High-Dose Atorvastatin Linked to Hyperglycemia

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NEW ORLEANS — Initial results from the PROVE IT–TIMI 22 study showed that patients with acute coronary syndrome who were treated with high-dose atorvastatin had significantly fewer deaths and cardiovascular events than did patients treated with a moderate-dose regimen of pravastatin.

But a new analysis of the results, which were first reported in the spring of 2004, shows that this benefit came with a price: an increased rate of hyperglycemia.

A post hoc evaluation of patients in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombosis in Myocardial Infarction 22 trial who developed impaired glycemic control during the study showed that patients who were treated with 80 mg/day atorvastatin had an 83% higher risk of having their glycosylated hemoglobin (HbA_{1c}) level rise above 6%, compared with patients treated with 40 mg/day pravastatin, Marc S. Sabatine, M.D., said at the annual scientific sessions of the American Heart Association.

The data available so far do not make it clear whether this link was primarily caused by a harmful effect of atorvastatin (Lipitor), a protective effect of pravastatin (Pravachol), or a combination of both mechanisms. In addition, this comparison of glycemic control between the two statin-treatment groups was not a prespecified analysis, and hence the finding must be confirmed by further research.

Despite this caution, the finding suggests that physicians should consider monitoring glycemic control in patients with acute coronary syndrome, especially those who are treated with an 80-mg/day dosage of atorvastatin, said Dr. Sabatine, a cardiologist at Brigham and Women's Hospital in Boston.

The analysis used data collected in PROVE IT–TIMI 22. The primary finding from this study of 4,162 patients with acute coronary syndrome was that aggressive lipid-lowering therapy with 80 mg atorvastatin daily led to a significant, 16% relative drop in the incidence of death or major cardiovascular events, compared with 40 mg pravastatin daily during a follow-up of 2 years. The results were first reported at the annual meeting of the American College of Cardiology last March, and were published a few weeks later (N. Engl. J. Med. 2004;350:1495-504).

The new analysis was done because results from prior studies had suggested that treatment with atorvastatin or simvastatin might boost the incidence of diabetes.

Dr. Sabatine and his associates looked at the rate of new-onset diabetes during the study; 82% of patients did not have diabetes at baseline. During follow-up, the incidence of new cases was 4.2% in the pravastatin group and 4.4% in the atorvastatin group, a difference that was not statistically significant.

A second analysis assessed glycemic control during the study, as reflected in serum levels of HbA_{1c}, which was measured several times during follow-up. The serum level of HbA_{1c} is a marker for glycemic control during the preceding 2-3 months. After 16 months of treatment, HbA_{1c} levels rose by an average of 0.37% in patients treated with atorvastatin, compared with an average 0.18% rise in those treated with pravastatin, Dr. Sabatine said.

In addition, 44% of patients who entered the study without diabetes and received atorvastatin had their HbA_{1c} level rise by at least 0.5% during the first 16 months of treatment, compared with 28% of patients treated with pravastatin.

In a multivariate analysis that took into account age, sex, body mass index, and baseline HbA_{1c} level, patients treated with 80 mg/day atorvastatin had an 83% higher risk of having their HbA_{1c} level rise by 0.5% or more, compared with patients treated with 40 mg/day pravastatin. ■

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'We were surprised by the magnitude of the effect. We had anticipated that it would be a few years at most, not the dramatic 7 to 10 years that we saw.'

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