Statins and Primary Atherosclerotic Cardiovascular Disease Prevention—What We Know, Where We Need to Go, and Why Are We Not There Already?

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The US Preventive Services Task Force (USPSTF) has updated recommendations pertaining to statin therapy use for primary prevention of atherosclerotic cardiovascular disease (ASCVD) in adults.\(^1,2\) For statin efficacy, the recommendations were based on an extensive updated evidence review that included 22 randomized clinical trials (RCTs).\(^1,2\) Compared with the 2016 USPSTF evidence review, additional data from 3 RCTs (1 new RCT and 2 older RCTs) were included in the updated 2022 evidence review.\(^1,2\) Harms were assessed using data from 19 RCTs and 3 large cohort studies.\(^1,2\) The evidence review found that statin therapy use in patients for primary prevention (ie, those without ASCVD at baseline) was associated with reductions in all-cause mortality, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, revascularization, and the composite cardiovascular outcome.\(^1,2\) Insufficient data were available for older adults, especially individuals older than 75 years. Importantly, the evidence review did not find any significant harm associated with statin therapy, suggesting a significant overall net benefit in primary prevention in appropriate groups of individuals.\(^1,2\)

The evidence review\(^2\) led to 3 clinical recommendations\(^1\) that are consistent with the 2016 USPSTF recommendations on this topic. A B statement (moderate net benefit) was made that clinicians initiate statins for primary prevention in adults aged 40 to 75 years with at least 1 CVD risk factor and a calculated 10-year CVD event risk 10% or greater. A C statement (small net benefit) was made that clinicians selectively offer statins in those with a 10-year risk of a cardiovascular event of 7.5% to less than 10%.\(^1,2\) The sex- and race-specific pooled cohort risk equations (PCE) may be used for 10-year ASCVD risk estimation.\(^3\) Given lack of sufficient data, the USPSTF concluded that “there was insufficient evidence to assess outcomes of statins in adults 76 years or older (I statement).”\(^1,2\)

These recommendations from the USPSTF\(^1,2\) are sensible and practical. A few issues need further discussion. First, these recommendations take a conservative approach with a B recommendation for adults aged 40 to 75 years with a 10-year ASCVD risk factor and a calculated 10-year CVD event risk 10% or greater and a nuanced approach among those with 10-year ASCVD risk of 7.5% to 10%. This is understandable, given the issues surrounding overestimation of ASCVD risk using PCE, as shown in some studies, and the dominant role that age plays in 10-year ASCVD risk estimation.\(^3\) On the other hand, statin therapy has been shown to be efficacious at much lower 10-year ASCVD risk levels. For example, the 10-year hard ASCVD event rates in 3 trials of pure primary prevention showed benefits of statin therapy ranging from 5.1% to 7.6%.\(^4\) Indeed, statin therapy shows efficacy at even lower 10-year ASCVD risk levels, and there is some indication that the relative benefits of statin therapy may be higher among individuals with lower 10-year ASCVD risk.\(^5\) For most therapies, treating individuals with lower ASCVD risk comes at a price of treating a large number of individuals for a longer period of time. With statin therapy, this strategy could still be considered by clinicians, given more than 40 years’ worth of efficacy and safety data; excellent cost-effectiveness, even for individuals with 10-year ASCVD risk of at least 5%;\(^6\) availability of statin therapy as a low-cost generic medication; and the characteristics of the disease in question, since atherosclerosis starts at a young age.\(^7\) Theoretically, a reduction of approximately 39 mg/dL (to convert to millimoles per liter, multiply by 0.0259) in low-density lipoprotein cholesterol (LDL-C) started at an early stage of atherosclerosis can retard atherosclerosis and could potentially lead to more events prevented compared with similar LDL-C reduction later in life, once atherosclerosis is more advanced.\(^7\) Intuitively, the benefit of any preventive therapy is a
function of the magnitude of effect of that therapy on the outcomes studied, the intensity of the therapy used, and duration for which the treatment is given.

Second, 10-year risk assessment using PCE does not include several important factors associated with risk of ASCVD (eg, family history of premature ASCVD, chronic kidney disease, borderline elevation of LDL-C between 160-189 mg/dL, presence of metabolic syndrome, premature menopause, history of preeclampsia, South Asian ancestry). Presence of some of these risk factors may increase short-term or long-term risk of ASCVD. Including these risk factors in risk calculation may also allow for more personalized risk discussion and decision-making between the patient and the clinician, especially when 10-year risk estimates are in borderline or intermediate ranges. This is also important because the 10-year ASCVD risk assessment estimates events on a 10-year time horizon. Most patients who initiate preventive therapies use those therapies for a much longer period of time. It is important to note that although most RCTs of statin therapy by design only evaluated a first ASCVD event, preventive therapies also are associated with reduced risk of second and subsequent cardiovascular events. The disability associated with first and subsequent myocardial infarction or stroke is not fully captured in these RCTs, given their short follow-up, but is extremely important to patients.

Third, a separate USPSTF evidence review and recommendation discuss the studies on coronary artery calcium score (CAC) but, understandably, do not recommend for or against its use, since studies to date have mostly been observational or epidemiological. Despite this, there is evidence from these epidemiologic studies that CAC may allow clarity in decision-making regarding statin therapy when there is uncertainty after 10-year ASCVD risk assessment or if a patient is unsure whether they can take a statin pill every day for a long period of time (disutility).11

Fourth, clinicians should consider titrating the intensity of therapy to the risk of the individual. Therefore, patients who belong to high-risk primary prevention groups (ie, LDL-C ≥190 mg/dL, diabetes with end-organ damage, or 10-year ASCVD risk ≥20%) may derive further benefit from the use of high-intensity statin therapy. Despite similar relative risk reduction, absolute risk reduction will be higher; therefore, the numbers needed to treat will be lower for these high-risk primary prevention groups with a larger LDL-C reduction. Some of the gaps in our understanding (eg, whether statin therapy improves cardiovascular outcomes in young adults with cardiovascular risk factors, what is the efficacy and safety of statin therapy in older adults, and whether a CAC-based preventive strategy improves cardiovascular outcomes) may be addressed as ongoing studies are completed.

It is said that guidelines do not implement themselves in clinical practice. Statin therapy is a prime example of this failure to implement guidelines effectively in clinical practice. Study after study has shown that statin therapy use remains low in primary ASCVD prevention.15 Clinical inertia, statin-associated adverse effects, and social media all play roles in suboptimal use of statin therapy in clinical practice.14 System-level interventions are needed to assist clinicians in implementing evidence-based statin therapy use in primary prevention. Thoughtful conversations are also needed with patients to counter the misinformation about statin therapy that is pervasive in social media.15

The USPSTF evidence review and recommendations identify several other issues that need to be highlighted. First, enrollment in most statin RCTs has been low among women, members of some racial and ethnic groups (eg, African American and Hispanic individuals), and individuals from outside the US, limiting wide generalizability of the findings. Additionally, we continue to see disparities in statin prescribing among women, members of racial and ethnic minority groups, and individuals from low socioeconomic strata, as described in detail in the USPSTF evidence review and recommendation statement.1,2 If clinicians want to reduce the rates of CVD in the US, they will need to ensure that preventive therapies are prescribed to patients in an equitable manner and that receipt of preventive therapies is not dependent on an individual’s sex, race, ethnicity, income, or the zip code of their residence. This becomes even more important as the next few iterative waves of the COVID-19 pandemic are projected to have direct and indirect impacts on CVD-related events in the years to come. Better efforts are needed to effectively implement CVD prevention in routine care and fully leverage the strengths of team-based care models in primary and specialty care.
ARTICLE INFORMATION
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REFERENCES


