The National Cholesterol Education Program Adult Treatment Panel III lipid management guidelines emphasize the importance of matching the intensity of lipid modification therapy to each patient’s risk of coronary heart disease. For many patients who are at low risk, nonpharmacologic interventions such as diet, exercise, and smoking cessation can be effective lipid-lowering strategies. However, many patients require the addition of drug therapy to achieve lipid targets. Currently available lipid-modifying drugs include bile acid sequestrants, fibrates, nicotinic acid, cholesterol absorption inhibitors, and statins. In addition, nonprescription agents such as plant sterols and stanol esters are available to modify plasma lipid levels. These agents can be used individually or coadministered to achieve lipid goals.

The reduction of low-density lipoprotein cholesterol (LDL-C) remains one of the primary methods of reducing the risk of coronary heart disease (CHD) and its complications. The optimal prevention program matches the intensity of risk reduction therapy with the individual’s absolute risk. To accomplish this, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines recommend starting with therapeutic lifestyle changes (TLC), a fundamental component of all treatment regimens, and moving to drug therapy if necessary to achieve the treatment goal.

As discussed elsewhere in this supplement, matching patients with the most appropriate lipid-modifying therapy is critical to success and begins with risk assessment. This article provides an overview of treatment strategies, with a focus on matching individual absolute risk with safe, cost-effective therapy that will encourage patient adherence. Adherence to treatment is essential for the achievement of LDL-C goals and subsequent reduction of CHD risk. The ATP III guidelines emphasize the importance of multiple follow-up office visits to monitor progress, adjust treatment, and provide motivation. Although results of lifestyle modification programs have been mixed, physician education and involvement in follow-up have been shown to improve adherence. In motivated patients who make the necessary changes, TLC interventions may reduce plasma cholesterol by as much as 15%.

Therapeutic Lifestyle Changes

Initiating and maintaining TLC is an important part of all lipid-lowering regimens and can be highly cost-effective when adhered to long term. The ATP III guidelines recommend TLC as first-line therapy for most patients without a history of CHD, CHD risk equivalents, or more than two risk factors. Components of TLC that have been shown to be effective in lowering LDL-C include a healthy diet, regular physical activity, smoking cessation, and weight loss.

Dietary changes should include a reduction of saturated fats to less than 7% of total calories and a reduction of dietary cholesterol intake to less than 200 mg/d. The addition of 2 g of plant sterols/stanol esters (commercially available in special margarines) and the incorporation of 10 g to 25 g of viscous fiber per day into the diet can further increase the LDL-lowering effectiveness of diet. Weight reduction can decrease LDL-C levels and ameliorate risk factors associated with the metabolic syndrome by improving insulin sensitivity and serum glucose uptake. Physical activity raises high-density lipoprotein cholesterol (HDL-C) levels and decreases the concentration of very low-density lipoprotein cholesterol (VLDL-C) and triglycerides. Smoking cessation also results in a reduction of CHD risk.

The ATP III guidelines recognize the management of metabolic syndrome—a constellation of symptoms that includes insulin resistance, obesity, hypertension, atherogenic dyslipidemia (elevated triglyceride concentrations, small LDL-C particles, and low levels of HDL-C), and prothrombotic and proinflammatory states—as a secondary target of risk-reduction therapy. Obesity and physical inactivity are key factors in the development of metabolic syndrome; therefore, a lipid-lowering strategy that includes TLC is essential to the management of the 47 million patients with this condition.

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Although this is an important reduction, it may not be adequate to reach target LDL-C levels in some patients. The ATP III guidelines recommend that if treatment goals are not achieved with 4 to 6 months of TLC, drug therapy should be considered.

### Targeting Different Components of the Cholesterol Metabolic Pathway

Five classes of lipid-modifying drugs are currently available in prescription form, including bile acid sequestrants, nicotinic acids, fibrin acid derivatives, cholesterol absorption inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). Each class targets a different step in the process through which cholesterol is metabolized. Circulating cholesterol is derived from two sources: de novo synthesis in peripheral tissues and intestinal absorption. Each source contributes approximately half of the total cholesterol found in the blood. However, of the cholesterol available for intestinal absorption, only 25% is derived from the diet. The remaining 75% is delivered to the intestine through biliary excretion and, to a much smaller degree, sloughing of intestinal cells. Several drugs that modify cholesterol metabolism in different ways are currently available.

### Agents Targeting Endogenous Cholesterol

- **Statins**—Statins, the most widely used lipid-modifying agents, decrease LDL-C by inhibiting cholesterol synthesis and reduce LDL-C up to 60% in a dose-dependent manner. The currently available statins are differentiated by the decrease in the LDL-C level achieved at a given dose. Several large clinical outcomes trials have demonstrated that statin use reduces the incidence of CHD events, including myocardial infarction, coronary death, stroke, and total mortality.

  Statins inhibit hydroxymethylglutaryl coenzyme A, the enzyme that catalyzes the rate-limiting step in cholesterol synthesis. These agents reduce plasma levels of total cholesterol, LDL-C, non–HDL-C, and triglycerides. Statins also increase levels of HDL-C.

- **Fish Oils**—Although the use of omega-3 long-chain fatty acids, or fish oils, is not addressed in the ATP III guidelines, these agents do have a favorable effect on plasma lipids, particularly triglycerides.

  A systematic review of lipid-lowering regimens found that dietary intake of long-chain fatty acids for 2 years decreased total cholesterol from baseline by 5% to 6.5%. In a study of 2033 men who were recovering from acute myocardial infarction, increased fatty fish intake decreased 2-year all-cause mortality by 29%. Although the exact mechanism by which these changes occur is poorly understood, the addition of fish oil to the diet of laboratory mice increased the activity of the rate-limiting enzyme responsible for bile acid synthesis. The increase in enzyme activity was associated with an increased cholesterol excretion.

- **Fibric Acids**—The ATP III guidelines did not consider fibric acids or fibrates an LDL-C–lowering drug option because fibrates possess minimal LDL-C-reducing capabilities. However, these agents are useful in patients with combined forms of hyperlipidemia and are especially effective in patients who have severe hypertriglyceridemia. It is thought that fibrates lower VLDL-C levels and increase HDL-C levels via an interaction with peroxisome proliferator–activated receptors (PPARs). The PPAR-mediated effects are thought to enhance clearance of triglyceride-rich lipoproteins.

  Poor tolerability and safety concerns with older fibrates such as gemfibrozil can limit adherence to fibrate therapy and therefore reduce the effectiveness of these agents. However, newer fibrates such as fenofibrate appear to be safer, better tolerated, and more effective.

- **Nicotinic Acid**—Nicotinic acid, or niacin, is the only lipid-lowering drug currently available as an over-the-counter medication. Nicotinic acids provide a moderate LDL-C–lowering action, but the primary use of these agents is in combination with statins for patients who have elevated triglyceride concentrations or low HDL-C levels, or both. The overall effectiveness of nicotinic acids may be limited because of side effects such as facial flushing. However, the tolerability of niacin therapy can be improved by using either sustained-release formulations of the drug or by slowly increasing the dose and providing patients with instructions on how to minimize side effects.

### Agents Targeting Exogenous Cholesterol

- **Cholesterol Uptake Inhibitors**—Ezetimibe is in a new class of drugs that specifically blocks absorption of intestinal cholesterol. Approximately 50% of the total cholesterol found in the gut after a meal is absorbed by the intestinal enteroocyte and is passed into the circulation in the form of a triglyceride-rich chylomcron. The unabsorbed cholesterol is eliminated with the feces. Ezetimibe inhibits as much as 54% of all intestinal cholesterol absorption without affecting uptake of triglycerides or lipid-soluble vitamins.

  Clinical trial evidence indicates that ezetimibe reduced LDL-C by 18%, with a 12% decrease in total cholesterol, a 41% decrease in triglyceride concentrations, and a 1% increase in HDL-C. The safety profile of ezetimibe was similar to that of placebo.

  Ezetimibe can be used as monotherapy in patients at low risk of CHD who require a modest reduction in their LDL level or in patients who cannot tolerate statin therapy.

- **Bile Acid Sequestrants**—Bile acid sequestrants reversibly bind to bile acids in the intestinal lumen, promoting their fecal elimination. As a result, the amount of bile acid that returns to the liver is reduced, activating the conversion of hepatic cholesterol into bile acids. These agents can reduce LDL-C levels by 15% to 25% and increase HDL-C levels. They are used as monotherapy when moderate reductions in LDL-C levels are required, or they are coadministered with statins, particularly in patients with severe dyslipidemia. The use of sequestrants is limited because of gastrointestinal side effects and the incompatibility of taking multiple tablets every day to obtain a clinical effect.

### Aggressive Lipid-Lowering Therapy and Adverse Events

Several well-designed clinical trials have demonstrated the benefits of aggressive lipid lowering with statins. How-
ever, many patients fail to achieve the benefits of statin therapy observed in clinical trials. A recent study by Foley et al. suggests that one explanation for this discrepancy is the failure of physicians to titrate the dose of statin to a level necessary to achieve the desired lipid reduction. Furthermore, it appears that lipid lowering with statins is not linear over the full dosing range, as increasing the dose twofold usually results in only a 6% further reduction in LDL-C levels.

The escalation of statin, which is generally well tolerated in most patients, results in a small increase in the incidence of statin-induced myalgias. Rare but serious adverse effects include rhabdomyolysis and hepatotoxicity. Liver function monitoring is important, and the drug should be stopped if liver function test values are elevated more than three times the upper limit of normal. Temporally associated muscle weakness should prompt immediate drug cessation and evaluation of the creatine kinase level. Routine testing of creatine kinase for myalgias is not warranted. If myalgias develop with initiation of statin therapy, stopping the drug with improvement of symptoms confirms the diagnosis. Thus, high-dose statin therapy has the potential to increase the risk of serious adverse events.

One approach to maximize the lipid-lowering effectiveness of statins and to minimize the potential for dose-related side effects is to coadminister them with agents that affect different steps involved in lipid metabolic pathways.

For many patients, this approach offers a potentially attractive therapeutic option. The proper coadministeration of two drugs is effective in producing lipid reductions that exceed those of monotherapy. By having an impact on lipid homeostasis by complementary mechanisms of action, coadministration of low-doses of two agents has a greater lipid-lowering effect compared with an increased dose of one agent. This ability is especially true when the lipid-modifying effect of a statin is augmented with a drug from another class.

Coadministration of lower doses of two agents may prove to be better tolerated than high-dose monotherapy, particularly when the lipid-lowering capacity of the add-on drug allows for reduction in the dose of the original therapy and offers a favorable side effect profile. Examples of agents frequently coadministered for lipid modification are described elsewhere in this supplement.

Comment
Lipid lowering reduces the risk of CHD and serious coronary events. However, to achieve optimal risk reduction, treatment strategies must be designed to meet the needs of each patient. Patients at lower risk can reduce their risk through the regular use of TLC, while others at higher baseline risk may require more intensive therapy using high doses of statins. However, because of the potential for more serious adverse events when using high-dose statin therapy, alternative approaches such as coadministering two agents with different, but complementary mechanisms of action may offer a more safe and effective way to achieve the desired clinical effects.

References