ABSTRACT

The emphasis in managing dyslipidemia should be given to achieving and maintaining lipid goals in order to optimally reduce the risk of coronary heart disease (CHD). The recently released guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) are reviewed in this article. The guidelines renew the emphasis on low-density lipoprotein cholesterol (LDL-C) as the primary target of therapy, and indicate an optimal LDL-C for all patients is less than 100 mg/dL. Most patients with dyslipidemia will require drug therapy to achieve this and other lipid-treatment goals. Currently, only a minority of patients, including those with established CHD, is achieving treatment goals. Use of appropriate doses of drugs and drug combinations may enhance the likelihood of achieving target lipid levels. ATP III continues to emphasize the importance of therapeutic lifestyle changes, particularly dietary intervention.


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istorically, the term “control” has been used to describe efforts to manage hypercholesterolemia and other abnormalities of serum lipid levels. In recent years, the more specific phrase, “treat to goal,” increasingly has displaced the more general term, “control,” as the preferred terminology in discussions related to management of dyslipidemia. The semantic transition reflects growing recognition of the need to achieve and maintain lipid levels that are associated with reduced cardiovascular risk. The most widely recognized goals for lipid levels are included in the clinical guidelines of the US National Cholesterol Education Program (NCEP). In May 2001, the NCEP released updated findings and recommendations regarding the scope of dyslipidemia and clinical strategies to treat lipid disorders. The updated guidelines retain many of the basic principles of past versions, including the traditional lipid-level goals and the emphasis on low-density lipoprotein cholesterol (LDL-C) as the primary target of therapy. The new guidelines have some notable changes, such as increased emphasis on use of lipid-lowering drug therapy in a larger number of patients, and recognition of certain high-risk patient categories that warrant a more aggressive approach to therapy. While retaining a traditional focus on intensive treatment in the setting of secondary prevention, the new guidelines place unprecedented emphasis on primary prevention. In keeping with previous versions, the new NCEP guidelines offer a variety of pharmacologic and nonpharmacologic methods for achieving lipid goals. While this wide array of tools for treating dyslipidemia is available
to clinicians and their patients, the effectiveness of these tools will be realized only when they are employed appropriately, regularly, and aggressively.

**SCOPE OF THE PROBLEM**

In the United States, 12.4 million people have coronary heart disease (CHD), and 500,000 people die of CHD each year. Blood lipid levels have a well-established association with CHD risk. Data from the Framingham Heart Study have shown a direct correlation between cholesterol levels and 40-year survival among people younger than 50 years of age. The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated a curvilinear relationship between rising cholesterol levels and CHD risk. Risk increased slightly as total cholesterol levels rose from 150 to 200 mg/dL, then the risk for CHD increased 2-fold at cholesterol levels of 250 mg/dL and 4-fold at levels of 300 mg/dL.

More than 70 million adults in the United States have total cholesterol levels of 200 mg/dL or higher, and 40% of these individuals have cholesterol values of 240 mg/dL or higher. The Lipid Research Clinics (LRC) Program provided the first conclusive evidence that reducing LDL-C levels will directly decrease risk for CHD. The LRC showed that an 11% reduction in LDL-C with cholesteryramine treatment was associated with a 24% reduction in CHD mortality and a 19% reduction in the incidence of nonfatal myocardial infarction. The LRC program also contained the earliest demonstrations of the principle that every 1% reduction in LDL-C leads to a 2% reduction in CHD risk.

Since publication of the LRC results, numerous clinical trials have added evidence from a variety of patient populations and with a variety of lipid-modifying therapies. The Scandinavian Simvastatin Survival Study (4S) showed impressive reductions in cardiovascular mortality and morbidity in CHD patients with high total and LDL-C levels. The trial also showed for the first time to show a reduction in overall mortality with lipid-lowering therapy. The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated a reduction in CHD risk in patients with elevated cholesterol levels but no evidence of CHD at enrollment. Subsequently, the Cholesterol and Recurrent Events (CARD) trial and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) showed that CHD risk could be reduced in patients who had normal or near-normal cholesterol levels. CARE provided evidence of benefit in a secondary prevention setting, whereas AFCAPS/TexCAPS was a primary prevention trial.

Although the bulk of current clinical data on the benefits of lipid-lowering therapy has come from trials involving 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase inhibitors (statins), other drugs have also proven beneficial. The Helsinki Heart Study, one of the early trials of lipid-modifying drug therapy, showed a reduction in CHD risk with the fibric acid derivative gemfibrozil. More recently, the Veterans Affairs HDL-C Intervention Trial (VA-HIT) demonstrated a benefit with gemfibrozil in patients who did not have elevated total or LDL-C but had low levels of high-density lipoprotein cholesterol (HDL-C). Earlier this year, the Diabetes Atherosclerosis Intervention Study (DAIS) showed a reduction in the progression of atherosclerosis in patients with diabetes who were treated with fenofibrate. The DAIS trial was notable in that it focused exclusively on patients with diabetes who had modest lipid abnormalities, a common finding in patients with diabetes. DAIS provided strong evidence that correction of even mild forms of dyslipidemia offers potentially important clinical benefits with respect to CHD risk.

Despite the availability of multiple therapies with proven efficacy for dyslipidemia, only a minority of patients actually achieve lipid goals that are associated with reduced CHD risk. One recent study of lipid management in the primary care setting showed that 38% of the treated patients achieved cholesterol goals established by the NCEP. Among patients with established CHD, only 18% achieved target lipid levels with treatment. The same trial demonstrated that drug therapy is not the total solution; lack of dietary intervention was an independent predictor of failure to achieve lipid goals.

The new NCEP recommendations retain the program’s historical endorsement of dietary modification and regular physical activity as essential elements of risk-reduction therapy. Just as clearly, the new guidelines reflect the growing recognition that many patients with dyslipidemia will require drug therapy to achieve lipid goals. The 2001 guidelines will almost triple the number of people who qualify for drug treatment from 13 million to 36 million. The number of patients who require dietary intervention will increase from more than 50 million to about 65 million.

The NCEP guidelines provide a blueprint for treating patients to lipid goals. The responsibility for following the blueprint rests with clinicians and their patients, who must share actively in the clinical effort by recognizing the importance of treating lipid disorders and by adhering to prescribed therapies, both pharmacologic and nonpharmacologic.

**HIGHLIGHTS OF THE 2001 NCEP GUIDELINES**

The current recommendations of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults represent the second update since the original guidelines were released in 1988. The recommendations of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) retain the same lipid targets embodied in ATP II, released in 1993. Consistent with prior versions of the guidelines, ATP III recognizes LDL-C as the primary target for therapy. An LDL-C level of less than 100 mg/dL is considered optimal for all adults. An LDL-C above 160 mg/dL, corresponding to a total cholesterol above 240 mg/dL, is considered high (Table 1). For total cholesterol, an optimal level is defined as less than 200 mg/dL and values of 240 mg/dL and greater are defined as high.

One notable change in ATP III relates to the definition of low HDL-C. Formerly defined as a value of less than 35 mg/dL, low HDL-C is now defined as any value less than 40 mg/dL. The change reflects the growing recognition of the importance of low HDL-C as an independent risk factor for CHD.

ATP III recommends an LDL-C goal of less than 160 mg/dL for people who do not have CHD and who have no more than 1 risk factor for CHD (Table 2). For these individuals, lipid-lowering drug therapy is recommended if the LDL-C level is 190 mg/dL or higher after an adequate trial of lifestyle modifications (eg, 3 months).

For patients with 2 or more CHD risk factors but no evidence of CHD, the LDL-C goal is less than 130 mg/dL (Table 2). Initiation of drug therapy in this patient group is based on risk assessment tables developed by investigators in the Framingham Heart Study. Drug therapy is recommended if the LDL-C level is 160 mg/dL or higher after lifestyle modification for patients whose 10-year CHD risk is less than 10%.

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**Table 1. ATP III Classification of LDL-L Total, and HDL-Cholesterol, and Triglycerides (mg/dL)**

<table>
<thead>
<tr>
<th>Category</th>
<th>LDL-Cholesterol</th>
<th>HDL-Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt; 100</td>
<td>≥ 60</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Near optimal/above optimal</td>
<td>100-129</td>
<td>≥ 60</td>
<td>150-199</td>
</tr>
<tr>
<td>Borderline high</td>
<td>130-159</td>
<td>≥ 60</td>
<td>200-499</td>
</tr>
<tr>
<td>High</td>
<td>≥ 190</td>
<td>≥ 60</td>
<td>≥ 500</td>
</tr>
<tr>
<td>Very high</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Three Categories of Risk that Modify LDL-C and Non-HDL-C Goals**

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Non-HDL-C Goal (mg/dL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalents</td>
<td>&lt; 100</td>
<td>&gt; 110</td>
</tr>
<tr>
<td>Multiple (≥2) risk factors</td>
<td>130</td>
<td>160</td>
</tr>
<tr>
<td>Zero to 1 risk factor</td>
<td>160</td>
<td>190</td>
</tr>
</tbody>
</table>

For patients with 2 or more CHD risk factors but no evidence of CHD, the LDL-C goal is less than 130 mg/dL (Table 2). Initiation of drug therapy in this patient group is based on risk assessment tables developed by investigators in the Framingham Heart Study. Drug therapy is recommended if the LDL-C level is 160 mg/dL or higher after lifestyle modification for patients whose 10-year CHD risk is less than 10%.

The NCEP guidelines provide a blueprint for treating patients to lipid goals. The responsibility for following the blueprint rests with clinicians and their patients, who must share actively in the clinical effort by recognizing the importance of treating lipid disorders and by adhering to prescribed therapies, both pharmacologic and nonpharmacologic.
ATP III suggests that individuals who already have CHD should strive for an LDL-C goal of less than 100 mg/dL (Table 2). Drug therapy should be considered for all CHD patients who have LDL-C levels of 130 mg/dL or greater and may be initiated simultaneously with lifestyle modification.

ATP III recognized for the first time that high triglycerides are an independent risk factor for CHD and recommends establishing a second treatment goal in patients with triglyceride levels above 200 once the LDL-C goal has been achieved. This goal is defined by non-HDL and is set 50 mg/dL above the LDL goal (Table 2). This recommendation is based on the fact that an increased triglyceride level signals the presence of cholesterol-rich remnant particles that are atherogenic and require additional treatment.

Another notable change embodied in ATP III is the recommendation to obtain a lipoprotein profile as the initial test for hypercholesterolemia. Earlier versions of the guidelines had recommended assessment of total cholesterol only, with lipoprotein assessments guided by the patient's cholesterol level.

Finally, ATP III recommends that hormone replacement therapy (HRT) not be considered as an alternative to lipid-lowering therapy in postmenopausal women. The recommendation stems from the panel's conclusion that clinical studies have failed to show that HRT reduces CHD risk but have shown an increased risk of thromboembolism and gallbladder disease.

The focus of the treatment of the metabolic syndrome as a target for therapy. The metabolic syndrome is a constellation of risk factors that greatly increase a patient's risk for CHD. Characteristics of the syndrome include obesity, central adiposity, high blood pressure, insulin resistance, and a particularly atherogenic form of dyslipidemia that includes elevated triglycerides, low HDL-C, and small, dense LDL particles.

The treatment of the focus of the metabolic syndrome is on lifestyle modification and management of associated risk factors. ATP III also recommends assessment of risk factors classified as life-habit factors in all patients, including atherogenic diet, obesity, and physical inactivity.

For patients who do not have CHD and are not at exceptionally high risk, ATP III recommends a 3-month trial of TLC before consideration is given to drug therapy for dyslipidemia. LDL-C response to intervention should be assessed after 6 weeks. If the response is inadequate, additional dietary modifications can be implemented, and referring the patient to a dietitian may be considered. Among patients who require drug therapy for dyslipidemia, nonpharmacologic interventions should continue to help maintain or augment the effects of drug treatment.

Options for Drug Therapy

Consistent with previous NCEP guidelines, ATP III cites a class of drugs that have proven effective for treatment of dyslipidemia: HMG-CoA reductase inhibitors (statins), bile acid sequestrants, niacin, and fibric acids (fibrates). ATP III recommends initiating drug therapy with a statin, bile acid sequestrant, or niacin to achieve LDL-C goals.

STATINS

As a class, the statins are the most potent lipid-lowering drugs, achieving LDL-C reductions that range as high as 55%. Since lovastatin, the first of the statins, was approved by the Food and Drug Administration in 1987, the agents have become the most widely used drugs in the treatment of dyslipidemia. The statins combine excellent lipid-lowering efficacy with a favorable safety profile. The most commonly reported side effects include nausea, fatigue, and changes in liver enzymes occurring in less than 3 of 100 patients and elevations in liver enzymes occurring in less than 3 of 100 patients, which tend to be dose dependent.

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Mylipity, in particular, is more common in patients who are taking drugs that can interfere with statin metabolism, including cyclosporine, nicoctinic acid, fibric acid derivatives, erythromycin, and azole antifungal agents.

In clinical trials of statins, between 4% and 7% of participants have withdrawn because of side effects. Outside the controlled environment of a clinical trial, the withdrawal rate is likely to be higher, given that the patients taking the drugs may have multiple medical disorders for which they are taking other drugs.

BILE ACID SEQUESTRANTS

Bile acid sequestrants lower cholesterol levels by binding to intestinal bile acids and blocking their reabsorption, leading to increased fecal excretion and resulting in depletion of the hepatic bile acid pool. Subsequently, bile acid synthesis from cholesterol increases, which stimulates hepatic cholesterol biosyn-

Table 3. Nutrient Composition of the TLC Diet

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Recommended Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated fat</td>
<td>Less than 7% of total calories</td>
</tr>
<tr>
<td>Polyunsaturated fat</td>
<td>Up to 10% of total calories</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Up to 20% of total calories</td>
</tr>
<tr>
<td>Total fat</td>
<td>25%-35% of total calories</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>50%-60% of total calories</td>
</tr>
<tr>
<td>Fiber</td>
<td>20-30 g/day</td>
</tr>
<tr>
<td>Protein</td>
<td>Approximately 15% of total calories</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Less than 200 mg/dl</td>
</tr>
<tr>
<td>Total calories (energy)</td>
<td>Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain</td>
</tr>
</tbody>
</table>

*Vats fatty acids are another LDL-C-raising fat that should be kept at a low intake.
1. Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains. Fruits, and vegetables. (Daily energy expenditure should include at least moderate physical activity (consisting approximately 200 Kcal per day).
thesis, increases expression of LDL-C receptors, and enhances LDL-C clearance.11

The original members of the drug class are colestipol and cholestyramine, the latter of which was used in the landmark LRC program that provided the first clear evidence that lipid-lowering therapy reduces CHD risk.12 Reported reductions in LDL-C with the agents range between 15% and 30%. Bile acid sequestrants increase HDL-C by about 5% and usually have little or no effect on triglycerides.13 In patients with hypertriglyceridemia, the older bile acid sequestrants can increase triglyceride levels.

Troubleome gastrointestinal side effects, especially constipation and flatulence, have limited the use of colestipol and cholestyramine, particularly with the emergence of statins. Additionally, the 2 older members of the drug class have the potential for drug interactions that can adversely affect absorption of drugs and fat-soluble vitamins.13,14

The addition of a new agent to the class could spark renewed interest in using bile acid sequestrants in the treatment of dyslipidemia. Colesevelam is a nonsystemic, nonabsorbed agent that has a high binding affinity for bile acids. Notably, colesevelam has not been associated with gastrointestinal distress and many of the drug interactions observed with colestipol and cholestyramine. In clinical trials, colesevelam has reduced LDL-C levels on average by 15% to 20% and has raised HDL-C levels by as much as 11%, although the overall effect on HDL-C appears to be fairly modest. Patient adherence to colesevelam has been exceptional in clinical trials, with compliance rates of up to 92%.15,16

As a nonsystemic agent that has relatively few side effects, colesevelam may appeal to many physicians and patients alike. The agent might be considered as initial therapy for patients with mixed dyslipidemia whose triglyceride levels are elevated but whose LDL-C levels are not.17

Nicotinic Acid

Available in many formulations without a prescription, nicotinic acid is the least expensive option for drug treatment of dyslipidemia. The lipid-modifying effects of the agents relate to inhibition of lipolysis in adipose tissue and a reduction in the hepatic secretions of apolipoprotein B particles.18 At full doses, nicotinic acid, or niacin, can lower LDL-C by as much as 25%. However, the primary effects of the agent are on HDL-C and triglycerides. During sustained treatment with 2 g of niacin or 3 g daily of crystalline niacin, HDL-C can increase by as much as 35%, accompanied by equally impressive decreases, as much as 50%, in triglycerides.19

The major downside to nicotinic acid is its side effects, which can be substantial. Many patients have pronounced vasodilatory responses that manifest as flushing, which often proves to be intolerable. Use of aspirin 30 minutes prior to the first daily dose can diminish these effects. Other potential risks include hyperglycemia, hyperuricemia, gout, upper gastrointestinal distress, and hepatotoxicity.20

Fibrates

Fibrate therapy usually produces only a modest reduction in LDL-C but increases HDL-C by 10% to 20%. The drugs have a pronounced effect on triglycerides, which can be decreased by as much as 50%. The impact on LDL-C appears related to triglyceride levels; nicotinic acid is the least effective option for patients who have high triglyceride levels.21

In the era of statin dominance, clinical interest in fibrates has been reinvigorated to some extent by results of the VA-HIT, which showed a 24% reduction in CHD death, nonfatal myocardial infarction, and stroke in high-risk CHD patients treated with gemfibrozil.22 The primary objective of this trial was to determine whether HDL-C risk could be reduced by raising HDL-C levels without significantly affecting LDL-C. As the results demonstrated, that objective was met.

The most notable adverse effect of fibrate therapy is the risk for gallstone formation, a risk that many clinicians and patients are unwilling to take. Other potential side effects include dyspepsia, myopathy, renal dysfunction, and abnormal liver function.23 Clinical use of fibrates also is hindered by a still-unexplained increase in non-CHD mortality observed in an early trial with clofibrate conducted by the World Health Organization.24

Combination Therapy

Although the clinical efficacy of statins is unquestioned, standard doses (used in clinical practice achieve LDL-C levels of less than 100 mg/dL in about 50% of patients. Because of concerns about side effects and possibly cost, many physicians are reluctant to prescribe high-dose statin therapy for patients who do not achieve lipid goals with starting doses.

Combination lipid-lowering therapy offers a potentially attractive option that addresses some of the concerns related to use of high-dose statins. The combination of 2 or more drugs achieves reductions in lipid levels that exceed those of monotherapy. By linking complementary mechanisms, combinations have a greater lipid-lowering effect compared to an increased dose of monotherapy, especially when the combination involves augmenting a statin with a drug from another class.25,26 Some combinations may prove to be better tolerated than high-dose therapy, particularly when a drug with a favorable side-effect profile, such as colesevelam, is the add-on therapy.27 Examples of combination strategies are discussed below.

Fibrate-Statin

This combination makes theoretical sense because of the complementary effects of these drugs on triglycerides (fibrate) and LDL-C (statin). The combination might prove especially attractive for patients with mixed hyperlipidemia characterized by elevated triglycerides and LDL-C.

Unfortunately, the risk of myopathy with the combination increases beyond what is normally observed with either drug class alone. For combination therapy, the drugs should be used in the lowest effective doses and used only in patients who have normal liver and kidney function. Correspondent drug therapy that may raise blood levels by interfering with metabolism should be recorded. Moreover, separating the drugs’ dosing schedules (fibrate in the morning, short-acting statin in the evening) may theoretically improve the safety of the combi-
nation, although it has not been studied. Substituting fenofibrate for gemfibrozil may minimize problems with myopathy, although the extent of the problem with this combination has not been widely studied.17–21

**STATIN-NIACIN**

This combination offers an alternative to fibrates-niacin for patients with mixed hyperlipidemia as well as for patients with only a cholesterol elevation. The combination is associated with fewer problems related to myopathy, although the vasodilatory effects of niacin can still prove difficult to tolerate. The addition of 2 g of niacin to a stable dose of statin was recently reported to add an additional 31% of LDL-C lowering.22 Additionally, niacin may worsen glycemic control in patients with diabetes or who have prediabetes symptoms. Lowering the niacin dose can reduce the side effects and still improve triglyceride and HDL-C levels, complementing the impact of a statin on LDL-C.

**FIBRATE-NIACIN**

Used infrequently, this combination may have some synergy with respect to the individual effects of the drugs on triglyceride and HDL-C levels and may prove useful in patients with very high triglyceride levels.23

**CONCLUSION**

According to ATP III recommendations, the emphasis of lipid-lowering therapy should be placed on reaching target lipid levels, which differ among patients depending on their risk of developing CHD. A majority of patients with dyslipidemia will likely require drug therapy to achieve lipid goals, which currently are met in only a minority of patients, including those with established CHD. Early, aggressive use of the variety of effective lipid-lowering agents available to clinicians is a key to achievement of lipid goals in more patients. Use of appropriate doses of drugs and drug combinations further enhances the likelihood of achieving target lipid levels. Although the emphasis on drug therapy has increased in the 2001 NCEP recommendations, dietary intervention, reduction in weight if applicable, and increased physical activity remain essential to reducing CHD risk with or without concomitant drug therapy.

**REFERENCES**