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Aggressive lipid reduction provides additional clinical benefit



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“Reduction of low-density lipoprotein [LDL] cholesterol, by any means, but especially with statins, is at the core of coronary heart disease protection,” said Dr. Evan A. Stein. “Greater absolute reduction in CHD [coronary heart disease] mortality and morbidity occurs in persons at highest risk of future CHD, and identifying individuals at high risk of CHD is important not only to initiate appropriate treatment and minimize morbidity and mortality, but also to maximize the cost-effectiveness of therapy.” In addition, he added, “preliminary evidence suggests that LDL cholesterol reduction beyond that achieved in previous controlled trials may

have a substantial impact on further lowering the risk of coronary heart disease.”

Two important interrelated questions remain to be answered: (1) Will reducing LDL cholesterol to very low (ie, <100 mg/dL) levels have a substantially greater impact on the residual risk of CHD in treated patients? (2) Will additional LDL cholesterol reduction beyond that already seen in clinical trials, with higher doses of any individual statin or of different statins, result in greater reductions in clinical end points (such as the effect on the arterial wall, as manifested by reductions in C-reactive protein, an inflammatory marker)?

Is more better?

Results of three studies suggest that aggressive LDL cholesterol re-

duction may provide extra clinical benefit compared with conventional therapy. In the Effect of Atorvastatin Versus Simvastatin on Atherosclerosis Progression (ASAP) study recently reported by Dutch investigators, 325 patients with familial hypercholesterolemia and LDL cholesterol >212 mg/dL were randomized to either simvastatin starting at 20 mg/day and increased to 40 mg/day at week 4, or atorvastatin starting at 40 mg/day and increased to 80 mg/day at week 4.

After 2 years, LDL cholesterol was reduced 19% more in the atorvastatin group. The change in carotid intima media thickness (IMT) from baseline was the primary efficacy measure. Carotid IMT decreased by a mean of 0.031 mm in the atorvastatin group and

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increased by 0.036 mm in the simvastatin group ($p = .0001$).

In the Post-Coronary Artery Bypass Graft (Post-CABG) trial, 2.5 to 5.0 mg/day of lovastatin was compared with 40 to 80 mg/day of the same statin in 1,351 patients who had undergone bypass surgery 1 to 11 years earlier. The percentage of saphenous vein grafts with atherosclerosis progression was 27% with the aggressive (ie, higher dosage) lovastatin regimen versus 39% for those with the less aggressive approach ($p < .001$).

In the Atorvastatin Versus Revascularization Treatment (AVERT) study, 80 mg of atorvastatin, sufficient to achieve a 46% reduction in LDL cholesterol to 75 mg/dL, produced additional clinical benefit of increasing the time to first ischemic event ($p = .03$) over a strategy of percutaneous intervention and usual lipid-lowering therapy of 18% in patients with stable CHD.

"Although these trials with surrogate or intermediate end points are promising, it will take large-scale trials with clinical end points of coronary artery disease [CAD] morbidity and mortality to confirm the effect of aggressive cholesterol lowering on cardiovascular disease and death," said Dr. Stein.

To date, despite the highly persuasive clinical trial evidence for morbidity and mortality benefits and the availability of five statins, physicians have not been successful at achieving LDL cholesterol goals in even high-risk patients. In the Lipid Treatment Assessment Project (L-TAP), which was a survey of frequent prescribers of lipid-lowering medications, only 18% of patients with CHD achieved their LDL cholesterol goal of ≤ 100 mg/dL (Figure 1), as established by the second Adult Treatment Panel (ATP II) of the

National Cholesterol Education Program in 1995 and reinforced by ATP III in 2001. Furthermore, most patients were not even being titrated to high doses of statin monotherapy.

When initiating statins, "there is a need to start with a dose likely to achieve goal," said Dr. Stein. Aggressive titration is also recommended, because these agents are safe and well tolerated at higher doses.

New treatment options

Some new lipid-lowering therapy options may soon make their way into the clinicians' armamentarium to assist them in achieving LDL cholesterol targets. Pitavastatin, currently in phase 3 studies in Japan and Europe, has been associated with moderate LDL cholesterol reductions of 37% to 47% at reported doses of 2 and 4 mg.

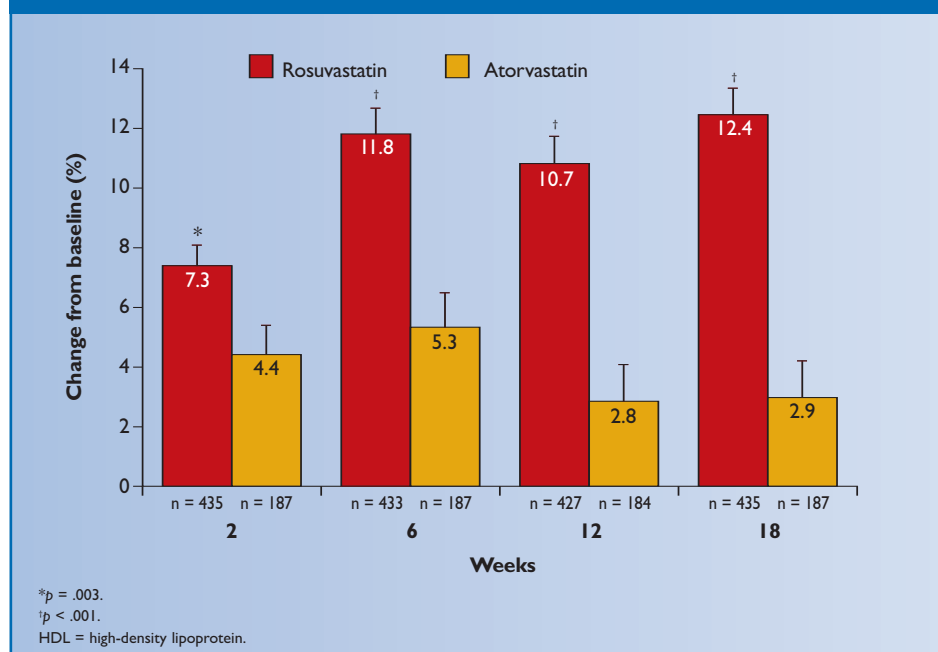
Rosuvastatin is associated with the greatest reductions in LDL cholesterol reported with a statin. With 80 mg/day of rosuvastatin, reductions in LDL cholesterol of 65% have been reported. A New Drug Application for rosuvastatin was filed with the U.S. Food and Drug Administration in 2001.

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Comparisons between rosuvastatin and other statins have been conducted. In a study comparing pravastatin 20 mg, simvastatin 20

FIGURE 2

Significantly greater increases in HDL cholesterol with rosuvastatin than with atorvastatin



mg, rosuvastatin 5 mg, and rosuvastatin 10 mg in patients with mild-to-moderate primary hypercholesterolemia, 67% of patients taking the 10-mg dose of rosuvastatin achieved their LDL cholesterol goal of < 100 mg/dL, compared with 41.9% of those taking the 5-mg dose of rosuvastatin, 19.4% with simvastatin, and 7.1% with pravastatin.

Rosuvastatin has also been compared with atorvastatin in 623 patients with heterozygous familial hypercholesterolemia. "There are 500,000 people with familial hypercholesterolemia in the United States," said Dr. Stein. "In these patients, the average age of onset of CHD is 40 to 50 years in men, and 10 years later in women." In the study, both agents were initiated at 20 mg/day, with forced titration at 6-week intervals to 40 mg and then 80 mg/day. At each time point, rosuvastatin was more effective at lowering LDL cholesterol. At week 18, LDL cholesterol was reduced by 57.9% in rosuvastatin recipients, compared with 50.4% in those taking atorvastatin. The most dramatic finding was that in the highest risk group of familial hypercholesterolemia—those with CAD—nearly 24% of patients achieved their LDL cholesterol goal of < 100 mg/dL on rosuvastatin, compared with only 3.2% on atorvastatin.

Another apparent advantage for rosuvastatin in this study was the significantly greater increase in high-density lipoprotein (HDL) cholesterol compared with atorvastatin. At 18 weeks, rosuvastatin increased HDL cholesterol by 12.4%, compared with a 2.9% increase with atorvastatin ($p < .001$; Figure 2). The mean

changes in HDL cholesterol were also superior with rosuvastatin at all dose levels when assessed by baseline triglycerides, which are known to heavily influence HDL response to statins, said Dr. Stein.

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New classes of agents are also in development, he said. Bile acid transport inhibitors are in early development; a cholesterol absorption inhibitor, ezetimibe, is in late-stage development. "Ezetimibe appears to block both the uptake of dietary cholesterol and the recycling of endogenously synthesized cholesterol present in the gastrointestinal tract," he said. As monotherapy, ezetimibe reduces LDL cholesterol by 20% with 10 mg, the only dose in clinical development.

Ezetimibe will most likely find its niche as combination therapy with statins, predicted Dr. Stein. When combined with 10 mg of simvastatin, ezetimibe has reduced LDL cholesterol by 51.9%. In the future, an 18% incremental reduction in LDL cholesterol may be possible by adding ezetimibe to statin therapy rather than a fourfold increase in the dose of the statin to achieve the same result. ■

FIGURE 1

Lipid Treatment Assessment Project: Majority of patients with CHD do not reach NCEP LDL cholesterol targets

