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Healthy Men Should Not Take Statins

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Should a 55-year-old man who is otherwise well, with systolic blood pressure of 110 mm Hg, total cholesterol of 250 mg/dL, and no family history of premature CHD be treated with a statin? —No.

EXTENSIVE EPIDEMIOLOGIC DATA DEMONSTRATE THAT higher cholesterol levels are associated with a greater risk of heart disease. At the population level, higher levels of cholesterol are associated with a diet greater in fatty foods, particularly trans fat and meat, and low intake of fruits and vegetables.

The important questions for clinicians (and for patients) are as follows: (1) does treatment of elevated cholesterol levels with statins in otherwise healthy persons decrease mortality or prevent other serious outcomes? (2) What are the adverse effects associated with statin treatment in healthy persons? (3) Do the potential benefits outweigh the potential risks? The answers to these questions suggest that statin therapy should not be recommended for men with elevated cholesterol who are otherwise healthy.

1. What is the benefit of statin therapy in healthy men with high cholesterol levels? Data from a meta-analysis of 11 trials including 65 229 persons with 244 000 person-years of follow-up in healthy but high-risk men and women showed no reduction in mortality associated with treatment with statins.[1] A 2011 Cochrane review of treatment with statins among persons without documented coronary disease came to similar conclusions.[2] The Cochrane review also observed that all but one of the clinical trials providing evidence on this issue were sponsored by the pharmaceutical industry. It is well established that industry-sponsored trials are more likely than non–industry-sponsored trials to report favorable results for drug treatment because of biased reporting, biased interpretation, or both of trial results.[6]

See also counter Viewpoint on page 1489, Editorial on page 1532, and online poll at www.jama.com.

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2. What adverse effects are associated with statin treatment in healthy persons? All treatments designed to prevent disease—such as death from coronary disease—can also result in adverse effects. Data from observational studies show much higher rates for statin-associated myopathy and other adverse events in actual use than the 1% to 5% rate reported in clinical trials. This underestimation of adverse events occurs because the trials excluded up to 30% of patients with many common comorbidities, such as those with a history of muscular pains, as well as renal or hepatic insufficiency.[3] Many randomized trials also excluded patients who had adverse effects of treatment during an open-label run-in period. For example, in the Treat to New Targets trial, after initial exclusions based on comorbidities, an additional 35% of eligible patients, or 16% of patients, were excluded during an 8-week, open-label, run-in phase because of adverse events, ischemic events, or participants' lipid levels while taking the drug not meeting entry criteria.[7] Additionally, the results of randomized trials of statin treatment likely underestimate common symptoms such as myalgia, fatigue, and other minor muscle complaints because these studies often only collect data on more quantifiable adverse effects such as rhabdomyolysis.

Numerous anecdotal reports as well as a small trial[8,9] have suggested that statin therapy causes cognitive impairment, but this adverse outcome would not have been captured in randomized trials. The true extent of cognitive impairment associated with statins remains understudied. It is disappointing that more data are not available on important adverse events associated with statin treatment, despite millions of prescriptions and many years of use. This information could be easily collected in observational studies and from registries. One population-based cohort study in Great Britain of more than 2 million statin users found that statin use was associated with increased risks of moderate or serious liver dysfunction, acute renal failure, moderate or serious myopathy, and cataract.[4] The risk of diabetes with statin use has been seen in randomized clinical trials such as JUPITER,

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which found a 3% risk of developing diabetes in the rosuvastatin group, significantly higher than in the placebo group. In observational data from the Women's Health Initiative, there was an unadjusted 71% increased risk and 48% adjusted increased risk of diabetes in healthy women taking statins.[5]

3. Do the potential benefits outweigh the potential risks? Based on all current evidence, a healthy man with elevated cholesterol will not live any longer if he takes statins. For every 100 patients with elevated cholesterol levels who take statins for 5 years, a myocardial infarction will be prevented in 1 or 2 patients.[7] Preventing a heart attack is a meaningful outcome. However, by taking statins, 1 or more patients will develop diabetes and 20% or more will experience disabling symptoms, including muscle weakness, fatigue, and memory loss.[3]

Nondrug Approaches to Reducing Coronary Risk

There are effective methods for reducing cardiovascular risk in otherwise healthy men: dietary modification, weight loss, and increased exercise. These strategies are effective in increasing longevity and also result in other positive benefits, including improved mood and sexual function[10] and fewer fractures. Although these strategies are challenging, prescribing a statin may undermine them. For example, some patients derive a false sense of security that because they are taking a statin they can eat whatever they want and do not have to exercise.

For some clinicians, evidence that statins reduce the risk of recurrent coronary events in patients with documented coronary disease leads to the belief that statins also "must" be beneficial for patients without coronary disease. However, recent history is rife with examples of interventions that are proven to work in patients with serious disease yet are not efficacious when generalized to patients without serious disease. For example, coronary artery bypass graft (CABG) surgery is lifesaving for patients with symptomatic left main disease. However, CABG surgery would not be a good choice for single-vessel coronary artery disease (CAD) because risks would outweigh benefits in less extensive CAD. Similarly, the benefits of carotid endarterectomy in preventing stroke outweigh the risks for symptomatic patients with tight carotid artery stenosis, but not for asymptomatic patients with less critical stenosis. In addition, the use of aspirin is similar to statins for prevention. The data show clear benefit for aspirin in secondary prevention of cardiovascular disease, but not for primary prevention. Practitioners should not be generalizing from other settings when good data indicate that statins are not effective in improving length or quality of life when used for primary prevention.

For the 55-year-old man in this scenario, his risk of myocardial infarction in the next 10 years based on the Framingham Risk Score varies from 10% to 20%. His risk is driven mostly by his age rather than by his cholesterol level. Increasing age has a much larger influence on risk for cardiovascular disease than do increasing levels of cholesterol. Recent data on increased risk of diabetes, cognitive dysfunction, and muscle pain associated with statins suggest that there is risk with no evidence of benefit. Advising healthy patients to take a drug that does not offer the possibility to feel better or live longer and has significant adverse effects with potential decrement in quality of life is not in their interest.

At the same time, there are significant opportunities for improvement in lifestyle counseling and interventions. Even small changes in diet and increases in physical activity and smoking cessation can lead to significant personal and population health benefits. Such positive lifestyle changes have the key advantage of helping patients feel better and live longer. Lifestyle counseling should remain the focus of primarily prevention efforts—at the physician and public health levels.

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