Preventive strategies for reducing coronary heart disease–related morbidity and mortality in patients with multiple risk factors

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Based on epidemiologic and clinical evidence, the National Cholesterol Education Program Adult Treatment Panel has identified low-density lipoprotein cholesterol as the primary target for lipid intervention to promote the reduction of high cholesterol through increased awareness and aggressive management of cardiovascular risk factors. These guidelines provide the basis for management of multiple risk factors and applied intervention using diet, exercise, and drug therapy to lower cholesterol levels. Data from primary- and secondary-prevention trials strongly support the rationale for aggressive therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to significantly reduce morbidity and mortality from coronary heart disease.

(Key words: acute coronary syndrome, atherosclerosis, coronary heart disease, low-density lipoprotein cholesterol, National Cholesterol Education Program guidelines, primary prevention, secondary prevention, unstable angina, statins)

For more than a decade, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel I, II, and III, or ATP I, II, and III) has promoted the reduction of high blood cholesterol levels (specifically low-density lipoprotein cholesterol [LDL-C]) through increased awareness and aggressive management of cardiovascular risk factors in an effort to reduce morbidity and mortality from coronary heart disease (CHD). The ATP III final report released earlier this year continues to recognize LDL-C as the primary target for lipid intervention.

Despite the educational efforts of the NCEP ATP I, II, and III and the availability of effective treatment, evidence suggests that many patients receiving lipid-lowering therapy are not reaching their LDL-C goals (ie, levels to or below those recommended in the NCEP guidelines). This fact has been evident in both patients with existing CHD and in primary prevention, underscoring the need for more systematic and aggressive management of patients with multiple risk factors, including elevated LDL-C levels, hypertension, family history of premature CHD, cigarette smoking, diabetes mellitus, and low levels of high-density lipoprotein cholesterol (HDL-C).

Findings from two large-scale surveys, the Lipid Treatment Assessment Project (L-TAP) and the National Health and Nutrition Examination Survey III (NHANES III), support these observations, particularly for patients at highest risk for CHD. Based on these surveys, approximately 70% of low-risk patients and only about 35% of high-risk patients were achieving their target LDL-C levels. Perhaps most disturbing is the fact that only 17% to 18% of patients with established CHD were reaching their LDL-C goals (Figure 1). Thus, both the L-TAP and NHANES III surveys show that application of lipid-lowering therapy is inadequate in many of those patients who are at greatest risk for the development of the macrovascular complications that progress to ischemic events.

As more is learned about the many factors that contribute to CHD, designing effective preventive strategies becomes more complex. Although the curvilinear correlation between serum cholesterol levels and CHD mortality rates is well established, a 25-year international study evaluating data from seven countries shows that the association varies considerably among cultures, suggesting that other factors such as dietary differences may be involved.

Although serum cholesterol is not the sole determinant of CHD risk, LDL-C reduction remains the foundation for preventing CHD-related morbidity and mortality. Preventive strategies emphasize LDL-C reduction for two reasons: (1) the clinical benefits are clearly established in a broad range of patient types, and (2) the goal is achievable through a combination of dietary modification and drug therapy, particularly with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Several landmark trials have established an association between aggressive use of statins and reductions in the incidence of CHD-related morbidity and mortality. The application of this knowledge in practice is now the issue for clinicians.

NCEP guidelines: setting the standards for prevention and care

The NCEP ATP III recently reviewed the appropriateness and success of the ATP II guidelines with the objectives of
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building on the existing guidelines and providing new recommendations for more intensive therapy in patients at high risk. Important issues for ATP III review and consideration included:

- The implications of recent clinical trials for both primary and secondary prevention;
- The appropriateness of current LDL-C target levels, both in patients at risk and those with established CHD;
- The predictive value of emerging risk factors in cholesterol management, such as lipoprotein(a), homocysteine, and C-reactive protein;
- New epidemiologic data and recommendations for special patient populations such as those with diabetes mellitus or peripheral vascular disease; and
- Recognition of the metabolic syndrome with clustering of risk factors in patients, such as elevated glucose level, high blood pressure, low HDL-C level, high triglyceride level, and abdominal obesity.

According to the ATP III final report, LDL-C will continue to be the primary target for lipid intervention, but its major new focus will be primary prevention in patients with multiple risk factors. As always, the NCEP ATP advises that an important aspect of prevention is matching the intensity of lipid management to the patient’s risk-factor status. However, ATP III guidelines are recommending that assessment of CHD risk be based on the determination of absolute risk, allowing for more complete and accurate estimation of risk. Furthermore, the new guidelines recommend even more intensive therapy for patients with CHD risk equivalents (Figure 2).

In keeping with this more intensive approach to lipid intervention, the ATP III guidelines reflect key adjustments to the established goal levels for LDL-C and the corresponding level of risk based on the presence of selected risk factors. Both ATP II and III guidelines share a similar philosophy and a number of core features. For a comparison of LDL-C cutpoints and major CHD risk factors identified by ATP II and III, see Figure 3. Some important differences between ATP II and III include:

- Lowering LDL-C to levels below 100 mg/dL in patients with established CHD or CHD risk equivalents,
- Defining HDL-C as a risk factor when levels are below 40 mg/dL,
- Classifying diabetes mellitus as a CHD risk equivalent, and
- Estimation of 10-year risk of myocardial infarction or coronary death using age, plasma cholesterol, HDL-C, sys
tolic blood pressure, cigarette smoking, and gender as terms in equations derived from the Framingham Heart Study.\textsuperscript{2,3}

It remains important for physicians to base their determination of a patient’s risk category and subsequent CHD management on clinical judgment in conjunction with the most recent scientific data.\textsuperscript{3}

Clinical support for aggressive lipid lowering with statins
Statin therapy has revolutionized our approach to the prevention of cardiovascular events. Several large, randomized, placebo-controlled clinical trials of approximately 5 years’ duration have demonstrated the efficacy of statins in the prevention of virtually all of the major complications associated with CHD and stroke. Coronary death has been reduced to such an extent that a significant decrease in total mortality has been documented in the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study\textsuperscript{7} and the Scandinavian Simvasstatin Survival Study (4S).\textsuperscript{8} Angiographic studies using various pharmacologic or nonpharmacologic modes of therapy alone or in combination have shown that aggressive LDL-C reduction is often associated with stabilization of lesion encroachment on the lumen of coronary arteries, and in some cases, regression of lesions.\textsuperscript{13-15} Data from all of these studies indicate a very low rate of adverse reactions.

When the ATP II guidelines\textsuperscript{2} were first released, the value of LDL-C reduction to levels equal to or below 100 mg/dL for those with established CHD was recommended based on somewhat preliminary evidence. However, the data that have accumulated since that time more clearly justify such aggressive LDL-C reduction, convincing ATP III to classify this lower value as the optimal level for LDL-C in all adults and a target for therapy in a broader group of patients than those identified by ATP II. In particular, three trials of aggressive statin therapy show significant clinical benefits for patients with CHD whose LDL-C levels are brought below 100 mg/dL.

The Post Coronary Artery Bypass Graft (Post CABG) study evaluated the effects of two lipid-lowering regimens versus placebo in patients who had CABG surgery. This was the first randomized, prospective study to investigate whether an aggressive approach to lipid lowering was more effective than a conventional method. In this large-scale trial, more than 1300 subjects (predominantly men ranging in age from 21 to 74 years) were evaluated. For men enrolled in the study, the criteria included at least two previous saphenous vein grafts inserted 1 to 11 years prior to trial initiation. A target LDL-C level of less than 85 mg/dL was established for patients randomly assigned to the aggressive treatment group, whereas the target level for those in the moderate-treatment group was between 130 mg/dL and 140 mg/dL.

Initially, patients in the aggressive-treatment group received lovastatin, 40 mg/d, whereas those in the moderate-treatment group received 2.5 mg/d. To help patients achieve their target LDL-C levels, either lovastatin dosages were later adjusted or therapy with cholestyramine, 8 g/d, was added. Treatment was continued for a mean of 4.3 years. At follow-up, the mean LDL-C levels were 93 mg/dL for the aggressive-treatment group and 134 mg/dL for the moderate-treatment group.\textsuperscript{9}

Angiograms during follow-up visits revealed that aggressive treatment significantly slowed the development of atherosclerosis within the grafts. Compared with the moderate-treatment group, the aggressive-treatment group had 31% fewer grafts per patient with substantial atherosclerosis progression (defined as a \( \geq 0.6 \) mm decrease in lumen diameter). The aggressive-treatment group also had substantial reductions in graft narrowing and new occlusions compared with the moderate-treatment group.\textsuperscript{9}

Clinically significant advantages of aggressive treatment were comparable in both diabetic and nondiabetic patients.\textsuperscript{16}

As expected, this prevention of atherosclerosis correlated with a marked decrease in ischemic events over time. After the study, there was a lower rate of revascularization procedures in the aggressive-treatment group (although this trend was not statistically significant).\textsuperscript{9}

In summary, findings from this study showed conclusively that aggressive lowering of mean LDL-C levels to below 100 mg/dL was associated with reduced disease progression and improved clinical benefit compared with results in patients with only moderate reductions to a mean LDL-C level near 130 mg/dL.\textsuperscript{2}

Another secondary prevention trial is the Atorvastatin Versus Revascularization Treatment (AVERT) study\textsuperscript{17} conducted to determine whether patients with stable angina and CHD could be treated medically with aggressive lipid lowering, thereby avoiding or delaying the need for revascularization. The AVERT study was an 18-month, open-label, randomized, multicenter trial in which approximately 300 patients were
Adult Treatment Panel II

- High LDL-C levels
  - >160 mg/dL for individuals with less than two risk factors listed below
  - >130 mg/dL for those with two or more risk factors listed below
  - >100 mg/dL for those who have established CHD

- Age
  - ≥45 years for men
  - ≥55 years for women or those with premature menopause without hormone replacement therapy

POSITIVE RISK FACTORS

- Family history of premature CHD (definite myocardial infarction or sudden death)
  - >55 years of age in first-degree male relative, or <65 years in first-degree female relative

- Current cigarette smoking

- Hypertension

- Low HDL-C level (<35 mg/dL)

NEGATIVE RISK FACTORS

- High HDL-C levels (≥60 mg/dL)
  (Subtract one risk factor from total number of risk factors.)

Adult Treatment Panel III

- High LDL-C levels
  - >160 mg/dL for individuals with zero to one risk factor listed below
  - >130 mg/dL for those with two or more risk factors listed below
  - >100 mg/dL for those who have established CHD or CHD risk equivalents

POSITIVE RISK FACTORS

- Low HDL-C level (<40 mg/dL)

NEGATIVE RISK FACTORS

- Diabetes mellitus regarded as CHD risk equivalent
treated with either atorvastatin calcium, 80 mg/d, or angioplasty followed by usual care. Patients were required to have stenosis of 50% or greater in one or two of the coronary arteries at baseline, and to have good ventricular function (ejection fraction ≥40%) and stable angina of no more than moderate severity. Some patients had no angina but had other symptoms suggestive of CHD. Patients assigned to atorvastatin discontinued taking all other lipid-lowering medications, whereas the use of these agents was not restricted in the angioplasty group.17

After 18 months, LDL-C levels in the atorvastatin group averaged 77 mg/dL, representing a 46% drop from baseline. The mean LDL-C level for the angioplasty group at the study endpoint was 119 mg/dL, which was 18% lower than baseline levels, but still greater than the 100 mg/dL recommended by the NCEP guidelines. The difference between groups in LDL-C reduction was statistically significant (P<.05).17 Seventy-two percent of the angioplasty group were treated with lipid-lowering drugs, but the dosage was low and therapy was started later in the study.

During follow-up, ischemic events were 36% less frequent in the atorvastatin group than in the angioplasty group. In addition, the time to first ischemic event was significantly delayed in the group receiving atorvastatin compared with the group receiving angioplasty.17 Thus, for patients with stable angina, aggressive lipid lowering with atorvastatin is at least as effective as angioplasty plus usual care, and may even be more effective in preventing or delaying subsequent ischemic events, reinforcing the point that dyslipidemia is a metabolic condition that responds well to medical therapy.

Most studies documenting the benefits of aggressive LDL-C reduction with statins have enrolled patients with stable coronary conditions versus those with recent myocardial infarctions or unstable angina. However, patients who are in the early period after these acute coronary syndromes are at greatest risk for recurrent ischemic events, especially within the first 6 months, and therefore are most in need of preventive care.18 The recently published Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study19 tested the hypothesis that early, rapid, and intensive LDL-C reduction with aggressive statin therapy over 16 weeks would reduce the incidence of early, recurrent ischemic events in patients with acute coronary syndromes. An early clinical benefit as demonstrated by reduced incidence of death and nonfatal ischemic events might be anticipated, because experimental evidence from animal models indicates that statins cause rapid physiologic changes in the endothelium.20-23

To further study this potentially rapid response of the endothelium to statin therapy, the MIRACL trial was conducted in approximately 3000 patients who were randomly assigned to receive either atorvastatin therapy, 80 mg/d, or placebo plus diet initiated between 24 and 96 hours after hospital admission for unstable angina or a non–Q-wave myocardial infarction.19 This dosage of atorvastatin produced a 40% reduction in LDL-C, with a mean level of 72 mg/dL at the study endpoint, which is well below the recommended NCEP cutpoint of 100 mg/dL for secondary prevention.

During the 16-week MIRACL study,19 a statistically significant reduction in the risk of the primary combined endpoint (ie, death, nonfatal acute myocardial infarction, resuscitated cardiac arrest, or recurrent worsening symptomatic myocardial ischemia with objective evidence requiring rehospitalization) was observed in patients receiving atorvastatin compared with those receiving placebo. A primary outcome event occurred in 14.8% of patients receiving atorvastatin compared with 17.4% of patients receiving placebo with an absolute risk reduction of 2.6% (Figure 4). Overall, patients in the atorvastatin group had a 16% relative risk reduc-

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tion in primary outcome events compared with those in the placebo group. Among secondary outcome events, there was a 26% decrease in the occurrence of acute angina requiring rehospitalization and a 50% decrease in stroke rate.\textsuperscript{19} The clinical benefits of atorvastatin at dosages of 80 mg/d strongly suggest that early, rapid, and intensive cholesterol-lowering therapy can reduce early, recurrent ischemic events in patients with unstable angina and non–Q-wave myocardial infarction.

Based on these results, further study of statins in patients immediately after episodes of acute coronary syndromes is needed to fully determine their clinical benefit. Additional large-scale trials studying the effects of early, aggressive lipid lowering with statins after myocardial infarction or acute angina are under way.\textsuperscript{24}

**Comment**

Findings from numerous clinical studies confirm the important role of LDL-C in the constellation of cardiovascular risk factors and the benefits of aggressive lipid intervention with statins for both primary and secondary CHD prevention. Nonpharmacologic interventions such as dietary modification, exercise, and smoking cessation also remain an essential part of any broad-based CHD preventive regimen, because the first key to protection is modifying risk factors that are within the patient’s control, including hypercholesterolemia, obesity, and tobacco use.

The presence of multiple risk factors mandates more intensive treatment in addition to lifestyle changes. According to NCEP ATP III guidelines,\textsuperscript{3} systematic and aggressive management of elevated LDL-C to define and achieve goal levels is recommended for all patients with CHD risk factors to prevent initial and subsequent ischemic events. In the presence of atherosclerosis, diabetes mellitus, predicted CHD risk of more than 20% in 10 years and/or established CHD, LDL-C levels of less than 100 mg/dL are the goal. However, it is important to note that the ceiling is \textit{not} the target. In patients at high risk, LDL-C levels should be well below 100 mg/dL for optimal benefit. Aggressive and proactive clinical management of the patient with multiple CHD risk factors on the part of the primary care physician and the cardiologist will result in prevention of atherosclerosis and a reduced rate of morbidity and mortality associated with ischemic events.

**References**


