

# Hyperlipidemia

**H**yperlipidemia is a group of disorders characterized by an excess of blood lipids such as cholesterol, triglycerides and lipoproteins. It affects one out of 100 people, with higher incidence among men than women. High blood cholesterol is a major contributor to the growing incidence of cardiovascular disease.

Causes of hyperlipidemia include high fat diet, obesity, habitual excessive alcohol intake, genetic factors, certain drugs, and diseases such as diabetes mellitus, hypothyroidism, Cushing's syndrome, and certain types of renal failure.

Every year, morbidity from coronary heart disease (CHD) in the U.S. costs more than \$200 billion, and CHD kills 500,000 Americans, making it the most common cause of death. Despite the well established connection between CHD and elevated serum cholesterol, this risk factor is generally undertreated. In 1996, only 30% of patients with CHD and hyperlipidemia received lipid-lowering agents from their cardiologists at a major teaching hospital.

To meet recommended goals for low-density lipoprotein (LDL) levels, approximately 52 million adults need to follow a well-balanced, low-fat diet with limited cholesterol intake, and 12.7 million need lipid-lowering drugs. Because diet,

exercise and smoking cessation combined often fail to lower blood lipids to optimal levels, the U.S. Food and Drug Administration (FDA) estimates that at least 35% of adults in the U.S. could benefit from a cholesterol-lowering agent.

Defining normal plasma total cholesterol levels is difficult because the incidence of CHD rises continuously with plasma cholesterol, and because statistically normal values in the U.S. are higher than optimal for CHD prevention.

Evidence from well-designed, prospective clinical trials suggests that lowering even average levels of total cholesterol and LDL can halt or reverse the progression of CHD.

Although pharmacological approaches to hyperlipidemia have included niacin, cholestyramine, and gemfibrozil, the mainstay of treatment is currently the statins because they are effective, well tolerated and easily administered. Niacin (nicotinic acid) reduces the rate of synthesis of very low-density lipoprotein (VLDL), the precursor of LDL, while fibric acid derivatives, such as gemfibrozil and clofibrate, accelerate the clearance of VLDL.

Bile acid sequestrants, such as cholestyramine and colestipol, and statins stimulate LDL clearance mostly through receptor-mediated mechanisms. Gastrointestinal side effects and cumbersome administration limit clinical use of the

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bile acid sequestrants.

Statins inhibit the rate-limiting step in cholesterol synthesis by blocking activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. They raise levels of beneficial high-density lipoprotein cholesterol (HDL-C) and may also lower triglycerides, VLDL and intermediate density lipoproteins.

Currently available statins have similar side effect profiles and differ only in their maximum potency. At maximum doses, simvastatin can lower LDL by 45% to 50%. Although statins may be even more effective in combination with other lipid-lowering drugs, the risk of myositis, rhabdomyolysis and renal failure increases when statins are combined with gemfibrozil, clofibrate, niacin, or other agents metabolized by the cytochrome P-450 system.

Ideally, the next generation of statins should be more effective at lowering lipids, with greater tolerability, improved compliance, and a reduced potential for adverse drug interactions. CenterWatch has identified a pipeline of 14 statins and other lipid-lowering agents in various phases of development.

Furthest along the pipeline is Crestor, or rosuvastatin calcium (ZD-4522). Astra-Zeneca received an FDA-approvable letter for Crestor in May 2002, submitted an amendment in February 2003, and is conducting additional trials.

In phase III trials, rosuvastatin was superior to currently available statins in lowering LDL and in raising HDL. Because it is not extensively metabolized by cytochrome P450 isozymes, there is a low risk of drug interactions. Its half-life of about 20 hours allows for once daily administration and little accumulation after repeated daily doses.

Rosuvastatin lowered LDL by 34% at a dose of 10 mg/day and by 65% at 80 mg/day, with 90% of the reduction occurring in the first two weeks of treatment. Other effects were 10%-35% decrease in triglycerides, marked reductions in total cholesterol and apolipoprotein-b, and 9%-14% increase in HDL.

Side effects included nausea, diarrhea, dry mouth and abdominal pain, but there were no cases of myopathy, nor any clinically relevant increases in liver function tests or creatine kinase.

In a randomized trial, 88% of patients with primary hypercholesterolemia taking rosuvastatin 5 or 10 mg/day achieved the NCEP goal for LDL, compared with 73% of patients taking pravastatin 20 mg/day, and 60% of patients taking simvastatin 20 mg/day. In a similar trial including patients with diabetes, CHD and peripheral vascular disease, 97% of patients taking rosuvastatin 10 mg/day met the NCEP LDL-C goal, compared with 61% of patients taking atorvastatin 10 mg/day.

Similar findings in large, independent European studies led to Crestor's approval in the Netherlands in 2002, completion of the Mutual Recognition Procedure in 13 other European countries, and approval in Canada and Singapore.

Another synthetic HMG-CoA reductase inhibitor that is not significantly metabolized by cytochrome P450 isozymes is pitavastatin, for which the Japanese company Kowa has submitted a new drug application. In patients with heterozygous familial hypercholesterolemia, pitavastatin reduced total cholesterol by 37%, LDL by 48%, and triglycerides by 23%, but it did not significantly raise levels of HDL-C.

For hyperlipidemia in postmenopausal women, Bristol-Myers Squibb is in phase III development of Premarin/Pravachol (estrogen/pravastatin). In a trial of 63 hypercholesterolemic menopausal women, this combined treatment brought the atherogenic index (cholesterol/HDL-C) from a moderate risk to a reduced risk category. Although hormonal replacement therapy alone increased triglycerides, adding the statin returned triglyceride levels to baseline.

Another once daily combination therapy is ezetimibe/simvastatin, in phase III development by Schering-Plough. Ezetimibe inhibits cholesterol absorption in the intestine, while simvas-

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atin (Zocor) inhibits production of cholesterol in the liver and should therefore have an additive benefit. This combination has been shown to reduce LDL by 52%, compared with 35% for Zocor alone.

HMG CoA reductase inhibitors currently in phase II development are the Novartis drug pitavastatin (NKS104) and Superstatin, from Bristol-Myers Squibb. The latter drug is said to be potentially far more potent than Lipitor, and to lower LDL levels by at least 60%.

An innovative approach is CETi-1, a cholesteryl ester transfer protein (CETP) vaccine in phase II testing by Avant Immunotherapeutics. The initial immunization and boosters are designed to induce antibodies against CETP, thereby blocking the transfer of cholesterol from HDL to LDL and raising serum HDL levels.

Using a focused combinatorial library of chemicals synthesized by robotics, Bristol-Myers Squibb designed BMS-201038 to be an oral inhibitor of the microsomal triglyceride transport protein (MTP). In a rat model of hypertriglyceridemia, BMS-201038 decreased plasma triglycerides and VLDL to approximately the same degree as did atorvastatin. Phase II testing of this drug is underway.

Forbes Medi-Tech is in phase II testing of its cholesterol transport inhibitor FM-VP4, an amphipathic analogue of phytosteranol, which is both water- and lipid-soluble. In animal mod-

els, FM-VP4 promoted weight loss, reduced total cholesterol levels by 52%-75%, and reduced by 75% the development of atherosclerotic lesions in apolipoprotein E-deficient (ApoE) mice.

In a phase I safety study of FM-VP4, there were no serious adverse events even at the highest dosages. The primary endpoint of the phase II study is the change in total and LDL cholesterol from baseline after four weeks of treatment.

To date, the statins have been the tried-and-true standard for lipid-lowering therapy. Most drugs in development for hyperlipidemia are new-and-improved statins designed for greater efficacy, better compliance and fewer drug interactions. A few combination therapies hope to achieve additive benefits by teaming a statin with a drug from a different class.

Pharmaceutical companies are also targeting multiple points along the lipid metabolism/absorption pathways. Whether through vaccine development or combinatorial chemicals synthesized by robotics, advances in technology may ultimately yield benefits applicable to the widespread problem of hyperlipidemia and its devastating implications for public health.

—Laurie Barclay, M.D.

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