

## Cholesterol-Lowering Statins: Diabetes and Other Side Effects

by Ann Gerhardt, MD

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Statins, the cholesterol-lowering drugs that have saved innumerable lives from heart attacks, have a dark side. Currently available statins include pravastatin (Pravachol), lovastatin (Mevacor), atorvastatin (Lipitor), rosuvastatin (Crestor) and simvastatin (Zocor).

Scientists probing statin study results for ancillary information have found possible associations of statins with **diabetes and hemorrhagic stroke**. The goal and design of most of these studies was to assess statins' effect on heart and vascular disease and death. The new concerns make you wonder how drugs proven to reduce vascular disease could also cause conditions that usually make vascular disease worse.

**First, some background.** Statins inhibit an enzyme in the metabolic pathway that the body uses to make cholesterol (yes, we do make cholesterol, since we need it for cell walls, neurologic function and hormones like adrenaline, cortisol, estrogen and testosterone). Normally the liver clears the body of excess cholesterol. People who can't maintain a healthy balance of incoming and out-going cholesterol tend to have more vascular disease.

Doctors strongly recommend taking a statin after experiencing a heart attack, stroke or other acute vascular event. These drugs dramatically reduce subsequent heart attacks, strokes and deaths from cardiovascular causes.

Some doctors suggest that anyone at risk of *ever* having vascular disease should take a statin. That would just about be everyone, since, if you live long enough, your arteries will stiffen and clog with plaque. Some even joke that we should put the drugs in our water supply.

**The problem with statin enthusiasm is that they don't reduce *all-cause* mortality.** So deaths from other maladies make up for those saved from vascular disease. Hence the ongoing furor over side-effects.

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## HEALTHY CHOICES FOR MIND AND BODY

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One study hinted that statin users risked more hemorrhagic strokes (strokes that result from bleeding into the brain). That study, called Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), compared 80 mg of atorvastatin to placebo. You can forget this potential problem, since subsequent analyses discounted that association.

### **The Women's Health Initiative (WHI) recently dropped the statins-cause-diabetes bombshell.**

Retrospective analysis of 153,840 post-menopausal women (age 50-79) found that taking a statin increased the risk of new diabetes diagnoses by 48%, after adjustment for some of the most obvious variables.

Like most WHI bombshells, the devil's in the details. *The WHI trial was **not** a direct comparison of women randomly assigned to statin or placebo.* The women's doctors, in 40 different geographic centers, had made independent clinical decisions, prior to the study, to use or not use statins.

### **It's easy to see that the women taking statins in the WHI were likely skewed to those at risk for diabetes.**

Doctors are more likely to prescribe a statin for people with diabetes or at risk of diabetes, because those patients are more likely to develop vascular disease. Doctors also prescribe statins for those who have high cholesterol, other risk factors or a strong family history of heart attack. Those risk factors often overlap with Metabolic Syndrome, the precursor for adult-onset diabetes.

There is a more practical reason that WHI statin-users might have been diagnosed with more diabetes - they have more lab testing done for monitoring. If you don't do the testing, you won't identify diabetes. Remember, WHI was not a study of statins and diabetes: The investigators took what information was available to them from the patients' usual care.

Another skewed trial was the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). In this trial

physicians reported a 25% higher risk of new diabetes cases, compared to the risk with placebo. The striking finding is that rosuvastatin reduced cardiovascular disease so much that, in spite of increased diabetes, the study was terminated after only 1.9 years.

Though the patients in JUPITER were randomly assigned to rosuvastatin or placebo, the whole study group was at higher than normal risk for diabetes. This study included only men with high CRP levels, a blood test that is often elevated in Metabolic Syndrome. The vast majority (78%) of new diabetes cases had had abnormal glucose levels at the start of the trial.

This suggests that, yes, rosuvastatin increases diabetes risk over that of placebo, but predominantly does so in people already predisposed to diabetes. (Metabolic Syndrome criteria include large waistlines, high triglycerides, low HDL-cholesterol, high blood pressure, gout and insulin resistance.) BUT, in spite of pushing these Metabolic Syndrome people into overt diabetes, the drug still lowered vascular risk.

There have been some studies not biased towards diabetes. These randomly assigned people to statin or no statin, and generated less striking diabetes results. Simvastatin, cerivastatin, atorvastatin and rosuvastatin all increased diabetes risk, but only by 1-20%. These are the more fat-soluble statins, the ones that also cause more statin-induced muscle aches. My cursory comparison of disparate studies puts pravastatin at the low and simvastatin at the high ends of the risk continuum.

It's interesting **that increasing statin dose does not seem to bring more diabetes doom**. Comparing data from three atorvastatin trials, (TNT, IDEAL and SPARCL) 80 mg of atorvastatin bumps up diabetes risk by ~2% over placebo, but only ~ 1% over 10 mg atorvastatin or 20 mg simvastatin.

This is all very disconcerting to cardiologists, who originally thought statins might decrease diabetes, based on the West of Scotland Coronary Prevention Study (WOSCOPS). The men in this study who took pravastatin (a more water-soluble statin) had 30% lower risk of new diabetes than those who took placebo. The study enrolled a different patient type – men with high cholesterol and no history of heart attack. Few had diabetes or significant risk factors for diabetes and the criteria for diabetes diagnosis were more strict than usual, so, overall, there were fewer diabetes diagnoses.

The LIPID trial of pravastatin more closely mimicked other statin trials. In it, elderly patients who had known coronary disease prior to the trial took pravastatin and had no increased incidence of diabetes. **Pravastatin is the most water-soluble statin, confirming the notion that a continuum within the statin drug class relates their fat-solubility to their likelihood of inducing diabetes in susceptible individuals.**

**Mechanisms:** Statins inhibit an enzyme that not only blocks cholesterol synthesis, but also blocks the body's ability to make other things, like isoprenoids. These compounds regulate many enzymes in the body and may be involved in glucose regulation. We know that statins reduce cells' production in test tubes of the glucose transporters used to take up glucose. Less transport means more insulin resistance, which can lead to metabolic syndrome and diabetes. Adding back mevalonate, blocked by statins but normally converted into either cholesterol or isoprenoids, can reverse this effect. Scientists postulate that isoprenoids, or some other downstream product of mevalonate, may mediate the effect on glucose transport.

Another possible mechanism related to the pancreas' ability to make insulin. Pancreatic cells bathed in a solution containing statins make less insulin. This only occurs with fat-soluble, not water-soluble statins.

**Other statin adverse effects:** We've known about possible liver damage, especially with high doses of statins, since the drugs came out. This is uncommon.

Statins may also cause muscle inflammation, called statin myopathy. The user may feel an array of symptoms, ranging from insidious, deep aches, to near paralysis from severe muscle wasting.

Normally these side effects occur in people taking high doses, but sometimes that is not the case. Statins are broken down in the body by liver enzymes - Taking a medicine that blocks these enzymes may raise statin blood levels enough to cause damage even on lower doses. One statin, cerivastatin (Baycol) was removed from the market because of 52 deaths from severe enough muscle damage to kill the kidneys.

Like all drugs, and most substances we put in our bodies, statins have potential side effects. Statins may push you into overt diabetes, especially if you have metabolic syndrome, but even then they reduce the risks of vascular disease and deaths from heart attack and stroke. So we shouldn't put them in the water supply, but instead take them as recommended – for prevention of

recurrence **after** vascular disease or diabetes is diagnosed. Choosing a more water-soluble statin should minimize the diabetes risk, and adopting a prudent diet and regular exercise routine would help even more.¶