Getting There: Statin Plus Ezetimibe for Low-Density Lipoprotein Cholesterol Goals

The clinical trial reported by Pearson et al in the current issue of the *Mayo Clinic Proceedings* brings the good news that the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines for lipid lowering can be met at a time when physicians are faced with the burden of increased prevalences of obesity, metabolic syndrome, and diabetes mellitus, all of which would be expected to increase the risk of coronary heart disease (CHD). Presently, two thirds of adults in the United States are overweight, and more than one third are obese. Statin drugs are understandably the first choice among lipid-lowering medications because of their ability to effectively lower low-density lipoprotein cholesterol (LDL-C) levels, their excellent safety profile, and their proven efficacy in clinical end point trials. However, primary care physicians may be hesitant to recommend maximal doses of statins because of the potential adverse effects of biochemical hepatitis and clinical myopathy. (High-dose rosuvastatin also has been associated with hematuria of unknown importance, a unique adverse effect among statins.) Indeed, 52% of the 5802 patients screened by Pearson et al had not achieved target LDL-C levels according to NCEP ATP III guidelines when physicians relied on statin monotherapy.

Ezetimibe is the first drug available for use from the class of cholesterol absorption inhibitors. The addition of 10 mg/d of ezetimibe to patients’ initial statin therapy in the treatment arm of the study by Pearson et al had an amazingly consistent LDL-C lowering effect of 24% to 26%, regardless of the patient’s statin drug brand or dose or the patient’s age, sex, ethnic background (9% black and 5% Hispanic), or presence or absence of diabetes mellitus or metabolic syndrome. More than half the patients had metabolic syndrome, and more than 77% (n=2345) were classified as having either CHD or CHD risk equivalent according to NCEP ATP III criteria. Even so, 71% of patients who received 10 mg/d of ezetimibe in addition to their initial statin therapy reached their LDL-C target goal compared with 21% with the addition of placebo. Ezetimibe administration also significantly lowered triglycerides, non–high-density lipoprotein cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein compared with placebo when added to existing statin therapy. Whether similar treatment efficacy could have been achieved by increasing the statin dose was not addressed in this study.

As reported by the INTERHEART study, 4% 90% to 94% of the risk of myocardial infarction worldwide is accounted for by the standard risk factors plus lifestyle factors including abdominal obesity, psychosocial factors, inadequate consumption of fruits and vegetables, insufficient physical activity, and pattern of alcohol consumption. Smoking, dyslipidemia, hypertension, and diabetes mellitus were the most predictive positive risk factors. We must not forget that the NCEP ATP III guidelines endorse therapeutic lifestyle change (TLC) to decrease CHD risk. Four targets of TLC include smoking cessation, an exercise program of at least 30 minutes for 5 days weekly, a prudent diet (Mediterranean diet, Dietary Approaches to Stop Hypertension [DASH] diet, or American Heart Association Step I diet), and weight reduction to a normal body mass index of less than 25 kg/m². The TLC modification should include 150 or more minutes of exercise weekly. Weight loss of 7% or greater was more effective than metformin therapy in the Diabetes Prevention Program for preventing progression to diabetes in persons with an elevated fasting glucose level. After a mean 2.8 years of follow-up in the Diabetes Prevention Program, lifestyle modification reduced the incidence...
of diabetes, a CHD risk equivalent, by 58% compared with
31% for metformin. However, implementing healthy lifestyle changes can be an uphill struggle for many patients and their physicians.

Before the publication of the study conducted by Pearson et al, the NCEP ATP III released a commentary on the latest guidelines in light of studies published since the release of the original guidelines. It suggested the option of reducing the LDL-C level below the previous goal of less than 100 mg/dL to a new target of less than 70 mg/dL for patients at “very high risk” of a CHD event including patients with acute coronary syndromes, diabetes, and multiple uncorrected risk factors (such as continued smoking). The rationale for this option is the observation that the number of CHD events decreases when lower LDL-C levels are achieved. However, the recently published Treating to New Targets study, which showed decreased numbers of CHD events in secondary prevention with more aggressive LDL-C lowering, failed to show a decrease in CHD mortality and showed a non–statistically significant but concerning increase in noncardiovascular mortality. Therefore, the role of more aggressive LDL-C lowering (<70 mg/dL vs <100 mg/dL) is still unclear.

The recent commentary on the last NCEP ATP III guidelines suggests that for individuals with moderate to high CHD risk, drug efficacy should be adequate to lower LDL-C levels by 30% to 40%. Although this degree of reduction can be achieved with moderate-dose statin therapy in many patients, other patients may benefit from combination therapy with a statin and an additional agent such as ezetimibe. It is reassuring that the combined ezetimibe and statin regimen studied by Pearson et al was not only effective in reducing LDL-C level but also had the same safety and tolerance profile of placebo added to statin therapy. Although not yet proved in clinical end point trials, the promise of statin plus ezetimibe therapy seems to be considerable.

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