ABSTRACT

The National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III) guidelines call for immediate intervention in individuals with established coronary heart disease (CHD). The significance of immediate intervention was based in part on our understanding of plaque stability versus morphology (i.e., the nature of the plaque, not the size, determines its vulnerability to thromboses). The sequelae of a ruptured plaque are dangerous and often deadly. Statins, through their ability to significantly reduce low-density lipoprotein cholesterol levels, can drastically reduce the risk of a future CHD event. This article reviews the epidemiologic statistics regarding CHD, with an emphasis on the lethality of this disease and the overall risk versus the risk of any side effects of statins. The guidelines recommend 2 types of treatment based on CHD risk: therapeutic lifestyle changes and drug treatment. Realistic outcomes with these types of therapies are reviewed as well as ongoing clinical studies and new drug therapies recently approved by the US Food and Drug Administration. Aggressive and early intervention to prevent CHD (both primary and secondary prevention) is essential, and it is quite safe. The onus is on primary care physicians to identify patients early and initiate statin therapy before the first clinical signs of CHD develop.

With the National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III) guidelines, the number of people who are eligible for lipid-lowering drug therapy has now reached more than 36 million. The guidelines call for immediate intervention in those with established coronary heart disease (CHD). The importance of early intervention was promoted after NCEP ATP II in a statement for healthcare professionals, issued by the American Heart Association Task Force on Risk Reduction: “A large number of patients with atherosclerotic disease are not receiving aggressive cholesterol-lowering therapy. Consequently, they are being deprived of a cost-effective, risk-reducing treatment...Intensive cholesterol reduction, initiated immediately, has the potential to significantly reduce both morbidity and mortality.” The significance of immediate intervention was based in part on our understanding of plaque stability. Libby described the vulnerable plaque based on autopsy studies from asymptomatic patients who died from myocardial infarction (MI). As shown in Figure 1, vulnerable...
plaques have a substantial lipid core and a thin fibrous cap that is easily disrupted by the mechanical forces on an artery wall, exposing the plaque to thrombogenic macrophages in the blood. Vulnerable plaques often maintain a well-defined lumen because they grow into the artery wall and do not disturb blood flow; however, these plaques can easily rupture and lead to thrombosis. Vulnerable plaques are often limited enough in size to remain undiagnosed after exercise testing. In contrast, stable plaques have a thick fibrous cap protecting a lipid-poor core. The lumen is usually decreased in size and is viewed as atherosclerotic disease on angiography. The morphology of a plaque— not its size— determines its danger level. As a result, patients with vulnerable plaques are difficult to identify clinically or through stress or exercise testing.

The sequelae of a ruptured plaque are dangerous and often deadly. Small ruptures cause partial occlusion, resulting in acute coronary syndrome (ie, chest pain, non-Q-wave MI). Large ruptures result in nearly 100% occlusion, which might occur in addition to established local stenosis, vasospasm, and thrombotic tendency. The result is usually a Q-wave MI or sudden death. In numerical terms, estimates of CHD event frequency in 2000 were 1.1 million for new or recurrent MI, with about 20% (250,000) resulting in death before hospitalization. The rates of post-MI complications vary by level of care but are estimated to be 10% for death within 1 month of hospitalization, 33% for development of heart failure, 21% for 1-year death rate for heart failure patients, and 18% and 35% for recurrent MI in men and women, respectively, within 6 years. The total number of CHD deaths per year is estimated to be 47% (more than 530,000). More than 1450 people are dying every day from CHD (roughly equivalent to 4 full 767 airplanes crashing daily). If patients question the safety of statins based on medical news reports in the lay press, it is important to place these reports in perspective. The number of deaths leading to the removal of cerivastatin from the market after 3 years was 54. During those 3 years, 1.5 million people died from heart disease. If patients do not want to initiate or continue statin therapy for fear of side effects, they need to understand that the side effect of inadequate treatment of CHD is often death. Statins are safe and effective drugs for reducing risk of CHD through lowering of low-density lipoprotein (LDL) cholesterol.

**RISK FACTORS FOR CHD**

As shown in Figure 2, 4-year risk of CHD increases with increasing LDL cholesterol level and decreasing high-density lipoprotein (HDL) cholesterol level. Total cholesterol level does not provide enough information to calculate CHD risk and should be used only as part of a comprehensive lipid panel.

**Figure 1. Vulnerable vs Stable Atherosclerotic Plaques**


**Figure 2. Risk of CHD According to LDL and HDL Levels**

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The NCEP ATP III guidelines calculate risk based on age, sex, smoking status, cholesterol subfractions, and blood pressure. The tool to calculate global risk assessment is simple and provides CHD risk data in minutes (Figure 3). Points are given for each degree of severity per risk factor. These points are then added and compared to a numeric scheme to determine 10-year CHD risk. Hypertension is an important factor because it usually occurs in conjunction with other metabolic risk factors (i.e., increased total cholesterol levels, decreased HDL cholesterol, increased triglycerides, increased body mass index, and increased blood glucose levels. As shown in Figure 4, most hypertensive patients have at least 1 other risk factor. Hypertension is one of the most common diseases in the United States, affecting 50 million Americans; therefore, most older hypertensive patients in primary care will likely be eligible for statin therapy. The cutpoints for drug or therapeutic lifestyle change (TLC) from the NCEP ATP III guidelines are based on LDL cholesterol levels and calculated global risk of CHD (Table 1).

Several noninvasive imaging modalities for determining atherosclerotic burden are either available or under investigation. These include B-mode ultrasonography for measurement of intima-media thickness of the carotid artery, aorta, and femoral artery; magnetic resonance imaging of coronary arteries; and electron-beam computed tomography of coronary arteries. Each has advantages and disadvantages. The latter has shown only 51% to 76% predictive accuracy and is costly. Global risk assessment based on the guideline-identified risk factors is much less expensive and more accurate. 

An important change in ATP III from ATP II is the identification of diabetes as a CHD risk equivalent—it poses the same risk of future CHD events as already having CHD. A diabetic patient can be considered a patient with heart disease who has not yet had an MI. This change in risk status with diabetes is based on the landmark study by Haffner et al showing that patients with type 2 diabetes but no prior MI had the same incidence of fatal or nonfatal MI during 7 years of follow-up as nondiabetic subjects with a previous MI (Figure 5).
NONPHARMACOLOGIC THERAPY

The NCEP ATP III guidelines increased the number of patients eligible for drug therapy to 36 million. The number of patients now eligible for TLC has increased to 65 million, with the largest increases in those with 0 or 1 risk factor or with 2 or more risk factors but a 10-year CHD risk of less than 10%. TLC involves increased physical activity, weight loss, and a diet that lowers saturated fat and cholesterol intake to levels of the previous Step II diet. It also adds dietary options to enhance LDL cholesterol lowering with consumption of plant stanols/sterols (2 g daily) or viscous soluble fiber (10–25 g daily).

The dietary recommendations might be difficult to maintain for any length of time and results regarding their effect on lipid levels has varied. A recent review of dietary intervention trials showed a modest reduction in total cholesterol levels of 12% to 18% in 4 studies, with the number of participants ranging from 412 to 10 612. Another meta-analysis showed benefits of Step I and Step II dietary changes via decreases in total cholesterol (10% and 13% for Step I and Step II, respectively), LDL (12% and 16%), triglycerides (8%) and total-to-HDL cholesterol ratio (10% and 7%). A study of 132 men and 132 women 25 to 49 years of age shows that diet in combination with exercise appears to have the greatest benefit. Study participants were randomized to 1 of 3 groups: control, hypocaloric NCEP diet, or hypocaloric NCEP diet with exercise. One hundred nineteen men and 112 women returned for testing after 1 year. The results showed that the only significant effect was increased HDL cholesterol, and this beneficial effect was due to exercise rather than diet (Figure 6).

Regardless of its effect on LDL, diet plays an important role in reducing CHD risk. Diabetes cannot be controlled without diet, and weight loss serves to reduce hypertension, abdominal obesity, and blood glucose levels—all risk factors for CHD and the metabolic syndrome. The key is to have realistic expectations of what can be achieved with TLC.

PHARMACOLOGIC THERAPY

As discussed by Ansell (see page S38), LDL cholesterol cutpoints might be further lowered based on

Table 1. LDL Cholesterol Cutpoints and Goals for Therapeutic Lifestyle Changes and Drug Therapy: NCEP ATP III Guidelines

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Cholesterol Level for Initiating TLC (mg/dL)</th>
<th>LDL Cholesterol Level for Considering Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalent (10-year risk &gt;20%)</td>
<td>100</td>
<td>130</td>
</tr>
<tr>
<td>2+ risk factors (10-year risk ≤20%)</td>
<td>≥130</td>
<td>≥130</td>
</tr>
<tr>
<td>0-1 risk factor†</td>
<td>&lt;160</td>
<td>≥160</td>
</tr>
</tbody>
</table>

* Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL (eg, nicotinic acid or fibrates). Clinical judgment also might call for deferring drug therapy in this subcategory.
† Almost all individuals with 0 to 1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0 to 1 risk factor is not necessary.

LDL = low-density lipoprotein; TLC = therapeutic lifestyle change; CHD = coronary heart disease; HDL = high-density lipoprotein.


Figure 5. Incidence of MI During 7-Year Follow-up in a Finnish Population

MI = myocardial infarction.
Data from Haffner et al.14
recent data from the Heart Protection Study and the Post-Coronary Artery Bypass Graft (Post-CABG) study. In clinical practice, it might be useful to immediately initiate statin therapy as well as TLC in patients at high risk for CHD and to treat to an LDL target level of 100 mg/dL or below.

**MISSED OPPORTUNITIES**

Primary care physicians (PCPs) cannot assume that patients with established CHD are receiving lipid-lowering therapy from the hospital or the cardiologist. It remains the responsibility of the PCP to ensure that the patient receives necessary medication to lower CHD risk. A study of 138 001 patients hospitalized for acute MI from 1470 hospitals during 1998 to 1999 showed that only 31.7% were discharged with lipid-lowering medication. Nearly one half of those with previous CHD, revascularization, or diabetes were discharged without lipid-lowering medication. Those more likely to receive drug therapy were patients with a history of CABG, smokers receiving counseling, and those taking beta-blocking agents and/or aspirin at discharge. Patients less likely to receive lipid-lowering drug therapy were elderly patients, patients treated at a non-teaching hospital, patients with hypertension or congestive heart failure, and patients undergoing CABG during hospitalization.19 Ideally, every post-MI patient should be discharged with the “angioplasty cocktail”: baby aspirin, an angiotensin-converting enzyme inhibitor, a beta blocker, clopidogrel, and a statin. It is an expensive regimen (about $2000), but angioplasty costs roughly $30 000, CABG costs $75 000, an emergency department visit costs several thousand dollars, and the average funeral costs about $9000.

A survey of 140 medical practices (80% of which were cardiology practices) showed that of the 48 586 outpatients with CHD, only 39% were taking lipid-lowering medications, and only 25% achieved LDL cholesterol levels below 100 mg/dL.20 Data from the Swedish Register of Cardiac Intensive Care showed that the 1-year mortality rate in nearly 20 000 patients more than doubled in patients who were not initiated on statin therapy prior to hospital discharge (4% vs 9.3%).

**LIPID-MODIFYING DRUGS**

Statins are one of 5 primary classes of available drugs that modify serum lipids. The major effect of statins is lowering of LDL cholesterol. In addition, statins decrease very-low-density lipoprotein (VLDL), the major carrier of triglycerides in the blood, and VLDL remnants, leading to decreased triglyceride levels. Statins have a modest if not negligible effect on HDL cholesterol levels (Table 3). Niacin can have significant effects on HDL cholesterol. Fibrates do not consistently affect LDL cholesterol levels; their main use is in addressing the secondary targets of triglycerides and HDL cholesterol. Resins have a modest effect on LDL cholesterol and total cholesterol but are difficult for patients to tolerate.22 The newest approved agent, the cholesterol absorption inhibitor, ezetimibe, has shown significant but small decreases in LDL, small decreases in triglycerides, and nominal increases in HDL levels.

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**Figure 6. Lipoprotein Changes After 1 Year of Lifestyle Intervention**

**A** Men

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>HDL</th>
<th>LDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>115</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>Control</td>
<td>110</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>Diet Only</td>
<td>105</td>
<td>85</td>
<td>70</td>
</tr>
<tr>
<td>Diet/Exercise</td>
<td>100</td>
<td>80</td>
<td>65</td>
</tr>
</tbody>
</table>

**B** Women

<table>
<thead>
<tr>
<th></th>
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<th>HDL</th>
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<td>80</td>
<td>65</td>
</tr>
</tbody>
</table>

TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

Data from Wood et al.20
A cohort study analyzing medical records of 2369 new users of antihyperlipidemic therapy at 2 health maintenance organizations from 1988 through 1990 showed that the rates of drug discontinuation over 1 year in these primary care settings varied greatly by drug class: 41% for resins, 46% for niacin, 37% for gemfibrozil, and 15% for lovastatin.23

COMBINATION THERAPY

Patients are often reluctant to take secondary medications, and significant risks are associated with some combination therapies. Statins can be combined with niacin to achieve LDL lowering with concomitant HDL cholesterol increases. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that baseline LDL cholesterol levels did not correlate with reduction in the rate of first acute major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death) in patients taking lovastatin. Decreases of 34%, 36%, and 41% occurred in patients with LDL cholesterol levels below 142 mg/dL, from 143 to 156 mg/dL, and above 157 mg/dL, respectively, in a 6605-patient cohort. Risk of first acute major coronary event was reduced much more dramatically in patients with low baseline HDL cholesterol (45% reduction for baseline HDL ≤34 mg/dL; 44% for baseline HDL 35-39 mg/dL; 15% for baseline HDL ≥40 mg/dL).24 The AFCAPS/TexCAPS study results are the basis for the HDL cholesterol cutoffpoint of 40 mg/dL in the NCEP ATP III guidelines. Raising HDL cholesterol levels might be important in reducing CHD risk.

Combining a statin with a fibrate can pose significant risks with regard to myopathy, but fibrates have been shown to reduce risk of CHD events, HDL cholesterol, and triglyceride levels. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed the benefit of fibrate therapy alone for a generally improved lipid profile (31% reduction in triglycerides, 6% increase in HDL cholesterol, unchanged LDL cholesterol) as well as 22% reduction in relative risk of CHD events/nonfatal MI (P = .006). The decrease in mortality appears to be predominantly related to the HDL increase.25 A meta-analysis of 17 population-based prospective studies of triglyceride and cardiovascular disease showed that the relative risk increased by 32% in men and 76% in women due to increased triglyceride levels.26 When adjusted for HDL cholesterol and other risk factors, these risks decreased to 14% (men) and 37% (women) but remained statistically significant. The impact of high triglyceride levels is thus unclear.26

A prospective study of 4559 men showed that elevated triglyceride level was a powerful additional CHD risk factor, but only in patients with a high (>5.0) LDL/HDL cholesterol ratio. When LDL cholesterol levels were high, the effect of increased triglycerides or CHD risk was significant; however, when LDL cholesterol levels were lowered, the effect of triglyceride elevation was not significant.27 The West of Scotland Coronary Prevention Study (WOSCOPS) showed that statin benefits were attained irrespective of any baseline

<table>
<thead>
<tr>
<th>Table 2. Compliant CHD Patients Might Not Achieve LDL Cholesterol Target With Diet Alone</th>
</tr>
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<tbody>
<tr>
<td>Treatment</td>
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<tr>
<td>NCEP Step II diet</td>
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<tr>
<td>Very-low-fat diet</td>
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</tbody>
</table>

CHD = coronary heart disease; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program.

Data from Aquilani et al.18

<table>
<thead>
<tr>
<th>Table 3. Effects of Lipid-Modifying Drugs on Serum Lipids</th>
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<tbody>
<tr>
<td>Drug Class</td>
</tr>
<tr>
<td>Resins</td>
</tr>
<tr>
<td>Niacin</td>
</tr>
<tr>
<td>Fibrates</td>
</tr>
<tr>
<td>Statins</td>
</tr>
<tr>
<td>Ezetimibe</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides.

Data from Gotto22; Bays.33
lipid measure, but the benefits are apparently due to LDL cholesterol lowering. Also, no increased risk from elevated triglycerides was observed in the patients taking statins.\textsuperscript{28} According to the NCEP ATP III guidelines, lowering non-HDL cholesterol to lower triglycerides is a secondary therapeutic target in patients with triglyceride levels above 200 mg/dL. Achieving target LDL levels remains the primary goal.

New Therapies and Future Studies

Rosuvastatin is the most recent statin to receive US Food and Drug Administration (FDA) approval. Clinical studies have shown that rosuvastatin can reduce LDL cholesterol levels by up to 63% after 6 weeks of treatment at doses up to 40 mg compared with 44% and 59% reductions with 10 and 80 mg atorvastatin, respectively. Significantly large increases in HDL cholesterol were also observed (up to 14.4% increase from baseline). Ninety percent of LDL cholesterol reduction occurred within the first 2 weeks of treatment with rosuvastatin.\textsuperscript{29} A recent review of the benefit-risk assessment of rosuvastatin 10 mg to 40 mg indicates that the ratio is favorable, with an adverse event profile similar to atorvastatin (10-80 mg), simvastatin (10-80 mg), and pravastatin (10-40 mg).\textsuperscript{30} The highest dose of rosuvastatin studied (80 mg) has been associated with myopathy and proteinuria.

A comparison of rosuvastatin, atorvastatin, simvastatin, and pravastatin across doses has recently been completed in the Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial. The results show that rosuvastatin had a greater effect on LDL cholesterol (Figure 7), HDL cholesterol, and total cholesterol compared with the other statins across doses in 2431 adults over 6 weeks of treatment and reduced triglyceride levels significantly more than simvastatin and pravastatin. The proportion of patients reaching both NCEP ATP III and the Joint European Task Force LDL cholesterol goals was higher with rosuvastatin than with the other statins. Drug tolerability was similar with all treatments.\textsuperscript{31} Rosuvastatin appears to be a potent agent for treating dyslipidemia through its effects on LDL cholesterol, HDL cholesterol, and triglycerides.

Pitavastatin is also under development. The published data on its safety and efficacy are limited. A study of 240 patients compared pitavastatin (2 mg) to pravastatin (10 mg). After 12 weeks of treatment, greater reductions in LDL cholesterol were observed with pitavastatin than with pravastatin (37.6% vs 18.4%, respectively; \( P < .05 \)). Pitavastatin also significantly lowered total cholesterol and triglycerides and increased HDL cholesterol compared with pravastatin. The adverse event profile was similar for both treatment groups, and neither treatment caused clinically relevant laboratory abnormalities.\textsuperscript{32}

Ezetimibe has also been recently approved by the FDA. It is not a statin but a cholesterol absorption inhibitor—it decreases LDL cholesterol by inhibiting cholesterol absorption at the intestinal brush border. Studies have shown significant though small decreases in LDL cholesterol of 18% in patients taking ezetimibe, with small decreases in triglycerides (8%) and nominal increases in HDL (1%).\textsuperscript{33} A recent study of ezetimibe in combination with a statin showed an incremental decrease in LDL cholesterol of 25% when ezetimibe was added to ongoing statin therapy. Triglycerides were also decreased by an additional 14% when ezetimibe was added to statin therapy.\textsuperscript{34} No data have been published regarding ezetimibe’s effect on reducing CHD events. Ezetimibe thus appears to be useful as monotherapy only in those who are unable to tolerate a statin. In those who are unable to tolerate therapeutic levels of a statin, ezetimibe can be given as add-on therapy. Ezetimibe is not associated with elevated liver function tests or myopathy.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{stellar LDL change.pdf}
\caption{STELLAR: LDL Cholesterol Percentage Change from Baseline}
\end{figure}

LDL = low-density lipoprotein.
Data from Jones et al.\textsuperscript{31}


