Weighing the Harms and Benefits of Using Statins for Primary Prevention: Raising the Risk Threshold

When the American College of Cardiology (ACC) and the American Heart Association (AHA) updated their guidelines for treatment of cholesterol levels in 2013, one recommendation was particularly controversial: use of statins for primary prevention of cardiovascular disease (CVD) among adults with 10-year risk of 7.5% or higher (1). The recommendation raised important questions about the "right" risk threshold at which to start statin therapy for primary prevention, particularly because many older adults exceed this threshold on the basis of age alone. The guidelines have since made their way into clinical practice, and "7.5%" has become instantly recognizable to primary care physicians and cardiologists. In 2018, an update to the guidelines largely affirmed this approach, although there was also an emphasis on the importance of patient preference and a suggestion that coronary artery calcium scores and clinical risk factors could help guide statin initiation decisions for primary prevention (2).

In 2016, the U.S. Preventive Services Task Force (USPSTF) released its own guidelines, which recommended statins for primary prevention among adults with 10-year CVD risk of 10% or higher and at least 1 clinical risk factor (B recommendation) (3). The guidelines also acknowledged that statins may be reasonable at lower risk thresholds (7.5% to 10%), depending on individual circumstances (C recommendation). Although these guidelines were more stringent than the initial 2013 ACC/AHA guidelines, they echoed the basic approach (using global CVD risk to guide initiation of statin therapy for primary prevention) and arrived at similar risk thresholds.

In this issue, Yebyo and colleagues challenge these risk thresholds through a careful accounting of long-term risks and benefits of statins (4). Specifically, they evaluated the 10-year CVD risk threshold at which the benefits of statins outweighed the harms (overall and for 4 specific statins), with separate estimates for men and women across 5-year age groups ranging from 40 to 44 years to 70 to 75 years. Using an approach developed by investigators at the National Cancer Institute, the authors projected disease-related events and drug-related adverse events over time while accounting for competing mortality. On the basis of 10-year CVD risk, they estimated the number of fatal and nonfatal cardiovascular events averted by statins and adverse events attributable to statins, including myopathy, hepatic dysfunction, and incident diabetes. The authors assigned weights to treatment outcomes so that benefits and harms could be quantified on a single scale and summed over a 10-year horizon to determine the risk threshold at which benefits outweighed harms.

Surprisingly, the authors consistently found that harms outweighed benefits until 10-year CVD risk thresholds substantially exceeded those recommended in current guidelines. For example, among men aged 70 to 75 years, benefits of statin therapy did not outweigh harms until 10-year CVD risk exceeded 21%. Among women in the same age group, risk would need to exceed 22% for there to be a net benefit. For younger adults, risk thresholds were lower, likely because of lower risk for adverse events from statins and lower competing mortality. However, at a 10-year CVD risk of 7.5%, benefits did not exceed harms for any age group, sex, or statin type. The lowest thresholds were 14% for men aged 40 to 49 years and 17% for women aged 40 to 49 years.

Given these findings, should physicians rethink how to incorporate the ACC/AHA or USPSTF guideline recommendations into practice, deprescribing for some patients and prescribing only for those at higher CVD risk? Before throwing the statins out with the bathwater, it is important to understand why Yebyo and colleagues' estimates differ from those in current guidelines, especially the effect of different methodological approaches and how adverse events were considered.

To evaluate the net benefit of statins, the ACC/AHA guidelines used a conceptually simple approach of calculating the 10-year CVD risk at which the number needed to treat was smaller than the number needed to harm. The USPSTF guidelines simplified the calculus even further—instead of formally calculating net benefit, they concluded that adverse events from statins were rare and that a moderate benefit from statins was likely when 10-year CVD risk exceeded 10%. In contrast, Yebyo and colleagues' approach was much more elaborate, incorporating age- and sex-specific expected benefit and risks for adverse effects associated with statin use and, most important, competing mortality. The effect of this approach was immediately apparent: within every CVD risk stratum, as age increased, the probability of net benefit from statin therapy decreased, reflecting both competing mortality and age-related risk for adverse events. The results paint a nuanced—if less optimistic—picture of the net benefits of statins, particularly in older adults who may not live long enough to benefit.

Yebyo and colleagues also included a wide range of adverse events, such as hemorrhagic stroke, acute kidney injury, and hepatic dysfunction, which were largely dismissed in the ACC/AHA and USPSTF guidelines. Accounting for this longer list of potential adverse events, which was derived from an as-yet unpublished network meta-analysis performed by the authors, inevitably tips the balance further away from net benefit and toward harm. Is inclusion of these adverse events justified? Some are likely to say no, pointing to a recent review of meta-analyses that found suggestive associations with statin use only for incident diabetes and myopathy (5), which echoes findings of the ACC/AHA and USPSTF

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guideline committees. Others are likely to find it reasonable because it avoids erroneous exclusion of adverse events associated with statin use, even if they are rare, although this leads to a worst-case scenario estimate of the net benefit.

The aggregated clinical trial evidence on statins for primary prevention is finite, so when the same studies lead to 3 different conclusions, which is correct? Perhaps only the patient can say. As others have shown, the CVD risk threshold for initiation of statin therapy for primary prevention is sensitive to patient preferences, including the burden of taking a pill daily (6). Some patients may favor a risk-averse approach in which harms associated with therapy are given greater weight than potential benefits, but others may prefer to give greater weight to potential benefits. The onus is on physicians to fairly summarize the evidence and guide patients through the decision-making process. The work by Yebyo and colleagues can support that decision making, particularly for older adults or those who are more concerned about harms of treatment. Indeed, primary prevention of CVD must be patient-centered, because healthy patients are asked to assume risk, benefits are experienced only as the absence of disease, and uncertainty lurks beneath every choice.

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