High-Dose Statin Therapy Increases the Risk of Diabetes

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(London, United Kingdom) — A meta-analysis of some of the more high-profile statin trials testing the effectiveness of high-dose therapy has revealed a significant increase in the risk of diabetes mellitus associated with statin use in high doses [1]. Compared with moderate-dose therapy across five statin trials, investigators report that treatment with high-dose statins increased the risk of diabetes by 12%.

Senior investigator Dr Kausik Ray (St George's University of London, UK) said that while there might be consequences from the raised blood glucose levels, researchers do not yet know what these long-term effects mean. The net benefit of high-dose statin therapy "is definitely in favor" of using the drugs, he said.

"One thing we do know is that there does appear to be a dose effect with statin therapy, with the risk of diabetes mellitus increasing with higher doses," Ray told heartwire. "Statins have multiple effects and cause a number of changes. What we're seeing is probably an off-target effect, and right now we have no obvious mechanisms. However, lowering LDL-cholesterol levels is probably more important than the increase in blood-sugar levels."

In their analysis, the number of patients needed to treat with high-dose statin therapy to prevent one cardiovascular event was 155, whereas the number needed to treat to cause one case of new-onset diabetes mellitus was 498. Overall, high-dose statin therapy reduced the risk of cardiovascular events in their meta-analysis by 16% compared with low- or moderate-dose statin therapy.

The results of the study are published in the June 22, 2011 issue of the Journal of the American Medical Association.

Previous Observed Diabetes Risk

Speaking with heartwire, Ray said that the idea for the meta-analysis began two years ago, when the signal for diabetes risk was observed in Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER). The group later performed an analysis of some of the early statin trials comparing the lipid-lowering drugs with placebo in 90 000 individuals and observed a significant 9% increase in the risk of diabetes mellitus. That study was reported in the Lancet in 2010 [2].
In this newest analysis, the researchers included large, randomized, controlled, hard-end-point studies that compared intensive-dose statin therapy with moderate-dose statin therapy followed for more than one year. The trials included in the meta-analysis were PROVE-IT, A to Z, TNT, IDEAL, and SEARCH, five trials that together included 32 752 patients without diabetes mellitus at baseline.

"We wanted to look at the different studies comparing the intensity of statin treatment," said Ray. "If the diabetes finding was a real finding, we would expect to see it in the statin trials that tested different intensities of treatment in about 33 000 subjects. The trials all ranged from two to five years in duration, and we had information from five trials comparing high versus low/moderate treatment doses. Our results support our initial findings. We observed a 12% increase in risk for those patients treated with high-dose statin therapy."

In total, 1449 patients treated with high-dose statin therapy developed diabetes compared with 1300 patients assigned to moderate-dose statin therapy. This translated into two additional cases of diabetes mellitus per 1000 patient-years. The odds ratio for new-onset diabetes was 1.12 (95% CI 1.04–1.22). Regarding benefit, 3134 patients treated with high-dose statin therapy and 3550 patients treated with moderate-dose therapy had a cardiovascular event, translating into 6.5 fewer outcomes per 1000 patient-years in the high-dose statin arm, or a relative reduction of 16%.

The investigators did observe differential effects with the different drugs. Whereas atorvastatin 80 mg and simvastatin 80 mg were both associated with similar risks of diabetes mellitus, the benefit differed significantly, with evidence in favor of atorvastatin (22% vs 5% risk reduction for cardiovascular events). The data, said Ray, support the recent Food and Drug Administration (FDA) decision to warn physicians to not start new patients on simvastatin 80 mg and to be vigilant to the risks of muscle toxicity caused by the drug in those who are still taking it.

**Getting Patients to Goal**

Speaking with heartwire about the results, Dr Brendan Everett (Brigham and Women's Hospital, Boston, MA), who was not involved in the analysis, agreed with the conclusions of Ray and colleagues, that the signal observed in this latest analysis supports the findings from JUPITER and the Lancet meta-analysis "and supports the idea of a dose effect, that there is an increasing risk of diabetes with increasing doses of statins."

Everett said the investigators helped clinicians by providing data on the relative benefits and relative harms of high-dose statin therapy. The number needed to treat to prevent one cardiovascular event and number needed to treat to cause one new case of diabetes mellitus clearly support the use of high-dose statin therapy in the patients studied in the five clinical trials.

"The benefits of statins for reducing important macrovascular events is so overwhelming that the balance is clearly on the side of benefit," said Everett. "This is an important point that shouldn't be forgotten."
**Dr Roger Blumenthal** (Johns Hopkins University Medical Center, Baltimore, MD) agreed, stating that while "it makes sense that higher doses [of statins] would have slightly higher adverse effects," there is still no proposed mechanism for the increased risk of diabetes. Like the others, he told *heartwire* that the benefits of moderate/high doses of statins outweigh the risks, although he added that some physicians might decide to downgrade the dose based on these new data.

In addition, **Dr Steven Nissen** (Cleveland Clinic, OH) told *heartwire* that the effect is likely real as it has been observed in enough trials and analyses. That said, "it is notable that despite the increase in the risk of diabetes mellitus, the reduction in cardiovascular morbidity and mortality is maintained," he added. "It leads me to believe that the effect is not very clinically significant."

Everett added that what is currently unknown is how the risks of diabetes mellitus differ in other patient populations. Clinicians need to understand their patients’ baseline risks of cardiovascular disease and diabetes mellitus when making a decision about high-dose statin therapy, and it will be important to determine whether patients at greater risk for adverse side effects can be identified. Researchers will also need to determine what effects high-dose statin therapy has on microvascular complications, such as retinopathy.

"The bottom line is that we need to follow up on the signal, but I don't believe the results should change treatment goals," said Everett. A failure to aggressively treat patients at high risk for cardiovascular events will result in an excess of clinical events, he added.

To *heartwire*, Ray suggested that clinicians monitor HbA1c levels when treating patients with high-dose statin therapy.

Like Ray, Everett said the results support the FDA decision regarding simvastatin 80 mg, that the drug is associated with more side effects without a corresponding balance of efficacy. In the interest of getting patients to treatment goal and trying to do so in a cost-efficient manner, some physicians had been using high-dose simvastatin. However, if they are unable to get to goal at 40-mg simvastatin, switching over to other, nongeneric drugs is not difficult, although it does involve extra paperwork when dealing with drug payers, he said.

This Sunday at the **American Diabetes Association (ADA) 2011 Scientific Sessions**, **Dr David Preiss** (University of Glasgow, Scotland), the first author of the analysis, will present their data at a special symposium organized by the ADA and FDA. The presentation will highlight the newly observed risks with high-dose statin therapy, as well as their *Lancet* analysis of 13 randomized trials comparing placebo and standard-therapy trials.

**References**


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