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Statins for Primary Prevention in Older Adults:

Uncertainty and the Need for More Evidence

Jerry H. Gurwitz, MD,

Meyers Primary Care Institute, a joint endeavor of University of Massachusetts Medical School, Fallon Health, and Reliant Medical Group, Worcester, Massachusetts; and Division of Geriatric Medicine, University of Massachusetts Medical School, Worcester

Alan S. Go, MD, and

Division of Research, Kaiser Permanente Northern California, Oakland; and Departments of Epidemiology, Biostatistics, and Medicine, University of California, San Francisco

Stephen P. Fortmann, MD

Kaiser Permanente Center for Health Research, Portland, Oregon; and Department of Public Health and Preventive Medicine, Oregon Health & Science University, Portland

Given the substantially increasing geriatric population, the need for evidence-based strategies to address the medical and societal consequences of these demographic trends has never been greater. In this context, statins for primary prevention of atherosclerotic cardiovascular disease (ASCVD) provide substantial potential social value by improving health and survival. However, using statins for primary prevention in older adults presents a clinical dilemma. Even though compelling evidence exists supporting statins for secondary prevention in individuals older than 75 years with clinical ASCVD, the same cannot be said for primary prevention. In this Viewpoint, we describe existing evidence on the benefits of statins for primary prevention in older adults, uncertainties about risks, and the need for a randomized trial before non–evidence-based prescribing patterns become irreversibly incorporated into practice.

Guidelines

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline¹ suggests that “a discussion of the potential ASCVD risk-reduction benefits, risk of adverse effects, drug-drug interactions, and consideration of patient preferences should

Corresponding Author: Jerry H. Gurwitz, MD, Meyers Primary Care Institute, 630 Plantation St, Worcester, MA 01605 (jgurwitz@meyersprimary.org).

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precede the initiation of statin therapy for primary prevention in older individuals [those >75 years of age].” Furthermore, despite the lack of evidence, the guideline states that “the Pooled Cohort Equations provide information on expected 10-year ASCVD risk for those 76 to 79 years of age that may inform the treatment decision.” Notably, the 10-year ASCVD risk estimated using the Pooled Cohort Equations for individuals older than 75 years, including those with an optimal risk factor profile, always exceeds 7.5%—the guideline-recommended treatment threshold. This represents one of the few instances in which a guideline-based recommendation for a lifelong therapy has been based solely on age, independent of any other factors. The recommendation does not incorporate quality-adjusted life expectancy, which has become increasingly important to consider with respect to screening or primary prevention that involves testing or drug therapy in older adults.

Data From Randomized Trials

Information about the benefits and risks of statins for primary prevention for adults older than 75 years is limited, as relatively few older individuals have participated in applicable trials. Underscoring this point, a 2013 Cochrane review of 18 randomized trials of statins for primary prevention of ASCVD included 56 934 patients with a mean age of only 57 years.² However, subgroup analyses from 3 trials (PROSPER, JUPITER, and HOPE-3) do provide some data about the efficacy of statins for primary prevention in older adults, and a relevant trial (STAREE) has recently been initiated in Australia.

The PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) trial studied men and women aged 70 to 82 years with either preexisting vascular disease or elevated predicted ASCVD risk because of smoking, hypertension, or diabetes mellitus. Patients were randomly assigned to receive pravastatin (40 mg/d) or placebo. In a subgroup analysis limited to primary prevention, statin therapy had no statistically significant effect on the primary composite outcome (coronary death, nonfatal myocardial infarction, and fatal or nonfatal stroke).³

The JUPITER (Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study examined the efficacy of rosuvastatin vs placebo in men 50 years or older and women 60 years or older with no history of ASCVD or diabetes, no recent lipid-lowering therapy, low-density lipoprotein cholesterol levels less than 130 mg/dL, and high-sensitivity C-reactive protein levels of 2.0 mg/L or greater at screening.⁴ The composite primary end point included myocardial infarction, unstable angina, stroke, arterial revascularization or cardiovascular death. Of 17 741 analyzed participants, 5595 (32%) were 70 years or older (median, 74 years). Statin therapy was protective for the primary end point in this older group of patients (hazard ratio, 0.61 [95% CI, 0.46–0.82]), but rates of all-cause death did not differ significantly between the statin group and the placebo group. Adverse events were more common in the rosuvastatin group but not significantly. Importantly, JUPITER was stopped early, limiting the completeness of adverse event ascertainment, and no cognitive or functional end points were reported.

The HOPE-3 (Heart Outcomes Prevention Evaluation) trial evaluated outcomes of rosuvastatin compared with placebo among persons who were considered at intermediate

ASCVD risk.⁵ The trial included men 55 years or older and women 65 years or older who had 1 or more additional risk factors (elevated waist-to-hip ratio, low level of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, or mild renal dysfunction). Women 60 years or older who had 2 or more risk factors were also included. Persons 65 years or older (mean, 71 years) comprised half of the 12 704 study participants. For the composite outcome of death from cardiovascular causes and nonfatal myocardial infarction or stroke, statin therapy was protective in this subgroup (hazard ratio, 0.75 [95% CI, 0.61–0.93]).

The recently launched Australian STAREE (Statin Therapy for Reducing Events in the Elderly) trial (NCT02099123) is assessing the efficacy of statins for primary prevention in older adults, randomly assigning persons 70 years or older without diabetes to atorvastatin (40 mg/d) vs placebo, with 2 coprimary clinical end points: a composite of all-cause death, dementia, or development of disability; and major adverse cardiovascular events (myocardial infarction, ischemic stroke, and cardiovascular death). The findings from the STAREE are expected sometime after 2020 and will be informative, although the trial will have limited ethnic diversity and will not evaluate a full range of patient-centered outcomes.

Risks of Statins

The risk for statin-associated adverse effects in older patients raises concerns. Myalgias are a major reason for drug discontinuation, and interactions with many commonly used drugs may increase these risks in older patients.⁶ The effect of these symptoms on functional status, risk of falls, and disability in older patients remains uncertain. Additional concerns have also been raised that statins could have an adverse influence on cognitive function. While a recent meta-analysis reported that statin therapy was not associated with cognitive effects, this conclusion was based on several small studies primarily limited to younger patients.⁷ A recent study simulating the effect of statins for primary prevention in adults aged 75 to 94 years suggested that statins are cost-effective in this population.⁸ However, in sensitivity analyses, just a 10% to 30% increased risk for adverse effects, such as treatment-related functional limitation or mild cognitive impairment, offset the benefit of ASCVD risk reduction.

A Closing Window

In the absence of clear evidence of net benefit for statins for primary prevention in adults older than 75 years and uncertainty about the risks of therapy, clinicians might reasonably follow a shared decision-making approach in discussing the use of statins for this indication with older patients. However, lack of evidence substantially challenges efforts to reach optimal health decisions for the aging population. Trends in prescription drug use, even before the 2013 ACC/AHA guideline, suggest that increasing numbers of individuals older than 75 years will likely be treated with statins for primary prevention in the absence of adequate information on benefits and risks.⁹ Furthermore, large numbers of persons aged 65 to 75 years who are currently receiving “evidence-based” treatment with statins are aging into non-evidence-based territory. To address the substantial knowledge gaps about statins for primary prevention in persons older than 75 years, a randomized placebo-controlled trial

is required—one that addresses a full range of outcomes, including health-related quality of life, function, and symptom burden related to statin therapy. Given the increasing use of statin therapy in older persons, the imperative for such a trial has never been greater, and the window to pursue it is closing fast.

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