



Should We Care Whether Statins Cause Diabetes?

The last few years have been really rough for medical professionals who treat patients with lipid disorders. One after the other of the different classes of lipid-lowering agents have come under unfavorable scrutiny. The allegations to date have all followed a common theme: These drugs may do nothing to further reduce cardiovascular disease (CVD) risk when added to baseline statin therapy. First it was ezetimibe, that benign blocker of cholesterol absorption. Ezetimibe failed to demonstrate an additional risk reduction when added to statin therapy, even though it produces a respectable reduction in low-density lipoprotein cholesterol (LDL-C) levels. Then it was fenofibrate's turn to be discredited. First was the very flawed Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, and then it was the more definitive Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, where fenofibrate added precious little, if anything, to baseline statin therapy. The biggest blow of all, from my perspective, was the damage that the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study did to my beloved niacin, which showed that niacin, in addition to statin therapy, did not offer any additional CVD risk reduction.

At least we can take comfort in the multitude of convincing trials that have shown unequivocally that statins do wonders to reduce CVD risk, both in primary and in secondary prevention settings. Statins have survived a number of assaults on their legiti-

macy over the years, such as the concerns that they can cause liver damage and precipitate fatal rhabdomyolysis. These complications are legitimate concerns, but they are, fortunately, infrequent occurrences. Statins have also survived other challenges that turned out to be invalid, such as the worry that they may increase the risk of tumor malignancy and that they might lead to some degree of mental impairment over the years. (Are my statins

demographic data from the published literature, on February 28, 2012 (after I had submitted this editorial for publication), the FDA added a black box warning to the package inserts of all statins concerning the risk of new-onset diabetes. But there's no need to push the panic button anytime soon, because the magnitude of the effect is relatively small in absolute terms and needs to be balanced against the benefits derived from these drugs.

The last few years have been really rough for medical professionals who treat patients with lipid disorders. One after the other of the different classes of lipid-lowering agents have come under unfavorable scrutiny.

the reason it seems to get harder and harder for me to come up with ideas for these editorials? Just kidding.)

Now, along comes a brand-new challenge to statins that's right up the metabolic alley of an aging endocrinologist such as me. This time the concern is that statins seem to cause a statistically significant increase in the rate of development of new cases of type 2 diabetes. What a brutal irony! Here we are passing out these drugs like candy in an effort to reduce strokes, heart attacks, and other vascular mishaps, and meanwhile they may actually be increasing the frequency of this dastardly vasculopathy! We were ready to dump these drugs into the water supply a few years back, and now they may actually be causing diabetes in some of our patients. Say it ain't so, Joe.

Unfortunately, it may be so. Indeed, based on clinical trial and epi-

Several major papers have now shown increases in the number of new diabetes cases with statin therapy. One study, published in the *Journal of the American Medical Association* in 2011, was a meta-analysis of 33,000 subjects enrolled in 5 major statin trials. This analysis showed that statins are, indeed, associated with 1 new case of type 2 diabetes for every 498 patients treated with a statin. That doesn't seem too bad, especially when you consider that a major CVD event, such as a heart attack or a stroke, was prevented for every 155 patients receiving a statin. Of course, a skeptic can always dismiss a meta-analysis because of issues over which trials were included and which were excluded, and the obvious fact that all such analyses are retrospective rather than prospective.

In January 2012, another major study pointing toward an increased

occurrence of new type 2 diabetes cases was published in the *Annals of Internal Medicine*. This was an analysis of more than 150,000 postmenopausal women who were participating in the landmark Women's Health Initiative (WHI) trial, which disabused some of our long-held beliefs about estrogen replacement therapy. This study showed that women taking statins had a 48% greater risk of developing

ened to include individuals whose only CVD risk factor is an elevated C-reactive protein (CRP) level. Subjects with elevated CRP levels were randomized in a double-blind fashion to receive either rosuvastatin or placebo. The trial confirmed a modest benefit of statins in these patients, but it also showed that the number of cases of new-onset diabetes was 25% higher in those receiving the statin; there were

people with only modestly elevated LDL-C levels, then the tradeoff may not be all that favorable. This assumes that the risk of new diabetes is constant across different populations on statins, which may be a shaky assumption.

On the other hand, if statins are used in high-risk patients where they really are preventing a significant number of strokes and heart attacks, then the collateral damage associated with producing a handful of new patients with diabetes may be a very acceptable cost of doing business. Of course, these types of calculations can be very challenging for the individual provider to make when facing a real patient sitting on the examination table. But the guiding principle should be to try to do the most good possible while minimizing any collateral harm that is caused. The bottom line is that statins remain a really good choice in patients with a high CVD risk, but the modest amount of collateral damage that may result from new-onset diabetes needs to be factored in when statins are contemplated in low-risk patients. ●

This time the concern is that statins seem to cause a statistically significant increase in the rate of development of new cases of type 2 diabetes.

new-onset diabetes than women not taking statins. However, the WHI was not designed to look for such an effect, so the statin data can essentially be considered purely observational. As such, there are huge limitations on what can actually be concluded from this finding. Perhaps the women taking statins were poorly matched with those who were not taking statins. Those being treated with statins may have had a greater prevalence of associated risk factors such as obesity and hypertension, which inherently predisposed them to needing statin therapy and to the development of new diabetes. The study authors performed multivariate analyses to try to reduce such bias, but such analyses can be an imperfect art.

But the noose is, indeed, starting to tighten a bit, particularly when one considers the new-onset diabetes results that emerged from the Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Men and Women with Elevated Levels of C-Reactive Protein (JUPITER) trial. This high-profile statin trial was set up to determine whether the indications for statin therapy should be broad-

270 cases of new diabetes in the rosuvastatin group vs 216 cases in the placebo group. It's a lot harder to dismiss these results, other than to observe that new-onset diabetes was not the focus of the study at the outset.

So it may be true that statins, by some still-unknown mechanism, do push you a bit along the spectrum from glucose intolerance to full-blown diabetes. But let's keep everything in perspective, before we make major changes in our therapeutic approach. Remember that the increase in new-onset diabetes is still a fairly minor one in absolute terms; it's roughly in the same ballpark as the increase in new cases of diabetes seen with diuretics or with beta-blockers. How meaningful is it that this modest handful has been nudged across the line to full-fledged diabetes? It all depends. It depends on the absolute number of CVD events prevented with the statins, as opposed to the modest amount of collateral damage they may cause by producing a few new cases of diabetes. If the absolute CVD risk reduction is minimal, because you're dealing with a low-risk population with a low absolute risk of CVD events, such as a group of young

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this editorial.

Disclaimer

The opinions expressed herein are those of the author and do not necessarily reflect those of Federal Practitioner, Quadrant HealthCom Inc., the U.S. Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.