

# Editorials

## For Hyperlipidemia, Go Where the Evidence Takes You: Give a Statin and Nothing Else

DANIEL L. SONTHEIMER, MD, MBA, *Cox Family Medicine Residency, Springfield, Missouri*

When prescribing treatment for patients with hyperlipidemia, physicians have an important choice to make. Although statins and nonstatins have been shown to reduce low-density lipoprotein cholesterol levels, only statins are known to effectively reduce all-cause mortality in men with coronary heart disease.<sup>1-4</sup> The clear and convincing evidence for this secondary prevention is compelling. Additionally, there is evidence for the use of statins for primary prevention in patients with coronary risk factors and without established coronary heart disease.<sup>5</sup>

Conversely, nonstatins, such as bile acid sequestrants, niacin, omega-3 fatty acids, and fibrates (including fenofibrate [Tricor] and gemfibrozil [Lopid]), have been shown to reduce cardiovascular mortality without improving all-cause mortality.<sup>1,3</sup>

Fibrates are particularly worrisome because they have been shown to increase mortality from noncardiovascular causes, based on results from a systematic review of 15 trials (risk ratio = 1.13; 95% confidence interval, 1.01 to 1.27).<sup>3</sup> This translates into one noncardiovascular death for every 132 patients treated for 4.4 years (number needed to harm = 132). This was supported by another systematic review of 12 trials involving 21,269 patients.<sup>1</sup> Additionally, fibrates have not been shown to be effective in secondary prevention of stroke, as demonstrated in a systematic review of eight trials that included approximately 10,000 patients.<sup>6</sup>

Studies evaluating the use of omega-3 fatty acids to reduce cardiac and all-cause mortality have yielded conflicting results. In a systematic review of 14 trials (of primary and secondary prevention) involving 20,260 patients, omega-3 fatty acid use reduced cardiac and all-cause mortality (risk ratio = 0.77; 95% confidence interval, 0.63 to 0.94).<sup>3</sup> The number needed to treat was 86, which translates into one less death for every 86 patients treated for 1.9 years. Another systematic review found that omega-3 fatty acids had no effect on all-cause or cardiovascular mortality.<sup>7</sup> However, this review included a trial that followed 3,114 men with angina who were advised to consume more fish or take fish oil supplements; eat more fruits, vegetable, and oats; both types of advice; or no advice.<sup>8</sup> Compared with the other three groups, the group advised to increase fish or



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► See related editorial on page 1056.

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fish oil consumption had a higher risk of cardiac mortality without a change in all-cause mortality over three to nine years of follow-up.

Ezetimibe (Zetia), which inhibits cholesterol absorption, has yet to be studied for patient-oriented outcomes. Although it has been shown to reduce cholesterol levels, it is unknown whether it reduces mortality. One study that examined carotid and femoral arterial intima-media thickness found no difference between the combination of ezetimibe and simvastatin (Zocor), and simvastatin alone.<sup>9</sup>

There is also a lack of evidence supporting the combination of statins and other agents compared with a higher dosage of statins. A 2009 systematic review revealed no difference in outcome or adverse events with either strategy in patients with low-density lipoprotein cholesterol levels requiring more than introductory dosages of statins to achieve the goals set by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III).<sup>10</sup> This review included a meta-analysis of 14 trials including 6,275 patients. No statistically significant difference in mortality was found (although there were wide confidence interval boundaries) between patients using various dosages and types of statins in combination with ezetimibe, compared with patients at high risk of coronary heart disease taking high-dosage statin monotherapy (odds ratio = 0.61; 95% confidence interval, 0.22 to 1.71). The authors concluded that there was no firm evidence to show that combining a statin with another agent (i.e., bile acid sequestrants, fibrates, ezetimibe, niacin, or omega-3 fatty acids) improved clinical outcomes (i.e., myocardial infarction, stroke, or all-cause mortality) more often than high-dosage statin monotherapy. These results demonstrate that maximal statin dosages can provide the same benefit as combination therapy for primary prevention in high-risk patients, avoiding the need for multidrug regimens.

Based on the current evidence, nonstatin therapy has no role in the treatment of patients with coronary

## Editorials

disease for secondary prevention of all-cause mortality, or in primary prevention for patients at high risk of coronary heart disease. However, patients who develop nonvascular complications from elevated triglyceride levels or other serum lipids may benefit from nonstatin therapy (e.g., fibrates to treat hypertriglyceride-induced pancreatitis<sup>11</sup>).

Only statins have patient-oriented evidence supporting their role in reducing all-cause mortality. The NCEP-ATP III guidelines offer a nine-step approach for reaching target lipid levels,<sup>12</sup> but the application to everyday practice is far simpler: If a patient with hyperlipidemia has coronary disease, prescribing a statin is the obvious choice.

Address correspondence to Daniel L. Sontheimer, MD, MBA, at daniel.sontheimer@coxhealth.com. Reprints are not available from the author.

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