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Statin Therapy for Healthy Men Identified as "Increased Risk"

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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? —**Yes.**

ATHEROSCLEROTIC CORONARY HEART DISEASE (CHD) is the most common cause of morbidity and mortality in the world. The "lipid hypothesis" of CHD is clearly established: (1) circulating cholesterol plays a central role in atherogenesis and is an integral component of the requisite lesion, the coronary plaque; (2) cholesterol levels beginning in childhood predict lifetime risk of atherosclerotic CHD events in a dose-response relationship; and (3) statins lower cholesterol levels and reduce CHD and cerebrovascular events directly proportional to the degree of low-density lipoprotein cholesterol (LDL-C) lowering. As a result, guidelines from around the world support a combined lifestyle and pharmacologic approach to cholesterol lowering directed at patients with elevated CHD risk.

Assuming a high-density lipoprotein cholesterol (HDL-C) level of about 40 mg/dL, the patient in this common clinical scenario would have an "intermediate" 10-year risk for developing CHD (approximately 10%) based on the Framingham Risk Score (FRS). As always, lifestyle change is the first-line therapy. However, if this patient's cholesterol level remains abnormal, despite sustained attempts at lifestyle optimization, statin therapy should be considered with the goal of reducing CHD risk. Current guidelines suggest an LDL-C goal of less than 130 mg/dL with an optional target of less than 100 mg/dL.[1] In the shared decision-making process, the clinician should explicitly inform this patient that a statin is likely to reduce the chance of a first CHD event and reduce the chance of stroke and may offer a survival benefit that is likely to become more evident over a lifetime.

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Evidence Supporting Primary Prevention

The WOSCOPS enrolled 6595 men aged 45 to 64 years with no previous history of myocardial infarction and a mean (SD) plasma cholesterol level of 272 (23) mg/dL. Treatment with pravastatin, 40 mg, resulted in a 31% reduction in myocardial infarction and CHD-related death (248 vs 174 events and 135 vs 106 deaths for placebo vs pravastatin, respectively).[2]

Similarly, the AFCAPS/TexCAPS randomized 6605 asymptomatic adults with a mean (SD) LDL-C level of 150 (17) mg/dL and low HDL-C (36 [5] mg/dL in men and 40 [5] mg/dL in women) to lovastatin, 20 to 40 mg, vs placebo. Treatment with lovastatin reduced the incidence of first major coronary events by 37% and myocardial infarction by 40% (183 vs 116 events and 95 vs 57 myocardial infarctions for placebo vs lovastatin, respectively).[3]

The JUPITER trial enrolled 17 802 healthy men and women with so-called normal LDL-C less than 130 mg/dL and elevated high-sensitivity C-reactive protein greater than 2.0 mg/L. Aggressive lowering of LDL-C in those randomized to receive rosuvastatin, 20 mg, reduced the risk of myocardial infarction, stroke, and revascularization by about 44% (251 vs 142 events for placebo vs rosuvastatin) and total mortality by 20% (247 vs 198 events, respectively). The effect of aggressive LDL-C lowering in JUPITER was substantial considering that the baseline median LDL-C was just 108 mg/dL.[4] Subanalysis demonstrated the largest absolute reduction in patients with a FRS of 11% to 20% (145 vs 74 events for placebo vs rosuvastatin; hazard ratio [HR], 0.51; 95% CI, 0.39-0.68) followed by those with FRS of 5% to 10% (59 vs 32 events; HR, 0.55; 95% CI, 0.36-0.84).[5]

Risk-Based, Individualized Treatment Decisions

Nearly all US adults have elevated cholesterol compared to their evolutionary ancestors. The debate over cholesterol therapy must therefore be rephrased. Clinicians should never treat elevated cholesterol levels in isolation. The main goal must be to direct risk-reducing, atherogenic lipoprotein–reducing therapies to those at the highest risk who are more likely to benefit.

What if the patient in this scenario is uncertain about his true risk and thus unclear about the absolute benefit of statin treatment? The best predictor of risk in intermediate-risk patients is the coronary artery calcium (CAC) scan.

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Knowing a patient's CAC score, a directly measured marker of the burden of coronary artery disease, enables the clinician to integrate risk exposure over a lifetime and to use this information to guide decision making. High CAC scores (>100) signify higher CHD risk and thus a lower estimated number needed to treat (NNT) with statins. In contrast, a CAC score of 0 equates to very low near-term (5-year) CHD risk and unfavorably high NNT.[6] The CAC scan is the single best test for reclassifying intermediate risk patients into their most appropriate treatment groups.

The argument of using a statin for the patient in this scenario can be supported by data from the Multi-Ethnic Study of Atherosclerosis (MESA). A 55-year-old patient with a total cholesterol of approximately 250 mg/dL and a normal blood pressure would have a 50% chance of having a CAC score of 0; this would translate to an estimated 10-year CHD event rate of less than 2% and an estimated 5-year NNT of approximately 300 using a 35% event reduction with statins. However, simple presence of CAC would increase that risk nearly 4-fold and reduce the estimated 5-year NNT to approximately 70. This patient also would have a 13% chance that the CAC score is greater than 100, which would suggest an estimated 10-year CHD event rate greater than 12% and an estimated 5-year NNT of approximately 45.

The CAC scan is a helpful tool that enables clinicians to direct statin treatment at the disease (coronary atherosclerosis) that they propose to treat and illustrates the concept of risk-based, individualized decision making. Statin therapy would not be recommended if a CAC scan revealed a score of 0.

Arguments Against Selective Use of Statins

Some physicians see no role for pharmacologic treatment of elevated cholesterol level to prevent CHD in any asymptomatic patient. What are the main points of contention?

1. Are statins safe? Adverse effects with statin therapy are rare. Approximately 5% of patients will develop muscle-related complaints that are generally reversible after drug discontinuation. Many of these patients can tolerate a different statin. There is no good peer-reviewed evidence that statins lead to cognitive impairment or memory loss, as has been anecdotally reported; one report suggested that statins may improve memory.[7] In appropriate middle-aged patients, the risk of type 2 diabetes associated with statins is mainly seen in those with preexisting glucose intolerance and is minimal in comparison with CHD event reduction.

2. Do statins lead to less adherence with a prudent lifestyle? In fact, there is evidence to the contrary; a recommendation from a physician for statin treatment may motivate overall healthy behaviors.[8] It is incumbent on physicians to refrain from paternalism/maternalism and to encourage sustained motivation for adherence to both lifestyle and medicine.

3. Is there a durable benefit to statin therapy, or should statins be prescribed only after a myocardial infarction? There is no apparent logic in waiting for a myocardial infarction or a stroke to occur before starting a risk-reducing therapy. A recent meta-analysis of trials confirms that statins retain their benefit after discontinuation of randomized therapy.[9]

4. Is statin therapy cost-effective? With the emergence of generic high-potency statins like simvastatin (~$4 a month) and atorvastatin, statin therapy is increasingly cost-effective, well below the typical willingness-to-pay threshold. Would it be more cost-effective to spend this money on walking trails, neighborhood renovation, and increased accessibility to fruits and vegetables? This is not likely, despite the critical importance of these approaches.

5. Do statins only work in men? In the recent meta-analysis by Kostis et al,[10] women derived just as much benefit from statins as men for primary prevention.

6. Do patients expect medications to prolong survival within 5 years? Most patients do not expect near-term survival benefit from medicine; they are concerned about myocardial infarction, stroke, venous thrombosis, and the resulting chronic disease and disability that may occur. They see their parents, who have vascular dementia and congestive heart failure, and seek safe strategies to reduce their risk. In fact, more than ever, the modern patient is focused on quality of life and not exclusively on longevity.

Conclusions

The cornerstone therapies for patients with elevated cholesterol levels will always be dietary modification and renewed emphasis on physical activity. Statin therapy is a critical adjunct for those identified to be at increased CHD risk.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.
Online-Only Material: The Author Audio Interview is available at http://www.jama.com.

REFERENCES

1. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110(2):227-239.
2. Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333(20):1301-1307.
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279(20):1615-1622.
4. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
5. Ridker PM, Macfadyen JG, Nordestgaard BG, et al. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity C-reactive protein and 5% to 10% and 10% to 20% 10-year risk. *Circ Cardiovasc Qual Outcomes*. 2010;3(5):447-452.
6. Blaha MJ, Budoff MJ, DeFilippis AP, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events. *Lancet*. 2011;378(9792):684-692.
7. Bernick C, Katz R, Smith NL, et al; Cardiovascular Health Study Collaborative Research Group. Statins and cognitive function in the elderly. *Neurology*. 2005;65(9):1388-1394.
8. Lytsy P, Burell G, Westerling R. Cardiovascular risk factor assessments and health behaviours in patients using statins compared to a non-treated population [published online April 15, 2011]. *Int J Behav Med*. doi:10.1007/s12529-011-9157-6.
9. Kostis WJ, Moreyra AE, Cheng JQ, Dobrzynski JM, Kostis JB. Continuation of mortality reduction after the end of randomized therapy in clinical trials of lipid-lowering therapy. *J Clin Lipidol*. 2011;5(2):97-104.
10. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol*. 2012;59(6):572-582.