Lipid-Lowering Drugs and Atherosclerosis

MAJOR DRUG CLASSES

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Therapeutic Overview

In 2004, there were nearly 1 million deaths from cardiovascular disease (CVD) in the United States. Of deaths resulting from CVD, the vast majority can be attributed to atherosclerosis and its complications. Each of the major complications of CVD, including acute coronary syndromes (myocardial infarction and unstable angina), sudden deaths, angina pectoris, stroke, claudication (exercise-induced leg pain), and congestive heart failure can be reduced by appropriate lifestyle and drug treatment interventions.

The major risk factors for atherosclerosis and its complications are known and are targets for treatment (Box 25-1). Lowering low-density lipoprotein (LDL) cholesterol (LDL-C) with hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, collectively known as the statins, is associated with decreased rate of death, acute coronary syndromes, strokes, and need for coronary artery revascularization by bypass surgery or angioplasty in patients at risk and with established congestive heart disease. Smoking cessation, diet and exercise, controlling blood pressure, daily low-dose aspirin, and increasing levels of high-density lipoprotein (HDL) cholesterol (HDL-C) also reduce the risk for atherosclerosis-related events (Fig. 25-1). Lipid-altering strategies shown to be effective include statins, fibric acid derivatives, bile acid sequestrants (resins), cholesterol absorption inhibitors, niacin, intestinal bypass, and removal of LDL by plasma apheresis. In general, for every 1% lowering of cholesterol, there is a 2% reduced risk of coronary artery disease.

Pathobiology of Atherosclerosis and Therapeutic Targets

Atherosclerosis is a systemic disease of the aorta, coronary, carotid, and peripheral arteries in response to endothelial injury by one or more risk factors (e.g., hypertension, oxidized LDL, tobacco, homocysteine, infection). The earliest lesions, fatty streaks, can be found in children and young men and women who die of noncardiac causes. Diffuse nonocclusive coronary plaque has been found in 25% to 50% of young adult men postmortem. The amount of fatty streak and plaque correlates with the prevalence of classic coronary risk factors even in children. The duration of exposure to risk factors (age) and genetics (family history of premature disease) are major determinants of how and when clinical manifestations may occur.

Atherosclerosis is primarily an inflammatory response to injury. At least six major processes occur in the development of atherosclerotic plaques (atheroma). Each is a potential therapeutic target that can be influenced by drugs, particularly the statin family of lipid-lowering drugs:

- Injury of the endothelial lining facilitating entry of monocytes and adherence of platelets
- Active and passive transport of lipid particles into the subendothelial space followed by oxidation
- Conversion of monocytes to macrophages that ingest oxidized LDL and transform to foam cells that coalesce into fatty streaks
- Inflammatory T lymphocyte responses
- Smooth muscle cells and fibroblasts provide a matrix skeleton of collagen, fibrin, and calcification
- Spontaneous death or digestion of foam cells with release of cholesterol and other lipids to form a lipid pool

Histological evidence suggests that plaque growth may be gradual over years, with bursts of growth from periodic intraplaque hemorrhage and repair. Gradual buildup of plaque over decades can lead to the gradual narrowing of coronary and other conduit arteries (carotid, femoral, popliteal), and, alternatively, can rupture, leading to
sudden occlusion, resulting in an acute ischemic syndrome (unstable angina, myocardial infarction, stroke, death, critical limb ischemia). Fibrous plaques are prevalent in the 4th and 5th decades of life, and symptoms (angina, claudication) from occlusive plaques peak in the 7th decade. Ruptures and fissures of plaques, which can lead to sudden occlusion with a superimposed thrombus resulting in acute ischemic events, occur predominantly in nonocclusive lesions. The prevalence of acute coronary syndromes in healthy men and women increases with age, from very rare in the 30s to more than 1% in men over 60 years and women over 70 years of age.

The type of plaque is a major determinant for risk of acute coronary events. Angina pectoris and claudication are usually caused by flow-limiting partially occlusive coronary or peripheral artery stenosis (>50% to 70%). The latter are composed of fibrocalcific plaques abundant in smooth muscle and fibrous tissue with or without a lipid core. Most people with hemodynamically significant stenosis remain asymptomatic until an acute event occurs. Most acute coronary events are the result of an occluding or partially occluding thrombus at the site of rupture of the fibrous cap in a nonocclusive (20% to 75%) coronary segment or intraplaque hemorrhage.

Most heart attacks and sudden cardiac deaths occur in persons without a history of angina or previous symptoms. Intraplaque hemorrhage from weakening of the walls of the vasa vasorum (small adventitial arteries supplying arteries with O2 and nutrients) can lead to plaque progression and sudden occlusion. Characteristics of vulnerable plaques include:

- A thin fibrous cap
- Increased inflammatory cells (macrophages and T lymphocytes capable of secreting matrix metalloproteinases that digest collagen)
- Few smooth muscle cells and collagen fibers
- A large lipid core

The endothelium, or luminal layer of cells of the arterial wall, provides a protective barrier and produces a wide variety of substances involved in regulating vascular tone, thrombosis, and cellular adhesion, migration, and growth. Coronary risk factors, including age, elevated LDL-C, low HDL-C, smoking, hypertension, and diabetes are associated with impaired endothelial function. Nitric oxide and prostacyclin are released in response to shear stress and autonomic tone. Each is a vasodilator with antithrombotic, antiplatelet, and antioxidant functions. Formation and release of prostacyclin and nitric oxide by the endothelium is impaired after a high-fat diet and in all stages of atherosclerosis in coronary and conduit vessels with or without plaque.

Lipid-lowering therapy can improve endothelial function, reduce coronary events and strokes, relieve symptoms, prevent new plaque formation, reduce rate of progression, and even induce regression of focal narrowing. Raising HDL-C enhances endothelial function and results in removal of cholesterol from cells and lipid pools, known as reverse cholesterol transport. In established coronary heart disease and for primary prevention, serum lipids are one of many interactive risk factors requiring lifestyle changes and drug therapy (see Fig. 25-1). Aspirin and other platelet antagonists (see Chapter 26) reduce risks of acute coronary syndrome and strokes by reducing thrombosis. Antihypertensive strategies (see Chapter 20) reduce wall stress and plaque rupture by various mechanisms.

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**BOX 25–1 Known and Putative Coronary Risk Factors**

**Major**
- Age/male gender
- Smoking
- Hypertension
- Elevated cholesterol/LDL-C
- Low HDL-C
- Diabetes
- Family history of premature coronary heart disease, peripheral vascular disease, or stroke

**Minor**
- Sedentary lifestyle
- Obesity
- Dietary saturated fats
- Triglycerides
- VLDL and IDL remnants

**Contributory**
- Chronic renal failure
- Radiation therapy
- Systemic lupus erythematosus

**Putative**
- Homocysteine
- Lp(a)
- Small LDL particles
- C-reactive protein
- Chronic infection

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**FIGURE 25–1** Atherosclerosis prevention. Intervention (treatment) involves (1) diet to decrease cholesterol and fats, (2) cessation of smoking, (3) drugs to reduce plasma cholesterol concentration, (4) control of blood pressure, (5) control of diabetes, and (6) regular moderate exercise.
Therapeutic uses of lipid-lowering drugs are summarized in the Therapeutic Overview Box.

Mechanisms of Action

Drugs that lower LDL-C can prevent the formation, slow the progression, and enhance the regression of atherosclerotic lesions. To appreciate how and why lipid-lowering compounds may be used both by themselves and in combination through their different mechanisms of action, it is essential to understand cholesterol balance by the body and the transport of lipoproteins and lipids in plasma and other fluids.

Cholesterol Balance

The dynamics of cholesterol ingestion, synthesis, and elimination are depicted in Figure 25-2. The sole sources of exogenous cholesterol are ingested animal-based food substances, including meats and dairy products. Dietary intake can vary from 0 to 1000 mg/day, with 30% to 75% typically absorbed.

Although cholesterol can be synthesized de novo in most cells, its main endogenous sources are the adrenals and liver. Because of the greater liver mass, hepatic synthesis is a major source of cholesterol. The normal rate of endogenous cholesterol synthesis varies from 600 to 1000 mg/day, with approximately 750 to 1250 mg secreted daily in bile. One half to two thirds of biliary cholesterol is reabsorbed, and the remainder is excreted in the stool. Total body cholesterol is estimated to be in excess of 125 g, of which greater than 90% is in cell membranes.

Synthesis of cholesterol originates with a reaction between acetyl coenzymeA (acetyl-CoA), a key intermediate for glycolysis, the citric acid cycle, and fatty acid degradation, and acetoacetyl-CoA to produce HMG-CoA. The next step is rate-limiting for cholesterol synthesis and involves the irreversible conversion of HMG-CoA to mevalonic acid (Fig. 25-3). The rate of this reaction is influenced by several factors, including time of day (predominantly at night), diet composition, excessive food intake, or obesity. Diets rich in saturated fats increase serum cholesterol primarily by down regulating hepatic clearance, whereas a diet of predominantly unsaturated fats or carbohydrates is generally associated with lower serum cholesterol. In addition, many other factors affect the rate of cholesterol synthesis, including a dynamic equilibrium with certain lipoproteins.

The liver is the primary organ for cholesterol uptake and degradation. Most cholesterol is converted to bile acids, which are secreted into the intestine to emulsify ingested fats, and are then reabsorbed and recycled. The total bile pool mass is estimated to be 2 to 3 g and is recycled approximately six times per day. Approximately half the cholesterol secreted in bile is reabsorbed, and the remainder is excreted. Rapid recycling normally limits the need for rapid synthesis of bile acids. Cholesterol is also secreted in bile as free cholesterol, which is fairly insoluble, requiring large amounts of bile. The enhanced synthesis and increased excretion of cholesterol in bile is a likely cause of cholesterol-containing gallstones in obese patients.

Lipoproteins and Lipids

Cholesterol, triglycerides, and phospholipids are transported in plasma and other fluids as lipoproteins, which have a lipid core encased in a protein coat. Triglycerides are assembled in the liver from fatty acids and glycerol. The largest plasma lipoprotein is the chylomicron, composed of triglyceride:cholesterol in 10:1 ratio. The shell is composed of phospholipid, cholesterol, and several apolipoproteins (Apo). Chylomicrons are usually present only after eating, especially a meal with a high fat content, but may be present in fasting persons with inadequate chylomicron metabolism. They are synthesized in the intestine and their principal role is to transport dietary fats to adipose tissue, muscle, and liver. The apolipoproteins associated with chylomicrons in the intestine are ApoB-48 and ApoA-I (Fig. 25-4). After chylomicrons have been secreted and enter the plasma, they acquire ApoE, ApoC-I, ApoC-II, and ApoC-III. ApoC-II is critical and acts with insulin to activate lipoprotein lipase in the capillary wall, liberating free fatty acids and glycerol from released triglycerides. The chylomicron remnants,
containing ApoA, ApoB, and ApoE, but having lost ApoC-II and ApoC-III, continue to circulate and are eventually removed by specific hepatic remnant receptors. This is the principal route by which dietary fat is transported and is referred to as the exogenous pathway. Fasting chylomicronemia resulting from inherited or acquired deficiency of lipoprotein lipase is usually associated with triglyceride levels greater than 2000 mg/dL, which may result in life-threatening pancreatitis.

The endogenous formation and transport of triglycerides is accomplished by very-low-density lipoprotein (VLDL) particles (see Fig. 25–4). Synthesized principally by the liver and to a lesser extent by the intestine, these particles are much smaller than chylomicrons. In contrast to chylomicrons, triglycerides in VLDL are obtained from fatty acids synthesized by the liver or released by adipose tissue and circulate to the liver. In addition to cholesterol and phospholipid, the wall of VLDL particles contains ApoB-100, ApoE, and ApoC-I, ApoC-II, and ApoC-III, the latter obtained from HDL. The internal composition is 5:1, triglyceride:cholesterol. ApoC-II on the VLDL surface results in lipoprotein lipase activation, releasing free fatty acids to muscle and adipose tissues and resulting in smaller, increasingly dense intermediate-density lipoprotein (IDL) particles. The surface ApoE on these VLDL remnants results in clearance of some particles via the same hepatic remnant receptors that bind chylomicron remnants.

Other IDL particles continue to lose triglycerides via lipoprotein lipase and hepatic lipase, resulting in contracted particles known as LDLs, which are approximately 2% the size of VLDL particles and 0.02% the volume of a chylomicron. LDL particles contain 50% to 60% cholesterol and less than 10% triglyceride and have one molecule of ApoB-100 on their surface. LDL particles vary in density and size. The small, dense particles are usually found in association with higher levels of serum triglycerides, are highly atherogenic because they readily cross the endothelial barrier, are more easily oxidized, and are more readily taken up by scavenger receptors. Atherogenicity is related to both LDL particle number and size. Every 1% increase in LDL-C increases the rate of coronary events by approximately 2%. In addition, both VLDL remnants and IDL particles have been found in atheroma. Lipoprotein(a) [Lp(a)] is a small particle formed in the liver, the size of LDL particles, containing Apo(a) linked
Apo(a) has a homology with plasminogen, resulting in competition for plasminogen receptors and decreasing thrombolysis.

The LDL surface protein ApoB-100 is recognized by LDL receptors located in pits on membranes of hepatocytes and other cells. When LDL particles bind, they and their receptors are endocytosed, and the LDL particle is incorporated into lysosomes and separated from its receptor, which is recycled. The coating of the particle is removed, and esterified cholesterol is hydrolyzed and released. The released cholesterol has three major effects on its own metabolism:

- Intracellular cholesterol affects cellular content of HMG-CoA reductase. Thus, as cholesterol concentrations increase, internal synthesis decreases.
- Increasing concentrations of cholesterol activate intracellular acyl-CoA, cholesterol acyl transferase.
- Increasing concentrations of cholesterol lower transcription of LDL receptors, whereas decreasing concentrations increase transcription. This enables cells to adjust cholesterol concentrations to their need.

The HDL lipoprotein particle is relatively small and dense and has a volume approximately 0.12% of the VLDL particle. The predominant apoproteins on the surface of HDL are ApoA-I, ApoA-II, ApoC-II, and ApoE. HDL is the major vehicle for transport of cholesterol from peripheral tissues (including macrophages and endothelial cells) to the liver for use or excretion. Increased numbers of circulating HDL particles are associated with less coronary and carotid atherosclerosis and decreased coronary events, strokes, and death rate. For every 1 mg/dL increase in HDL-C, there is an approximate 2% to 3% decrease in the risk of coronary artery disease. HDL particles improve endothelial function, reduce oxidation of LDL particles, reduce cellular damage by oxidized LDL, have antiinflammatory properties, enhance production and prolong the t1/2 of prostacyclin, and inhibit platelet aggregation.

VLDL and IDL particles also exchange triglycerides for cholesterol with HDL particles, which is facilitated by cholesterol ester transfer protein. The clearance of these particles via remnant and LDL receptors facilitates hepatic clearance of cholesterol. Each of these mechanisms contributes to the antiatherosclerotic process known as reverse cholesterol transport. Treatment strategies designed to raise HDL levels alone or in association with decreasing triglycerides have been associated with less atherosclerosis progression, disease regression, and decreased coronary event rates in persons with atherosclerosis. Low levels of HDL-C (<45 mg/dL in men and 50 mg/dL in women) are associated with increasing risk for coronary disease and strokes at normal and low levels of LDL-C. Figure 25-5 demonstrates how HDL particles impact vascular endothelial function and tone. Total and HDL-C are measured in the nonfasting state to assess the risk of coronary heart disease in adults.

A low total cholesterol (<200 mg/dL) and a normal or high HDL-C (>45 mg/dL in men and 55 mg/dL in women) in the absence of other risk factors or a family history of atherosclerosis generally infers a low risk. In persons with other risk factors and an increase in total cholesterol and less than average HDL-C, lipids and lipoproteins are

**FIGURE 25–4** Lipoprotein metabolism depicting: (1) the exogenous pathway where ingested free fatty acids are converted to triglycerides, combined with ApoB-48, and covered by phospholipid to form chylomicrons in intestinal lymph; and (2) the endogenous pathway where triglycerides synthesized in the liver combine with ApoB-100 to form VLDLs in the liver. Both chylomicrons and VLDLs acquire ApoC from HDLs. ApoC serves as a cofactor to activate lipoprotein lipase in the vascular epithelium, delivering fatty acids to target tissues such as fat and muscle. HDLs recover ApoC for reuse as the chylomicrons and VLDLs are metabolized. Remnant particles are removed by the liver and secreted as LDLs, which contain cholesterolester as their predominant component.
measured in the fasting state (approximately 12 hours) to eliminate the postprandial increase in triglycerides. Total cholesterol, triglycerides, and HDL-C are measured, and the LDL-C is calculated by the Fredrickson equation:

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\text{LDL-C} = \frac{\text{total cholesterol}}{\text{HDL-C}} - \frac{\text{VLDL-C}}{2}
\]

VLDL-C is calculated by dividing the triglyceride levels by 5, based on the 1:5 ratio of cholesterol to triglycerides in VLDL particles. The formula is inaccurate when the triglycerides are greater than 350 to 400 mg/dL, an indication for direct measurement of LDL-C.

Although ideal total cholesterol is less than 150 mg/dL and LDL-C is less than 100 mg/dL, the average person in the United States, with or without coronary heart disease, has cholesterol of 205 mg/dL and an LDL-C of 135 mg/dL. The major cause of elevated cholesterol in the United States and industrialized world is an increased intake of saturated fats. Approximately 5% of persons have primary hypercholesterolemia, which can be divided into polygenic hypercholesterolemia (3.8%), familial combined hyperlipidemia (1.5%), and familial hypercholesterolemia (0.2%), the latter caused by a decreased number or activity of LDL receptors. The heterozygous form of familial hypercholesterolemia appears in approximately 0.2% of people, whereas the homozygous form is rare (0.000001%). Heterozygotes have serum cholesterol concentrations approximately twice normal and LDL-C levels greater than 240 mg/dL. Homozygotes have cholesterol concentrations six times normal and may show evidence of coronary heart disease in childhood and adolescence. Many homozygotes die before 10 to 12 years of age, and almost all experience a myocardial infarction by 20 years of age.

Polygenic hypercholesterolemia and familial combined or mixed hyperlipidemia (increased cholesterol and triglycerides) are much more common, involving increased absorption of dietary fats, overproduction of lipids, or decreased clearance of lipoprotein particles. A deficiency in lipoprotein lipase activity, either inherited or acquired with obesity, excess dietary carbohydrates, and diabetes, results in high levels of fasting triglycerides (200 to 10,000 mg/dL) and chylomicronemia. The lipoproteins that promote atherosclerosis and the vasculoprotective effect of HDL particles are depicted in Figure 25-6.

A classic inheritable atherogenic lipoprotein phenotype is present in 5% to 10% of the population, nearly all diabetics, the metabolic syndrome associated with insulin resistance (hypertension, truncal obesity, elevated insulin), and nearly 50% of persons with premature coronary artery disease. The phenotype is characterized by increased small dense LDL particles, decreased HDL particles with less of the larger buoyant type, and moderately increased VLDL remnant particles rich in triglycerides and cholesterol. Elevated triglyceride levels increase the risk in men and, particularly, women with elevated cholesterol. This is likely due to the association with small LDL particles and low HDL-C, and the atherogenicity of VLDL remnant particles. Elevated Lp(a) is the most common abnormal lipid in patients with a family history of premature coronary heart disease. In addition to increasing thrombosis and decreasing thrombolysis, Lp(a) is a small LDL-like particle that is easily oxidized and atherogenic. Low HDL-C and increased triglycerides and isolated low HDL-C are common causes of premature coronary artery disease. Ironically, hypercholesterolemia accounts for less than 10% of premature coronary artery disease.
HMG-CoA Reductase Inhibitors

The **statins** inhibit the enzyme HMG-CoA reductase, the initial rate-limiting step in cholesterol synthesis (see Fig. 25-3). Statins act as **competitive inhibitors** for the active site on the reductase enzyme, with a higher affinity than HMG-CoA. Inhibition of cholesterol synthesis, particularly in hepatocytes, decreases intracellular pools, which triggers an increase in LDL receptor number and activity. This leads to an increased clearance of LDL particles. Plasma concentrations of LDL-C and the number of LDL particles decrease, and less LDL is available to react with cells in blood and vessel walls. Statins also lower plasma lipids, including LDL-C and triglycerides, by inhibition of hepatic VLDL synthesis, resulting in decreased numbers of VLDL, IDL, and LDL particles. The structure of **simvastatin**, a typical HMG-CoA reductase inhibitor, is shown in Figure 25-7.

Lovastatin, pravastatin, and simvastatin are derivatives of fungal products, whereas fluvastatin, atorvastatin, and rosuvastatin are synthetic. Lovastatin and simvastatin are both prodrugs requiring hydrolysis in the liver to become active. Rosuvastatin and pravastatin are active drugs, and fluvastatin has active metabolites that do not reach the systemic circulation. Although atorvastatin is active, its metabolites also contribute significantly to lowering cholesterol.

The statins vary in their abilities to increase LDL receptors and hence increase the clearance of LDL particles. The LDL-C-lowering effect of comparable doses of each of the statins is summarized in Table 25-1, although all doses are not necessarily available commercially. Note that a **doubling of dose** results in only a **5% to 6% further reduction in LDL-C**. The effects of the statins on ApoB, VLDL-C, IDL-C, and triglycerides are proportional to the decrease in LDL-C. With cessation of therapy, lipids return to pretreatment levels within 4 weeks.

Fibric Acid Derivatives

Phenoxyisobutyric acid, or fibric acid, is the parent compound for several drugs that lower plasma cholesterol and triglyceride concentrations, known collectively as the **fibrates** or fibric acid derivatives, and include gemfibrozil, fenofibrate, and clofibrate. The structure of gemfibrozil is shown in Figure 25-7.

Fibrates have a broad spectrum of lipid-modulating and pleiotropic effects related to their capacity to mimic the structure and biological functions of free fatty acids. Their mechanisms of action are only partially understood but appear to activate transcription factors belonging to the nuclear hormone receptor superfamily, the **peroxisome proliferator-activated receptors** (PPARs). PPAR-α mediates the action of fibrates on HDL-C levels via transcriptional induction of synthesis of major HDL apolipoproteins (ApoA-I and ApoA-II) and increased synthesis of lipoprotein lipase. Fibrates decrease hepatic ApoC-III transcription, reducing inhibition of lipoprotein lipase and enhancing clearance of triglyceride-rich lipoproteins. Other functions altered by the actions of fibrates on PPAR-α result in increased fatty acid uptake, decreased fibrinogen and high sensitivity C-reactive protein, and increased cholesterol efflux. The effect of fibrates on raising HDL and reducing triglyceride-rich chylomicron and VLDL particles and lipid content is mediated by decreasing production of hepatic VLDL containing less ApoC-III, and induction of hepatic and systemic expression of lipoprotein lipase. Increasing the activity of endothelial lipoprotein lipase enhances release of VLDL surface fragments to form nascent HDL and increases production of ApoA-1. Decreasing triglyceride content and number of VLDL remnants reduces the cholesterol ester transfer protein transfer of triglycerides to HDL particles in exchange for cholesterol.
Bile Acid Sequestrants

Cholestyramine, colestipol, and colesevelam are bile acid absorbants for use in the treatment of hypercholesterolemia. They are large copolymers that act by exchanging Cl⁻ for negatively charged bile salt anions. They are poorly absorbed and pass out of the gastrointestinal tract with the stool. These bile resins are particularly of value in patients intolerant to statins and in combination with statins and niacin when the additional lowering of LDL-C is sought.

Cholesterol Absorption Inhibitors

Ezetimibe is currently the only cholesterol absorption inhibitor on the market in the United States. Ezetimibe does not inhibit cholesterol synthesis or increase bile acid excretion. Rather, it appears to act at the brush border of the small intestine to inhibit cholesterol absorption, leading to a decreased delivery to the liver. This reduces hepatic cholesterol and increases LDL receptor-mediated clearance of cholesterol from the blood. This distinct mechanism is complementary to that of the HMG-CoA reductase inhibitors.

Niacin

Niacin (see Fig. 25-7) was observed in the mid-1950s to lower serum triglycerides and cholesterol. It was the first drug with lipid-modulating effects shown to reduce recurrent coronary events and mortality in men who had recovered from a myocardial infarction. After absorption, niacin is enzymatically converted to nicotinamide adenine dinucleotide. However, nicotinamide does not have hypolipidemic activity.

Niacin reduces release of fatty acids from fat stores, decreasing the rate of hepatic triglyceride synthesis and VLDL production. It also increases hepatic clearance of HDL-C but inhibits uptake of ApoA-1, resulting in its increased availability for development of HDL particles. The decrease in anabolism of VLDL triglyceride-rich particles, which are metabolized to IDL and LDL, results in decreased LDL-C and LDL particle numbers and an increase in the less atherogenic, larger, more buoyant LDL particles.

Pharmacokinetics

Selected pharmacokinetic parameters of individual drugs are listed in Table 25-2. All the lipid-lowering drugs are taken by oral administration; thus their absorption may be affected by the presence of food.

Atorvastatin and rosuvastatin, the two most potent statins, have a $t_{1/2}$ of 14 to 20 hours, compared with less than 4 hours for the other statins. Because of their long $t_{1/2}$, atorvastatin and rosuvastatin can be taken once in the morning. The statins differ in their bioavailability and in the effect of food on their absorption. Lovastatin absorption is enhanced by food, whereas fluvastatin and pravastatin absorption is reduced by food; thus they are taken at bedtime. The absorption of simvastatin, rosuvastatin, and atorvastatin is unaffected by food. All statins are subject to high (approximately 60%) first-pass metabolism by the liver. Their varying hydrophilic or lipophilic natures do not appear to correlate with lipid-lowering effects, side effects, or toxicity.
Fibrates are metabolized by the liver and excreted by the kidneys and should be discontinued in acute renal failure and used with caution in chronic renal failure. Because immunosuppressive drugs may impair renal function, fibrates should be used with caution in transplant patients.

After oral administration, ezetimibe is absorbed and conjugated extensively to a pharmacologically active phenolic glucuronide. After a single dose in fasting adults, mean ezetimibe peak plasma concentrations are attained within 4 to 12 hours. Food administration (high-fat or nonfat meals) has no effect on absorption. Ezetimibe is highly bound to plasma proteins and metabolized in the small intestine and liver via glucuronide conjugation, with subsequent biliary and renal excretion.

Both crystalline and slow-release niacin are available over the counter. The minimal effective dose is approximately 1g/day. The plasma t1/2 of crystalline niacin is approximately 1 hour. When given by mouth, peak concentrations are achieved within 1 hour.

### Relationship of Mechanisms of Action to Clinical Response

The effect of each drug class on lipid parameters depends to a large extent on the fasting levels of lipids. For example, at a triglyceride level of 1000 mg/dL, gemfibrozil can lower triglycerides by 50%, whereas at 250 mg/dL, gemfibrozil may yield a 20% decrease. The magnitude of effect also depends upon diet, absorption, metabolism, and other genetic factors.

### HMG-CoA Reductase Inhibitors

The antiatherosclerotic effects of statins cannot be explained solely by their effects on lipids. These agents also cause many other important effects, which are different for each drug. These include platelet inhibition and antithrombosis; enhanced fibrinolysis and effects on clotting factors; effects on tissue factors, blood viscosity and flow; reduced leukocyte adhesiveness; enhanced endothelial function; inhibition of LDL-C oxidation; reduction of circulating inflammatory markers; and atherosclerotic plaque stabilization by decreasing lipid content, reducing numbers of macrocytes and T lymphocytes and reducing vascular smooth muscle cell growth.

In healthy middle-aged and elderly men and women with increased risk factors, there is evidence that statins can provide a 20% to 30% reduction in total and CVD mortality, coronary events, strokes, and need for coronary revascularization. The benefits are more pronounced in men and women with established vascular disease of any type (coronary heart disease, peripheral vascular disease, stroke), including the elderly, diabetics, and those with congestive heart failure. There is evidence of benefit of statins in men and women with atherosclerosis of all ages and baseline cholesterol levels, if above 135 mg/dL. Clinical studies indicate that men and women with coronary or other vascular disease, diabetes, and older men with hypertension show similar benefits regardless of levels of LDL-C: an approximate 25% reduction in total mortality, cardiovascular mortality, and recurrent fatal and nonfatal myocardial infarctions.

Statins are the lipid-altering drugs of choice and should be given to all persons with atherosclerosis of any type. They are also indicated in diabetes in men and women with multiple risk factors and a 20% or greater 10-year risk of a coronary event. A reasonable approach would be to choose a dose that reduces LDL-C by 35% or greater.

### Fibric Acid Derivatives

The fibrates are particularly effective in modulating the atherogenic lipoprotein profile. Specifically, they reduce fasting and postprandial triglycerides by reducing VLDL, VLDL remnants, and IDL; increase LDL particle size; and increase HDL particle number and cholesterol content. The effects depend on fasting lipid parameters. Fenofibrate can lower LDL-C by up to 25% in patients with isolated hypercholesterolemia and has a moderate LDL-C-lowering effect (15% to 25%) in hypertriglyceridemia and mixed lipid disorders. Gemfibrozil is neutral or can increase LDL-C by up to 10%, particularly in patients with isolated hypertriglyceridemia. A major antiatherosclerotic effect of fibrates results from lowering triglycerides and a resultant shift in LDL mass to the larger and buoyant particles (up to 50% change), which are less easily oxidized and less capable of entering the subendothelial space.

The fibrates also reduce the magnitude of both fasting and postprandial hyperlipidemia. Although epidemiological evidence implicating lipids in atherosclerosis is predominantly in fasting states, there is considerable evidence that postprandial increases in triglycerides and VLDL
receptors and LDL particles help explain the increase in coronary artery disease risk in diabetes and the metabolic syndrome. Impaired postprandial triglyceride metabolism is associated with endothelial dysfunction, possibly related to cytotoxicity of triglycerides.

Gemfibrozil is used for treatment of adults with very high elevations of serum triglycerides, who present a risk of pancreatitis and who do not respond adequately to dietary changes. Gemfibrozil should also be considered in less severe hypertriglyceridemia in patients with a history of pancreatitis or recurrent abdominal pain typical of pancreatitis.

Gemfibrozil is also used for reducing the risk of developing coronary heart disease in patients with elevated triglycerides and LDL-C and low HDL-C without a history of or symptoms of existing coronary heart disease and who have had an inadequate response to weight loss, dietary therapy, exercise, and other drugs, such as the statins and niacin. Although there is some disagreement, clinical trials generally support the efficacy of fibrate therapy for treatment of atherosclerotic vascular disease. However, considering the safety and efficacy of statin therapy in all forms of atherosclerosis, the statins remain the first choice when cholesterol levels are greater than 135 mg/dL. Fibrate therapy should be considered in patients with vascular disease or diabetes who are intolerant to statins. In addition, fibrates can be used cautiously in combination with statins to further decrease non-HDL-C and increase HDL-C.

**Bile Acid Sequestrants**

Before the statins were developed, the bile acid sequestrants were the most often prescribed cholesterol-lowering drugs. Clinical trials demonstrated that lowering LDL-C with bile resins can reduce coronary event rates in men with hypercholesterolemia and improve coronary endothelial function. In contrast to the statins, niacin, and fibrates, which have antiatherothrombotic properties, the resins are effective in primary and secondary prevention of coronary heart disease because of the decrease in LDL-C and ApoB, having effects similar to a very low-fat diet.

As discussed, the usual bile acid pool is 2 to 3 g but is recycled up to six times per day. When bile acids are excreted, plasma cholesterol is converted to bile acids. The resultant decrease in cholesterol results in an increase in LDL receptors and greater hepatic uptake of LDL. Concentrations of LDL-C are reduced by 10% to 25% in response to bile acid sequestrants, in a dose-dependent fashion. VLDL and plasma triglyceride concentrations may increase as much as 20%. Usually this effect disappears within 2 to 3 months, but changes are not predictable. The bile absorbants should be avoided when triglyceride levels are greater than 250 to 300 mg/dL. They have no consistent effect on HDL levels.

**Cholesterol Absorption Inhibitors**

Ezetimibe reduces total cholesterol, LDL-C, and ApoB, with minimal effects on triglycerides and HDL-C in hypercholesterolemia. Administration with an HMG-CoA reductase inhibitor is effective in improving serum total cholesterol, LDL-C, ApoB, triglycerides, and HDL-C beyond either treatment alone. The effects of ezetimibe either alone or in addition to an HMG-CoA reductase inhibitor on cardiovascular morbidity and mortality have not been established. It is indicated for cholesterol and LDL lowering in patients who are intolerant of statins or in whom abnormal liver function or side effects benefit from a reduction in the statin dose.

**Niacin**

The major antiatherosclerotic effect of niacin appears to be its ability to raise HDL-C, which is considerable and greater than that of the fibrates. In contrast to the fibrates, niacin is very effective in individuals with isolated low HDL-C. Like the statins, nonlipid pleiotropic effects of niacin are also important for preventing coronary events and progression of atherosclerosis. Table 25-3 summarizes the effects of niacin. Clinical trials have shown that niacin reduces nonfatal and recurrent myocardial infarctions and is associated with relatively less new lesion formation and more coronary plaque regression.

The effect of niacin is also highly dependent on fasting lipids. In patients with elevated triglycerides and low HDL-C, niacin will usually reduce triglycerides by 15% to 25%, increase HDL-C by 20% to 30%, and reduce LDL-C

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**TABLE 25–3 Pleiotropic Effects of Niacin**

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<tr>
<th>Lipoprotein</th>
<th>Vascular</th>
<th>Thrombosis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases HDL</td>
<td>Stabilizes plaque and new lesion formation</td>
<td>Inhibits thrombosis</td>
<td>Limit ischemia and reperfusion injury, possibly by preservation of glycolysis</td>
</tr>
<tr>
<td>↑ HDL-C</td>
<td>↓ lipid core by reverse cholesterol transport</td>
<td>↑ fibrinolysis</td>
<td>↓ Platelet adhesion and aggregation</td>
</tr>
<tr>
<td>↑ ApoA-I</td>
<td></td>
<td>↓ coagulation factors</td>
<td>↓ fibrinogen</td>
</tr>
<tr>
<td>↓ ApoA-II</td>
<td></td>
<td></td>
<td>↓ blood viscosity</td>
</tr>
<tr>
<td>↑ large HDL</td>
<td>↓ Vascular inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ Small LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ LDL oxidation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>Improves endothelial function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ LDL-C</td>
<td>↑ NO synthase activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ VLDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>triglycerides</td>
<td>↑ Vasodilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces Lp(a)</td>
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</tbody>
</table>
minimally. Average reduction in LDL-C by 2 g of niacin is approximately 15%. A slow-release product that reduces the side effect of flushing without a loss of efficacy is available. The cholesterol-lowering effect of niacin can be enhanced by coadministration with statins and resins. Niacin is used as an adjunct to diet for reduction of LDL-C and triglycerides, to increase in HDL-C in patients with hypercholesterolemia and mixed lipid disorders, and to slow progression or promote regression of atherosclerotic disease in individuals with a history of myocardial infarction or coronary heart disease. Although it is not approved for use in individuals with isolated low HDL-C in coronary heart disease, many consider it effective. Niacin is of particular value in combination with statins. The combination results in a marked reduction of atherogenic lipoproteins (number of small dense LDL particles, Lp(a), VLDL remnants), increases HDL-C, and increases the non-lipid antiatherothrombotic effects. High doses of statins plus niacin have been shown to induce coronary artery lesion regression and reduction in event rates beyond that of statins alone. Vitamin E, which is often taken as an antioxidant supplement, interferes with the benefits of niacin, probably by inhibiting the increase in the protective HDL-2b fraction.

**Combination Therapies**

Combination therapies are often required in mixed lipid disorders, statin-intolerant patients, treatment of individuals with non-HDL-C, and when targeting a low HDL-C along with elevated LDL-C.

In patients with statin-induced abnormal liver function testing (two to three times normal), combining a lower dose of a statin with ezetimibe or a bile resin can safely provide an additional 15% to 20% reduction of LDL-C. Similarly, in statin-intolerant patients, a combination of high-dose niacin and bile resins or ezetimibe can reduce LDL-C by up to 40% to 50%. The strategy of combining low-dose statins with ezetimibe to reduce toxicity should be used only when necessary, because some pleiotropic effects of statins may be lost.

The combination of a statin with niacin is very effective in decreasing LDL-C, ApoB, triglycerides, and LDL particle numbers while increasing HDL-C and LDL particle size. Although relatively safe, liver function should be monitored. Lovastatin plus niacin is available as a single tablet given at bedtime, which increases compliance.

Generally, statins should not be used with gemfibrozil, a warning that is less of a concern with fenofibrate. In patients with hypertriglyceridemia or elevated non-HDL-C, the drug of choice is a statin targeting LDL-C to less than 100 mg/dL and non-HDL-C to less than 130 mg/dL. If this is not achieved, in diabetics and patients with established atherosclerosis, careful combination of gemfibrozil with pravastatin, fluvastatin, simvastatin, and atorvastatin might be considered. Patients must be warned of the possibility of muscle weakness and pain and the potential for rhabdomyolysis. At the onset of symptoms, both drugs should be stopped and serum creatine kinase determined. Rhabdomyolysis can occur as early as a few weeks or any time thereafter and result in irreversible renal failure.

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**Pharmacovigilance: Side Effects, Clinical Problems, and Toxicity**

Adverse effects of the various drug classes are listed in the Clinical Problems Box.

**HMG-CoA Reductase Inhibitors**

The statins are relatively safe, except for possible drug interactions. Mild elevation in creatine kinase activity and mild elevation of hepatic alanine aminotransferase are not uncommon and are usually, but not always, clinically insignificant. Statins should be avoided in active liver disease and avoided or used with great caution in chronic liver disease. However, there have been no confirmed cases of fatal liver disease associated with statins.

Severe rhabdomyolysis, while very rare, can occur with each statin. Muscle aches or weakness should trigger discontinuation and measurement of creatine kinase. In cardiac transplant patients receiving immunosuppressive drugs, myositis develops in 30% within 1 year of initiating lovastatin therapy. In a few patients it progresses to severe rhabdomyolysis and acute renal failure. In the general population the incidence of myositis is less than 1% but increases to 5% in patients on lovastatin and gemfibrozil or immunosuppressive drugs. Discontinuation of drug is recommended in patients with risk factors that may lead to renal failure caused by rhabdomyolysis (i.e., severe infection, hypotension, major surgery, trauma, or uncontrolled seizures).

Up to 10% of patients have gastrointestinal symptoms, including diarrhea, constipation, nausea, dyspepsia, excess flatus, and abdominal pain or cramps. Other rare effects, which are difficult to confirm, include thrombocytopenia, visual blurring, alopecia, proteinuria (especially rosuvastatin), depression, insomnia, and sensory and motor neuropathy. Statins have been reported to cause erectile dysfunction, but improved endothelial function could enhance erectile function. Because these drugs inhibit cholesterol synthesis, the potential exists for inhibition of synthesis of adrenal and gonadal steroid hormones and of bile acids. However, there is substantial evidence indicating that this does not occur. The levels of other end products of mevalonic metabolism, such as dolichol, required for glycoprotein synthesis, and ubiquinone, the potent antioxidant used for mitochondrial electron transport, are not significantly affected by statins.

Statins have been used safely in children over 8 years of age and do not interfere with sexual maturation, menarche, or growth and development. Because their effect on fetal development and fertility is unknown, they should be avoided during pregnancy and breastfeeding.

**Fibric Acid Derivatives**

Clofibrate use has diminished because of the increased incidence of cholelithiasis and a possible increased incidence of carcinoma. Both clofibrate and gemfibrozil have...
been associated with increasing suicidal and accidental deaths.

Gemfibrozil and fenofibrate enhance the anticoagulant effect of warfarin and associated compounds. Doses of warfarin must often be reduced as much as 50% in patients taking these compounds. Other side effects are principally gastrointestinal and consist of abdominal pain and, less frequently, nausea, vomiting, and diarrhea. The increased ratio of cholesterol to bile in patients treated with gemfibrozil and fenofibrate makes them more susceptible to gallbladder disease.

Fibric acid derivatives should not be used in pregnancy unless the potential benefit is very high, such as in pancreatitis or severe hypertriglyceridemia (>2000 mg/dL). The contraindication of combining gemfibrozil with lovastatin and rosuvastatin has been emphasized.

### Bile Acid Sequestrants

The bile resins are insoluble, have the consistency of course sand, and must be mixed with fluids to be ingested. They tend to cause gastrointestinal bloating, excess flatus, and constipation with nausea and indigestion. A diet high in fluids and fiber is necessary to minimize these effects.

Because of the exchange of chloride ions for bile acids, excess chloride absorption may result in a hyperchloremic metabolic acidosis. Transient rises in alkaline phosphatase and transaminase activities have been reported.

Binding of bile acids decreases their emulsifying action, and excess fat may appear in stool. Because they may interfere with absorption of fat-soluble vitamins, supplementation is indicated. They may also interfere with intestinal absorption of thiazide diuretics, phenobarbital, thyroxine, warfarin, and digoxin, all compounds that undergo enterohepatic circulation. It is generally advisable not to administer resins with other drugs. Bedtime is a convenient and safe time for thyroid supplements, warfarin, and digoxin. A time differential of 1 hour before and 4 hours after is recommended when coadministration is indicated.

### CLINICAL PROBLEMS

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors (statins)</td>
<td>Muscle pain and weakness, myositis, increased liver enzymes, rosuvastatin-increased microalbuminuria</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Gastrointestinal distress, constipation, flatus, but colesevelam better tolerated</td>
</tr>
<tr>
<td>Niacin</td>
<td>Decrease absorption of fat-soluble vitamins and some drugs</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>Flushing, increase uric acid and gout, dyspepsia, dry skin, hepatotoxicity</td>
</tr>
<tr>
<td>Fibric acids</td>
<td>Mild gastrointestinal distress</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia, gallstones, myopathy, increase in violent deaths</td>
</tr>
</tbody>
</table>

### Cholesterol Absorption Inhibitors

Ezetimibe is contraindicated in liver disease and renal failure where blood levels may rise significantly. It must also be used with caution in patients on cyclosporine and other immunosuppressive drugs that may alter renal function. Gemfibrozil and fenofibrate increase blood levels of ezetimibe, but their own blood levels are not affected by ezetimibe. Rare patients complain of bloating, but clinical trials show that ezetimibe has adverse events similar to placebo.

### Niacin

Side effects are generally noted within 30 minutes of niacin ingestion. Intense flushing and pruritus of the trunk, face, and arms can occur. Gradual dose titration of niacin over days to weeks results in a marked reduction in flushing and tolerance in more than 70% to 80% of users. Symptoms are caused by release of prostaglandin D in the skin and can be partially inhibited by ingestion of aspirin. Bedtime use of sustained-release niacin reduces flushing and increases compliance.

Additional side effects include nausea, diarrhea, and dyspepsia and aggravation of peptic ulcer disease. Elevations of transaminase and creatine kinase concentrations are common but not generally of concern. Serum urate concentrations may increase, with an increased incidence of gouty arthritis. An increased incidence of cardiac dysrhythmias has been reported.

### Lifestyle Interventions and Drugs in Atherosclerosis

Prevention and treatment of atherosclerosis need to be comprehensive and targeted to each of the major and contributing risk factors (see Box 25-1). Both food choices and calories consumed should be tailored for weight control, lipid management, and hypertension. Because cholesterol levels increase with dietary fat and age, a basic recommendation is to decrease caloric intake and lower the proportion of dietary fat to less than 30% and saturated fat to less than 7% to 10%. This requires a shift to foods rich in monounsaturated fats, such as olive oil, lean meat, and certain vegetables.

Patients with abnormal lipid profiles, hypertension, diabetes, and obesity should be encouraged to consult with dietitians. Simply recommending a low-fat diet often results in inappropriate increases in starches and sugars and increased triglycerides and lowered HDL-C. Smoking cessation, weight loss, and moderate exercise, along with an increase in monounsaturated fats and decrease in saturated fats, will result in an increase in HDL-C, decrease in LDL-C, and improvement in the ratio of cholesterol to HDL-C.

The effect of dietary intervention varies widely. Diets high in fiber, antioxidant-containing fruits and vegetables,
and cold water fish rich in omega-3 polyunsaturated fats have been shown to reduce first and recurrent coronary events independent of drugs. Patients with established atherosclerosis should be placed on drug therapy with appropriate dietary advice. The argument for dietary change as a principal component in prevention of atherosclerosis is based on the following:

- Patient is in control.
- Change should be life-long.
- Benefits are additive to drug therapy.
- Drug doses may be able to be reduced.
- Primary prevention by diet may eliminate the need for expensive drugs.

New Horizons

Future drugs will be designed to prevent the early stages of atherosclerosis and progression, induce regression, and provide plaque stability by novel mechanisms. These may include potent intracellular antioxidants that increase HDL-C and lower LDL-C and inhibit formation of vascular endothelial adhesion molecules; synthetic HDL; inhibitors of cholesterol ester transfer protein that increases HDL levels and reduces cardiovascular event rates alone or in combination with the statins; potent antiinflammatories targeted to T lymphocytes; and inhibition of matrix metalloproteinases responsible for plaque instability.

Physician awareness, patient education, and society’s ability to pay for prevention remain problematic. Only half of patients with proven coronary artery disease and elevated total cholesterol are receiving treatment, and nearly half stop therapy after 1 to 2 years despite having insurance. Statins are cost saving in patients with coronary disease and strokes. Only 35 to 40 patients with intermediate to high risk is assessed by increased LDL-C and C-reactive protein need to be treated to prevent one coronary event. Resolution of compliance and cost issues will determine whether continuing advances in treatment of coronary artery disease and other forms of atherosclerosis will occur.

TRADE NAMES

(In addition to generic and fixed-combination preparations, the following trade-named materials are some of the important compounds available in the United States.)

HMG-CoA Reductase Inhibitors (statins)
- Atorvastatin (Lipitor)
- Fluvastatin (Lescol)
- Lovastatin (Mevacor, Altovyl)
- Pravastatin (Pravachol)
- Rosuvastatin (Crestor)
- Simvastatin (Zocor)

Bile Acid Sequestrants
- Colesevelam (Welchol)
- Colestipol (Colestid)
- Cholestyramine (Questran)

Fibric Acid Derivatives
- Fenofibrate (Fantast, Lofibra, Tricor)
- Gemfibrozil (Lopid)

Niacin
- Crystalline niacin (nicotinic acid)
- Sustained-release niacin (Niaspan, Slo-Niacin)

Cholesterol Absorption Inhibitor
- Ezetimibe (Zetia)

FURTHER READING


SELF-ASSESSMENT QUESTIONS

1. The lipid-transporting particle in blood that serves as the major vehicle for transporting cholesterol from peripheral tissues to the liver is the:
   A. Chylomicron.
   B. High-density lipoprotein.
   C. Low-density lipoprotein.
   D. Very-low-density lipoprotein.
   E. None of the above because it depends on how long the particle is in the blood.

2. Which of the following agents has the greatest impact to decrease triglyceride levels?
   A. Bile acid sequestrants
   B. Cholesterol absorption inhibitors
   C. Fibric acids
D. Niacin
E. Statins

3. The major mechanism by which statins reduce circulating cholesterol is:
   A. Activation of peroxisome proliferation activating receptor (PPAR) alpha.
   B. Decreased production of apolipoprotein B-100.
   C. Increased degradation of cholesterol.
   D. Increased LDL receptor expression.
   E. Induction of lipoprotein lipase.

4. An agent that lowers blood cholesterol by decreasing cholesterol absorption is:
   A. Niacin.
   B. Gemfibrozil.
   C. Simvastatin.
   D. Cholestyramine.
   E. Ezetimibe.