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THE PHARMACOLOGICAL TREATMENT OF DYSLIPIDEMIA

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INTRODUCTION

This review discusses the drugs and other substances used to treat abnormal blood lipid levels (dyslipidemia) in order to retard arteriosclerosis. The relationship between dyslipidemia and morbidity and/or mortality from arteriosclerotic cardiovascular disease (ASCVD) has long been established (1–4). More recently the results of primary prevention trials with a variety of drugs have shown that correction of primary dyslipidemia decreases the incidence of disease or death from ASCVD (5–8). In addition, pharmacotherapeutic intervention in dyslipidemia can arrest the progression of preexisting, clinically evident, or surgically corrected ASCVD (9, 10). The reader is referred to other recent reviews of this topic for additional information (11–16).

PRIMARY DYSIPLIDEMIAS

Alterations in normal lipoprotein metabolism lead to a variety of dyslipidemic states (Table 1). Most are associated with abnormally high levels of serum total cholesterol (TC) which are usually a reflection of increased concentrations of low-density lipoprotein cholesterol (LDLC) which accounts for 60–70% of the total cholesterol level. Thus, it is most common to see a direct correlation between hypercholesterolemia, elevated LDLC levels, and ASCVD. However, many patients with premature coronary heart disease have "normal" or borderline high-serum cholesterol levels but low levels of

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high-density lipoprotein cholesterol (HDLC) (17). This condition, referred to as relative hypercholesterolemia, is commonly observed in patients with isolated hypertriglyceridemia (18), which produces a high ratio of LDLC to HDLC. It has also been associated with enhanced rates of atherogenesis. In such cases, reductions of LDLC levels should be pursued to lower the LDLC/HDLC ratio, despite seemingly borderline or normal total cholesterol levels. On the other hand, hypercholesterolemia resulting from an isolated elevation in HDLC would not warrant therapeutic intervention. We therefore elected to use the term "dyslipidemia" rather than "hyperlipidemia" when referring to alterations in serum lipoprotein levels that predispose to atherosclerosis.

Most hypercholesterolemic dyslipidemias are attibutable to defects in receptor-mediated catabolism of LDL that are caused by genetic or environmental factors (19). Several hypertriglyceridemic conditions result from the oversecretion of triglycerides (TG) by the liver or the inability to remove triglyceride-rich lipoproteins. The one most clearly associated with an increased rate of ASCVD is dysbetalipoproteinemia which is caused by the failure to remove very low-density lipoprotein (VLDL) remnant particles (also called intermediate density lipoproteins (IDL)) from the serum (20). A classification of the primary dyslipidemias, a description of their characteristic serum-lipoprotein patterns, and the drugs most commonly used in their treatment are shown in Table I.

SECONDARY DYSLIPIDEMIAS

These are lipoprotein abnormalities associated with metabolic or endocrine disorders such as diabetes mellitus, hypothyroidism, obesity, and kidney disease. Treatment of the first two disorders favorably influences lipoprotein levels (see below). Obesity (21) and excessive alcohol intake (22) frequently cause oversecretion of VLDL particles that leads to hypertriglyceridemia. This condition usually normalizes with weight loss or abstinence from alcohol, respectively. Dyslipidemic patients with renal insufficienty who undergo frequent hemodialysis may improve if orally supplemented with carnitine, which is reduced because it is removed in dialysis.

Another group of secondary dyslipidemias arise as a side effect of drugs used for conditions unrelated to lipoprotein abnormalities. These may be corrected by discontinuing the responsible drug, switching to a therapeutically equivalent alternative without the dyslipidemic effect, or, as a last resort, adding a hypolipidemic drug to counteract the effect. One example of this type of dyslipidemia is that caused by oral thiazide diuretics which may lower HDLC and/or raise triglyceride and LDLC levels in blood (23). A list of nonhypolipidemic drugs known or thought to affect serum lipids is given in Table 2.

Table 1 Primary Dyslipidemias

Disorder	Possible phenotypes	Lipid abnormalities TC	CHYLO	VLDLC	IDLC	LDLC	HDLC	Tgs	Most commonly used drugs*
Primary hyperchylomicronemia	Type I		↑ ↑ ↑					↑ ↑ ↑	- - - -
Familial or polygenic hypercholesterolemia	Type IIA	↑ ↑ ↑				↑ ↑ ↑			NA - RESIN - PRO - LOV - NEO
(Familial) combined hyperlipidemia	Type IIB (variably, IIA or IV)	↑ ↑		↑		↑ ↑		↑	NA - RESIN - PRO - LOV - GEM
Familial dysbetalipoproteinemia	Type III	↑ ↑		↑ ↑	↑ ↑ ↑	↑ ↑		↑ ↑	GEM - NA - CLO - LOV
Familial hypertriglyceridemia	Type IV			↑ ↑			↓	↑ ↑	NA - GEM - FO - CLO
Severe hypertriglyceridemia	Type V	↑	↑ ↑ ↑	↑ ↑ ↑	↑	↓	↓	↑ ↑ ↑	NA - GEM - FO - CLO - NOR
Relative hypercholesterolemia	- - - - -						↓ ↓		NA - LOV - GEM

↑ = abnormally increased
↓ = abnormally decreased

TC = total cholesterol
VLDLC = very low density lipoprotein cholesterol
IDLC = intermediate density lipoprotein cholesterol
LDLC = low density lipoprotein cholesterol
HDLC = high density lipoprotein cholesterol
Tgs = triglycerides
CHYLO = chylomicrons

NA = nicotinic acid
RESIN = cholestyramine, colestipol
PRO = probucol
LOV = lovastatin
GEM = gemfibrozil
CLO = clofibrate
FO = fish oil
NOR = norethyndrone
NEO = neomycin

*Drugs listed randomly; order does not imply therapeutic preference

Table 2 Other agents with potential effects on blood lipid levels

Possibly adverse	Possibly beneficial
Thiazide diuretics	pindolol
Some β-blockers	guanabcnz
Anabolic steroids	prazosin
Androgenic hormones	terazosin
Glucocorticoids	Phenytoin
Vitamin A analogs	terbutaline
Zinc	cimetidine
Ethanol (excess)	ethanol (moderate)
Progesterones	estrogens
Isotretinoin	carnitine

DRUGS USED FOR PRIMARY DYSLIPIDEMIAS

There are several categories of drugs used to treat dyslipidemia. Since diet is the first line therapy, each of the drugs described below should be used in conjunction with a low saturated fat, low cholesterol diet (13). A list of the most common drugs, their side effects, drug interactions, and usual costs are given in Table 3. Their structures are given in Figure 1 and their sites of action on lipoprotein metabolic pathways are shown in Figure 2.

It is possible that pharmacological or dietary interventions that increase HDLC will decrease coronary risk (see Helsinki trial below). Nevertheless, we focus upon those drugs that primarily lower VLDLC, IDLC, or LDLC levels. At present, relative hypercholesterolemia is most appropriately treated by lowering LDLC, and only secondarily by raising HDLC levels.

Ion Exchange Resins

Two resins are currently available and will be described jointly since they are almost identical in their chemical behavior, preparation forms, and mechanisms of action.

Cholestyramine is a chloride salt of a basic anion-exchange resin and colestipol is a copolymer of diethyl enetriamine and choloroepoxypropane. These drugs come in powder form and can be administered suspended in fluids or mixed with pureed foods. The dose ranges are 5–30 gm/day for colestipol and 4–24 gm/day for cholestyramine given before two or three meals. Higher doses are poorly tolerated, difficult to comply with, and unlikely to significantly enhance the effects on blood lipids.

The resins are hydrophilic, insoluble in water, unaffected by digestive enzymes, and nonabsorbable. They transit through the gut unchanged, bind to bile salts in the intestine, and are excreted in the stools without ever entering the systemic circulation. The enterohepatic circulation of bile acids is in-

Table 3 Summary of major drugs used for primary dyslipidemia

Drugs category	Drugs	Proven to reduce ASCVD†	Long-term safety*	Compliance characteristics	General effects on serum lipoproteins					
					TC	VLDLC	IDLC	LDLC	HDLC	Tgs
Ion exchange resins	Cholestyramine colestipol	Yes	Yes	Poor	↓ ↓ ↓	-or ↑	-	↓ ↓ ↓	-	-or ↑
Antioxidant	Probucol	N.T.	N.T.	Good	↓ ↓	-	-	↓ ↓	↓	-
Fibrates	Gemfibrozil	Yes	Yes	Good						
	Clofibrate	Yes	No	Good	↓ ↓	↓ ↓	↓ ↓	↑ ↓	↑ ↑	↓ ↓
Nutrients	Nicotinic acid	Yes	Yes	Variable	↓ ↓	↓ ↓	↓	↓ ↓	↑ ↑	↓ ↓
	Omega-3 fatty acids	N.T.	N.T.	Good	↓ or-	↓ ↓	↓	-or ↑	-or ↑	↓ ↓
HMG CoA Reductase inhibitors	Lovastatin Simvastatin Pravastatin	N.T.	N.T.	Good	↓ ↓ ↓ ↓	↓	↓	↓ ↓ ↓ ↓	-or ↑	↓

↓ = lowers ↑ = increases - = no effect ? = not well established

†Efficacy proven in placebo-controlled clinical trial of at least 5 years' duration.

*No proven life-threatening drug-related toxicity found after at least five years of therapy in placebo-controlled clinical trial

N.T. = not tested

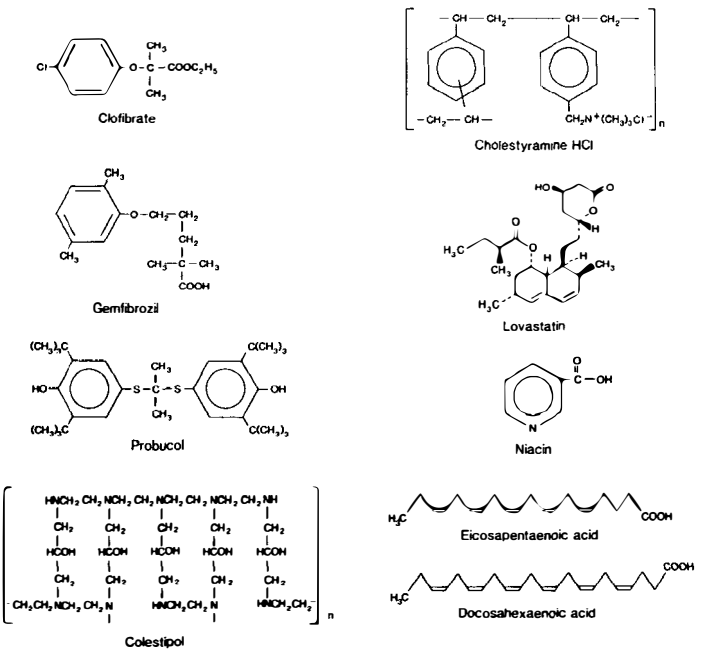

Figure 1 The major drugs currently used to treat hyperlipidemias.

terrupted because they are bound and excreted with the resins. This increases the need for hepatic bile acid synthesis which, in turn, enhances cholesterol turnover in the hepatocyte. The increased demand is met by increased de novo cholesterol synthesis and enhanced synthesis of high-affinity LDL receptors. The latter effect lowers serum cholesterol levels as the liver removes more LDL from the circulation (Figure 2).

The range of effects on serum lipoprotein concentrations after chronic resin administration is as follows: TC: −10 to −30%; TG: 0 to +40%; LDLC: −10 to −35%; and HDLC: 0 to +20%. In controlled trials the mean reduction in LDLC in compliant patients has ranged from 10–25% (5, 24).

Resins are indicated for the treatment of isolated or relative hypercholesterolemia in order to lower the LDLC/HDLC ratio. Because of their tendency to elevate triglycerides, they should be avoided in hypertriglyceridemic patients or used only if triglyceride elevations are mild (<300 mg/dl).

Both resins have been shown to be safe and effective in clinical trials (5, 24). Cholestyramine administration was associated with reduced morbidity and mortality from ASCVD in the Lipid Research Clinics Coronary Primary Prevention trial (LRC-CPPT) (6). The LRC-CPPT was a randomized, double-blind seven-year study examining the effects of the drug (or placebo) in 3,800

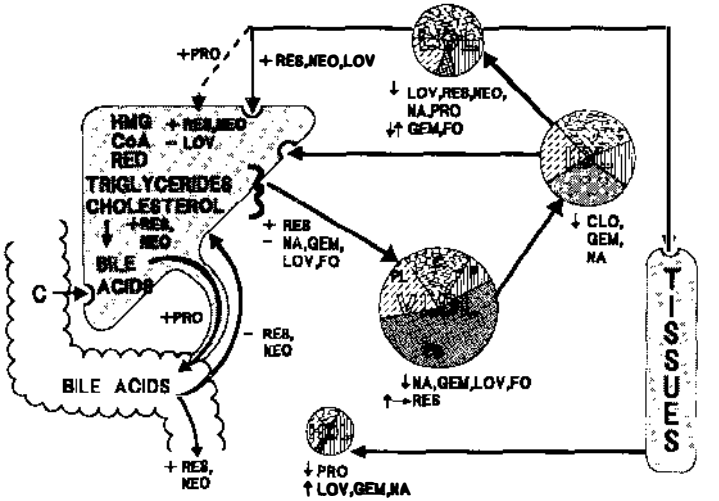

Figure 2 The effects of drugs on lipoprotein metabolism. Briefly, the liver secretes TG-rich VLDL particles which, following TG hydrolysis by lipoprotein lipase, become cholesteryl ester-rich IDL particles. IDL is either removed by hepatic LDL receptors or is converted into LDL. LDL provides cholesterol to tissues via receptor mediated (→) and nonreceptor mediated (- - - →) removal mechanisms. HDL (derived from the liver and intestines) removes free cholesterol from tissues. + − = pathway enhanced or inhibited. ↑↓ = effect on the respective serum lipoprotein cholesterol levels. Abbreviations: drugs - PRO = probucol; RES = resins; NEO = neomycin; LOV = lovastatin; NA = nicotinic acid; GEM = gemfribrozil; CLO = clofibrate; FO = fish oil. Lipoproteins - very low density = VLDL; intermediate density = IDL; low density = LDL; high density = HDL. Lipoprotein constituents - TG = triglyceride; C = cholesterol; PL = phospholipid; P = protein. HMG CoA Red is β-hydroxy-β-methyglutaryl coenzyme A reductase, the rate-limited enzyme in cholesterol biosynthesis.

asymptomatic men. The treatment produced an average 9% decrease in serum cholesterol levels (LDLC, −13%) and a 19% decrease in cardiac deaths. In patients with maximal therapeutic effect due to good compliance to the drug, serum cholesterol levels decreased by 19% and coronary risk by 39%. Because this trial involved the use of a nonabsorbable, nonsystemic drug in a well-designed study, it provided the clearest confirmation to date that decreasing LDLC levels can lower ASCVD risk in humans.

The frequent gastrointestinal side effects of the resins, although not disabling or life-threatening, make it difficult for many patients to take these drugs, especially in view of the need to do so for a lifetime. Bile acid-binding resins can interfere with the absorption of coadministered medications such as diuretics, digitalis, antiarrhythmics, antihypertensive drugs, or oral anticoagulants, and Vitamin K. This interaction can be avoided by taking the drugs two or more hours before the resins.

No irreversible or serious side effects from these drugs have been recorded

over many years of use. The only biochemical abnormality noted was recurrent mild (1–3 fold over normal) elevations of serum transaminase levels in 1–2% of patients. Because resins are not absorbed, this effect may be secondary to changes in hepatic metabolism or excretion of bile acids. Resins are possibly the safest of all the drugs available for treatment of dyslipidemia, but good compliance is often difficult to achieve.

Probucol

This drug is a bisphenol and is structurally related to tocopherol. It was originally developed as an industrial antioxidant, and was later found to have hypocholesterolemic activity in animals and man.

Probucol comes in 250 mg and 500 mg tablets and is used in the standard dose of 500 mg (2 tablets) twice a day. It is extremely water-insoluble and has a very low rate of enteric absorption that can be enhanced if the drug is taken immediately after or with meals. Probucol is highly bound to and transported in lipoproteins, and its incorporation into LDL alters the particle apparently increasing its hepatic uptake via non-LDL receptor-mediated mechanisms (25, 26) (Figure 2). The drug has a half life of over a month, and may therefore remain in circulation for three to five months after discontinuation. However its effects on blood lipids disappear within 3–6 weeks. Its antioxidant properties apparently prevent LDL uptake by scavenger pathways in macrophagcs, and thus appear to reduce foam cell formation. The drug enhances hepatic excretion of bile acids, that in turn may accelerate LDL removal by the liver. Probucol has a remarkable HDLC lowering effect (24); however, it appears to enhance reverse cholesterol transport as evidenced by the disappearance of cholesterol deposits from tissues in animals and patients treated with this drug (27). Thus, the effects of probucol are intriguing since it enhances LDL removal by receptor independent pathways in the liver and yet prevents LDL uptake by scavenger pathways in the macrophages. It lowers HDLC levels but appears to accelerate the removal of excess tissue cholesterol. Obviously, much work remains before the mechanism of its action is fully elucidated.

The range of effects of probucol on serum lipoprotein concentrations is as follows: TC: −10 to −30%; LDLC: −5 to −25%; and HDLC: −5 to −40% (25, 26). In controlled trials the range of LDLC reduction has been −7 to −20% (28, 29). Probucol is indicated for the treatment of primary hypercholesterolemia. It can be used in familial combined hyperlipidemia if triglyceride elevations are mild (<300 mg/dl) and/or controlled by diet.

Results are not available from placebo-controlled, clinical trials to establish the long-term safety of probucol or its effects on ASCVD morbidity or mortality. Chronic use of the drug is rarely associated with any important clinically evident side effects. A prolongation of the QT interval on

electrocardiography found in about 50% of patients taking to this drug has not been associated with any clinically relevant, cardiovascular effects (29). Fatal cardiac arrhythmias have occurred in dogs or monkeys given probucol together with an extremely high fat diet (29). This myocardial toxicity was attributed to the inordinately high tissue levels of probucol found under these extreme experimental conditions and may not be applicable to the regular use of the drug in patients.

Fibrates

CLOFIBRATE This drug is a chlorphenoxy-methyl propanoic acid ethyl ester prepared in capsules of 500 mg each. The usual dose is 1 gm (2 capsules) twice a day. It is most useful in the treatment of the rare, type III dysbetalipoproteinemia, a highly atherogenic condition generally resistant to resins or probucol. Lovastatin, nicotinic acid, and other fibrates may also be effective in this condition (30–32). The goal of drug treatment is to lower the abnormally elevated IDLC levels found in this disorder.

Clofibrate is now seldom, if ever, prescribed for any other dyslipidemic condition because of an unexpectedly high incidence of cholelithiasis and malignant tumors of the colon in a placebo-controlled, primary prevention trial in hypercholesterolemic men conducted by the World Health Organization (33). This drug has been largely replaced in the USA by gemfibrozil; the latter has similar pharmacokinetic features, mechanism of action, and indications, but appears to be safer since in a recent five-year trial in 4,081 men it did not significantly increase the incidence of cholelithiasis or carcinoma (See below). Two other fibrates, fenofibrate and bezafibrate, have been widely used in other countries for over a decade; they have equal or greater therapeutic efficacy and are expected to be marketed in the USA in the near future.

GEMFIBROZIL This drug is a dimethylphenoxy-dimethyl pentanoic acid prepared in capsules of 300 mg. The usual dose is 600 mg (2 capsules) twice a day. The drug is highly bound to plasma proteins; the unbound fraction may be increased in conditions accompanied by low-serum protein concentrations—such as nephrotic syndrome or chronic liver disease—or by high blood urea nitrogen concentrations, such as in uremic nephropathy.

Gemfibrozil's effects are primarily on hepatic synthesis and secretion of VLDL cholesterol (34) (Figure 2). It also stimulates the activity of lipoprotein lipase, and increases biliary excretion of neutral steroids and catabolism of VLDL and IDL (35). Gemfibrozil primarily affects serum triglycerides, decreasing their levels by 10–80% depending on the lipoprotein disorder. The drug is particularly useful when severe hypertriglyceridemia (greater than 750 mg/dl) places the patient at risk for acute pancreatitis. When the drug alone

fails to normalize serum triglyceride levels, a combination with nicotinic acid or fish oil may achieve maximal trigylceride lowering.

Fibrates have variable effects on LDLC levels, depending on the type of dyslipidemia. In patients with elevated LDLC levels, fibrates may reduce LDLC as effectively as resins (36). However, in hypertriglyceridemic patients normal baseline LDLC levels may not change (37) and may even increase with treatment (38). Why this occurs is not known, and is of some concern, given the known atherogenic potential of LDLC. Fenofibrate raises LDL levels by reducing the rate of LDL removal from plasma in these patients (39). Whether gemfibrozil does the same is not known.

Gemfibrozil raises HDLC levels (34–37), and thus may be effective in the treatment of relative hypercholesterolemia by lowering the LDLC/HDLC ratio. Decreasing this ratio may be more important than the absolute lowering of LDLC levels, and the occasional rise in LDLC may be more than offset by a rise in HDLC to produce an overall favorable effect on the atherosclerotic process.

Although gemfibrozil is approved in the United States only for treatment of isolated hypertriglyceridemia (i.e. triglycerides greater than 750 mg/dl), the results of the Helsinki Trial (described below) suggest that gemfibrozil may be beneficial to any patient with non-HDL cholesterol (VLDLC + LDLC) levels above 200 mg/dl, regardless of their total serum triglyceride levels.

The Helsinki Heart study was a randomized, placebo-controlled, clinical trial involving over 4,000 men in which gemfibrozil therapy was compared to placebo for five years (7). There was a statistically significant decrease in all cardiac endpoints in the gemfibrozil treated group. Nevertheless, overall mortality was not reduced by the drug. Decreased cardiac morbidity and mortality were associated with a 10% elevation of HDLC and a lowering of serum VLDL by 40%, triglycerides by 34%, and LDL by 9%.

The results were within the range of effect of this drug on serum lipoprotein levels: TC: −2 to −10%; TG: −10 to −50%; LDLC: +15 to −10%; HDL: +5 to +25%. This study provided the strongest support to date of the proposition that lowering the LDLC/HDLC ratio may beneficially influence ASCVD morbidity and mortality. However, the marked decrease in VLDLC levels may also have been beneficial. Further studies will be needed to understand the mechanism(s) behind the gemfibrozil-induced reduction in heart disease.

Nicotinic Acid

Nicotinic acid (niacin) is a vitamin of the B group; its chemical name is pyridine-3-carboxylic acid. It is available in standard or slow-release tablets in amounts of 25–500 mg. The drug is absorbed rapidly on an empty stomach and as it reaches peak plasma concentrations may cause an acute dilation in blood vessels of the skin that results in flushing and, occasionally, itching.

This is presumably caused by release of prostacyclin and may be minimized by concomitant ingestion of aspirin (40). Its use in sustained-release form or taking the drug at mealtimes can also help reduce these side effects, which gradually diminish as a tolerance to the vasodilation effect develops (41). Although niacinamide (an alternate vitamin form) does not cause these cutaneous side effects, it also has no beneficial effect on serum lipids. The hypolipidemic dose range of 0.25–3 gm/day is far greater than the Recommended Dietary Allowance of 20 mg/day, thus its mode of action is apparently unrelated to its function as a vitamin.

Nicotinic acid affects lipoprotein metabolism through (*a*) inhibition of lipolysis in adipose tissue, (*b*) increased activity of lipoprotein lipase, (*c*) decreased hepatic secretion of VLDL, and (*d*) reduced rate of synthesis of LDL (42). It also increases serum HDLC levels (Figure 2) (41).

The primary indications for nicotinic acid are combined hyperlipidemia and isolated (or relative) hypercholesterolemia. The drug affects serum lipid levels rapidly (within one week) with typical changes as follows: TG and TC: −10 to −30%; LDLC: −10 to −20%; HDLC: +5 to +30%; and VLDLC: −15 to −40%. Of all the hypolipidemic drugs, niacin has the widest range of beneficial effects on blood lipid levels and does not adversely affect one lipoprotein fraction while beneficially affecting another. Thus, niacin would be the drug of choice for most types of dyslipidemia were it not for the multiplicity, and sometime seriousness, of its side effects (see Table 4).

Chronic administration may result in impaired glucose tolerance in nondiabetics and in overt diabetes in prediabetic patients. It can also induce hyperuricemia which, with glucose intolerance, is associated with increased ASCVD risk (43, 44). In addition, large doses of niacin (greater than 2 gm/day) can increase the incidence of gastritis, abnormal liver function tests, and, rarely, severe toxic hepatitis. Irreversible chronic active hepatitis has reportedly been precipitated by large doses of niacin (45). The sustained-release forms of niacin have been suggested to be more hepatotoxic than the unmodified forms (41). Niacin may interact with some antihypertensive drugs to increase postural hypotension.

Niacin was studied in the Coronary Drug Project, a trial examining the effects of several hypolipidemic drugs on the secondary prevention of coronary heart disease (44). Men with previous myocardial disease (n=1,119) were given 3 g/day of nicotinic acid for an average of six yr. At the end of the trial, the drug on average had lowered serum cholesterol by 10%, reduced nonfatal myocardial infarctions by 7%, but produced no decrease in cardiac or overall mortality. The reduction in nonfatal myocardial infarction was statistically similar to that found in the LRC-CPPT trial (6) with cholestyramine (i.e. a 2% decrease in risk for every 1% decrease in TC). There was, however, an increased incidence of atrial fibrillation and other cardiac arrythmias. In-

Table 4 Therapeutic characterstics of commonly used dyslipidemic drugs

Drug	Dosage	Common side effects	Uncommon side effects	Drug interactions	Cost per day $
Cholestyramine (Questran)	8–24 gm daily (mixed with 4–6 oz suitable liquid) given in 1–3 divided doses before meals.	Dyspepsia, constipation, nausea, abdominal pain, exacerbation of hemorrhoids, or anal fissures or hernias. Elevation of triglycerides.	Vomiting, skin rash, easy bruising.	May decrease absorption of other drugs.	1–3
Colestipol HCl (Colestid)	10–30 gm daily (mixed as above).	Same as above.	Same as above.	Same as above.	1.5–3
Probucol (Lorelco)	500 mg with meals BID.	Increased bowel movement. Prolonged QT interval on ECG.	Diarrhea, dyspepsia, skin rash.	None known.	1.5
Lovastatin (Mevacor)	20–80 mg/day (1–4 tablets/day).	None known.	Elevated liver enzymes, myopathy.	High SGOT, SGPT after alcoholic beverage excess. May potentiate coumadin effect.	1.5–6

Nicotinic acid (Nicobid, Nico-400, Nicolar, or generics)	1–3 gm daily, given in 2 divided doses.	Flushed skin, itching, dyspepsia, decreased glucose tolerance, hyperuricemia, abnormal liver function tests.	Hepatotoxicity, diabetes, gout, peptic ulcer, skin rash.	Enhanced hypotensive effects of antihypertensives.	.09–26 (generic) 2–6 (time-release)
Gemfibrozil (Lopid)	1200 mg/day (2 capsules BID).	Generally none, but increased LDLC levels in Type IV.	Elevated CPK. Myositis. PVC's.	May enhance effects of anticoagulants, antidiabetics, or other highly protein bound drugs.	1.25–1.85
Fish Oil (MaxEPA, Super-EPA, Promega, Protochol)	3–6 capsules 2–3 times a day with meals. (Capsules contain 300–500 mg n-3 fatty acids/gm of oil.)	Generally none but increased LDL levels in Types IIB and IV.	Diarrhea, dyspepsia.	May potentiate anticoagulant effects.	.8–2.4

terestingly, nine years after discontinuing the drug, the men who had taken niacin had experienced a significant reduction in overall mortality compared to the placebo group (8). Thus, niacin is the only hypolipidemic drug that has been associated with reduced overall mortality, even though the reasons for this late effect are completely unknown.

HMG-CoA Reductase Inhibitors

HMG-CoA reductase is an important, rate-limiting enzyme in the cholesterol biosynthetic pathway. The newest class of hypolipidemic drugs reduces cholesterol synthesis by competitively inhibiting this enzyme (46, 47). As was noted earlier for ion exchange resins, the depletion of hepatic cholesterol stores (in this case by decreased de novo synthesis) increases the intracellular need for cholesterol and thus stimulates the synthesis of LDL receptors. As receptor density on the hepatocyte increases, plasma LDL levels decrease (Figure 2) (48).

The only HMG-CoA reductase inhibitor currently approved for use in the United States is lovastatin. Simvastatin is available in some European countries. In early stages of development are pravastatin (CS514) and SRI-62320. The latter compound was produced by chemical synthesis; the others are microbially-derived compounds. Lovastatin and simvastatin are actually prodrugs; in vivo, their lactone ring is cleaved to yield active, β-hydroxy acid (46) (Figure 3). It appears that appropriate doses of all these drugs will produce similar reductions in serum LDLC levels (49–52).

Lovastatin is indicated for patients with primary hypercholesterolemia. It is

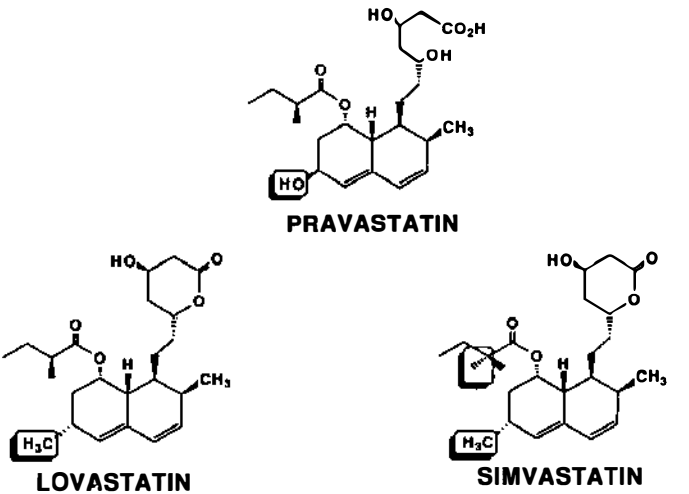

Figure 3 The structures of three HMG-CoA reductase inhibitors.

available in 20 mg tablets, and doses of 20–80 mg/day may reduce LDLC levels by 20–60%. The drug raises HDLC levels by 5–10% and lowers triglycerides by 25% in most patients. Although lovastatin clearly inhibits HMG-CoA reductase in man (53), the mechanism by which it lowers serum LDLC levels is more complicated than simply reducing cholesterol synthesis. Comparing the effects of lovastatin in patients with heterozygous and homozygous familial hypercholesterolemia provides an insight into its mode of action. The former group has functional LDL receptors (but only 50% of the normal amount); the latter group has few or no functional receptors. Lovastatin reduces LDLC levels in heterozygotes, presumably by maximizing receptor synthesis (54), but it is much less effective in the homozygotes, whose receptor activity cannot be increased (55).

Studies on the effects of lovastatin on LDL kinetics in patients with nonfamilial hypercholesterolemia revealed, unexpectedly, that the drug did not enhance LDL catabolism but reduced LDL production rates (56). Nevertheless, this finding does not necessarily conflict with the hypothesis that lovastatin stimulates LDL receptor activity because LDL production would in fact decrease if the removal rate of IDL, the direct precursor of LDL, were increased. This is not unlikely since IDL has a greater affinity for the LDL receptor as LDL itself does (57) (Figure 2). Thus, lovastatin may reduce LDL levels by either stimulating receptors to remove more IDL, or by reducing VLDL secretion rates.

The incidence of side effects from lovastatin are relatively low, especially compared to other hypolipidemic drugs. Various gastrointestinal symptoms, headache, or rash have been reported but have rarely led to discontinuation. In about 2% of patients, lovastatin causes marked (i.e. greater than 3 times over the upper limit of normal) asymptomatic elevation of hepatic transaminases (58), and myopathy in about 0.5% of patients. This last effect was seen mostly in patients with complicated histories who were also receiving therapy with immunosuppressive drugs or with niacin or gemfibrozil (59). Although lovastatin in very large doses has caused cataracts in dogs (46), no such effect has been detected in long-term human trials (60).

The greatest toxicological concerns surrounding the HMG-CoA reductase inhibitors relate to cataract development and hepatic injury. The relative abilities of three of these drugs to inhibit cholesterol synthesis in the lens and liver are given in Table 5. Whether these differences in tissue specificity will have pharmacological and/or toxicological significance in humans is not known.

Neomycin

This aminoglycoside antibiotic is largely unabsorbed when taken orally. At a dose of 1–3 gm/day, it lowers serum cholesterol by precipitating bile acids and preventing their resorption in the ileum (61). It can reduce total serum

Table 5 IC_{50}* values for [^{14}C]-acetate incorporation into cholesterol

	IC_{50} (nM)	
	Rat lens	Rat liver
Pravastatin	472 ± 62	48 ± 11
Lovastatin	4 ± 1	33 ± 13
Simvastatin	4 ± 1	19 ± 6

*IC_{50} is the concentration of drug which produces a 50% inhibition of cholesterol synthesis.

cholesterol levels by 10–20% (62) but the potential for nephrototoxicity and/or ototoxicity exists if used in patients with impaired renal or hepatic function. Patients free of these conditions are unlikely to suffer such side effects. Gastrointestinal malabsorption of nutrients is not an uncommon side effect. Hypercholesterolemia is not currently an approved indication for neomycin.

OTHER AGENTS BENEFICIALLY AFFECTING DYSLIPIDEMIA

Insulin

The use of insulin to achieve glycemic control in diabetes often has a beneficial effect on the elevated cholesterol and triglyceride levels frequently found in this condition (63, 64). By normalizing glucose metabolism, free fatty acid flux from adipose tissue is reduced and, in turn, slows hepatic trigylceride synthesis and lowers VLDL secretion rates (65). In addition to its action on serum VLDL triglyceride levels, insulin therapy lowers LDL levels, perhaps via increased LDL receptor activity (66), and raises HDLC levels (67).

Estrogen and Oral Contraceptive Hormones

The diminution of natural estrogens with menopause frequently leads to increased levels of LDLC and an attendant rise in cardiovascular risk (68–70). Estrogen replacement therapy lowers elevated LDLC and raises HDLC levels in these patients (68), and reduces the risk for coronary artery disease (70). The beneficial effects of such therapy are especially evident in women who have undergone bilateral oophorectomy (69). Thus, estrogen replacement therapy should be considered in the postmenopausal patient, especially if dyslipidemia is present.

Some combinations of estrogenic compounds and various progestinic drugs can affect blood lipids adversely. The effects are quite variable with the

different preparations, however those containing the lowest amounts of estrogen and androgenic progestins are less likely to have a deleterious effect on plasma lipid levels (70a, 70b).

Norethindrone Acetate

This is a progestinic substance shown to be effective in lowering triglycerides in females who are resistant to other therapies (71). It is indicated only for prevention of hyperlipidemia-induced recurrent pancreatitis. The recommended dose is 5 mg/day. Long-term treatment should be avoided because of the lowering of HDLC and the lack of controlled, long-term safety data.

Thyroxine (D- and L- Isomers)

The optical isomer of the natural hormone L-thyroxine has documented hypocholesterolemic activity. Both isomers appear to stimulate the expression of LDL receptors (72, 73). When D-thyroxine was used in a large clinical trial as an alternative to niacin (44), it was found to be associated with an increased incidence of cardiac mortality and morbidity, presumably due to enhancement of arrhythmias and the general hypermetabolic effects. As a result, the use of D-thyroxine is no longer recommended for treatment of hyperlipidemia.

The use of L-thyroxine may decrease serum cholesterol levels in dyslipidemic subjects who have low or borderline-low levels of circulating thyroid hormone (T4 less than 6 mg/dl) (74).

Fish Oils

The use of fish oils rich in n-3 fatty acids (FAs) to lower serum cholesterol and triglyceride levels has recently attracted widespread attention (75–77). Fueled by observations among Greenland Eskimos that the consumption of high levels of n-3 FAs was associated with reduced serum lipid levels and cardiovascular disease rates (78), many studies have examined the effects of these unique fatty acids on lipoprotein levels in humans (see 79).

There are two major n-3 fatty acids found in fish oils: eicosapentaenoic acid (C20:5; EPA) and docosahexaenoic acid (C22:6; DHA) (Figure 1). EPA, like arachidonic acid, is a substrate for cyclooxygenase and lipoxygenase. Although the products of these two enzymes (prostaglandins, thromboxanes, prostacyclins, and leukotrienes) have a wide variety of biologic effects (see 77, 78), the extent to which these metabolites influence lipoprotein metabolism is not known.

EPA and DHA are found almost exclusively in marine animals. Oily fish such as salmon, mackeral, herring, and sardine are rich sources, as opposed to low-fat fish such as cod, sole, perch, etc. (80, 81). Fish oil may be obtained in

liquid (e.g. cod liver oil), encapsulated or emulsified forms. Preparations containing ethyl esters of n-3 FAs are also available.

A wide range of doses of n-3 FAs has been employed in the treatment of hyperlipidemia. Doses as low as 2–3 g (6–9, 1–g capsules) per day have been effective in lowering elevated triglyceride levels (82–84). Reductions of 30-40% are not uncommon with these doses in hypertriglyceridemic patients. HDLC and LDLC levels may rise slightly (0–5%) with fish oil treatment. The marked reduction in serum TG levels stems from a decrease in TG synthesis and VLDL secretion from the liver (85–87) (Figure 2).

LDLC and serum apolipoprotein B levels occasionally increase with fish oil supplementation in hypertriglyceridemic patients (types IIb, IV and V) (88–90). This effect is shared by other hypotriglyceridemic drugs such as the fibrates. The mechanism of this effect is not known; however, animal studies suggest that fish oil may inhibit the activity of the LDL receptor (91, 92).

Because n-3 FAs are a natural component of the human diet and have been so for thousands of years, they are quite free of side effects. Their ability to inhibit platelet function (93) has led to increases in bleeding times, especially when combined with aspirin (94), although clinically significant bleeding has not been reported (95). Potentially harmful chemical compounds may be found in some fish oil preparations but these are unrelated to the n-3 FAs they contain. For example; cod liver oil contains large amounts of vitamins A and D that can reach toxic levels in the tissues if more than 15–20 gm/day are consumed chronically.

The clearest indication for the use of n-3 FAs is hypertriglyceridemia (types IV, V, and perhaps type III) (79). N-3 FAs should not be used to treat elevated LDL cholesterol levels as they have been largely ineffective and, as noted above, may even elevate normal or borderline levels of LDLC in hypertriglyceridemic patients. When triglyceride levels are very high (greater than 1,000 mg/dL), fish oil can very effectively and rapidly reduce them and lower the risk of acute pancreatitis.

There have been no controlled clinical trials to examine the effects of n-3 FAs on cardiovascular morbidity and mortality. However, epidemiological studies have compared fish-eating to non-fish-eating populations (93) and fish-eaters to non-fish-eaters within the same populations (96, 97). In these studies fish consumption was associated with reduced mortality from cardiovascular disease. Restenosis following percutaneous transluminal coronary angioplasty was significantly reduced by n-3 FAs (95) and the development of atherosclerotic plaque has been retarded in animals given fish oil (99).

COMBINED DRUG THERAPY

The drug combinations most useful in the treatment of dyslipidemia are listed in Table 6. Coadministration of two different types of drugs to normalize

Table 6 Combined drug therapies for dyslipidemia

Combination	Advantages
Resins	
+ Nicotinic acid	Enhanced LDLC reduction and HDLC elevation. Blunting of hypertriglyceridemic effect of resins.
+ Probucol	Enhanced LDLC reduction. Reduction of constipation due to resins.
+ Gemfibrozil	Enhanced LDLC reduction and blunting of LDLC elevation due to gemfibrozil. Additional hypotriglyceridemic effect or blunting of hypertriglyceridemic effect of resins.
+ Lovastatin	Enhanced LDLC reduction. Blunting of hypertriglyceridemic effect of resins.
+ Fish oil	Prevention of LDLC elevation from fish oils and of triglyceride elevation by resins in combined hyperlipidemia. Diarrhea and constipation from either agent may be ameliorated.
Lovastatin	
+ Gemfibrozil	Enhanced LDLC reduction in isolated hypercholesterolemia or blunting of LDLC elevation due to gemfibrozil in combined hyperlipidemia. Enhanced hypotriglyceridemic effect.
+ Nicotinic acid	Enhanced LDLC and triglyceride reduction in combined hyperlipidemia.
Nicotinic Acid	
+ Fish Oil	Enhanced hypotriglyceridemic effect. Blunting of LDLC elevation due to fish oils in combined hyperlipidemia.

serum lipoprotein levels is justifiable for the reasons given in the table. In addition, combination therapies may reduce the overall cost of treatment and decrease potential toxicity from large doses of single drugs. Drug combination should be attempted (*a*) if there is no effective response to a single drug given at its maximum recommended or tolerated dose or (*b*) if there is evidence of side-effects at optimally effective doses of a single agent. As a rule there should be adequate documentation of the effects of monotherapy before initiating a combined therapeutic regimen.

CONCLUSION

The incidence of coronary heart disease has been reduced by lowering elevated levels of atherogenic lipoproteins (VLDL and, especially, LDL) and

possibly by increasing abnormally low levels of HDL (lowering LDLC/HDLC ratio). Dietary intervention to reduce saturated fat and cholesterol intake is the first step in any treatment regimen. If dietary changes fail to normalize lipid levels, pharmacological intervention is indicated. First-line drugs would be resins, nicotinic acid, and possibly gemfibrozil because of their proven ability to lower ASCVD risk and their lack of serious long-term toxicity (13). The relatively new drug, lovastatin, is a potent hypocholesterolemic drug, and probucol may be more antiatherogenic than hypolipidemic. Trials to document their long-term safety and their effects on ASCVD are under way. The role (156) of fish oil in the treatment of hypertriglyceridemia is promising but its effects on ASCVD have not been rigorously examined. Regardless of the means employed, correction of dyslipidemia will reduce the risk for ASCVD.

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