VIEW ON THE NEWS

## Benefits Eclipse Rare Events

Over the many years of placebo-controlled statin trials, physicians have encountered inconsistent reports on the risk of new-onset diabetes with statins.

A recent meta-analysis of statin/placebo trials with 91,140 participants found a 9% increased risk of diabetes with number needed to harm, or cause one case of new-onset diabetes per year, as 1,020.

This new meta-analysis examining the dose-response association, giving the number needed to harm with intensive versus moderate dose statin therapy as 498 per year, with both high-dose simvastatin and atorvastatin associated with this effect.

What is clear from this meta-analysis is that the number needed to treat with higher- versus lower-dose statin to prevent cardiovascular events is 155 per year, which in subanalyses is significant for the more frequent nonfatal MI and coronary revascularizations but not for the fewer cardiovascular deaths and nonfatal strokes. This cardiovascular preventive effect of intensive versus moderate statin dosing was significant for atorvastatin but not for simvastatin. This plus the recent Food and Drug Administration recommendation to no longer increase simvastatin from 40 to 80 mg in those not attaining LDL cholesterol goals but to switch to another statin (see article on p. 11), suggests that use of 80-mg dose simvastatin for intensive statin-lowering therapy will decrease.

Although a mechanism for possible myocyte insensitivity to carbohydrate oxidation with the use of simvastatin has recently been shown (J. Physiol. 2009;587:219-30), thus increasing the probability of this association as causal, nonetheless, the absolute low frequency of new-onset diabetes of 1/500 to 1/1,000 per year, can be used to reassure worried patients that the greater cardiovascular preventive effects of statin therapy significantly outweigh the possible but much smaller risk of diabetes.

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# Diabetes Risk Rises With Statin Dose

BY MARY ANN MOON

FROM JAMA

The risk of developing type 2 diabetes rises with increasing doses of statin therapy, according to the findings of a large meta-analysis.

"Our findings suggest that clinicians should be vigilant for the development of diabetes in patients receiving intensive statin therapy," said Dr. David Preiss of the BHF Glasgow (Scotland) Cardiovascular Research Centre at the University of Glasgow, and his associates.

Several recent studies have suggested that statin therapy may raise the risk of diabetes, and some have indicated that the risk is higher at higher doses of the drugs.

Dr. Preiss and his colleagues conducted a meta-analysis of five large (at least 1,000 subjects each) randomized clinical trials that compared moderate-dose with intensive-dose statin therapy and followed patients for a minimum of 1 year. These trials were intended to compare cardiovascular outcomes, but they also tracked adverse events, blood glucose levels, and the use of diabetes medications, so cases of new-onset diabetes could be identified.

Overall, 32,752 subjects who did not have diabetes at baseline were followed for a mean of 5 years. During that time 2,749 subjects (8%) developed diabetes.

There were 149 more cases of diabetes among subjects taking intensive statin

VITALS

**Major Finding:** Two additional cases of incident diabetes per 1,000 patient-years developed in subjects taking intensive statin therapy, compared with those taking moderate statin therapy.

**Data Source:** A meta-analysis of five large randomized controlled trials comparing intensive with moderate statin therapy in 32,752 participants who were followed for a mean of 5 years.

**Disclosures:** Dr. Preiss' associates reported ties to numerous industry sources.

therapy than in those taking moderate statin therapy, for an odds ratio of 1.1.

"In absolute terms, there were two additional cases of diabetes per 1,000 patient-years among those receiving intensive-dose therapy (mean 18.9 cases per 1,000 patient-years with high-dose statin treatment vs. 16.9 cases per 1,000 patient-years with moderate-dose therapy), corresponding to a number needed to harm of 498 per year," the investigators said.

This dose-response relation persisted across several subgroups of patients, regardless of age, HDL cholesterol level, body mass index, or fasting plasma glucose level at baseline. The dose-response relation also was comparable between subjects receiving simvastatin and those receiving atorvastatin, Dr. Preiss and his associates said (JAMA 2011;305:2556-64).

However, more intensive statin therapy also provided clear cardiovascular benefits compared with less intensive statin therapy. "When expressed in absolute terms, there was one additional case of diabetes for every 498 patients treated for 1 year, compared with one fewer patient experiencing a cardiovascular event for every 155 patients treated for 1 year," they noted.

"We hypothesize that given that cardiovascular risk from diabetes is modest in the first decade after diagnosis, and as the benefit of statin therapy increases over time and in absolute terms with increasing age, net cardiovascular benefit in high-risk individuals will still strongly favor statin therapy," the investigators said.

The mechanism by which statins raise diabetes risk is not known. The data on subgroups in this meta-analysis do not shed light on the issue since all subgroups were at comparable risk. ■