EDITORIAL

Statins for Primary Prevention
The Debate Is Intense, but the Data Are Weak

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A recent issue of *JAMA* contains the latest US Preventive Services Task Force (USPSTF) recommendation statement on statins for prevention of cardiovascular disease in adults,[1] along with the accompanying evidence report and systematic review[2] on which the recommendations are based. The evidence report summarized data from 19 trials including a total of 71 344 patients and concluded that statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and cardiovascular disease (CVD) events. Thus, the task force recommended "initiating use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors and a calculated 10-year CVD event risk of 10% or greater (B recommendation)" or "7.5% to 10% (C recommendation)."[1] Although the task force did their usual careful job of reviewing the evidence, the evidence for treating asymptomatic persons with statins does not appear to merit a grade B or even a grade C recommendation.

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The task force evidence report estimated an absolute benefit for use of statins of 0.40% for all-cause mortality and 0.43% for cardiovascular mortality and indicated that the absolute benefit was greater for patients at greater baseline risk.[2] Notably, the evidence report did not exclude studies that included patients taking statins for secondary prevention, who have a higher baseline risk of cardiac events and death and thus are more likely to benefit from therapy that inflates the benefit attributed to a primary prevention population. The task force did perform a sensitivity analysis that excluded 3 trials with persons for whom there were prior "hard" cardiovascular events and obtained similar results of benefits (eTable 5 in the article by Chou et al[2]). This sensitivity analysis did not exclude WOSCOPS, which included patients receiving statins for secondary prevention—5% had angina and 3% had intermittent claudication,[3] accounting for 15% of the total weight in the meta-analysis. In contrast, a meta-analysis of 11 studies and 65 229 patients receiving statins for primary prevention, in which patients receiving statins for secondary prevention were excluded, found no benefit of statins for reducing all-cause mortality.[4] The confidence intervals of these 2 analyses overlap, and the difference between these findings likely reflects differences in studies included.

The USPSTF and authors of the evidence report did not have access to the primary data (clinical study reports and anonymized patient-level data) from the statin clinical trials. Rather, they had to rely on peer-reviewed published reports as the basis for these recommendations. Exacerbating the potential bias, all of the trials included in the task force evidence report[2] were industry-sponsored except 1 trial,[5] and that trial contributed 0.2% of the weight to the mortality calculation. Industry-sponsored studies have been shown to report greater benefit and lesser adverse effects than noncommercially sponsored trials of the same drugs.[6] Whether this is true for statins and primary prevention of CVD is unknown.

Among the 19 randomized clinical trials of statins vs placebo or no statin included in the evidence report for the task force recommendations, only 15 reported all-cause mortality, 10 reported cardiovascular mortality, 12 reported fatal and nonfatal myocardial infarction, and 13 reported fatal and nonfatal stroke.[2,7] Reliance on selective reporting of the most important outcomes, which are likely included in the clinical trial data, makes reporting bias possible. Furthermore, after all-cause mortality, the comparative incidence of serious adverse events between treatment and control groups is arguably the second most important measure of the effect of active therapy in randomized clinical trials.

Understanding the evidence base in evaluating harms of statin therapy is also critically important. Although the benefits of any preventive therapy accrue according to risk of disease (greater benefit in higher-risk patients), the harms of therapy usually distribute equally over all risk levels. Thus, persons at low risk have little chance of benefit but equal chance of harms and thus are more likely to have a net harm. The evidence base for harms of statins, despite the introduction of these drugs more than 20 years ago, is incomplete. Many of the trials did not ask about commonly reported statin effects, such as muscle pains and weakness, and only recorded myopathy, for which an increase in creatine kinase levels was required. Because most muscle problems do not involve an increase in creatine kinase levels, this leads to a significant underestimate of muscle problems. Other studies have estimated that closer to 20% of statin users have muscle problems.[8] Additionally, the actual trial data are largely held by the Cholesterol Treatment Trialists' Collaboration on behalf of the industry sponsor and have not been made available to other researchers, despite multiple requests over many years.[9]

Although reported rates of adverse events in clinical trials are low, this does not reflect the experience of clinicians who see patients who are taking statins. For instance, the experience of an NPR reporter with a calculated 2.9% risk of heart disease over 10 years using the recommended American College of Cardiology/American Heart Association (ACC/AHA) risk calculator,[10] but still prescribed a statin, and experiencing adverse effects from the medication, is typical of what many

clinicians see in practice. She reported that "going for a walk was like slogging through mud" until "I ditched the statin. The weakness evaporated. I could run again."[11]

Using shared decision making, including discussion of the actual data on risks and benefits, would be an important step forward. Decision aids, such as that available from the Mayo Clinic website,[12] can help promote shared decision making, and such decision aids should be integrated into the electronic health record to facilitate their clinical use.[13] Using the current data, the decision aid shows that of 100 people who take a statin for 5 years, only 2 of 100 will avoid a myocardial infarction, and 98 of the 100 will not experience any benefit. There will be no mortality benefit for any of the 100 people taking the medicine every day for 5 years. At the same time, 5 to 20 of the 100 will experience muscle aches, weakness, fatigue, cognitive dysfunction, and increased risk of diabetes. All will have to take a pill every day, and they and their health plans will pay for these medications. The association between use of statins and cognitive dysfunction is controversial, with studies indicating both an increased risk and no increased risk. Most but not all studies show an increased risk of diabetes with statin use. The diabetes risk is more common for high-dose compared with moderate-dose statins.[14] The US Food and Drug Administration issued safety label changes in 2012 stating that "Information about the potential for generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels has been added to the statin labels."[15]

Even though the evidence may be insufficient to support statin treatment for asymptomatic patients, these new guidelines may have a beneficial effect. Many patients are treated with statins, even though their risk of a cardiovascular event in the next 10 years is less than 7.5%; in fact, the ACC/AHA Pooled Cohort Equations recommend statin treatment for patients with 10-year risk below this level, as well as persons who meet the risk level only because of age.[10] If physicians follow the task force recommendation and do not recommend treatment for primary prevention unless risk is greater than 10% in the presence of a risk factor, many patients would potentially avoid unnecessary treatment. In addition, the task force assigned a Grade C recommendation for statin use for persons between ages 40 and 75 years who have between a 7.5% and 10% 10-year CVD event risk and a risk factor and did not recommend for or against statins for any persons older than 75 years, many of whom are currently receiving statins. An analysis of the Medical Expenditure Panel Survey found that the rate of statin use for primary prevention among persons older than 79 years had increased from 8.8% in 2000 to 34.1% in 2012.[16]

There are unintended consequences of the widespread statin use in healthy persons. For example, people taking statins are more likely to become obese and more sedentary over time than nonstatin users, likely because these people mistakenly think they do not need to eat a healthy diet and exercise as they can just take a pill to give them the same benefit.[17]

The USPSTF recommendations for statin use for primary prevention of CVD are not likely to end the debate about the use of statins for asymptomatic persons. However, it is worth taking a step back and asking why this debate is so contentious. Although the estimates of the benefits of statins for primary prevention used by the task force may be inflated, even if these estimates are accurate, this is still a relatively weak intervention. The task force evidence report estimated that to prevent one death from any cause over a 5-year period, 244 patients would need to take a statin daily.[2] In that sense, whether a clinician concludes that the existing meta-analyses show that statins produce a statistically significant benefit or produce a statistically nonsignificant result, the benefit is relatively small. Certainly, one reason the debate is intense is because of the large market for statins if these drugs are recommended for primary prevention. The global market for statins has been estimated to be a staggering $20 billion annually in the last decade.[18,19] For that kind of investment, better data on risks and benefits should be required.

In deciding on any therapy, it is important to understand the risks and benefits, particularly for healthy people. It is incumbent on clinicians to be sure that before recommending that a patient take a daily pill that has multiple adverse effects, there is evidence that the medication will lead to a better quality of life, longer life, or both. Such evidence is lacking for statins in primary prevention. Thus, while the task force summarized the available evidence well, the limitations of the evidence were not considered sufficiently. Given the serious concerns about the harms of the reliance on statins for primary prevention, it is in the interest of public health and the medical community to refocus efforts on promoting a heart-healthy diet, regular physical activity, and not smoking.

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