



Statins and Risk of New-Onset Diabetes Mellitus

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For any prescription drug, the potential benefits to health must be balanced against potential risks. Understanding these potential risks can help physicians and patients make informed decisions on whether to use a medication. Recently, statins, a class of medications prescribed to treat high cholesterol levels, have been found to modestly increase the risk of developing diabetes mellitus. It is clear that statins can prevent future major cardiovascular events, such as heart attack, stroke, and deaths from cardiovascular causes, in patients who have had a previous heart attack or those with multiple cardiovascular risk factors. However, the associations between diabetes mellitus and statin use have raised concerns over the widespread use of statin medications in patients at lower risk for cardiovascular disease. In this Patient Page, we describe the indications for statin therapy, the most common adverse effects, and recent concerns about new-onset diabetes mellitus to help patients and providers make more informed decisions about the use of this important class of medications in at-risk individuals.

Why Should High Cholesterol Be Treated?

Cardiovascular disease is a major cause of illness and death worldwide. Elevated blood cholesterol levels (specifically the low-density lipoprotein [LDL] cholesterol) are associated with a higher risk of heart attack, stroke, and heart failure. It has become clear that elevated LDL cholesterol levels predict future events, and modern risk scores such as the Framingham Risk Score use LDL cholesterol level as an important predictor of future cardiac events.¹ In addition, as new large trials shed light on the important role of LDL in cardiac disease, the optimal LDL cholesterol level has been progressively lowered in national guidelines.

What Are Statins?

Statins are a class of medications called 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. These drugs block a critical step in the production of LDL cholesterol in the liver, thereby reducing the blood levels of LDL cholesterol. Aside from lowering LDL, statins reduce inflammation and promote health of the lining of the blood vessels. Currently, the statin class of drugs collectively is the most commonly

prescribed class of medication used to treat high LDL cholesterol.

In general, statins are safe and well tolerated. If common and minor adverse effects (eg, muscle aches) develop, switching to another statin or altering the dose or frequency of administration may be recommended. Some studies report memory loss for patients using statins, which reverse when stopping the statin. The risk of more severe effects (eg, liver failure or muscle inflammation) is quite rare, and close monitoring with attention to interacting medications can help to prevent them.

How Beneficial Are Statins, and Are There Alternatives?

Statins have a long track record of improving clinical outcomes in patients with high LDL cholesterol. Treatment of elevated LDL cholesterol levels with statins leads to a dramatic drop in the risk of heart attack, stroke, and death from cardiovascular causes in those with and without diabetes mellitus (Figure A).² Over 4 years, for every 40-mg/dL drop in the LDL cholesterol level, there is a 13% reduction in the risk of death from any cause in patients without diabetes mellitus and

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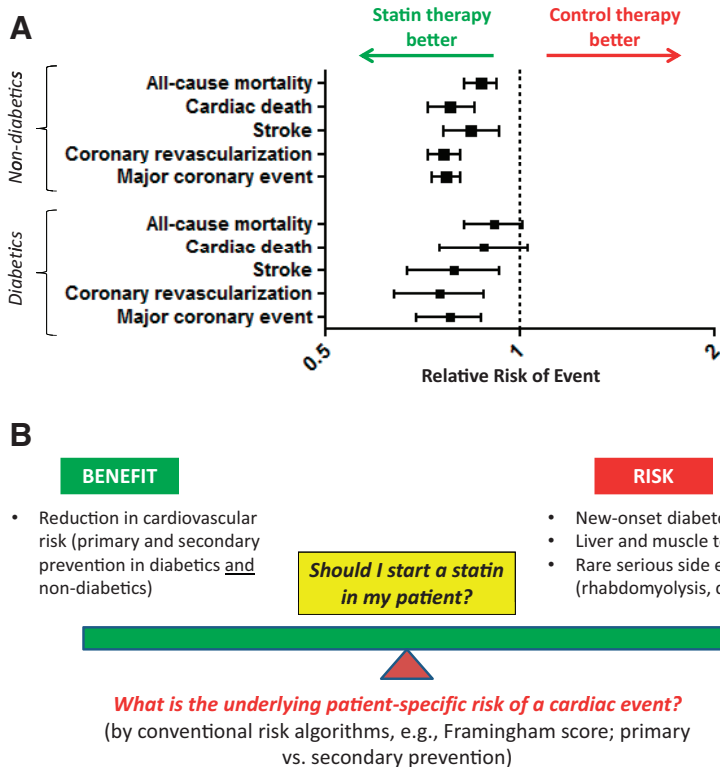


Figure. A, Relative risk of experiencing a cardiac event or death by diabetes status (for a near 40 mg/dL reduction in LDL cholesterol) from a meta-analysis of 14 clinical trials of statin therapy. Bars to the left represent better outcomes on statin therapy. Adapted from Kearney et al.³ **B**, Risk-benefit of statin initiation in at-risk patients.

a 9% reduction in patients with diabetes mellitus.² These cardiovascular health and survival benefits occur within the first year using a statin and increase over time. Although other medications used to treat high cholesterol (eg, fibrates, niacin, and bile acid sequestrants) can be effective in reducing the LDL cholesterol level, they have not yet shown a similar degree of benefit for heart health as compared with statin therapy.

Can Statins Cause Diabetes Mellitus?

Careful review of findings from many trials combined does show that statins can modestly raise blood sugars, and more patients who are on statin therapy are diagnosed with diabetes mellitus compared with those not on statins. Although patients on statins do have a higher risk of developing diabetes mellitus during the studies, they also experience a significant drop in cardio-

vascular events. In 1 study, diabetes mellitus was diagnosed in 27% more patients receiving a statin (rosuvastatin) compared with patients receiving placebo (an identical appearing pill that does not contain medication), but patients receiving the statin had a significant 54% lower risk of heart attack, 48% lower risk of stroke, and 20% lower risk of death from any cause.³ Although risk of new-onset diabetes mellitus is seen with all statins, it is not true that 27% of patients prescribed a statin will develop diabetes mellitus. Many people treated with placebo also developed diabetes mellitus. The findings do show that new-onset diabetes mellitus is more common in the patients who received statin treatment.

Although diabetes mellitus is a serious disease, risk and benefit must be considered at the same time. Combining information from 13 individual studies (involving a total of 91 140 patients) showed that treating 255

patients with statins for 4 years led to 1 extra case of diabetes mellitus, whereas 5.4 cardiovascular events were prevented.⁴ Therefore, although the risk of diabetes mellitus is higher in patients receiving statins, statins ultimately benefit cardiac health in people with established heart disease or risk factors for heart disease. More importantly, the strongest predictors of whether a patient will develop diabetes mellitus (regardless of whether he/she takes a statin) still include older age, increased weight, and higher blood sugar levels before statin use. Statins may be simply unmasking diabetes mellitus that would have developed anyway based on these other very important risk factors.

The effect of statins on glucose are small, and it takes combining many studies that involve thousands of patients for doctors to be confident in a consistent but weak association between statin therapy and the development of new-onset diabetes mellitus or worsening of diabetes mellitus. In patients without diabetes mellitus, fasting sugars are increased by 3 mg/dL for patients using statins compared with those not using statins, and it took data from >345 000 patients to detect this difference in a clinical setting.⁵ In patients with diabetes mellitus and hemoglobin A1c near 7.5% before starting statins, atorvastatin and rosuvastatin (2 potent and widely used statin drugs) both increased hemoglobin A1c by ≈0.3%.⁶ Thus, whereas there is an effect of statins on glycemia, the exacerbation of diabetes mellitus is relatively small, and especially so compared with the cardiovascular protection provided to those with cardiovascular risk similar to the participants in the trials.

What If I Already Have Diabetes? Will Statin Therapy Make It Worse?

There are a wealth of clinical data showing that patients with diabetes mellitus benefit greatly from statin therapy to prevent cardiac events. The current data do not support discontinuing statins if you have diabetes mel-

litus or if you are newly diagnosed with diabetes mellitus. It also remains important to increase your exercise as tolerated, make healthy food choices, and control portion sizes to help remain healthy and to lose excess weight if you have or are at risk for diabetes mellitus.

What Does This US Food and Drug Administration Advisory Mean to Me?

The long-term implications of statin-induced diabetes mellitus are unknown and will become clearer as we continue to follow patients in trials of statin therapy over a longer period of time. Although it is clear that statins prevent heart disease in patients at high risk or with established cardiac disease, the use of statins in patients at lower risk (for primary prevention before any cardiac events have occurred) is less certain. Although large studies suggest that using statins to achieve lower LDL cholesterol may benefit lower-risk populations,⁷ the risk of statin-induced diabetes mellitus is important and unknown in this population. If diet and exercise cannot achieve LDL goals established by national guidelines, statin therapy should be strongly considered.

In conclusion, as we obtain further data to define the risks and clinical implication of statin-induced diabetes mellitus, patients and their physicians should continue to have a candid discussion of risks of heart disease and appropriateness of statin therapy. Patients at high risk for cardiovascular events (as determined by modern risk metrics, like the Framingham score) continue to merit statin therapy (Figure, B). Physicians should monitor blood sugar control in patients at risk for diabetes mellitus in whom statins are used but should continue to prescribe statins when indicated to prevent future cardiovascular disease. Patients should continue to take statins to reduce their risk of heart attack, stroke, and death from cardiovascular causes.

Disclosures

None.

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