New-onset type 2 diabetes and statins: What is the relationship?

David Preiss is the lead author of a recent meta-analysis that found high-dose statin therapy to be associated with an increased risk of new-onset type 2 diabetes. Here, Dr Preiss provides background to these findings that have received much media interest.

David Preiss is a Clinical Research Fellow at the British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow.

Statins are the most prescribed medication worldwide and a quarter of the population over the age of 50 in developed countries are on a statin (British Heart Foundation, 2011). Numerous large randomised statin trials – and meta-analyses of these trials – have established the ability of these agents to lower the risk of major cardiovascular (CV) events in people with and without diabetes (Baigent et al, 2010). However, given the vast numbers of people on statins, it is important to examine and quantify any risks that are identified.

Statins have a good track record of safety and are generally well tolerated. Until recently, the only significant side-effect associated with statin therapy has been myopathy and occasional rhabdomyolysis, especially on high-dose simvastatin (Thompson et al, 2003). However, publication of the JUPITER (Justification for the use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial (Ridker et al, 2008), in which 17 802 people were treated with either rosuvastatin 20 mg or placebo and followed-up for a median 1.9 years, led to speculation that statin therapy may increase the risk of developing diabetes. In the JUPITER trial, those receiving rosuvastatin were at 25% increased risk of developing diabetes than those receiving placebo.

Colleagues and I formed a collaboration with investigators from most of the large placebo- and standard care-controlled statin trials and analysed data to investigate for the development of diabetes. In our 2010 meta-analysis of >90 000 people without diabetes at baseline from 13 trials, we found that statin therapy was indeed associated with a 9% increased risk of developing diabetes over 4 years (Sattar et al, 2010). Yet in absolute terms the risk was low (one additional case per 1000 person-years of statin therapy) and CV benefit appeared to comfortably outweigh this risk. Meta-regression analysis failed to find a clear relationship between LDL-cholesterol lowering and risk of developing diabetes across these trials. Given that new-onset diabetes was not the primary endpoint of these trials, methods of diabetes diagnosis varied somewhat between the trial protocols.

Most of the 13 trials we analysed used only modest statin regimens, while the 25% higher risk of new-onset diabetes seen in the JUPITER trial – and the more recently published 44% higher risk in the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial (Waters et al, 2011; atorvastatin 80 mg vs placebo in people with previous stroke or transient ischemic attack) – were in populations receiving more intensive statin therapy. Therefore, the next step was to examine trials comparing high-dose statins with moderate doses to see if a dose-dependent relationship between statin therapy and increased risk of new-onset diabetes could be found.

We investigated the five large trials comparing high-dose statin therapy with moderate doses published to date: the TNT (Treating to New Targets) trial (LaRosa et al, 2005), the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial (Pedersen et al, 2005), the A to Z (Aggrastat to Zocor) trial (de Lemos et al, 2004), the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction) trial (Cannon et al, 2004), and the SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) trial (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine

[SEARCH] Collaborative Group et al, 2010). Investigators from all of these trials collaborated in our meta-analysis, providing data from >32 000 people without diabetes at baseline – 2749 of whom developed diabetes and 6684 experienced a major CV event (i.e. CV death, non-fatal myocardial infarction, non-fatal stroke or coronary revascularisation). A major advantage of this analysis was that we were able to directly compare the risk of new-onset diabetes and benefit of reduced CV events, allowing clinicians and patients to put the findings in context.

We found that high-dose statin therapy led to a 12% increase in new-onset diabetes and a 16% reduction in major CV events compared with moderate dose statin therapy over 5 years (Preiss et al, 2011). In absolute terms, treatment with high-dose statins increased new-onset diabetes by two cases per 1000 person-years of treatment, while reducing the number of people who experienced a major CV event by 6.5 – a ratio of approximately 1 to 3. Subgroup analyses did not provide convincing evidence that there was a particular group at higher risk of developing diabetes while receiving a high-dose statin.

We compared the risks and benefits of simvastatin 80 mg with atorvastatin 80 mg. While the risk of new-onset diabetes was similarly increased by both agents versus moderate dose therapy, atorvastatin 80 mg led to a 22% reduction in major CV events compared with only 5% for simvastatin 80 mg. Given the myopathy risks associated with of simvastatin 80 mg (SEARCH Collaborative Group et al, 2008), and given that atorvastatin will soon be off-patent, atorvastatin appears the better option for high-dose treatment.

The available data show that statins increase the risk of new-onset diabetes in a dose-dependent way, but important questions remain: What is the explanation for this increased risk? Should these findings change how we treat our patients?

A small number of studies conducted in animal models suggest that statins may interfere slightly with insulin signalling in skeletal muscle and adipose tissue (Nakata et al, 2006; Mallinson et al, 2009), but these findings are far from conclusive at present. Other studies have shown that statin therapy may indeed lead to a slight increase in glycaemia (Koh et al, 2010).

In my view, our recent findings (Preiss et al, 2011) should not lead to a change in guidelines for statin prescribing in general, and certainly not in people with established diabetes. However, it may be sensible to screen those treated with statins – especially those on high doses – for diabetes every year or two. In addition, people should be informed of the increased risk of developing diabetes associated with high-dose statins; most will compare the risk of new-onset diabetes with the CV benefit conferred and still conclude that the benefits of statin therapy comfortably outweigh any risks. Finally, clinicians should think twice before prescribing statins to those people in who statin therapy has not shown benefit, such as those with heart failure. ■

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