Lipid Management Update

Clinical Lipidology and Thrombosis Update

Is Hypertriglyceridemia a Risk Factor in Patients with Normal Cholesterol Levels?

The most convincing argument for the importance of elevated triglycerides comes from the fact that large trials, primarily with fibrates as their intervention, have shown selective benefits in patients with triglycerides >200 mg/dL, according to W. Virgil Brown, MD, Emory University School of Medicine, Atlanta, GA. A substudy of the Helsinki Heart Study, for example, which divided patients into groups above and below median HDL levels and then into those with triglycerides above and below 200 mg/dL revealed a "terrific" benefit (~70% reduction) in coronary death plus MI for gemfibrozil versus placebo in patients with high triglycerides and low HDL. In those with other risk factors, the reduction was only 20% (34% for the overall study). Furthermore, the Israeli BIP study with fibrates, despite showing only borderline benefits overall in a hypercholesterolemic population, showed a 40% reduction in the fourth of patients with triglycerides >200 mg/dL.

Detecting Lipid Abnormalities Sooner

"I really believe very strongly that if we are going to change the residual risk we see with our current approaches, we've got to catch ongoing disease long before there's any clinical evidence that we can currently measure," Brown stated, "and apply risk reduction in a more selective fashion."

Based on the strong suspicion that stiffness of major vessels is an early indicator of superoxide damage and endothelial dysfunction, Brown and colleagues conducted a study among about 250 healthy, middle-age subjects with no evidence of vascular disease, but with a spectrum of other risk factors. Measuring arterial stiffness with MRI and angiography, investigators found, after first excluding all individuals with ECG or stress test abnormalities, that vessels were stiffer in subjects with higher LDLs and lower HDLs. Among men, only weight and C-reactive protein stood out significantly (with positive trends for other factors). In women, however, lower arterial compliance was strongly correlated with triglyceride levels and other indices of VLDL remnant accumulation.

"Our conclusion was that women without evidence of vascular disease have an increased arterial stiffness in the arteries of the lower extremities associated with concentrations of VLDL and perhaps chlyomicron remnants," Brown said. Men showed weaker trends in the same direction.

"From the physiological perspective, elevated triglycerides could be the etiology of the entire atherogenic phenotype," Brown concluded, also observing that triglyceride-lowering interventional trials with vascular endpoints in hypertriglyceridemic individuals are badly needed.

What Is the Maximum CHD Reduction Risk that Is Possible with Lipid-Lowering Drugs?

The central insight into the relationship between lipid levels and coronary heart disease (CHD) risk is not that it is not a threshold relationship, but a continuously graded one, stated Neil J. Stone, MD, Northwestern Memorial Hospital, Chicago, IL. The Heart Protection Study also showed not only similar CHD reduction, but similar lower all-cause mortality at all levels of LDL with simvastatin in high-risk subjects.

Additionally, the PROVE IT-TIMI- 22 trial looking at LDL levels below 100 mg/dL, compared pravastatin-treated patients with LDL reduced to 95 mg/dL (2.5 mmol/dL) and atorvastatin-treated patients reaching a median of 63 mg/dL (1.6 mmol/dL), finding a 16% relative risk reduction for those attaining the lower LDL level – "leading to the idea that we should be treating aggressively," Stone stated.

Results of the TNT Study comparing 10 mg and 80 mg of atorvastatin, showed the higher atorvastatin dose to bring LDL levels to a median of 77 mg/dL (as compared with 101 mg/dL) with a 22% relative risk reduction for major cardiovascular events, suggesting a goal of 70 mg/dL for highest risk patients, Stone said.

The Cholesterol Treatment Trialists review of 90 thousand

patients in 14 cholesterol-lowering trials revealed an overall risk reduction of 20% for statin therapy, and showed also that benefits were consistent regardless of subgroups with or without prior MI, age >65, female gender, treated or untreated hypertension or diabetes. It showed that a 1 mmol/dl LDL reduction sustained for 5 years could produces a 23% reduction in major vascular events.

All of the cited results support NCEP ATPIII (National Cholesterol Education Program Adult Treatment Panel) recommendations. Stone noted that ATP III extended concern beyond LDL awareness to include those with atherogenic dyslipidemia, with metabolic syndrome, elevated apo B, diabetes or familial combined hyperlipidemia. Furthermore, Helsinki Heart Study analysis identified those with BMI >30, LDL/HDL ratio >5 and triglycerides >204 mg/dL as the greatest benefactors from lipid lowering. Other studies revealed correlations between risk and abdominal obesity such that Stone became an active advocate of measuring waist circumference—to the point that one patient asked, "Are you my doctor or my tailor?"

Recent clinical trials have reconfirmed the benefits of niacin in reducing recurrent coronary events despite some glucose increases. It has also become apparent that with a statin/niacin combination, anti-oxidants impair the action of niacin and should be avoided. While niacin appears to be better for raising HDL, fibrates are better for lowering triglycerides.

In answer to the question, what may be done beyond statin therapy when LDL is already low? The answer is that in those with diabetes, low HDL or metabolic syndrome, fibrates or niacin can help.

Beyond Statin Therapy

Christie M. Ballantyne, MD, Director of the Center for Cardiovascular Disease Prevention at Methodist DeBakey Hospital in Houston, TX, moderated a lively session where three cardiologists traded ideas on optimum managements of the following case.

The case of an asymptomatic 55-year-old man on a heart-healthy diet, with no evidence of active disease on exam was presented. Waist circumference was measured at 42 inches. Lab results included total cholesterol of 195 mg/dL, LDL 120 mg/dL, triglycerides 255 mg/dL, HDL 30 mg/dL, and fasting blood glucose 120 mg/dL. The patient's NCEP risk was noted as moderate.

Frank Sacks, MD, Professor of Cardiovascular Disease Prevention at the Harvard School of Public Health, Cambridge, MA commented that the patient meets all of the criteria of metabolic syndrome, and as such his NCEP risk should actually be doubled. "This is the scenario where we want to consider going after more lowering of LDL than might be acceptable otherwise. I'd also initiate combination therapy with a statin, and either niacin or a fibrate to lower triglycerides and LDL, and increase the HDL"

C. Noel Bailey Merz, MD, Director, Preventive and Rehabilitation Cardiac Center at Cedars-Sinai Medical Center, Los Angeles, CA, suggested a fibrate over niacin in cases of significantly elevated triglycerides, but would go on to niacin or possibly omega-3 fatty acids if fibrates were not effective.

Dr. Ballantyne noted that fibrates can have impressive triglyceride-lowering effects (although less so in diabetics).

Dr. Roger Blumenthal, MD, Clinical Director of Heart Disease Prevention at Johns Hopkins University School of Medicine in Baltimore, MD recommended a statin plus a fibrate, and suggesting that even a third additional drug agent might be indicated in this kind of biochemical profile.