Elevated low-density lipoprotein cholesterol (LDL-C) is closely associated with an increased risk of cardiovascular morbidity and mortality. Results from numerous well-designed clinical trials indicate that interventions designed to modify lipid levels significantly reduce the risk of coronary heart disease (CHD), particularly in patients at highest risk. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines recommend matching the intensity of lipid-lowering therapy to the patient’s risk of CHD. However, despite the existence of evidence-based treatment guidelines and the availability of many safe and effective lipid-modifying modes of therapy, optimal CHD risk reduction rarely is achieved.

The prevention and treatment of coronary heart disease (CHD) continue to be a significant challenge for healthcare providers. Coronary heart disease is the single largest killer of both women and men in the United States, and if all forms of major cardiovascular disease were eliminated, life expectancy would lengthen by approximately 7 years. Despite strong clinical evidence that reduction of low-density lipoprotein cholesterol (LDL-C) levels decreases the morbidity and mortality associated with CHD, many patients have dyslipidemia that remains undiagnosed and untreated. Therefore, effective prevention strategies must be designed and implemented to improve the treatment of lipid disorders and to reduce CHD risk.

Adult Treatment Panel III Clinical Guidelines for Lipid-lowering Therapy
The third edition of the National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP III) guidelines recommends matching the aggressiveness of LDL-C-lowering therapy to the patient’s absolute risk of CHD. This is done using a scoring system based on Framingham risk factors. Patients with the highest risk, including those with a history of CHD, patients with two or more risk factors that confer a 10-year risk of greater than 10%, and patients with CHD risk equivalents such as diabetes, are targeted for the most intensive lipid lowering. The ATP III also identifies patients with conditions such as the metabolic syndrome as ideal candidates for lipid modification, particularly through weight loss, dietary changes, exercise, and other therapeutic lifestyle changes (TLC).

Low-density lipoprotein cholesterol treatment goals vary depending on the number of risk factors present (Table). Patients at highest risk and, subsequently, having the lowest treatment goals, are those with a history of CHD and the presence of CHD risk equivalents. A risk equivalent places an individual at a 20% or more risk of having a CHD event during the next 10 years and includes peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes mellitus, and the presence of multiple risk factors. A second category of risk includes patients with two or more risk factors in whom the 10-year risk of CHD is less than 20%. A third risk category is made up of those individuals who have zero to one risk factor and a 10-year risk of less than 10%.

Clinical Trials Supporting the Benefits of Aggressive Lipid-lowering Therapy
The Framingham study was among the first of a series of epidemiologic studies to establish the correlation between elevated plasma cholesterol levels and CHD. In 1994, the first of several large interventional trials, the Scandinavian Simvastatin Survival Study (4S) was published. Results from this study demonstrated that compared with placebo, lipid-lowering modes of therapy reduced the risk of major coronary events. Data from this trial, as well as several other prospective clinical outcomes trials, have demonstrated that every 1% decrease in LDL-C is associated with an approximate 1% decrease in CHD-related mortality. Current research efforts are focused on confirming the existence of a linear relationship between lipid lowering and reduction of risk of CHD.

One of the first trials to provide supportive data for this hypothesis was the Post Coronary Artery Bypass Graft (Post-CABG) trial published in 2000. Data from this trial suggested that a ther-
Table
Low-Density Lipoprotein Cholesterol (LDL-C) Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories*

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>LDL-C Level at Which to Initiate TLC (mg/dL)</th>
<th>LDL-C Level at Which to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Equivalents (10-Year Risk &gt;20%)</td>
<td>&lt;100</td>
<td>≥100</td>
<td>≥130 (100 to 129: drug optional)†</td>
</tr>
<tr>
<td>Two or More Risk Factors (10-Year Risk ≥20%)</td>
<td>&lt;130</td>
<td>≥130</td>
<td>10-year risk 10% to 20%: ≥130</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-year risk &lt;10%: ≥160</td>
</tr>
<tr>
<td>Zero to One Risk Factor (10-Year Risk &lt;10%)</td>
<td>&lt;160</td>
<td>≥160</td>
<td>≥190 (160 to 189: drug optional)</td>
</tr>
</tbody>
</table>

† Some authorities recommend use of drug therapy in this category if an LDL-C level of less than 100 mg/dL cannot be achieved by TLC.

A therapeutic approach that lowered LDL-C level by 40% to an approximate LDL-C of 80 mg/dL was significantly more effective in reducing risk of CHD compared with moderate LDL-C-lowering therapy that elicited a 13% decrease in LDL-C and achieved an LDL-C level of approximately 125 mg/dL. Aggressive lipid lowering was associated with a 31% reduction in progression of graft disease.

The findings of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study also suggested that acute LDL-C lowering within 96 hours of an episode of unstable angina could reduce death and nonfatal ischemic events. Just as remarkably, there was a 50% reduction in stroke rates due to early and aggressive lipid-lowering therapy. The MIRACL study, however, only followed up a small number of patients with acute coronary syndrome for 16 weeks; therefore, application of these findings is limited.

More robust support for aggressive and empiric lipid-lowering therapy was provided by the Heart Protection Study (HPS), which reported the results of lipid-lowering therapy in 20,536 adults with CHD, other occlusive arterial disease, or diabetes who were followed up for approximately 5 years. In this study, a continuous 20% reduction in risk of CHD was seen in patients who had a baseline LDL-C level of 116 mg/dL and was similar to that seen in patients who had a baseline LDL-C level of 154 mg/dL. This seems to indicate that if there is a lower threshold at which point risk reduction ceases to exist (eg, <80 mg/dL), it is a much lower value than is typically seen in Western populations.

Three recently published studies reported positive results associated with even greater and more aggressive lipid-lowering therapy. Although not a true outcomes trial, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial revealed that for patients with CHD, intensive lipid-lowering treatment reduced progression of coronary atherosclerosis compared with moderate therapy.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial was designed to compare LDL-C lowering to less than 100 mg/dL (as recommended by the current NCEP guidelines), with even more aggressive lowering of LDL-C to approximately 62 mg/dL. The primary endpoint (composite of all-cause mortality, myocardial infarction, documented unstable angina requiring hospitalization, revascularization, and stroke) was reduced by 16% with more aggressive therapy. The benefits of this lipid-lowering strategy were seen in as early as 30 days.

The Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE) trial added to the positive results seen in the other studies by assessing whether aggressive LDL-C lowering compared with usual care in patients with CHD would reduce cardiovascular complications. Usual care could include diet, behavior modification, or antihyperlipidemic medication alone or in combination. In this study, 2442 patients were randomly assigned to receive 3-hydroxy-3-methylglutaryl...
coenzyme A reductase inhibitor (statin) therapy to achieve either an LDL-C level of less than 80 mg/dL or therapy sufficient to obtain the LDL-C goal as recommended by the current NCEP guidelines. Reduction of LDL-C levels to less than 80 mg/dL elicited a 17% reduction in the primary endpoint (composite of cardiac death, myocardial infarction, stroke, and hospitalization) and a 47% reduction in risk of nonfatal myocardial infarction compared with patients in the usual care group.

Combination therapy also is assuming a more prominent clinical role for lipid lowering. The benefit of the coadministration of a statin and the cholesterol absorption inhibitor ezetimibe was studied in the Ezetimibe Add-On Statin for Effectiveness (EASE) trial. In this trial, 10 mg of ezetimibe was added to ongoing statin therapy. The group receiving the coadministration of ezetimibe and a statin had a 25% reduction in LDL-C levels compared with a 2% reduction for statin alone. Additionally, more than 75% of patients receiving ezetimibe and a statin achieved their LDL-C target level compared with 20% of patients on statin therapy alone.

Coadministration of niacin and a statin also has been proved to significantly reduce cardiac event rates. Fibrates may be cautiously added to statin therapy, but extreme vigilance for rhabdomyolysis is warranted.

The clinical findings reviewed here suggest that the optimal LDL-C level may be well below the current NCEP target levels. In fact, the NCEP recently published an update to the ATP III in which LDL-C lowering to less than 70 mg/dL is suggested as a therapeutic option for patients at very high risk. Currently, several prospective randomized trials are under way to assess the degree of LDL-C reduction required to realize the greatest reduction in risk of CHD. Patients enrolled in the Treating to New Targets (TNT) trial will undergo LDL-C–reducing therapy to 75 mg/dL or lower for 5 years to assess the impact of aggressive LDL-C–lowering therapy on risk of CHD.

Two other larger studies, the Incremental Decrease in Endpoints through Aggressive Lipid Lowering (IDEAL) and the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), also are designed to compare the effect of conventional and aggressive statin dosing on risk of CHD in patients with varying baseline LDL-C concentrations. The data from these studies have the potential to lower the LDL-C target goals. Consequently, new therapeutic strategies such as the coadministration of two or more agents with complementary mechanisms of action may be required to achieve the optimal LDL-C level.

Achieving Target Lipid Levels in Clinical Practice

Despite the known benefits of reducing LDL-C levels, clinicians and healthcare systems often do not identify and appropriately treat many patients who require lipid-modification therapy. Even with the availability and widespread use of pharmacologic agents, patients are frequently unable to achieve target lipid levels and gain the clinical and economic benefits of reduction of risk of CHD observed in clinical trials. The National Health and Nutrition Examination Survey III found that only 65% of individuals eligible for cholesterol-lowering therapy actually received treatment, and of those patients who received therapy, few had achieved the goals established in the NCEP guidelines. Furthermore, only 25% of patients receiving lipid-lowering medication had reached the LDL-C target levels established by the NCEP.

To optimize the effectiveness of therapeutic guidelines for primary and secondary prevention, ATP III recommends the use of multidisciplinary methods targeting patients, clinicians, and healthcare systems. The Figure provides patient-oriented recommendations, and include the following:

- Providing simplified medication regimens and explicit instructions of how and when medications should be taken,
- Using prompts,
- Encouraging involvement of family members,
- Reinforcing and rewarding persistent adherence, and
- Maintaining regular contact.

Although direct-to-consumer advertising has been loudly criticized, it appears that in the case of cholesterol awareness, these advertisements have prompted patients to become partners.
in their own care and, in many instances have motivated patients to ask their physicians about life-saving medications. As a clinician, it is easier to address this issue with a patient whose curiosity already has been piqued by such advertising.

The ATP III recommendations targeted toward physicians include educating them about current guidelines, using chart audits and patient outcomes data to provide feedback on the clinical impact of therapy, encouraging the use of simplified treatment regimens, and concentrating on difficult-to-treat patients. For healthcare systems, the ATP III recommends development of protocols that initiate lipid interventions before discharge of patients hospitalized for coronary events, formation of multidisciplinary lipid-management clinics, frequent contact with patients via telephone or electronic means, and collaboration with community pharmacists to encourage patient adherence.

The following case presentations illustrate the decision-making process in the development of a lipid-lowering treatment strategy for patients typically seen in primary care practice.

**Illustrative Case Presentations**

**Case 1**

A 68-year-old woman arrives in the emergency department with chest pain. The findings on an electrocardiogram are consistent with ischemia. She still has pain despite intravenous administration of nitroglycerine. She is taken to the cardiac catheterization laboratory, and she is found to have a 90% stenosis of the left circumflex artery. She undergoes a successful angioplasty. The remainder of her coronary arteries have minimal disease. She is discharged within 48 hours, at which time her lipid profile ordered in the emergency department is still not available.

The decision to be made postdischarge for this patient is when to initiate statin therapy.

This case illustrates the appropriate timing of initiation of lipid-lowering therapy. Currently, several trials, including PROVE-IT and MIRACL, suggest that early and aggressive initiation of statin therapy can reduce recurrent ischemia as early as 30 days. Additionally, improvement of endothelial function is evident within the first month of statin use. Finally, long-term compliance is much better when secondary prevention strategies such as statin, aspirin, and β-blocker therapy are initiated during the hospital stay. Initiation during the hospital stay reduces the likelihood that physicians caring for patients with coronary disease will overlook these medications and ensures that patients understand that these medications are inexorably linked to reducing the risk of another ischemic event.

A study examining compliance with secondary prevention strategies initiated at hospital discharge found not only tremendous increase in the number of patients on lipid-lowering therapy with these medications at 1 year postdischarge, but also saw a 50% reduction in recurrent ischemic events among patients who started therapy at the time of their hospitalization. Two years after the Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) was implemented, aspirin use increased from 68% to 92%; β-blocker use, from 12% to 62%; angiotensin-converting enzyme use, from 6% to 58%; and statin use, from 6% to 86%. Additionally, the number of patients with an LDL-C level of less than 100 mg/dL increased from 6% to 86%. These findings have led to the recommendation from the American College of Cardiology and the American Heart Association that all patients be discharged from a hospitalization for an acute ischemic event on statin therapy unless contraindicated.

**Case 2**

A 59-year-old man had an angioplasty of the right coronary artery and is seen 6 weeks later by his family physician. His lipid profile on atorvastatin calcium (10 mg/d) therapy reveals an LDL-C level of 103 mg/dL. He always worries about “side effects,” though he is tolerating this medication well.

His family physician needs to assess whether this patient can be considered to be at his LDL-C target level for the time being, as well as consider other treatment options that may help him achieve his LDL-C target level.

This case is illustrative of implementation of the new guidelines as set forth by the updated ATP III guidelines for patients at high risk for CHD which were released in 2004, as well as the need to sometimes use coadministration therapy to achieve these aggressive goals. Two years ago, an LDL-C level of 103 mg/dL in a patient with coronary artery disease may have been acceptable, but now with the newer guidelines, an LDL-C level of closer to 70 mg/dL would be optimal. If one were to simply increased the dose of atorvastatin calcium to 20 mg/d or 40 mg/d, one could expect the LDL-C level to decrease to 90 mg/dL. At this point, coadministration therapy with ezetimibe could be considered for greater LDL-C reduction and for achieving the LDL-C goals shown in the EASE trial. Most patients with coronary artery disease will require coadministration therapy to reduce their LDL-C level to the newly recommended ultralow levels with concomitant reduction in secondary ischemic events.

**Comment**

Clinical trial data clearly indicate that reduction of LDL-C levels is an effective means to decrease the risk of CHD. The ATP III treatment guidelines recommend that patients with a history of CHD, multiple risk factors, or CHD equivalents be targeted for the most aggressive therapy. To optimize the risk-reduction benefits of lipid-lowering therapy, physicians must work with their patients and the healthcare system to implement treatment guidelines and maximize patient adherence to appropriate therapy.

**References**


