
Making the Case for Selective Use of Statins in the Primary Prevention Setting

Members of the Archives of Internal Medicine editorial board recently wrote,1(p619)

. . . opioids for persons with chronic nonmalignant pain, and statin medications for persons without coronary artery disease are . . . examples of the widespread use of medications with known adverse effects despite the absence of data for patient benefit for these indications.

We disagree that “less is more” when it comes to statins for primary prevention of cardiovascular disease (CVD). In accord with current National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, we believe there is compelling evidence to support the use of statins for primary prevention in patients at high risk (Framingham risk score, >10%) for developing coronary heart disease (CHD) over the next 10 years.2

The argument made by the Archives Redberg et al3 is based on the assertion that statin therapy does not decrease near-term (<5-year) all-cause mortality.3 Before disregarding the benefits of statins, we must place this assertion in context—can we expect any drug or lifestyle intervention to reliably produce a survival benefit in asymptomatic individuals within a few years?

An effective primary prevention intervention must either prolong survival or reduce patient suffering. A fundamental goal of primary prevention must also include reduction of morbidity—particularly myocardial infarction, stroke, ischemia-related hospitalizations, and invasive revascularization procedures resulting in over $475 billion in direct and indirect costs in 2009.4 While not always fatal, major vascular events often result in severe pain and lifelong disability.

All-Cause Mortality Data for Statin Therapy. Three meta-analyses of the large statin primary prevention randomized controlled trials (RCTs) have been published since 2009.3,5,6 Among these publications is a 2010 study by Ray et al,3 which included 11 RCTs involving 65,229 participants without known CHD. Using previously unpublished data of strictly primary prevention patients, the authors found that statins resulted in a nonsignificant 9% risk reduction in all-cause mortality (relative risk [RR], 0.91; 95% confidence interval [CI], 0.83-1.01) over an average treatment duration of 3.7 years.3 Unfortunately, an analysis of cardiovascular morbidity was not undertaken.

A 2009 meta-analysis by Brugts et al5 examined 10 RCTs, 9 of them the same as those analyzed by Ray et al3 but also including the primary prevention subgroup from the Heart Protection Study. A total of 70,388 participants were included, 6% of whom had known CHD but could not be eliminated owing to data constraints. Treatment with statins significantly reduced the risk of all-cause mortality by 12% (odds ratio [OR] 0.88; 95% CI, 0.81-0.96) over a mean follow-up of 4.1 years.5 A significant decrease in all-cause mortality remained after excluding the 3 trials that included participants with known CHD (OR, 0.87; 95% CI, 0.78-0.97) or after excluding JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), the largest and most controversial of the primary prevention trials (OR, 0.89; 95% CI, 0.81-0.97).

A 2011 Cochrane meta-analysis of statins in primary prevention analyzed 14 RCTs (including 16 trial arms) dating from 1994 to 2006, representing a total of 34,272 patients. For inclusion, the authors required enrollment of 10% of participants or less with known CVD. The individual trials had observation periods ranging from 1.3 to 5.3 years. Treatment with a statin resulted in a 17% reduction in all-cause mortality (RR, 0.83; 95% CI, 0.73-0.95).6 The authors cautioned that any conclusions about mortality benefit with statin therapy are limited owing to inconsistencies in individual RCT data quality, study design, and emphasis on combined end points as primary outcomes.

Overall, 2 of the 3 statin primary prevention meta-analyses indicate a modest but statistically significant 12% to 17% RR reduction in all-cause mortality at 5 years of follow-up or less. If the only goal of statin therapy is to prolong near-term (≤5-year) survival, then the evidentiary support would have to be considered less than robust.

Cardiovascular Morbidity Data for Statins—The Message Is Clear. The meta-analysis by Brugts et al5 also analyzed the effect of statins on cardiovascular morbidity. These findings suggest a significant decrease in major coronary events (OR, 0.70; 95% CI, 0.61-0.81), major cerebrovascular events (OR, 0.81; 95% CI, 0.71-0.93), nonfatal myocardial infarction 0.56 (OR, 0.56; 95% CI, 0.41-0.76) and revascularizations (OR, 0.67; 95% CI, 0.59-0.76).5 These results corroborate those of the Cochrane meta-analysis demonstrating a 34% reduction in revascularizations (RR, 0.66; 95% CI, 0.53-0.83) and a 30% reduction in combined fatal and nonfatal CVD end points (RR, 0.70; 95% CI, 0.61-0.79).5

Despite these impressive treatment effects on CVD morbidity and modest effects on mortality, the authors of the Cochrane review emphasize that “caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.”5(p62) We agree that statins are not likely to benefit patients with low coronary risk (10-year Framingham risk score, <10%) but emphasize that it is paramount to make the distinction between low-risk and high-risk primary prevention cohorts. Patients without known CHD but with diabetes,
hypertension, hyperlipidemia, and tobacco use are at increased risk for developing CHD and are likely to benefit from statin primary prevention in accord with ATP III guidelines.2

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1. Redberg R, Katz M, Grady D. Diagnostic tests: another frontier for less is more: or why talking to your patient is a safe and effective method of reassurance. Arch Intern Med 2011;171(7):619.

COMMENTS AND OPINIONS

Needed Assumptions for Potential Savings From Greater Use of $4 Generic Drugs

The study by Zhang and colleagues1 suggests patient and societal savings of $6 billion from more widespread use of $4 discounted generic medication programs. While possible, such savings depend on a number of unstated assumptions on marginal profitability, scalability, and absence of negative societal costs.

First, for each additional script sold under such a program, gross margin has to be positive. If not, the store must recoup the loss from increased prices on other goods sold. This would mean some patient savings are others’ costs, reducing societal savings. Walmart initially sacrificed margin but made some up on increased foot traffic and on branded medications.2 At current enrollments, they likely earn positive gross margin on $4 generics as a standalone product,3 but other pharmacy chains may not.

Second, the economics of the program have to persist with increase in scale. Without better knowledge of the cost of increased pharmacy size and extra pharmacy staff, it is not clear how costs could rise with sales. If these new customers did not increase Walmart’s foot traffic, program rev-

EDITORS’ NOTE

To Make the Case—Evidence Is Required

Minder et al disagree that statins for primary prevention are an example of a widely used medication with no known benefit and definite risks. Although they concede that the evidence that statins prolong survival is “less than robust,” they state that such evidence cannot be expected from trials in which patients were only treated for a few years. To support their belief in statin use for primary prevention they cite a meta-analysis (Brugts et al1) that includes data from studies of both primary and secondary prevention, where most of the benefit occurred in the studies of secondary prevention. Importantly, Minder et al do not acknowledge the commonly reported adverse effects associated with statins, including memory loss, muscle pains, weakness, and liver function abnormalities.

For a medicine to be recommended to healthy patients for a lifetime of use, there should be robust evidence that this regime will reduce suffering or extend life, and evidence that the benefit outweighs adverse effects. Until there is such data for statins for primary prevention, we will continue to classify it as an intervention without known benefit, but with definite risks, in our Less Is More series.

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