LDL Lowering to Remain Focus of ATP Guidelines

BY BRUCE JANCIN
Denver Bureau

CHICAGO — Lowering LDL cholesterol using statins will remain the main focus of cardiovascular prevention in the next generation of clinical practice guidelines, according to one expert.

"Lately, because of controversies concerning new medications we've had, some people say maybe LDL shouldn't be the focus of the clinical guidelines. There are four strong reasons why that's not true: the breadth and depth of the supporting genetic, epidemiologic, experimental, and clinical trial evidence," Dr. Neil J. Stone said at the annual meeting of the American Thyroid Association. Dr. Stone is a cochair of the National Heart, Lung, and Blood Institute's Adult Treatment Panel (ATP) IV, along with Dr. Scott M. Grundy, chairman of the department of clinical nutrition at the University of Texas at Dallas.

Dr. Stone, who also served on ATP I and III, provided a glimpse into the future of the dyslipidemia guidelines and the thinking of those who fashion them, and also fielded audience criticism that the guidelines are too LDL centric and described the high bar that's been set for acceptance of new therapies, including the novel thyroid hormone analogues many endocrinologists are interested in using to lower LDL.

He stressed that statins, the drugs of choice for lowering LDL cholesterol, are among only three therapies with well-established safety and efficacy in lowering LDL while reducing cardiovascular events. The others are bile acid sequestrants and partial ileal bypass, which surgically excludes the last 100 cm of terminal ileum.

"Any new therapy that's going to rival statins would have to lower LDL by at least 30%-50%, as can be attained by statins now available," said Dr. Stone, professor of clinical medicine at Northwestern University, Chicago.

Moreover, before any new therapy can win large-scale acceptance, it will need to demonstrate both safety and efficacy in a large-scale randomized clinical trial, conducted over a period of at least several years, with hard cardiovascular outcomes such as acute MI and mortality, not just surrogate imaging or biomarker end points, the cardiologist added.

This point was brought home for him by the defining experience of serving on the independent data safety monitoring board of the landmark Heart and Estrogen Replacement Study (HERS), a double-blind randomized clinical trial that some prominent physicians dismissed during the organizing stages as a waste of time. After all, the critics noted, hormone therapy had already been shown to reduce LDL and slow carotid intimal medial thickening, and ATP II recommended it for cardiovascular risk reduction.

Yet HERS ultimately demonstrated an increased cardiovascular event rate in hormone-treated patients, leading to a strong recommendation against giving such therapy to women with coronary heart disease. A similarly unexpected negative finding resulted from the first large randomized trial of torcetrapib, the once highly promising but now abandoned HDL-boosting/LDL-lowering cholesterol esterase transport protein inhibitor.

'Any new therapy that's going to rival statins would have to lower LDL by at least 30%-50%,' as statins do.

DR. STONE

The best bet in the near future for important new advances in lipid-lowering therapy to arrive on the scene, in Dr. Stone's view, will be in agents piggybacked on top of statin therapy to reduce the residual cardiovascular risk remaining in statin-treated patients.

Expected to report results within this time frame are the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial evaluating a simvastatin\fenofibrate combination in 10,000 patients with type 2 diabetes, as well as the 3,300-subject Atherothrombosis Intervention in Metabolic Syndrome with Low HDL\High Triglycerides and Impact on Global Health Outcomes (AIM HIGH), featuring a long-acting niacin (Niaspan)\simvastatin combination. Both double-blind randomized trials are sponsored by the National Heart, Lung, and Blood Institute.

Audience members asked what they should do about the growing number of statin-intolerant patients they're encountering as the drugs become more widely prescribed. "People who can't tolerate statins are filling our schedules and are very frustrating," Dr. Stone agreed, while noting they constitute only a small percentage of all patients prescribed the drugs. In the setting of statin intolerance he urged greater use of bile acid sequestrants, as well as an emphasis on plant-based diets, which reduce LDL in adherent individuals to an extent comparable to starting doses of statins. It's also important to identify and treat hypothyroidism in statin-intolerant patients because it makes treatment of their myositis much easier.

As for the newer investigational thyroid hormone analogues turning heads with their statin-sized LDL lowering and evidence of additive LDL lowering when combined with statins, Dr. Stone said preliminary studies look promising—just as they once did for estrogen replacement and torcetrapib—and he reiterated the need for large definitive, double-blind, randomized trials with hard end points. He noted that d-thyroxine was recommended for lipid lowering in the late 1960s and early 1970s but was dropped because of arrhythmic problems in the Coronary Drug Project.

Dr. Stone disclosed that although in the past he has received honoraria for consulting services, as of last May 1st he has cancelled all consulting activities. ■

Inflammation Ups PAD Risk in Women

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Women with metabolic syndrome have an increased risk of developing symptomatic peripheral artery disease, mediated mainly by the syndrome's associated inflammation and endothelial activation, according to a prospective study of more than 27,000 women.

"The bottom line is if you account for the inflammation associated with the metabolic syndrome, there is no residual risk associated with the syndrome itself," Dr. Aruna D. Pradhan said at the annual scientific sessions of the American Heart Association.

She reported on 27,111 middle-aged female health professionals free of known cardiovascular disease when they enrolled in the Women's Health Study. At entry, one-quarter met criteria for the metabolic syndrome. At that time 28% of those with metabolic syndrome had diabetes, as did 1.8% of the others.

During a median 13.3 years of prospective follow-up, 114 women developed symptomatic peripheral artery disease (PAD). In an unadjusted first-pass analysis, women with metabolic syndrome at baseline were 62% more likely to go on to develop PAD. And for each additional metabolic syndrome–defining risk factor present beyond the requisite minimum three out of five, the risk of PAD increased by 26%.

However, women with metabolic syndrome also were slightly older, less likely to exercise, more likely to smoke, and had a higher body mass index in addition to their much greater prevalence of diabetes. Upon adjustment for these factors in a Cox multivariate proportional hazards analysis, the presence of the metabolic syndrome remained a significant risk factor for PAD. Indeed, women with metabolic syndrome had an adjusted 48% greater likelihood of PAD, and this risk climbed by another 21% for each additional metabolic syndrome–defining trait present, according to Dr. Pradhan of Brigham and Women's Hospital, Boston.

But the nearly 7,000 women with metabolic syndrome also differed from the more than 20,000 others in another important way: they had markedly higher levels of biomarkers of systemic inflammation.

The median plasma level of high-sensitivity C-reactive protein (hsCRP) among participants with metabolic syndrome at baseline was 3.98 mg/L, compared with 1.53 mg/L in women without metabolic syndrome. Levels of soluble intercellular adhesion molecule-1 (ICAM-1) averaged 374 ng/mL in the metabolic syndrome group and 333 ng/mL in the comparison arm. As the number of metabolic syndrome elements present increased from zero to five, median CRP increased from 1.0 to 5.9 mg/L and median ICAM-1 rose from 321 to 413 ng/mL.

When hsCRP and ICAM-1 levels were folded into the multivariate adjustment model, metabolic syndrome was no longer associated with a significantly increased risk of PAD, suggesting that systemic inflammation is the driving force in the development of PAD, not the high triglycerides, low HDL, or other components of the metabolic syndrome. ■

PAD Prognosis Linked to Stenotic Lesion Location

BY MITCHEL L. ZOLER
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MUNICH — For peripheral arteial disease, like real estate, it's all about location.

In a review of 400 patients, those with proximally located peripheral arterial disease (PAD) within aortoiliac vessels, were more than twice as likely to die or have a cardiovascular disease event during follow-up as patients with PAD lesions located exclusively in distal, infrailiac arteries, Dr. Victor Aboyans reported at the annual meeting of the European Society of Cardiology.

"This is the first study showing general prognosis differences in PAD patients according to disease location, independent of associated risk factors," said Dr. Aboyans, a senior physician at Dupuytren University Hospital in Limoges, France.

The study reviewed all 400 patients who underwent an initial, lower-limb angiography examination at the hospital during 2000-2005. Their average age was 68 years, and 78% were men. Arterial stenoses of 50% or more were located by two experienced vascular physicians.

Aortoiliac lesions were found in 211 patients. Many of these patients had lesions in distal arteries, too, although 56 of these patients only had aortoiliac stenoses. The other 189 patients in the study had stenotic lesions confined to distal parts of the lower vasculature, including femoro-popliteal disease and infragenicular disease.

During follow-up through April 2007, the rate of total death in the patients with aortoiliac stenoses was about 2.5-fold higher than those PAD patients who only had distal lesions in an analysis that adjusted for differences in patient age, gender, smoking status, diabetes, heart failure, and several other comorbidities and variables, Dr. Aboyans said. A second 2.5-fold increased risk was calculated for the incidence of cardiovascular disease events in the patients with proximal disease, compared with those who only had infra-iliac stenoses. ■