Rationale for Aggressive Lipid Lowering in High-Risk Patients

Jerome D. Cohen, MD

According to current guidelines from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the target low-density lipoprotein cholesterol (LDL-C) level for patients with established coronary heart disease (CHD) or CHD risk equivalents is less than 100 mg/dL, with an optional target of less than 70 mg/dL. More recent data suggest, however, that the physiologically normal level of LDL-C and the level at which atherogenesis is initiated is much lower. Overall, the data convincingly demonstrate that LDL-C lowering is associated with a significant reduction in CHD events, regardless of preexisting CHD. The NCEP ATP III treatment guidelines, published in 2002 and updated in 2004, do not reflect more recent findings on intensive lipid-lowering therapy, which are likely be addressed in the NCEP ATP IV guidelines, scheduled to be released in 2011. Drug options for LDL-C lowering include statins (the drug of choice), bile acid sequestrants, nicotinic acid, fibrates, and selective cholesterol absorption inhibitors.

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Current guidelines from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) state that the target low-density lipoprotein cholesterol (LDL-C) level for patients with established coronary heart disease (CHD) or CHD risk equivalents (eg, diabetes, peripheral or cerebral vascular disease, Framingham 10-year CHD risk >20%) is less than 100 mg/dL, with a target of less than 70 mg/dL considered an option. However, data now suggest that the physiologically normal level of LDL-C and the level at which atherogenesis is initiated is much lower.

Although the average total cholesterol level in US adults is 200 mg/dL, mean values in individuals from hunter-gatherer societies and in wild primates range from 70 to 140 mg/dL. These hunter-gatherer populations show no evidence of atherosclerosis. Thus, it has been estimated that LDL-C levels of 50 to 70 mg/dL are physiologically normal and the levels for which humans are genetically adapted. This notion is supported by data from the MRFIT (Multiple Risk Factor Intervention Trial) study, involving more than 360,000 men in the United States who were followed longitudinally for morbidity and mortality. As illustrated in Figure 1, the relationship between total serum cholesterol levels and the 10-year risk of death due to CHD in this population was strong, continuous, and graded over the entire range of total cholesterol concentrations. Thus, current target goals for LDL-C may lead to substantial undertreatment of patients at risk for CHD events.

Aggressive Lowering of LDL-C Levels

Data from the Heart Protection Study conducted in the United Kingdom support the value of LDL-C lowering even in patients with relatively low LDL-C values at baseline. This study included 20,536 participants aged 40 to 80 years.
with an increased 5-year risk of CHD death due to prior disease (eg, myocardial infarction or other CHD, occlusive disease of noncoronary arteries, type 1 or type 2 diabetes, treated hypertension). Notably, the total cholesterol threshold level for entry into the study was 135 mg/dL or above, meaning that a large number of patients with “normal” cholesterol levels were allowed entry. The results indicated that vascular events (eg, total CHD, total stroke, revascularization) were reduced by 24% in patients receiving simvastatin compared with those receiving placebo (P <.0001). Importantly, the relative risk reduction was similar across groups when results were stratified by baseline LDL-C values. The Heart Protection Study 5 was one of the first to demonstrate that treatment of LDL-C levels considered “normal” is associated with clinical benefit.

Cannon and colleagues 6 conducted a meta-analysis of trials comparing intensive (high-dose) and moderate (standard-dose) statin therapy in patients with CHD or acute coronary syndromes. 6 The analysis included data from 4 trials comparing more vs less aggressive cholesterol lowering: PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22), TNT (Treating to New Targets), A-to-Z (Aggrastat to Zocor), and IDEAL (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering). A total of 27,548 patients were enrolled.

Patients were randomly assigned to receive standard-dose or high-dose statin. The following regimens were used in these studies 6:

- PROVE IT-TIMI 22: pravastatin (40 mg) vs atorvastatin (80 mg)
- TNT: atorvastatin (10 mg vs 80 mg)
- A-to-Z: placebo followed by simvastatin (20 mg) vs simvastatin alone (40 mg increased to 80 mg)
- IDEAL trial: simvastatin (20 mg titrated to 40 mg) vs atorvastatin (80 mg)

More aggressive therapy was associated with a statistically significant greater reduction in LDL-C levels and an improvement in clinical outcomes compared with less aggressive therapy. Mean LDL-C concentrations during treatment ranged from 97 to 104 mg/dL in the standard therapy arms and from 65 to 81 mg/dL in the intensive therapy groups. Overall, in the pooled analysis, mean LDL-C concentrations decreased from 130 mg/dL at baseline to a mean of 101 mg/dL in the standard-dose group and 75 mg/dL in the intensive therapy group. Overall, intensive treatment with statins was associated with a 16% reduction in these clinical events (P = .00003). Similarly, the pooled analysis found a 16% reduction in coronary death or any cardiovascular event among those receiving high-dose rather than standard-dose statin therapy. 7

Another analysis of the PROVE IT-TIMI study evaluated the relationship between achieved LDL-C concentrations and clinical events among patients in the intensive therapy arm. 7 Patients were stratified into subgroups by the LDL-C concentration achieved at 4 months: >80 to 100 mg/dL, >60 to 80 mg/dL, >40 to 60 mg/dL, or ≤40 mg/dL. 7 The results indicated that there was a relationship between the achieved LDL-C levels and the rates of the primary composite end point, which included instances of any of the following outcomes: death, myocardial infarction, stroke, revascularization, and unstable angina requiring hospital admission. 7 The rates of the primary composite end point were 26.1%, 22.2%, 20.4%, and 20.4%, respectively, in the 4 LDL-C categories, showing that lower LDL-C levels were associated with progressively lower risk. 7 A multivariable analysis found that the 2 groups with the lowest LDL-C levels had significantly lower end point rates than the >80 to 100 mg/dL group (the referent group against which hazard ratios were calculated) (Figure 2). Patients in the >40 to 60 mg/dL group achieved 33% risk reduction, compared with 39% in the ≤40 mg/dL group. 7

Data from the TNT trial also support intensive lipid-lowering therapy. 8 Overall, these data suggest that further clinical benefit is achieved by lowering LDL-C concentrations to very low levels. 8 The study included patients with established CHD who had mean LDL-C levels less than 130 mg/dL after an 8-week open-label run-in period during which they were treated with atorvastatin at 10 mg/dL. 8 During this period, LDL-C levels were reduced to a mean of 98 mg/dL. At the completion of this phase, patients were randomized to continue atorvastatin at 10 mg/dL or to receive aggressive therapy (atorvastatin, 80 mg/dL). 8 Results indicated that aggressive therapy was...
associated with significantly lower LDL-C concentrations than standard therapy (77 vs 101 mg/dL). Aggressive therapy was also associated with a 22% reduction in the composite clinical outcome of death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke (P < .001).8

Overall, the results of these studies demonstrate that there is a relationship between reduced LDL-C levels and reduced CHD risk in the secondary prevention setting (ie, in patients with preexisting CHD). Figure 3 summarizes the relationship between LDL-C levels during statin therapy and clinical event rates in secondary prevention trials. Notably, the relationship is relatively linear and extends down to LDL-C concentrations substantially below 100 mg/dL.8

Although aggressive lowering of LDL-C levels appears to reduce CHD risk, the safety of this approach needs to be considered. In the TNT trial, significantly more patients receiving intensive therapy (atorvastatin, 80 mg/day) experienced treatment-related adverse events (8.1% vs 5.8%; P < .001) or discontinued therapy because of treatment-related adverse events (7.2% vs 5.3%; P < .001), compared with those in the standard therapy group (atorvastatin, 10 mg/d).8 There was also a small but significant increase in the rate of persistently elevated liver transaminase levels in the intensive therapy vs the standard therapy group (1.2% vs 0.2%; P < .001). However, there were no statistically significant differences between treatment groups in the rates of myalgia (4.8% vs 4.7%; P = .72) or any indication that intensive therapy was associated with an increase in persistently elevated creatinine kinase levels or with the development of rhabdomyolysis.8

In the PROVE IT-TIMI trial, there was no apparent relationship between the LDL-C level achieved and the development of adverse events. These events included muscle side effects (eg, myalgia, myositis, elevated creatinine kinase levels), elevated liver enzyme levels, other adverse events (eg, hemorrhagic stroke, retinal events, suicide or death due to trauma), or treatment discontinuation related to adverse events.7 Overall, the benefit-risk ratio of more vs less aggressive lipid-lowering therapy is favorable for secondary prevention.

### Primary Prevention

Data from the primary care setting (ie, patients with no preexisting CHD) also indicate that there is a continuous and positive relationship between LDL-C concentrations and the risk of CHD events (Table 1); these studies include WOSCOPS (West of Scotland Coronary Prevention Study), AFCAPS (Air Force Coronary Atherosclerosis Prevention Study), and ASCOT (Anglo-Scandinavian Cardiac Outcome Trial).2 For example, the lipid-lowering arm of the therapy group (atorvastatin, 10 mg/d).8

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**Figure 2.** Coronary heart disease event rate by achieved low-density lipoprotein cholesterol (LDL-C) levels from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22) study.6

**Figure 3.** Relationship between low-density lipoprotein cholesterol (LDL-C) levels and coronary heart disease (CHD) events in patients with existing CHD (ie, secondary prevention). Reprinted with permission from LaRosa et al.8 Abbreviations: 4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events Trial; HPS, Heart Protection Study; LIPID, Long-Term Intervention With Pravastatin in Ischaemic Disease; TNT, Treating to New Targets trial.

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ASCOT study included 10,305 patients aged 40 to 79 years who had hypertension and at least 3 other risk factors for cardiovascular disease but were not considered hyperlipidemic by standard guidelines (ie, total cholesterol <251 mg/dL)\(^9\). Patients were randomly assigned to receive atorvastatin 10 mg (n=5168) or placebo (n=5137), and the primary end point was nonfatal myocardial infarction or fatal CHD. The trial was stopped early after 3.3 years (instead of continuing to the planned 5-year duration) because significantly fewer primary events had occurred in the atorvastatin group (n=154) than in the placebo group (n=200).\(^9\) Rates for the primary end point were 1.9% and 3.0%, respectively, for the atorvastatin and placebo groups, amounting to a 36% risk reduction for atorvastatin-treated patients (P=.0005).\(^9\)

Significant reductions in risk were also achieved for individual components of the primary end point, including fatal or nonfatal stroke (27%; P=.024), total cardiovascular events (21%; P=.0005), and total coronary events (29%; P=.0005). There were fewer deaths in the atorvastatin group than in the placebo group (185 vs 212 deaths), although the difference was not statistically significant.\(^9\)

Notably, the reduction in clinical events was evident early in the study, and the difference between groups continued to widen over time. Given that the trial was discontinued early, the long-term benefits of lipid-lowering therapy may be even greater than the early results indicate.

The most recent study evaluating statin therapy in the primary prevention setting was JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin),\(^10\) which included 17,802 healthy men and women with LDL-C levels less than 130 mg/dL and high-sensitivity C-reactive protein (CRP) levels of at least 2.0 mg/L. Participants were randomly assigned to receive either rosuvastatin (20 mg/d) or placebo, with a primary end point of a first major cardiovascular event (ie, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed death from cardiovascular causes).\(^10\) The trial was stopped after 1.9 years because of a statistically significant benefit in favor of rosuvastatin-treated patients.

Patients receiving rosuvastatin experienced a 50% reduction in LDL-C concentrations (median at 12 months, 55 mg/dL) and a 37% reduction in high-sensitivity CRP levels (median at 12 months, 2.2 mg/L).\(^10\) The rates for the primary end point in the rosuvastatin and placebo groups were 0.77 and 1.36 per 100 person-years of follow-up, respectively, a 44% risk reduction for rosuvastatin-treated individuals.\(^10\)

Rosuvastatin was also associated with significant reductions in the individual components of the primary end point, including fatal or nonfatal myocardial infarction (54%), fatal or nonfatal stroke (48%), arterial revascularization or unstable angina (47%), and nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (47%).\(^10\) Other adverse events, such as myopathy, hepatic injury, and cancer, did not occur more frequently in the rosuvastatin group, even though LDL-C concentrations were less than 55 mg/dL in half of patients and less than 44 mg/dL in 25%. As with secondary prevention, the benefit-risk ratio for primary prevention is also very favorable.

In addition to these trials, the benefit of lipid-lowering for reducing clinical events has also been demonstrated in nonpharmacologic intervention studies. For example, the POSCH (Program on the Surgical Control of the Hyperlipidemias) trial compared diet plus partial ileal bypass with diet alone in adults with a prior myocardial infarction and a plasma cholesterol level of at least 220 mg/dL.\(^11\) At 5 years, ileal bypass was associated with a number of clinical benefits, including reductions in overall mortality, mortality from atherosclerotic CHD, and confirmed or suspected myocardial infarction and unstable angina.\(^11\) Regression analysis demonstrated a linear relationship between LDL-C levels and clinical end points.\(^12\)

Overall, the results of these studies convincingly demonstrate that LDL-C lowering is associated with a significant reduction in CHD events, both in patients with and patients without pre-existing CHD. Although the absolute benefit is greater in patients with CHD (because they have a higher baseline risk), the benefit is also clearly evident in otherwise healthy individuals. Indeed, there are few therapeutic areas in which the proof of clinical benefit has been demonstrated as clearly and convincingly as in lipid-lowering therapy.

**Treatment Recommendations**

Current NCEP ATP III treatment guidelines were published in 2002 (with an update in 2004)\(^1\) and therefore do not reflect the more recent findings demonstrating the benefit of intensive lipid-lowering therapy. The studies discussed in the present report and others will most likely be addressed in the ATP IV guidelines, scheduled to be released in 2011. Experts have speculated that ATP IV will address several issues, such as lowering goals for LDL-C in primary and secondary prevention, the routine use of CRP levels in risk stratification, the use of other secondary targets (eg, high-density lipoprotein cholesterol [HDL-C], non-HDL-C, apolipoprotein B, and LDL particle concentrations), and the use of lifetime risk instead of 10-year risk estimates.

The current recommendations are summarized in Table 2. For high-risk patients (ie, those with CHD or CHD

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**Table 1. Relationship Between Low-Density Lipoprotein Cholesterol (LDL-C) Levels and Coronary Heart Disease (CHD) Events in the Primary Care Setting**

<table>
<thead>
<tr>
<th>Study</th>
<th>CHD Events, %</th>
<th>LDL-C mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>3.8</td>
<td>120</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>5.9</td>
<td>135</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT</td>
<td>3.5</td>
<td>124</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>5.8</td>
<td>153</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>8.2</td>
<td>195</td>
</tr>
</tbody>
</table>

**Abbreviations:** AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; ASCOT, Anglo-Scandinavian Cardiac Outcome Trial; WOSCOPS, West of Scotland Coronary Prevention Study.
Table 2. NCEP ATP III Goals and Initiation Levels for Therapeutic Lifestyle Changes (TLC) and Drug Therapy by Risk Category\textsuperscript{13}

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C, mg/dL</th>
<th>Initiation Level for TLC</th>
<th>Initiation Level for Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD or CHD risk equivalents (10-year risk, &gt;20%)</td>
<td>&lt;100 (optional: &lt;70)</td>
<td>≥100</td>
<td>≥100 (&lt;100: consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: ≥2 risk factors (10-year risk, 10%-20%)</td>
<td>&lt;130 (optional: 100)</td>
<td>NA</td>
<td>≥130 (100-129: consider drug options)</td>
</tr>
<tr>
<td>Moderate risk: ≥2 risk factors (10-year risk, &lt;10%)</td>
<td>&lt;130</td>
<td>NA</td>
<td>≥160</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt;160</td>
<td>NA</td>
<td>≥190 (160-189: drug therapy optional)</td>
</tr>
</tbody>
</table>

Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III.

Risk equivalents), the recommended LDL-C goal is less than 100 mg/dL. An LDL-C goal of less than 70 mg/dL is a therapeutic option for these patients and should be encouraged, particularly in patients at very high risk. If the LDL-C level is 100 mg/dL or greater in high-risk patients, a lipid-lowering drug should be administered in conjunction with therapeutic lifestyle changes (TLC).\textsuperscript{13}

For moderately high-risk patients (ie, those with ≥2 risk factors), the LDL-C goal is less than 130 mg/dL, with an optional target of 100 mg/dL. When the LDL-C level in these patients is between 100 and 129 mg/dL at baseline or with TLC, an LDL-C-lowering agent designed to lower concentrations to less than 100 mg/dL is a therapeutic option.\textsuperscript{13}

More recent guidelines from the American Heart Association and American College of Cardiology (AHA/ACC), published in 2006, recommend an LDL-C goal of less than 100 mg/dL for all patients with CHD.\textsuperscript{14} These guidelines further state that an LDL-C level of less than 70 mg/dL is a reasonable goal for all patients with CHD.

The NCEP ATP III guidelines recommend intensive LDL-C lowering with TLC in all patients who have elevated levels. For patients with CHD or CHD risk equivalents, a cholesterol-lowering drug should be added to TLC in all patients with LDL-C levels of 100 mg/dL or higher and is an option for those LDL-C levels in the range of 70 to 99 mg/dL.\textsuperscript{1}

Patients without CHD but with multiple risk factors and a 10-year risk of more than 20% should be treated similarly. Based on their demonstrated ability to reduce LDL-C levels and improve clinical outcomes, statins are generally considered the drug of first choice.\textsuperscript{1} The relative degrees of LDL-C-lowering potential for different statins are summarized in Figure 4.\textsuperscript{15}

If LDL-C goals are not achieved within 6 weeks with initial drug therapy, treatment should be intensified, either by increasing the statin dose or by adding another lipid-lowering agent.\textsuperscript{1} The major classes of drugs in addition to statins include bile acid sequestrants, nicotinic acid, fibrates, and selective cholesterol absorption inhibitors, with each having advantages and therapeutic niches.\textsuperscript{1} Bile acid sequestrants have additive lipid-lowering effects relative to statins and lack systemic toxicity because they are not absorbed. Nicotinic acid is effective for reducing LDL-C and triglyceride levels, and for raising HDL-C levels, but its long-term use can be limited by adverse events, particularly flushing.\textsuperscript{1}

Fibrates are generally used for lowering elevated levels of triglycerides, because their potential to lower LDL-C levels is modest.\textsuperscript{1} Selective cholesterol absorption inhibitors have shown moderate reductions (<20%) in LDL-C levels when used as monotherapy and may be used in combination with statins (enabling statin doses to be reduced) or in place of them in statin-intolerant patients.\textsuperscript{1}

**Conclusion**

There are now convincing data that aggressive lipid lowering is effective for reducing the risk of CHD events and overall mortality in various populations. The benefit is greatest in patients at high risk (ie, those with CHD or CHD risk equivalents) but has also been demonstrated in otherwise healthy individuals. Evidence indicates that there is a linear relationship between lipid levels and the

<table>
<thead>
<tr>
<th>Statin, mg</th>
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<tbody>
<tr>
<td>Pravastatin</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>10</td>
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<td>10</td>
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Figure 4. Low-density lipoprotein (LDL) cholesterol lowering potential of various statins at different doses.\textsuperscript{15}
risk of CHD events, suggesting that LDL-C concentrations below 70 mg/dL are optimal. New NCEP ATP guidelines, to be published in 2011, are likely to reflect this more aggressive approach. Fortunately, a variety of therapeutic options are allowing a greater proportion of patients to achieve their LDL-C treatment goals.

References

JAOA Peer Reviewer Seminar
On Tuesday, November 1, 2011, JAOA—The Journal of the American Osteopathic Association will host a peer reviewer seminar during the American Osteopathic Association’s 116th Annual Osteopathic Medical Conference and Exposition in Orlando, Florida. Osteopathic physicians, researchers, and others interested in best practices in peer review are invited to attend this event, which will be held from 1:15 PM to 3:15 PM. The room will be announced at a later date. Contact JAOA staff at jaoa@osteopathic.org for more information.