

Lower Cholesterol Below Current Guidelines

If diabetes patients can lower their cholesterol below the current guidelines, their risk of MI may be lowered and CHD may be stabilized.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

New clinical data shows that intensive cholesterol-lowering to targets below currently recommended levels significantly reduces the risk of myocardial infarction (MI) and stroke in patients with diabetes and stable coronary heart disease (CHD).

James Shepherd, MD, of Glasgow, UK, presented the diabetic portion of the Treating to New Targets (TNT) study at the American Diabetes Association 65th Annual Meeting and Scientific Sessions.¹ The main trial was first presented during the American College of Cardiology Scientific Sessions earlier this year, by John LaRosa, MD, State University of New York Downstate Medical Center, Brooklyn, and subsequently published in *The New England Journal of Medicine*.^{2,3}

TNT was the first large randomized clinical trial to compare 80 mg and 10 mg atorvastatin (Lipitor, Pfizer) as secondary prevention in patients with stable CHD. Eligible patients were aged 35 to 75 years and had clinical evidence of CHD. After a washout period of 1 to 8 weeks, 15,464 patients were entered an open-label run-in phase with 10 mg atorvastatin.

CONTROL LDL CHOLESTEROL

To be eligible for enrollment, patients had to have their LDL cholesterol ≤ 130 mg/dL at the end of the run-in phase. A total of 10,001 patients reached this level and were then randomized to treatment with either 10 mg or 80 mg of atorvastatin daily. Mean follow-up was 4.9 years.

Over the course of the trial, investigators looked for a risk reduction in composite vascular phenomenon of coronary death, nonfatal MI, fatal and nonfatal stroke and

resuscitative cardiac arrest, according to Dr. Shepherd. Risk reduction was the primary endpoint of the study.

To assess the benefit of treatment to different LDL levels, the target was <100 mg/dL in the atorvastatin 10-mg group and 75 mg/dL in the atorvastatin 80-mg group. Total cholesterol and triglycerides decreased significantly in the atorvastatin 80-mg group, and nonsignificant increases in HDL were seen in both groups.

Compared to the 10-mg/dL dose, 80 mg/dL atorvastatin decreased the risk of first major cardiovascular events by 22%.

In the main portion of the TNT study, high-dose atorvastatin decreased first major cardiovascular events by 22% compared to the lower dose (8.7% vs 10.9%; $P < .001$). Nonfatal MI was also decreased by 22% (4.9% vs 6.2%; $P = 0.004$), and fatal or nonfatal stroke was reduced by 25% (2.3% vs 3.1%; $P = 0.02$). A trend toward a decrease in coronary mortality was observed with atorvastatin 80 mg (2.0% vs 2.5%; HR, 0.80; $P = .09$).

WHAT ABOUT DIABETICS IN TNT?

Diabetes is a coronary risk equivalent, Dr. Shepherd said. "The recent ATP III guidelines have been changed to include the fact that diabetic patients should be treated for their vascular risk as if they had existing coronary disease," he said.

There were 1,500 diabetic patients in TNT, which is roughly 15% of the total cohort. Half were randomized

HOW LOW CAN YOU GO?

There are numerous benefits to lowering LDL cholesterol. However, LDL levels between 100 and 130 mg/dl may still cause myocardial infarction and other coronary events in a substantial number of patients.

John C. LaRosa, MD, president, SUNY Downstate Medical Center, and colleagues enrolled patients in the Treating To New Targets (TNT) study to determine if lowering the current guideline in patients with stable coronary heart disease was as safe and effective as in patients with acute coronary syndromes. Dr. LaRosa is chairman of the TNT steering committee.

According to a news release from the American College of Cardiology, optimal treatment targets for patients with coronary heart disease (CHD) are still the subject of substantial debate. In March, Dr. LaRosa first presented this study at the 54th Annual Scientific Sessions in Orlando. One major goal of the study was to decrease LDL levels to 75 mg/dL in the enrolled patients.

"Is it useful to get LDL cholesterol levels down so low? And secondly, is it safe? These are landmark questions," Dr. LaRosa said in the news release.

The study was also published in *The New England Journal of Medicine*. Investigators evaluated the patients for sign of a first major cardiovascular event. This was defined as either death from CHD, nonfatal myocardial infarction that was not caused by a hospital procedure, resuscitation after cardiac arrest or fatal or nonfatal stroke.

After 4.9 years follow-up, those patients who were given 10 mg atorvastatin had LDL levels of 101 mg/dL. However, patients who received 80 mg of atorvastatin decreased their LDL level to 77 mg/dL. Investigators concluded in *The New England Journal of Medicine* that if patients with stable coronary heart disease were treated with 80 mg of atorvastatin, a clinical benefit was seen in regards to substantial coronary events.

LaRosa JC, Grundy SM, Waters DD, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. *NEJM*. 2005;352:1425-1435.

on a double-blind basis to receive atorvastatin 10 mg and half received atorvastatin 80 mg. Patients were followed over 4.9 years of the study, just like the main cohort. The average age of the diabetic patients was 63 years. There were more women, more hypertension, more peripheral vascular disease and more were overweight patients compared to the main cohort.

Among the diabetic patients in TNT, there was a 25% reduction in the primary endpoint among those treated with the high-dose statin compared to those treated with the lower dose, Dr. Shepherd said.

CARDIOVASCULAR RISKS

"We confirm that, cardiovascular risk is significantly increased among diabetic versus nondiabetic patients. We also show that, in this trial, if you are aggressive in your intervention with a statin, you will get a significant reduction of major cardiovascular events (25% in this trial) versus more conventional and modest atorvastatin intervention," Dr. Shepherd said.

Secondary efficacy outcomes in the diabetic patients were consistent with the general cohort and there were no problems in terms of side effects.

"The TNT study achieved lower event rates than the other secondary prevention trials which are out there in diabetic patients," Dr. Shepherd concluded. "It suggests to me – and I hope it suggests to you – that we should really be aggressive in our intervention in diabetic patients.

Not only with their glucose control, but with their cardiovascular risk control. We should be using multifactorial intervention to achieve the kind of benefits that we see in the TNT results."

TNT'S MAIN RESULTS

According to TNT's lead investigator Dr. LaRosa, the TNT results herald "a new era in the treatment of established coronary disease," showing that additional lowering of LDL cholesterol is warranted in stable CHD patients. In an accompanying commentary to the TNT study report in *The New England Journal of Medicine*, Bertram Pitt, MD, University of Michigan School of Medicine, was more cautious. He called for "further reassurance" before a "major shift" is made in current goals for LDL cholesterol levels in patients with stable CHD. ■

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1. Shepherd J. Intensive lipid lowering with atorvastatin in patients with diabetes and stable coronary disease. Presented at the American Diabetes Association 65th Annual Meeting and Scientific Sessions. June 10-14, 2005. San Diego.
2. LaRosa JC. Effect of lowering low density lipoprotein cholesterol substantially below currently recommended levels in patients with coronary heart disease: Results of the Treating to New Targets study. Late Breaking Clinical Trials 2. American College of Cardiology Annual Scientific Session 2005, March 6-9 2005. Orlando.
3. LaRosa JC, Grundy SM, Waters DD; Treating to New Targets (TNT) Investigators. Intensive lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.