Atherosclerotic vascular disease is the leading cause of death in industrialized nations. The presence of high plasma levels of total cholesterol (TC) and its major carrier, low-density lipoprotein (LDL), are strongly correlated with the development and progression of coronary heart disease (CHD). Conversely, a low level of high-density lipoprotein (HDL) is an independent risk factor for CHD. An increased level of triglycerides (TG) often is present in patients with CHD. Traditionally, CHD risk assessment focused on determining serum levels of TC, LDL-choles-

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ABSTRACT

PURPOSE: To review the pharmacologic properties of the 5 major classes of lipid-modifying agents and summarize the findings from major clinical studies assessing the efficacy and safety of single lipid-modifying agents and combination pharmacotherapy for lipid disorders.

Epidemiology: Coronary heart disease (CHD) affects 13 million Americans and is the cause of 1 in every 5 deaths in the United States. Almost 50% of the adult population has a low-density lipoprotein cholesterol (LDL-C) level ≥130 mg/dL (considered borderline-high to high). It has been estimated that a population-wide decrease in total cholesterol levels of 10% would reduce the incidence of CHD by 30%.

Review Summary: Of the 5 classes of lipid-modifying agents (statins, bile acid sequestrants [BAS], fibrates, niacin, and cholesterol absorption inhibitors [ezetimibe]), all but ezetimibe have been shown to reduce the risk of cardiovascular events during long-term treatment. Statins are the most potent at reducing LDL-C levels, whereas fibrates are most potent at reducing triglyceride levels, and niacin is most potent at increasing levels of high-density lipoprotein cholesterol. Eight of the 10 possible combinations of classes have been studied in clinical trials. Combination therapy provides additional favorable changes in lipid levels compared with monotherapy, and combinations with complementary mechanisms are particularly useful in patients with mixed hyperlipidemia. Caution should be exercised when combining a statin with a fibrate because of the increased risk of myopathy. Hepatic enzyme levels should be monitored when statins are combined with niacin or ezetimibe. The combination of a statin plus a BAS does not increase the incidence of adverse events relative to either agent given alone.

Type of Available Evidence: Randomized controlled trials, nationally recognized guidelines, systematic reviews/meta-analyses.

Grade of Available Evidence: Good.

Conclusion: As the latest guidelines from the National Cholesterol Education Program Adult Treatment Panel III mandate more aggressive treatment of lipid disorders linked to CHD, it is likely that use of combination therapy for lipid disorders will increase. A number of possible combinations are available, all providing incremental lipid-lowering efficacy compared with monotherapy. However, physicians should carefully assess patient needs, potential adverse events, and drug interactions when choosing the right combination for an individual patient.

terol (LDL-C), HDL-cholesterol (HDL-C), and TG. Non-HDL-C level, which includes the cholesterol from the TG-rich very low-density lipoproteins (VLDL), VLDL-remnants, LDL, and lipoprotein (a) is now also used as a treatment measure in patients with elevated TG.24 However, recent evidence suggests that direct measurement of apolipoprotein B, a major protein of LDL, intermediate-density lipoprotein (IDL), and VLDL, and apolipoprotein AI (apo AI), the major protein of HDL, are better indices of CHD risk than TC, LDL-C, or HDL-C.3,6

The value of lowering lipid levels with pharmacotherapeutic agents to reduce cardiovascular event rates is well established, but the optimal level of LDL-C has not yet been determined. Recent studies (including the Treating to New Targets, or TNT Study) showed that intensive lowering of LDL-C levels in patients with CHD reduced cardiovascular event rates2,3 and slowed atherosclerotic progression.2 In fact, in these studies, a target LDL-C level of <70 mg/dL conferred greater benefit than a level of <100 mg/dL, and more intensive lipid-lowering therapy (atorvastatin 80 mg/day) was more effective than less intensive treatment (atorvastatin 10 mg/day).4

The National Cholesterol Education Program (NCEP) has established new lipid-lowering guidelines for primary and secondary prevention of CHD.2,3 Under these guidelines, the threshold to initiate drug therapy and the target cholesterol level, in particular the LDL-C level, depends on the presence or absence of CHD, CHD risk equivalents, and associated risk factors (Table 1). The NCEP Adult Treatment Panel (ATP) III guidelines focus on multiple risk factors and contain a modified classification of optimal lipid and lipoprotein levels. In this classification, the optimal target for LDL-C is <100 mg/dL with an optional target of <70 mg/dL for patients at very high risk, and there are new definitions of low HDL-C (≤40 mg/dL) and high TG levels (>150 mg/dL). The guidelines provide recommendations for complete screening of TC, LDL-C, HDL-C, and TG, encouraging the use of plant sterols and soluble fiber, and treatment using non-HDL-C guidelines for patients with TG ≥200 mg/dL.2,3

In addition to measurement of lipid protein levels, important prognostic information can be derived from levels of highly sensitive C-reactive protein (hsCRP), a measure of inflammatory activity within atherosclerotic blood vessels.18 In fact, hsCRP levels may be even stronger predictors of cardiovascular events than LDL-C levels,11 and the prognostic value of hsCRP is now reflected in treatment guidelines.2 In some of the recent studies of intensive lipid-lowering described above, the better outcomes and slower progression of atherosclerosis were directly linked to reduced hsCRP levels.12,13

Lifestyle and dietary modifications are recommended for patients with hypercholesterolemia.2 Dietetic modifications typically reduce LDL-C by 5% to 13%.14-18 However, many patients do not adhere to these modifications over the long term, and many require greater reductions of LDL-C to reach NCEP goals. Indeed, analysis of the National Health and Nutrition Examination Survey and the Lipid Treatment Assessment Project reveals that >90% of patients with CHD do not meet treatment goals using lifestyle and dietary modifications alone.19,20 Furthermore, although a high proportion of patients achieve LDL-C goals using a single cholesterol-lowering agent,21 there is a patient subgroup who will require combination drug therapy with agents from different classes to achieve LDL-C goals.

This review evaluates the literature on the different classes of lipid-lowering agents focusing on basic pharmacology, clinical efficacy in terms of lipid-modifying effects and risk reduction of cardiovascular events (nonfatal myocardial infarction [MI] or fatal CHD, the most common endpoint in clinical trials), and the risks associated with these therapies as part of single-agent or combination lipid-modifying regimen. A detailed description of risk reduction for a wide range of outcomes is not addressed in detail in this manuscript.

<table>
<thead>
<tr>
<th>Table I. National Cholesterol Education Program—Adult Treatment Panel III Guidelines for Low-Density Lipoprotein-Lowering Initiation and Goals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>CHD or CHD risk equivalents</td>
</tr>
<tr>
<td>(10-year risk &gt;20%)</td>
</tr>
<tr>
<td>Moderately high risk</td>
</tr>
<tr>
<td>≥130 (≥10% risk)</td>
</tr>
<tr>
<td>No CHD and (2 risk factors$</td>
</tr>
<tr>
<td>(10-year risk 10%-20%)</td>
</tr>
<tr>
<td>Moderate risk</td>
</tr>
<tr>
<td>No CHD and ≥2 risk factors$</td>
</tr>
<tr>
<td>(10-year risk ≤20%)</td>
</tr>
<tr>
<td>Lower risk</td>
</tr>
<tr>
<td>0-1 risk factor$</td>
</tr>
</tbody>
</table>

*Adapted with permission from the National Cholesterol Education Program, Adult Treatment Panel III.2 Full report available at: www.nhlbi.nih.gov/guidelines/cholesterol.

1Drug therapy advisable on the basis of clinical trials. When LDL-C lowering therapy is employed, it should be of an intensity to achieve a 30% to 40% decrease in LDL-C in high-risk patients and to a goal LDL-C of <100 mg/dL in moderately high-risk patients.

2Very high risk favors the optimal LDL-C goal of <70 mg/dL, and in patients with high triglycerides, non-HDL-C <100 mg/dL.

3Positive risk factors for CHD are cigarette smoking, hypertension, low HDL cholesterol (<40 mg/dL), age (>45 years in men, >55 years in women), diabetes, obesity, physical inactivity, and atherogenic diet.

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.
**Basic Pharmacology of Lipid-Modifying Agents**

The basic pharmacology of lipid-modifying agents is summarized in Table 2 and reviewed below.

**Inhibitors of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (Statins)**

The statins are the most potent and generally well-tolerated agents for treating dyslipidemias. Approved agents in the United States include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and rosuvastatin. Cerivastatin was withdrawn from the market after reports of fatal rhabdomyolysis, with the majority of deaths associated with combination therapy using cerivastatin and gemfibrozil. The mechanism of action of statins is reversible (competitive) inhibition of the hepatic enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis.

The first effect of statins is a reduction in the amount of cholesterol synthesized. Secondly, in response to decreased free cholesterol in the hepatocytes, synthesis of LDL receptors increases. Increased expression of LDL receptors leads to increased removal of LDL-C from the blood, thereby reducing plasma LDL-C levels.

Most statins are active as administered; however, lovastatin and simvastatin are prodrugs that are metabolized to active forms in the liver. Statins undergo extensive first-pass metabolism via the hepatic portal system and typically less than 20% of these agents reaches systemic circulation. Three statins, lovastatin, simvastatin, and atorvastatin, are metabolized by the CYP3A4 isozyme of the cytochrome P450 microsomal enzyme system, and consequently have drug interactions with other agents metabolized by CYP3A4 (Table 2). Statins are not safe in pregnant or nursing women (pregnancy category X), and should not be used in patients with active or chronic hepatic disease or cholestasis because of potential hepatotoxicity. Statins are generally well tolerated; myopathy is a rare event, occurring at an incidence of 1.2 per 10,000 person-years.

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Table 2. Basic Pharmacology of Lipid-Modifying Agents*

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Distribution and Metabolism</th>
<th>Drug Interactions</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>HMG-CoA reductase inhibition</td>
<td>Extensive first-pass metabolism, plasma protein binding, metabolized by liver and excreted into bile</td>
<td>Cyclosporine, macrolides, cytochrome P450 inhibitors (3A4 isozyme)</td>
<td>Active or chronic hepatic disease, cholestasis, pregnancy</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Anion exchange binding of bile acids in intestine</td>
<td>No systemic absorption, excreted in feces</td>
<td>Decreased absorption of other agents</td>
<td>Familial dysbetalipoproteinemia, or TG &gt;400 mg/dL</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Agonists for peroxisome proliferator-activated receptor-α</td>
<td>Rapid and nearly complete absorption, widely distributed, excretion of glucuronidate metabolite in urine</td>
<td>Warfarin and other drugs that bind strongly to plasma proteins; caution with statins (myopathy)</td>
<td>Severe hepatic or renal insufficiency, pregnancy</td>
</tr>
<tr>
<td>Niacin</td>
<td>Agonist for a newly discovered G-protein coupled receptor, HM74b</td>
<td>Nearly complete absorption, metabolized in liver, major metabolite excreted in urine</td>
<td>Vasodilator effect may cause dizziness and syncope when used with anti-hypertensives</td>
<td>Active or chronic hepatic disease, hyperuricemia or gout, pregnancy, peptic ulcer</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor (ezetimibe)</td>
<td>Acts at the brush border of the small intestine and inhibits the absorption of cholesterol through the NPC1LI protein</td>
<td>Glucuronidated in liver, enterohepatic circulation, excreted in bile</td>
<td>Mean AUC values of total ezetimibe and ezetimibe reduced 55% and 80%, respectively with concomitant cholestyramine; fibrates increased oral bioavailability 1.5- to 1.7-fold</td>
<td>Combination with a statin in patients with active liver disease or unexplained persistent elevations in serum transaminases</td>
</tr>
</tbody>
</table>

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TG = triglyceride; AUC = area under the plasma concentration-time curve.

*See text for further details and references.

†With the exception of pravastatin and rosuvastatin.

‡Although all possible drug-drug interactions have not yet been studied with the second-generation bile acid sequestrant, colesevelam HCl, this agent did not inhibit absorption of other coadministered agents in clinical studies (except sustained-release verapamil); see text for details.
**Bile Acid Sequestrants**

Bile acid sequestrants (BASs), also called resins, are among the oldest and safest of lipid-modifying agents as they are not absorbed into systemic circulation. The conventional BAS agents, cholestyramine and colestevol, usually are prepared as powders mixed with water or orange juice, although colestevol also is formulated as a tablet. A newer, specifically engineered BAS, colesevelam HCl, is a hydrophilic polymer taken as a tablet. Both the conventional BASs and colesevelam are positively charged chemicals that bind to the negatively charged bile acids. Due to the large size of the polymers, BASs are not absorbed and are excreted with their bile acid cargo in the stool. Typically, about 95% of bile acids are reabsorbed by enterohepatic recycling; BASs disrupt this process, depleting the endogenous bile acid pool by around 40% and increasing hepatic bile acid synthesis from cholesterol. This process reduces hepatic cholesterol and increases the expression of LDL receptors, an end-product effect that is similar to that of the statins and cholesterol absorption inhibitors (see below). However, BASs upregulate HMG-CoA reductase, so the overall effect on lowering plasma LDL-C is attenuated. Inhibition of HMG-CoA reductase by statins substantially increases the effect of BASs, providing a rationale for use of these agents in combination pharmacotherapy. All BASs significantly reduce levels of LDL-C and apolipoprotein B, and increase levels of apo AI and HDL-C.

Because BASs are not absorbed, there are no systemic drug-drug interactions with metabolic enzymes. However, studies show that coadministered conventional BASs decrease the bioavailability of thiazides, glipizide, propranolol, digoxin, and others. As BASs tend to increase TG, and because they have not been well studied in patients with very high TG levels, they should not be used in patients with familial dysbetaIipoproteinemia or with significantly elevated TG levels (>300 mg/dL). Colesevelam did not significantly elevate TG levels in moderately dyslipidemic study subjects. In addition, colesevelam was found to have no significant effect on the bioavailability of digoxin, fenofibrate, lovastatin, metoprolol, quinidine, valproic acid, or warfarin. However, a decrease in verapamil maximum plasma concentration and the area under the plasma concentration-time curve (AUC) was observed during coadministration of colesevelam and sustained-release verapamil, but the clinical significance of this is unclear, given the high degree of variability in verapamil bioavailability. There are no adequate and well-controlled studies in pregnant women receiving colesevelam; however, it is the only BAS with a pregnancy category B label; all other BASs carry a pregnancy category C label.

**Fibrates**

There are currently 2 fibric acid derivatives or fibrates used in the United States: gemfibrozil and fenofibrate; cipofibrate and bezafibrate are used internationally but not in the United States. Fibrates primarily are used for the treatment of hypertriglyceridemia. Fibrates are agonists at the nuclear peroxisome proliferator activated receptor-α (PPAR-α), where they modulate the transcription of several target genes implicated in lipoprotein homeostasis—upregulating the lipoprotein lipase and apo AI genes and downregulating the apo C-III gene. The net result is a potent reduction in the level of plasma TG and an increase in HDL-C. The effect of fibrates on LDL-C is variable, and may result in a moderate reduction, no effect, or an increase in LDL-C.

All fibrates are rapidly and almost completely absorbed, with high levels of plasma protein binding. They are conjugated with glucuronidate and excreted in the urine. They hold the potential for drug-drug interactions with other agents that bind to plasma proteins (Table 2), and hepatic enzymes should be monitored when fibrates are combined with statins. Myopathy is a potential adverse effect, especially when statins and certain fibrates (eg, gemfibrozil) are combined; fenofibrate appears to be a safer choice of a fibrate for coadministration with a statin. Myopathies are contraindicated in patients with severe hepatic and renal disease, and should be used with caution in pregnant patients (pregnancy category C).

**Niacin (Nicotinic Acid)**

This class of lipid-modifying agents is unique in that niacin is available as a nutritional supplement, in addition to extended- and sustained-release formulations available only by prescription. Niacin is indicated for the treatment of low HDL-C and for the reduction of TG and LDL-C. Despite its wide availability, relatively low cost, and broad-spectrum beneficial effects on plasma lipids, adverse effects limit its use in certain patients (see below). Until recently, the exact mechanism of action of niacin was unknown, but several independent research groups have now characterized and cloned a plasma membrane receptor that mediates the effects of niacin. The nicotinic receptor is a member of the large family of G-protein coupled receptors. Ligand binding initiates a signal transduction pathway via the inhibitory Gi/o proteins. The nicacin receptor is localized on adipose tissue where niacin causes a decrease in intracellular cyclic adenosine monophosphate leading to inactivation of protein kinase A and suppression of hormone-sensitive lipase. This action limits the lipolysis of TG and reduces the transport of free fatty acids to the liver, thereby reducing the hepatic synthesis of TG. In the hepatocyte, niacin receptor-mediated action reduces TG by decreasing the synthesis and esterification of fatty acids, which increases apolipoprotein B degradation. A decrease in TG synthesis increases proteolysis of apolipoprotein B.
leading to a reduction of the hepatic production and secretion of VLDL. Because VLDL is a precursor of IDL and LDL, reduction in VLDL results in decreased levels of both IDL and LDL. The exact mechanism by which niacin increases plasma HDL-C is still unclear; however, it appears that niacin reduces the hepatic clearance of HDL-apo AI, thereby increasing the plasma levels of HDL-apo AI and reverse cholesterol transport.

The efficacy and tolerability of niacin recently has been reviewed. Pharmacologically active doses of niacin (≥1 g/day) are nearly completely absorbed, but in its crystalline form niacin has a half-life of only about 1 hour. Thus, 2 or 3 doses per day are needed. Flushing is the most common side effect, occurring in up to 50% of patients. Myopathy has been reported with the coadministration of niacin with a statin but these patients usually were on a high dose of statin that by itself may cause myopathy. The true incidence of myopathy with coadministration of niacin with a statin is difficult to determine, but is likely to be around 2 to 4 cases per 1000 treated. Drug interactions are not prevalent with niacin, although a vasodilatory effect may cause dizziness and/or syncope in patients taking antihypertensive medication. Co-administration with ethanol, or with hot beverages such as tea or coffee, may increase the side effect of flushing. Niacin should be discontinued or used with caution during pregnancy (pregnancy category C). Additionally, niacin administered to patients with diabetes mellitus can result in increased hyperglycemia, so patients with diabetes taking niacin may require changes to their hypoglycemic therapy. Unlike immediate-release niacin agents, however, it appears that extended- or prolonged-release niacin formulations may not further deteriorate the diabetic condition. Conversely, prolonged-release, but not extended-release (ER), formulations appear to be associated with a greater risk of hepatic injury than are immediate-release formulations. The existence of gouty arthritis also is a relative contraindication for niacin, as increased levels of plasma uric acid are noted. Niacin also is contraindicated in patients with peptic ulcers as it can increase acid secretion via the release of histamine.

### Table 3. Summary of Outcomes Trials With Single Pharmacotherapy by Drug Class

<table>
<thead>
<tr>
<th>Class/Agents</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>CHD† % Adverse</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC LDL-C HDL-C TG Apo B Risk Reduction Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>↓4% to ↓25% ↓18% to ↓85% ↑5% to ↑15% ↓7% to ↓30% ↓9% to ↓29%</td>
<td>Slight ↑ transaminase in 0.5% to 2% of cases; slight ↑ creatine kinase, caution for myopathy</td>
<td>1 to 6 years</td>
<td>45, 1994&lt;sup&gt;a&lt;/sup&gt;; WOSCOPS, 1995&lt;sup&gt;b&lt;/sup&gt;; CARE, 1996&lt;sup&gt;c&lt;/sup&gt;; LIPID, 1998&lt;sup&gt;d&lt;/sup&gt;; AFCAPS, 1999&lt;sup&gt;e&lt;/sup&gt;; HPS, 2002&lt;sup&gt;f&lt;/sup&gt;; ALLHAT-LLT, 2002&lt;sup&gt;g&lt;/sup&gt;; ASCOT-LLA, 2003&lt;sup&gt;h&lt;/sup&gt;; CARDS, 2004&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bile Acid</td>
<td>↓8% to ↓8% ↑16% to ↑23% ↑6% to ↑32 %</td>
<td>↑TG; GI complaints, constipation common</td>
<td>5 to 7 years</td>
<td>NHLBI-T2CIS, 1984&lt;sup&gt;j&lt;/sup&gt;; LRCCPPT1, 1984&lt;sup&gt;k&lt;/sup&gt;; LRCCPPT2, 1984&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓4% to ↓8% ↓5% to ↓20% ↑6% to ↓20% to ↓50%</td>
<td>7% to 34%</td>
<td>Dyspepsia, GI complaints, gall bladder disease, myositis</td>
<td>5 to 6 years</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓10% to ↓16% ↓4% to ↓25% ↑15% to ↓26% to ↓50% to ↓35% to ↓50%</td>
<td>13%</td>
<td>13% cases ↑ plasma urate; 9% ↑ fasting glucose 6 years</td>
<td>CDP, 1975&lt;sup&gt;q&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**TC** = total cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **HDL-C** = high-density lipoprotein cholesterol; **TG** = triglycerides; **apo B** = apolipoprotein B; **CHD** = coronary heart disease; **GI** = gastrointestinal; **4S** = Scandinavian Simvastatin Survival Study; **WOSCOPS** = West of Scotland Coronary Prevention Study; **CARE** = Cholesterol and Recurrent Events; **LIPID** = Long-Term Intervention with Pravastatin in Ischaemic Disease; **AFCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **HPS** = Heart Protection Study; **ALLHAT-LLT** = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; **CARDS** = Collaborative Atorvastatin Diabetes Study; **ND** = not determined; **GI** = gastrointestinal; **NHLBI-T2CIS** = NHLBI Type II Coronary Intervention Study; **LRCCPPT1** = Lipid Research Clinics Coronary Primary Prevention Trial I; **LRCCPPT2** = Lipid Research Clinics Coronary Primary Prevention Trial II; **CDP** = Coronary Drug Project; **HHS** = Helsinki Heart Study; **VA-HIT** = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; **BIP** = Bezafibrate Infarction Prevention; **LEADER** = Lower Extremity Arterial Disease Event Reduction.

<sup>a</sup>CHD risk reduction = reduction in the risk of the combined endpoint of CHD death or nonfatal myocardial infarction.
**Cholesterol Absorption Inhibitors**

At present, ezetimibe is the only member of this drug class. Recent research indicates that ezetimibe selectively inhibits a newly discovered transporter that moves cholesterol from bile acid micelles in the brush border of enterocytes. The transporter is a Niemann-Pick C1-like 1 (NPC1L1) protein localized at the brush border of enterocytes. Ezetimibe significantly reduces cholesterol absorption in animals homozygous for wild-type NPC1L1, but has no effect in NPC1L1 knock-out mice. This suggests that NPC1L1 is the cellular target of ezetimibe, although researchers were unable to demonstrate ezetimibe binding to the NPC1L1 protein.

Ezetimibe reduces the overall delivery of cholesterol to the liver, decreasing hepatic cholesterol and promoting the upregulation of LDL receptors, thus decreasing the concentration of LDL-C in the plasma. However, ezetimibe also increases cholesterol synthesis, so the overall effect on lowering plasma LDL-C is attenuated. Inhibition of HMG-CoA reductase by statins substantially increases the effect of ezetimibe, providing a rationale for using these agents in combination pharmacotherapy. Ezetimibe is conjugated to its active glucuronide form, which undergoes enterohepatic circulation. This process increases its elimination half-life to about 22 hours.

There generally are few drug interactions associated with ezetimibe, although coadministered cholestyramine did decrease levels of ezetimibe and coadministration with fibrates increased plasma levels of ezetimibe. In patients taking ezetimibe and cyclosporine concomitantly, the potential for increased exposure to both ezetimibe and cyclosporine from this combination should be weighed against the benefits gained from alterations in lipid levels, and these combination therapy patients should be carefully monitored. A study investigating concomitant administration of ezetimibe and warfarin found that ezetimibe had no significant effect on the bioavailability of warfarin in 12 healthy subjects; however, more recently there have been postmarketing reports of increased international normalized ratios in patients who had ezetimibe added to warfarin. At present, the only contraindication to the use of ezetimibe is for combination therapy with a statin in patients who have active liver disease or unexplained persistent elevations in serum transaminases, but caution is recommended for patients with chronic or severe liver disease. This is because the AUC of the drug is increased in these patients, and the effect of such an increase is not yet known. Ezetimibe has not been studied in pregnant women and can be used only if the benefit justifies the risk to the fetus (pregnancy category C).

**Single-Agent Pharmacotherapy for Lipid Disorders Related to Risk of Coronary Heart Disease**

A comparison of the results from major clinical studies of the 4 classes of lipid-modifying agents is presented in Table 3. These results are from prospective clinical outcome trials with long duration of treatment. Clinical outcomes data are available for all classes of agents except the cholesterol absorption inhibitors, as the only available example of this class, ezetimibe, is too new to have completed clinical trials with cardiovascular endpoints.

**Statins**

There are 9 major clinical studies of the effect of statins on plasma lipids and cardiovascular outcome. These studies have a mean duration of more than 5 years. The efficacy of statins in reducing mean total cholesterol is dose-related and ranges from 4% to 25%, decreases in mean LDL-C from 18% to 55%, and reduction of mean TG from 7% to 30%. In studies in which it was determined, mean apolipoprotein B decreased from 18% to 54%.

In general, the statins are well tolerated. In these clinical trials, the incidence of transient elevation of liver enzymes (alanine and aspartate transaminases), creatine kinase, and myopathy was similar in the treatment and placebo groups.

Meta-analysis of clinical endpoint trials shows that statin therapy significantly reduces the risk of major cardiovascular events (fatal CHD or nonfatal MI) by 27% (P < .0001). The significant risk reduction with statins has been seen in both primary and secondary prevention studies and across a range of patient groups, including men and women, smokers, and those with diabetes or hypertension. Patients at greatest risk show the greatest benefit with statin therapy. As seen in Table 3, the statins are the most potent agents for reducing total cholesterol and LDL-C. Statins also are associated with a moderate increase in HDL-C and decrease in TG.

**Bile Acid Sequestrants**

BASs reduce total cholesterol by 11% to 14% and LDL-C by 16% to 23%; HDL-C levels are increased by 4% to 8%. The reduction in the relative risk of CHD associated with BAS monotherapy is approximately 19% and the progression of CHD has been shown to be inversely proportional to the combination of the increase in HDL-C and the decrease in LDL-C achieved with BAS therapy. BAS may produce either no change or an increase in plasma TG. The primary adverse effect noted in the large-scale trials was gastrointestinal complaints such as constipation, nausea, bloating, and flatu-
ience, although the incidence and/or severity of these side effects may potentially be lower with colesevelam. Colesevelam is indicated for use in patients with elevated LDL-C levels due to primary hypercholesterolemia as an adjunct to diet and exercise, and may be administered alone or in combination with a statin (see below). In addition to lowering mean LDL-C by up to 15% at the recommended starting dose, colesevelam at 3.8 g/day also increases median HDL-C by 3% to 8.1%. In contrast to conventional BASs, preliminary data suggest that colesevelam may not adversely affect LDL particle size. To date, there are no outcome data for colesevelam, but the reductions in CHD risk seen with other BASs suggest that this is a class effect.

Fibric Acid Derivatives

The differential efficacy of fibrates on lipid constituents in the plasma is apparent in Table 3. Fibrates are most effective in lowering elevated TG levels, generally to a greater degree than statins, with relatively minor effects on TC. They also elevate HDL-C levels and reduce LDL-C. Fibrates have been shown to be effective in both primary and secondary prevention of CHD. In the Helsinki Heart Study, treatment with gemfibrozil reduced the incidence of cardiac events by 34% relative to placebo in middle-aged men with elevated non-HDL-C but no evidence of CHD. The risk reduction associated with gemfibrozil was 22% in men with pre-existing CHD in the Veterans Affairs HDL-C Intervention Trial. In the Bezafibrate Infarction Prevention (BIP) study, results suggested that bezafibrate is particularly effective in reducing risk of cardiac events in patients with high baseline TG levels (≥200 mg/dL). Adverse effects include dyspepsia and other gastrointestinal complaints, gallbladder disease, and myositis.

Niacin

Niacin (vitamin B3) is most potent in elevating HDL-C and lowering TG. It has more moderate efficacy against elevated LDL-C and total cholesterol. Niacin is the only lipid-modifying agent that has been shown to reduce levels of lipoprotein(a). A 27% decrease in risk from CHD was ascribed to niacin treatment in the Coronary Drug Project (CDP). About 13% of patients on niacin saw a slight, but significant, increase in plasma urate, and 24% developed an increase in fasting glucose levels. A recent report showed that diabetic patients from the CDP had a significant reduction in cardiovascular events and that such benefit was greater the higher the glucose level.

Ezetimibe

Five clinical studies of ezetimibe monotherapy were recently reviewed. In studies of relatively short duration, ezetimibe produced mean decreases of 15% to 20% in plasma LDL-C and up to 8% mean reductions in TG, and small increases in TC and HDL-C. Ezetimibe was well tolerated and safe. More clinical studies of greater duration and numbers are needed to assess the efficacy of this first-in-class agent to prevent CHD.

Combination Pharmacotherapy for Lipid Disorders Related to the Risk of Coronary Heart Disease

Pairing of the 5 existing classes of lipid-modifying agents for combination pharmacotherapy gives 10 possible 2-way combinations. Of these possibilities, 8 combinations have been tested in clinical trials. As expected, the statins were employed in most combination treatments, paired with BASs, fibrates, niacin, and cholesterol absorption inhibitors. BASs have been paired with statins, fibrates, niacin, and ezetimibe, and there also are a few reports of combination treatment with fibrates and niacin. Two 2-way combinations that are yet to be assessed for efficacy (although pharmacokinetic studies have been done) are ezetimibe paired with a fibrate or ezetimibe paired with niacin. Most studies assessed the safety and lipid-lowering efficacy of the combinations, and were therefore of limited duration and not designed to assess clinical outcomes. However, CHD risk reduction was evaluated using estimates based on the Framingham Offspring Study and The Münster Heart Study (PROCAM study), in the trials of atorvastatin plus fenofibrate and simvastatin plus niacin (the HDL-Atherosclerosis Treatment Study [HATS]). Additionally, the latter study included angiographic assessment of coronary artery stenosis, as well as a composite clinical endpoint, including death from cardiovascular causes, nonfatal MI, and revascularization procedures. A more recent combination study showed that niacin plus simvastatin caused greater reduction in carotid artery intima-media thickness than did simvastatin alone.

Statins and Bile Acid Sequestrants

Combination treatment with statins and BASs produces a potent complementary lowering of plasma cholesterol and LDL-C levels, greater than that seen with either agent alone (Table 4). In early combination studies, mean reductions in LDL-C levels of nearly 50% were seen with maximal daily doses of lovastatin (40-80 mg/day) and colestipol (20-30 g/day). More moderate doses of lovastatin (20 mg/day) or atorvastatin (10 mg/day) and colestipol (10 or 20 g/day) still reduced mean LDL-C by nearly 50% over 6 or 12 weeks of treatment. More recent studies occurring over shorter treatment times show the potent LDL-C reducing actions of moderate doses of statins plus colesevelam, with decreases of 32% to 48%. The effects of statin-
BAS combinations on HDL-C appear to be related to the dose of BAS, with median or mean increases of ≥10% seen with colesevelam 3.8 g/day or colestipol 20 g/day, and single-digit increases seen with lower doses of these drugs or with cholestyramine (8-16 g/day). Changes in TG levels were variable between studies. The incidence of adverse effects from the combination of statins and BASs is neither increased nor decreased compared with that seen when these agents are given alone.

**Statins and Fibrates**

Combination therapy with statins and fibrates is less potent in reducing plasma LDL-C than is the combination of statins and BASs, but more efficacious in elevating HDL-C and reducing TG (Table 5).61,99-110 Combination therapy with moderate doses of statins (10-20 mg/day) and gemfibrozil (1.2 g/day), fenofibrate (200 mg/day), or ciprofibrate (100 mg/day) produce mean decrements in TG levels in the range of 41% to 56% after 6 months to 2 years.103-106,110 Statin-fibrate combination therapy also shows impressive increases in HDL-C, greater with fenofibrate than gemfibrozil, along with reductions in fibrinogen; however, it is not known whether other combinations also have this effect. As expected, the combination of a statin and a fibrate increases the risk of hepatic enzyme elevations compared with monotherapy, but most studies do not report clinically significant sequelae from these elevated laboratory values. Caution is needed with combined statin-fibrate therapy due to the increased risk of myopathy, which has been fatal in some cases.111,112 However, as mentioned previously, the risk of myopathy may be lower with micronized fenofibrate than with other fibrates when combined with statins.96,97

**Statins and Niacin**

The combination of a statin and niacin provides even better elevation in HDL-C than do statin-BAS or statin-fibrate combinations (Table 6).83,113-122 Except for a single study that reported an increase in HDL-C of only 2% with lovastatin plus niacin,116 the combination of a statin and niacin typically increases mean

### Table 4. Summary of Clinical Trials With Combination Pharmacotherapy: Statins Plus Bile Acid Sequestrants*

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine + lovastatin</td>
<td>↓25% to ↓43%</td>
<td>↑1% to ↑13%</td>
<td>1% to 2% constipation; 4% to 13% GI discomfort</td>
<td>7 weeks to 2.5 years</td>
</tr>
<tr>
<td>Cholestyramine + atorvastatin</td>
<td>↓31%</td>
<td>↓45%</td>
<td>↓4% to ↓13%</td>
<td>60% constipation</td>
</tr>
<tr>
<td>Cholestyramine + simvastatin</td>
<td>↓29%</td>
<td>↓42%</td>
<td>↓1% to ↓1%</td>
<td>ND</td>
</tr>
<tr>
<td>Colesevelam HCl + fluvastatin</td>
<td>↓18% to ↓22%</td>
<td>↓3% to ↓26%</td>
<td>ND</td>
<td>16% to 30% constipation; 8% to 22% flatulence; 11% to 19% dyspepsia</td>
</tr>
<tr>
<td>Colesevelam HCl + lovastatin</td>
<td>↓13%</td>
<td>↓24%</td>
<td>↑5% to ↑29%</td>
<td>None noted</td>
</tr>
<tr>
<td>Cholestyramine + pravastatin</td>
<td>↓24% to ↓32%</td>
<td>↓45% to ↓46%</td>
<td>↓1% to ↓1%</td>
<td>23% ↓CK; 43% ↑ALT; 18% ↑AST; 11% to 45% GI disorders</td>
</tr>
<tr>
<td>Colesevelam HCl + atorvastatin</td>
<td>↓31%</td>
<td>↓48%</td>
<td>↑1% to ↑11%</td>
<td>37% GI complaints</td>
</tr>
<tr>
<td>Colesevelam HCl + lovastatin</td>
<td>↓21%</td>
<td>↓3% to ↓32%</td>
<td>↑9%</td>
<td>7% to 8% diarrhea; 4% to 7% constipation</td>
</tr>
<tr>
<td>Colesevelam HCl + simvastatin</td>
<td>↓28% to ↓29%</td>
<td>↓12% to ↓4%</td>
<td>↑10% to ↑12%</td>
<td>34% to 35% GI complaints</td>
</tr>
</tbody>
</table>

*All data are mean values unless otherwise indicated.

 ND = not determined; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B; CK = creatine kinase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal.
HDL-C levels by 16% to 42%. In the one study that investigated the differential effects of the combination on HDL-C subfractions, the HDL2 subfraction was increased by 113% to 189% compared with an 8% to 15% increase in the HDL3 subfraction; the HDL2 subfraction may be more cardioprotective than the HDL3 subfraction. Statin plus niacin also effectively lowers LDL-C to an extent similar to that seen with other combinations of lipid-modifying agents. However, in most studies, levels of TG reduction were not as impressive as those seen with the combination of statins and fibrates. As expected with niacin administration, there is a notable incidence of flushing as a result of vasodilatation and, as with all statin treatments, a tendency for hepatic enzyme levels to be elevated.

**STATINS AND EZETIMIBE**

A number of studies have evaluated the efficacy and safety of statin-ezetimibe combinations (Table 7). Potent reductions of about 50% in the level of LDL-C were observed with moderate effects on TG levels. HDL-C levels typically increase by 2% to 10%, although a single study with a small number of patients (n=13) showed a moderate decrease. The combination of statin-ezetimibe is generally well tolerated, with few adverse effects reported, although during such combinations hepatic enzyme levels should be monitored for potential elevations. In postmarketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported, regardless of causality. Most patients who developed rhab-
domyolysis also were taking a statin. The manufacturer suggests that all patients starting therapy with ezetimibe should be advised of the risk of myopathy and told to promptly report any unexplained muscle pain, tenderness, or weakness.15

**OTHER COMBINATIONS**

With regard to nonstatin combinations, there are fewer studies to compare; although such combinations are a necessary option for those patients who cannot tolerate statin therapy. BASs plus fibrates are potent reducers of LDL-C and TG, but less reliable at elevating levels of HDL-C.16,34-38 No significant adverse effects are noted with this combination (Table 8). The combination of a BAS and niacin (Table 9) produces reliable decreases in LDL-C and TG in most studies, as well as increases in HDL-C.18,122,139,140 Combination therapy with a BAS and ezetimibe has been evaluated in 2 studies to date.29,142 only 1 of which reported the change in lipid levels from baseline (Table 10).142 (The other reported the change from BAS-based regimen.141) In both studies, the addition of ezetimibe to BAS therapy resulted in additional lowering of LDL-C. The combination of fibrates and niacin appears to be safe and effective with moderate lowering of LDL-C. The combination of fibrates and niacin (Table 9) produces reliable decreases in LDL-C and TG, but less reliable at elevating levels of HDL-C.90,134-138 No significant adverse effects are noted with this combination (Table 9).

**Table 6. Summary of Clinical Trials With Combination Pharmacotherapy: Statins Plus Niacin**

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin + ER niacin</td>
<td>↓27% to ↓40%</td>
<td>↑28% to ↑30%</td>
<td>ND</td>
<td>28%↑ALT; 21%↑CK; 60% flushing</td>
</tr>
<tr>
<td>Pravastatin + ER or SR niacin</td>
<td>↓29% to ↓41%</td>
<td>↑16% to ↑26%</td>
<td>ND</td>
<td>↑ALT/CK; 28% flushing; 30% GI complaints</td>
</tr>
<tr>
<td>Lovastatin + IR niacin</td>
<td>↓22% to ↓30%</td>
<td>↑2% to ↑11%</td>
<td>ND</td>
<td>1%↑uric acid</td>
</tr>
<tr>
<td>Lovastatin + ER niacin†</td>
<td>↓29% to ↓39% to ↓45%</td>
<td>↑17% to ↑41%</td>
<td>↓49% to ↓38%</td>
<td>5% to 10% flushing; ≤1%↑ALT/AST</td>
</tr>
<tr>
<td>Simvastatin + SR niacin</td>
<td>↓3% to ↓43%</td>
<td>↑29% to ↑38%</td>
<td>ND</td>
<td>26%↑AST; 23%↑CK; 19%↑insulin</td>
</tr>
<tr>
<td>Atorvastatin + ER niacin</td>
<td>ND</td>
<td>↓55%</td>
<td>↑42% to ↓69%</td>
<td>None reported</td>
</tr>
<tr>
<td>Rosuvastatin + ER niacin</td>
<td>↓29% to ↓36% to ↓38%</td>
<td>↑17% to ↑24% to ↑2%</td>
<td>↓34% to ↓42%</td>
<td>29% to 39% flushing; 5% to 7% pruritus</td>
</tr>
<tr>
<td>Pooled statins§ + ↓24%</td>
<td>↓32%</td>
<td>↑25% to ↑32%</td>
<td>ND</td>
<td>3%↑AST; 5% flushing</td>
</tr>
</tbody>
</table>

*All data are mean values unless otherwise indicated.
† In single, fixed-dose formulation (Advicor®); ‡ Data presented are medians; § Lovastatin, pravastatin, or simvastatin.
ER = extended-release; SR = sustained-release; IR = immediate-release; ND = not determined; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ADVOCATE = 1; Advicor Versus Other Cholesterol-Modulating Agents Trial Evaluation; CK = creatine kinase; GI = gastrointestinal.

**EFFECTS OF COMBINATIONS ON hsCRP**

There are limited data on the effects of combination therapy on plasma levels of hsCRP, possibly because much of the clinical data on the combinations predate the findings on the importance of hsCRP. Those that do provide these data indicate that ezetimibe plus a statin is more effective than a statin alone in reducing hsCRP levels.126,127 In addition, the fixed combination of lovastatin/ER niacin may dose-dependently reduce hsCRP levels, although the study in which this was reported did not have a control group, so it is difficult to determine whether this effect is related to the statin, niacin, or both.119

**TRIPLE COMBINATION THERAPY**

If 2 combinations of lipid-modifying agents improve the plasma lipid profiles without significantly increasing adverse effects, then it is logical to investigate the use of 3 or more lipid-modifiers in combination pharmacotherapy to improve efficacy when clinically indicated. To date, only a small number of trials have investigated this possibility, although some of these
Table 7. Summary of Clinical Trials With Combination Pharmacotherapy: Statins Plus Cholesterol Absorption Inhibitors*  

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>LDL-C</td>
<td>HDL-C</td>
<td>TG</td>
</tr>
<tr>
<td>Studies reporting changes from placebo baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin + ezetimibe</td>
<td>↓37% to ↓43%</td>
<td>↓50% to ↓58%</td>
<td>↑15% to ↑10%</td>
<td>↓4% to ↓30%</td>
</tr>
<tr>
<td>Atorvastatin + ezetimibe</td>
<td>↓41%</td>
<td>↓55%</td>
<td>↑7%</td>
<td>↓33% to ↓45%</td>
</tr>
<tr>
<td>Lovastatin + ezetimibe</td>
<td>↓29%</td>
<td>↓39%</td>
<td>↑9%</td>
<td>↓22%</td>
</tr>
<tr>
<td>Pravastatin + ezetimibe</td>
<td>↓27%</td>
<td>↓38%</td>
<td>↑8%</td>
<td>↓18%</td>
</tr>
<tr>
<td>Studies reporting changes from statin baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin or atorvastatin + ezetimibe</td>
<td>↓19%</td>
<td>↓21%</td>
<td>↓3%</td>
<td>↓11%</td>
</tr>
<tr>
<td>Any statin + ezetimibe</td>
<td>↓17%</td>
<td>↓25%</td>
<td>↑3%</td>
<td>↓14%</td>
</tr>
</tbody>
</table>

*All data are mean values unless otherwise indicated.
TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; MS = musculoskeletal; URTI = upper respiratory tract infection.

Table 8. Summary of Clinical Trials With Combination Pharmacotherapy: Bile Acid Sequestrants Plus Fibrates*  

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TC</td>
<td>LDL-C</td>
<td>HDL-C</td>
<td>TG</td>
</tr>
<tr>
<td>Cholestyramine + bezafibrate</td>
<td>↓28% to ↓35%</td>
<td>↓37% to ↓39%</td>
<td>↓1% to ↑2%</td>
<td>↓19% to ↓39%</td>
</tr>
<tr>
<td>Colestipol/cholestyramine + gemfibrozil</td>
<td>↓17%</td>
<td>ND</td>
<td>↑18%</td>
<td>↓50%</td>
</tr>
<tr>
<td>Colestipol + fenofibrate</td>
<td>↓36%</td>
<td>↓41%</td>
<td>↑14%</td>
<td>↓30%</td>
</tr>
<tr>
<td>Colestipol + bezafibrate</td>
<td>↓17%</td>
<td>↓23%</td>
<td>↑14%</td>
<td>↓19%</td>
</tr>
</tbody>
</table>

*All data are mean values unless otherwise indicated.
1Data presented are medians.
ND = Not determined; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B; GI = gastrointestinal; ALP = alkaline phosphatase.
studies have been of long duration. Triple combination therapies tested for safety and efficacy predominantly have employed a statin, BAS, and niacin. However, other triple combinations tested clinically include the combination of a statin, BAS, and probucol (the latter being an older lipid-lowering drug with antioxidant properties), a statin plus fibrate plus BAS, and a fibrate plus niacin plus BAS. These limited studies show improved lipid profiles in the selectively small number of patients treated, with no significant adverse effects compared with use of each agent alone; however, larger studies are needed to establish triple combination therapy as a viable treatment strategy. Triple combinations usually are reserved for patients who are unable to meet LDL-C targets with a single agent or dual therapy.

**Combination Pharmacotherapy in a Single Formulation**

In an effort to increase patient compliance, new combination formulations for lipid disorders recently were approved and others are in development. The first combination drug for the treatment of atherosclerosis is marketed as Advicor® (Kos Pharmaceuticals, Inc, Miami, Fla), containing ER niacin and lovastatin in doses of 500 mg/20 mg and 1000 mg/20 mg. Vytorin™ (Merck/Schering-Plough Pharmaceuticals, North Wales, Penn), a fixed-dose formulation of the first cholesterol absorption inhibitor, ezetimibe (10 mg), in combination with simvastatin (10, 20, 40, or 80 mg), was recently approved for use in patients with primary hypercholesterolemia or mixed hyperlipidemia. The US Food and Drug Administration (FDA) also recently approved the fixed combination of amlodipine and atorvastatin (Caduet®, Pfizer Labs, NY) in a single tablet in doses of 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg for patients with lipid disorders and comorbidities for a calcium channel blocker.

Although not combined in the same tablet/capsule, Pravigard PAC® (Bristol-Myers Squibb, Princeton, NJ),

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**Table 9. Summary of Clinical Trials With Combination Pharmacotherapy: Bile Acid Sequestrants Plus Niacin***

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colestipol + niacin (3–12 g/day)</td>
<td>TC ↓23% to LDL-C ↓32% to HDL-C ↑43% to TG ↓18% to Apo B ↓28% to 3% to 5% gouty arthritis</td>
<td>2 to 4 years</td>
<td>Blankenhorst et al, 1987; Cashin-Hemphill et al, 1990; Brown et al, 1990</td>
<td></td>
</tr>
</tbody>
</table>
| Cholestyramine or 
colestipol + ER niacin (1–2 g/day) | TC ↓11% to LDL-C ↓19% to HDL-C ↑36% to TG ↓13% to Apo B ↓19% to 2% ↑aminotransferases | 48 weeks | Guyton et al, 1998 |

*All data are mean values.

**Table 10. Summary of Clinical Trials With Combination Pharmacotherapy: Bile Acid Sequestrants Plus Ezetimibe***

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Effects on Lipids and Lipoproteins</th>
<th>Adverse Effects</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesevelam + ezetimibe</td>
<td>TC ↓25% to LDL-C ↓39% to HDL-C ↑2% to TG NS ND</td>
<td>None reported</td>
<td>12 weeks</td>
<td>Zema, 2005</td>
</tr>
</tbody>
</table>

*All data are mean values.

NS = no significant change (percentage change not reported); ND = not determined; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B.
which consists of the copackaging of 20 mg, 40 mg, and 80 mg pravastatin sodium with 81- and 325-mg doses of buffered aspirin for a total of 6 different formulations, also has been FDA approved. Other fixed-dose combination formulations in various stages of development include simvastatin-ER niacin, pravastatin sodium-aspirin, atorvastatin calcium-cholesterol ester transfer protein (CETP) inhibitor, and a statin combined with a PPAR agonist. Combined formulations for the other 6 pair-wise combinations of lipid-modifying agents shown in Tables 4-10 also are theoretically possible, and have the general advantage that combined formulations may increase patient compliance.

**DRUG THERAPIES IN DEVELOPMENT**

Although current agents are effective and well tolerated as monotherapy to control severe or combined dyslipidemias and achieve clinically relevant effects, 2 or more agents often are required, which may confer an additional side effect burden despite the fact that lower doses of individual drugs are often effective. Drugs currently in development may enhance our ability to achieve NCEP-ATP III lipid goals and may prove to be sufficiently potent to use as monotherapy even in difficult-to-treat patients. Included in this category is the novel “super statin” pitavastatin, which is already available in Japan and is expected to receive regulatory approval soon in the United States and Europe. Other drugs in development include those that modify lipid levels through novel mechanisms and may prove useful as mono- or adjunctive therapy; examples include the reverse cholesterol transport activators such as recombinant human apolipoprotein A-1 Milano (ETC-216), which has been shown to induce significant regression of atherosclerosis; and dual PPAR agonists such as muraglitazar, which have been shown to have both fibrate and thiazolidinedione-like effects. In addition, CETP inhibitors (such as JTT-705 and torcetrapib, both in phase II), bile acid transport inhibitors, and acyl-CoA cholesterol acyl-transferase inhibitors have been shown to have lipid-modifying effects. As well as providing enhanced lipid-modifying efficacy, these novel agents may also provide additional primary and secondary protection against cardiovascular events.

**COMMENTARY ON COMPARING DIFFERENT DRUG COMBINATIONS**

The effect of lipid-modifying drugs on CHD outcomes can be secondary to lipid-modifying effects and nonlipid effects such as reduction of hsCRP levels. The preventive effects also can be primary, independent of lipid effects. Many studies have demonstrated an association between improved lipid profile and CHD outcomes, but it is not known to what extent the absolute cardiovascular risk is reduced by individual drugs and drug combinations in specific patient groups. Indeed, even with marked reduction in LDL-C to “normal” levels possible with statin therapy, the cardiovascular event rate, although substantially reduced, is still higher than in a healthy population. It is clear that the relationship between lipid levels and CHD risk is confounded by baseline characteristics and demographic variables. Although the studies reviewed reveal some potential advantages of specific agents in particular patients, this manuscript does not address the place of these drugs in the treatment of specific patient subgroups, such as patients with diabetes, those with abnormal lipid profiles with no CHD risk factors, those with metabolic syndrome, elderly patients, women, and patients of nonwhite ethnicity.

Because the efficacy in terms of improvement in lipid and lipoprotein profiles and incidence of CHD varied substantially between single or combination therapy, it is not possible to determine from this review whether the differences in efficacy among various agents are statistically and clinically significant.

**CONCLUSION**

Recent detailed understanding of the molecular path-

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<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Apo B</th>
<th>Adverse Effects</th>
<th>Study Duration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin + bezafibrate</td>
<td>↓11%</td>
<td>↓39%</td>
<td>↑50%</td>
<td>↓38%</td>
<td>ND</td>
<td>None reported</td>
<td>12 months</td>
<td>Luria and Sapoznikov, 1993</td>
</tr>
<tr>
<td>Niacin + gemfibrozil</td>
<td>↓17%</td>
<td>↓20%</td>
<td>↑22%</td>
<td>↓55%</td>
<td>ND</td>
<td>↓Weight</td>
<td>12 months</td>
<td>Spencer et al, 1996</td>
</tr>
</tbody>
</table>

*All data are mean values. ND = Not determined; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; apo B = apolipoprotein B.*
ways involved in the genesis of atherosclerotic lesions, the heterogeneity of lipoproteins, the identification of emerging risk factors, and the mechanism of action of lipid-modifying agents creates new opportunities for the improved diagnosis and treatment of patients at risk for developing CHD. Many patients will require more aggressive combination pharmacotherapy in order to meet NCEP-ATP III recommended cholesterol targets, and this approach is supported by the results of clinical studies employing combination therapy for the treatment of lipid disorders. In addition, combination therapy may be needed in patients refractory to single-treatment modalities, and allows the use of lower dosages of individual agents. Future diagnosis and treatment of patients at risk for developing CHD will be improved by the recognition of new genetic and environmental factors contributing to the increased risk of, and protection from, the development of dyslipidemias and the associated risk of CHD.

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