

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Shih SC, Bost JE, Pawlson LG. Standardized health plan reporting in four areas of preventive health care. *Am J Prev Med*. 2003;24(4):293-300.
2. Parsons A, McCullough C, Wang J, Shih S. Validity of electronic health record-derived quality measurement for performance monitoring. *J Am Med Inform Assoc*. 2012;19(4):604-609.
3. Begum R, Ryan MS, Winther CH, et al. Small practices' experience with EHR, quality measurement, and incentives. *Am J Manag Care*. 2013;19(11 spec No. 10):esp12-esp18.

## Formulation of Treatment Recommendations for Statins

**To the Editor** Drs Ridker and Wilson<sup>1</sup> proposed that statin guidelines formulate treatment recommendations through consideration of "... patient populations for whom clinical trials have demonstrated benefit." They failed to provide a clear definition of benefit. The authors cited approximately 20 randomized clinical trials; however, the measures of benefit varied widely between some of these trials.

In addition, the vascular events terminology is insufficiently specific. Efficacy measures in randomized clinical trials of statins often include outcomes that differ in their clinical importance, ranging from death to clinician-driven end points such as revascularization procedures and hospitalizations.

For example, in the Scandinavian Simvastatin Survival Study (4S),<sup>2</sup> in which participants with a history of coronary heart disease were enrolled, the primary efficacy measure was total mortality. In the Subcutaneous Heparin and Angioplasty Restenosis Prevention (SHARP) trial,<sup>3</sup> in which participants with chronic kidney disease were enrolled, the modified efficacy outcome was a broad composite of events (ie, nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure). In fact, a reduction in revascularization procedures contributed most to the statistically significant result in SHARP.<sup>4</sup> Even though total mortality was reduced in the 4S trial (relative risk, 0.70 [95% CI, 0.58-0.85];  $P < .001$ ), this was not the case in SHARP (rate ratio, 1.02 [95% CI, 0.94-1.11];  $P = .63$ ).

Despite the qualitative differences in the benefit demonstrated in these 2 clinical settings, Ridker and Wilson<sup>1</sup> endorsed statin therapy equally for patients with chronic kidney disease as for patients with a history of coronary heart disease. The authors suggested incorporation of the number needed to treat metric into clinical decision making, but the number needed to treat for which outcome?

Guidelines that use oversimplified and ambiguous references to benefit or lack of benefit (without specification of the efficacy measures tested in the relevant trials) are unlikely to be usable by clinicians and patients. In our view, before guideline panels engage in interpretation and application of evidence, they should first specify for guideline users a hierarchy of outcomes that is specific and transparent.<sup>5</sup>

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1. Ridker PM, Wilson PW. A trial-based approach to statin guidelines. *JAMA*. 2013;310(11):1123-1124.
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**To the Editor** The Viewpoint on formulation of statin guidelines by Drs Ridker and Wilson<sup>1</sup> may have unintentionally implied to the clinical community that it is acceptable to focus on selected evidence over the totality of the evidence. Ridker and Wilson's example of trial-based recommendations for primary cardiovascular disease prevention includes subgroups identified through only 6 trials; however, a recent Cochrane Collaboration systematic review<sup>2</sup> on the effect of statins for primary cardiovascular disease prevention identified 18 trials.

In concert with recommendations from the Institute of Medicine, we favor using systematic reviews of the evidence over evidence from individual trials to draw conclusions about the effectiveness of an intervention.<sup>3</sup> Systematic reviews have a transparent, reproducible method that assesses the totality of evidence on a topic, including the risk of bias in the identified studies, and synthesizes that information quantitatively, when appropriate, through meta-analyses. When clinical practice guidelines use systematic reviews to support recommendations, opportunities for bias are minimized.

We are encouraged that the US cholesterol guidelines will incorporate systematic reviews,<sup>4</sup> even though earlier guidelines did not. Similar to the authors, we believe that guidelines should be updated frequently to account for accrual of new data, but we also argue that systematic review updates provide the appropriate framework to do so.

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1. Ridker PM, Wilson PW. A trial-based approach to statin guidelines. *JAMA*. 2013;310(11):1123-1124.
2. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;1:CD004816.
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**In Reply** We concur with Dr O'Sullivan and Ms Brown that only those trials that use actual clinical outcomes should inform practice. For the great majority of trials that we cited, the common end point was inclusive of myocardial infarction, stroke, revascularization for unstable angina, or vascular death. How one chooses to weight those outcomes is a matter of opinion, and thus we differ somewhat from O'Sullivan and Brown in that we believe a reduction in the need for angioplasty or bypass surgery is a relevant benefit for patients.

By contrast, we firmly believe that studies based on surrogate end points should have little if any role in guideline discussions. We respectfully disagree with Drs Huffman, Ebrahim, and Dickersin that comprehensive is better than relevant or that meta-analysis automatically trumps individual trial data. The 6 studies evaluated in our analysis of primary prevention include all trials ever conducted that address the fundamental hypotheses of whether or not statin therapy reduces hard clinical events in populations known at the baseline evaluation to be free of cardiovascular disease.

We are surprised to learn that the Cochrane meta-analysis of statins in primary prevention<sup>1</sup> included not only these core relevant studies but also analyzed studies in which the trial's primary aim was to address changes in surrogate end

points such as carotid thickness, low-density lipoprotein cholesterol level, blood pressure, and bone density. Our omission of such trials was intentional, and we believe well within the fundamental spirit of the Institute of Medicine recommendation to rely on hard evidence and on the simple concept of "what works and in whom?"<sup>2</sup> We note that other high-quality meta-analyses such as those routinely performed by the Cholesterol Treatment Trialist Collaboration also elect to exclude surrogate end point studies.

Surrogate end point trials tend to be of small sample size and add virtually no power to the overall analysis. Thus, the Cochrane approach comes to a similar conclusion as our approach, although we believe it puts an unfortunate distance between the actual trial data and the clinician responsible for patient care.

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1. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013;1:CD004816.
2. Ridker PM. What works and in whom? a simple, easily applied, evidence-based approach to guidelines for statin therapy. *Circ Cardiovasc Qual Outcomes*. 2012;5(4):592-593.

## CORRECTION

**Incorrect Language:** In the Original Investigation entitled "Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels" published in the November 6, 2013, issue of *JAMA* (2013;310[17]:1829-1836. doi:10.1001/jama.2013.280386), incorrect language was used. The fourth sentence of the Results section of the Abstract should read "At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages with events were 19.9% in the no testosterone therapy group vs 25.7% in the testosterone therapy group, with an absolute risk difference of 5.8% (95% CI, -1.4% to 13.1%)." The fifth sentence in the third paragraph of the Results section, the sentence should read "The Kaplan-Meier estimated cumulative percentages with events among the no testosterone therapy group vs testosterone therapy group at 1 year after coronary angiography were 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7." This article has been corrected online.