Statins for Primary Cardiovascular Disease Prevention
Time to Curb Our Enthusiasm

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In the US, more than 126 million adults have been diagnosed with cardiovascular disease (CVD).\(^1\) Reducing the morbidity and mortality associated with CVD is a public health imperative. Accordingly, considerable resources and effort have been invested in determining not only how to effectively treat symptomatic coronary artery disease or ischemic stroke, but also on prevention of clinical CVD. Although elevated low-density lipoprotein (LDL) is associated with higher rates of CVD,\(^2\) there is uncertainty regarding the net benefit to risk ratio of using statins to reduce LDL among persons without CVD (primary prevention). This contrasts with the established role of LDL reduction for persons with established CVD (secondary prevention).

The US Preventive Services Task Force (USPSTF) has updated its 2016 recommendations on the use of statins for the primary prevention of clinical CVD.\(^3\) Two of us (M.H.K. and R.F.R.) wrote about the 2016 recommendations,\(^4\) and in this Editorial we update our comments for the 2022 recommendations.\(^5\)

The updated evidencesynthesis\(^6\) found that statins yielded a slightly smaller, but still statistically significant, reduction in all-cause mortality (pooled relative risk, 0.92; 95% CI, 0.87-0.98), as well as for myocardial infarction and stroke (Table). The USPSTF recommendations should be considered in the context of a meta-analysis, published in 2010,\(^8\) which included only trials that enrolled patients receiving high-risk primary prevention; this study showed no benefit on all-cause mortality with statins. The benefit for CVD mortality was not statistically significant (pooled relative risk, 0.91; 95% CI, 0.81-1.02). Notably, there was no significant statistical heterogeneity (I\(^2\) = 0) across the 12 trials (n = 75,138) examined. The null result was robust in sensitivity analyses that excluded trials that stopped early, trials that included patients receiving secondary prevention, good-quality trials, trials with at least 3 years of follow-up, and trials with participants with a median baseline LDL lower than 160 mg/dL.\(^6\) The lack of benefit on CVD mortality found in the 2022 evidence review\(^6\) and the lack of benefit on all-cause mortality in the purely high-risk primary prevention meta-analysis\(^8\) call into question the reliability of the all-cause mortality benefit reported in the sys-

<table>
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<tr>
<th>Date of USPSTF systematic review</th>
<th>No. of RCTs/No. of participants</th>
<th>Pooled relative risk (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All-cause mortality</td>
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<tr>
<td>2022(^6)</td>
<td>22/90,624</td>
<td>0.92 (0.87-0.98)</td>
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<td>2016(^7)</td>
<td>19/71,344</td>
<td>0.86 (0.80-0.93)</td>
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Abbreviations: CVD, cardiovascular disease; RCT, randomized clinical trial; USPSTF, US Preventive Services Task Force.
tematic review that accompanies the 2022 USPSTF recommendations. Because 19 of the 22 included trials were industry sponsored, potential bias in the randomization processes, as well as the potential for exaggeration of net benefits, are of greater concern than for trials whose sponsors were disinterested with regard to the outcomes.

In contrast with its 2016 recommendations, the USPSTF no longer recommends use of low-intensity statins in certain situations. This change is driven by the fact that 17 of the 22 trials had fixed-dose statin groups, including 12 which used moderate-intensity statins. We are unaware of any RCTs that directly compare either different statin intensities in terms of clinical CVD outcomes or fixed-dose vs titrate-to-LDL goal approaches. While it is understandable that the Task Force was limited by lack of data on dosing, this change is unfortunate for patients because the frequency of adverse effects increases as the statin dose increases.

Finally, the 2022 recommendations no longer note the “uncertainty in individual risk prediction” in contrast with the 2016 recommendations, which more clearly acknowledged that cardiac risk prediction is not an exact science. Refining the accuracy of prediction of risk for individuals remains a major issue for primary prevention. It is disappointing that there was no sex-specific analysis in the evidence review, as women have lower cardiovascular risk than men at all ages until age 75 years and are more likely to experience adverse drug effects than men. Thus, the risk-benefit profile for statins is less favorable for women than men, which is neither discussed nor recognized in the current USPSTF recommendations.

Many of the caveats and concerns noted in the Editorial accompanying the 2016 USPSTF recommendations are still present with the 2022 recommendations. These include the heterogeneous inclusion criteria across studies and the inclusion of participants not receiving primary prevention who either had symptoms consistent with clinical CVD or known coronary artery disease equivalents, such as carotid artery atherosclerosis. As noted previously, a meta-analysis of statins for patients receiving high-risk primary prevention found no benefit on all-cause mortality. Additionally, as the data for many trials of statin therapy remain unavailable, the USPSTF does not have access to participant-level data. The trials for which there is no data transparency are those with data housed at the Cholesterol Treatment Trialists’ (CTT) Collaborative at Oxford University. The CTT does not allow academic researchers and others access to the data from 24 trials comparing statins with a control group, starting in 1995. The CTT states that it is just the repository of data and cannot allow others access because the data are owned and controlled by the industry sponsors of the trials. In 2022, there is no reason for participant-level data from these trials to remain unavailable for independent analysis.

At present, there are further reasons to curb our enthusiasm about the use of statins for primary prevention of CVD. There is a difference between statistically significant and clinically meaningful benefit. The purported benefits of statins in terms of relative risk reduction are fairly constant across baseline lipid levels and cardiovascular risk score categories for primary prevention. Therefore, the absolute benefit for those in lower-risk categories is likely small given that their baseline absolute risk is low, while the chance of adverse effects is constant across risk categories.

Use of the PCE to risk-stratify individuals is problematic. The cut points of 5%, 7.5%, 10%, and 20% are arbitrary given the linear “continuum of risk” without a threshold effect that exists within the relationship between CVD risk and CVD occurrence. Additionally, the PCE itself is an imperfect tool to assess baseline 10-year absolute risk. The PCE was derived and validated in studies that enrolled individuals (mostly White males) between 1968 and 1990. Thus, the PCE does not reflect the recent decreases in rates of CVD that have accrued owing to population-wide health improvements from reduced rates of smoking, shifts in dietary patterns and exercise, and blood pressure control. In a multiethnic prospective cohort from 2000 to 2002, the PCE overestimated CVD events by 86% in men and 67% in women. When applied to 6 cohorts from 1971 to 2014 (n = 26 689), the PCE overestimated 10-year risk of CVD by an average of 20% across risk groups, which would have down-staged 11.7 million adults from a 10-year CVD risk of greater than 10% to less than 10%, and 11.8 million adults from a 10-year CVD risk of greater than 7.5% to less than 7.5%. Furthermore, the PCE propagates the unavoidable variability and uncertainty in the clinical inputs (eg, total cholesterol, high-density lipoprotein, systolic blood pressure); a 10% higher or lower variation in these inputs would result in up to a 24% change in the risk categorization of individuals. Such issues with discrimination and calibration present challenges in applying the USPSTF guidelines to individuals in informing discussions about their potential for clinical benefits from statin use.

The USPSTF concluded that, among 19 RCTs and 3 observational studies examined (a different data set than the data set for the review of benefits, which was 22 RCTs), statins did not have any statistically significant harms, namely in terms of myalgias, incident diabetes, liver enzyme elevations, cancer, kidney effects, cognitive harms, or cataracts. However, in clinical practice, adverse events are commonly reported with use of statins. For example, in observational data, statin-associated muscle symptoms affect up to 1 in 10 individuals. Even if, as has been argued, statin-associated muscle symptoms are at least partly due to the nocebo effect, the extent to which muscle symptoms lead to either dose-reduction or discontinuation of statins (usually with subsequent cessation of these symptoms) should not be discounted. Although the USPSTF analysis did not find a statistically significant increase in incident diabetes, a prior meta-analysis of 13 trials (n = 91 140) found that 1 extra case of diabetes per 255 patients over 4 years of statin treatment could be attributed to statin use. Furthermore, individuals with other risk factors for glycemic intolerance and people with preexisting diabetes are likely to be at increased risk of progression to diabetes and worsened glycemic control, respectively.

When assessing the potential harms of statins, it is prudent to keep in mind that although the purported benefits of statins will accrue to a few patients in the future, everyone prescribed a moderate-intensity statin is at risk immediately for the harms. Consider-
eration of adverse effects is especially important for a primary prevention drug, which is prescribed to healthy people who feel perfectly well.

The practice of medicine is an art as well as a science. As the USPSTF and other professional societies, including the American College of Cardiology/American Heart Association and the European Society of Cardiology/European Atherosclerosis Society have all emphasized, shared decision-making of the anticipated benefits, harms, and uncertainties in predicting CVD are essential in determining whether to initiate a medication that a patient may possibly take for the remainder of their life. Although there are patient-facing decision-support aids for statins, they are underused. These aids would be more useful if quality-of-life data were collected in statin trials and could be added to decision-making tools. In addition, consideration should be given to deprescribing statins for adults 76 years or older, other older individuals unlikely to derive benefit from statins for primary prevention, and individuals who are at risk of polypharmacy because of medications taken for other conditions.

In the US, about $25 billion is spent annually on statins. Cardiovascular disease incidence and mortality are the upshot of myriad social determinants. Although statins lower LDL cholesterol in individuals, investments at the community level to construct a more salubrious environment that enables healthy eating and promotes physical activity are likely to have more widespread multiplicative and pleiotropic effects on the biological and psychosocial risks of CVD, as well as on improving quality of life. The 2022 USPSTF recommendations are an opportunity to pause and refocus efforts to meaningfully improve CVD outcomes for all, rather than extol the marginal, likely small, and uncertain absolute benefits of statins for the few in primary CVD prevention.

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REFERENCES


