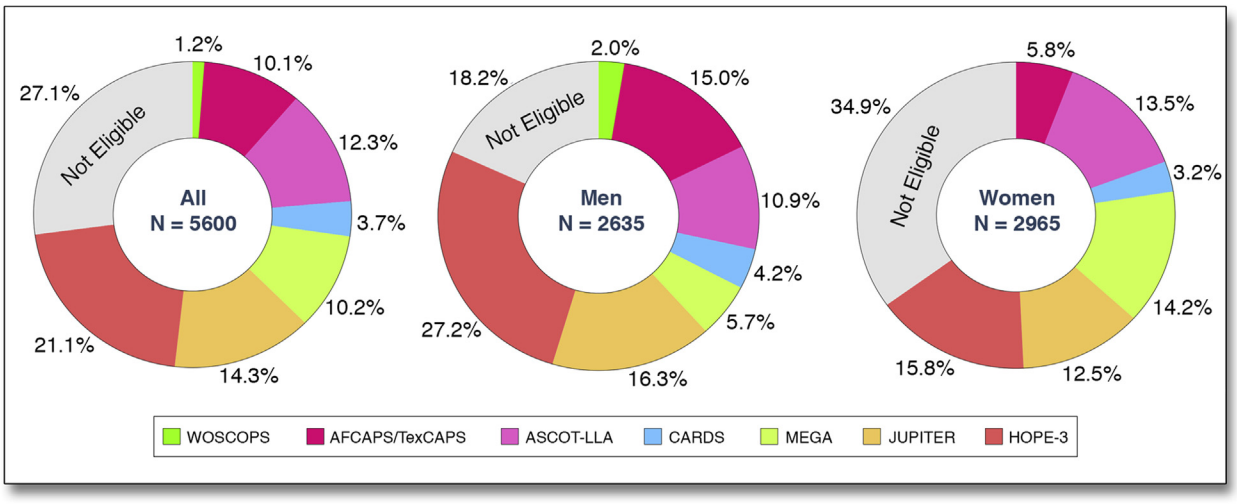
RESULTS

A total of 6,814 men and women were included in MESA. After exclusion of individuals taking lipid-lowering medication (n = 1,100) or with missing information (n = 114), 5,600 individuals were available for this study. Baseline characteristic of the study population are shown in Table 1. Median age was 61 years, and 53% were women.

STATIN ELIGIBILITY BASED ON RANDOMIZED STATIN TRIALS. Based on enrollment criteria used in 7 high-quality RCTs of statin therapy (trial-based approach), 4,085 individuals (73%) were eligible for primary prevention using statins (Figure 2). More men than women met enrollment criteria (82% vs. 65%, respectively). Notably, among those >55 years of age, 91% qualified for trial-based statin therapy (Online Figure 1). Baseline characteristics of participants stratified by statin eligibility are presented in Table 2. Individuals eligible for statins were older and had a higher burden of cardiovascular risk factors, including higher blood pressure and more atherogenic lipid profile than individuals who did not fulfill enrollment criteria in any RCT of statin therapy. When we assessed statin eligibility by each trial individually, 55% of MESA participants qualified for statin therapy based on HOPE-3 trial alone. For comparison, statin eligibility varied from 1% (WOSCOPS) to 18% (JUPITER) in the other 6 trials (Online Figure 2, Online Table 1). More than one-half of statin-eligible individuals met enrollment criteria in 2 or more of the 7 RCTs.

CAC DISTRIBUTION AMONG STATIN ELIGIBLE INDIVIDUALS. Among the 4,085 individuals meeting

FIGURE 2 Statin Eligibility in MESA Using a Trial-Based Approach



Diagrams illustrate the fraction of individuals from MESA who met enrollment criteria in RCTs of statin therapy. Individuals were selected consecutively in chronological order clockwise starting 12 o'clock; that is, first we selected individuals according to WOSCOPS criteria (1995), then we selected additional individuals according to AFCAPS/TexCAPS criteria (1998) and so on. RCT = randomized controlled trial; other abbreviations as in Figure 1.

TABLE 2 Baseline Characteristics of MESA Participants Stratified by Eligibility for Trial-Based Statin Therapy

	All		Men		Women	
	Trial-Based Eligible (N = 4,085)	Not Trial-Based Eligible (N = 1,515)	Trial-Based Eligible (n = 2,156)	Not Trial-Based Eligible (n = 479)	Trial-Based Eligible (n = 1,929)	Not Trial-Based Eligible (n = 1,036)
Age, yrs	65.0 (58.0–72.0)	51.0 (48.0–55.0)	64.0 (56.0–71.0)	50.0 (47.0–53.0)	66.0 (60.0–73.0)	52.0 (48.0–56.0)
Systolic blood pressure, mm Hg	127.0 (114.0–144.0)	114.0 (103.0–125.0)	125.0 (114.0–140.0)	115.0 (107.0–125.0)	131.0 (115.0–148.0)	113.0 (102.0–125.0)
Diastolic blood pressure, mm Hg	73.0 (66.0–80.0)	70.0 (64.0–76.0)	75.0 (70.0–82.0)	73.0 (68.0–79.0)	69.0 (63.0–76.0)	68.0 (62.0–75.0)
Plasma cholesterol concentration, mmol/l						
Total cholesterol	5.1 (4.6–5.8)	4.8 (4.3–5.2)	4.9 (4.4–5.6)	4.6 (4.2–5.0)	5.4 (4.8–6.0)	4.8 (4.4–5.2)
HDL cholesterol	1.2 (1.0–1.5)	1.3 (1.1–1.6)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	1.4 (1.2–1.7)	1.4 (1.2–1.7)
LDL cholesterol	3.2 (2.6–3.7)	2.8 (2.4–3.2)	3.1 (2.6–3.7)	2.8 (2.4–3.2)	3.3 (2.7–3.8)	2.8 (2.4–3.2)
% of current smokers	13	15	15	16	10	15
C-reactive protein, mg/l	2.2 (1.0–4.5)	1.4 (0.6–3.8)	1.7 (0.8–3.5)	0.8 (0.4–1.7)	3.0 (1.3–6.2)	1.9 (0.8–4.9)
% of diabetes	14	3	14	3	13	2
% of hypertension	53	21	49	16	58	23
10-year ASCVD risk, %*	12.5 (6.4–22.3)	2.2 (1.1–4.1)	14.7 (8.3–24.1)	3.9 (2.5–6.3)	10.0 (4.8–19.3)	1.5 (0.8–2.9)

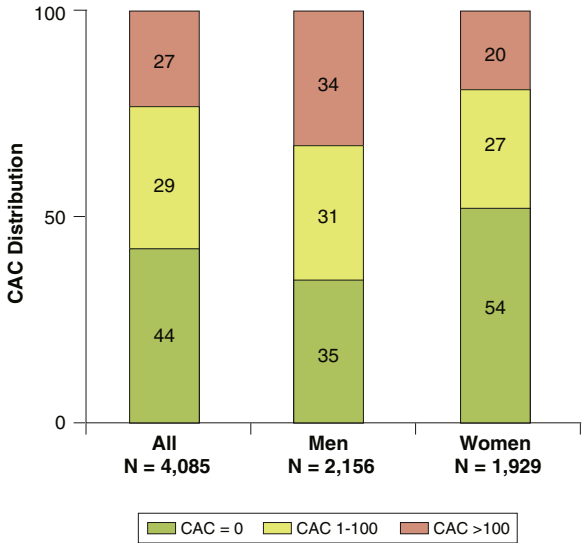
Values are median (interquartile range) or %. *The 10-year ASCVD risk calculated with the pooled cohort equations.
Abbreviations as in Table 1.

enrollment criteria in RCTs of statin therapy, nearly one-half had no detectable CAC (CAC = 0), and more than one-fourth had CAC >100 (Figure 3). The burden of CAC differed in a sex-specific manner. The CAC = 0 status was more common among women than men; the opposite was the case for CAC >100. Overall, the number needed to screen (NNS) to identify 1 person with CAC = 0 was 2.3, and the NNS to find 1 with CAC >100 was 3.7 (Table 3). The NNS to identify 1 person with either CAC = 0 or CAC >100 was <2. The distribution of CAC among individuals meeting enrollment criteria in each of the 7 statin trials varied considerably. Using MEGA criteria would have included the most individuals (59%) with no CAC, whereas using WOSCOPS criteria would have included the fewest (38%) with no CAC (Online Figure 3).

CLINICAL EVENTS IN STATIN-ELIGIBLE INDIVIDUALS. Among those who qualified for trial-based statin therapy, we observed 332 ASCVD events during 10-year follow-up, of which 208 were CHD events (Table 4). Kaplan-Meier cumulative-event curves for ASCVD and CHD by CAC score (0, 1 to 100, and >100) are shown in Figure 4. There was a strong relationship between the burden of CAC and both ASCVD and CHD events (Table 4, Online Table 2). Among individuals with no CAC, the event rates were low (3.9 for ASCVD and 1.7 for CHD per 1,000 person-years), whereas the event rates were considerably higher in individuals with CAC >100 (18.9 for ASCVD and 12.7 for CHD per 1,000 person-years). Compared with a CAC score of 0, CAC scores above 100 were associated with an adjusted hazard ratio of 5.2 (95% confidence interval [CI]: 3.9 to 6.4) for ASCVD and 8.0 (95% CI: 5.3 to 12.1) for CHD. Interestingly, event rates were similar in men and women separately when stratified by CAC score (Table 4).

NNT STRATIFIED BY CAC GROUP. Assuming a 30% relative risk reduction with statin therapy, the NNT_{10} to prevent 1 ASCVD event among individuals meeting enrollment criteria in RCTs of statin therapy was 87 for those with CAC = 0 compared with 19 for

FIGURE 3 Distribution of CAC Among Individuals Eligible for Statin Therapy Using a Trial-Based Approach



In individuals for whom trial-based evidence supports efficacy of statin therapy, 44% had no sign of CAC. CAC = coronary artery calcium score.

TABLE 3 NNS for Subclinical Atherosclerosis Among Individuals Eligible for Trial-Based Statin Therapy

	All (N = 4,085)	Men (n = 2,156)	Women (n = 1,929)
CAC = 0			
NNS	2.3	2.8	1.9
CAC >100			
NNS	3.7	3.0	5.1
CAC = 0 or >100			
NNS	1.4	1.4	1.4

CAC = coronary artery calcium score; NNS = number needed to screen to identify 1 individual with the value(s) in question.

those with CAC >100 (Figure 5). For CHD events, the NNT_{10} to prevent 1 event was 197 for those without CAC compared to 28 for those with CAC >100. For ASCVD events there was no sex difference, but women with CAC = 0 had a higher NNT to prevent 1 CHD event than men. As most statin trials have mean follow-up time of ≤5 years, we also calculated NNT for 5 years (NNT_5) (Online Figure 4). The NNT_5 ranged from 194 (CAC = 0) to 40 (CAC >100) for ASCVD and from 725 (CAC = 0) to 54 (CAC >100) for CHD events. Notably, among women with CAC = 0 (54% of all women), the estimated NNT_5 to prevent 1 CHD event was >1,000. In a secondary sensitivity analysis, we recalculated the NNT_{10} assuming 40% relative risk reduction by long-term statin therapy. In this analysis, the NNT_{10} was as low as 14 for ASCVD events and 21 for CHD events in those with CAC >100 (Online Figure 5).

DISCUSSION

Among MESA participants, as many as 73% met enrollment criteria in 1 or more of 7 high-quality RCTs of statin therapy for primary prevention and would therefore be eligible for trial-based statin therapy. In these trial-based eligible individuals, the burden of CAC differed substantially with nearly one-half having CAC = 0 and, thus, very low event rates. In those with CAC = 0, the NNT to prevent 1 event (ASCVD or CHD) was unfavorably high, with an NNT_{10} of 87 for ASCVD and 197 for CHD. In contrast, in the large subpopulation with CAC score >100, event rates were much higher and associated with considerably more favorable NNT_{10} (19 for ASCVD and 28 for CHD). Hence, for health care providers who prefer a trial-based approach to primary prevention with statins, knowing the CAC score may help targeting of treatment to those at highest risk for ASCVD and, thus, to those who are likely to benefit the most from statin therapy.

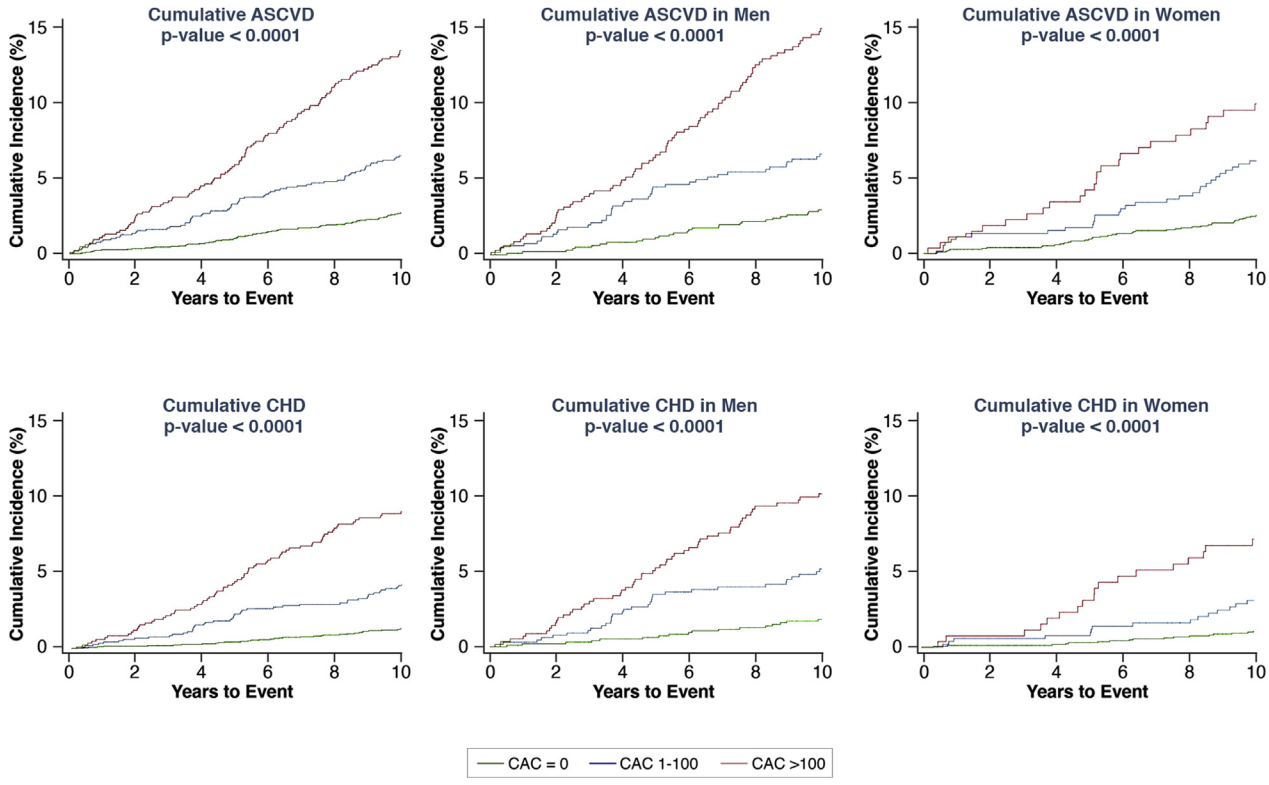
TRIAL-BASED STATIN THERAPY FOR PRIMARY PREVENTION: IS IT REASONABLE TO TREAT ALL? In 1995, the first larger RCT of statin use in primary prevention (WOSCOPS) (10) was published in which the efficacy of statin therapy was documented in a selected subgroup of high-risk men with hypercholesterolemia. Only 1% of MESA participants met enrollment criteria for WOSCOPS. Since then, primary prevention with statins has proven effective in other carefully selected individuals with specific risk-factor profiles, progressively expanding the indication for primary prevention with statins. Based on enrollment

TABLE 4 Relationship Between Coronary Artery Calcium and Clinical Events in Individuals Eligible for Trial-Based Statin Therapy

		ASCVD Events Hazard Ratio (95% Confidence Interval)			CHD Events Hazard Ratio (95% Confidence Interval)		
Subclinical Atherosclerosis	N (%)	n (%)	Event Rate per 1,000 Person-Years	Hazard Ratio*	n (%)	Event Rate per 1,000 Person-Years	Hazard Ratio*
All							
CAC = 0	1,798 (44)	64 (3.6)	3.85 (3.02–4.93)	1.00 (reference)	28 (1.6)	1.67 (1.16–2.43)	1.00 (reference)
CAC 1–100	1,185 (29)	98 (8.3)	9.44 (7.74–11.50)	2.53 (1.84–3.46)	63 (5.3)	5.99 (4.68–7.70)	3.69 (2.36–5.76)
CAC >100	1,102 (27)	170 (15.4)	18.86 (16.22–21.91)	5.19 (3.88–6.94)	117 (10.6)	12.68 (10.58–15.20)	8.01 (5.29–12.13)
Men							
CAC = 0	765 (35)	28 (3.7)	3.97 (2.74–5.75)	1.00 (reference)	17 (2.2)	2.40 (1.49–3.86)	1.00 (reference)
CAC 1–100	667 (31)	55 (8.2)	9.49 (7.29–12.37)	2.49 (1.58–3.93)	40 (6.0)	6.83 (5.01–9.31)	2.98 (1.69–5.26)
CAC >100	724 (34)	115 (15.9)	19.35 (16.12–23.23)	5.23 (3.44–7.94)	81 (11.2)	13.36 (10.75–16.61)	6.01 (3.54–10.20)
Women							
CAC = 0	1,033 (54)	36 (3.5)	3.77 (2.72–5.23)	1.00 (reference)	11 (1.1)	1.14 (0.63–2.06)	1.00 (reference)
CAC 1–100	518 (27)	43 (8.3)	9.37 (6.95–12.63)	2.54 (1.63–3.96)	23 (4.4)	4.94 (2.28–7.43)	4.39 (2.14–9.00)
CAC >100	378 (20)	55 (14.6)	17.89 (13.74–23.31)	4.99 (3.27–7.62)	36 (9.5)	11.37 (8.20–15.77)	10.31 (5.23–20.33)

*Adjusted for race and MESA site.
ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; other abbreviations as in Tables 1 and 3.

FIGURE 4 Cumulative Incidence of ASCVD and CHD Stratified by CAC Burden, Among Individuals Eligible for Statin Therapy in a Trial-Based Approach



CHD = coronary heart disease; other abbreviations as in Figures 1 and 3.

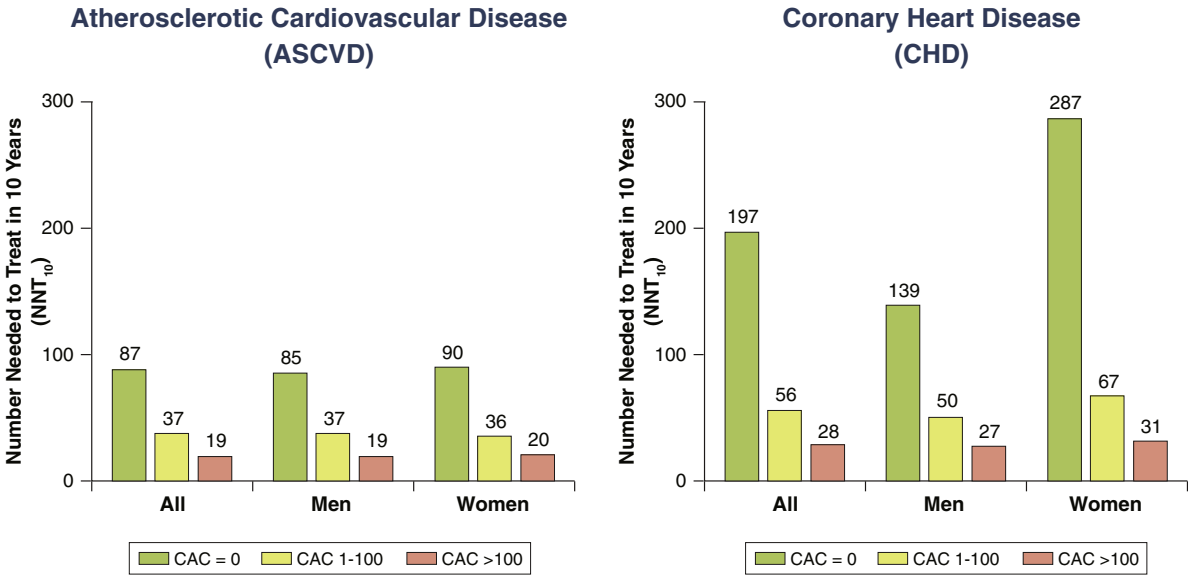
criteria used in the first 6 of the 7 RCTs (10-15), 52% of MESA participants were eligible for primary prevention with statin therapy. Similar results were recently reported from 2 European population-based cohort studies, the Copenhagen General Population Study (56%) (8) and the Rotterdam Study (53%) (25).

In 2016, RCT evidence for primary prevention with statins became stronger and more inclusive, with publication of the HOPE-3 trial (16). This pragmatic trial had enrolled "intermediate-risk" persons without known ASCVD in whom clear trial-based evidence for efficacy of statins was still lacking. The HOPE-3 trial provided important missing evidence, and 55% of MESA participants were statin-eligible based solely on enrollment criteria for this trial. Considering not only HOPE-3 but the totality of evidence from all 7 randomized statin trials, 73% of MESA participants 40 to 84 years of age qualified for trial-based primary prevention with statins, increasing to 91% when considering only those >55 years of age. This proportion would most likely be even higher in a real-world population (26).

Hence, after publication of the statin arm of HOPE-3, near-complete RCT evidence has now been provided for a universal, pragmatic approach to primary prevention of ASCVD based on a fixed low-to-moderate statin dose from 55 years of age, a provocative concept introduced by Wald and Law (27) in 2003. However, a critical question is whether such a pragmatic approach is reasonable in countries where a simple test is available that could distinguish between those who need and those who do not need to take a statin pill every day for the rest of their lives.

PRECISION MEDICINE: CAC TO GUIDE TRIAL-BASED STATIN ALLOCATION. Over the short term, people without atherosclerosis are at low risk for ASCVD and the higher the burden of atherosclerosis, the higher the risk for ASCVD. Although CAC is not a marker of the earliest coronary atherosclerotic lesions, those with CAC = 0 are at very low risk for ASCVD and mortality for up to 15 years (18,21,28-33). At the other end of the risk spectrum, those with CAC >100 have a risk for a first ASCVD event that approaches that seen

FIGURE 5 **Estimated Number Needed to Treat in 10 Years to Prevent 1 ASCVD or CHD Event Stratified by CAC Burden Among Individuals Eligible for Statin Therapy Under a Trial-Based Approach**



Abbreviations as in Figures 1, 3, and 4.

for a recurrent event in patients with established ASCVD (secondary prevention) (19). Thus, in primary prevention, it makes sense to identify those with CAC = 0 to avoid overtreatment and those with CAC >100 to avoid undertreatment and ensure long-term adherence to a cost-effective treatment (34).

In the present study, we confirmed that CAC = 0 at baseline examination was associated with very low CHD and ASCVD event rates for at least 10 years, known as the power of zero (35). Of course, to prevent events, there need to be events to prevent (19). Nearly one-half of MESA participants who were eligible for trial-based statin therapy had CAC = 0. In that low-risk population (CAC = 0), the NNT_5 to prevent 1 CHD event was high (>500 in men and >1,000 in women, assuming 30% event reduction with statin therapy). Screening just 3 persons who were eligible for trial-based statin therapy would identify 1 who did not need this treatment. At the other end of the risk spectrum, more than one-fourth of MESA participants had CAC >100 and a high 10-year event rate. Most events occurred in this high-risk subpopulation. Overall, just 2 persons need to be screened to find just 1 with either CAC = 0 (do not treat) or CAC >100 (treat and ensure long-term adherence).

The size of the study population and length of follow-up allowed us to assess the benefit of CAC assessment in men and women separately. The NNS to find 1 person with CAC = 0 or CAC >100 in men was similar to that in women (<2), but more women than men had CAC = 0, whereas the opposite was the case for CAC >100. Notably, the 10-year cumulative ASCVD risk was >15% in both men and women with CAC >100, that is, far above the current 7.5% 10-year ASCVD risk threshold for statin therapy identified by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Thus, as the ACC/AHA guidelines currently recommend that statin therapy might be considered in selected individuals with CAC ≥300 (Class IIb recommendation), our results suggest that this cut point may reasonably be lowered to 100 in future guidelines. Given that the price for CAC testing is now low (U.S. ≈$100), the additional information on ASCVD risk that CAC provides (especially when treatment decision is uncertain) may be worth the expense and, under some circumstances, even be cost-effective (36). In patients with detectable CAC, knowing this may increase adherence to preventive medication (37), which may further improve ASCVD outcome (38). These considerations are obvious topics for evidence-based and meaningful patient-physician discussions on initiation of statin therapy for primary prevention (39).

STUDY LIMITATIONS. First, our ability to consider all exclusion criteria used in the randomized statin trials

was limited. However, potential exclusion criteria were not mentioned in the trial-based proposal and are often ignored in routine clinical practices (40). Second, although we excluded individuals taking lipid-lowering medication at baseline examination, MESA participants were informed about their CAC scores, which may have led to selective uptake of preventive measures (including statin) among individuals with high CAC scores that could have influenced event rates. However, this would be expected to weaken the association among CAC and ASCVD and CHD events and, thus, cannot explain our results. Third, we assumed a 30% relative risk reduction with statin therapy based on Cochrane analyses (22), although that may have varied according to both treatment time and dose/type of statin. Fourth, most statin trials have a follow-up of ≤5 years. However, using 5 years of follow-up instead of 10 years did not affect the main results or conclusion.

Strengths of our study include the high-quality assessment of risk factors at baseline (enabling assessment of enrollment criteria in the 7 RCTs), adjudicated events over 10 years of follow-up and the size of the study population that allowed sex-specific assessment of the trial-based approach to statin therapy in a modern, multiethnic population.

CONCLUSIONS

After the HOPE-3 trial, most of the middle-aged and elderly MESA participants free of ASCVD would meet enrollment criteria used in at least 1 randomized statin trial. Evidence from RTCs now supports primary prevention with statins in nearly all men and women >55 years of age. However, nearly one-half of those considered statin-eligible based on RCTs had CAC = 0 and a very low event rate, and one-fourth had CAC >100 and a high event rate. For health care providers and patients who are reluctant to enter into treatment of all with statins from age 55 years, this information may help in shared decision making aimed at targeting prevention to those at highest risk.

ACKNOWLEDGMENTS The authors thank the investigators, the staff, and the participants of the MESA study for their valuable contributions. A complete list of participating MESA investigators and institutions can be found at the MESA Website.

ADDRESS FOR CORRESPONDENCE: Dr. Martin Bødtker Mortensen, Department of Cardiology, Aarhus University Hospital, Palle Juul Jensens Boulevard 99, Aarhus N, Jylland 8200, Denmark. E-mail: martin.bodtker.mortensen@clin.au.dk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among individuals with trial evidence supporting statin efficacy, quantification of subclinical atherosclerosis using the Agatston CAC score can be used to identify individuals with questionable (if CAC = 0) and substantial (if CAC >100) benefit of statin therapy.

TRANSLATIONAL OUTLOOK: Future research is needed to evaluate how best to incorporate CAC-guided allocation of statin therapy in routine clinical practice.

REFERENCES

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016;37:2315–81.

3. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart 2014;100 Suppl 2:ii1–67.

4. Ridker PM, Wilson PWF. A trial-based approach to statin guidelines. JAMA 2013;310:1123–4.

5. Ridker PM, Cook NR. Statins: new American guidelines for prevention of cardiovascular disease. Lancet 2013;382:1762–5.

6. Ridker PM, Rose L, Cook NR. A Proposal to incorporate trial data into a hybrid ACC/AHA algorithm for the allocation of statin therapy in primary prevention. J Am Coll Cardiol 2015;65:942–8.

7. Ridker PM. What works and in whom? A simple, easily applied, evidence-based approach to guidelines for statin therapy. Circ Cardiovasc Qual Outcomes 2012;5:592–3.

8. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. Primary prevention with statins: ACC/AHA risk-based approach versus trial-based approaches to guide statin therapy. J Am Coll Cardiol 2015;66:2699–709.

9. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.

10. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301–7.

11. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615–22.

12. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial: Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58.

13. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685–96.

14. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with

pravastatin in Japan (MEGA study): a prospective randomised controlled trial. Lancet 2006;368:1155–63.

15. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.

16. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016;374:2021–31.

17. MESA Coordinating Center. MESA website. 2015. Available at: http://www.mesa-nhlbi.org. Accessed May 24, 2017.

18. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011;378:684–92.

19. Martin SS, Blaha MJ, Blankstein R, et al. Dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. Circulation 2014;129:77–86.

20. Bittencourt MS, Blaha MJ, Blankstein R, et al. Polypill therapy, subclinical atherosclerosis, and cardiovascular events-implications for the use of preventive pharmacotherapy: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2014;63:434–43.

21. Nasir K, Bittencourt MS, Blaha MJ, et al. 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). J Am Coll Cardiol 2015;66:1657–68.

22. Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. JAMA 2013;310:2451–2.

23. Ebrahim S, Taylor FC, Brindle P. Statins for the primary prevention of cardiovascular disease. BMJ 2014;348:280.

24. Ridker PM, MacFadyen JG, Fonseca FAH, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER). Circ Cardiovasc Qual Outcomes 2009;2:616–23.

25. Pavlovic J, Greenland P, Deckers JW, et al. Comparison of ACC/AHA and ESC guideline recommendations following trial evidence for statin use in primary prevention of cardiovascular disease: results from the population-based Rotterdam study. JAMA Cardiol 2016;1:708–13.

26. Leening MJG, Heeringa J, Deckers JW, et al. Healthy volunteer effect and cardiovascular risk. Epidemiology 2014;25:470–1.

27. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.

28. 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.

29. Hecht HS. A zero coronary artery calcium score: priceless. J Am Coll Cardiol 2010;55:1118–20.

30. Greenland P. When nothing is really something: new evidence of the importance of zero coronary calcium. J Am Coll Cardio Img 2015;8:910–2.

31. Valenti V, Ó Hartaigh B, Heo R, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-up of 9,715 individuals. J Am Coll Cardiol Img 2015;8:900–9.

32. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage Study. J Am Coll Cardiol 2016;68:881–91.

33. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. J Am Coll Cardio Img 2009;2:692–700.

34. Rossello X, Pocock SJ, Julian DG. Long-term use of cardiovascular drugs: challenges for research and for patient care. J Am Coll Cardiol 2015;66:1273–85.

35. Blaha MJ, Silverman MG, Budoff MJ. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease? Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. Circ Cardiovasc Imaging 2014;7:398–408; discussion, 408.

36. Pletcher MJ, Pignone M, Earnshaw S, et al. Using the coronary artery calcium score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes 2014;7:276–84.

37. Mamudu HM, Paul TK, Veeranki SP, Budoff M. The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. Atherosclerosis 2014;236:338–50.

38. Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. J Am Coll Cardiol 2016;68:789–801.

39. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA guidelines. J Am Coll Cardiol 2015;65:1361–8.

40. Pocock SJ, Gersh BJ. Do current clinical trials meet society's needs?: a critical review of recent evidence. J Am Coll Cardiol 2014;64:1615–28.

KEY WORDS cardiovascular disease, guideline, lipoproteins, primary prevention, statin

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