Drug Therapy

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DRUG TREATMENT OF LIPID DISORDERS

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

MECHANISMS OF ATHEROGENESIS

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

In healthy persons, these lipoproteins function to distribute and recycle cholesterol (Fig. 1).[12] Hepatic overproduction of VLDL can lead to increases in the serum concentrations of VLDL, remnant lipoprotein, and LDL,[13,14] depending on the ability of the body to metabolize each of these types of lipoprotein.[15-17] The most common and important lipid disorder involving this mechanism is familial combined hyperlipidemia (also referred to as mixed hyperlipemia).[13,18] The primary disorders of lipoprotein metabolism are described in Table 1 and have been reviewed elsewhere.[5,19,20]

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

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SECONDARY CAUSES OF HYPERLIPIDEMIA

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

TARGET SERUM LIPOPROTEIN CONCENTRATIONS

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

A serum triglyceride concentration of more than 200 mg per deciliter (2.3 mmol per liter; approximately the 90th percentile for older men and women)[41] is considered somewhat elevated, and a concentration of more than 400 mg per deciliter (4.5 mmol per liter; >95th percentile) is considered high according to the National Cholesterol Education Program guidelines.[21] A reasonable target is a triglyceride concentration of 200 mg per deciliter or less, because higher values are associated with a doubling of the risk of cardiovascular disease when serum total cholesterol concentrations exceed 240 mg per deci-

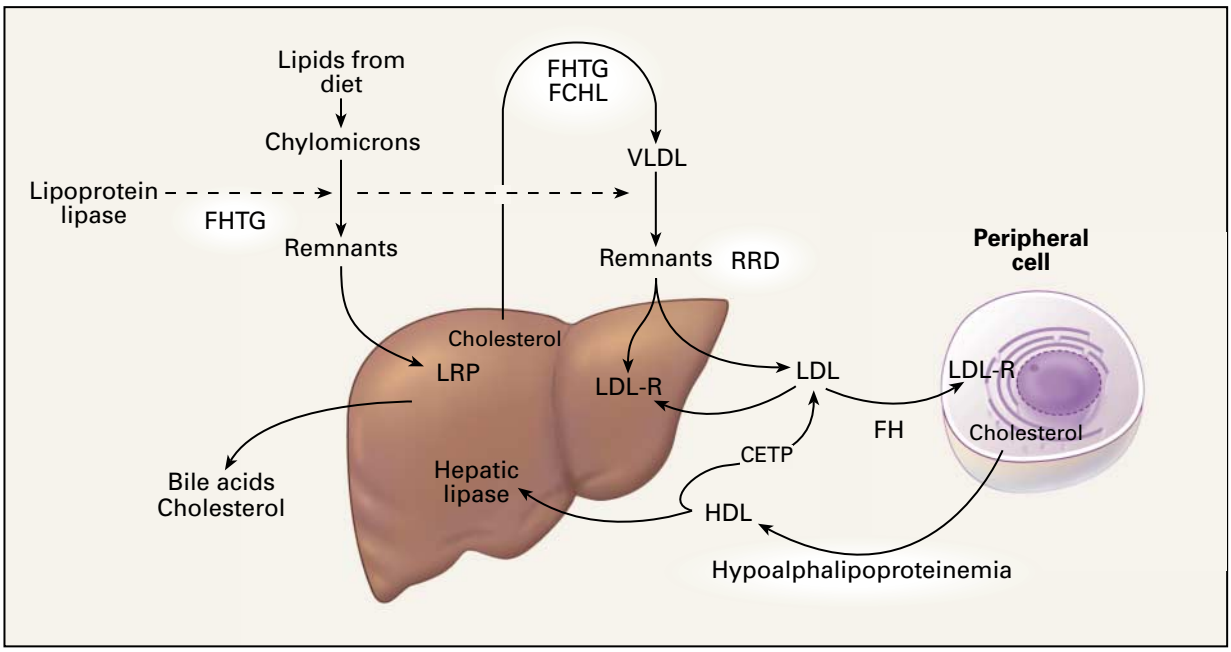

Figure 1. Pathways of Lipid Transport.

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

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

liter (6.2 mmol per liter) or the ratio of serum LDL cholesterol to HDL cholesterol exceeds 5:1.[42,43] Reasonable targets for serum HDL cholesterol concentrations are 45 mg per deciliter (1.2 mmol per liter) in men and 55 mg per deciliter (1.4 mmol per liter) in women — the respective means in these populations.[41]

DIETARY TREATMENT OF HYPERLIPIDEMIA

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

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

STATINS

Drugs of the statin class are structurally similar to hydroxymethylglutaryl–coenzyme A (HMG-CoA), a precursor of cholesterol, and are competitive in-

TABLE 1. PRIMARY LIPOPROTEIN DISORDERS AMENABLE TO TREATMENT WITH DIET AND DRUG THERAPY.*

DISORDER	MECHANISMS	COMPLICATIONS	TREATMENT†
Familial hypertriglyceridemia‡	Decreased serum triglyceride removal resulting from decreased LPL activity Increased hepatic secretion of triglyceride-rich VLDL	Pancreatitis at triglyceride concentrations >2000 mg per deciliter (22.6 mmol/liter); low risk of CAD	Diet and weight loss Fibrate Nicotinic acid n−3 fatty acids Oxandrolone
Familial combined hyperlipidemia‡	Increased hepatic secretion of apolipoprotein B–containing VLDL and conversion to LDL Accumulation of VLDL, LDL, or both, depending on efficiency of their removal	CAD, PVD, stroke	Diet and weight loss Statin Nicotinic acid Fibrate§
Remnant removal disease (familial dysbetalipoproteinemia)	Increased secretion of VLDL Impaired removal of remnant lipoproteins resulting from homozygosity (ϵ_2/ϵ_2) or heterozygosity (ϵ_2/ϵ_3 or ϵ_2/ϵ_4) for apolipoprotein E ϵ_2	PVD, CAD, stroke	Diet, weight loss Fibrate§ Nicotinic acid Statin
Familial or polygenic hypercholesterolemia	Diminished LDL-receptor activity Defective apolipoprotein B that is poorly recognized by LDL receptor	CAD, occasionally PVD, stroke	Diet Statin Bile-acid–binding resin Nicotinic acid
Familial hypoalphalipoproteinemia (low HDL syndrome)¶	Diminished apolipoprotein AI formation, increased removal, increased CETP or hepatic lipase activity	CAD, PVD, (may be associated with hypertriglyceridemia)	Exercise and weight loss Nicotinic acid Fibrate§ Statin

*LPL denotes lipoprotein lipase, VLDL very-low-density lipoprotein, CAD coronary artery disease, PVD peripheral vascular disease, HDL high-density lipoprotein, and CETP cholesterol-ester transfer protein.

†The treatments may be given alone or in combination; the primary treatment is listed first, followed by other treatments in decreasing order of importance.

‡Diabetes mellitus can greatly exacerbate the condition. The hyperlipidemia of diabetes is closest mechanistically to familial combined hyperlipidemia.

§Combined treatment with a fibrate and a statin can increase the risk of myopathy.

¶This disorder is characterized by low concentrations of HDL cholesterol.

TABLE 2. RISK FACTORS FOR CARDIOVASCULAR DISEASE IDENTIFIED BY THE NATIONAL CHOLESTEROL EDUCATION PROGRAM AND OTHERS.*

NATIONAL CHOLESTEROL EDUCATION PROGRAM	OTHERS
Age (≥45 years for men, after menopause for women)	Serum Lp(a) lipoprotein concentration 20 mg/dl (frequency distribution, 75th percentile) or 40 mg/dl (90th percentile)
Hypertension (even if treated)	Serum homocystine concentration >10 nmol per liter (≥50th percentile)
Smoking	Small, dense LDL particles
Diabetes mellitus	Ratio of serum VLDL cholesterol to triglycerides >0.3 (90th percentile) or >0.25 (75th percentile)
History of cardiovascular disease in first-degree relatives (<55 years of age for men, <65 years for women)	High concentrations of plasma fibrinogen, factor VIII, factor VII, plasminogen-activator inhibitor type 1 (associated with hypertriglyceridemia); resistance to protein C inactivation of factors V and VIII
Serum HDL cholesterol concentration <35 mg/dl	Insulin resistance with hyperinsulinemia
	Visceral (intraabdominal) obesity
	High serum C-reactive protein concentrations
	High white-cell count, hematocrit, or both
	DD genotype for angiotensin-converting enzyme
	Arcus senilis, vascular bruits, missing or asymmetric pulses in the legs
	Deficiency of antioxidant vitamins
	Chlamydia infection

*Data obtained from the National Cholesterol Education Program,[21] Maher et al.,[22] Welch and Loscalzo,[23] Chambless et al.,[24] Diaz et al.,[25] and Bachmaier et al.[26] LDL denotes low-density lipoprotein, VLDL very-low density lipoprotein, and HDL high-density lipoprotein. To convert values for cholesterol to millimoles per liter, multiply by 0.026.

TABLE 3. THRESHOLD SERUM TOTAL AND LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL CONCENTRATIONS FOR THE INITIATION OF DIETARY AND DRUG TREATMENT, ACCORDING TO THE NUMBER OF RISK FACTORS FOR CARDIOVASCULAR DISEASE AND THE PRESENCE OR ABSENCE OF CARDIOVASCULAR DISEASE.*

CATEGORY	THRESHOLD FOR INITIATION OF DIETARY THERAPY		THRESHOLD FOR INITIATION OF DRUG THERAPY	
	TOTAL CHOLESTEROL	LDL CHOLESTEROL	TOTAL CHOLESTEROL	LDL CHOLESTEROL
	milligrams per deciliter			
0 or 1 Risk factor for cardiovascular disease	240	160	275	190
≥2 Risk factors for cardiovascular disease	200	130	240	160
Cardiovascular disease	160	100	200	130

*To convert values for cholesterol to millimoles per liter, multiply by 0.026.

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

Lipid-Altering Effects

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

TABLE 4. CHARACTERISTICS OF STATINS.*

CHARACTERISTIC	LOVASTATIN	PRAVASTATIN	SIMVASTATIN	ATORVASTATIN	FLUVASTATIN	CERIVASTATIN
Maximal dose (mg/day)	80	40†	80	80	40	0.3
Maximal serum LDL cholesterol reduction produced (%)	40	34	47	60	24	28
Serum LDL cholesterol reduction produced (%)‡	34	34	41	50	24	28
Serum triglyceride reduction produced (%)‡	16	24	18	29	10	13
Serum HDL cholesterol increase produced (%)‡	8.6	12	12	6	8	10
Plasma half-life (hr)	2	1–2	1–2	14	1.2	2–3
Effect of food on absorption of drug	Increased absorption	Decreased absorption	None	None	Negligible	None
Optimal time of administration	With meals (morning and evening)	Bedtime	Evening	Evening	Bedtime	Evening
Penetration of central nervous system	Yes	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	10	20	13	2	<6	33
Mechanism of hepatic metabolism	Cytochrome P-450 3A4	Sulfation	Cytochrome P-450 3A4	Cytochrome P-450 3A4	Cytochrome P-450 2C9	Cytochrome P-450 3A4, 2C8

*The synthetic statins atorvastatin and cerivastatin contain only the active enantiomers; fluvastatin contains both active and inactive enantiomers.[61] LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

†An 80-mg dose has also been studied, which reduces serum LDL cholesterol concentrations by 38 to 39 percent and is safe.[62] However, the approved maximal dose is 40 mg per day.

‡This effect was elicited by a daily dose of 40 mg of lovastatin, pravastatin, simvastatin, atorvastatin, and fluvastatin and by a daily dose of 0.3 mg of cerivastatin in patients with hypercholesterolemia.[63] Reductions in LDL cholesterol of 30 to 32 percent are more typical of once-daily treatment with lovastatin[63] and twice-daily treatment with pravastatin.[62]

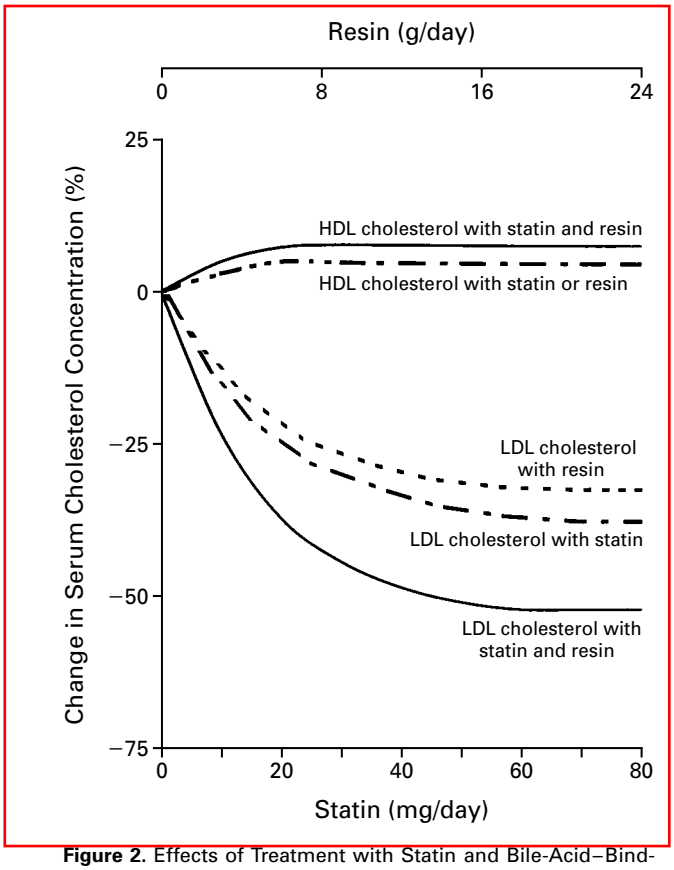

Figure 2. Effects of Treatment with Statin and Bile-Acid–Binding Resin, Alone or in Combination, on Serum High-Density Lipoprotein (HDL) and Low-Density Lipoprotein (LDL) Cholesterol Concentrations.

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

by treatment with a statin ranges from 24 to 60 percent (Table 4).

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

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

Absorption and Metabolism

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

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

Adverse Effects

The most common adverse effects of statins are gastrointestinal upset, muscle aches, and hepatitis. Rarer problems are myopathy (defined as muscle pain with serum creatine kinase concentrations of more than 1000 U per liter), rash, peripheral neuropathy, insomnia, bad or vivid dreams, and difficulty sleeping or concentrating (Table 5).[76-79] For patients who have adverse central nervous system effects, a statin with no penetration of the central nervous system, such as pravastatin, can be tried. Cataracts have occurred in animals treated with high doses of lovastatin, simvastatin, and fluvastatin, but not in humans given these or any other statin.[80,81]

Hepatotoxicity occurs in less than 1 percent of patients given high doses, and it is very rare during treatment with low doses. Myotoxicity is even rarer.[82] Hepatotoxicity and myotoxicity are both more common among patients who are receiving drugs that are metabolized by cytochrome P-450 enzyme systems. Four of the six statins are metabolized by the cytochrome P-450 3A4 system, fluvastatin is metabolized by the cytochrome P-450 2C9 system, and pravastatin is metabolized by sulfation and possibly other mechanisms. Drugs that inhibit cytochrome P-450 3A4 or 2C9 retard the metabolism of statins and include antibiotics, antifungal drugs, HIV-protease inhibitors, and cyclosporine (Table 6).[83] Drugs that induce cytochrome P-450 3A4, such as barbiturates and carbamazepine, reduce serum statin concentrations. For patients who are receiving either type of drug, pravastatin, which is not metabolized by any cytochrome P-450 enzyme, provides an alternative. Warfarin and fluvastatin are common substrates for cytochrome P-450 2C9, and warfarin levels may increase if the two drugs are given concomitantly.[83]

The symptoms of hepatitis induced by statins — fatigue, sluggishness, anorexia, and weight loss — resemble those of an influenza-like syndrome. Serum

TABLE 5. SIDE EFFECTS OF LIPID-LOWERING DRUGS.*

DRUG AND SITE OR TYPE OF EFFECT	EFFECT
Statins	
Skin	Rash
Nervous system	Loss of concentration, sleep disturbance, headache, peripheral neuropathy
Liver	Hepatitis, loss of appetite, weight loss, and increases in serum aminotransferases to 2 to 3 times the upper limit of the normal range
Gastrointestinal tract	Abdominal pain, nausea, diarrhea
Muscles	Muscle pain or weakness, myositis (usually with serum creatine kinase >1000 U/liter), rhabdomyolysis with renal failure
Immune system	Lupus-like syndrome (lovastatin, simvastatin, or fluvastatin)
Protein binding	Diminished binding of warfarin (lovastatin, simvastatin, fluvastatin)
Bile-acid–binding resins	
Gastrointestinal tract	Abdominal fullness, nausea, gas, constipation, hemorrhoids, anal fissure, activation of diverticulitis, diminished absorption of vitamin D in children
Liver	Mild serum aminotransferase elevations, which can be exacerbated by concomitant treatment with a statin
Metabolic system	Increases in serum triglycerides of approximately 10 percent (greater increases in patients with hypertriglyceridemia)
Electrolytes	Hyperchloremic acidosis in children and patients with renal failure (cholestyramine)
Drug interactions	Binding of warfarin, digoxin, thiazide diuretics, thyroxine, statins
Nicotinic acid	
Skin	Flushing, dry skin, pruritus, ichthyosis, acanthosis nigricans
Eyes	Conjunctivitis, cystoid macular edema, retinal detachment
Respiratory tract	Nasal stuffiness
Heart	Supraventricular arrhythmias
Gastrointestinal tract	Heartburn, loose bowel movements or diarrhea
Liver	Mild increase in serum aminotransferases, hepatitis with nausea and fatigue
Muscles	Myositis
Metabolic system	Hyperglycemia (incidence, approximately 5 percent; higher in patients with diabetes), increase of 10 percent in serum uric acid
Fibrates	
Skin	Rash
Gastrointestinal tract	Stomach upset, abdominal pain (mainly gemfibrozil), cholesterol-saturated bile, increase of 1 to 2 percent in gallstone incidence
Genitourinary tract	Erectile dysfunction (mainly clofibrate)
Muscles	Myositis with impaired renal function
Plasma proteins	Interference with binding of warfarin, requiring reduction in the dose of warfarin by approximately 30 percent
Liver	Increased serum aminotransferases

*Data obtained from Abramowicz[76] and *Physicians' Desk Reference*.[63]

TABLE 6. DRUGS AND SUBSTANCES THAT INTERFERE WITH THE METABOLISM OF STATINS.*

MECHANISM OF ACTION	EFFECT	DRUG OR SUBSTANCE
Inhibits cytochrome P-450 3A4	Raises serum drug concentrations	Clarithromycin, erythromycin, troleandomycin, cyclosporine, tacrolimus, delavirdine mesylate, ritonavir, fluconazole, itraconazole, ketoconazole, fluoxetine, grapefruit juice, mibefradil, nefazodone, verapamil
Induces cytochrome P-450 3A4	Lowers serum drug concentrations	Barbiturates, carbamazepine, griseofulvin, nafcillin, phenytoin, primidone, rifabutin, rifampin, troglitazone
Inhibits cytochrome P-450 2C9	May raise serum fluvastatin concentrations	Amiodarone, cimetidine, trimethoprim–sulfamethoxazole, fluoxetine, fluvoxamine, isoniazid, itraconazole, ketoconazole, metronidazole, sulfinpyrazone, ticlopidine, zafirlukast
Induces cytochrome P-450 2C9	May lower serum fluvastatin concentrations	Barbiturates, carbamazepine, phenytoin, primidone, rifampin

*Data obtained from *Physicians' Desk Reference*[63] and Hanston and Horn.[83] Common substrates have been described previously in detail.[83]

aminotransferase concentrations are usually only moderately elevated (e.g., two to three times the upper limit of the normal range). Serum LDL cholesterol concentrations are often much lower than expected, and serum HDL cholesterol concentrations are low. The symptoms subside almost overnight after the drug is discontinued, but serum aminotransferase concentrations may not return to normal for several weeks, depending on the degree of the elevation. On the other hand, minor, isolated elevations in serum aminotransferase concentrations (such as increases to 1.5 times the upper limit of the normal range) can be ignored in the absence of symptoms. The recommended intervals for the measurement of serum aminotransferases vary among the drugs; the initial measurements should be done 2 to 12 weeks after treatment is started and every 6 months during long-term treatment.[82]

When lovastatin is given with nicotinic acid or with derivatives of fibric acid (commonly referred to as fibrates), myopathy and myositis occur in approximately 1 percent of patients.[84-88] Patients who are at higher risk for myositis when they receive combined treatment with a statin and a fibrate are small-framed, older persons with impaired renal function.[89] As a general rule, high doses of statin should not be given to patients who are taking a fibrate. The frequency of

myopathy among patients who are taking lovastatin alone at a dose of 80 mg per day is reported to be 0.2 percent,[82] but it is higher among patients who are also taking cyclosporine or erythromycin.[84]

Indications

Statins are useful in treating most of the major types of hyperlipidemia. The classic indication is heterozygous familial or polygenic hypercholesterolemia, in which LDL-receptor activity is reduced. Statins increase LDL-receptor activity by inhibiting the synthesis of cholesterol.[53] They also reduce the formation of apolipoprotein B–containing lipoproteins and their entry into the circulation[50,54,90] and can reduce high serum concentrations of triglycerides and remnant lipoproteins.[64,91-93] As a result, statin therapy is also indicated in patients with combined or familial combined hyperlipidemia, remnant removal disease, and the hyperlipidemia of diabetes[94] and renal failure.[95]

BILE-ACID–BINDING RESINS

Once a mainstay of lipid-lowering therapy, bile-acid–binding resins are now largely used as adjuncts to statin therapy for patients in whom further lowering of serum cholesterol concentrations is indicated. The available bile-acid–binding resins are cholestyramine and colestipol. A 5-g dose of colestipol is approximately equivalent to a 4-g dose of cholestyramine. When given in doses of 4 to 8 g or 5 to 10 g twice daily with meals as a suspension in juice or water, these resins decrease serum LDL cholesterol concentrations by 10 to 20 percent.[62,96] Recently, 1-g tablets of colestipol have become available. No one formulation of cholestyramine or colestipol is consistently preferred by patients.

Lipid-Altering Effects

Resins bind bile acids (not cholesterol) in the intestine, thereby interrupting the enterohepatic circulation of bile acids and increasing the conversion of cholesterol into bile acids in the liver. Hepatic synthesis of cholesterol is also increased, which in turn increases the secretion of VLDL into the circulation, raises serum triglyceride concentrations, and limits the effect of the drug on LDL cholesterol concentrations. The increase in serum triglyceride concentrations can represent a major complication in patients who are prone to hypertriglyceridemia.

The chief indication for therapy with a bile-acid–binding resin is to reduce serum LDL cholesterol concentrations in patients who are already receiving a statin (Fig. 2).[62] The statin-induced inhibition of cholesterol synthesis increases the efficacy of the bile-acid–binding resin. In addition, serum HDL cholesterol concentrations increase by about 0.5 mg per deciliter (0.04 mmol per liter) when a bile-acid–binding resin is added to the treatment regimen of patients who are already receiving a statin.[96,97] Combination therapy can potentially reduce the risk of events related to heart disease by more than 50 percent.[31]

Adverse Effects

Bile-acid–binding resins cause abdominal fullness, gas, and constipation in 30 percent of patients (Table 5).[62,96,97] The dose can be adjusted to minimize these symptoms, and fiber (such as 3 tsp [10.2 g] of psyllium-husk fiber) or a glass of prune juice can be added to the daily diet, especially when treatment is started, to help avoid constipation. Stool softeners are less useful for this purpose.

Cholestyramine can cause hyperchloremic acidosis in children or in patients with renal failure because chloride ions are released in exchange for bile acid.[98] Colestipol may not have this effect. Both resins may reduce the absorption of vitamin D and other fat-soluble vitamins, but this effect is negligible, except possibly in children.[98] Bile-acid–binding resins can bind polar compounds, including warfarin, digoxin, thyroxine, thiazide diuretics, folic acid, and statins. To avoid such an effect, these substances should be given one hour before or four hours after the resin.

Indications

Treatment with bile-acid–binding resins should be restricted to patients who have hypercholesterolemia but not hypertriglyceridemia. This group includes patients with polygenic or heterozygous familial hypercholesterolemia and those with the hypercholesterolemic form of familial combined hyperlipidemia.

NICOTINIC ACID

Lipid-Altering Effects

The cholesterol-lowering effect of nicotinic acid was first reported in 1955.[99] Its primary action is to inhibit the mobilization of free fatty acids from peripheral tissues, thereby reducing hepatic synthesis of triglycerides and secretion of VLDL (Fig. 3).[100] Nicotinic acid may also inhibit the conversion of VLDL into LDL.[101] The ability of nicotinic acid to increase serum HDL concentrations, by up to 30 percent at the maximal dose, exceeds that of all other drugs.[100] In addition, nicotinic acid causes a shift in the form of LDL from small, dense particles to large, buoyant particles and lowers serum Lp(a) lipoprotein concentrations by about 30 percent.[102]

Nicotinic acid has proved most effective in preventing heart disease when it is given in combination with other drugs, such as a bile-acid–binding resin[30,31,103] or a fibrate.[104] Treatment with nicotinic acid has also been reported to reduce the rates of nonfatal and fatal myocardial infarction and the total 15-year mortality rate.[105,106] The ability of combination therapy with nicotinic acid and a statin to prevent cardiovascular disease has not been studied, but the combination lowers serum LDL cholesterol concentrations more than treatment with either drug alone,

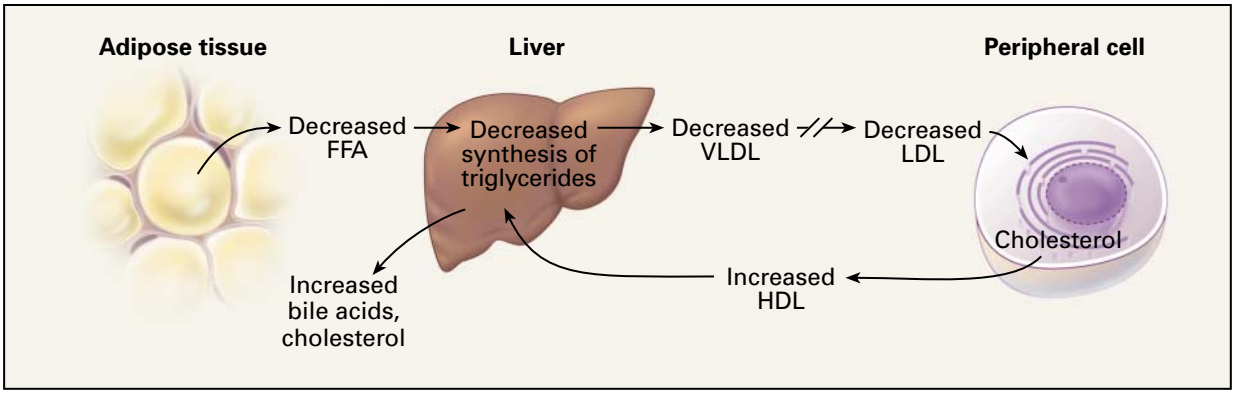

Figure 3. Mechanisms of Action of Nicotinic Acid.

Nicotinic acid inhibits the mobilization of free fatty acids (FFA) from peripheral adipose tissue to the liver. As a consequence of this decrease or an additional hepatic effect, the synthesis and secretion of very-low-density lipoprotein (VLDL) are reduced, and the conversion of VLDL to low-density lipoprotein (LDL) is decreased.[96] Nicotinic acid can also increase serum high-density lipoprotein (HDL) cholesterol concentrations by up to 30 percent; the mechanism responsible for this effect is unknown. Reproduced from Knopp et al.[100] with the permission of the publishers.

without increasing adverse effects.[107,108] Combination therapy also reduces serum triglyceride and remnant lipoprotein concentrations, raises serum HDL cholesterol concentrations, and improves the LDL-subclass profile[109] more than does monotherapy.[107,108]

Adverse Effects

The predominant adverse effect of nicotinic acid is flushing of the skin, an effect that about 10 percent of patients find intolerable (Table 5). The administration of 325 mg of aspirin 30 to 60 minutes before each dose of nicotinic acid reduces the severity of flushing, and the aspirin can often be discontinued after a few days as tachyphylaxis develops in response to the prostaglandin-mediated flush. Patients can also minimize flushing by taking nicotinic acid at the end of a meal and by not taking it with hot liquids. With the use of these precautionary measures, nicotinic acid can be started at a moderate dose, such as 250 to 500 mg twice daily, depending on the patient's size. The daily dose can be increased at monthly intervals by 500 or 1000 mg, to a maximum of 3000 mg, if serum aminotransferase, glucose, and uric acid concentrations do not increase excessively. With each increase in the dose, flushing may recur.

Other adverse effects include conjunctivitis, nasal stuffiness, loose bowel movements or diarrhea, acanthosis nigricans, and ichthyosis (Table 5). Hepatitis is more frequent in patients who are taking nicotinic acid than in those who are taking statins, especially at doses of more than 2000 to 3000 mg of nicotinic acid daily. The symptoms and time course of nicotinic-acid–induced hepatitis are similar to those associated with statins.

Timed-release formulations of nicotinic acid are designed to minimize cutaneous flushing. However, the absence of flushing may indicate poor gastrointestinal absorption.[100,102] Other drawbacks of such formulations are hepatotoxicity at doses of 2000 mg per day or higher[100,110] and smaller decreases in serum triglyceride concentrations and smaller increases in serum HDL cholesterol concentrations than are induced with plain nicotinic acid.[100,110] Nonetheless, some timed-release formulations are useful in patients who cannot tolerate plain nicotinic acid and are equivalent to plain nicotinic acid with respect to the effects on serum lipid and aminotransferase concentrations.[102]

Indications

The changes in serum triglyceride and HDL cholesterol concentrations that are induced by nicotinic acid are curvilinear, whereas the changes in serum LDL cholesterol concentrations are linear (Fig. 4).[111] Thus, a daily dose of 1500 to 2000 mg of nicotinic acid will substantially change the serum triglyceride and HDL cholesterol concentrations without causing many of the mucocutaneous and hepatic adverse effects seen with higher doses. This dose is often ideal for patients with familial combined hyperlipidemia. These patients usually need to take a statin as well, and because it is tolerated better, the statin should be given first. The patients may then be more receptive to moderate doses of plain or timed-release nicotinic acid. Higher doses of nicotinic acid (3000 to 4500 mg daily) may be needed to reduce serum LDL cholesterol concentrations substantially in patients with familial hypercholesterolemia even when statins and a bile-acid–binding resin are given concomitantly.

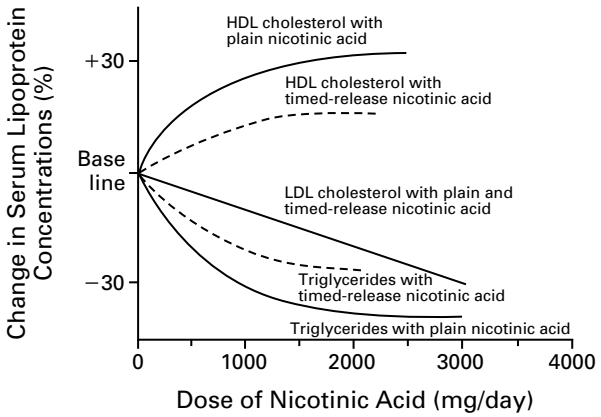

Figure 4. Effects of Plain and Timed-Release Nicotinic Acid on Serum Lipoprotein Concentrations.

Low doses of plain nicotinic acid have more favorable effects than most timed-release forms on serum triglyceride and high-density lipoprotein (HDL) cholesterol concentrations. The plain and timed-release forms have similar effects at any given dose on serum low-density lipoprotein (LDL) cholesterol concentrations. The majority of the effects on serum triglyceride and HDL cholesterol concentrations occur with lower doses of nicotinic acid.

FIBRATES

Lipid-Altering Effects

The prototypical fibric acid is clofibrate (ethyl *p*-chlorophenoxyisobutyrate). Clofibrate and related drugs resemble, in part, short-chain fatty acids and increase the oxidation of fatty acids in both liver and muscle (Fig. 5). The increase in fatty-acid oxidation in the liver is associated with increased formation of ketone bodies (an effect that is not clinically important)[112] and decreased secretion of triglyceride-rich lipoproteins. In muscle, the increase in fatty-acid oxidation is associated with an increase in both lipoprotein lipase activity and the uptake of fatty acids.[113] These drugs act by activating the nuclear transcription factor peroxisome proliferator-activated receptor α (PPARα), up-regulating the expression of the LDL cholesterol and apolipoprotein AI genes, and down-regulating the expression of the apolipoprotein CII gene.[114,115]

The fibrates are the most effective triglyceride-lowering drugs.[28] Patients with very high serum triglyceride concentrations have low serum LDL cholesterol concentrations, and these may increase during treatment with a fibrate. If the increase is substantial, a low-dose statin may be added to the regimen. Conversely, in patients with high serum LDL cholesterol concentrations and moderately high serum triglyceride concentrations, fibrates can lower serum LDL cholesterol concentrations.[116] Fibrates also increase the buoyancy of LDL particles, a potentially favorable effect.[117] Fenofibrate, which was recently approved for use in the United States, may lower serum LDL cholesterol concentrations more effectively than does clofibrate or gemfibrozil.[118-120] Bezafibrate and ciprofibrate are available in Europe but not in the United States.

Treatment with gemfibrozil reduced the frequency of heart disease in a placebo-controlled study of patients with high serum VLDL and LDL cholesterol concentrations[121] and in a secondary-prevention trial in men with low serum HDL cholesterol concentrations.[122-124] Treatment with clofibrate produced similar results.[125] Treatment with bezafibrate and gemfibrozil is also associated with regression of coronary artery disease on angiography.[126,127]

Adverse Effects

The adverse effects of fibrates are listed in Table 5. Of the three fibrates that are available in the United States, clofibrate and fenofibrate cause fewer gastrointestinal symptoms than gemfibrozil. Other adverse effects include erectile dysfunction, especially in men treated with clofibrate, and myositis in patients with impaired renal function. The fibrates are largely excreted by the kidney and therefore accumulate in the serum in patients with renal failure.[128] Because fibrates displace warfarin from albumin-binding sites, patients who are taking a fibrate may need up to 30 percent less warfarin. All the fibrates increase biliary cholesterol concentrations and can cause gallstones.[125,128,129] In one placebo-controlled study, the mortality rate was increased among patients who were receiving clofibrate, as a result of diseases of the biliary tract and cancer.[125] There was no increase in the risk of death or cancer among patients who were treated with clofibrate in another study[105] or among those who received gemfibrozil.[121]

Indications

The primary indications for fibrate therapy are serum triglyceride concentrations of more than 1000 mg per deciliter (11.5 mmol per liter), remnant removal disease, and low serum HDL cholesterol concentrations. However, they may also be useful in patients with combined hyperlipidemia.

OTHER THERAPIES

Dietary supplementation with soluble fiber, such as psyllium husk, oat bran, guar gum and pectin, and fruit and vegetable fibers, lowers serum LDL cholesterol concentrations by 5 to 10 percent.[130,131] Sitostanol, a plant sterol incorporated into margarine, inhibits gastrointestinal absorption of cholesterol.[132] The n−3 fatty acids can lower serum triglyceride concentrations by up to 30 percent at a daily dose of 3 g and by about 50 percent at a daily dose of 9 g.[133] In postmenopausal women, oral estrogen therapy can lower serum LDL cholesterol concentrations by approximately 10 percent and raise serum HDL cho-

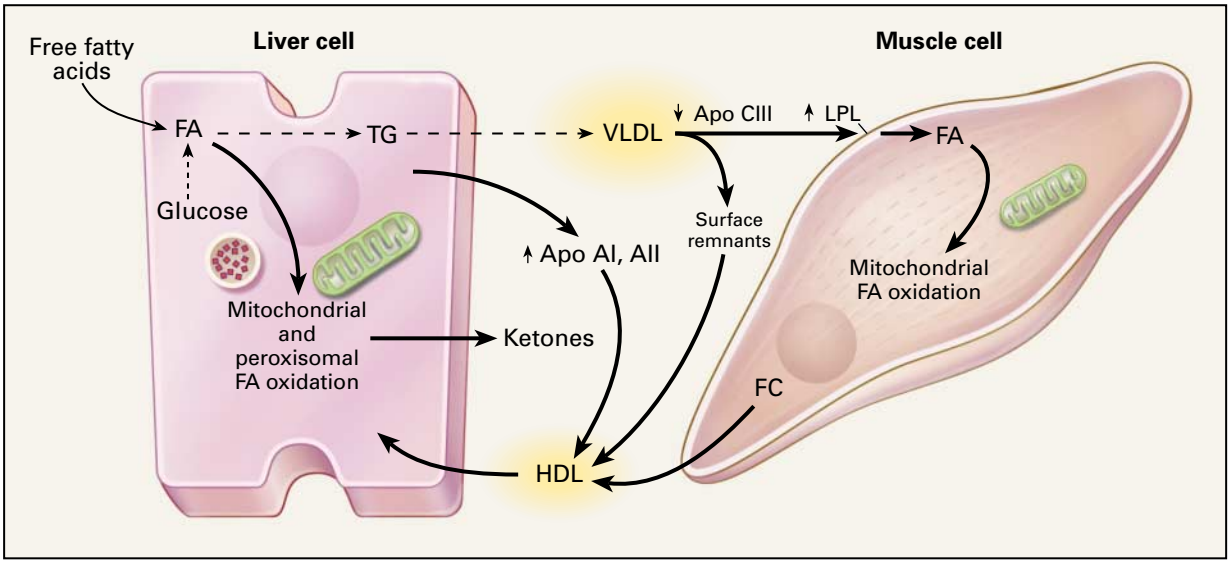

Figure 5. Metabolic Effects of Fibrates.

Bold lines indicate increased transport, and dashed lines diminished transport. Fibrates enhance the oxidation of fatty acids (FA) in liver and muscle and reduce the rate of lipogenesis in the liver, thereby reducing hepatic secretion of very-low-density lipoprotein (VLDL) triglycerides (TG). The increased uptake of triglyceride-derived fatty acids in muscle cells results from an increase in lipoprotein lipase (LPL) activity in adjacent capillaries and a decrease in the apolipoprotein CIII (Apo CIII) concentration mediated transcriptionally by peroxisome proliferator-activated receptor α (PPARα). The decrease in apolipoprotein CIII reduces the inhibition of LPL activity. The enhanced catabolism of VLDL generates surface remnants, which are transferred to high-density lipoprotein (HDL). HDL concentrations are further augmented by an increase in PPARα-mediated transcription of apolipoprotein AI (Apo AI) and apolipoprotein AII (Apo AII). Ultimately, the rate of HDL-mediated reverse cholesterol transport may increase. Fibrates activate PPARα, which binds to a PPARα response element in conjunction with the retinoid X receptor. Other effects of fibrates include an increase in the size of LDL particles, increased removal of LDL, and a reduction in the levels of plasminogen activator inhibitor type I.

lesterol concentrations by about 15 percent.[7,134,135] However, the risk of venous thrombosis doubles or triples,[135,136] and there is no overall reduction in the risk of recurrence of coronary disease among women.[136] Women with serum triglyceride concentrations above 300 mg per deciliter (3.4 mmol per liter) should be treated with transdermal estrogen. Rarely, an anabolic steroid such as oxandrolone or stanozolol is used to reduce the hepatic secretion of triglycerides.[137] In patients with severe hypercholesterolemia, apheresis with dextran sulfate can be used to trap lipoproteins containing apoprotein B.[138]

CONCLUSIONS

Patients with severe hypertriglyceridemia are best treated with diet and a fibrate, alone or in combination with nicotinic acid, n−3 fatty acids, possibly a statin, or as a last resort, an anabolic steroid, to prevent pancreatitis. The presence of hypertriglyceridemia with low serum LDL cholesterol concentrations may not be associated with atherosclerosis. If a patient has vascular disease of any type or a family history of vascular disease, treatment is the same as for familial combined hyperlipidemia (Table 1).

Among patients with familial combined hyperlipidemia, the most appropriate treatment depends on the findings at presentation. Patients with the hypertriglyceridemic form should be treated first with diet and then nicotinic acid, and those with the hypercholesterolemic form should receive dietary therapy and a statin. The most effective therapy in patients with elevations of both serum LDL cholesterol and triglycerides is the combination of nicotinic acid (up to 2000 mg daily) and a statin with dietary therapy. If plain or timed-release nicotinic acid must be discontinued because of adverse effects, a fibrate can be given alone or in combination with a statin. This combination, however, increases the risk of myopathy. Treatment with both nicotinic acid and fibrate causes a shift in the form of LDL from small, dense particles to large, buoyant particles, an effect that is potentially beneficial in patients with combined hyperlipidemia.[43]

Fibrates are the most appropriate treatment for patients with remnant removal disease since these drugs curb the overproduction of VLDL. Such patients are often very sensitive to diet and exercise as well. A statin given in combination with a fibrate increases the removal of remnant lipoproteins. Nicotinic acid can also be given in combination with or

as an alternative to a fibrate. Of all the hyperlipidemic disorders, remnant removal disease is the most responsive to drug therapy, as it is to dietary therapy, but the use of drugs in combination is required for best results.

Patients with polygenic or heterozygous familial hypercholesterolemia should be given a statin and placed on the Step II diet. A bile-acid–binding resin can be added to lower the serum LDL cholesterol concentration further. If the serum HDL cholesterol concentration is low, nicotinic acid is the preferred second drug. All three drugs are often required in patients with heterozygous familial hypercholesterolemia.

Patients with hypoalphalipoproteinemia, who have low serum HDL cholesterol concentrations, have a variable response to weight loss, exercise, diet, and lipid-lowering drugs. In patients with hypertriglyceridemia, serum HDL cholesterol concentrations almost always increase as serum triglyceride concentrations fall. Nicotinic acid usually increases serum HDL cholesterol concentrations by 30 percent, fibrates by 10 to 15 percent, statins by 5 to 10 percent, and bile-acid–binding resins by 1 to 2 percent, supporting the rationale for combined drug therapy. Patients who have low serum HDL cholesterol concentrations in isolation probably should not be treated unless they have other risk factors for atherosclerosis, existing heart disease, or a family history of heart disease.

Cardiovascular disease accounts for nearly 50 percent of all deaths in the United States. Clinical trials and pathophysiological evidence support the use of aggressive therapy in patients with arteriosclerotic vascular disease and in those with several risk factors for the disease. Combination therapy with lipid-lowering drugs is advisable, especially in patients with combined hyperlipidemia.

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REFERENCES

1. Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. N Engl J Med 1998;339:861-7.
2. Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Bureau of Disease Study. Lancet 1997;349:1269-76.
3. Mortality statistics. In: Center for Health Statistics. Washington State Heart Disease and Stroke Prevention Plan. Olympia: Washington State Department of Health, 1995:1.
4. White AA. Mapping and geographic display of data. Stat Med 1995;14: 697-9.
5. Levine GN, Keaney JF Jr, Vita JA. Cholesterol reduction in cardiovascular disease: clinical benefits and possible mechanisms. N Engl J Med 1995;332:512-21.
6. Williams KJ, Tabas I. The response-to-retention hypothesis of early atherogenesis. Arterioscler Thromb Vasc Biol 1995;15:551-61.
7. Knopp RH, Zhu X-D, Bonet B. Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. Atherosclerosis 1994;110: Suppl:S83-S91.
8. Rapp JH, Lespine A, Hamilton RL, et al. Triglyceride-rich lipoproteins isolated by selected-affinity anti-apolipoprotein B immunosorption from human atherosclerotic plaque. Arterioscler Thromb 1994;14:1767-74.
9. Coresh J, Kwiterovich PO Jr. Small, dense low-density lipoprotein particles and coronary heart disease risk: a clear association with uncertain implications. JAMA 1996;276:914-5.
10. Oram JF, Yokoyama S. Apolipoprotein-mediated removal of cellular cholesterol and phospholipids. J Lipid Res 1996;37:2473-91.
11. Fielding CJ, Fielding PE. Molecular physiology of reverse cholesterol transport. J Lipid Res 1995;36:211-28.
12. Knopp RH. The effects of oral contraceptives and postmenopausal estrogens on lipoprotein physiology and atherosclerosis. In: Halbe HW, Rekers H, eds. Oral contraception into the 1990s. Carnforth, England: Parthenon Publishing, 1989:31-45.
13. Chait A, Albers JJ, Brunzell JD. Very low density lipoprotein overproduction in genetic forms of hypertriglyceridaemia. Eur J Clin Invest 1980; 10:17-22.
14. Ginsberg HN. Is hypertriglyceridemia a risk factor for atherosclerotic cardiovascular disease? A simple question with a complicated answer. Ann Intern Med 1997;126:912-4.
15. Brunzell JD. Familial lipoprotein lipase deficiency and other causes of the chylomicronemia syndrome: In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic bases of inherited disease. 7th ed. Vol. 2. New York: McGraw-Hill, 1995:1913-32.
16. Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622-30.
17. Hokanson JE, Austin MA, Zambon A, Brunzell JD. Plasma triglyceride and LDL heterogeneity in familial combined hyperlipidemia. Arterioscler Thromb 1993;13:427-34.
18. Goldstein JL, Schrott HG, Hazzard WR, Bierman EL, Motulsky A. Hyperlipidemia in coronary heart disease: genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. J Clin Invest 1973;52:1544-68.
19. Ginsburg HN, Goldberg IJ. Disorders of lipoprotein metabolism. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., eds. Harrison's principles of internal medicine. 14th ed. Vol. 2. New York: McGraw-Hill, 1998:2138-49.
20. Havel RJ, Rapaport E. Management of primary hyperlipidemia. N Engl J Med 1995;332:1491-8. [Erratum, N Engl J Med 1995;333:467.]
21. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 1993;269:3015-23.
22. Maher VMG, Brown BG, Marcovina SM, Hillger LA, Zhao X-Q, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). JAMA 1995;274:1771-4.
23. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998;338:1042-50.
24. Chambless LE, Fuchs FD, Linn S, et al. The association of corneal arcus with coronary heart disease and cardiovascular disease mortality in the Lipid Research Clinics Mortality Follow-up Study. Am J Public Health 1990;80:1200-4.
25. Diaz MN, Frei B, Vita JA, Keaney JF Jr. Antioxidants and atherosclerotic heart disease. N Engl J Med 1997;337:408-16.
26. Bachmaier K, Neu N, de la Maza LM, Pal S, Hessel A, Penninger JM. Chlamydia infections and heart disease linked through antigenic mimicry. Science 1999;283:1335-9.
27. Stone NJ. Secondary causes of hyperlipidemia. Med Clin North Am 1994;78:117-41.
28. Brunzell JD, Bierman EL. Chylomicronemia syndrome: interaction of genetic and acquired hypertriglyceridemia. Med Clin North Am 1982;66: 455-68.
29. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med 1997;336:153-62. [Erratum, N Engl J Med 1997;337:1859.]
30. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987;257:3233-40. [Erratum, JAMA 1987;259:2698.]
31. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323:1289-98.
32. American Diabetes Association. Management of dyslipidemia in adults with diabetes. Diabetes Care 1999;22:Suppl 1:S56-S59.
33. Haffner SM, Lehto S, Rönnemaa T, Pyörala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondi-

abetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
34. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
35. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1301-7.
36. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001-9.
37. Sacks FM, Moyé LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. Circulation 1998;97:1446-52.
38. The West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998;97:1440-5.
39. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453-60.
40. Grundy SM. Statin trials and goals of cholesterol-lowering therapy. Circulation 1998;97:1436-9.
41. Lipid Metabolism Branch, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute. The Lipid Research Clinics population studies data book. Vol. 1. The Prevalence Study: aggregate distribution of lipids, lipoproteins and selected variables in 11 North American populations. Bethesda, Md.: National Institutes of Health, 1980:1-136.
42. Assmann G, Schulte H. Relation of high-density lipoprotein cholesterol and triglycerides to incidence of atherosclerotic coronary artery disease (the PROCAM experience): Prospective Cardiovascular Munster Study. Am J Cardiol 1992;70:733-7.
43. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. JAMA 1996;276:882-8.
44. Knopp RH, Walden CE, Retzlaff BM, et al. Long-term cholesterol-lowering effects of 4 fat-restricted diets in hypercholesterolemic and combined hyperlipidemic men: the Dietary Alternatives Study. JAMA 1997; 278:1509-15.
45. Walden CE, Retzlaff BM, Buck BL, McCann BS, Knopp RH. Lipoprotein lipid response to the National Cholesterol Education Program Step II diet by hypercholesterolemic and combined hyperlipidemic women and men. Arterioscler Thromb Vasc Biol 1997;17:375-82.
46. Denke MA. Cholesterol-lowering diets: a review of the evidence. Arch Intern Med 1995;155:17-26.
47. Labarthe DR. Dietary fiber: further epidemiological support for a high-intake dietary pattern. Circulation 1996;94:2696-8.
48. Retzlaff BM, Walden CE, McNeney WB, Buck BL, McCann BS, Knopp RH. Nutritional intake of women and men on the NCEP Step I and Step II diets. J Am Coll Nutr 1997;16:52-61.
49. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779-85.
50. Davignon J, Montigny M, Dufour R. HMG-CoA reductase inhibitors: a look back and a look ahead. Can J Cardiol 1992;8:843-64.
51. Mabuchi H, Haba T, Tatami R, et al. Effects of an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase on serum lipoproteins and ubiquinone-10 levels in patients with familial hypercholesterolemia. N Engl J Med 1981;305:478-82.
52. Mabuchi H, Sakai T, Sakai Y, et al. Reduction of serum cholesterol in heterozygous patients with familial hypercholesterolemia: additive effects of compactin and cholestyramine. N Engl J Med 1983;308:609-13.
53. Bilheimer DW, Grundy SM, Brown MS, Goldstein JL. Mevinolin and colestipol stimulate receptor-mediated clearance of low-density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Proc Natl Acad Sci U S A 1983;80:4124-8.
54. Arad Y, Ramakrishnan R, Ginsberg HN. Effects of lovastatin therapy on very-low-density lipoprotein triglyceride metabolism in subjects with combined hyperlipidemia: evidence for reduced assembly and secretion of triglyceride-rich lipoproteins. Metabolism 1992;41:487-93.
55. Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation 1995;92: 2419-25.
56. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol per liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. Am J Cardiol 1993;72:1031-7.
57. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279:1615-22.
58. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
59. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. Arch Intern Med 1997;157: 1305-10.
60. Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke: a meta-analysis of randomized, controlled trials. Ann Intern Med 1998;128:89-95.
61. Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. Ann Pharmacother 1995;29:743-59.
62. The Pravastatin Multicenter Study Group II. Comparative efficacy and safety of pravastatin and cholestyramine alone and combined in patients with hypercholesterolemia. Arch Intern Med 1993;153:1321-9.
63. Physicians' desk reference. Montvale, N.J.: Medical Economics, 1999.
64. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. JAMA 1996;275:128-33.
65. Davidson MH, Stein EA, Dujovne CA, et al. The efficacy and six-week tolerability of simvastatin 80 and 160 mg per day. Am J Cardiol 1997;79: 38-42.
66. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. Lancet 1996;348:1079-82. [Erratum, Lancet 1997; 349:214.]
67. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. JAMA 1998;279:1643-50.
68. McPherson R, Tsoukas C, Baines MG, et al. Effects of lovastatin on natural killer cell function and other immunological parameters in man. J Clin Immunol 1993;13:439-44.
69. Kobashigawa JA, Katznelson S, Laks H, et al. Effect of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621-7.
70. Llorente-Cortés V, Martínez-González J, Badimon L. Esterified cholesterol accumulation induced by aggregated LDL uptake in human vascular smooth muscle cells is reduced by HMG-CoA reductase inhibitors. Arterioscler Thromb Vasc Biol 1998;18:738-46.
71. Cignarella A, Brennhausen B, von Eckardstein A, Assmann G, Cullen P. Differential effects of lovastatin on the trafficking of endogenous and lipoprotein-derived cholesterol in human monocyte-derived macrophages. Arterioscler Thromb Vasc Biol 1998;18:1322-9.
72. Colli S, Eligini S, Lalli M, Camera M, Paoletti R, Tremoli E. Vastatins inhibit tissue factor in cultured human macrophages: a novel mechanism of protection against atherothrombosis. Arterioscler Thromb Vasc Biol 1997; 17:265-72.
73. Kaesemeyer WH, Caldwell RB, Huang J, Caldwell RW. Pravastatin sodium activates endothelial nitric oxide synthase independent of its cholesterol-lowering actions. J Am Coll Cardiol 1999;33:234-41.
74. Jahn CE, Schaefer EJ, Taam LA, et al. Lipoprotein abnormalities in primary biliary cirrhosis: association with hepatic lipase inhibition as well as altered cholesterol esterification. Gastroenterology 1985;89:1266-78.
75. Travia D, Tosi F, Negri C, Faccini G, Moghetti P, Muggeo M. Sustained therapy with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors does not impair steroidogenesis by adrenals and gonads. J Clin Endocrinol Metab 1995;80:836-40.
76. Abramowicz M, editor. Choice of lipid-lowering drugs. Med Lett 1996;38:67-70.
77. Vgontzas AN, Kales A, Bixler EO, Manfredi RL, Tyson KL. Effects of lovastatin and pravastatin on sleep efficiency and sleep stage. Clin Pharmacol Ther 1991;50:730-7.
78. Roth T, Richardson GR, Sullivan JP, Lee RM, Merlotti L, Roehrs T. Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. Clin Cardiol 1992;15:426-32.
79. Partinen M, Pihl S, Strandberg T, et al. Comparison of effects on sleep of lovastatin and pravastatin in hypercholesterolemia. Am J Cardiol 1994; 73:876-80.
80. deVries ACJ, Cohen LH. Different effects of the hypolipidemic drugs pravastatin and lovastatin on the cholesterol biosynthesis of the human ocular lens in organ culture and on the cholesterol content of the rat lens in vivo. Biochim Biophys Acta 1993;1167:63-9.
81. Laties AM, Keates EU, Taylor HR, et al. The human lens after 48 weeks of treatment with lovastatin. N Engl J Med 1990;323:683-4.
82. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med 1991;151:43-9.

83. Hanston PD, Horn JR. Drug interactions with HMG CoA reductase inhibitors. Drug Interactions Newsletter 1998:103-6. (Vancouver, Wa.: Applied Therapeutics.)
84. Illingworth DR, Tobert JA. A review of clinical trials comparing HMG-CoA reductase inhibitors. Clin Ther 1994;16:366-85.
85. Leitersdorf E, Muratti EN, Eliav O, et al. Efficacy and safety of a combination fluvastatin-bezafibrate treatment for familial hypercholesterolemia: comparative analysis with a fluvastatin-cholestyramine combination. Am J Med 1994;96:401-7.
86. Wiklund O, Angelin B, Bergman M, et al. Pravastatin and gemfibrozil alone and in combination for the treatment of hypercholesterolemia. Am J Med 1993;94:13-20.
87. Feher MD, Foxton J, Banks D, Lant AF, Wray R. Long-term safety of statin-fibrate combination treatment in the management of hypercholesterolaemia in patients with coronary artery disease. Br Heart J 1995;74: 14-7.
88. Smit JWA, Jansen GH, de Bruin TWA, Erkelens DW. Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in combination, does not induce muscle damage. Am J Cardiol 1995;76: 126A-128A.
89. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264:71-5.
90. Arad Y, Ramakrishnan R, Ginsberg HN. Lovastatin therapy reduces low density lipoprotein apoB levels in subjects with combined hyperlipidemia by reducing the production of apoB-containing lipoproteins: implications for the pathophysiology of apoB production. J Lipid Res 1990;31: 567-82.
91. Broyles FE, Walden CE, Hunninghake DB, Hill-Williams D, Knopp RH. Effect of fluvastatin on intermediate density lipoprotein (remnants) and other lipoprotein levels in hypercholesterolemia. Am J Cardiol 1995; 72:129A-135A.
92. Knopp RH, Walden CE, Heiss G, Johnson JL, Wahl PW. Prevalence and clinical correlates of beta-migrating very-low-density lipoprotein: Lipid Research Clinics Program Prevalence Study. Am J Med 1986;81:493-502.
93. Vega GL, East C, Grundy SM. Lovastatin therapy in familial dysbetalipoproteinemia: effects on kinetics of apolipoprotein B. Atherosclerosis 1988;70:131-43.
94. Knopp RH, Frohlich J, Jokubaitis LA, Dawson K, Broyles FE, Gomez-Coronado D. Efficacy and safety of fluvastatin in patients with non-insulin-dependent diabetes mellitus and hyperlipidemia. Am J Med 1994; 96:69S-78S.
95. Vega GL, Grundy SM. Lovastatin therapy in nephrotic hyperlipidemia: effects on lipoprotein metabolism. Kidney Int 1988;33:1160-8.
96. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351-64.
97. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365-74.
98. Packard CJ, Shepherd J. The hepatobiliary axis and lipoprotein metabolism: effects of bile acid sequestrants and ileal bypass surgery. J Lipid Res 1982;23:1081-98.
99. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. Arch Biochem Biophys 1955;54:558-9.
100. Knopp RH, Ginsberg J, Albers JJ, et al. Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. Metabolism 1985;34:642-50.
101. Grundy SM, Mok HYI, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. J Lipid Res 1981;22:24-36.
102. Knopp RH, Alagona P, Davidson M, et al. Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night vs. plain niacin in the management of hyperlipidemia. Metabolism 1998;47:1097-104.
103. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990;264:3007-12.
104. Carlson LA, Rosenhamer G. Reduction of mortality in the Stockholm Ischaemic Heart Disease Secondary Prevention Study by combined treatment with clofibrate and nicotinic acid. Acta Med Scand 1988;223:405-18.
105. Clofibrate and niacin in coronary heart disease. JAMA 1975;231: 360-81.
106. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol 1986;8:1245-55.
107. Davignon J, Roederer G, Montigny M, et al. Comparative efficacy and safety of pravastatin, nicotinic acid and the two combined in patients with hypercholesterolemia. Am J Cardiol 1994;73:339-45.
108. Stein EA, Davidson MH, Dujovne CA, et al. The efficacy and tolerability of low dose simvastatin and niacin, alone and in combination, in patients with combined hyperlipidemia: a prospective trial. J Cardiovasc Pharmacol Ther 1996;1:107-16.
109. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol: a meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213-9.
110. McKenney JM, Proctor JD, Harris S, Chinchili VM. A comparison of the efficacy and toxic effects of sustained- vs. immediate-release niacin in hypercholesterolemic patients. JAMA 1994;271:672-7.
111. Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia: a prospective trial. Arch Intern Med 1994;154:1586-95.
112. Ide T, Oku H, Sugano M. Reciprocal responses to clofibrate in ketogenesis and triglyceride and cholesterol secretion in isolated rat liver. Metabolism 1982;31:1065-72.
113. Nikkilä EA, Huttunen JK, Ehnholm C. Effect of clofibrate on postheparin plasma triglyceride lipase activities in patients with hypertriglyceridemia. Metabolism 1977;26:179-86.
114. Auwerx J, Schoonjans K, Fruchart J-C, Staels B. Transcriptional control of triglyceride metabolism: fibrates and fatty acids change the expression of the LPL and apo C-III genes by activating the nuclear receptor PPAR. Atherosclerosis 1996;124:Suppl:S29-S37.
115. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart J-C. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation 1998;98:2088-93.
116. Knopp RH, Brown WV, Dujovne CA, et al. Effects of fenofibrate on plasma lipoproteins in hypercholesterolemia and combined hyperlipidemia. Am J Med 1987;83:50-9.
117. de Graaf J, Hendriks JC, Demacker PN, Stalenhoef AF. Identification of multiple dense LDL subfractions with enhanced susceptibility to in vitro oxidation among hypertriglyceridemic subjects: normalization after clofibrate treatment. Arterioscler Thromb 1993;13:712-9.
118. Jen S-L, Chen J-W, Lee W-L, Wang S-P. Efficacy and safety of fenofibrate or gemfibrozil on serum lipid profiles in Chinese patients with type IIb hyperlipidemia: a single-blind, randomized, and cross-over study. Chung Hua I Hsueh Tsa Chih (Taipei) 1997;59:217-24.
119. Brown WV, Dujovne CA, Farquhar WJ, et al. Effects of fenofibrate on plasma lipids: double-blind, multicenter study in patients with type IIA or IIB hyperlipidemia. Arteriosclerosis 1986;6:670-8.
120. Knopp RH, Walden CE, Warnick GR, Albers JJ, Ginsberg J, McGinnis BM. Effect of fenofibrate treatment on plasma lipoprotein lipid, high-density lipoprotein cholesterol subfractions, and apolipoproteins B, AI, AII, and E. Am J Med 1998;83:75-84.
121. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety in treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987;317:1237-45.
122. Rubins H. The Veterans Affairs HDL Intervention Trial (VA-HIT). Presented at plenary session XII of the 71st Annual Meeting of the American Heart Association, Dallas, November 11, 1998.
123. Ferguson JJ. Highlights of the 71st scientific sessions of the American Heart Association. Circulation 1999;99:2486-91.
124. Abramowicz M, editor. Choice of lipid-lowering drugs. Med Lett 1998;40:117-22.
125. The Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978;40:1069-118.
126. Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, de Faire U. Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. Lancet 1996;347:849-53.
127. Frick MH, Syvanne M, Nieminen MS, et al. Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Circulation 1997;96:2137-43.
128. Schonfeld G. The effects of fibrates on lipoprotein and hemostatic coronary risk factors. Atherosclerosis 1994;111:161-74.
129. The Coronary Drug Project Research Group. Gallbladder disease as a side effect of drugs influencing lipid metabolism: experience in the Coronary Drug Project. N Engl J Med 1977;296:1185-90.
130. Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WC. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. JAMA 1996;275:447-51.
131. Truswell AS. Dietary fibre and plasma lipids. Eur J Clin Nutr 1995; 49:Suppl 3:S105-S109.
132. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. N Engl J Med 1995;333:1308-12.
133. Rambjor GS, Wålen AI, Windsor SL, Harris WS. Eicosapentaenoic

acid is primarily responsible for hypotriglyceridemic effect of fish oil in humans. Lipids 1996;31:Suppl:S45-S49.
134. Knopp RH, Zhu X-D, Lau J, Walden CE. Sex hormones and lipid interactions: implications for cardiovascular disease in women. The Endocrinologist 1994;4:286-301.
135. Knopp RH. Estrogen, female gender, and heart disease. In: Topol E, ed. Textbook of cardiovascular medicine. Philadelphia: Lippincott-Raven, 1998:195-218.
136. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280:605-13.
137. Albers JJ, Taggart HM, Applebaum-Bowden D, Haffner S, Chesnut CH III, Hazzard WR. Reduction of lecithin-cholesterol acyltransferase, apolipoprotein D and the Lp(a) lipoprotein with the anabolic steroid stanozolol. Biochim Biophys Acta 1984;795:293-6.
138. Mabuchi H, Koizumi J, Shimizu M, et al. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Am J Cardiol 1998;82:1489-95.