

EXAMINING THE DYSLIPIDEMIA CONSTELLATION

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A FORUM ON NEW TREATMENT ADVANCES

NCEP ATP III guidelines incorporate global risk assessment



Antonio M. Gotto, MD, DPhil

The National Cholesterol Education Program's Adult Treatment Panel III (ATP III) guidelines for coronary heart disease (CHD) risk stratification incorporate the concept of global risk assessment to determine the intensity and appropriateness of lipid-modifying treatment, said Antonio M. Gotto, Jr, MD, DPhil.

The United States guidelines for lipid management represent a synthesis of constantly emerging and evolving data in the field of lipid disorders, he said. The most recent guidelines, ATP III, include several changes from previous ATP guidelines.

Global risk as treatment determinant

ATP III guidelines establish 3 major categories of risk that determine the

aggressiveness of treatment: (1) those with CHD or with a risk-factor profile equivalent to having CHD (high risk); (2) those with 2 or more risk factors (moderate or intermediate risk); and (3) those with 0 or 1 risk factors (low risk).

The identification of a high-risk CHD-equivalent group is an important modification from previous ATP guidelines. Included in this category are patients who have other forms of vascular disease (such as peripheral or cerebrovascular disease or aortic aneurysm), those with diabetes, and those with a 10-year risk for CHD >20%.

Global risk calculation is incorporated in ATP III in the form of a modified version of the Framingham algorithm. In patients with no history of CHD and 2 or more risk factors in addition to an elevated level of low-density lipoprotein (LDL) cholesterol, global risk should be calculated to determine at what LDL cholesterol level to initiate drug therapy (Table). The importance of applying global

risk in the selection of patients for treatment was exemplified in the recent Heart Protection Study (HPS), in which patients with CHD or with a high-risk profile benefited from statin therapy, regardless of their baseline LDL cholesterol, said Dr. Gotto. The only lipid inclusion criterion in HPS was a total cholesterol ≥ 135 mg/dL.

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"The risk reduction with statin therapy in HPS was approximately 24% whether the LDL cholesterol at baseline was <100 mg/dL, was 100 to 130 mg/dL, or was >130 mg/dL," he said.

Emerging risk factors

"Because the modified Framingham

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score used by the ATP III reflects the contributions of the traditional major risk factors (ie, smoking, total cholesterol, high-density lipoprotein [HDL] cholesterol, age, blood pressure, and sex), they do not consider the risks associated with emerging risk factors, such as homocysteine, lipoprotein(a), or inflammatory markers," Dr. Gotto noted. "The presence of such factors may influence clinical judgment in favor of initiating more aggressive intervention, especially in patients who appear to be at borderline risk based on traditional risk factors alone."

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That is, these emerging risk factors may help justify drug therapy for patients with a 10-year risk of CHD events of 10% to 20%, based on the Framingham calculation. Recently, the American Heart Association and the Centers for Disease Control released a joint statement (*Circulation*. 2003;107:499-511) recommending the use of the inflammatory marker C-reactive protein in exactly this manner, he said.

In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL cholesterol-lowering drugs, even though use of drugs may not be cost-effective by current standards.

LDL goals

Previous ATP guidelines recommended an LDL cholesterol goal of ≤ 100 mg/dL in patients in the highest risk category. In ATP III, the LDL cholesterol goal is < 100 mg/dL for patients with the highest 10-year risk ($> 20\%$); this reflects uncertainty about how low LDL cholesterol should be in this population. Some authorities believe that

LDL cholesterol levels much lower than 100 mg/dL are optimal in patients at highest risk, but there is very little evidence, at present, to support this recommendation. Several clinical trials are in progress to test the hypothesis that LDL cholesterol levels much lower than 100 mg/dL provide further risk reduction in patients at highest risk of CHD events.

Another change from previous ATP guidelines is the redefinition of low HDL cholesterol as < 40 mg/dL, as opposed to < 35 mg/dL in previous guidelines. Triglyceride classification cut points are lowered from previous guidelines ("normal" being defined as < 150 mg/dL) to give more attention to moderate elevations, and non-HDL cholesterol (ie, total cholesterol minus HDL cholesterol) is identified as a secondary target of treatment in persons with high triglycerides (> 200 mg/dL).

Secondary prevention

In secondary prevention, key among ATP III recommendations for patients following an acute coronary event is that therapy be started before or at the time of discharge. There are 2 perceived advantages with this approach: (1) patients are particularly motivated to undertake and adhere to risk-lowering interventions at that time, and (2) failure to initiate indicated therapy early contributes to a treatment gap characterized by potentially inconsistent and fragmented patient follow-up (> 200 mg/dL).

Recognition of metabolic syndrome

The ATP III guidelines recognize the importance of the metabolic syndrome as a secondary target of therapy. This cluster of risk factors, including abdominal obesity, hypertension, low HDL cholesterol, insulin resistance, and hyperglycemia, acts synergistically to enhance the risk for coronary and cardiovascular morbidity and mortality. ATP III considers a diagnosis of metabolic syndrome to be the presence of any 3 of these 5 risk factors.

"The presence of this constellation of risk factors identifies a group of patients who are at higher risk than those with isolated LDL cholesterol elevation," said Dr. Gotto. An 11-year longitudinal study (*JAMA*. 2002;288:2709-2716) determined that compared with those without this syndrome, patients with the metabolic syndrome had a relative risk for CHD mortality of 3.77 and for all-cause mortality of 2.43.

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In a post hoc analysis of the Scandinavian Simvastatin Survival Study (4S), individuals who had the lipid triad of low HDL cholesterol, an elevated level of triglycerides, and an elevated level of LDL cholesterol derived greater benefit from simvastatin than patients whose only lipid abnormality was an elevation of LDL cholesterol (*Circulation*. 2001;104:3046-3051).

Those with the lipid triad were more likely to have other components of the metabolic syndrome. A retrospective analysis of the Helsinki Heart Study also demonstrated that the greatest benefit was derived from gemfibrozil among the patients with the lipid triad (*Circulation*. 1992;85:365-367).

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Continuing research may enhance understanding of this high-risk group of patients and identify novel approaches for prevention, said Dr. Gotto. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a new study sponsored by the National Institutes of Health and the National Heart, Lung, and Blood Institute, is attempting to determine whether tight glucose control, tight blood pressure control, and statin therapy will reduce major coronary events in patients with type 2 diabetes. ■

Table

NCEP ATP III LDL cholesterol goals for different risk categories			
Risk category	LDL goal (mg/dL)	LDL level at which to initiate therapeutic lifestyle changes (mg/dL)	LDL level at which to consider drug therapy (mg/dL)
0-1 risk factor	< 160	≥ 160	≥ 190 (160-189: LDL-lowering drug optional)
2+ risk factors (10-year risk $\leq 20\%$)	< 130	≥ 130	10-year risk 10%-20%: 130 10-year risk <10%: 160
CHD or CHD risk equivalents (10-year risk >20%)	< 100	≥ 100	≥ 130 (100-129: drug optional)

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; CHD = coronary heart disease; LDL = low-density lipoprotein.
Source: NCEP ATP III.