

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***DRUG TREATMENT OF LIPID DISORDERS**

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**A**RTERIOSCLEROSIS of the coronary and peripheral vasculature is the leading cause of death among men and women in the United States<sup>1</sup> and worldwide.<sup>2</sup> 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<sup>3</sup>; nationwide, the mortality rate for cardiovascular disease is approximately 50 percent.<sup>4</sup>

**MECHANISMS OF ATHEROGENESIS**

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

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

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

**SECONDARY CAUSES OF HYPERLIPIDEMIA**

Closely related to the numerous risk factors for cardiovascular disease are conditions that cause hyperlipidemia,<sup>27</sup> 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,  $\beta$ -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.<sup>19,20,28</sup>

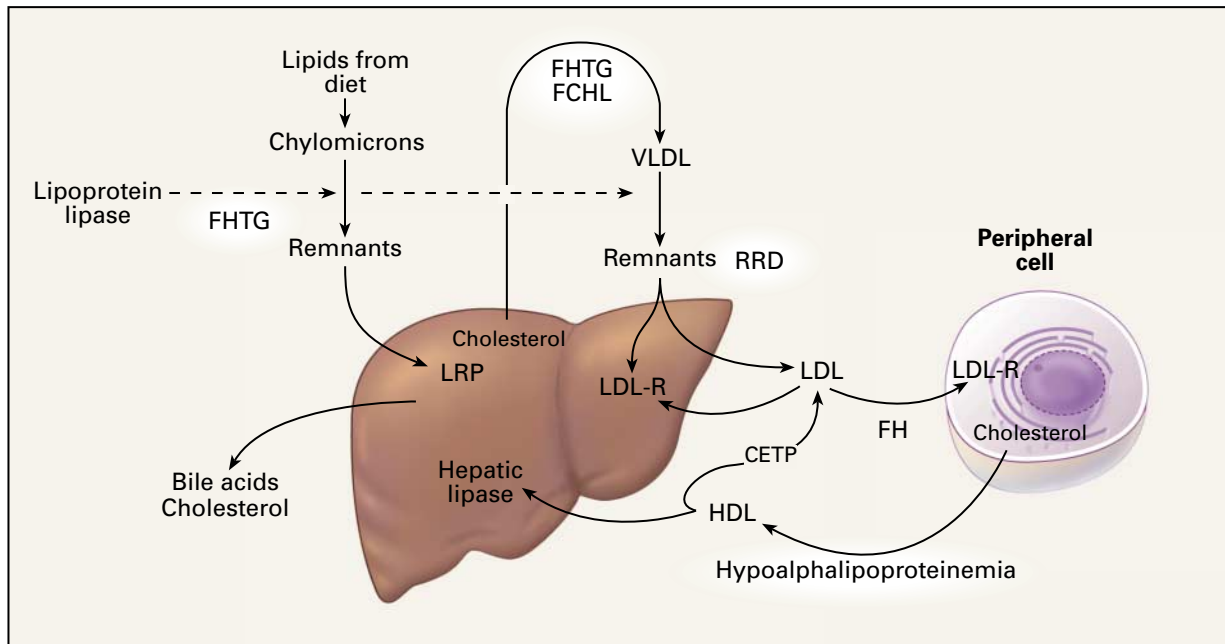
**TARGET SERUM LIPOPROTEIN CONCENTRATIONS**

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).<sup>21</sup> 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).<sup>21,29-31</sup> Persons with diabetes also fall in this third category, even those with no apparent cardiovascular disease.<sup>21,32,33</sup> Reducing serum LDL cholesterol concentrations below the target levels does not necessarily result in a proportional reduction in the risk of cardiovascular disease,<sup>34-39</sup> because of the attenuation of the cholesterol-heart disease relation at lower serum cholesterol concentrations.<sup>40</sup> 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.<sup>21</sup> 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)<sup>41</sup> 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.<sup>21</sup> 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-

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**Figure 1.** Pathways of Lipid Transport.

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

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

liter (6.2 mmol per liter) or the ratio of serum LDL cholesterol to HDL cholesterol exceeds 5:1.<sup>42,43</sup> 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.<sup>41</sup>

#### 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,<sup>21</sup> 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 con-

tains 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.<sup>44-46</sup> In addition, diet can help to reduce weight to an ideal level, increase the intake of vitamins, and reduce blood pressure and insulin resistance.<sup>44-48</sup> 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.<sup>44</sup> 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.<sup>49</sup>

#### 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 ( $\epsilon_2/\epsilon_2$ ) or heterozygosity ( $\epsilon_2/\epsilon_3$ or $\epsilon_2/\epsilon_4$ ) for apolipoprotein E $\epsilon_2$	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 ( $\geq 45$ 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 ( $\geq 50$ th 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,<sup>21</sup> Maher et al.,<sup>22</sup> Welch and Loscalzo,<sup>23</sup> Chambless et al.,<sup>24</sup> Diaz et al.,<sup>25</sup> and Bachmaier et al.<sup>26</sup> 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.<sup>50</sup> These drugs lower serum LDL cholesterol concentrations<sup>51,52</sup> by up-regulating LDL-receptor activity as well as reducing the entry of LDL into the circulation.<sup>50,53,54</sup> 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<sup>34-36,55-58</sup> and reduce the risk of death from any cause by about 30 percent.<sup>35,56,58</sup> 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.<sup>31,34-36,38,55-60</sup>

**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

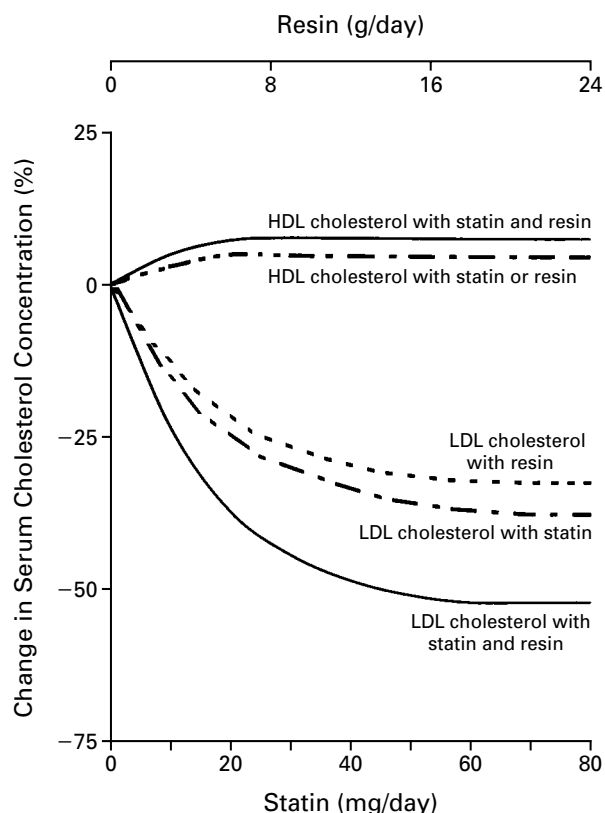
**TABLE 4.** CHARACTERISTICS OF STATINS.\*

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.<sup>61</sup> 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.<sup>62</sup> 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.<sup>63</sup> Reductions in LDL cholesterol of 30 to 32 percent are more typical of once-daily treatment with lovastatin<sup>63</sup> and twice-daily treatment with pravastatin.<sup>62</sup>



**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.<sup>62</sup>

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

All the statins lower serum triglyceride concentrations, with atorvastatin<sup>64</sup> and simvastatin<sup>65</sup> having the greatest effect. In general, the higher the base-line serum triglyceride concentration, the greater the decrease induced by statin therapy.<sup>65</sup> 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<sup>66,67</sup> include decreased fibrinogen levels and viscosity,<sup>66</sup> increased immune tolerance after transplantation,<sup>68,69</sup> diminished uptake of aggregated LDL by vascular smooth-muscle cells,<sup>70</sup> increased free cholesterol and decreased cholesterol ester concentrations within macrophages,<sup>71</sup> suppression of the release of tissue factor,<sup>72</sup> and activation of endothelial nitric oxide synthase.<sup>73</sup>

### 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.<sup>61</sup> 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.<sup>61,74</sup> 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.<sup>75</sup>

### 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).<sup>76-79</sup> 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.<sup>80,81</sup>

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.<sup>82</sup> 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).<sup>83</sup> 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.<sup>83</sup>

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
<b>Statins</b>	
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)
<b>Bile-acid-binding resins</b>	
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
<b>Nicotinic acid</b>	
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
<b>Fibrates</b>	
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<sup>76</sup> and *Physicians' Desk Reference*.<sup>65</sup>

**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, sulfapyrazone, ticlopidine, zafirlukast
Induces cytochrome P-450 2C9	May lower serum fluvastatin concentrations	Barbiturates, carbamazepine, phenytoin, primidone, rifampin

\*Data obtained from *Physicians' Desk Reference*<sup>65</sup> and Hanston and Horn.<sup>83</sup> Common substrates have been described previously in detail.<sup>83</sup>

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.<sup>82</sup>

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.<sup>84-88</sup> 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.<sup>89</sup> 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,<sup>82</sup> but it is higher among patients who are also taking cyclosporine or erythromycin.<sup>84</sup>

#### 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.<sup>53</sup> They also reduce the formation of apolipoprotein B-containing lipoproteins and their entry into the circulation<sup>50,54,90</sup> and can reduce high serum concentrations of triglycerides and remnant lipoproteins.<sup>64,91-93</sup> As a result, statin therapy is also indicated in patients with combined or familial combined hyperlipidemia, remnant removal disease, and the hyperlipidemia of diabetes<sup>94</sup> and renal failure.<sup>95</sup>

#### 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.<sup>62,96</sup> 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).<sup>62</sup> 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.<sup>96,97</sup> Combination

therapy can potentially reduce the risk of events related to heart disease by more than 50 percent.<sup>31</sup>

#### Adverse Effects

Bile-acid-binding resins cause abdominal fullness, gas, and constipation in 30 percent of patients (Table 5).<sup>62,96,97</sup> 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.<sup>98</sup> 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.<sup>98</sup> 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

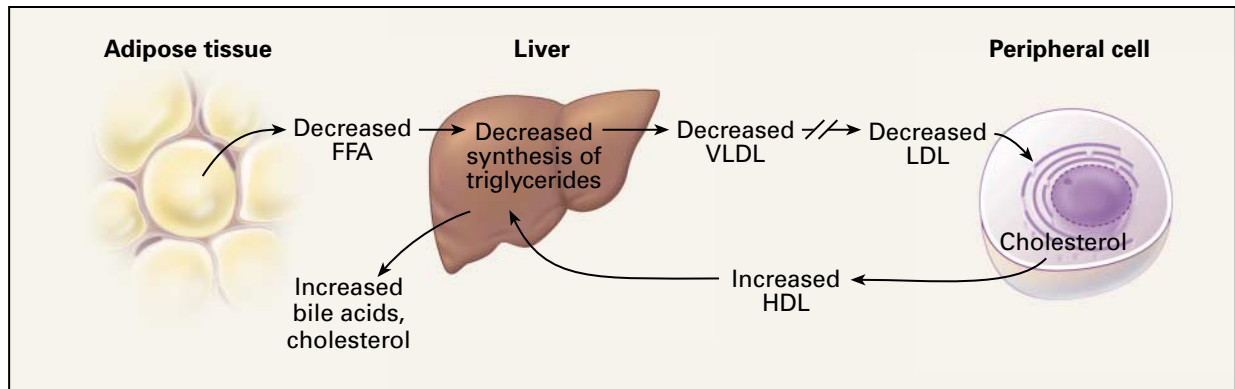
Treatment with bile-acid-binding resins should be restricted to patients who have hypercholesterolemia but not hypertriglyceridemia. This group includes patients with polygenic or heterozygous familial hypercholesterolemia and those with the hypercholesterolemic form of familial combined hyperlipidemia.

#### NICOTINIC ACID

##### Lipid-Altering Effects

The cholesterol-lowering effect of nicotinic acid was first reported in 1955.<sup>99</sup> 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).<sup>100</sup> Nicotinic acid may also inhibit the conversion of VLDL into LDL.<sup>101</sup> 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.<sup>100</sup> 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.<sup>102</sup>

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<sup>30,31,103</sup> or a fibrate.<sup>104</sup> 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.<sup>105,106</sup> 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.<sup>96</sup> 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.<sup>100</sup> with the permission of the publishers.

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

#### 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.

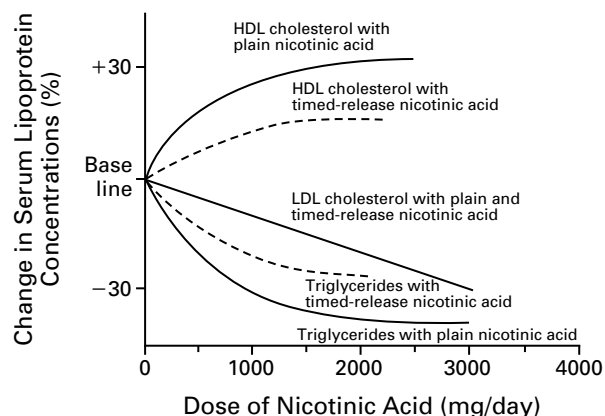
Other adverse effects include conjunctivitis, nasal stuffiness, loose bowel movements or diarrhea, acanthosis nigricans, and ichthyosis (Table 5). Hepatitis is more frequent in patients who are taking nicotinic acid than in those who are taking statins, especially at doses of more than 2000 to 3000 mg 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.<sup>100,102</sup> Other drawbacks of such formulations are hepatotoxicity at doses of 2000 mg per day or higher<sup>100,110</sup> and smaller decreases in serum triglyceride concentrations and smaller increases in serum HDL cholesterol concentrations than are induced with plain nicotinic acid.<sup>100,110</sup> 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.<sup>102</sup>

#### 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).<sup>111</sup> 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)<sup>112</sup> 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.<sup>113</sup> These drugs act by activating the nuclear transcription factor peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ), up-regulating the expression of the LDL cholesterol and apolipoprotein AI genes, and down-regulating the expression of the apolipoprotein CII gene.<sup>114,115</sup>

The fibrates are the most effective triglyceride-lowering drugs.<sup>28</sup> 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.<sup>116</sup> Fibrates also increase the buoyancy of LDL particles, a potentially favorable effect.<sup>117</sup> Fenofibrate, which was recently approved for

use in the United States, may lower serum LDL cholesterol concentrations more effectively than does clofibrate or gemfibrozil.<sup>118-120</sup> 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<sup>121</sup> and in a secondary-prevention trial in men with low serum HDL cholesterol concentrations.<sup>122-124</sup> Treatment with clofibrate produced similar results.<sup>125</sup> Treatment with bezafibrate and gemfibrozil is also associated with regression of coronary artery disease on angiography.<sup>126,127</sup>

### Adverse Effects

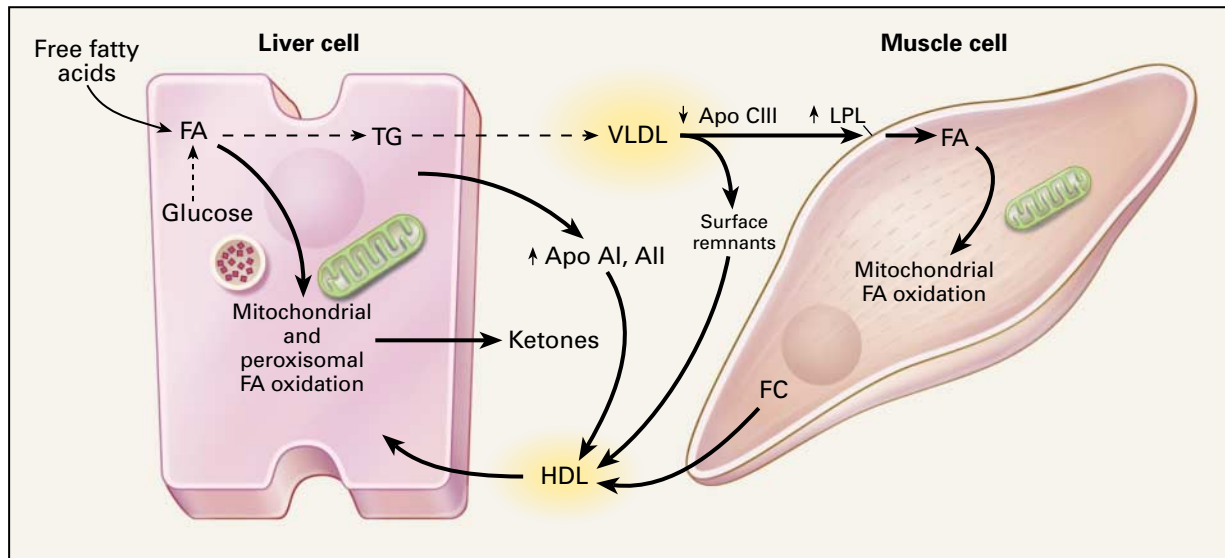
The adverse effects of fibrates are listed in Table 5. Of the three fibrates that are available in the United States, clofibrate and fenofibrate cause fewer gastrointestinal symptoms than gemfibrozil. Other adverse effects include erectile dysfunction, especially in men treated with clofibrate, and myositis 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.<sup>128</sup> 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.<sup>125,128,129</sup> 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.<sup>125</sup> There was no increase in the risk of death or cancer among patients who were treated with clofibrate in another study<sup>105</sup> or among those who received gemfibrozil.<sup>121</sup>

### 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.<sup>130,131</sup> Sitostanol, a plant sterol incorporated into margarine, inhibits gastrointestinal absorption of cholesterol.<sup>132</sup> 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.<sup>133</sup> 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  $\alpha$  (PPAR $\alpha$ ). 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 PPAR $\alpha$ -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 PPAR $\alpha$ , which binds to a PPAR $\alpha$  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.<sup>7,134,135</sup> However, the risk of venous thrombosis doubles or triples,<sup>135,136</sup> and there is no overall reduction in the risk of recurrence of coronary disease among women.<sup>136</sup> 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.<sup>137</sup> In patients with severe hypercholesterolemia, apheresis with dextran sulfate can be used to trap lipoproteins containing apoprotein B.<sup>138</sup>

### 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 hyperlip-

idemia, 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.<sup>43</sup>

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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