Lipid Ratio Flags CVD Risk in Elderly

BY MITCHEL L. ZOLER
Philadelphia Bureau

NEW YORK — The ratio of LDL cholesterol to HDL cholesterol was the most powerful measure of cardiovascular disease risk in a retrospective analysis of data on almost 6,000 elderly patients.

The analysis also suggested that patients over age 70 years won't benefit from statin therapy if their serum level of HDL cholesterol at baseline exceeds 45 mg/dL, Chris J. Packard, Ph.D., said at an international symposium on triglycerides and HDL.

Previous studies showed that elevated LDL cholesterol is not a risk factor for cardiovascular disease in the elderly. Yet in a large trial first reported in 2002, during a mean follow-up of 3.2 years, use of 40 mg pravastatin/day cut the risk of new cardiovascular disease events by a significant 15%, compared with placebo, in patients aged 70-82 who had established vascular disease or elevated risk factors for vascular disease (Lancet 2002;360:1623-30).

This finding from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial raised the question of why statins lowered risk in patients with an average age of 75 who are usually not harmed by high LDL cholesterol levels, said Dr. Packard, a biochemist and research director at Glasgow Royal Infirmary, Scotland.

In the new analysis, pravastatin's benefit was confined to the two quintiles with the lowest baseline levels of HDL cholesterol (all were below 45 mg/dL). In these patients, the use of pravastatin was associated with a 33% reduction in cardiovascular events, compared with placebo. Among the 60% of patients with a baseline HDL cholesterol level above 45 mg/dL, the use of pravastatin was not linked with any reduction in events.

Statin therapy's impact on HDL was greatest in the 25% of patients with the lowest baseline HDL cholesterol levels. In this group, use of pravastatin was linked to a mean increase of 10.7%. In the 25% who started with the highest HDL cholesterol levels, statin therapy was linked to a 4.8% increase.

Further analysis showed that the change in HDL cholesterol level, by itself, was not linked to the change in risk, Dr. Packard said at the symposium, sponsored by the Giovanni Lorenzini Medical Foundation. Nor was the change in risk linked with changes in serum levels of C-reactive protein. But elderly patients with a significant reduction in the ratio of LDL to HDL cholesterol had, on average, a significant reduction in cardiovascular disease risk. ■

Non-HDL Cholesterol And Myocardial Infarction

BY DIANA MAHONEY
New England Bureau

NEW ORLEANS — Measuring non-HDL cholesterol level may be a better primary screen for risk of first nonfatal myocardial infarction in women than measuring the level of LDL cholesterol, reported Wildon R. Farwell, M.D.

Recent studies have implicated non-HDL cholesterol—including triglyceride-rich very low-density–lipoprotein cholesterol and intermediate-density–lipoprotein cholesterol—as atherogenic, Dr. Farwell said at the annual meeting of the Society of General Internal Medicine.

He and his colleagues at Brigham and Women's Hospital, Boston, analyzed data on nearly 19,000 women from the Women's Health Study who neither had a diagnosis of hyperlipidemia nor took cholesterol medication. They confirmed 118 self-reported cases of first nonfatal MI and used Cox proportional hazards models to control for cardiovascular risk factors.

The mean values of LDL and non-HDL cholesterol in the 118 MI patients were 116.3 mg/dL and 147.5 mg/dL, respectively. Non-HDL cholesterol level was a more significant predictor of risk than LDL cholesterol level. The hazard ratio for the highest tertile of non-HDL cholesterol was 2.91, compared with 1.51 for LDL. Similarly, the hazard ratios for the middle non-HDL and LDL tertiles were 1.81 and 0.92, Dr. Farwell said.

The non-HDL tertile measures were defined as less than 130.1 mg/dL, from 130.1 to 159.4 mg/dL, and greater than 159.4 mg/dL. For LDL cholesterol, the tertile measures were defined as less than 102.1 mg/dL, from 102.1 to 126.6 mg/dL, and greater than 126.6 mg/dL.

"While LDL cholesterol is important, non-HDL cholesterol may be the more important predictor, at least in some groups of people," Dr. Farwell said. ■

MINDFUL PRACTICE

Intensive Cholesterol Lowering

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 63-year-old white male with a history of hypertension and type 2 diabetes presents for follow-up after hospitalization, during which he underwent coronary angiography with stenting of a 90% left anterior descending lesion. He has other diffuse disease but no vessels amenable to additional intervention. He is on aspirin, clopidogrel, hydrochlorothiazide, a β-blocker, glyburide, and a statin. He has been on a statin for 5 years and volunteers that he has "muscle aches" at the current dosage. His blood pressure is 126/76 mm Hg, and his total cholesterol is 210 mg/dL (LDL cholesterol 96 mg/dL, HDL cholesterol 45 mg/dL, and triglycerides 207 mg/dL). You know that diabetes is a "CHD risk equivalent" and, therefore, the Adult Treatment Panel III guidelines recommend a goal LDL cholesterol of less than 100 mg/dL. Your colleagues advise treating to a goal LDL cholesterol of less than 70 mg/dL. You seek evidence showing that this will further reduce his risk.

The Question

In patients with coronary artery disease who are at goal with their cholesterol level according to the national treatment guidelines, does further reduction of cholesterol by intensification of statin therapy reduce cardiovascular outcomes?

The Evidence

We went to PubMed (www.pubmed.gov) and entered "intensive cholesterol lowering," limiting the search to randomized, controlled trials.

Our Critique

This was a well-designed study, the results of which will shape practice guidelines. Experts have expressed concern over the increased risk. Some experts suggest that 25% of diabetics may need more than one lipid-lowering drug simultaneously to reduce LDL cholesterol levels to less than 70 mg/dL.

Patient Preferences & Clinical Decision

You discuss the results with the patient. He says that some months, he has difficulty affording his high out-of-pocket expenses for his medication and diabetic supplies. You are aware of the evidence that only 60% of patients remain on statins at 12 months after a coronary event. You use the evidence as a motivational device to change his diet and start exercise, but he gives you plenty of signs that he may continue to be noncompliant with his drugs and probably noncompliant with diet and exercise. You refer him to the U.S. Department of Agriculture site www.mypyramid.gov for assistance. You agree to recheck the cholesterol level in 1 year. He agrees to report his progress to you in 3 months.

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J.C. LaRosa, et al.

Intensive lipid lowering with atorvastatin in patients with stable coronary disease (N. Engl. J. Med. 2005;352:1425-35).

► **Design and Setting:** Double-blind, parallel-group design. Patients were recruited from 14 countries in four continents between July 1998 and December 1999.

► **Subjects:** Men and women aged 35-75 years were included if they had clinically evident coronary heart disease (CHD, defined as previous MI or previous or present angina with evidence of atherosclerotic CHD) and had undergone coronary revascularization. Patients were excluded if they had statin hypersensitivity; liver disease or hepatic dysfunction; nephrotic syndrome; uncontrolled diabetes, hypothyroidism, or hypertension; an MI, coronary revascularization or severe/unstable angina in the last month; planned surgery for atherosclerosis; ejection fraction < 30%; valvular disease; GI disease limiting drug absorption; a survival-limiting disease; or elevated creatinine kinase. Also excluded were patients who were pregnant or breastfeeding, on immunosuppressants, or abusing alcohol.

► **Intervention:** Patients discontinued lipid-lowering agents and completed a 1- to 9-week washout period. Subjects with LDL cholesterol levels of 130-250 mg/dL or a triglyceride level of 600 mg/dL or less entered an 8-week run-in period of open-label treatment with atorvastatin 10 mg. Next, subjects with LDL cholesterol less than 130 mg/dL were randomly assigned to double-blind therapy with either 10 mg or 80 mg of atorvastatin per day.

► **Outcomes:** Primary efficacy outcome was occurrence of a major cardiovascular event (death from CHD; nonfatal, non-procedure-related MI; resuscitation after cardiac arrest; or fatal or nonfatal stroke). Secondary outcomes included a major coronary event, a cerebrovascular event, hospitalization for HF, peripheral-artery disease, death from any cause, any cardiovascular event, and any coronary event.

► **Results:** Of 18,469 patients screened, 10,001 were randomized. Mean LDL was 77 mg/dL and 101 mg/dL on atorvastatin 80 mg and 10 mg, respectively. Those on 80 mg of atorvastatin had a reduction in the primary end point, compared with the 10-mg group (hazard ratio 0.78; 95% confidence interval 0.69-0.89). The 80-mg group vs. the 1-mg group had reductions in nonfatal non–procedure-related MI (HR 0.78; 95% CI 0.66-0.93), fatal or nonfatal stroke (HR 0.75; 95% CI 0.59-0.96), and hospitalization for HF (HR 0.74; 95% CI 0.59-0.94). The 80-mg group vs. the 10-mg group had more deaths from noncardiovascular causes (HR 1.25; 95% CI 0.99-1.57). Also, the 80-mg group vs. 10-mg group had more adverse events (8.1% vs. 5.8%; $P < .001$), had higher rates of discontinuation (7.2% vs. 5.3%; $P < .001$), and was more likely to have persistent elevation of AST and/or ALT (1.2 % vs. 0.2%, $P < .001$). No differences in treatment-related myalgias or rhabdomyolysis occurred.