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Hypocholesterolemic Drugs and Coronary Heart Disease

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PREVENTION OF CORONARY HEART DISEASE AS THE GOAL

Atherosclerosis is the primary cause of coronary heart disease. Markedly lowering blood cholesterol can halt and even reverse to some extent the progression of atherosclerosis. For these reasons, prevention should be the goal, with the focus on decreasing elevated blood cholesterol. About 20% of Americans between 20 and 75 years of age have blood total cholesterol levels above 240 mg/dL, a level requiring management, and up to 40% of some middle aged groups have this elevation.

Although hypercholesterolemias are linked to specific genetic mutations, most have a multifactorial basis that can respond to lifestyle changes. Even though the physician is justified in immediately prescribing a cholesterol-lowering drug to patients with very high blood cholesterol and additional risk factors, strong advice should also be given on the need and benefits of adding life style changes. These changes include reduction of body weight; decreased dietary total fat, chole-

sterol, saturated fatty acids, and trans fatty acids; and increased exercise and stress management. In fact, a recent study employing intensive lifestyle changes in patients with coronary heart disease achieved a 37% lowering of LDL (low-density lipoprotein) cholesterol, a 91% decline in anginal episodes, and a decline in coronary artery stenosis within a year—all without drugs. A prescription for lifestyle changes should accompany the one for a hypocholesterolemic drug.

WHEN TO TREAT HYPERCHOLESTEROLEMIAS?

Principal risk factors for heart disease are elevated levels of LDL cholesterol, a family history of heart disease, and hypertension. Other risks include being male, smoking, low levels of high density lipoprotein (HDL) cholesterol, diabetes mellitus, hyperhomocystinemia, high levels of lipoprotein a (Lpa), and high blood levels of C-reactive protein. (Table 23.1). C-Reactive protein is a marker for cellular inflammation.

TABLE 23.1 Treatment Guidelines for Patients with Hypercholesterolemia

Treatment guidelines	LDL cholesterol ^a	
	Initiation level (mg/dL)	Minimal goal (mg/dL)
Dietary treatment		
Without CHD or two other risk factors ^b	≥160	<160 ^c
Without CHD and with two or more other risk factors ^b	≥130	<130 ^d
With CHD	>100	<100
Drug treatment		
Without CHD or two other risk factors ^b	≥190	<160
Without CHD and with two or more other risk factors ^b	≥160	<130
With CHD	>130	<100

LDL, low-density lipoproteins; CHD, coronary heart disease.
^aClassification: <130 mg/dL is the desirable LDL cholesterol level; 130-159 mg/dL is borderline-high-risk; >160 mg/dL is high-risk.

^bPatients have a lower initiation level and goal if they are at high risk because they already have definite CHD or because they have any two of the following factors: male sex, family history of premature CHD, cigarette smoking, hypertension, low high-density lipoprotein (HDL) cholesterol (<35 mg/dL), hyperhomocysteinemia (>16 μM), high plasma levels of Lp(a) (>30 mg/dL), diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.

^cRoughly equivalent to total cholesterol level <240 mg/dL.

^dRoughly equivalent to total cholesterol level <200 mg/dL.

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Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults.

Homocysteine blood levels (>15 μmol/L) promote atherosclerosis, perhaps by stimulating proliferation of arterial wall smooth muscle cells. Supplementing the diet with folic acid can reduce high levels. Lp(a) is a modified LDL particle that is both atherogenic and prothrombic.

Although development and clinical expression of coronary heart disease (CHD) are determined by the interaction of numerous risk factors, lowering blood cholesterol is the major approach to prevention and suppression of heart disease, the number one cause of death in Western society. The risk of CHD is directly proportional to blood cholesterol levels (Fig. 23.1), and a lowering of cholesterol, specifically LDL cholesterol, decreases the incidence of heart attacks.

The results of several large clinical trials using the statin drugs (discussed later) show that the tested drugs decreased the risk of both primary and secondary cardiovascular events. The incidence of myocardial infarction and death from cardiovascular disease was reduced in patients with hypercholesterolemia who never had a

heart attack (primary prevention) and in those with heart disease (secondary prevention). Furthermore, the statins decreased the risk of a first heart attack in subjects with even average LDL cholesterol levels. In addition to decreased clinical expression of heart disease, aggressive lowering of blood cholesterol with the statin drugs can partially reverse atherosclerosis in the sense of reducing the degree of stenosis (closure) of coronary arteries. Guidelines for initiation and goals of treatment of hypercholesterolemias are outlined in Table 23.1.

MANAGEMENT OF HYPERLIPIDEMIAS WITH DRUGS

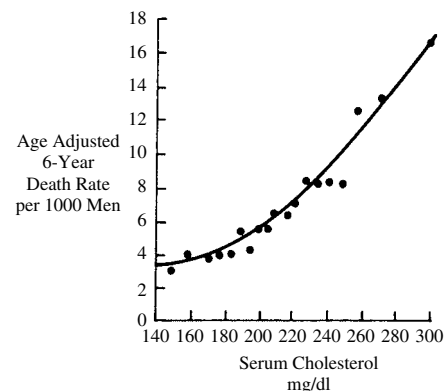
Drug Treatment of Polygenic and Familial Hypercholesterolemia

Statins

Mechanism of Action

The statin family of six closely related hypocholesterolemic drugs are all potent competitive inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), the rate-limiting enzyme in cholesterol biosynthesis. The liver is their target organ, and decreased hepatic cholesterol synthesis ultimately leads to increased removal of LDL particles from the circulation. As a consequence, all other hypocholesterolemic drugs have been relegated to secondary status.

Clinical trials with lovastatin (*Mevacor*), simvastatin (*Zocor*) and pravastatin (*Pravachol*) provided much of the evidence supporting the observation that lowering



Key points

- (1) The risk increases steadily and particularly above 200 mg/dl.
- (2) The magnitude of the increased risk is large—fourfold at the top 10% as compared to the bottom 10%.

FIGURE 23.1

Relationship of serum cholesterol to deaths from coronary heart disease in 36,662 men aged 35–37 years during an average followup period of 6 years. Each point represents the median value for 5% of the population. (From Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. NIH Publication 88-2925, 1988).

of blood cholesterol lowers the risk of CHD. Reductions in CHD risk appear to be due to multiple consequences of inhibiting the cholesterol synthesis pathway. Drug-induced inhibition of hepatic cholesterol synthesis leads to lowering of liver cholesterol concentrations and feedback up-regulation at the gene level of both HMG CoA reductase and the LDL receptor (mechanisms IV and VII in Fig. 23.2). As long as the statin is present at adequate concentration in the liver, the extra HMG CoA reductase activity is not expressed. However, the increased hepatic LDL receptor protein results in increased rates of removal of LDL particles from the circulation by the liver, lowering of

blood LDL-cholesterol levels, slowing of atherosclerosis, and decreased risk of heart attack. An overview of lipoprotein metabolism and the sites where drugs can influence plasma lipoprotein levels is provided in Figure 23.2.

The reduced risk of CHD achieved with the statins may also be due to drug actions independent of lowering blood cholesterol. Many important molecules besides cholesterol are generated by intermediates in the complex cholesterol synthesis pathway. These include the isoprenes geranylgeranyl and farnesyl, which are covalently attached to some proteins (isoprenylation) and target them to membranes where they function. The re-

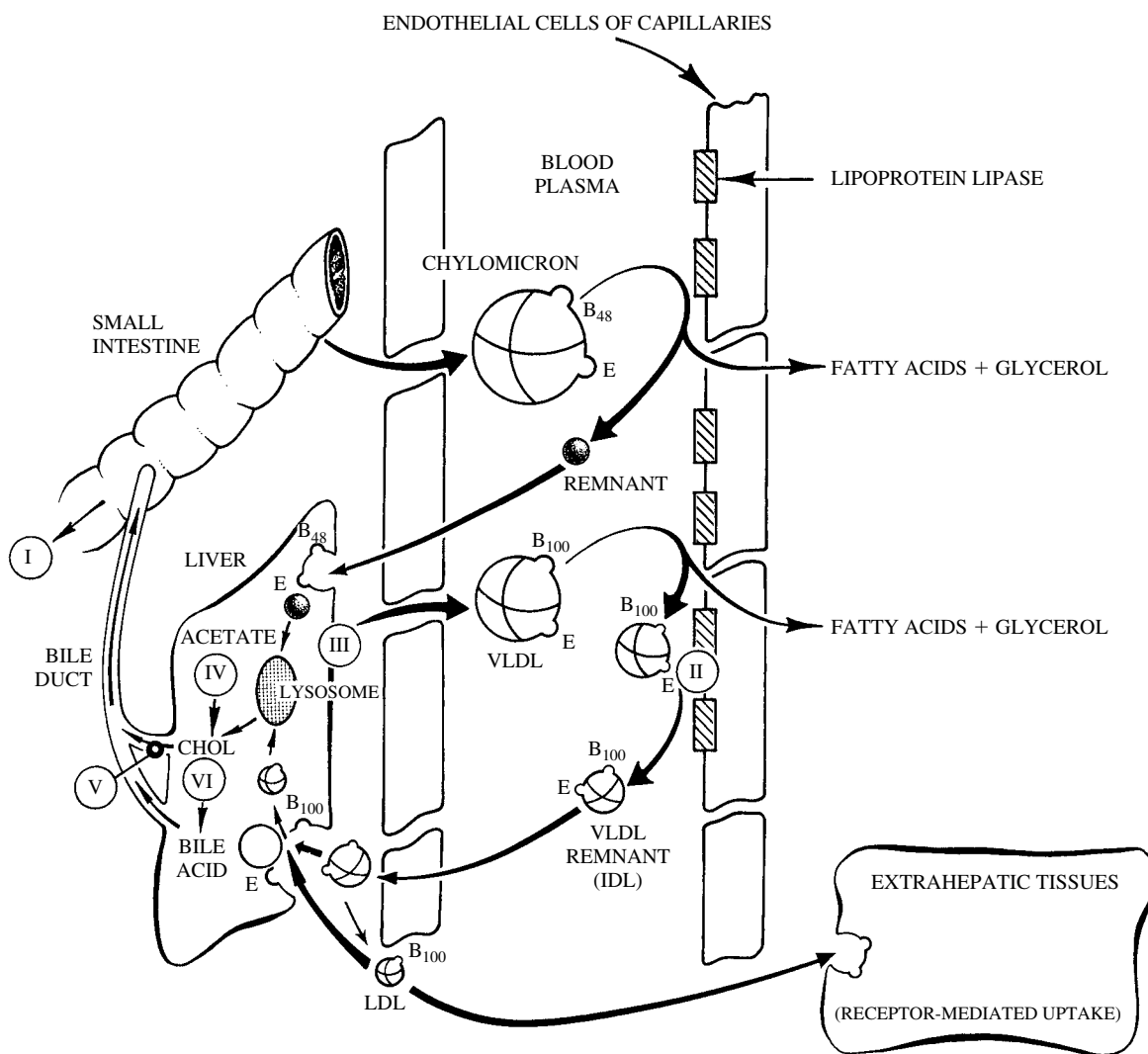


FIGURE 23.2

Partial summary of lipoprotein metabolism in humans. I to VII are sites of action of hypolipidemic drugs. I, stimulation of bile acid and/or cholesterol fecal excretion; II, stimulation of lipoprotein lipase activity; III, inhibition of VLDL production and secretion; IV, inhibition of cholesterol biosynthesis; V, stimulation of cholesterol secretion into bile fluid; VI, stimulation of cholesterol conversion to bile acids; VII, increased plasma clearance of LDL due either to increased LDL receptor activity or altered lipoprotein composition. CHOL, cholesterol; IDL, intermediate-density lipoprotein.

ported capacities of statins to inhibit proliferation of arterial wall smooth muscle cells and to improve endothelial cell functions may be due to inhibited protein isoprenylation in these cells secondary to HMG CoA reductase inhibition.

Clinical Uses

With the possible exception of atorvastatin, the statins are used to lower LDL cholesterol in familial or polygenic (multifactorial) hypercholesterolemia (type IIa) and in combination with triglyceride-lowering drugs to treat combined hyperlipidemia (type IIb) when both LDL and VLDL (very low density lipoproteins) are elevated (Table 23.2). However, the statins probably should not be given with the fibrates (triglyceride-lowering drugs, discussed later), since this combination may greatly increase statin toxicity. Atorvastatin, the most potent of the available statins (Fig. 23.3), has also been shown to lower blood triglycerides significantly.

This effect may be due to decreasing hepatic cholesterol and cholesterol ester levels to such an extent that hepatic formation of VLDL is impaired. The statins also have been claimed to reduce blood cholesterol levels modestly in some patients with homozygous familial hypercholesterolemia, a condition often fatal in childhood or in early adulthood.

The statins may lower the risk of CHD by decreasing inflammation, an important component of atherogenesis. Lovastatin decreased elevated plasma levels of C-reactive protein, a marker for cellular inflammation, and acute coronary events in patients with relatively low plasma cholesterol levels. Recent studies also suggest that use of statins may decrease the risk of stroke, dementia, and Alzheimer's disease and may improve bone

density in postmenopausal women. These broad actions may be related to the hypocholesterolemic, antiproliferative, antiinflammatory, or antioxidant properties of the statins or some combination of these properties.

Adverse Effects

The statins generally appear to be well tolerated, with muscle pain and liver dysfunction seen in 1 to 2% of patients. However, the consequences of 20 to 30 years of continuous use are unknown. This fact has been

TABLE 23.2 Classification of Hyperlipoproteinemias

Disorders	Type ^a	Lipoprotein(s) Elevated	Main Lipid(s) Elevated	Mechanism	Increased Risk
Polygenic or familial hypercholesterolemia	IIa	LDL	Chol	Deficient LDL receptor activity. Abnormal Apo B ₁₀₀ . High-fat diet, excess calories, inactivity.	CHD, stroke
Familial combined hyperlipidemia	IIb	LDL, VLDL	Chol, TG	Increased VLDL production, increased conversion of VLDL to LDL.	CHD, stroke
Familial dyslipoproteinemia	III	IDL (β-VLDL)	Chol, TG	Decreased plasma clearance of VLDL and chylomicron remnants due to abnormal Apo E (E ₂ for normal E ₃).	CHD, stroke
Familial hypertriglyceridemia	IV	VLDL	TG	Overproduction of VLDL; low LPL activity.	Pancreatitis, CHD if HDL is low

^aTypes I and V are not shown. Type I is a rare elevation of chylomicrons treatable only by diet (removing long chained fatty acids). Type V involves elevation of both chylomicrons and VLDL and can be viewed as an extreme type IV. Chol, cholesterol; TG, triglyceride; CHD, coronary heart disease; LDL, low density lipoproteins; LPL, lipoprotein lipase; VLDL, very low density lipoprotein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein.

dramatically reinforced by the recent recognition of a potentially fatal consequence of statin use. A relatively common side effect of the statins (perhaps 1% of patients) is myositis, that is, inflammation of skeletal muscle accompanied by pain, weakness, and high levels of serum creatine kinase. Rhabdomyolysis, i.e., disintegration of muscle with urinary excretion of myoglobin and kidney damage, was considered to be a rare and extreme toxic outcome. However, cerivastatin (*Baycol*) has now been withdrawn from the market by its manufacturer (Bayer) because of 31 deaths linked to fatal rhabdomyolysis. The risk of muscle damage is said to increase with simultaneous use of the triglyceride-lowering fibrates. Pravastatin may be less toxic than other statins because it does not readily penetrate extrahepatic cells and may be more confined to the liver after oral dosage.

Drug Interactions

Most of the statins (lovastatin, simvastatin, atorvastatin, and cerivastatin) are metabolized by the cytochrome P450 3A4 system of intestines and liver to more water-soluble metabolites that are excreted in both the bile and urine. Drugs that inhibit P450 3A4, such as itraconazole, cyclosporine, and erythromycin, can vastly (10-fold) increase plasma statin levels and thus increase the risk of toxicity. Unexpectedly, grapefruit juice can inhibit intestinal metabolism of the statins and can result in an 8- to 10-fold increase in simvastatin serum levels. Since fluvastatin is metabolized by cytochrome P450 2C9, which is also responsible for metabolism of warfarin, warfarin toxicity may be increased if these drugs are simultaneously given. Grapefruit juice should obviously not be consumed within several hours of statin administration. Drugs that induce the P450 3A4 system, such as barbiturates, can accelerate statin metabolism and suppress statin blood levels.

Other Hypocholesterolemic Drugs

Resins

Mechanism of Action

Prior to the introduction of the statins in the mid to late 1980s, the bile acid-sequestering drugs cholestyramine (*Questran*) and colestipol (*Colestid*) were primary drugs for lowering plasma cholesterol. Today they are second-line drugs that can safely be given with a statin to enhance cholesterol lowering or as an alternative for patients intolerant to a statin or concerned with statin's potential for toxicity. Alone, the resins can achieve 20 to 25% reductions in LDL cholesterol, but when used with a statin, such as lovastatin, reductions of 50% and more can be seen.

These drugs are basically anion exchange resins that remain in the gut, bind intestinal bile acids, and greatly increase their fecal excretion (mechanism I in Fig. 23.2).

The lowered concentration of bile acids returning to the liver by the enterohepatic circulation results in derepression of 7- α -hydroxylase, the rate-limiting enzyme for conversion of cholesterol to bile acids. This results in increased use of cholesterol to replace the excreted bile acids and lowering of hepatic cholesterol (mechanism VI in Fig. 23.2). Thus, similar to the statins, the ultimate actions of the bile acid-sequestering resins are up-regulation of transcription of the LDL receptor gene, increased hepatic receptor activity, and lowering of plasma LDL cholesterol (mechanism VII in Fig. 23.2).

Clinical Uses

The bile acid sequestering resins lower elevated LDL cholesterol and therefore are useful in the treatment of type IIa hyperlipoproteinemia. However, because the resins can raise plasma VLDL in some patients, they are not recommended for treatment of combined hyperlipidemias (type IIb) when both LDL cholesterol and VLDL triglycerides are high or in other conditions of elevated triglycerides.

Adverse Effects

The resins are interesting drugs because they have profound metabolic effects without truly entering the body. Perhaps for this reason they are relatively safe, with constipation being the chief complaint. Because the resins are given as the chloride salt and the chloride is exchanged for the negatively charged bile salt, bile acid resins can lead to hyperchloremic acidosis in vulnerable patients (children and patients with kidney failure).

Drug Interactions

The principal precaution with use of the bile acid resins is the possibility of impaired absorption of other drugs given orally at the same time. Cholestyramine and colestipol can bind many other drugs, such as digoxin, phenobarbital, chlorothiazide, and warfarin, and delay or prevent their absorption. For this reason, other drugs should always be taken at least 1 hour before or 4 to 6 hours after the resin. The resins can also decrease absorption of fat-soluble vitamins.

Nicotinic Acid (Niacin)

Nicotinic acid has three special features as a hypolipemic drug: it has multiple beneficial effects on serum lipoproteins, it is the least expensive, and it is the least well tolerated.

Mechanism of Action

Nicotinic acid decreases formation and secretion of VLDL by the liver (mechanism III in Fig. 23.2). This action appears secondary to its ability to inhibit fatty acid mobilization from adipose tissue. Circulating free fatty acids provide the main source of fatty acids for hepatic

triglyceride synthesis, and lowering triglyceride synthesis lowers VLDL formation and secretion by the liver. Since plasma VLDL is the source of LDL, lowering VLDL can ultimately lower LDL. In addition, nicotinic acid shifts LDL particles to larger (more buoyant) sizes. The larger LDL particles are thought to be less atherogenic. Nicotinic acid can also significantly increase plasma HDL levels; the mechanism is unknown.

Clinical Uses

Used alone, nicotinic acid can decrease plasma LDL cholesterol levels by 15 to 30%. It can also be used in combination therapy with the statins or the bile acid-sequestering resins to augment reduction of very high LDL levels. Because nicotinic acid can lower plasma triglycerides by 40% or more, it is useful in treating familial hypertriglyceridemia type IV (Table 23.3), and in combination with the statins it is useful in treating combined hyperlipidemia type IIb. As described later with the fibrates, patients with high plasma triglycerides plus low HDL are at increased risk for CHD. Nicotinic acid is useful for treating these patients, since it can both lower triglycerides and raise HDL.

Adverse Effects

Compliance with nicotinic acid therapy can be poor because the drug can produce an intense cutaneous flush. This can be reduced by beginning the drug in stepped doses of 250 mg twice daily and increasing the dose monthly by 500 to 1000 mg per day to a maximum of 3000 mg per day. Taking nicotinic acid on a full stomach (end of meal) and taking aspirin before dosage can reduce the severity of flushing. Time-release forms of nicotinic acid may also decrease cutaneous flushing. Nicotinic acid can cause gastrointestinal (GI) distress,

liver dysfunction (especially at high doses), decreased glucose tolerance, hyperglycemia, and hyperuricemia. Thus, it is contraindicated in patients with hepatic dysfunction, peptic ulcer, hyperuricemia, or diabetes mellitus. A paradox associated with nicotinic acid is that it is the most widely available hypolipidemic drug (it is sold over the counter), yet its use requires the closest management by the physician.

When to Treat Hypertriglyceridemias

The guidelines for use of drugs to treat familial hypertriglyceridemia type IV are less well defined than those for hypercholesterolemia. One should account for plasma HDL in deciding to treat hypertriglyceridemias with the intent of decreasing the risk for CHD. Moderate hypertriglyceridemia (200–500 mg/dL) without low HDL may not be an independent risk factor for CHD. However, the results of a recent clinical trial indicate that hypertriglyceridemia is an independent risk factor for ischemic stroke. Results of the Helsinki Heart Study showed that the reduced risk of CHD with use of gemfibrozil (discussed later) was correlated with elevation of HDL plus reduction of VLDL triglyceride rather than reduction of LDL cholesterol. Gemfibrozil has little effect on plasma LDL.

Low HDL cholesterol (<35 mg/dL) is an independent risk factor for CHD. HDL appears to antagonize atherogenesis by at least two mechanisms. HDL can mobilize cholesterol from extrahepatic cells (such as arterial wall foam cells) and transport it to the liver for disposal (reverse cholesterol transport); HDL also has antioxidant properties. HDL contains the potent antioxidant enzyme paraoxonase, which may protect LDL lipids from oxidation. Thus, hypertriglyceridemia with

TABLE 23.3 Summary of Major Hypolipidemic Drugs

Drug	Reduced CHD Risk	Lipoprotein Affected	Hyperlipoproteinemia Treated		Principal Adverse Effects
			Singly	In Combination	
Statins	Yes	Reduces LDL	II _a	II _b with niacin	Myositis, liver dysfunction, rhabdomyolysis with cerivastatin
Bile acid-sequestering resins	Yes	Reduces LDL	II _a	Severe II _a with statin or niacin	GI distress, hyperchloremic acidosis
Nicotinic acid (niacin)	Yes	Reduces LDL Reduces VLDL Raises HDL	II _a , II _b IV	II _b with fibrates; severe IV with fibrates	Cutaneous flush, GI distress, liver dysfunction, hyperglycemia, hyperuricemia
Fibrates	Yes	Reduces VLDL Reduces IDL Raises HDL	III, IV	II _b with niacin; severe IV with niacin	GI distress, myositis, gallstone risk, erectile dysfunction

concurrent low HDL cholesterol should be treated to reduce the risk of CHD. Treatment of hypertriglyceridemia independent of HDL levels may also be worthwhile to decrease the risk of ischemic cerebrovascular disease. Very high plasma triglycerides (>1000 mg/dL) are clearly a risk factor for pancreatitis and must be treated for this reason.

As with drugs that lower LDL cholesterol, dietary plus other lifestyle changes should accompany drug therapy of hypertriglyceridemia. Reduction of body weight to ideal is probably the single most important dietary goal. Because patients with familial hypertriglyceridemia may have increased liver capacity to synthesize fat from carbohydrate, attention should be given to restricting excessive carbohydrate and alcohol.

Fibrates

Mechanism of Action

The three structurally related fibrates available in the United States are gemfibrozil (*Lopid*), fenofibrate (*Tricor*) and clofibrate (*Atromid-S*). They share common uses and toxicities. The fibrates typically lower VLDL triglyceride by 40% or more and elevate plasma HDL cholesterol by 10 to 15%. The reduction of plasma triglycerides in humans appears due to increased lipoprotein lipase (LPL) activity. The fibrates activate a nuclear receptor (transcription factor) termed peroxisomal proliferation activated receptor (PPAR) that is a member of the steroid hormone receptor superfamily. PPAR increases transcription of the LPL gene and decreases transcription of the apolipoprotein CIII gene (apo CIII). Since LPL is responsible for catabolism of VLDL triglyceride and apo CIII is an inhibitor of LPL activity, the combined consequences of these changes are increased LPL activity and enhanced removal of triglyceride from the circulation (mechanism II in Fig. 23.2).

The elevation of HDL levels by fibrates may be due to two drug actions: induced synthesis of apo-A1, the principal apoprotein of HDL, and increased assembly of new HDL particles in the circulation. Surface components of VLDL contribute to formation of HDL, as the VLDL particles are reduced in size through the action of LPL. The increased rate of catabolism of VLDL caused by the fibrates would provide more components for assembly of HDL particles.

Clinical Uses

The fibrates are mainly used to treat two hyperlipidemias, familial hypertriglyceridemia (type IV) and dysbetalipoproteinemia (type III). They are also useful in the treatment of hypertriglyceridemia associated with type II diabetes (secondary hyperlipidemia). The fibrates are the drugs of choice in treating hypertriglyceridemias, particularly those associated with low levels of HDL cholesterol. The fibrates additionally appear to

shift LDL particles to larger, hence less atherogenic, species.

Type III or dysbetalipoproteinemia is a rare condition in which cholesterol-enriched VLDL remnants, called β -VLDL, accumulate in the plasma. They are atherogenic particles. Dysbetalipoproteinemia is a genetic condition associated with expression of an unusual form of apolipoprotein E (apo E2 versus the normal E3) that leads to reduced plasma clearance of these lipoproteins by the liver. Through stimulation of LPL and perhaps other lipases, the fibrates accelerate clearance of these β -lipoproteins. Both plasma cholesterol and triglyceride levels are elevated in dysbetalipoproteinemia and in combined hyperlipidemia, type IIb. However, the drug treatments are different for the two conditions. Type IIb hyperlipoproteinemia requires use of agents that lower both LDL and VLDL particles; for example, a statin plus niacin, niacin alone, or niacin in combination with a fibrate. Care should be taken in distinguishing between types IIb and III as the cause of the elevated cholesterol plus triglyceride. This can be achieved by examining the profile of the elevated plasma lipoproteins separated by electrophoresis. A broad β -band is seen in type III but distinct β - and pre- β -bands are seen in type IIb.

Adverse Effects

The fibrates are generally well tolerated, with GI distress being the most likely complaint. Other adverse effects include myositis and erectile dysfunction, particularly with clofibrate. There is ongoing concern about the fibrates increasing the risk of gallstones, although the extent of risk is unclear. Because clofibrate was associated with increased mortality in early clinical trials, it should be considered as a second-line drug.

Drug Interactions

The fibrates potentiate the actions of the coumarin anticoagulants, such as warfarin, so care should be taken to reduce the dose of simultaneously administered anticoagulants, and plasma prothrombin should be frequently measured until the level stabilizes. As mentioned earlier, great care should be given to combining a statin with a fibrate, since this combination may increase the risk of myositis and perhaps rhabdomyolysis. Table 23.4 summarizes major interactions of drugs that lower cholesterol.

Other Approaches to Prevention of Coronary Heart Disease with Drugs

Probucol

Probucol (*Lorelco*) is a hypocholesterolemic drug with few side effects that modestly (15–30%) decreases elevated plasma LDL cholesterol levels. The marginal

TABLE 23.4 Summary of Major Drug Interactions

Drug	Interactions and Special Precautions
Statins	Inhibition of cytochromal P450 3A4 can greatly increase serum statin levels. Grapefruit juice inhibits intestinal P450 3A4 and raises serum statins. Fluvastatin may increase warfarin toxicity because both compete with P450 2C9 for metabolism. Cerivastatin can cause fatal rhabdomyolysis; risk with other statins unclear.
Bile acid resins	Interferes with absorption of many drugs (give other drugs 1 hr before or 6 hr after the resin). May interfere with absorption of fat-soluble vitamins.
Nicotinic acid (niacin)	Cutaneous flush can limit compliance. Giving niacin after meals and use of aspirin may decrease flushing. Gradually increase niacin dose to maximum.
Fibrates	Potentates coumarin anticoagulants. Therefore, reduce dose of anticoagulant and monitor plasma prothrombin. Use clofibrate as second-line drug because it increased death rate in an early study. Avoid use with statins, since the combination may increase risk of myositis and rhabdomyolysis.

LDL-lowering action plus reports that it can lower HDL cholesterol resulted in its discontinuation as a hypocholesterolemic drug. However, it still may reduce the risk of CHD because it is a powerful antioxidant.

The oxidation hypothesis of atherosclerosis states that oxidation of lipids in LDL is required for LDL uptake by macrophages and smooth muscle cells in the intima of arteries, leading to their transformation to foam

cells, an early event in atherogenesis. A recent clinical trial reported that use of probucol decreased the rate of restenosis of coronary arteries by 50% in patients who underwent angioplasty. Fluvastatin also has potent antioxidant properties that may contribute to its antiatherosclerotic effects. These findings suggest that reducing high plasma lipids may not be the only approach to retarding the progression of atherosclerosis and decreasing the risk of coronary heart disease.

Study Questions

Use the following information to answer questions 1 through 4:

A 54-year white man (5', 11"; 189 lb) has a plasma total triglyceride of 105 mg/dL and total cholesterol of 431 mg/dL. Plasma HDL is 53 mg/dL. Electrophoresis of his plasma lipoproteins shows an intense β -band; all others are normal. He is taking itraconazole for a persistent fungal infection. He had two older brothers who both died of myocardial infarction at 57 and 63 years of age.

- What hyperlipoproteinemia does this patient most likely have?
 - Type IIa
 - Type IIb
 - Type III
 - Type IV
- What is the most likely biochemical basis of this patient's hyperlipidemia?
 - Abnormal apolipoprotein E content of serum β -lipoproteins.
 - Increased transcription of the HMG CoA reductase gene in liver.
 - Overproduction of VLDL particle by the liver.
 - Reduced hepatic LDL-receptor activity.
 - Reduced lipoprotein lipase activity.

- What drugs would be contradicted in this patient if his use of itraconazole was not discontinued?
 - Cholestyramine
 - Gemfibrozil
 - Niacin
 - Probucol
 - Simvastatin
- If the patient was treated with cerivastatin, what adverse effects would be of greatest potential concern?
 - Constipation
 - Hepatic dysfunction
 - Hyperglycemia
 - Intense cutaneous flush
 - Rhabdomyolysis

Use the following information to answer questions 5 through 8:

A 42-year-old white woman (5', 4"; 207 lb) has a plasma total triglyceride of 1042 mg/dL and total cholesterol of 368 mg/dL. Plasma HDL cholesterol is 72 mg/dL. Electrophoresis of the plasma lipoproteins shows an intense pre- β -band; all others are normal or absent. Blood glucose is normal. She is not taking any medications.

5. What hyperlipoproteinemia does this patient most likely have?
 (A) Type IIa
 (B) Type IIb
 (C) Type III
 (D) Type IV
6. What is the greatest health risk to this patient based upon the provided information?
 (A) Coronary heart disease
 (B) Decreased digestion of dietary fat
 (C) Hepatic disease
 (D) Pancreatitis
 (E) Stroke
7. Which of the following individual drugs or drug combinations can safely be used to produce maximum lowering of her elevated plasma lipids?
 (A) Atorvastatin
 (B) Atorvastatin + gemfibrozil
 (C) Cholestyramine + niacin
 (D) Cholestyramine + gemfibrozil
 (E) Niacin + gemfibrozil
8. If the patient is given fenofibrate to treat her condition, what enzyme or receptor activity will most increase?
 (A) Cholesterol 7- α -hydroxylase
 (B) Cytochrome P450 2C9
 (C) HMG CoA reductase
 (D) Lipoprotein lipase
 (E) Low-density lipoprotein receptor
6. **D.** Pancreatitis. Extremely high plasma triglycerides, as in this patient, present a serious risk of acute pancreatitis.
7. **E.** Niacin + gemfibrozil. Niacin and gemfibrozil each can reduce plasma triglycerides. In combination a greater reduction should be observed. Although atorvastatin is reported to lower triglycerides, it is mainly a hypocholesterolemic drug. A statin should not be combined with a fibrate. Cholestyramine is a hypocholesterolemic drug that may aggravate hypertriglyceridemia, and therefore, it should not be used in this patient.
8. **D.** Lipoprotein lipase. Fenofibrate is a hypotriglyceridemic drug that lowers plasma triglycerides by increasing the activity of lipoprotein lipase, the enzyme responsible for disassembly of triglycerides in serum lipoproteins (VLDL, IDL and chylomicrons).

ANSWERS

1. **A.** Type IIa or familial hypercholesterolemia. Because triglycerides are normal, the contribution of VLDL cholesterol to the total cholesterol is slight (about 105/5, or 21 mg) and taking into account HDL cholesterol, it is clear LDL accounts for the increase in cholesterol. This is confirmed by an intense β -lipoprotein band on electrophoresis. High LDL cholesterol without elevation of other lipids defines type IIa. The condition is probably genetic because of the premature death of his brothers due to heart attacks.
2. **D.** Reduced hepatic LDL-receptor activity. Familial hypercholesterolemia is most often due to deficient LDL-receptor activity. A less likely possibility, although not considered in this question, is reduced LDL clearance from the circulation due to defective apolipoprotein B₁₀₀.
3. **E.** Simvastatin. Itraconazole inhibits cytochrome P450 3A4. This cytochrome is responsible for metabolism of simvastatin. Therefore, itraconazole can increase serum level of simvastatin and increase its toxicity.
4. **E.** Rhabdomyolysis. Cerivastatin increases the risk of death from rhabdomyolysis.
5. **D.** Type IV. The patient's very high triglycerides are due to elevated VLDL, because electrophoresis showed only an intense pre- β -band. The high cholesterol is due to VLDL being composed of about 20% cholesterol and not to elevated LDL. VLDL cholesterol is about 208 mg/dL (1042/5) and 72 mg/dL for HDL. LDL cholesterol (about 88 mg/dL) must account for the remainder.
6. **D.** Pancreatitis. Extremely high plasma triglycerides, as in this patient, present a serious risk of acute pancreatitis.
7. **E.** Niacin + gemfibrozil. Niacin and gemfibrozil each can reduce plasma triglycerides. In combination a greater reduction should be observed. Although atorvastatin is reported to lower triglycerides, it is mainly a hypocholesterolemic drug. A statin should not be combined with a fibrate. Cholestyramine is a hypocholesterolemic drug that may aggravate hypertriglyceridemia, and therefore, it should not be used in this patient.
8. **D.** Lipoprotein lipase. Fenofibrate is a hypotriglyceridemic drug that lowers plasma triglycerides by increasing the activity of lipoprotein lipase, the enzyme responsible for disassembly of triglycerides in serum lipoproteins (VLDL, IDL and chylomicrons).

SUPPLEMENTAL READING

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Case Study A Plan for Therapy

Mrs. Jones, a sedentary 52-year-old black woman, complains of chest pain upon exertion. The patient is divorced with two daughters, 28 and 31 years old. She provides full-time care for three grandchildren aged 1 to 4. Her mother is living, 78 years old, but her father died of a myocardial infarction at age 53. She has one older brother, 59 years old, who is said to be in good health. The patient neither smokes nor takes alcohol. She consumes a typical American diet of about 40% calories from fat and participates in no regular exercise. She is taking no medication. She says that “taking care of the kids is a handful.” Provide a diagnosis and possible treatment plan.

Physical findings

Height: 62 inches
Weight: 173 pounds
Blood pressure:
144/98 mmHg

Fasting blood chemistry

Total cholesterol: 246 mg/dL
LDL cholesterol: 177 mg/dL
HDL cholesterol: 53 mg/dL
Triglyceride: 131 mg/dL
Glucose: 108 mg/dL

ANSWER: The patient has heterozygous familial hypercholesterolemia (type IIa) that is aggravated by lifestyle factors (obesity, high fat diet, stress, no exercise). Her LDL cholesterol is markedly elevated; other lipids are normal; she has angina; and she has a family history of heart disease. Her hypertension would probably improve with a decrease in body weight.

TREATMENT PLAN: Based upon the criteria for initiating drug therapy of hypercholesterolemia, the physician

decides to begin treatment with 40 mg per day of pravastatin. The patient is also referred to a dietitian for advice on diet and weight control.

OUTCOMES: Two months later the patient is reexamined. Her body weight is 164 pounds and blood LDL cholesterol is 114 mg/dL. Her blood pressure is 136/92. She is encouraged to continue to lose weight and take the cholesterol-lowering drug. She complains of the drug cost.

FOLLOW-UP: When the patient is examined 3 months later, her body weight and blood pressure continue to improve (157 pounds, 128/87 mm Hg) but her LDL cholesterol has increased to 167 mg/dL. She says she has stopped taking the drug because she can't afford it. The physician explains that there is a much less expensive cholesterol drug called niacin, but it can produce a bad itch if not taken in the proper way. The physician begins the patient on 250 mg/day of time-release niacin and advises her to take the medicine after her major meal and to take aspirin if she has skin problems. The physician sees her regularly over the next several months, gradually increasing the niacin dose to 2 g/day. She seems to tolerate the drug well (liver enzymes are unchanged, glucose and other blood chemistries are normal). Her blood LDL cholesterol stabilizes at about 130 mg/dL. The physician encourages her to continue losing weight and to exercise regularly to augment the reduction in her blood cholesterol.

