10 – Lipid-modifying and antiatherosclerotic drugs

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> *"In the great majority of cases ordinary atheroma (Greek, meal or porridge) is to blame; this consists of softening, the precursor of arteriosclerosis, with yellowish fatty (cholesterol) areas in the endarterium."*
>
> *Paul Dudley White, 1944*[1]
>
> *Very large reductions in coronary disease might attend pharmacologic achievement of LDL levels characteristic of "traditional" populations such as hunter-gatherers and Arctic Eskimos.*
>
> *Modified from Domanski, 2007*[2]

Blood lipid assessment forms an essential step in the evaluation of almost every cardiac patient, whether young, middle aged, or older. Physicians may help guide younger patients toward long-term cardiovascular health by addressing early risk factors, whereas middle-aged and older patients may need a more intensive approach because of their near-term risk for coronary disease. The widespread availability, persuasive and substantial clinical database, and relative safety of the statins have established pharmacologic control of blood lipids as an increasingly acceptable strategy. Of the lipid aims, the early reduction of low-density-lipoprotein cholesterol (LDL-C) levels by statins is the current key to lessening clinical cardiovascular disease.[2-4] Since the last edition of this book, results of a major clinical trial in primary prevention have demonstrated the utility of the inflammatory marker C-reactive protein (CRP) in identifying individuals at increased risk despite having low to normal levels of LDL-C.[5] Patients in this trial who attained LDL-C levels less than 50 mg/dL experienced greater reductions in cardiovascular morbidity and mortality than the rest of the study cohort.[6] These findings are indicative of two major trends in current research: (1) the potential benefit of high-intensity therapy to very low LDL-C levels, and (2) the growing recognition of the role of vascular inflammation in the genesis of arterial disease (Fig. 10-1) and the increased integration of inflammatory markers in cardiovascular risk assessment. These developments and their translation into clinical practice hold the potential to improve patient outcomes.

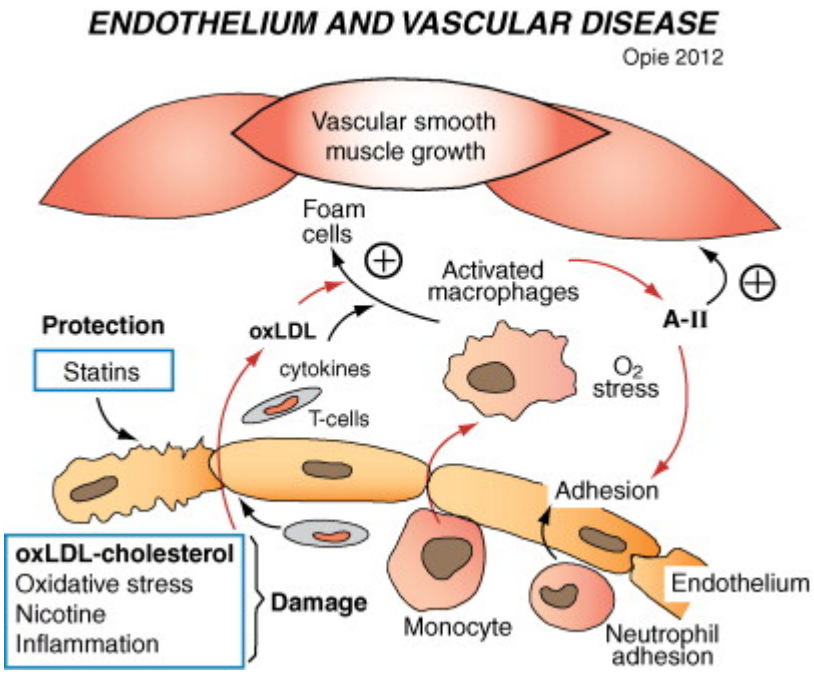

Figure 10-1 From endothelial damage to atheroma: the proposed role of the vascular endothelium in atherogenesis. Note early endothelial damage, prompted by several factors including oxidized low-density lipoprotein (oxLDL) cholesterol, and hypothetically prevented by treatment. Neutrophils roll on and adhere to the damaged endothelium to promote adhesion of macrophages. Vascular cell adhesion molecule (VCAM) promotes the binding of macrophages to the endothelium, after which they penetrate the endothelium to become activated and, by uptake of oxLDL, to become foam cells. Activated macrophages also synthesize angiotensin II (A-II) that in turn promotes oxidative stress that stimulates the formation of VCAM. A-II also promotes growth of vascular smooth muscle cells, an integral part of atherogenesis. *O2*, Oxygen.
(Figure © L.H. Opie, 2012.)

Inflammation and atherogenesis

Atherosclerotic inflammation is triggered when circulating LDL enters the arterial wall and is retained through interaction with proteoglycans in the extracellular matrix.[7] LDL modification within the arterial wall occurs through a series of oxidative steps, which damages the endothelium and stimulates an immune and inflammatory response with increased production of chemoattractant molecules, cytokines, and adhesion molecules.[8] In addition to LDL oxidation, hypertension and cigarette smoking can also cause endothelial dysfunction. Subsequently, the dysfunctional endothelium is more permeable to circulating monocytes and T-cells; both are transported into the intima, where the monocytes are converted into macrophages. Activated macrophages and T-cells release a variety of mediators that collectively exacerbate inflammation and oxidation within the vessel wall.[9],[10] Macrophages also synthesize angiotensin II, which further disrupts normal endothelial function. Foam cells are formed when macrophages ingest oxidized LDL through receptors, including CD36. Growth of the atherosclerotic lesion is characterized by smooth muscle cell proliferation and increased production of matrix metalloproteinases, which can cause deterioration of elastin and collagen within the extracellular matrix. Mature plaques typically consist of a lipid-rich necrotic core encased by a weakened fibrous cap. Inflammatory cells may make mature plaques more prone to rupture by promoting the deterioration of fibrous caps.

C-reactive protein.

Much interest has centered on CRP, a general measure of inflammation that is produced in the liver in response to interleukin-6. This inflammatory marker is used to assess patients at intermediate risk (10% to 20% 10-year risk) according to traditional risk factor assessment.[11] A high level of CRP is an independent risk factor for atherogenesis and adds to the predictive value of other risk factors. It is unclear whether CRP plays a causal role in atherosclerosis or whether it is simply a marker of the atherosclerotic inflammatory response. Experimental studies have suggested that CRP may contribute to atherogenesis by promoting endothelial dysfunction and altering the behavior of monocytes, macrophages, and smooth muscle cells.[12]

However, individuals with genetically determined CRP elevations over a lifetime do not appear to be at increased cardiovascular risk.[13]

The cutoff values are less than 1 mg/L for low risk and greater than 3 mg/L for high risk, the latter tertile indicating an approximate doubling of the relative risk compared with the low-risk tertile. Elevated CRP is associated with obesity and the metabolic syndrome, and levels can be reduced through weight loss, increased physical activity, and smoking cessation. Apparently healthy persons at increased risk because of age, elevated CRP (>2 mg/L), and one additional cardiovascular risk factor should be treated with a statin as in the JUPITER trial with rosuvastatin 20 mg daily (see later).[5] Because statins lower both LDL-C and CRP, it is currently unclear whether reducing CRP, and inflammation more generally, has an independent effect on cardiovascular risk apart from LDL-C reduction. At least two trials with antiinflammatory agents that do not affect lipids are currently planned to begin in the near future.[10]

Prevention and risk factors

Primary prevention.

Primary prevention in patients without evident coronary disease remains a highly desirable aim. Lifestyle interventions (diet, smoking cessation, and physical activity) are the first line of treatment and may achieve cholesterol reduction in many patients. The national American campaign, promoting dietary management and other lifestyle measures, has resulted in a reduction of mean blood cholesterol levels and a fall in coronary heart disease (CHD) mortality rates. Clinical trials of statins in the past decade have demonstrated safety and clinical event reduction across the spectrum of cardiovascular risk, even in populations with low baseline risk such as the Japanese.[14] Still debated, however, are the fiscal and ethical issues related to the cost-effectiveness of lipid drug therapy in lower-risk primary prevention.[15]

Global risk evaluation: Adult treatment panel III.

Rather than assign patients to primary or secondary prevention, the 2004 U.S. Adult Treatment Panel III (ATP III) argued for three risk categories that use the concept of global risk (Table 10-1): high (CHD or equivalent); medium (two or more risk factors, 10-year risk of 20% or less); and low (zero to one major risk factor, 10-year risk 10% or less). LDL-C values form the primary basis for treatment decisions (Table 10-2). In the updated ATP III guidelines, the patient's absolute risk for developing CHD in the next 10 years determines the aggressiveness of lipid intervention.[16] This global risk is calculated using an algorithm based on the Framingham Heart Study that considers not only total cholesterol, but also high-density-lipoprotein cholesterol (HDL-C), smoking, age, hypertension, and sex. Also featured in ATP III is the concept of the *CHD equivalent,* a risk factor that identifies a patient who should receive treatment as aggressively as someone with a history of heart attack, angina, or revascularization. Included in this category of risk factors are diabetes, noncoronary atherosclerosis (peripheral vascular disease or stroke), and aortic aneurysm.

Table 10-1 -- LDL-C Goals Based on Global Risk in Latest American and European Guidelines

	LDL-C Goal
ATP III Risk Categories and LDL-C Goals (Highest to Lowest)	
CHD CHD Risk Equivalents Other cardiovascular disease or	<100 mg/dL (2.6 mmol/L) (for <70 mg/dL or 1.8 mmol/L; see Table 10-2)
Diabetes mellitus *or*	
Aortic aneurysm *or*	
10-year risk greater than 20%	
Multiple (2+) Risk Factors	<130 mg/dL (3.4 mmol/L)
0—1 Risk Factors	<160 mg/dL (4.1 mmol/L)
European Guidelines Risk Priorities (Highest to Lowest)	
Patients with **established CVD**Asymptomatic patients who have **Multiple risk factors** *or* **Markedly raised levels of single risk factors** *or* **Type 2 diabetes** *or* **type 1 diabetes with microalbuminuria** **Close relatives** of	<96 mg/dL (2.5 mmol/L)<115 mg/dL (3 mmol/L) <115 mg/dL (3 mmol/L)
Patients with early-onset CVD *or*	
Asymptomatic, high-risk patients	

	LDL-C Goal
ATP III Risk Categories and LDL-C Goals (Highest to Lowest)	
Other individuals encountered in routine practice	<115 mg/dL (3 mmol/L)

ATP III, U.S. Adult Treatment Panel III; *CHD,* coronary heart disease; *CVD,* cardiovascular disease; *LDL-C,* low-density-lipoprotein cholesterol.

ATP III and joint European guidelines.[16],[17],[18]

Table 10-2 -- LDL-C Treatment Thresholds for Diet and for Drugs

Risk Category	LDL-C Goal	Diet, Lifestyle Initiation Level	Drug Treatment Initiation Level
0-1 Other risk factors*	<160 mg/dL (4.14 mmol/L)	≥160 mg/dL	≥190 mg/dL (4.91 mmol/L)
			(160-189 mg/dL; LDL-C–lowering drug optional)
2+ Other risk factors (10-year risk ≤20%)	<130 mg/dL (3.36 mmol/L)	≥130 mg/dL	10-year risk 10%-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL *or* <70 mg/dL (1.8 mmol/L)[†]	≥100 mg/dL	≥100 mg/dL[†]

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[3]

CHD, Coronary heart disease; *LDL-C,* low-density-lipoprotein cholesterol.

* Almost all people with 0 to 1 other risk factors have a 10-year risk less than 10%: thus 10-year risk assessment in people with 0 to 1 risk factor is not necessary.

† Revised to lower levels in light of the PROVE-IT and REVERSAL trials.[22],[23] Clinical judgment may call for deferring drug therapy in this subcategory.

Other algorithms.

Besides the ATP III model, a number of other algorithms are available for estimating absolute risk, including guidelines of the Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice,[17] the PROCAM risk calculators of the International Task Force (see http://www.chd-taskforce.com), and the Reynolds Risk Score incorporating CRP (see http://www.reynoldsriskscore.org). Differences in the data sets used and the methods for calculation may yield different risk predictions, but these schemas share a common intention: to facilitate the discrimination of higher-risk patients from lower-risk ones. Both U.S. and European guidelines prioritize categories of patients and modify the LDL-C goal accordingly (see Table 10-1).

Secondary prevention.

The latest guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) on secondary prevention support aggressive risk reduction therapies for patients with established coronary and other atherosclerotic vascular disease (Table 10-3).[18] For patients at very high risk for future CHD, results from two clinical trials demonstrated the cardiovascular benefit of lipid lowering to levels significantly less than those prescribed by ATP III.[19],[20] Thus the updated 2011 AHA-ACC guidelines support the recommended LDL-C goal of less than 100 mg/dL (2.6 mmol/L) for all patients with CHD and other clinical forms of atherosclerotic disease, but allow for an optional goal of less than 70 mg/dL (1.8

mmol/L) in such patients. These guidelines do not modify the ATP III recommendations for patients without atherosclerotic disease who have diabetes or multiple risk factors and a 10-year risk level for CHD greater than 20% (LDL-C < 100 mg/dL). Although *drug-induced LDL-C reduction remains an essential component* of cardiovascular risk factor management, total risk can also be modified through blood pressure (BP) control, dietary changes, increased exercise, weight loss, and strictly no smoking.

Table 10-3 -- Lipid Management in Secondary Prevention

Lifestyle and Diet
1. Daily exercise and weight control. *(Evidence: B)*
2. Reduce saturated fats, avoid trans fatty acids, limit cholesterol. *(Evidence: B)*
3. Omega-3 fatty acids from fish* or fish oil capsules (1 g/day). *(Evidence: B)*
Lipids and Statins
1. Statins. Aim: LDL-C of <100 mg/dL (2.6 mmol/L). *(Evidence: A)*
2. Lipid profile, all patients. *(Evidence: B)*
3. Statins for triglycerides ≥200 mg/dL (2.26 mmol/L); aim to lower non–HDL-C to <130 mg/dL (3.4 mmol/L). *(Evidence: B)*
4. Statins plus fibrates for triglycerides >500 mg/dL (5.65 mmol/L), to prevent acute pancreatitis. *(Evidence: C)*
5. Statins dosed to reduce LDL-C to <100 mg/dL (2.6 mmol /L), AND by ≥30%. *(Evidence: C)*
Beyond Statins
1. Cholestyramine[†] and/or niacin for statin intolerance, or for statin failure despite higher-dose and higher-potency. *(Evidence: B)*
2. Niacin or fibrate therapy for elevated non–HDL-C despite statin therapy: *(Evidence: B)* or fish oil. *(Evidence: C)*
3. Ezetimibe: consider if above fail. *(Evidence: C)*
For Very High-Risk Patients
1. If triglycerides ≥200 mg/dL (2.26 mmol/L), non–HDL-C goal is <100 mg/dL (2.6 mmol/L). (*Evidence: B)*
2. Statin aim is LDL-C to <70 mg/dL (1.8 mmol/L). *(Evidence: C)*

Modified from Smith et al.[18]

HDL-C, High-density-lipoprotein cholesterol; *LDL-C,* low-density-lipoprotein cholesterol.

Evidence levels: A: Data from multiple randomized clinical trials or metaanalyses. B: Data from single randomized trial or nonrandomized trials. C: Only consensus opinion of experts, case studies, or standard of care.

Very high risk:[18]- Established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥ 200 mg/dL (2.26 mmol/L) plus non–HDL-C ≥ 130 mg/dL (3.4 mmol/L) with low HDL-C <40 mg/dL (1.03 mmol/L), and (4) patients with acute coronary syndrome.

* Not for pregnant or lactating women because of mercury risk.

† Or colesevelam, colestipol.

Blood lipid profile

Total blood cholesterol and LDL-C.

Optimal total blood cholesterol levels are less than 200 mg/dL (5.2 mmol/L)[3],[16] or even much lower at 150 mg/dL (3.9 mmol/L), but it bears reemphasizing that cholesterol level is only part of the patient's absolute global risk. Furthermore, the LDL-C level is the real goal of therapy. Both European and American guidelines emphasize a low LDL-C (<100 mg/dL) as the prime aim of therapy in patients with established coronary disease or equivalent risks. In other patients, higher values of up to 115 mg/dL (3 mmol/L) are acceptable according to the European guidelines, with the Americans being somewhat more tolerant, going up to 130 or even 160 mg/dL as the risk level falls (see Table 10-1). Every reduction in LDL-C of 40 mg/dL (1 mmol/L) is accompanied by a 22% reduction in vascular events.[21]

It has been unclear whether there is a lower limit of LDL-C beyond which no further benefit occurs or whether *"lower is better."* This argument is now largely settled in patients with recent acute coronary syndrome (ACS) because LDL-C values of only 62 mg/dL (1.60 mmol/L) gave convincingly better clinical outcomes than levels of 95 mg/dL (2.46 mmol/L).[22] An alternate interpretation of this study is that high-dose atorvastatin was better at reducing the increased levels of CRP (see previous discussion) found in recovering ACS patients than was low-dose pravastatin. However, in a companion study involving patients with stable coronary disease and much lower values of CRP, high-dose atorvastatin reduced atheroma volume at an LDL-C of 79 mg/dL.[23] In a third series, an LDL-C value of approximately 75 mg/dL (2 mmol/L) marked the point at which progression and regression of the atheroma volume were in balance.[24] The primary prevention JUPITER study (see later) suggests that even lower LDL-C levels may be ideal: a subgroup of patients achieving LDL-C levels less than 50 mg/dL experienced a 65% reduction in cardiovascular events compared with placebo, whereas risk reduction was 44% in the study overall.[6] Thus a provisional conclusion, subject to further verification, is that an LDL-C level between 50-70 mg/dL (2 mmol/L) may be a desirable aim with statin therapy.[25]

High-density lipoproteins.

HDLs are a new focus of interest. In vitro, HDL aids in clearing cholesterol from the foam cells that develop in diseased arteries (Fig. 10-2), either by returning cholesteryl ester directly to the liver through the SR-BI receptor or through transfer to the apolipoprotein (apo) B–containing lipoproteins in exchange for triglycerides (reverse cholesterol transport mediated by cholesteryl ester transfer protein [CETP], see later). HDL is also hypothesized to exert antiinflammatory and antioxidant effects.[26]

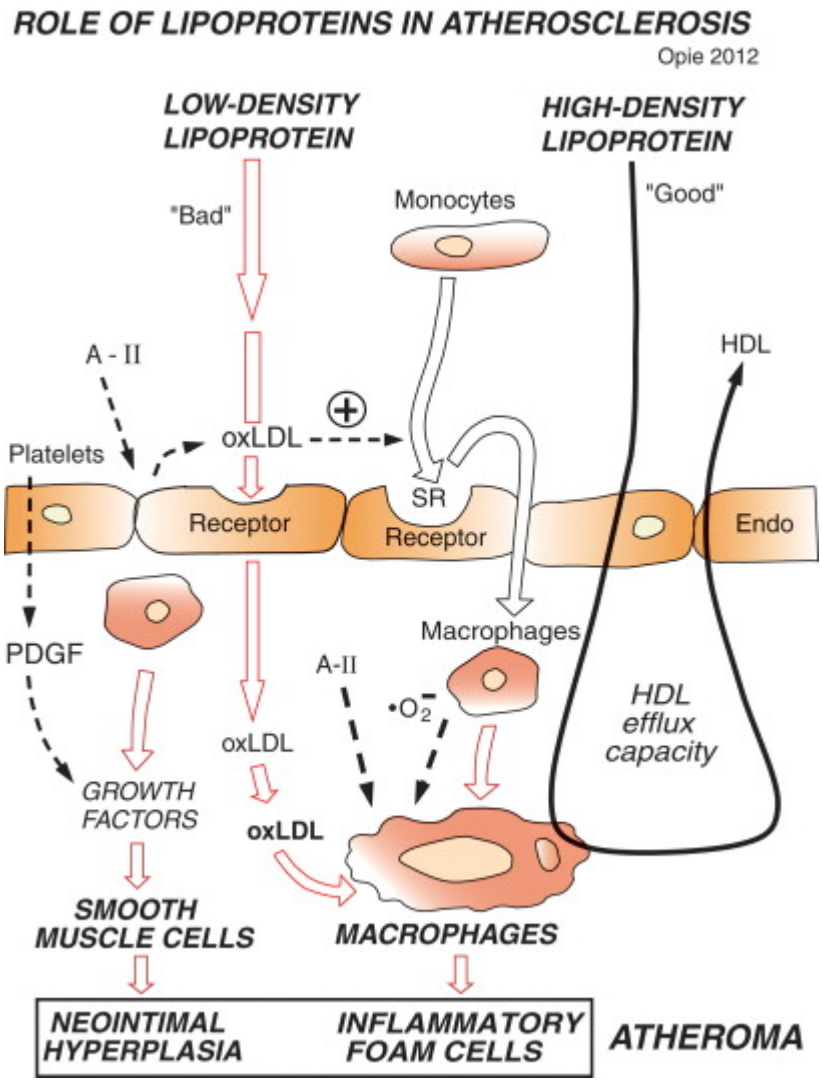

Figure 10-2 Proposed round trip of cholesterol through the vascular endothelium and intima. Oxidized low-density lipoprotein (oxLDL) promotes the formation of foam cells. LDL that remains unoxidized can potentially be reexported. High-density lipoprotein (HDL) acts hypothetically to help export lipid from the foam cells; free radicals form either in the endothelium (endo) or in foam cells. *A-II,* Angiotensin II; *O2,* oxygen; *PDGF,* platelet-derived growth factor; *receptor,* receptor for oxLDL; *SR,* scavenger receptor.
(Figure © L.H. Opie, 2012.)

A low HDL-C is an independent risk factor that is strongly and inversely associated with risk for CHD.[3] In the CARE study, every 10-mg/dL decrease in HDL-C led to a similar 10% increase in risk.[27] Because this is a continuously variable relation, and because a low HDL-C is often associated with other lipid abnormalities such as high triglycerides, an HDL-C of less than 40 mg/dL (<1.03 mmol/L) is seen in ATP III in part as a marker for other risk factors, as in the metabolic syndrome (see later). A value of 60 mg/dL (1.6 mmol/L) or more is a negative (protective) risk factor, although it remains to be proven that raising HDL-C is in itself cardioprotective.[3] Even minor elevations of HDL-C to only 42 mg/dL (1.1 mmol/L) are associated with protection in some large studies.[28] Overall, normalization of HDL-C is desirable, but not as essential as reduction of LDL-C (to <100 mg/dL). Evidence is mixed regarding the potential benefit of increasing HDL-C even when LDL-C levels are very low (<70 mg/dL), with some studies showing that HDL-C levels remain predictive of risk and others showing that it is not.[29],[30] The combination of low HDL-C and high triglycerides is believed to play a contributory role in increasing cardiovascular risk, although there is insufficient evidence to make the same claim about each of these lipid components separately.[31] The AIM-HIGH study[32] (see later), which investigated the effect of raising HDL-C with niacin, did not show cardiovascular benefit in CHD patients who were already treated with a statin to a baseline mean LDL-C of 71 mg/dL. Although ATP III and European guidelines do not propose a target value for HDL-C, they do

recommend correction when possible by lifestyle modification (exercise, modest alcohol intake, loss of weight, nonsmoking). A low HDL-C is often part of a lipid triad known as *atherogenic dyslipidemia,* with the other two components being elevated triglycerides and small, dense LDL particles. The lipid triad is a risk factor in its own right[33] and is commonly found in patients with the metabolic syndrome, type 2 diabetes, and premature CHD.[3] Lifestyle modification, combined with nicotinic acid or fibrates, are the recommended treatments for patients exhibiting the lipid triad.[3]

Cholesteryl ester transfer protein and HDL-C.

Novel drug development aimed at raising HDL-C include strategies for inhibiting the CETP. CETP facilitates the exchange of cholesteryl ester with triglycerides during HDL reverse cholesterol transport, but it is unclear whether its actions are pro- or antiatherogenic. Trials with the CETP inhibitor torcetrapib were halted because of excess mortality and morbidity, possibly caused by molecule-specific increases in BP; a decrease in serum potassium; and increases in serum sodium, bicarbonate, and aldosterone.[34] Two other CETP inhibitors are currently in clinical trials: dalcetrapib, which raises HDL-C but has little effect on LDL-C concentrations, and anacetrapib, which raises HDL-C and lowers LDL-C.[35],[36] Other experimental approaches to exploiting the protective properties of HDL center on mimetic and naturally occurring variants of apo A-I, the primary protein in HDL, and stimulation of apo A-I synthesis.[37]

Blood triglycerides.

Although triglyceride levels are commonly high in patients with coronary artery disease, the specific role of hypertriglyceridemia in atherogenesis remains controversial because it often occurs in conjunction with the lipid triad of obesity, hypertension, and diabetes mellitus. Epidemiologically, an elevated triglyceride level can be an independent risk factor, even with adjustment for HDL-C.[38] Values of more than 150 mg/dL are considered elevated (1.69 mmol/L; versus the prior cutoff of 200 mg/dL)[3], and values below that level are associated with reduced cardiovascular risk even after major reduction of the LDL-C.[38] Levels of more than 1000 mg/dL (11.3 mmol/L) confer increased risk for pancreatitis and require treatment with prescription-strength ω-3 fatty acids, nicotinic acid, or a fibrate. A recent statement from the AHA suggests that fasting triglycerides less than 100 mg/dL are optimal and recommends treatment with intensive dietary and lifestyle therapy, which can lower triglyceride levels by 50% or more.[39] An elevated triglyceride level (>200 mg/dL; 2.3 mmol/L) may be viewed with special concern when combined with high blood LDL-C or low blood HDL-C values. Elevated triglyceride and low HDL-C levels are believed to directly increase cardiovascular risk and should be treated initially with lifestyle modification, followed by niacin, a fibrate, or intensification of LDL-C lowering therapy if necessary.[31]

Metabolic syndrome.

The ATP III guidelines recognize as a secondary target of treatment the cluster of risk factors known as the *metabolic syndrome.* According to ATP III, metabolic syndrome can be diagnosed when three or more of the five basic ingredients are present (see Table 11-1), and it greatly enhances the risk for coronary morbidity and mortality at any level of LDL-C. The underlying pathologic findings of the metabolic syndrome appears to be linked to obesity and insulin resistance. After appropriate control of LDL-C, if elevated, first-line therapy is weight control and increased physical activity. Achieving a significant increase in HDL-C, although very desirable, may require fibrates or nicotinic acid or the development of future therapies.

Non-HDL cholesterol.

Non-HDL cholesterol is a secondary target of treatment in patients with triglyceride levels greater than 200 mg/dL (2.26 mmol/L) and may aid in cardiovascular risk stratification.[3],[40] Measuring non-HDL cholesterol is believed to capture the risk associated with triglyceride-rich particles such as very-low-density lipoprotein (VLDL) and to include all of the apo B–containing particles. The non-HDL cholesterol value is calculated by subtracting the HDL-C value from the total cholesterol value. Treatments that target non-HDL cholesterol include intensified lifestyle measures and possibly drug therapy in high-risk persons. The treatment goals for non-HDL cholesterol are determined by adding 30 mg/dL (0.76 mmol/L) to the LDL-C goals specified in Table 10-2.

Apolipoprotein B and other risk markers.

Apo B, a key atherogenic lipoprotein, is a more sensitive measure of lipid-based risk than LDL-C.[40] The

apo B level reflects the total number of atherogenic apo B–containing lipoproteins and provides information on LDL particle size, which is difficult to measure directly. The ratio of apo B to apo A-I has been shown to be directly related to the risk for myocardial infarction (MI) in a very large 52-country study,[41] and it has outperformed total cholesterol: HDL-C ratios in cardiovascular risk stratification.[42] The apo B: apo A-I ratios are particularly valuable in patients with the metabolic syndrome or type 2 diabetes, which can be characterized by normal LDL-C levels but small LDL particles. High levels of lipoprotein(a) and homocysteine are two other emerging risk factors. Overall, in practice, LDL-C remains the major aim of lipid-lowering therapy, although these alternative measures can help determine the intensity of treatment for patients who appear to be at borderline risk based on traditional risk factors alone.

Cholesterol in special population groups

Secondary hyperlipidemias.

Diabetes mellitus, hypothyroidism, nephrotic syndrome, and alcoholism should be excluded and remedied if possible. Among drugs causing adverse lipid changes are diuretics, β-blockers, progestogens, and oral retinoids.

Diabetic patients.

Patients with diabetes constitute a high-risk group and warrant aggressive risk reduction. Increasingly, type 2 diabetes is regarded as a risk category in its own right and, hence, as a CHD equivalent (see Table 10-1). In recent years, there has been growing awareness of the overlapping pathophysiologic characteristics of CHD and type 2 diabetes, with increased coordination between cardiologists and diabetologists in addressing the joint risk.[43] In patients with type 2 diabetes, there may be a preponderance of smaller, denser, atherogenic LDL particles, even though the LDL-C level may be relatively normal. Metaanalysis of 14 randomized trials with a follow-up of at least 2 years indicates that lipid-lowering drug treatment significantly reduces cardiovascular risk in both diabetic and nondiabetic patients.[44] In terms of absolute risk, it is likely that diabetic patients benefit more than nondiabetic patients in both primary and secondary prevention.

The Diabetes Association Intervention Study (DAIS) reported increased LDL particle size and increased angiographic coronary lumen size in diabetic patients who responded to fenofibrate.[45] The Collaborative Atorvastatin Diabetes Study (CARDS) was a multicenter, randomized, placebo-controlled primary-prevention trial in patients with type 2 diabetes with at least one other risk factor who were treated with atorvastatin, 10 mg/day, compared with placebo. The trial was stopped early because of a favorable clinical benefit of the statin.[46] Taken together with a large subgroup analysis from the Heart Protection Study (HPS),[47] there are strong arguments for considering statin therapy, in addition to lifestyle modification and BP control, in all patients with type 2 diabetes. In the ACCORD Lipid study in patients with type 2 diabetes, combination therapy with simvastatin and fenofibrate did not show increased benefit in cardiovascular event reduction compared with simvastatin alone; however, a subgroup analysis suggests that combination therapy may be beneficial in diabetic patients with both high triglycerides and low HDL-C.[48]

Older adult patients.

Although the relation between cholesterol and coronary disease weakens with age, physicians should continue to consider lipids as a modifiable risk factor in older adults. The absolute risk for clinical coronary disease in older adults is much higher because age is a powerful risk factor and because BP, another risk factor, often increases with age. Furthermore, consider the cumulative effect of lifetime exposure to a coronary risk factor on an older adult patient. The PROSPER study found coronary but no overall mortality benefit with statin treatment in older adults (see section on pravastatin), although this trial may have been too short (3 years) to show major decreases in cerebrovascular disease.[28] The SAGE study confirmed the safety and benefit of intensive treatment with atorvastatin, 80 mg/day, in older adult patients with stable coronary syndromes, but failed to demonstrate the superiority of intensive versus moderate treatment in reaching the primary end point of total ischemia duration from baseline to 1 year.[49] While awaiting further research, judicious application of statin therapy to higher-risk older adults is appropriate.

Women.

Women have a lower baseline risk for CHD than men at all ages except perhaps beyond 80 years.[3] Risk

lags by about 10 to 15 years, perhaps because of a slower rate of increase in LDL-C, higher levels of HDL-C, or ill-understood, protective genetic factors in the heart itself. It is not simply a question of being pre- or postmenopausal. In large statin trials such as the HPS, women experience relative risk reduction comparable to that seen in men.[47] In the MEGA trial, low-dose pravastatin was given to low-risk Japanese patients; 69% were women, who had marginally less CHD risk reduction than men, possibly because of their lower initial risk.[14] The JUPITER trial, which enrolled 6801 women (38% of study population), showed that women experienced similar risk reduction as men, primarily because of reductions in risk for revascularization and unstable angina.[50] A metaanalysis conducted by the JUPITER investigators found that statins reduced cardiovascular events in women in primary prevention trials by one-third.[50]

Pregnant women.

As a group, lipid-lowering drugs are either totally or relatively contraindicated during pregnancy because of the essential role of cholesterol in fetal development. Bile acid sequestrants may be safest, whereas statins must not be used (see Table 12-10; also see “Contraindications and Pregnancy Warning” in the later section on statins).

Dietary and other nondrug therapy

Lifestyle and risk factors.

Nondrug dietary therapy is basic to the management of all primary hyperlipidemias and frequently suffices as basic therapy when coupled with weight reduction, exercise, ideal (low) alcohol intake, and treatment of other risk factors such as smoking, hypertension, or diabetes. Regular exercise may also increase insulin sensitivity and lessen the risk of type 2 diabetes. If lifestyle recommendations, including diet, were rigorously followed, CHD would be largely eliminated in those younger than age 70.[51] However, high-intensity lifestyle modification is required to prevent progression or even to achieve regression of CHD.

Diet.

Changes in diet are an absolute cornerstone of lipid-modifying treatment. As a general aim, saturated fats should be less than 7% of the calories, and total fat less than approximately 30% (Table 10-4). Monounsaturates, such as *olive oil,* are relatively beneficial within the framework of total lipid reduction, and patients, especially hypertensive older adults, should limit sodium intake (see Chapter 7). The dietary fatty acid recommendations can be simplified to reducing *trans*-fatty acids and saturated fatty acids, which are largely of animal origin, and increasing other fatty acids from plants or fish oils. Exceptions are coconut oil and crustacean flesh, such as lobsters and prawns, which are high in saturated fatty acids.

Table 10-4 -- Suggested Nutrient Composition for Diet

Nutrient	Recommended Intake
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat*	25%-35% of total calories
Carbohydrate	50%-60% of total calories
Fiber	20-30 g/day
Protein	<15% of total calories
Cholesterol	<200 mg/day
Total calories (energy)	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain

From Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[3]

* US guidelines suggest a range of total fat consumption, provided saturated fats and trans-fatty acids are kept low. A higher intake of unsaturated fats can help reduce triglycerides and raise high-density-lipoprotein cholesterol in patients with the metabolic syndrome.

A *Mediterranean-type diet* confers increased postinfarct protection,[52] as discussed under post-MI management in Chapter 12. Patients are told to eat more bread, more fiber (10 to 25 g/day), more fresh vegetables, more fish, and less meat, with “no day without fruit” and canola margarine to replace butter and cream. Olive oil is often used. The better the adherence to this diet, the better the survival rate[53] (see “ω-3 Fatty Fish Oils” later). Higher-risk individuals may require a stricter diet with reduced intake of cholesterol-raising nutrients, saturated fats less than 7% of total calories, and dietary cholesterol less than 200 mg/day. Vegetable oils containing polyunsaturated linoleic acid are not as ideal as once thought, and total lipid intake must be restricted. *In brief, the ideal diet is low in total fat and cholesterol, high in fiber, and high in fresh vegetables and fruit, with modest sodium restriction*. Much the same diet benefits hypertensives (see Chapter 7) and is recommended by the AHA, the American Diabetes Association, and the American Cancer Society.[54]

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Drug-related lipidemias

Cardiac drugs and blood lipid profiles

β-Blockers and diuretics may harmfully influence blood lipid profiles (Table 10-5), especially triglyceride values. Diuretics, in addition, tend to increase total cholesterol unless used in low doses. Nonetheless, cardiac drugs known to be protective, such as β-blockers, should not be withheld on the basis of their lipid effects alone, especially in postinfarct patients when there is clear indication for the expected overall benefit. Statins appear to counter some of the effects of β-blockers on blood lipids.

Table 10-5 -- Effects of Antihypertensive Agents on Blood Lipid Profiles (Percentage Increase or Decrease)

Agent	TC	LDL-C	HDL-C	TG
Diuretics				
Thiazides[126]	14	10	2	14
Low-dose TZ[127]*	0	0	0	0
Indapamide[128]	0 (+9)	0	0	0
Spironolactone[129]	5	?	?	31
β-Blockers				
Grouped (>1 year)[130]	0	0	–8	22
Propranolol[126]	0	–3	–11	16
Atenolol[126]	0	–2	–7	15
Metoprolol[126]	0	–1	–9	14
Acebutolol[127]*	–3	–4[†]	–3	6
Pindolol[126]	–1	–3	–2	7
α-Blockers				
Grouped	–4	–13	5	–8
Doxazosin[127]*	–4[†]	–5[†]	2	–8
αβ-Blocker				
Labetalol[126]	2	2	1	8
Carvedilol[131]	–4	?	7	–20
CCBs				
Grouped[126]	0	0	0	0
Amlodipine[127]*	–1	–1	1	–3
ACE Inhibitors				
Grouped	0	0	0	0
Enalapril[127]	–1	–1	3	–7
Angiotensin Receptor Blockers				
Losartan[128]	(0)[‡]	(0)	(0)	(0)
Central Agents				
MD + TZ	0	0	0	0

ACE, Angiotensin-converting enzyme; *CCBs,* calcium channel blockers; *HDL-C,* high-density-lipoprotein cholesterol; *LDL-C,* low-density-lipoprotein cholesterol; *MD,* methyldopa; *TC,* total cholesterol; *TG,* triglyceride; *TZ,* thiazide.

* Chlorthalidone 15 mg/day; acebutolol 400 mg/day; doxazosin 2 mg/day; amlodipine 5 mg/day; enalapril 5 mg/day; data placebo-corrected.

† <0.01 versus placebo over 4 years.

‡ (0) = no long-term data.

β-blockers.

β-Blockers tend specifically to reduce HDL-C and to increase triglycerides. β-Blockers with high intrinsic sympathomimetic activity or high cardioselectivity may have less or no effect (as in the case of carvedilol with added α-blockade). The fact that β-blockers also impair glucose metabolism is an added cause for concern when giving these agents to young patients (see Chapter 7, p. 250). Nonetheless, note the strong evidence for protective effects of β-blockers in postinfarct and heart failure patients (see Chapter 1, pp. 10-13). In stable effort angina, calcium channel blockers may have a more favorable effect on triglycerides and HDL-C than β-blockers. In hypertensives, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and calcium channel blockers are all lipid neutral.

Diuretics.

Doses should be kept low (see Chapter 7, p. 239). In ALLHAT, chlorthalidone, 12.5 to 25 mg daily over 5 years increased total cholesterol by 2 to 3 mg/dL.[55] In the ALPINE study, hydrochlorothiazide, 25 mg, combined with atenolol in most patients, increased blood triglycerides and apo B, while decreasing HDL-C.[56]

Lipid-neutral cardiac drugs.

Cardiac drugs that have no harmful effects on blood lipids include the ACE inhibitors; the angiotensin receptor blockers; the calcium channel blockers; vasodilators such as the nitrates and hydralazine; and the centrally acting agents, such as reserpine, methyldopa, and clonidine. The α-blockers, including prazosin and doxazosin, favorably influence the lipid profiles.

Oral contraceptives.

When oral contraceptives are given to patients with ischemic heart disease or with risk factors such as smoking, possible atherogenic effects of high-estrogen doses merit attention. In postmenopausal women, the cardiovascular benefits of hormone replacement therapy (HRT) have not been supported by clinical trials (see “Estrogens” later).

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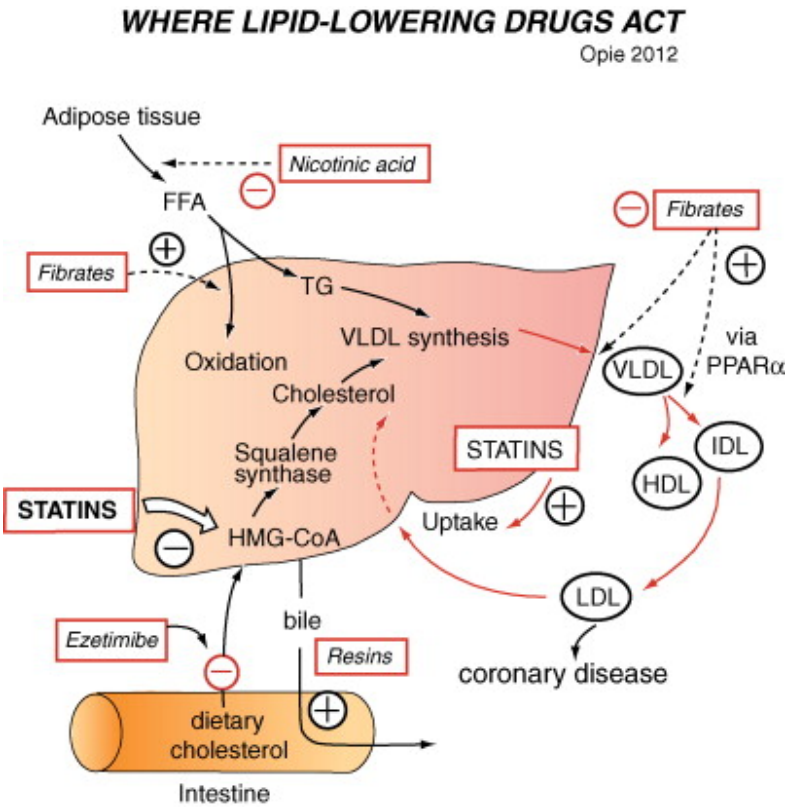
The statins: 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors

The currently available lipid-lowering drugs can be divided into the statins, the bile acid sequestrants, nicotinic acid, the fibrates, and cholesterol absorption inhibitors. These all reduce LDL-C. Of these drugs, statins are now usually the first drugs of choice because of their relatively few side effects and predictable benefits for treating LDL-C. All of the statins decrease hepatic cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (Fig. 10-3). They are highly effective in reducing total cholesterol and LDL-C, they usually increase HDL-C, and long-term safety and efficacy are now established. Many are now available in generic form. The landmark Scandinavian Simvastatin Survival Study (4S) showed that simvastatin used in secondary prevention achieved a reduction in total mortality and in coronary events.[57] This was soon followed by a successful primary prevention study with pravastatin in high-risk men.[58] Successful primary prevention of common events has been found in patients with LDL-C values near the U.S. national average.[59] An interesting recent concept is that lipid-lowering drugs may act in ways beyond regression of the atheromatous plaque, for example, by improving endothelial function, stabilizing platelets, reducing fibrinogen (strongly correlated with triglyceride levels), or inhibiting the inflammatory response associated with atherogenesis.[60] These *nonlipid or pleiotropic* benefits have primarily been extrapolated to humans based on experimental studies showing substantial nonlipid cardiovascular protection with statins. One proposed mechanism for the antiinflammatory effects of statins following ACS is reduction of phospholipase A2 biomarkers.[61] Statins have also been investigated for potential beneficial effects on disease states unrelated to atherosclerosis, such as arrhythmias, cancer, and Alzheimer's and other neurodegenerative disorders. A possible example is the reduction of stroke by statins. In 61 studies with 55,000 vascular deaths, statins reduced the incidence of stroke, sometimes strikingly, despite a lack of association with blood cholesterol levels.[62] Currently, the dominant view is that apparent pleiotropic effects can largely be explained by lipid reduction, especially of LDL-C (Fig. 10-4).



Bile acid sequestrants: The resins

Bile acid sequestrants—*cholestyramine (Questran), colesevelam (Welchol),* and *colestipol (Colestid)*—bind to bile acids to promote their secretion into the intestine. There is increased loss of hepatic cholesterol into bile acids and hepatic cellular cholesterol depletion, the latter leading to a compensatory increase in the hepatic LDL receptor population so that the blood LDL is more rapidly removed and total cholesterol falls (see Fig. 10-4). There may be a transitory compensatory rise in plasma triglycerides that is usually ignored, but may require co-therapy. Colesevelam received an additional FDA indication in 2008 for improved glycemic control in the treatment of type 2 diabetes, as combination therapy with metformin, sulfonylureas, or insulin. The major trial conducted with resins was the Lipid Research Clinics Coronary Primary Prevention Trial, in which cholestyramine modestly reduced CHD in hypercholesterolemic patients and improved blood lipid profiles, yet without effect on overall mortality.[97] Regarding *drug interactions,* watch for interference with the absorption of digoxin, warfarin, thyroxine, and thiazides, which need to be taken 1 hour before or 4 hours after the sequestrant. Impaired absorption of vitamin K may lead to bleeding and sensitization to warfarin. Poor palatability is the major problem. *Combination therapy* is often undertaken, and coadministration with a statin may exploit the complementary mechanisms of action of these two drug classes. Resins may increase triglycerides, so a second agent such as nicotinic acid or a fibrate may be required to adequately lower triglycerides. Resins should be used with caution in patients with hypertriglyceridemia. Long-term therapy with resins may result in a compensatory increase in HMG-CoA reductase activity that tends to increase cholesterol levels.

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Inhibition of lipolysis by nicotinic acid (niacin)

Nicotinic acid was the first hypolipidemic drug to reduce overall mortality.[98] It is the cheapest compound and can be bought over the counter. The basic effect of nicotinic acid may be decreased mobilization of free fatty acids from adipose tissue, so that there is less substrate for hepatic synthesis of lipoprotein lipid (see Fig. 10-3). Consequently there is less secretion of lipoproteins so that LDL particles, including triglyceride-rich VLDL, are reduced. Nicotinic acid is the drug that best increases HDL-C, and is recommended for the *lipid triad* (small dense LDL, high triglycerides, low HDL-C).[3] The lipid-lowering effects of nicotinic acid are not shared by nicotinamide and have nothing to do with the role of that substance as a vitamin.

The AIM-HIGH study, an outcomes study examining the effect of adding extended-release niacin to simvastatin in patients with cardiovascular disease, was stopped early because of lack of efficacy.[99] Niacin demonstrated no incremental benefit in cardiovascular event reduction for patients already optimally treated with lipid-lowering therapy to a mean LDL-C of 71 mg/dL at baseline; in addition, there was an unexplained increase in ischemic stroke in the niacin arm. After 36 months, there was only a 4 mg/dL difference in HDL-C between treatment groups, and it may be that the study was underpowered to show benefit with niacin on top of statin therapy. Interestingly, niacin was found to induce carotid plaque regression in a small study using intravascular ultrasound and was superior to ezetimibe, which did not.[100] Prescribing patterns with niacin should not be altered; the ongoing HPS2-THRIVE study with similar design and endpoints will provide further information on the effects of increasing HDL-C levels and reducing triglycerides with niacin.

Dose, side effects, and contraindications.

The dosage required for lipid lowering is up to 4 g daily, achieved gradually with a low starting dose (100 mg twice daily with meals to avoid gastrointestinal discomfort) that is increased until the lipid target is reached or side effects occur. A lower target dosage (1.5 to 2 g daily) still has a marked effect on blood lipids with better tolerability and only two daily doses. If taken with meals, flushing is lessened. *Niaspan* is an extended-release formulation with an initiation starter pack that titrates up the dose to reduce side effects. The recommended maintenance dose is 1 to 2 g once daily at bedtime.

On the debit side, this drug has numerous subjective *side effects,* although these can be lessened by carefully building up the dose. Through ill-understood mechanisms, nicotinic acid causes prostaglandin-mediated symptoms such as flushing, dizziness, and palpitations. Flushing, which is very common, lessens with time and with use of the extended-release formulation. *Caution* should be used in patients with peptic ulcer, diabetes, liver disease, or a history of gout. Impaired glucose tolerance and increased blood urate are reminiscent of thiazide side effects, also with an unknown basis. Hepatotoxicity may be linked to some *long-acting preparations* (extended-release capsules or tablets), whereas flushing and pruritus are reduced. Myopathy is rare. Use in pregnant women is questionable. Nicotinic acid and statin co-therapy gives a better effect on the lipid levels at the cost of an increased (albeit low) risk of hepatotoxicity and of myopathy.

The fibrates

As a rule, none of the fibrates reduces blood cholesterol as much as do the statins or nicotinic acid. Their prime action is to decrease triglyceride, thereby increasing HDL-C, and to increase the particle size of small, dense LDL. Like nicotinic acid, they are therefore suitable for use in atherogenic dyslipidemia.[3] They are first-line therapy to reduce the risk for pancreatitis in patients with very high levels of plasma triglycerides and may be useful with more modest triglyceride elevations or when the prime problem is a low HDL-C.[101] At a molecular level, fibrates are agonists for the nuclear transcription factor peroxisome proliferator–activated receptor-α (PPAR-α) that stimulates the synthesis of the enzymes of fatty acid oxidation, thereby reducing VLDL triglycerides.[3] Although all belong to the same group, structural differences between the compounds seem important because of the very different results of large-scale trials on clofibrate (unfavorable) and gemfibrozil (favorable).

Class warnings.

There are five warnings or reservations for this class of drugs, as found in the fenofibrate package insert. First, the early experience with clofibrate suggested that fibrates may increase mortality. This fear has not been borne out by trials of other fibrates, and gemfibrozil has significant coronary benefits. Second, hepatotoxicity may occur, with a pooled analysis of 10 placebo-controlled trials showing elevated transaminases in 5.3% of patients given fenofibrate compared to 1.1% on placebo. Third, cholelithiasis is a risk, because fibrates act in part by increasing biliary secretion of cholesterol; however, again this was not found in the Veterans Affairs Cooperative Studies Program High-density lipoprotein cholesterol Intervention Trial (VA-HIT) study. Fourth, there is an important drug interaction with concomitant oral anticoagulants, so that the warfarin dose needs to be reduced. Fifth, combined therapy with statins should be avoided unless the potential beneficial effects on lipids outweigh the increased risk for myopathy (see later section on “Combination Therapy”).

Gemfibrozil (lopid)

Major trials.

This agent was used in the large Helsinki Heart Study in a primary prevention trial on 2000 apparently healthy men with modest hypercholesterolemia observed for 5 years.[102] With a dose of 600 mg twice daily, there was a major increase in HDL-C (12%), a decrease in total cholesterol and LDL-C (8% to 10%), and a substantial reduction in triglycerides with an overall reduction in coronary events. Although the total death rate was unchanged, the study was not powered to assess mortality. An open-label follow-up found mortality reduction after 13 years.[103] Despite the theoretical risk of gallstone formation, none was found.

Benefit in men with low HDL-C.

The VA-HIT was a secondary intervention trial in men with CHD whose primary abnormality was a low HDL-C: less than 40 mg/dL (1 mmol/L), with a mean of 32 mg/dL.[101] The LDL-C was 140 mg/dL (3.6 mmol/L) or less, with a mean of 112 mg/dL. Over 5 years, the mean HDL-C was 6% higher, the mean triglyceride 31% lower, and the total cholesterol 4% lower, whereas the mean LDL-C level did not change. There was a 24% reduction in the outcome of death from CHD, nonfatal MI, and stroke. The 5-year NNT to prevent one major outcome event was 23, which compared well with the major statin trials. This trial showed that major reduction of total cholesterol or LDL-C was not essential to achieve outcome benefit.

Dose, side effects, contraindications.

This agent is currently licensed in the United States for treatment of the lipid triad. The dose is 1200 mg given in two divided doses 30 minutes before the morning and evening meals. *Contraindications* are hepatic or severe renal dysfunction, preexisting gallbladder disease (possible risk of increased gallstones, not found

in the HIT study), and simvastatin. There are *drug interactions* to consider. Because it is highly protein bound, gemfibrozil potentiates warfarin. When combined with statins, there is an increased risk for myopathy with myoglobinuria and a further rare risk for acute renal failure (for perspective, see "Combination Therapy" section).

Bezafibrate

This agent (*Bezalip* in the United Kingdom; not available in the United States) resembles gemfibrozil in its overall effects, side effects, and alterations in blood lipid profile. Uniquely among fibrates, it is also a PPAR-γ agonist, thereby theoretically stimulating the enzymes that regulate glucose metabolism. Hence plasma glucose tends to fall with bezafibrate, which may be useful in diabetics or those with abnormal glucose metabolic patterns. In patients with coronary artery disease, bezafibrate slows the development of insulin resistance.[104] As with other fibrates, warfarin potentiation is possible, and co-therapy with statins should ideally be avoided. In addition, myositis, renal failure, alopecia, and loss of libido have occurred. The dose is 200 mg two to three times daily; however, once daily is nearly as good, and there is now a slow-release formulation available (*Bezalip-Mono,* 400 mg once daily). Some increase in plasma creatinine is very common and of unknown consequence. The major problem with this agent is that, unlike gemfibrozil and the statins, there are as yet no major long-term outcome trials with clear results. In the Bezafibrate Infarction Prevention (BIP) study, patients with a low HDL-C and modest elevations of LDL-C experienced trends in favor of bezafibrate, but no clear advantage was observed except post hoc in a subgroup of patients with initial triglyceride levels greater than 250 mg/dL.[105]

Fenofibrate (tricor, trilipix, lipofen, antara, lofibra)

Fenofibrate is a prodrug converted to fenofibric acid in the tissues. The licensed indications are as adjunctive therapy to diet to reduce LDL-C and total cholesterol, triglycerides, and apo B and to increase HDL-C. Fenofibrate is also indicated for treatment of hypertriglyceridemia, although the effect on the risk for pancreatitis in patients with very high triglyceride levels, typically exceeding 2000 mg/dL, has not been well studied. The Trilipix formulation, which contains fenofibric acid rather than the ester, has an indication for mixed dyslipidemia in combination with statin therapy. Tablets are 48 or 145 mg for Tricor, but other formulations have slightly altered dosing. The dose for Tricor is 48 to 145 mg once daily (half-life of 20 hours), taken with food to optimize bioavailability. Predisposing diseases such as diabetes and hypothyroidism need to be excluded and treated. The DAIS suggests that treatment with fenofibrate in patients with type 2 diabetes reduces progression of atherosclerosis, with a nonsignificant trend to cardiovascular event reduction.[45] The FIELD study similarly attempted to assess the effect of fenofibrate on cardiovascular disease events in patients with type 2 diabetes, but failed to reach the primary endpoint of reduction in coronary events, possibly because the study design allowed for initiation of statin therapy in both the placebo and fenofibrate treatment arms.[106] Despite these null findings, FIELD did show a decrease in total cardiovascular events, primarily caused by significant reductions in nonfatal MI and revascularizations. However, the ACCORD Lipid study, which examined the effects of fenofibrate in patients with type 2 diabetes treated with simvastatin, found no cardiovascular benefit with the drug, except in a subgroup of individuals with low baseline HDL-C and high triglycerides.[48] Post hoc analyses of three other fibrate trials, including the Helsinki Heart Study, BIP, and FIELD, similarly suggested benefit with a fibrate in a subgroup of patients with atherogenic dyslipidemia.[48] Thus the cumulative body of evidence indicates that the prime lipid-lowering therapy for prevention of macrovascular complications in most diabetic patients remains a statin.

Weight reduction, increased exercise, and elimination of excess alcohol are recognized in the package insert as essential steps in the overall control of triglyceride levels. In addition, there is a warning that cyclosporine co-therapy may cause renal damage with decreased excretion of fenofibrate and increased blood levels. Note risk of bleeding in patients given warfarin (bold warning in package insert). Animal data suggest a deleterious effect in pregnancy. Avoid in nursing mothers (carcinogenic potential in animals). Use with caution in older adults or patients with renal dysfunction (renal excretion).

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Cholesterol absorption inhibitors: Ezetimibe

Cholesterol absorption inhibitors selectively interrupt intestinal absorption of cholesterol and other phytosterols. The first of this drug class to reach the market, ezetimibe (*Zetia*), acts at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to decreased delivery of intestinal cholesterol to the liver,[107] which reduces hepatic cholesterol and increases cholesterol clearance from the blood. This mechanism is complementary to that of the statins. This drug has a half-life of 22 hours and is not metabolized by the CYP system.

Ezetimibe monotherapy is an option for patients with statin intolerance, and combination therapy with statins is effective in those requiring large LDL-C reductions. Its clinical benefit in primary and secondary prevention has yet to be established.

Indications.

As monotherapy in primary hypercholesterolemia, ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL-C, and apo B. Combination therapy with simvastatin is approved in the United States for lipid indications similar to ezetimibe alone, but is also licensed to increase HDL-C (which it modestly elevates). In homozygous familial hypercholesterolemia, ezetimibe may be combined with atorvastatin or simvastatin, used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis), or used if such treatments are unavailable. Ezetimibe is indicated as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

Dosage and effect.

The recommended dosage of ezetimibe is 10 mg once daily, administered with or without food. The daily dose of ezetimibe may be taken at the same time as the HMG-CoA reductase inhibitor, according to the dosing recommendations for the statin. As fixed-dose monotherapy, ezetimibe produces an approximate 12% reduction in total cholesterol, an 18% reduction in LDL-C, and modest beneficial effects on triglycerides and HDL-C, with no apparent safety concerns. No dosage adjustment is necessary in patients with mild hepatic insufficiency, but the effects of ezetimibe have not been examined in patients with moderate or severe hepatic insufficiency. No dosage adjustment is necessary in patients with renal insufficiency or in geriatric patients. As *co-therapy*, the lipid effects of ezetimibe and a statin appear to be additive. For example, with pravastatin, 10 to 40 mg, LDL-C fell by 34% to 41% and triglycerides by 21% to 23%, and HDL-C rose by 7.8% to 8.4%, with a safety profile similar to pravastatin alone.[108] Coadministration of a resin may dramatically decrease the bioavailability of ezetimibe; therefore its dosing should occur either 2 or more hours before or 4 or more hours after administration of the resin.

Combination therapy

Combined statin plus fibrate.

Statins alone are not the answer to all lipid problems.[3] In secondary prevention, the currently ideal lipid levels may be difficult to achieve with only a statin, and the increase in HDL-C is especially limited. In primary prevention, for patients with severe hypercholesterolemia or familial combined hyperlipidemia with marked triglyceride elevations, combination of a statin with a fibrate is increasingly seen as an option. The statin is very effective in the reduction of LDL-C, whereas the fibrate reduces triglycerides, increases LDL particle size, and increases HDL-C. Two reservations are, first, the lack of any unambiguously favorable large-scale outcome studies with such combinations and, second, the fear of myopathy. The latter is now increasingly seen as a rather rare event during combination therapy.[74],[109],[110] When statins are metabolized through CYP3A4 (see Table 10-6), the risk of adverse interaction with fibrates is greater during co-therapy with erythromycin, azole antifungals, and antiretrovirals.[109] A logical combination would be a statin and a fibrate that are metabolized by noncompeting pathways, for example, fluvastatin or rosuvastatin with fenofibrate. Hepatotoxicity seems to be a consistent but rare side effect of statins, also during statin-fibrate therapy.[111]

Combined statin plus resin or nicotinic acid.

Another choice is between a statin plus a resin, or a statin plus nicotinic acid. In the FATS angiographic trial, men with coronary disease at high risk for cardiovascular events received either lovastatin or nicotinic acid, combined with colestipol. Both regimens were equally effective on blood lipids, and angiographically measured coronary stenosis was lessened, although side effects were worse on the nicotinic acid regimen.[112] A combination preparation has reached the market that pairs extended-release nicotinic acid at doses of 500, 750, and 1000 mg with lovastatin, 20 mg (*Advicor*). This agent is indicated for treating primary hypercholesterolemia and mixed dyslipidemias where the lipid triad is present.

Ezetimibe plus statin.

Two studies on carotid arterial lesions found that ezetimibe plus a statin (Vytorin) does less well than expected[111] or has adverse effects.[98] When ezetimibe was added to a statin in patients with a well-controlled lipid profile to decrease LDL-C, which it did, the carotid-media thickness paradoxically increased; when niacin was added to the statin, HDL-C was increased, triglycerides decreased, and there were fewer major cardiovascular events than with ezetimibe.[98] On the benefit side, the combination of simvastatin plus ezetimibe reduced the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease in the SHARP trial.[113],[114] Note that this study could equally well argue for lipid-lowering with a statin in dialysis patients.[115] The FDA updated the prescribing information for Vytorin to include data from SHARP.[116] Although it approved the ezetimibe-simvastatin combination for use in chronic kidney disease as a new indication, ezetimibe without simvastatin was not approved because the relative contributions of simvastatin and ezetimibe were not assessed in the trial. Also for this reason, the prescribing information for ezetimibe alone (Zetia) does not contain data from SHARP. *FDA recommendations to reduce myopathy with simvastin are also applicable to Vytorin.* In brief, Vytorin should not be used with the conazole group of drugs, some antibiotics, HIV protease inhibitors, cyclosporine, and gemfibrozil. The 10-mg dose should not be exceeded in patients taking amiodarone, verapamil, and diltiazem. The 20-mg dose should not be exceeded with amlodipine and ranolazine (Ranexa). The 80-mg dose should not be started.[84]

Niacin plus laropiprant.

Niacin plus laropiprant (Tredaptive) is approved in the European Union as a modified-release tablet in a dose of 1 g nicotinic acid and 20 mg laropiprant for dyslipidemia and primary hypercholesterolemia. Laropiprant minimizes the flushing side effect of using niacin alone.[117] Tredaptive is approved for use in

combination with statins, but may be used as monotherapy if statins are inappropriate or not tolerated. However, it is not approved by the FDA and is being tested for clinical event reduction in the large HPS2-THRIVE trial.

Other combinations.

Because of the enormous popularity of the statins, it is likely that various other combinations will be considered in the future, such as a statin with low-dose aspirin and other cardioprotective drugs. Some experts have put forth the concept of a “polypill” that combines several heart-beneficial agents as a potential approach.

Natural antiatherosclerotic agents

Estrogens.

Despite observational studies that noted an association between HRT and reduced coronary risk in women, prospective, randomized clinical trials, including the secondary prevention Heart Estrogen/Progestin Replacement Study and the primary prevention Women's Health Initiative, have reported no clinical cardiovascular benefits with HRT compared with placebo.[118],[119] An increased risk for thrombotic complications in the early years of HRT makes such therapy even less attractive for cardiovascular risk management. Caveats are the following: (1) in younger women closer to menopause there was no increase in cardiovascular disease and short-term use for relief of vasomotor symptoms can be justified;[120] and (2) the lipid pattern matters, in that a high LDL-C/HDL-C of 2.5 or more is associated with an increased CVD risk (odds ratio 1.83) whereas those with a low ratio less than 2.5 had no increase when given conjugated equine estrogen with or without medroxyprogesterone.[121]

Dietary antioxidants.

In the light of the negative mega-studies showing no cardiovascular protection by vitamin E, either as primary or secondary prevention (see Chapter 12, p. 464), enthusiasm for antioxidant supplements has cooled. A Mediterranean diet, which in the United States is associated with decreased all-cause mortality, is likely to contain adequate amounts of antioxidants mixed in the right proportions.

ω-3 fatty fish oils.

Prescription-strength fish oil (Lovaza) is FDA approved to decrease triglycerides 500 mg/dL or more at a dose of 4 g/day. Nonprescription fish oil may also be protective, at least in the postinfarct period and when the benefit is largely independent of any change of blood lipid levels and may relate to sodium channel blockade. Several good epidemiologic studies relate intake of ω-3 fish oils to decreased sudden death or increased life span.

Plant sterol and stanol margarines.

Plant sterols can be converted to the corresponding stanol esters that interfere with the intestinal uptake of cholesterol, to cause "cholesterol malabsorption." Daily intake of 2 to 3 g reduces LDL-C by approximately 6% to 15%.[3] In the United States, *Benecol* margarine is available (dose, 2 to 2.5 g/day).

Folic acid.

The role of homocysteine as a risk factor remains controversial.[3] Nonetheless, convincing studies show that reducing homocysteine with folic acid fails to lower the coronary risk[122],[123] so that there is little point in searching for homocysteinemia (unless genetic excess is suspected).

Alcohol.

There is a U-shaped relation between alcohol intake and coronary artery disease, with modest intake rates having a protective effect and higher rates an adverse effect, the latter probably by elevation of triglycerides and BP. Modest quantities of alcohol may promote protection by giving a more favorable blood lipid profile and, in particular, increasing HDL-C. In addition, red wine contains flavonoids that give experimental coronary vascular protection, perhaps by an antioxidant effect. However, the potential for abuse makes it difficult to give a whole-hearted endorsement to alcohol consumption as a preventive measure. Dealcoholized red wine has favorable vascular compliance effects when given to humans.[124] For teetotallers, a liberal intake of red grape juice or cranberry juice could be equally protective.

Juices, tea, and nuts.

In a variety of studies, red fruit juices such as cranberry juice, purple or red grape juice, black tea, and nuts have shown varying degrees of benefit on lipid profiles or vascular function. Almonds are well-studied, with a dose-response benefit.[125] Full-dose unblanched almonds (approximately 75 g/day) reduced LDL-C of hyperlipidemic subjects by 9%, reduced conjugated dienes (evidence of oxidized LDL) by 14%, and raised HDL-C by 4%. Herbal remedies are unsupported by data.

Summary

1. ***Primary prevention.*** In primary prevention of cardiovascular disease, global risk factor assessment and correction is the current favored approach. The atherogenic components of blood lipids and especially LDL are an important part of an overall risk factor profile that includes factors that cannot be changed, such as age, sex, and family history of premature disease, and those that can, such as BP, diet, smoking, exercise, and weight. Elevated CRP can help identify individuals at increased risk despite having low to normal LDL-C. The ideal blood cholesterol and LDL-C levels appear to be falling lower and lower, and a Mediterranean diet is a currently recommended dietary approach.
2. ***Secondary prevention.*** In secondary prevention, strict LDL-C lowering (recent ultralow aim for very high risk: LDL-C <70 mg/dL or 1.8 mmol/L) is an essential part of a comprehensive program of risk-factor modification. Strict dietary modification is required. Among the cardiac drugs tending to cause hyperlipidemias are β-blockers (especially propranolol) and thiazide diuretics; however, when these drugs are indicated, their protective effect overrides the relatively small changes in blood lipids, especially with statin co-therapy.
3. ***Increasing use of statins***. The decisive 4S and several other studies have shown substantial total and cardiac mortality reduction when statins (HMG-CoA reductase inhibitors) are given to postinfarct patients with modest to severe hypercholesterolemia. The HPS extends the benefits of statins to all high-risk patients defined by any clinical vascular disease or by diabetes, regardless of baseline total cholesterol or LDL-C. Statins have few serious side effects or contraindications.
4. ***Statins in primary prevention***. Although lifestyle and dietary measures remain the basis of primary prevention, the impressive results of one large statin trial (JUPITER), in individuals with blood cholesterol levels that are within the normal range, without known coronary disease, but with elevated levels of CRP, raise important issues for the future prevention of coronary disease.
5. ***Fibrates.*** Fibrates act differently from statins at a molecular level to modify tissue fatty acid metabolism by stimulation of PPAR-α, and clinically to decrease triglyceride, increase HDL-C, and decrease LDL particle size, with only a modest fall in LDL-C. Fibrates appear to have the most benefit in patients with low HDL-C and high triglyceride levels, which is part of the adverse risk profile (lipid triad) of the metabolic syndrome.
6. ***Combination therapy.*** Combination therapy is now increasingly used to achieve goal lipid levels. The principle is to combine two different classes of agents with different mechanisms of action, such as a statin and a fibrate or nicotinic acid. Most sources warn against these combinations because of the fear of muscle or renal damage or hepatotoxicity. Nonetheless, there is a growing consensus that judicious use of combination therapy, when required, is likely to confer more benefits than harm. Caution is still required, with regular clinical observation, patient education about side effects, and monitoring of CK and blood liver enzymes. An additional combination, approved for use in chronic kidney disease, is that of simvastatin with a cholesterol absorption inhibitor, ezetimibe.
7. ***Interactions with antiretrovirals.*** Recent FDA warnings relate to all statins except pravastatin and pitavastatin. Specifically, there are dose limitations for atorvastatin and rosuvastatin, with major contraindications for use with simvastatin and lovastatin.
8. ***Side effects.*** Hyperglycemia and new diabetes, first noted with rosuvastatin, are now recognized. Although this metabolic harm is more than outweighed by the overall cardiovascular benefits of statin therapy, periodic checks for glycemia are strongly advised.
9. ***HRT.*** HRT in postmenopausal women can no longer be linked to major cardiovascular benefit. *Dietary antioxidants* may be obtained in adequate amounts by following the Mediterranean-type diet, whereas vitamin E supplements, in particular, have not given protection either in secondary prevention or as primary prevention in high-risk individuals.

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