Biomarkers Don't Predict Cardiovascular Events

BY BRUCE JANCIN

BARCELONA — C-reactive protein was among 17 novel biomarkers of inflammation and atherosclerosis that failed to predict future cardiovascular events in statin-treated patients with established coronary heart disease, in a post hoc subanalysis of the landmark Treating to New Targets (TNT) study.

Only 1 of the 18 biomarkers assessed in the study was predictive of major cardiovascular events: osteopontin. At baseline, when TNT participants had already been on atorvastatin (Lipitor) at 10 mg/day for 8 weeks, a low osteopontin level was associated with a significant 16% increase in cardiovascular event risk during the median 4.9 years of follow-up, Dr. John J.P. Kastelein reported at the annual congress of the European Society of Cardiology.

In contrast, on-treatment levels of the traditional lipid risk factors—LDL cholesterol, HDL cholesterol, and triglycerides—were powerful predictors. The implication is that the appropriate treatment strategy in patients with established CHD is to put them on a statin, titrate to a dose that achieves guideline-recommended lipid levels, and don't bother with the novel biomarkers, said Dr. Kastelein, professor of medicine and chairman of the department of vascular medicine at the Academic Medical Center of the University of Amsterdam.

The TNT study, which randomized 10,001 patients with stable CHD to 10 or 80 mg/day of atorvastatin for a median of 4.9 years, was the first study to show that lowering LDL to a target of 75 mg/dL led to significantly fewer major cardiovascular events than did treatment to the previously accepted target of 100 mg/dL (N. Engl. J. Med. 2005;352:1425-35).

The new TNT subanalysis was a post hoc nested case-control study that utilized stored plasma samples from 507 TNT participants who experienced a major cardiovascular event—CHD death, nonfatal MI, fatal or nonfatal stroke, or resuscitated cardiac arrest—and 1,020 controls who did not. The biomarkers were measured in samples obtained after 8 weeks on low-dose atorvastatin during the study run-in period and again in samples gathered after 1 year of randomized treatment.

The novel biomarkers do not offer increased predictive power over the standard lipids.

DR. KASTELEIN

An on-treatment elevated LDL cholesterol level was associated with a 2.1-fold increased risk of major cardiovascular events, a high HDL cholesterol level was linked to a 65% reduction in risk, and elevated triglycerides were associated with a 27% increase in risk.

Among the 17 novel biomarkers that proved to have no predictive value were markers of general inflammation, including CRP, lipoprotein-associated phospholipase A2, adiponectin, and soluble intercellular adhesion molecule-1, receptor for advanced glycation end products (RAGE), and soluble vascular adhesion molecule-1.

Others, in addition to osteopontin, included cystatin C, lipoprotein (a), N-terminal pro-brain natriuretic peptide, myeloperoxidase, soluble CD-40 ligand, insulin, neopterin, monocyte chemotactic protein-1, and matrix metalloproteinase-9.

The main TNT trial as well as this analysis were sponsored by Pfizer. ■

Liraglutide May Help Lower Heart Risk in Type 2 Diabetes

BY BRUCE JANCIN

BARCELONA — Liraglutide, a once-daily investigational human glucagon-like peptide-1 analogue, achieved impressive reductions in multiple cardiovascular risk biomarkers in type 2 diabetes patients in a meta-analysis of six phase III randomized trials.

The trials, which collectively included 3,967 patients with type 2 diabetes followed for 6 months, variously compared liraglutide with rosiglitazone, glimepiride, exenatide, insulin glargine, and placebo.

Liraglutide was the only agent to significantly reduce triglycerides, with a mean 7.7 mg/dL reduction.

DR. GARBER

Liraglutide reduced hyperlipidemia to a significantly greater extent than any of the other antidiabetic medications. The same was true for plasma brain natriuretic peptide (BNP), a marker of cardiovascular risk; indeed, liraglutide was the sole agent to significantly reduce BNP. And liraglutide was second only to rosiglitazone in its magnitude of C-reactive protein reduction, Dr. Alan Garber reported at the annual congress of the European Society of Cardiology.

Rosiglitazone produced an unwelcome mean 31% increase in BNP compared with baseline, in contrast to the 12% decrease with liraglutide. And while liraglutide resulted in a significant mean 5 mg/dL reduction in total cholesterol, rosiglitazone-treated patients had an 11 mg/dL increase, noted Dr. Garber, professor of medicine, biochemistry, and molecular biology at Baylor College of Medicine, Houston.

Neither glimepiride, exenatide, insulin glargine, nor placebo resulted in significant changes over time in BNP or total cholesterol, the endocrinologist added.

Liraglutide was the only agent to significantly reduce triglycerides, achieving a mean 7.7 mg/dL reduction. The mean LDL decrease of 7.7 mg/dL seen with liraglutide was significantly more robust than that of other therapies, as was the 3.5 mg/dL decrease in free fatty acids achieved with the glucagon-like peptide-1 analogue. The mean reduction in C-reactive protein with liraglutide was 23%, while rosiglitazone achieved a 43% reduction.

In the six phase III trials, liraglutide reduced mean hemoglobin A_{1c} values by 1.0%-1.5%, systolic blood pressure by 2-6 mm Hg, and body weight by a mean of 1.8 kg. Exenatide reduced body weight by 1.3 kg, while insulin glargine and glimepiride resulted in significant gains of 1.6 and 2.1 kg, respectively.

Some of the benefits of liraglutide can be attributed to the weight loss; however, there is also evidence to indicate an additional direct beneficial effect of the agent itself independent of weight loss, according to Dr. Garber.

Liraglutide has received marketing approval in Europe and is now undergoing Food and Drug Administration review for possible marketing approval as an adjunct to diet and exercise and in combination therapy with oral antidiabetic drugs to improve glycemic control in patients who have type 2 diabetes.

Novo Nordisk has provided the FDA with an estimate that liraglutide reduces the risks of fatal and nonfatal myocardial infarction and stroke by at least 20% on the basis of the clinical investigators' reported observations.

Dr. Garber disclosed that he is on the speakers bureaus and advisory boards for Novo Nordisk, GlaxoSmithKline, Merck, and Roche. ■

Plasma Lipid Levels Can Be Measured After Eating

BY NEIL OSTERWEIL

BOSTON — Nonfasting lipid status may be a better marker for impaired lipid metabolism than fasting lipids, according to a prospective study.

The findings suggest that patients need not deny themselves a good breakfast or lunch before having their blood drawn for plasma lipid testing.

Dr. István Reiber and Dr. Izabella Mezõ from the Szent György Hospital in Székesfehérvár, Hungary, compared fasting and postprandial lipid levels among 102 nondiabetic patients (44 men), and found that the only significant differences in any lipid parameters were between fasting and nonfasting triglycerides.

It is well known that there are no significant changes in total cholesterol and HDL cholesterol levels between the fasting and postprandial state. In addition, recent study findings suggest that nonfasting triglyceride concentrations in plasma are more predictive of cardiovascular events than are conventional measures of fasting triglycerides, the investigators wrote in a scientific poster presented at a symposium sponsored by the International Atherosclerosis Society.

The study participants had never received lipid-lowering drugs. They underwent separate venous blood draws following an overnight fast, 3 hours after eating their usual breakfasts, and 3 hours after their usual lunches.

Overall, total cholesterol in the fasting state was 5.51 mmol/L, 5.48 mmol/L after breakfast, and 5.69 mmol/L after lunch, a difference that was not significant.

HDL levels also were comparable between the fasting and postprandial states, at 1.12 mmol/L, 1.14 mmol/L (breakfast), and 1.20 mmol/L (lunch), respectively. Triglyceride levels, however, were significantly higher after eating, rising from 2.21 mmol/L in the fasting state, to 2.31 mmol/L after breakfast, and 2.94 mmol/L after lunch.

The researchers also found that both postprandial triglyceride measures correlated significantly with fasting triglycerides. All volunteers who had fasting triglyceride levels below 1.5 mmol/L had postprandial triglyceride levels below 2.0 mmol/L.

In addition to being more convenient, allowing patients to have their lipids measured in a nonfasting state is preferable because after all, "atherosclerosis is a postprandial story," the researchers wrote, referring to the fact that people are in a postprandial state at least 20 hours daily.

Lipid measures 2-4 hours after meals provide a better early predictor for cardiovascular disease than do fasting lipids, concluded the investigators, who advised intervention whenever a patient has triglycerides higher than 2.0 mmol/L with elevated LDL and decreased HDL. Their suggested triglyceride treatment targets are fasting triglycerides lower than 1.0 mmol/L, or 2-4 hour postprandial triglycerides lower than 3.0 mmol/L.

Neither investigator disclosed relevant conflicts of interest. ■