Overview of Pharmacologic Therapy for the Treatment of Dyslipidemia

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Summary

Although the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines stress the importance of nonpharmacologic lipid modification interventions such as diet and exercise, the guidelines also recognize that many patients will require drug therapy to achieve low-density lipoprotein cholesterol (LDL-C) target goals. Currently available lipid-modifying drugs include bile acid sequestrants (or resins), fibrates, niacin, and statins, with each class exerting different effects on the lipid profile. In addition, weight loss agents such as plant stanols and sterols have been shown to be effective in modifying plasma lipids. Of these agents, the statins are the most effective, most widely prescribed, and best-tolerated form of lipid-lowering drug therapy. New formulations of other drugs, such as niacin and bile acid sequestrants, can also improve treatment regimes and reduce side effects, thereby improving patient compliance with these therapies. In patients who have high levels of LDL-C and triglycerides together with low concentrations of high-density lipoprotein cholesterol (HDL-C), combination therapy may be required. Ezetimibe, a selective cholesterol absorption inhibitor, is the first of a new class of lipid-lowering agents and provides a new agent for the management of patients with dyslipidemia. Data from the ezetimibe clinical development program suggests that this agent can be used alone or in combination with statins to reduce LDL-C, improve compliance, and bring more patients to ATP III target goal.

KEYWORDS: Atherosclerosis, Cholesterol, Coronary heart disease, Drug therapy, Dyslipidemia

A dult Treatment Panel III (ATP III) stresses the importance of initiating therapeutic lifestyle changes (TLC) and reiterates that TLC forms the foundation for all drug therapy. However, diet modification and regular physical activity are often not adequate to achieve the aggressive new treatment goals outlined by the guidelines. In addition, long-term patient compliance with TLC is often poor. Consequently, ATP III encourages the addition of drug therapy if TLC fails to reduce low-density lipoprotein cholesterol (LDL-C) to goal after 3 months. For patients at high risk, ATP III recommends that drug therapy may be initiated along with TLC from the onset of treatment. Utilization of appropriate drug therapy offers a real chance for patients to reduce LDL-C and can significantly decrease the risk for coronary heart disease (CHD). Numerous clinical trials completed in the past several decades have demonstrated the effectiveness of lipid-lowering agents in decreasing the need for percutaneous transluminal coronary angioplasty and decreasing coronary events and stroke, arterial stenosis, and cardiovascular and overall mortality.1-3

The treatment goals and lipid thresholds for initiating drug therapy are based on the presence of CHD or CHD risk equivalents, the number of major risk factors, and the estimated 10-year risk of CHD.4 For patients with the highest risk for coronary events, ATP III identified an LDL-C threshold of >130 mg/dL for initiation of drug (after a 3-month trial of TLC) and a goal of <100 mg/dL. For patients with a baseline LDL-C between 100 mg/dL and 129 mg/dL, ATP III recommends that drug therapy is optional, and physicians are encouraged to use their professional clinical judgment to determine the nature of therapy required to reduce CHD risk.

Results of the Heart Protection Study have subsequently demonstrated benefit with statins for patients at high risk, even when the baseline LDL-C is <130 mg/dL. For patients with moderate risk without definite CHD or CHD risk equivalents but with >2 major risk factors and a 10-year risk of 10% to 20%, the threshold is >130 mg/dL and the target is also <130 mg/dL. For patients at moderate risk but with a 10-year risk <10%, the LDL-C threshold is >160 mg/dL. For patients without CHD and with 0 to 1 major risk factor, drug treatment should be considered if LDL-C cholesterol is >190 mg/dL after 3 months of TLC, with a goal of <160 mg/dL. In all cases, TLC should be encouraged and supported (Table 1).

At any level of LDL-C, the risk for CHD may be increased by the presence of the metabolic syndrome. Consequently, this syndrome is a secondary therapeutic target after the LDL-C goal is achieved. The metabolic syndrome is characterized by the presence of at least 3 of the following risk factors: abdominal obesity, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), hypertension, and elevated fasting glucose. The meta-
bolic syndrome may also be characterized by elevated levels of lipoprotein(a) and homocysteine, and a prothrombotic and pro-inflammatory state. These emerging risk factors suggest the existence of subclinical atherosclerotic disease and indicate the need for a more aggressive strategy in patients who appear healthy based on traditional risk factors.4

Once the decision has been made to initiate drug therapy, patients should be provided with the agent that offers the greatest opportunity to achieve target LDL-C levels with minimal titration (Table 2). Several classes of agents are currently available for the pharmacologic treatment of lipid abnormalities, including fibrates, nicotinic acids, bile acid sequestrants, and statins (Figure 1). In addition, plant sterols and stanol esters have been used to effectively modify lipid levels.

### Current Lipid-Modifying Drugs—Statins

Of the 4 classes of lipid-modifying drugs, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are the most widely prescribed, best tolerated, and most effective agents. Statins decrease LDL-C by competitively inhibiting HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. The resultant reduction in hepatocyte cholesterol concentration stimulates increased expression of hepatic LDL-C receptors, which remove LDL-C from the circulation. Several large clinical trials with statins have demonstrated their efficacy in lowering LDL-C by 24% to 60% in hypercholesterolemic patients in a dose-dependent manner and in reducing triglycerides by 10% to 29%.3 In addition, statins may increase HDL-C by up to 12%.5 The currently available statins are differentiated by the LDL-C lowering potency elicited at a given dose. Large clinical outcome trials have demonstrated unequivocally that statins reduce the incidence of CHD events, including myocardial infarction, coronary death, stroke, and total mortality.5,6

Although statin monotherapy is well tolerated and associated with few adverse effects, the most serious side effect is hepatic and skeletal muscle toxicity. Elevated transaminase levels occur in approximately 1% of patients regardless of dose.6 Myopathy is less common than increases in liver enzymes, but can in rare instances lead to rhabdomyolysis and acute renal failure. With statin monotherapy, myopathy occurs in approximately 1 in 1,000 patients and is dose-related. This issue is particularly pertinent with the recent withdrawal of cerivastatin and the U.S. Food and Drug Administration’s delay of the approval of rosuvastatin. Hence, there remains some debate as to whether clinicians should uptitrate statins to their highest dose. It should be noted, however, that statin monotherapy rarely causes myopathy and rhabdomyolysis, and these conditions are more common when statins are combined with gemfibrozil or when used in patients with hepatic or renal failure, acute infection, and hypothyroidism.7

### Bile Acid Sequestrants

Bile acid sequestrants have been in clinical use for more than 30 years. These agents bind bile acids in the intestine and thereby interrupt the process by which nearly 90% of bile acids are returned to the liver for reuse. Since bile acids are formed from cholesterol, sequestrants reduce total body cholesterol. When the bile acid pool is depleted due to sequestrant-induced excretion, hepatic synthesis of bile acids is increased, leading to a reduction in hepatic cholesterol. This reduction also triggers a secondary activation of HMG-CoA reductase, however, that causes an increased cholesterol production that can attenuate the cholesterol-lowering effect of bile acid sequestrants. The addition of a statin to bile acid sequestrant therapy can block the secondary activation of HMG-CoA reductase.

Bile acid sequestrants can be used as monotherapy when moderate reductions in LDL-C are required to achieve goal or as add-on therapy to statins, particularly in patients with severe dyslipidemia. Although effective in reducing LDL-C by 15% to 30% over the dose range, compliance is limited because many patients consider bile acid sequestrants to be unpalatable, and their use may be associated with undesirable GI side effects.3 Colesevelam, a high-capacity polymer that selectively binds bile acids in the intestine, is the newest bile acid sequestrant. Because of its selectivity, colesevelam may help reduce the bothersome side effects, although compliance remains an issue, as patients are required to take up to 6 tablets at a time.

### Nicotinic Acids

Nicotinic acid (niacin) is the oldest lipid-lowering drug available, having first been used in the 1950s. Nicotinic acids are most commonly used in their rapid-release form and provide an LDL-C reduction in the range of 10% to 20% at doses of 1,500 mg/day to 4,000 mg/day.1 It is also the most powerful agent for elevating

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**FIGURE 1** ATP III Treatment Recommendations for Drug Therapy

<table>
<thead>
<tr>
<th>Start statin or bile acid sequestrant or nicotinic acid</th>
<th>Consider higher dose of statin or add a bile acid sequestrant or nicotinic acid</th>
<th>If LDL-C goal not achieved, intensify LDL-lowering therapy</th>
<th>If LDL-C goal not achieved, intensify drug therapy or refer to a lipid specialist</th>
<th>Q 4-6 mo</th>
<th>Monitor response and adherence to therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate LDL-C-lowering drug therapy 6 wks</td>
<td>If LDL-C goal not achieved, intensify LDL-lowering therapy 6 wks</td>
<td>If LDL-C goal not achieved, intensify LDL-lowering therapy 6 wks</td>
<td>If LDL-C goal not achieved, intensify LDL-lowering therapy 6 wks</td>
<td>Monitor response and adherence to therapy</td>
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HDL-C, with increases of 10% to 15% even at modest doses. In addition, niacin is effective in lowering triglycerides and is a helpful agent in the management of patients with mixed dyslipidemia. Nicotinic acid reduces hepatic synthesis of triglycerides and limits secretion of triglyceride-rich, very-low-density lipoprotein cholesterol (VLDL-C) by inhibiting the mobilization of free fatty acids from the peripheral tissues. In addition, niacin may also inhibit the conversion of VLDL-C to LDL-C and initiate a shift in LDL-C from the small, dense particles to large, buoyant, less atherogenic LDL-C particles.

The primary drawback with niacin is tolerability. Patients experience GI upset, flushing, itching, and skin irritation in the face and neck with initial dosing. Most of these bothersome side effects can be overcome with proper initiation, titration, and patient education; however, nicotinic acids remain undertused. More serious side effects are evident at higher doses. Although rare, high doses of niacin can elicit gout, clinical hepatitis, hypertriglyceridemia, and negatively impact glycemic control.

Nearer, extended-release preparations of niacin have been developed to overcome many of these undesirable side effects. Studies utilizing the newer preparations as monotherapy demonstrated favorable dose-related effects on LDL-C and HDL-C; the trials also demonstrate that the agents are generally well tolerated. Extended-release niacin has also been shown to be effective in improving lipid parameters when used in combination with statins, particularly for patients who have elevated triglycerides and/or low HDL-C. An older formulation of sustained-release niacin given in combination with simvastatin has also been shown to increase HDL-C 26%, reduce LDL-C 42%, retard stenosis, and reduce the combined endpoints of death, myocardial infarction, stroke, and revascularization in patients with known coronary disease, low HDL-C, and normal LDL-C.

**Fibrates**

Fibrates fibrates act on the liver, resulting in decreased secretion of VLDL-C and increased lipoprotein lipase activity in skeletal muscle. Thus, the lipid-modifying effects of fibrates are secondary to changes in these LDL-C precursors. In patients with very high triglycerides, fibrates may increase LDL-C levels.

Fibrates may be used in combination with niacin or bile acid sequestrants since these drugs appear to be additive in lowering LDL-C and raising HDL-C. When fibrates are given in combination with a sequestrant, the administration of the 2 drugs must be separated by at least 2 hours to ensure full bioavailability of the fibrates. Combinations of fibrates with statins are very effective in lowering LDL-C and increasing HDL-C, particularly in patients with mixed hyperlipidemia, characterized by elevated triglycerides and LDL-C. Statin-fibrate combinations have been historically limited by fear of the increased risk of myopathy. However, the absolute risk has been estimated to be as low as 0.12%. The combination of a statin with gemfibrozil has been most often reported although this may be due to much greater use of this fibrate to date. When the choice is made to use a statin and fibrate in combination, these drugs should be used only in the lowest effective doses and only in patients who have normal liver and kidney function.

**Plant Stanols**

Plant stanols decrease LDL-C by approximately 10% in modestly hypercholesterolemic patients. These compounds reduce cholesterol absorption from the intestine by competing for the limited space available in mixed micelles that deliver lipids for absorption into the intestinal mucosal cell. Plant stanols are nonprescription, and their use should be encouraged for patients at low risk, requiring only modest LDL-C reductions. These agents are not recommended as primary therapy for moderate- to high-risk patients requiring more aggressive lipid lowering. Plant stanols are generally well tolerated, and the LDL-C-lowering effect appears to be additive to statin or fibrate therapy.

Despite the efficacy of statins and other lipid-modifying agents in reducing coronary events, the issues of tolerability, untoward side effects, and safety remain concerns with many agents, particularly when administered at high doses or in combination. This
problem restricts use when patients cannot tolerate statins or when statin up-titration is limited due to safety concerns. In these cases, physicians and patients are limited to agents such as bile acid sequestrants, niacin, or other less-effective therapies.

A promising new alternative therapy is the recently approved selective inhibitor of intestinal cholesterol absorption, ezetimibe. Ezetimibe appears to have significant potential for use as monotherapy for patients at low risk for CHD who require a modest reduction in their LDL-C or for those who do not tolerate statin therapy. In addition, when ezetimibe is used in combination with a low-dose statin in patients at moderate to high risk for CHD, the drug can elicit a reduction in LDL-C comparable to that seen at the highest statin doses, with a safety profile similar to placebo. Thus, ezetimibe appears to be a safe and effective lipid-modifying agent that can help patients achieve target while minimizing tolerability and safety concerns that lead to poor adherence and reduced clinical and economic effectiveness.

## Pharmacoeconomic Outcomes of Lipid-Lowering Therapies

The assessment of the economic impact of drug treatment is complex and involves the consideration of many factors, including drug costs, costs related to the diagnosis, treatment, and management of CHD events, and direct and indirect costs associated with lost productivity and quality of life. Most of the direct and indirect costs of CHD are related to the cost of hospitalization, invasive procedures such as angioplasty, and loss of quality of life. Therefore, the real cost benefits of lipid-modification therapy are related not only to the reduction in morbidity and mortality but also to the reduction of direct and indirect costs. Now that several clinical trials have clearly shown the benefit of cholesterol lowering on cardiovascular morbidity and mortality, the debate surrounding lipid drugs may shift from their efficacy and safety to that of their cost and cost-effectiveness. Of course, safe and efficacious drugs cannot improve cost-effectiveness without a commitment on the part of patients and physicians to implement and adhere to treatment in order to realize the clinical and economic outcome benefits observed in clinical trials.

The Scandinavian Simvastatin Survival Study (4S) demonstrated that statin use in a high-risk secondary prevention population is cost effective in all subgroups analyzed. Furthermore, 4S data indicated that cost-effectiveness increases as the number of CHD risk factors increases. When certain indirect costs such as loss of job productivity and disability are taken into consideration, statin therapy provides a cost saving, particularly in young men. The West of Scotland Coronary Prevention Study (WOSCOPS) suggested that in a primary prevention cohort, the use of pravastatin was relatively cost effective in those patients at highest risk.

The cost-effectiveness of providing statin therapy to high-risk patients for the reduction of CHD is supported by these pharmacoeconomic analyses of WOSCOPS and 4S. However, when the usual starting dose of most statins is doubled, the result is only about a 6% additional LDL-C reduction while the increase in cost can be as much as 2-fold. This illustrates the reality that the greater the need to achieve LDL-C target goals, the greater the cost. Multiple upward titrations of statins have the potential to significantly increase the overall cost of treatment as drug costs, office visits, and patient monitoring costs are added with each move from the starting dose. In addition, undesirable side effects of many statins are dose-related, use of high statin doses may lead to added costs for intensified monitoring. Novel therapies currently in development have the potential to minimize costs associated with multiple statin titrations and side-effect monitoring. Safe and effective new agents that can be used either as monotherapy or in combination with low-dose statins hold promise to provide additional cost-effective strategies for the reduction of LDL-C.

### DISCLOSURES

Dr. Lipsey received an honorarium for participating in the symposium on which this article is based. He disclosed having no financial interest/relationships with commercial entities related to his presentation materials.

### REFERENCES