ABSTRACT

Primary preventive measures for cardiovascular disease are centered on lifestyle changes such as diet, exercise, and weight management. If these lifestyle changes do not prove adequate in optimizing lipid levels, drug treatment should be considered. Four classes of lipid-lowering agents are presented briefly, including their respective lipoprotein effects, contraindications, and common adverse effects. These agents include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), nicotinic acid, fibric acid derivatives, and bile acid sequestrants. An investigational class of agents, cholesterol absorption inhibitors, is mentioned. Four of the 5 landmark monotherapy statin clinical trials reviewed for achievement of low-density lipoprotein cholesterol (LDL-C) levels did not reach new guideline levels of <100 mg/dL nor did they reach older LDL-C goals. The use of starting doses and the nonlinear dose-response curve of statins may be responsible for this finding. Results of a clinical study evaluating the combination of a statin and colesevelam (a bile acid sequestrant) demonstrated a more pronounced reduction in LDL-C, total cholesterol, and triglycerides as well as an improved increase in high-density lipoprotein cholesterol with combination therapy as compared to monotherapy. To achieve new LDL-C goals, clinicians should use more aggressive treatment strategies, including combination therapy.

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VER THE PAST 30 YEARS, CLINICAL STUDIES HAVE EVALUATED THE ROLE OF CHOLESTEROL IN CARDIOVASCULAR DISEASE. APPROXIMATELY 10 YEARS AGO THERE WAS NO MEDICAL EVIDENCE THAT LOWERING CHOLESTEROL WOULD LENGTHEN LIFE, BUT RECENT CLINICAL STUDIES HAVE RESULTED IN A DRAMATIC INCREASE IN THE ABILITY TO MODIFY THE CAUSES OF CORONARY HEART DISEASE (CHD). MOST OF THIS NEWFOUND SUCCESS HAS BEEN WITH SECONDARY PREVENTATIVE MEASURES. SPECIFICALLY, A META-ANALYSIS OF 5 RANDOMIZED CONTROLLED STUDIES INVOLVING 3-HYDROXY-3-METHYLGUTARYL COENZYME A REDUCTASE INHIBITORS (STATINS) WITH FOLLOW-UP FOR AT LEAST 4 YEARS PROVIDED A RELATIVE REDUCTION IN RISK OF MAJOR CORONARY EVENTS BY 31% AND OF ALL-CAUSE MORTALITY BY 21%.

Primary preventative measures stressed in the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP III) published guidelines on detection, evaluation, and treatment of high blood cholesterol in adults are based on lifestyle changes, including dietary changes, increased physical
activity, and weight control. After a decision has been made to include lipid-lowering agents to these lifestyle modifications, the patient's blood lipids must be followed with alterations in the pharmacologic regimen as necessary. In light of ATP III's strict guidelines for appropriate lipid management, practitioners must treat hyperlipidemia more aggressively. This paper presents the rationale behind combination therapy and its use in aggressive lipid management strategies.

**LIPID MANAGEMENT GOALS OF ATP III**

While ATP III is based on ATP I and II, ATP III calls for more intensive low-density lipoprotein cholesterol (LDL-C)-lowering therapy and primary prevention in people with multiple risk factors. According to ATP III, the optimal level is <100 mg/dL for LDL-C, <200 mg/dL for total cholesterol, and ≥40 mg/dL for high-density lipoprotein cholesterol (HDL-C). Prior to intervention with lipid-lowering agents, causes of secondary dyslipidemia such as diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drug-related abnormalities should be ruled out in all patients with hyperlipidemia. If secondary dyslipidemic causes are present, they should be excluded and/or treated prior to initiation of primary prevention measures.

To achieve ATP III lipid goal levels in clinical practice, the optimal treatment program must include individualization for each patient and include agents with proven benefit in clinical trials. Major classes of therapeutic agents for lipid management emphasizing uses and limitations are discussed so that selection of the most appropriate agent for an individual patient can be facilitated.

**LIPID-LOWERING AGENTS**

Currently, several different pharmacological classes of agents, including the statin group, nicotinic acid, fibric acid derivatives, and bile acid sequestrants, are available in the United States and provide favorable changes in the lipid profile. A new class of agents, cholesterol absorption inhibitors, is still under clinical investigation.

**STATINS**

Lovastatin, simvastatin, atorvastatin, fluvastatin, and pravastatin are all statins approved by the Food and Drug Administration (FDA) to lower LDL-C levels. These agents are associated with reductions in LDL-C by 18% to 55% and in triglycerides by 7% to 30%. Additional lipoprotein effects include elevations in HDL-C by 5% to 15%. In clinical trials, these agents demonstrated the ability to reduce all-cause mortality, major coronary events, stroke, deaths due to CHD, and the need for coronary procedures. Use of statins is limited by a contraindication in concurrent active, or chronic or active liver disease, and during pregnancy. Drug-related adverse effects such as myopathy and increased liver enzymes also have been associated with statin use. Drug interactions have been observed with the following agents: cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors; therefore, their concomitant use with statins should be used with appropriate caution.

**NICOTINIC ACID**

Nicotinic acid is available as an over-the-counter agent in the United States. Immediate-release, extended-release, and sustained-release formulations of nicotinic acid are available. Clinical trials have demonstrated that lowering LDL-C by 5% to 25% and triglycerides by 20% to 50%, and increasing HDL-C by 15% to 35% resulted in a reduction in major coronary events and in a possible reduction in total mortality rates. The hallmark adverse effect of nicotinic acid is flushing; additional adverse events include hyperglycemia, hyperuricemia, upper gastrointestinal distress, and hepatotoxicity. Similar to the statins, nicotinic acid is contraindicated in patients with concurrent chronic liver disease. The combination of statins and nicotinic acid increases the risk of hepatic dysfunction. Severe gout is an additional contraindication, and diabetes, hyperuricemia, and peptic ulcer disease are relative contraindications.

**FIBRIC ACID DERIVATIVES**

In clinical trials, gemfibrozil, fenofibrate, and clofibrate (fibric acid derivatives) have reduced major coronary events. Favorable lipid effects with these agents include reductions in LDL-C by 5% to 20% (an effect that may be increased in patients with elevated triglycerides), reductions in triglycerides by 20% to 50%, and elevations in HDL-C by 10% to 20%. Use of fibric acid derivatives in patients with concurrent severe hepatic disease is absolutely contraindicated and an unacceptable alternative (along with nicotinic acid and
statins) for lipid management in these patients. In addition, patients suffering from severe renal disease should not be treated with fibric acid derivatives. Other adverse effects observed with fibric acid derivatives include dyspepsia, gallstones, and myopathy, as well as unexplained non-CHD deaths reported in a World Health Organization study.3

**Bile Acid Sequestrants**

Cholestyramine, colestipol, and colesevelam (bile acid sequestrants) are available in the United States. Decreases in LDL-C by 15% to 30% and increases in HDL-C by 3% to 5% as well as no changes or increases in triglyceride levels have been observed with these agents.3 Clinical studies of bile acid sequestrants have reported a reduction in major coronary events and CHD deaths. These agents are not absorbed systemically and, therefore, are not associated with the liver toxicities observed with nicotinic acid and statins. In addition, bile acid sequestrants may be used in combination with statins, fibric acid derivatives, and nicotinic acid. Absolute contraindications to these agents include dysbetalipoproteinemia and triglyceride levels greater than 400 mg/dL. Bile acid sequestrants are relatively contraindicated in patients with triglyceride levels greater than 200 mg/dL. Adverse effects include gastrointestinal distress, constipation, and decreased absorption of other drugs.3

Bile acid sequestrants offer an effective treatment alternative to patients who are intolerant of statins or who experience liver enzyme elevations caused by statins, fibric acid derivatives, or nicotinic acid. In addition, patients who prefer to receive nonsystemic therapy, such as young adults or women of childbearing potential, may prefer bile acid sequestrants over systemic agents. Of the agents in this class, colesevelam binds bile acids with high specificity due to the spacing of hydrophobic side chains along the polymer backbone, which may theoretically reduce the possibility of some drug-to-drug interactions. Colesevelam uses the combination of ionic binding via primary amines, the optimal length of the hydrophobic side chains, and the presence of quaternary amines on the hydrophobic side chains to allow for affinity, specificity, and a high capacity for bile salts.4

**Cholesterol Absorption Inhibitors**

The cholesterol absorption inhibitors represent a new class of lipid-lowering agents. Early evidence demonstrates the possibility of an additive effect to that achieved with statin treatment.5 The exact mechanism of action of these agents is currently unknown.6 Cholesterol absorption inhibitors are metabolized in the intestine and undergo rapid enterohepatic recycling that may result in systemic accumulation. Importantly, no data are currently available regarding toxicity, adverse effects, contraindications, and outcomes.

**Target LDL-C Levels with Statin Therapy in Clinical Trials**

ATP III recommends an LDL-C goal of less than 100 mg/dL for patients with CHD or CHD equivalent.3 This level of LDL-C was not achieved by most of the landmark clinical trials involving statin therapy. In the Scandinavian Simvastatin Survival Study (4S), patients at high risk of coronary heart disease received 10 mg to 40 mg of simvastatin per day.7 The mean baseline LDL-C level was 188 mg/dL and at endpoint was 122 mg/dL. This endpoint value for LDL-C did not meet the ATP II recommendations of ≤100 mg/dL; nor did it meet the more stringent recommendations of ATP III.

Endpoint LDL-C levels were above ATP III guidelines in other studies as well. In the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, median baseline LDL-C levels of 150 mg/dL were reduced to 112 mg/dL after a mean follow-up period of 6.1 years with 40 mg of pravastatin per day in patients with CHD.8 Similarly, in the West of Scotland Coronary Prevention Study (WOSCOPS), patients at moderately high risk for CHD who received 40 mg of pravastatin per day had mean baseline levels of 192 mg/dL LDL-C reduced to 144 mg/dL.9 In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), low-risk patients received 20 to 40 mg of lovastatin per day.10 At baseline, the study patients' mean LDL-C levels were 153 mg/dL; after 1 year, the LDL-C levels reached 115 mg/dL.

The Cholesterol and Recurrent Events (CARE) study was the only statin landmark clinical trial in which patients achieved mean LDL-C levels in accordance with ATP III goals.11 In the CARE study, baseline LDL-C levels were 139 mg/dL; after 5 years of therapy with 40 mg of pravastatin per day, LDL-C levels were reduced to 97 mg/dL (32%). The results of these clinical studies suggest that more aggressive ther-
apy is needed in order to achieve ATP III goals. In addition, most of the patients enrolled in these landmark studies were receiving starting doses of statins. Whether an increased titration of statin dose would have resulted in LDL-C levels low enough to meet guidelines is addressed next.

**Dose Response Characteristics**

A 54-week, open-label, randomized, active-controlled study of 318 patients with documented atherosclerosis and baseline LDL-C levels of 173 mg/dL evaluated the ability of 4 statins to reach ATP II LDL-C goal of ≤100 mg/dL. Initially, daily starting doses of 10 mg of atorvastatin, 10 mg of simvastatin, 20 mg of lovastatin, and 20 mg of fluvastatin were given. Investigators were allowed to up-titrate doses every 12 weeks as necessary. A significantly greater number of patients treated with atorvastatin monotherapy achieved goal LDL-C levels as compared to those patients treated with the monotherapy of the other statins (P < .05). However, despite this significant difference, 21% of patients receiving atorvastatin did not meet ATP II’s goal LDL-C levels with monotherapy. An even greater percentage of patients did not meet the LDL-C goals with monotherapy of the other statins (Figure 1).

An analysis of controlled clinical trials evaluating statins, bile acid sequestrants, or niacin and reductions in LDL-C was conducted to determine treatment implications of these agents’ dose-responses. The dose-response for monotherapy with statins, bile acid sequestrants, or niacin is nonlinear and most of their beneficial effects on LDL-C can be achieved at low doses. Two thirds of the anticipated maximum response of statins can be expected with one fourth of the highest dose. In general, doubling the dose of statin monotherapy leads to an additional 6% decrease in LDL-C.

These dose-response findings were confirmed in the CURVES study, a dose-response trial. Patients with hypercholesterolemia (n = 534) were randomized to receive atorvastatin, simvastatin, pravastatin, lovastatin, or fluvastatin in an open-label 8-week study. At endpoint, atorvastatin was associated with significantly greater reductions in LDL-C as compared to milligram-equivalent doses of the other statins (P < .01). However, regardless of the statin used, doubling of dose resulted in an additional 6% lower LDL-C on average.

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**Table. Clinical Trials Evaluating Combination Therapy to Reach LDL-C Goals**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment group Regimen</th>
<th>Δ% Stenosis (P)</th>
<th>% Event reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>FATS (L + R)²⁵</td>
<td>D + R + L</td>
<td>↓46</td>
<td>↓0.7 (0.02)</td>
</tr>
<tr>
<td>USCF-SCOR²⁶</td>
<td>D + R + N ± L</td>
<td>↓39</td>
<td>↓1.5 (0.04)</td>
</tr>
<tr>
<td>SCRIP²⁷</td>
<td>D + (R+N +L+F)+E, BP</td>
<td>↓21</td>
<td>—</td>
</tr>
<tr>
<td>HARP²⁸</td>
<td>D+P+N+C+F</td>
<td>↓41</td>
<td>↑2.1</td>
</tr>
<tr>
<td>Post-CABG²⁹</td>
<td>D+L+C</td>
<td>↓37-40</td>
<td>↓0.054</td>
</tr>
<tr>
<td>Malloy, et al²⁵</td>
<td>R+L+N +L</td>
<td>↓65-68</td>
<td>—</td>
</tr>
<tr>
<td>Grundy, et al²⁶</td>
<td>L+R</td>
<td>↓52</td>
<td>—</td>
</tr>
<tr>
<td>Pan, et al²¹</td>
<td>P+C</td>
<td>↓47-56</td>
<td>—</td>
</tr>
<tr>
<td>Simons, et al²³</td>
<td>S+R</td>
<td>↓46-53</td>
<td>—</td>
</tr>
<tr>
<td>Davignon, et al²³</td>
<td>P+N</td>
<td>↓49</td>
<td>—</td>
</tr>
<tr>
<td>Vacek, et al²⁴</td>
<td>L+N</td>
<td>↓37</td>
<td>—</td>
</tr>
</tbody>
</table>

C = cholestyramine; D = diet; E = exercise program; F = fibrate-type drug; L = lovastatin; N = nicotinic acid; P = pravastatin; R = resin; S = simvastatin.
COMBINATION STATIN AND BILE ACID SEQUESTRANT THERAPY

What are the options for patients who cannot achieve goal LDL-C levels on statin monotherapy or for those who cannot tolerate high doses of statin therapy? Several studies have shown that a combination approach to LDL-C lowering with statins and niacin or with statins and bile acid sequestrants may reduce LDL-C while minimizing the concentration of drugs taken (Table). Data in some studies have shown that combination therapy can reduce LDL-C to a greater extent than can be achieved by monotherapy. Moreover, this combination approach also has reduced cardiovascular events, in some cases up to 70%.

In a randomized, placebo-controlled, double-blind study, colesevelam (a bile acid sequestrant) was administered in combination with a starting dose of simvastatin. Of the 589 patients screened for the study, 258 were randomized to the active treatment period, and 241 patients (123 men and 118 women) completed the study. Patients were randomized into 7 treatment groups based on daily treatment with placebo, 3.8 gm of colesevelam, 10 mg of simvastatin, 2.3 mg of colesevelam, 20 mg of simvastatin, 3.8 mg of colesevelam per day plus 10 mg of simvastatin per day, and 2.3 mg of colesevelam plus 20 mg of simvastatin per day. Analysis of demographic data showed the 7 treatment groups were similar in terms of age, body weight, body mass index, and baseline LDL-C.

As shown in Figure 2, treatment with 10 mg and 20 mg of simvastatin alone reduced LDL-C by 26% and 34%, respectively. Additive LDL-C reduction was observed with the combinations of 3.8 mg of colesevelam plus 10 mg of simvastatin or 2.3 mg of colesevelam plus 20 mg of simvastatin per day, resulting in a 42% decrease in both groups. Intergroup statistical analysis revealed that the LDL-C-lowering effects of combination colesevelam and simvastatin were statistically superior to either agent alone (P < .05).

In all cases, decreases in total cholesterol were statistically significant versus placebo for each of the active treatment groups shown. Combination treatments of 2.3 mg of colesevelam plus 20 mg of simvastatin and of 3.8 gm of colesevelam plus 10 mg of simvastatin produced the greatest reductions in total cholesterol of 29% and 28%, respectively. These combination treatment regimens produced results that were additive based on either agent alone and were statistically superior to reductions in total cholesterol relative to colesevelam or simvastatin alone.

Increases in HDL-C from baseline to endpoint were significant for all active treatment groups. The combination of 3.8 mg of colesevelam plus 10 mg of simvastatin showed the greatest increase in HDL-C (10%). Triglycerides were significantly decreased in all groups shown. Treatment group comparisons revealed that patients treated with 10 mg or 20 mg of simvastatin alone or a combination of colesevelam and simvastatin had statistically significant decreases in triglycerides as compared to patients treated with placebo or with colesevelam alone. A 12% reduction in triglycerides was observed with both coadministration groups: 2.3 mg of colesevelam plus 20 mg of simvastatin 20 mg and 3.8 mg of colesevelam plus 10 mg of simvastatin.

Figure 2. Combination Statin Plus Bile Acid Sequestrant Demonstrates Additive Benefit

LDL-C and Total-C values are expressed as mean, whereas HDL-C and TG values are expressed as median.
LDL-C = low-density lipoprotein cholesterol; Total-C = total cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides.
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OPTIMIZATION OF DRUG THERAPY

When selecting the most appropriate lipid-lowering agent, specific patient characteristics must be considered. Concurrent medical conditions, such as liver disease, make the use of statins, nicotinic acid, and fibric acid derivatives limited. In addition, lifestyle characteristics of patients should be taken into account. Women of childbearing potential should not be given statins without appropriate counseling due to the FDA's category X classification assigned to these agents. An acceptable alternative in these patients may be bile acid sequestrants.

Compliance is another consideration in selecting the most appropriate agent. Adherence to LDL-lowering therapy is critical in achieving benefits observed in clinical trials. A retrospective cohort study has estimated 1-year probability rates of drug discontinuation as 46% for niacin, 41% for bile acid sequestrants, 37% for gemfibrozil, and 15% for statins. These results suggest that in patients with a lifestyle not conducive to good compliance, niacin may not be the most appropriate lipid-lowering agent. After the ideal agent has been selected and instituted, response to therapy should be assessed every 6 weeks.

DISCUSSION

Although several different classes of lipid-lowering agents are available in the United States, statins are the most commonly prescribed. Results of landmark clinical trials with statins have not demonstrated achievement of ATP III's lipid management goals or those of the old ATP II guidelines. The use of statin monotherapy may be partially responsible for this observation.

One explanation for the difficulty observed in getting patients at high risk or with diagnosed coronary artery disease to achieve NCEP goals may be the relatively flat dose-response curve of the statin class. Combination therapy of a statin plus a bile acid sequestrant has proven more effective with fewer adverse effects than a higher dose of a single agent. Colesevelam plus simvastatin demonstrated improved reduction in LDL-C, total cholesterol, and triglycerides and greater elevations in HDL-C as compared to statin monotherapy. In providing effective lipid management for women, the physician must be aware of combination treatment strategies in order to meet current NCEP treatment goals.


