On-Statin Lipid Levels Best Predict Cardiac 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 study.

Indeed, only 1 of the 18 biomarkers that were assessed in the study proved predictive of major cardiovascular events: osteopontin.

At baseline, when Treating to New Targets (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 the risk of cardiovascular events 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 marked contrast to the underperformance of the novel biomarkers, on-treatment levels of the traditional lipid risk factors—LDL cholesterol, HDL cholesterol, and triglycerides—were powerful predictors of major cardiovascular events.

The implication is that the appropriate treatment strategy in patients with established coronary heart disease (CHD) is to put them on statins, titrate to a dose that achieves guideline-recommended lipid levels, and dispense with focusing on novel biomarkers, which do not offer increased predictive power over the standard lipids.

Of 18 novel biomarkers assessed, 17 proved to have no predictive value. Osteopontin was the exception.

DR. KASTELEIN

"Until further evidence is available and/or guidelines recommend otherwise, clinical decisions around statin therapy might continue to focus on traditional contributors to cardiovascular risk, such as lipid levels, prior medical history, and lifestyle factors," 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 clinical trial to demonstrate that lowering LDL to a target of 75 mg/dL resulted in 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 undertaken to shed light on the potential utility of the much-discussed novel biomarkers in managing cardiovascular disease.

The post hoc nested case-control study 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.

An on-treatment elevated LDL cholesterol level was associated with a 2.1-fold increase in the 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 A_2, adiponectin, 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. ■

Metabolic Syndrome Linked To Peripheral Artery Disease

BY KATE JOHNSON

Women with metabolic syndrome have an increased risk of developing symptomatic peripheral artery disease, compared with healthy women, according to a new analysis of the Women's Health Study.

"In this generally low-risk population of women, the excess risk associated with [metabolic syndrome] may be mediated through heightened inflammation and/or endothelial activation," reported Dr. Aruna Pradhan of Brigham and Women's Hospital, Boston, and colleagues.

The prospective cohort study included a subgroup of 27,111 women, aged at least 45 years, who were enrolled in the Women's Health Study and followed for a median of 13 years (Circulation 2009 Sept. 8 [doi:10.1161/circulationaha.109.863092]).

About one-quarter of the study population (6,920) had metabolic syndrome, defined according to the ATP (Adult Treatment Panel) III guidelines as the presence of three or more of the following traits: a waist circumference of 88 cm or more; a triglyceride level of 150 mg/dL or greater; HDL cholesterol levels lower than 50 mg/dL; a blood pressure of at least 130/85 mm Hg; and abnormal glucose metabolism as identified by a fasting blood glucose level of at least 100 mg/dL.

Incident symptomatic peripheral artery disease (PAD), defined as intermittent claudication and/or peripheral artery surgery inclusive of catheter-based interventions, occurred in 114 women, 70 of them with metabolic syndrome and 44 without.

The hazard ratio for PAD with metabolic syndrome, compared with PAD without metabolic syndrome, was 1.62 on univariate analysis, and 1.48 after adjustment for patient age and smoking status.

Hazard ratios for PAD were 0.98 with elevated body mass index, 1.39 for elevated triglycerides, 1.50 for hypertension, 1.60 for low HDL cholesterol, and 2.05 for dysglycemia.

Even among women who did not have metabolic syndrome, the risk for PAD increased with the number of metabolic syndrome traits. Compared with women who did not have any traits, those who had one or two traits had a 2.5-fold increased risk of PAD.

The hazard ratios for PAD were 0.98 with elevated body mass index, 1.39 for elevated triglycerides, 1.50 for hypertension, 1.60 for low HDL cholesterol, and 2.05 for dysglycemia, reported the authors.

By comparison, the hazard ratio associated with current smoking was 12.7.

"Smoking was by far the strongest risk in this population," the researchers wrote. "This study underscores the importance of abstinence from smoking for the prevention of PAD." ■

Screen for Metabolic Syndrome Before Prescribing Tricyclics

BY BRUCE JANCIN

ISTANBUL, TURKEY — The use of tricyclic antidepressants to treat depression and/or anxiety was associated with a sharply increased risk of metabolic syndrome, compared with other antidepressant classes, a large prospective Dutch cohort study has shown.

The specific components of the metabolic syndrome exacerbated by tricyclic antidepressants (TCAs) were hypertension, abdominal obesity, and hypertriglyceridemia, Arianne K.B. van Reedt Dortland reported at the annual congress of the European College of Neuropsychopharmacology.

There are two clear take-home messages of this analysis from the Netherlands Study of Depression and Anxiety (NESDA), according to Ms. Reedt Dortland of Leiden (the Netherlands) University Medical Center:

► It is important to screen for these elements of the metabolic syndrome in patients who are being considered for TCA therapy or who are already on it.

► When one or more of these elements is present, an alternative type of antidepressant is highly preferable to minimize the patient's risk of developing cardiovascular disease or diabetes.

NESDA is an ongoing 8-year prospective multicenter study involving 261 patients with current major depressive disorder only, 266 with a current pure anxiety disorder, and 690 with both, all diagnosed according to DSM-IV criteria.

A total of 328 patients were treated with a selective serotonin reuptake inhibitor, 49 received a TCA, 110 were on a serotonergic/noradrenergic reuptake inhibitor, and 730 were not on antidepressant medication.

During the first 4 years of follow-up, patients who were on a TCA were at a 2.3-fold increased risk of meeting criteria for the metabolic syndrome after adjustment for age, gender, physical activity, years of education, smoking status, and alcohol use, compared with patients who were not on antidepressant medication.

Specifically, patients on TCA therapy were at 2.3-fold increased risk for hypertension, 1.9-fold increased risk for abdominal obesity, and 2.6-fold increased risk for hypertriglyceridemia.

In contrast, the use of selective serotonin reuptake inhibitors or selective norephinephrine reuptake inhibitors was not associated with an increased rate of metabolic syndrome or any of its components.

NESDA, which will run through 2012, is funded by the Dutch Ministry of Health.

Ms. Reedt Dortland reported having no potential conflicts of interest in connection with the study. ■