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Drug Treatment of Lipid Disorders

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Arteriosclerosis of the coronary and peripheral vasculature is the leading cause of death among men and women in the United States[1] and worldwide.[2] In 1992, for example, cardiovascular disease accounted for 38 percent of deaths from all causes among men and 42 percent of all deaths among women in Washington State[3]; nationwide, the mortality rate for cardiovascular disease is approximately 50 percent.[4]

Mechanisms of Atherogenesis

Central to the pathogenesis of arteriosclerosis is the deposition of cholesterol in the arterial wall.[5,6] Nearly all lipoproteins are involved in this process, including cholesterol carried by very-low-density lipoprotein (VLDL),[7,8] remnant lipoprotein,[8] and low-density lipoprotein (LDL), particularly the small, dense form.[9] Conversely, cholesterol is carried away from the arterial wall by high-density lipoprotein (HDL).[10,11]

In healthy persons, these lipoproteins function to distribute and recycle cholesterol (Figure 1).[12] Hepatic overproduction of VLDL can lead to increases in the serum concentrations of VLDL, remnant lipoprotein, and LDL,[13,14] depending on the ability of the body to metabolize each of these types of lipoprotein.[15,16,17] The most common and important lipid disorder involving this mechanism is familial combined hyperlipidemia (also referred to as mixed hyperlipemia).[13,18] The primary disorders of

lipoprotein metabolism are described in Table 1 and have been reviewed elsewhere.[5,19,20]

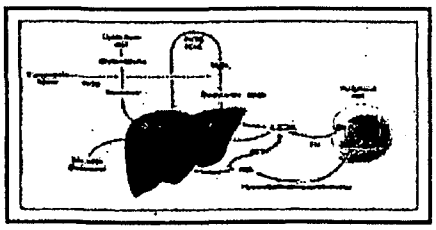

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Figure 1. Pathways of Lipid Transport.

Cholesterol is absorbed from the intestine and transported to the liver by chylomicron remnants, which are taken up by the low-density lipoprotein (LDL)-receptor–related protein (LRP). Hepatic cholesterol enters the circulation as very-low-density lipoprotein (VLDL) and is metabolized to remnant lipoproteins after lipoprotein lipase removes triglyceride. The remnant lipoproteins are removed by LDL receptors (LDL-R) or further metabolized to LDL and then removed by these receptors. Cholesterol is transported from peripheral cells to the liver by high-density lipoprotein (HDL). Cholesterol is recycled to LDL and VLDL by cholesterol-ester transport protein (CETP) or is taken up in the liver by hepatic lipase. Cholesterol is excreted in bile. The points in the process that are affected by the five primary lipoprotein disorders — familial hypertriglyceridemia (FHTG), familial combined hyperlipidemia (FCHL), remnant removal disease (RRD, also known as familial dysbetalipoproteinemia), familial hypercholesterolemia (FH), and hypoalphalipoproteinemia — are shown.

The effects of drug therapy can also be understood from these pathways. Statins decrease the synthesis of cholesterol and the secretion of VLDL and increase the activity of LDL receptors. Bile-acid–binding resins increase the secretion of bile acids. Nicotinic acid decreases the secretion of VLDL and the formation of LDL and increases the formation of HDL. Fibrates decrease the secretion of VLDL and increase the activity of lipoprotein lipase, thereby increasing the removal of triglycerides. Adapted from Knopp.[12]

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Table 1. Primary Lipoprotein Disorders Amenable to Treatment with Diet and Drug Therapy.

The chief risk factors for cardiovascular disease are listed in Table 2.[6,10,11,21,22,23,24,25,26] When these risk factors occur in combination with hyperlipidemia and low serum HDL concentrations, early cardiovascular disease is commonplace.[21] Keys to prevention and treatment are the elimination or modification of risk factors, if possible, in conjunction with treatment of the specific lipid disorder.

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Table 2. Risk Factors for Cardiovascular Disease Identified by the National Cholesterol Education Program and Others.

Secondary Causes of Hyperlipidemia

Closely related to the numerous risk factors for cardiovascular disease are conditions that cause hyperlipidemia,[27] including obesity, diabetes mellitus, hypothyroidism, and the nephrotic syndrome; alcohol ingestion; and therapy with oral estrogen, isotretinoin, sertraline hydrochloride, human immunodeficiency virus (HIV)–protease inhibitors, ß-adrenergic antagonists, glucocorticoids, cyclosporine, and thiazide diuretics. In general, each condition should be treated and any offending medications discontinued before a program to lower serum lipid concentrations is initiated. Patients with severe hyperlipidemia usually have two disorders — for example, diabetes mellitus and familial combined hyperlipidemia, familial hypertriglyceridemia, or remnant removal disease.[19,20,28]

Target Serum Lipoprotein Concentrations

The threshold serum total cholesterol and LDL cholesterol concentrations above which diet and drug therapy should be initiated, as well as the goals of therapy, have been defined by the National Cholesterol Education Program (Table 3).[21] The target serum LDL cholesterol concentration is less than 160 mg per deciliter (4.3 mmol per liter) for patients with no risk factors for heart disease or only one risk factor, less than 130 mg per deciliter (3.4 mmol per liter) for patients with two or more risk factors, and less than 100 mg per deciliter (2.6 mmol per liter) for those with cardiovascular disease (Table 3).[21,29,30,31] Persons with diabetes also fall in this third category, even those with no apparent cardiovascular disease.[21,32,33] Reducing serum LDL cholesterol concentrations below the target levels does not necessarily result in a proportional reduction in the risk of cardiovascular disease,[34,35,36,37,38,39] because of the attenuation of the cholesterol–heart disease relation at lower serum cholesterol concentrations.[40] Drug therapy is not recommended for premenopausal women and men under 35 years of age unless they have serum LDL cholesterol concentrations of more than 220 mg per deciliter (5.7 mmol per liter), because their immediate risk of heart disease is low.[21] The presence of risk factors and a family history of the disease could lower this threshold.

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Table 3. Threshold Serum Total and Low-Density Lipoprotein (LDL) Cholesterol Concentrations for the Initiation of Dietary and Drug Treatment, According to the Number of Risk Factors for Cardiovascular Disease and the Presence or Absence of Cardiovascular Disease.

A serum triglyceride concentration of more than 200 mg per deciliter (2.3 mmol per liter; approximately the 90th percentile for older men and women)[41] is considered somewhat elevated, and a concentration of more than 400 mg per deciliter (4.5 mmol per liter; >95th percentile) is considered high according to the National Cholesterol Education Program guidelines.[21] A reasonable target is a triglyceride concentration of 200 mg per deciliter or less, because higher values are associated with a doubling of the risk of cardiovascular disease when serum total cholesterol concentrations exceed 240 mg per deciliter (6.2 mmol per liter) or the ratio of serum LDL cholesterol to HDL cholesterol exceeds 5:1.[42,43] Reasonable targets for serum HDL cholesterol concentrations are 45 mg per deciliter (1.2 mmol per liter) in men and 55 mg per deciliter (1.4 mmol per liter) in women — the respective means in these populations.[41]

Dietary Treatment of Hyperlipidemia

Dietary treatment of hyperlipidemia is a necessary foundation for drug treatment. Depending on the degree of hyperlipidemia, the Step I and Step II diets can be introduced sequentially,[21] or the Step II diet can be begun immediately (or when drug therapy is begun) if the patient is already restricting his or her intake of saturated fatty acids to less than 10 percent of total calories or if the risk of cardiovascular disease is high. The Step I diet contains no more than 30 percent of calories from fat, less than 10 percent of calories from saturated fatty acids, and less than 300 mg of cholesterol (7.8 mmol) per day. The Step II diet contains no more than 30 percent of calories from fat, less than 7 percent of calories from saturated fatty acids, and less than 200 mg of cholesterol per day.

In long-term studies the Step II diet decreased serum LDL cholesterol concentrations 8 to 15 percent.[44,45,46] In addition, diet can help to reduce weight to an ideal level, increase the intake of vitamins, and reduce blood pressure and insulin resistance.[44,45,46,47,48] Diets more restricted in fat than the Step II diet result in little additional reduction in serum LDL cholesterol concentrations, raise serum triglyceride concentrations, and lower serum HDL cholesterol concentrations.[44] The risk of heart disease can also be reduced with the use of some diets that include a moderate intake of monounsaturated and polyunsaturated fat, such as the Mediterranean diet.[49]

Statins

Drugs of the statin class are structurally similar to hydroxymethylglutaryl–coenzyme A (HMG-CoA), a precursor of cholesterol, and are competitive inhibitors of HMG-CoA reductase, the last regulated step in the synthesis of cholesterol.[50] These drugs lower serum LDL cholesterol concentrations[51,52] by up-regulating LDL-receptor activity as well as reducing the entry of LDL into the circulation.[50,53,54] Given alone for primary or secondary prevention of heart disease, these drugs can reduce the incidence of coronary artery disease by 25 to 60 percent[34,35,36,55,56,57,58] and reduce the risk of death from any cause by about 30 percent.[35,56,58] Therapy with a statin also reduces the risk of angina pectoris and cerebrovascular accidents and decreases the need for coronary-artery bypass grafting and angioplasty.[31,34,35,36,38,55,56,57,58,59,60]

Lipid-Altering Effects

The characteristics of the six currently available statins are listed in Table 4. The dose required to lower serum LDL cholesterol concentrations to a similar degree varies substantially among the statins. In addition, the response to increases in the dose is not proportional, because the dose–response relation for all six statins is curvilinear (Figure 2). In general, a doubling of the dose above the minimal effective dose decreases serum LDL cholesterol concentrations by an additional 6 percent. The maximal reduction in serum LDL cholesterol concentrations induced by treatment with a statin ranges from 24 to 60 percent (Table 4).

View this table: **Table 4.** Characteristics of Statins.
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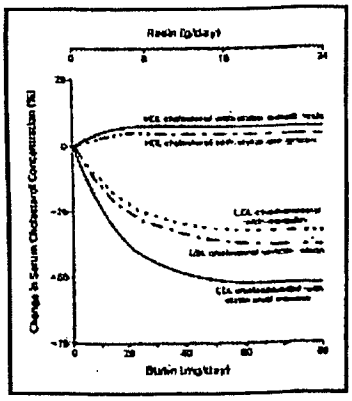

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Figure 2. Effects of Treatment with Statin and Bile-Acid–Binding Resin, Alone or in Combination, on Serum High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) Cholesterol Concentrations.

The effects of both drugs decline exponentially with increasing doses. Resin denotes bile-acid–binding resin given as cholestyramine. Data were obtained from the Pravastatin Multicenter Study Group II.[62]

All the statins lower serum triglyceride concentrations, with atorvastatin[64] and simvastatin[65] having the greatest effect. In general, the higher the base-line serum triglyceride concentration, the greater the decrease induced by statin therapy.[65] Statins are a useful adjunct in the treatment of moderate hypertriglyceridemia in patients with familial combined hyperlipidemia, but they are often insufficient. Statins are ineffective in the treatment of patients with chylomicronemia.

Other benefits of some statins[66,67] include decreased fibrinogen levels and viscosity,[66] increased immune tolerance after transplantation,[68,69] diminished uptake of aggregated LDL by vascular smooth-muscle cells,[70] increased free cholesterol and decreased cholesterol ester concentrations within macrophages,[71] suppression of the release of tissue factor,[72] and activation of endothelial nitric oxide synthase.[73]

Absorption and Metabolism

Since lovastatin is better absorbed when taken with food, it should be taken with meals (Table 4). On the other hand, pravastatin is best taken on an empty stomach or at bedtime.[61] Food has less of an effect on the absorption of the other statins. Because the rate of endogenous cholesterol synthesis is higher at night, all the statins are best given in the evening.

The statins are eliminated in part by the kidneys (Table 4), and serum concentrations may be higher in patients with renal disease. The predominant route of excretion is through the bile, after hepatic transformation. Patients with hepatic disease should be given lower doses or treated with another type of drug.[61,74] None of the statins should be given to pregnant women because they are teratogenic at high doses in animals. Statin therapy does not affect adrenal or gonadal steroidogenesis.[75]

Adverse Effects

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