Treating dyslipidemia in the high-risk patient

How low should LDL levels be pushed and how important are other lipoproteins in our efforts to reduce CV risk? Here's an update.

Dyslipidemia is a primary contributor to coronary heart disease (CHD), the No. 1 cause of death in the United States.\(^1,2\) Mortality rates from CHD have declined sharply over the last 3 decades as a result of improvements in acute care and in secondary prevention, notably by means of lipid-lowering statin therapy.\(^1,4\) Studies confirm that the decline in cardiovascular events is largely due to decreases in low-density lipoprotein (LDL)-cholesterol and other atherogenic particles.\(^2,5\) Still, despite these gains, CHD continues to be a major threat, and the search to find ways to lower CHD risk further continues. Additional avenues being explored include reducing triglycerides and raising high-density lipoprotein (HDL)-cholesterol through lifestyle intervention and other means in patients with mixed dyslipidemia whose statin therapy is already optimal.\(^2\) This article reviews the LDL-cholesterol lowering “standard of care” and discusses the potential of addressing other lipoproteins to reduce the residual cardiovascular risk that frequently remains.

Lower LDL levels remain the primary target

The National Cholesterol Education Program (NCEP) has focused on reduction of serum levels of LDL-cholesterol for the primary and secondary prevention of CHD. This approach is biologically reasonable, because LDL is the major atherogenic lipoprotein and is directly implicated in the development of atherosclerosis. Further, the benefit of LDL lowering has been validated by the results of many randomized clinical trials using a combination of lifestyle changes and statins.\(^2\)

Data on 90,000 patients confirm efficacy of lowering LDL

In an important meta-analysis, the Cholesterol Treatment Trialists’ (CTT) Collaborators compiled data from more than...
90,000 people in 14 large-scale, randomized statin trials that included high-risk populations. The investigators found that each 39-mg/dL (1-mmol/L) reduction in LDL-cholesterol sustained over 5 years reduced the incidence of a first major coronary event by 23% and the incidence of CHD death by 19%. In the high-risk subgroup with preexisting CHD, a 39-mg/dL (1-mmol/L) reduction in LDL-cholesterol prevented 14 deaths per 1000 participants. These benefits were significant even in the first year of treatment ($P < .0001$) and were greater in subsequent years. The nearly linear relationship between lower LDL-cholesterol levels and fewer major vascular events held true regardless of baseline LDL-cholesterol levels, even when the baseline levels were <100 mg/dL.

The greatest absolute benefit was noted in the high-risk and very-high-risk groups, especially in individuals with diabetes and those older than 75 years. Moreover, long-term follow-up comparing the original statin-treated participants with the original placebo group showed that lowering LDL-cholesterol continued to reduce cardiovascular risk for 10 years after the study ended.

Optimal LDL levels may be even lower than we thought
Observational studies have suggested that the relationship between cholesterol and CHD mortality has no apparent lower threshold, and that the physiologic norm for LDL-cholesterol may be lower than that typically seen in Western countries. For example, in a study done in the 1970s in an urban Chinese population of more than 9000 middle-aged men and women, the mean baseline total cholesterol level was 162 mg/dL, and only 7% of deaths were attributed to CHD in 13 years of follow-up. Nevertheless, there was an independent and strongly positive ($P < .001$) relationship between total cholesterol and risk of CHD death, starting at a level as low as 147 mg/dL, which may be equivalent to an LDL-cholesterol of 100 mg/dL. Some data indicate the physiologic norm for LDL-cholesterol levels may be in the range of 50 to 70 mg/dL, which is much lower than the US average of approximately 130 mg/dL.

Lower LDL-cholesterol protects against atherosclerosis
Lifetime exposure to a lower LDL-cholesterol level may be responsible for a lower burden of atherosclerotic disease later in life. Analyses of data from major statin clinical trials indicate that atherosclerosis does not progress when LDL-cholesterol levels are maintained at <67 mg/dL, while other data suggest that CHD event rates could be minimized at LDL-cholesterol levels of 57 mg/dL for primary prevention and 30 mg/dL for secondary prevention.

Intensive regimens yield better outcomes
Controlled clinical trials have compared more intensive and less intensive statin and lifestyle modification regimens in high-risk subjects, most of whom already had CHD. These trials found that lower LDL-cholesterol values achieved by more intensive regimens produced incremental CHD benefits. Major findings of these trials are summarized in Table 1.

Treating to New Targets (TNT)
After an 8-week run-in period with atorvastatin 10 mg/d, the TNT researchers randomized 10,000 patients with stable CHD and mean baseline LDL-cholesterol levels of 98 mg/dL to atorvastatin 80 mg/d or continued with atorvastatin 10 mg/d. Patients in the high-dose group achieved a mean LDL-cholesterol level of 77 mg/dL, which was associated with a 22% relative reduction in risk of a major cardiovascular event ($P < .001$) and significant reductions in stroke (25%) and cerebrovascular events (23%).

PROVE IT
The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial enrolled 4162 patients who had been hospitalized for acute coronary syndrome within the previous 10 days. Patients were randomly assigned to intensive (atorvastatin 80 mg/d) or moderate (pravastatin 40 mg/d) therapy for 24 months—in addition to therapeutic lifestyle interventions. Median LDL-cholesterol levels fell from 106 mg/dL at baseline to 62 mg/dL in the intensive-therapy group and to 95 mg/dL in
At 2 years, the primary end point—a composite of cardiovascular events—was 16% lower \((P=.005)\) in patients on intensive therapy than in patients on moderate therapy, with the greatest apparent benefit in those with baseline LDL-cholesterol levels of at least 125 mg/dL.\(^{12}\) Favorable outcomes were more closely related to the on-treatment levels of LDL-cholesterol and C-reactive protein than to the specific agent used.\(^{18}\)

Taken together, the TNT and PROVE IT trials show that in high-risk patients with

### Table 1

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Daily statin treatment; patient population</th>
<th>Mean baseline LDL-C level</th>
<th>Mean achieved LDL-C level,(^*) % reduction</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial (ALLHAT-LLT)</strong>(^{15})</td>
<td>Pravastatin 40 mg vs usual care; ≥55 y, moderately hypertensive and hypercholesterolemic</td>
<td>146 mg/dL</td>
<td>104 mg/dL, 29% (pravastatin); 121 mg/dL, 17% (usual care)</td>
<td>CHD event rates not significantly reduced, except in blacks (27%, (P=.03))</td>
</tr>
<tr>
<td><strong>Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA)</strong>(^{14})</td>
<td>Atorvastatin 10 mg vs placebo; hypertensive, multiple risk factors</td>
<td>132 mg/dL</td>
<td>90 mg/dL, 32% (atorvastatin); 126 mg/dL (placebo)</td>
<td>Atorvastatin 10 mg added to an antihypertensive regimen reduced major CV events by 36% ((P=.0005))</td>
</tr>
<tr>
<td><strong>Heart Protection Study (HPS)</strong>(^{13})</td>
<td>Simvastatin 40 mg vs placebo; high-risk coronary or other occlusive arterial disease, or diabetes</td>
<td>132 mg/dL</td>
<td>89 mg/dL, 33% (simvastatin); 128 mg/dL (placebo)</td>
<td>Significant 18% decrease in coronary deaths, even in individuals with baseline LDL-C &lt;116 mg/dL</td>
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<tr>
<td><strong>Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL)</strong>(^{11})</td>
<td>Atorvastatin 80 mg vs simvastatin 20 mg; history of MI</td>
<td>122 mg/dL</td>
<td>80 mg/dL, 34% (atorvastatin); 100 mg/dL, 17% (simvastatin)</td>
<td>Nonsignificant reduction in primary outcome, but significant reductions in selected secondary outcomes: 13% ((P&lt;.02)) for major CV events, 16% ((P&lt;.001)) for any CHD event, 16% ((P&lt;.001)) for any CV event</td>
</tr>
<tr>
<td><strong>Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)</strong>(^{16})</td>
<td>Pravastatin 40 mg vs placebo; 70-82 y with CVD or at high risk</td>
<td>147 mg/dL</td>
<td>97 mg/dL, 34% (pravastatin)</td>
<td>15% ((P=.014)) reduction in composite incidence of coronary death, nonfatal MI, and stroke vs placebo</td>
</tr>
<tr>
<td><strong>Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT—TIMI 22)</strong>(^{12})</td>
<td>Atorvastatin 80 mg vs pravastatin 40 mg; hospitalized for ACS</td>
<td>106 mg/dL</td>
<td>62 mg/dL, 42% (atorvastatin, 80 mg); 95 mg/dL, 10% (pravastatin, 40 mg)</td>
<td>Intensive therapy reduced risk of death and major CV events early in treatment vs standard therapy</td>
</tr>
<tr>
<td><strong>Treating to New Targets (TNT)</strong>(^{10})</td>
<td>Atorvastatin 80 mg vs atorvastatin 10 mg; stable CHD</td>
<td>98 mg/dL</td>
<td>77 mg/dL, 21% (80 mg); 101 mg/dL, (10 mg)</td>
<td>Intensive therapy reduced rate of major CV events by 22% vs moderate therapy</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndromes; CHD, coronary heart disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

\(^*\)PROVE IT values reflect the median.
CHD, achieving LDL-cholesterol levels of 60 to 80 mg/dL results in better outcomes than regimens that achieve LDL-cholesterol levels of approximately 100 mg/dL.

Moving the goal posts
The 2002 NCEP Adult Treatment Panel III (ATP III) guidelines recommend LDL-cholesterol goals depending on the patient’s level of risk, with <100 mg/dL as the goal for those in the highest risk category. Statin-treated patients in the Heart Protection Study (HPS) achieved a mean LDL-cholesterol level of 89 mg/dL, and investigators reported a “highly significant” 18% reduction in coronary deaths (P=.0005), even in individuals who entered the study with baseline LDL-cholesterol level of <116 mg/dL. No indication of a threshold effect was found. For that reason, the HPS investigators suggested that reducing LDL-cholesterol still further with dietary and statin therapy might produce even greater reductions in cardiovascular events.

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The 2004 update of the NCEP guidelines took into account the findings of the HPS and several other statin trials—most of them secondary prevention studies—that provided further evidence for the benefit of lowering LDL-cholesterol to levels well below 100 mg/dL. The mean achieved LDL-cholesterol levels in these trials and the impact on CHD events are summarized in Table 1. The more intensive vs less intensive LDL-cholesterol lowering trials discussed earlier provided evidence that reducing LDL-cholesterol levels to <70 mg/dL is a “therapeutic option” for people at very high CHD risk. The “very-high-risk” category includes those with established cardiovascular disease and additional risk factors such as diabetes mellitus, continued cigarette smoking, metabolic syndrome, and acute coronary syndrome.

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Guidelines for secondary prevention jointly issued by the American Heart Association and the American College of Cardiology in 2006 and endorsed by the National Heart, Lung, and Blood Institute (NHLBI) agree that a goal of <70 mg/dL is “reasonable” for all patients with CHD and other clinical forms of atherosclerotic disease, even those whose baseline LDL-cholesterol level is between 70 and 100 mg/dL.

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Lowering LDL may cause atherosclerosis to regress
Intensive lipid lowering has shown prom-
ise in inducing regression of atherosclerotic plaque.\textsuperscript{20,21} The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial compared the effects on atheroma volume, as measured by intracoronary intravascular ultrasound, of intensive (atorvastatin 80 mg/d) vs moderate (pravastatin 40 mg/d) lipid lowering over 18 months in patients who had 1 or more vessels with a luminal narrowing of 20% or more.\textsuperscript{20} In the intensive treatment group, which attained a mean LDL-cholesterol level of 79 mg/dL, the 0.4% reduction in atheroma volume indicated no disease progression from baseline and a significantly lower progression rate ($P=0.02$). By contrast, the group on moderate treatment that achieved a mean LDL-cholesterol level of 110 mg/dL had a 2.7% increase in atheroma volume, indicating net progression of atheroma volume compared with baseline.\textsuperscript{20}

**ASTEROID shows actual regression**

A study of the effect of rosuvastatin on disease progression (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden, or ASTEROID) evaluated the effect of rosuvastatin 40 mg/d on coronary disease progression assessed by intravascular ultrasound at baseline and after 24 months, with the patients serving as their own controls.\textsuperscript{21} The results showed the mean change in percent atheroma volume (PAV), a measure of disease progression and regression, for the entire vessel being measured was $-0.98\%$, compared with baseline ($P<0.001$). A second efficacy measure, change in atheroma volume in the 10-mm subsegment with the greatest disease severity, also showed a reduction, with a mean change of $-6.1$ mm\textsuperscript{3} compared with baseline ($P<0.001$).\textsuperscript{21} The ASTEROID investigators attributed disease regression to intensive statin treatment, leading to an LDL-cholesterol mean of 61 mg/dL, together with significantly increasing HDL-cholesterol levels to 49 mg/dL, up 5% from baseline.\textsuperscript{21}

**Combination therapy fails to ENHANCE atherosclerosis regression**

In a controversial study in patients with familial hypercholesterolemia utilizing B-mode ultrasound measurements of carotid intima-media thickness, lowered LDL-cholesterol levels did not result in regression of atherosclerosis. The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial evaluated simvastatin 80 mg plus ezetimibe 10 mg compared with simvastatin 80 mg alone.\textsuperscript{22} Despite a significant 16.5% greater lowering of LDL-cholesterol with combination therapy ($P<0.01$), no difference was observed in progression of carotid intima-media thickness between the 2 treatment groups.

**No LDL is too low for safety**

Given the physiologic importance of cholesterol in the body, the very low cholesterol levels achieved with intensive statin therapy in some trials has raised questions about the safety of such an approach.\textsuperscript{23} A substudy of the PROVE IT-TIMI 22 trial focused on the 11% of 1825 atorvastatin-treated patients whose LDL-cholesterol levels had dropped to 40 mg/dL or lower after 4 months of treatment. There were fewer cardiovascular events in this group compared with the patients with LDL-cholesterol levels between 80 and 100 mg/dL, and no relationship between this low level and adverse events over 24 months.\textsuperscript{23} Similarly, the TNT study group analyzed cardiovascular events across quintiles of LDL-cholesterol and found that the lowest quintile (LDL <64 mg/dL, mean 54 mg/dL) had the lowest event rate, without a difference in adverse events over 5 years.\textsuperscript{24}

**LDL isn’t the whole story**

It is clear from the statin clinical trials that cardiovascular events occur even after LDL-cholesterol is optimally treated. Why is this so? One possibility is that levels of other lipids—too-high triglycerides or too-low HDL-cholesterol—also contribute to CHD risk. These lipid abnormalities often cluster with other risk factors, including obesity, insulin resistance, hyperglycemia, and hypertension. Such patients are considered to have mixed, or atherogenic, dyslipidemia, and frequently include those with metabolic syndrome and type 2 diabetes. In patients whose triglyceride levels remain high (>200 mg/dL) or HDL-cholesterol levels...
low (<40 mg/dL) even after they have achieved their LDL-cholesterol goals, the NCEP ATP III guidelines recommend non−HDL-cholesterol as a secondary target of therapy. Non−HDL-cholesterol (calculated as total cholesterol minus HDL-cholesterol) is a measure of all the atherogenic, apolipoprotein B-containing lipoproteins (LDL, intermediate-density lipoprotein [IDL], and very-low-density lipoprotein [VLDL]).

In mixed, or atherogenic, dyslipidemia, the LDL particles are usually smaller and the calculated LDL-cholesterol content does not reflect the increased particle number. Several observational studies suggest that non−HDL-cholesterol is a better predictor of risk at any given LDL-cholesterol level.

**The IDEAL predictor**
To highlight the predictive value of non−HDL-cholesterol, Kastelein and colleagues analyzed pooled data from TNT and IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering). IDEAL was a large (N=8888), randomized clinical trial in which patients with established CHD were assigned to usual-dose or high-dose statin treatment. In the investigators’ statistical models, while LDL-cholesterol levels were positively associated with cardiovascular outcome, that relationship turned out to be less significant than the relationship with non−HDL-cholesterol and apolipoprotein B. The ratio of total cholesterol to HDL (Total/HDL) and the ratio of apolipoprotein B to apolipoprotein A-I were each more closely associated with outcome than any of the individual proatherogenic lipoprotein parameters.

Another post hoc analysis of TNT data has shown that HDL-cholesterol levels in patients receiving statins predicted major cardiovascular events. Among subjects with LDL-cholesterol levels <70 mg/dL, those in the highest quintile of HDL-cholesterol were at less risk for major cardiovascular events than those in the lowest quintile (P=.03). Both of these analyses support the concept that there is residual CHD risk after optimal statin treatment, and that the easily obtained non−HDL-cholesterol and HDL-cholesterol levels are predictive of that risk.

**Setting goals for non−HDL-cholesterol**
The ATP III−recommended goal for non−HDL-cholesterol is 30 mg/dL above the LDL goal, since maximum acceptable cholesterol carried in the triglyceride-rich lipoproteins (VLDL/IDL) is one-fifth of the acceptable triglyceride level (150/5=30 mg/dL). Thus, a high-risk person whose LDL-cholesterol goal is <100 mg/dL would have a non−HDL-cholesterol goal of <130 mg/dL. ATP III recommends lowering non−HDL-cholesterol by intensifying statin therapy to further reduce LDL as well as considering the addition of niacin or a fibrate to further decrease VLDL and triglycerides. Although not specifically recommended by ATP III, omega-3 fatty acids at a sufficient dose (3-4 g/d of eicosapentaenoic acid + docosahexanoic acid) can reduce triglycerides as monotherapy, or when added to statins.

**Total atherogenic particles**
A 2008 consensus conference report from the American Diabetes Association and the American College of Cardiology states that in patients with high cardiometabolic risk, LDL-cholesterol levels alone do not adequately capture risk and that measurements of total atherogenic particles are better. These measurements include non−HDL-cholesterol, apolipoprotein B, and the number of LDL particles identified by nuclear magnetic resonance. In individuals in the highest-risk category (known clinical cardiovascular disease or diabetes plus 1 or more CHD risk factors in addition to dyslipidemia), the report recommends a non−HDL-cholesterol goal of <100 mg/dL and an apolipoprotein B goal of <80 mg/dL.

**Combining therapies: AIM-HIGH and ACCORD**
Two ongoing trials are comparing combination therapy (statin with either niacin or a fibrate) with statin therapy alone in patients with atherogenic dyslipidemia to assess the incremental benefit of combination therapy. AIM-HIGH (Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides and Impact on Global Health outcomes) is a 5-year study in 3300 patients with vascular disease and low HDL-
cholesterol. This study is designed to find out whether lowering LDL to <80 mg/dL with simvastatin plus niacin can delay the time to a first major cardiovascular event for longer than simvastatin therapy alone. The 6-year ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) randomizes patients with type 2 diabetes into 2 groups, 1 receiving statin-fibrate combination therapy and the other statin monotherapy. ACCORD is designed to find out whether raising HDL-cholesterol and lowering triglycerides along with targeted reductions in LDL-cholesterol will improve CHD outcomes more than LDL lowering alone.

Raising HDL-cholesterol is promising, but complex

Improving residual CHD risk after statin treatment has emphasized raising HDL-cholesterol as a therapeutic target. The validity of raising HDL-cholesterol is supported by epidemiologic evidence showing an inverse relationship between HDL-cholesterol levels and cardiovascular risk: an increase of 1 mg/dL in HDL-cholesterol is associated with a 2% to 3% decrease in risk of cardiovascular disease. Therapeutic lifestyle changes, such as weight loss, exercise, and smoking cessation are effective at increasing HDL-cholesterol and these interventions are always encouraged. Most statins modestly (5%-10%) increase HDL-cholesterol, with rosuvastatin generally producing the largest increases, as shown in the ASTEROID study.

Niacin raises HDL

Currently, the most efficacious HDL-raising drug is niacin. As monotherapy, niacin can increase HDL-cholesterol by 15% to 35%. The problem is that niacin often causes flushing, a side effect patients find unpleasant enough that they don’t continue therapy. Extended-release preparations cause less flushing than immediate-release forms of niacin, and specific flush-reducing agents (laropiprant) are under investigation to improve tolerance.

Fibrates, alone and combined, with statins

By activating the nuclear transcription factor peroxisome proliferator-activated receptor-α, fibrates increase HDL-cholesterol by 8% to 35%. The Veterans Affairs HDL Intervention Trial (VA-HIT) studied the effects of gemfibrozil in men with CHD and HDL-cholesterol <40 mg/dL. After a median follow-up of 5 years, gemfibrozil raised HDL-cholesterol by 6% more than placebo and lowered triglycerides by 31% more (P<.001 for both), but did not affect levels of LDL-cholesterol. Compared to placebo, gemfibrozil treatment reduced the risk of CHD death and nonfatal myocardial infarction by 22% (P=.006). In post hoc analysis, each 5-mg/dL increase in HDL-cholesterol was associated with an 11% decrease in the risk of these CHD events.

The Helsinki Heart Study reported similar results with gemfibrozil in a population without CHD. Fibrates may be combined with statins: small studies using rosuvastatin and fenofibrate and atorvastatin and fenofibrate have shown positive effects on dyslipidemia. Gemfibrozil may be associated with increased risks of myositis, whereas fenofibrate combined with statins has not shown this effect.

High hopes, sobering findings, for torcetrapib

The glycoprotein cholesteryl ester transfer protein (CETP) can make HDL particles smaller and more readily removed by the kidneys, with the overall effect of a reduction in HDL-cholesterol. Inhibiting this effect, then, should raise HDL levels. Expectations were high for torcetrapib, the first CETP inhibitor, which had been shown to increase HDL-cholesterol by >50% in early clinical trials. However, a clinical outcomes trial comparing torcetrapib and atorvastatin with atorvastatin alone was stopped early because the combination therapy was associated with a higher incidence of adverse cardiovascular events, including total mortality. Significant increases in average systolic blood pressure with torcetrapib were reported, but it is not clear if this was the cause of the unfavorable outcome. Further, substantial HDL-cholesterol increases of 54% and 61% achieved with torcetrapib in 2 surrogate outcomes trials did not have a beneficial effect on atherosclerosis. Other CETP inhibitors are currently in
Investigative approaches for increasing HDL-cholesterol levels include IV and oral therapies such as apolipoprotein A1-Milano, apolipoprotein A1-mimetic peptides, and phospholipid-directed therapies.

 References


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