High-Dose Statin Aids Renal Function in CHD

BY BRUCE JANCIN
Denver Bureau

ATLANTA — Intensive atorvastatin therapy in patients with stable coronary heart disease resulted in impressive improvement in kidney function over the course of 5 years in a post hoc analysis of the landmark Treating to New Targets trial, Dr. James Shepherd reported at the annual meeting of the American College of Cardiology.

A dose of 10 mg/day of atorvastatin (Lipitor) in TNT also thwarted the anticipated age-related decline in renal function, but the benefit was significantly greater with 80 mg/day, according to Dr. Shepherd of the University of Glasgow.

"Given that renal disease is now recognized as an important and independent predictor of increased cardiovascular risk, any delay in progression of renal disease has to be a good thing," he observed. "Pushing the dose of atorvastatin—or of any statin, for that matter—should give you lower LDL and will more greatly improve renal function over the course of time, according to these results."

TNT was a double-blind study in which 10,001 patients with stable coronary disease were randomized to 10 or 80 mg/day of atorvastatin and followed for 5 years. The primary end point was major coronary events, which showed a 22% relative risk reduction with high-dose therapy.

The new post hoc renal analysis involved nearly 8,000 TNT participants with baseline and follow-up measurements of creatinine clearance. Glomerular filtration rate (GFR) was estimated using both the Cockcroft-Gault formula and the abbreviated Modification of Diet in Renal Disease (MDRD) equation, which is considered by most nephrologists to be more reliable.

'Any delay in progression of renal disease has to be a good thing' due to its role as a predictor of increased CV risk.

DR. SHEPHERD

The typical annual age-related decline in renal function is 1-2 mL/min per 1.73 m^2 in patients with good blood pressure. But this tail off wasn't seen in TNT. Instead, estimated GFR by MDRD actually increased from a mean baseline of 65 mL/min per 1.73 m^2 by 5.6% over the course of 5 years in patients assigned to 10 mg/day of atorvastatin, and by a significantly greater 8.4% in the 80-mg group.

Among the roughly one-third of TNT participants with baseline stage 3 or worse chronic kidney disease as defined by a GFR of less than 60 mL/min per 1.73 m^2, significantly more in the high-dose atorvastatin group improved to less than stage 3 disease. Moreover, significantly fewer patients in the high- than the low-dose atorvastatin group declined from a baseline GFR of at least 60 mL/min per 1.73 m^2 to stage 3 or worse chronic kidney disease. (See box.)

The clinical significance of what Dr. Shepherd termed "these exciting data" lies in the fact that an estimated 8 million Americans have stage 3 chronic kidney disease—defined by a GFR of 30-59 mL/min per 1.73 m^2—or worse, with stage 3 being the threshold at which significant increases in cardiovascular events and all-cause mortality are seen. If individuals with earlier stage disease are included, an estimated 20 million Americans have chronic kidney disease.

On-treatment LDL cholesterol levels averaged roughly 100 mg/dL with 10 mg of atorvastatin and 80 mg/dL with 80 mg of the statin. On-treatment LDL cholesterol levels correlated with GFR improvement such that the lower the LDL cholesterol, the greater the improvement over time in GFR.

High-dose atorvastatin was not associated with additional safety concerns in TNT. Thus, high-dose therapy conferred greater reduction in cardiovascular risk with the added benefit of improved renal function—and with no additional safety issues, compared with low-dose therapy, Dr. Shepherd said.

TNT was funded by Pfizer Inc. Dr. Shepherd is a member of the study's steering committee and a consultant to Pfizer. ■

Dose-Dependent Gains in Kidney Function Seen in TNT

	80 mg atorvastatin	10 mg atorvastatin
Patients with baseline GFR <60 mL/min who improved to >60	45%	37%
Patients with baseline GFR >60 mL/min who worsened to <60	7%	9%

Note: Based on a study of nearly 8,000 patients.
Source: Dr. Shepherd

ELSEVIER GLOBAL MEDICAL NEWS

Ezetimibe/Simvastatin Outdoes Statin Alone for Lowering CRP

BY BRUCE JANCIN
Denver Bureau

ATLANTA — The ezetimibe/simvastatin combination pill Vytorin has a markedly greater anti-inflammatory effect, as reflected by reduction of C-reactive protein, than either agent alone, Dr. Christie M. Ballantyne said at the annual meeting of the American College of Cardiology.

It's already established that Vytorin produces greater LDL reductions than does statin monotherapy. To learn more about the combination agent's effect on C-reactive protein (CRP), Dr. Ballantyne and coinvestigators conducted a posthoc pooled analysis of three multicenter, randomized, double-blind, placebo-controlled clinical trials.

The pooled analysis included 3,083 patients with baseline LDL of 145-250 mg/dL who were randomized to 12 weeks of placebo, ezetimibe at 10 mg/day, various doses of Vytorin comprised of ezetimibe 10 mg plus simvastatin 10-80 mg, or simvastatin monotherapy at 10-80 mg/day.

Ezetimibe alone wasn't significantly more effective than placebo at lowering CRP levels. In combination with the various doses of simvastatin, however, it reduced CRP by a mean of 31%, compared with 14.3% in the pooled simvastatin monotherapy group, reported Dr. Ballantyne, professor of medicine at Baylor College of Medicine, and director of the Center for Cardiovascular Disease Prevention at Methodist DeBakey Heart Center, Houston.

Simvastatin monotherapy lowered LDL by a mean of 38%, while Vytorin dropped it by 52.5%, he added.

The CRP cutpoint associated with reduced cardiovascular event rates in previous studies has been 2 mg/dL. In the pooled analysis, 47.7% of Vytorin-treated patients achieved both an LDL of less than 100 mg/dL and a CRP below 2 mg/dL, as did a collective 22.2% of patients on simvastatin monotherapy.

The more stringent target of an LDL below 70 mg/dL plus a CRP of less than 2 mg/dL was met by 21.6% of the Vytorin group and 3.2% of patients on simvastatin alone.

The clinical significance of reducing CRP in patients at high cardiovascular risk has yet to be established.

DR. BALLANTYNE

That said, Dr. Ballantyne was quick to add that the clinical significance of reducing CRP in patients at increased cardiovascular risk has yet to be established and is the subject of ongoing randomized prospective studies.

Audience members inquired as to the mechanism underlying the apparent synergy between ezetimibe and simvastatin in robustly lowering CRP, an especially striking effect given ezetimibe's trivial impact as monotherapy.

"That's a good question. I wish I had the answer," Dr. Ballantyne replied.

Dr. Ballantyne is a consultant to Merck/Schering-Plough, which markets Vytorin. ■

Ezetimibe/Simvastatin Combo Safe, Effective in Kidney Disease

BY MARY ANN MOON
Contributing Writer

Adding ezetimibe to simvastatin was found to be safe in a pilot study of patients with chronic kidney disease, and the combined regimen decreased LDL cholesterol by approximately 40%, according to Martin Landray, Ph.D., of the University of Oxford (England) and his associates.

The 6-month study involved 203 patients treated for chronic kidney disease at eight British medical centers. One-fourth of the patients required dialysis. The mean age was 60 years. A total of 102 were randomly assigned to receive 20 mg simvastatin plus 10 mg ezetimibe daily, and the rest received simvastatin plus a placebo.

Both treatments significantly lowered LDL cholesterol levels at 1-, 3-, and 6-month follow-ups, but the addition of ezetimibe cut these levels a further 27% (21 mg/dL). The addition of ezetimibe also decreased total cholesterol levels by a further 16% and apolipoprotein B levels by a further 15% (Am. J. Kidney Dis. 2006;47:385-95).

These beneficial effects were noted in patients who required dialysis and in those who did not, although the study had limited power to assess possible differences between the two groups because of relatively small numbers of subjects, the investigators said.

Compliance with the combined therapy was similar to that with simvastatin monotherapy and approached 90% at 6 months. No serious adverse events were attributed to either treatment. There was no elevation of creatine kinase levels, and the drugs did not appear to affect blood calcium, phosphate, or retinol concentrations.

There was no excess risk with the combined therapy for gastrointestinal symptoms, although more patients taking ezetimibe reported having diarrhea. There also were no reports of myopathy. However, "the size and duration of this pilot study are insufficient to detect a moderate excess risk for serious myopathy or other safety outcomes reliably or [to] assess possible effects on major clinical events," Dr. Landray and his associates noted.

These results suggest that combined therapy with simvastatin plus ezetimibe "is a potent yet well-tolerated cholesterol-lowering regimen," they said. The researchers are now conducting a large-scale randomized trial examining the effects of lowering cholesterol on cardiovascular outcomes in patients with chronic kidney disease. ■