Hyperlipidemias

I. OVERVIEW

Coronary heart disease (CHD) is the cause of about half of all deaths in the United States. The incidence of CHD is correlated with elevated levels of low-density lipoprotein (LDL) cholesterol and triacylglycerols and with low levels of high-density lipoprotein (HDL) cholesterol. Other risk factors for CHD include cigarette smoking, hypertension, obesity, and diabetes. Cholesterol levels may be elevated as a result of an individual's lifestyle (for example, by lack of exercise and consumption of a diet containing excess saturated fatty acids). Hyperlipidemias can also result from a single inherited gene defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors. Appropriate lifestyle changes in combination with drug therapy can lead to a decline in the progression of coronary plaque, regression of preexisting lesions, and reduction in mortality due to CHD by 30 to 40 percent. Antihyperlipidemic drugs must be taken indefinitely, because when therapy is terminated, plasma lipid levels return to pretreatment levels. The lipid-lowering drugs are listed in Figure 21.1. Figure 21.2 illustrates the normal metabolism of serum lipoproteins and the characteristics of the major genetic hyperlipidemias.

II. TREATMENT GOALS

Plasma lipids consist mostly of lipoproteins, which are spherical macromolecular complexes of lipids and specific proteins (apolipoproteins). The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very-low-density lipoprotein (VLDL) and chylomicrons, and HDL. The occurrence of CHD is positively associated with high total cholesterol and even more strongly with elevated LDL cholesterol in the blood. In contrast to LDL cholesterol, high levels of HDL cholesterol have been associated with a decreased risk for heart disease (Figure 21.3). Reduction of the LDL level is the primary goal of cholesterol-lowering therapy. Figure 21.4 shows the current goals in the treatment of hyperlipidemia. Recommendations for the reduction of LDL cholesterol to specific target levels are influenced by the coexistence of CHD and the number of other cardiac risk factors. The higher the overall risk of heart disease, the more aggressive the recommended LDL-lowering therapy.

A. Treatment options for hypercholesterolemia

In patients with moderate hyperlipidemia, lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL levels and increases in HDL levels. However, most patients are
Hyperlipidemias

Figure 21.2
Metabolism of plasma lipoproteins and related genetic diseases. Roman numerals in the white circles refer to specific genetic types of hyperlipidemias summarized on the facing page. CM = chylomicron, TG = triacylglycerol; VLDL = very-low density lipoprotein, LDL = low-density lipoprotein, IDL = intermediate-density lipoprotein, apo CII = apolipoprotein CII found in chylomicrons and VLDL.

1. The intestinal mucosa secretes TG-rich chylomicrons (produced primarily from dietary lipids); the liver secretes TG-rich VLDL particles.

2. Extracellular lipoprotein lipase, activated by apo CII, degrades TG in CM and VLDL.

3. LDLs bind to specific receptors on extrahepatic tissues and on the liver, where they are endocytosed.

4. CM remnants bind to specific receptors on the liver, where they are endocytosed.

Type I [FAMILIAL HYPERCHYLOMICRONEMIA]
Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels. De/ficiency of lipoprotein lipase or de/ficiency of normal apolipoprotein CII (rare). Type I is not associated with an increase in coronary heart disease. Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.

Type II [FAMILIAL HYPERCHOLESTEROLEMIA]
Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels. Caused by defects in the synthesis or processing of LDL receptors. Ischemic heart disease is greatly accelerated. Treatment: Diet. Heterozygotes: Cholestyramine and niacin, or a statin.

Type II A [FAMILIAL HYPERCHOLESTEROLEMIA]
Similar to Type II but with VLDL also increased, resulting in elevated serum TG as well as cholesterol levels. Relatively common. Caused by overproduction of VLDL by the liver. Treatment: Diet. Drug therapy is similar to that for Type IIA.

Type II B [FAMILIAL COMBINED (MIXED) HYPERLIPIDEMIA]
Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels. Type II B is relatively common. Caused by overproduction of VLDL by the liver. Treatment: Diet. Drug therapy is similar to that for Type IIA.

Type III [FAMILIAL DYSBETALIPOPROTEINEMIA]
Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels. Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E. Xanthomas and accelerated vascular disease develop in patients by middle age. Treatment: Diet. Drug therapy includes niacin and/or fenofibrate, or a statin.

Type IV [FAMILIAL HYPERTRIGLYCERIDEMIA]
VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels. Cause is overproduction and/or decreased removal of VLDL TG in serum. This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic. Treatment: Diet. If necessary, drug therapy includes niacin and/or fenofibrate.

Type V [FAMILIAL MIXED HYPERTRIGLYCERIDEMIA]
Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels. Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect. Occurs most commonly in adults who are obese and/or diabetic. Treatment: Diet. If necessary, drug therapy includes niacin, and/or fenofibrate, or a statin.
II. Treatment Goals

**Type I [FAMILIAL HYPERCHYLOMICRONEMIA]**
- Massive fasting hyperchylomicronemia, even following normal dietary fat intake, resulting in greatly elevated serum TG levels.
- Deficiency of lipoprotein lipase or deficiency of normal apolipoprotein CII (rare).
- Type I is not associated with an increase in coronary heart disease.
- Treatment: Low-fat diet. No drug therapy is effective for Type I hyperlipidemia.

**Type IIA [FAMILIAL HYPERCHOLESTEROLEMIA]**
- Elevated LDL with normal VLDL levels due to a block in LDL degradation. This results in increased serum cholesterol but normal TG levels.
- Caused by defects in the synthesis or processing of LDL receptors.
- Ischemic heart disease is greatly accelerated.
- Treatment: Diet. Heterozygotes: Cholestyramine and niacin, or a statin.

**Type IIB [FAMILIAL COMBINED (MIXED) HYPERLIPIDEMIA]**
- Similar to Type IIA except that VLDL is also increased, resulting in elevated serum TG as well as cholesterol levels.
- Caused by overproduction of VLDL by the liver.
- Relatively common.
- Treatment: Diet. Drug therapy is similar to that for Type IIA.

**Type III [FAMILIAL DYSBETALIPOPROTEINEMIA]**
- Serum concentrations of IDL are increased, resulting in increased TG and cholesterol levels.
- Cause is either overproduction or underutilization of IDL due to mutant apolipoprotein E.
- Xanthomas and accelerated vascular disease develop in patients by middle age.
- Treatment: Diet. Drug therapy includes niacin and fenofibrate, or a statin.

**Type IV [FAMILIAL HYPERTRIGLYCERIDEMIA]**
- VLDL levels are increased, whereas LDL levels are normal or decreased, resulting in normal to elevated cholesterol, and greatly elevated circulating TG levels.
- Cause is overproduction and/or decreased removal of VLDL TG in serum.
- This is a relatively common disease. It has few clinical manifestations other than accelerated ischemic heart disease. Patients with this disorder are frequently obese, diabetic, and hyperuricemic.
- Treatment: Diet. If necessary, drug therapy includes niacin and/or fenofibrate.

**Type V [FAMILIAL MIXED HYPERTRIGLYCERIDEMIA]**
- Serum VLDL and chylomicrons are elevated. LDL is normal or decreased. This results in elevated cholesterol and greatly elevated TG levels.
- Cause is either increased production or decreased clearance of VLDL and chylomicrons. Usually, it is a genetic defect.
- Occurs most commonly in adults who are obese and/or diabetic.
- Treatment: Diet. If necessary, drug therapy includes niacin, and/or fenofibrate, or a statin.

*Figure 21.2 (continued).*
unwilling to modify their lifestyle sufficiently to achieve LDL treatment goals, and drug therapy may be required. Patients with LDL levels higher than 160 mg/dL and with one other major risk factor, such as hypertension, diabetes, smoking, or a family history of early CHD, are candidates for drug therapy. Patients with two or more additional risk factors should be treated aggressively, with the aim of reducing their LDL level to less than 100 mg/dL and, in some patients, to as low as 70 mg/dL.

B. Treatment options for hypertriacylglycerolemia

Elevated triacylglycerol (triglyceride) levels are independently associated with increased risk of CHD. Diet and exercise are the primary modes of treating hypertriacylglycerolemia. If indicated, niacin and fibric acid derivatives are the most efficacious in lowering triacylglycerol levels. Triacylglycerol reduction is a secondary benefit of the statin drugs (the primary benefit being LDL cholesterol reduction). [Note: The major lipid component of VLDL is composed of triacylglycerol.]

III. DRUGS THAT LOWER THE SERUM LIPOPROTEIN CONCENTRATION

Antihyperlipidemic drugs target the problem of elevated serum lipids with complementary strategies. Some of these agents decrease production of the lipoprotein carriers of cholesterol and triglyceride, whereas others increase the degradation of lipoprotein. Still others decrease cholesterol absorption or directly increase cholesterol removal from the body. These drugs may be used singly or in combination. However, they are always accompanied by the requirement that dietary saturated and trans fats be low, and the caloric content of the diet must be closely monitored.

A. HMG CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors (commonly known as statins) lower elevated LDL cholesterol levels, resulting in a substantial reduction in coronary events and death from

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**Figure 21.3**
Effect of circulating LDL and HDL on the risk of coronary heart disease (CHD). LDL = low-density lipoprotein; HDL = high-density lipoprotein.

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**Figure 21.4**
Goal lipoprotein levels achieved with dietary or drug therapy for the prevention of coronary heart disease. [Note: Lower goals for total and LDL cholesterol are recommended for patients with a history of heart disease.]
III. Drugs That Lower The Serum Lipoprotein Concentration

CHD. This group of antihyperlipidemic agents inhibits the first committed enzymatic step of cholesterol synthesis, and they are the first-line and more effective treatment for patients with elevated LDL cholesterol. Therapeutic benefits include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity. The value of lowering the level of cholesterol with statin drugs has now been demonstrated in 1) patients with CHD with or without hyperlipidemia, 2) men with hyperlipidemia but no known CHD, and 3) men and women with average total and LDL cholesterol levels and no known CHD.

1. Mechanism of action:

a. Inhibition of HMG CoA reductase: Lovastatin [LOE-vah-stat-in] simvastatin [sim-vah-STAT-in], pravastatin [PRAH-vah-stat-in], atorvastatin (a-TOR-vah-stat-in), fluvastatin [FLOO-vah-stat-in], pitavastatin [pit-AV-a-STAT-in] and rosuvastatin [roe-SOO-va-stat-in] are analogs of HMG, the precursor of cholesterol. Lovastatin and simvastatin are lactones that are hydrolyzed to the active drug. Pravastatin and fluvastatin are active as such. Because of their strong affinity for the enzyme, all compete effectively to inhibit HMG CoA reductase, the rate-limiting step in cholesterol synthesis. By inhibiting de novo cholesterol synthesis, they deplete the intracellular supply of cholesterol (Figure 21.5). Pitavastatin, rosuvastatin and atorvastatin are the most potent LDL cholesterol–lowering statin drugs, followed by simvastatin, pravastatin, and then lovastatin and fluvastatin.

Figure 21.5
Inhibition of HMG CoA reductase by the statin drugs. HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein; VLDL = very–low-density lipoprotein.
b. Increase in LDL receptors: Depletion of intracellular cholesterol causes the cell to increase the number of specific cell-surface LDL receptors that can bind and internalize circulating LDLs. Thus, the end result is a reduction in plasma cholesterol, both by lowered cholesterol synthesis and by increased catabolism of LDL. [Note: Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ.] The HMG CoA reductase inhibitors, like the bile acid sequestrant cholestyramine, can increase plasma HDL levels in some patients, resulting in an additional lowering of risk for CHD. Decreases in triglyceride also occur.

2. Therapeutic uses: These drugs are effective in lowering plasma cholesterol levels in all types of hyperlipidemias (Figure 21.6). However, patients who are homozygous for familial hypercholesterolemia lack LDL receptors and, therefore, benefit much less from treatment with these drugs. [Note: These drugs are often given in combination with other antihyperlipidemic drugs; see below.] It should be noted that, in spite of the protection afforded by cholesterol lowering, about one fourth of the patients treated with these drugs still present with coronary events. Thus, additional strategies, such as diet, exercise, and additional agents, may be warranted.

3. Pharmacokinetics: Pravastatin and fluvastatin are almost completely absorbed after oral administration. Oral doses of lovastatin and simvastatin are from 30 to 50 percent absorbed. Similarly, pravastatin and fluvastatin are active as such, whereas lovastatin and simvastatin must be hydrolyzed to their acid forms. All are biotransformed, with some of the products retaining activity. Excretion takes place principally through bile and feces, but some urinary elimination also occurs. Their half-lives range from 1.5 to 2 hours. Some characteristics of the statins are summarized in Figure 21.7.

4. Adverse effects: It is noteworthy that during the 5-year trials of simvastatin and lovastatin, only a few adverse effects, related to liver and muscle function, were reported (Figure 21.8).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atorvastatin</th>
<th>Fluvastatin</th>
<th>Lovastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Simvastatin</th>
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<td>Serum LDL cholesterol reduction produced (%)</td>
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<td>24</td>
<td>34</td>
<td>34</td>
<td>50</td>
<td>41</td>
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<td>Serum triacylglycerol reduction produced (%)</td>
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<td>10</td>
<td>16</td>
<td>24</td>
<td>18</td>
<td>18</td>
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<td>Serum HDL cholesterol increase produced (%)</td>
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<td>8</td>
<td>9</td>
<td>12</td>
<td>8</td>
<td>12</td>
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<tr>
<td>Plasma half-life (hr)</td>
<td>14</td>
<td>1–2</td>
<td>2</td>
<td>1–2</td>
<td>19</td>
<td>1–2</td>
</tr>
<tr>
<td>Penetration of central nervous system</td>
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<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal excretion of absorbed dose (%)</td>
<td>2</td>
<td>&lt;6</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>13</td>
</tr>
</tbody>
</table>

Figure 21.6
Effect of simvastatin on serum lipids of 130 patients with type 2 diabetes treated for 6 weeks. LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triacylglycerol.

Figure 21.7
Summary of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors. LDL = low-density lipoprotein; HDL = high-density lipoprotein.
III. Drugs That Lower The Serum Lipoprotein Concentration

a. **Liver:** Biochemical abnormalities in liver function have occurred with the HMG CoA reductase inhibitors. Therefore, it is prudent to evaluate liver function and measure serum transaminase levels periodically. These return to normal on suspension of the drug. [Note: Hepatic insufficiency can cause drug accumulation.]

b. **Muscle:** Myopathy and rhabdomyolysis (disintegration or dissolution of muscle) have been reported only rarely. In most of these cases, patients usually suffered from renal insufficiency or were taking drugs such as cyclosporine, itraconazole, erythromycin, gemfibrozil, or niacin. Plasma creatine kinase levels should be determined regularly.

c. **Drug interactions:** The HMG CoA reductase inhibitors may also increase warfarin levels. Thus, it is important to evaluate international normalized ratio (INR) frequently.

d. **Contraindications:** These drugs are contraindicated during pregnancy and in nursing mothers. They should not be used in children or teenagers.

B. **Niacin (nicotinic acid)**

*Niacin* [NYE-a-sin] can reduce LDL (the “bad” cholesterol carrier) levels by 10 to 20 percent and is the most effective agent for increasing HDL (the “good” cholesterol carrier) levels. Niacin can be used in combination with statins, and a fixed-dose combination of lovastatin and long-acting niacin is available.

1. **Mechanism of action:** At gram doses, niacin strongly inhibits lipolysis in adipose tissue, the primary producer of circulating free fatty acids (Figure 21.9). The liver normally uses these circulating fatty acids as a major precursor for triacylglycerol synthesis. Therefore, a reduction in the VLDL concentration also results in a decreased plasma LDL concentration. Thus, both plasma triacylglycerol (in VLDL) and cholesterol (in VLDL and LDL) are lowered (Figure 21.10). Furthermore, niacin treatment increases HDL cholesterol levels. Moreover, by boosting secretion of tissue plasminogen activator and lowering the level of plasma fibrinogen, niacin can reverse some of the endothelial cell dysfunction contributing to thrombosis associated with hypercholesterolemia and atherosclerosis.

2. **Therapeutic uses:** Niacin lowers plasma levels of both cholesterol and triacylglycerol. Therefore, it is particularly useful in the treatment of familial hyperlipidemias. Niacin is also used to treat other severe hypercholesterolemas, often in combination with other antihyperlipidemic agents. In addition, it is the most potent anti-hyperlipidemic agent for raising plasma HDL levels, which is the most common indication for its clinical use.

3. **Pharmacokinetics:** Niacin is administered orally. It is converted in the body to nicotinamide, which is incorporated into the cofactor nicotinamide-adenine dinucleotide (NAD\(^+\)). Niacin, its nicotinamide derivative, and other metabolites are excreted in the urine. [Note: Nicotinamide alone does not decrease plasma lipid levels.]

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Figure 21.8  
Some adverse effects and precautions associated with 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase inhibitors.

Figure 21.9  
Niacin inhibits lipolysis in adipose tissue, resulting in decreased hepatic VLDL synthesis and production of LDLs in the plasma.
4. **Adverse effects:** The most common side effects of niacin therapy are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated. The sustained-release formulation of niacin, which is taken once daily at bedtime, reduces bothersome initial adverse effects. Some patients also experience nausea and abdominal pain. Niacin inhibits tubular secretion of uric acid and, thus, predisposes to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

C. The fibrates: Fenofibrate and gemfibrozil

*Fenofibrate* (fen-oh-FIH-brate) and *gemfibrozil* (jem-FI-broh-zill) are derivatives of fibric acid that lower serum triacylglycerols and increase HDL levels. Both have the same mechanism of action. However, *fenofibrate* is more effective than *gemfibrozil* in lowering plasma LDL cholesterol and triglyceride levels.

1. **Mechanism of action:** The peroxisome proliferator–activated receptors (PPARs) are members of the nuclear receptor supergene family that regulates lipid metabolism. PPARs function as ligand-activated transcription factors. Upon binding to their natural ligands (fatty acids or eicosanoids) or hypolipidemic drugs, PPARs are activated. They then bind to peroxisome proliferator response elements, which are localized in numerous gene promoters. In particular, PPARs regulate the expression of genes encoding for proteins involved in lipoprotein structure and function. Fibrate-mediated gene expression ultimately leads to decreased triacylglycerol concentrations by increasing the expression of lipoprotein lipase (Figure 21.11) and decreasing apolipoprotein (apo) CII concentration. Fibrates also increase the level of HDL cholesterol by increasing the expression of apo AI and apo AII. *Fenofibrate* is a prodrug, producing an active metabolite, fenofibric acid, which is responsible for the primary effects of the drug.

2. **Therapeutic uses:** The fibrates are used in the treatment of hypertriacylglycerolemias, causing a significant decrease in plasma triacylglycerol levels. *Fenofibrate* and *gemfibrozil* are particularly useful in treating Type III hyperlipidemia (dysbetaIipoproteinemia), in which intermediate-density lipoprotein particles accumulate. Patients with hypertriacylglycerolemia (Type IV [elevated VLDL] or Type V [elevated VLDL plus chylomicron] disease) who do not respond to diet or other drugs may also benefit from treatment with these agents.

3. **Pharmacokinetics:** Both drugs are completely absorbed after an oral dose. *Gemfibrozil* and *fenofibrate* distribute widely, bound to albumin. Both drugs undergo extensive biotransformation and are excreted in urine as their glucuronide conjugates.

4. **Adverse effects:**

a. **Gastrointestinal effects:** The most common adverse effects are mild gastrointestinal (GI) disturbances. These lessen as the therapy progresses.
b. **Lithiasis:** Because these drugs increase biliary cholesterol excretion, there is a predisposition to the formation of gallstones.

c. **Muscle:** Myositis (inflammation of a voluntary muscle) can occur with both drugs, and muscle weakness or tenderness should be evaluated. Patients with renal insufficiency may be at risk. Myopathy and rhabdomyolysis have been reported in a few patients taking *gemfibrozil* and *lovastatin* together.

d. **Drug interactions:** Both fibrates compete with the coumarin anticoagulants for binding sites on plasma proteins, thus transiently potentiating anticoagulant activity. INR should, therefore, be monitored when a patient is taking both drugs. Similarly, these drugs may transiently elevate the levels of sulfonylureas.

e. **Contraindications:** The safety of these agents in pregnant or lactating women has not been established. They should not be used in patients with severe hepatic and renal dysfunction or in patients with preexisting gallbladder disease.

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**D. Bile acid–binding resins**

Bile acid sequestrants (resins) have significant LDL cholesterol–lowering effects, although the benefits are less than those observed with statins.

1. **Mechanism of action:** *Cholestyramine* (koe-LES-tir-a-meen), *colestipol* (koe-LES-tih-pol), and *colesevelam* (koh-le-SEV-e-lam) are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine (Figure 21.12). The resin/bile acid complex is excreted in feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. Lowering the bile acid concentration causes hepatocytes to increase conversion of cholesterol to bile acids, resulting in a replenished supply of these compounds, which are essential components of the bile. Consequently, the intracellular cholesterol concentration decreases, which activates an increased hepatic uptake of cholesterol-containing LDL particles, leading to a fall in plasma LDL. [Note: This increased uptake is mediated by an upregulation of cell-surface LDL receptors.] In some patients, a modest rise in plasma HDL levels is also observed. The final outcome of this sequence of events is a decreased total plasma cholesterol concentration.

2. **Therapeutic uses:** The bile acid–binding resins are the drugs of choice (often in combination with diet or *niacin*) in treating Type IIA and Type IIB hyperlipidemias. [Note: In those rare individuals who are homozygous for Type IIA, that is, for whom functional LDL receptors are totally lacking, these drugs have little effect on plasma LDL levels.] *Cholestyramine* can also relieve pruritus caused by accumulation of bile acids in patients with biliary obstruction. It is also used to treat diarrhea.

3. **Pharmacokinetics:** *Cholestyramine*, *colestipol*, and *colesevelam* are taken orally. Because they are insoluble in water and are very large (molecular weights are greater than $10^6$), they are neither absorbed nor metabolically altered by the intestine. Instead, they are totally excreted in feces.

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**Figure 21.12**

Mechanism of bile acid–binding resins.
4. **Adverse effects:**

   a. **GI effects:** The most common side effects are GI disturbances, such as constipation, nausea, and flatulence. Colesevelam has fewer GI side effects than other bile acid sequestrants.

   b. **Impaired absorptions:** At high doses, cholestyramine and colestipol (but not colesevelam) impair the absorption of the fat-soluble vitamins (A, D, E, and K).

   c. **Drug interactions:** Cholestyramine and colestipol interfere with the intestinal absorption of many drugs (for example, tetracycline, phenobarbital, digoxin, warfarin, pravastatin, fluvastatin, aspirin, and thiazide diuretics). Therefore, drugs should be taken at least 1–2 hours before, or 4–6 hours after, the bile acid–binding resins.

**E. Cholesterol absorption inhibitor**

Ezetimibe [eh-ZEH-teh-mib] selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe lowers LDL cholesterol by 17 percent and triacylglycerols by 6 percent, and it increases HDL cholesterol by 1.3 percent. Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation (a Phase II reaction), with subsequent biliary and renal excretion. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma, with a half-life of approximately 22 hours. Ezetimibe has no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E. Patients with moderate to severe hepatic insufficiency should not be treated with ezetimibe.

**F. Combination drug therapy**

It is often necessary to use two antihyperlipidemic drugs to achieve treatment goals in plasma lipid levels. For example, in Type II hyperlipidemias, patients are commonly treated with a combination of niacin plus a bile acid–binding agent such as cholestyramine. (Note: Remember that cholestyramine causes an increase in LDL receptors that clears the plasma of circulating LDL, whereas niacin decreases synthesis of VLDL and, therefore, also the synthesis of LDL.) The combination of an HMG CoA reductase inhibitor with a bile acid–binding agent has also been shown to be very useful in lowering LDL cholesterol levels (Figure 21.13). Simvastatin and ezetimibe as well as simvastatin and niacin are currently available combined in one pill to treat elevated LDL cholesterol. However, more clinical information is needed to determine whether the combination statin-ezetimibe produces equal or better long-term benefits that the use of a high dose of a statin. Until this uncertainty is resolved, many experts recommend maximizing statin dosages and adding niacin or fibrates to achieve goal HDL-cholesterol and triglyceride levels. However, combination drug therapy is not without risks. Liver and muscle toxicity occur more frequently with lipid-lowering drug combinations. Figure 21.14 summarizes some actions of the antihyperlipidemic drugs.

![Figure 21.13](image-url)

*Figure 21.13*

Response of total plasma cholesterol in patients with heterozygous familial hypercholesterolemia to a diet (low in cholesterol, low in saturated fat) and antihyperlipidemic drugs.

Treatment guidelines for hyperlipidemia are shown in Figure 21.15.
III. Drugs That Lower The Serum Lipoprotein Concentration

<table>
<thead>
<tr>
<th>TYPE OF DRUG</th>
<th>EFFECT ON LDL</th>
<th>EFFECT ON HDL</th>
<th>EFFECT ON TRIGLYCERIDES</th>
</tr>
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<tr>
<td>HMG CoA reductase inhibitors (statins)</td>
<td>↓↓↓↓</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓</td>
<td>↑↑↑↑</td>
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<tr>
<td>Niacin</td>
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<td>Bile acid sequestrants</td>
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<td></td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>↓</td>
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</tbody>
</table>

**Figure 21.14**
Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

**Figure 21.15**
Treatment guidelines for hyperlipidemia. *Note that diet and exercise are integral to all treatments of hyperlipidemia. LDL= low-density lipoprotein.
21. Hyperlipidemias

Study Questions

Choose the ONE best answer.

21.1 Which one of the following is the most common side effect of antihyperlipidemic drug therapy?

A. Elevated blood pressure.
B. Gastrointestinal disturbance.
C. Neurologic problems.
D. Heart palpitations.
E. Migraine headaches.

Correct answer = B. Gastrointestinal disturbances frequently occur as a side effect of antihyperlipidemic drug therapy. The other choices are not seen as commonly.

21.2 Which one of the following hyperlipidemias is characterized by elevated plasma levels of chylomicrons and has no drug therapy available to lower the plasma lipoprotein levels?

A. Type I.
B. Type II.
C. Type III.
D. Type IV.
E. Type V.

Correct answer = A. Type I hyperlipidemia (hyperchylomicronemia) is treated with a low-fat diet. No drug therapy is effective for this disorder. The other choices are not seen as commonly.

21.3 Which one of the following drugs decreases de novo cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase?

A. Fenofibrate.
B. Niacin.
C. Cholestyramine.
D. Lovastatin.
E. Gemfibrozil.

Correct answer = D. Lovastatin decreases cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Fenofibrate and gemfibrozil increase the activity of lipoprotein lipase, thereby increasing the removal of very-low-density lipoprotein (VLDL) from plasma. Niacin inhibits lipolysis in adipose tissue, thus eliminating the building blocks needed by the liver to produce VLDL and, therefore, very-low-density lipoprotein (VLDL). Cholestyramine lowers the amount of bile acids returning to the liver via the enterohepatic circulation.

21.4 Which one of the following drugs causes a decrease in liver triacylglycerol synthesis by limiting available free fatty acids needed as building blocks for this pathway?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Gemfibrozil.
E. Lovastatin.

Correct answer = A. At gram doses, niacin strongly inhibits lipolysis in adipose tissue—the primary producer of circulating free fatty acids. The liver normally utilizes these circulating fatty acids as a major precursor for triacylglycerol synthesis. Thus, niacin causes a decrease in liver triacylglycerol synthesis, which is required for VLDL production. The other choices do not inhibit lipolysis in adipose tissue.

21.5 Which one of the following drugs binds bile acids in the intestine, thus preventing their return to the liver via the enterohepatic circulation?

A. Niacin.
B. Fenofibrate.
C. Cholestyramine.
D. Fluvastatin.
E. Lovastatin.

Correct answer = C. Cholestyramine is an anion-exchange resin that binds negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus preventing the bile acids from returning to the liver by the enterohepatic circulation. The other choices do not bind intestinal bile acids.