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Statin Trials, Cardiovascular Events, and Coronary Artery Calcification

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

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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 2017;■:■-■)

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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.

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