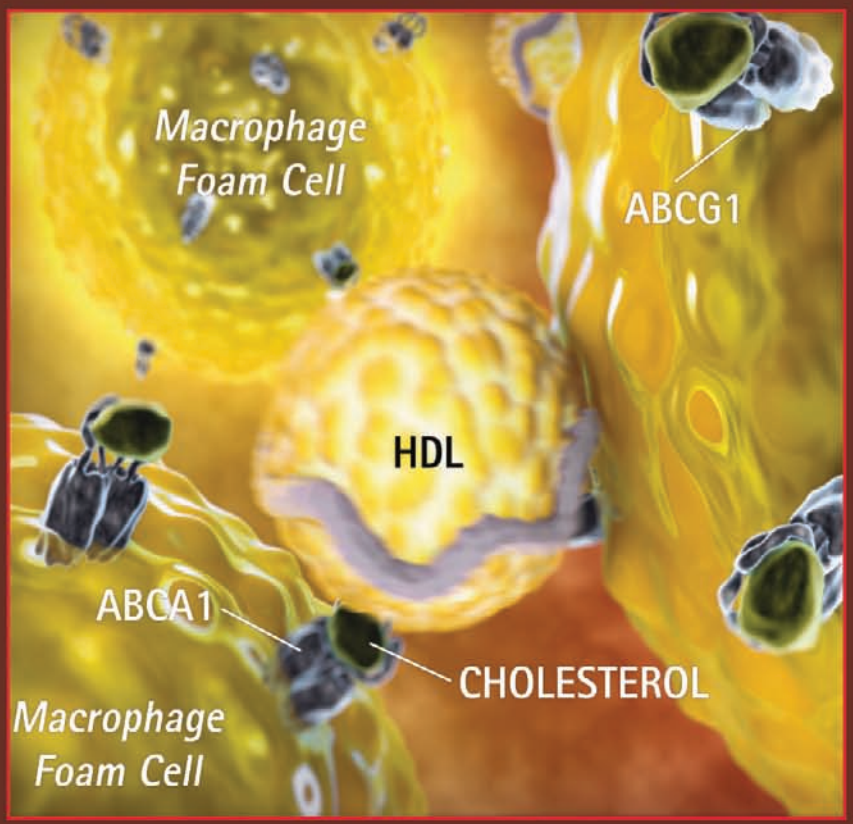
Clinical Challenges

LIPID DISORDERS

Peter P. Toth · Domenic A. Sica



FOREWORD BY SCOTT M. GRUNDY

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CLINICAL CHALLENGES IN LIPID DISORDERS

Edited by

Peter P. Toth and Domenic A. Sica

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Foreword

Cholesterol and a highly diverse array of lipid species play critical roles in the structural and functional integrity of biological organisms. Cholesterol is a modulator of cell membrane fluidity and is a key precursor to steroid hormones and bile acids. Cholesterol is vital to our well-being: a highly elaborate series of biochemical systems has evolved to both produce cholesterol and absorb dietary and biliary sources of cholesterol and to then distribute this cholesterol systemically via the formation and speciation of different lipoproteins. Lipids serve as structural constituents of cell membranes and specialized neural tissues, perform cell signaling functions, and are a vital source of oxidizable fuel. The astounding variety of lipid species participating in human intermediary metabolism, during both health and disease, is amply illustrated by the burgeoning field of lipidomics.

Despite enormous strides, cardiovascular disease remains the leading cause of morbidity and mortality in Western nations. Secondary to increased mechanization and availability of food (among other causes), many developing nations must also address the steep elevation in the incidence of cardiovascular disease. Atherosclerosis is an insidious and chronic disease. Atherosclerosis is etiologic for myocardial infarction, ischemic stroke, peripheral arterial disease, and a high percentage of sudden death. Epidemiologic investigation throughout the world has established a causal link between cholesterol and risk for developing all forms of atherosclerotic disease. Since the mid 1970s, a large number of prospective, randomized, placebo-controlled clinical trials with a variety of lifestyle modifications and pharmacologic agents have established beyond doubt that decreasing serum levels of cholesterol is associated with reductions in cardiovascular morbidity and mortality.

Since 1985, the National Cholesterol Education Program (NCEP) has been dedicated to educating healthcare providers and patients about the relationship between serum cholesterol and risk for cardiovascular disease. From its inception, the NCEP has applied a highly rigorous, scientific, and evidence-based approach to the development of guidelines for identifying and managing dyslipidemia. The NCEP emphasizes the need for combining dietary modification and therapeutic lifestyle change (weight loss, increased exercise, smoking cessation) with pharmacologic intervention as indicated. In its Adult Treat Panels (ATP) I and II, the NCEP established the importance of reducing serum levels of low-density lipoprotein cholesterol (LDL-c) in both the primary and secondary prevention settings, and provided guidelines for the screening and treatment of children with dyslipidemia.

In 2001, the NCEP ATP III continued to place primary emphasis on LDL-c reduction. Among the most important of the new recommendations were the following: (i) risk stratified LDL-c targets; (ii) need for quantitative 10-year risk assessment (low, moderate, high risk) using the Framingham risk model in patients with 2 or more risk factors for coronary heart disease (CHD); (iii) introduction of non-HDL-c as a secondary target of therapy in patients with baseline serum triglyceride levels >200 mg/dl with non-HDL-c targets defined as the LDL-c target plus 30 mg/dl; (iv) HDL-c <40 mg/dl is a categorical risk factor for CHD; (v) CHD risk equivalents, defined as diabetes mellitus, peripheral arterial disease, abdominal aortic aneurysm, history of ischemic cerebrovascular accident or presence of a carotid atheromatous plaque that causes $>50\%$ occlusion of the vessel lumen, or a

10-year Framingham risk that exceeds 20%; and (vi) the metabolic syndrome was defined which identified a group of patients with insulin resistance, multiple risk factors for CHD, and heightened risk for cardiovascular disease. In an addendum to ATP III, two new risk categories were established based on new clinical trial evidence, which included moderately high risk (10-year risk of 10–20%) and very high risk (patients with established CHD who have had a recent acute coronary syndrome, smoke, have diabetes mellitus, or have multiple poorly controlled components of the metabolic syndrome). For patients with moderately high and very high risk, therapeutic options for LDL-c lowering were defined as <100 mg/dl and <70 mg/dl, respectively.

Although all of these recommendations are evidence-based, compliance with the guidelines, especially among patients with moderately high or greater risk, is suboptimal. It is certainly the goal of all practicing healthcare providers to deliver high quality, state-of-the-art care that meets national guidelines. For primary care providers, there are innumerable diseases and syndromes that a patient can present with. Dyslipidemia is, however, highly prevalent and its treatment is a true cornerstone in any approach to CHD risk reduction. Familiarity and facility with these guidelines is crucial if dyslipidemia is to be managed in an optimal manner.

In *Clinical Challenges in Lipid Disorders*, Drs Toth and Sica and their contributing authors address the diagnosis and treatment of dyslipidemia in a novel manner. The book is organized according to a series of questions. These questions are carefully crafted to reflect many of the most important questions and concerns primary care providers express at conferences and other settings. Recent evidence shows that many providers continue to treat dyslipidemia less aggressively than they should due to concerns over possible toxicity from lipid-lowering agents. Hepatotoxicity, myopathy, drug interactions, and combination therapy are addressed in a detailed but practical way. The authors emphasize the need for risk assessment and stratification. Similarly, the book provides in-depth explorations of how the NCEP concluded that the various CHD risk equivalents impart the level of risk they do; the epidemiology linking dyslipidemia to CHD and why measurement and treatment of non-HDL-c and low levels of serum high-density lipoprotein cholesterol are important. It provides immediately applicable advice on how to counsel patients about weight loss and lifestyle modification, details the role of dietary adjuncts (plant sterols and dietary fiber) in lipid management, reviews the efficacy and risk/benefit considerations of lipid-modifying drugs for specific forms of dyslipidemia, and discusses approaches to the treatment of dyslipidemia in women and more elderly patients, among other topics.

This volume is an excellent resource on dyslipidemia and successfully strikes that fine balance between concept and practical application in the practice setting. It will provide a considerable amount of insight into many key issues regarding risk assessment and lipid management for mid-level providers, primary care physicians, cardiologists, and endocrinologists. Guidelines are continually updated and refined. Cholesterol guidelines will continue to evolve. Understanding and appropriately applying these guidelines is crucial to any national effort aimed at significantly reducing the morbidity and mortality attributable to cardiovascular disease. All of us must make this a high and urgent priority.

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Preface

The busy clinician needs to be knowledgeable about best practices for an ever expanding array of conditions. Dyslipidemia is a widely prevalent and highly heterogeneous condition. Clinical lipidology is a newly recognized specialty in medicine. Our understanding of how lipids and lipoproteins influence risk for cardiovascular disease is evolving rapidly. The pace of research and the sheer volume of new information offered by clinical trials are challenging to keep up with for even the most astute clinician.

Clinical Challenges in Lipid Disorders is published at an opportune time. Many important, recent developments in clinical lipidology warrant immediate application in clinical practice. This book was not intended to be encyclopedic in scope. Instead its aim is to focus on important day-to-day questions that the busy clinician might want to have quickly yet authoritatively answered. These questions are among the most frequently asked by primary care and specialty audiences at national and international conferences, and they poignantly reflect where potential gaps in knowledge about dyslipidemia exist. Addressing these questions in an evidence-based manner is fundamental to any effort directed at improving the identification and management of all forms of dyslipidemia. In that context, this book may be viewed as being particularly comprehensive in nature.

Clinical Challenges in Lipid Disorders covers the basic and clinical science of dyslipidemias. In so doing, it thoughtfully addresses aspects of the diagnosis and management of dyslipidemias where the available data can be quite unsettled and confusing. Such is the case for the chapters addressing the diagnosis and management of children, women, the elderly, those with familial hypercholesterolemia, as well as the newly hospitalized patient with an acute coronary syndrome. Chapters focused on Framingham risk scoring, the metabolic syndrome, low HDL-cholesterol, and elevated non-HDL-cholesterol are worthy of careful reading. This book is also particularly informative on the topics of fibrate therapy, niacin use, and the oft debated use of nutriceuticals and dietary supplements as lipid-altering therapies. *Clinical Challenges in Lipid Disorders* also contains a large amount of information related to various aspects of statin therapy, including proposed pleiotropic effects as well as insightful discussions of the muscle and hepatic side effects that seem to weigh heavily on the use of this drug class. As the reader will quickly determine, this book both recognizes and answers the most pervasive questions in the field of clinical lipidology and does so with a cutting edge balance between conceptual development and clinical utility. It is our ardent hope that this information will empower healthcare providers of all disciplines to more aggressively identify and treat the many forms of lipid disorder encountered in daily practice.

Peter P. Toth
Domenic A. Sica

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How well do various lipids and lipoprotein measures predict cardiovascular disease morbidity and mortality?

K. C. Maki, M. R. Dicklin

BACKGROUND

Atherosclerotic cardiovascular disease (CVD), mainly comprised of coronary heart disease (CHD) and stroke, is the leading cause of mortality in the world. Evidence favoring a causal relationship between elevated blood cholesterol and risk of CHD has been available for nearly a century, originally supported by data from animal models, anecdotal reports, and small studies in humans [1–3]. However, until the mid-20th century, epidemiological data to support the 'lipid hypothesis' and to refute the belief that atherosclerosis is an inevitable consequence of aging, was lacking. In the 1950s, Ancel Keys examined the relationships between dietary fat, blood cholesterol level, and CHD rates in seven countries with average blood cholesterol ranging from 160 mg/dl (4.13 mmol/l, Japan) to 260 mg/dl (6.72 mmol/l, Finland) [3–4]. The Seven Countries Study showed that CHD incidence varied as much as 10-fold between countries and that the risk of death from CHD was proportionate to the average blood cholesterol level. Migration studies helped to answer the next question, which was whether these findings were simply due to genetic differences between countries. Individuals migrating from countries with lower saturated fat and cholesterol intakes to countries with higher saturated fat and cholesterol intakes experienced rises in blood cholesterol, which were later accompanied by increases in CHD incidence [3, 5].

Another landmark investigation, The Framingham Heart Study (FHS), had a major impact on CHD risk prediction. Initiated in 1948 and continuing today, the Framingham study measured various characteristics of thousands of residents in Framingham, Massachusetts and followed them over decades to determine what 'risk factors' were associated with the development of CHD and other cardiovascular events [6]. The first use of the term 'risk factor' in the medical literature was in a 1961 publication from the Framingham Heart Study [6]. Data from the Framingham investigation provided compelling, prospectively derived evidence supporting a relationship between elevated cholesterol and CHD risk [7]. Over the years, findings from observational studies from around the world have consistently supported this association [8–12].

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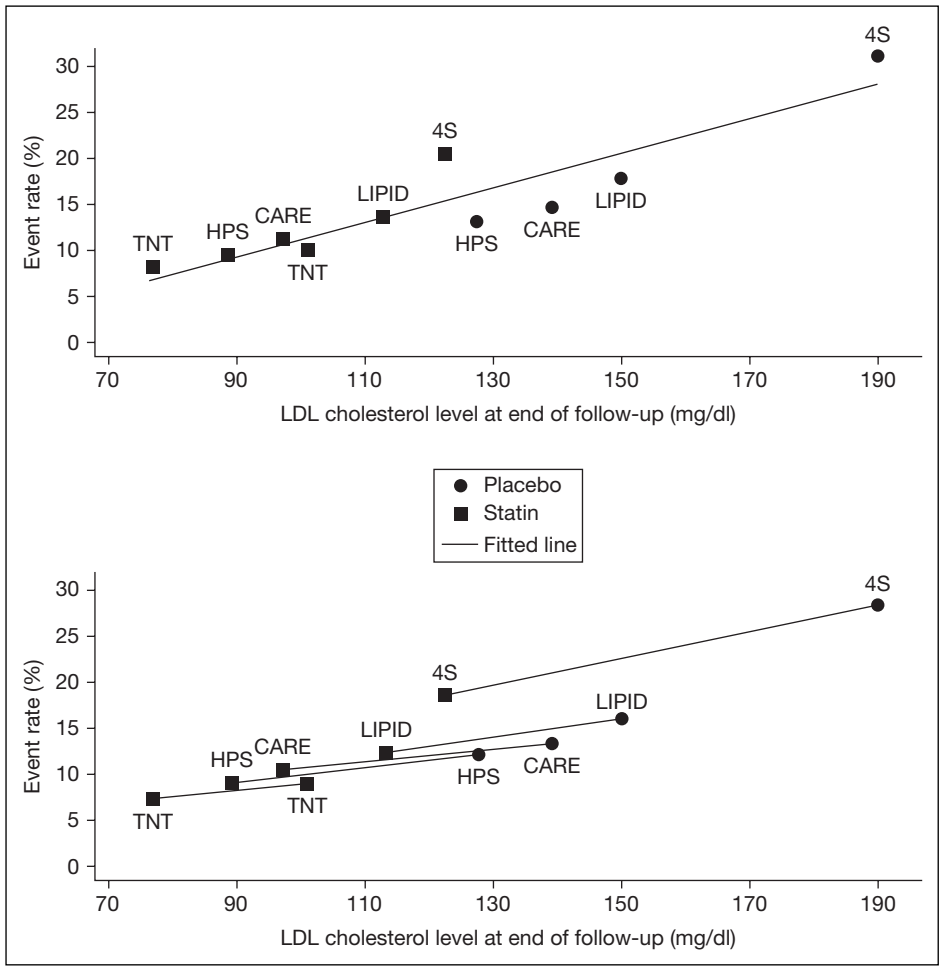

Figure 1.1 **Top.** Event rate assuming a single association between low-density lipoprotein cholesterol (LDL-c) and outcome across trials. **Bottom.** The LDL-c outcome associations found within each study. 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Study; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease Study; TNT = Treating to New Targets Study. With permission from [23].

The results from the Lipid Research Clinics Coronary Primary Prevention Trial, published in 1984, provided the first evidence from a randomized clinical trial to show that lowering the circulating cholesterol level with drug treatment (a bile acid binding agent) reduced CHD events [13]. There is now a large body of evidence from clinical trials using dietary and drug interventions to support the consensus that lowering cholesterol prevents CVD morbidity and mortality, including that from CHD, stroke, and peripheral arterial disease (Figure 1.1) [14–23]. Various countries and organizations have released guidelines for the management of disturbances in the lipid profile in order to reduce CVD risk. Despite a large body of clinical trial evidence demonstrating the efficacy of cholesterol-lowering for reducing major CVD events, many questions remain regarding the optimal ways to assess and manage disturbances in the circulating lipid and lipoprotein profile in clinical practice.

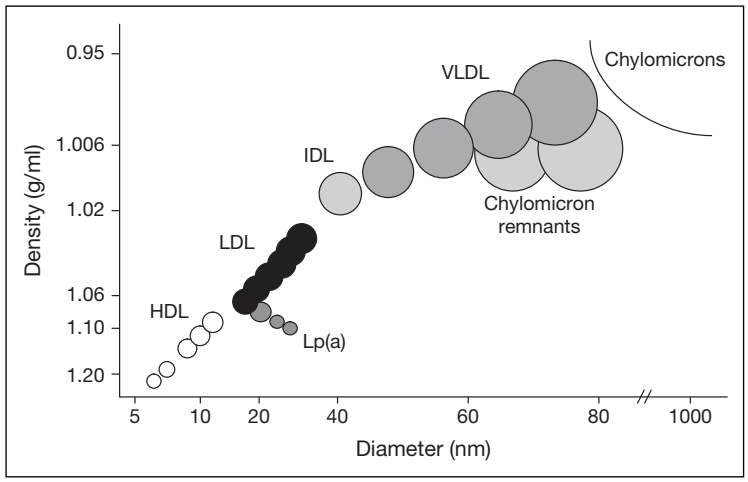

Figure 1.2 Relative sizes and densities of circulating lipoprotein particles. Adapted from [24]. Figure by courtesy of Dr James Otvos, LiopScience, Inc.

This chapter will examine the major circulating lipids and lipoproteins, their relationships to cardiovascular morbidity and mortality, and summarize areas where controversy or uncertainty remain.

CIRCULATING LIPIDS AND LIPOPROTEINS

Cholesterol and triglycerides (TG) are not water-soluble, thus they are carried in the blood in lipoproteins. The five main classes of circulating lipoproteins include (Figure 1.2) [24]:

- Chylomicron particles
- Very-low-density lipoproteins (VLDL)
- Intermediate-density lipoproteins (IDL)
- Low-density lipoproteins (LDL)
- High-density lipoproteins (HDL)

Lipoprotein metabolism will not be discussed in detail in the present chapter. However, the following is a brief overview of the major lipoprotein classes and their functions. Chylomicron particles are the largest and most TG-rich lipoproteins. These are the major vehicles for transporting dietary fat from the intestines to peripheral tissues. The liver takes up chylomicron remnants after delipidation by lipoprotein lipase in peripheral tissues (e.g., adipose and muscle). VLDL particles are also TG-rich and are secreted by the liver for the purpose of transporting TG and cholesterol to the peripheral tissues. As VLDL particles undergo delipidation, they become IDL and ultimately LDL particles. LDL particles, and to a lesser extent other partially TG-depleted particles, are taken up by the liver and their cholesterol content is recycled for synthesis of new lipoproteins or other hepatic products such as bile acids. Nascent HDL particles are secreted by the liver and intestine and participate in reverse cholesterol transport from the peripheral tissues back to the liver. Higher circulating levels of HDL are associated with lower CVD risk, whereas higher circulating levels of all of the other lipoproteins discussed above are associated with increased risk.

In clinical practice, lipoprotein particles are not usually measured *per se*. Instead, lipoprotein cholesterol (total, non-HDL, LDL, HDL) and the total circulating TG concentration are typically reported. The circulating chylomicron content is normally very low in the fasting state. Therefore, the fasting lipid profile can be characterized using the following measured or calculated values:

- Total cholesterol (TC)
- Non-HDL-c
- LDL-c
- HDL-c
- TG

Guidelines for cholesterol management have generally identified LDL-c as the primary target for therapy. If the fasting TG concentration is <400 mg/dl (2.25 mmol/l), the LDL-c level is often calculated using the Friedewald equation [25]. This equation estimates the VLDL-c concentration from the TG level (TG/5 if in mg/dl or TG/2.2 if in mmol/l). Thus, the LDL-c concentration is estimated as TC minus HDL-c minus estimated VLDL-c. The LDL-c calculated with this method includes the cholesterol carried by true LDL particles, as well as that carried by IDL and lipoprotein (a) particles. Lipoprotein (a) particles are LDL particles that also contain apolipoprotein (a), which is structurally similar to plasminogen.

Non-HDL-c is calculated as the TC concentration minus the HDL-c concentration. Non-HDL-c represents all of the cholesterol carried by potentially atherogenic lipoproteins including: LDL, lipoprotein (a), IDL, VLDL and chylomicron remnant particles. Thorough understanding of the impact of disturbances in the circulating lipoprotein profile on CVD risk requires an understanding of the three major lipoprotein categories (LDL, TG-rich lipoproteins and HDL) and their associations with CVD risk.

LOW-DENSITY LIPOPROTEIN

LDL-c

Lipid treatment guidelines generally focus on LDL-c as the primary target for lipid-altering therapies. There is a strong linear relationship, independent of other major CHD risk factors, between LDL-c concentration and CHD risk. Clinical intervention trials of dietary, surgical (ileal bypass), and drug therapies for lowering LDL-c have consistently reported reductions in CHD events [26]. The largest body of evidence is from trials of statin drugs. Figure 1.3 shows the proportional effects on major vascular events per 1.0 mmol/l (38.7 mg/dl) LDL-c reduction in statin outcomes trials that, in aggregate, included more than 90 000 men and women [27]. Significant reductions in risk were observed for myocardial infarction and CHD death, revascularization procedures, ischemic stroke (but not hemorrhagic stroke) and a composite of all major vascular events. These benefits were observed in all of the major subgroups studied, including men and women, young and older subjects, and those with or without other major risk factors such as smoking, hypertension, and diabetes mellitus. The benefits were also evident at all starting levels of LDL-c [16, 27].

Each 1% reduction in LDL-c has been estimated to reduce the CHD event risk by approximately 1% over five years [28]. However, the true long-term benefit from lowering LDL-c may be underestimated due to the short length of a typical clinical trial (<10 years) compared to the period over which atherosclerotic disease develops (decades). As shown in Figure 1.1, the slope of the line for the relationship between the mean on-treatment LDL-c level and CHD events is steeper for the relationship across studies than the slopes observed within studies. This observation is consistent with the possibility that the individual studies

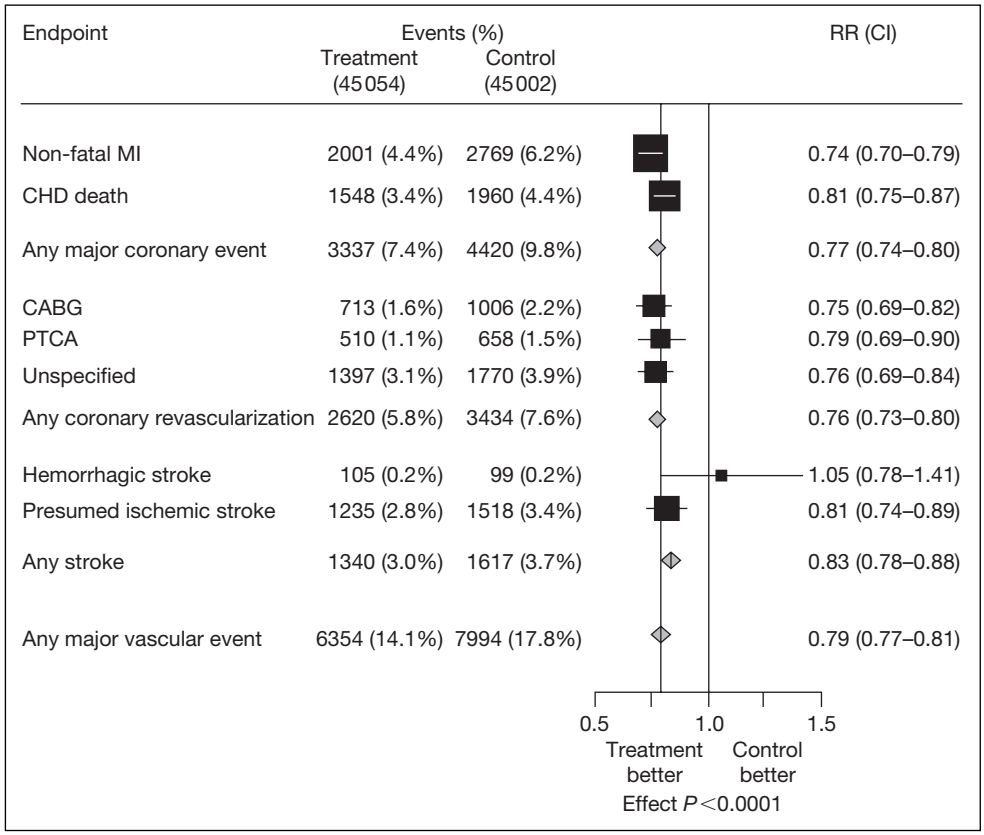

Figure 1.3 Proportional effects on major vascular events per mmol/l (38.7 mg/dl) LDL-c reduction in statin outcomes trials. CABG = coronary artery bypass graft; CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RR = relative risk. With permission from [27].

underestimated the size of the treatment effect because of their relatively short duration relative to the longer period of time during which the subjects were exposed to higher pre-treatment LDL-c levels.

Gene mutation studies and inter-country observational comparisons suggest that each 1% lowering of LDL-c might produce a 2–3% reduction in CHD if maintained over an extended period [29–30]. For example, Cohen *et al.* [30] reported on the effects of variations in proprotein convertase subtilisin/kexin type 9 serine protease gene (*PCSK9*) among participants in the Atherosclerosis Risk in Communities Study (Figure 1.4). PCSK9 is involved in the degradation of LDL receptors. High levels of its expression lead to a reduced number of LDL receptors and increased circulating concentrations of LDL-c, whereas nonsense or missense mutations result in reduced LDL receptor degradation and lower levels of circulating LDL-c [31]. Among subjects with a nonsense mutation (2.6% of black participants), LDL-c was lower by a mean of 28% and CHD events were lower by 88%. Subjects with a missense mutation (3.2% of white participants) had a mean LDL-c concentration that was 15% lower, which was associated with a 47% lower CHD risk. These results imply that even

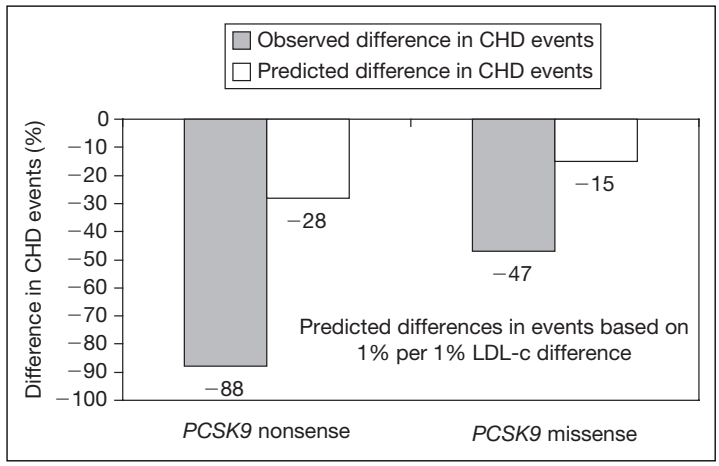

Figure 1.4 Predicted and observed differences in CHD events associated with sequence variations in *PCSK9* that result in chronically reduced levels of LDL-c. CHD = coronary heart disease; LDL-c = low-density lipoprotein cholesterol; *PCSK9* = pro-protein convertase subtilisin/kexin type 9 serine protease gene. Adapted with permission from [30].

relatively small reductions in LDL-c, if maintained over an extended period, could substantially lower CVD risk.

Populations with an LDL-c level <100 mg/dl have very low rates of CHD, and the benefits of reducing LDL-c appear to extend to levels less than 100 mg/dl (2.58 mmol/l) [28]. Results from secondary prevention trials suggest that aggressive lowering of LDL-c to very low levels is beneficial [28]. Based on these data, the US National Cholesterol Education Program (NCEP) Expert Panel issued a more aggressive, but optional, LDL-c treatment target of <70 mg/dl (1.80 mmol/l) for individuals at very high risk for a CHD event [28]. However, because of the cost and additional risk associated with very aggressive LDL-c reduction to these levels, which often requires high-dose statin therapy or the use of multiple cholesterol-lowering medications, the Expert Panel did not feel that the evidence was sufficient to warrant a stronger recommendation.

NON-HDL-c AND APOLIPOPROTEIN B

Non-HDL-c

Non-HDL-c represents all of the cholesterol carried by potentially atherogenic particles. When the circulating TG concentration is in the normal range (<150 mg/dl, 1.7 mmol/l), a large majority of the cholesterol carried by potentially atherogenic lipoproteins is contained in LDL particles. However, when the TG concentration is elevated, particularly if ≥200 mg/dl (2.25 mmol/l), a substantial quantity of cholesterol may be carried by atherogenic remnants of VLDL and chylomicron particles [32]. In this situation, LDL-c alone will not accurately reflect the total burden of circulating atherogenic particles and non-HDL-c may be a better predictor of CVD risk than LDL-c. Results from several epidemiological studies suggest that non-HDL-c may be more strongly related to CVD event risk than LDL-c [33–34]. For example, in the apolipoprotein-related Mortality Risk Study, non-HDL-c was more strongly associated with CHD mortality than LDL-c, particularly among women (Figure 1.5) [33]. However, some uncertainty exists regarding whether non-HDL-c is always superior to LDL-c in predictive value because a proportion of non-HDL-c represents

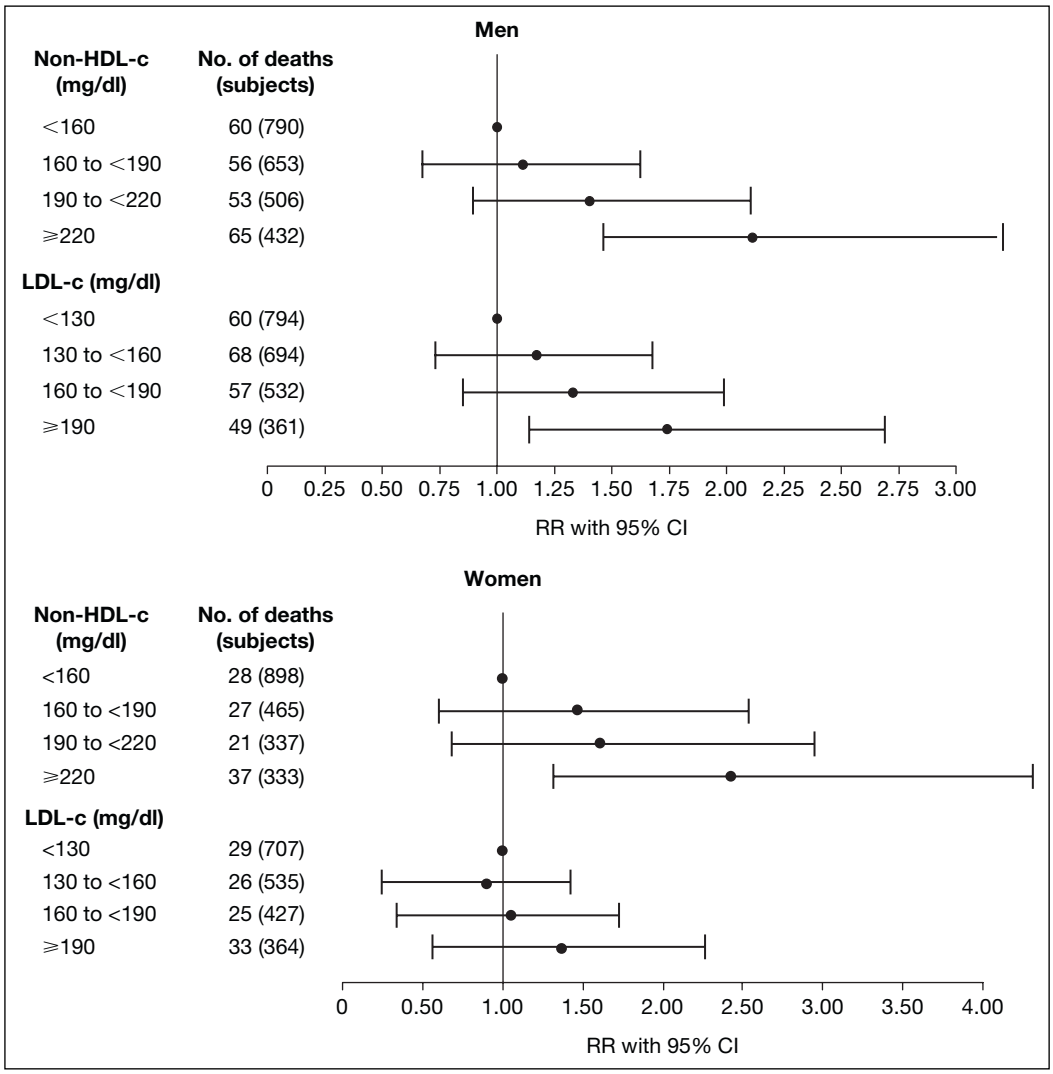

Figure 1.5 Cardiovascular disease mortality by non-HDL cholesterol and LDL cholesterol levels in men and women. CI = confidence interval; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; RR = relative risk. With permission from [33].

cholesterol carried by particles that are too large to enter the arterial wall (large VLDL and chylomicron particles), whereas the atherogenicity of LDL particles is well established.

The Third Adult Treatment Panel (ATP III) of the US NCEP has taken the position that non-HDL-c should be a secondary target for cholesterol-lowering therapy for patients with high TG (≥200 mg/dl, 2.25 mmol/l) after the LDL-c concentration has been lowered to within the goal range. Non-HDL-c targets are each 30 mg/dl (0.78 mmol/l) above the

Table 1.1 Relative risks and 95% confidence intervals for coronary heart disease during 6 years of follow-up for the fifth vs the first quintile of selected biomarker levels in the Health Professionals Follow-Up Study

Biomarker	*Relative risk and 95% confidence interval (Quintile 5 vs Quintile 1)*[1]	*P-trend*
LDL-c	2.07 (1.24–3.45)	<0.001
Non-HDL-c	2.75 (1.62–4.67)	<0.001
ApoB	2.98 (1.76–5.06)	<0.001

[1]From a multivariate model adjusted for age, smoking status, month of blood draw, body mass index, parental history of myocardial infarction before age 60, diabetes, hypertension, alcohol intake and physical activity.
ApoB = apolipoprotein B; LDL-c = low-density lipoprotein cholesterol; non-HDL-c = non-high-density lipoprotein cholesterol.
Adapted with permission from [34].

LDL-c target for each risk category. They do not recommend non-HDL-c targets for patients without elevated TG.

Apolipoprotein B

Each VLDL, IDL, LDL and chylomicron particle contains one molecule of apolipoprotein B (apoB). Chylomicrons and their remnants contain apoB-48, which is synthesized by the intestine. In the fasting state, apoB-48 accounts for <1% of the total circulating apoB concentration [35]. VLDL, IDL, and LDL particles contain apoB-100 of hepatic origin. Since each of these lipoproteins contains only one molecule of apoB, the circulating apoB concentration is a direct indication of the number of potentially atherogenic particles. The Canadian Cardiovascular Society guideline group has adopted an apoB target of <90 mg/dl (<0.85 g/l) for high-risk patients [36]. The recent report of the 'Thirty- person/Ten-country Panel' suggests an even lower optimal apoB target of <80 mg/dl [37].

As is the case for non-HDL-c, a fraction of apoB is carried by particles that are too large to enter the arterial wall (large VLDL and chylomicron particles). However, most apoB (and non-HDL-c) is carried by smaller particles with atherogenic potential (smaller VLDL, LDL, IDL, and chylomicron remnant particles). Some investigators have argued that apoB should replace LDL-c as the primary target for lipid-altering therapies [37]. Indeed, as illustrated in Table 1.1, results from several large observational studies have found stronger relationships between both non-HDL-c and apoB with CHD risk than for LDL-c [34, 38–39]. Although the interpretations of results from trials of lipid-altering therapies have generally focused on the effects of these interventions on LDL-c, the therapies used (particularly statins) also generally lower non-HDL-c and apoB and cannot be interpreted as pure LDL-c interventions. Furthermore, to date, no large outcome trial has specifically tested a lipid intervention in subjects selected for having hypertriglyceridemia, the group for which it would be anticipated that non-HDL-c and apoB might have the greatest advantages over LDL-c for predicting risk.

An additional consideration for apoB that does not apply to non-HDL-c, is the added cost associated with obtaining this measurement. Since non-HDL-c can be calculated from values typically reported in the standard lipid profile, there is essentially no additional cost. A question that remains controversial is whether the additional discriminatory ability of

apoB is sufficiently superior to that of LDL-c and/or non-HDL-c to justify the cost of its measurement. To date, the available data have provided no clear answer to this question, which remains a source of substantial controversy [37, 40].

TG, TG-RICH LIPOPROTEINS, ATHEROGENIC REMNANTS

Elevated TG is generally accepted as a risk factor for CHD, although its independent predictive ability after accounting for other risk factors has long been the source of debate [26, 41–42]. In the Munster Heart Study, the incidence of major coronary events for subjects with TG <200 mg/dl was considerably less (4.4%) than for subjects with TG between 200 and 399 mg/dl (9.3%) and between 400 and 799 mg/dl (13.2%) [41]. This association remained significant after adjustment for other traditional CHD risk markers, although it is uncertain whether this would hold true after adjustment for additional risk markers that were not measured such as remnant lipoprotein levels and the number of circulating atherogenic lipoprotein particles.

At present, the degree to which elevated TG *per se* is responsible for the increase in CHD risk associated with hypertriglyceridemia, as opposed to associated lipid and other metabolic and hemodynamic abnormalities is uncertain. Excess TG in the blood may have direct CHD-promoting actions by increasing blood viscosity, making blood flow more sluggish and less capable of transporting oxygen to the tissues [43]. However, when the circulating TG concentration is elevated, levels of atherogenic TG-rich remnant lipoproteins and small, dense LDL particles are also elevated and HDL-c is often depressed. In addition, hypertriglyceridemia is associated with other metabolic and hemodynamic disturbances, including insulin resistance, glucose intolerance and elevated blood pressure. Thus, the intercorrelations between elevated TG and other lipid and non-lipid correlates of risk make untangling the relationships between TGs, lipoprotein particle levels, and CHD risk statistically problematic. In addition, most population studies have not measured, and cannot therefore account for, all of the relevant variables (e.g., apolipoproteins or lipoprotein particle numbers). In the authors' opinion, the available evidence, albeit incomplete, supports the view that lipoprotein particle numbers are likely more important risk determinants of CVD risk than cholesterol or TG concentrations *per se*, which are really surrogate measures of the numbers of circulating lipoprotein particles.

In the NCEP ATP III report, the importance of the association between TG elevation and CHD risk was acknowledged by including the presence of high TG (≥200 mg/dl, 2.25 mmol/l) in the determination of lipoprotein cholesterol treatment targets [26]. In patients with TG <200 mg/dl (1.7 mmol/l), most of the cholesterol in atherogenic particles is carried by LDL. So, targeting LDL-c lowering is a logical choice in those individuals. However, patients with elevated TG typically have increased levels of TG-rich lipoprotein remnants [22, 26]. Therefore, focusing on LDL-c alone in patients with elevated TG will underestimate the burden of atherogenic lipoproteins and, consequently, CHD risk [44–45].

LDL PARTICLE SIZE

Although sometimes referred to interchangeably, LDL and LDL-c are not the same. The convention of using the cholesterol in lipoproteins originated because, in a clinical setting, lipids were easier to measure than lipoproteins. At a population level, utilizing cholesterol measurement for CHD risk determination is adequate because lipoprotein levels are strongly correlated with the number of lipoprotein particles in most situations. However, as noted above, these relationships may not hold up well for all subsets of the population, particularly those with elevated TG.

Moreover, it has been proposed that a gradient of atherogenicity exists across the spectrum of atherogenic lipoprotein particles. In particular, some investigators have proposed

Table 1.2 Associations of large and small low-density lipoprotein particle concentrations with carotid intimal-medial thickness after adjustment for low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations in the Multi-Ethnic Study of Atherosclerosis

Parameter	*Difference (SE) in IMT in μm per SD*[1]	P-*value*
Large LDL-P	30.3 (9.4)	0.001
Small LDL-P	34.8 (10.1)	0.001
LDL-c	11.8 (7.8)	0.130
HDL-c	−17.3 (5.7)	0.003
Triglycerides	−1.6 (5.1)	0.750

[1]Model also included terms for age, sex, race, hypertension and smoking. HDL-c = high-density lipoprotein cholesterol; IMT = intimal-medial thickness; LDL-c = low-density lipoprotein cholesterol; LDL-P = low-density lipoprotein particle; SD = standard deviation; SE = standard error.
Adapted with permission from [55].

that small, dense LDL particles are more atherogenic than larger, more buoyant particles [46–47]. As reviewed by Packard [47], small, dense particles appear to bind less readily to hepatic LDL receptors, prolonging their time in the circulation. In contrast, these particles bind more readily to proteoglycans in the arterial wall and have greater susceptibility to oxidative modification, an important step in unregulated LDL uptake by macrophages, contributing to foam cell formation.

Based on LDL particle size, two phenotypes have been defined. Individuals with LDL pattern A have a predominance of large, buoyant LDL particles, whereas those with pattern B have a predominance of small, dense LDL particles [48]. Conversion between LDL subclass patterns appears to be a threshold phenomenon, with transition to pattern B occurring when the fasting TG level rises above a threshold level [49–50]. This threshold varies between individuals, but is within the range of 100–250 mg/dl (1.1–2.8 mmol/l) for most of the population [48–49]. Thus, among those with high or very high TG concentrations, even very large reductions in TG level induced by drug therapies will not generally produce an increase in LDL particle size unless the TG level is reduced below the individual's threshold for conversion from pattern B to pattern A [49–50].

Despite the strong theoretical basis for the idea that small, dense LDL particles have enhanced atherogenicity, this has been difficult to demonstrate because the LDL subclass pattern is only one component of a larger group of metabolic characteristics including elevated TG, low HDL-c, obesity, and insulin resistance [48–49, 51–52]. In a review of 70 studies evaluating the relationship of CHD risk with LDL particle size and number, small LDL particle size was found to be significantly associated with CHD risk in nearly all of the studies. However, in multivariate analyses, LDL size was rarely found to be a significant predictor of CHD risk, suggesting that other features associated with LDL particle size may account for part or all of its association with CHD risk [53].

In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), both large and small LDL particle concentrations, but not LDL particle size, were significantly associated with CHD events once their correlation was taken into account [54]. Consistent with this finding, results from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that both small and large LDL particles were associated with greater carotid intimal-medial

thickness (a surrogate for atherosclerosis), and to a similar degree, in models that adjusted for the inverse correlation between the two particle types (Table 1.2) [55].

In addition, data from a variety of sources have supported the atherogenicity of remnants of TG-rich particles such as IDL and chylomicron remnants [32]. Thus, the relative atherogenicity of various apoB-containing particles is uncertain, leading one prominent authority in the field to declare the following [56]:

> "For the practicing clinician, however, the major argument for extending measurement of subclasses into the mass market is the hypothesis that one subclass is more atherogenic than another. Because evidence clearly indicates that all apoB-containing particles are atherogenic, this reasoning is akin to the argument that an Uzi submachine gun is more deadly than an M16 or an AK47. Obviously all are potentially lethal, and although this assertion may interest gun aficionados, it matters little to law enforcement or to general public safety if the sole objective is disarmament!"

HIGH-DENSITY LIPOPROTEIN

HDL-c

HDL particles facilitate reverse cholesterol transport by removing cholesterol from peripheral tissues, including foam cells in the arterial wall, and delivering it to the liver for excretion. HDL has also been suggested to be directly antiatherogenic by performing vasodilatory, antithrombotic, anti-inflammatory, antioxidative, anti-apoptic, and anti-infectious functions at the arterial wall [57–58].

Data from epidemiological observational studies have consistently shown an inverse correlation between HDL-c and CHD [59]. However, like small, dense LDL particles, the HDL-c concentration is strongly related to TG, remnant lipoproteins, and small, dense LDL particles, potentially confounding the degree to which HDL or HDL-c contributes directly to CHD risk [49, 51]. Multivariate analyses from clinical trials evaluating the effects of lipid-altering drugs on HDL-c (while adjusting for their effects on LDL-c and TG or TG-rich lipoprotein levels) support the hypothesis that raising HDL-c contributes to the effects of drug therapies, including statins, to reduce atherosclerosis progression and CHD event rates [29, 60–62].

Although HDL-c levels have been strongly inversely associated with CHD risk in population studies, and evidence from drug trials suggests that raising HDL-c contributes to the observed benefits, the available data for interventions to target HDL-c are not as robust as is the case for interventions targeting LDL-c and apoB-containing lipoproteins. The NCEP ATP III recommendations included low HDL-c (<40 mg/dl) as a major CHD risk factor for risk stratification [26], and identified HDL-c as a potential target for lipid-altering therapy, but did not establish specific treatment goals for HDL-c. The Canadian guidelines take a slightly different approach, suggesting targets for LDL-c and a secondary target for the TC/HDL-c ratio, thus recommending that patients with low HDL-c receive more aggressive treatment (Table 1.3).

Various assertions have been made about the relative protective effects of smaller and larger HDL particles, as well as the importance of the number of particles vs the HDL-c level [54, 63–65]. At present, no consensus exists among experts regarding these issues beyond the conclusion that when it comes to HDL-c or HDL particles, higher is generally better.

LIPOPROTEIN CHOLESTEROL AND APOLIPOPROTEIN RATIOS

The TC/HDL-c ratio reflects the balance of cholesterol carried by atherogenic and protective particles. Because the TC/HDL-c ratio includes the atherogenic VLDL and TG-rich lipoprotein remnants, it might be expected to be a more potent predictor of CHD risk than the LDL-c/HDL-c ratio, particularly among subjects with elevated TG [45]. The apoB/apoAI ratio represents the relative quantities of circulating atherogenic and protective particles. An

Table 1.3 Comparison of lipid goal approaches in two national treatment guidelines: US National Cholesterol Education Program and Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias

Risk status[1]	*US guidelines*	*Canadian guidelines*
High risk or CHD and CHD risk equivalents[2]	LDL-c <100 mg/dl (2.59 mmol/l)	LDL-c <2.5 mmol/l (97 mg/dl) and TC:HDL-c <4.0
Moderate risk or multiple (2+) risk factors[3]	LDL-c <130 mg/dl (3.36 mmol/l)	LDL-c <3.5 mmol/l (135 mg/dl) and TC:HDL-c <5.0
Low risk or 0–1 risk factor	LDL-c <160 mg/dl (4.14 mmol/l)	LDL-c <4.5 mmol/l (174 mg/dl) and TC:HDL-c <6.0

[1]US NCEP risk categories include CHD and CHD risk equivalents, multiple (2+) risk factors, and 0–1 risk factor. Canadian risk categories include high, moderate, and low risk.
[2]CHD includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease, transient ischemic attacks or stroke of carotid origin or 50% obstruction of a carotid artery), diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%.
[3]Risk factors include cigarette smoking, hypertension (BP ≥140/90 mmHg or on antihypertensive medication), low HDL-cholesterol (<40 mg/dl), family history of premature CHD (CHD in male first-degree relative <55 years of age; CHD in female first-degree relative <65 years of age), and age (men <45 years; women <55 years).
CHD = coronary heart disease; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol.
Adapted with permission from [26, 67].

elevated apoB/apoAI ratio explained nearly half (49.2%) of the global population attributable risk for CHD in the INTERHEART study [66].

Because these ratios provide information on both atherogenic and anti-atherogenic lipoproteins, they tend to be more powerful predictors than their component parts. However, little information is available from intervention studies to judge potential interactions or the use of treatment targets based on these ratios. For example, does a TC/HDL-c ratio of 4.0 confer the same risk at HDL-c concentrations of 40 and 80 mg/dl (1.0 and 2.1 mmol/l)? In the absence of such information, treatment recommendations have generally favored targets for individual lipoprotein cholesterol levels or identified a ratio as a secondary treatment goal (Table 1.3) [26, 36, 67].

SUMMARY

Population studies have shown that a large percentage of the variation in CHD incidence within and between countries can be accounted for by lipid-related risk factors. The risk for developing CHD with increased LDL-c levels is well documented and LDL-c has consistently been identified as the primary target for intervention. However, in recent years, the atherogenicity of other apoB-containing particles has become better established, suggesting that efforts toward prevention should not focus solely on LDL-c, especially in patients with elevated TGs, an indication of increased levels of atherogenic TG-rich lipoprotein remnants.

Thus, support is increasing for the use of alternative or supplementary measures of atherogenic lipoprotein burden such as non-HDL-c and apoB concentrations. In addition,

suggestive, but inconclusive, data from drug trials support the view that raising the HDL-c concentration contributes to the benefits on CHD event rates and atherosclerosis prevention. For these reasons, ratios such as the TC/HDL-c ratio and the apoB/apoAI ratio show promise, although more data will be needed to establish whether targeting specific reductions or levels of these ratios is superior to a focus on the individual components.

Investigation and debate continue regarding the relative atherogenicity of different lipoprotein subclasses, such as small and large LDL and HDL particles. At present, these issues remain unresolved. Accordingly, clinical and public health efforts should emphasize maintaining a low burden of circulating atherogenic lipoproteins throughout the life cycle for CVD prevention. Dyslipidemia management should focus primarily on LDL-c, non-HDL-c, apoB and/or TC/HDL-c treatment goals as recommended by national guidelines, with secondary emphasis on raising HDL-c and lowering TG concentrations, particularly through lifestyle intervention (e.g., physical activity and weight loss), which will simultaneously improve other elements of the CVD risk profile.

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2

Framingham risk scoring or risk factor counting: which is more sensitive and how do I use this information to determine patient-specific lipid goals?

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BACKGROUND

The report of the first Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) in 1988 established low-density lipoprotein cholesterol (LDL-c) as the primary target for coronary heart disease (CHD) risk reduction [1]. Risk factor scoring was emphasized for the ATP II report in 1994 [2]. Major categorical risk factors that modified the intensity of therapy for elevated LDL-c included:

- Hypertension (systolic ≥140 or diastolic ≥90 or treated)
- Low HDL-c (<40 mg/dl)
- Family history of premature CHD
  - — Male first-degree relative <55 years of age
  - — Female first-degree relative <65 years of age
- Cigarette smoking
- Diabetes mellitus

Also, for HDL-c ≥60 mg/dl, one risk factor was subtracted from the tally because of the decreased risk associated with high HDL-c levels. This allowed categorization into a low risk group (0–1 risk factor) and an intermediate risk group (2 or more risk factors). Those with CHD were considered the highest risk group and due to their highest absolute risk merited the lowest LDL-c goals and the most intensive LDL-c lowering drug regimens.

In 2001, the ATP III report suggested several changes in CHD risk evaluation [3]. Diabetes mellitus was considered a 'coronary risk equivalent' along with peripheral vascular disease, symptomatic carotid artery atherosclerotic disease, or aortic abdominal aneurysm. In addition, Framingham risk scoring for 'hard' CHD (this excluded the softer endpoint of angina pectoris) was introduced. ATP III used a modified version of the 1998 Framingham risk score [4]. This updated ATP III Risk Assessment Tool requires the user to input values of

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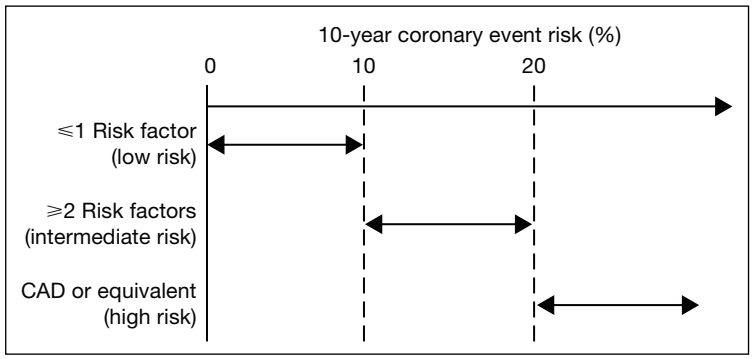


Figure 2.1 Risk factor categories and approximate 10-year coronary (hard CHD) event risk.

A	B	C	D
From the Framingham Heart Study		Enter values here	
CHD (MI and Coronary Death) Risk Prediction			*National Cholesterol Education Adult Treatment Panel III*
Risk factor	Units	(Type over placeholder values in each cell)	Notes
Gender	male (m) or female (f)	m	
Age	years	55	
Total cholesterol	mg/dl	240	
HDL	mg/dl	39	
Systolic blood pressure	mmHg	135	
Treatment for hypertension (only if SBP>120)	yes (y) or no (n)	n	
Current smoker	yes (y) or no (n)	y	
Time frame for risk estimate	10 years	10	
Your Risk (The risk score shown is derived on the basis of an equation. Other NCEP materials, such as a ATP III print products, use a point-based system to calculate a risk score that approximates the equation-based one.)		21%	*If value is < the minimum for the field, enter the value is > the maximum for the field, enter the*

Figure 2.2 Risk calculator for Framingham 'hard events' of CHD. Downloaded on 3 Feb 2008 at http://hp2010.nhlbihin.net/atpiii/riskcalc.htm. Source: NHLBI.

age, sex, total and HDL-c, systolic blood pressure (BP) and smoking status and use of antihypertensive medication. The Risk Assessment Tool then employs the weighted Framingham multivariable equations to estimate an absolute 10-year risk for hard CHD events. As noted above, diabetes was not included in this risk score, since it was considered a CHD risk equivalent, meriting secondary prevention intensity of LDL-c lowering. Whether done by paper from published tables or on a downloadable risk calculator, the Risk Assessment Tool can be used to place the patient in either a low (<10% 10-year risk), intermediate (10–20% 10-year risk) or high risk (>20% 10-year risk, CHD, or CHD equivalent) category (Figure 2.1). The value of this was that risk factor counting could potentially lead to an underestimation of risk (Figure 2.2), as in the example of a 55-year-old male who is a current smoker with a total cholesterol of 240 mg/dl, HDL-c of 39 mg/dl, and a systolic BP of 135 mmHg. His 10-year risk is 21% and it was felt that he deserved intensive therapy consistent with high short-term absolute risk of CHD. Any patient with a 10-year Framingham risk >20% has a CHD risk equivalent.

In 2004, these guidelines were revised due to new information from clinical trials that resulted in new optional goals for those felt to have the highest risk and those with high-risk

Table 2.1 Evolution of ATP Lipid Guidelines for the National Cholesterol Education Program (NCEP)

ATP I (1988)	*ATP II (1993)*	*ATP III (2001)*	*ATP III Update (2004)*
■ Emphasis on primary prevention 'know your cholesterol'	■ Emphasis on secondary prevention with goal for LDL-c ≤100 mg/dl	■ Emphasis on person with 2 or more risk factors ■ Framingham risk scoring for 'hard' CHD introduced	■ Lower LDL-c thresholds with optional goals for 1) very high risk 2) moderately high risk primary prevention
■ Focus on LDL ■ Rx: lifestyle, resins, niacin; fibrates, statins not first-line	■ Risk assessment guided Rx ■ Statins included in major drugs	■ LDL-c goal <100 mg/dl for CHD and CHD ■ Non-HDL-c and metabolic syndrome secondary targets	

primary prevention (Table 2.1) [5]. Those felt to have the highest risk had established cardiovascular disease (CVD) and either:

- A history of an acute coronary syndrome;
- Diabetes mellitus;
- Multiple risk factors as in the metabolic syndrome; or
- Severe, less well treated risk factors such as cigarette smoking.

Those with high-risk primary prevention were patients whose Framingham risk score did not exceed 20%, but in whom the following high-risk features were felt to intensify the risk:

- Advancing age
- More than 2 risk factors
- Severe risk factors (continued cigarette smoking and/or a strong positive family history of premature CHD)
- High triglycerides (200 mg/dl or greater) plus elevated non-HDL-c (>160 mg/dl)
- Low HDL-c (<40 mg/dl)
- Metabolic syndrome
- Emerging risk factors such as
  - — Elevated C-reactive protein (CRP)
  - — Abnormal coronary calcium score (>75th percentile)

Some argue that LDL-c goals are not required. They point to the Heart Protection Study (HPS), a landmark clinical trial, where treatment with simvastatin 40 mg over a wide range of LDL-c resulted in significantly lower rates of the primary endpoint of fatal and non-fatal CHD [6]. Indeed, the striking reductions in risk could be shown when data from similar studies were pooled to result in a proportional reduction in LDL-c (seen on a log scale) at every value of LDL-c studied [6]. Thus, the ATP III panel recommended that when statins are used in those at risk, one should always give a dose that resulted in at least a 30% reduction in LDL-c. It should be emphasized, however, that those with LDL-c of 160 mg/dl have (other risk factor burden being equal) a much higher absolute risk of CHD than those with an LDL-c of 100 mg/dl prior to initiation of the statin and likely merit more intensive therapy.

The Framingham risk scoring algorithm has been validated in multiple populations [7]. In general, it has excellent ability to discriminate risk in all populations studied (i.e., it can discriminate higher risk from lower risk individuals very well). It has also been shown to be

Table 2.2 Remaining lifetime risk for coronary heart disease at selected index ages, by age-specific tertile of Framingham risk score

	Lifetime risk for CHD (%)					
	Men			*Women*		
Index age	*FRS tertile 1%*	*FRS tertile 2%*	*FRS tertile 3%*	*FRS tertile 1%*	*FRS tertile 2%*	*FRS tertile 3%*
40*	36	35	42	12	17	30
50†	38	43	45	23	28	34
60†	32	36	41	19	27	34

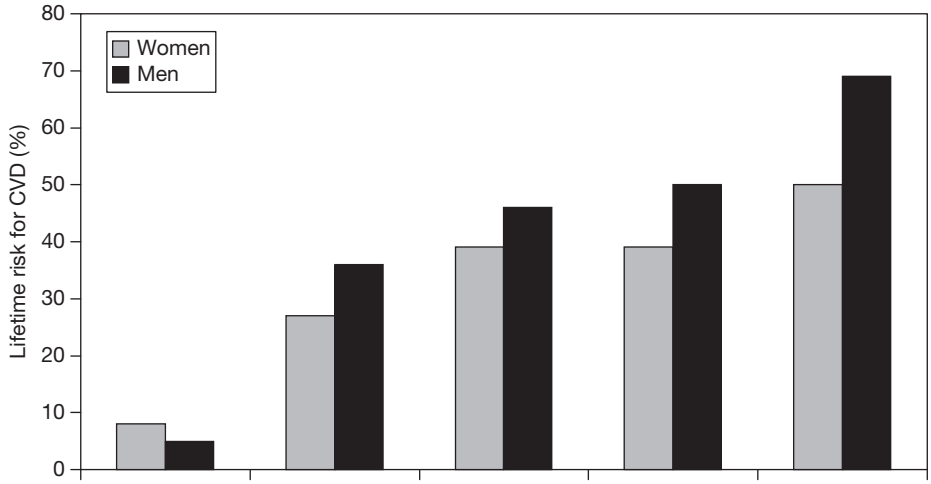
*Lifetime risk through age 80
†Lifetime risk through age 94

very well calibrated for white and black men and women in the US [8]. It tends to overestimate absolute 10-year risks for some populations, such as Asian-Americans, Hispanic-Americans, and American-Indians, as well as native Chinese. However, this problem can be easily overcome with simple recalibration using population-specific mean risk factor levels and underlying CHD event rates [7]. Despite the robust applicability of the Framingham risk score and its obvious face validity, there is concern that multivariable risk scoring has not been widely adopted in clinical practice, and data are sparse regarding the clinical impact of this treatment selection algorithm.

In addition, another concern has arisen with regard to the utility of multivariable risk scoring. Framingham [3, 4] and other multivariable risk equations [9, 10] weight the impact of age extremely heavily. This is generally appropriate, given that short-term risks for CHD do increase dramatically with increasing age. However, the effect of this is that, when treatment thresholds are applied to the absolute risk estimates, younger adults (aged less than 45 in men and less than 65 in women) rarely exceed treatment thresholds, even in the face of significant risk factor burden [11, 12]. This can hinder effective risk communication with patients that need to implement therapeutic lifestyle change or adhere to medical therapy, since they will be told they are in the low risk group even if they have markedly elevated risk factors. A number of potential solutions have been offered to overcome this problem. One of the most promising appears to be consideration of longer-term and lifetime risks for CHD and CVD.

Lifetime risk calculation estimates the absolute risk of developing the disease of interest (in this case CHD or CVD) prior to dying [13–15]. As such, this method takes into account both risk for CVD, risk of dying of something else first, and remaining lifespan. These estimates thus provide more 'real-world' estimates of population burden of disease, and individual risk, than Kaplan-Meier-based or Cox-based long-term risk estimates that do not account for competing risks.

One could consider just extrapolating the Framingham risk score (FRS) 10-year risk estimate to stratify long-term risk. It would seem logical that the risk factors that determine short-term risk would also work in the long term. However, the weighting of the covariates in the 10-year Framingham risk equations work poorly in discriminating long-term risk, likely because of changes in risk factors over time, and the importance of competing risk [16]. Thus, Lloyd-Jones *et al.* [16] recently demonstrated that the utility of the FRS for discriminating long-term risk is relatively poor, especially for men. In men at ages 40, 50 and 60 years, lifetime risks for CHD were quite similar for those in the lowest vs highest tertiles of 10-year FRS for their age (Table 2.2).



Risk factors	All optimal	⩾1 Not optimal	⩾1 Elevated	1 Major	⩾2 Major
SBP	<120 and	120–139 or	140–159 or	⩾160 or	⩾160 or
DBP	<80	80–89	90–99	⩾100	⩾100
	and	or	or	or	or
Total	<180	180–199	200–239	⩾240	⩾240
cholesterol	and	and	and	or	or
Diabetes	No	No	No	Yes	Yes
	and	and	and	or	or
Smoking	No	No	No	Yes	Yes

Figure 2.3 Lifetime risk for cardiovascular disease based on aggregate risk factor burden at age 50 years in men and women from the Framingham Heart Study.

In contrast, a simple algorithm of counting aggregate risk factor burden does a remarkable job of stratifying remaining lifetime risk for CVD. In one study [17], Framingham participants were stratified according to their risk factor burden at age 50. At 50 years of age, average lifetime risks were 51.7% (95% confidence interval [CI], 49.3–54.2) for men and 39.2% (95% CI 37.0–41.4) for women. (To put these numbers in perspective, the lifetime risk for breast cancer at age 50 for women is only 11.1%.) Single risk factors considered in isolation did a modest job of discriminating higher and lower lifetime risk for CVD. Of all the single risk factors, diabetes at age 50 was associated with the highest remaining lifetime risk for CVD. When aggregate risk factor burden (i.e., risk factor counting) was considered, there was a marked difference in remaining lifetime risk for CVD. Men and women who had all optimal risk factors (*see* Figure 2.3 for definitions) at age 50 had remaining lifetime risks for CVD of only 5% and 8%, respectively. In short, those who reached age 50 with optimal risk factor levels had almost abolished their remaining lifetime risk for CVD. With increasing risk factor burden, lifetime risks for CVD increased dramatically. For men and women with two or more major risk factors at age 50, remaining lifetime risks were substantial, at 69% and 50%, respectively [17].

Of importance, risk factor counting at age 50 stratified more than just remaining lifetime risk for CVD. Aggregate risk factor burden was also associated strongly with median survival. Overall median survivals at age 50 were 30 years for men and 36 years for women. However, median survivals were >39 years for men and women with all optimal risk factors at age 50, compared with only 28 years in men and 31 years in women [17]. These

substantial differences further highlight the importance of aggregate risk factor burden in middle age as a determinant of both morbidity (i.e., CVD events) and overall longevity. A large pooling project recently confirmed these findings using the same risk factor counting scheme among more than 45 000 men and women from 16 different US cohort studies, and followed for 650 000 person-years for different endpoints, including the occurrence of CVD death, non-fatal myocardial infarction (MI) or CHD death, and stroke [18].

In light of these data, one might consider the example of a 50-year-old non-smoking, non-diabetic man with total cholesterol of 240 mg/dl, HDL-c of 38 mg/dl, and an untreated systolic BP of 135 mmHg who would have an average lifetime risk for CVD of nearly 70% and median survival more than 11 years shorter than that for a man with optimal risk factor levels at age 50 [17]. One could easily argue that the lifetime risk concept might encourage him to do a better job of risk factor prevention than simply telling him that over the next 10 years his estimated hard CHD risk is only 8%, as estimated by the FRS. An even more striking contrast is provided by a hypothetical woman at age 50 with an identical risk factor burden whose lifetime CVD risk of 50% and >8 years shorter median survival is compared to a 10-year Framingham risk of 'hard' CHD of only 2% [17].

The above results regarding risk factor counting and lifetime risks for CVD were recently extended in the Chicago Heart Association Detection Project in Industry cohorts using an even simpler risk factor counting scheme [19]. Men and women ages 40–59 years were stratified into five groups on the basis of risk factor burden: favorable risk factor profile (untreated BP <120/<80 mmHg, total cholesterol <200 mg/dl, non-smoking, and body mass index [BMI] <25 kg/m^2); 0 elevated but >1 unfavorable; or any 1, any 2, or ≥3 elevated (systolic ≥140 mmHg or diastolic ≥90 mmHg or treated hypertension; total cholesterol ≥240 mg/dl; current smoking; or BMI ≥30 kg/m^2). Remaining lifetime risks for CVD and non-CVD death were estimated through the age of 85 years. Eight thousand and thirty-three men and 6493 women were followed for 409 987 person-years; 2582 died of CVD, and 3955 died of non-CVD causes. A greater risk factor burden was associated with a higher incidence of both CVD and non-CVD death. Compared with participants with ≥3 risk factors, those with favorable profiles had substantially lower lifetime risks for CVD death (20.5% vs 35.2% in men, 6.7% vs 31.9% in women) and for non-CVD death. Thus, those with fewer risk factors in middle age had markedly longer median survival (>35 vs 26 years in men, >35 vs 28 years in women) [19].

A number of other studies have used risk factor counting algorithms to define short- and long-term risks for CVD and other outcomes. These studies, some of which are reviewed below, have shown robust associations of risk factor burden with events.

For example, Framingham Heart Study (FHS) investigators have examined number of risk factors in association with overall survival and survival free of comorbidity to age 85 years [20]. They followed-up 2531 men and women who were examined between the ages of 40 and 50 years and observed overall rates of survival and survival free of CVD to age 85 and beyond. Low levels of the major risk factors in middle age predicted overall survival and morbidity-free survival to age 85 years. Overall, 35.7% survived to age 85, and 22% survived to age 85 free of major morbidities. Factors positively associated with survival to age 85 included female sex, lower systolic BP, lower total cholesterol, better glucose tolerance, absence of current smoking, and higher level of education attained. Factors associated with survival to age 85 free of MI, unstable angina, heart failure, stroke, dementia, and cancer were nearly identical. The investigators observed a strong gradient in association with the number of risk factors present at ages 40–50 (Table 2.3). When adverse levels of 4 of these factors were present in middle age, fewer than 5% of men and approximately only 15% of women survived to age 85 [20].

An identical analysis [21] among Japanese-American men enrolled in the Honolulu Heart Program cohort found similar results. The count of adverse risk markers and risk factors measured at ages 45–64 years was strongly associated with the probability of surviving to age 90 or beyond. The probability of survival to oldest age was as high as 69% with no risk

Table 2.3 Probability of survival to age 85 or older, based on number of conditions/risk factors* present at ages 40 to 50 years

	No. of conditions present at ages 40 to 50*				
	0	***1***	***2***	***3***	***≥4***
Women (%)	65	53	35	27	14
Men (%)	37	32	24	14	2

*Systolic blood pressure ≥140 mmHg, total cholesterol ≥240 mg/dl, smoking, glucose intolerance, education less than completion of high school.

factors, and as low as 22% with 6 or more risk factors. The probability of exceptional survival to age 85 years (without CVD, cancer, Parkinson disease, chronic obstructive pulmonary disease or diabetes, or physical or cognitive impairment) was 55% with no risk factors but decreased to 9% with 6 or more risk factors [21].

Among 366 000 men and women from the Multiple Risk Factor Intervention Trial (MRFIT) screened and the Chicago cohorts [22], low risk status was defined as follows: serum cholesterol level <200 mg/dl, untreated BP <120/80 mmHg, absence of current smoking, absence of diabetes, and absence of major electrocardiographic abnormalities. Compared with those who had higher burden of risk factors, those with low risk factor burden had between 73% and 85% lower risk for CVD mortality, 40–60% lower total mortality, and 6–10 years greater life expectancy in all cohorts [22].

Seventeen-year mortality data from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Follow-Up Study indicate that the risk for fatal CHD was 51% lower for men and 71% lower for women with none of three major risk factors (hypertension, current smoking, and total cholesterol ≥240 mg/dl) compared with those with one or more risk factors. Had all three major risk factors not occurred, it is estimated that 64% of all CHD deaths among women and 45% of CHD deaths in men could have been avoided [23].

A study of 84 129 women enrolled in the Nurses' Health Study [24] identified five healthy lifestyle factors, including absence of current smoking, drinking 1/2 glass or more of wine per day (or equivalent alcohol consumption), 1/2 h or more per day of moderate or vigorous physical activity, BMI <25 kg/m^2, and dietary score in the top 40% (including diets with lower amounts of *trans* fats, lower glycemic load, higher cereal fiber, higher marine omega-3 fatty acids, higher folate, and higher polyunsaturated to saturated fat ratio). When three of the five healthy lifestyle factors were present, risk for CHD over 14 years was reduced by 57%; when four were present, risk was reduced by 66%; and when all five factors were present, risk was reduced by 83% [24].

The utility of risk factor counting algorithms has been demonstrated to extend beyond association with morbidity and mortality endpoints. For example, investigators from the Chicago Heart Association Detection Project in Industry have also observed that risk factor burden in middle age is associated with quality of life at follow-up in older age (about 25 years later). A greater number of risk factors in middle age is associated with lower scores at older ages on assessment of social functioning, mental health, walking, and health perception in women, with similar findings in men [25]. Similarly, a greater number of risk factors in middle age is associated with higher average annual total and CVD-related Medicare costs (once Medicare eligibility is attained) [26].

Thus, CVD risk factor counting algorithms, which have been derived from multiple different cohorts but are generally similar, provide effective means for predicting future risk

for overall mortality and fatal and non-fatal CVD events, as well as the occurrence of non-CVD death. These risk factor counting algorithms, applied to middle-aged populations, have also been shown to be associated with quality of life and healthcare costs at older ages. They have also highlighted the importance of primordial prevention of risk factors. Specifically, those who reach middle age free of risk factors have substantially prolonged longevity, lower lifetime risks for disease, greater disease-free longevity, and greater health-related quality of life at older ages, compared to those with one or more than one risk factor present in middle age. Thus, greater efforts are needed to prevent the development of risk factors not just to prevent disease once risk factors are present, suggesting the clinical relevance of risk factor counting schemes.

SUMMARY

There is little doubt that the Framingham risk score, with its consideration of important clinical covariates (that are also targets of therapy) and estimation of absolute 10-year risks, represents a substantial advance in our understanding of CHD risks. The FRS has also provided the basis of a rational treatment algorithm in the ATP III guidelines. However, it should also be noted that simple risk factor counting schemes provide remarkable discrimination of short-term and especially long-term risks for cardiovascular events, non-cardiovascular death, morbidity and health-related quality of life measures. Therefore, risk factor counting methods deserve consideration in clinical practice decision-making regarding primary prevention of CVD.

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3

What is the metabolic syndrome, how do I treat it and is it a high-risk condition?

K. L. Wyne

BACKGROUND

The metabolic syndrome, also known as the dysmetabolic syndrome, syndrome X, or the insulin resistance syndrome, refers to the clustering of cardiovascular (CV) disease (CVD) risk factors that are present in many individuals who are at increased risk for cardiovascular events. The criteria for metabolic syndrome include a combination of categorical and borderline risk factors that can be readily measured in clinical practice. Identification of the metabolic syndrome was not done in clinical practice prior to the definition proposed by the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) because the prior definitions utilized factors that were not typically measured in the routine practice of medicine. The definition has since been refined as we attempt to create a worldwide definition with racial/ethnic-specific criteria. Therapies targeted to specific components of the metabolic syndrome, such as decreasing weight, improving glycemic control, managing dyslipidemia, decreasing blood pressure, and reducing the prothrombotic state, should help to minimize the realized cardiovascular risk, particularly if initiated early.

A clustering of CVD risk factors that appeared in certain patients was identified as syndrome X by Reaven in 1988 [1]. However, this was not a new disease process, having first been described in the German literature in 1923 [2]. Subsequent reports in the 1960s further refined the constellation of factors without determining the significance of the clustering [3, 4]. The reason for the renewed interest by Reaven in 1988 was to emphasize the important causal role of insulin resistance in this cluster of abnormalities. The risk factors identified by Reaven included glucose intolerance, hypertension, elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-c). The list of risk factors has been expanded to include central obesity, impaired fibrinolysis, alterations in uric acid metabolism, and a proinflammatory state [5–8]. This syndrome has been referred to as the insulin resistance syndrome, syndrome X, dysmetabolic syndrome or metabolic syndrome (MS). The term 'metabolic syndrome' has rapidly become the international designation for this constellation of factors.

DIAGNOSTIC CRITERIA

Reports on the prevalence of the MS have varied considerably because of the lack of uniform definitional criteria. Current estimates are that up to 40% of the adult population in the

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Table 3.1 Clinical criteria to identify the metabolic syndrome

Components	*WHO 1998*	*NCEP ATP III 2001*	*IDF 2005*	*AHA/NHLBI 2005*
Required:	Diabetes or IGT or insulin resistance[a] + any 2 metabolic factors	Any 3 of the 5 factors	Waist circumference[b] + any 2 metabolic factors	Any 3 of the 5 factors
Obesity	BMI >30 kg/m^2 or Waist:Hip ratio >0.9 (M), >0.85 (F)	Waist circumference (cm) >102 (M) >88 (F)	Waist circumference (cm) Europid* ≥94 (M) ≥80 (F) S. Asian** ≥90 (M) ≥80 (F) Japanese ≥85 (M) ≥90 (F)	Waist circumference (cm) >102 (M) (>40 in) >88 (F) (>35 in)‡
TG (mg/dl)	>150	>150	>150†	>150†
HDL (mg/dl)		<40 (M) <50 (F)	<40 (M)† <50 (F)†	<40 (M) <50 (F)†
BP (mmHg)	>140/90	>130/>85	>130 or >85†	>130 or >85†
FPG (mg/dl)		>110	>100†	>100†
Micro-albuminuria	Albumin excretion >2.5 mg/mmol (M) and >3.5 mg/mmol (F)			

‡≥90cm (M) ≥80cm (F) for Asian-Americans;
†Or on drug treatment.
WHO = World Health Organization; EGIR = the European Group for the Study of Insulin Resistance; ATP III NCEP=National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); IDF = International Diabetes Federation; F = female; and M = male.
[a]Defined as the lowest quartile of HOMA-S
[b]IDF recommends the use of ethnicity-specific waist circumference cut-points based on language spoken at home rather than country of birth
*Europids includes Europeans, Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations
**South Asians includes South Asians, Chinese, ethnic South and Central Americans

United States has the MS depending on the definition utilized [9–16]. In 1998, the World Health Organization (WHO) proposed a definition for the MS that included the presence of hypertension, dyslipidemia, glucose intolerance, and microalbuminuria [17]. The NCEP ATP III re-emphasized that the MS is a collection of categorical and borderline risk factors for coronary heart disease (CHD) (Table 3.1) [18]. However, ATP III proposed a new definition which utilized components that were typically measured in these patients (blood pressure [BP], lipids and glucose) or could be easily measured in clinical practice (waist circumference). A subsequent consensus conference on management, held by the American Heart Association (AHA), the National Heart, Lung, and Blood Institute (NHLBI), and the American Diabetes

Table 3.2 Ethnic-specific values for waist circumference. Central obesity is most easily measured by waist circumference using the guidelines in Table 3.2 which are gender- and ethnic-group (not country of residence) specific. The consensus group acknowledges that these are pragmatic cut-points taken from various different data sources and that better data will be needed to link these to risk

Country/ethnic group	*Waist circumference*	
Europids in the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male Female	>94 cm >80 cm
South Asians based on a Chinese, Malay and Asian-Indian population	Male Female	>90 cm >80 cm
Chinese	Male Female	>90 cm >80 cm
Japanese	Male Female	>85 cm >90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available	

*In future epidemiological studies of populations of Europid origin, prevalence should be given using both European and North American cut-points to allow better comparisons

Association (ADA), recommended lifestyle modifications leading to weight reduction and increased physical activity as first-line therapy for the MS [19]. This conference also reviewed data supporting the ATP III definition for the MS. At that time they did not formally revise the criteria but they did add a footnote specifying that the new ADA cut-point of 100 mg/dl [20] should be used to define an elevated blood glucose as a criterion for the MS [21].

One shortcoming of the ATP III and WHO definitions is the lack of racial and ethnic group-specific criteria for obesity. This issue was addressed by a group convened in 2000 by the International Association for the Study of Obesity and supported by the WHO (Western Pacific Region) and the International Obesity Task Force (IOTF) [22]. They redefined overweight as a body mass index (BMI) >23 and obesity as >25 in Asians. Central obesity was defined as >80 cm for women and >90 cm in men. Another working group, with representatives from these same organizations, reported in 2004 that urban Asians with a BMI of 23–24 have an equivalent risk of type 2 diabetes, hypertension, and dyslipidemia as a BMI of 25–29.9 in Caucasian people [23]. This set the stage for an international conference to bring together these definitions.

The International Diabetes Federation (IDF) hosted the 1st International Congress on 'Prediabetes' & the Metabolic Syndrome in April 2005 with a goal of developing a worldwide consensus definition of MS [17, 24]. Their goal was to emphasize the role of central obesity and insulin resistance as contributing factors. Additionally, they created ethnic-specific criteria for the measurement of waist circumference (Table 3.2). They suggested that in future epidemiological studies the prevalence of the MS should be reported using both European and North American cut-points to allow for better comparisons. They also recommended

Table 3.3 Criteria for risk factors for the metabolic syndrome in children

Criteria	**Any three of the five**
Triglycerides	>110 mg/dl
HDL	<40 mg/dl
Abdominal obesity	>90th percentile waist circumference[a]
Fasting glucose	>100 mg/dl[b]
Blood pressure	
Systolic	>90th percentile[a]
Diastolic	>90th percentile[a]

[a]for age, sex and height
[b]cut-point updated to reflect the most current ADA recommendation

that ethnic group-specific cut-points be used for people of the same ethnic group, regardless of where the person resides. For example, a person from South Asia who is living in the United States should have South Asian cut-points applied to their evaluation rather than the higher cut-points currently employed for the US population.

The modifications to the definition proposed by the IDF were then adopted in the United States in 2005 by a Consensus Scientific Statement from the American Heart Association/National Heart, Lung, and Blood Institute [21]. The Scientific Statement maintained the original ATP III criteria with the following modifications:

1. A lower waist circumference cut-point (e.g., 90 cm [35 inches] in men and 80 cm [31 inches] in women) appears to be appropriate for Asian-Americans.
2. The threshold for the glucose criteria to be decreased to 100 mg/dl, in accordance with the revised ADA criteria for impaired fasting glucose.
3. The cut-points for the metabolic parameters now include the specific threshold value or the fact that the person is on specific drug therapy. The specific criteria for the WHO, ATP III, IDF and AHA/NHLBI definitions are listed in Table 3.1.

PREVALENCE OF METABOLIC SYNDROME IN THE US

Analysis of the data from the Third National Health and Nutrition Examination Survey (1988–1994) (NHANES III) showed that unadjusted and age-adjusted prevalences of the MS were 21.8% and 23.7%, respectively [16]. The prevalence increased from 6.7% (age 20–29 years) to 43.5% (age 60–69 years) and 42.0% (age ≥70). The age-adjusted prevalence in the NHANES III was similar for men (24.0%) and women (23.4%) [10]. The prevalence increased significantly in subsequent years such that the NHANES 1999–2002 survey found an unadjusted prevalence of the MS in adults of 34.5% (33.7% among men and 35.4% among women). When these same data were analysed using the IDF definition, the unadjusted prevalence of the MS was 39.0% among all participants with a similar prevalence in men and women. The IDF definition did lead to higher estimates of prevalence in all the demographic groups, especially among Mexican-American men. Only about 7% of the individuals identified met criteria for only one of these two definitions.

Estimating the true prevalence of MS in children has proven difficult. Evaluation of the NHANES III data for adolescents (aged 12–19) using a modification of the ATP III definition (Table 3.3) revealed a 4.2% prevalence of MS (6.1% of males and 2.1% of females) [25]. These data were then projected to estimate that approximately 910 000 US adolescents have the MS. This number is likely an underestimate because the data for the NHANES III was collected prior to the onset of the current epidemics of obesity and type 2 diabetes. A recent

evaluation of children and adolescents (age 4–20) found that the overall prevalence of the MS was 38.7% in moderately obese and 49.7% in severely obese subjects [26]. In this cohort, no overweight or non-obese subject met the criteria for the MS. Analysis of the data from the next NHANES survey, (NHANES 1999–2002) using criteria modified from the ATP III definition shows a prevalence, depending on the subgroup studied, ranging from 0.7 to 23% [27]. The analysis is limited by the fact that there are incomplete metabolic data on the children that were included in the study. With that as a limitation, the authors studied three groups: a) children 2–18 years old with data on at least three or four of the five diagnostic criteria but not missing blood glucose data ($n = 5172$); b) a subsample of 12–18-year-olds who had fasting glucose data but were not overweight or obese using the IOTF standards ($n = 1064$); and c) 12–18-year-olds with blood glucose data who were overweight or obese ($n = 641$). They found a prevalence of MS of 2%, 0.7%, and 23%, respectively. Two percent of those that were overweight or obese with fasting blood glucose data met all five diagnostic criteria for MS. More than 10% of those with fasting blood data had hyperglycemia. Low HDL-c and elevated triglycerides were the abnormalities most commonly present. While it is difficult to compare between the NHANES III and NHANES 1999–2002 data, there appears to be a modest increase in the prevalence of the MS in children over this time period. While the increase is not of the magnitude seen in the adult population, it is a problem that needs attention to try to prevent the development at a young age of the MS-related complications. The IDF has recently proposed a definition for evaluation of CV risk factors and the MS in children and adolescents [28]. This definition will need to be tested on a variety of populations for validation but will likely show a similar prevalence of the MS as that found in the recent studies.

ETIOLOGY OF THE METABOLIC SYNDROME

CENTRAL OBESITY AND INSULIN RESISTANCE

Central obesity is a surrogate marker for the accumulation of adipose tissue in the metabolically active depots that are present in the truncal region. These depots include the mesenteric, perinephric, and the omental fat. Research has shown that different adipose depots have different metabolic activities based on the profile of cytokines that are produced locally. These adipocyte-derived cytokines are now referred to as adipocytokines and include free fatty acids (FFAs), leptin, adiponectin, plasminogen activator inhibitor 1 (PAI-1), and resistin. The alterations in fat metabolism associated with overnutrition and physical inactivity lead to elevated circulating FFA levels because the adipocytes are too full and cannot store any more fat. These FFAs need to be stored somewhere so they get deposited in non-adipose tissues, including muscle, liver, heart and the pancreatic β-cell. Unfortunately, these tissues are not able to store large amounts of fat, thus the excess accumulation of FFAs becomes toxic to the cells leading to the loss of β-cell function, insulin resistance in the muscles, fatty liver, and a stiff heart. This process has been termed 'lipotoxicity' and is thought to play a major role in the development of type 2 diabetes. In addition to needing a place to store the excess FFAs, the insulin resistance leads to a reduced expression of lipoprotein lipase (LPL) and increased circulating levels of apoCIII, an inhibitor of LPL. Taken together, these contribute to the increase in circulating triglycerides and a decrease in HDL cholesterol. As the adipose depot expands to try to accommodate the FFAs delivered to it, the levels of adiponectin decrease and leptin increases to communicate the size of the adipose depot to the rest of the body. The overproduction of PAI-1 contributes to the prothrombotic state. The altered constellation of adipocytokines contributes to the development of endothelial dysfunction, resulting in hypertension and accelerated atherogenesis. Increased blood pressure results from sympathetic activation, adipocyte derived production of angiotensin II, and increased intravascular volume secondary to sodium retention, among

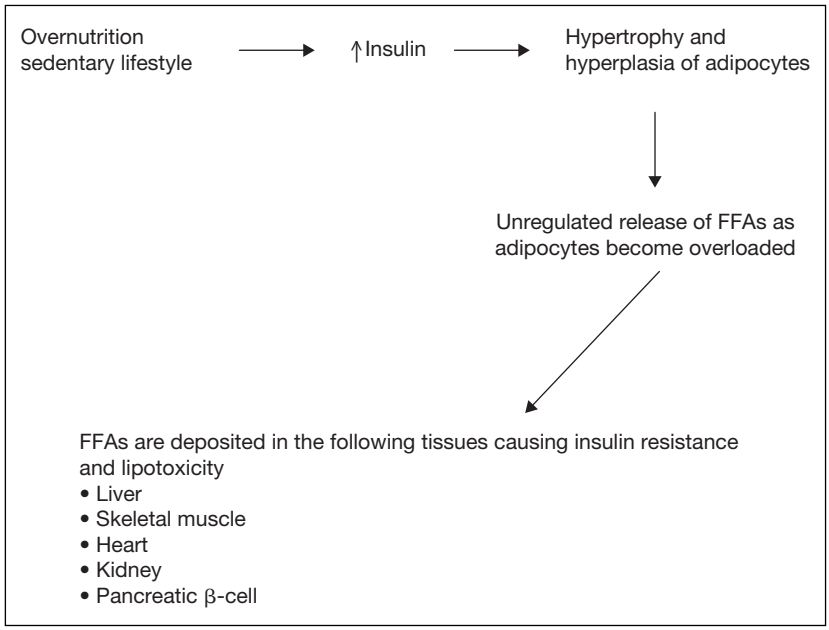

Figure 3.1 Events leading to lipotoxicity and insulin resistance.

other mechanisms. In the setting of insulin resistance, there is increased flux of FFAs into the liver which can result in increased very-low-density-lipoprotein (VLDL) secretion and risk for the development of hepatic steatosis (Figure 3.1).

The localization of the excess fat to the truncal depots appears to have a strong genetic component as evidenced by studies of fat depots and insulin resistance in different ethnic populations. Consequently, the guidelines for MS have emphasized measuring the waist circumference as it is a better surrogate for insulin resistance and metabolic risk than is BMI. In fact, the IDF definition requires the presence of central obesity, using ethnic group-specific measurements.

MANAGEMENT OF THE METABOLIC SYNDROME

Management of MS begins with the initiation of therapeutic lifestyle changes (TLC), with a goal of weight loss and increased physical activity. In addition to lifestyle changes, pharmacologic therapy should be considered for each component with a goal of attaining targets such that they no longer meet criteria as a component of MS.

CENTRAL OBESITY AND OVERWEIGHT

The use of waist circumference in the criteria focuses attention on the association of obesity, physical inactivity, genetic factors and insulin resistance. It is important that the waist circumference be measured correctly and thus in a reproducible manner. The Scientific Statement from the AHA/NHLBI provides specific guidelines as to how to measure the waist circumference. This document specifies that to 'measure waist circumference, locate

the top of the right iliac crest. Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, ensure that it is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration' [29].

Most persons with insulin resistance have abdominal obesity. Components of TLC are: reduced intake of saturated fats and cholesterol, therapeutic dietary options for enhancing LDL lowering (plant stanols/sterols and increased viscous [soluble] fiber), weight reduction, and increased regular physical activity. TLC should also be the initial intervention for MS. TLC is the most cost-effective means to reduce risk for CHD.

Realistic goals must be set for weight loss upon initiation of TLC. To have sustained benefit, one must have slow, steady and maintained weight loss over time (i.e., reducing body weight by 7–10% over 6–12 months). For this reason, 'fad' diets should be discouraged. Unfortunately, most people give up after a brief period of time because they fail to understand that they must make a complete lifestyle change to prevent the development of CV disease and diabetes. Pharmacologic interventions have not typically been associated with major and sustainable amounts of weight loss. However, there are agents in development that may result in greater amounts of weight lost. The agents which appear to have the most promise are a new class of compounds that target the endocannabinoid system. This system consists of endogenous ligands and two types of G-protein-coupled cannabinoid receptors: CB1, located in several brain areas and in a variety of peripheral tissues; and CB2, which localizes to the immune system [30]. The endocannabinoid system contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects. One such compound, rimonabant, is a selective CB1 blocker which has been shown to reduce waist circumference, HDL-c, triglycerides, insulin resistance, and prevalence of the MS [31]. It has also been associated with a decrease in tobacco use [32]. Unfortunately, this compound is yet to gain regulatory approval in the United States and its ultimate approval will likely hinge on studies addressing its propensity to cause depression in treated patients.

Bariatric surgery is another option that must be considered as it has been shown to be the most effective strategy for weight loss. The criteria for such surgery are very specific, thus it is only an option for those with a BMI above 40 kg/m^2 or 35–40 kg/m^2 with significant comorbidities [33].

DYSLIPIDEMIA

If triglycerides are elevated, ATP III recommends the following changes: weight control, regular physical activity, smoking cessation, restriction of alcohol use (in selected persons), and avoidance of high-carbohydrate diets. If these are not successful, then pharmacologic therapy should be instituted with a fibrate, nicotinic acid, or fish oil supplements. Fibrates are generally the first-line agent because they are well tolerated and will improve all components of the atherogenic dyslipidemia. Of the fibrates available in the United States, fenofibrate is the preferred agent as it has the least potential for drug interactions that might result in myopathy [34]. The introduction of extended release prescription niacin has made the use of nicotinic acid more acceptable to patients. However, the practitioner must remember to advise the patient to take an aspirin at least 30 min before taking even the slow release niacin. Other strategies, albeit anecdotal, to avoid the flushing with niacin include eating apple sauce prior to taking it or taking Alka-Seltzer prior to the dose for the first three days of therapy. High doses ($\geq$2 g/day) generally should be used cautiously in persons with type 2 diabetes as the nicotinic acid will lower FFAs which, if low enough, may impair the ability of the pancreas to secrete insulin leading to a worsening of hyperglycemia and an elevation in triglyceride levels. Additionally, there is usually a rebound in FFA levels after the niacin wears off, which can acutely increase insulin resistance. A prudent strategy is to have

the patient notify the practitioner who manages their diabetes at the time they initiate therapy with nicotinic acid. Supplements of long chain omega-3 polyunsaturated fatty acids, which are present in fish oil, can be purchased without a prescription but require doses up to 10–12 g/day, which are not well tolerated. There is a purified form, containing mainly omega-3 fatty acid ethyl esters, which has been approved for use in the United States and is available by prescription for the treatment of hypertriglyceridemia. This omega-3 product was associated with a decrease in mortality in the GISSI-P trial which may provide an additional benefit when using this agent to lower triglyceride levels [35].

All of the above strategies to lower triglycerides will also raise HDL. However, it is important that the strategies used to raise HDL have efficacy, which has been demonstrated in randomized outcomes trials. While epidemiologic studies have demonstrated an association between high HDL and fewer vascular events, these observations are not able to tell us how to raise HDL to those levels. This point was recently reinforced when clinical trials, notably the ILLUMINATE Trial, with a cholesteryl ester transfer protein (CETP) inhibitor were stopped after an increase in CV events was observed [36]. Although the subjects attained very high HDL levels, it appears that it does matter how the HDL gets to that level. It is still possible that other agents of this class may become available for clinical use, as most of the excess CV risk was attributable to effects that are not mediated by HDL particles and were specific to torcetrapib, including increased blood pressure, increased adrenal secretion of aldosterone, reduced serum K, and increased serum bicarbonate. While there are outcomes data using fibrates in patients with low HDL and mildly elevated triglycerides [37], the most potent HDL-c raising agent is nicotinic acid. Statins have a modest effect on raising HDL-c. In populations selected specifically because they have low HDL-c, the use of statins has been shown to be associated with angiographic regression of atherosclerosis and to be effective in primary prevention of CV events [38–40]. Whether this can be attributed to the effects on HDL-c raising, LDL-c lowering or other beneficial effects of the statin is unknown. Thiazolidinediones (TZD), which improve insulin resistance, have also been demonstrated to raise HDL-c and their effect is more pronounced in patients with lower baseline HDL-c levels. The magnitude of HDL-c increase that occurs with thiazolidinedione therapy is more than what would be expected from improving glucose control alone. It is possible that the TZD-induced improvement in insulin resistance leads to lower serum triglyceride levels, which results in less enrichment of HDL with triglyceride, and less HDL lipolysis by hepatic lipase leading to an increase in HDL2. Additionally, TZDs initiate cholesterol efflux from the macrophage/foam cells and that cholesterol is picked up by the HDL particle. Although triglycerides and HDL are separate criteria for the MS syndrome, most interventions will have a clinically relevant impact on both of these components.

BLOOD PRESSURE

No particular antihypertensive agents were recommended by ATP III for management of hypertension in patients who also have MS. JNC7 recommends diuretics as first-line agents unless there is a compelling indication to use a specific agent for the added benefit of treating a comorbidity such as coronary artery disease (CAD), heart failure, or diabetic nephropathy. However, both diuretics and ß-blockers in high doses can worsen insulin resistance, fasting blood sugar, and atherogenic dyslipidemia. Utilizing low doses of thiazide diuretics as per JNC7 recommendations will minimize the risk of worsening concurrent dyslipidemia. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are also useful for their cardiac benefits and for renal protection in the presence of diabetes. If hypertension and MS are present in a patient who is at high risk for diabetes or meets the glucose criteria for MS, one should consider use of ACE inhibitors or ARBs to maximally decrease the progression rate of diabetic nephropathy. However, most people will need multiple agents to control their BP; thus ACE inhibitors and ARBs

will typically be used in combination with a low dose thiazide diuretic (i.e., 12.5 mg daily of hydrochlorothiazide) and a long acting ß-blocker. The availability of fixed dose combination pills has improved compliance and adherence to these multi-drug regimens. *Post hoc* analyses of trials involving ACE inhibitors and ARBs have suggested that these agents may decrease the likelihood of being diagnosed with diabetes. However, this hypothesis was formally tested in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication trial (DREAM) which found no positive effect of ramipril on the progression to diabetes in patients with impaired fasting glucose or impaired glucose tolerance [41]. There are emerging data which shed light on a possible mechanism by which alteration of the renin–angiotensin system activity could impact insulin resistance and, thus, progression to type 2 diabetes. Insulin has been shown to stimulate angiotensin II production suggesting that hypertension may be a surrogate marker for hyperinsulinemia in someone at risk for MS or diabetes. In addition, the local renin–angiotensin system plays a role in adipocyte differentiation. Angiotensin II produced by mature adipocytes inhibits the differentiation of adipocyte precursors, thus decreasing the percentage of small insulin-sensitive adipocytes. The lack of small adipocytes will in turn lead to ectopic fat deposition in the liver, skeletal muscle, and pancreas, leading to lipotoxicity. There may also be interplay between angiotensin and insulin signaling in the endothelial cell. An ARB, telmisartan, has been shown to activate peroxisome proliferator-activated receptor-γ (PPAR-γ) *in vitro*, but at pharmacologic concentrations that are much higher than those achieved at currently used doses. Despite the negative results of the DREAM trial, given the CV benefits of ACE inhibitors and ARBs, they should still be a component of the therapy of hypertension in the MS patient.

INSULIN RESISTANCE AND HYPERGLYCEMIA

At this time the most effective therapy in preventing the progression to diabetes mellitus is the institution of intensive lifestyle changes. There is growing interest in the possibility that drugs used to treat type 2 diabetes will delay onset of type 2 diabetes and will reduce CVD risk when MS is present. Acarbose (which reduces glucose absorption), metformin (which reduces hepatic gluconeogenesis), and the thiazolidinediones (pioglitazone and rosiglitazone, which decrease insulin resistance and maintain β-cell function), have all been shown to prevent or delay the development of diabetes [42–46]. There has been a great deal of debate over whether these agents are preventing diabetes or merely delaying the rise in glucose. Evaluation of these subjects after stopping the drug for anywhere from 11 days to 8 months has generally shown that the glucose rises as soon as the drug is stopped suggesting there has not been an alteration in the underlying physiology and that the drug has merely been keeping the glucose in the normal range. One study, using troglitazone, which is no longer available, showed a sustained decrease in the glucose for at least 8 months after stopping the drug while another study did not find such a decrease 3 months after stopping rosiglitazone [42]. Nonetheless, the data hint that there may be some benefits in slowing the progression to diabetes, if the therapy is started early enough, which is before significant β-cell function has been lost [47].

PROTHROMBOTIC STATE AND PROINFLAMMATORY STATE

Patients with metabolic syndrome have a prothrombotic and proinflammatory state which is characterized by elevations of fibrinogen, PAI-1, C-reactive protein (CRP), tumor necrosis factor-alpha, interleukin-6, and coagulation factors. Only CRP is available for routine measurement if the practitioner chooses to obtain the test. ATP III recommends aspirin prophylaxis in patients with MS when their 10-year risk for CHD is >10% by Framingham risk scoring. Contrary to a widespread misconception, MS is not defined by NCEP ATP III as a

high risk condition. In order to derive any given patient's LDL-c and non-HDL-c target, these patients should undergo comprehensive risk factor evaluation and a Framingham risk score should be calculated. Elevated CRP (>3 mg/l) is an emerging risk factor for CVD. The AHA and Centers for Disease Control and Prevention (CDC) recently issued guidelines for measurement of CRP in clinical practice. They suggested that such measurements can be made at the physician's discretion, but testing should be limited to individuals determined to be at intermediate risk by Framingham scoring to find those with high CRP levels whose risk category should be raised to high. These guidelines emphasized that CRP testing still belongs in the category of optional, based on clinical judgment, rather than recommended routinely because the magnitude of its independent predictive power remains uncertain.

The question remains as to whether any other therapies are available in addition to lifestyle changes and aspirin therapy. Studies have shown that glucose-lowering agents such as metformin and thiazolidinediones decrease parameters of the prothrombotic and proinflammatory state (i.e., fibrinogen, PAI-1, CRP, tumor necrosis factor-alpha and interleukin-6). However, outcomes studies are not yet available to determine if these changes are associated with a decrease in CVD. While awaiting data from ongoing studies, the use of such therapies can only be considered at the discretion of the healthcare provider and whenever possible should be discussed with the patient.

METABOLIC SYNDROME AS A PREDICTOR OF VASCULAR DISEASE

Analysis of the Framingham database has revealed that MS alone predicted ~25% of all new-onset CVD [48]. However, MS alone, without the presence of diabetes, generally did not raise 10-year risk for CHD to >20%. The Atherosclerosis Risk in Communities (ARIC) study database showed that over an average of 11 years of follow-up men and women with the MS were approximately 1.5 and 2 times more likely to develop CHD or stroke than were control subjects after adjustment for age, smoking, LDL cholesterol, and race/ARIC center (sex interaction, $P < 0.03$) [49]. Elevated BP and low levels of HDL-c exhibited the strongest associations with CHD. Application of MS criteria to the San Antonio Heart Study found that the ATP III criteria for MS did not increase the identification of individuals at risk for CVD beyond applying the Framingham Risk Score. This discrepancy may reflect the need for ethnic-specific criteria, as emphasized by the new IDF definition. Nevertheless, the ATP III criteria for MS have been applied to a number of databases and have been found to be associated with the presence of vascular disease (i.e., coronary heart disease, cardiovascular disease, stroke and death), suggesting that it has clinical utility in identifying patients at increased risk of vascular disease [49–53].

METABOLIC SYNDROME AS A PREDICTOR OF TYPE 2 DIABETES

The question as to whether the ATP III criteria for MS predict risk for type 2 diabetes has been raised because this definition differs from the WHO criteria in that it does not require a measurement of insulin resistance. In some populations, the WHO criteria are a better predictor of risk of type 2 diabetes [54]. The ability of the ATP III criteria to predict insulin resistance was recently tested in a cohort of obese, non-diabetic individuals. In this study, insulin resistance was calculated from insulin-mediated glucose uptake as measured by the euglycemic–hyperinsulinemic clamp technique. The ATP III criteria for MS had a sensitivity of 52% and a specificity of 85% for predicting insulin resistance. These data are consistent with other studies looking at utilization of ≥2 criteria from ATP III to identify MS and insulin resistance. Interestingly, this study showed that more insulin-resistant individuals ($n = 87$) were identified by simply using a fasting triglyceride >130 mg/dl and/or a triglyceride-to-HDL ratio of >3.0 than by using the ATP III criteria [55]. Although these data need to be validated in non-Caucasian populations, this is a parameter that can be easily calculated

from laboratory results that are typically obtained in patients. These data suggest that perhaps subjects who have MS with triglycerides and HDL as two of the qualifying components may merit further evaluation for the presence of type 2 diabetes.

The San Antonio Heart Study has shown that both the WHO and the ATP III criteria predict risk of type 2 diabetes as well as impaired glucose tolerance on a 2-hour oral glucose tolerance test [56]. The predictability of the criteria for MS was improved if the glucose criterion was lowered to 5.4 mmol/l (97 mg/dl), which is close to the level recommended in the new ADA criteria for impaired fasting glucose. These data suggest that application of the criteria for MS could be used to predict risk of type 2 diabetes rather than performing a glucose tolerance test. An alternative way to apply these data would be that if a patient is at risk for diabetes (i.e., has a family history of diabetes in a first- or second-degree relative) and has MS, but the fasting glucose does not meet criteria for type 2 diabetes (i.e., $>$126 mg/dl), then one should consider performing a glucose tolerance test.

LOOK TO THE FUTURE

The question as to whether treating insulin resistance slows progression of MS and/or the development of diabetes will need to be addressed again in the near future when compounds in development become available. There is a great deal of interest in rimonabant, as already mentioned, for its metabolic effects. Whether the beneficial effect on glucose lowering and improving cardiovascular risk factors is due to weight loss or an intrinsic effect of the drug remains to be determined. The class of compounds that activate both PPAR-α and -γ have been shown to improve dyslipidemia and hyperglycemia; however, there are concerns about increased CV risks with these agents [57]. The next generation in this family may be the compounds that activate PPAR-α, -γ, and -δ or, perhaps, only the PPAR-δ. These may have even greater benefits in treating the MS. Analogs of glucagon-like peptide-1 (GLP-1), such as exenatide (exendin-4), have promise for benefits beyond merely lowering glucose. Exenatide is now available for the treatment of type 2 diabetes. There has been a great deal of interest in the use of exenatide in people with MS as a subset of the people in the glucose control studies lost weight while taking exenatide [58]. It is important to wait for prospective randomized trials to determine if exenatide would benefit people with MS. If patients were to lose significant amounts of weight while taking exenatide then they would likely see an improvement in all of the components of the MS. However, the safety and efficacy must be established in prospective clinical trials before considering such use in people who do not have type 2 diabetes as that is not currently an FDA approved use of exenatide. There is still a need to explore the possibility that metformin has non-glycemic benefits, which may explain why there was a decrease in MI (39%; $P < 0.010$) in the group that received metformin in the UK Prospective Diabetes Study (UKPDS) [59]. These classes of agents raise hope that we may be able to slow or stop the morbidity and mortality that is increasing with the growing epidemic of obesity and diabetes.

SUMMARY

The MS refers to the clustering of CV disease risk factors that are present in many individuals who are at increased risk for CV events and/or type 2 diabetes. Identification of MS allows early identification of individuals at risk for CVD and type 2 diabetes. ATP III introduced the identification of the MS into its clinical guidelines in an effort to achieve CVD risk reduction beyond LDL-lowering therapy. Because MS is relatively uncommon in the absence of obesity and physical inactivity, lifestyle modification leading to weight reduction and increased physical activity represents first-line clinical therapy. Smoking cessation is also important. When lifestyle changes fail to reduce risk sufficiently, drug therapy might be required to achieve the treatment goals recommended in current guidelines. Standard therapies

for each component apply in patients with MS. One must keep in mind that management of insulin resistance with insulin-sensitizing agents in the absence of diabetes has not been shown to reduce CVD risk; however, such studies are ongoing and, if positive, will require that their use be added to the existing guidelines.

Identification of individuals with MS may allow for earlier diagnosis and management of risk for both CV disease and type 2 diabetes. In addition to identifying risk, there remains a need to test and treat these individuals. If lifestyle interventions are not successful then patients will need pharmacologic therapy to treat the components of MS. The cost of initiating such therapy must be weighed against the cost of not attempting early intervention to prevent the progression to the devastating side effects, which include CV disease and type 2 diabetes.

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4

Should all patients admitted to the hospital with an acute coronary syndrome initiate statin therapy?

J. A. Farmer, P. H. Jones

BACKGROUND

Despite a recent decline in age-adjusted mortality, coronary artery disease (CAD) and its complications remain the most common cause of death in the United States. The etiology of atherosclerosis is multifactorial and is best regarded as a syndrome with multiple underlying potential factors which influence the initiation and progression of obstructive atherosclerotic vascular disease. The lipid hypothesis, which was introduced over 100 years ago, was developed as a theory to explain the central role of hypercholesterolemia in atherosclerosis. However, the ability of the clinician to modify the lipid profile was limited prior to the advent of pharmacologic agents (statins) which inhibit the rate limiting enzyme in cholesterol synthesis (3-hydroxy 3-methylglutaryl CoA reductase). Statin therapy has been demonstrated to reduce the risk for coronary and cerebral atherosclerosis-related events in multiple clinical trials [1, 2]. However, the utilization of statin therapy has been predominantly regarded as a long-term strategy to prevent the onset of, or slow the progression of, atherosclerosis. Statins were not felt to play a significant role in acute coronary syndromes (ACS) due to the fact that early clinical trials did not reveal benefit until several years of therapy had been completed. However, recent prospective controlled clinical trials have demonstrated that intensive statin therapy in ACS is of benefit in the reduction of cardiovascular (CV) morbidity and mortality. This review will focus on the pathophysiology of ACS, the potential role of intensive statin therapy, and the clinical trial evidence supporting the early and intensive use of these drugs.

PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

The initial concept of the pathogenesis of myocardial infarction (MI) or unstable angina was related to progressive and unrelenting deposition of atheromatous debris in the vessel wall until 100% obstruction to flow occurred. However, this concept was challenged by angiographic and thrombolytic studies which were performed in acute MI [3, 4]. The angiographic studies revealed that the majority of acute MIs involved culprit lesions which were

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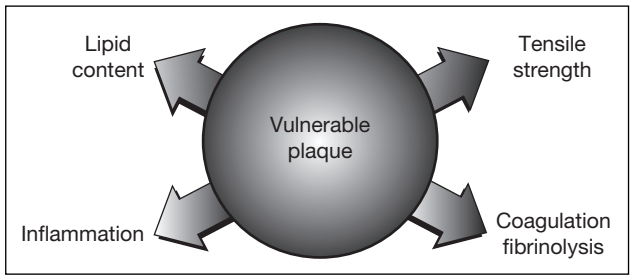

Figure 4.1 Determinants of plaque vulnerability.

characterized by non-obstructive atherosclerotic plaques which become unstable, rupture or fissure, and promote overlying thrombus formation. ACS have multiple underlying pathophysiologic features which predispose to the sudden progression of plaque and vascular occlusion. The concept of the vulnerable plaque was promoted to explain the sudden transition from a non-obstructive lesion to the obstructive lesion characteristic of an ACS. (Figure 4.1) [5]. Pathology studies have demonstrated several characteristics of an atherosclerotic plaque which predispose to clinical instability, including a thin fibrous cap, a lipid core exceeding 40% of the plaque volume (especially manifest by cholesterol in the thrombogenic droplet phase), inflammatory cell infiltrates and a lack of calcification. Atheromatous plaques give rise to ACS secondary to plaque rupture, erosion of the plaque surface with thrombus formation, intraplaque hemorrhage with sudden expansion of the lesion, and/or a coexistent hypercoagulable state.

Inflammation has been demonstrated in ACS, and inflammatory cell infiltrates may play a significant role in a plaque's loss of architectural integrity [6]. Circulating monocytes become localized in vascular areas prone to develop atherosclerosis and subsequently transform into the macrophage cell line. These macrophages have been demonstrated to produce a variety of enzymes (collagenase, gelatinase, etc.) which have been collectively termed the matrix metalloproteinase system [7]. The matrix metalloproteinase system is involved in degradation of the collagen matrix within the vessel wall and its activity is correlated with a progressive increase in plaque vulnerability to rupture or fissuring. In addition, lymphocytes have been demonstrated to synthesize γ-interferon, which reduces the production of collagen and further decreases the tensile strength of an atheromatous plaque (Figure 4.2) [8]. Cytokines such as interleukin-1β and CD-40 ligand are also inflammatory molecules, which are intimately involved in processes central to atherosclerosis [9]. The dysfunctional endothelium produces a variety of adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1] and a variety of selectins), which bind inflammatory cells and subsequently induce their transmigration from the vascular space into the vessel wall. Elevated levels of apoprotein (apo) B-containing lipoproteins, as well as low levels of high-density lipoprotein (HDL) particles, result in increased circulating levels of interleukin-1β and CD-40 ligand, which are also elevated during an ACS. Reductions in apoB-containing lipoproteins by statins have been shown to decrease the levels of these cytokines, which may potentially contribute to the reduction in the morbidity and mortality associated with an ACS [10].

C-reactive protein (CRP) has been identified as a readily available marker of systemic inflammation [11]. The development of high sensitivity assays has expanded the potential pathophysiologic role of CRP in atherogenesis (Figure 4.3). Endothelial cell receptors for CRP have been identified in pathology studies [12]. Increased exposure of cultured endothelial

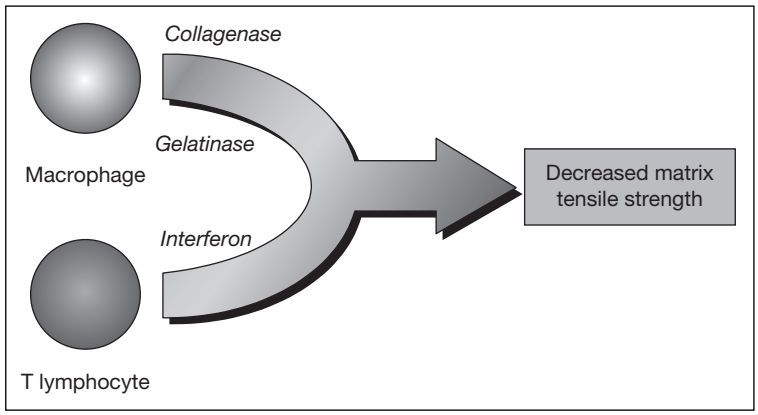

Figure 4.2 Inflammatory cells and plaque stability.

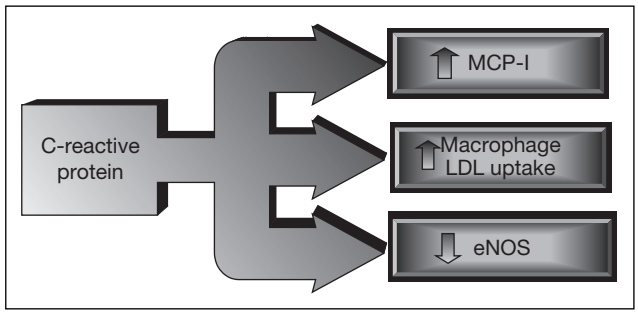

Figure 4.3 C-reactive protein and atherosclerosis.

cells to CRP is associated with reduced nitric oxide (NO) production and enhanced expression of adhesion molecules [13]. NO is produced by normally functioning endothelium and is a potent vasodilator and antiplatelet agent. CRP has been shown to reduce the bioavailability of NO, which predisposes to enhanced platelet aggregation and vasoconstriction, both of which are clinical hallmarks of ACS [14]. Tissue factor (previously termed thromboplastin) is an initiator of the coagulation cascade due to the recognition and binding of factor VIIIa which leads to fibrin formation following the activation of factor IX and X [15]. CRP has been demonstrated to increase the expression of tissue factor and thus may play a role in the hypercoagulability associated with ACS [16].

Plaque rupture with the subsequent generation of an overlying, occlusive thrombus is not the only mechanism by which an ACS may occur (Figure 4.4). Pathology studies have demonstrated coronary occlusions without evidence of definite plaque disruption. Erosion of the endothelial lining of a non-occlusive lesion may also result in progressive clot formation and resultant vascular occlusion. Abnormalities in endothelial function may play a central role in clot formation in the absence of frank plaque rupture [17]. The endothelium produces a variety of vasoconstrictor and vasodilatory mediators which affect platelet function. NO, angiotensin II, and endothelin are all produced by the normally functioning

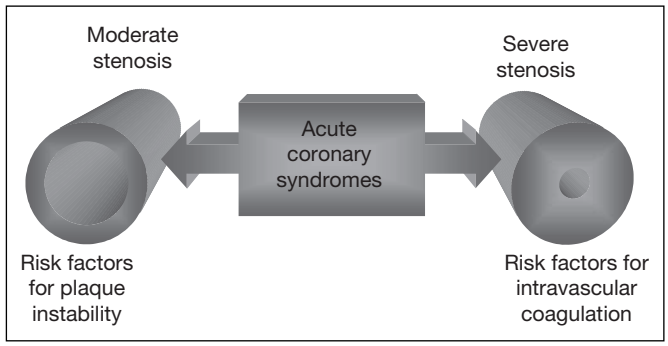

Figure 4.4 Acute coronary syndromes and severity of stenosis.

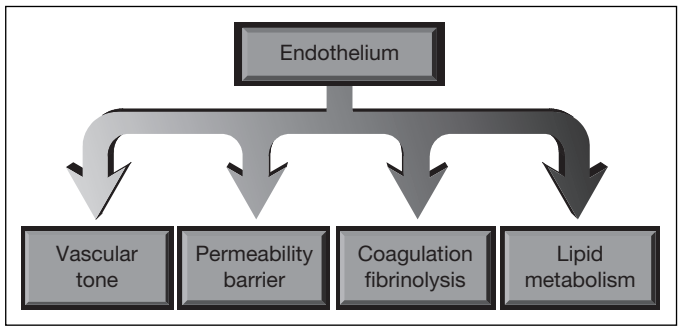

Figure 4.5 Endothelial function.

endothelium and are in physiologic balance [18]. Endothelial dysfunction is associated with a relative increase in angiotensin II and endothelin which results in vasoconstriction, increased platelet aggregation, impaired vascular repair, and increased inflammation. Classic cardiac risk factors, including dyslipidemia, hypertension, cigarette smoking, and diabetes mellitus, are all associated with a relative reduction in the bioavailability of NO, which links the reduction in this endothelium-derived molecule to atherosclerosis.

Physiological abnormalities of the endothelium may be demonstrated in the absence of pathologic plaque rupture or erosion. The normally functioning endothelium modulates a variety of physiologic processes including vasomotor tone, lipid metabolism, coagulation, and fibrinolysis (Figure 4.5). Endothelial dysfunction is characterized by increased vasoconstriction, increased platelet aggregation, impaired fibrinolysis, and coagulation abnormalities. Hypercoagulability may play a significant role in the pathogenesis of ACS in the absence of physical plaque disruption. The normally functioning endothelium is the source of tissue plasminogen activator (tPA) which decreases the risk of clot formation. Endothelial dysfunction is associated with a relative increase in the production of plasminogen activator inhibitor (PAI-1). Circulating levels of PAI-1 may be increased in hypertension, diabetes, and dyslipidemia, and could contribute to clot propagation in an ACS [19]. Tissue factor levels are also elevated with traditional risk factors including hypertension, dyslipidemia and diabetes [20]. Tissue factor and markers of impaired fibrinolysis such as PAI-1 have been

classified as emerging risk factors in the pathogenesis of the ACS. Inflammation, plaque rupture, plaque erosion, endothelial dysfunction, hypercoagulability, and impaired fibrinolysis may all contribute to the pathogenesis of an ACS and are potential targets for statin therapy.

STATINS AND ACUTE CORONARY SYNDROMES

Based on the relationship between lipids and atherosclerotic disease, statins are utilized to modify the long-term effect of LDL particles on the initiation and progression of atherosclerosis. The recent recognition of the non-lipid, or pleiotropic, effects of statins raises the possibility that these drugs may be useful in modifying the clinical course immediately following an ACS [21]. The role of inflammation across the spectrum of atherogenesis has been well documented and statins have been demonstrated to modify several components of the inflammatory response. As mentioned, pathology studies of vulnerable plaque have demonstrated the presence of inflammatory cells, which may play a significant role in plaque rupture. Matrix metalloproteinase production by inflammatory cells degrades the collagen matrix and increases plaque instability. Statin therapy has been demonstrated to reduce matrix metalloproteinase activity [22]. Furthermore, inflammatory cells produce modulators, such as γ-interferon, which reduce collagen synthesis and decrease the tensile strength of atheromatous plaque [23]. Statins also potentiate collagen production. Oxidized lipoproteins, such as oxidized low-density lipoproteins (oxLDL), induce macrophages to produce inflammatory molecules, which increase the expression of adhesion molecules, further enhancing the attachment and migration of inflammatory cells into the subendothelial space. The imbalance between pro- and anti-inflammatory pathways not only contributes to the pathogenesis of an ACS, but may be favourably modified by statin therapy. Statins reduce several pro-inflammatory mediators, including soluble CD-40 ligand, interleukin-1, interferon-γ, and interleukin-6 [24, 25, 26]. These markers are not easily measured clinically; however, they provide insight into the potential beneficial mechanisms of statin therapy in the clinical setting of an ACS. As discussed, elevated serum CRP is a marker of an adverse prognosis in ACS [27]. CRP stimulates endothelial expression of adhesion molecules, reduces the bioavailability of NO, and stimulates tissue factor production by macrophages, among other effects [28]. Statins significantly reduce levels of CRP in both experimental and clinical studies, which may extend their clinical benefits beyond simply reducing LDL levels [29].

Endothelial dysfunction can be demonstrated in subjects who have various traditional cardiovascular risk factors and statins have been shown to improve endothelial function [30]. NO is generated by the activation of endothelial nitric oxide synthase (eNOS). Arginine is enzymatically degraded by eNOS, with the production of citrulline and NO, which is a potent vasodilator and antiplatelet agent. Statins are a positive agonist for eNOS activity [31]. Since CRP has been demonstrated to decrease NO availability secondary to the inhibition of eNOS [32], statin-mediated reductions in CRP may lead to increased rates of NO production. The net result of enhanced NOS is an increase in coronary blood flow, which can be measured either directly by angiographic flow studies or indirectly by the utilization of clinically validated non-invasive surrogate measurements (e.g., flow-mediated dilatation and reactive hyperemia). The impairment of flow-mediated dilatation has been demonstrated to be an adverse prognostic marker following an ACS [33]. Importantly, the improvement of endothelial function with statins occurs before a meaningful alteration of the lipid profile [34], providing a theoretical benefit in ACS. The statin effect on endothelium-mediated vasodilation is partially linked to the increased production of NO and may be associated with decreased platelet aggregation. The increase in flow-mediated dilatation is not limited to hyperlipidemic patients and may be demonstrated at all levels of baseline LDL-c. The argument for starting statins early in the course of an ACS is supported by the evidence for both vasodilation and decreased platelet aggregation, independent of baseline lipid levels.

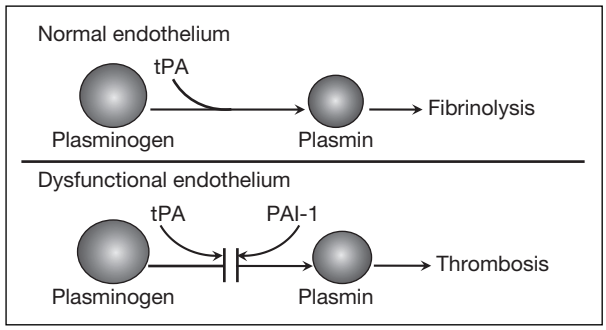

Figure 4.6 Fibrinolytic balance and the endothelium.

Endothelial cell repair is mediated by a variety of cellular elements including endothelial progenitor cells which are produced in, and released from, the bone marrow [35]. The number of colony-forming units of endothelial progenitor cells may be quantitated in peripheral blood and are correlated with the Framingham risk score, such that an increased risk score is associated with a reduction in endothelial progenitor cells. Endothelial dysfunction, as measured by a reduction in flow-mediated dilatation, has also been linked to decreased levels of endothelial progenitor cells. Recent investigations have shown that the circulating levels of endothelial progenitor cells are a more accurate predictor of vascular reactivity than is the presence or absence of conventional risk factors. Statins increase endothelial repair following mechanical injury to the vasculature [36] and this has been correlated with an increase in circulating levels of endothelial progenitor cells by a posited dual mechanism. The proliferative capacity of these cells is limited by the natural aging process, which is inhibited by statin therapy. Atorvastatin has been shown to increase the proliferative capacity of endothelial progenitor cells by regulating the expression of various cell cycle proteins [37]. Thus, statins may enhance both endothelial repair and decrease the adverse pathophysiologic aspects of endothelial dysfunction.

Statins beneficially impact activity of the coagulation cascade. Increased levels of tissue factor have been found in subjects with an ACS. Statins reduce circulating levels of tissue factor, which has implications for the initiation and progression of an intravascular thrombus [38]. As stated, increased levels of PAI-1 have been found in patients with several CV risk factors, including obesity, diabetes, dyslipidemia and hypertension. A relative imbalance between procoagulant and fibrinolytic mediators increases the risk for an ACS (Figure 4.6). Statin therapy reduces the production of PAI-1, which may improve the efficacy of either exogenously administered or endogenously generated plasminogen activators and, hence, decrease the risk of developing an occlusive vascular thrombus [39].

CLINICAL TRIALS IN ACS

Epidemiologic observations and *in vitro* studies are best regarded as hypothesis-generating and require analysis in a controlled prospective clinical trial to establish efficacy in human subjects. Clinical trials have clearly established the benefit of statin therapy in subjects in both the primary and secondary prevention settings. However, the utilization of statins during ACS had not been employed until recently. The first randomized, placebo-controlled statin trial, the Simvastatin Scandinavian Survival Study (4S), enrolled subjects who were a minimum of 3 months removed from an acute MI [40]. The administration of simvastatin reduced both total and CV mortality over five years; however, since therapy was not

administered during the earliest, most vulnerable phase following an MI, any opportunity to show clinical benefit in the first 6 months of treatment (compared to placebo) was lost.

In the past decade, several prospective clinical trials have addressed the role of statin therapy in ACS. However, trial design flaws and other study-specific problems have produced conflicting results. The Pravastatin Acute Coronary Treatment (PACT) and Prevention of Ischemic Events by Early Treatment with Cerivastatin (PRINCESS) were terminated for administrative or regulatory reasons [41]. The PRINCESS trial has not yet been published. The Aggrastat to Zocor (A to Z) study was a complex trial utilizing an early intensive versus a delayed conservative statin treatment regimen and did not demonstrate a statistically significant difference between the two treatment arms [42]. The Fluvastatin On Risk Diminishment After Acute Myocardial Infarction (FLORIDA) did not reach its primary endpoint but was underpowered and of relatively short duration (540 patients followed over a 12 month trial duration) [43]. However, two major, well designed clinical trials have addressed this important clinical question.

MYOCARDIAL ISCHEMIA REDUCTION WITH AGGRESSIVE CHOLESTEROL LOWERING (MIRACL)

The MIRACL study was designed to test the hypothesis that statin therapy would be beneficial when given in the early phase of an ACS [44]. This initial phase of an ACS is a clinically unstable state, with high rates of mortality and recurrent MI during the first 30 days. The incidence of adverse events declines after 1 month and reaches a plateau in the ensuing 6 months. Previous statin trials had excluded subjects with unstable angina or history of an acute MI 3 to 6 months prior to randomization. The MIRACL study was based on the premise that in addition to the beneficial effects associated with LDL-c lowering, additional clinical improvement may be demonstrated by improving endothelial function, reducing platelet aggregability, improving fibrinolysis, and decreasing systemic inflammatory tone.

The MIRACL trial was a prospective, placebo-controlled trial with 3086 patients randomized to receive intensive statin therapy (atorvastatin 80 mg/day) vs a matching placebo. Statin therapy began within one to eight days following hospital admission for an ACS, which was defined as unstable angina or a non-Q-wave MI. The trial duration was only 16 weeks because of ethical concerns in the placebo arm, since the 4S Trial had already demonstrated that statin therapy would reduce total mortality and morbidity when initiated at a minimum of 3 months after an ACS. The primary endpoint was a composite, defined as total mortality, non-fatal acute MI, cardiac arrest requiring resuscitation, or recurrent symptomatic MI requiring hospitalization. The primary endpoint occurred in 228 (14.8%) patients in the atorvastatin group compared to 269 (17.4%) subjects who were randomized to placebo. The reduction in the primary endpoint was positive but of borderline statistical significance ($P = 0.048$). Intensive therapy with atorvastatin did not result in a significant reduction in total mortality, non-fatal MI, or cardiac arrest. The majority of the benefit in the primary endpoint occurred in the reduction of symptomatic ischemia requiring hospitalization. Importantly, atorvastatin did not reduce the number of acute coronary events documented in the first 5 weeks (70% of total ischemic events in the MIRACL study). The need for revascularization was prospectively defined as a secondary endpoint and was not altered by atorvastatin. Despite these caveats, the MIRACL study was the first trial to show benefit of statin therapy in ACS and paved the way for more definitive studies.

THE PRAVASTATIN OR ATORVASTATIN EVALUATION AND INFECTION THERAPY (PROVE-IT)-TIMI-22

The PROVE-IT study was designed to further test the hypothesis that the institution of statin therapy at differing intensities in an ACS would be of clinical benefit [45].

Additionally, the trial was designed to test the potential clinical benefit of more intensive LDL-c reductions over 2 years. Pravastatin therapy had been demonstrated to be of clear clinical benefit in preventing CV events among patients with established CHD and relatively normal LDL-c levels in the Cholesterol And Recurrent Events (CARE) trial [46]. The PROVE-IT study randomized 4162 subjects who had been hospitalized within the previous 10 days with an acute MI (with or without electrocardiographic evidence of ST segment elevation) or high risk unstable angina. Subjects were randomly assigned, whether or not they were on statin treatment prior to the ACS event, to either the dose of pravastatin which had been utilized in stable CHD clinical trials (40 mg/day) or atorvastatin 80 mg/day. The primary endpoint was defined as a composite of total mortality, MI, unstable angina requiring hospitalization, revascularization, and stroke. The mean LDL-c level prior to randomization was 106 mg/dl, and pravastatin 40 mg decreased low-density lipoprotein to 95 mg/dl, with an interquartile range of 79 to 113 mg/dl. In comparison, 80 mg of atorvastatin decreased LDL-c to a mean of 62 mg/dl. After 2 years, the atorvastatin group had a 16% reduction in the primary endpoint compared to the pravastatin group. Importantly, the benefit of intensive lipid-lowering therapy was demonstrable after 1 month (albeit not statistically significant). The risk of having a secondary endpoint (CHD death, MI and revascularization) was also reduced (14%) by intensive lipid-lowering therapy. Both of the statins were well tolerated, with no significant difference in risk for myopathy.

While the PROVE-IT study demonstrated clinical benefit over 2 years by initiating intensive statin dosing and achieving aggressive LDL-c reductions compared to more conventional statin dosing, it is still unclear if there is an early (<30 day) benefit in reducing the high rate of events after ACS. The question of whether non-LDL-c effects of statins are clinically relevant within weeks following an ACS and whether maximum doses of statins are required in order to see pleiotropic effects has not been adequately addressed in the clinical trials performed to date. The failure of maximum statin dosing in the A to Z trial to demonstrate either early or late benefit, even with the other issues that complicated the trial's interpretation [47], suggests that we still are not certain when, and at what dose, to start statins in the acute setting of myocardial ischemia/injury. While the PROVE-IT investigators have found correlates of which patients had the best outcomes, such as those who had both LDL-c <70 mg/dl and a high-sensitivity CRP (hs-CRP) <2 mg/dl, this was true whether the patient received atorvastatin or pravastatin, thus not helping the clinician firmly decide on the issue of statin dosing [48]. We await the results of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT) in 10 000 ACS subjects randomized to either simvastatin 40 mg or simvastatin/ezetimibe 40/10 mg to confirm if very low on-treatment LDL-c levels from a combination drug regimen achieves incremental benefit compared to the same statin equally dosed as monotherapy. In the meantime, the AHA/ACC Secondary Prevention Guidelines offer the best guidance for clinicians at this time [49]. They recommend that statins be initiated in hospital for all ACS patients, with a reasonable LDL-c goal of <70 mg/dl, and that clinicians should use a statin dose that can be expected to achieve, at minimum, a ≥30–40% reduction in LDL-c.

SUMMARY

The contemporary management of ACS with medical and revascularization techniques has resulted in a significant improvement in morbidity and mortality. Statin therapy has clearly demonstrated a reduction in CV morbidity and mortality in both primary and secondary prevention settings. Lipid-lowering agents, in general, had not been considered to be of immediate necessity in the management of ACS due to the perception that they required months or years to attain their clinical benefit. Experimental data have suggested that statins may have direct effects on cellular function aside from their LDL-c lowering efficacy. These potential benefits, which include improvement of endothelial function, a reduction in

platelet aggregation, and a decline in thrombotic factors, were the basis for clinical trials, which demonstrated the benefit of intensive statin therapy initiated early in the course of ACS. These data now support the addition of statins to other proven therapies, such as aspirin, β-blockers, anticoagulants, modulation of the renin–angiotensin system, and revascularization, all of which reduce the mortality and morbidity following an ACS.

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5

What are CAD risk equivalents and how did these clinical entities come to be so defined?

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BACKGROUND

Coronary heart disease (CHD) remains the number one cause of mortality in both men and women in this country despite the many diagnostic and therapeutic interventions developed over the last several decades. Unfortunately, the diagnosis of CHD often comes too late with myocardial infarction (MI) or CHD death as the initial presentation in 62% of men and 42% of women with undiagnosed CHD [1]. In 2004, there were 452 327 deaths due to CHD, which is approximately one of every five deaths in the United States or about one death every minute [2].

Atherosclerosis can start early, often beginning in childhood, with the risks for developing early atherogenesis including: elevated LDL-c, low HDL-c, elevated blood pressure, family history of premature onset coronary disease, body mass index (BMI) greater than 25 kg/m^2 and cigarette smoking [3, 4]. In transplant and necropsy studies, fatty streaks and atheromatous plaque have been found in one of six children aged 12–18 years old when associated with these risk factors [3, 5]. In some individuals atheromatous plaques can become inflamed and unstable and give rise to acute coronary syndromes years later, while in others the disease can have a somewhat indolent course and remain clinically silent [6].

Approximately half the men and 64% of the women who die suddenly of CHD have no previous symptoms of this disease [2]. This suggests that our current standard testing is not very sensitive at detecting asymptomatic patients who are at high risk for CHD-related events. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines state that individuals with established CHD have an absolute 10-year risk for a recurrent acute MI or CHD death that exceeds 20%. However, there are a number of asymptomatic individuals without established CHD who will also be at high risk for a CHD event, whose risk approaches those with established CHD; these individuals are designated as having a CHD risk equivalent [7].

The following is a list of clinical entities that the NCEP-ATP III guidelines have designated as CAD risk equivalents (Table 5.1):

- Peripheral artery disease
- Abdominal aortic aneurysm (AAA)

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- Symptomatic carotid artery disease
- Diabetes mellitus
- Multiple risk factors resulting in a 10-year Framingham hard risk score that exceeds 20%

NCEP-ATP III CHD EQUIVALENTS

PERIPHERAL ARTERY DISEASE

Peripheral arterial disease (PAD) is defined by the ATP III guidelines as a CHD risk equivalent based on five clinical trials. Three of the studies (Edinburgh Artery Study [8], the Multicenter Study of Osteoporotic Fracture [9], and a study by McKenna *et al.* [10] all utilized the ankle-brachial index (ABI). Using a Lipid Research Clinics (LRC) protocol, the San Diego study [11] used non-invasive testing of lower limb flow. A study by Poulias *et al*. [12] evaluated patients undergoing aortofemoral bypass. When these studies were analysed in aggregate, the annual CHD event rates ranged from 2% to 3.8% and, thus, support the concept that PAD, whether diagnosed by ABI, lower limb blood flow studies or clinical symptoms, is a CHD risk equivalent.

The clinician needs a high index of suspicion for PAD as only one in five patients will have symptomatic intermittent claudication, defined as cramping or pain in leg muscles brought on by a predictable amount of ambulation (or other form of exercise) and relieved by rest, even in those with ABI <0.9 [8, 13]. Other manifestations of lower extremity ischemia can include femoral bruit, reduced peripheral pulses, arthralgia, lower back or buttock pain, and a sense of 'heaviness' in the leg with exertion.

PAD when diagnosed using the ABI is 95% sensitive and 99% specific for PAD [14]. The definitions for ABI values are as follows: normal 0.95–1.20; mild to moderate PAD <0.9; severe PAD <0.4. In those with the most severe PAD, 5-year mortality rates approach 60% and severe PAD (as evidenced by an ABI <0.4) is a stronger predictor of cardiovascular mortality than in those with a history of prior cardiovascular disease [15].

Following the publication of the ATP III guidelines, several other studies reaffirmed the risk of PAD as a CHD equivalent. ABI in the Rancho Bernardo Study revealed a correlation of ABI with carotid intima-media thickness studied in 637 subjects [14]. In this analysis, an ABI of 1.10–1.26 was associated with the lowest cardiovascular risk and carotid atherosclerosis, and thus suggested new cut-points for ABI: normal >1.1–1.29 and low normal 1.0–1.09. A substudy of the Framingham Study shows ABI in the elderly to be an important factor in predicting CHD, transient ischemic attack (TIA), stroke and PAD. In this evaluation, 251 men and 423 women with mean age of 80 years were followed for 4 years and the following were found: 20% had low ABI <0.9 (25% in those over 85 years), 18% of those with low ABI had claudication, and 33% with normal ABI and 55% with low ABI had coronary artery disease (CAD) at baseline.

When comparing patients with low ABI to those with normal ABI, patients experienced a 1.2-fold increase in risk of CHD, a 1.5-fold higher risk of death, and twice the risk of stroke or TIA [16, 17]. Other studies showed overall risk of all-cause mortality to be 2–4 times higher with low ABI. Death from CAD increased six-fold in middle age and three-fold in the elderly with a low ABI [16, 17]. Patients with PAD have a risk of MI or CHD death that exceeds 20% in 10 years. Screening individuals for ABI should be considered in smokers over 40 years, non-smokers greater than 60 years of age, diabetics, and patients with multiple poorly controlled risk factors [8, 13].

ABDOMINAL AORTIC ANEURYSM (AAA)

Abdominal aortic aneurysm is another CHD equivalent as evidenced by a study by Hertzer *et al*. [18] where 300 men and 43 women (aged 45–89) were followed for 6–11 years after

Table 5.1 CHD equivalents summary

Current NCEP CHD equivalents [7]	*Emerging CHD equivalents [51, 52, 54]*
Peripheral artery disease	Metabolic syndrome with >3 risk factors
Abdominal aortic aneurysm	Plus either family history of premature CHD or elevated CRP
Symptomatic carotid artery disease	Carotid artery IMT *via* ultrasound ≥1 mm or
Asymptomatic carotid artery	>75th percentile
disease with stenosis >50%	Coronary artery calcium score *via* CT >100 or
Diabetes mellitus	>75th percentile
Multiple risk factors with a 10-year	
Framingham risk >20%	**Emerging CHD risk factors [31, 56]**
	Estrogen deficiency
	Lipoprotein(a)
	Endogenous tissue plasminogen activator
	Plasma fibrinogen
	Lipoprotein associated phospholipase A_2 ($LpPLA_2$)

surgery for AAA. Results in this study showed the annual CHD mortality to be as follows: 1.9% in subjects with no symptoms or prior history of CHD and normal ECG; 2% in subjects with no symptoms but prior MI by electrocardiogram (ECG); and 3.9% in subjects with angina/prior MI (30%). Because the rate of CHD events is at least twice that of CHD mortality, patients with no previous history of CHD events would easily fall into the CHD risk equivalent category [18]. Screening is recommended for AAA as per the U.S. Preventive Task Force for patients with major risk factors such as age >65 years, history of smoking, and family history of AAA [19].

The Society of Vascular Surgery recommends one-time ultrasound screening for all men aged 60–85 years and all women aged 60–85 years with an associated CVD risk factor. If there is a family history of AAA, then screening should occur at 50 years of age [20]. If the abdominal aorta measures less than 3 cm, then no further action is needed. However, if the aorta measures greater than 3 cm, it is considered to be significantly enlarged and should be regarded as a CHD equivalent and followed according to established guidelines [20].

SYMPTOMATIC CAROTID ARTERY DISEASE OR ASYMPTOMATIC CAROTID DISEASE WITH ADVANCED STENOSIS

The guidelines reviewed three studies of patients with symptomatic carotid disease (TIA or stroke), including the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [21], the European Carotid Surgery Trial (ECST) [22] and a study by Norris *et al*. [23]. Taken in aggregate these studies revealed a 10-year incidence of CHD mortality ranging from 19% to 30% and CHD event rates ranging from 27% to 83%.

A high CHD event rate has been documented by four studies in which individuals were asymptomatic but had advanced carotid artery stenosis >50%. The Asymptomatic Carotid Atherosclerosis Study [24], the Veteran Affairs Cooperative Study Group [25], the Mayo Asymptomatic Carotid Endarterectomy Study [26], and the Carotid Artery Surgery Asymptomatic Narrowing Operation versus Aspirin (CASANOVA) trial [27] demonstrated that, in asymptomatic persons, the 10-year CHD mortality rates ranged from 19% to 51% and CHD event rates ranged from 30% to 35%. Consequently, individuals with symptomatic carotid disease and those asymptomatic with carotid artery stenosis >50% constitute a risk group defined as a CHD equivalent.

DIABETES MELLITUS (DM)

In NCEP-ATP III, DM was redefined from a CHD risk factor to a CHD risk equivalent [7]. Several studies such as the Finnish population based study (East–West study) [28], the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) trial [29], and the Heart Outcomes Prevention Evaluation (HOPE) trial [30] have shown that the absolute risk for CHD events in individuals with DM approximates that for recurrence rates in patients without diabetes with clinical CHD [31]. Diabetic patients have twice the mortality rate from acute MI compared to non-diabetics, and diabetic patients experience worse outcomes than patients without diabetes after revascularization [32].

Women with DM and CHD have a higher CHD-related morbidity and mortality than diabetic men. Women with diabetes also have a 50% greater likelihood of CHD death compared to men with diabetes. Part of this excess risk for cardiovascular events among diabetic women may be attributable to their higher likelihood for having other associated risk factors such as hypertension and dyslipidemia compared to diabetic men [33].

Many diabetic patients have undiagnosed asymptomatic CAD such that autopsy data on 293 diabetics and 1763 non-diabetics without clinical evidence of CAD revealed that 75% of diabetics had at least one high grade coronary lesion defined as having grade 3 or higher atherosclerosis in the left main coronary artery, or grade 4 or higher atherosclerosis in the left anterior descending, right or circumflex arteries. Of note, 58% of the diabetics in this analysis also had multi-vessel high grade disease [34]. The Detection of Silent Myocardial Ischemia in Asymptomatic Diabetes (DIAD) Study [35] evaluated 1123 diabetic patients without CAD who were randomized to either stress testing and 5-year follow-up or to follow-up only. Of the 522 patients randomized to adenosine stress testing, 22% were found to have silent ischemia, suggesting that silent ischemia occurs in approximately one in five asymptomatic diabetic patients.

In general, patients with DM without evident CHD have a 10-year risk for major coronary events that approximates the risk of a patient with CHD [28]. However, in diabetic patients in whom there is no evidence of subclinical atherosclerosis by virtue of negative coronary artery calcium screening, the risk in these individuals may be less than that of a CHD equivalent [36]. In addition, younger diabetic patients with no other CHD risk factors frequently exhibit a 10-year incidence of CHD less than 20%. However, those individuals still have a high lifetime risk for CHD [7].

HIGH RISK PATIENTS WITH MULTIPLE RISK FACTORS AND A 10-YEAR FRAMINGHAM RISK >20%

NCEP-ATP III places a strong focus on primary prevention in persons with multiple risk factors and recommends that a patient's 10-year risk be quantified with a Framingham risk score (FRS). The FRS is a calculation of the risk for developing CHD over a 10-year period based on points allocated for age, total cholesterol, HDL-c, systolic blood pressure and cigarette smoking. An FRS $\geq$20% confers a level of risk identical to established CHD [7].

The Canadian guidelines also recommend a global risk assessment using the FRS. The Canadian guidelines recognize an FRS $\geq$20%, DM, and any form of atherosclerotic disease as CHD risk equivalents. Screening is recommended routinely for men over 40 years old and women who are postmenopausal or over 50 years old. In addition, screening for CHD is recommended for people with DM, hypertension, smoking, abdominal obesity, family history of premature atherosclerotic CVD (ASCVD), manifestations of hyperlipidemia, or evidence of symptomatic or asymptomatic atherosclerosis [37].

The European Atherosclerosis Society Guidelines on CHD prevention in clinical practice differ in the method of risk stratification. The task force recommends the use of the

Systematic Coronary Risk Evaluation System (SCORE) Model and Risk Charts as recently developed. As in the Framingham Heart Study, the SCORE Model and Risk Chart is now defined in terms of the absolute 10-year probability of developing a fatal cardiovascular event. SCORE is derived from a large database of prospective European studies and predicts any kind of fatal atherosclerotic endpoint over a 10-year period. SCORE integrates smoking, systolic blood pressure, and either total cholesterol or the total cholesterol:HDL ratio. Since the European guidelines utilize mortality and not CHD events, the CHD equivalent is defined as a fatal risk >5% [38]. Definition of high risk CHD or equivalent for developing a fatal CHD event from the EAS guidelines include: (1) established CHD; and (2) asymptomatic subjects who have: (a) multiple risk factors resulting in a 10-year risk >5% now or extrapolated to age 60; (b) markedly raised levels of a single risk factor (total cholesterol >320 mg/dl, LDL cholesterol >240 mg/dl, or blood pressure >180/110 mmHg); or (c) type 1 or type 2 DM with microalbuminuria [33].

The Framingham risk model has been validated in both Caucasian and African-American populations and can be applied to other ethnic groups after recalibration for differing prevalence of risk factors and underlying rates of CHD [39]. However, the FRS may not correctly identify subjects with a low short-term risk but high lifetime risk for CHD, likely due to changes in risk factor status over time [40]. For example, middle-aged men and women in the lowest 10-year cumulative risk of CHD could have lifetime risks that are as much as 10 times higher because rates of diabetes and hypertension increase sharply with age, thus altering the long-term risk in an unpredictable fashion. Current methods of lifetime risk estimation cannot account for changes in risk factor status over time due to aging, changes in lifestyle, or medication [40].

In dealing with one of the groups, i.e., women, in which the Framingham risk model has been less accurate, investigators from The Reynolds Center for Cardiovascular Research and Disease Prevention evaluated 35 risk factors in 24 558 healthy US women age 45 years or older [41]. The Reynolds Risk Score utilized the standard Framingham risk factors but added both high-sensitivity C-reactive protein (hs-CRP) and a parental history of myocardial infarction before age 60. This new algorithm, incorporating family history and CRP, reclassified 1.5% of women with a 10-year CVD risk of 5–10%, and 21.2% with a 10–20% CVD risk into a CHD equivalent status.

The Chicago Heart Association Detection Project in Industry Study sought to estimate lifetime risk for CHD and non-CHD death and median survival by risk factor stratification in middle-aged men and women. Populations in their middle age years (40–59 years old) were evaluated for favourable risk factor profile: blood pressure <120/80 untreated, total cholesterol <200 mg/dl, non-smoker and BMI <25 kg/m^2; and unfavourable risk factor profile of elevated blood pressure >140/90, or treated hypertension, total cholesterol >240 mg/dl, current smoker or body mass index >30 kg/m^2. As expected a greater risk burden was associated with a higher incidence of CHD and non-CHD death: those with favourable risk factors in middle age had both a lower lifetime risk of CHD death and markedly longer survival [42].

Those at high risk as evidenced by a 10-year Framingham risk score >20% or the SCORE model used by EAS for mortality >5% have CHD risk equivalent status. However, those with multiple risk factors at a young age, who have a 10-year risk below 20% may actually have a lifetime risk that would place them in a high risk category consistent with CHD equivalency.

The pro-protein convertase subtilisin/kexin type 9 serine protease (*PCSK9*) gene promotes degradation of LDL receptor proteins and individuals with the nonsense mutation of this gene have lower levels of LDL-c throughout their lifetime, with a resultant 88% decrease in the prevalence of CHD [43]. Brown and Goldstein [44] have speculated that the reason for the marked decrease in CHD in these individuals is because they have low levels of LDL-c throughout their lifetime and that if we were to intervene early in those with an increased

lifetime risk (i.e., diabetics, metabolic syndrome, smokers, positive family history, hypertensives) the benefit would impact these lifetime high risk individuals in a similar manner as does the *PCSK9* mutation.

Although not included in the FRS, a family history of premature CHD in a first-degree relative is an independent risk factor for CHD and as such is used as one of the standard non-modifiable risk factors in the NCEP-ATP III guidelines [7]. Even though a family history, *per se*, does not necessarily place a person at a CHD equivalent risk, in some individuals it may indicate such a risk. When a family history of premature CHD is associated with multiple risk factors [45] or metabolic syndrome [46] or emerging risk factors such as the presence of a positive coronary artery calcium score (CACS) [47], the resultant combination of family history plus any or all of these other risk factors may very well portend a risk equivalent to a CHD equivalent.

EMERGING RISK FACTORS AS CHD EQUIVALENTS (Table 5.1)

Other factors that potentially influence risk assessment include the metabolic syndrome and emerging risk factors such as CRP, lipoprotein(a), homocysteine, factor VII, endogenous tissue plasminogen activator, plasma fibrinogen, and lipoprotein associated phospholipase A_2 ($LpPLA_2$), to name a few [31]. These emerging risk factors are probably most useful in subjects where the treatment options are the most contentious, such as those at a moderate or moderate high risk for asymptomatic atherosclerosis. Evaluation of ABI, carotid ultrasonography, electrocardiogram (ECG), graded exercise stress testing and CACS on computed tomography are some of the technologies used to assist in defining those who may have CHD or a CHD risk equivalent. Among this group of emerging risk factors and technologies those currently exhibiting the greatest potential for discerning CHD risk equivalency will be highlighted.

METABOLIC SYNDROME AND ELEVATED CRP

The metabolic syndrome is associated with an increased risk CHD events by approximately 1.74-fold and this effect appears independent of baseline lipid levels or Framingham risk score [48, 49]. The NCEP did not define the metabolic syndrome as a CHD risk equivalent. It is imperative that patients diagnosed with the metabolic syndrome undergo FRS evaluation so that their risk is appropriately stratified. Older patients with four or five components of the metabolic syndrome will have a 10-year projected CHD risk exceeding 20%. Consistent with this, individuals with four or five metabolic risk factors in both the WOSCOPS and AFCAPS studies appeared to exceed the 20% 10-year risk threshold when treated with a placebo [49, 50]. In addition, the 20% CHD event rate was broached in the Treating to New Targets (TNT) trial in those with four or five metabolic risk factors even when treated with a low dose of atorvastatin [51].

Although not conclusive, a recent *post hoc* analysis of the AFCAPS/TexCAPS study investigated the risk associated with metabolic syndrome in patients with a baseline LDL-c <130 mg/dl [52]. Those with a baseline LDL-c 100–130 mg/dl and a 10–20% 10-year risk who had metabolic syndrome had an actual 10-year CHD incidence rate of 25%, significantly above the CHR risk equivalent threshold. In a separate analysis of this subgroup, both a positive family history for CHD and a CRP >1 mg/l indicated a better way to identify those at greater CHD risk, as well as identifying those who may likewise benefit the most from intervention with statin therapy [53]. Taken together, these two analyses are merely hypothesis-generating but suggest that the combination of metabolic syndrome, even in patients with lower LDL-c levels, when associated with greater than three metabolic risk factors and/or either an elevated CRP or a family history of premature CHD, may confer CHD equivalent risk status.

ULTRASOUND MEASURED CAROTID INTIMA-MEDIAL THICKNESS AND CALCIUM SCORE ON COMPUTED TOMOGRAPHY

New imaging methods to non-invasively detect asymptomatic individuals at high risk for CHD events include magnetic resonance angiography, computed tomography to evaluate coronary calcium burden, and B-mode ultrasound to measure carotid intima-media thickness. All of these imaging methods have been shown to provide information about the presence and distribution of atherosclerotic disease [38]. Of these imaging modalities, carotid artery ultrasonography and coronary calcium scoring have emerged as the leading technologies for assessing CHD risk equivalency.

Ultrasonography of the carotid artery assessing the intima-media thickness (CIMT) can be considered in individuals who have multiple risk factors to determine if a patient has early asymptomatic carotid disease [54]. CIMT can be a reasonable surrogate for CHD if the stenosis exceeds 50% [7]. In the Dallas Heart Study, the presence of coronary artery calcium when associated with a family history of myocardial infarction was a predictor of atherosclerosis in young subjects compared to older adults, especially young adults with two or more risk factors, including hypertension, DM, smoking, hypercholesterolemia, low HDL and hypertriglyceridemia [47].

The Screening for Heart Attack Prevention and Education (SHAPE) task force recently recommended screening for subclinical atherosclerosis using computed tomography, carotid artery ultrasound, or both, for all asymptomatic 'at risk' men aged 45–75 years and women aged 55–75 years old [55]. The SHAPE trial considered a positive test for atherosclerosis a CACS $\geq$1 or CIMT $\geq$50th percentile or presence of carotid plaque. However, those considered high risk or CHD equivalent were further subcategorized as having a CACS $>$100 or $>$75th percentile or a CIMT $\geq$1 mm or $>$75th percentile. These individuals would be treated to the same goals as high risk CHD equivalent patients from the NCEP-ATP III guidelines.

Other lifestyle risk factors such as obesity, physical inactivity, atherogenic diet and emerging risk factors such as elevated levels of lipoprotein(a), homocysteine, $LpPLA_2$, various prothrombotic factors and impaired fasting glucose do not meet the rigorous criteria of having been tested in prospective studies, available as a commercial assay, shown to have additive predictive power to that of standard lipid values, or additive predictive value to the FRS [56, 57]. Further development of these and other emerging risk factors will potentially allow us to better define and refine CHD equivalent risk in the future (Table 5.1).

CONCLUSIONS

CHD risk equivalents as defined by the NCEP-ATP III guidelines include peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease and asymptomatic carotid disease with $>$50% stenosis, DM, and a 10-year calculated Framingham risk $>$20%. Extension of the Framingham risk from a relatively short 10-year period to one over a lifetime may allow us to better define CHD equivalency, especially in younger individuals and thus allow the option to intervene therapeutically at a much earlier stage of disease. For those individuals who do not meet current criteria for CHD equivalency, newer imaging technologies such as coronary artery calcium scoring by computed tomography scanning and CIMT by ultrasonography may be recommended to further delineate individuals who may have a CHD equivalent state and therefore require the most intensive therapeutic intervention. Emerging risks associated with the growing epidemics of obesity and metabolic syndrome have the potential to unmask another high risk CHD equivalent group. In those with metabolic syndrome, superimposing other risk factors, such as inflammatory markers and a family history of premature CHD disease, may allow further refinement of a subgroup of patients whose risk equals a CHD equivalent status. Anyone diagnosed with the

metabolic syndrome should have an FRS calculated. Many of these patients, especially if they are older and have four or five components of the metabolic syndrome, will achieve CHD risk equivalency. As both technology and evidence based on new emerging risk factors evolve, our ability to refine and define CHD risk equivalents will improve our ability to better direct therapy to those individuals most at risk for a CHD event.

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6

When should children and adolescents be screened for dyslipidemia and how should they be treated?

J. A. Brothers, S. R. Daniels

BACKGROUND

In the United States, cardiovascular disease (CVD) kills more people every year than all forms of cancer and other causes of death combined [1]. Data are compelling that CVD starts in childhood [2–5], with the progression of endothelial damage beginning in the first decade of life in those with dyslipidemia [6–8]. Dyslipidemia, defined as elevated LDL-cholesterol (LDL-c), low HDL-cholesterol (HDL-c), and/or elevated triglycerides (TG), appears to be the main component in the development of CVD. What is most concerning in the modern era is the increasing number of children and adolescents with abnormal cholesterol; this is likely related to poor dietary choice, limited physical activity, and the rise in childhood overweight [9, 10]. This chapter reviews the current recommendations for how physicians, nurses, and advance practice nurses/nurse practitioners should screen children and adolescents and a discussion of the treatment and management options for young patients with dyslipidemia.

SCREENING FOR DYSLIPIDEMIA

Current guidelines for screening and treatment of dyslipidemia in children and adolescents are based on the recommendations published in 1992 by The National Cholesterol Education Program (NCEP) Expert Panel on Blood Cholesterol Levels in Children and Adolescents [11]. NCEP proposed using a two-tiered approach: one that is population-based and an individual-based one that targets children and adolescents at increased risk for dyslipidemia, especially elevated LDL-c. The population-based approach focuses on dietary and lifestyle management of cholesterol and encourages children to maintain a healthy body weight, exercise regularly, and refrain from smoking. This approach is especially relevant to nurses and advanced practice nurses/nurse practitioners who want to take an active role in CVD prevention in children in school- and community-based settings. School nurses are especially poised to help implement nutrition and dietary programs, physical activity recommendations, and other preventive education aimed at reducing CVD risk in the pediatric population [12].

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Table 6.1 Classification of lipoprotein concentrations in children

Cholesterol	*Acceptable*	*Borderline*	*High*
Total	<170 mg/dl	170–199 mg/dl	≥200 mg/dl
LDL-c	<110 mg/dl	110–129 mg/dl	≥130 mg/dl
HDL	≥40 mg/dl		
Triglycerides	<150 mg/dl	150–499 mg/dl	≥500 mg/dl

To identify children at increased risk for developing premature CVD, the NCEP recommends that children ≥2 years of age have a fasting lipoprotein analysis if a first- or second-degree relative has documented CVD (e.g., angina pectoris, peripheral or cerebral vascular disease, myocardial infarction, documented coronary artery disease, or sudden death) by age 55 years if male and 65 years if female. A fasting lipoprotein analysis should also be obtained in children and adolescents with no significant family history but who are at increased risk of early heart disease due to other risk factors, including:

- Overweight
- Hypertension
- Diabetes
- Smoking
- Poor diet
- Sedentary lifestyle

The lipoprotein analysis should include the total cholesterol (TC), HDL-c, TG, and a calculated LDL-c. The LDL-c can usually be determined indirectly from the Friedewald formula: LDL-c = TC − (HDL-c + TG/5) [13]. The practitioner should request that the laboratory measure the LDL-c directly if the TG are >400 mg/dl, as the Friedewald formula is not accurate when TG are significantly elevated. If the initial lipoprotein analysis reveals the LDL-c to be 'borderline' or 'high,' a repeat analysis should be performed. The classification of LDL-c levels is based on fasting lipoprotein data from the Lipid Research Clinics (LRC) Program Prevalence Study [14] and the Third National Health and Nutrition Examination Survey [15]. The categorization as 'borderline' or 'high' is based on lipoprotein values that correspond to the 75th and 95th percentiles, respectively. These categories are shown in Table 6.1.

For a child who does not have a family history of premature CVD but has a parent with a TC >240 mg/dl, a random TC level can be obtained. If this level is 'borderline' or 'high', then a repeat level should be obtained with the average taken of these two measurements. If the average is still ≥170 mg/dl, then a fasting lipoprotein analysis should be obtained. Some physicians will obtain a fasting lipid profile initially instead of a random TC. Screening children in whom the family history is unknown is at the judgment of the practitioner. In all cases, the average LDL-c values of at least two separate fasting measurements should be used to base further evaluation and treatment recommendations.

Once a child has been identified with elevated LDL-c, a more thorough evaluation is necessary. A complete family history should include identifying first- and second-degree relatives who have a history of hypercholesterolemia, premature CVD, diabetes mellitus, overweight, and hypertension. A complete past medical history and review of systems should be performed to rule out any potential secondary causes of hypercholesterolemia, focusing on medications, physical activity, sedentary time, tobacco use, and dietary habits. A complete physical examination should be performed, including height, weight, body

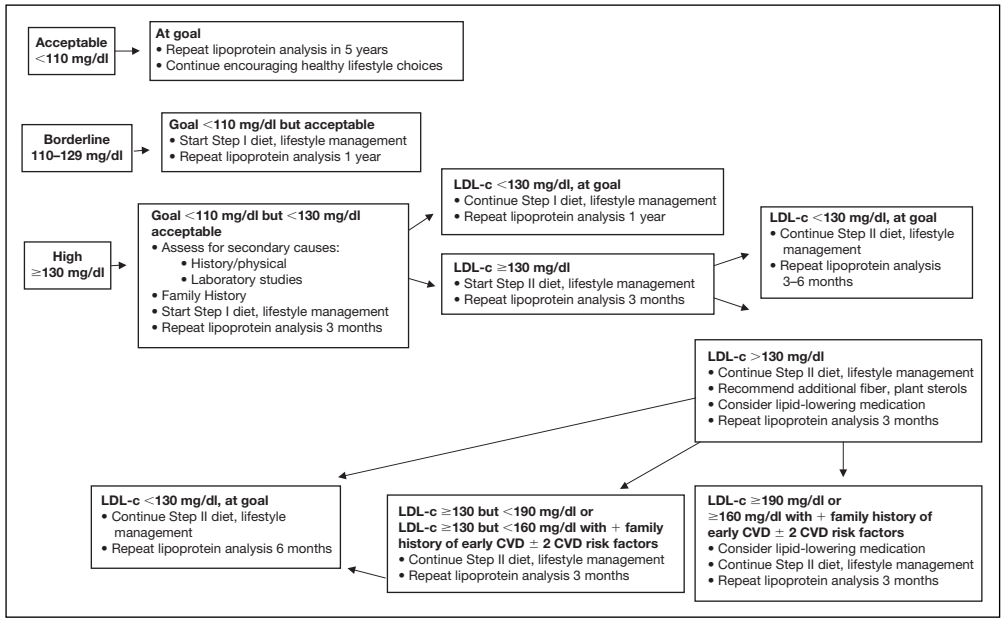

Figure 6.1 Goal LDL-c concentrations.

mass index (BMI = weight in kilograms divided by the square of height in meters), waist circumference, blood pressure, pubertal stage, and assessment of thyroid and liver size. A thorough skin examination should evaluate for acanthosis nigricans (a marker for insulin resistance), eye xanthelasma, and tuberous and tendon xanthomas. Additional laboratory studies should be obtained, including liver, renal, and thyroid function tests; glucose levels; and a urinalysis. In patients with familial hypercholesterolemia (FH), the family should also be educated about the genetic nature of their disorder. An evaluation algorithm is outlined in Figure 6.1, with recommendations based on baseline and goal levels of LDL-c concentrations.

While the NCEP guidelines highlight the importance of both a population-based and individual-based high risk approach for CVD prevention, several limitations have been noted. First, the accuracy and usefulness of family history as a way to screen children for CVD risk factors have been questioned [16–18]. This is because parents may not know their cholesterol status, young parents may not have developed elevated cholesterol or clinical cardiovascular disease, and/or children may live in single parent homes without knowledge of the other parent's risk history [19, 20]. Second, when setting the 75th and 95th percentile cutoff points, the guidelines set the standards for all children and adolescents but did not take into account differences between sex, race/ethnicity, age, and pubertal status. Because girls tend to have higher cholesterol levels than boys [14, 15, 21], more girls will be referred for treatment; however, when compared to men, women have a lower overall risk of premature CVD [22]. Similarly, African-American children tend to have higher TC levels but also have higher HDL-c levels when compared to Caucasian children; thus, the sensitivity is increased but the specificity is decreased [21]. Third, TC and LDL-c levels fluctuate throughout childhood and adolescence, with the highest levels found among children aged 9–11 years, decreasing throughout adolescence, and then increasing thereafter into adulthood [14, 15, 21]. Lastly, the guidelines focus on evaluation and treatment only based on

Table 6.2 Summary of dietary guidelines for all children and adolescents. With permission from [24, 25]

Goal	*Recommendation*
Overall healthy eating habits	Consume a variety of fruits, vegetables, grains, whole grains, low-fat or non-fat dairy products, legumes, poultry, lean meats. Eat more broiled or baked fish. Limit juice intake and sugar-sweetened beverages and foods.
Appropriate body weight	Balance dietary calories with physical activity and energy needs to attain normal growth and development. Appropriate changes should be made to achieve weight loss when indicated.
Desirable lipid profile	After age 2 years, limit foods high in saturated fat (<10% of daily calories), *trans*-fat and cholesterol (<300 mg/day). Encourage use of whole grains and unsaturated fat from vegetables, fish, legumes, nuts.
Desirable blood pressure	Limit salt intake to <6 g/day. Maintain a healthy body weight. Focus on a diet rich in vegetables, fruits, and low-fat or non-fat dairy products.

LDL-c levels. However, this was prior to the obesity epidemic and the concomitant increased prevalence of low HDL-c and high TG. There are no recommendations for screening and treatment for what have now become the more common lipoprotein abnormalities in children: low HDL-c and elevated TG. To address these issues, the American Heart Association (AHA) recently proposed that children are at long-term increased risk of CVD when TG levels are >150 mg/dl and HDL-c ≤40 mg/dl [5].

DIETARY AND LIFESTYLE TREATMENT OF DYSLIPIDEMIA

DIETARY TREATMENT

Population-based approach

As described above, the NCEP outlined primary prevention guidelines in a two-tiered approach. With the population-based method, a diet with limited saturated fat intake is recommended for all healthy children ≥2 years of age, regardless of family history. The goal is <10% of total daily calories from saturated fat, ≤30% of total calories from fat, and <300 mg/day from cholesterol. This is known as the AHA Step I diet [11, 23]. As outlined in Table 6.2, the AHA more recently published guidelines that emphasize not only dietary total and saturated fat content, but also food choices and overall eating habits, particularly increasing intake of poly- and mono-unsaturated fats, omega-3 fatty acids, and high-fiber foods [24, 25].

Individual-based approach

If a child's average cholesterol is elevated (i.e., TC ≥170 mg/dl and/or LDL-c ≥110 mg/dl), the Step I AHA diet should be initiated along with other lifestyle changes, most importantly weight management, decreased sedentary time, and increased physical activity. These changes should be implemented for 3–6 months and then a repeat fasting lipoprotein analysis should be obtained. If the LDL-c is not <130 mg/dl, then a more restrictive diet may be necessary, with further reduction of daily saturated fat to <7% and dietary cholesterol

<200 mg/day. This has been called the AHA Step II diet [11]. This further reduction in fat and cholesterol should be undertaken in conjunction with a medical dietitian to ensure that all the requirements for protein, carbohydrates, and vitamins are met for appropriate growth and development.

Concerns with utilizing a 7% restricted saturated fat diet in children and adolescents have been addressed. Two recent studies found no adverse effects in children following this diet. One was a longitudinal, randomized controlled clinical trial of 663 initially pre-pubertal children with elevated LDL-c levels. They were placed on a low-fat, low-cholesterol diet (saturated fat <8% and total fat <28% of calories, dietary cholesterol <150 mg daily). No adverse changes in growth, iron stores, nutrition, or physical well-being were found after 3 years. LDL-c levels were significantly lower in the low-fat, low-cholesterol group than the control group [26]. Another dietary intervention study randomized 540 babies and their families at 7 months of age into a low-saturated fat diet (intervention) group and another 522 infants and their families into an unrestricted diet (control) group. Families were subsequently followed until 10 years of age. Those in the intervention group consumed a lower-saturated fat, lower-calorie diet and had lower cholesterol levels without any significant differences in long-term metabolic or neurologic growth when compared to the control group [27, 28].

LIFESTYLE TREATMENT

Physical activity

Exercise prescription should be targeted toward a consistent program, with the goal of 60 min or more of vigorous play or aerobic activity per day. Children should also be encouraged to make more active choices, such as walking or bicycling to school or using the stairs instead of the elevator, when possible. Attention should be paid to sedentary behaviors, focusing on the amount of time spent watching television, 'surfing' the internet, and playing video games. Parents can also act as role models for their children by living an active lifestyle and planning family events that promote exercise.

Other lifestyle assessments

The child should have lifestyle assessments at each pediatric office visit with height, weight, and BMI plotted on age- and gender-specific growth curves [29, 30]. In a child who is overweight (BMI ≥85th but <95th percentile) or obese (BMI ≥95th percentile), parent and child education should be offered regarding dietary and exercise management and referral to a nutritionist or registered dietitian may be helpful. In addition, blood pressure should be monitored at every routine visit in children ≥3 years of age with a goal blood pressure <95th percentile for age, sex, height, and weight [5, 31]. Tobacco and alcohol use should be assessed and prevention discussed after the age of 9 years.

LIPID-LOWERING MEDICATION

While the threshold for initiation of drug therapy in children should be high, it may be necessary to institute lipid-lowering medication to bring the LDL-c to the targeted goal (*see* Figure 6.1). The NCEP recommends considering medication in children ≥10 years in whom lifestyle and dietary intervention has been implemented for 6–12 months, but who continue to have elevated LDL-c. Criteria for drug therapy include LDL-c ≥190 mg/dl or LDL-c ≥160 mg/dl with a family history of premature CVD and/or ≥2 traditional risk factors [11]. Choice of therapies is influenced by the lipid diagnosis, age and sex of the child, and age at which family members developed CVD. Since males on average develop CVD 10 years earlier than females, greater latitude exists in treatment of the young or adolescent female.

Table 6.3 Lipid-lowering medications for use in children and adolescents

Medication class	*Names and dosing*	*Lipid profile change*	*Common side effects*
Bile acid sequestrants	Cholestyramine: Start 4 g/day; Max 24 g ÷ BID to TID Colestipol: Granules: Start 5 g/day; Max 30 g ÷ BID to TID Tab: Start 2 g/day. Max 16 g ÷ BID to TID	Decrease LDL-c Increase TG	Constipation, flatulence, abdominal distention Decreased absorption of fat-soluble vitamins and certain medications May increase TG level; should not be used if TG ≥400 mg/dl
HMG-CoA reductase inhibitors (statin)	Atorvastatin: 10–20 mg QHS Lovastatin: 10–40 mg QHS *Pravastatin: 20 mg QHS (8–13 years); 20–40 mg QHS (14–18 years) Simvastatin: 5–40 mg QHS	Decrease LDL-c Increase HDL-c Decrease TG	Gastrointestinal upset, muscle pain, myopathy and elevated creatine kinase levels, rhabdomyolysis, elevated liver enzymes
Cholesterol absorption inhibitor	Ezetimibe: 10 mg daily	Decrease LDL-c	In adults, fatigue, abdominal pain, diarrhea
Niacin	Immediate release: Start 250 mg QD; Max 1 g TID Sustained release: Start 500 mg QD; Max 2 g BID Niaspan: Start 500 mg QD; Max 2 g QD	Decrease LDL-c Increase HDL-c Decrease TG	Flushing, headache, abdominal pain, nausea and vomiting, elevated liver enzymes Flushing may be diminished by administration of aspirin (81–325 mg) 30 min prior to use
Fibrates	Fenofibrate: Start 54 mg QD; Max 160 mg/day Gemfibrozil: Start and Max 600 mg BID 30 min before meals Bezafibrate: 10–20 mg/kg/day	Increase HDL-c Decrease TG	Gastrointestinal distress, mild anemia, elevated liver enzymes, myopathy and myositis

*Approved for pre-pubescent children (age 8 and older)

Recently, the AHA published guidelines for treatment of children at higher CVD risk than the general population; these patients have lower LDL-c cutoff levels, need more aggressive intervention with lower LDL-c goals, and may require combination drug therapy to reach appropriate cholesterol levels [32]. A second scientific statement was subsequently published, focusing mainly on new evidence for the link between lipid abnormalities and early CVD, summarizing the results of clinical trials using statins in children with hypercholesterolemia, and reviewed the revised guidelines regarding treatment and management of children and adolescents with significant lipid abnormalities [33]. These scientific statements are intended for use by general practitioners as well as those specializing in lipid management; however, the more complicated children should likely be referred to a lipid specialist for further evaluation and treatment.

Table 6.3 summarizes the lipid-lowering medications used in children and adolescents, including the recommended dosing, usual change in lipid profile, and major side effects. As

with all medications, the side effect profile should be reviewed carefully with the patient and his/her family prior to initiation and patients should be counseled appropriately on which symptoms to be concerned about. Dosing differs based on the medication. It is recommended that medication be started at the lowest recommended dose and titrated up slowly, following the fasting lipid profile to determine successful treatment.

BILE ACID SEQUESTRANTS

The current NCEP guidelines recommend bile acid sequestrants as first-line therapy for elevated cholesterol in children and adolescents. These medications include cholestyramine and colestipol. Their mechanism of action is through binding bile acids in the intestine and decreasing their absorption. This leads to the upregulation of the LDL receptor on the surface of hepatocytes, increased hepatic conversion of cholesterol to bile acids, and improved clearance of LDL-c from the circulation [34]. Several studies in children with FH found bile acid sequestrants lowered LDL-c by 10–20% at a dose of 8 or 10 g/day [35–39]. Because these medications are not systemically absorbed, they are an extremely safe medication for this population.

Unfortunately, cholestyramine is only prepared in powder formulation that must be mixed with liquid and can be unpalatable. Colestipol is offered in granules and tablets but the tablets are quite large and cannot be cut or crushed, making them more difficult for pediatric usage. Further, the poor palatability and gastrointestinal side effects makes adherence to these medications difficult and patient compliance low [35–39]. They also have the potential for decreasing the absorption of fat-soluble vitamins and folic acid. For this reason, a multivitamin with folate and possibly vitamin D supplementation should be considered. Colesevelam, a non-resin bile acid sequestrant which comes in pill form, may be more palatable with less gastrointestinal side effects than cholestyramine and colestipol. While it has not been FDA approved for the pediatric population, a current clinical trial is underway in conjunction with a statin in children with heterozygous FH [40]. While the bile acid sequestrants have a moderate lipid-lowering ability, the poor compliance with these medications makes it less likely that they will be able to lower LDL-c to target levels in many children and adolescents with dyslipidemia.

HMG-COA REDUCTASE INHIBITORS

3-hydroxyl-3-methyglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line therapy for elevated LDL-c in the adult population and are becoming increasingly popular for use in certain pediatric and adolescent patients as well [32, 33]. Statins lower LDL-c by inhibiting the rate-limiting enzyme in cholesterol biosynthesis, HMG-CoA reductase, and by upregulating LDL receptors in the liver. They improve removal of very low-density lipoproteins (VLDL) and intermediate-density remnants, which accounts for their actions on reducing TG levels [41] and they increase HDL-c levels modestly by increasing hepatic biosynthesis of its major apolipoprotein, apoAI [42].

Demonstrated therapeutic benefits of statin therapy in adults include reduced major coronary artery and stroke events, coronary artery disease mortality, and overall total mortality [43–46]. Because of the interest in using statins in children and adolescents, several clinical trials have evaluated the safety and efficacy of different statins in children with FH and all were found to have similar safety and efficacy profiles as in adults [47–54]. A recent meta-analysis of these clinical trials confirmed this by showing that statins are not only effective in lowering TC and LDL-c and raising HDL-c but also that there was no significant difference in adverse events (including liver and muscle toxicity) or sexual development between treatment and placebo groups [55]. Further, in the longest follow-up study of statin use in the pediatric population to date (average treatment of 4.5 years), Rodenburg

et al. [56] demonstrated that long-term use of pravastatin was safe and that earlier treatment with a statin resulted in smaller carotid intima-media thickness. Atorvastatin, simvastatin, pravastatin, and lovastatin have been FDA approved for use in boys ≥10 years and postmenarchal girls, but pravastatin is the only statin approved for prepubescent children with FH (age ≥8 years) [57]. In select patients with very high LDL-c levels, additional risk factors, or a strong family history of premature CVD, statin therapy may be initiated prior to age 10 years [32, 33].

Although uncommon, potential adverse effects include gastrointestinal upset, elevated liver enzymes, myositis and increased creatine kinase (CK) levels, and rhabdomyolysis [58]. For this reason, baseline liver function tests should be obtained prior to starting therapy and repeated 4 weeks after medication initiation and with any dose uptitration. They should then be rechecked 8 weeks and then 3 months later. If normal, routine liver function tests should be monitored every 3–6 months [33]. Statin medications are contraindicated in those patients with acute liver disease (e.g., acute viral hepatitis) but appear to be safe in those with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis [59]. If a patient has a minor elevation in liver transaminase levels (<3 times the upper limit of normal), they should be rechecked in 2–6 weeks; this is usually not an indication to stop therapy as these fluctuations are usually transient. However, if levels are >3 times the upper limit of normal, they should be rechecked immediately. If they continue to be elevated at this level, the statin should be discontinued and repeat transaminase levels should be checked 2 weeks later [60]. Once levels have returned to normal, the same statin can be restarted at a lower dose or a different statin may be used. Further, prior to starting therapy, muscle symptoms should be evaluated and a baseline CK level obtained; symptoms should be assessed at every visit, but an additional CK level need only be obtained if a patient is having muscle-related symptoms. If a patient with muscle symptoms has a CK level >10 times the upper limit of normal, the statin should be immediately discontinued [58]. Female patients should be counseled that statins are potentially teratogenic and that statin use is contraindicated in pregnancy [61]. Physicians should document that female patients are not pregnant at start of therapy and that they are using adequate birth control if sexually active. With the increasing number of children and adolescents being treated with statin therapy, more studies are needed to assess longer-term compliance, safety, and effectiveness on clinical endpoints as these patients reach adulthood.

CHOLESTEROL ABSORPTION INHIBITORS

Ezetimibe is a relatively new lipid-lowering medication that is indicated for reducing LDL-c and TC levels [62]. In adults, it is sometimes prescribed as monotherapy, but most commonly it is used in conjunction with an HMG-CoA reductase inhibitor [63]. It works by preventing absorption of biliary and dietary cholesterol at the brush border of the small intestine, which causes less cholesterol to be circulated to the liver. This leads to reduced hepatic cholesterol stores and increased cholesterol clearance from the bloodstream [64, 65].

Clinical trials in adults have shown that 10 mg daily of ezetimibe affords a modest (approximately 20% on average) reduction in LDL-c levels. It is well tolerated with minimal side effects, the most common being fatigue, abdominal pain, and diarrhea [66]. This medication is especially useful for people intolerant of or unable to take a statin. Ezetimibe at 10 mg/day has been approved for children >10 years of age; however, there are limited studies using ezetimibe in patients younger than 17 years of age [67, 68]. While there are clinical trials currently underway evaluating the safety and efficacy of ezetimibe and a statin in children with heterozygous FH, it will likely be used as adjunctive therapy in children with persistently elevated LDL-c despite treatment with other drugs [32]. Long-term studies in the pediatric population are needed with both combination therapy as well as monotherapy, especially for those children who are statin-intolerant.

NIACIN

Nicotinic acid, or niacin is indicated for elevated LDL-c, elevated TG, and low HDL-c [69]. It is the only medication found to lower lipoprotein (a) [70]. Niacin decreases the mobilization of fatty acids from visceral adipose tissue, which is associated with reduced hepatic VLDL secretion [71]. It appears to raise HDL by decreasing the catabolism of HDL apoAI, resulting in the recirculation from the liver to peripheral cells of apoAI deficient HDL particles, effectively enhancing reverse cholesterol transport [72, 73]. Niacin comes in three forms: immediate-release, sustained- or slow-release (both over-the-counter), and an extended-release prescription form, Niaspan.

To date, there have been no randomized, clinical trials assessing the safety and efficacy of niacin therapy in children and adolescents. One retrospective review of 21 children with heterozygous FH found that those treated with 500–2250 mg of niacin daily over an average of 8.1 months had reduced TC levels by 23% and LDL-c levels by 30%. However, 76% of the children had reversible adverse effects (e.g., flushing, abdominal pain, itching, headache, nausea, and vomiting) that led to discontinuation of the medication in 38% [74]. Six (29%) had elevation of serum aspartate aminotransferase levels that appeared to be dose-related. These side effects were similar to those found in adults; other side effects seen in adults include hyperglycemia, hyperuricemia, peptic ulcer disease and myopathy (rare) [75]. Because of the lack of safety and efficacy data and the potential for serious adverse events, niacin is generally not recommended for use in the pediatric population, except as adjunctive therapy in children with severe FH who are being closely supervised by a lipid specialist [11, 76].

FIBRIC ACID DERIVATIVES

Fibric acid derivatives, or fibrates, reduce TG and increase HDL-c but have minimal effect on LDL-c levels. Fibrates promote the lipolysis of VLDL by inducing lipoprotein lipase activity; increase hepatic biosynthesis of apoAI and AII, which leads to increased hepatic secretion of HDL; and decrease the enrichment of LDL and HDL particles with triglycerides, thereby rendering them less favorable targets for lipolysis by hepatic lipase [77]. The most commonly used fibrates are fenofibrate and gemfibrozil. Fibrates are generally well tolerated; the most common side effects are gastrointestinal distress, gallstone formation, hepatic transaminase elevation, mild anemia, and increased risk for myopathy and myositis, notably when used in conjunction with statin therapy [78]. Two studies in small numbers of children with FH found that bezafibrate significantly lowered TC and LDL-c and increased HDL-c levels without significant side effects [79, 80]. In general, fibrates are used for treatment of severe hypertriglyceridemia (i.e., level $\geq$500 mg/dl), with a lower threshold to start medication in children with extremely elevated triglycerides (i.e., $\geq$1000 mg/dl) as their risk for pancreatitis is high.

NON-PRESCRIPTION DIETARY SUPPLEMENTS

There has been strong interest in complementary and alternative therapies for cholesterol management in children but there have been few rigorous clinical trials. Plant sterols and stanols decrease LDL-c by inhibiting cholesterol absorption. When consumed at a dose of 2 g/day, they have been shown to reduce LDL-c levels by 4–15% without significant side effects [81–84]. There have been concerns regarding the potential for decreased fat-soluble vitamin malabsorption with chronic therapy; more studies are warranted to determine the long-term safety and efficacy of this therapy in children. Nevertheless, the AHA recommends the use of these products in children with moderate to severe hypercholesterolemia, but with the caution that they should be monitored for possible decreased absorption of fat-soluble vitamins and β-carotene [25]. Increasing dietary intake of fiber has been advocated for all children over 2 years of age, along with the recommended Step I diet [85, 86]. The impact of

dietary fiber on cholesterol levels in children is varied. One crossover clinical trial using 6 g/day of psyllium fiber-enriched cereal vs placebo in children with hypercholesterolemia found no change in cholesterol levels [87] but a similarly designed study found a 7% reduction in LDL-c levels in the fiber compared with placebo group [88]. Another alternative therapy, garlic, has not been shown to have an effect on cholesterol levels in children. One study found that after 8 weeks of either garlic extract or placebo, there was no significant change in cholesterol levels or other CVD risk factors in a group of 30 children with FH [89].

Controversy exists regarding the use of omega-3 fatty acids and antioxidant vitamins in hyperlipidemic children. Engler *et al*. performed a double-blind crossover clinical trial in 20 children with FH or familial combined hyperlipidemia using either 1.2 g/day of docosahexaenoic acid (DHA) or placebo for 6 weeks after first being placed on the AHA Step II diet. While those who received DHA had increased levels of TC, LDL-c, and HDL-c and no change in TG, there was a significant shift in the lipoprotein subclasses toward less atherogenic particles compared with the placebo phase [90]. They also found that endothelial function improved in the DHA-treated phase compared with placebo [91]. While high-dose fish oil is known to reduce serum TG levels in adult patients with hypertriglyceridemia, the discrepant findings from this study may be because high-dose omega-3 was not used (only 1.2 g/day) and the patients did not have significantly elevated baseline triglycerides (mean 133 ± 68 mg/dl). Another study evaluated the use of vitamins C and E in a randomized, double-blind, placebo-controlled trial in children with hypercholesterolemia after 6 weeks on the AHA Step II diet and found that antioxidant vitamins improved endothelial function compared with baseline [92]. These studies suggest that, in addition to lipoprotein levels, vascular endpoints may be an additional way to monitor children at increased risk for premature CVD. However, additional research is needed before these therapies can be recommended for use in the pediatric population.

SUMMARY

In conclusion, children with hypercholesterolemia are at increased risk of premature CVD. The current screening and treatment guidelines proposed by the NCEP for primary prevention of CVD are useful but do have potential limitations. Modifications to these guidelines are necessary to better address the changing lipoprotein profile of children taking into consideration the obesity epidemic and the more recent studies of pharmacologic management in children with dyslipidemia.

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7

Management of dyslipidemia in women

R. Gadi, E. A. Meagher

BACKGROUND

Cardiovascular (CV) mortality amongst women is now reaching almost epidemic proportions. Approximately 500 000 women die of cardiovascular diseases (CVD) per annum [1]. This accounts for close to half of all female mortality and is more than the next seven causes of death combined. For at least 20 years, the number of women dying from CVD has exceeded the number of men dying from CVD (Figure 7.1). These data underscore the need to actively identify risk factors that contribute to CVD in women and aggressively implement CVD risk management strategies.

IDENTIFYING CARDIOVASCULAR RISK

Identification of patients at risk requires an understanding of current risk factors that go beyond the traditional, well-known risk dynamic of increasing age, postmenopausal status, smoking status, and family history. A significant barrier to accurately profiling the CVD epidemic in women is a lack of awareness of the disease as a problem by at least 50% of the population. Lack of awareness of CVD risk warrants special attention and should be the key initial focus if risk management strategies are to be successfully implemented in women.

CARDIOVASCULAR RISK ASSESSMENT

The first step in CVD risk management is to determine and stratify the level of risk for individual patients. There are numerous useful tools available to aid in this process. One of them is the Framingham risk assessment tool shown in Figure 7.2, which quantifies the absolute risk of coronary heart disease (CHD) over 10 years [2]. This tool, which can be accessed at http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm, is incorporated into a variety of national guidelines which have established lipid targets based on 10-year risk estimates, and include the National Cholesterol Education Program (NCEP), the American Heart Association (AHA) Evidence Based Guidelines for Cardiovascular Risk Reduction in Women, and the American Diabetes Association guidelines (Table 7.1). All recommend a comprehensive assessment of CV risk irrespective of gender [3–6]. The evaluation should include a complete and thorough medical history to identify a known history of CVD or CVD risk equivalents (diabetes, other vascular disease, and chronic kidney disease

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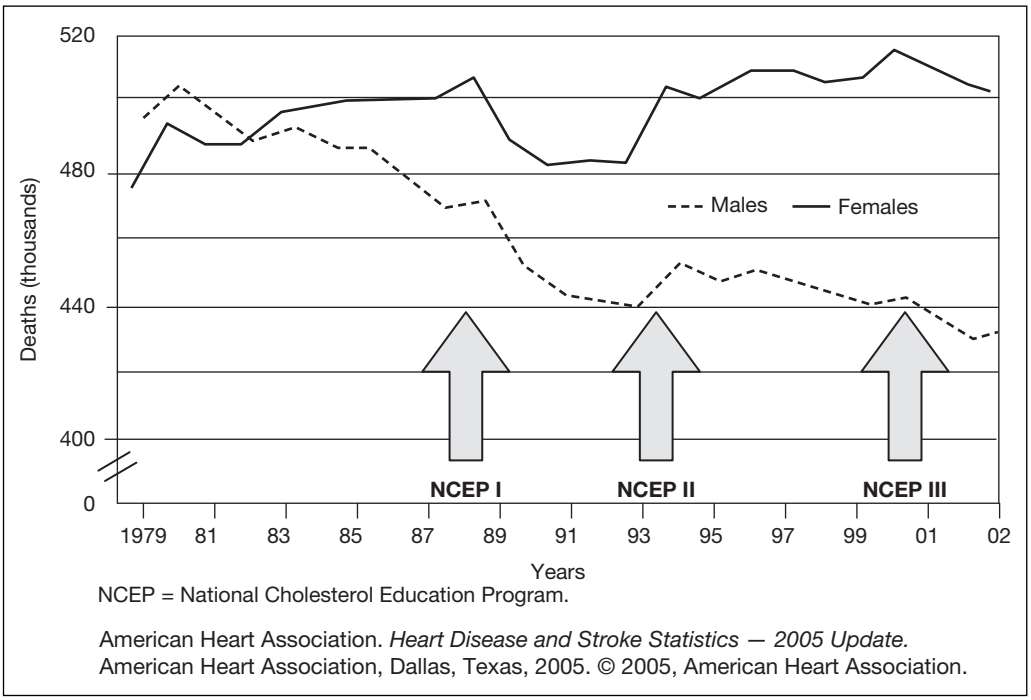

Figure 7.1 Heart disease is the leading cause of death among women in the United States. The incidence of CVD is widespread in both men and women. Publication of the first and subsequent NCEP guidelines appears to coincide with a decrease in CVD deaths among men but not among females where the absolute risk is on the rise.

[CKD]), hypertension, hyperlipidemia, metabolic syndrome, diabetes, thyroid disease and obesity (Table 7.2). A family history for each of these should also be determined, as should a family history of premature CVD. A laboratory workup should initially include a complete fasting lipid panel and a fasting glucose level. In patients who have known hyperlipidemia, a thyroid-stimulating hormone (TSH) level should be obtained to rule out hypothyroidism, the most common secondary cause of hypercholesterolemia. There is a significant focus in all guidelines on primary prevention in patients with multiple risk factors. Guidelines typically use Framingham projections of 10-year risk to identify those particular individuals with multiple risk factors who are then candidates for more intensive treatment, including those with the metabolic syndrome.

The AHA evidence-based guidelines for CVD prevention in women describe risk groups based on the Framingham global risk and other clinical characteristics that help to determine the aggressiveness of a preventive treatment strategy (Table 7.3). For example, a high-risk group, based on the Framingham global risk score, corresponds to an absolute risk of CHD in the next 10 years of ≥20%, an intermediate risk would be classified as 10–20% absolute risk, and a lower risk is ≤10%. Importantly, subclinical CVD is being identified more frequently with the availability of tools such as the ultra-fast computed tomography (CT) scan. In an update to the 2004 guidelines, the AHA acknowledged a growing appreciation of the limitations of risk stratification with the Framingham risk function in diverse populations of women, including the narrow focus on short-term (10-year) risk of myocardial infarction (MI) and coronary artery disease (CAD), lack of inclusion of family history, overestimation or underestimation of risk in the non-white poulation, and the documentation of subclinical

Step 1: Age

Years	Points
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Step 2: Total Cholesterol

TC (mg/dl)	Points at age 20–39	Points at age 40–49	Points at age 50–59	Points at age 60–69	Points at age 70–79
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

Step 3: HDL-cholesterol

HDL-c (mg/dl)	Points
≥60	–1
50–59	0
40–49	1
<40	2

Step 4: Systolic blood pressure

Systolic BP (mmHg)	Points if untreated	Points if treated
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Step 5: Smoking status

	Points at age 20–39	Points at age 40–49	Points at age 50–59	Points at age 60–69	Points at age 70–79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Step 6: Adding up the points

Age	____
Total cholesterol	____
HDL-cholesterol	____
Systolic blood pressure	____
Smoking status	____
Point total	____

Step 7: CHD risk

Point/total	10-Year risk	Point/total	10-Year risk
<9	<1%	20	11%
9	1%	21	14%
10	1%	22	17%
11	1%	23	22%
12	1%	24	27%
13	2%	≥25	≥30%
14	2%		
15	3%		
16	4%		
17	5%		
18	6%		
19	8%		

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001; 285:2486–2497.

Figure 7.2 Assessing CHD risk in women.

Table 7.1 Goals for lipid management

Parameter	*ATP III+ Update*[1]	*Women*[2]	*ADA Position*[3]
Optimal LDL-c	<100 mg/dl	<100 mg/dl	<100 mg/dl
Very high risk (2004 Update)[4]	<70 mg/dl		
Optimal TG	<150 mg/dl	<150 mg/dl	<150 mg/dl
Optimal HDL-c	>40 mg/dl	>50 mg/dl	>40 mg/dl men >50 mg/dl women
LDL-c goal for CHD or equivalents	<100 mg/dl	<100 mg/dl	<100 mg/dl
Non-HDL goal	<130 mg/dl	<130 mg/dl	

[1]Expert Panel. *JAMA* 2001; 285:2486–2497.
[2]Mosca L *et al*. *Circulation* 2007; 115:1481–1501.
[3]American Diabetes Association. *Diabetes Care* 2008; 31(suppl 1):S26–S27.
[4]Grundy SM *et al*. *Circulation* 2004; 110:227–239.
ADA = American Diabetes Association; ATP III = Third Adult Treatment Panel of the National Cholesterol Education program; CHD = coronary heart disease; LDL-c = low-density lipoprotein cholesterol; TG = triglycerides.

Table 7.2 CVD risk assessment

History	*Examination*
Age Postmenopausal status Hypertension Diabetes Hypothyroidism Renal disease Other vascular disease Family history of premature CVD Female member <60 years Male member <50 years Cigarette smoking Obesity	Height, weight, waist circumference Blood pressure Thyroid examination Examination of eyes with fundoscopy Cardiovascular examination Stigmata of dyslipidemia: xanthelasma, thickened tendons
Laboratory workup Comprehensive metabolic panel to include fasting glucose, creatinine level, and liver function tests Fasting lipid panel: total cholesterol, LDL-c, HDL-c, and non-HDL-c TSH Optional labs: hs-CRP and Lp(a)	

Table 7.3 Risk stratification for CVD prevention in women

- High (>20%) – CHD, CVA, PAD, AAA, DM, CKD
- At risk (10–20%) – Subclinical CHD, metabolic syndrome, multiple risk factors, marked elevation of single RF, family history of premature CVD
- Optimal (<10%) – no risk factors and healthy lifestyle

AAA = abdominal aortic aneurysm; CHD = coronary heart disease; CKD = chronic kidney disease; CVA = cerebrovascular accident; DM = diabetes mellitus; PAD = peripheral arterial disease; RF = risk factor.

disease among many women who score as being at low risk [4]. Finally, despite a Framingham risk score that differentiates low or intermediate risk, if a single risk factor is sufficiently abnormal, women may transition into the high risk category [4].

LIPOPROTEINS AND CVD

Increased LDL-c levels have been definitively linked to the development of CVD in both men and women. Data from the Lipid Research Clinics Program Follow-up Study, a mortality study with baseline data gathered from 1972 through 1976 from 2406 men and 2056 women aged 40–64 years, clearly established the association between increased LDL-c and CVD incidence/mortality over a 19-year time frame [7]. There is abundant evidence showing a reduction in clinical events in both men and women when LDL-c levels are lowered [8, 9–15]. The current guidelines from the NCEP Adult Treatment Panel (ATP III), as well as the more recent AHA evidence based guidelines for CVD prevention in women underscore the importance of LDL-c reduction as the primary goal of therapy [3, 4]. LDL-c levels are generally lower in women than in men until menopause when levels increase and LDL particles become smaller and more dense and, therefore, more atherogenic [16, 17].

The guidelines also recognize non-HDL-c as a secondary target for therapy [3, 4]. Despite the fact that non-HDL-c, which includes all atherogenic lipoproteins, has been shown to be a strong predictor of CV mortality in women, it is significantly underutilized as a test in CVD risk assessment [18].

The Framingham Heart Study established both HDL-c and triglycerides as important predictors for coronary events [2]. Castelli *et al*. [19] obtained fasting lipid profiles on 1025 men and 1445 women aged 49–82 years between 1969 and 1971. During the 4-year follow-up period, CVD developed in 79 of the men and 63 of the women. This association was noted to be independent of total and LDL-c levels and applied to both genders [19]. This and a subsequent analysis by the same author were the first data to suggest that triglyceride and HDL levels may have greater predictive potential in women when compared with men [19, 20]. More recently, the Lipid Research Clinics Follow-Up Study also demonstrated that both HDL-c and triglycerides were better predictors of coronary risk and CV mortality in women than was total cholesterol or LDL-c [21]. Importantly, this study showed that when HDL-c level is <50 mg/dl in women compared with ≥ 50 mg/dl, there is a three- to four-fold increase in CVD mortality irrespective of the baseline LDL-c level. In 1995, a meta-analysis performed by Hokanson *et al*. [22] supported this observation by showing a 1 mmol/l increase in triglycerides to be associated with a 76% increased risk of CVD in women versus 32% in men. The synergy between low HDL-c and elevated triglyceride levels in women described in the Framingham data set is of particular relevance given the increasing prevalence of combined dyslipidemia and its association with excess CVD morbidity and mortality.

There are two significant differences in lipoprotein levels between genders. First, women have on average HDL-c levels 10 mg/dl greater than men [3, 4]. Second is the change that occurs in these levels throughout a woman's lifecycle, particularly during the pre-, peri-, and postmenopausal periods [23]. The former is well described in the ATP III and the AHA women's guidelines. The latter is thought to contribute to the sharp increase in CV mortality that occurs in the early postmenopausal period. A study of the influence of menopause on serum lipids and lipoproteins was undertaken to examine the serum lipid profiles at 6-week intervals for 2–3 years in 1360 premenopausal women undergoing the menopause. Results from the study characterized the increase in total and LDL-c and triglyceride levels and the decrease in HDL-c that occur spanning the perimenopausal period (Figure 7.3) [23].

Lipoprotein (a) (Lp(a)) is emerging as a risk factor for CVD [3]. Data from the Heart and Estrogen/Progestin Replacement Study indicate that Lp(a) is an independent predictor of the risk of recurrent CVD in postmenopausal women [24]. This may have important implications for therapy, because Lp(a) is unaffected by diet, exercise, and most lipid-modifying medications, with the exception of niacin, which decreases it. According to the ATP III guidelines, Lp(a) measurement can be considered in patients with less obvious risk but who may warrant more aggressive evaluation based on the presence of one significantly abnormal risk factor [3].

The role of inflammation in the development and progression of atherosclerosis has received increased attention in recent years [25]. C-reactive protein (CRP), an acute-phase marker of systemic inflammation, has been identified as an independent risk factor for CV events, adding predictive value to that of individual lipoprotein fractions. Data from the Women's Health Study indicate that high sensitivity (hs)-CRP is related to several CV risk factors in women, including age, body mass index (BMI), blood pressure, cigarette smoking, and, to a lesser extent, HDL-c [25]. In one prospective follow-up study of 28 263 women over 3 years, CRP was found to be the strongest predictor of CVD, proving superior to several other markers of inflammation and to homocysteine and lipoprotein levels [26]. However, this marker also correlates with other risk factors and may lose its predictive value when adjustment for the confounding effect of other risk factors occurs [27]. It has been suggested that screening patients for an elevation in hs-CRP may help clinicians identify patients, otherwise treated in a limited fashion, who are candidates for more aggressive primary prevention strategies [28].

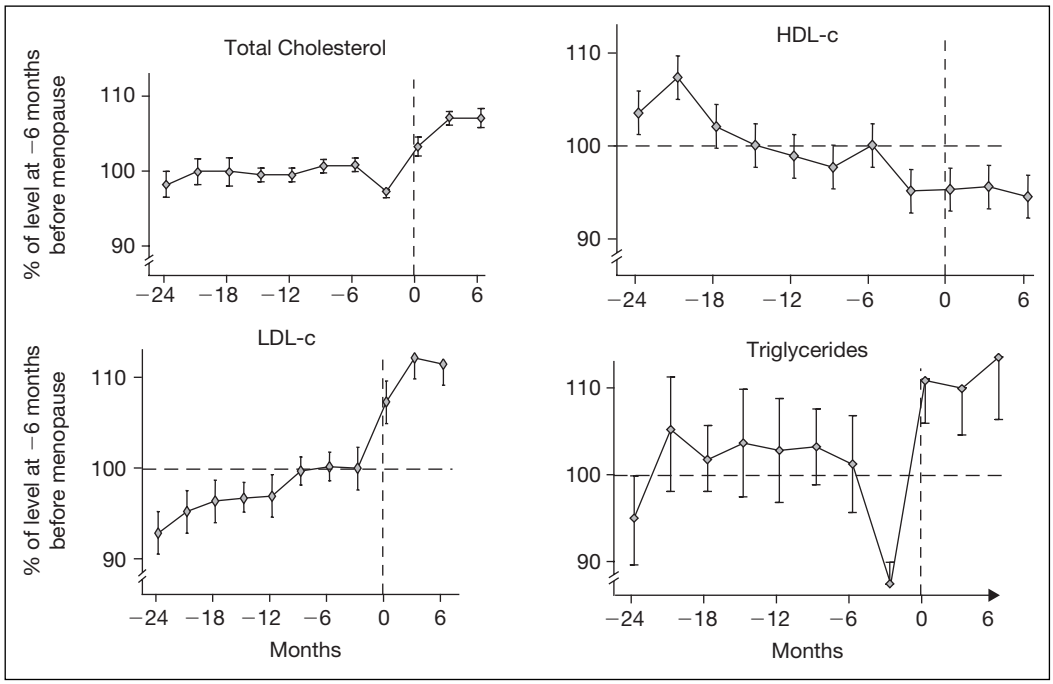

Figure 7.3 Change in lipids after menopause. Adapted with permission from [23].

LIPID GOALS

Current lipid treatment goals as put forward by various advisory bodies are presented in Table 7.1. Elevated LDL-c is the primary target of therapy with elevated non-HDL-c as a secondary target of therapy for patients with triglyceride levels ≥150 mg/dl. An optimal LDL-c is defined as <100 mg/dl. *Statin therapy is indicated in all women with a high CV risk regardless of the LDL-c level*. An optimal level of HDL-c is defined as >50 mg/dl for women. An optimal non-HDL is <130 mg/dl. Niacin or fibrate therapy is indicated for women who are classified as high or intermediate risk and have a low HDL or an elevated non-HDL after LDL-c goal is reached [4]. Both genders respond equally well to risk factor management. However, even when women are identified as having risk factors for CVD, there is lower physician utilization of accepted therapies compared with men [29–31]. When comparing women and men with similar CV profiles, women are significantly less likely than men to undergo additional coronary evaluation (38% vs 62%; $P = 0.002$) or coronary revascularization (2% vs 5%; $P = 0.03$) [32]. Less aggressive lipid-modifying strategies are employed when treating women when compared to men with similar risk profiles. In the Heart and Estrogen/Progestin Replacement Study, approximately half of the women with established CVD were not receiving lipid-modifying medications [31]. In a prospective 3-year study (randomization between 1992 and September 1994) of 825 men and women with CHD, use of lipid-modifying therapy increased and LDL-c decreased in men, but utilization of therapy and, not surprisingly, LDL-c levels remained unchanged in women despite LDL-c levels above goal in the women enrolled in the study [29]. This difference may partially derive from the paucity of relevant data at the time of this study [29].

Dyslipidemia is one of the most important modifiable risk factors for CHD [3, 4]. However, women had largely been excluded from the original primary and secondary prevention trials. Most of the available data on lipid modification therapy in women was derived from subgroup analyses of the relatively small female populations enrolled in clinical trials, which not surprisingly clearly showed that women benefit from such therapy [8–11]. An additional explanation for laxity in the approach to CVD risk in women may be the widely held belief that CV risk is more time-dependent in women, increasing markedly only after the menopause [33]. The results of various large-scale observational studies documenting an increase in CVD after menopause and a decline in risk with the use of estrogen laid the foundation for starting CV risk assessment after menopause and initiating hormone replacement therapy (HRT) as a preventive strategy [1, 34–35]. Given our present understanding of the progressive nature of atherosclerosis [36], it now seems that the time demarcation at menopause may be an artificial distinction and that the presence of risk factors in women warrants the initiation of risk intervention strategies much earlier.

LIFESTYLE AND BEHAVIORAL CHANGES

The first step to reducing overall CHD risk involves therapeutic lifestyle changes. To this end, clinicians need to encourage women to adopt a healthy lifestyle, including smoking cessation, beginning a low-fat and possibly reduced carbohydrate diet, weight control, and regularly engaging in physical activity. Specific therapeutic lifestyle recommendations are presented in detail in ATP III [3]. As a general recommendation, patients should reduce their dietary intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day), increase their intake of foods that lower LDL-c (plant stanols/sterols and soluble fiber), reduce weight, and incorporate regular physical activity into their daily routine (30 min or more on most days of the week) [4].

DRUG THERAPY

Pharmacological treatment options exist for the management of dyslipidemia in both genders. It is recognized, however, that women and, importantly, minority women are less likely than men to receive optimal lipid management, despite the fact that they receive equal benefit from lipid management [37]. Furthermore, giving attention to appropriate lipid management in the postmenopausal years is particularly relevant given that the Women's Health Initiative (WHI) demonstrated that HRT did not prevent CV events in women despite some beneficial lipid effects. Part of this study randomized 16 608 primary prevention postmenopausal women between the ages of 50 and 79 years to receive either estrogen plus progesterone or placebo [38]. The primary efficacy outcome of the trial was CHD (non-fatal MI or death due to CHD). After a mean follow-up of 5.2 years, the Drug and Safety Monitoring Board recommended terminating this part of the study because of an increased incidence of the CHD endpoint, stroke, breast cancer and thromboembolic events. Despite the fact that there may be some benefit for colorectal cancer, hip fractures and total fractures in addition to the known benefit of HRT on lipoproteins, it is recommended that combined HRT not be used for CVD prevention in women [38]. The subsequent analysis of the estrogen alone arm of the WHI again showed a failure to prevent coronary events as well as noting an increase in stroke rate [39]. These data have important clinical implications. As women deemed to be at risk for CVD discontinue HRT, their lipoprotein profiles typically deteriorate with LDL-c and HDL-c values increasing and decreasing, respectively.

Fortunately, several lipid-lowering trials have shown an unequivocal benefit of statin therapy in both men and women. Meta-analysis of data from five trials in which 30 817 participants were randomized to statin or control therapy for at least 4 years demonstrated that

total cholesterol was reduced by 20%, LDL-c by 28%, triglycerides by 13% and HDL-c was increased by 5% [39]. Overall, statin treatment reduced risk of major coronary events by 31%, fatal CHD by 29% and all-cause mortality by 21%. The Heart Protection Study randomized 5082 women (25%) and 15 454 men (75%) with known CHD between ages 40 and 80 years to receive simvastatin 40 mg or placebo in a 2×2 factorial design and they were followed for 5 years. The study demonstrated that overall reductions in major vascular events with statin therapy were similar in both men and women (25% and 20%, respectively) and were unaffected by age [12]. Among the 3421 patients with entry LDL-c levels below 100 mg/dl, a similar reduction in risk of major events is seen when compared with those participants with higher baseline LDL-c levels. This effect was independent of gender. Two recent trials, the Prospective study of Pravastatin in Elderly at Risk [40] and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)–Lipid Lowering Arm [32], had contradictory findings, which showed no benefit with statin therapy in women. However, these trials were of shorter duration and few events occurred in the women enrolled in these trials.

Statins have proved to be extremely safe and well tolerated in the majority of patients. Their most common serious adverse effects, hepatotoxicity and myopathy, occur at very low rates [41]. The risk of myopathy increases with advanced age, especially in women, in patients with multi-system disease, and in patients taking specific concomitant medications [41]. With appropriate care, statins can be used safely in these patients. Statins are classified as category X drugs, which are contraindicated during pregnancy. Women of childbearing potential who use statins should be counseled about the need for adequate contraception and prenatal planning.

COMBINATION THERAPY FOR THE TREATMENT OF DYSLIPIDEMIA

Cardiovascular events continue to occur despite aggressive LDL-c lowering. There is an increasing body of evidence from numerous 'proof of concept' studies in support of combination drug therapy in the management of dyslipidemia in high-risk patients. Two large randomized clinical endpoint studies of combination regimens are underway. Until the results of these studies are available, we must examine the available data that evaluate this approach.

STATIN/NIACIN

The combination of a statin plus niacin is perhaps one of the most useful combinations for treating dyslipidemia in women, as it adds the favorable effects of niacin on atherogenic dyslipidemia to the LDL-c lowering action of statins. In numerous clinical studies, this combination has shown improvements across the lipid profile [42–45]. In a small study of fluvastatin and niacin, LDL-c levels were reduced by 54.6% in women versus 38.2% in men ($P < 0.0005$) [42]. The Familial Atherosclerosis Treatment Study (FATS) found that combination therapy with niacin, colestipol, and/or lovastatin also resulted in a better reduction in coronary artery stenosis in women than men among individuals with familial hypercholesterolemia [46]. A 10-year evaluation of triple therapy with lovastatin, niacin and colestipol in these same patients subsequently enrolled in the FATS 10-year follow-up showed that this triple therapy was associated with a significant reduction in LDL-c (−48%) and triglyceride levels (−36%), an increase in HDL-c (+23%) and a significant lower rate of death and cardiovascular events ($P < 0.05$) [47]. The HDL-Atherosclerosis Treatment Study (HATS) was a placebo-controlled secondary prevention study of 160 patients with CHD designed to look at the impact of the combination of simvastatin and niacin with or without antioxidant vitamins on the progression of CHD [48]. The primary endpoint was the mean change in the percent stenosis caused by the most severe lesion from the initial arteriogram to the final arteriogram. The mean HDL-c was 31 mg/dl at baseline and was increased by 24%. The

mean LDL-c was 125 mg/dl at baseline and was decreased by 42%. A significant reduction in events was associated with the use of simvastatin and niacin in combination. Antioxidant vitamins appeared to attenuate the beneficial effects of simvastatin and niacin on CV outcomes [48]. This may possibly be related to the fact that antioxidant vitamins may interfere with the HDL-c raising impact of niacin therapy [49].

A large phase III randomized National Institutes of Health (NIH) sponsored study, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM HIGH) study, is underway to evaluate the vascular endpoint effect of simvastatin combined with extended release niacin in high-risk men and women with atherogenic dyslipidemia.

STATIN/FIBRATE

Combining statin therapy with a fibrate is another good option for patients with mixed dyslipidemia [50–52]. Although no outcome studies have been performed with this combination, one study showed a reduction in projected coronary risk with the combination of pravastatin or simvastatin with gemfibrozil or ciprofibrate [51]. As mentioned, myopathy is a potential concern when using this combination, but the risks can be attenuated by avoiding use in patients with renal impairment, avoiding the use of gemfibrozil with statin therapy, using moderate statin doses, and appropriately monitoring patients [41, 53]. A large phase III NIH sponsored randomized study, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, is underway to evaluate the effect of simvastatin combined with fenofibrate therapy on a wide range of vascular endpoints.

PATIENT CASE STUDY 1

The patient is a 66-year-old postmenopausal woman who comes to the office for a routine examination. She is a non-smoker and has a history of treated hypertension and depression. Her current medications include a calcium channel blocker (diltiazem, 240 mg/day) and a selective serotonin reuptake inhibitor (SSRI: nefazodone 150 mg/dl). She is uncertain about a family history of premature CHD. She works as an administrative assistant and follows no specific diet or exercise regimen. On physical examination the following were recorded: height 5′5″, weight 171 lbs, BMI 28.4 kg/m^2, waist circumference 37 inches, blood pressure 139/82 mmHg. Laboratory testing revealed serum creatinine 1.4 mg/dl, estimated glomerular filtration rate 52 ml/min/1.73 m^2, fasting blood glucose 104 mg/dl, total cholesterol 241 mg/dl, LDL-c 156 mg/dl, HDL-c 44 mg/dl, and TG 248 mg/dl.

Using the Framingham point score to estimate this patient's 10-year risk for a 'hard' CHD event, she has a Framingham 10-year risk of 11% [3]. This score is based heavily on her age (contributing 12 points) and treated systolic blood pressure (contributing 4 points), her total cholesterol level (3 points), with a smaller contribution by her low HDL-c (1 point), combining for a total of 20 points. The lipid profile results indicate combined dyslipidemia with high total cholesterol and triglycerides, borderline high LDL-c, and low HDL-c.

This patient has three major risk factors (age, hypertension, and low HDL-c) according to the NCEP risk criteria. Since her family history of premature CHD is unknown, this is a possible fourth risk factor. Thus, according to the NCEP definitions, she is considered to be in a moderately high-risk category, with two or more risk factors and a 10-year risk between 10% and 20% [6]. It is important to establish the therapeutic goal for each individual patient. For this case, the lipid goals include the following: an LDL-c of $<$130 mg/dl with the option of reducing it to $<$100 mg/dl, HDL-c $>$50 mg/dl, and triglyceride $<$150 mg/dl. Finally, the non-HDL-c goal is always 30 points higher than the stated LDL-c goal. To achieve these goals the following approach should be considered. Therapeutic lifestyle change (TLC) should be the first approach to therapy, with a particular emphasis on dietary modification and optimizing

her exercise regimen. However, consideration should also be given to initiating drug therapy since she is at moderately high risk of future CVD events. Statins are the first drug of choice in elderly patients, having been shown to be safe and effective, as well as reducing the risk of CVD in this population [3, 12, 40]. Drug therapy in this patient must take into account her decreased renal function as well as potential drug interactions with medications she is currently taking (nefazodone and diltiazem). Because both of these medications have the potential to inhibit metabolism of certain statins, great care should be exercised to choose the statin least likely to be affected by interactions with these drugs. Pravastatin and rosuvastatin are not significantly metabolized by the cytochrome system and would be appropriate choices for this patient. Given her other medications and reduced kidney function, it would be important to start this patient on the lowest statin dose and then carefully titrate the dose higher if necessary. The patient's kidney and liver function should be monitored regularly. Once goal LDL-c is achieved, attention should be directed to other components of the lipid profile.

If the patient is compliant with diet and exercise, there is a good chance that the fasting glucose values will return to <100 mg/dl and the triglyceride value can show dramatic responses to reduced dietary carbohydrate and fat intake. In the event that TLC is ineffective, then combination drug therapy can be considered. Omega-3 fatty acids can be effective as adjunctive therapy for the management of elevated triglyceride levels with minimal toxicity. Alternatively, the addition of a fibrate can be considered, but the possibility of liver function test elevations and myopathy make this approach less attractive given the modest degree of elevation of her triglyceride levels. A final combination therapeutic approach would be the addition of prescription niacin. This intervention as mentioned previously would increase HDL-c levels in addition to reducing LDL-c and triglyceride levels. The downside of this approach is the small potential of aggravating her mildly elevated glucose level and the development of flushing in response to treatment. Both of these can be effectively managed clinically by reducing simple carbohydrate intake and the ingestion of 325 mg of aspirin 1 h prior to the nighttime dose of niacin.

PATIENT CASE STUDY 2

Patient 2 is a 52-year-old woman who presented to the emergency room with chest pain and was admitted to the telemetry unit. She was diagnosed with an MI by elevated cardiac markers and with compatible electrocardiographic findings. A cardiac catheterization revealed a 90% right coronary artery occlusion that was successfully treated with angioplasty and stent placement. Her family history is significant for premature CHD. Her mother was diagnosed with CHD at the age of 48 and underwent coronary artery bypass surgery. During the hospitalization she was noted to have hypertension with blood pressure 152/84 mmHg and heart rate of 72 bpm. She was started on an enteric-coated aspirin (325 mg/day), clopidogrel (75 mg/day), lisinopril (20 mg/day), metoprolol (50 mg/day) and atorvastatin (20 mg/day).

She presented for follow-up 6 weeks after being discharged. In the office her physical examination revealed height 5′2″, weight 134 lbs, BMI 24.5 kg/m^2, waist circumference 28 inches, and blood pressure 134/76 mmHg. Laboratory testing revealed total cholesterol 170 mg/dl, LDL-c 98 mg/dl, HDL-c 50 mg/dl, and TG 150 mg/dl.

As per the revised ATP III guidelines, this patient, given her recent hospitalization with an acute MI, meets criteria for the designation of very high risk. The benefits of LDL-c lowering are greatest in patients who are at very high risk. The NCEP and the AHA guidelines [1, 3] advocate that patients implement and maintain therapeutic lifestyle changes, including adherence to appropriate diet and regular exercise. An LDL-c goal of <70 mg/dl is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk.

Therapy should begin with a statin at a dose that will reduce LDL-c levels by 30–40% [6]. After 6 weeks of drug therapy, LDL-c should be measured. If treatment goals are not met, drug therapy may be intensified by either increasing the dose of the statin or using combination therapy. Increases in the statin dose are limited by the increasing risk of adverse effects and the so-called 'rule of 6's', which states that doubling the statin dose will only reduce LDL-c levels by an additional 6% [54]. The addition of ezetimibe therapy is an efficacious approach to further lowering of LDL-c in those patients who fail to reach target LDL-c goal with appropriate dose statin monotherapy.

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8

In high and very high-risk patients, is it true that when it comes to LDL-c, lower is better and can a serum LDL-c be driven too low?

W. B. Borden, M. H. Davidson

BACKGROUND

Amongst the various targets for cardiovascular (CV) risk factor modification, low-density lipoprotein cholesterol (LDL-c) is both a powerful determinant of CV risk and a target highly amendable to intervention. Multiple epidemiologic studies have demonstrated the linear association between increasing levels of cholesterol and CV events such as the development of CV disease, death from coronary heart disease (CHD), and all-cause mortality [1, 2]. Similarly, multiple randomized clinical trials have demonstrated that reductions in LDL-c decrease the incidence of myocardial infarction (MI), ischemic stroke, and overall mortality [3]. Anthropologic studies of non-human primates and primitive hunter-gatherer populations indicate that the default level for LDL-c may be significantly lower than that currently observed [4–6]. Subgroup analyses of large clinical trials that assessed patients who either started trials with baseline low LDL-c or achieved very low LDL-c levels suggest that the target LDL-c for minimizing CV risk may actually be significantly lower than currently recommended goals [7–13].

The approach to lowering LDL-c involves both lifestyle modifications and pharmacologic therapy. The global risk profile involves elevated LDL-c as well as other known modifiable risk factors such as hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c), hypertension, smoking, high-fat high-carbohydrate diets, sedentary lifestyles, obesity, and impaired glycemic control, as well as non-modifiable risk factors such as age and family history of premature onset atherosclerotic disease. With 25% of the entire United States population and more than 40% of Americans over the age of 60 having multiple risk factors, drug therapy targeting LDL-c alone fails to recognize the interplay between LDL-c and these other risk factors, [14, 15]. Moreover, such an approach inappropriately subjects patients to the risks of medications without incorporating the benefits of effective non-pharmacologic therapies such as low-fat low-carbohydrate diets, smoking cessation, and regular aerobic exercise. Without global risk reduction, even with LDL-c lowering, high-risk individuals will still be left with significant residual cardiovascular risk. Therefore, while LDL-c lowering is important, the approach to treating high-risk individuals must include global CV risk profile modification with lifestyle changes in conjunction with pharmacologic therapy.

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However, when thinking about LDL-c lowering, in addition to global risk reduction, the clinician is faced with the question of how low an LDL-c should be sought. Mindful of current recommendations in the Adult Treatment Panel III (ATP III), the clinician will have already assessed the risk level of the patient and classified the patient as low, moderate, moderately high, or high risk [16, 17]. The relative risk reduction with LDL-c lowering should be the same in all patients. However, the absolute risk reduction will vary in that in patients who have higher baseline CV risk, a 30 or 40% relative risk reduction will result in a much greater absolute risk reduction than in a patient who starts with a lower initial CV risk. The benefit received by patients from LDL-c reduction depends greatly on their individual CV risk. This varying benefit must be weighed against the risks and costs of pharmacologic LDL-c lowering. As we will discuss in this chapter, in high- and very high-risk individuals the evidence does support aggressive LDL-c lowering, combined with global CV risk reduction to the lowest possible levels, even less than current guideline recommendations.

This chapter will review the epidemiologic support for lower LDL-c goals as being consistent with the natural state of humans. Building on these observational data, the chapter will review the randomized controlled studies that have demonstrated the specific benefits of lower LDL-c. Lastly, the safety of aggressive LDL-c lowering will be addressed.

WHAT LDL-c DOES NATURE INTEND?

The modern Western diet, combined with more sedentary lifestyle, leads to elevated baseline total cholesterol in both men and women. Cohorts of men, all younger than 39 years old, showed serum total cholesterol values in the range of 190–210 mg/dl [1]. In that same study of the young male cohorts, those individuals with the highest serum levels of cholesterol, 240 mg/dl or greater, had 1.31 to 1.49 times greater all-cause mortality compared to those individuals whose serum cholesterol was less than 200 mg/dl. Modern population studies in a variety of demographic groups have demonstrated a clearly positive linear relationship between elevated serum cholesterol and CV mortality. Assessing cholesterol levels and ischemic heart disease in different countries over the 40-year time span from 1950 to 1990 showed a ten-fold difference in ischemic heart disease with 80% of that variation associated with elevated serum cholesterol levels [2]. A direct relationship exists between higher total cholesterol and risk for both CV and all-cause mortality. However, the modern diet and resultant cholesterol levels may not represent the natural diet and resultant cholesterol levels for human beings in their natural state.

Assessing the physiologic needs of cells for cholesterol can be done through examining *in vitro* cell cultures. When fibroblasts are cultured, they take up LDL-c through the LDL receptor pathway until the cell has obtained enough cholesterol to meet its physiologic needs. At that point, cells downregulate the LDL receptor. Studies of fibroblasts have shown that the amount of LDL-c required for metabolism is approximately 2.5 mg/dl. Knowing that there exists a 10:1 gradient between plasma and interstitial LDL-c, an extrapolation can be made that a plasma LDL-c level of 25 mg/dl is sufficient for cell metabolism [18].

Anthropologic studies show that in the natural state the human diet consisted of foods high in lean protein, polyunsaturated fats, and fiber and that our hunter-gatherer ancestors had low rates of atherosclerotic disease relative to contemporary populations [4]. Studies of our evolutionary predecessors, such as baboons, demonstrate that baseline very-low-density lipoprotein cholesterol (VLDL-c) and LDL-c levels are lower than those of modern humans, in the 40–50 mg/dl range. When groups of baboons are fed a human diet, their LDL-c levels increase significantly compared to baboons feeding from their natural environment [5]. Even though hunter-gatherer populations likely received two-thirds of their energy intake from animal-derived sources, differences in the composition of animals fats, with higher levels of monounsaturated, polyunsaturated, and omega-3 fatty acids, likely

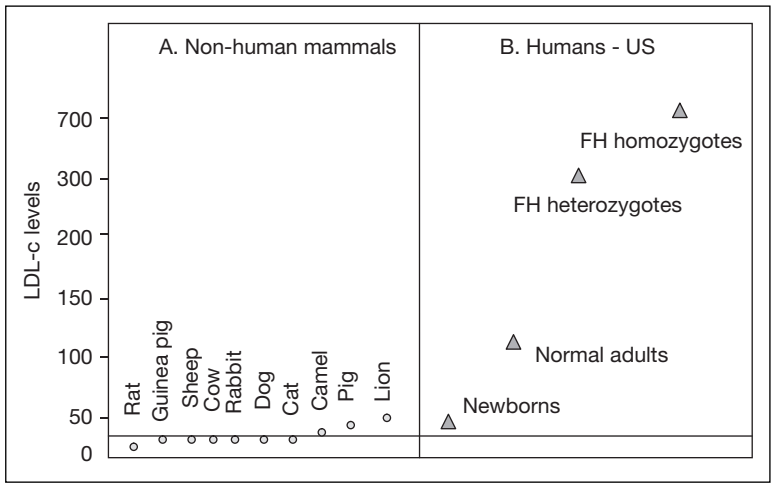

Figure 8.1 Variation of LDL-c levels amongst non-human and human mammals. The LDL-c levels for many non-human mammals (Panel A) are below 50 mg/dl. Human levels of LDL-c also average less than 50 mg/dl at birth and then increase later in life (Panel B). Pathologically elevated LDL-c levels can be seen in familial hypercholesterolemia (FH) heterozygotes and homozygotes (Panel B).

led to more favorable blood lipid profiles [6]. These anthropologic data provide some guidance as to the optimal LDL-c level for our genetic composition (Figure 8.1).

Two genetic polymorphisms provide additional insight into the long-term impact of very low LDL-c levels on the risk for developing CHD. Hypobetalipoproteinemia is a condition defined genetically by a variety of gene mutations, such as apolipoprotein genotype 2/3 and truncation of apolipoprotein B, and clinically as a baseline LDL-c of less than 75 mg/dl. Hypobetalipoproteinemia is associated with increased longevity and resistance to the development of atherosclerotic disease [19]. Another set of loss of function mutations affect the proprotein convertase subtilisin/kexin type 9 serine protease (*PCSK9)* gene, which leads to lower serum levels of LDL-c. When PCSK9 is overexpressed, hepatic cells have lower levels of LDL-c receptors and, thus, are less able to clear LDL-c from the plasma. When a *PCSK9* mutation prevents its expression, hepatocytes have increased levels of LDL-c receptors and plasma LDL-c levels fall. Two nonsense mutations of the *PCSK9* gene (426C→G and 2037C→A) led to a 28% reduction in LDL-c and a subsequent 88% reduction in the risk of CHD disease compared to individuals without the mutation [20]. These two groups of patients support the conclusion that lifetime exposure to low serum levels of LDL-c are associated with increased longevity secondary to reduced risk for CV morbidity and mortality.

IS LOWER REALLY BETTER?

While the prospective observational cohort data provide the background for understanding the relationship between LDL-c and risk for CHD, clinical trial data show that lowering LDL-c through lifestyle modification and/or pharmacologic intervention improves outcomes and that this benefit extends even to patients with the lowest baseline levels of LDL-c. In patients with CHD and a total cholesterol of at least 214 mg/dl, lowering LDL-c by 35% with simvastatin reduces the risk of death by 30% [21]. Moreover, the effectiveness of aggressive lipid lowering can be substantial. When compared to percutaneous coronary intervention and usual-care lipid lowering, the Atorvastatin vs Revascularization Treatment study

evaluating aggressive lipid lowering with atorvastatin 80 mg daily demonstrated a 36% decrease in ischemic events [22]. While this study only included patients whose baseline LDL-c was at least 115 mg/dl, the aggressive lipid-lowering group reached an LDL-c of 77 mg/dl compared to 119 mg/dl in the percutaneous coronary intervention group, without any increase in serious adverse events in the atorvastatin 80 mg group. These studies set the stage for subsequent investigations that both more broadly define high-risk individuals and more aggressively treat patients even when their baseline LDL-c is low.

The Heart Protection Study (HPS) evaluated lipid lowering in a high-risk population defined as having coronary artery disease (CAD), other occlusive arterial disease, or diabetes mellitus [7, 23]. The group receiving simvastatin 40 mg daily had a 12% reduction in all-cause mortality, largely driven by a decrease in coronary and vascular deaths. Interestingly, even the subgroup whose baseline LDL-c was less than 116 mg/dl benefited from simvastatin therapy with a decrease in LDL-c to approximately 70 mg/dl and an event rate similar to all of the patients in the treatment arm of the study who received simvastatin 40 mg. There was no significant increase in adverse outcomes in the group assigned to simvastatin therapy. Statin therapy in diabetics has also been shown to be beneficial in the Collaborative Atorvastatin Diabetes Study (CARDS) which lowered LDL-c in patients with type 2 diabetes to 68 mg/dl at 6 months and was stopped early due to demonstrated benefit in the primary endpoints of time to first acute CHD event, coronary revascularization, or stroke [8, 23]. This study further supports the concept that the CV benefits of LDL-c lowering extend even to high-risk individuals who already have low baseline LDL-c, such as those with LDL-c values of 133 mg/dl and 118 mg/dl in HPS and CARDS, respectively.

The Antihypertensive and Lipid Lowering Heart Attack – Lipid Lowering Trial (ALLHAT-LLT) compared therapy with pravastatin 40 mg daily to usual care, defined as treatment for LDL-c at the discretion of the primary care physician, in older adults with hypercholesterolemia, hypertension, and at least one additional coronary risk factor [24]. While this study did not confirm the mortality benefit seen in the HPS, likely secondary to extensive statin drop-in in the placebo group and statin drop-out in the pravastatin group, the pravastatin group was only able to achieve a reduction of LDL-c to 104 mg/dl, a 16.7% decrease compared to usual care. In contrast, compared to control subjects, the HPS showed a 33% decrease in LDL-c to an average of 90 mg/dl. ALLHAT-LLT provided more support of the concept that adequate LDL-c reduction is necessary in order to achieve significant reductions in CV event rates.

The Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) evaluated hypertensive patients with at least three other CV risk factors (e.g., left ventricular hypertrophy, microalbuminuria, high total cholesterol to HDL-c ratio, family history of premature CHD, etc.), but non-fasting total cholesterol of less than about 250 mg/dl. At enrollment, both the treatment and placebo groups had LDL-c levels of approximately 132 mg/dl. The treatment group was given atorvastatin 10 mg daily. The study was stopped after a mean follow-up of 3.3 years because of a 36% decrease in major coronary events in the atorvastatin group which met the pre-specified level of significance for stopping the trial early. At trial closure, the atorvastatin group had a mean LDL-c of 91 mg/dl compared to 128 mg/dl in the placebo group. While inclusion criteria for ASCOT-LLA sought patients whose physicians did not intend to pharmacologically treat their cholesterol levels, the study shows that benefit can be derived from even moderate lipid lowering.

Significant LDL-c lowering is associated with changes in rates of coronary atheromatous plaque progression. In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, patients with established CAD were randomized to therapy with either atorvastatin 80 mg/day or pravastatin 40 mg/day. These treatment groups attained mean LDL-c levels of 79 and 100 mg/dl, respectively. Serial intravascular ultrasonography demonstrated that patients in the atorvastatin group experienced net stabilization of coronary plaque growth, while those in the pravastatin group experienced significant progression of

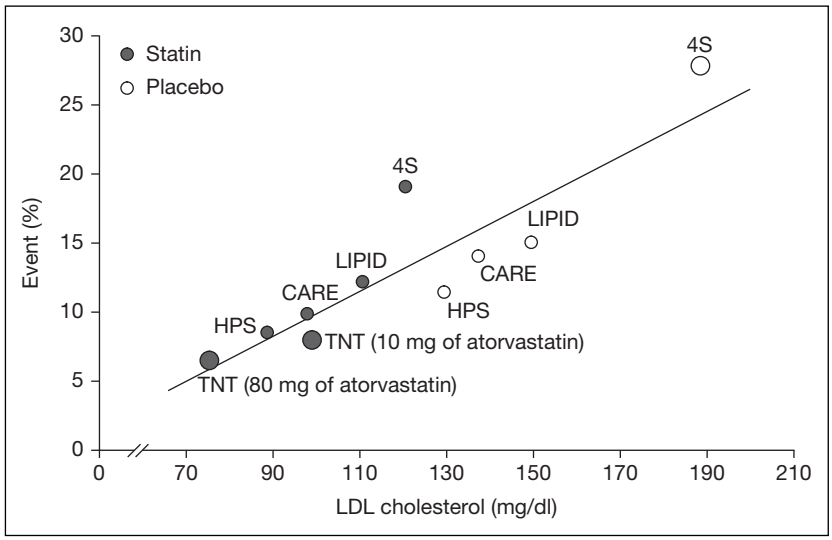

Figure 8.2 Cardiovascular event rates compared to LDL-c levels in secondary-prevention statin therapy studies. 4S = Scandinavian Simvastatin Survival Study [21]; CARE = Cholesterol and Recurrent Events Trial [49]; HPS = Heart Protection Study [7]; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease [50]; TNT = Treating to New Targets [9]. Event rates for HPS, CARE, and LIPID are for death from CHD and non-fatal myocardial infarction. Event rates for 4S and the TNT Study also include resuscitation after cardiac arrest. To convert values for LDL cholesterol to mmol/l, multiply by 0.02586. Adapted with permission from [9].

their disease [25]. A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) also evaluated changes in atheromatous plaque volume in response to statin therapy. In this trial, patients with CAD were treated with rosuvastatin 40 mg/day. Patients achieved a mean LDL-c of 60.8 mg/dl and experienced significant regression of coronary atheroma with a mean change in percent atheroma volume of −0.98% (P <0.001 vs baseline), a mean change in atheroma volume in the most diseased 10-mm subsegment of −6.1 mm^3 (P <0.001 vs baseline), and a mean change in total atheroma volume of −14.7 mm^3 (P < 0.001 vs baseline) [26].

The Treating to New Targets (TNT) study sought to more definitively address the lowest level of LDL-c at which CV benefits still accrue [9]. By treating patients with CAD whose baseline LDL-c was less than 130 mg/dl with either atorvastatin 10 mg or 80 mg, serum LDL-c levels of 77 mg/dl and 101 mg/dl, respectively, were achieved. When comparing high- and low-dose atorvastatin therapy, the more intensively treated group of patients experienced an additional 22% relative risk reduction in major CV events. The only significant adverse event difference between the groups was a higher rate of persistent liver enzyme elevations in the high-dose atorvastatin group of 1.2% compared to the low-dose atorvastatin group with a rate of 0.2% (P <0.001). Subgroup analyses of the TNT trial have shown similar benefit in patients with diabetes and with the metabolic syndrome [27, 28]. Moreover, even when stratifying TNT patients according to achieved LDL-c, there was a significant trend for decreased CV events as LDL-c fell to lower and lower levels, including the group with LDL-c values less than 64 mg/dl [10]. Thus, TNT demonstrated that compared to patients in the low-dose atorvastatin group, who nearly achieved ATP III goals of an LDL-c less than 100 mg/dl, those patients who achieved even lower LDL-c levels experienced even greater reductions in CV risk (Figure 8.2).

A higher risk group, those patients with a history of a known acute MI, was studied in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial comparing high-dose atorvastatin of 80 mg/dl to usual-dose simvastatin of 20 mg/dl [29]. The study did not meet its pre-specified primary endpoint; however, the high-dose atorvastatin group only reached a mean LDL-c level of 81 mg/dl, higher than that seen in other studies, while the simvastatin group reached an LDL-c of 104 mg/dl. The study did show a significant reduction in secondary endpoints, including decreases in non-fatal MI by 17% ($P = 0.02$), peripheral arterial disease by 24% ($P = 0.02$), and coronary revascularization by 23% ($P < 0.001$).

Multiple studies have demonstrated benefit with intensive lipid lowering in patients with a recent acute coronary syndrome (ACS) [11, 12, 30]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study, the patients randomized to either atorvastatin 80 mg/day or pravastatin 40 mg/day achieved serum LDL-c levels of 62 mg/dl and 95 mg/dl, respectively [11]. Lower LDL-c on treatment was associated with significant reductions in both the primary and secondary composite CV endpoints of this trial. A subgroup analysis of patients with pre-treatment LDL-c values of less than 125 mg/dl did not reach statistical significance for the primary endpoint; however, the study was neither designed nor powered to evaluate this. One subgroup of interest from PROVE IT-TIMI 22 were patients who achieved an LDL-c of less than 40 mg/dl and had improved outcomes with a hazard ratio of 0.61 (95% confidence interval [CI] 0.40–0.91) compared to patients with an on-treatment LDL-c of 80–100 mg/dl [13]. A similar study assessing ACS was the Z phase of the A to Z trial, which was the second of two over-lapping phases of a trial in ACS patients comparing an aggressive strategy of simvastatin 40 mg/day for 30 days followed by an escalation to 80 mg/day to a less aggressive strategy of placebo for 4 months followed by simvastatin 20 mg/day. The Z phase of the A to Z trial showed that the aggressive strategy achieved an LDL-c of 63 mg/dl at 8 months, though the results only showed a trend toward benefit on the primary CV endpoint of major adverse CV events compared to the less aggressive strategy. The subgroups assessing patients whose baseline LDL-c was 100–130 mg/dl and less than 100 mg/dl both showed similar trends with reductions in the primary outcome of 13% and 17%, respectively, with neither reaching statistical significance [12].

A meta-analysis of 14 major statin lipid-lowering trials was performed by the Cholesterol Treatment Trialists' (CTT) Collaborators [3]. Statin therapy reduced all-cause mortality by 12% per mmol/l reduction in LDL-c (approximately 39 mg/dl). In the subgroup analysis of patients whose baseline LDL-c was less than 100 mg/dl, there was a relative risk (RR) in major coronary events of 0.75 (95% CI 0.56–1.01) with statin therapy. This meta-analysis serves as the key summarizing study demonstrating the mortality benefit of LDL-c lowering and that this benefit extends to patients whose baseline LDL-c levels already meet guideline-based targets.

CAN THE LDL-c BE DRIVEN TOO LOW?

While higher levels of cholesterol are associated with increased CV events, some studies have raised the question of whether low levels of cholesterol may also be linked to higher overall mortality [31]. This raises the provocative question as to whether there is a 'J-curve,' such that at lower cholesterol levels, total mortality increases due to disease processes such as cancer or intracerebral hemorrhage [32–37]. A second, though no less important, question is whether the aggressive pharmacologic therapy necessary to achieve very low LDL-c levels may result in adverse effects that negate the benefit of the LDL-c lowering [38]. (Table 8.1). The potential adverse events linked to aggressive and presumably excessive lowering of LDL-c fall into four major categories: hemorrhagic stroke, cancer, musculoskeletal abnormalities, and hepatic dysfunction [39–42].

Table 8.1 Patient characteristics likely to enhance safety of high-dose* statins based on eligibility criteria for subjects participating in endpoint clinical trials, adverse event reporting and package inserts†

Patient characteristics‡	*Safety criterion or characteristic/medication to avoid*
Age	<75 years§
Body size	Use with caution if small body frame, especially if female patient
	If frail, evaluate appropriate use in terms of life expectancy and goals of care
Race/ethnicity	Asian: rosuvastatin starting dose 5 mg due to decreased clearance
Statin use	Prior statin use
	No history of statin intolerance
Hepatic function	No active hepatic disease
	ALT and AST $\leq 2 \times$ ULN
Renal function	Creatinine $\leq 1.5 \times$ ULN
	Glomerular filtration rate >60 ml/min/1.73 m^2
	No history of nephrotic syndrome
	Discontinue before intravenous dye administration
Thyroid function	TSH in normal range
Muscle function	CK $< 3 \times$ ULN unless explanation
	Use with caution if history of muscle disease
	Discontinue before strenuous exercise (e.g. marathon)
Immune function	No chronic immunosuppressive therapy (especially cyclosporine)
Cytochrome P450 inhibitors	No concomitant use of:
	Macrolide antibiotics (especially erythromycin and clarithromycin)
	Antiviral drugs (especially HIV protease inhibitors)
	Systemic azole antifungals (itraconazole and ketokonazole)
	Verapamil (simvastatin)
	Diltiazem (lovastatin, atorvastatin)
	Amiodarone (simvastatin)
	Nefazadone
	Grapefruit juice >1 quart/day
Other lipid-lowering therapy¶	No fibrates (especially gemfibrozil)
	No niacin?
Alcohol intake	<2 drinks per day
	Avoid if alcoholism present
Left ventricular ejection fraction	≥30%
Intercurrent illness, surgery, or trauma	If severe illness, major surgery, or major trauma, discontinue lipid-lowering medications until recovered
Multiple comorbidities or medications	Evaluate appropriate use in terms of life expectance and goals of care

*Atorvastatin 80 mg, simvastatin 80 mg, rosuvastatin 40 mg; †the risk–benefit ratio should be carefully evaluated for patients exceeding 1 or more criterion; patients should be carefully monitored for musculoskeletal and/or hepatic toxicity. ‡Exclusion criteria for clinical trials also included blood pressure <160/<100 mmHg, hemoglobin A_1C <8.5%, hemodynamically important valvular heart disease, and cancer dignosis other than non-melanoma skin cancer less than 5 years ago; the relationship of these characteristics to increased risk of serious adverse muscle effects has not been established, but hypertension and diabetes were associated with an increased risk of serious hepatic adverse effects in one study [11]; §age up to 80 years at baseline in IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering); others have recommended age <70 years as cut-point for safety [65]; ¶other concomitant lipid-lowering therapies excluded from high-dose statin trials; limited safety data with higher doses of statins although reported rates of rhabdomyolysis with moderate-dose statins used in combination with niacin are much lower than when statins are used with fibrates.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; HIV = human immunodeficiency virus; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.
With permission from [38].

HEMORRHAGIC STROKE

The concern regarding hemorrhagic stroke dates back at least to the Multiple Risk Factor Intervention Trial (MRFIT) which showed that total cholesterol levels less than 160 mg/dl were associated with a two-fold increase in the risk of hemorrhagic stroke [43]. Subgroup analyses of PROVE IT-TIMI 22 and TNT, two of the studies that most aggressively treated LDL-c to low levels, both showed no increased risk of hemorrhagic stroke [13, 44]. The CTT meta-analysis also showed no difference between treatment groups in hemorrhagic stroke; moreover, there was a significantly decreased rate of ischemic stroke [3].

CANCER

The MRFIT trial also suggested that a total cholesterol level less than 160 mg/dl was associated with increased risk of death from pancreatic and hepatic cancer and that an inverse relationship was found between serum total cholesterol levels and lung cancer, lymphoma, and leukemia [43]. The more recent Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial of pravastatin versus placebo in older adults showed an increase in new cancer diagnoses with a RR of 1.25 [95% CI 1.04–1.51] for pravastatin [45]. The authors of PROSPER interpreted the increase in new cancer diagnoses as inconsistent with the remainder of the studies and potentially due to play-of-chance. A meta-analysis of 23 statin treatment arms assessing safety showed an increase in newly diagnosed cancers that correlated specifically with lower LDL-c levels, but not with the degree of LDL-c reduction [46].

The findings in these three publications are discordant with the observations gleaned from the remainder of the large randomized controlled trials, which have shown no difference in cancer rates between statin-treated and placebo-treated patients. The CTT meta-analysis showed no evidence of increased cancer risk with lowering of LDL-c [3]. While limited data do show an increased cancer risk with significant LDL-c lowering, there may be confounders complicating an association that may not be causal, such as seen in patients with comorbid conditions leading to their low LDL-c.

MUSCULOSKELETAL ABNORMALITIES

The risk of rhabdomyolysis is quite low with statin therapy. Rates of rhabdomyolysis range from 0% to a high of 0.6% for simvastatin; however, most trials have had rates of less than 0.07% [38]. Myalgias are significantly more common with statin therapy than is the case for rhabdomyolysis. One retrospective analysis of pooled data from 49 atorvastatin therapy trials showed myalgia rates of up to 1.5% with atorvastatin 80 mg/day compared to a rate of 0.7% in the placebo arms [47]. This same analysis revealed that myopathy with serum creatine kinase elevations greater than 10 times the upper limit of normal without muscle symptoms had a rate of 0.06% with atorvastatin 80 mg/day compared to 0% in atorvastatin 10 mg/day and in placebo patients. The CTT meta-analysis did not show any significant increase in the rates of rhabdomyolysis with statin therapy [3].

HEPATIC DYSFUNCTION

When achieving LDL-c levels of less than 100 mg/dl, persistent hepatic transaminase elevations to more than three times the upper limit of normal were reported with a frequency of less than 1.3% with both high-dose atorvastatin and simvastatin [38]. The rate of liver enzyme elevations correlates with higher statin doses and not to the magnitude of LDL-c reduction *per se* [46]. Discontinuing or lowering the statin dose typically results in the return of elevated liver enzymes to normal.

THE RISK–BENEFIT RATIO

The benefit of LDL-c lowering has been clearly demonstrated into the range of 70 mg/dl. PROVE IT-TIMI 22 has shown LDL-c lowering into the low 60 mg/dl range to be beneficial, a finding supported by multiple subgroup analyses of the other large randomized clinical trials. Cholesterol is a necessary component of the cell membrane and a precursor for bile acids, steroid hormones, and vitamin D synthesis. Therefore, a lower limit to the benefit in LDL-c reduction likely does exist. However, that lower asymptote has yet to be defined. One review of the literature suggests that an LDL-c of 57 mg/dl for primary prevention and 30 mg/dl for secondary prevention would be sufficient to achieve a CV event rate of zero [48]. However, this suggestion comes from a secondary analysis of data and would need to be confirmed with prospective studies.

When reviewing the safety literature, the risks with very low LDL-c are minimal, with the exception of a potentially small increase in the risk of cancer. The main considerations are the adverse effects of statins or other lipid-lowering drugs [49, 50]. In general, statins are highly effective at achieving LDL-c levels at or below 70 mg/dl with minimal side effects. The main concerns are myalgias and hepatic transaminase elevations that increase in frequency at higher doses of these medications.

Thus, the clinician needs to engage in quantitative, global CV risk assessment. If a patient has a high absolute risk, then he or she will likely benefit from the relative risk reduction that accompanies decreasing LDL-c to very low levels. If not otherwise contraindicated and if prescribed in a monitored fashion, the benefits outweigh the adverse effects associated with lipid-lowering agents for these high-risk patients. This lowering of LDL-c must also be part of a larger treatment plan aimed at lessening the global risk profile of the patient.

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9

How should we approach the statin-treated patient with myalgia?

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BACKGROUND

The 3-hydroxy-3-methylglutaryl–CoA reductase inhibitors (statins) have repeatedly demonstrated 30% reductions in clinical cardiovascular endpoints with only minimal drug related adverse events [1, 2]. Over the past 2 decades, the use of these drugs has grown to over 100 million statin prescriptions per year, yet some estimates suggest that less than 50% of the patients who would benefit from statins are taking these drugs [3]. Some untreated patients are reluctant to take these drugs due to myopathic symptoms or due to reports in the media regarding myopathy. Physician and public concerns about statin myopathy were magnified with the withdrawal of cerivastatin from the market, secondary to its increased tendency to cause rhabdomyolysis. Although the statins have an impressive safety profile and a proven track record for reducing cardiovascular events, there is disproportionate public concern over the small potential for statin related side effects [4]. Musculoskeletal pain complaints are ubiquitous in patients both on and off statins, and the challenge to the physician is to present the patient with an accurate perspective of the risk of cardiovascular disease compared to that of a statin related adverse event.

This chapter will review terminology used to define myopathic complications and then discuss proposed mechanisms of myotoxicity. A discussion of the incidence, risk factors and clinical features of myopathy will then be presented. Finally, the evidence concerning prevention, monitoring, and treatment of myopathic patients will be discussed.

TERMINOLOGY

The ACC/AHA/NHLBI helped standardize the terminology used when discussing statin related muscle symptoms and disease. This set of definitions is the most widely used in the literature [5]. In this set of definitions, myopathy is a broad term for any muscle symptom or pathology, whereas myalgia refers to muscle symptoms without creatinine kinase (CK) elevation. Myositis refers to muscular symptoms with an elevation in CK and rhabdomyolysis is defined as muscle symptoms with marked CK elevation greater than 10 times the upper limit of normal with a creatinine elevation and the occasional presence of brown urine with urinary myoglobin (Table 9.1) [5]. Both the National Lipid Association (NLA) and the US Food and Drug Administration (FDA) have also used slightly different definitions for muscle

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Table 9.1 Muscle toxicity and rhabdomyolysis. Definitions from American College of Cardiology/American Heart Association/National Heart Lung Blood Institute Clinical Advisory [5]

Term	*Definition*
Myalgia	Muscle ache or weakness without CK elevation
Myopathy	Any disease of the muscle
Myositis	Muscle symptoms with increased CK levels
Rhabdomyolysis	Muscle symptoms associated with marked CK elevations, typically substantially >10 times upper limit of normal

CK = creatinine kinase.

complaints related to statins [6]. These organizations mainly differ in their definitions of rhabdomyolysis and what degree of CK elevation constitutes myopathy. The FDA defines rhabdomyolysis as CK >50 times upper limit of normal or >10 000 IU/l with renal compromize while the NLA Safety Task Force on statins has defined rhabdomyolysis as CK >10 000 IU/l or 10× the upper limit of normal plus an elevation in serum creatinine requiring medical intravenous (IV) hydration therapy. Most of the arbitrary nature of these definitions stems from the fact that rhabdomyolysis is a clinical diagnosis and that currently there is no adequate confirmatory urine or blood test. There is a need for a more objective and consistent definition that can be used clinically and in research studies. Throughout this review the term myopathy will be used as a broad term that includes the entire spectrum of muscle related side effects including myalgia, myositis and rhabdomyolysis, and for the sake of clarity, the ACC/AHA/ NHLBI terminology will be used for all statin related muscle disorders.

PUTATIVE MECHANISMS OF MYOTOXICITY

The mechanisms of statin-induced myopathy have not been determined; however, mechanisms have been proposed and require further elucidation. One proposed mechanism of statin myotoxicity is a deficiency of ubiquinone also known as co-enzyme Q10 (Co-Q10), which is a product of the HMG-CoA reductase pathway (Figure 9.1) [7]. Co-Q10 is an isoprenoid that plays a key role in the electron transport chain, and a reduction in this coenzyme could cause abnormal mitochondrial respiratory function. However, this theory has several limitations. Several studies in humans and animals have shown that statin treatment may decrease serum Co-Q10 levels, but myocyte Co-Q10 levels have not been consistently shown to decrease and in some instances may increase [8, 9]. In an *in-vitro* human study, cerivastatin induced myocyte apoptosis, but this did not correlate with Co-Q10 levels; furthermore, co-administration of cerivastatin with mevalonate prevented apoptosis but did not increase Co-Q10 levels [10, 11].

Another proposed mechanism of myopathy is reduced cholesterol levels, which may result in alterations in myocyte membrane cholesterol content [12]. However, two key findings argue against this mechanism: 1) myotoxicity does not occur *in vitro* when cholesterol is lowered by inhibiting squalene synthetase (Figure 9.1), a distal enzyme in the cholesterol synthesis cascade [13]; and 2) inherited disorders of the distal cholesterol synthetic pathway result in reduced cholesterol levels without associated clinical myopathy (Figure 9.1) [14].

Most recently it has been proposed that statins may induce myopathy by depleting key isoprenoids that control myofiber apoptosis. Isoprenoids are lipids that are a product of the HMG-CoA reductase pathway [15]. Isoprenoids are linked to proteins by either farnesylation

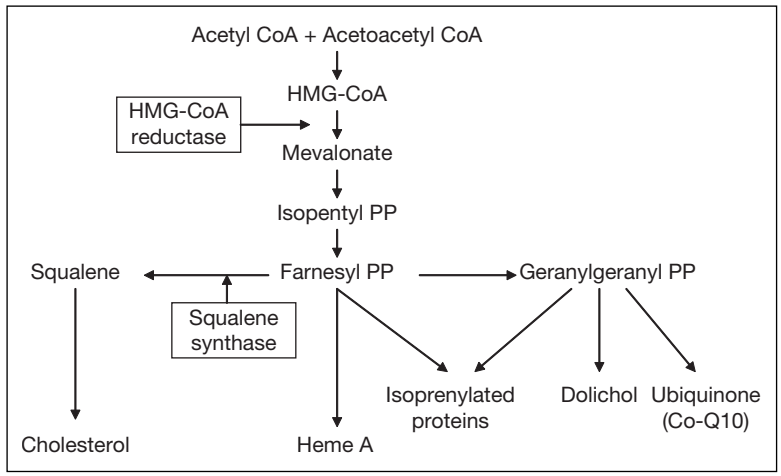

Figure 9.1 Cholesterol biosynthetic pathway. CoA = coenzyme A; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; PP = pyrophosphate. With permission from [7].

or geranylgeranylation. A reduction in the farnesylation or geranylgeranylation of proteins is thought to increase levels of cytosolic calcium which activates a cascade of events leading to the activation of capsase-3, a proteolytic enzyme that has a central role in cell death (Figure 9.2) [15]. Additional support for the apoptosis theory includes studies with vascular smooth muscle cells that demonstrated statin-induced apoptosis is prevented by supplementation with isoprenoids including farnesyl pyrophosphate and geranylgeranyl pyrophosphate [16]. Finally, it has been suggested that in some cases of myopathy there may be an immunologic mechanism. The exact mechanism is uncertain but may involve a statin-induced stress response in the endoplasmic reticulum, resulting in upregulation of major histocompatibility complex-1 (MHC-1) expression and antigen presentation by muscle fibers [17].

INCIDENCE

Although the incidence of statin-induced myopathy is low, the rate of myopathy in clinical trial populations is artificially depressed because high-risk patients for statin complications tend to be excluded from clinical trials. A systematic review of 20 clinical trials by Law *et al*. [18] revealed a myopathy and minor muscle pain incidence of 195 cases (95% confidence interval [CI], −17 to 27) per 100 000 patient-years (Table 9.2) and a minor muscle pain incidence of 190 cases (95% CI −38 to 410) per 100 000 patient-years. Myopathy was defined as muscle pain, or weakness sufficient to consult a physician or stop taking medications, while minor muscle pain was defined as muscle pain or weakness elicited on a questionnaire yet insufficient to consult a physician or stop medication. The incidence of rhabdomyolysis incidence was 1.6 cases (95% CI −2.4 to 5.5) per 100 000 patient-years.

Data from the FDA adverse events reporting system (AERS) indicate a rhabdomyolysis incidence of 0.70 (95% CI 0.62–0.79) per 100 000 patient-years [18]. Although the AERS database is an important tool, adverse events are reported on a voluntary basis, thus resulting in possible under-reporting of the true incidence.

To obtain 'real world' data in patients more representative of clinical practice, it is also useful to look at databases from epidemiological cohort studies or from closed systems such as US managed care organizations for additional assessments of the incidence of myopathy. Based on a review of 2 cohort studies the incidence of rhabdomyolysis was 3.4 (95% CI

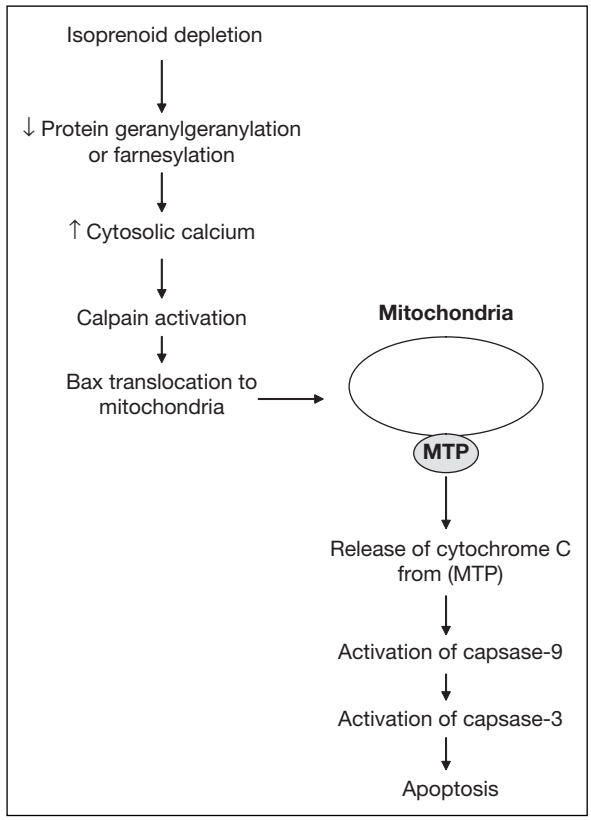

Figure 9.2 Putative role of isoprenoid depletion in statin-induced myopathy [15]. MTP = mitochondrial transition pore. With permission from [15].

Table 9.2 Incidence of muscle related side effects occurring in clinical trial participants [18]

	Minor muscle pain[3]	*Myopathy*[4]	*Rhabdomyolysis*[5]
Incidence per 100 000 person-years[1]	5150	97	4.4
Placebo corrected[2] per 100 000 person-years	190	5	1.6

[1]100 000 person-years = 100 000 people treated for 1 year with a statin
[2]Placebo corrected = incidence in treatment group minus incidence in placebo group
[3]Muscle pain tenderness or weakness not severe enough to stop statin
[4]Muscle pain tenderness or weakness severe enough to stop statin
[5]CK >10 times upper limit of normal or >2000 U/l

1.6–6.5) per 100 000 patient-years with a mortality rate of 0.3 per 100 000 patient-years [19, 20]. The incidence of myopathy defined as diffuse muscle symptoms with CK elevations was 11 (95% CI 4–27) per 100 000 patient-years. Although myalgias are the most common side effect of statin therapy and the most likely to reduce patient adherence, prospective

data on the incidence of myalgia in the community setting are quite limited. Two prospective observational trials, however, suggest a myalgia rate of 10–15% [21, 22].

CLINICAL FEATURES

The clinical presentation of statin-induced myopathy ranges from complaints of mild fatigue to fulminant rhabdomyolysis requiring hospitalization. Frequent symptoms include myalgia, weakness, low back and proximal muscle pain or generalized aching. Some patients have reported tendon pain and nocturnal cramping of muscles. It is important to note that in one study of statin-induced rhabdomyolysis, fatigue (74%) was almost as common as muscle pain (88%) for the chief complaint [23].

The temporal relationship between initiation of statin therapy and onset of symptoms is poorly defined as is the time between cessation of statin therapy and resolution of symptoms. In the Prediction of Muscular Risk in Observational Conditions (PRIMO) Study, 7924 hyperlipidemic patients treated with high-dose statin therapy were enrolled in a 12-month prospective observational study. Muscle symptoms were reported by 832 patients (11%). The median time of myalgia onset was 1 month following initiation of statin therapy but could occur at any time. Muscular pain prevented performance of daily activities in 315 patients (4% of total patients participating in the study) and 31 patients (0.4% of all patients participating in the study) were confined to bed [21]. In a smaller retrospective study at the University of Wisconsin, 13 years of inpatient and outpatient data were reviewed and 45 patients with statin-induced myopathy were identified. The long-term outcomes of patients with statin-associated myopathy or rhabdomyolysis were analysed [24]. Eight of these patients met the criteria for a diagnosis of rhabdomyolysis, while the remaining had mild to moderate elevation in CK levels with symptoms. The median duration of statin therapy before symptom onset was 6.3 months with a range of 1 week to 4 years and the duration of myalgia after cessation of statin was 2.3 months with a range of 1 week to 4 months. This study was limited by its small sample size ($n = 45$), and its retrospective observational study design. The patient population was from a tertiary care center, leading to referral bias as these patients were more likely to be different from those treated in a community setting.

RISK FACTORS

Identifying patients with an increased proclivity for statin-induced myopathy could allow clinicians to make more cost-effective decisions concerning monitoring and screening. Key variables include patient characteristics, and concurrent use of other medications that may alter the pharmacokinetics of statins. The clinician's choice of currently available statins may play a role, but comparative randomized trials in safety are limited.

Increased rates of myopathy have been documented in patients who perform sporadic heavy exercise. The elderly, particularly those with a small body mass index, are thought to have a higher incidence of myopathy. Heavy alcohol consumption and use of crack cocaine increase the risk of rhabdomyolysis (Table 9.3) [25]. Patients with biliary tract obstruction also have increased risk of statin myopathy as these drugs are primarily excreted via the bile. Finally, some have suggested that a significant number of patients with statin-induced rhabdomyolysis have underlying inherited metabolic muscle defects such as McArdle disease, carnitine palmityl transferase II deficiency, or genetic diseases of impaired fatty acid oxidation [26].

PHARMACOLOGIC PROPERTIES THAT INCREASE THE RISK OF MYOPATHY

Any variable that increases the serum concentration of a statin may increase the risk of myopathy. Myopathy rates seem to correlate best with statin doses, and appear independent of

Table 9.3 Putative risk factors for statin myopathy. With permission from [25].

Endogenous risks	*Exogenous risks*
Advanced age (>80 years)	Alcohol consumption
Hypertension	Heavy exercise
Diabetes mellitus	Surgery with severe metabolic demands
Small BMI	**Drugs affecting statin metabolism**
Renal disease	Fibrates
Hepatic disease	Nicotinic acid
Hypothyroidism	Cyclosporine
Genetic polymorphisms of CYP-450 isozymes	Azole antifungals
Metabolic muscle disease	Macrolide antibiotics
McArdle disease	Protease inhibitors
Carnitine palmityl transferase II deficiency	Nefazadone
Myadenylate deaminase deficiency	Verapamil
	Amiodarone
	Warfarin
	Grapefruit juice (>1 quart/day)

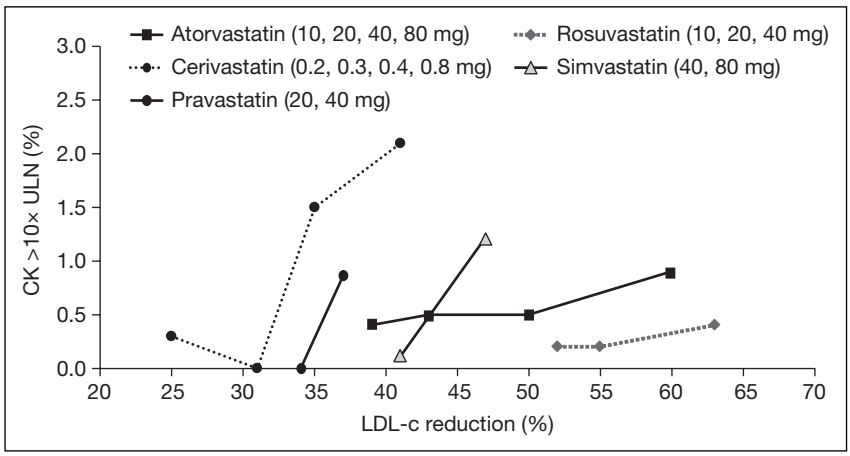

Figure 9.3 Incidence of myopathy and relationship to statin dosing and % LDL-c reduction. CK = creatinine kinase; LDL-c = LDL-cholesterol; ULN = upper limit of normal. With permission from [27].

LDL-c reduction [27] (Figure 9.3). Drug interactions can increase the risk of statin myopathy either by interfering with hepatic metabolism or gut wall transport. Gemfibrozil, a fibric acid derivative, has demonstrated one of the highest rates of rhabdomyolysis when combined with most statins. The two fibrates available in the US are gemfibrozil and fenofibrate. When combining with a statin, fenofibrate is the preferred drug since it has less risk of rhabdomyolysis compared with gemfibrozil. The risk of rhabdomyolysis when fenofibrate is combined with a statin is considerably lower, because of some differences in fibrate metabolism. Recently, it has been shown that statins undergo significant glucurondiation when metabolized, and if glucurondiation is inhibited then statin clearance is impeded and statin

Table 9.4 Pharmacologic characteristics of statins [26]

	Lovastatin	*Pravastatin*	*Simvastatin*	*Fluvastatin*	*Atorvastatin*	*Rosuvastatin*
CYP-450 pathway	CYP-3A4	None*	CYP-3A4> CYP-3A5	CYP-2C9> CYP-3A4> CYP-2C8	CYP-3A4	CYP-2C9 <10%, CYP-2C19
Bioavailability (%)	<5	18	<5	19–29	12	20
Absorption (%)	30	34	60–80	98	30	Rapid
Lipophilicity (%)	Yes	No	Yes	Yes	Yes	No
Half-life (h)	2.9	1.3–2.8	2–3	0.5–2.3	15–30	20.8
Urinary excretion (%)	10	20	13	5	2	10
Fecal excretion (%)	83	70	58	95	98	90

*Pravastatin metabolized by sulfation; h = hours

blood levels increase to potentially toxic levels [28]. Gemfibrozil competes with statin drugs for the hepatic microsomal enzymes uridine diphosphate glucuronosyl transferase (UGT) 1A1 and UGT 1A3, which are required for glucurondiation, while fenofibrate utilizes a different set of hepatic microsomal enzymes for glucurondiation and has a minimal effect on the metabolism of statins [28]. Thus, although fibrates alone can cause myopathy and rhabdomyolysis, gemfibrozil particularly, when combined with a statin, increases the rhabdomyolysis risk 10- to 15-fold [29].

The pharmacokinetic and pharmacodynamic properties of a statin may also play a role in the incidence of myopathy and rhabdomyolysis. Most statins are metabolized predominantly by the hepatic microsomal CYP-450 3A4 system with the exception of pravastatin (which undergoes sulfation), and rosuvastatin and fluvastatin which are metabolized to varying degrees via the CYP-450 2C9 system (Table 9.4) [26]. Concurrent administration of a statin with other drugs metabolized by the same CYP-450 isozyme can lead to higher levels of the statin and a greater risk for myopathy [30]. Many commonly prescribed drugs are substrates for the CYP-3A4 isozyme including macrolide antibiotics, azole antifungals, nondihydropyridine calcium channel blockers, and protease inhibitors. Fluvastatin and to a much lesser extent rosuvastatin are CYP-2C9 substrates and may interact with diclofenac, warfarin, and tolbutamide. Pravastatin and rosuvastatin are the most hydrophilic and are thought to be less likely to penetrate the myocyte membrane than more lipophilic statins; however these less lipophilic statins have an incidence of rhabdomyolysis equal to the other more lipophilic statins [6]. Choice of statin may be more important in moderate to severe chronic kidney disease, as severe renal insufficiency is an established risk factor for statin myopathy. Fluvastatin and atorvastatin are minimally excreted in the urine and may have a safety advantage in chronic kidney disease patients (Table 9.4) [31].

SCREENING AND MONITORING

The AHA/NHLBI Statin Advisory panel recommended measurement of CK prior to the initiation of therapy; however the NLA Statin Safety Assessment Task Force did not consider a baseline CK necessary, as this has not been shown to be cost-effective [5, 6]. A reasonable approach may be to include screening baseline CK values for high-risk groups such as patients with renal dysfunction, hepatic dysfunction or on known agents that cause myopathy (Table 9.5) [6]. CK elevations are common in the general population and are elevated in

Table 9.5 Recommendations to health professionals regarding muscles and statin safety. With permission from [6]

Patient monitoring
1. Routine CK levels in asymptomatic patients are not recommended
2. Obtain baseline CK in high-risk patients (renal dysfunction, liver disease, polypharmacy)
3. Consider CK levels in patients with muscle related symptoms
4. Rule out other etiologies in other symptomatic patients or those with elevated CK levels (hypothyroidism, trauma, seizures, infection, strenuous physical activity)
5. Exacerbating factors should be considered (concomitant medications and herbal remedies)

Management of muscle symptoms
1. If intolerable muscle symptoms develop discontinue statin regardless of CK levels and rechallenge only after patient becomes asymptomatic
2. If muscle symptoms are tolerable and CK elevation is mildly elevated (<10 times upper limit of normal) then statin may be continued and muscle symptoms can be used as guide to stop or continue treatment
3. If muscle symptoms are tolerable and CK elevation is moderate to severe then discontinue statin therapy and weigh risk and benefits
4. If muscle symptoms are tolerable and CK elevation is associated with elevated creatinine or need for IV hydration then discontinue therapy

certain ethnic groups such as African-Americans, and are frequently elevated with physical activity or strenuous muscle exertion.

Myalgia symptoms should be monitored during statin therapy and other preventive measures include using the lowest statin dose that achieves the lipid goal and discontinuing therapy prior to extensive exercise or lengthy surgery. The NLA Statin Safety Assessment Task Force does not recommend monitoring CK in asymptomatic patients. Moderate to marked (CK >10× ULN) CK elevations during statin therapy are rare, while mild CK elevations (<5× ULN) are more common and are often related to exercise [6].

The NLA recommends measuring CK in patients experiencing myalgia to aid the clinician in assessing the degree of muscle damage and in making a decision regarding discontinuation of therapy (Table 9.5). The evaluation of symptomatic patients should include a measurement of thyroid-stimulating hormone (TSH) and a careful review of concomitant medications and herbal remedies (e.g., red rice fungus) and assessment of recent physical activity patterns [32].

Statins should be discontinued in patients reporting intolerable myalgia regardless of CK level. The clinician may choose to rechallenge the patient with the same statin and reduce the dose or use a different statin. Patients with tolerable muscle complaints and no or mild CK elevation can be continued at current or reduced dosing at the clinician's discretion. In the patient with moderate or severe CK elevations or rhabdomyolysis then the statin should be discontinued [32].

MANAGEMENT OF MYOPATHY

The mainstay of therapy for myalgia and myositis is cessation of statin therapy. This is only considered after excluding known precipitants of myopathy, particularly hypothyroidism, strenuous physical activity, or use of alcohol or cocaine. For patients with clinically significant rhabdomyolysis the treatment requires hospitalization for intravenous hydration and possible alkalinazation of the urine to prevent precipitation of myoglobin in the renal tubules [33].

There is significant interest in the role of CoQ10 for prevention or management of myopathy. Statins inhibit the production of mevalonate which is necessary for the production of cholesterol and CoQ10. CoQ10 is critical for electron chain transport during oxidative

phosphorylation in the mitochondria. CoQ10 supplementation has been used with some success in patients with inherited mitochondrial disorders and primary enzyme deficiencies [34, 35].

Evidence supporting the use of CoQ10 for statin-induced myopathy consists of case reports and a few small studies. In a small trial with cancer patients, high-dose lovastatin (2–45 mg/kg/day for 7 days) was used for the treatment of solid tumors in 81 patients. CoQ10 100 mg qid was used in one arm of the study to prevent statin myopathy [7]. The 56 patients receiving CoQ10 had a reduction in the severity of myopathy. However, the study did not have a placebo comparison group. In another small study, 41 patients with myopathic pain on statins, were enrolled in a prospective randomized, blinded trial of vitamin E 400 IU versus treatment with CoQ10 100 mg daily for 30 days. During the study, statin brand and dose were unchanged. A serum CK level was measured and a validated analog scale for pain assessment performed at baseline and after 30 days of therapy. Pain improved in 18 of 21 patients in the CoQ10 group and only 3 of 20 in the vitamin E group ($P < 0.001$). This study was limited by its small size, lack of a comparator placebo group, and short time course [36]. Recently, in a double-blind, placebo-controlled study, 44 patients with a history of statin myalgia, were randomized to CoQ10 100 mg daily or placebo. CoQ10 supplementation did not improve the tolerability of simvastatin 10 mg when titrated to 40 mg/day over a 12 week time period. The study used intention-to-treat analysis and three primary endpoints were measured: 1) number of patients tolerating simvastatin at 40 mg/day; 2) number of patients remaining on simvastatin therapy at 12 weeks; and 3) change in myalgia score from baseline to end of treatment. The CoQ10 treatment group did not differ significantly from placebo when considering any of the endpoints [37].

There have been important inconsistencies in our understanding of the relationship between CoQ10 and statin-induced myopathy. Serum CoQ10 levels and intramuscular levels do not correlate. Intramuscular levels of CoQ10 are usually not reduced by low-dose statins (simvastatin 20–40 mg) [38]. For these reasons, and the lack of a definitive randomized controlled trial, the NLA does not recommend prophylactic therapy with CoQ10 [32].

MANAGEMENT OF DYSLIPIDEMIA AFTER MYOPATHY OR RHABDOMYOLYSIS

The NLA Muscle Expert Panel recommends discontinuing statin therapy if the patient has CK elevations ≥10 times the upper limit of normal or rhabdomyolysis [6]. Dietary therapy should be re-emphasized including daily supplementation of diet with plant stanols found in certain commercially available margarines and orange juice products. Resuming statin therapy is controversial and should only be considered in those patients at highest risk of cardiovascular disease, where the benefits of treatment outweigh any risks. If the patient and clinician decide to resume treatment with a statin, a lower dose may be considered in possible conjunction with ezetimibe. Treatment with ezetimibe alone may be an option; however, there are a few case reports of biopsy-proven myopathy with CK elevations on ezetimibe monotherapy [39]. A recent NLA report evaluated these sporadic cases of myopathy on ezetimibe, but concluded that definitive causation could not be determined, particularly without rechallenging the patient with ezetimibe [40]. Other lipid-lowering drugs including niacin, fibrates, and bile acid sequestrants may also be considered; however, there have been a few case reports of myopathy with fibrates when used as monotherapy [41]. In patients without major triglyceride abnormalities the bile acid sequestrants may be the safest choice.

A recent randomized controlled clinical trial reported the outcomes of patients with myopathy, randomized to several different lipid-lowering therapies. Patients were randomized to fluvastatin XL 80 mg daily, ezetimibe 10 mg daily, or both. After 12 weeks of therapy there was no difference in incidence of myalgia or CK elevations in the fluvastatin monotherapy group compared to either the combination therapy group or when compared to the ezetimibe monotherapy group. The results of this study suggest that agents with

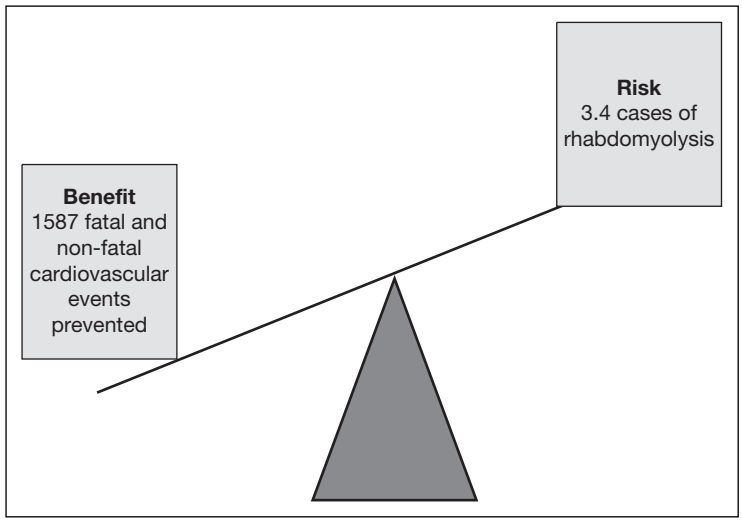

Figure 9.4 Risk–benefit analysis of treating 100 000 patients with a statin for 1 year. Benefit calculation based on data from 4S study [42]. Risk calculation based on data from [18].

lower myopathic potential, such as fluvastatin or ezetimibe can be safely used and tolerated when given to myalgia patients [42].

SUMMARY

Clinicians are still challenged by a small but significant number of patients who are not willing or not able to take a statin. Within the spectrum of myopathic complications, myalgia is the least severe yet most common and may have the largest impact on patient adherence to therapy. Randomized clinical statin trials, which tend to include healthier populations and exclude patients with prior statin myopathy, show a myalgia rate of 3%; however, observational studies in unselected patients suggests a much higher myalgia rate occurring in about 10–15% of patients taking a statin. Clinically significant rhabdomyolysis is at the other end of the myopathic spectrum and is rare (3 per 100 000 patient-years) but potentially lethal.

Patients who experience myalgia should have a serum CK level measured but pre-treatment CK evaluation is controversial and has not been proven to be cost-effective. Patients with CK values $\geq 10\times$ upper limit of normal, or with increases in serum creatinine, should stop statin therapy and secondary causes of CK elevation should be considered. Patients with myalgia and normal or mild increases in CK (<10 upper limit of normal) may require a statin holiday or a reduction in dose. Patients who have intolerable myalgia, and or moderate to high CK elevations after repeated trials of different statins may require alternative therapy including emphasis on diet, plant stanols, ezetimibe, niacin and bile acid sequestrants. Other lipid-lowering agents such as fibrates and niacin may be considered but fibrates also carry some risk of myopathy alone and in combination with a statin.

Small clinical trials and case reports have been published concerning CoQ10 as a potential treatment or prophylactic measure for statin myopathy. The NLA Muscle Expert Panel does not recommend CoQ10 until better evidence from randomized trials becomes available.

In conclusion, it is important to maintain perspective by looking at the risk of statin myopathy as it compares with the benefits of preventing atherosclerotic cardiovascular complications (Figure 9.4) [18, 43]. The statins play a critical role in the prevention of

atherosclerotic cardiovascular disease. These drugs have proven efficacy in reducing cardiovascular events and are well tolerated by the majority of patients. As in all treatment decisions, the potential benefits of therapy must outweigh the risks. In the case of statin therapy the benefit–risk ratio is overwhelmingly positive.

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Pleiotropic effects of statins and their relevance to cardiovascular outcomes

J. K. Liao

BACKGROUND

Elevated serum cholesterol levels are strongly associated with coronary atherosclerotic disease [1] and atherosclerosis is mediated, in part, by the uptake of modified low-density lipoprotein (LDL) into the vascular wall [2]. Since the conversion of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) to mevalonate is the early rate-limiting step in cholesterol biosynthesis, blocking the formation of mevalonate and subsequent cholesterol synthesis by statins has been proposed to be the predominant mechanism underlying the beneficial effects of statins. Indeed, therapeutic doses of statins potently reduce serum cholesterol levels in humans [3] and a number of large clinical trials have demonstrated that statins markedly decrease the incidence of cardiovascular (CV) events in hypercholesterolemic individuals [3–6].

There is increasing evidence, however, that statins may also exert effects beyond cholesterol lowering. These cholesterol-independent or 'pleiotropic' vascular effects of statins appear to involve improved endothelial function, enhanced stability of atherosclerotic plaques, decreased oxidative stress and inflammation, and inhibition of the thrombogenic response (Figure 10.1). The mechanism underlying statin pleiotropy involves inhibition of isoprenoids, the downstream products of mevalonate, which serve as lipid attachments for intracellular signaling molecules. In particular, inhibition of small GTPase family proteins, Rho, Ras, and Rac, whose proper membrane localization and function are dependent upon isoprenylation, may play an important role in mediating the pleiotropic effects of statins (Table 10.1). Thus, the pleiotropic effects of statins may contribute to many of the beneficial effects of statin therapy in CV disease (Table 10.2).

EVIDENCE FOR STATIN PLEIOTROPY IN CLINICAL TRIALS

Although reduction of low-density lipoprotein cholesterol (LDL-c) plays an important role in the beneficial effects of statins, several lines of evidence also implicate non-lipid mediated effects that may contribute to outcome benefits. In the recent Heart Protection Study (HPS) and Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), the relative risk reduction conferred by statin treatment was independent of the pre-treatment lipid levels [7, 8]. These large prospective trials raise the question whether individuals with coronary heart disease (CHD) could benefit from statin drugs independently of cholesterol levels. Furthermore, subgroup analysis of the West of Scotland Coronary Prevention (WOSCOP) and Cholesterol

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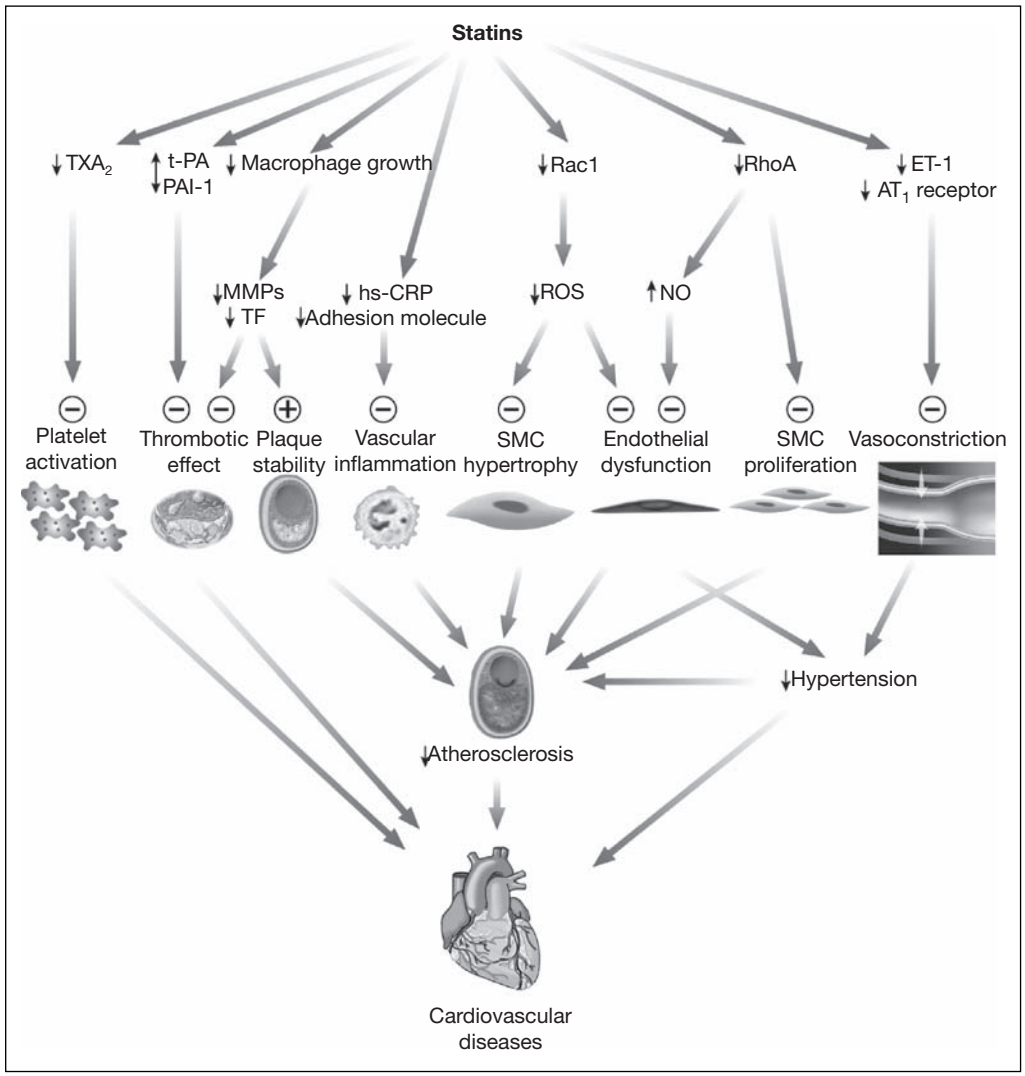

Figure 10.1 Pleiotropic effects of statins. Diagram illustrating various non-cholesterol effects of statins on vascular wall cells and platelets. AT_1 = angiotensin-1; ET-1 = endothelin-1; hs-CRP = high-sensitivity C-reactive protein; MMP = matrix metalloproteinase; NO = nitric oxide; PAI = plasminogen activator inhibitor-1; Rac1 = Ras-related C3 botulinum toxin substrate; RhoA = Ras homolog gene family, member A; ROS = reactive oxygen species; TF = transfer factor; t-PA = tissue plasminogen activator; TXA_2 = thromboxane A_2.

And Recurrent Events (CARE) studies indicate that, despite comparable serum cholesterol levels among the statin-treated and placebo groups, statin-treated individuals had significantly lower risks for CHD compared to age-matched, placebo-controlled individuals [5, 9]. Indeed, when the statin treatment group was divided into quintiles of percentage LDL-c reduction, it was found that there was no difference in the 4.4-year coronary event rate for quintiles 2 through 5 (LDL-c reductions of 23–41%). Hence, there was no apparent association between coronary event rate and the level of LDL-c reduction. Furthermore, meta-analyses of cholesterol lowering trials suggest that the risk of myocardial infarction (MI) in

Table 10.1 Rho GTPases in mediating statin pleiotropy

Effect	*Mediator*	*Benefit*
Reduction in activity of NAD(P)H oxidase	Rac1	Reduction of oxidative stress
Decrease in synthesis of endothelin-1	Rho	Improvement of endothelial function
Decrease in the expression of AT_1-receptor	Rho	Improvement of endothelial function
Decrease in the expression of tissue-type plasminogen activator	Rho	Reduction in thrombosis
Increase in the expression of plasminogen activator inhibitor-1	Rho	Reduction in thrombosis
Decrease in the expression of adhesion molecules	Rho	Reduction of inflammation
Increase in eNOS activity	Rho	Improvement of endothelial function
Increase in number and differentiation of circulating endothelial cells	Rho, Rac1	Increase in neovascularization and re-endothelialization
Inhibition of apoptosis	Rho, Rac1	Increase in cell survival

Table 10.2 Cholesterol-independent effects of statins

Effect	*Benefit*
Increased synthesis of nitric oxide Decreased synthesis of endothelin-1 Inhibition of LDL-c oxidation	Improvement of endothelial dysfunction
Reduced number and activity of inflammatory cells Reduced levels of C-reactive protein	Reduced inflammatory response
Reduced macrophage cholesterol accumulation Reduced production of metalloproteinases	Stabilization of atherosclerotic plaques
Inhibition of platelet adhesion/aggregation Reduced fibrinogen concentration Reduced blood viscosity	Reduced thrombogenic response

individuals treated with statins is significantly lower compared to individuals treated with other cholesterol-lowering agents or modalities despite comparable reduction in serum cholesterol levels [10]. Indeed, application of the Framingham risk score to WOSCOPS produced a coincidence between predicted and observed risk in the placebo group, but underestimated the benefit of the pravastatin group by 31% [11].

Despite these subgroup analyses of previous clinical trials suggesting that the beneficial effects of statins could extend to mechanisms beyond cholesterol reduction, data from a meta-analysis of lipid lowering trials, however, indicate that lipid modification alone accounts for the clinical benefits associated with statin therapy [12]. Indeed, the slope of the relationship between cholesterol reduction and mortality risk reduction was similar for statins and non-statins, while the mortality risk reductions realized over statin treatment periods of 2 years and longer were found to be a consequence of cholesterol reduction alone (Figure 10.2, *left panel*). However, this type of meta-analysis does not take into account the differences in terms of the length of the individual trials with respect to CV benefits and whether the overall or primary endpoint was being evaluated. For example, in the non-statin lipid lowering trials such as the Lipid Research Clinic – Coronary Primary Prevention Trial (LRC-CPPT) using the bile acid resin, cholestyramine [13], or the Program on the Surgical Control of the Hyperlipidemias (POSCH) using partial ileal bypass surgery [14],

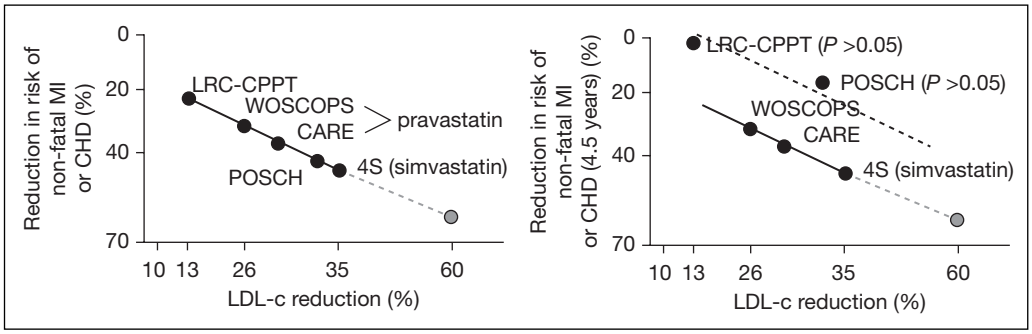

Figure 10.2 Relationship between LDL-c reduction and cardiovascular outcomes. (*Left panel*) Decrease in LDL-c (% reduction) is correlated with reduction in risk of non-fatal myocardial infarction (MI) or coronary heart disease (CHD) in statin (WOSCOPS, CARE, and 4S) and non-statin (LRC-CPPT and POSCH) trials. Note that the relationship (slope) holds between statin and non-statin trials suggesting that the beneficial effects of statins are likely due only to cholesterol lowering. (*Right panel*) Decrease in LDL-c (% reduction) is correlated with reduction in risk of non-fatal myocardial infarction (MI) or coronary heart disease (CHD) in statin (WOSCOPS, CARE, and 4S) and non-statin (LRC-CPPT and POSCH) trials after 4.5 years of treatment. Note that the non-statin trials (LRC-CPPT and POSCH; *dashed lines*) show less cardiovascular benefits than statin trials (WOSCOPS, CARE, and 4S), and no longer fall on the same slope (*solid line*). 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol And Recurrent Events; LRC - CPPT = Lipid Research Council - Coronary Primary Prevention Trial; POSCH = Program on the Surgical Control of the Hyperlipidemias; WOSCOPS = West of Scotland Coronary Prevention Study.

benefits from therapy were reported only after 7.4 and 9.7 years, respectively; whereas most of the statin trials showed benefits at much earlier time-points (e.g., within 5 years). Thus, if one compares the benefits after 5 years for all lipid lowering trials, one finds that the non-statin drugs or interventions do not provide the same level of risk reduction for a given decrease in LDL-c as do the statins (Figure 10.2, *right panel*). Indeed, the benefits of cholesterol lowering after ileal bypass surgery in the POSCH study were not realized at 4.5 years, despite significant LDL-c reduction of 34% within the first 3 months after the surgical procedure. These results suggest that the beneficial effects of statins occur rapidly and may not be entirely dependent on the degree to which cholesterol is reduced.

Another potentially important benefit of statin therapy is their anti-inflammatory effect. The involvement of inflammatory cells is critical to the progression of atherosclerosis. Markers of inflammation such as high-sensitivity C-reactive protein (hs-CRP) have been shown to add further prognostic information about patients at risk of CV disease who may benefit from statin therapy [15]. For example, increased concentrations of hs-CRP, an acute phase reactant that reflects varying degrees of systemic inflammation, are predictive of increased risk for CAD in apparently healthy men and women [16, 17]. In CARE [18] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) [15], changes in hs-CRP did not correlate with changes in LDL-c reduction, suggesting a cholesterol-independent effect of statins. Nevertheless, despite having low or normal LDL-c, patients who had elevated hs-CRP derived greater benefits from statin therapy than those with low hs-CRP levels [15].

The anti-inflammatory effects of statins were also observed in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study [19], where individuals achieving hs-CRP levels of less than 2 mg/dl and LDL-c of greater than 1.8 mmol/l (70 mg/dl) had similar CV event rates as individuals who achieved LDL-c values of less

than 1.8 mmol/l (70 mg/dl) but hs-CRP of greater than 2 mg/dl, suggesting that a lesser inflammatory intensity confers as much protection as lower cholesterol levels in patients with a history of acute coronary syndrome [20]. Similarly, in the Reversal of Atherosclerosis With Lipid Lowering (REVERSAL) trial, the benefits of CRP and total atheroma volume reduction in the coronary arteries by atorvastatin exceeded that of pravastatin, even at similar cholesterol reductions [21, 22]. Indeed, the differences in outcome reduction in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and A to Z acute coronary syndrome trials were not explained by the degree of LDL-c lowering or achieved LDL-c levels, but by reduction in CRP [23, 24]. Further studies, such as the ongoing randomized placebo-controlled Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [25], which is enrolling patients with modestly increased serum levels of LDL-c (<3.4 mmol/l or 130 mg/dl) and elevated hs-CRP (>2 mg/dl), are still needed to help address the question whether CRP is an additional non-lipid associated CV risk factor which can be modified by statin therapy.

Whereas myocardial infarction (MI) is closely associated with serum cholesterol levels, neither the Framingham Heart Study nor the Multiple Risk Factor Intervention Trial (MRFIT) demonstrated a significant correlation between ischemic stroke and serum cholesterol levels [26, 27]. An intriguing result of large clinical trials with statins, however, is the associated reduction in ischemic stroke [28]. For example, the recent HPS shows a 28% reduction in ischemic strokes in over 20 000 people with cerebrovascular disease or other high-risk conditions [29]. The proportional reductions in stroke were about one-quarter in all subgroups studied, including those aged over 70 years at entry and those presenting with different levels of blood pressure (BP) or lipids, even when the pre-treatment LDL-c was below 3.0 mmol/l (116 mg/dl). Indeed, in the recent Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, high-dose atorvastatin (80 mg/day) reduced the incidence of secondary strokes by 16% ($P = 0.03$) [30]. Thus, the findings of these large statin trials raise the interesting question of how a class of cholesterol-lowering agents can reduce ischemic stroke when ischemic stroke is not related to cholesterol levels *per se*. It appears likely that there are pleiotropic effects of statins, which are of some benefit in decreasing ischemic stroke rate. Some of these beneficial effects are attributed to the effects of statins on endothelial function.

EFFECTS OF STATINS ON VASCULAR FUNCTION

Acute plasma LDL apheresis improves endothelium-dependent vasodilatation [31] suggesting that statins could restore endothelial function, in part, by lowering serum cholesterol levels. However, in some studies with statins, the restoration of endothelial function occurs before there is a significant reduction in serum cholesterol levels, suggesting that there are additional effects on endothelial function beyond that which is gained from cholesterol reduction. Indeed, in patients, statin therapy has been found to rapidly improve vasomotor response to endothelium-dependent agonists [32], to enhance coronary blood flow [33], and to reduce surface expression of such adhesion molecules as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) [34]. The mechanism is due, in part, to a statin's ability to increase endothelial cell production of the vasodilator nitric oxide (NO) [11, 35]. Furthermore, statins have been shown to restore endothelial nitric oxide synthase (eNOS) activity in the presence of hypoxia [36] and oxidized low-density lipoprotein (ox-LDL) [11], circumstances which lead to endothelial dysfunction. Statins also increase the expression of tissue-type plasminogen activator (t-PA) [37] and inhibit the expression of endothelin-1, a potent vasoconstrictor and mitogen [38]. Statins, therefore, exert many favorable effects on the endothelium and attenuate endothelial dysfunction in the presence of known atherosclerotic risk factors.

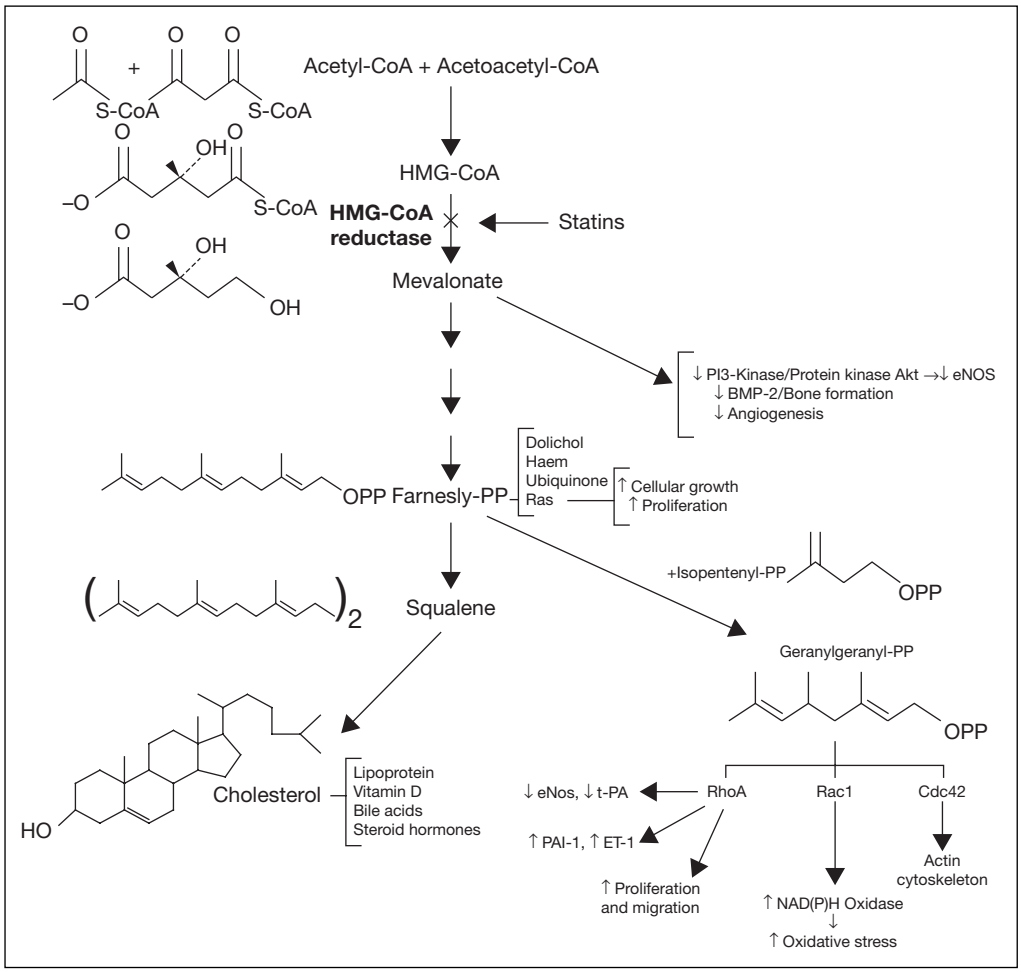

Figure 10.3 Biological actions of isoprenoids. Diagram of cholesterol biosynthesis pathway showing the effects of inhibition of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins. Decrease in isoprenylation of signaling molecules such as Ras, Rho and Rac leads to modulation of various signaling pathways. BMP-2 = Bone morphogenetic protein-2; eNOS = endothelial nitric oxide synthase; ET-1 = endothelin-1; PAI-1 = plasminogen activator inhibitor-1; t-PA = tissue-type plasminogen activator.

MECHANISMS UNDERLYING THE PLEIOTROPIC EFFECTS OF STATINS

STATINS AND ENDOTHELIAL FUNCTION

The realization that inhibition of HMG-CoA reductase by statins not only reduces cholesterol production, but also prevents the formation of various isoprenoid intermediates, has given rise to the concept of statin pleiotropism along the vascular wall (Figure 10.3). Farnesyl pyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), for example, serve as important lipid attachments for the post-translational modification of a variety of proteins, including the subunit of heterotrimeric G-proteins and small GTP-binding protein Ras, and Ras-like proteins, such as Rho, Rab, Rac, Ral or Rap. Protein isoprenylation allows the covalent attachment, subcellular localization, and intracellular trafficking of several

membrance-associated proteins. While the effects of statins on Ras and Rho isoprenylation are reversed in the presence of FPP and GGPP, respectively, the effects of statins on eNOS expression are only reversed with GGPP and not by FPP or LDL-c [39]. Indeed, direct inhibition of geranylgeranyl transferase or Rho leads to increases in eNOS expression [39, 40]. These findings are consistent with a non-cholesterol-lowering effect of statins and suggest that inhibition of Rho by statins mediates the increase in eNOS expression. Indeed, statins upregulate eNOS expression by prolonging eNOS messenger ribonucleic acid (mRNA) half-life but not eNOS gene transcription [39]. Since hypoxia, oxidized LDL, and cytokines such as tumor necrosis factor-α (TNF-α) decrease eNOS expression by reducing eNOS mRNA stability, the ability of statins to prolong eNOS half-life may make them effective agents in counteracting conditions which downregulate eNOS expression.

Furthermore, Kureishi *et al*. [35] have reported that statins can activate protein kinase Akt. The serine-threonine kinase Akt is an important regulator of various cellular processes including cell metabolism and apoptosis. Stimulation of receptor tyrosine kinases and G-protein-coupled receptors leads to the activation of PI 3-kinase, the products of which, namely 3′-phospholipids, induce the phosphorylation and activation of Akt. Indeed, inhibitors of PI 3-kinase such as wortmannin block the effects of statins on Akt activation [35]. Akt has been shown to modulate several targets, such as caspase-9 (an inducer of apoptosis or programmed cell death) and eNOS by phosphorylation. Consequently, activation of Akt by statins inhibits apoptosis and increases NO production in cultured endothelial cells. Therefore, in addition to stabilizing eNOS mRNA by inhibition of Rho, there is increasing evidence that activation of the PI 3-kinase/Akt pathway may also contribute to the endothelium-dependent effects of statins, although the precise mechanisms by which PI 3-kinase is activated by statins are not yet identified.

Since several vasoconstrictors counteract the vasodilating effect of NO, endothelial dysfunction and the development of atherosclerosis may also be attributed to the release of potent vasoconstrictors like endothelin (ET)-1 or angiotensin II (Ang II). Circulating concentrations and tissue immunoreactivity of ET-1 are increased in patients with severe atherosclerosis. ET-1 acts as a vasoconstricting and mitogenic agent. Exposure to ox-LDL leads to increased production and release of ET-1 [41], which promotes the neointimal proliferation of atherosclerotic lesions. Statins have been shown to inhibit pre-proET-1 mRNA expression in a concentration-dependent manner and to reduce immunoreactive ET-1 in bovine endothelial cells, a phenomenon which has been suggested to be mediated by Rho proteins [38, 42]. Furthermore, statins modulate the renin–angiotensin system by downregulating the expression of angiotensin receptor subtype 1 (AT_1) in a Rho A-dependent manner [43].

Another potential mechanism by which statins may improve endothelial function is through their antioxidant effects. For example, statins attenuate Ang II-induced free radical production in vascular smooth muscle cells (SMC) by inhibiting Rac1-mediated NAD(P)H oxidase activity and downregulating AT_1-receptor expression [44]. More recently, Wassmann *et al*. reported that atorvastatin reduced vascular mRNA expression of essential NAD(P)H oxidase subunits p22phox and nox1 by a mechanism which might involve the translocation of Rac1 from the cytosol to the cell membrane. Since NO is scavenged by reactive oxygen species (ROS), these findings indicate that the antioxidant properties of statins may also contribute to their ability to improve endothelial function. Furthermore, withdrawal of statin treatment in mice has been shown to impair endothelium-dependent relaxation by increasing vascular superoxide anion generation *via* a pathway involving the Rac-dependent activation of the gp91phox-containing vascular NAD(P)H oxidase [45]. ROS directly affects endothelial function, and the endothelium itself has also been shown to generate ROS [46].

STATINS AND INFLAMMATION

Atherosclerosis is a complex inflammatory process that is characterized by the presence of monocytes or macrophages and T lymphocytes in atherosclerotic lesions. Inflammatory

cytokines secreted by these macrophages and T lymphocytes can modify endothelial function, SMC proliferation, rates of collagen degradation, and tendency toward thrombosis. An early step in atherogenesis involves monocyte adhesion to the endothelium and subsequent penetration into the subendothelial space. Statins have been shown to reduce the number of inflammatory cells in atherosclerotic plaques and, therefore, possess anti-inflammatory properties. The mechanisms have yet to be fully elucidated, but may involve inhibition of adhesion molecule and cytokine (interleukin [IL] 6 and 8) expression, both of which are involved in the recruitment of inflammatory cells into the subendothelial space. In addition, a recent study has shown that statins can suppress the inflammatory response independently of HMG-CoA reductase inhibition by binding directly to a novel regulatory site of the β_2 integrin, leukocyte function antigen-1. This regulatory site serves as a major counter-receptor for ICAM-1 on leukocytes [47]. The mechanism of the anti-inflammatory properties of statins was further elucidated by Yoshida *et al*. [48] who recently demonstrated that cerivastatin reduced monocyte adhesion to vascular endothelium by decreasing expression of integrin adhesion molecules and actin polymerization through the inactivation of RhoA.

A clinical marker of low-grade systemic inflammation is hs-CRP, which is an acute phase reactant produced by the liver in response to pro-inflammatory cytokines such as IL-6. Elevated levels of hs-CRP have been shown to be predictive of increased risk for coronary artery disease (CAD) [49]. CRP could contribute to the development of atherosclerosis by binding to modified LDL within atherosclerotic plaques [50] and inhibiting eNOS [51, 52]. However, further studies are needed to more fully elucidate the role CRP plays in atherosclerosis.

STATINS AND RE-ENDOTHELIALIZATION AND ANGIOGENESIS

Stimulation of re-endothelialization or neovascularization is a therapeutic aim to reduce ischemia-induced tissue injury. Postnatal neovascularization is mainly attributed to angiogenesis, e.g., proliferation, migration, and remodeling of pre-existing endothelial cells. However, some studies recently demonstrated that bone marrow-derived circulating endothelial cells are also involved in this process. Circulating endothelial cells can be grown out of isolated $CD133^+$ or $CD34^+$ cells. Transplantation of these cells leads to postnatal neovascularization in the ischemic hind limb, augments ischemia-induced neovascularization *in vivo* [53], and even improves post-ischemic cardiac function [54].

Recent studies reveal that statins also promote vasculogenesis. Llevadot *et al*. [55] demonstrated *in vitro* that simvastatin induces the proliferation, migration, and survival of circulating endothelial cells. The signal pathway for this effect includes activation of protein kinase Akt, which was confirmed by functional blocking with dominant negative Akt overexpression. Dimmeler *et al*. [56] showed *in vitro* and *in vivo* that statins not only increase the number of circulating endothelial cells, but also induce their differentiation. This might be of clinical relevance since it has been recently reported by Walter *et al*. [57] that induction of these cells with statin treatment is associated with an accelerated re-endothelialization after carotid balloon injury.

In contrast, some studies report an anti-angiogenic effect of statins, which might be mediated by RhoA [58]. These conflicting effects of statins may be related to the dose used. Low doses of a statin may activate endothelial Ras and promote Akt and eNOS phosphorylation leading to an angiogenic effect, whereas higher statin doses are anti-angiogenic although they promote an increase in eNOS protein expression [59]. This suggestion remains controversial since high doses of statins have also been shown to be angiogenic [60]. Further studies are necessary to clarify these issues.

STATINS AND SMOOTH MUSCLE PROLIFERATION

The proliferation of vascular SMCs is a central event in the pathogenesis of vascular lesions, including post-angioplasty restenosis, transplant vasculopathy, and venous graft occlusion

[61]. Recent studies have shown that statins attenuate vascular proliferative disease such as transplant-associated arteriosclerosis [61]. In contrast to atherosclerosis, transplant-associated arteriosclerosis is more dependent upon immunological mechanisms as opposed to lipid disorders, although hypercholesterolemia exacerbates the immunologic process [62]. Inhibition of isoprenoid but not cholesterol synthesis by statins decreases platelet-derived growth factor (PDGF)-induced DNA synthesis in vascular SMCs [63, 64]. Treatment with statins decreases PDGF-induced Rab hyperphosphorylation and cyclin-dependent kinase (Cdk)-2, -4 and -6 activities. This correlates with increases in the level of Cdk inhibitor, $p27^{Kip1}$, without concomitant changes in $p16^{INK4}$, $p21^{Waf1}$, or p53 levels. These findings indicate that statins inhibit vascular SMC proliferation by arresting the cell cycle between the G1/S phase transition. It remains to be determined whether the upregulation of $p27^{Kip1}$ is responsible for the cell cycle arrest and whether there are differences between different statins in terms of $p27^{Kip1}$ activity.

Since the small GTP-binding proteins, Ras and Rho, require post-translational modification for membrane localization and activity and are implicated in cell cycle regulation, they are likely targets for the direct antiproliferative vascular effects of statins. Ras can promote cell cycle progression *via* activation of the MAP kinase pathway [65], whereas Rho causes cellular proliferation through destabilizing $p27^{Kip1}$ protein [66]. Interestingly, inhibition of vascular SMC proliferation by statins is reversed by GGPP, but not FPP or LDL-c [63]. Direct inhibition of Rho by *Clostridium botulinum* C3 transferase, which ADP-ribosylates and inactivates Rho, or by a dominant-negative Rho, mutant, increases $p27^{Kip1}$ and inhibits Rab hyperphosphorylation and SMC proliferation following PDGF stimulation. Taken together, these findings indicate that Rho mediates PDGF-induced SMC proliferation and that inhibition of Rho by statins is the predominant mechanism by which statins inhibit vascular SMC proliferation.

STATINS AND THROMBOLYSIS

Plasminogen activator inhibitor type-1 (PAI-1) is the major endogenous inhibitor of t-PA and it also plays a pivotal role in the regulation of fibrinolysis. High PAI-1 plasma levels and decreased levels of t-PA activity have been shown to be associated with CAD. PAI-1 mRNA has also been found in human atherosclerotic lesions underlining its role in the development of these disorders. There is increasing evidence from *in vitro* studies that statins positively affect the fibrinolytic system of cultured endothelial cells. In these studies, a decrease in PAI-1 and an increase in t-PA were observed after treating endothelial cells with statins [37, 67]. Statins may, therefore, interfere with the progression of the atherosclerotic plaque as well as with thrombotic events in hyperlipidemic patients independently of their ability to reduce plasma cholesterol, but further studies have to delineate the physiological significance of this.

SUMMARY

CLINICAL IMPLICATIONS

Although the reduction of plasma cholesterol levels by statins improves CV outcomes, statins may exert other cholesterol-independent effects on the vascular wall. These additional properties include beneficial effects on endothelial function and blood flow, decreasing LDL-c oxidation, enhancing the stability of atherosclerotic plaques, inhibiting vascular SMC proliferation and platelet aggregation, and reducing vascular inflammation. Because statins also reduce plasma cholesterol levels in normocholesterolemic subjects, it is often difficult, if not impossible, to separate the cholesterol lowering from the pleiotropic effects. Nevertheless, it is likely that both direct and indirect effects of statins play important roles in vascular protection. Further studies are needed to determine which of these effects are predominant, in terms of clinical outcome, in patients with low or average cholesterol levels.

Sorting out these issues will help physicians improve the outcomes of patients with CV disease without elevated cholesterol levels.

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11

An update on the 'rubber chicken' treatment of dyslipidemia: therapeutic lifestyle change and the alphabet soup of behavior modification

M. A. Denke

BACKGROUND

Take a walk anywhere in the United States and bear witness to the harsh reality: few Americans are participating in healthy lifestyles. The health risks of high-calorie, low fruit and vegetable intake, combined with an inactive lifestyle, apply not only to the primary consumer – consenting adults – but also to their children who are silently inducted into the choice. Unhealthy lifestyles have fundamental disregard for two laws of nature: (1) food choices confer health consequences; and (2) consuming more calories than you expend leads to weight gain.

Naming obesity as an 'epidemic' rather than a disease [1] holds hope for patients that a stealth virus, prion or gene is responsible for their weight gain. For most patients, behavior is the primary cause of the disease. Asking patients to accept personal responsibility for their choice of lifestyle will not make you a popular clinician. It will also take clinical skills. Helping a patient make positive lifestyle changes takes time, effort, and persistence. Recidivism rates are high. The pay-off – cardiovascular risk reduction including improvements in dyslipidemia – is well worth the effort, even if success is not achieved in every patient. Success can be enhanced using the proven strategies reviewed here.

THERAPEUTIC LIFESTYLE CHOICES: FLEXING THE RUBBER CHICKEN

Therapeutic lifestyle changes (TLC) are effective treatments of dyslipidemia (Table 11.1). The evidence is profound, reproducible, and irrefutable. Instituting these changes, however, is a challenge. Initiating conversation regarding lifestyle often brings humorous responses that deserve a vaudevillian 'bonk' with a rubber chicken:

'I'm following the *sea*food diet – I *see* the *food* and I eat it'
'Quit smoking – yeah, I'll do that *when I die*, I promise you.'
'Exercise doesn't make you live longer, it only makes it *seem* longer'

It isn't difficult to answer with humor: 'I want to see *less of you* on the next visit.'

The sad state of affairs is that most patients who really need to make lifestyle changes feel they 'don't have the time' to make these changes. Ask a patient why they can't make the

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Table 11.1 Lifestyle intervention

Lipid target	*Lifestyle intervention*	*Observational association with lipids*	*Proven benefits of intervention*
LDL	Smoking cessation	No consistent effects	No consistent effects
	Physical activity	No consistent effects	No significant effects observed in meta-analysis of aerobic exercise [2]
	Diet and weight loss	33% of non-shared variance in LDL-c in twins reared apart could be explained by calorie intake; 39% by total fat intake [3];	Dietary meta-analysis showed 10% saturated fat restriction produced a 19 mg/dl reduction in LDL-c, 7% restriction a 25 mg/dl reduction [4], with greater reductions when exercise was part of the intervention Participants in cardiac rehab programs lower LDL-c on average 20 mg/dl [5]
TG	Smoking cessation	No consistent effects	No consistent effects
	Physical activity	BMI correlates better to TG than physical activity scores [6]	Aerobic exercise meta-analysis in CHD patients found 19 mg/dl average reduction in TG [2] The greater the exercise intensity, the greater the TG lowering [7] with ranges from 5–38 mg/dl
	Diet and weight loss	21% of the genetic variance in TG in twins reared apart could be explained by calorie intake [3]	Dietary meta-analysis showed either 10% or 7% saturated fat restriction produced 15 mg/dl reduction in TG [4]
HDL	Smoking cessation	Non-smokers have a 3.5 mg/dl higher HDL than smokers [8]	Average increase HDL-c of 3.9 mg/dl; women have greater increases than men [9]
	Physical activity	Active persons have a 1.2 mg/dl higher HDL-c than inactive persons [8]	Meta-analysis of aerobic exercise trials in CHD patients show 3.7 mg/dl increase in HDL [2] The greater the exercise intensity, the greater the HDL raising [7] with ranges from 2–8 mg/dl
	Diet and weight loss	15% of non-shared variance inHDL-c in twins reared apart could be explained by calorie intake; 21% by total fat intake [3]; For every 1 kg/m^2 increase in BMI, there is a corresponding 0.7 mg/dl reduction in HDL [8]	Active weight loss causes transient reductions in HDL 2–5 mg/dl [10]; HDL levels following weight loss are 2–5 mg/dl higher if fat restriction is not a component of the diet [11]

BMI = body mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LDL-c = low-density lipoprotein cholesterol; TG = triglyceride.

Table 11.2 Addressing smoking cessation: the 5 A's. Adapted with permission from [12]

Ask about smoking status.
Advise all smokers to quit.
Assess willingness of smokers to quit.
Assist all patients motivated to quit in their attempt to quit; determine a quit date.
Arrange follow-up 1 week after agreed upon quit date.

time and prepare yourself for a nearly endless list of more urgent or important things to do. Many patients claim that as soon as these other priorities are managed, they will have time to devote themselves to making healthy choices. This is a fantasy! Lifestyle is a choice that every person makes every minute of every day. A poor lifestyle is not by default, it is a choice. Lifestyle choices have consequences.

As healthcare professionals, we must develop effective strategies for helping patients change. Lifestyle therapies typically include four goals: smoking cessation, achievement of ideal body weight, adoption of cholesterol-lowering diets, and participation in regular physical activity. Since physical activity, cholesterol-lowering diet, and ideal body weight are inextricably linked, only two interventions need to be initiated in the office:

1. Cessation of cigarette smoking; and
2. Adopting a healthy diet and healthy weight.

ALPHABET SOUP AND SMOKING CESSATION

From 1965 to 2006, cigarette smoking habits have had an impressive decline in prevalence, from 42.4% of the US population to 20.9% of the population. Putting these numbers into the day to day practice of medicine gives a different feel: at least one in five of your patients smoke! Smoking cessation is an excellent model for the problems inherent to all lifestyle choices. Smoking is a bad habit and prone to relapse and remission due to the complex interaction between biological, psychological, behavioral and social factors. Helping patients quit is not easy but it is not impossible.

The Agency for Healthcare Research and Quality has issued practice guidelines [12] for smoking cessation. The recommendations are often summarized as the '5 A's' approach which asks the clinician to address smoking during every patient encounter (Table 11.2). The guidelines are based on the evidence: the spontaneous quit rate among smokers ranges from 1 to 3%; 6–10% of smokers quit following physician advice to quit; 11–20% successfully quit following behavioral therapy programs; drug therapy may increase the percentage of successful quitting in motivated patients to 30%. Following the '5 A's' respects a clinician's time. Motivation is a key predictor of success, so assistance for quitting is not offered unless a patient is motivated to quit. An excellent review detailing this 'how to' approach is available [13].

ALPHABET SOUP AND HEALTHY DIETS, HEALTHY WEIGHTS, AND HEALTHY LEVELS OF PHYSICAL ACTIVITY

As with the prevalence of smoking, population figures for saturated fat intake appear to be falling. From 1971 to 2000, total dietary fat has fallen from 36.9% of calories to 32.8% of calories and saturated fat has fallen from 13.5% to 10.9% of calories – very close to the Step One guidelines of 10% [14]. Putting these figures into a clinical perspective, however, leads to a different conclusion. Americans are eating more calories – 7% by self report in men and 21% by self report in women [15]. Although percent calories from saturated fat have declined, the actual grams of saturated fat have increased. This suggests that our ready-to-eat foods

contain less saturated fat but the larger portion sizes cancel out any benefit. Saturated fat intake by grams is linearly related to changes in low-density lipoprotein cholesterol (LDL-c).

From 1960 to 2002, the average weight for a man in the US has increased nearly 24 lbs, resulting in an increase in average body mass index (BMI) from 25.1 to 27.8 kg/m^2, with similar increases observed among women [16]. Rather than continuing to preach the cholesterol-lowering diets of the 1960s to lean patients who needed to change food choices to reduce intake of saturated fat and dietary cholesterol, a streamlined 2007 approach to dietary modification would be recommended that patients simply eat less. The National Institutes of Health (NIH) guidelines on obesity [17] concluded that sufficient clinical trial evidence supports the expectation that weight-losing diets can reproducibly achieve a 5–10% weight loss. Little difference in magnitude of weight loss has been seen in clinical trials comparing diets of different fat/carbohydrate/protein compositions; one trial [18] reports greater benefit with low-carbohydrate diets – a finding not born out from weight loss registries, where the greatest long-term success has been with low-fat diets [19]. Perhaps the 'success' of carbohydrate restriction lies in the fact that increases in carbohydrate intake accounts for the majority of the increase in overall calories [14].

Irrespective of diet composition, a 5–10% weight loss is sufficient to improve dyslipidemia [17]. How to achieve this weight loss is another matter. The outstanding success of the lifestyle arm in the Diabetes Prevention Program (DPP) provides a template for lifestyle intervention [20]. The basic behavioral model underlying programs such as the DPP was based on 'ABC' – in order to change lifestyle **B**ehaviors, environmental **A**ntecedents and **C**onsequences that influence these behaviors must also be modified. Introducing lifestyle change in the clinical setting should include some acknowledgement of the patient's willingness to change. Table 11.3 summarizes a stepped approach for lifestyle interventions [21].

It would be remiss not to mention growing evidence that another lifestyle habit – adequate sleep – should be included in our definition of a healthy lifestyle. Sleep deprivation has been associated with insulin resistance and changes in leptin and grehlin secretion [25]. Evidence is growing that sleep deprivation may be one of the contributing factors to the societal rise in obesity.

CUTTING THE SOUP COURSE IS NOT THE SAME AS MAKING A LIFESTYLE CHANGE

Bariatric surgery for weight loss – where the stomach and duodenum are surgically modified to prohibit consumption of large meals – is growing in popularity. Physicians should be mindful that although the procedure achieves weight loss, it does not require patients to increase their physical activity or improve their diet [26]. Since the Lyon Diet Heart Study achieved significant cardiovascular event reduction without changes in serum lipids [27], the importance of a healthy diet should not be underrated.

CASES: PREPARING YOUR CHICKEN FOR THE SOUP TUREEN

If you use rubber chickens in the soup, it won't taste good. You need real meat. All clinicians advise patients regarding medical conditions, but few of us have received formal training in counseling. There are major distinctions between advice and counsel, illustrated in Webster's New Dictionary of Synonyms [28]:

> Advice implies '. . . real or pretended knowledge or experience, often professional or technical, on the part of the one who advises and may apply to any of the affairs of life. Counsel often stresses the fruit of wisdom or deliberation, and presupposes weightier occasions than *advice* or more authority or a closer personal relationship in the one who counsels.'

Table 11.3 Effective strategies for lifestyle intervention

Advise	*Advice*	*Rationale*
All patients on all visits	Maintain your weight	Natural history is weight gain; small gains in weight may be easily preventable
Patients motivated to change	Your weight loss goal is . . . [21]	e.g., if current weight = 236 lbs 5% goal = 225 lbs 10% goal = 212 lbs
	Your physical activity goal is . . . [22]	150 minutes/week physical activity (expends 1000 kcal/week) same effect achieved if activity comprises 4 bursts of activity/day 200 minutes/week physical activity achieves superior results
	Your daily calorie intake should be . . . [23]	Patients <200 lbs = 1200–1500 calories/day Patients >200 lbs = 1500–1800 calories/day Low-fat diets have been associated with better long-term success for maintaining weight
	Keep a daily log of your food intake and physical activity [24]	Teach patients to record daily food intake and daily physical activity in a diary
Patients ready to change today	Get help from a behavioral therapist (trainer, dietitian, clinical nurse specialist)	DPP used 16 sessions over a 24-week period to develop personalized strategies to change behaviors including self-monitoring, goal-setting, problem-solving, stimulus control, contingency contracting and self-reinforcement
	Let me help you monitor progress	Monitor progress in person initially once a month and over time once every 2 months
	Let me help you develop a successful strategy	Identify a patient's motivation for weight loss, specific barriers to success, and help problem-solve by identifying possible solutions for these barriers

Changing your own habits – from *advising* patients to *counseling* them – is the best way to trade those rubber chicken counseling skills for real ones. One technique – motivational interviewing – is a great skill for clinicians to use in their office practice. Motivational interviewing will outshine outdated counseling skills in our most difficult patients, the patients we really want to change [29].

CASE REPORT 1

'Dreamgirl' is a 44-year-old executive. Her father had his first myocardial infarction at age 30 and was diagnosed with familial hypercholesterolemia post-infarction. All family members were tested and she was found to have inherited one defective LDL receptor gene. Since age 35 after all of her children were born she has been religiously taking statin therapy, at maximum dose, PLUS a cholesterol absorption inhibitor and a bile acid binding resin. Her LDL-c has fallen from 330 mg/dl (untreated) to 190 mg/dl. She is referred to you

for any new therapies to further lower her LDL-c. She is highly motivated and follows a rigorous exercise program giving her a svelte BMI of 22.3. She describes herself as a 'picky eater' and often eats on the run as she follows a 'road warrior' schedule with extensive foreign travel. She does not smoke and has no other coronary risk factors other than her hypercholesterolemia and her family history.

Strategy

The search for means to lower LDL-c by diet should focus on adjustable factors: excess body weight and excess saturated fat. Several carefully controlled trials of diet vs statin vs combination therapy have proven that dietary therapy is additive to statin therapy. Specifically, for Dreamgirl, controlling saturated fat could lead to an additional 6% reduction in LDL-c even in persons taking drug therapy [30]. Dreamgirl is lean so our focus should be on restricting dietary saturated and trans fat and dietary cholesterol. There are three main sources of dietary saturated and trans fat: dairy, meat, and baked goods. Dietary cholesterol comes from all meats including fish, shellfish, egg yolks, and dairy products. You appropriately refer Dreamgirl to a registered dietitian for education; she tells you that she will comply but the soonest she will have time will be in 4 months – she expects you, the lipid expert, to get her started today.

Pitfalls

Before you tell Dreamgirl she has a genetic condition and that the >50% lowering she has achieved by drugs is the best she can do, and before you start the canned lecture about red meat, get some data. Find out what she is eating. A simple and direct way to find out about her diet is to ask what she has eaten in the past 24 h. Her recall is provided in Table 11.4 along with streamlined suggestions to either reduce saturated/trans fat or to improve other aspects of her diet (a Mediterranean style diet, which contains ample fruits, vegetables, fish and grains). Dreamgirl is a patient whose diet is dictated by convenience – fortunately many healthy options are also convenient. Dreamgirl has asked for your direction so it is acceptable to give that direction.

CASE REPORT 2

'Bubba' is a 58-year-old mechanic. A heavy smoker since age 18, he moved up the ladder from mechanic's assistant to office manager. He recently suffered a non-fatal myocardial infarction. His referral to you was prompted by his inability to tolerate niacin which was prescribed for low HDL-c. He has otherwise been compliant with his post-infarction regimen of aspirin, a β-blocker and statin therapy. Last week, he started cardiac rehabilitation therapy. His LDL-c is on target at 65 mg/dl, but HDL-c is low at 31 mg/dl, fasting triglycerides are 211 mg/dl, and fasting serum glucose is 98 mg/dl. He continues to smoke but has cut back from 3 packs per day (ppd) to 1 ppd. He is 'heavy built' (his own words) with a BMI of 32.6 and waist circumference of 46″, and 'exercises his wrists' at work using computers and during his home hobby of making deer-meat sausages.

STRATEGY

Bubba has two reversible causes of his low HDL – cigarette smoking and body weight/physical inactivity. He fits the criteria for having 'metabolic syndrome' and his borderline high serum glucose suggests he in on the way towards developing type 2 diabetes mellitus. There are many things about Bubba's lifestyle that could be changed to reduce his risk. Your tact, however, should focus on a limited number of changes that Bubba can

Table 11.4 Case report 1: Dreamgirl's dietary recall

Mealtime	*Choices and location*	*Option 1 – LDL-c lowering*	*Option 2 – moves towards a Mediterranean diet*
Breakfast	Large cappuccino with two squirts of hazelnut and topped with crème from the local deli One muffin	Substitute non-fat milk for crème topping to reduce saturated fat Substitute low-fat muffin for regular muffin to reduce saturated and trans fat	Remove those 'empty calories' from the high fructose corn syrup used in this sugary drink; substitute this breakfast with black coffee, fresh fruit and nut-containing biscotti
a.m. snack	None typically except glazed donut at work brought Fridays from local deli	Substitute 1/2 bagel from same deli to reduce sat/trans fat Substitute microwave oatmeal as oatfiber has LDL-c-lowering properties	Add lox and low-fat cream cheese to the bagel Add nuts and raisins to the oatmeal
Lunch	Turkey wrap	Remove part of the tortilla wrap – likely contains trans fat	Add fruit cup or raw vegetables Consider tunafish wrap
p.m. snack	None typically; rare visit to the snack machine for packaged muffin/sweet roll	Chocolate covered peanuts will have less trans+saturated fat	Plain nuts or dried fruit & nut mixture will add nuts and fruit
Dinner	Small order Nachos and fast food item such as fries, burrito, or small hamburger	To reduce sat/trans fat: Salad order with chicken from same fast food place Explore deli options of prepared pasta salad with olive oil and garlic	Easy home meal: canned chicken and vegetable soup with toast or saltine crackers; apple or orange stored in refrigerator for longer shelf-life
Bedtime snack	None typically; enjoys Chai Tea with milk or fudge brownie	Substitute dark chocolate square for brownie; use low-fat milk in tea to reduce saturated fat	Add fruit to the dark chocolate

commit to and succeed at. Unlike Dreamgirl, Bubba is not coming to you for advice; he is coming because he was told to come. The traditional strategy of offering advice, as you did with Dreamgirl, is unlikely to work.

Bubba's risk for another cardiovascular event would be 54% lower if he stopped smoking [31]! Change in body weight and increases in physical activity would also improve his HDL; we cannot readily quantify the benefit from clinical trials as the benefits of lifestyle changes for raising HDL have not been directly tested.

Pitfalls

Do not make the mistake of giving Bubba his umpteenth lecture on why he should quit smoking. Those lectures did not work the first time, did not work the second time, and are not likely to work the umpteenth time. Your 'hazards of cigarette smoking' lecture/sermons were created and dutifully recorded on the premise that scaring a patient will increase their motivation to quit. Bubba has just personally experienced an even scarier, major health event that should have convinced him to quit, and yet it did not. He did, however, reduce the number of cigarettes he smokes. It is time to try something new, and this does not necessarily mean a prescription for the latest smoking cessation drug.

What Bubba needs from you is 'motivational interviewing.' This skill does not depend on *lecturing*, but rather on *interviewing* the patient. The technique guides a patient towards an understanding of their own personal barriers to making a behavioral change. Once these barriers are identified by the patient, the clinician guides (*not* directs) the patient into figuring out his own solution to these barriers. The premise of motivational learning is that a patient is more likely to accept and act upon opinions that they voice themselves.

As always, start with the steps of the Five A's' (Table 11.2) – but when you get to Step 3, reflect what Bubba has told you – he has cut back on his smoking. Bubba has the knowledge that smoking is bad for his health but he has not figured out how to get rid of a behavior he is addicted to. The tendency for most physicians is to whip out the prescription pad and give him one of the various drugs approved to help with smoking cessation. Resist this tendency.

Explore why Bubba hasn't quit: 'If I heard you correctly, it sounds like you would like to quit since you have cut back dramatically on how much you smoke.' Wait for a response – don't ask any questions or offer advice. He may tell you how difficult it will be to quit. Using your motivational interviewing skills, acknowledge what he just said – that it would be difficult. Wait for his response. Bubba may joke that he might commit suicide during the quitting process. Acknowledge that this is a possibility, but it is more likely that his wife would murder him for his bad behavior before he even attempted to take his own life. (Humor is a good method to tell the patient you are listening and *heard* the problem.) If Bubba gives you some hint that he would like to quit, now is the time to ask him some specifics of how he sees the importance of quitting and his own self-confidence to quit. 'On a scale from 0 to 10, with 10 being the highest, how important is it to you to quit smoking?' If his answer is '5', Bubba needs some help exploring his own conflicts about quitting. Ask why he didn't choose a lower number like one or two. Listen for his response. Then ask 'What would it take you to get to a 9 or 10?' Listen for his response and you have begun the dialog exploring what it would take for Bubba to quit. If Bubba tells you he feels it is important to change his smoking habits, then explore his confidence that he can quit. 'On a scale of 0 to 10, how confident are you that you can quit?' If Bubba expresses concern about his success, acknowledge how difficult the problem is. Ask what he thinks it would take to get his confidence to a nine or ten. Bubba already knows there are medications that might take the edge off his addiction. Let the idea come from him.

Bubba may tell you that he is not ready to quit. If your interview regarding intention to quit smoking came up with a 'when I am dead' answer, either drop the issue or try to 'unstick' his resistance by reflecting his stance: 'It appears that you see no problem with your cigarette smoking.' (Get some training if you choose this latter response.) Shift gears to explore his interest in lifestyle modification with weight loss or more physical activity. Again, use motivational interviewing and reflective listening to understand where Bubba is coming from: what he thinks is important and not important to change and how confident he is that he can make a change. Take a diet history (*see* Table 11.5) and use this as a stepping stone to figuring out how he can improve his diet. Take a history of his daily activities and explore with him ways to add activity to his day and to schedule adequate time for a good night's sleep (*see* Table 11.6). Use this to explore a formal exercise program.

Table 11.5 Case report 2: Bubba's diet history

Mealtime	*Choices and location*	*Option 1 – LDL-c lowering*	*Option 2 – moves towards a Mediterranean diet*
Breakfast	2 bacon, egg and cheese burritos on the way to work 32 oz cola soft drink	Change entrée to fajita (steak or chicken); guacamole OK (mono fat) but no cheese or sour cream (sat fat) Change cola to diet drink or black coffee to reduce calories	Add fruit cup to bring fruit and fiber into the diet Change entrée to bagel with cream cheese and lox to bring fish and dairy into the diet Tea has antioxidants and may provide an alternative beverage
a.m. snack	4 'pigs in a blanket' kolaches	Change entrée to fresh fruit and low-fat yogurt to reduce sat/trans fat and calories	Consider the combination of dried fruit and nuts to bring nuts and fruit into the diet Mixed raw vegetables (carrot sticks, celery, peppers, radishes, jalapenos, pickles) to brings vegetables into the diet while reducing calorie intake
Lunch	4–6 pieces of pizza at the all-you-can-eat Pizza Buffet 32 oz fountain drink	Include salad bar selection at the same buffet and reduce to 2 pieces of pizza (avoiding double stuffed crusts and extra cheese) to reduce sat/trans fat and calories Change to diet drink	Tuna fish salad sandwich on wholegrain bread to bring fish into the diet Carrot sticks to bring vegetables and reduce calories
p.m. snack	Large order of french fries with 20 oz cola on the way home from work	Get home first and then have a small bowl of cereal with low-fat milk to bring fiber and grain into the diet and to reduce sat/trans fat	Other alternatives: Toast with olive spread Toast with peanut butter Celery with peanut butter Raw vegetable snacks as above
Dinner	Deer-meat sausage with 4 homemade biscuits and gravy 6 pack of beer	Deer-meat is low in fat and saturated fat; no need to change the sausage. Make biscuits and gravy with vegetable oil or olive oil rather than lard/margarine Limit to 2 beers (calories)	Add non-starchy vegetables to the meal (e.g., green beans, cauliflower, asparagus, carrots, onions, summer squash)

Table 11.6 Case report 2: Bubba's daily activity

Reported activity	*Possible easy modifications*
Alarm goes off at 5:30; shower, shave and out the door by 6:00; drive to work and get there by 7:00	One hour commute is long; a job closer to home or a home closer to work would free up time
Parks closest to the back door entryway	Park farthest from the back door entryway
At the desk, handles customer orders	Explore ways to add a few steps to the job – instead of pointing where the requested item is, could he walk the customer to it?
10 am cigarette break	Take a walk during the break
Lunch break – drives to pizza place	Can he walk to the pizza place? Walk to a different restaurant? Bring his lunch and walk to a park to eat?
2 pm cigarette break	Take a walk during the break
5 pm goes through drive-through for snack to eat on the commute home	Can he wait to eat until he is home? If not, can he park the car and walk inside the fast food place?
6 pm – home, lets dog out in backyard	Walk the dog around the neighbourhood
7 pm – 9 pm deer sausage activity	
9pm – Midnight favourite TV shows	Discuss earlier time to bed to ensure 7–8 h sleep/rest

SUMMARY

The benefits of lifestyle modification are irrefutable. Success in modification requires some understanding of behavior and behavior modification, and for many clinicians this will require an updating of their counseling skills. Lifestyle contributes to cardiovascular risk through multiple risk factor pathways. Investing the time to interview a patient and understand how the patient views their disease can place you in a good position to guide a patient towards adopting healthier lifestyle habits.

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12

What is the best place for fibrate therapy in reducing cardiovascular risk?

J. M. McKenney

INTRODUCTION

As we begin the 21st century, statins are generally seen as first-line therapy to reduce cardiovascular (CV) risk. Randomized, controlled clinical trials involving over 100 000 people have clearly established their ability to reduce all consequences of atherosclerotic vascular disease, including sudden coronary death, CV and total mortality, non-fatal myocardial infarction (MI), unstable angina, revascularization procedures, acute coronary syndrome, stroke, and peripheral vascular disease [1]. All patient groups benefit from statin treatment, including the elderly as well as the young, men and women, and patients with chronic kidney disease, hypertension, and diabetes. Patients with sufficient future risk of a CV event are candidates for medical management with a statin regardless of their baseline low-density lipoprotein cholesterol (LDL-c), for we have learned that lowering LDL-c irrespective of where we begin lowers CV risk. We have also been advised by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) to lower LDL-c at least 30–40%, more if possible, to attain a significant risk reduction [2]. We are now beginning to combine two LDL-c lowering drugs to intensify the lowering that can be achieved. In the pipeline of future risk reduction therapies are newer cholesterol absorption inhibitors, squalene synthetase inhibitors, and microsomal triglyceride (TG) transfer protein inhibitors, all drugs designed to be added to statin therapy to extend LDL-c lowering.

In spite of this, CV events continue to occur, even in patients receiving maximal LDL-c lowering therapy. In an analysis of 14 large randomized, placebo-controlled clinical trials, involving 90 056 subjects, major coronary heart disease (CHD) events were reduced from 24 to 40% with 5 years of statin therapy [1]. Based on an analysis of these trials, lowering LDL-c 50% in everyone at risk would be predicted to lower first CV events by about 50%. These are heady numbers. But, they also tell us that a substantial number of people are still left to experience an event in spite of receiving our most effective treatment; accordingly, the search for additional approaches to extend our ability to prevent CV events is imperative.

NON HDL-c AND ATHEROGENIC DYSLIPIDEMIA

NCEP ATP III established non-high-density lipoprotein cholesterol (non-HDL-c) as the second goal of treatment after patients have been treated to their LDL-c goal and are left with

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Table 12.1 Targets (mg/dl) for lipid-altering therapy after LDL-c goal in patients with triglycerides ≥200 mg/dl [2, 4]

Patient category	*LDL-c target*	*Non-HDL-c target*	*ApoB target*
No CHD, ≤2 RF	<160	<190	<130
No CHD, ≥2 RF	<130	<160	<110
CHD or CHD risk equivalent	<100	<130	<90
CHD with very high risk	<70	<100	<70

ApoB = apolipoprotein B; CHD = coronary heart disease; RF = risk factor(s).

a triglyceride level above 200 mg/dl [3]. Non-HDL-c is the sum of very-low-density lipoprotein cholesterol (VLDL-c) and LDL-c or the remainder of high-density lipoprotein cholesterol (HDL-c) subtracted from total cholesterol. If LDL-c is at the treatment goal, an elevated non-HDL-c represents an elevated VLDL-c but actually it means much more than that, as will be discussed below. Importantly, an elevated non-HDL-c is now commonplace in populations because of the high and growing prevalence of the metabolic syndrome, insulin resistant diabetes, and obesity. A close correlate to non-HDL-c is apolipoprotein B (apoB). Non-HDL-c reports the cholesterol content carried in VLDL and LDL particles while apoB reports the concentration (number) of VLDL and LDL particles, as each of these particles contain one apoB. The goals of non-HDL-c as recommended by ATP III and apoB as suggested by Grundy are shown in Table 12.1 [4].

The reason NCEP ATP III established non-HDL-c as a secondary goal was to give the clinician an easy way to clinically address high blood triglycerides and the atherogenic particles that accompany it. NCEP ATP III considered recommending apoB to guide treatment instead of non-HDL-c, but did not since this analyte is not standardized in labs across the US and results may be disparate. Further, numerous investigators have reported a strong correlation between non-HDL-c and apoB in predicting future CV risk. Conversely, the risk prediction with LDL-c is generally inferior to either that of non-HDL-c or apoB [5–10]. For example, in a 10-year follow-up of 15 632 initially healthy women aged 45 or greater who were participants in the Women's Health Study, the adjusted hazard ratio for future CV events was 1.62 for LDL-c, 2.51 for non-HDL-c, and 2.50 for apoB [6]. Similarly, in 18 225 men initially free of CHD in the Health Professionals Follow-up Study who were followed for 6 years, the relative risk in the highest quintile compared to the lowest quintile for the occurrence of a non-fatal MI or fatal CHD was 1.81 for LDL-c, 2.76 for non-HDL-c, and 3.01 for apoB [5].

Virtually all patients with a triglyceride level above 200 mg/dl (and an elevated non-HDL-c) have atherogenic dyslipidemia. This lipid disorder is characterized by cholesterol-enriched VLDL remnant particles, small dense LDL-c, low HDL-c, and increased numbers of VLDL and LDL particles. This is why non-HDL-c is not simply an elevated VLDL-c. Furthermore, management of patients with an elevated non-HDL-c is much more than just lowering blood triglyceride levels; it is reducing the number and changing the composition of cholesterol-carrying particles. To do this, we will need therapies with properties other than those which mainly lower LDL-c, such as niacin and fibrates.

The process by which patients develop atherogenic dyslipidemia is complex but understanding it helps one better appreciate the array of problems contained in this dyslipidemia and also how to match therapies to remedy it. Patients with atherogenic dyslipidemia secrete triglyceride-enriched VLDL particles from their liver, which contain apoCIII. Under normal circumstances, lipoprotein lipase in capillary beds hydrolyses triglycerides in this particle, but apoCIII inhibits this enzyme leaving VLDL particles loaded with triglycerides (and serum triglyceride levels high). Triglyceride molecules from the VLDL particle are

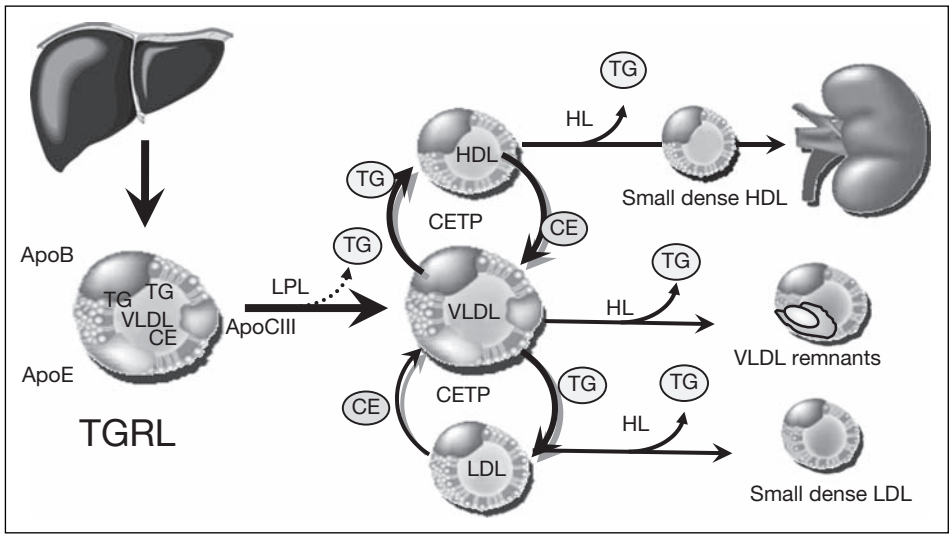

Figure 12.1 Patients with atherogenic dyslipidemia secrete a triglyceride-enriched VLDL particle from their liver which contains apoCIII. ApoCIII inhibits the activity of lipoprotein lipase from removing triglyceride content from VLDL particles. As a result, triglyceride molecules from the VLDL particle are exchanged for cholesteryl ester molecules from LDL and HDL particles under the influence of cholesteryl ester transfer protein (CETP). Hepatic lipase removes triglycerides from VLDL particles creating a cholesterol-enriched, highly atherogenic VLDL remnant particle. Hepatic lipase also removes triglycerides from HDL and LDL particles leaving cholesterol-deficient, small HDL and LDL particles, which is also highly atherogenic. The net results of the secretion of triglyceride-rich lipoproteins are cholesterol-enriched VLDL remnant particles, cholesterol-deficient small dense LDL particles, cholesterol-deficient small HDL particles, and an overall increase in the number of atherogenic particles [11]. Adapted from *Expert Rev. Cardiovasc Ther* 2004; 2: 485–501; with permission of Future Drugs Ltd.

exchanged for cholesteryl esters in LDL and HDL particles by cholesteryl ester transfer protein (CETP) (Figure 12.1) [11]. This causes VLDL particles to become cholesterol-enriched; as triglycerides are removed by hepatic lipase, a highly atherogenic, cholesterol-enriched VLDL remnant particle emerges that is smaller in size and able to penetrate into the subendothelial space of artery walls. This contributes to the pathogenesis of atherosclerosis, and leads to CV events [12–13]. The triglyceride-enriched, cholesterol-depleted HDL particles, when acted on by hepatic lipase, become cholesterol-depleted, small HDL particles, some of which may be eliminated by the kidney, which further lowers blood HDL-c levels. Finally, the triglyceride-enriched, cholesterol-depleted LDL particles, when acted on by hepatic lipase, form cholesterol-depleted, small dense LDL particles, which are also highly atherogenic [14]. The net result of the secretion of triglyceride-rich lipoproteins is: cholesterol-enriched VLDL remnant particles, cholesterol-depleted small dense LDL particles, cholesterol-depleted small HDL particles which are more rapidly catabolized and cleared from serum, and an overall increase in the number of atherogenic particles.

An elevated non-HDL-c level includes LDL-c (and small dense LDL particles), as well as VLDL-c (and cholesterol-enriched VLDL remnant particles), and inherently speaks to an increased particle number as well. A low HDL-c accompanies elevated VLDL-c levels. Non-HDL-c serves as a good surrogate for the multiple lipid abnormalities encountered in patients with atherogenic dyslipidemia. Some health professionals use so-called advanced lipid testing and spend hundreds of dollars to try to quantify the components of atherogenic dyslipidemia, but a simple non-HDL-c in a patient with a triglyceride above

Table 12.2 A sampling of randomized, placebo-controlled efficacy trials with fibrates

Reference	*Drug, daily dose*	*LDL-c baseline (% change)*	*TG baseline (% change)*	*HDL-c baseline (% change)*	*Non-HDL-c baseline (% change, estimated)*
Schonfeld, 1994 [15]	Gemfibrozil 900 mg, FH	302 mg/dl (−19%)	96 mg/dl (−18%)	55 mg/dl (−7%)	321 mg/dl (−20%)
	Fenofibrate 300 mg, FH	332 mg/dl (−26%)	119 mg/dl (−28%)	45 mg/dl (8%)	355 mg/dl (−26%)
	Gemfibrozil 900 mg, CHL	239 mg/dl (−18%)	244 mg/dl (−50%)	48 mg/dl (6%)	288 mg/dl (−23%)
	Fenofibrate 300 mg, CHL	201 mg/dl (−30%)	258 mg/dl (−47%)	38 mg/dl (19%)	234 mg/dl (−29%)
Broijersen, 1996 [16]	Gemfibrozil 1200 mg CHL	163 mg/dl (9%)	466 mg/dl (−60%)	30 mg/dl (19%)	273 mg/dl (−21%)
Steinmetz, 1996 [17]	Fenofibrate 200 mg HBC	212 mg/dl (−21%)	178 mg/dl (−32%)	40 mg/dl (12%)	245 mg/dl (−23%)
	CHL	210 mg/dl (−20%)	290 mg/dl (−53%)	32 mg/dl (33%)	277 mg/dl (−29%)
Tricor, 2004 [18]	Fenofibrate 145 mg HBC	228 mg/dl (−31%)	102 mg/dl (−24%)	58 mg/dl (10%)	250 mg/dl (−30%)
	CHL	220 mg/dl (−20%)	232 mg/dl (−36%)	47 mg/dl (15%)	266 mg/dl (−23%)
	High TG	128 mg/dl (15%)	432 mg/dl (−46%)	34 mg/dl (20%)	218 mg/dl (−14%)
	Very high TG	103 mg/dl (45%)	726 mg/dl (−55%)	30 mg/dl (23%)	231 mg/dl (−19%)
Brown, 1986 [19]	Fenofibrate 300 mg HBC	220 mg/dl (−25%)	154 mg/dl (−33%)	49 mg/dl (10%)	252 mg/dl (−23%)
	CHL	180 mg/dl (−12%)	349 mg/dl (−48%)	42 mg/dl (15%)	259 mg/dl (−21%)
Oli, 2004 [20]	Fenofibrate 200 mg	150 mg/dl (−4%)	316 mg/dl (−46%)	35 mg/dl (22%)	214 mg/dl (−16%)
	Gemfibrozil 1200 mg	156 mg/dl (1%)	313 mg/dl (−37%)	34 mg/dl (9%)	219 mg/dl (−10%)

CHL = combined hyperlipidemia; FH = familial hypercholesterolemia; HBC = high blood cholesterol; TG = triglycerides.

200 mg/dl tells the whole story in a much simpler and less expensive manner. Other therapies that help correct the underlying problem are needed. In this chapter, the potential of fibrates for non-HDL-c focused therapy is explored.

EFFICACY OF FIBRATES

Fibrates are thought of principally as triglyceride-lowering agents, but they also have other important effects on key lipoproteins (Table 12.2) [15–21]. Given their 'broad spectrum' of

beneficial effects on triglycerides, HDL-c and usually LDL-c, they are one of the first agents to consider for the management of patients with atherogenic dyslipidemia.

Fibrates have a prominent role in the management of very high triglycerides (≥500 mg/dl) to prevent pancreatitis. Triglyceride reductions in these patients approach 50% [16, 18, 21]. Fibrate therapy is associated with a 25% increase in serum HDL-c in patients with hypertriglyceridemia [18]. This is partly due to the reduced enrichment of HDL particles with triglycerides and increased hepatic apoAI and apoAII biosynthesis which help to drive hepatic HDL secretion. In any population, the higher the triglyceride level, the greater the triglyceride reduction achieved with a fibrate and, inversely, the greater the increase in HDL-c [18, 19]. Patients with hypertriglyceridemia often have low LDL-c and treatment with a fibrate may raise their LDL-c 10–35% [16, 18, 20]. This is due to lipolysis of triglycerides from triglyceride-rich VLDL particles by lipoprotein lipase and a quick conversion to LDL particles, producing the so-called beta shift phenomenon. It is not known whether this increase in LDL-c increases CHD risk.

In the treatment of atherogenic dyslipidemia, focus should be given to patients with high serum triglycerides (i.e., 200–500 mg/dl) as triglyceride levels in this range are associated with increased CV risk. In these patients, fibrates lower triglycerides and VLDL-c about 20–50% and raise HDL-c and apoAI by 10–20% (Table 12.2). LDL-c levels are usually reduced 10–30% but rarely may remain the same or increase (mostly in patients with low baseline LDL-c levels and triglycerides above 300 mg/dl) [15–20]. Evidence from the Helsinki Heart Study with gemfibrozil 1200 mg daily suggests that these changes in LDL-c may not be detrimental. A *post hoc* analysis from this study found that the reduction in CHD events was similar in patients with a reduction, an increase, or no change in LDL-c levels [22]. VLDL-c is usually reduced substantially with a fibrate, in the 20–50% range. This reduction is proportional to the triglyceride level; the higher the triglyceride level, the greater the reduction in VLDL-c with a fibrate. The reduction in non-HDL-c is similar to the LDL-c reduction in hypercholesterolemic patients, but superior in patients with combined hyperlipidemia (increased cholesterol and triglycerides), highlighting the lipid profile best suited for fibrate therapy (Table 12.2) [14, 17–19]. In fact, the higher the triglyceride level, the greater is the reduction in non-HDL-c owing importantly to a reduction in VLDL-c [18]. Even in those instances where LDL-c increases with fibrate therapy, non-HDL-c is still lowered owing to a substantial reduction of VLDL-c. In most, but not all studies, fenofibrate appears to be more effective in lowering LDL-c and triglyceride levels and raising HDL-c than is gemfibrozil (Table 12.2) [23].

The lipid-altering efficacy of fibrates persists when they are added to a statin, the most common circumstance in which fibrate therapy is used (Table 12.3) [24–31]. Fibrates lower TG and VLDL-c levels an *additional* 20–40% and raise HDL-c levels an *additional* 10–20% when added to a statin (Table 12.3). They also lower non-HDL-c on average an additional 7–12% over that achieved with a statin. The LDL-c is most often changed little or may be increased slightly with fibrate therapy, especially in those with higher baseline triglyceride levels. The same response pattern is seen with the addition of a fibrate to ezetimibe, colestipol, and colesevelam except that the TG reduction with the latter two bile acid sequestrants is attenuated [32–34].

In addition to changes in the main lipoproteins with fibrate therapy, treatment also affects other components of the atherogenic dyslipidemia profile. The 10–20% reduction in apoB is important and suggests these drugs lower particle number. Studies have also shown that fibrates reduce VLDL remnants appreciably, especially the larger particles [30]. The effect on LDL particles themselves appears to be reflected in a reduction in small particle numbers and an increase in large, supposedly less atherogenic, 'fluffy' LDL particles [35]. Overall, there is an increase in LDL particle size and a decrease in LDL particle number.

There is some evidence that these changes are related to improved outcomes. Analysis of the Diabetes Atherosclerosis Intervention Study (DAIS) suggests that these changes may have contributed to the overall reduction in atherosclerosis progression. In DAIS,

Table 12.3 The *additional* change in lipids when a fibrate is added to statin therapy

Statin, daily dose Fibrate, daily dose (Reference)	***LDL-c baseline, % change with statin,* additional *% change with fibrate***	***TG baseline, % change with statin,* additional *% change with fibrate***	***HDL-c baseline, % change with statin,* additional *% change with fibrate***	***Non-HDL-c baseline, % change with statin,* additional *% change with fibrate* (estimated)**
Atorvastatin 10 mg Fenofibrate 200 mg (Koh 2005) [24]	134 mg/dl, −40%, +11%	301 mg/dl, −25%, −39%	46 mg/dl, 0%, +15%	197 mg/dl −36%, −7%
Ezetimibe 10 mg + simvastatin 20 mg, Fenofibrate 160 mg (Farnier 2007) [25]	166 mg/dl, −47%, +1%	223 mg/dl, −29%, −21%	45 mg/dl, +9%, +10%	210 mg/dl −45%, −12%
Multiple statins Gemfibrozil 1200 mg (Murdock 1999) [26]	150 mg/dl, −26%, +5%	314 mg/dl, −1%, −41%	33 mg/dl, +6%, +9%	213mg/dl −19%, −11%
Simvastatin 20 mg Fenofibrate 160 mg (Grundy 2005) [27]	163 mg/dl, −26%, −6%	234 mg/dl, −20%, −23%	44 mg/dl, +10%, +19%	213 mg/dl −26%, −12%
Atorvastatin 10 mg Gemfibrozil 900 mg (Wagner 2003) [28]	152 mg/dl, −35%, +7%	162 mg/dl, −13%, −18%	46 mg/dl, +4%, 0%	184 mg/dl −30%, 0%
Rosuvastatin 10 mg Fenofibrate 200 mg (Durrington 2004) [29]	144 mg/dl, −46%, +9%	310 mg/dl, −30%, −36%	39 mg/dl, +10%, +17%	202 mg/dl −46%, 0%
Simvastatin 10 mg Fenofibrate 200 mg (Vega 2003) [30]	159 mg/dl, −28%, +5%	321 mg/dl, −24%, −38%	35 mg/dl, 6%, +16%	239 mg/dl −31%, −7%
Fluvastatin ER 80 mg Fenofibrate 200 mg (Derosa 2004) [31]	191 mg/dl −25%, −11%	161 mg/dl −17%, −12%	41 mg/dl +14%, +15%	224 mg/dl −28%, −10%

418 patients with type 2 diabetes randomly received micronized fenofibrate 200 mg daily or placebo for approximately 40 months [36]. Quantitative coronary angiography demonstrated significantly less progression of focal atherosclerosis in subjects receiving fenofibrate. A *post hoc* analysis revealed that a portion of this benefit could be attributed to an increase in LDL particle size, reductions in LDL-c, triglycerides and apoB, and an increase in HDL-c [37]. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) reported a statistically significant 22% reduction in major CHD events and total mortality in 2531 men treated with gemfibrozil 1200 mg per day [38]. A *post hoc* analysis of 364 of the men in this trial who had a new CHD event during the 5.1 years of follow-up was compared with 697 age-matched men who did not experience a new CHD event [39]. While LDL-c was not changed by gemfibrozil in the overall study, LDL particle number in the *post hoc* analysis was reduced, as was small LDL particle number, and HDL particle number was increased; these changes were significant independent predictors of new CHD events. In this analysis, changes in LDL or HDL particle size were not related to CHD events.

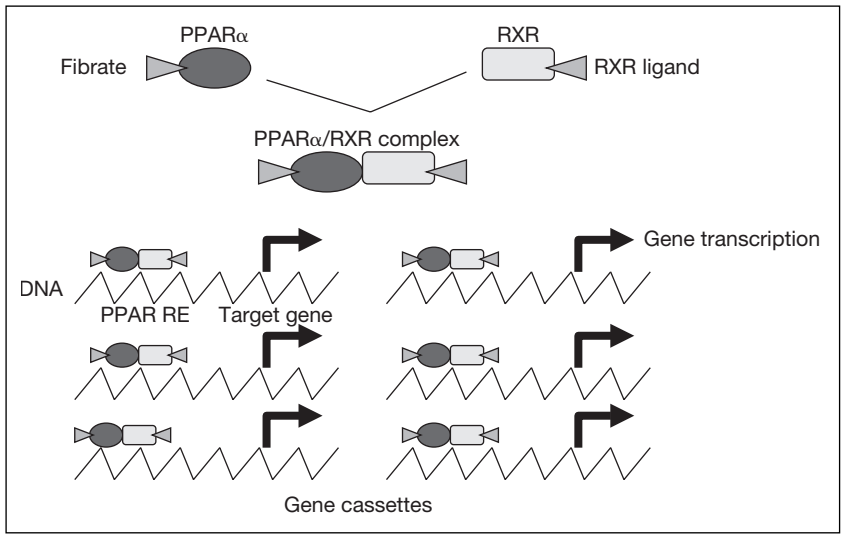

Figure 12.2 PPARα activation and gene transcription. Peroxisome proliferator-activated receptor α (PPARα) is a member of the superfamily of nuclear receptors that regulate the expression of genes that are involved in lipid metabolism, vascular function, and inflammation. Fibrates serve as a ligand for the activation of PPARα which then undergoes heterodimerization with RXR which itself is activated by a ligand. The PPARα/RXR complex interacts with specific peroxisome proliferator response elements (PPREs) in promoter regions of DNA that regulate target genes. With permission from [40].

FIBRATE MECHANISM OF ACTION

In spite of the fact that fibrates have been used for decades, we are only now beginning to understand the mechanisms by which they exert their effects. Some of these mechanisms are related to the lipid-altering efficacy of these compounds, while other mechanisms are linked to non-lipid effects.

Fibrates are agonists of the nuclear receptor, peroxisome proliferator-activated receptor α (PPARα) [40]. PPARα is one member of a superfamily of nuclear receptors which currently number 48 and counting. PPARα activation by a fibrate causes the upregulation or suppression of well over 100 genes, many of which are currently unknown and which regulate a variety of biological functions. The specific genes under the influence of PPARα receptors are those involved in cholesterol metabolism, vascular function, and inflammation.

The process of gene activation or suppression is complex and begins with an interaction between a specific ligand with the ligand-binding domain on the PPARα nuclear receptor (Figure 12.2). Endogenous ligands for PPARα include fatty acids, eicosanoids, hormones, and vitamins [41]. Fibrates are synthetic ligands for PPARα. Gemfibrozil is a less potent PPARα agonist than is fenofibrate. Once activated by binding to the ligand, PPARα undergoes heterodimerization with another nuclear receptor, retinoid X receptor (RXR), which is required for transcriptional PPARα activity [40]. The activated PPARα/RXR complex then interacts with DNA at specific binding sites called peroxisomal proliferator response elements (PPREs) in the promoter regions of positively and negatively regulated target genes [42]. Once bound to its PPRE, the receptor complex can activate or repress the expression of a target gene. Through this process, PPARα activation can control the expression of entire cassettes of genes, operating as the central nexus of control for cellular, tissue, organ and

organism responses [40]. Each nuclear receptor appears to be without overlapping effects and controls a specific set of genes. However, while this may turn on or off transcription of genes which regulate lipid metabolism and vascular function in a beneficial way, it may also turn on or off genes which produce adverse effects.

Lipid Metabolism: PPARα activation plays an important role in the mitochondrial β-oxidation of fatty acids which is a major source of cell energy. Perhaps that is why PPARα nuclear receptors are mostly found in metabolically active, energy-requiring tissues where there are high amounts of fatty acids, such as the liver, kidney, heart and skeletal muscle [43]. Through the activation of the PPARα/RXR complex, genes involved in fatty acid (FA) uptake and transport and β-oxidation are upregulated, including FA transport protein-1, FA translocase, FA acetyl-coenzyme A synthase, and carnitine palmitoyl transferase (Table 12.4) [44–46]. The enhanced catabolism of free fatty acids resulting from PPARα activation reduces the production of triglyceride-rich VLDL because less free fatty acid mass can be reassimilated into triglycerides in the liver [40]. This leads to a reduction in the secretion of VLDL particles into the systemic circulation and therefore lower triglyceride levels. With a reduction in VLDL particles, there is less substrate to produce LDL particles and so LDL-c levels may also drop.

Activation of PPARα by fibrates also results in the regulation of genes which are involved in triglyceride catabolism in the systemic circulation. One such gene is for apoCIII which is repressed by PPARα activation leading to a reduction in the synthesis of this apolipoprotein (Table 12.4) [47–48]. Since apoCIII inhibits the activity of lipoprotein lipase (LPL), its downregulation frees the enzyme to hydrolyse triglycerides in triglyceride-rich lipoproteins. In addition, the gene for LPL is upregulated, further enhancing lipolytic activity directed at triglyceride-rich VLDL and chylomicron particles [48–49]. The net result of the action of these two genes is the rapid removal of triglycerides from newly secreted triglyceride-rich lipoproteins and the conversion of VLDL particles to smaller VLDL remnant and LDL particles, which if not taken up by peripheral cells, are removed from the systemic circulation by hepatic receptors which bind with apolipoprotein E and B on the surface of VLDL or LDL particles (called BE or LDL receptors). Additionally, because apoCIII synthesis is reduced and occupies less space on the surface of VLDL particles, it is believed that this may allow apoE to bind more freely to hepatic BE receptors, which would facilitate the removal of remnant VLDL particles from the systemic circulation [45].

Activation of PPARα by a fibrate also induces the transcription of genes responsible for the synthesis of apoAI and apoAII proteins, which are the primary apoprotein constituents of HDL [50–52]. An increase in apoAI and apoAII may result in an increase in HDL-c levels and HDL particle number. Additionally, through the upregulation of LPL, lipolysis of triglycerides carried in the HDL particle should result in an increase in the number of small HDL particles.

Vascular Function: PPARα activation in monocytes, macrophages, endothelial cells, and vascular smooth muscle cells produces a number of effects which affect vascular function and inflammation (Table 12.4) [40]. The effect of PPARα activation on inflammation appears to come about through a negative feedback mechanism [53, 54]. This was demonstrated when mice bred without PPARα nuclear receptors were found to have a prolonged inflammatory response but mice with functioning PPARα receptors had less inflammation [55]. Other studies have shown that PPARα activation represses the transcription of enzymes in endothelial cells which are involved in redox responses, nitric oxide signaling, and the release of vascular cell adhesion molecules (VCAM) [53, 56, 57]. The demonstration that tumor necrosis factor-α (TNF-α) induction of VCAM from endothelial cells is suppressed with PPARα activation could be important because this is an early important step in the development of atherosclerosis [56]. This effect is lost in PPARα-deficient mice and adhesion molecule expression is increased. Mechanistically, there is evidence that this may occur through inhibition of the proinflammatory mediator nuclear factor kappa B (NF-κB) [58].

Table 12.4 Effect of PPARα activation by fibrates on genes regulating lipid metabolism and vascular function [40, 45–48]

Target gene	*Function of the gene product*	*How the gene expression is affected by PPARα agonist*
ApoCIII	Inhibitor of LPL activity. Inhibits VLDL clearance. Increases TG levels	↓
Lipoprotein lipase	Hydrolyses triglyceride-rich VLDL and chylomicron particles. Reduces TG levels	↑
ApoAI, apoAII	Major proteins of HDL. Increases HDL-c and number of HDL particles	↑
ABCA1 ABCG1	Proteins for transporting cholesterol across cell membranes (e.g., macrophages). May enhance reverse cholesterol transport	↑
SR-B1	Hepatic receptors for HDL and for transporting cholesterol across cell membranes	↑
Fatty acid transport protein Fatty acid translocase FS acetyl-coenzyme A synthase Carnitine palmitoyl transferase I	Enzymes involved in the oxidation of fatty acids, a major source of cellular energy	↑
Vascular inflammation		
Cell adhesion molecule-1	Repression of endothelial inflammatory response	↓
Interleukin-6 CRP COX-2 fibrinogen	Decreases circulating levels of inflammatory markers and mediators. Attenuates the inflammatory pressure on the vessel wall	↓
P16	Regulates vascular smooth muscle proliferation and migration	↑
Procoagulant tissue factor in the macrophage	Repression of a contributor to plaque thrombogenicity	↑

In vascular smooth muscle, PPARα activation has been shown to reduce circulating levels of inflammatory markers and mediators, including interleukin-6 and C-reactive protein (CRP) [59]. In addition to modulating cytokine signaling, PPARα appears to regulate vascular smooth muscle proliferation and migration [60, 61].

In macrophages, activation of PPARα receptors has been shown to increase the transcription of transmembrane transport proteins, including ATP binding cassette A1 (ABCA1) and the scavenger receptor B1 (SR-B1) [41]. These proteins move cholesterol out of macrophages to the cell surface where lipid-poor apoAI (nascent HDL) may pick it up for transport to the liver [62]. There is much to be learned about how to effectively move unwanted cholesterol from peripheral cells out of the body, but the ability to upregulate transmembrane transport proteins, ABCA1 and SR-B1, through PPARα activation is important since it is an initiating event in this process.

Activation of PPARα receptors in macrophages has also been shown to repress the production of a potent procoagulant tissue factor [63, 64]. In lymphocytes, PPARα activation limits generation of inflammatory molecules, including the expression of interferon-γ and TNF-α [65].

Table 12.5 Fibrate outcome studies

	n	*Rx*	*LDL-c (mg/dl) mean change*	*HLD-c (mg/dl) mean change*	*TG (mg/dl) mean change*	*Relative change in CHD events*	*Relative change in non-fatal MI*	*Relative change in total mortality*	*Relative change in CHD mortality*
FIELD [66]	9795	F	119 (−6%)	43 (+1%)	153 (−22%)	−11% $P = 0.16$	−24% $P = 0.01$	11% $P = 0.18$	19% $P = 0.22$
HHS [67]	4081	G	189 (−8%)	47 (11%)	175 (−35%)	−34% $P < 0.05$	−34% $P = 0.02$	6% NS	−27% NS
VA-HIT [38]	2531	G	112 (0%)	32 (6%)	160 (−31%)	−22% $P = 0.006$	−23% $P = 0.02$	−11% $P = 0.23$	−22% $P = 0.07$
BIP [68]	3090	B	148 (NR)	35 (18%)	145 (−21%)	−9.4% $P = 0.26$	−13% $P = 0.18$	5% $P = 0.62$	7% $P = 0.61$
WHO Study [69]	15745	C	NR	NR	NR	−20% $P < 0.05$	−25% $P < 0.05$	+22% $P< 0.05$	+13% $P > 0.05$
CDP [70]	3892	C	NR	NR	177 (−16%)	−7% (NS)	−5% (NS)	0% (NS)	−8% (NS)

B = bezafibrate; BIP = Bezafibrate Infarction Prevention; C = clofibrate; CDP = Coronary Drug Project; F = fenofibrate; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; G = gemfibrozil; HHS = Helsinki Heart Study; NR = not recorded; NS = not significant; VA-HIT = Veteran Affairs High-Density Lipoprotein Cholesterol Intervention Trial; WHO = World Health Organization.

The array of non-lipid effects associated with PPARα activation is broad based and could be important in explaining how fibrates affect atherosclerosis. What is needed is more fundamental research to define these effects at a cellular and molecular level, and clinical research to demonstrate whether these non-lipid effects truly contribute to improved outcomes in patients with increased CV risk.

THE EVIDENCE OF BENEFIT

The bottom line with any drug or class of drugs is its ability to reduce mortality and morbidity. So the fundamental question is: can fibrates reduce CV events and prolong life (reduce mortality)? The answer is somewhat equivocal.

Fibrate Trials. The 6 large, randomized, placebo-controlled, multi-year trials which have been conducted with fibrates are summarized in Table 12.5. Both of the clofibrate studies enrolled men with CHD [69, 70]. During the 5- to 8.5-year follow-up in the Coronary Drug Project, CHD events and deaths were not different between the clofibrate and placebo treatment groups. During the 5.3-year follow-up in the World Health Organization (WHO) study, patients receiving clofibrate experienced significant reductions in CHD events, but significant increases in death (Table 12.5). Most disturbingly, the increase in deaths in this study was due mostly to increases in non-CHD causes, including malignant neoplasms and cholecystectomies. Concerns over these results caused use of clofibrate to plummet and ultimately the drug was withdrawn from US formularies. These findings stifled further development of this class of drugs for more than a decade.

The two gemfibrozil studies involved only men who were randomly assigned to receive gemfibrozil 600 mg bid or placebo for a 5-year follow-up [38, 67]. Subjects in the VA-HIT

had CHD and a lipid profile resembling atherogenic dyslipidemia (low HDL-c and borderline high TGs). Conversely, subjects in the Helsinki Heart Study (HHS) were free of CHD and had a non-HDL-c >200 mg/dl. Both studies found significant reductions in major CHD events and non-fatal MI (Table 12.5). In the HHS, there were no differences in total or CHD mortality or in the occurrence of cancer or cholecystectomies between gemfibrozil and placebo. However, in a 3.5-year follow-up after the study (total of 8.5 years from the beginning of the study), the investigators found significantly more deaths in patients treated with gemfibrozil, mostly due to an increase in cancer deaths [21, 71]. The authors evaluated these data extensively and concluded that the increased death rate was most likely due to a chance variation around the mean. In the VA-HIT trial, there was also a significant reduction in major CHD events and non-fatal MI and, in contrast to other fibrate trials, CHD mortality was significantly reduced. Total mortality trended lower but did not reach statistical significance. There was no difference in the occurrence of cancer between study groups.

The only fenofibrate endpoint trial conducted to date was the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [66]. The results of this study were disappointing and confounded. Fenofibrate is the most widely used fibrate in the US and theoretically would be ideal for the management of patients with diabetic dyslipidemia, the patient population studied in FIELD. The study investigators reported a significant reduction in non-fatal MI (−24%; $P = 0.01$) and total cardiovascular events (cardiovascular death, MI, stroke, and revascularization) (−11%; $P = 0.035$), but not in the primary endpoint, non-fatal MI and CHD death (−11%; $P = 0.16$). Differences between treatment groups with regard to death were not significant, but total, CV, and CHD mortality all trended higher at 11–19%. Additionally, fenofibrate-treated subjects experienced more thromboembolic disease (pulmonary embolism $P = 0.022$ and deep venous thrombosis $P = 0.074$) and had a greater occurrence of pancreatitis ($P = 0.031$), a 15% higher plasma creatinine, and a 45% increase in plasma homocysteine. On a positive note, there was less albuminuria progression ($P = 0.002$), fewer non-traumatic lower extremity amputations ($P = 0.04$), and less retinopathy needing laser treatment ($P = 0.003$) in diabetic subjects receiving fenofibrate. The reduction in total CV events with fenofibrate was not significantly different in subjects with triglyceride levels above or below 150 mg/dl or in those with or without the metabolic syndrome or a low HDL-c/high TG lipid profile, parameters which typically show differences in lipid response with fibrate therapy (*see* Table 12.2). Also puzzling was the fact that total CV events (but not major CHD events) were significantly reduced with fenofibrate in patients with no prior history of CV disease (−19%; $P = 0.001$) but not in those with a prior CV history ($P = 0.85$).

FIELD was a confounded study [66, 72]. During the study, 19% of patients allocated to fenofibrate and 36% of patients allocated to placebo started other lipid-lowering therapy, most often a statin. The initiation of other lipid-lowering therapy was more likely to occur in patients receiving placebo, in those with prior CHD history, and in those with higher total and LDL cholesterol levels. When the other lipid-lowering therapy was started, 26% of placebo patients and 38% of fenofibrate patients discontinued their assigned study drug. These and other problems with the study severely interfered with the integrity of the random allocation of blinded treatments, thus destroying the homogeneity of study treatment arms.

Analysis of the Fibrate Trials: With all of the fibrate trials considered together, it appears that only one of the six trials studied a population with mixed hyperlipidemia. None included patients with a mean triglyceride level above 200 mg/dl. Only two, the VA-HIT trial [38] and the Bezafibrate Intervention Prevention (BIP) trial [68], included patients with low HDL-c (Table 12.5). In fact, the lipid profiles of patients in these trials appear more like a population that should be treated with a LDL-c lowering statin. *Post hoc* analysis of patients with high triglycerides/low HDL-c in these trials showed strong risk reduction effects [68, 72, 73]. For example, in the HHS, an LDL-c/HDL-c ratio of >5 and a triglyceride level >200 mg/dl defined the population receiving the greatest benefit from gemfibrozil, a 70% lowering in CHD events [73]. There was no difference in total mortality in this subgroup

but the number of deaths was very small. In the BIP trial, patients with an HDL-c <35 mg/dl and a triglyceride ≥200 mg/dl achieved the greatest benefit with bezafibrate, a 42% significant reduction in major CHD events [68]. No information is provided on mortality outcomes in this subpopulation. One can point to the VA-HIT study as corroborating these results in that people with borderline high TG and low HDL-c demonstrated a significant reduction in CHD events and death [74]. These data argue that if the investigators had selected a population better suited for fibrate therapy, at least for treatment with gemfibrozil or bezafibrate, the results of these studies might have been quite different [72].

It is surprising and concerning that most of the fibrate trials did not demonstrate a reduction in mortality, whether CHD, CV, or all-cause. The initial reports of increased mortality came from the WHO trial where total mortality was increased by both coronary and non-cardiovascular mortality, including an increase in cancer deaths [69]. Subsequently, increases in total and/or CHD mortality were also reported in the HHS with gemfibrozil [67], in the BIP study with bezafibrate [68], and in the FIELD trial in diabetic patients with fenofibrate (Table 12.5) [66]. A recent meta-analysis of 17 fibrate trials, all containing a control group, using random allocation to treatment arms and continuing for at least 6 months, showed that fibrate therapy had a negligible effect on total mortality (i.e., no reduction) and a significant 13% increase in non-cardiovascular mortality [75]. There are no explanations why this increase in deaths occurred.

Importantly, most of the fibrate trials found that fibrates reduce major CHD events (CHD death and non-fatal MI) and non-fatal MI alone (Table 12.5). A significant reduction in major CHD events was obtained in the two gemfibrozil studies, HHS [67] and VA-HIT [38], and in one of the two clofibrate studies (the WHO Study) [69]. In the FIELD trial, reduction in major CHD events did not achieve significance (mostly because of an increase in CHD mortality) but non-fatal MI, revascularization procedures, and total cardiovascular events were significantly reduced [66]. The benefit on coronary events did not extend to strokes. Strokes were significantly reduced in only one of the three fibrate trials in which it was reported; −9% in the FIELD trial ($P = 0.36$), −14% in the BIP trial ($P = 0.36$), and −31% in VA-HIT ($P = 0.036$) [38, 66, 68].

DIFFERENCES AMONG FIBRATES

The two fibrates available in the United States, gemfibrozil and fenofibrate, have similarities, but also important differences, especially regarding safety issues. For example, both gemfibrozil and fenofibrate can increase the risk of myotoxicity when combined with a statin, but gemfibrozil appears to be associated with a greater risk than fenofibrate. One group of investigators found 5.5 cases of rhabdomyolysis per million fenofibrate prescriptions compared with 59.6 cases per million gemfibrozil prescriptions in the FDA's spontaneous adverse event reporting system (AERS) database [76]. Most cases occurred in patients taking a fibrate with a statin, and, in the case of gemfibrozil, 90% of the reported cases occurred in patients receiving cerivastatin. This is consistent with our current understanding that the risk of muscle toxicity increases as statin blood concentrations increase. There are several reasons for believing cerivastatin levels were high in the rhabdomyolysis cases including the high bioavailability of cerivastatin compared with other statins, frequent use of the top cerivastatin daily dose, 0.8 mg, and a drug interaction with gemfibrozil.

However, even when cerivastatin was removed from this analysis, gemfibrozil is still more likely to increase the risk of muscle toxicity. For example, another investigator group reported 0.58 cases of rhabdomyolysis occurred per million fenofibrate prescriptions compared to 8.6 cases of rhabdomyolysis per million gemfibrozil prescriptions in the FDA AERS database when these fibrates were used in combination with any statin other than cerivastatin [77]. When cerivastatin was the statin in the fibrate combination, the corresponding rates of rhabdomyolysis were 140 and 40 cases per million prescription with gemfibrozil and

Table 12.6 Effect of fibric acid derivatives on the C_{max} ratio (C_{max} of statin with a fibrate/C_{max} of the statin alone) [79]

Statin	*With gemfibrozil*	*With fenofibrate*
Atorvastatin	1.3	1.0
Fluvastatin	1.1	1.2
Lovastatin	2.8	NA
Pravastatin	1.8	1.4
Rosuvastatin	2.2	1.2
Simvastatin	2.1	1.0

fenofibrate, respectively. The pharmacy benefits management group of the Veterans Administration, reported the rate of rhabdomyolysis or acute tubular necrosis to be 0.16% with gemfibrozil-statin combination therapy (149 cases out of 93 677 patients) and 0% with a fenofibrate–statin combination (no cases out of 1830 patients) [78]. These data collectively show that fenofibrate is less likely than gemfibrozil to produce myotoxicity when added to a statin, even if the statin is not cerivastatin. The reason for this disparity may at least in part relate to pharmacokinetic drug interactions between fibrates and statins.

When given in combination with a statin, gemfibrozil results in an increased serum concentration (C_{max}) of the statin; fenofibrate does not act in a similar way (Table 12.6) [79]. Several mechanisms for this interaction have been described [80]. Gemfibrozil and its major metabolite, a 1-O-β-glucuronide, inhibits the transport protein, OATP1B1, mediated transport of the statin into the hepatocyte which could lead to an increased plasma concentration of the statin and diminished LDL-c lowering efficacy [81]. Gemfibrozil is also an inhibitor of CYP2C8. However, many of the dugs used in the treatment of diabetes, including rosiglitazone, pioglitazone, repaglinide, and glimepiride, are metabolized by these enzymes and increased statin area under the curve (AUC) has been reported in patients given gemfibrozil concurrently [79]. Recently, it has been shown that statins undergo glucuronidation *via* UDP glucuronosyl transferases, UGT1A1 and UGT1A3, and subsequent lactonization [82, 83]. Gemfibrozil utilizes the same enzyme system for glucuronidation and renal elimination and thus competes for these enzymes with statins. The result is higher concentrations of the active, open acid form of statins. By this mechanism, gemfibrozil increases the AUC and C_{max} of most statins (except atorvastatin and fluvastatin) (Table 12.6). Conversely, fenofibrate utilizes UDP glucuronosyl transferases, UGT1A9 and UGT2B7, for glucuronidation and does not compete with the enzymes that metabolize statins; thus statin blood levels do not change substantially [80, 84–86]. The exception of atorvastatin is noteworthy as, until recently, it was believed that atorvastatin levels would increase 2- to 5-fold as do other CYP3A4 metabolized, lipophilic statins, simvastatin and lovastatin. However, two recent studies suggest atorvastatin plasma levels rise only 1.2- to 1.5-fold when gemfibrozil is given concurrently [84, 86].

Fenofibrate therapy can cause serum creatinine values to increase. In the FIELD trial, fenofibrate-treated patients experienced an average increase in serum creatinine values of 12%, which returned to baseline after drug withdrawal [66]. The serum creatinine increase with fenofibrate does not appear to be associated with a significant decrease in glomerular filtration rate (GFR) nor are cases of advanced renal failure reported with long-term fenofibrate treatment [38, 66–70, 87]. Some investigators have found that fenofibrate increases creatinine production and does not alter renal function *per se* but this has not been a uniform finding [87, 88]. Regardless, since about 60% of fenofibrate is eliminated *via* the kidney, the

National Lipid Association Safety Task Force has recommended that increasing serum creatinine levels in fenofibrate-treated patients, that cannot otherwise be explained, should cause health professionals to consider discontinuing fenofibrate therapy, especially if the calculated GFR drops below 60 ml/min/1.73m^2 [89]. Gemfibrozil undergoes predominantly hepatic metabolism prior to elimination. It undergoes very little renal excretion as the intact parent molecule. Older recommendations on dosage adjustment for gemfibrozil in the setting of renal failure have been inconsistent. Despite there being less than definitive dosing studies for gemfibrozil in renal failure, the National Kidney Foundation recognizes gemfibrozil as the fibrate of choice in patients with renal transplants and with chronic renal failure who require a fibrate for the management of a dyslipidemia [90]. The National Lipid Association Safety Task Force, however, recommends a more cautious dosing approach and suggests that the dose of gemfibrozil should be halved in patients with a GFR between 15 and 59 ml/min/1.73 m^2 and that it be avoided altogether if the GFR is $<$15 ml/min/1.73 m^2 [89].

Fenofibrate also increases homocysteine an average of 45–55% during chronic therapy [66, 89]. Increases are apparent within 8 weeks of starting therapy and persist until therapy is discontinued. The relevance of this increase is not known. The worry is that increasing levels of homocysteine may create a hypercoagulable state, a concern that was heightened recently when a significant increase in venous thromboembolic events was reported in fenofibrate-treated patients in the FIELD trial [66]. Most concerning of all was that a *post hoc* tertile analysis showed a diminishing reduction in CV events as homocysteine levels rose in fenofibrate-treated patients [91]. Gemfibrozil therapy appears to have little if any effect on homocysteine levels.

THE PLACE OF FIBRATE THERAPY IN CV RISK REDUCTION

The evidence supports the recommendations of NCEP ATP III, which advises health professionals to consider fibrate therapy in the management of patients with atherogenic dyslipidemia and in the management of very high triglycerides to prevent pancreatitis. Further, fibrate therapy should principally be used as add-on therapy with a statin or other LDL-c lowering therapy. The evidence is strong that lowering LDL-c lowers CV risk and death and so statin therapy, or alternative LDL-c lowering agents in statin-intolerant patients, remains the treatment of choice in patients at moderate to very high CV risk. This includes patients with atherogenic dyslipidemia, even if they have a 'low' LDL-c as they often do. Studies have demonstrated that lowering LDL-c at least 30–40% even in those with baseline levels $<$100 mg/dl will reduce CV risk [92, 93]. This is the approach recommended by NCEP ATP III. A valid treatment approach is to first identify patients with sufficient CV risk to warrant medical management, target LDL-c lowering with a statin or alternative therapy to a defined goal, and, in those who still have a triglyceride level $\geq$200 mg/dl after achieving this goal, establish a secondary goal defined by non-HDL-c and utilize lifestyle modification, intensified LDL-c lowering, and/or add-on fibrate or niacin therapy to achieve the new non-HDL-c goal [2, 3].

The main dilemma for the health professional is deciding which fibrate to use and how. Gemfibrozil and fenofibrate have similar efficacy in patients with atherogenic dyslipidemia alone and with a statin. Fenofibrate, but not gemfibrozil, causes a troublesome increase in homocysteine which may blunt its ability to reduce CV events. Gemfibrozil, but not fenofibrate, may increase the risk of muscle toxicity when used in combination with a statin through a pharmacokinetic drug interaction. There is more evidence supporting gemfibrozil's ability to reduce CV events and death, especially in patients with atherogenic dyslipidemia, than fenofibrate which appears to reduce events but not deaths, whether deaths from CHD, CV, or any cause. In neither case has a fibrate demonstrated the ability to reduce events and death when added to a statin. A study is ongoing which will soon address

this issue. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is studying approximately 5519 patients with diabetes to determine whether there is a difference in the occurrence in major CHD events between treatment with simvastatin monotherapy and the combination of simvastatin and fenofibrate during a 5.6-year mean study period [94]. This trial is scheduled to conclude in 2009.

Considering all of the evidence presented in this chapter, gemfibrozil has the better of two problematic profiles. Its use, however, should be restricted to patients who have a triglyceride over 200 mg/dl after receiving LDL-c lowering therapy to goal with either atorvastatin or fluvastatin, neither of which appears to be significantly affected by the pharmacokinetic drug interaction. Alternatively, gemfibrozil may be combined with other statins if lower statin doses are used and careful monitoring is in place. Medications which extend the LDL-c lowering of these statins, such as a bile acid sequestrant like colesevelam or a cholesterol absorption inhibitor like ezetimibe, may be added to the regimen without increasing the risk of myotoxicity. Fenofibrate is best considered as an alternative to gemfibrozil until we better understand its relationship to a diminished CV event rate reduction as homocysteine levels increase and to the increased mortality associated with its use.

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Niacin for dyslipidemia management and atheroprevention: why, when and how?

E. A. Brinton

BACKGROUND

With a brief report by Altschul *et al*. [1] in 1955, niacin became the first pharmacologic agent known to favorably alter serum lipid concentrations in humans. In 1959, niacin was the first lipid-altering agent reported to reduce xanthomata [2]. In 1975, niacin became the first lipid-altering agent proven to reduce cardiovascular disease (CVD) events [3], and in 1986 it was the first lipid therapy to show a reduction in total mortality [4]. Niacin is recognized as the most effective agent for raising high-density lipoprotein (HDL) levels [5] while HDL is recognized as the most potent natural inhibitor of atherogenesis. [5] Niacin is also the only agent which effectively lowers all proatherogenic lipoproteins, not only LDL, IDL and VLDL, but lipoprotein (a) (Lp(a)) as well [6], which may be the most potent adverse lipoprotein on a per-particle basis. As noted below, niacin also has many non-lipid actions which should have favorable effects on atherosclerosis [7, 8]. Niacin is the only effective lipid-altering agent which is also both a natural product and a vitamin. Thus, it has a unique historical and practical status among lipid therapies.

LIPID EFFECTS

At its highest recommended dose of 2 g, once-daily extended-release (ER) niacin lowers low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG) moderately, about 17% and 35%, respectively. It is also the most effective agent available for raising HDL-c, by about 26%, and for lowering Lp(a), by about 24% [9]. Niacin is the broadest and most versatile lipid agent, as the National Cholesterol Education Program Adult Treatment Panel III Guidelines (NCEP ATP III) states: 'Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia' [10].

In contrast to the statins, with which most of the lipid benefit occurs with low doses, the lipid dose–response curve for niacin tends to be fairly linear [9]. Although this means that one can usually obtain greater lipid effects, if desired, by pushing to higher doses, it also means that the response at lower doses may be disappointing. Thus, dose uptitration is very important clinically, as are measures to improve tolerance to side-effects (*see* below), which also tend to be dose-related. The other niacin formulations, immediate-release (IR) and sustained-release (SR), tend to provide lipid effects comparable to those of the ER formulation,

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although IR niacin can be given at much higher doses than ER or SR niacin, and thus may achieve higher maximal lipid responses.

HOW DOES NIACIN WORK?

Niacin has many complex effects on lipid and lipoprotein metabolism. Although many of these effects are well understood, mechanisms of many of the most important of niacin's effects remain elusive despite more than half a century of research and clinical experience with this important lipid treatment agent.

In 2001, a G protein-coupled receptor for niacin was described, GPR109A [11]. In 2003, three groups identified this receptor as the human orphan receptor HM74A, homologous in the mouse to the 'protein upregulated in macrophages by interferon-gamma' (PUMA-G). [12–14]. This receptor is located in adipocytes and immune cells (spleen, lung, lymphoid cells, macrophages and epidermal Langerhan cells). In adipocytes, binding of niacin to GPR109A reduces intracellular hydrolysis of stored TG and subsequent release of free (non-esterified) fatty acids (FFA) into the plasma. This, in turn, tends to reduce hepatic FFA and TG content, reducing VLDL synthesis and plasma TG levels. While this may help account for the ability of niacin to reduce TG and VLDL levels, the decrease in FFA is brief and soon rebounds above baseline, so its significance is unclear [15, 16]. Furthermore, niacin has been shown to reduce activity of diacyl glycerol acyl transferase-2 (DGAT2), a key enzyme in the synthesis of TG and this may better explain its ability to reduce VLDL production and TG levels [17]. This is also hypothesized to be a mechanism by which niacin lowers Lp(a), in that Lp(a) appears to be a derivative of LDL, and thus ultimately may be a derivative of VLDL [17].

The effects of the binding of niacin to GPR109A in immune cells might contribute to anti-inflammatory, and thus anti-atherogenic, effects of the drug [18], but this has not been established. Meanwhile, it seems unlikely that any immune-cell effect could account for the lipid changes with niacin.

The lipid effect of niacin likely of greatest importance is the increase in HDL-c levels. It has long been clear that niacin's primary effect on HDL metabolism has been to reduce the rate of clearance or catabolism of the major HDL protein, apoAI, from the plasma. Binding of apoAI to the β-chain of adenosine triphosphate (ATP) synthase on the surface of the hepatocyte might mediate such clearance [19]. Niacin has been shown to reduce uptake of apoAI by Hep G2 cells, a transformed hepatocyte cell line [20], which might relate to the β-chain binding. This effect could account for much or most of the ability of niacin to increase HDL levels. In contrast, the effect of niacin on HDL is probably not related to its binding to GPR109A, since this receptor is not found in hepatocytes, nor does it appear to modulate HDL uptake or catabolism.

In addition to its beneficial lipid effects, niacin appears to have many other properties, such as anti-inflammatory, antioxidative, antithrombotic, profibrinolytic and pro-endothelial effects, which would be expected to reduce atherogenesis [7, 8].

REDUCTION IN ATHEROSCLEROSIS AND CVD EVENTS

Nine published clinical trials have shown efficacy of niacin in reducing atherosclerosis, CVD events, or both, as recently reviewed by Guyton [15]. Unfortunately, only two of these, the CDP (Coronary Drug Project) [3] and ARBITER 2 (Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial) [21], employed niacin separately, either in monotherapy or added to statin therapy. All other trials added niacin simultaneously with other lipid agents, making it difficult to assess the impact of niacin *per se*.

The oldest niacin study, the CDP, remains the most important due to its use of niacin monotherapy, about 3 g/day of the IR form (vs placebo), and its focus on CVD events [3]. Treatment continued for about 6 years in 1119 men with prior CVD events. Several major CVD-related endpoints were significantly reduced, including total mortality, although the

latter effect did not become statistically significant until extended follow-up was completed [4]. A major drawback of the CDP is the fact that HDL-c levels were measured in only a small subset of patients, so the contribution of baseline and on-treatment HDL-c is unknown. Also, it was done long before other preventive measures were developed, and so its relevance to current treatment situations is unclear, especially the ability of niacin to add to atheroprevention with statin treatment.

Fortunately, ARBITER 2 directly addressed this question by studying the effect of adding 1g/day ER niacin or matching placebo in subjects already taking statin monotherapy, change in carotid intima-media thickness (CIMT) being the primary outcome measure [21]. During 1 year of treatment, CIMT progressed significantly in those on statin plus placebo, whereas there was no significant CIMT progression in those given niacin in addition to the statin [21]. During a second year of follow-up, all subjects received niacin, and at the end of 2 years CIMT was reduced from baseline both in those receiving 2 years and 1 year of added niacin treatment [22].

Although only two of the niacin clinical trials, the CDP and the Stockholm Heart Study, employed CVD events as the primary endpoint, several other trials provided CVD endpoint data. Among the remaining seven studies, which focused on surrogate measures of atherosclerosis, coronary angiography or CIMT, three others, FATS (Familial Atherosclerosis Treatment Study) [23], HATS (HDL Atherosclerosis Treatment Study) [24] and AFREGS (Armed Forces Regression Study) [25] also noted statistically significant reductions in CVD events as a secondary finding. Furthermore, only one published clinical endpoint trial of niacin, HARP (Harvard Atherosclerosis Reversibility Project) [26], has failed to show a statistically significant atherosclerosis benefit, and even this study showed a favorable trend towards fewer clinical CVD events. Thus, with all studies taken together, the scientific support is strong for the use of niacin in atheroprevention.

The Stockholm Heart Study [27] compared niacin plus clofibrate vs placebo for 5 years in patients with a recent myocardial infarction, and found a CVD event rate reduction similar to that in the CDP. Since clofibrate has not otherwise been shown to reduce CVD events, the Stockholm results support the positive findings with niacin monotherapy in the CDP. Unfortunately, like the CDP, the Stockholm study was not done against the backdrop of modern therapy for lipid and blood pressure reduction, and HDL-c levels were not measured.

The remaining six published niacin trials used coronary angiography as the primary endpoint, and all studied niacin in combination with one or more other lipid agents: two with gemfibrozil [25, 26], five with bile acid sequestrants [23, 25, 26, 28, 29] and four with statins [23, 24, 26, 29]. As noted above, five of these six studies showed statistically significant benefit with niacin combination treatment. Interestingly, four of these five reported net regression, on average, of the severity of coronary atherosclerosis, [23–25, 29] while only two of several studies testing statin monotherapy have shown a similar benefit [30, 31]. The only completed trial of niacin effects on CIMT showed regression of atherosclerosis, on average, with the addition of niacin to statin monotherapy [22], while recent studies of aggressive statin monotherapy [32] and the addition of ezetimibe to high-dose statin [33] failed to show atheroregression by CIMT.

Although intuitively niacin should be most effective in patients with low HDL-c levels, this has not been well tested in published niacin trials. Three of the studies showing regression of atherosclerosis recruited patients for low baseline HDL-c [22, 24, 25], but none have tested carefully for the impact of low versus normal versus high baseline HDL-c on the ability of niacin to reduce progression of atherosclerosis or reduce CVD events.

DOES ADDING NIACIN TO A STATIN HELP REDUCE CARDIOVASCULAR EVENTS?

Not only does the combination of niacin and a statin produce excellent lipid effects [34, 35], but the addition of niacin to a statin provides lipid benefits beyond those of a statin alone [36].

Clinical endpoint trials provide evidence that greater lipid benefit relates to greater atherosclerosis benefit. Four published trials have shown reduced progression and even regression of atherosclerosis resulting from the combination of niacin with a statin (with or without other lipid agents) [23, 24, 26, 29], but they do not answer two key questions: (1) the degree of contribution of each agent, and (2) whether it is beneficial to add niacin to the regimen of a patient already taking a statin. The ARBITER 2 trial [21] (along with its extension, ARBITER 3 [22]) does address this question, showing that the addition of niacin to statin monotherapy reduced progression of atherosclerosis by CIMT [21], and eventually induced its regression [22]. Although this study has been criticized for its small number of patients and relatively short period of follow-up, it is the only trial to date which directly addresses the issue of atherosclerosis-related benefits of adding niacin to a statin. Surprisingly, as modest as the evidence for niacin may be, there is no direct clinical trial evidence to date regarding the addition of any other lipid agent to a statin. Other studies of niacin with a statin, such as HATS [24], suggest greater atherosclerosis benefit with the combination of niacin plus a statin indirectly by comparing favorably with separate trials employing statin monotherapy.

Three large ongoing studies promise to greatly enhance our understanding of the potential for niacin as a potent adjunct to statins in atheroprevention. The ongoing study NTCØØ384293 (A Worldwide, Double-Blind, Randomized, Placebo-Controlled Study of MK0524A Coadministered With Intensive LDL-c Lowering Therapy Compared to Intensive LDL-c Lowering Therapy Alone on Carotid Artery Intima Media Thickening) [37] employs the atherosclerosis endpoint of CIMT and will compare effects of 2 years' treatment with ER niacin (given with a prostaglandin D_2 receptor subtype 1 (DP1) inhibitor, laropiprant, *see* below) plus simvastatin versus those of simvastatin alone in about 900 subjects with heterozygous familial hypercholesterolemia. Results are expected in about 2009. AIM HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes) [38] is testing CVD events over about 5 years with ER niacin plus simvastatin versus simvastatin alone in about 3300 subjects with low HDL-c and the metabolic syndrome. Results are expected in about 2012. A third study, HPS2-THRIVE (Heart Protection 2-Treatment of HDL to Reduce the Incidence of Vascular Events) [39] will study effects on CVD events over 4–5 years in about 20 000 subjects, with prior CVD (about two-thirds) or diabetes mellitus type 2 (about one-third). It will study the same medication regimens as in ACHIEVE, and results are expected in about 2013.

NIACIN TOXICITY: WHAT TO MEASURE? HOW TO MINIMIZE?

Niacin is reported to worsen insulin resistance by 36–63% when measured by intravenous glucose tolerance test [39, 40–42], but only by 15–21% when measured by an insulin clamp [42, 43–45]. Increased insulin resistance probably accounts for the tendency of niacin to increase serum glucose; however, the latter effect is rather small, on average 5–10% [24, 46–48], suggesting that there are compensatory changes which minimize glucose increases, and increased insulin secretion is a primary candidate for such compensation [42]. Most studies also suggest that the glucose increase is temporary, reversing over months [47, 48] to years [46], and data suggest the mechanism of adaptation to be increased β-cell function [42]. Fortunately, among patients with diabetes, any glucose increase generally can be controlled in the usual course of diabetes treatment [47, 48]. In patients without diabetes, niacin is not reported to increase conversion to the diabetic state [3]. Most importantly, niacin appears to reduce CVD equally well in patients with diabetes and impaired fasting glucose subjects as in normoglycemic individuals [46], and equally well whether fasting glucose increases more or less than 10 mg/dl or decreases [46]. Together, these data strongly suggest that niacin is a good agent for CVD prevention in patients with diabetes or pre-diabetes [49]. It is wise, how-

ever, to measure glucose levels periodically during niacin use, and to respond with glucose-lowering measures if needed. It does not appear that the tendency for glucose increases differs among niacin formulations.

The potential for serious hepatotoxicity with niacin use has been of concern ever since a report of such in the early 1960s [50]. The risk, however, appears to be almost entirely with dietary-supplement SR formulations at a dose of 1g/day or higher [51, 52]. In contrast, IR and once-daily ER niacin appear to have minimal hepatotoxicity up to 3 g/day [53]. It is not known if the greater toxicity with SR niacin is an intrinsic property of this formulation, due to the very slow rate of drug release, or if it is simply due to the fact that a very slow-release product causes uninterrupted hepatic exposure when given in multiple daily doses. Despite the lack of liver toxicity at moderate doses of the more commonly used ER formulation, the Food and Drug Administration (FDA) has placed warnings in the package insert for prescription ER niacin that transaminase levels be monitored before and during niacin use and that it not be given in cases of underlying liver disease [54].

Myopathy has been reported with niacin, but the cases have been rare and either very mild or associated with predisposing factors (*see* Guyton and Bays [55] for a review). The FDA has placed warnings regarding myopathy risk with the combination of niacin with a statin in the package insert of prescription niacin products [54]; however, there is no good evidence that this combination has a risk of myopathy beyond that of a statin alone [55], and the FDA has approved a fixed-dose tablet containing a statin and niacin (Advicor®) [56]. Similar considerations apply to the newly approved combination of ER niacin with simvastatin (Simcor®). Due to the lack of tendency for myopathy, measurement of creatine kinase levels during niacin treatment is not needed, except if warranted by the use of other agents such as statins or fibrates.

Niacin raises uric acid levels by competitive inhibition of renal tubular secretion of uric acid [57] and can precipitate a gouty attack in patients with or even without a prior history of such (*see* Guyton and Bays [55] for a review). Any hyperuricemia (or gout) resulting from niacin treatment can be treated either with the usual treatments for these disorders or, if necessary, by discontinuation of the niacin. Active gout, however, is considered a relative contraindication to niacin use [55].

Niacin causes an increase in gastric acid secretion [58] and can cause or exacerbate peptic ulcer disease [59]. Gastrointestinal upset may be more common with SR than with IR niacin [60]. Although this complication in particular [61] and dyspepsia in general [62] are uncommon with niacin, active peptic ulcer disease is a contraindication to niacin use [54, 55]. Atrial fibrillation was reported to increase 62% with niacin in older men with established CVD studied in the CDP trial [3]. This has not been reported in other niacin trials (generally in subjects without CVD), however, and is rarely noted in clinical use. Blurred vision due to macular edema has been reported with niacin; however, its frequency appears to be limited to a few case reports, it resolves upon discontinuation of the drug [63], and does not appear to be associated with fluorescein leakage on retinal angiography [64]. Niacin may rarely cause acanthosis nigricans or other rashes, but these are generally minor and seldom of clinical importance [6, 55].

HOW CAN NIACIN TOLERABILITY BE MAXIMIZED?

Niacin is not used in many patients for whom it would be beneficial. Although toxicity (discussed above) and cost are concerns for some, the underuse appears most often due either to a lack of tolerability by the patient, or due to physician perception of lack of tolerability on the part of the patient [55]. Given the relative infrequency of adverse gastrointestinal or joint symptoms with niacin, its poor tolerability is mainly due to flushing.

Hepatotoxicity (*see* above) and flushing are determined largely by niacin dose and by selection among the three types of formulations: IR, SR and ER. IR is the formulation used

in most of the atherosclerosis and CVD event trials (*see* above) and is available primarily as various dietary supplement products, but also as an FDA-regulated prescription product (Niacor®). Peak plasma levels are reached 30–60 min after oral administration of the IR form and the drug is rapidly excreted in the urine with a half-life of 20–45 min [65]. Although the half-life of the lipid effect of IR niacin is long enough to warrant once-daily administration, in order to reduce the amount per dose while maximizing the daily dose it is usually given two or three times daily. SR niacin products employ various time-release mechanisms and are available as a variety of dietary supplement products. Although SR preparations traditionally are given two or more times daily, some come with instructions to be taken once daily. ER niacin is a proprietary hydro-gel release formulation available only by prescription (Niaspan®). It is said to have a release rate intermediate between IR and SR, although published comparisons of absorption kinetics between ER and SR niacin are lacking. A new ER formulation, combined with the flush-reducing DP1 inhibitor, laropiprant (Cordaptive®), is currently under review by the FDA. No data are yet available directly comparing the efficacy, safety, tolerability or pharmacokinetics of these two ER niacin products.

Differences in lipid-lowering efficacy among the various niacin formulations have been found in some [66] but not other studies [67]. Any true differences are relatively minor and do not tend to drive the selection of a niacin product. Instead, niacin product selection is mainly dictated by the following factors: (1) flushing – less with SR and ER than with the IR formulation [66]; (2) hepatotoxicity – less with IR and ER than with SR [53]; (3) cost – less for dietary supplement IR and SR products than for branded ER and IR niacin; and (4) quality – better assured for prescription IR and ER products than for dietary supplement IR and SR products. Regarding this last point, the American Heart Association has stated that 'dietary supplement niacin must not be used as a substitute for prescription niacin. It should not be used for cholesterol lowering because of the potential for very serious side effects' [68].

Flushing is noted by most patients as they begin niacin therapy, being reported in about 70% of patients even with a 500 mg dose of ER niacin given once daily at bedtime [56]. The number of flushing episodes experienced is several-fold higher when using an IR versus the ER formulation [67]. The 750 mg and 1 g tablets of ER niacin were reformulated in 2007, resulting in significant reductions in the intensity and duration of flushing, although its frequency was little reduced [69].

Niacin tolerability and safety can be maximized by (1) taking niacin once daily at bedtime; (2) using prescription ER niacin; (3) starting at a low dose and then gradually uptitrating; (4) taking niacin with or 30 min after aspirin or another non-steroidal anti-inflammatory agent [70, 71] or possibly with diphenhydramine; (5) taking the dose with a low-fat, high-fiber snack [54]; (6) avoiding other concurrent factors which could predispose to flushing such as exposure to external heat or ingestion of alcohol or hot or spicy foods [55] and (7) possibly taking sufficient omega-3 oil to change the prostaglandin products of niacin-induced cyclooxygenase activity.

A type of 'flush-free' niacin, inositol hexaniacinate, consists of six niacin molecules attached to an inositol backbone. Unfortunately, the lack of flushing appears to be due to a lack of release of free niacin, which prevents any lipid (or other) benefits [55]. Niacinamide also does not cause flushing but lacks lipid benefits.

Recently, the major mechanism of the niacin flush has been elucidated. First, niacin binds to the GPR109A receptor in epidermal Langerhan cells [72] which is analogous to the PUMA-G/HM74A receptor in mice. This binding induces production of various prostaglandins by cyclooxygenase 1 [18]. The binding of one of these products, PGD2, to the DP1 receptor on dermal blood vessel cells activates vasodilatation and flushing [73]. Knowledge of this mechanism has been applied to the development of an inhibitor of the final step, the binding of PGD2 to DP1. The first such agent, laropiprant (MK0524) is reported to inhibit up to three-quarters of niacin flushing, even when administered simultaneously with niacin [74]. Laropiprant is currently being evaluated by the FDA and, if

approved, it promises to reduce flushing with niacin sufficiently to obviate the need for its slow uptitration, for concurrent aspirin use, and perhaps also for most other anti-flushing measures.

Development of other niacin adjuncts and of niacin analogs is underway. Non-niacin agonists for the GPR109A receptor are being considered, but are problematic for two important reasons. First, the binding of niacin to the GPR109A receptor is the major trigger for niacin-induced flushing, so other agonists may well cause similar side-effects. Second, niacin binding to this receptor appears not to account for much of its lipid effects, so the ability of other GPR109A ligands to favorably alter lipids is in doubt [16].

SUMMARY

Niacin is recommended as an adjunct to a statin when non-lipid risk factors and especially residual dyslipidemia suggest high residual CVD risk [75]. Also, niacin can be used as monotherapy or in combination with any other lipid agent. Although it is often used primarily in patients with low HDL-c levels, few of the clinical trials with atherosclerosis or CVD endpoints have focused on these patients, and it is probably useful regardless of baseline HDL. Importantly, ongoing clinical trials should clearly delineate the ability of niacin to add to CVD event reduction in statin-treated patients with and without low baseline HDL-c. If clearly positive, these results should greatly increase the clinical imperative for wider niacin use. Meanwhile, primarily due to concerns about tolerability, niacin use is currently quite limited, being confined largely to occasional adjunctive use with statins or with fibrates for extra HDL raising and/or TG and LDL lowering. Nevertheless, recent and ongoing advances in the ability to reduce flushing and in our understanding of the occasional problems with safety suggest that the use of niacin can and should increase significantly in the near future.

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Which dietary supplements have proven efficacy for impacting serum lipids and cardiovascular outcomes and are any vitamins harmful to the cardiovascular system?

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BACKGROUND

Healthy nutrition practices together with other lifestyle behaviors including physical activity, a healthy body weight, and non-smoking are recommended for the prevention and treatment of cardiovascular disease (CVD). On the basis of a large database of clinical trial and epidemiologic evidence, diet and lifestyle recommendations have been made. The recommendations emphasize a food-based approach for building healthy dietary patterns to decrease risk of many chronic diseases, including CVD [1, 2]. Because certain dietary patterns, such as those high in fruits and vegetables, are consistently associated with decreased risk of CVD, there has been interest in identifying the key bioactive nutrients and phytochemicals that confer a protective effect. Many of these have been identified, and include B vitamins [folic acid, vitamin B6, vitamin B12, and niacin), antioxidant vitamins (vitamin C, vitamin E, vitamin A, selenium, and β-carotene), omega-3 fatty acids, plant stanols and sterols, and soluble fiber. There has been an impetus for marketing these as dietary supplements that reduce CVD risk. The popularity of nutritional supplements has led to the emergence of nutraceuticals, defined as foods or supplements that are purported to have a medicinal effect on health. Unfortunately, there are many instances where the scientific evidence base is insufficient to support the health benefits presented on the labels of supplements and foods. In addition, as science advances, many questions are emerging about the benefits and risks associated with these products.

In this chapter, we summarize the results of randomized clinical trials of dietary supplements that are recommended for CVD risk reduction. In most cases, such as for vitamin B12, folic acid, and vitamin B6, which lower homocysteine concentrations, and for antioxidant vitamins, which include vitamin C, vitamin E, selenium, and β-carotene, there is little effect

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of supplementation on CVD events and mortality. In some instances, adverse effects have been reported. In contrast, other supplements, such as niacin and omega-3 fatty acids have shown protective effects for secondary prevention of CVD in randomized clinical trials. Plant stanols and sterols and soluble fiber are often recommended for CVD risk reduction because they lower total and low-density lipoprotein (LDL) cholesterol when used alone or in conjunction with statins. However, they have not been studied in long-term clinical trials that have evaluated coronary morbidity and mortality.

On the basis of the evidence, there are clinical practice recommendations for supplements that are applied widely. In some cases, there is robust evidence that justifies recommendations that have been made for nutrient supplements. In other instances, the database is emerging or lacking, and for some, because of reported adverse effects, recommendations NOT to use them are warranted. Thus, the purpose of this chapter is to provide an overview of the current understanding of the evidence for popular dietary supplements, and to give practitioners guidance about appropriate recommendations for clinical practice. Herbal products, which have a very limited database, are outside the scope of this chapter but there are recent reviews for interested readers [3–5].

NIACIN

Niacin (nicotinic acid) has been recognized as a cholesterol-lowering agent for over 50 years [6]. However, its use in clinical practice has been limited due to adverse side-effects including cutaneous flushing and hepatic toxicity [7]. There is renewed interest in using niacin to treat dyslipidemia with the development of new formulations that reduce flushing and have a low incidence of hepatic toxicity [8, 9]. Numerous studies have shown that niacin in gram doses (1–3 g/day) increases high-density lipoprotein (HDL)-c and decreases triglycerides, LDL-c and lipoprotein (a) [6, 10–16]. Niacin is the most effective agent for raising HDL-c, resulting in increases of 15–35%. Niacin also lowers LDL-c by 5–25% and triglycerides (TG) by 20–50% [17]. Triglyceride levels are lowered via inhibition of hepatic triglyceride and very-low-density lipoprotein (VLDL) production and inhibition of lipolysis in adipose tissue [16, 18]. The HDL-c raising effect of niacin is due to decreased HDL degradation [19]. The usual daily dose of niacin is 1.5–3 g/day for immediate-release (IR) (crystalline) niacin, 1–2 g/day for sustained-release (SR) niacin, and 1–2 g/day for extended-release (ER) niacin [20].

A reduced frequency of cardiovascular (CV) events has been reported when niacin is taken alone or combined with statin drugs. The Coronary Drug Project evaluated the long-term efficacy and safety of lipid-influencing drugs, including niacin, in 8341 men with a previous myocardial infarction (MI) [21]. For patients taking niacin (3 g/day), the incidence of non-fatal MI and cerebrovascular endpoints (stroke or transient ischemic attack [TIA]) were reduced by 26% and 24%, respectively, relative to placebo after 5 years ($P < 0.05$). Niacin also lowered total cholesterol by 10% and triglycerides by 26%. Nine years after the conclusion of the study, all-cause mortality was 11% lower in the niacin group compared with the placebo group ($P < 0.001$), primarily due to a reduction in coronary heart disease (CHD) death [22], suggesting there may be long-term CV benefits of niacin treatment.

The HDL Atherosclerosis Treatment Study (HATS) evaluated the effect of combination therapy of niacin plus a statin on coronary stenosis and the occurrence of a first CV event [23]. One hundred and sixty men and women with clinical coronary disease were randomly assigned to one of four treatments: niacin plus simvastatin; antioxidant vitamins (800 IU vitamin E, 1000 mg vitamin C, 25 mg β-carotene, and 100 μg selenium); niacin, simvastatin and antioxidant vitamins; or placebo. After 3 years, 3% of participants in the niacin plus simvastatin group had a CV event (death from coronary causes, confirmed MI or stroke, or revascularization for worsening ischemic symptoms) compared with 24% in the placebo group ($P = 0.03$) (Figure 14.1). In addition, simvastatin plus niacin was the only treatment group that produced a regression in stenosis (0.4% regression). Including the antioxidant

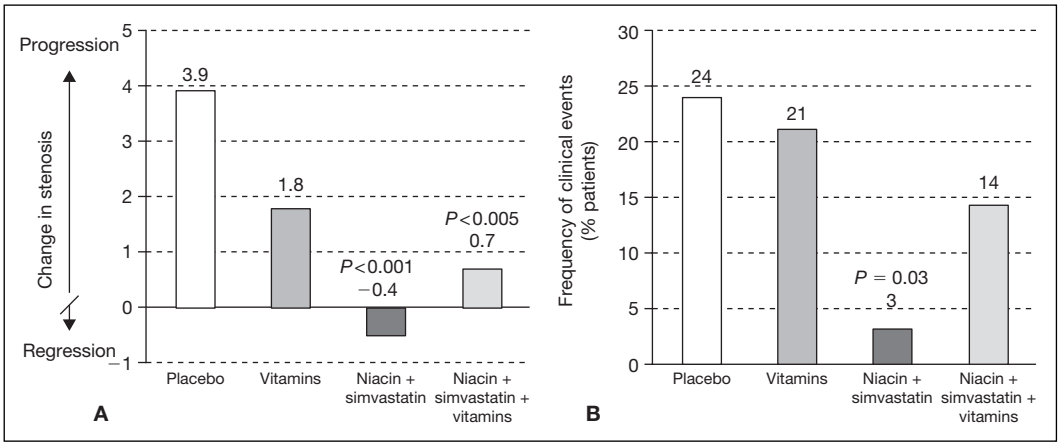

Figure 14.1 Percent change in stenosis (A) and frequency of clinical events (B) over 3 years of treatment with placebo, antioxidant vitamins (800 IU vitamin E, 1000 mg vitamin C, 25 mg β-carotene, and 100 μg selenium), niacin + simvastatin, or niacin, simvastatin, and antioxidant vitamins in the HDL atherosclerosis treatment study (HATS) [23, 125]. Niacin + simvastatin was the only treatment to cause a regression in stenosis. There was also a reduced frequency of clinical events in the niacin + simvastatin group compared with placebo. Adapted with permission from [125].

cocktail with the drug regimen blunted the benefits of the simvastatin plus niacin treatment. Stenosis progressed by 3.9% in the placebo group, by 1.8% in the antioxidant cocktail group, and by 0.7% in the simvastatin/niacin plus antioxidants group. The Familial Atherosclerosis Treatment Study (FATS) and Cholesterol-Lowering Atherosclerosis Study (CLAS) also reported either decreased rates of atherosclerosis progression or regression of coronary stenosis with niacin in combination with a LDL-lowering drug [24, 25].

There is also a benefit noted with a combination of niacin and statin therapy on the lipid and lipoprotein profile. Specifically, there is a greater decrease in triglycerides and LDL-c and an increase in HDL-c with combination therapy than with either treatment taken alone [26, 27]. In the largest trial, 2 g/day of ER niacin with 40 mg/day lovastatin reduced LDL-c 42% in hypercholesterolemic men and women, which was significantly greater than the LDL-c reduction of 32% with lovastatin alone and 14% reduction with niacin alone ($P < 0.05$) [26]. Similarly, HDL-c increased 30% with the combination therapy compared with an increase of 6% with lovastatin alone and 24% with niacin alone. Triglycerides decreased 43% with the combination treatment compared with a 20% and 23% decrease with lovastatin and niacin alone.

Overall, current evidence indicates that niacin effectively improves the lipid profile and reduces CV risk when used alone or in combination with LDL-c lowering medications. Of note, the upper limit for niacin established by the Institute of Medicine, or the largest daily intake that is unlikely to cause harm, is 35 mg [28]. However, the dose needed to raise HDL-c is 1–3 g/day. Flushing occurs in almost all patients taking IR niacin [21], which has limited its use. SR niacin was developed to reduce flushing, but hepatic toxicity occurred at a greater frequency [29, 30]. The ER formulation reduces the incidence of flushing by 80% compared with IR niacin, and has an equivalent lipid-lowering efficacy [14] and a rare incidence of hepatic toxicity (≤1%) [11, 13, 31]. Mild hyperglycemia (5% increase in fasting plasma glucose) results from 2 g/day ER niacin [32]. However, the favorable effects of niacin on lipids and lipoproteins appear to outweigh any increase in glucose levels [33]. Although ER niacin

has been shown to be safe and tolerable, monitoring liver blood tests while using niacin is recommended.

FISH AND FISH OIL

Fish and fish oil are rich sources of long chain omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The association between fish consumption and coronary heart disease (CHD) mortality has been evaluated in population studies with over 220 000 individuals who were followed for an average of 11.8 years [34]. Compared with individuals who rarely eat fish, the risk of death from CHD is 38% lower for individuals who consume the most fish (≥5 times a week) [34]. Individuals who consume five or more servings of fish per week also have a greater reduction in risk of stroke (~31% lower risk) compared with those who eat fish less than one time per month [35]. Two case-controlled studies have also found that risk of sudden death from cardiac causes or fatal ischemic heart disease (IHD) was lower in subjects with lower baseline plasma phospholipid concentrations of EPA and DHA [36, 37].

Randomized, clinical trials evaluating omega-3 fatty acids have shown a protective effect of fish and fish oil on CVD risk. The favorable effects on overall and cardiac mortality are similar to that seen with statins (Figure 14.2) [38]. The two largest clinical trials are the Gruppo Italiano por lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study and the Diet and Reinfarction Trial (DART) [39, 40]. The GISSI study enrolled 11 000 recent MI survivors and randomized them to receive supplements of either 850 mg/day EPA + DHA or placebo for 3.5 years [40]. There was a 15% significant reduction in the primary endpoint of death, non-fatal MI, and non-fatal stroke in subjects who took EPA + DHA ($P < 0.05$), as well as a 20% reduction in all-cause mortality and 45% reduction in sudden death ($P < 0.05$). The DART was a randomized controlled trial where 2033 male MI survivors were randomized to receive dietary advice to either: (a) reduce fat intake and increase the ratio of polyunsaturated to saturated fat in their diet; (b) increase fatty fish intake to at least two servings a week; or (c) increase cereal fiber intake [39]. In two years, men who had been advised to eat fish had a 29% reduction in all-cause mortality compared with men who were not advised to increase fish intake ($P < 0.05$).

Although most clinical trials have observed a benefit of fish or fish oil in the secondary prevention of CHD, not all studies have shown a protective effect. These include a study by Nilsen *et al*. [41], which found no clinical benefit of 3.5 g/day EPA + DHA for 12–24 months on cardiac events in 300 patients who had an acute MI. It was subsequently suggested that the lack of benefit of omega-3 fatty acids in this study may have been due to a habitually high fish consumption in this Norwegian population [42]. In another trial conducted by Burr *et al*. [43] in 3114 men with angina, subjects who were advised to consume two servings of fish/week or three 0.5 g MaxEPA capsules/day of fish oil had a higher cardiac death rate (11.5% vs 9.0%; $P = 0.02$) and a greater risk of sudden cardiac death (4.6% vs 3.0%, $P = 0.02$) than subjects not on the fish/fish oil treatment. This increase in risk was largely attributed to the group taking fish oil capsules. Some researchers have questioned the results reported in the study due to incomplete data collection and the use of inadequate measures of compliance [44].

ANTIARRHYTHMIC EFFECTS

The primary beneficial effect of omega-3 fatty acids appears to be in preventing cardiac arrhythmias. Omega-3 fatty acids prevent spontaneous or medication-related tachycardia/arrhythmias in cultured neonatal cardiomyocytes [45] and reduced the risk of ventricular fibrillation (VF) by approximately 75% when a MI was surgically induced in dogs [46]. Calò *et al*. [47] also found that the incidence of atrial fibrillation (AF) after coronary artery

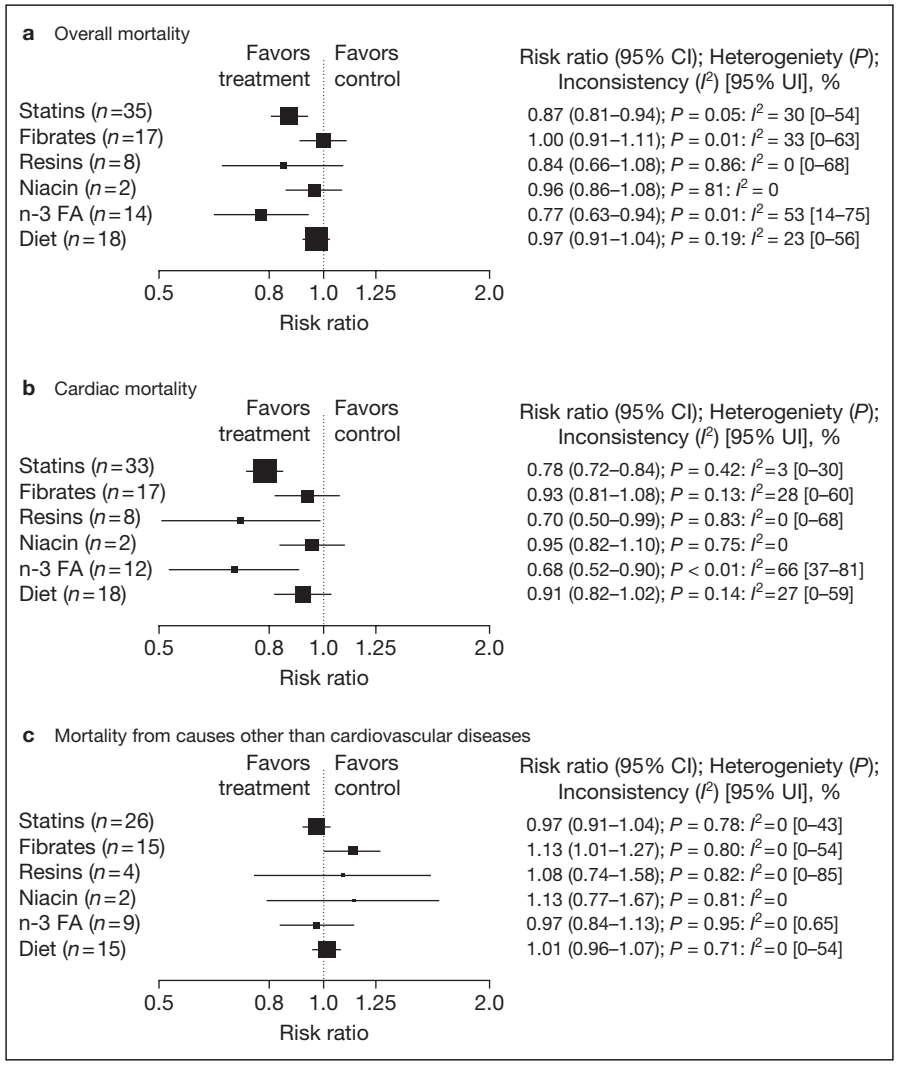

Figure 14.2 Summary estimates for overall mortality (a), cardiac mortality (b), and mortality from causes other than cardiovascular diseases (c) for different types of lipid-lowering interventions [38]. The risk of overall and cardiac mortality was significantly reduced for statins and omega-3 fatty acids. UI = uncertainty interval. Reprinted with permission from [38].

bypass graft surgery was reduced when patients took 850–882 mg/day of EPA + DHA from at least 5 days before surgery until discharge from the hospital. Postoperative AF developed in 27/81 patients in the usual care group (33.3%) and in 12/79 patients of the EPA + DHA group (15.2%) ($P = 0.013$).

Clinical studies on the antiarrhythmic effects of fish oil supplementation in humans with implantable cardioverter defibrillators (ICDs), however, have been inconsistent. Raitt *et al.* [48] conducted a randomized, double-blind, placebo-controlled trial of 1.8g/day EPA + DHA for a median of 718 days in 200 patients with ICDs and observed no overall

effect on the incidence of ventricular tachycardia (VT) or VF in the 2-year study period. In a subset of 133 patients that had an episode of sustained VT prior to enrollment, there was a greater number of patients with VT or VF events compared with individuals in the control group ($P = 0.007$), suggesting that fish oil could be arrhythmogenic in this population.

Alternatively, the Fatty Acid Antiarrhythmia Trial (FAAT) conducted by Leaf *et al*. [49] in 402 patients with ICDs found that supplementation with 4 g/day of fish oil had a trend toward antiarrhythmic benefits. Patients taking a fish oil supplement tended to have a delay in time to the first ICD event (VT or VF) or of death from any cause (risk reduction of 28%; $P = 0.057$). In the Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA), there was no evidence of a protective effect of intake of omega-3 fatty acids from fish oil (2 g/day) when given to 546 patients with an ICD and prior malignant VT or VF for a median of 356 days (range 14–379 days) [50]. The primary endpoint of VT, VF or death from any cause occurred in 33% of patients taking placebo and 30% of patients taking fish oil (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.64–1.16; $P = 0.33$). In summary, studies of EPA + DHA supplementation in patients with ICDs have not consistently demonstrated reductions in either CHD mortality or the incidence of ventricular arrhythmias. The current recommendations of the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC) are that omega-3 fatty acid supplementation be considered for patients with ventricular arrhythmias and underlying CHD [51, 52]. Currently, the AHA/ACC does not have guidelines for fish oil supplementation or oily fish meals in patients with ICDs. For patients with CHD, the AHA recommends consuming ~1 g of EPA + DHA per day (equivalent to approximately 1 serving of fatty fish/day) [53]. EPA + DHA supplements could be considered in consultation with a physician.

OTHER EFFECTS OF FISH OIL

In patients with hypertriglyceridemia, omega-3 fatty acids lower triglycerides in a dose-dependent manner, with a larger decrease in triglycerides in subjects with higher baseline levels. Two to four grams of EPA + DHA per day can lower triglycerides by 20–40% and increase HDL-c 1–3% without significantly affecting total cholesterol [54]. Intake of 2–4 g/day EPA + DHA also increases LDL-c 5–10% [54], but the increase in LDL-c is often accompanied by favorable increases in LDL particle size [55–57]. Omega-3 fatty acids have a small, dose-dependent, blood pressure (BP) lowering effect in hypertensive individuals (−3.4 mmHg systolic and −2.0 mmHg diastolic with an average 5.6 g/day fish oil) [58] and have been shown to suppress expression of cell adhesion molecules by endothelial cells, to enhance endothelial nitric oxide production, and to reduce platelet aggregation [59–63].

There is no strong evidence to differentiate EPA from DHA as the primary active component that is protective against CVD. In fact, similar changes in lipids and lipoproteins have been reported with purified EPA and DHA in patients with type 2 diabetes [64]. Although most supplementation trials have compared a combination of EPA + DHA, the Japan EPA Lipid Intervention Study (JELIS) study compared 1800 mg of EPA daily with a statin versus a statin alone in 18 645 patients with a total cholesterol ≥6.5 mmol/l (≥250 mg/dl). There was a 19% relative reduction in major coronary events in patients in the EPA group compared with the statin only group (2.8% vs 3.5%) over a mean follow-up of 4.6 years ($P = 0.011$) [65]. Additional randomized, prospective studies are needed, however, to determine the independent effects of EPA and DHA.

B VITAMINS

Supplementation with folic acid, vitamin B6, and vitamin B12 has been proposed as a strategy to reduce CVD risk because these vitamins lower total plasma and serum homocysteine (tHcy) levels. Homocysteine is an amino acid produced in the metabolism of

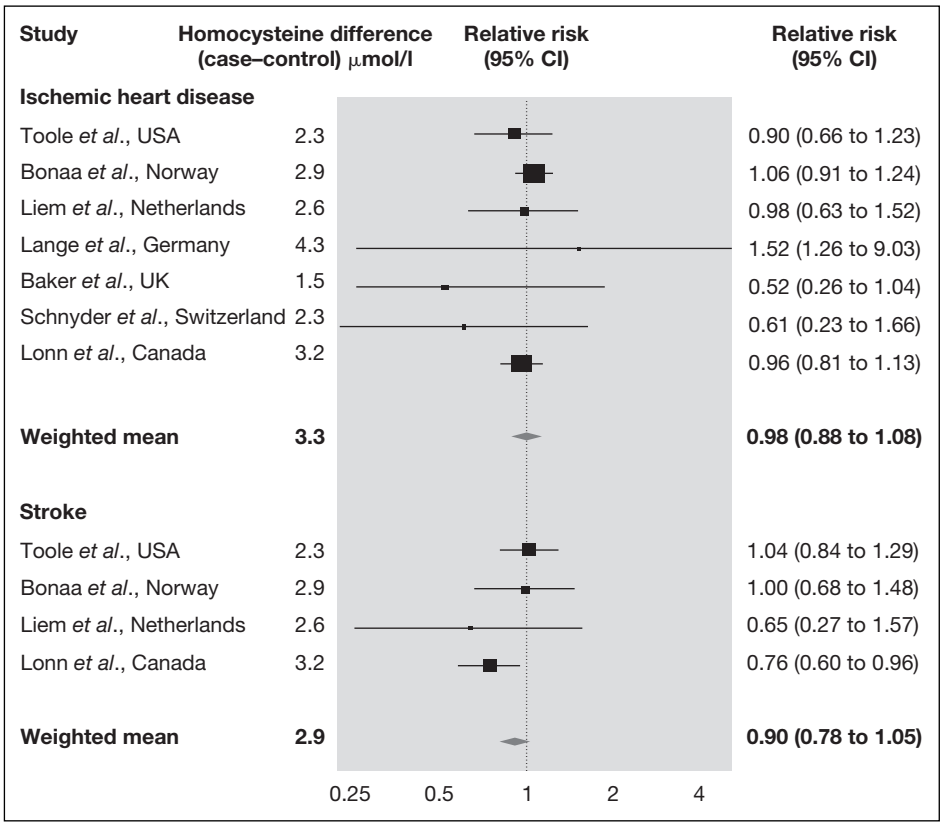

Figure 14.3 Meta-analyses of randomized trials of lowering homocysteine concentrations on ischemic heart disease and stroke events. Overall, there was no significant effect of homocysteine lowering on the risk of ischemic heart disease and stroke. Reprinted with permission from [126].

methionine that can be metabolized through one of two vitamin-dependent pathways: (1) re-methylation requiring folic acid and vitamin B12; or (2) trans-sulfuration requiring vitamin B6 [66]. Supplementation with 0.5–5.0 mg/day of folic acid significantly reduces tHcy by 25%, and taken with 0.5 mg/day of vitamin B12 further reduces tHcy by an additional 7% [67].

The homocysteine 'hypothesis for atherosclerosis' was introduced by McCully in 1969 after observing premature atherothrombosis in children with homocystinuria [68, 69]. Subsequently, tHcy was found to have a graded and independent association with IHD events (fatal and non-fatal MI and sudden cardiac death) in case–control and retrospective studies [70, 71]. The relationship between tHcy and CVD risk is attenuated in prospective studies, however, suggesting that elevated tHcy may be a consequence rather than a cause of vascular disease [72].

Despite compelling evidence that B vitamins lower tHcy, clinical trials to date do not support a beneficial effect of B vitamin supplementation on CVD risk. Three large, multicenter, double-blind, randomized studies have evaluated the impact of B vitamins on secondary prevention of stroke and MI. The results from these and smaller clinical trials are summarized in Figure 14.3 and are described below.

In the Vitamin Intervention for Stroke Prevention (VISP) study, 3680 adults with a non-disabling stroke were randomly assigned to receive a daily high-dose formulation of B vitamins (25 mg B6, 0.4 mg B12, and 2.5 mg folic acid) or a low-dose formulation (200 μg B6, 6 μg B12 and 20 μg folic acid) for 2 years [73]. Pre-therapy tHcy levels were identical between treatment groups at randomization (13.4 μmol/l) and on average there was a 2 μmol/l greater reduction in tHcy for the high-dose group versus the low-dose group. However, treatment with the high-dose formulation had no effect on stroke, CHD events, or death compared with the low-dose group (6.7% had a CHD event in the low-dose group compared with 6.3% in the high-dose group). In a subsequent analysis, subjects with very low and high B12 levels at baseline were excluded (25th to 95th percentiles were studied) to eliminate those with vitamin B12 malabsorption, those taking B12 supplements, and those with renal impairment [74]. In this cohort, there was a 21% reduction in the risk of events (ischemic stroke, coronary disease or death) in the high-dose versus the low-dose group ($P = 0.049$).

In the NORVIT (Norwegian Vitamin Trial), 3749 men and women who had an acute MI were randomized into one of four supplementation groups: (1) 0.8 mg folic acid, 40 mg B6 and 0.4 mg B12/day; (2) 0.8 mg folic acid and 0.4 mg B12/day; (3) 40 mg B6/day; or (4) placebo for a median of 40 months [75]. Plasma tHcy decreased by ~27% in patients in the folic acid groups compared with the B6- and placebo-treated patients. However, there was no effect on the primary endpoint of the composite of recurrent MI, stroke, and sudden death due to coronary disease. In the group that received 0.6 mg folic acid, 40 mg B6, 0.4 mg B12, there was a 22% increase in the primary endpoint ($P = 0.05$) and 30% increase in non-fatal MI compared with placebo ($P = 0.05$). It is possible that the increased CVD risk could be due to an adverse interaction between folic acid, vitamin B6, and vitamin B12 [76]. There was also a non-significant 17% decrease ($P = 0.52$) in the incidence of stroke in this group compared with placebo. Vitamin B6 was not associated with any endpoint benefit.

The Heart Outcomes Prevention Evaluation-2 (HOPE-2) included 5522 patients aged 55 and older with a history of vascular disease or diabetes [77]. Patients were randomized to receive a combined supplement containing 2.5 mg folic acid, 50 mg B6, and 1 mg B12, or placebo daily for an average of 5 years. Mean tHcy decreased in the group receiving active treatment. However, there was no significant effect on the primary outcome of death from CV causes, MI, and stroke (18.8% event rate in the active therapy group vs 19.8% in the placebo group). There was an increase in the number of patients hospitalized for unstable angina in the active treatment group, but also a 25% reduction in stroke in the active treatment group compared with placebo.

In summary, although elevated tHcy is associated with increased CVD risk in observational studies, the results from three large clinical trials suggest that reducing tHcy with B vitamin supplementation does not confer any benefit and may even increase CVD risk in patients with established CV disease. This finding supports the hypothesis that elevated tHcy may be a consequence of CVD, rather than a cause. Presently, the AHA does not recommend folic acid and B vitamin supplements to reduce the risk of CVD [2, 78]. Instead, it is recommended that emphasis be placed on meeting current recommended daily allowances (RDAs) for folate, vitamin B6, and vitamin B12 by consuming vegetables, fruits, legumes, nuts, lean meats, fish, and fortified grains and cereals [79]. Supplements should only be used when the diet does not provide adequate amounts of these vitamins.

ANTIOXIDANT VITAMINS

The hypothesis that antioxidant vitamins reduce the risk of CVD is based on evidence that oxidative stress is atherogenic. *In vitro* experiments have shown that antioxidant vitamins decrease formation of reactive oxygen species and decrease LDL oxidative susceptibility [80]. Epidemiologic and observational studies have also reported that diets rich in antioxi-

dants (e.g., high in fruits and vegetables), as well as in specific antioxidants (e.g., vitamin E, vitamin C and β-carotene), are associated with reduced CVD risk [81, 82]. In addition, antioxidant supplements have been shown to reduce the progression of atherosclerosis in animal models [83, 84]. However, the data from clinical trials (both primary and secondary prevention studies) fail to support a beneficial effect of antioxidant vitamin supplements on CVD events, as reviewed by Kris-Etherton *et al*. [85].

A recent meta-analysis assessed the effect of antioxidant supplements on mortality in 68 randomized primary and secondary prevention trials that included 232 606 participants [86]. These trials involved adults and compared β-carotene, vitamin C, vitamin E, vitamin A and selenium, either alone or combined, versus placebo or versus no intervention. When all trials were analysed together, there was no significant effect of antioxidant supplements on mortality (relative risk [RR] 1.02; 95% CI 0.98–1.06). In an analysis of the 47 low-bias trials that had adequate randomization procedures and satisfactory follow-up, antioxidant supplements significantly increased mortality (RR; 1.05; 95% CI; 1.02–1.08) (Figure 14.4). Specifically, β-carotene (RR 1.07; 95% CI 1.02–1.11), vitamin A (RR 1.16; 95% CI 1.1–1.24), and vitamin E (RR 1.04; 95% CI 1.01–1.07), singly or combined, significantly increased mortality in the low-bias risk trials. Vitamin C and selenium had no significant effect on mortality. Although adverse effects of antioxidant supplements are implicated, there are limitations of this meta-analysis. Importantly, the studies that evaluated changes in mortality tended to enroll older participants (the average age was 62 years), which means that there could still be a clinical benefit if antioxidant supplementation began at a younger age and for a longer period of time [87]. This analysis also combined studies of different durations, design and supplement combinations as well as non-homogeneous populations.

The findings of the Women's Antioxidant Cardiovascular Study (WACS) were published after the meta-analysis of Bjelakovic *et al*. [86], and reported consistent results [88]. The WACS was a randomized, double-blind, placebo-controlled trial evaluating the individual and combined effects of vitamin C (500 mg/day synthetic vitamin C [ascorbic acid]), vitamin E (600 IU of natural vitamin E [*d* alpha tocopherol acetate] every other day), and β-carotene (50 mg of Lurotin every other day) over an average of 9.4 years in women at high CVD risk. A total of 8171 women with either a history of vascular disease or with at least 3 cardiovascular risk factors were randomized into the trial. There was no overall effect of ascorbic acid (RR 1.02; 95% CI 0.92–1.13), vitamin E (RR 0.94; 95% CI 0.85–1.04), or β-carotene (RR 1.02; 95% CI 0.92–1.13) on the primary combined endpoint of CVD morbidity and mortality, including incident MI, stroke, coronary revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), and cardiovascular mortality, nor on the individual secondary outcomes. A significant reduction in the primary outcome with vitamin E was observed among the pre-specified subgroup of women with prior CVD (RR 0.89; 95% CI 0.79–1.00; $P = 0.04$). There were no significant interactions between antioxidant supplements for the primary endpoint, but those randomized to both active ascorbic acid and vitamin E experienced fewer strokes (*P*-value for interaction, 0.03).

Taken together, the majority of clinical trial evidence has not demonstrated a benefit of antioxidant supplementation on CVD morbidity and mortality [86, 89, 90]. The lack of efficacy of antioxidant supplements has been demonstrated consistently for different doses of antioxidants and in diverse population groups [85]. Some analyses have even suggested an increase in mortality from β-carotene, vitamin E, and vitamin A supplements [86, 89, 90]. One suggested reason for an adverse response could be that, by decreasing free radicals, antioxidants interfere with defense mechanisms for removing damaged cells [91]. Based on available evidence, the AHA currently recommends consumption of antioxidant-rich foods such as fruits, vegetables, whole grains, and nuts; but does not support the specific use of antioxidant vitamin supplements [2, 85].

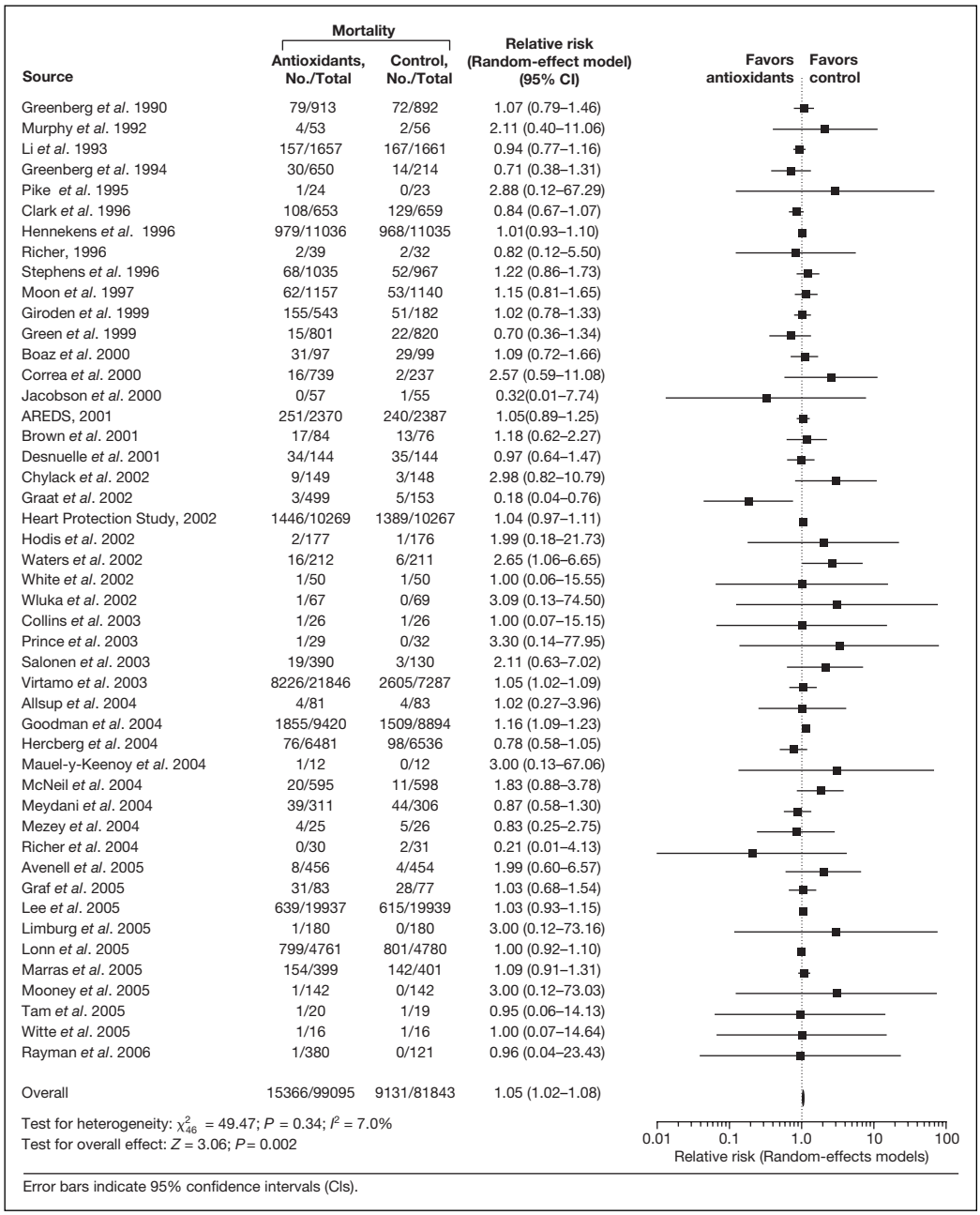

Figure 14.4 Intervention effect of antioxidant supplements versus placebo on mortality in trials with a low risk of bias. In trials with a low risk of bias, mortality was significantly increased in the supplemented group (RR 1.05; 95% CI 1.02–1.08). With permission from [86].

PLANT STANOLS AND STEROLS

Plant stanols and sterols have a potent LDL-lowering effect and are recommended by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III as a therapeutic option for maximum LDL-c lowering with diet [92]. Two to three g/day of plant sterols or stanols lowers plasma LDL-c by 6–15% with no significant effects on HDL-c or triglycerides [20]. This reduction in total and LDL cholesterol is seen in individuals with hypercholesterolemia and type 2 diabetes, as well as in healthy adults and children [20, 93]. The NCEP ATP III recommends 2 g/day of plant sterols and/or stanols as a therapeutic option to enhance LDL-c lowering [92]. This recommendation is based on studies that have demonstrated maximum cholesterol reduction at this dose and no further significant cholesterol lowering at higher doses.

Plant stanols and sterols are structurally related to cholesterol and are present naturally in small amounts in nuts, seeds, and vegetable oils. The most common phytosterols are β-sitosterol, campesterol, and stigmasterol. Sitostanol is the most common plant stanol, which is a saturated derivative of sitosterol. The usual dietary intake of plant sterols and stanols without supplementation ranges from 150 to 400 mg/day [94], so supplements are needed to achieve the recommended intake of 2 g/day. Plant stanols and sterols are now supplemented in many foods like margarine, low-fat milk, yogurt, cereal bars, and orange juice. In addition, a gel-cap stanol and sterol supplement is available.

There is considerable evidence that plant stanols and sterols lower cholesterol levels by displacing cholesterol from mixed micelles, resulting in reduced intestinal cholesterol absorption and higher fecal excretion of cholesterol [95, 96]. However, since there is an equivalent reduction in total and LDL cholesterol when stanols and sterols are consumed once a day at lunch or dinner compared with three times a day at each meal, it appears that there is another mechanism responsible for the reductions beyond inhibiting cholesterol absorption [97, 98]. One hypothesis is that plant stanols and sterols increase cholesterol efflux out of enterocytes and into the intestinal lumen by inducing a greater expression of cholesterol transporters including adenosine triphosphate-binding cassette (ABC)G5 and ABCG8 [97, 99].

Combining sterols or stanols with cholesterol-lowering medications such as statins has an additive cholesterol-lowering effect that has been replicated in several studies [100–103]. In a multicenter, randomized, double-blind study, treatment with 400 μg/day cerivastatin over 4 weeks reduced LDL-c by 32% versus placebo, and treatment with a sterol-ester enriched margarine (2 g sterols/day) reduced LDL-c by 8%. The combination of sterol-ester margarine and cerivastatin taken together was additive, resulting in a 39% reduction in LDL-c [103]. In a second study by Blair *et al*. [100], 67 women and 100 men with LDL-c ≥130 mg/dl who had been taking a stable dose of a statin drug for at least 90 days were randomized to consume either 3 servings/day of a plant stanol ester spread that provided 5.1 g/day of plant stanol esters or a placebo for 8 weeks. The plant stanol ester spread reduced LDL-c cholesterol by 17% compared with a 7% reduction in the placebo group.

Most (80–95%) plant stanols and sterols are not absorbed [94] and they are considered safe by the United States Food and Drug Administration. A reduction in plasma levels of β-carotene and other lipophilic carotenoids following sterol/stanol supplementation has been consistently reported [94], but is not associated with any adverse health outcomes [104]. Increasing consumption of high-carotenoid fruits or vegetables (≥5 servings/day) such as carrots, pumpkin, apricots, spinach, or broccoli prevents the decline in plasma carotenoid concentrations observed with stanol/sterol supplementation [105].

To date there have been no long-term clinical trials evaluating the effects of stanols/sterols on CV events. However, several recent studies have examined the relationship between plasma stanol and sterol levels with the incidence of CV events or presence

of CHD [106–109]. The results of these studies have been inconsistent. In the Prospective Cardiovascular Münster (PROCAM) study, there was a 1.8-fold increased risk of coronary events in subjects with sitosterol levels in the upper quartile (>5.25 μmol/l) compared with the lower three quartiles ($P < 0.05$) [106]. In contrast, in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Population study, which compared 373 cases of coronary artery disease (CAD) with 758 controls, there was a 21% reduced risk of future CAD in the highest tertile of sitosterol concentration (not significant) after adjusting for traditional risk factors [107]. The Longitudinal Aging Study Amsterdam (LASA) study reported that high plasma concentrations of sitosterol were associated with a significant 28% reduction in risk of CHD in 1242 subjects older than 65 years [108]. In the Dallas Heart Study, there was no relationship between plant sterol levels and family history of CHD or coronary calcium in the 3252 study participants [109]. In summary, recent studies have found differing associations between plant stanol and sterol levels with CHD and CV events. Although the PROCAM study reported an adverse association between plasma sitosterol levels and coronary disease risk, three other studies suggest no negative association or even a beneficial effect of elevated sitosterol levels. Randomized clinical trials are needed to determine if there is a causal relationship between plant stanols and sterols and CVD risk.

SOLUBLE FIBER

Soluble fiber (10–25g/day) is also recommended by the NCEP ATP III as a therapeutic option for maximum LDL-c lowering with diet [10]. Dietary fiber is a component of plant foods that cannot be digested in the human small intestine [110]. Soluble fiber is a type of dietary fiber that dissolves or swells when hydrated and is often metabolized (fermented) by bacteria in the large intestine. In contrast, insoluble fiber usually does not dissolve in water and is not metabolized by bacteria in the large intestine. The major sources of soluble fiber in the diet are oats and oat bran, beans and peas (i.e., legumes), citrus fruits, strawberries and apples. Foods high in insoluble fiber include whole-wheat breads, wheat cereals, most other grains, and vegetables such as cabbage, carrots, Brussels sprouts and cauliflower.

Several large cohort studies [111–117] have reported that an increased intake of dietary fiber (>25 g/day) is associated with a reduced risk of CHD and CVD. An analysis of ten cohort studies including 91 058 men and 245 186 women found that each 10 g/day increase in dietary fiber was associated with a 14% lower risk of all coronary events and a 27% lower risk of coronary mortality [118]. These associations were independent of other dietary factors, sex, age, baseline body mass index, smoking, and history of hypertension, diabetes, and hypercholesterolemia. Some studies have reported a stronger relationship between soluble fiber intake and CV events and progression of carotid atherosclerosis compared with insoluble fiber [115, 117, 119]. There also is a greater LDL-c lowering capacity with soluble fiber compared with insoluble fiber. The hypocholesterolemic effect of soluble fiber is primarily due to the binding of bile acids in the small intestine [120]. This reduces bile acid absorption and increases fecal excretion of bile acids. As a result, cholesterol is removed from the blood and converted into bile acids in the liver to replace the bile acids lost in the stool.

Clinical trials have consistently demonstrated a cholesterol-lowering effect of soluble fiber. Brown *et al*. [121] conducted a meta-analysis of 67 studies that evaluated the cholesterol-lowering effects of soluble fibers including oats, psyllium, pectin, and guar gum. The average dose of soluble fiber was 9.5 g/day, which was given for an average of 49 days. Soluble fiber reduced total and LDL cholesterol by 1.10 mg/dl and 1.13 mg/dl, respectively, per gram of soluble fiber. These diets also significantly reduced HDL-c, but to a lesser extent (0.07 mg/dl per gram of soluble fiber), and did not significantly affect triglycerides.

Soluble fiber also has an additive cholesterol-lowering effect when combined with statins. In a study by Moreyra *et al*. [122] of 68 men and women with hyperlipidemia, LDL-c fell 55 mg/dl in patients taking 10 mg of simvastatin plus placebo for 8 weeks. However, in patients taking 10 mg of simvastatin plus 15 g psyllium (Metamucil), LDL-c decreased 63 mg/dl ($P = 0.03$), which was a similar reduction to that seen with 20 mg of simvastatin alone.

To achieve the upper end of the ATP III soluble fiber recommendation, there must be a major emphasis on fruits, vegetables, cereal grains, and legumes. Nonetheless, it is a challenge to consume 25 g of soluble fiber each day. A lower intake of soluble fiber (5–10 g/day) will still achieve 3–5% LDL-c lowering. There are soluble fiber supplements available, but it is important to note that some provide calories and many do not deliver the same variety of nutrients that soluble fiber-rich foods do.

SUMMARY

There has been great interest from consumers, physicians, researchers, and many industry sectors on the effects of dietary supplements on CV events and CVD risk factors. Some supplements, including omega-3 fatty acids and niacin, have demonstrated protective effects in randomized, controlled clinical trials. The marine-derived omega-3 fatty acids reduce the risk of sudden death and overall mortality in men and women with established CVD, in addition to decreasing triglyceride levels. Likewise, niacin supplementation reduces the incidence of CV events and decreases the progression of coronary stenosis in clinical trials. Plant stanols/sterols and soluble fiber reduce total and LDL-c alone and in conjunction with statins and are recommended by the NCEP ATP III to achieve maximum LDL-c lowering. However, long-term studies have not been conducted to determine the effects of these supplements on atherosclerosis progression and CVD events. Based on clinical and epidemiologic evidence that these nutrients can reduce CVD risk and/or improve lipid and lipoprotein levels, specific nutrient recommendations have been made by the American Heart Association and the NCEP ATP III [20, 78, 123, 124]. These nutrient recommendations are summarized in Table 14.1.

On the other hand, B vitamins (folic acid, vitamin B6, vitamin B12) and antioxidants (vitamin E, vitamin C, β-carotene, selenium) held great promise for decreasing CVD risk based on findings from observational studies and from studies using *in vitro* and animal models that demonstrated a protective effect. However, the randomized controlled clinical trials conducted with various antioxidant and B vitamin supplements have not demonstrated efficacy, and, some have even demonstrated adverse effects. As a result, these supplements are not currently recommended for CVD risk reduction [2, 78].

There is convincing evidence that certain dietary patterns decrease risk of CVD. In contrast, there are many examples of single nutrients or nutrient cocktails delivered as supplements that have not yielded protective effects. It is important to recognize that a supplement provides a single nutrient or a nutrient cocktail, whereas foods provide a wide variety of nutrients and phytochemicals that may be protective against CVD. Thus, the best advice is to recommend a healthy diet that meets food-based guidelines and not rely heavily on supplements to deliver a nutritionally adequate dietary pattern. Table 14.2 presents food-based dietary patterns that are recommended for CVD risk reduction by the AHA and the National Heart, Lung, and Blood Institute (NHLBI) [2]. Beyond this, supplements with demonstrated efficacy that are currently recommended by the AHA and NHLBI are warranted when indicated. These include marine-derived n-3 fatty acids, niacin, stanols/sterols and soluble fiber. At this juncture, supplements not on this list do not have a convincing evidence base to warrant their use and, for some use is contraindicated because of adverse effects.

Table 14.1 Recommended supplements and pharmacologic agents to reduce CVD risk[a]. Adapted with permission from [3]

Supplement		*Biologic actions*	*Recommended dose for clinical benefits*	*Diet*	*Supplement/ fortified foods*	*Prescription drug*	*Adverse effects*
Niacin (nicotinic acid)		↑HDL-c 15–35% ↓TG 20–50% ↓LDL-c 5–25%	1–3 g/day	Not possible to achieve clinically significant lipid/lipoprotein effects with diet only	Niacin supplements: typically 500 mg/tablet or capsule	Crystalline nicotinic acid 1.5–3 g/day; Sustained-release nicotinic acid 1–2 g/day; Extended-release nicotinic acid (Niaspan®) 1–2 g/day	Flushing of the face, neck, and chest Glucose intolerance and hepatotoxicity for some forms
EPA + DHA[b]	Primary prevention	Antiarrhyrthmic; anti-inflammatory;	500 mg/day	2 servings of fatty fish/week	Fish oil supplement: about 110–500 mg/ soft gel or packet	Omacor 840 mg/capsule (465 mg EPA + 375 mg DHA)	Increases LDL-c by 5–10%
	Secondary prevention	↓ CVD risk factors	1 g/day	1 serving of fatty fish/day or fish oil supplement	Fortified foods: eggs, bread, juice, etc.		
	TG lowering	↓TG	2–4 g/day	Fish oil supplement			
Sterols/ Stanols		↓LDL-c 6–15%	2 g/day	Not possible to achieve a clinically significant LDL-c lowering effect with diet only	Stanol supplement: Benecol: 2 softgels = 1.1 g stanol ester Fortified foods: margarine/spread; yogurt; orange juice; cereal bar, etc.	N/A	Decreased plasma levels of β-carotene and other lipophilic carotenoids

Soluble fiber	↓LDL-c 3–5% (for 5–10 g/day)	10–25 g/day	Cereal grains, fruits, vegetables, legumes (varies 1–5 g)	Soluble fiber supplements: Psyllium: (e.g., Metamucil) ~4–10 g fiber/serving (powder) or 0.5–1.0 g fiber/capsule Methylcellulose: (e.g., Citrucel) ~0.5 g methylcellulose/capsule or 2 g methylcellulose/serving Polycarbophil: (e.g., Fibercon) ~500 mg polycarbophil/capsule Fortified foods – cereal, bread, etc.	N/A	Flatulence and bloating; may cause stomach cramps

[a] Physician monitoring of supplement use is recommended for all patients on an ongoing basis

[b] There are no current recommendations for patients with ICDs

Table 14.2 Two examples of daily dietary patterns that are consistent with AHA-recommended dietary goals at 2000 calories

Eating pattern	*DASH**	*TLC†*	*Serving sizes*
Grains‡	6 to 8 servings per day	7 servings§ per day	1 slice bread; 1 oz dry cereal¶; ½ cup cooked rice, pasta, or cereal
Vegetables	4 to 5 servings per day	5 servings§ per day	1 cup raw leafy vegetable, ½ cup cut-up raw or cooked vegetable, ½ cup vegetable juice
Fruits	4 to 5 servings per day	4 servings§ per day	1 medium fruit; ¼ cup dried fruit; ½ cup fresh, frozen, or canned fruit; ½ cup fruit juice
Fat-free or low-fat milk and milk products	2 to 3 servings per day	2 to 3 servings per day	1 cup milk, 1 cup yogurt, 1½ oz cheese
Lean‖ meats, poultry, and fish	<6 oz per day	5 oz per day	
Nuts, seeds, and legumes	4 to 5 servings per week	Counted in vegetable servings	$^1/_3$ cup (1½ oz), 2 tbsp peanut butter, 2 tbsp or ½ oz seeds, ½ cup dry beans or peas
Fats and oils	2 to 3 servings# per day	Amount depends on daily calorie level	1 tsp soft margarine, 1 tbsp mayonnaise, 2 tbsp salad dressing, 1 tsp vegetable oil
Sweets and added sugars	5 or fewer servings per week	No recommendation	1 tbsp sugar, 1 tbsp jelly or jam, ½ cup sorbet and ices, 1 cup lemonade

*Dietary Approaches to Stop Hypertension. For more information, please visit www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf.
†Therapeutic Lifestyle Changes. For more information, please visit http://www.nhlbi.nih.gov/cgi-bin/chd/step2intro.cgi. TLC includes 2 therapeutic diet options for LDL lowering: plant stanol/sterol (add 2 g/day) and soluble fiber (add 5–10 g/day).
‡Whole-grain foods are recommended for most grain servings to meet fiber recommendations.
§This number can be less or more depending on other food choices to meet 2000 calories.
¶Equals ½ to 1¼ cups, depending on cereal type. Check the product's Nutrition Facts Label.
‖Lean cuts include sirloin tip, round steak, and rump roast; extra lean hamburger; and cold cuts made with lean meat or soy protein. Lean cuts of pork are center-cut ham, loin chops, and pork tenderloin.
#Fat content changes serving counts for fats and oils: for example, 1 tbsp of regular salad dressing equals 1 serving; 1 tbsp of low-fat dressing equals ½ serving; 1 tbsp of fat-free dressing equals 0 servings.
Reproduced with permission from [2].

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Why do lipid-lowering agents affect serum transaminase levels, are these drugs toxic to the liver and can they precipitate liver failure?

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BACKGROUND

Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide. The established linear relationship between the risk for a cardiovascular (CV) event and low-density lipoprotein cholesterol (LDL-c) suggests that for every 40 mg/dl reduction in LDL-c, there is a >20% reduction in the risk for major coronary and vascular events [1]. Studies have substantiated the efficacy of reducing lipid-related risk factors using 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins, with considerable reduction in vascular events in all study groups and at virtually all levels of cholesterol [2].

Although the lower threshold of LDL-c benefit has not been established, intensive lowering of LDL-c to values beyond those recommended in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines [3] has been suggested for added cardiovascular benefits [4]. Indeed, recent studies confirmed that more intensive statin therapy conferred additional benefits [5–7]. These have led to a national trend toward using higher doses of statins in those populations at risk for cardiovascular events. Furthermore, lipid lowering is now recommended for a wide range of people at cardiovascular risk, including those with average and below-average lipid levels [3, 8].

Approximately 25 million individuals receive statins each year worldwide [2]. Given the widespread use of statins, the safety of these drugs assumes considerable importance. In general, these agents are well tolerated. A clinically important effect and relevant to the current review is the concern for liver injury. Although rare, significant injury to the liver can occur. In this review we address the putative mechanisms of serum transaminase elevation and hepatic safety with the use of lipid-lowering agents, especially the statins. We also summarize the current recommendations for their use.

WHY DO LIPID-LOWERING AGENTS AFFECT SERUM TRANSAMINASE LEVELS?

Currently available lipid-lowering agents used in clinical practice, either alone or in combination to achieve target reduction in lipids, include HMG-CoA reductase inhibitors (statins),

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fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil), a cholesterol absorption inhibitor (ezetimibe), bile acid sequestrants (the resins cholestyramine and colestipol, or colesevelam, a polymer) and niacin. The most extensive data on the use and safety of these compounds is with statins.

Lipid-lowering agents are known to affect serum transaminase levels. Initial studies in animals suggested that statins might cause liver injury. In dogs, lovastatin caused slight elevations in alanine aminotransferase (ALT) but no histologic liver damage [9]. In contrast, lovastatin administered in high doses (100 to 200 mg/kg/day) to rabbits was associated with hepatic necrosis [10]. A similar pattern of injury was seen in guinea pigs given high doses of simvastatin [11]. Rabbits and guinea pigs appear to be uniquely sensitive to statins, perhaps because of low basal levels of HMG-CoA reductase. However, in humans who do not receive such high doses, statins do not predictably cause hepatocellular necrosis.

Serum transaminases (aspartate aminotransferase [AST] and ALT) are released in response to statin therapy as a result of hepatocyte injury, altered cell membrane integrity, or as an adaptive response to enzyme induction. While AST is also present in skeletal muscle and red cells, ALT is only present in the liver. The cellular mechanisms underlying the statin-induced elevation in transaminases and liver injury are not well understood. It has been postulated that the statins affect serum transaminases by one or more of several mechanisms. These include:

1. *Disruption of hepatocytes*: Covalent binding of the drug to intracellular proteins may disrupt actin. Disassembly of actin fibrils at the surface of the hepatocyte in turn causes blebs and rupture of the cell membrane [12].
2. *Disruption of surface transport proteins*: Interruption of hepatic uptake and metabolism of the drug due to interference with transport proteins may influence its toxicity. In a study of healthy human volunteers, concomitant use of rifampin with atorvastatin significantly increased total area under the plasma concentration–time curve (AUC) of atorvastatin metabolites (acid and lactone forms) [13]. Rifampin inhibited the hepatic uptake transporter organic anion transporter 1B1 (OATP1B1) and influenced the kinetics of atorvastatin and its metabolites. These metabolites are pharmacologically equipotent with the parent drug. They have a long half-life and are responsible for the majority of circulating inhibitory activity of 3-HMG-CoA reductase inhibitor. The inhibition of hepatic uptake can result in increased systemic exposure to atorvastatin and its active metabolites and predispose to adverse reactions with continued use [14, 15].
3. *Cytolytic T-cell activation*: Covalent binding of a drug to P-450 enzymes may act as an immunogen, activating T cells and cytokines and stimulating a multifaceted autoimmune response. This is possible given that most statins are metabolized by P-450 enzymes [16].
4. *Apoptosis (programmed cell death) of hepatocytes*: In a recent study, a variety of lipophilic statins (lovastatin, simvastatin, fluvastatin and atorvastatin) but not the hydrophilic statin (pravastatin) reduced the viability of cultured human hepatocytes [17]. The lipophilic statins stimulated caspase-9 activity by reducing the expression of bcl-2 and enhanced caspase-8 activity through activation of the Fas/FADD system, both of which lead to hepatocyte apoptosis through the activation of caspase-3.
5. *Mitochondrial disruption*: Statins decrease the biosynthesis of mevalonic acid and its products, including farnesyl pyrophosphate, an intermediate metabolite of ubiquinone/coenzyme Q10 (CoQ10; Figure 15.1). CoQ10, an isoprenoid, plays an important role in cellular energy transduction in the mitochondrial electron transport system. CoQ10 is a vital electron and proton carrier and supports ATP synthesis in the mitochondrial inner membrane, and stabilizes cell membranes, thereby preserving cellular integrity and function [18]. Although no data support depletion of CoQ10 levels within the hepatocytes in

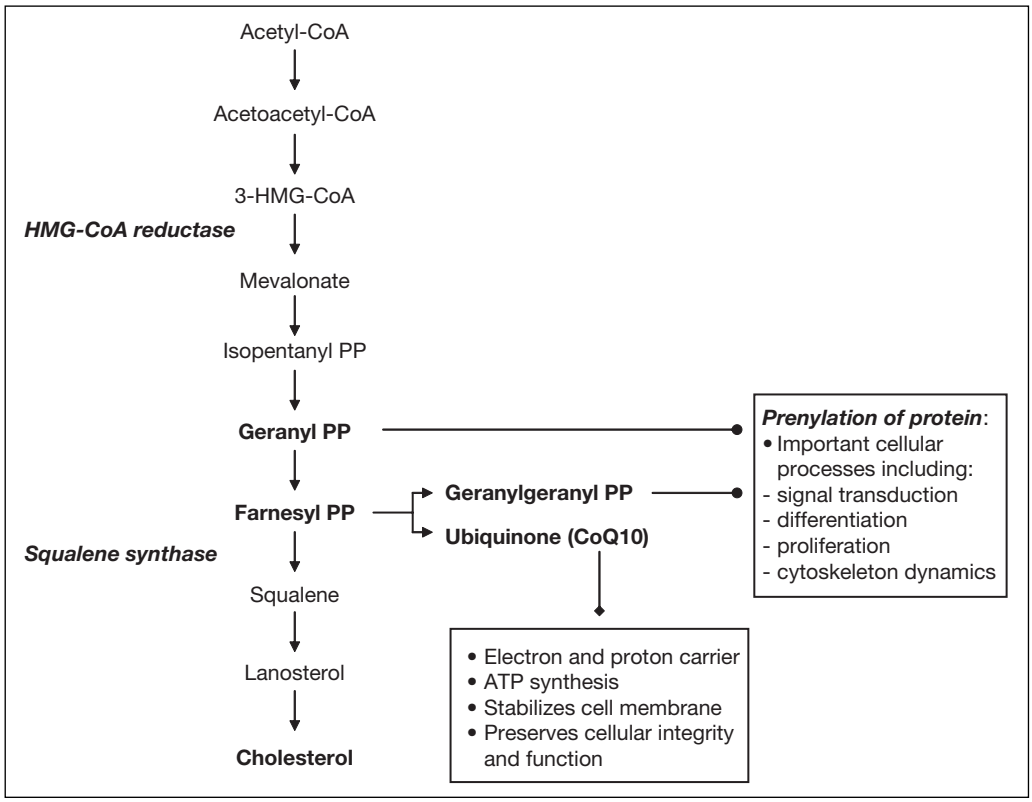

Figure 15.1 Hepatic biosynthesis of cholesterol. Several important intermediates and its derivatives in the biosynthesis of cholesterol with putative functions are shown.
3-HMG-CoA = 3-hydroxy 3-Methylglutaryl coenzyme A; CoQ = coenzyme Q; PP = pyrophosphate.

humans on statin therapy, it can be hypothesized as one of the mechanisms in statin hepatotoxicity.

6. *Impaired prenylation of proteins*: The mevalonic acid metabolites farnesyl pyrophosphate and geranylgeranyl pyrophosphate are required for the posttranslational modification or isoprenylation of essential regulatory proteins in mammalian cells. Prenylated proteins are involved in important cellular processes including signal transduction, differentiation, proliferation, and cytoskeleton dynamics. Thus, statins may lead to a prenylation defect and contribute to hepatocyte injury. At present there is no direct evidence to support this. However, in neonatal rat myocytes, pravastatin and lovastatin reduced the prenylation of proteins [19] which was reversed by the addition of farnesol and geranyl geraniol. In contrast, inhibition of cholesterol synthesis by squalene synthase inhibitors did not induce myotoxicity *in vitro* [20]. Taken together, these findings suggest that farnesyl and geranylgeranyl pyrophosphate depletion may contribute to statin-associated myotoxicity and could be a factor in hepatocyte injury as well.

ARE LIPID-LOWERING AGENTS TOXIC TO THE LIVER?

Although liver histology is the ideal tool for defining the pattern of drug injury, it is often not available and at best describes a condition 'compatible with', thus lacking specificity.

'Drug induced hepatotoxicity' (DIH) is therefore defined based on abnormal liver biochemical tests, with or without features of liver disease in the presence of a suspected agent. This includes the activity of serum ALT, AST and alkaline phosphatase (AP), which is expressed with respect to the upper limit of normal (ULN) [21]. It may suggest a hepatocellular injury [ALT/AST $>3 \times$ ULN], a cholestatic injury [AP $>2 \times$ ULN], or a mixed pattern. Elevated transaminases in the context of drug therapy could therefore represent:

- *Adaptive responses to drugs:* Asymptomatic alterations in liver biochemical tests without clinically significant liver injury, which are usually a response to enzyme induction.
- *Adverse drug reactions:* Undesirable manifestations (clinical or biochemical) that occur at doses recommended for treatment or prophylaxis.
- *DIH:* The liver injury has either been characterized histologically or is suggested by liver dysfunction (i.e., hyperbilirubinemia), in addition to elevations in ALT/AST. In fact, accompanying hyperbilirubinemia is a cardinal sign of 'DIH' indicating hepatocyte injury severe enough to affect global liver function. This requires discontinuation of the offending agent.

Clinically significant elevations in liver biochemical tests defined by ALT $\geq 3 \times$ ULN with a total bilirubin $\geq 3 \times$ ULN characterize Hy's rule [22]. This estimates a case-fatality of 10% or higher in the presence of acute hepatocellular jaundice and is thus of prognostic value in 'DIH'. However, the sensitivity and specificity of Hy's rule need to be validated.

The above details clearly show the difficulty in accurately defining DIH. The changes in liver biochemical tests upon exposure to lipid-lowering agents, especially statins, lack a 'signature' pattern of liver injury. It can be speculated that the abnormal liver enzymes due to statins may actually be a part of an *adaptive response* to statins or represent *adverse drug reactions* and rarely constitute *true hepatotoxicity*. The *adverse drug reactions* can usually be distinguished by a longer latent period (weeks to months) than with *true hepatotoxicity* (a few days).

The plausible hepatic manifestations of statin-related liver injury include:

1. Asymptomatic elevation of transaminase levels;
2. Hepatitis, characterized by necroinflammation;
3. Cholestasis;
4. Acute liver failure.

LIPID-LOWERING AGENTS AND ASYMPTOMATIC ELEVATION OF TRANSAMINASE LEVELS

STATINS

The most common clinical hepatic manifestation with statins is an asymptomatic elevation in transaminases [23–25], often referred to as 'transaminitis'. This has consistently been seen across all the relevant studies and in long-term endpoint trials [26]. It is probably a result of an adaptive response or an adverse drug reaction to the statins, or of an underlying comorbid condition (e.g., non-alcoholic fatty liver disease [NAFLD]. Statins are prescribed to patients with hyperlipidemia with or without the metabolic syndrome and who often have underlying NAFLD that commonly presents with transaminase elevations. Initial studies that assessed statin safety provide limited information on underlying NAFLD and baseline liver enzyme levels, which can confound data on transaminase elevation [26].

Although there is a clear association between statin therapy and transaminase elevation, lack of baseline data may make it more difficult to confirm causality in an individual. Considerable spontaneous fluctuations in transaminase levels can occur over time. Further, many of these patients are on multiple medications that may influence statin metabolism and

some may use other herbal or over-the-counter preparations that can alter transaminase levels. Thus, a precise incidence of statin-related transaminase elevation cannot be ascertained.

Lovastatin

Lovastatin provides the longest available risk and benefit profile among statins with 24 million patient-years of use [27]. Despite initial concerns of hepatic necrosis in animal studies, this was not predictably observed in human clinical trials. Transaminase elevation was the only consistent liver biochemical abnormality in about 15 000 patients on lovastatin in the EXpanded Clinical Evaluation of Lovastatin (EXCEL) [28] and Air Force/Texas Coronary Arteriosclerosis Prevention Study (AFCAPS/TexCAPS) [29]. In EXCEL, increased ALT values were dose-related ($P < 0.001$ for trend) and occurred after 90 days in the study [27]. On logistic regression analysis, the risk factors for increased ALT were daily intake of alcohol, increasing weight, higher baseline ALT values, and increasing doses of lovastatin. In AFCAPS/TexCAPS [29], an ALT/AST elevation $>10 \times$ ULN was similar in lovastatin (0.2%) and placebo (0.1%) groups. Also, there were no differences in ALT elevation $\geq 3 \times$ ULN between the lovastatin (0.6%) and placebo (0.4%) groups. Further, 127 lovastatin-treated participants had ALT elevations of 2–3 $\times$ ULN and were monitored on continued treatment. Of these 127 individuals, 72% had a subsequent decrease in ALT levels, in 14% the ALT levels remained in the same range, and the other 14% progressed to $>3 \times$ ULN with no adverse hepatic outcome.

Pravastatin

A meta-analysis of the three major randomized clinical trials of pravastatin – the Cholesterol and Recurrent Events (CARE), the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID), and the West of Scotland Coronary Prevention Study (WOSCOPS) – assessed safety data from more than 112 000 person-years of exposure [30]. Importantly, there were no significant differences in serious non-cardiovascular adverse events between the groups receiving pravastatin and placebo. In particular, the percentage of patients with ALT levels $\geq 3 \times$ ULN was 1.4% with both pravastatin and placebo.

Simvastatin

In the Heart Protection Study (HPS), 1.4% of subjects on simvastatin had ALT levels 2–4 $\times$ ULN compared to 1.3% of the placebo group [31]. Alanine aminotransferase levels $>4 \times$ ULN were seen in 0.4% of simvastatin- and 0.3% of placebo-treated participants. Further, there was no difference in the rate of treatment discontinuation because of elevated ALT between the simvastatin and placebo groups (0.05% vs 0.03%, respectively). Similarly, elevated transaminase ($>3 \times$ ULN) was seen in about 1% of subjects in the Scandinavian Simvastatin Survival Study (4S) trial [32].

Atorvastatin

As reported in the atorvastatin new drug application, persistent ALT elevations were low (0.2–0.6%) except at the 80 mg dose (2.3%), and occurred in 0.7% of patients for all atorvastatin doses combined [33]. This was confirmed in an analysis of pooled data on atorvastatin (10–80 mg) in 16 495 dyslipidemic patients from 44 completed trials [34]. Persistent ALT/AST elevation of $>3 \times$ ULN was similar in the atorvastatin (0.5%) and placebo (0.3%) groups. Continued atorvastatin treatment was well tolerated. The Anglo-Scandinavian Cardiac Outcomes Study (ASCOT) further supports the hepatic safety of atorvastatin [35].

Rosuvastatin

The incidence of clinically significant ALT increases was low and similar across all doses: 0.1–0.5% (5–40 mg) [36]. In most cases, the increases were transient and either resolved or

improved with continued treatment, with or without downward dose titration. In addition, clinically significant ALT increases occurred in the same proportion (0.2%) as in other statin comparator groups, which included 10–40 mg of pravastatin ($n = 1260$).

The above trials confirm ALT elevations with statins, but do not provide evidence of clinical hepatotoxicity. Moreover, ALT elevation is dose-related, not predictive of progressive liver disease, and is not a useful monitoring tool. In addition, the overall incidence of hepatic adverse events is similar to that with placebo, occurs infrequently, and rarely requires treatment discontinuation.

FIBRIC ACID DERIVATIVES

While fibrates provide greater reductions in triglyceride levels than statins (20–50% vs 7–30% from baseline) and greater increases in HDL-c levels (10–20% vs 5–15% from baseline), they are less effective in reducing LDL-c levels (5–20% vs 18–55%) [37]. Fibrates do, however, improve LDL particle size, from small dense particles to larger particles that may be less atherogenic [38]. Thus, fibrates may conceivably be associated with improvement in CV outcomes when used in combination with statins. This issue is being investigated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [39]. The fibrates are generally well tolerated. Notable hepatobiliary adverse effects include cholelithiasis, mildly elevated transaminase levels, and an increase in the need for gallbladder surgery [40, 41]. Although rare case reports of fibrate-induced acute and chronic hepatitis exist, no such events were found in the clinical trials. The combined use of fibrates and statin, especially gemfibrozil, significantly increases the risk of myopathy [42]. However, no serious liver injury has been described.

CHOLESTEROL ABSORPTION THERAPY (EZETIMIBE) – ALONE OR IN COMBINATION

While the incidence of ALT $\geq 3 \times$ ULN was similar between ezetimibe monotherapy and placebo groups (0.5% vs 0.3%) [43, 44], in combination with statins an increase in ALT values $\geq 3 \times$ ULN occurred in a comparable manner to that seen with statins alone [45]. This was statin dose-related and seen with the highest statin combination dose (ezetimibe 10–simvastatin 10 vs 80 mg) (0.5% vs 3.8%) [46]. No cases of liver failure, liver transplantation or death have been reported to date. Thus, ezetimibe in combination with a statin increases the incidence of transaminitis without significant clinical complications.

NIACIN

Serious hepatic toxicity from niacin was largely confined to the use of sustained-release (SR) formulations given as unregulated nutritional supplements [47]. Over 50% of subjects (8/15) developed hepatitis on SR niacin, compared with none of the 67 subjects using regular niacin [48]. Further, when immediate-release (IR) and SR niacin were compared in a randomized controlled clinical trial, none of the 23 patients on IR niacin developed hepatotoxic effects, whereas 12 of 23 patients (52%) taking SR niacin did, which mainly occurred with doses >1500 mg/day [49]. In contrast, hepatotoxicity has been rarely observed with an extended-release (ER) formulation available only by prescription (Niaspan®) [50]. Treatment with 1000–3000 mg prolonged-release (PR) nicotinic acid (niacin) produced statistically significant elevations in AST levels ($P < 0.05$–0.001 vs placebo and/or baseline) but ALT levels remained unaltered [51, 52].

The COMParative Effects on Lipid Levels of *Niaspan* (COMPELL) study evaluated the efficacy and safety of statins in combination with other lipid-lowering agents [53]. In this study, rosuvastatin alone (20 mg), a combination of low-dose atorvastatin (20 mg) or rosuvastatin (10 mg) with low-dose niacin ER 1000 mg or simvastatin (20 mg)/ezetimibe (10 mg) combinations were equally efficacious in lipid lowering. All drug regimens were generally

well tolerated. All groups had small increases within the normal range in liver transaminases except one patient, who on rosuvastatin had reversible liver enzyme elevation >3 × ULN. Thus, drug combinations in appropriate dosages can provide adequate control of lipids with no additional risk of hepatotoxicity.

HEPATITIS AND CHOLESTASIS

In all the major clinical trials, there were no reports of statistically significant or clinically important increases in the incidence of hepatitis and cholestasis with lipid-lowering agents, particularly for the statins. However, there are isolated reports of drug-induced autoimmune hepatitis [54–57] that could be potentially serious if not detected and treated in a timely and appropriate manner.

Statins may induce or unmask autoimmune hepatitis (AIH), which although very rare, should be ruled out in individuals with moderate to marked increase in transaminases (>3–10 × ULN). The presence of abnormal AST, increased γ globulins and AST:alkaline phosphatase >3 warrants evaluation of AIH. The *definite* diagnosis of AIH requires exclusion of other similar diseases; laboratory findings that indicate substantial immunoreactivity (γ-globulins ≥1.5 normal, increased titers ≥1:80 of antinuclear antibody [ANA], smooth muscle antibody (SMA) or antibodies to liver kidney microsome type 1 [anti-LKM1]); and histologic features of interface hepatitis. AIH is *probable* when findings are compatible with, but are insufficient for, a definite diagnosis (i.e., γ-globulins <1.5, titers of ANA, SMA or anti-LKM1 ≤1:40, history of previous blood products or alcohol use; or presence of other liver-related autoantibodies like antibodies to soluble liver antigen/liver pancreas [anti-SLA/LP], anti-actin, antibody to liver cytosol type 1 [anti-LC1], and perinuclear anti-neutrophil cytoplasmic antibodies [pANCA]).

CAN LIPID-LOWERING AGENTS PRECIPITATE LIVER FAILURE?

Liver failure as a result of statin therapy has rarely been reported and is thought to be an idiosyncratic reaction. According to the Food and Drug Administration adverse event reporting system (AERS), 38 cases of liver failure have been reported in persons on statins. While eight of these subjects had other known causes of liver failure, no other recognizable cause was identified in the remaining 30 cases [58]. The projected incidence of statin-induced acute liver failure (1:114 000) is similar to that in the general population (1:130 000) [27]. In a review of the AERS of the World Health Organization, the calculated rate of death per million prescriptions resulting from serious liver injury that could be attributed to statin therapy was: atorvastatin 0.07%, fluvastatin 0.05%, simvastatin 0.02%, pravastatin 0.04% and lovastatin 0.04% [59]. Moreover, there is no evidence that minor asymptomatic elevations of ALT and AST precede acute liver failure, nor is there support for routine screening or monitoring for acute liver failure [60].

Significant liver damage thus appears to be extremely uncommon with statins, especially given the magnitude of their use worldwide. The liver transplant data over a 12-year period (1990–2002) showed that out of 51 741 liver transplants, only three patients had acute liver failure that was attributable to statins [61]. Of these, two were receiving cerivastatin (taken off the market) and one was on simvastatin. There is also no identifiable evidence of death due to liver failure caused by statin therapy in the available literature.

ELEVATED TRANSAMINASES ON LIPID-LOWERING AGENTS: HOW TO MONITOR AND MANAGE?

The available evidence does not support routine monitoring of transaminases in asymptomatic patients on statins [26, 60, 62, 63]. The purpose of monitoring is not to determine

Table 15.1 Key message for monitoring serum transaminases in subjects on statins

- Ideally, a baseline transaminase level prior to initiation of statin therapy
- Follow up levels in 3 months
  - If normal, follow up during routine medical evaluation
  - If abnormal, other etiologies should be ruled out
- For transaminases $<3\times$ ULN, with normal bilirubin and prothrombin time
  - Repeat hepatic panel in 1–2 weeks for rare possibility of acute liver failure
  - Repeat in 3–6 months; if normal, follow up during routine medical evaluation
- For transaminases $>10 \times$ ULN, with or without abnormal bilirubin and prothrombin time
  - Discontinue all potentially hepatotoxic agents
- For transaminases between 3–10 $\times$ ULN
  - Discontinue potentially hepatotoxic agents if abnormal bilirubin and prothrombin time
  - Monitor at 6 weeks and 3 months if normal bilirubin and prothrombin time
  - If still high, monitoring should be individualized or switch to alternative agents
- Monitor transaminase levels following increase in the dose of statins

whether statins cause a significant increase in transaminases, but whether they cause serious liver dysfunction or failure which can be predictably identified. While exceedingly rare cases of liver failure on statins have been reported, routine monitoring of transaminase levels did not help identify these patients, which was likely due to an idiosyncratic reaction. Instead, this monitoring may lead to alteration or discontinuation of statin therapy, depriving a considerable number of patients of the modifiable, life-protecting benefit of statin therapy. Further, one will need to monitor 100 000 patients each year for an average of 3 years for transaminase levels to detect 110 patients who have consecutive elevations in ALT to identify 0.1 person who may experience liver failure [58]. However, from a medico-legal perspective, one cannot abrogate transaminase monitoring until changes in the prescribing information for marketed statins occur.

It should therefore become standard practice to document transaminase levels prior to initiation of statin therapy. Then a follow-up test can be performed after 3 months of treatment. If normal, this may be followed during routine medical evaluations of patients. If it is abnormal, then other etiologies for transaminase elevation should be excluded. The subject should be evaluated clinically. A full hepatic panel including measures of hepatic synthetic functions should be performed. If the AST and ALT are $>10 \times$ ULN or associated with hepatic synthetic dysfunction (i.e., elevated bilirubin or prolonged prothrombin time), all potentially hepatotoxic drugs should be discontinued.

For transaminase levels $<3 \times$ ULN, normal bilirubin and prothrombin time, the likelihood of developing severe hepatotoxicity is low. Such patients can be followed up with repeat measurements within a week or two and then at 3–6 month intervals. The early monitoring provides data on the likelihood of acute liver failure while subjects with persistent elevations should be evaluated for chronic liver disease, especially NAFLD. Statins do not need to be discontinued in subjects with this degree of transaminase elevation. Finally, if statin-induced hepatotoxicity is diagnosed or cannot be excluded in the setting of abnormal transaminases ($>3 \times$ ULN), we recommend that statins be held and an alternative antihyperlipidemic therapy be considered. The key points about monitoring of transaminases on statins are shown in Table 15.1.

SUMMARY

The lipid-lowering agents, especially statins, are associated with asymptomatic elevations in transaminases. The elevation of ALT and AST $>3 \times$ ULN can be seen with all statins and is dose-related. Further, this is often transient and resolves spontaneously in the majority of

Table 15.2 Scales for assigning confidence and type of evidence* codes to the answers given to task force questions

Scale	*Description*
Confidence	
1	Very confident
2	Confident
3	Marginally confident
4	Not confident
Type of evidence	
A	• Well-designed RCTs, including RCTs conducted in patients who reported adverse events
B	• Single RCT with a highly statistically significant result • Well-conducted retrospective case–control studies with adverse events as primary endpoints • Managed care claims database analysis with a highly statistically significant result
C	• Reports to regulatory agencies judged to exceed population averages and reporting bias • Multiple case studies with non-blinded dechallenge and rechallenge • Strong trends, not reaching statistical significance, for safety issues in large RCTs • Well-conducted prospective cohort study giving a result that is statistically well above population average • Metabolic or clinically surrogate studies
D	• Undocumented opinion of experienced research investigators and clinicians • Poorly controlled or uncontrolled studies • Non-definitive evidence from regulatory agency reporting systems or managed care claims databases
U	• Unknown, no appropriate evidence, or evidence considered subject to bias

RCT = randomized controlled clinical trial.
*Support for evidence for or against contention that a potential human adverse experience is related to use of statins. Adapted with permission from [64].

subjects even if the statins are continued at the same dose. The cellular mechanisms of statin-related elevations of transaminases have not been well defined. Moreover, the data from clinical trials are confounded by the fact that the patients most likely to receive statin therapy are also the most likely to experience elevated transaminases due to obesity, NAFLD, diabetes mellitus, old age and multiple medications. Liver failure is extremely rare and has been reported in patients on statin therapy, but a causal relation cannot be established from these data alone because the rate of liver failure is similar to that observed in a population not receiving statin therapy. The liver failure may represent an idiosyncratic reaction and routine monitoring of transaminase levels is not helpful in identifying these patients. Thus, the key features of transaminase elevations attributed to statins include:

- A dose-related effect
- A class effect
- Most elevations occur within the first 3–6 months of therapy and reverse in the majority even when continued
- They do not predict the development of liver failure and are thus not a useful monitoring tool
- Isolated transaminase elevations do not predictably represent hepatotoxicity in the absence of hyperbilirubinemia.

An assessment of statin safety and recommendations from the Liver Expert Panel and the National Lipid Association Statin Safety Assessment Task Force are summarized in Tables

Table 15.3 An assessment of statin safety by hepatologists – a summary

Question	*Response*	*Level of evidence*
Are elevations in serum transaminase levels associated with statin therapy?	Yes	1A
Are statin-associated transaminase elevations indicative of liver damage or dysfunction?	No	2C
Does statin therapy increase the incidence of liver failure, liver transplants or death associated with liver failure in the general population?	Yes	2D
Should liver enzymes and liver function tests be monitored in patients receiving long-term statin therapy?	No	2B
Are any of the following conditions a contraindication for statin therapy?		
Chronic liver disease	No	2B
Compensated cirrhosis	No	3D
Decompensated cirrhosis or acute liver failure	Yes	2D
Can statins be used in patients with non-alcoholic fatty liver disease (NAFLD) including steatohepatitis (NASH)?	Yes	1B

Adapted with permission from [64].

Table 15.4 The National Lipid Association Statin Safety Assessment Task Force: recommendations to healthcare professionals regarding the liver and statin safety

1. Obtain transaminase levels prior to initiating statins. If abnormal, investigate to determine the etiology.
2. The available evidence does not support routine monitoring of liver biochemical tests. Until there is a change in the FDA-approved prescribing information for statins, it is appropriate to continue to measure transaminase levels before starting therapy, 12 weeks later, after a dose increase, and periodically thereafter.
3. The clinician should be alert to signals of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level and elevated prothrombin time (rather than simple elevations in liver transaminase levels).
4. The preferred biochemical test to ascertain significant liver injury is fractionated bilirubin. In the absence of biliary obstruction, it is a more accurate prognosticator of liver injury than isolated transaminase levels.
5. Should the clinician identify objective evidence of significant liver injury in a patient receiving a statin, the statin should be discontinued. Other etiologies should be sought and, if indicated, the patient should be referred to a specialist.
6. For an isolated asymptomatic transaminase level 1–3 $\times$ ULN, there is no need to discontinue the statin.
7. An isolated asymptomatic transaminase level $>3 \times$ ULN during a routine evaluation of a patient on a statin should be repeated and, if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment.
8. Patients with chronic liver disease including non-alcoholic fatty liver disease may safely receive statins.

FDA = US Food and Drug Administration; ULN = upper limit of normal.
Adapted with permission from [65].

15.2–15.4 [64, 65]. However, it should also be emphasized that many factors limit our understanding of statin-induced hepatotoxicity. These include the relatively rare incidence of toxicity, lack of animal models, under-reporting and issues of drug interactions which can confound the establishment of causality in cases of suspected toxicity.

In conclusion, while the available evidence confirms the association between statin therapy and elevated serum transaminase levels, the incidence of transaminase elevations appears to be similar between statin and placebo groups. Although exceedingly rare, the risk of acute liver failure exists with statin therapy but is probably no higher than that associated with other commonly used drugs or the background rate in the general population. Hence, the risk of liver injury with statin therapy should not preclude its use in patients at risk for cardiovascular events.

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16

Should we treat a low serum HDL-c and what specific lifestyle changes and drugs can be used to raise a low HDL-c?

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BACKGROUND

Circulating cholesterol is distributed in macromolecular complexes called lipoproteins that have varying impacts on the risk for atherosclerosis. Lipoproteins that contain apolipoprotein (apo) B, such as low-density lipoprotein (LDL) and lipoprotein (a), are clearly atherogenic. Remnant particles catabolized from endogenously produced, triglyceride-rich particles, such as very-low-density lipoprotein (VLDL), may also be atherogenic [1, 2]. Conversely, the available evidence suggests that high-density lipoprotein (HDL), in general, is anti-atherosclerotic through a variety of potential protective mechanisms [3].

In contrast to the impressive experimental and clinical evidence that illustrates the primary role of LDL cholesterol (LDL-c) in cardiovascular (CV) risk management, the optimization of HDL-c levels with pharmacologic or lifestyle therapy lacks a broad evidence base, despite being theoretically attractive. Should clinicians treat a low level of HDL cholesterol (HDL-c)? The answer would depend on the clinician's judgment and the overall risk factor profile for the individual patient. This chapter will discuss the regulation of circulating levels of HDL, propose a rationale for the clinical management of this lipoprotein, and review established and evolving therapeutic interventions that target HDL.

HIGH-DENSITY LIPOPROTEIN AND ATHEROSCLEROSIS

Epidemiologic studies, such as the Framingham Heart Study, demonstrate an inverse relationship between the risk for atherosclerosis and levels of HDL-c [4]. The protective benefit found with progressively increasing levels of HDL-c is independent of other CV risk factors. The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) has designated levels of HDL-c <40 mg/dl (1.03 mmol/l) as a risk factor for coronary artery disease (CAD) [5]. Conversely, elevated levels of HDL-c (>60 mg/dl [1.55 mmol/l]) favorably modify the overall risk factor profile (Table 16.1). In Framingham risk scoring, an HDL-c >60 mg/dl allows the subtraction of one point from the overall risk score, hence it is a 'negative risk factor'.

Many etiologies for low HDL-c exist and are increasingly better understood (Table 16.2) [6]. Likewise, multiple mechanisms have been proposed as an explanation for the protective

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Table 16.1 Classification of HDL-c levels, according to several authorities

	Low	*Optimal or desirable*
ATP III (2001)	<40 mg/dl (1.0 mmol/l)	≥60 mg/dl (1.55 mmol/l)*
Expert Group (2002)	<40 mg/dl	≥40 mg/dl for CHD or high risk patients
AHA (2004) in women	≤50 mg/dl (1.29 mmol/l) for women	>50 mg/dl
ADA (2007) in diabetic patients	≤40 mg/dl	>40 mg/dl >50 mg/dl for women may be considered

*ATP III designates this as a 'high' level of HDL-c and does not specify a goal for HDL-c, *per se* (see text).
ADA = American Diabetes Association; AHA = American Heart Association; ATP III = Third Adult Treatment Panel; CHD = coronary heart disease. HDL-c = high-density lipoprotein cholesterol.
Adapted with permission from Toth [3]; ATP III [5]; Sacks FM. *Am J Cardiol* 2002; 90:139–143; Mosca L, Appel LJ, Benjamin EJ *et al*. *Arterioscler Thromb Vasc Biol* 2004; 24:e29–e50; and American Diabetes Association. *Diabetes Care* 2007; 30:S4–S41.

Table 16.2 Selected etiologies for Low HDL-c

Etiology	*Description*
Lifestyle	Overweight/obesity and smoking are associated with depressed HDL-c.
Hypertriglyceridemia	Overproduction/impaired removal of TG-rich lipoproteins may enrich TG in HDL and enhance apoAI catabolism.
Mutations related to apoAI	Mutations in expression of this protein can lead to HDL deficiency.
Mutations related to LCAT	LCAT mediates the esterification of HDL-c and thus maturation of HDL particles. Mutations can yield autosomal recessive forms of low HDL called familial LCAT deficiency and fish-eye disease.
Mutations related to PLTP	PLTP contributes to remodeling of HDL. Four missense mutations have been identified, one of which is associated with decreased lipid transfer.
Mutations related to ABCA1	Mutations in ABCA1 result in impaired lipid efflux to apoAI, yielding HDL deficiency. Such mutations are present in the autosomal recessive disorder Tangier disease.
Mutations related to CETP and hepatic lipase	Gain-of-function mutations in these factors decrease HDL-c.

ABCA1 = adenosine triphosphate-binding cassette A1; apo = apolipoprotein; HDL-c = high-density lipoprotein cholesterol; LCAT = lecithin cholesterol acyltransferase; PLTP = phospholipid transfer protein; TG = triglyceride.
Adapted with permission from [6].

role of HDL. Investigators have coined the term *reverse cholesterol transport* (RCT) to describe HDL's potential to remove atherogenic cholesterol from the peripheral vasculature with subsequent hepatic excretion [7]. However, while HDL-mediated RCT has been extensively studied, its quantitative contribution to CV risk reduction remains arguable.

HDL originates from the synthesis of apoAI in the liver and ileum. The particle subsequently progresses through a series of maturation steps that increase its size and cholesterol

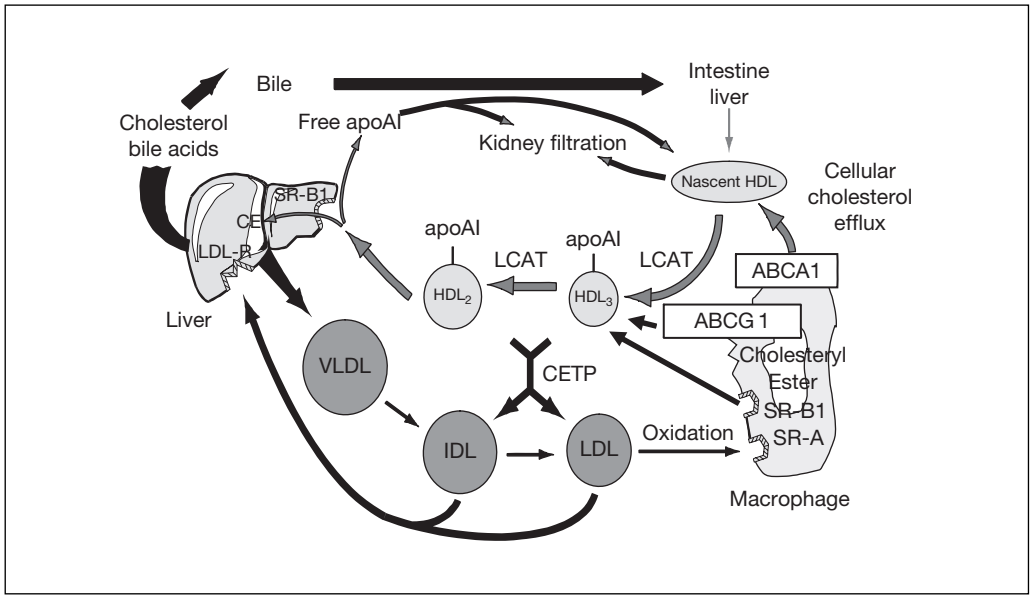

Figure 16.1 Schematic representation of reverse cholesterol transport. Nascent HDL is secreted from the liver and the intestine as a small disk-shaped molecule containing phospholipids, free cholesterol and primarily apoAI. Other apolipoproteins are rapidly added as the particle gains lipid. Free cholesterol is adsorbed from both peripheral cells and the liver cell membranes through action of the ABCA1 transporter. This cholesterol is converted into cholesteryl ester (CE) by lecithin : cholesterol acyltransferase (LCAT). CE leaves the surface to form an inner core, causing the particle to become a spherical structure. These more-mature HDL no longer bind as well with the ABCA1 and instead acquire cholesterol through another transporter ABCG1. Through the action of CETP, HDL exchanges CE for triglyceride (TG) with TG-rich lipoproteins, as they circulate. At the liver, hepatic triglyceride lipase (HTGL) on the surface of the hepatocytes can hydrolyse this TG, and SR-B1 can take up CE, leaving the particle to continue circulating in the plasma. ApoE-containing HDL can bind to the LDL-receptor–related protein (LRP), which results in these HDL particles entering the hepatocyte and transferring to the lysosomal compartments where hydrolysis of lipids and proteins occur.
Adapted with permission from Lipidsonline.com, Linsel-Nitschke and Tall. *Nat Rev Drug Discovery* 2005; 4:193–205, and WV Brown. *J Clin Lipidol* 2007; 1:7–19.

content (Figure 16.1). Mature HDL has several potential metabolic fates. The cholesterol of HDL can be exchanged for triglyceride through the action of cholesteryl ester transfer protein (CETP), resulting in the movement of cholesterol into apoB-containing lipoproteins (LDL and VLDL) [8]. Additionally, HDL may deliver cholesterol to the liver where it is recognized by the scavenger receptor class B type 1 (SR-B1) receptor. HDL also acquires apoE, allowing recognition, binding, and removal from the circulation by the LDL (apoB/E) receptor [9].

The transformation of circulating monocytes into foam cells occurs early in the atherosclerotic process, with macrophages accumulating lipids through uptake of minimally modified or oxidized LDL. The efflux of cholesterol from lipid-laden foam cells is an important step in RCT (Figure 16.1). Such efflux is at least partially mediated by adenosine triphosphate (ATP)-binding cassettes (ABC), which are transport facilitators that exist in a variety of subclasses with differing physiologic functions [10]. The ABCA1 transporter modulates the migration of cholesterol from lipid-laden foam cells [11]. Cholesterol may also leave the

foam cell by passively diffusing down concentration gradients or by interacting with the SR-B1 receptor [12]. Following efflux from the foam cell, cholesterol is accepted by lipid-poor apoAI, which is the major protein of HDL.

Defects in the ABCA1 transporter system are the basis of the genetic disorder Tangier disease [13]. Extremely low levels of HDL-c and apoAI characterize individuals with Tangier disease. Additionally, massive amounts of cholesterol may accumulate in lymphoid tissue (e.g., tonsils), which may take on a yellow to orange discoloration. Interestingly, although low levels of HDL-c are a feature of Tangier disease, premature atherosclerosis is not the rule, thus emphasizing the complex nature of HDL function.

In addition to the well-documented role of ABCA1 in reverse cholesterol transport, a second member of the family (ABCG1) plays a role in the modulation of cholesterol efflux from the macrophage [14]. The regulation of the binding cassettes is both complex and multifactorial. Cholesterol loading of the macrophage is associated with increased activity of both ABCA1 and G1, which would allow increased cholesterol efflux from the foam cell. Additionally, a class of nuclear receptors termed liver X receptors (LXRs) play a role in the regulation of the ATP-binding cassettes [15]. Oxysterols, which are formed by enzymatic modification of cholesterol, are the normal endogenous ligands that bind to LXRs. The interaction of oxysterols with the LXR system subsequently upregulates ABCA1 and G1 activity, yielding an efflux of cholesterol from the macrophage. The activity of LXRs plays a central role in the modulation of cholesterol trafficking from the macrophage and in the subsequent uptake of cholesterol by HDL [16].

Niemann-Pick type C disease is a neurovisceral disorder that results from the deficiency of a lysosomal enzyme called acid sphingomyelinase, in which unesterified cholesterol and other lipids accumulate in endosomes and lysosomes and impair the trafficking of cholesterol to other cell compartments [17]. Many patients with this disease have low HDL-c as a consequence of abnormal ABCA1 regulation, which inhibits lipidation of apoAI. Boadu *et al*. [17] have demonstrated that *in vitro* treatment with the non-oxysterol LXR agonist TO-901317 normalizes the expression and activity of ABCA1 in human fibroblasts, as well as corrects ABCG1 expression and HDL particle formation.

While increasing reverse cholesterol transport is considered to be a major mechanism by which elevated levels of HDL confer protection from atherosclerosis, other mechanisms have also been proposed. Considerable evidence indicates that atherosclerosis has a major inflammatory component [18]. As noted above, the chemotaxis of monocytes to, and migration of monocytes across, the endothelium is an initiating event in atherosclerosis. HDL may manifest an anti-inflammatory effect by decreasing expression of cellular adhesion molecules (e.g., vascular cell adhesion molecule-1 and intercellular adhesion molecule-1) that might otherwise facilitate this initiating event [19, 20].

However, the role of HDL in systemic inflammation is complex. In the absence of significant systemic inflammation, HDL has a complement of antioxidant enzymes that effectively decreases the degree and extent of progressive inflammation [21]. HDL then exhibits a protective antioxidant effect upon LDL. Increased levels of HDL may thus reduce foam cell generation by decreasing the oxidation of LDL particles, consequently diminishing their recognition and uptake by the macrophage scavenger receptor. However, increased exposure to systemic inflammation may inactivate the antioxidant enzymes localized in HDL, resulting in progressive accumulation of oxidized lipids in macrophages [22]. The increase in oxidized lipids also adversely affects the function of HDL, converting it to a proinflammatory particle. Apolipoprotein AI may also be chemically altered by reactive oxygen species, thus impairing the ability of HDL to modulate RCT *via* the ABCA1 pathway [23].

Prostacyclin is a potent vasodilator and a significant inhibitor of platelet aggregation. HDL may either increase the production or prolong the half-life of prostacyclin, leading to beneficial effects on platelet aggregation [24].

Table 16.3 General features of the metabolic syndrome

Risk factor	*Defining level*
Abdominal obesity* (waist circumference)†	
Men	≥102 cm (≥40 in)
Women	≥88 cm (≥35 in)
Elevated triglycerides	>150 mg/dl (1.7 mmol/l) or on drug treatment for elevated TG‡
Low HDL-c	
Men	<40 mg/dl (1.03 mmol/l)
Women	<50 mg/dl (1.29 mmol/l) or on drug treatment for decreased HDL-c‡
Raised blood pressure	≥130 mmHg systolic or ≥85 mmHg diastolic or on drug treatment for hypertension
Fasting glucose	≥100 mg/dl or on drug treatment for elevated glucose

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. The simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
†To measure waist circumference, locate top of right iliac crest. Place a measuring tape in a horizontal plane around abdomen at level of iliac crest. Before reading tape measure, ensure that tape is snug but does not compress the skin and is parallel to floor. Measurement is made at the end of a normal expiration. Some US adults of non-Asian origin (e.g., white, black, Hispanic) with marginally increased waist circumference (e.g., 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. A lower waist circumference cutpoint (e.g., ≥90 cm [35 inches] in men and ≥80 cm [31 inches] in women) appears to be appropriate for Asian-Americans.
‡Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL-c. Patients taking one of these drugs are presumed to have high TG and low HDL.
Adapted with permission from [25].

CLINICAL MANAGEMENT OF LOW HDL

Isolated low HDL-c (i.e., in the absence of other coronary risk factors) is uncommon. More frequently, low HDL-c is present in the triad of lipid abnormalities called *atherogenic dyslipidemia* (low HDL-c, elevated triglycerides, and small dense LDL particles or elevated LDL-c). This phenotype is observed in patients with diabetes or the constellation of metabolic risks called the *metabolic syndrome* (Table 16.3) [25]. Other clinical scenarios that decrease HDL-c may include the use of tobacco products, the use of some pharmacologic agents (e.g., noncardioselective beta-blockers and androgens), and several genetic syndromes (e.g., primary hypoalphalipoproteinemia) [26].

The ATP III designates low levels of HDL-c as an independent risk factor for the development of atherosclerosis, but does not specify a target level for therapy [5]. The unwillingness to do so is largely due to the fact that few trials have demonstrated that raising HDL-c reduces the risk for coronary events. Nevertheless, Figure 16.2 presents a simple algorithm

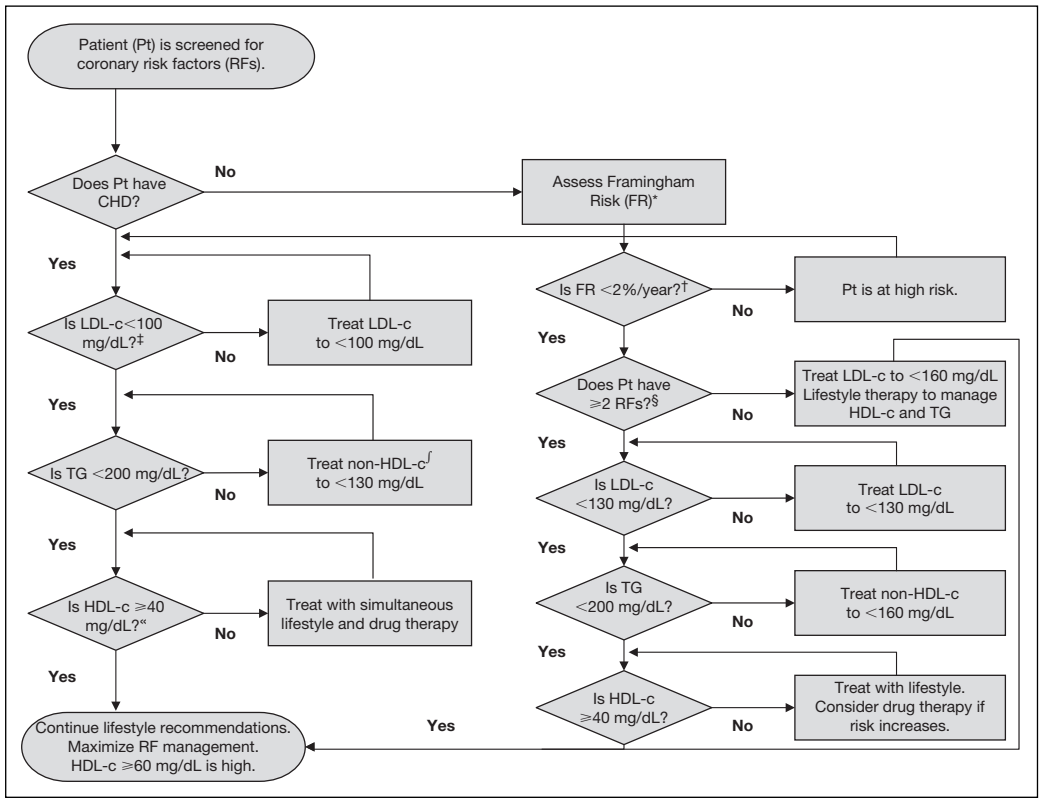

Figure 16.2 HDL-c in clinical treatment decision-making. Derived largely from the recommendations of ATP III [5], this algorithm suggests HDL's current role in guiding treatment decisions. Although HDL appears to be a tertiary concern after LDL-c and non-HDL-c, its importance as a coronary risk factor is well recognized. Additional clinical trials that clarify the clinical effects of raising HDL-c are needed.
To convert from mg/dl to mmol/l, multiply LDL-c, HDL-c, and non-HDL-c by 0.02586 and TG by 0.01129.
*Framingham risk estimation is available online at http://hp2010.nhlbihin.net/atpiii/calculator.asp.
†A patient is at high risk according to Framingham if his or her risk is greater than 20% over 10 years (or 2%/year).
‡ATP III also recommends an optional LDL-c goal of <70 mg/dl (1.80 mmol/l) for patients at highest risk for CHD (e.g., those with pre-existing disease plus diabetes or multiple other uncontrolled risk factors).
§Other coronary risk factors (RF) besides LDL-c include age (≥45 years for men; ≥55 years for women); smoking; hypertension; family history of premature CHD; and HDL-c <40 mg/dl. The presence of HDL-c ≥60 mg/dl (1.55 mmol/l) permits the subtraction of one RF from the total number. Patients with no CHD and fewer than 2 other risk factors are generally considered low risk. Diabetes is considered a coronary risk equivalent, and its presence automatically places a patient in the high-risk category.
∫Non-HDL-c can be calculated by subtracting HDL-c from the total cholesterol value.
«Some authorities recommend that the definition of low HDL-c in women be <50 mg/dl (1.29 mmol/l), to account for women's tendency to have higher HDL-c values compared with men. Therefore, for women, an HDL-c ≥50 mg/dl (1.29 mmol/l) may be desirable.

that may help guide treatment decisions based on HDL-c. As such, in the patient with low HDL-c values, assessing the global risk for near-term CV disease, using a risk prediction model such as the one developed from the Framingham Heart Study (available online at http://hp2010.nhlbihin.net/atpiii/calculator.asp) provides a therapeutic starting point. In

concordance with ATP III recommendations, addressing abnormal LDL-c is the first priority. Once LDL-c is under control, if HDL-c remains low, the clinician may consider intervention(s) to raise it, especially in patients who have pre-existing CV disease or who are at high risk for atherosclerosis in the next decade. Weight loss and increased physical activity are emphasized. If triglycerides are 200 mg/dl (2.26 mmol/l) or greater, non-HDL-c becomes a secondary target, with a treatment goal that is 30 mg/dl (0.76 mmol/l) greater than the patient's LDL-c goal. Non-HDL-c may be calculated by subtracting the HDL-c value from the total cholesterol level.

LIFESTYLE THERAPY

Lifestyle measures directed at the optimization of body weight and increased physical activity should be the primary strategy to manage low levels of HDL-c [5]. Increased aerobic physical activity can be expected to raise HDL-c levels by 9% (an approximate increase of 3.7 ± 1.3 mg/dl, or 0.10 ± 0.03 mmol/l) [27]. Dietary fat restriction and caloric substitution with carbohydrates, as well as consumption of *trans* fats, may decrease HDL-c; replacement of saturated fats with monounsaturated fats, such as olive oil, may help maintain HDL-c while offering other CV benefits [28]. Smoking can depress HDL-c levels in smokers compared with non-smokers. Discontinuing the use of tobacco products generally returns HDL-c to levels comparable to those seen in non-smokers [29].

Lifestyle measures should be given a thorough trial prior to the initiation of pharmacologic therapy, although the duration of lifestyle therapy must take into account the patient's overall risk for CV disease in the next few years. High-risk patients with isolated low HDL-c should receive simultaneous lifestyle and drug treatment to reduce their greater near-term risk.

DRUG THERAPY

If lifestyle measures fail to optimize HDL-c, a variety of drug therapies are available (Table 16.4). Of the traditional lipid-modifying agents, nicotinic acid has the greatest effect on HDL-c, but statin and fibrate therapies have more substantive evidence of clinical benefit. Omega-3 fatty acids may be consumed as part of the diet or through dietary supplements, with a highly purified prescription preparation also available. Resins and cholesterol absorption inhibitors have minimal effects on HDL-c and are thus excluded from the discussion below. In general, available drugs that raise HDL-c have favorable effects on other lipid fractions. One exception is prescription omega-3 fatty acids, which may induce an increase in LDL-c, although the clinical importance of this effect remains unclear.

STATINS

Statins have evolved as the primary pharmacologic agent in the treatment of dyslipidemia. Statins have a complex mechanism of action including partial inhibition of the rate-limiting enzyme in cholesterol synthesis (HMG CoA reductase) and upregulation of the LDL (apoB/E) receptor [30]. The primary effect of statins is to lower circulating LDL-c concentrations. Statins also modulate a variety of effects that may be lipid-independent and that may contribute to their other observed benefits, including improvements in endothelial function, inflammation, coagulation, and other factors [31]. The effect of statins on increasing circulating levels of HDL-c is generally modest and ranges from 5% to 10%. The mechanism by which statin therapy increases circulating levels of HDL-c is multifactorial. Statins may raise HDL by inhibition of CETP, inhibition of Rho kinase, and increases in apoAI gene transcription through an effect on peroxisome proliferator-activated receptor (PPAR)-α [32]. However, the relative contributions of these various proposed pathways remain controversial.

Table 16.4 Summary of major classes of lipid-modifying drugs and their effects on HDL

Drug class	*Nicotinic acid*	*Statins*	*Fibrates*	*Omega-3 fatty acids*	*Resins*	*Cholesterol absorption inhibitors*
Available in US	Various preparations	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin	Gemfibrozil, clofibrate, fenofibrate	Various preparations	Cholestyramine, colestipol, colesevelam	Ezetimibe
Increase in HDL-c	15–35%	5—15%	10–20%	5–10%	3–5%	1–3%
Major use	To lower LDL-c, TG; to raise HDL-c	To lower LDL-c	To lower TG; raise HDL-c	To lower very high TG	To lower LDL-c	To lower LDL-c
Usual starting dose/Maximum FDA-approved dose	Crystalline: 1.5–3g/4.5 g Sustained-release: 1–2 g/2 g Extended-release: 1–2 g/2 g	Lovastatin: 20 mg/80 mg Pravastatin: 20 mg/80 mg Simvastatin: 20 mg/80 mg Fluvastatin: 20 mg/80 mg Atorvastatin: 10 mg/80 mg Rosuvastatin: 10 mg/40 mg	Gemfibrozil: 600 mg bid/1200 mg Fenofibrate: 200 mg daily/200 mg Clofibrate: 1000 mg bid/ 2000 mg	Prescription formulation: 4 g/4 g	Cholestyramine: 4–16g/24 g Colestipol: 5–20 g/30 g Colesevelam: 2.6–3.8 g/4.4 g	Ezetimibe: 10 mg

FDA = Food and Drug Administration; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; TG = triglyceride

Additionally, statin therapy increases the levels of larger subfractions of HDL (α–1 HDL) that have been proposed to be markers of more effective RCT [33]. In clinical trials, statin therapy has reduced CV morbidity and mortality across the spectrum of at-risk patients, and this benefit appears to be related linearly to a decrease in LDL-c [34]. The quantitative effect of the relatively modest increase in HDL-c associated with statin therapy in CV risk reduction is unclear.

FIBRIC ACID DERIVATIVES

The mechanism of action of the fibric acid derivatives, or fibrates, is mediated by activation of the nuclear receptor PPAR-α [35]. Activation of the PPAR-α receptor modulates multiple aspects of lipoprotein metabolism and inflammation. The primary effect of fibrates in dyslipidemia is a decrease in triglyceride-rich lipoproteins coupled with an increase in HDL, with relatively minimal effects on LDL. However, fibrates may alter the phenotype of LDL from a small, dense form to a larger, more buoyant, and potentially less atherogenic one [35]. Fibric acid derivatives may increase HDL-c from 5 to 20%, and a greater increase in HDL-c is demonstrable in subjects with a higher degree of pretreatment hypertriglyceridemia [35]. The beneficial effect of fibric acid derivatives on triglyceride-rich lipoproteins is due to an increased catabolic rate secondary to activation of lipoprotein lipase, coupled with a reduction in hepatic synthesis. The enhanced degradation of triglyceride-rich lipoproteins induced by fibric acid derivatives is linked to a secondary increase in HDL-c. Fibric acid derivatives also increase HDL by increasing synthesis of apoAI and apoAII. Gemfibrozil has reduced the rates of CV morbidity and mortality compared with placebo in clinical trials, including the Helsinki Heart Study and the Veterans Affairs HDL Intervention Trial (VA-HIT) [36, 37]. Fenofibrate therapy was also analysed relative to placebo in a large (9795 subject) cohort of diabetic subjects in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [38]. Fenofibrate therapy did not reduce the primary endpoint of coronary events (CHD death or non-fatal myocardial infarction) in that trial, but the fact that a considerable number of the placebo patients began statin therapy during this study may have influenced the results.

NICOTINIC ACID

Nicotinic acid is an essential B vitamin that has been utilized to prevent pellagra in a dose range of 1–5 mg/day. However, at high doses nicotinic acid reduces triglycerides, LDL-c, chylomicrons (and their remnant particles), and lipoprotein (a) [39]. Nicotinic acid is also a relatively potent agent in raising HDL-c concentrations, with expected increases in HDL-c ranging from 15 to 35%. Nicotinic acid reduced risk for myocardial infarction and stroke in the Coronary Drug Project and has also been associated with regression of coronary atherosclerosis in combination with other hypolipidemic agents [40–42].

The mechanism by which nicotinic acid exerts its beneficial effect on circulating HDL-c levels is complex and multifactorial. Nicotinic acid had long been considered to increase HDL levels solely by decreasing the intrinsic catabolic rate of HDL and thus prolonging its availability within the circulation [43]. Nicotinic acid also decreases lipolysis in peripheral adipose tissue, resulting in a secondary reduction in circulating free fatty acids. The delivery of free fatty acids to the liver is a primary step in triglyceride-rich lipoprotein synthesis, and the diminished availability of substrate due to nicotinic acid therapy thus decreases VLDL synthesis. The recent discovery of the G protein-coupled nicotinic acid receptor has added to current understanding regarding nicotinic acid's mechanism of action [44]. The interaction of nicotinic acid and its receptor in the periphery enhances the expression of the ABCA1 membrane cholesterol transporter and alters intracellular trafficking.

OMEGA-3 FATTY ACIDS

Epidemiologic observations have linked the consumption of a diet rich in marine-derived omega-3 fatty acids to a significant reduction in the incidence of CAD [45]. This phenomenon was first observed in Greenland Eskimos, although these early studies were controversial because detailed pathologic evaluations were not performed. However, additional studies in multiple diverse populations have since confirmed that diets rich in omega-3 fatty acids are related inversely to CV risk. The reduction in CV morbidity and mortality occurs despite a diet relatively high (>30%) in fat.

Omega-3 fatty acids have multiple potentially beneficial CV effects, including the capacity to decrease platelet aggregation, reduce inflammation, promote vasodilation, and improve the lipid profile [46, 47]. Marine-derived omega-3 fatty acids inhibit the sterol regulatory element binding protein-1c (SREBP-1c), which is a key gene transcription factor [47]. The SREBP-1c complex is predominantly located in the liver and regulates enzymes that are involved in lipid synthesis. The net result of inhibition of SREBP-1c is a reduction in the hepatic synthesis of triglyceride-rich lipoproteins, amongst other mechanisms. The major effect of the consumption of omega-3 fatty acids is a reduction in circulating triglyceride-rich lipoproteins, although the effect of marine fish oils on HDL-c levels is modest and ranges between 5 and 10% [48].

The preponderance of epidemiologic data supports the beneficial effects of an increased intake of marine omega-3 fatty acids in CV risk reduction, and meta-analysis has demonstrated a roughly 7 to 14% reduction in CAD mortality for each 20 g per day of fish intake, although not all studies have shown such positive results [49–52]. The Gruppo Italiano per lo Studio della Sopravvivenza nell' infarto micardico (GISSI) –Prevenzione trial offers support for these epidemiologic observations. This prospective trial found that the administration of a highly purified source of omega-3 fatty acids at a dose of 1 g per day, in addition to standard therapy and a Mediterranean diet, resulted in a 14% risk reduction for death, nonfatal myocardial infarction, and stroke [53].

EMERGING THERAPIES FOR HDL ELEVATION

A variety of emerging therapies have been proposed as potential candidates for optimizing HDL-c levels.

CETP inhibitors – Until recently, the most promising HDL-based treatments in the pipeline had been agents that inhibit CETP. A large glycoprotein, CETP modulates the exchange of cholesterol from HDL to the atherogenic apoB-containing particles, such as VLDL and LDL [54]. Controversial observations that a genetic deficiency of CETP was associated with markedly elevated HDL-c levels (hyperalphalipoproteinemia) and potentially increased longevity stimulated interest in CETP as a therapeutic target [55].

The molecule torcetrapib was developed as a pharmacologic inhibitor of CETP. The administration of torcetrapib markedly improves the lipid profile, with a significant increase in HDL-c coupled with a reduction in LDL-c [56]. However, further study has raised concerns about both the efficacy and safety of this particular drug, and of CETP inhibitors in general. Three studies that assessed vascular endpoints (percent change in atheroma measured by intravascular ultrasonography and carotid intima-media thickness assessed by B mode ultrasonography) reported no benefit from the addition of torcetrapib to a background of atorvastatin, even though adjuvant torcetrapib was found to increase HDL-c by 50–60% and to generate additional LDL-c reductions above and beyond those seen with statin therapy alone [57–59]. While the use of vascular endpoints as surrogates for clinical events remains debatable, less ambiguous was a large-scale randomized trial of over 15 000 subjects that was discontinued prematurely because of excess total mortality in the group receiving torcetrapib, again despite a substantial HDL-c increase [60].

The reasons behind the failure of this promising therapy remain unclear. Torcetrapib induced unexpected elevations of blood pressure [61]. The absolute increase in blood pressure with torcetrapib, though relatively modest, may have been a clinical marker of other adverse vascular effects, although other explanations are also possible [62]. Despite the disappointing results with torcetrapib, other CETP inhibitors remain in various stages of development.

Reconstituted HDL – Intravenous injection of reconstituted HDL has been advocated as an innovative approach to increasing HDL through facilitation of RCT. Such particles typically consist of apoAI and phospholipid, but may also include apoE and other lipids [63]. Infusion of reconstituted HDL appears to promote a number of antiatherogenic effects, such as inhibition of adhesion molecule expression, attenuation of proinflammatory cytokines, and reductions in LDL oxidation [63].

The novel compound CSL–111 is a reconstituted HDL compound synthesized from soybean phosphatidylcholine and combined with apoAI obtained from human plasma [64]. CSL-111 resembles HDL both chemically and physiologically. The effects of reconstituted HDL infusions have been analysed in 183 subjects with documented CAD who underwent intravascular ultrasound quantification of plaque burden [64]. CSL-111 infusion did not reduce atheroma volume relative to placebo, but it did improve both plaque characteristics and coronary score as evaluated by quantitative coronary angiography over a four-week trial.

ApoAI Milano is a mutation of apoAI first identified in an Italian population in Limone Sul Garda [65]. The defect is associated with enhanced longevity. Human studies utilizing intravenous administration of apoAI Milano have demonstrated plaque regression [66]. Therefore, reconstituted HDL containing apoAI Milano may prove to be a promising approach for future investigation [63]; however, an oral agent would be of even more significant clinical advantage, if it could be developed.

ApoAI mimetic peptides – The role of apoAI mimetic peptides is under active clinical investigation [67]. Experimental studies have demonstrated that the administration of apoAI is associated with regression of atherosclerosis in laboratory animals. ApoAI has been characterized and consists of 243 amino acids. The initial impression was that it would need to be parenterally administered in order to avoid degradation in the gastrointestinal tract. Subsequent research demonstrated, however, that the lipid-binding properties of this compound were a function of class A amphipathic helices with a hydrophobic face which binds lipids in a similar manner to apoAI [68]. A peptide which has been designated 4F has been synthesized with four phenylalanine residues on the hydrophobic face [67]. The biologic properties of 4F have been studied and were demonstrated to induce cellular cholesterol efflux in experimental studies. A derivative of 4F synthesized from D-amino acids (designated D-4F) has been demonstrated to be bioavailable in human studies, and clinical trials are currently underway with this compound.

Rimonabant – Rimonabant is a selective endocannabinoid-1 receptor blocker that reduces weight significantly in prospective clinical trials, compared with placebo [69–71]. In addition to weight loss, the administration of rimonabant significantly improves abnormal lipid profiles. Its administration was followed by an 11% reduction in circulating triglyceride concentrations and an increase in HDL-c levels of 27%. In an overweight population with a high prevalence rate of the metabolic syndrome, treatment with rimonabant 20 mg/day decreased the prevalence of metabolic syndrome by 53.6% (from 42.2% at baseline to 19.6% after 1 year of therapy) [69]. Although rimonabant is already marketed in a number of other countries, at the time of this writing, the US Food and Drug Administration has withheld approval of this drug in the United States, pending additional safety data [72].

SUMMARY

Prospective clinical trials have established that optimization of the lipid profile is beneficial to CV risk reduction. The role of LDL as a therapeutic target is well recognized, but HDL is

less so, despite epidemiologic evidence that high HDL-c is cardioprotective. Reverse cholesterol transport, antioxidant activity, anti-inflammatory activity, and alteration of prostacyclin have all been implicated as potential mechanisms in the HDL-mediated reduction in CV risk. However, increased circulating levels of HDL-c do not necessarily assure reduced risk. Multiple genetic conditions are associated with low levels of HDL-c without an increased risk for premature atherosclerosis.

Although evidence-based clinical precepts related to low HDL-c have proved hard to articulate, it is key to consider low HDL-c in the context of the patient's overall risk profile. In the absence of other CV risks, a less aggressive approach that emphasizes weight loss and increased aerobic exercise is a reasonable prescription for a low HDL-c patient. In patients at high risk or with pre-existing CV disease, the presence of low HDL-c concentrations assumes additional importance, and simultaneous lifestyle and drug intervention may be considered if LDL-c and non-HDL-c are at NCEP-defined target values.

Nicotinic acid, fibric acid derivatives, omega-3 fatty acids, and statin therapy all may improve HDL-c levels (albeit the relative quantitative effect of each drug may vary). In addition, controlled prospective clinical trials have demonstrated these agents to be beneficial. Development of novel pharmacologic agents that dramatically increase circulating HDL-c levels (i.e., torcetrapib) has stalled because of concerns about increased mortality risk and other toxicities. Nevertheless, other pharmacologic advances that target HDL-c levels and HDL's functionality are in various stages of development, and their clinical efficacy will need to be determined.

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17

What is familial hypercholesterolemia and how should it be treated?

P. M. Moriarty, C. A. Gibson, J. M. Backes

BACKGROUND

Familial hypercholesterolemia (FH) is one of the most common inherited disorders with a frequency as high as 1:70 [1]. The disease has a plethora of mutations with dysfunction of the low-density lipoprotein (LDL) receptor representing the most common gene defect. FH results in decreased LDL catabolism, hypercholesterolemia, tendon xanthomas, and premature cardiovascular disease (CVD). The severity of symptoms occurs based on a gene dose effect, in that homozygotes are more harshly affected than heterozygotes. Patients who are homozygous for FH typically die before the age of 50 from the clinical manifestations of CVD. Until the advent of 3-hydoxy-3-methylglutary-coenzyme A reductase (HMG-CoA) inhibitors (statins), pharmacotherapy was not very successful in lowering the plasma levels of low-density lipoprotein cholesterol (LDL-c). Despite the use of this class of medications and others (resins, niacin, ezetimibe), there is still a significant percentage of patients who are unable to achieve appropriate cholesterol levels and thus remain at risk of developing CVD. For these drug-resistant patients, LDL apheresis has proven successful in reducing cholesterol levels and CVD.

In this chapter, we will review the diagnosis of FH and the use of appropriate screening measures. We will also examine presently available medications and drugs in development which may be used to treat hypercholesterolemia. Finally, we will assess the clinical application, patient qualification, and outcome data related to the use of LDL apheresis for treating FH.

WHAT IS FAMILIAL HYPERCHOLESTEROLEMIA AND HOW SHOULD IT BE SCREENED?

FH is an autosomal co-dominant disorder caused by a mutation in the gene that encodes the LDL receptor protein and is characterized by elevated plasma LDL-c with normal triglycerides, tendon xanthomas (cholesterol deposits), and premature coronary atherosclerosis [2]. Because this disorder results in a diminished ability to clear LDL-c from the circulation

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by the LDL receptor, FH is associated with severe elevations in total cholesterol and LDL-c. A substantial change in the number or functional status of LDL receptors directly influences serum cholesterol levels. With mutations in the genetic coding for the LDL receptor, the control of LDL uptake and cholesterol homeostasis in hepatocytes is severely affected, causing accumulation of cholesterol within the liver. The total and LDL-c levels of individuals with two mutated LDL receptor alleles (FH homozygotes) are much more affected than those with one mutant allele (FH heterozygotes), with levels typically two- or more fold higher than the population average.

HOMOZYGOUS FH

Homozygous FH is an extremely rare disorder, occurring in approximately one case per 1 million persons in the United States and Europe. Patients with homozygous FH can be classified into one of two groups based on the amount of LDL receptor activity. The first group includes patients with <2% of normal LDL receptor activity (receptor negative). The second group consists of patients with 2–25% of normal LDL receptor activity (receptor defective mutations). Homozygous FH patients display very high levels of circulating, cholesterol-rich, apolipoprotein (apo) B-containing lipoproteins with typical total cholesterol levels ranging between 500 mg/dl and 1000 mg/dl [3]. As a consequence, complications of homozygous FH are manifested in premature CVD and mortality in childhood or early adulthood. Without treatment, receptor-negative homozygous FH patients seldom live to reach 30 years of age. Patients with LDL receptor defects have a better prognosis but most develop atherosclerotic disease by the third decade.

The clinical diagnosis of homozygous FH is usually made in childhood during the first decade of life, when cutaneous and tendon xanthomas appear on the hands between the webs of the fingers, wrists, elbows, knees, heels, or buttocks [3]. Tendon xanthomas are not present in persons with non-familial hypercholesterolemia. If tendon xanthomas are present, FH or familial defective apolipoprotein B-100 is the correct diagnosis. Other clinical features typically present include deposits of fatty material around the eyes (xanthelasmas) and the cornea (arcus cornealis).

HETEROZYGOUS FH

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele and occurs in approximately 1 in 500 persons, or roughly 500 000 individuals in the United States and more than 10 million people worldwide [3, 4]. The prevalence of heterozygous FH in Europe is similar to that of the United States [3] but in select populations such as Afrikaners, Ashkenazi Jews, Christian Lebanese, and French Canadians, the disease is more frequent due to the founder effect [5], in which a subpopulation is formed through the immigration of a small number of 'founder' subjects [6].

Heterozygous FH is one of the most common genetic disorders, characterized by increased total cholesterol, elevated plasma LDL-c (200–400 mg/dl) and normal triglyceride levels. Because heterozygous FH is caused by the inheritance of one mutant LDL receptor allele, patients have hypercholesterolemia from birth. However, the clinical manifestations of the disease, such as xanthomas, are not usually detected in childhood despite having elevated levels of LDL-c [7]. Instead, clinical features of the disease are most often detected in adulthood after a first cardiac event.

FAMILIAL DEFECTIVE APOLIPOPROTEIN (APO) B-100

Familial defective apoB-100 (FDB) is an autosomal dominant inherited disorder of lipoprotein metabolism that results from a point mutation in the apoB gene and is associated with significantly elevated plasma total and LDL-c levels [8]. The substitution of

Table 17.1 Simon Broome Register diagnostic criteria for familial hypercholesterolemia

	Description
Criteria	
A	Total cholesterol concentration >7.7 mmol/l in adults or a total cholesterol concentration >6.7 mmol/l in children <16 years of age; low-density lipoprotein cholesterol concentration >4.9 mmol/l in adults or >4.0 mmol/l in children
B	Tendon xanthomas in the patient or a first-degree relative
C	DNA-based evidence of mutation in the LDLR or apoB gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of raised total cholesterol concentration >7.5 mmol/l in a first- or second-degree relative
Diagnosis	
Definite	A 'definite' familial hypercholesterolemia (FH) diagnosis requires either criteria *A* and *B* or criterion *C*
Probable	A 'probable' FH diagnosis requires either criteria *A* and *D* or criteria *A* and *C*

With permission from: Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolemia. *BMJ* 1991; 303:893–896.
Scientific Steering Committee on behalf of the Simon Broome Register Group. Mortality in treated heterozygous familial hypercholesterolemia: implications for clinical management. *Atherosclerosis* 1999; 142:105–112.

glutamine-for-arginine at position 3500 of apoB-100 leads to defective binding of apoB-100 to the LDL receptor and accumulation of LDL in the plasma [9]. In contrast to heterozygous FH, patients with FDB have normal LDL receptors while FH patients have defective ones. Patients can be easily tested for FDB and identified through molecular analysis [10], even though they may have only slightly elevated serum cholesterol levels and do not present with tendon xanthomas [11].

MUTATIONS IN PCSK9

A mutation in *PCSK9*, a gene which encodes proprotein convertase subtilisim/kexin type 9 (*PCSK9*) is associated with hypercholesterolemia and CVD [12].

One mutation, Asp374Tyr, is associated with severe disease and found in the UK and Norway [13]. The mechanism for causing hypercholesterolemia is not fully understood but a recent publication on patients with a loss of function in PCKS9, through a nonsense mutation, are found to have lower levels of LDL-c and reduced CHD [14]. The authors of the article state that their results support the hypothesis that lifelong reduction of LDL-c can lower the risk of CVD even in patients with non-lipid related cardiovascular risk factors.

DIAGNOSTIC CLASSIFICATION OF FH

Currently, three groups have developed diagnostic classification tools for FH patients. These groups include the Simon Broome Familial Hyperlipidaemia Register in the United Kingdom, the Dutch Lipid Clinic Network, and the Make Early Diagnosis to Prevent Early Deaths (MEDPED) Program in the United States [6]. The diagnostic criteria of the Simon Broome Register for FH include cholesterol levels, clinical features, molecular diagnostic technologies, and family history [15]. Based on these criteria, individuals can be classified as a 'definite' or 'probable' FH (*see* Table 17.1). Patients with elevated cholesterol levels and the presence of tendinous xanthomata, or an identified mutation in the LDL receptor gene or

Table 17.2 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia (FH)*

Criteria	*Points*
Family history	
1st-degree relative with known premature (men <55 years; women <60 years) coronary and vascular disease, or 1st-degree relative with known LDL-c above the 95th percentile	1
1st-degree relative with tendinous xanthomata and/or arcus cornealis, or	
Children aged <18 years with LDL-c >95th percentile	2
Clinical history	
Patient with premature (men <55 years; women <60 years) coronary artery disease	2
Patient with premature (men <55 years; women <60 years) cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis prior to age 45 years	4
Cholesterol levels (mmol/l)	
LDL-c ≥8.5	8
LDL-c 6.5–8.4	5
LDL-c 5.0–6.4	3
LDL-c 4.0–4.9	1
DNA analysis	
Functional mutation in the LDLR gene	8
Diagnosis is based on the total number of points obtained	
'Definite' FH diagnosis requires more than 8 points	
'Probable' FH diagnosis requires 6–8 points	
'Possible' FH diagnosis requires 3–5 points	

*World Health Organization. Familial hypercholesterolemia – report of a second WHO Consultation. World Health Organization, Geneva, Switzerland: 1999. (WHO publication no. WHO/HGN/FH/CONS/99.2).
LDL-c = low-density lipoprotein cholesterol
Reproduced with permission from [16].

Table 17.3 US MEDPED Program diagnostic criteria for familial hypercholesterolemia

Total cholesterol cutpoints (mmol/l)				
Age (years)	*First-degree relative with FH*	*Second-degree relative with FH*	*Third-degree relative with FH*	*General population*
<20	5.7	5.9	6.2	7.0
20–29	6.2	6.5	6.7	7.5
30–39	7.0	7.2	7.5	8.8
≥40	7.5	7.8	8.0	9.3

Note: Diagnosis (FH is diagnosed if total cholesterol levels exceed the cutpoint). With permission from [17].
FH = familial hypercholesterolemia.

the apoB-100 gene, are classified as 'definite'. Patients with elevated cholesterol levels and a family history of hypercholesterolemia or heart disease are classified as 'probable'.

The Dutch Lipid Clinic Network criteria assign different point values for family history of heart disease or hypercholesterolemia, clinical history, presence of tendinous xanthomata or arcus cornealis, elevated LDL-c levels, and/or an identified mutation in the LDLR gene. A diagnosis is based on the score derived from the LDL-c level, history of premature CVD,

and presence of tendon xanthomas or corneal arcus [16]. A 'definite' FH diagnosis requires more than 8 points, 'probable' FH diagnosis requires 6 to 8 points, and a 'possible' FH diagnosis requires 3 to 5 points (*see* Table 17.2).

The MEDPED diagnostic criteria use cutpoints for total cholesterol levels specific to an individual's age and family history [17], with cutpoints differing for individuals with first-, second-, and third-degree relatives with FH and for the general population (see Table 17.3).

HOW IS FAMILIAL HYPERCHOLESTEROLEMIA TREATED?

HOMOZYGOUS FH AND PHARMACOLOGIC THERAPY

Homozygous FH is a rapidly progressive disease, leading to angina pectoris, myocardial infarction (MI), or sudden death before age 30 [3]. While therapeutic lifestyle changes (TLC) and drug therapy play major roles in treating homozygous FH, traditional therapies will not achieve LDL-c goals. In addition, homozygotes do not respond adequately to existing therapies. This population has a greatly reduced number of functional hepatic LDL receptors, a mechanistic target for many lipid-altering medications (e.g., statins and bile acid sequestration [BAS] agents), thus producing less LDL-c reduction with certain lipid-altering agents [18, 19].

Raal *et al*. investigated the effects of atorvastatin among patients ($n = 35$) with homozygous FH. Significant LDL-c reductions of 17% and 28% were produced with daily doses of 40 mg and 80 mg, respectively [18]. The same investigators evaluated expanded doses of simvastatin (maximum of 160 mg/day) in a similar population ($n = 12$) and achieved LDL-c reductions up to 31% [19]. Studies with ezetimibe in homozygous patients have produced conflicting results. Patients with homozygous FH ($n = 33$) were randomized to receive ezetimibe 10 mg daily with their ongoing statin therapy [20]. After 12 weeks, ezetimibe produced an additional 20% reduction in LDL-c compared to baseline. Conversely, other investigators report only modest reductions in LDL-c (9%) when ezetimibe was added to statin therapy in six Japanese homozygotes [21]. Pharmacotherapy targeting LDL-c reduction is effective among patients with homozygous FH, but substantially less compared to populations without homozygosity for FH.

HETEROZYGOUS FH AND PHARMACOLOGIC THERAPY

Aggressively lowering LDL-c to reduce CV risk among patients with heterozygous FH is imperative. Without effective treatment, approximately 30% of women and at least 50% of men will have a CV event by age 60. Initial treatment for heterozygous FH is TLC, which involves dietary and exercise regimens that can substantially improve lipoprotein status and therein CV risk. However, non-pharmacologic therapy alone will not achieve LDL-c goals, then warranting the use of pharmacotherapy such as statins [22]. The statins substantially improve prognosis for this population and have established an excellent safety record [23]. Despite the potency of statins, most heterozygotes will require additional medications to achieve their LDL-c goal. Several agents are available that can be added to statin therapy in order to achieve the requisite LDL-c reduction.

As monotherapy, maximal dose statin therapy lowers LDL-c in patients with heterozygous FH by approximately 55% [22]. This reduction is variable and somewhat less when compared to treatment responses in those without FH. Higher doses of statins are required to achieve increased LDL-c reductions, which makes adverse effects (typically dose-dependent) more likely [23]. Many patients may require lower doses of combination therapy to attain LDL-c goals or to achieve maximal LDL-c reduction. Combining agents has become more commonplace and is generally regarded as reasonably safe in most patients.

Commonly used lipid-altering agents that have been administered with a statin include the BAS, cholesterol absorption inhibitors (ezetimibe), and niacin (Table 17.4) [24–41].

Table 17.4 Mean lipoprotein changes of various lipid-altering combinations

Regimen	*% Change from baseline*			
	TC	*LDL-c*	*HDL-c*	*TG*
Statin + BAS	−29 to −40	−42 to −61	+4 to +18	−12 to +19
Statin + niacin	−23 to −31	−29 to −45	+26 to +41	−30 to −42
Statin + fibrate	−26 to −37	−24 to −50	+14 to +34	−32 to −57
Statin + ezetimibe	−25 to −49	−39 to −60	+5 to +9	−18 to −40
Statin + BAS + niacin	−56	−57 to −66	+27 to +32	−45

BAS = bile acid sequestrant; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

Certain fibrates such as bezafibrate and fenofibrate may also modestly lower LDL-c levels when added to a statin, but are considered more effective for treating other types of dyslipidemia (e.g., hypertriglyceridemias and familial combined hypercholesterolemia) [24, 33, 42]. The combined use of statins and BAS or ezetimibe appears to minimally increase the common adverse effects seen with statin therapy such as myalgias and elevated transaminases, while providing substantial additional LDL-c reduction [43]. Stein *et al*. [44] evaluated the effectiveness of adding ezetimibe to ongoing statin therapy vs doubling the statin dose in patients ($n = 621$) with heterozygous FH. After four weeks, those receiving the statin/ezetimibe combination experienced significantly greater reductions in LDL-c (−22.8% vs −8.6%; $P < 0.01$) compared to those having doubled their statin dose. Similarly, when BAS were co-administered with statins for primary hypercholesterolemia or heterozygous FH, further reductions in LDL-c of ~15–25% were observed [41, 45].

Nicotinic acid (niacin) improves all major lipoproteins and has demonstrated LDL-c reductions of 15–30% in heterozygotes [22]. The safety of niacin when used as monotherapy or with other lipid-altering agents is dependent upon the formulation. Niacin is available as a nutritional supplement in numerous formulations (i.e., crystalline immediate-release [IR] and sustained-release [SR]), as well as by prescription as extended-release ((ER) [Niaspan®, Abbott Labs, North Chicago, IL, USA]). The IR and ER products have a low incidence of elevated liver function tests (LFTs) [46], which does not appear to be increased with the addition of a statin [36]. However, higher rates of flushing, particularly with IR, limit their use. Conversely, SR formulations generally cause less flushing but are associated with serious liver toxicity in up to 50% of patients at doses ≥2000 mg/day [47]. Another concern with niacin is the lack of regulation and consistency with the vast array of agents marketed as dietary supplements (IR and SR). In contrast, the prescription ER formulation has a more favorable safety profile and is thus approved by the Food and Drug Administration (FDA).

Additional safety measures should be employed when prescribing higher doses or combining lipid-altering agents. Baseline measures of LFTs and creatinine kinase (CK) levels and periodic monitoring of LFTs upon follow-up are suggested. For patients reporting muscle symptoms possibly associated with drug therapy, additional monitoring of CK levels is prudent [48]. Identifying certain populations more susceptible to drug toxicities is also essential. Typically, factors such as advanced age or frailty (diminished muscle mass), multiple disease states and the use of interacting medications (CYP3A4 inhibitors), greatly predispose individuals to adverse effects.

The age at which to initiate drug therapy in persons with FH is controversial. For heterozygotes, Adult Treatment Panel III (ATP III) suggests that LDL-lowering agents be initiated in young adulthood with statins considered first-line therapy [49]. Additionally, a recent publication demonstrating the safety and efficacy of pravastatin in children with heterozygous

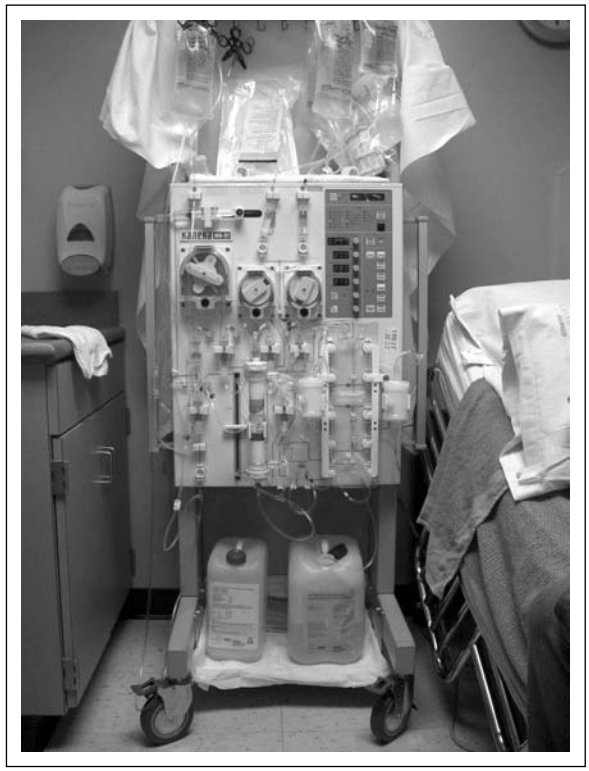

Figure 17.1 Dextran Sulfate Adsorption (DSA [Liposorber®]) apheresis apparatus (Kaneka Corporation; Japan).

FH, strongly encourages early initiation (>8 years old) of statin therapy in this population [50]. Treatment for patients with homozygous FH consists primarily of LDL apheresis, with the addition of a statin providing moderate additional efficacy; however, treatment guidelines addressing this are lacking.

AGENTS IN DEVELOPMENT

A number of novel drugs are currently in development that may potentially play a role in the future treatment of FH. Acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitors have been associated with decreased cholesterol levels by diminishing secretion of apoB-containing lipoproteins and preventing cholesterol absorption. Avasimibe and eflucimibe were two of the early ACAT inhibitors studied; however, the manufacturers recently discontinued development of these compounds apparently due to safety concerns [51]. Another agent, SMP-797 (Dainippon Sumitomo Pharma Co Ltd), differs from other ACAT inhibitors because of its greater water solubility and an ability to more markedly reduce LDL-c. Clinical trials of SMP-797 are ongoing in Europe and Japan. Another class with potential promise is the antisense inhibitors of apoB. The compound ISIS-301012 (ISIS Pharmaceuticals), maximally reduces LDL-c by 35% among patients with mild dyslipidemia [52]. Further, in a small study involving three homozygous patients, ISIS-301012, when co-administered with ongoing lipid-altering agents including high-dose statins, reduced LDL-c by an additional 50% [53]. Recently, a potential future lipid-lowering drug (BMS-201038), which inhibits the microsomal triglyceride transfer protein (MTP), demonstrated a significant reduction (>50%) of LDL-c in patients with

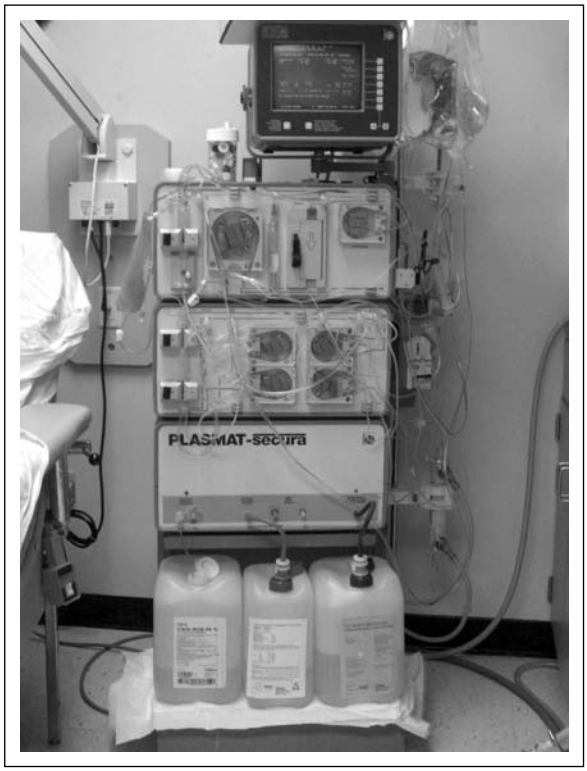

Figure 17.2 Heparin-induced extracorporeal lipoprotein precipitation (Plasmat Secura [Help®] apheresis machine). B. Braun Medical Inc., Germany.

homozygous FH [54]. Inhibition of MTP results in the reduced production of hepatic apoB by inhibiting the production of very low-density lipoproteins, the precursor to LDL [55]. However, treatment is associated with elevated liver enzymes and hepatic fat accumulation.

The investigational agents described above have significant potential. Much work remains to be done in establishing their safety and clinical efficacy particularly as relates to their reducing the incidence of acute CV events.

LDL APHERESIS

Apheresis (Greek: *to take away*) is an extracorporeal procedure in which a patient's blood/plasma passes through an apparatus and its basic components can be separated and removed (Figure 17.1). It may be applied therapeutically for curing, preventing, or relieving the symptoms of certain diseases (neurological, autoimmune, hematological, and cardiovascular). There are generally two types of apheresis devices, centrifugation (plasma exchange) and membrane separation, which utilize semi-selective or specific separation by methods such as filtration, adsorption, or precipitation. Plasma exchange therapy for the removal of LDL-c was first described by De Gennes in 1967 [56]. The procedure's non-selectiveness results in the removal of not only LDL-c, but also albumin and other plasma proteins. In 1980, the first semi-selective apheresis process (cascade filtration) for the removal of LDL-c was developed [57]. Other selective apheresis devices using adsorption or precipitation have been developed for the specific removal of LDL-c and apoB-containing

Table 17.5 Food and Drug Administration criteria required for LDL apheresis

Patient characteristic	*LDL cholesterol (mg/dl)*
Homozygous FH	≥500
Heterozygous FH and failure of medical therapy	≥300
Heterozygous FH with documented coronary disease and failure of medical therapy	≥200

FH = familial hypercholesterolemia; LDL = low-density lipoprotein.

Table 17.6 Acute % lipid changes following LDL apheresis

Parameter (mg/dl)	*% reduction*
Total cholesterol (TC)	40–70
Low-density lipoprotein cholesterol (LDL-c)	40–80
High-density lipoprotein cholesterol (HDL-c)	0–30
Lipoprotein (a)	50–70
Triglycerides	30–60

Note: High variation of values may be partially due to differences in treated plasma and blood volumes.

lipoproteins without disturbing plasma levels of albumin, electrolytes, immunoglobulins, or hemoglobin.

The clinical application of LDL apheresis has been accepted worldwide and in 1996 received approval from the US FDA). Presently, only dextran sulfate adsorption (Liposorber®) (*see* Figure 17.1) and heparin extracorporeal LDL precipitation (HELP®) (*see* Figure 17.2) devices are approved for use in North America. Patient qualification is based on uncontrolled plasma cholesterol levels where dietary control has been ineffective and maximum drug therapies have been either ineffective for attaining LDL-c goals or poorly tolerated. These can include: **Group A:** Functional hypercholesterolemic homozygotes with LDL-c >500 mg/dl; **Group B:** Functional hypercholesterolemic heterozygotes with LDL-c >300 mg/dl; **Group C:** Functional hypercholesterolemic heterozygotes with LDL-c >200 mg/dl; and documented coronary heart disease (CHD) (Table 17.5).

On average, LDL apheresis therapy is performed every 2 weeks. A single session (2 h) treats about 3 l of plasma (flow rate <100 cc/min) of which only 300–500 cc is extracorporeal at any one time. This isovolemic procedure requires two anticubital vein sites for access. Adverse effects are rare and typical for an apheresis device [58] with hypotension (<2%) being the most common. LDL-c levels can be acutely reduced by 80% (Table 17.6), depending on the volume of plasma 'treated', with potential long-term LDL-c reductions of 20–40% [59]. Figure 17.3 demonstrates the precipitate filter pre-and post-LDL apheresis.

Due to the small number of patients treated with LDL apheresis and the unethical question of sham (or placebo) therapy for these patients, there is a lack of large multicenter controlled trials. The Hokuriko study [60], the largest and longest (6 years) LDL apheresis trial, examined the safety and efficacy of LDL apheresis. FH heterozygote patients (n = 43) receiving LDL apheresis combined with lipid-lowering therapy (low-dose statin + probucol

Table 17.7 Acute changes to vascular markers following LDL apheresis [65–80]

Marker	*Acute changes (%)*
Pro-inflammatory	
MCP-1	−15 to −18
MMP-9	−20
TIMP-1	−30
LBP	−27
Lp-PLA2	−22
VCAM-1	−10 to −20
ICAM-1	−10 to −16
E-selectin	−6 to −31
Fibrinogen	−10 to −65
Oxidized LDL	−65
CRP	−10 to −80
Vascular function	
Nitric oxide	25 to 45
VEGF	15
IGF-I	−37
Bradykinin	0 to >2000
ET-1	−15 to −75
PGI2	300
Thrombotic	
Tissue factor	−26
Von Willebrand's factor	−29 to −56
Thrombin	−55
Factor V	−57 to −74
Factor VII	−4 to −36
Factor XI	−27 to 82
Factor XII	−32 to 73
sCD40L	−16
Homocysteine	−15 to −25
Fibrinogen	−10 to −65
Fibrinolytic	
Plasminogen	−23 to −50
Protein S	−11 to −35
Protein C	−32 to −48
Antithrombin	−11 to −25
Hemorheology	
Plasma viscosity	−11 to −18
Blood viscosity	−5 to −15
RBC aggregation	−31 to −52
RBC deformability	45
Fibrinogen	−10 to −65

CRP = C-reactive protein; ET-1 = endothelin-1; ICAM-1 = intercellular adhesion molecule-1; IGF-1 = insulin-like growth factor 1; LBP = lipopolysaccharide binding protein; Lp-PLA2 = lipoprotein-associated phospholipase A2; MCP-1 = monocyte chemoattractant protein-1; MMP-9 = matrix metalloproteinase-9; PGI2 = prostaglandin I2; sCD40L = soluble CD40 ligand; sCD430L = soluble CD430 ligand; TIMP-1 = tissue inhibitor of metalloproteinase-1; VCAM-1 = vascular cellular adhesion molecule-1; VEGF = Vascular endothelial growth factor.
High variation of values may be partially due to differences in treated plasma and blood volumes.

Fig. 17.3. Precipitate filter before (left) and after (right) LDL apheresis.

and resin or fibrate) were compared to 87 heterozygous FH patients on similar combination lipid-lowering medications but not undergoing apheresis. Kaplan-Meier analyses of the coronary events including non-fatal MI, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and death from CHD, found the rate was 72% lower in the LDL apheresis group (10%) compared to the drug only group (36%) ($P = 0.008$).

Observational studies examining changes to vascular function following LDL apheresis therapy have demonstrated immediate improvement of endothelial function [61], myocardial perfusion [62], microvascular flow [63], and coronary vasodilatation [64]. Furthermore, LDL apheresis modifies a sizeable number of other vascular markers and pathologic processes (Table 17.7) associated with CVD such as inflammatory markers, hemorheologic measures, as well as thrombotic and fibrinolytic factors.

Most private health insurers and Medicare cover LDL apheresis treatments as described by the FDA. The procedure is covered in both the hospital outpatient and physician office. The billing code is CPT 36516. The diagnosis codes include ICD-9-CM 272.0 (pure hypercholesterolemia) or 272.2 (mixed hyperlipidemia). Some of the hindrances that may influence the use of LDL apheresis include the cost of treatments (~$2500), training of nursing staff, and convincing patients of the need for chronic therapy.

SUMMARY

Familial hypercholesterolemia is a common genetic disease that until recently had not significantly benefited from medical management. Despite the major advances achieved in the

treatment of FH and CVD there is still a lack of uniformly approved systems for diagnosing the disease. HMG-CoA reductase inhibitors alone or in combination with other medications have greatly reduced the levels of plasma cholesterol thus lowering the risk of premature CVD. In cases of continued hypercholesterolemia despite maximal pharmacotherapy, LDL apheresis has proven to be a safe and effective means for lowering LDL-c.

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18

Should plasma levels of lipoprotein (a) be measured? Guiding principles from bench to bedside

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BACKGROUND

Elevated plasma concentrations of lipoprotein (a) (Lp(a)) have been identified as a risk factor for coronary heart disease (CHD), and in fact, Lp(a) excess is the most common inherited lipid disorder in patients with premature CHD; however, there are a number of issues that complicate the use of Lp(a) measurement in clinical practice. Lp(a) consists of a low-density lipoprotein (LDL)-like moiety to which is covalently attached the unique glycoprotein apolipoprotein (a) (apo(a)). Studies have revealed that Lp(a) is highly heterogeneous in its composition, owing to the fact that apo(a) is present in varying sizes in different Lp(a) species. This variability has been attributed to the presence of different numbers of identically-repeated plasminogen-related kringle domains in apo(a) that are a hallmark of this apolipoprotein. The size variation in Lp(a) has resulted in significant challenges in the design of immunologically-based measurement strategies that are independent of Lp(a) isoform size. Additionally, the isoform size distribution of Lp(a) varies according to ethnic group, thereby complicating the design of population studies aimed at addressing the contribution of Lp(a) to CHD risk. Despite the inherent complexities associated with Lp(a) that can hinder interpretation of epidemiological data, meta-analyses have consistently demonstrated that Lp(a) is an independent risk factor for CHD. However, evidence has also been provided to suggest that the CHD risk attributable to Lp(a) can be lessened through the lowering of plasma LDL concentrations.

Despite the evidence suggesting a role for elevated plasma Lp(a) concentrations (in excess of 25–30 mg/dl) as a risk factor for CHD, prospective studies evaluating the effect of lowering of Lp(a) on CHD risk have yet to be conducted. This reflects the relative resistance of Lp(a) concentrations to lowering by methods that work well for LDL modification including lifestyle modifications and pharmacotherapy. In fact, it has been clearly shown that Lp(a) levels are largely genetically determined, and are controlled by steps involved in the production of this lipoprotein rather than its catabolism *per se*.

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Extensive studies ranging from *in vitro* experimentation to animal models to clinical investigations have been undertaken to determine the mechanism by which Lp(a) contributes to atherogenesis. The simplest hypotheses stemmed from the assumption that Lp(a) function can be attributed to either its LDL-like or plasminogen-like constituents, thereby reflecting either proatherogenic or prothrombotic effects, respectively. However, many studies have uncovered additional roles for Lp(a) which reflect the unique properties of apo(a) itself rather than homology to LDL and plasminogen. Despite the intensive research in this area, definitive mechanisms by which Lp(a) contributes to the development of CHD remain to be identified.

So given the many uncertainties concerning the role of Lp(a) in atherogenesis, coupled with the difficulties in measuring its concentration in plasma, should screening for elevated Lp(a) levels be performed in the general population? In an attempt to address this question, this chapter will evaluate the state of our knowledge with respect to how Lp(a) levels are determined and the clinical evidence for Lp(a) as a risk factor for CHD, and will further examine the body of evidence that has been generated regarding the role of Lp(a) in atherogenesis. Finally, recommendations for the measurement and use of Lp(a) in clinical practice will be provided.

LIPOPROTEIN (a) STRUCTURE: DOES FORM REFLECT FUNCTION?

The Lp(a) particle exhibits an interesting duality of structure that forms the basis for hypotheses regarding its function. Lp(a) contains a moiety that is essentially indistinguishable from LDL [1] on the basis of lipid composition and the presence of a single molecule of apolipoprotein B-100 (apoB-100). However, Lp(a) constitutes a unique lipoprotein class based on the presence of the highly glycosylated apo(a) moiety that is covalently linked to apoB-100 *via* a single disulfide bond (Figure 18.1). apo(a) is highly homologous to the serine protease zymogen plasminogen. Both of these proteins contain kringle domains: plasminogen comprises five kringle units (designated I–V) followed by a serine protease domain that that can be cleaved by plasminogen activators to form the active enzyme plasmin. Plasmin, in turn, plays a key role both in fibrinolysis as well as in pericellular proteolytic processes such as regulation of extracellular matrix turnover [2]. apo(a), on the other hand, contains sequences that are highly similar to plasminogen kringle IV followed by domains that are homologous to the kringle V and protease domains of plasminogen [3] (Figure 18.2). Interestingly, the apo(a) protease-like domain is catalytically inactive [4], which implies obvious functional differences between apo(a) and plasminogen.

The apo(a) kringle IV domain can be subdivided into ten types based on amino acid sequence [3] (Figure 18.2). These kringle domains (designated kringle IV type 1 to kringle IV type 10) are all present in one copy per apo(a) molecule with the exception of kringle IV type 2 [5]. This kringle is present in varying numbers of copies which gives rise to Lp(a) isoform size heterogeneity *in vivo* [5, 6]. This is a key structural property of Lp(a), the functional significance of which is at the forefront of Lp(a) research. Structure-function analyses have helped to map functional features to different apo(a) kringle IV types: for example, kringle IV type 9 contains a free sulfhydryl group that has been shown to participate in covalent bond formation with apoB-100 in the Lp(a) particle [7].

A number of the kringle domains in apo(a) and plasminogen contain lysine-binding sites (LBS) that mediate binding interactions with lysine-containing sequences in target proteins. These sites have been shown to be important for the fibrinolytic function of plasminogen; similar (and potentially competing) functions have been proposed for the high affinity LBS present in apo(a) kringle IV type 10 [8, 9]. apo(a) kringle IV types 5–8 each contain lower affinity LBS [9, 10], several of which have been implicated in the process of Lp(a) particle assembly [10, 11].

Many properties of Lp(a) have been described over the past decade that do not reflect its similarity to either LDL or plasminogen, and have been interpreted to reflect unique

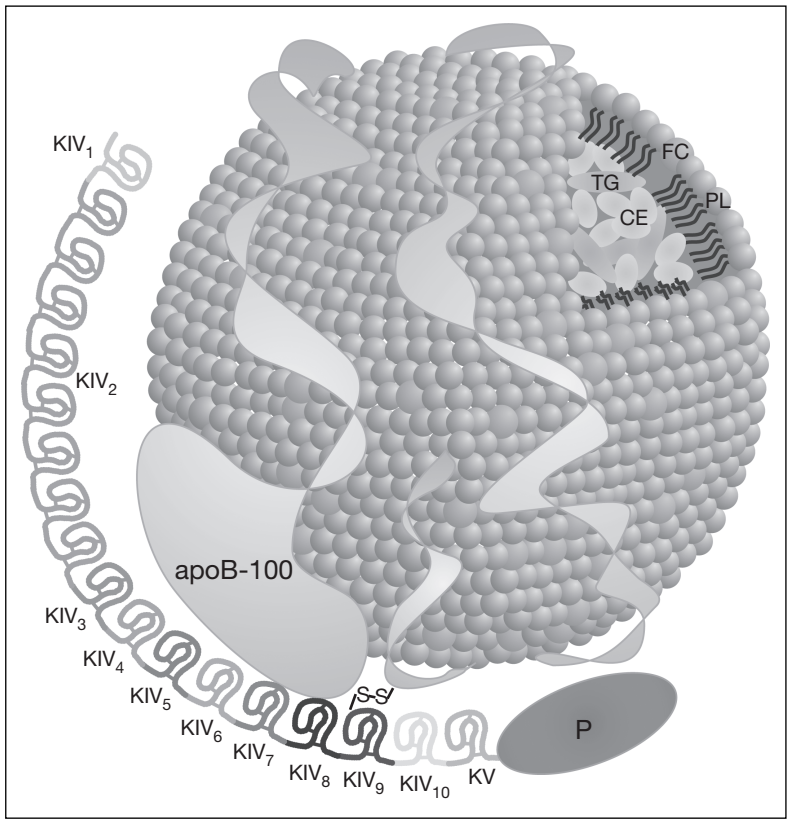

Figure 18.1 Structure of Lp(a). Lp(a) consists of a moiety that resembles low-density lipoprotein (LDL) covalently linked to the unique glycoprotein apoliproprotein(a) (apo(a)). The LDL moiety consists of a central core of triglycerides (TG) and cholesteryl esters (CE) that is surrounded by an outer shell of phospholipids (PL) and free cholesterol (FC) as well as a single molecule of apolipoprotein B-100 (apoB-100). Apo(a) consists of ten different types of plasminogen kringle IV-like domains, followed by domains resembling the kringle V and protease regions of plasminogen; the KIV type 2 unit is present in different numbers of copies in different alleles of apo(a). Apo(a) is covalently linked to apoB-100 by a single disulfide bond. Adapted with permission from [7].

properties of apo(a). This may result from properties of apo(a) that are distinct from plasminogen including the extreme glycosylation modification of apo(a) [1], the unique sequence of particular kringle motifs, and its inactive protease domain.

DETERMINATION OF PLASMA LIPOPROTEIN (a) CONCENTRATIONS

In addition to the size heterogeneity of Lp(a), the concentrations of this lipoprotein in plasma vary greatly in the population, ranging over 3 orders of magnitude from less than 0.1 mg/dl to in excess of 100 mg/dl. It is well accepted that, under normal conditions, Lp(a) levels are determined by the rate of production of the particle, rather than its clearance from the circulation [12]. The precise step(s) in production that contribute to control of Lp(a) levels have not been identified. There is a general inverse correlation between Lp(a) levels and apo(a) isoform sizes such that Lp(a) particles containing smaller apo(a) isoform sizes are associated

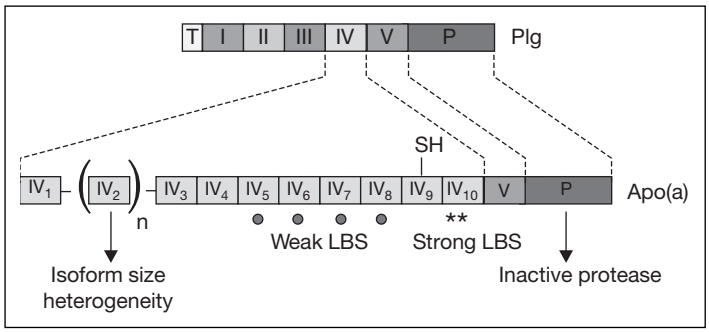

Figure 18.2 Topology of apo(a) vs. plasminogen. Plasminogen consists of an amino-terminal tail region (T) followed by five types of kringles (designated I–V) and a latent protease domain. apo(a) consists of multiple copies of a sequence resembling plasminogen kringle IV as well as kingle V-like and protease-like domains. The apo(a) protease domain cannot be activated by plasminogen activators and has no potential protease activity. There are ten different types of KIV-like sequence in apo(a). Types 1 and 3–10 are present in single copy in all apo(a) isoforms whereas KIV type 2 is found in different numbers of copies in different individuals, which gives rise to the Lp(a) isoform size heterogeneity observed in the population. Intrinsic function have been ascribed to certain kringles: KIV types 5–8 contain low-affinity lysine binding sites (LBS) while KIV type 10 contains a higher-affinity LBS. KIV type 9 contains the unpaired cysteine residue that participates in disulfide bond formation with apoB-100 in the Lp(a) particle.

with higher plasma Lp(a) levels [13]; this has been postulated to arise as a result of less efficient secretion of larger apo(a) species from hepatocytes [14]. Although this correlation underlies the strong contribution of the gene encoding apo(a) (*LPA*) to Lp(a) levels in the Caucasian population [15], this effect is not as pronounced in the African population [16].

Interestingly, therapeutic modulation of plasma Lp(a) levels has proven to be difficult. Data clearly demonstrate that strategies effective in lowering LDL levels, such as statin administration, have little or no impact on Lp(a) levels [17]. This has been interpreted to suggest that the presence of the apo(a) molecule in Lp(a) particles interferes with LDL receptor-mediated uptake of Lp(a). Despite reports of modulation of Lp(a) levels by factors including sex steroids, dietary fat, and aspirin (reviewed in [17], the only compound that consistently lowers Lp(a) levels is niacin [18]. However, this effect is not Lp(a)-specific since niacin is well known to have effects on other aspects of lipid metabolism.

CLINICAL EVIDENCE FOR LIPOPROTEIN (a) AS A RISK FACTOR FOR CHD

Retrospective case–control studies have consistently revealed that Lp(a) levels are elevated in cases versus matched controls. On the other hand, the results of prospective studies designed to assess the contribution of elevated plasma concentrations (greater than a risk threshold of 25–30 mg/dl as defined by Dahlen and coworkers in the 1970s) to future risk for CHD have been less consistent [17, 19]. Indeed, results from the prospective studies range from findings of no association of Lp(a) with CHD risk whatsoever [20, 21], to either weak [22] or strongly positive associations [23–27]. The variability in these reports may reflect differences in study design, including sample storage, Lp(a) measurement methodology, or ethnic composition of the subjects. Importantly, meta-analyses of prospective data have consistently shown that Lp(a) is an independent risk factor for CHD [28, 29]. Despite this, the inability to specifically and consistently lower plasma Lp(a) levels to prospectively evaluate effects on future CHD risk is one of the considerations that have prevented placing Lp(a) into the category of established risk factors. As such, elevated Lp(a) concentration is currently designated as an emerging risk factor for CHD according to the Adult Treatment Panel III (ATP III) guidelines.

Studies have been published suggesting that the risk associated with elevated Lp(a) levels can be modulated by both non-lipid and lipid factors. Indeed, although there is little or no correlation between plasma concentrations of Lp(a) and other vascular risk factors, a number of studies suggest that the risk attributable to elevated Lp(a) concentrations is dependent upon the concomitant presence of other such risk factors. For example, in the Familial Atherosclerosis Treatment Study (FATS), Lp(a) concentrations were a strong predictor of events at baseline, but lost their predictive value when LDL cholesterol was reduced to <100 mg/dl in the treatment group [30]. More recently, in the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study [31], Lp(a) concentrations were investigated as a CHD risk factor using a prospective cohort of 9133 French and Northern Irish men aged 50–59, without a history of CHD. Elevated Lp(a) concentrations increased the risk for myocardial infarction (MI) and angina pectoris, and the effect was most pronounced in men with a high LDL cholesterol concentration. The results of the Quebec Cardiovascular Study suggest that Lp(a) is not, in fact, an independent risk factor for ischemic heart disease in men, but increases the risk associated with elevated apoB and total cholesterol, and appears to attenuate the beneficial effects of elevated HDL cholesterol [32]. Similar interactions of elevated Lp(a) concentrations with other risk factors were found in the Prospective Cardiovascular Münster (PROCAM) study in which a high concentration of Lp(a) further increased the risk of MI in men with high or moderately elevated estimated global risk (i.e., risk of a coronary event $>10\%$ in 10 years), but not in men with a low estimated global risk [33].

In a very recent report, baseline Lp(a) concentrations were measured in a large prospective study of 27 791 initially healthy women in the Women's Health Study, who had been followed up for 10 years. The findings indicated that extremely elevated Lp(a) concentrations (greater than the 90th percentile) were associated with increased cardiovascular risk, especially in women with high LDL concentrations [34]. Interestingly, no risk gradient was observed in individuals with lower plasma Lp(a) concentrations. This raises the possibility that previous studies that did not evaluate for thresholds may have missed relationships between Lp(a) and risk, and further suggest that the current risk threshold for Lp(a) (above 30 mg/dl; [35]) may be too low, especially in some populations.

A relatively new area of study in the Lp(a) field concerns the identification of small apo(a) isoform size as a risk factor for CHD independently of elevated plasma LDL levels. A comparatively small number of studies have been sufficiently powered to determine the independent contribution of apo(a) isoform size to Lp(a) risk. For example, in the Bruneck Study, it was shown that small apo(a) sizes are an independent risk factor for advanced carotid atherosclerosis, although risk is further increased in combination with elevated Lp(a) concentrations [36]. On the other hand, these investigators reported that plasma Lp(a) concentrations, but not small apo(a) isoform sizes, were predictive of risk for early atherosclerosis and that this association was only present when LDL cholesterol concentrations were concomitantly elevated. Interestingly, although a relationship between cardiovascular (CV) disease and Lp(a) concentrations associated with small apo(a) isoform sizes in both Caucasian as well as African-American men has been documented [37], this association has not been consistently observed in women [37–39].

Results of a study by Wu *et al*. [40] suggest that small apo(a) isoform size (<22 kringle IV repeats) is associated with lower endothelium-dependent, flow-mediated dilation of the brachial artery irrespective of plasma Lp(a) concentrations. Additionally, Emanuele *et al*. [41] reported that the percentage of subjects with at least one small apo(a) isoform was significantly higher in those patients who presented with acute MI versus those with unstable angina; small apo(a) isoform size, but not elevated Lp(a) concentrations, was an independent predictor of acute MI vs unstable angina pectoris in a multivariate logistic regression model. Strong evidence for a role of apo(a) isoform size and risk for the development of angina was also provided by Rifai *et al*. [42] who demonstrated that while both Lp(a)

concentrations and small apo(a) isoforms were associated with risk for angina, only the association between apo(a) size and risk remained significant in a multivariate model.

OVERCOMING CHALLENGES IN LIPOPROTEIN (a) MEASUREMENT

The data generated from epidemiological studies have been clearly complicated by bias in the measurement of Lp(a). For immunologically-based studies, this bias largely results from the isoform size heterogeneity of Lp(a). Depending on the location of epitopes for antibodies used in the assays, Lp(a) measurement may be isoform-size dependent. Through ground-breaking work by Marcovina *et al*. [17], an enzyme-linked immunosorbent assay (ELISA) has been developed that is insensitive to apo(a) isoform size. This, in conjunction with the development of a WHO-recognized International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) secondary reference material, has allowed the assessment of a number of available assays for isoform-size bias [43]. Although challenges still exist in the selection of an appropriate calibrator for the assay, ELISAs performed using the appropriate reagents can yield reliable data for the measurement of Lp(a) levels. Marcovina *et al*. [17] have also provided recommendations for the measurement of Lp(a) in clinical practice and in epidemiological studies; these guidelines are summarized below:

- Assays for measuring Lp(a) levels in clinical and epidemiological studies must be validated for their ability to produce accurate values independent of apo(a) isoform size values in the samples.
- Because of the potential impact on Lp(a) measurement, stringent conditions for blood collection and storage must be developed and followed. Effects of collection/storage on individual assays must be determined.
- Lp(a) values should not be measured in terms of mass (which reflects the contributions of lipid and carbohydrate), but rather in terms of nmol/l of Lp(a) protein. This will allow direct comparison of data from different studies.
- The WHO-approved IFCC secondary reference material with the assigned value of 107 nmol/l should be used as a point of reference for assay calibration.
- If methods sensitive to isoform size are used for risk assessment, samples with values in excess of 50 nmol/l should be re-measured by referral laboratories using validated methods. This should minimize the chance of misclassification due to method inaccuracy.

Interestingly, recent studies by Berglund's group [44] have revealed that in individuals heterozygous for apo(a) isoform sizes, the small apo(a) allele is not consistently dominant with respect to Lp(a) levels; this appears to depend upon the size of the larger isoform, particularly in Caucasians. Interesting evidence is also emerging that within individuals each allele size affects not only the level of that allele, but also the level of the other allele [45]. Taken together, these findings suggest that future epidemiological studies should perhaps consider the measurement of allele-specific Lp(a) concentrations such that the relative contribution of each isoform to total Lp(a) concentrations can be determined.

THE BASIS FOR LIPOPROTEIN (a) PATHOGENICITY: EVIDENCE FROM *IN VITRO* AND *IN VIVO* STUDIES

Many studies using both *in vitro* studies as well as animal models have been undertaken to attempt to identify the role of Lp(a) in atherogenesis [7, 46]. These studies have largely been predicated on a key observation that Lp(a) becomes deposited in atherosclerotic lesions to an extent that is proportional to plasma Lp(a) concentrations [47]. Further to this, it was reported that Lp(a) is preferentially retained in this milieu [48] which allows local accumulation of Lp(a) in the arterial wall and which likely reflects the ability of Lp(a) to interact

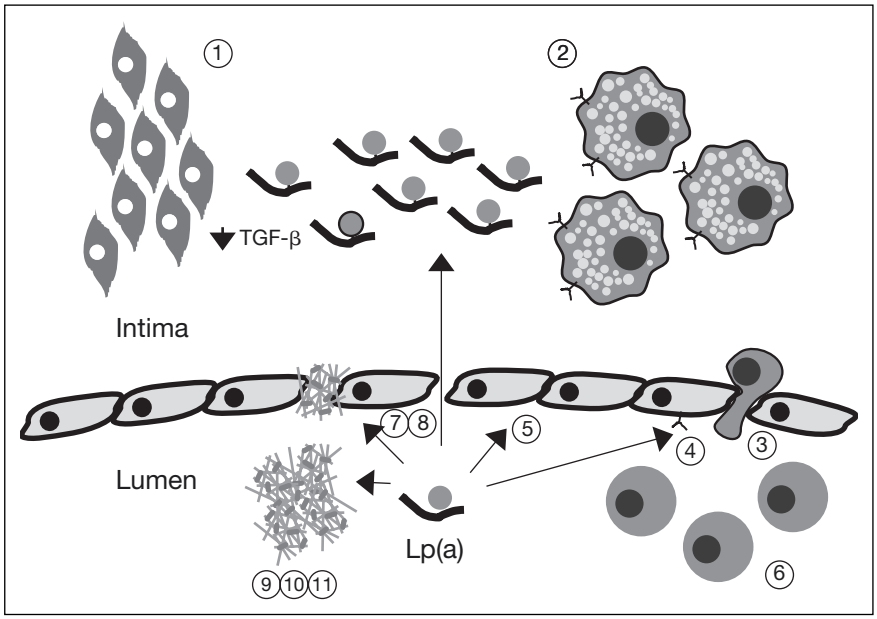

Figure 18.3 Potential pathogenic mechanisms of Lp(a). Lp(a) can penetrate the endothelial layer and become deposited in the intima, where it can promote smooth muscle cell migration and proliferation (1) by decreasing TGF-β activation, and can promote macrophage foam cell formation (2). Lp(a) has numerous proatherogenic effects of the endothelium, including stimulation of monocyte chemoattractant activity (3), induction of proinflammatory adhesion molecules (4), and stimulation of endothelial contraction through rearrangement of the actin cytoskeleton (5). Lp(a) also induces expression of the proinflammatory cytokine interleukin (IL)-8 by monocytes (6). Lp(a) also has several prothrombotic effects, including inhibition of plasminogen activation on the surface of endothelial cells and platelets (7), increasing endothelial cell PAI-1 (plasminogen activator inhibitor-1) expression (8), inhibition of TFPI (tissue factor pathway inhibitor) activity (9), inhibition of plasminogen activation on fibrin (10), and increasing platelet responsiveness to agonists such as thrombin (11).

with a variety of different extracellular matrix components including fibrinogen, vitronectin and collagen [7]. However, the identification of a definitive mechanism whereby Lp(a) can contribute to the development of atherosclerosis remains elusive, largely due to challenges in testing observations made *in vitro* to relevant animal modes. This, in turn, reflects the unusual species distribution of Lp(a), which is only found in hedgehogs, Old World monkeys and humans.

Mechanistic studies have identified both proatherosclerotic and prothrombotic roles for Lp(a) (Figure 18.3). Indeed, many *in vitro* studies have probed structure–function relationships involving different kringle modules of apo(a), the results of which are summarized in Figure 18.4. Clearly, Lp(a) can contribute to the progression of atherosclerosis and the precipitation of CV events at all possible levels, including lipid deposition, stimulation of inflammatory responses, modulation of vascular cell phenotype, and prevention of thrombolysis (Figures 18.3, 18.4). The most fruitful strategy going forward will be to combine an understanding of the biochemistry of apo(a)/Lp(a) with informative animals models to elucidate in greater detail the mechanistic basis for the harmful effects of Lp(a).

Despite challenges inherent in the interpretation of data generated using surrogate animal models for Lp(a), the balance of opinion in the field is that single and double transgenic animals (i.e., overexpressing both human apo(a) and LDL), can be useful tools to understand the role of Lp(a) in atherosclerosis. Indeed, transgenic apo(a) mouse and rabbit models have

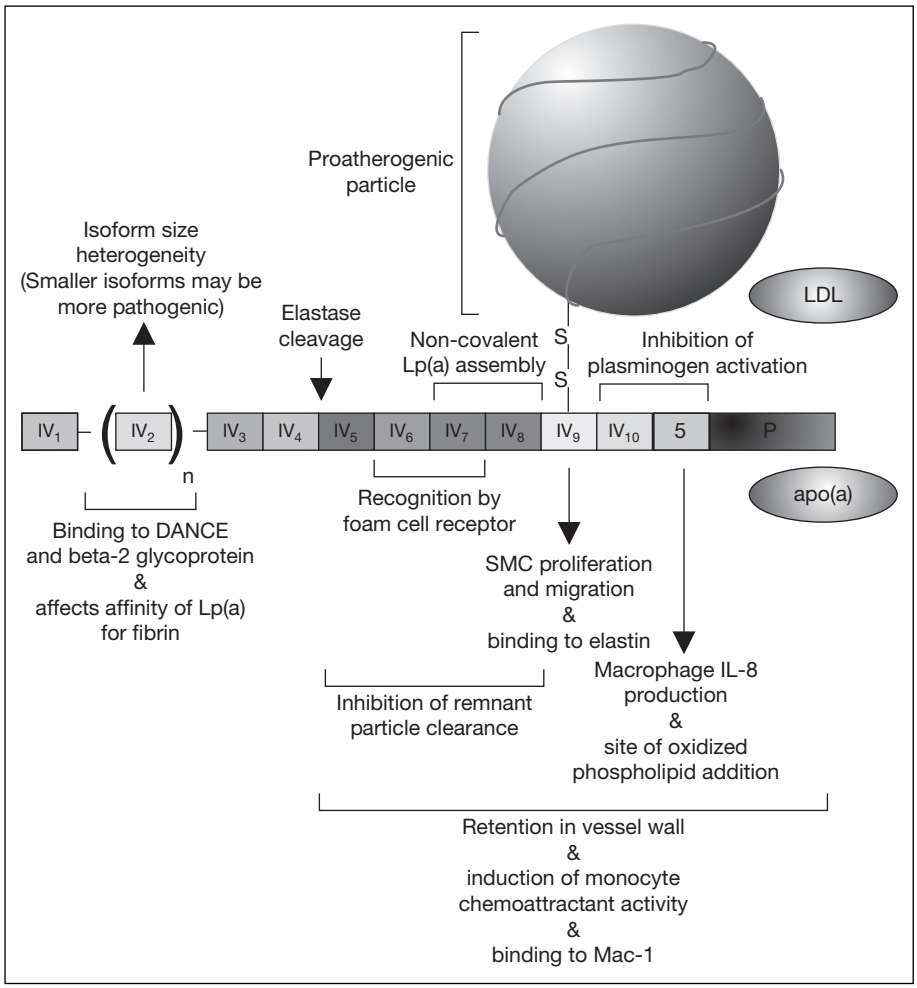

Figure 18.4 Potential pathogenic mechanisms have been mapped to specific function domains on Lp(a). The LDL moiety of Lp(a) likely has all the proatherogenic effects of LDL itself. Generation of apo(a) fragments using either recombinant protein expression or proteolytic cleavage (the elastase cleavage site between KIV types 4 and 5 is shown) has yielded information of the domains in apo(a) responsible for particular pathogenic mechanisms or interaction with specific substrates, as shown in the Figure. Certain functional effects of apo(a) have yet to be mapped to a specific domain. Adapted with permission from [7].

been used to study processes such as Lp(a) assembly, structure–function relationships in Lp(a), regulation of the expression of the gene encoding apo(a), and mechanisms of Lp(a) involvement in the process of atherosclerosis (expanded upon below) [46].

Studies using apo(a) transgenic rabbits are in agreement with data from transgenic mice in that apo(a) deposition in both models was coincident with the presence of accumulated intimal smooth muscle cells and decreased active transforming growth factor (TGF-β) [49]. The possibility that Lp(a) might modulate smooth muscle cell phenotype by promoting dedifferentiation was suggested by the enhanced staining for markers of activated or immature smooth muscle cells in this study [49]. A somewhat different effect of Lp(a) on smooth

muscle cell phenotype was reported in transgenic apo(a) rabbits constructed in the Watanabe Heritable Hyperlipidemic (WHHL) rabbit background [50]. The advanced, complex lesions observed in the transgenic animals showed notable calcification, unlike the less advanced lesions in the non-transgenic WHHL rabbits; examination of advanced human lesions also showed association of Lp(a) deposition with areas of calcification [50]. Interestingly, it was shown that Lp(a) promotes calcification of cultured smooth muscle cells, as evidenced by stimulation of calcium uptake, promotion of an osteogenic pattern of protein expression, and promotion of an osteoblast-like phenotype (i.e., upregulated osteoblast-specific factor-2 and alkaline phosphatase activity) [48]. The role of apo(a) in aortic calcification remains unclear, however, particularly in light of several recent reports suggesting that no relationship exists between coronary calcium and either Lp(a) concentrations or apo(a) isoform sizes [51]. A recent report using the same WHHL rabbit line expressing human apo(a) described above [52] has further shown that Lp(a), in the context of hypercholesterolemia, enhances coronary artery lesion size; the increased coronary atherosclerosis in these animals was associated with a higher incidence of chronic ischemia and MI [52]. This study underscores the ability of Lp(a) to further contribute to the burden of atherosclerosis in hypercholesterolemic animals.

A recent study has been published using transgenic mice expressing apo(a) at a high level which may shed light on the role of Lp(a) *in vivo*. Specifically, mice expressing both low and high concentrations of apo(a) (~35 mg/dl and 700 mg/dl, respectively) in a transgenic human apoB background were used [53]. It was reported that high levels of oxidized phospholipids were present in Lp(a) from the high apo(a)-expressing mice, but not in LDL from mice with human apoB alone. This likely results from the preferential transfer of oxidized phospholipids to Lp(a) that has been previously suggested to occur in human plasma (see above). The significance of this finding in the context of how Lp(a) contributes to atherosclerosis is unclear. However, it is tempting to speculate that the deposition of Lp(a) containing these oxidized phospholipids in the developing lesion may contribute to both proatherosclerotic and proinflammatory processes; such an effect would be magnified by the preferential retention of Lp(a) in this milieu. This study is the first to report the use of transgenic mice expressing high concentrations of Lp(a); apo(a) and Lp(a) concentrations in previous transgenic models have been over an order of magnitude lower.

In another recent study using a transgenic mouse model, Devlin *et al*. [54] reported the overexpression of a fragment of apo(a) (containing kringle IV types 5–8, each containing a weak lysine-binding site; Figure 18.2). Compared to control animals, these mice had greatly enhanced atherosclerosis and markedly elevated non-HDL cholesterol. Accordingly, these investigators found using a perfused mouse liver model that this four-kringle apo(a) species, as well as full-length apo(a) inhibited the clearance of cholesterol-rich remnant particles. The molecular basis of this observation is the subject of ongoing study and may help to shed light on our understanding of the effect of Lp(a) on the catabolism of other lipoproteins.

Surprisingly, very few *in vitro* mechanistic studies performed to date, and no studies performed in animal models, have considered the role of apo(a) size in atherogenesis. The exception to this is the effect of apo(a) isoform size on fibrin binding and plasminogen activation to plasmin. In this regard, recent studies indicate that smaller Lp(a) isoforms bind more avidly to fibrin [55], and inhibit plasmin formation to greater extents [56]. Contradictory evidence has been provided, however: larger isoforms of Lp(a) (as well as larger isoforms of free apo(a)) were reported to be more effective in reducing plasmin formation on fibrin [57]. Clearly, more studies are required in order to understand the molecular mechanism(s) by which small apo(a) isoform size can confer risk independently of plasma Lp(a) concentrations. Interesting recent data suggest that small apo(a) isoforms may be preferentially retained in the intima of atherosclerotic lesions relative to large isoform sizes, irrespective of corresponding plasma Lp(a) concentrations [58]. The molecular basis for this intriguing

observation may help in our understanding of the inherently pathogenic nature of small apo(a) isoforms.

GUIDELINES FOR MEASUREMENT OF LIPOPROTEIN (a) IN THE CLINIC

Based on the current lack of treatment available for elevated Lp(a) levels, coupled with the inability to place Lp(a) into the category of established or traditional risk factors, we cannot recommend measurement of Lp(a) levels in the general population at this time. However, we do recommend that Lp(a) levels be determined using best practices identified by Marcovina *et al*. (see above) in the following subset of patients:

- Individuals at high risk for CHD with:
  - Elevated apoB or LDL cholesterol levels
  - Family history of CHD
  - Premature MI with otherwise normal risk profile
- Individuals who respond poorly to statins for LDL-c lowering

In these scenarios, clinicians could utilize the measurement of Lp(a) levels to decide upon a more aggressive course of treatment for modifiable risk factors such as elevated LDL. Based on the lack of data from highly-powered studies and the labour-intensive nature of measuring apo(a) isoform sizes, we do not recommend apo(a) phenotyping in the clinic at this time.

Although the data do suggest that Lp(a) lowering might be beneficial for some subgroups of patients, we lack sufficient information at present on how to define such subgroups with respect to Lp(a) concentrations, apo(a) size and the presence of other risk factors. Further, there are no current guidelines defining a suitable clinical target for Lp(a) lowering. Moreover, there is no therapeutic agent currently available that has been shown to lower plasma Lp(a) levels long-term, and there is a lack of available evidence demonstrating the utility of such an approach with respect to risk reduction.

FUTURE CONSIDERATIONS: WHAT'S NEXT FOR LIPOPROTEIN (a)?

Clearly, more insights from basic research approaches are required to provide fundamental information in areas such as defining the route of Lp(a) catabolism and to gain insights into the role of Lp(a) in both pathophysiological and physiological contexts. Additionally, we need more mechanistically-based studies to understand the basis for reports that small apo(a) isoform sizes are more atherogenic than larger apo(a) species. In addition, larger carefully-designed clinical studies are required to more clearly define the role of Lp(a) levels and isoform size in CHD risk, particularly in different populations. Such studies would be greatly enhanced by the utilization of best practices for measurement of Lp(a), as detailed above. Finally, as more fundamental information on apo(a) biology becomes available, efforts should be accelerated to identify a strategy for specific lowering of Lp(a) levels. This, in turn, would enable the design and execution of prospective studies in which prospective lowering of Lp(a) levels could be correlated with CHD risk.

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19

Clinical utilization of advanced lipid testing

W. C. Cromwell

INTRODUCTION

Laboratory measurements of plasma lipids (cholesterol and triglycerides) and lipoprotein lipids (very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol) have been used for clinical assessment and management of coronary heart disease (CHD) risk since the Friedewald formula was introduced in 1972 for estimating LDL cholesterol [1]. Lipoprotein particles that transport cholesterol and triglycerides in plasma are the direct mediators of atherogenesis. LDL particles (and to a lesser extent VLDL, intermediate-density lipoprotein [IDL] and remnant particles) promote atherosclerosis, while HDL particles entering the artery wall oppose this process. The overall risk of cardiovascular disease depends on the balance between these atherogenic and anti-atherogenic particles.

Due to the difficulty in measuring lipoprotein particles directly, plasma triglycerides (TG) have come to serve as a surrogate measure of VLDL levels, while LDL cholesterol (LDL-c) and HDL cholesterol (HDL-c) values serve as indicators of the concentrations of LDL and HDL particles. Few people have regarded the surrogate relationship of lipids to lipoproteins as a clinical limitation. Data from genetic, epidemiologic and clinical intervention trials have demonstrated that, at a population level, abnormal lipid levels are strongly related to atherosclerosis and CHD events.

As a result, lipid values are used for both risk assessment and to monitor the progress of therapeutic interventions [2]. For risk assessment, Adult Treatment Panel III (ATP III) guidelines recommend that elevated LDL-c along with age, gender, blood pressure (BP), HDL-c, diabetes, smoking, family history, and metabolic syndrome all be taken into account to determine the patient's global CHD risk [2, 3]. The assigned risk category defines the corresponding LDL-c treatment goal needed to lessen that risk. When used for risk management, lipid measurements are not employed in conjunction with other information, but as a standalone measure of progress towards a treatment goal. The LDL-c level indicates which patients have lowered their risk to acceptable levels (as inferred from their treatment goal having been reached) and which have not (indicating a need for more aggressive treatment). Recognizing the potential contribution to risk of other atherogenic lipoproteins besides LDL, such as VLDL remnants, ATP III designated LDL + VLDL cholesterol (non-HDL cholesterol or non-HDL-c) as 'atherogenic cholesterol' and recommended its use as a secondary therapy target in patients with elevated triglyceride levels (200–500 mg/dl) [2].

Nevertheless, practical limitations to this approach are encountered in clinical practice. Numerous trials have demonstrated a curvilinear relationship of LDL-c with CHD events in

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which risk is linked strongly to increasing LDL-c when LDL-c is high, but more weakly when LDL-c levels are moderate to low [3, 4]. LDL-c levels are thus relatively insensitive discriminators of risk when they approach the levels designated as treatment goals for high-risk (<100 mg/dl) or moderately high-risk (<130 mg/dl) patients. In prospective epidemiologic trials substantial variability in CHD risk is present across a wide range of cholesterol values, as well as among patients followed in placebo and active therapy groups of clinical intervention trials [5, 6]. Additionally, on-trial lipid values are often weak predictors of CHD risk in intervention studies [6–9].

The association of CHD outcomes with various measures of lipoproteins other than those based on cholesterol content of the particles present has been extensively studied to determine if this higher level of information could aid providers in clinical decision-making. To help define the potential clinical utility of this information this chapter will focus on the following questions:

1. What is the relationship between lipids and lipoproteins?
2. How are lipoproteins measured?
3. What lipoprotein abnormalities are commonly encountered in clinical practice?
4. How do lipoprotein measures relate to CHD risk?
5. What is the potential clinical utility of 'advanced lipid tests'?

WHAT IS THE RELATIONSHIP BETWEEN LIPIDS AND LIPOPROTEINS?

Data from many groups have established that chylomicrons, VLDL, IDL, LDL and HDL particles are linked in a continuous metabolic cascade that results in the generation of particle populations varying in size, density, and core lipid content [10]. Two processes are primarily responsible for the variability seen in amount of cholesterol carried per particle. First, the sizes of particles vary within a given lipoprotein class resulting in substantial differences in the volume of individual particles. Persons with elevated TG are likely to have VLDL particles that are larger and more triglyceride-rich compared to people with low or normal levels of serum triglycerides, and LDL and HDL particles that are smaller and more cholesterol-poor [11]. Even small changes in size result in large changes in particle volume. For example, although LDL diameters differ by what seems to be only a small amount, typically up to about 3 nm (approximately 12%), the volume differences of the spherical lipid core are substantial, because they scale according to the third power of the radius. For LDL particles differing by 3 nm in diameter, there is approximately 40% less core cholesterol in the smaller particle. On this basis alone, the person with the smaller LDL particles will require almost 70% more particles to carry the same amount of LDL cholesterol than the person with larger particles [12].

The second process modulating lipoprotein cholesterol content is cholesterol ester transfer protein (CETP) mediated pair-wise exchange of TG and cholesterol between cholesterol-rich (LDL and HDL) and triglyceride-rich (VLDL, IDL, and remnants) particles. When TG levels are elevated or LDL levels are decreased, even modestly, this exchange process alters LDL and HDL particles to become partially depleted in core cholesterol and enriched in core TG [12, 13]. In a physiologic attempt to re-establish the normal ratio of cholesterol/triglyceride in the particle core, these compositionally abnormal particles become a substrate for hepatic lipase and endothelial lipase, which partially hydrolyse core triglycerides. In response to loss of TG from the core and remodeling of the surface phospholipid–apoprotein coat, particles are transformed into smaller, denser LDL and HDL particles.

Due to variations in LDL composition and size, the amount of cholesterol carried inside lipoprotein particles is highly variable among individuals with the same measured cholesterol levels. Consequently, even the most accurate cholesterol measurements will, for many individuals, provide an inaccurate measure of circulating lipoprotein particles [6, 12–15].

HOW ARE LIPOPROTEINS MEASURED?

Measurement of lipoproteins is complicated by the fact that particles are not composed of a single molecular species, but a multi-molecular aggregate of protein and thousands of molecules of cholesterol and other lipids. As a result, no unique chemical entity is present that allows for quantification of individual lipoprotein subclasses. Several analytical methods have been used to overcome this limitation and provide information beyond that gained from standard lipid testing. Although collectively termed 'advanced lipid tests', individual tests measure related, but distinctly different, lipoprotein characteristics.

Some tests serve as alternative measures of lipoprotein particle concentration. Apolipoprotein B-100 (apoB) serves as an alternative to LDL-c to provide an estimate of LDL particle concentration, since all LDL and VLDL particles contain a single molecule of apoB protein and >90% of apoB is on LDL [16]. Similarly, apolipoprotein AI (apoAI) serves as an alternative to HDL-c for estimating HDL particle concentration. However, unlike apoB, the number of apoAI molecules per HDL varies from 1 to 4 apoAI per HDL particle. Nuclear magnetic resonance (NMR) spectroscopy provides another means to measure lipoprotein particle concentrations [17]. Two phenomena make NMR quantification of numbers of lipoprotein subclass particles possible: (1) lipoprotein subclasses of different size in plasma emit distinctive NMR signals whose individual amplitudes can be accurately and reproducibly measured; and (2) measured subclass signal amplitudes are directly proportional to the numbers of subclass particles emitting the signal, irrespective of variation in particle lipid composition. NMR spectroscopy serves as a direct measure of total LDL particle concentration (LDL-P), as well as the subclass particle concentrations of very low-density lipoprotein (VLDL-P) (large VLDL-P, medium VLDL-P, small VLDL-P), intermediate-density lipoprotein (IDL-P), LDL (large LDL-P, small LDL-P), and HDL (large HDL-P, medium HDL-P, small HDL-P).

Other tests provide information regarding lipoprotein subclass size or density. Gradient gel electrophoresis (GGE) involves the movement of lipoproteins, under the influence of an electric current, through a semi-solid gel matrix of polyacrylamide. As the concentration of polyacrylamide increases from the top to the bottom of the gel, cross-linkages forming the matrix become progressively tighter resulting in a series of increasingly smaller 'pores' through which lipoproteins travel. Movement of particles through the gel continues until lipoproteins encounter pores too small to allow continued migration. Particle diameters are estimated by comparing the distance(s) traveled in the gel by a subject's lipoprotein particles to the distances traveled by non-lipoprotein size standards (various proteins and latex beads of known diameter). Lipoprotein size is reported by different laboratories in a variety of ways including: large (pattern A), small (pattern B) or intermediate (pattern AB) particle size (based on the largest peak present); average particle size (weighted average of all subclasses identified as a continuous variable); and percentages of particles present in predefined size ranges (determined by comparing the area of a predefined region to the integrated area under the curve for all subclasses identified on optical density scanning). Due to variability in stain uptake, GGE is not able to reliably measure the absolute concentrations (numbers) of lipoprotein particles present in a given subclass.

Density gradient ultracentrifugation (DGU) involves separating lipoproteins of differing densities by spinning them in a defined salt solution at very high speeds. This spinning creates a progressively increasing density (gradient) of salt from the top to the bottom of the tube. Lipoprotein particles move to that position of the tube where the density of the salt solution matches the density of the lipoprotein particle. The degree of subclass separation (resolving power) that can be achieved for LDL, HDL and VLDL particles is determined by the density range of the salt solution employed. In order for individual subclasses of VLDL, LDL, or HDL particles to be measured with precision, separate salt solutions must be used that have narrow density ranges that match the unique density of VLDL, LDL, and HDL

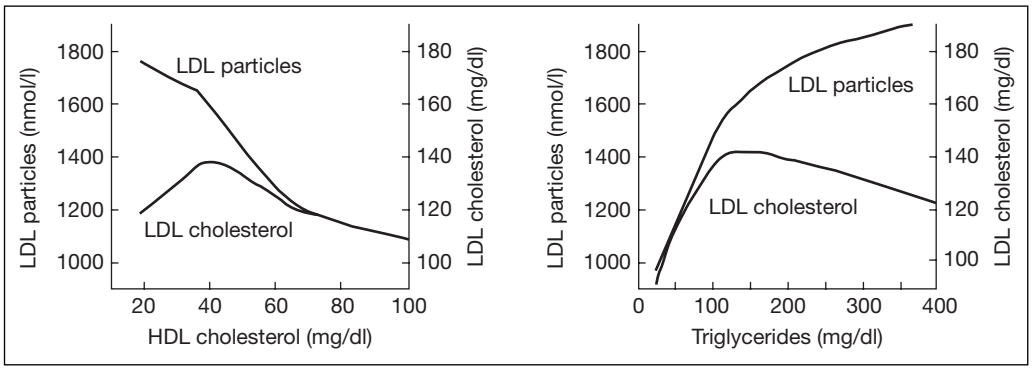

Figure 19.1 Relations in the Framingham Offspring Study ($n = 3437$) of NMR-measured LDL particles (LDL-P) and Friedewald-calculated LDL cholesterol (LDL-c) to HDL-c and triglycerides. With permission from [14].

particles, respectively. If a single solution gradient is used for ultracentrifugation, general partitioning of HDL, LDL, and VLDL classes is achieved. However, individual HDL, LDL, and VLDL subclasses blur together limiting the identification of individual lipoprotein particle subclasses. Following ultracentrifugation, lipid testing is performed to quantify the cholesterol or TG present in the separated solution. However, because the amount of cholesterol or triglyceride carried inside lipoprotein particles varies significantly between individuals, lipid testing performed following separation by ultracentrifugation is not capable of measuring the absolute concentration (number) of lipoprotein particles present.

WHAT LIPOPROTEIN ABNORMALITIES ARE COMMONLY ENCOUNTERED IN CLINICAL PRACTICE?

As noted previously, patients with elevated TG typically have cholesterol-poor LDL and HDL particles, either because they are smaller in size, have a core lipid content enriched in triglycerides and depleted of cholesterol ester, or both. Termed the 'atherogenic lipid phenotype' or the 'lipid triad', the combination of elevated TG, low HDL-c, and normal or minimally elevated LDL-c is commonly encountered in patients with insulin resistance, metabolic syndrome and type 2 diabetes mellitus. Lipoprotein abnormalities accompanying this phenotype include increased number of large VLDL particles, increased number of small LDL particles, decreased number of large HDL particles and increased concentration of apoB [10, 18–19]. Because the quantity of LDL (assessed by LDL-c) appeared not to be elevated, many authors concluded that increased numbers of non-LDL apoB containing lipoproteins (VLDL, IDL and remnant particles) were responsible for the elevated apoB levels observed. Confounding this conclusion are data indicating that, with the exception of type III dyslipoproteinemia, more than 90 percent of apoB is bound to LDL, even in the setting of elevated TG levels [16]. This is supported by data from the Framingham Offspring Study (Figure 19.1) demonstrating discordance between low LDL-c and increased NMR-measured LDL-P among subjects with elevated TG or reduced HDL-c [14].

Many studies have addressed the prevalence and magnitude of discordance between cholesterol and particle measures in the general population and in selected high-risk populations, such as those with diabetes or cardiometabolic risk [20–25]. There is a high prevalence of discordance between LDL-c and particle measures of LDL quantity (apoB or NMR-measured LDL-P) overall (~30–40%), and an even higher prevalence in patients with diabetes or cardiometabolic risk even when LDL-c is at low (<100 mg/dl) or very low

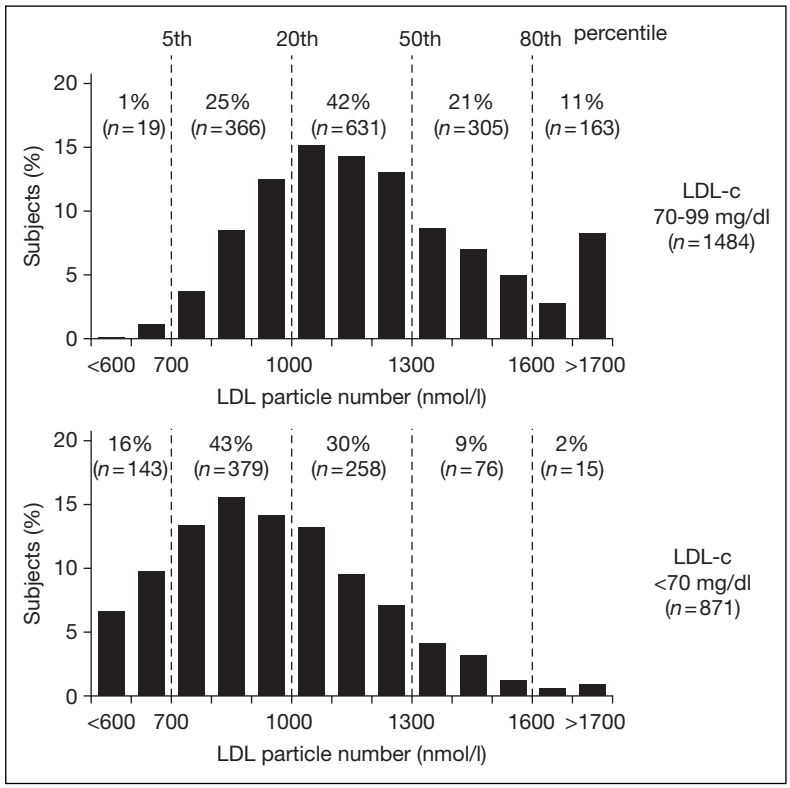

Figure 19.2 Distribution of LDL particle number among 2355 patients with type 2 diabetes mellitus and LDL cholesterol between 70–99 mg/dl (top) or <70 mg/dl (bottom). LDL particle number concentrations of 700, 1000, 1300, and 1600 correspond closely to the 5th, 20th, 50th and 80th percentile values of subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) reference population [33]. With permission from [21].

(<70 mg/dl) values. The magnitude of LDL particle number heterogeneity among 2355 patients with type 2 diabetes mellitus and LDL-c <100 mg/dl is shown in Figure 19.2 [21]. Of the 1484 patients with low LDL-c (70–99 mg/dl), only 385 (26%) had correspondingly low levels of LDL-P <1000 nmol/l (<20th percentile), while 468 (32%) had LDL-P values >1300 nmol/l (>50th percentile). Even among the 871 patients with LDL-c values <70 mg/dl (< 5th percentile), 349 (40%) had LDL-P >1000 nmol/l (>20th percentile) and 91 (10%) had LDL-P >1300 nmol/l (>50th percentile). Discordance between non-HDL-c and the particle measures is less in individuals with elevated triglycerides, but is still substantial. For example, in the Quebec Cardiovascular Study, non-HDL-c and apoB were discordant (difference of >15 percentile units) in more than one-third of subjects [22].

Collectively these data demonstrate that patients with elevated TG and decreased HDL-c harbour substantial lipoprotein abnormalities, the magnitude of which is not discernible from traditional lipid testing.

HOW DO LIPOPROTEIN MEASURES RELATE TO CHD RISK?

To date, over 100 trials examining the relationship of cardiovascular disease (CVD) risk with alternative lipoprotein measures have reported, at times, conflicting results. Beyond differences in population characteristics, study design, and lipoprotein assay methods, analytic

factors such as variability in cholesterol content of lipoprotein particles, as well as substantial intercorrelations of lipid and lipoprotein measures contribute to the varying results reported to date. A comprehensive review of these data for each lipoprotein class is beyond the scope of this chapter. Given the central role of LDL quantification in risk assessment and management, as well as the variable risk harboured by individuals near or at designated LDL-c targets of therapy, this chapter will focus on understanding the CVD risk implications of alternative LDL measures.

The associations of CVD risk with LDL particle size and LDL particle number in more than 70 cross-sectional and prospective epidemiologic and clinical intervention trials were reviewed recently [15]. With few exceptions, small LDL particle size was found to be significantly associated with CVD risk in univariate analyses. Many authors cite indirect lines of evidence that implicate atherogenic properties of small-sized LDL, such as easier entry into the arterial wall, reduced systemic clearance secondary to decreased affinity for the LDL receptor, increased localized retention due to binding with arterial wall proteoglycans, and enhanced oxidizability in several *in vitro* models [26]. Collectively, these findings imply that small LDL is a potent atherogenic lipoprotein, the measurement of which may be of some particular utility in enhancing CVD risk prediction and better evaluating response to lipid therapy [27–29].

However, the origin of this risk association remains controversial. Small-sized LDL particles are most commonly present as a component of a broader pathophysiology characterized by high TG, low HDL-c, increased LDL particle number, obesity, insulin resistance, diabetes and the metabolic syndrome [20, 30–32]. As a result, it is unclear if the increased risk associated with small LDL size in univariate analyses is a reflection of an increased atherogenic potential of small LDL particles, or simply a consequence of the broader pathophysiology of which small LDL is a part. The degree to which small versus large LDL particle numbers are differentially related to development of atherosclerosis was examined recently in the Multi-Ethnic Study of Atherosclerosis (MESA). Baseline blood samples were used to examine relations of NMR-measured lipoprotein subclass concentrations and particle size with carotid intima-media thickness (CIMT). In an analysis of 5538 subjects not on lipid-lowering medications, the relationships between lipoprotein variables were determined individually, as well as in models that included both small and large LDL subclass concentrations together to assess the independent association of each LDL subclass with CIMT [33]. Due to a strong inverse correlation of small and large LDL particle concentrations, small LDL confounded the association of large LDL with CIMT. Both small and large LDL particle concentrations were significantly associated with subclinical atherosclerosis, independent of each other, traditional lipids, and established risk factors. Further, in agreement with prior trials showing that LDL size is rarely a significant predictor of CVD risk following adjustment for HDL-c, TG and LDL particle concentration [15], no significant association was demonstrated between LDL particle size and atherosclerosis after accounting for the concentrations of the large and small LDL particles. Similar findings were reported in the VA-HDL Cholesterol Intervention Trial (HIT) trial, where both large and small LDL particle concentrations, but not LDL particle size, were significantly associated with coronary events once their correlation was taken into account [34].

An alternative explanation for the relationship of small LDL size with CHD risk is the increased number of LDL particles present when size is small. Many prospective epidemiologic and clinical intervention trials demonstrate that measures of LDL particle concentration by apoB [6–9, 35, 36] or NMR-measured LDL-P [15, 33, 34, 37–39] are more significantly predictive of CHD risk than LDL-c. Recent data from the Framingham Heart Study offer new insights by comparing the ability of alternative measures of LDL to provide CVD risk discrimination at relatively low potential target levels, as well as the degree to which non-HDL-c predicts risk better than LDL-c because it accounts for other atherogenic lipoproteins besides LDL. In multivariable models adjusting for non-lipid CVD risk factors, NMR-measured LDL-P was

related more strongly to future CVD in both sexes than LDL-c or non-HDL-c [13]. Subjects with a low level of LDL-P (<25th percentile) had a lower CVD event rate (59 events per 1000 person-years) than those with an equivalently low level of LDL-c or non-HDL-c (81 and 74 events per 1000 person-years, respectively). The event-free survival curves for Framingham participants with concordant or discordant LDL-c and LDL-P levels greater or less than the median were substantially worse for discordant individuals with low LDL-c and high LDL-P than for the group with high LDL-c and low LDL-P. Differences in LDL-c had little effect on event-free survival within both the high and low LDL-P participants.

Another confounding question is the degree to which inclusion of TG-rich remnants and other atherogenic particles besides LDL is responsible for non-HDL-c and apoB being better risk markers than LDL-c [2, 40]. The problem with this interpretation is that NMR-measured LDL-P, which quantifies only LDL and not TG-rich particles, predicts CVD risk at least as well as apoB and consistently better than non-HDL-c [13, 34, 39]. If TG-rich particles were making an important additive contribution to prediction, LDL-P would be expected to predict less well than non-HDL-c. This question was recently examined directly in the Framingham Offspring Study, taking advantage of the availability of both LDL and VLDL particle concentrations measured by NMR [13]. VLDL particle numbers added to LDL-P provided little or no improvement in CVD risk prediction beyond that given by LDL-P alone. Thus, it appears that apoB and non-HDL-c are better risk predictors than LDL-c not because they account for TG-rich lipoproteins, but because they are better measures (albeit surrogate measures) of the LDL particles that create much of the risk.

WHAT IS THE POTENTIAL CLINICAL UTILITY OF 'ADVANCED LIPID TESTS'?

Information from 'advanced lipid tests' could be used either to aid assessment of individual risk or as potential targets of therapy in management of individual risk. While global risk assessment is useful at a population level, substantial heterogeneity of CVD risk is present among patients in the same risk category, especially among patients judged to be at moderately high risk with a 10-year Framingham risk score of 10–20%. To better stratify individual risk, many advocate the judicious use of 'emerging biomarkers' with the expectation that abnormal values infer the presence of greater risk and the need for more aggressive therapy [41]. In this manner, 'advanced lipid tests' have been viewed as risk assessment tools capable of identifying additional risk that might otherwise be missed by conventional lipid testing. If increased risk appears to be present, the clinician is motivated to choose more aggressive lipid targets of therapy.

Questions have been raised regarding the degree to which use of emerging biomarkers may significantly improve global risk assessment. A growing expectation is that an emerging biomarker should not be considered for broad clinical use unless the CVD risk associated with addition of the emerging biomarker to global risk assessment is significantly stronger than risk observed for global risk assessment alone [42]. Because lipid factors included in global risk assessment (TG, HDL-c) are highly inter-related with multiple lipoprotein parameters (particle size, density, number), it is not surprising that information present in 'advanced lipid tests' frequently fails to add significantly to risk prediction in global risk assessment models.

Alternatively, particle measures of LDL quantity (apoB and NMR-measured LDL-P) have been advocated for risk management as adjunct targets of therapy [40, 43, 44]. By advocating that patients at risk for CVD be managed to target LDL levels, we implicitly expect that achieved LDL levels higher or lower than the target values signify, respectively, risk that remains unacceptably high (requiring more aggressive treatment) or risk that has been made acceptably low by the therapy. As noted previously, evidence from prospective epidemiologic and clinical intervention trials demonstrate that this expectation is satisfied better by particle measures of LDL quantity (apoB or NMR-measured LDL-P) than with LDL-c.

Table 19.1 Integrating lipoprotein particle number (apolipoprotein B or NMR-measured LDL-P) and lipid management

		LDL particle number (Apolipoprotein B or NMR-measured LDL-P)	
		At goal	***Not at goal***
LDL-c	At goal	No further therapy	Further LDL-lowering therapy
	Not at goal	Consider further LDL-lowering therapy	
HDL-c	At goal	No further therapy	Further LDL-lowering therapy
	Not at goal	Consider HDL-raising therapy	Further LDL-lowering therapy (Priority 1) Further HDL-raising therapy (Priority 2)
TG	At goal	No further therapy	Further LDL-lowering therapy
	Not at goal	Consider TG-lowering therapy	Further LDL-lowering therapy (Priority 1) Further TG-lowering therapy (Priority 2)

Table 19.2 Targets for alternative LDL measures

Patient risk category	***LDL cholesterol goal****	***LDL particle number goals***	
		NMR-LDL measured LDL-P	***Apolipoprotein B******
Very high risk	<100 mg/dl (<70 mg/dl optional based on clinical judgment)	< 1000 nmol/l	< 80 mg/dl
High risk	<100 mg/dl	< 1000 nmol/l	< 80 mg/dl
Moderately high risk	<130 mg/dl	< 1300 nmol/l	< 100 mg/dl

*LDL cholesterol values <100 mg/dl and < 130 mg/dl correspond to 20th and 50th percentile values, respectively, in the Framingham Offspring population [12].
**NMR-measured LDL-P <1000 nmol/l and <1300 nmol/l correspond to population equivalent cut-points (20th and 50th percentile) of a contemporary reference population consisting of >6900 subjects enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) [33].
***Apolipoprotein B values correspond to 25th and 50th percentile values, respectively, in the Framingham Offspring population [44].

An approach to incorporating LDL particle number into clinical management of dyslipidemia is presented in Tables 19.1 and 19.2. If LDL particle number is elevated, consideration may be given to adjusting the dosage or combination of therapy used to achieve LDL particle targets appropriate for the clinical setting. When LDL particle number is elevated in conjunction with abnormal HDL-c or TG levels, the first priority is placed on LDL lowering with therapy to affect HDL-c or TG levels being the second priority. The effect of lipid-lowering therapies on LDL particle number, LDL-c, HDL-c and TG is shown in Table 19.3 [43]. Among patients with small LDL size, due to elevated numbers of small LDL particles, combining niacin or fibrates with statins decreases triglycerides, raises HDL cholesterol, and increases LDL size. The effect of this combination is a greater reduction in LDL particle number than

Table 19.3 LDL particle number and lipid altering efficacy of common lipid-altering agents

Lipid-altering agent	*Change in LDL particle number (%)*	*Change in LDL-c (%)*	*Change in triglyceride (%)*	*Change in HDL-c (%)*
Statins	↓18–55***	↓18–55	↓7–30	↑5–15
Nicotinic acid (niacin)*	↓10–25	↓5–25	↓20–50	↑15–35
Fibric acids (fibrates)*	↓5–20***	↓5–20**	↓20–50	↑10–20
Ezetimibe	↓15–25***	↓17–22	↓4–11	↑2–5
Bile acid sequestrants	↓15–30***	↓15–30	No change to increased	↑3–5
Fish oils****	Trials in progress	No change to increased	↓ 20–50	No change to increased
Phytosterols/phytostanols	Trials in progress	↓ 10–15	No change to decreased	No change to increased

*In patients with elevated numbers of small LDL particles, combination with statins usually decreases triglycerides, raises HDL cholesterol, and increases LDL size – causing LDL-P to be decreased more than LDL-c.
**Fibrates may increase LDL-c blood levels in some patients with hypertriglyceridemia. This is the so-called 'beta-effect' of fibrates and can occur secondary to a large increase in the conversion of VLDL to LDL as lipoprotein lipase is activated.
***Combination of NMR and apoB Data.
****The lipid-altering effects of oil listed are with administration of −5–9 g of omega-3 fatty acids per day.
With permission from [43]

LDL-c. Fibrates have been shown to exert discordant effects on LDL particle number versus LDL-c. Although fibrates may increase LDL-c blood levels in some patients with hypertriglyceridemia (the so-called 'beta-effect' of fibrates), an overall reduction in LDL-P commonly occurs secondary to a reduction in small LDL particle number only partially offset by increase in large LDL particle number.

FUTURE DIRECTIONS

The potential clinical utility of 'advanced lipid tests' has usually been examined in the same way that new CVD biomarkers are evaluated, with the aim of determining whether they provide independent prediction additive to traditional risk factors. While this may be a reasonable approach in judging the value of lipoprotein particle size/density information for CHD risk assessment, particle measures of LDL quantity (apoB and NMR-measured LDL-P) are not new biomarkers, but alternative measures of LDL. As such, apoB and LDL-P have greater worth as secondary targets of therapy by adjudicating when LDL levels have been adequately reduced for the degree of clinical risk present.

Many trials are underway to further elucidate the clinical value of lipoprotein information. First, additional clinical trials evaluating the relationship of cholesterol versus particle measures of LDL quantity with CHD risk among discordant individuals at low levels of these values are ongoing. Second, studies are investigating whether the greater CHD risk relationship of non-HDL-c versus LDL-c is attributable to the inclusion of non-LDL lipoproteins, or whether non-HDL-c simply serves as a better surrogate measure of LDL than LDL-c. Finally, future trials will generate data to examine the difference in CHD risk at low levels of apoB or NMR-measured LDL-P versus non-HDL-c at specified target levels.

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20

Should we treat dyslipidemia in the elderly and is there an upper age limit to instituting lipid-lowering therapy?

J. G. Robinson

BURDEN OF DISEASE

Contrary to popular misconception, cardiovascular (CV) disease is by far the leading cause of death and the leading cause of disability after age 65 (Figure 20.1) [1, 2]. Blood pressure (BP) control, smoking cessation, and aspirin prophylaxis have all been shown to prevent CV disease in the elderly as well as middle-aged populations [3–6]. Although statin therapy has been shown to reduce CV risk in elderly subjects as old as 80 years with clinical evidence of CV disease or diabetes, there is little evidence to support cholesterol-lowering therapy in primary prevention for those >80 years of age. Several arguments for and against lowering cholesterol with advancing age merit consideration.

EPIDEMIOLOGIC EVIDENCE

The association between total and low-density lipoprotein cholesterol (LDL-c) and CV risk diminishes with advancing age. Most epidemiologic studies have observed a decline in serum cholesterol levels after age 65, due to the premature death before age 65 of those with high cholesterol, as well as to increasing comorbidity, weight loss, and declining cholesterol synthesis [7, 8]. After age 80, total cholesterol levels are inversely related to coronary heart disease (CHD) mortality for both men and women.

CLINICAL TRIAL EVIDENCE

Only three morbidity/mortality trials of statin therapy have enrolled subjects as old as 80 years, the Heart Protection Study (HPS), Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), and the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) studies. In a prospective meta-analysis of 14 statin trials, those over age 65 (n = 6446) had a 19% reduction in the risk of major CV events, similar to the 22% reduction in risk experienced by those aged ≤65 years (n = 7902) [6]. However, this benefit appears to have been driven primarily by those with clinical evidence of CV disease or diabetes. In the 5-year HPS, in which >20 000 subjects had CV disease or diabetes, those aged 70–80 (n = 5806) had a reduction in risk similar to those <65 years (18% vs 24%,

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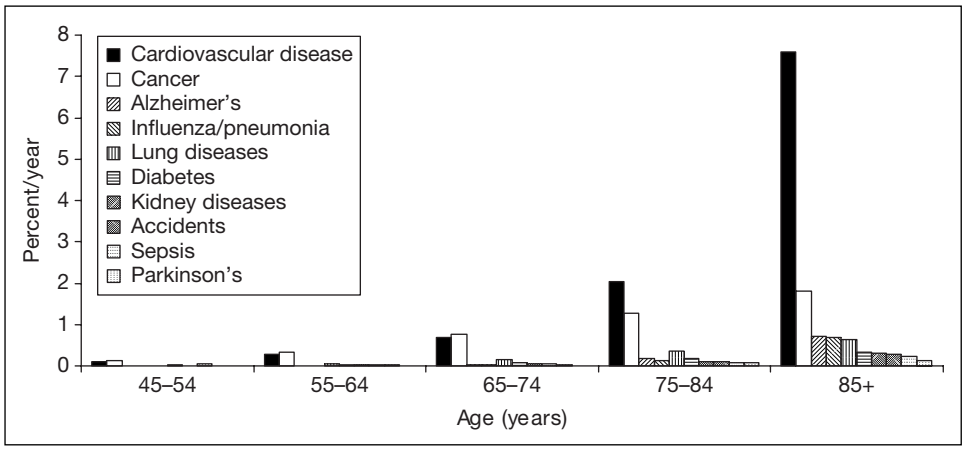

Figure 20.1 Top 10 causes of death with advancing age in the United States, 2004. Data from [1].

respectively) with simvastatin 40 mg [9]. Furthermore, the absolute benefit was greater in those aged >70, in whom the risk of an event over the 5-year treatment period was higher.

In contrast, there is little evidence supporting the use of statins for primary prevention in the elderly. In PROSPER, with 5804 subjects aged 70–82 years, the 1259 subjects without clinical evidence of CV disease had a non-significant reduction in CV events (6%) compared to the 22% risk reduction in those with a history of CV disease [10]. However, PROSPER had several limitations precluding any definitive conclusions regarding the efficacy of statin therapy for primary prevention in elderly patients. PROSPER was underpowered to detect a 22% reduction in risk (56% power), it may have been too short (≈3 years) in duration, and/or LDL-c reduction may have been inadequate (34% to a mean LDL-c of 97 mg/dl).

Some evidence of an attenuated benefit of lower levels of LDL-c-reduction in older patients may also be obtained from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Study – Lipid-Lowering Trial (ALLHAT-LLT) [11]. In ALLHAT-LLT, 55% of the over 10 000 subjects were ≥ age 65 (few were ≥ age 75), and approximately half had CV disease or diabetes. The rate of CHD events and stroke did not differ between the pravastatin 40 mg and usual care groups in this study. Similar CHD event rates occurred in those with and without CHD at baseline. The non-significant 9% difference in CHD events has been attributed to the less-than-expected 17% difference in LDL-c between the 2 groups; however, this degree of risk reduction is still less than the 1:1 relationship between LDL-c reduction and CHD risk commonly observed in placebo-controlled statin trials [12].

The Study Assessing Goals in the Elderly (SAGE) randomized 893 subjects aged 65–85 years with myocardial ischemia to atorvastatin 80 mg or pravastatin 40 mg for 1 year. The mean achieved LDL-c in the atorvastatin group was 67 mg/dl and in the pravastatin group was 98 mg/dl. Atorvastatin 80 mg resulted in a significant reduction in all-cause mortality compared to placebo, despite the small sample size, with a trend toward fewer major CV events in the atorvastatin group. The data from these studies suggest that LDL-c reduction is but one of several treatment targets in the elderly and may not be the most important one, particularly in those older patients who are without clinical evidence of CV disease or diabetes.

AGE >80 YEARS

Although data for those >80 years of age are not available from clinical trials, some observational studies have been performed. In an analysis of Medicare data from >9000 patients

Table 20.1 Characteristics of patients most likely and least likely to experience benefit from cholesterol-lowering therapy to reduce cardiovascular risk

Characteristic	*Rationale*
Most likely to benefit	
Patients with clinical evidence of cardiovascular disease or diabetes	Clear evidence of benefit from clinical trials in patients <80 years with these conditions
Least likely to benefit	
Poorly controlled blood pressure (SBP >160 mmHg or DBP >100 mmHg)	Evidence of increased hemorrhagic stroke risk
Any condition likely to limit survival to <5 years, including cancer, Stage 3 or 4 congestive heart failure, or hemodialysis	Disease course unlikely to be affected by lowering LDL-c
Moderate to severe cognitive dysfunction or dementia	33% mortality at 5 years
Nursing home residence or self-reported difficulty with ≥3 instrumental activities of daily living	>30% mortality at 5 years
Poor self-assessed health	38% mortality at 5 years
LDL-c <100 mg/dl	Evidence of excess mortality in elderly persons with an untreated LDL-c level <100 mg/day May represent serious comorbidities or malnutrition
Underweight Men <142 lb (63.9 kg) Women <115 pounds (51.8 kg)	2-fold greater mortality than higher weight individuals
Unexplained weight loss >10 lb (4.5 kg)	
Excessive alcohol intake (>2 drinks/day)	Increased risk of statin myotoxicity
Known drug contraindications	Increased risk of muscle and liver toxicity

aged >80, no mortality benefit was found over 3 years in those receiving a statin (hazard ratio [HR] 0.97 [0.87–1.09]), although an 11% reduction in mortality was found for those aged 65–79 years (n >14 000) [13]. There was, however, a trend towards benefit in those aged 80–85 compared to those over age 85. Also, in a patient cohort with a history of CHD, domiciled in a long-term care facility, CHD rates were significantly lower in those who were aged 81–100 years and stroke rates were lower in those aged 81–90 years who received a statin. This benefit was independent of the condition(s) that resulted in their residence in a long-term care facility [14, 15].

MORE ARGUMENTS FOR AND AGAINST CHOLESTEROL LOWERING IN THE ELDERLY

Futility in the face of competing causes of mortality has been offered as an argument against treating hypercholesterolemia with advancing age. It should be noted that after age 65, 40% of deaths are due to CV causes, whereas a competing cause of death is actually more likely to occur in those aged 50–64, in whom only 29% of deaths are attributable to CV disease. In the SAGE trial, a significant total mortality benefit was observed in elderly subjects with CHD who received atorvastatin 80 mg compared to pravastatin 40 mg. However, there are identifiable competing conditions in which preventive therapy would not be expected to offer any substantial benefit, such as moderate–severe cognitive dysfunction and dementia, being underweight or having substantial unexplained weight loss, high-grade or metastatic cancer, Class III or IV heart failure, chronic lung disease, end-stage renal disease, liver disease, and advanced Parkinson's disease (Table 20.1; *see also* Figure 20.1) [16–18].

Another argument for treating hypercholesterolemia in the elderly is that most elderly persons now live long enough to experience a benefit from risk factor intervention, since clinical trials have demonstrated a risk reduction benefit over a period of approximately 5 years. In the US in 2004 the average remaining life expectancy at age 65 years was 17 years for men and 20 years for women, regardless of health [19]. Life expectancy is expected to continue to increase while disability and the need for long–term care is decreasing among the elderly [20].

RISK STRATIFICATION

The available clinical trial evidence supports the current cholesterol management guidelines in the US, Canada, and Europe that recommend lowering LDL cholesterol in patients with CV disease and diabetes [21–23], with the caveat that the oldest subjects in clinical trials have been ≤82 years at the initiation of treatment. Since a CV benefit has yet to be demonstrated in patients >70 years without clinical evidence of CV disease or diabetes, evidence-based recommendations for cholesterol treatment cannot be made for this group of patients, including those who are characterized as high risk with a >20% 10-year risk of CHD by Framingham scoring [21]. In the absence of clinical trial evidence of benefit, it is not unreasonable to manage selected patients according to current guidelines for primary prevention. The risk stratification algorithms for primary prevention patients have an upper age limit. The European Systematic Coronary Risk Evaluation system (SCORE) algorithm does not allow risk prediction in persons over age 65 and the Framingham risk scoring used by both US and Canadian guidelines does not allow risk prediction after age 79. The Framingham risk scoring algorithm will therefore be most useful in identifying cholesterol goals in those over age 65, with the caveat that it should only be used in regions of Europe with high-risk populations, as defined in the European guidelines. For persons over age 80 in the US, Canada, and high-risk European countries, or over age 65 in low-risk European countries, the approach to treating hypercholesterolemia should be mindful of the patient's wishes (or not) and whether the patient is expected to have a good to excellent level of function over the next 5 years and thus benefit from preventive therapies to maintain their quality of life. Characteristics of patients likely or not to experience a benefit from CV risk factor management are provided in Table 20.1 [24].

CHOLESTEROL TREATMENT GOALS

As a reminder, cholesterol management should be part of an overall approach to risk factor control, including hypertension treatment, smoking cessation, and acquisition of healthy lifestyle habits related to diet, physical activity, and weight control.

CHD OR CHD EQUIVALENT

All guidelines identify an LDL-c goal <100 mg/dl for patients at high risk of a CV event in the next 10 years, including those with existing CHD, other CV disease, diabetes, or multiple risk factors conferring a >20% 10-year CHD risk [21–23]. The US guidelines additionally identify non-high-density lipoprotein cholesterol (non-HDL; defined as total cholesterol – HDL-c) as the secondary target of therapy with a goal 30 mg/dl higher than that for LDL-c. High-risk elderly patients having an expectation of a good quality of life over the next 5 years should be considered candidates for statin treatment. However, in the absence of clinical trial data, initiation of drug treatment can be considered optional in elderly patients with a baseline LDL-c <100 mg/dl (in light of the excess mortality associated with untreated LDL-c levels <100 mg/dl), especially if malnutrition is suspected as a contributor to the low LDL-c level [16].

The US National Cholesterol Education Program Adult Treatment Panel has recommended an optional LDL-c goal <70 mg/dl for very high-risk patients such as those with established coronary artery disease plus another high-risk condition such as diabetes, metabolic syndrome, smoking or other poorly controlled risk factors, ≥2 risk factors, and those with a history of an acute coronary syndrome [25]. More recently, this more aggressive LDL-c goal of <70 mg/dl has been recommended as a reasonable goal for all patients with CHD [26]. However, in the absence of trials comparing moderate to aggressive LDL-c reduction in the elderly, it is reasonable to consider LDL-c < 100 mg/dl an acceptable target for those >70 years. There are a number of reasons not to attempt to achieve an LDL-c goal <70 mg/dl in most patients aged >70. It should first be noted that <25% of elderly patients with CHD reach the LDL-c goal of <100 mg/dl [13]. Furthermore, high-dose statins are typically required in many patients to achieve an LDL-c <100 mg/dl [27]. High-dose statins appear to be relatively safe in properly selected patients <80 years who have enrolled in clinical trials, but the margin of safety may be lower in those who are >75 years, have multiple comorbidities, or are receiving a variety of concomitant medications [28]. Furthermore, there is attenuation of benefit with progressively greater LDL-c reduction below 100 mg/dl in middle-aged patients [29, 30], which is likely to be more pronounced with advancing age.

Finally, in high-risk patients, lifestyle and drug therapy should be initiated simultaneously if optimal LDL-c reduction and adherence are to occur [31].

PRIMARY PREVENTION

US and international guidelines identify LDL-c goals ranging from <100 to <160 mg/dl for primary prevention, depending on the estimated level of CV risk over the ensuing 10 years [21–23]. While these are not evidence-based recommendations in subjects >70 years of age due to the lack of demonstrated benefit in randomized trials, in properly selected patients <80 years of age it is reasonable to initiate cholesterol-lowering therapy according to the current guidelines. It may also be reasonable to treat patients in average to excellent health between the ages of 80 and 90 years since they are likely to live at least another 5 years [32], the duration over which significant risk reduction has been demonstrated in clinical trials.

By virtue of age and the presence of isolated systolic hypertension, which affects >80% of persons after age 70 [33], the vast majority of persons aged 70–79 have at least a 10% 10-year CHD risk and thus an LDL-c goal <130 mg/dl. In those ≥65 years with a 10–20% 10-year risk of CHD (US), or a ≥5% risk of fatal CV disease (Europe), an optional LDL-c goal <100 mg/dl is recommended [22, 25]. Those with a >20% 10-year CHD risk are considered at high risk with an LDL-c goal <100 mg/dl. Weight control and regular, moderate physical activity are critical for the prevention of both CV disease and diabetes [21, 34]. A heart-healthy diet is recommended for all patients, regardless of their level of risk [35]. Although the Women's Health Initiative reported that 8 years of a low-fat diet (without lowering saturated fat intake) did not reduce CV events in postmenopausal women, subgroup analysis found a 19% reduction in CV risk in those women with the lowest intakes of saturated and *trans* fats, which was consistent with the 10% reduction in LDL-c observed in these women [36]. If after 3 months of lifestyle therapy the LDL-c goal has not been achieved, drug treatment is recommended.

DRUG CHOICE

Statins are recommended as first-line drug therapy for hypercholesterolemia based on their extensive record of efficacy and safety [25]. Statin therapy should be initiated at a daily dose expected to result in at least a 30–40% reduction in LDL-c, and in some patients >50% reductions may be desirable (Table 20.2). To enhance safety in the elderly, depending on age,

Table 20.2 Approximately equivalent statin doses to achieve LDL-c reduction (from manufacturer's prescribing information)

	Approximately 30–40% LDL-c reduction	*Approximately 50% LDL-c reduction*	*Approximately 60% LDL-c reduction*
Atorvastatin	10 mg	40–80 mg	
Fluvastatin XL	80 mg		
Lovastatin	40–80 mg		
Pravastatin	40–80 mg		
Rosuvastatin	5–10 mg	20–40 mg	40 mg
Simvastatin	20–40 mg		
Simvastatin/ezetimibe	10/10 mg	20–80/10 mg	80/10 mg

gender, body size, comorbidities, renal function, Asian ancestry, and other patient characteristics, it may be prudent to initiate statin therapy at half the starting dose and titrate upward as necessary (Table 20.3). Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and simvastatin/ezetimibe have been reported to be at least as effective in lowering LDL-c in those ≥65 as those <65 years of age [37–44].

Only higher doses of atorvastatin or rosuvastatin, or simvastatin coadministered with ezetimibe, lower LDL-c by >50%, the level of LDL-c reduction required to achieve an LDL-c <100 mg/dl in most patients [27]. In addition, recent trials of high-dose atorvastatin (80 mg) have shown additional 11–21% reductions in CV risk beyond that experienced by those receiving a moderate statin dose (simvastatin 20–40 mg, pravastatin 40 mg, or atorvastatin 10 mg), although whether the same incremental benefit occurs with advancing age is as yet unknown [45–47]. Since CV risk reduction is directly correlated with the degree of LDL-c reduction, the addition of ezetimibe to statin therapy should further reduce CV events [12]. Clinical trials evaluating the efficacy of ezetimibe–statin combination therapy are in progress. Caution is warranted when using high-dose statin therapy in patients with advancing age, as discussed below.

In those patients who are not at their LDL-c goal, each doubling of the statin dose results in an additional 5–7% reduction in LDL-c. Similar reductions in LDL-c can be obtained from the addition of stanol or sterol margarines, increasing soluble fiber, improving diet, increasing physical activity, or losing a moderate amount of weight. Another option for further reducing LDL-c is to add ezetimibe, which blocks intestinal uptake of cholesterol from dietary and biliary sources. The addition of ezetimibe to already present statin therapy lowers LDL-c an additional 20% in elderly subjects [41] and may be a reasonable addition if a LDL-c level well below 100 mg/dl is being sought. Niacin 1.5 to 2 g daily and bile acid sequestering agents will lower LDL-c by an additional 15% when added to statin monotherapy, but may be of somewhat limited use in elderly persons due to their potential for causing side effects [48]. Niacin is associated with significant cutaneous side effects in a large proportion of users, may transiently worsen glucose intolerance, and may exacerbate gout. Additional concerns with niacin in the elderly are the risks for gastrointestinal bleeding, atrial fibrillation, and increased risk of muscle toxicity when used with statins. Few studies have evaluated the muscle safety of niacin used in combination with statins but the little evidence available has not shown an increase in the myotoxic effects of statins in properly selected patients [49]. Bile acid binding agents, except for colesevelam, which appears to have fewer problems associated with its use, are notorious for causing constipation and altering absorption of coadministered drugs.

Table 20.3 Patient characteristics likely to enhance statin safety in the elderly

Characteristic	*Likely to enhance statin safety*
Age	Avoid high-dose statins if age >80 years[†]
Body size	Use with caution if small body frame, especially if female If frail, evaluate appropriate use in terms of life expectancy and goals of care
Race/ethnicity	Asian: rosuvastatin starting dose 5 mg due to decreased clearance
Statin use	A history of prior statin use without adverse effects
Hepatic function	No active hepatic disease ALT and AST ≤2 times ULN
Renal function	Glomerular filtration rate >60 ml/min/1.73 m^2 Start at half of recommended starting dose if GFR 30–60 ml/min/1.73 m^2, with careful titration thereafter Use with caution and at very low doses if GFR <30 ml/min/1.73 m^2 Absence of nephrotic syndrome Discontinue prior to intravenous dye administration
Thyroid function	TSH in normal range
Muscle function	CK <3 times ULN unless an explanation exists Use with caution if history of muscle disease Discontinue prior to strenuous exercise (e.g., marathon)
Immune function	Avoid using with chronic immunosuppressive therapy (cyclosporine or danazol)
Cytochrome P450 inhibitors	Potent inhibitors (avoid concomitant use) – Macrolide antibiotics (especially erythromycin, clarithromycin, and telithromycin) – Antiviral drugs (especially HIV protease inhibitors) – Systemic azole antifungals (itraconazole, ketoconazole, and fluconazole) – Risperidone – Nefazadone – Grapefruit juice >1 quart/day Weak inhibitors (avoid or reduce maximum dose) – Verapamil – Diltiazem – Amiodarone
Other lipid-lowering therapy[‡]	Avoid concomitant use with gemfibrozil Use lower dose of fenofibrate with caution Avoid fenofibrate if moderate or severe renal impairment Perhaps avoid concomitant use (or reduce dose) with niacin ≥1 g daily
Alcohol intake	<2 drinks per day Avoid if alcoholism present
Congestive heart failure	Avoid or use lower starting doses if NYHA Class 3 or 4 heart failure
Intercurrent illness, surgery, or trauma	If severe illness, major surgery or major trauma, discontinue lipid-lowering medications until recovered
Multiple comorbidities or medications	Evaluate appropriate use in terms of life expectancy and goals of care

[†]Age up to 80 years at baseline in IDEAL and HPS; [‡]Others have recommended age <70 years as cut-point for safety [49]. ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; GFR = glomerular filtration rate; HIV = human immunodeficiency virus; TSH = thyroid stimulating hormone.

When considering the addition of adjuvant LDL-c- lowering drugs to achieve more aggressive LDL-c targets, the need for intensification of risk factor management, including hypertension treatment, should be evaluated. As an example, when on-treatment LDL-c is 100 mg/dl, adding another drug to reduce LDL-c by an additional 30–70 mg/dl would be expected to result in a 12% reduction in CV risk over 5 years [30]. In comparison, lowering systolic BP by 10 mmHg would be expected to reduce CV risk by over 25% and can usually be accomplished at much lower cost, particularly when generic medications are used [29, 50, 51]. Polypharmacy in the elderly is a particular concern. Multiple lipid-lowering drugs are probably not indicated in elderly subjects who are likely to be receiving multiple concomitant medications and who may inherently have a greater risk of adverse effects.

OTHER LIPIDS

Treatment of non-HDL-c can generally be approached through intensification of both lifestyle changes and drug therapy targeted to lowering LDL-c. In the absence of clinical trial data demonstrating a beneficial effect on CV disease or mortality when added to statin therapy, the use of drug therapy to lower triglycerides or raise HDL-c is not indicated for CV prevention. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is evaluating the incremental CV benefit and safety of fenofibrate added to simvastatin [52]. Fibrates markedly increase the risk of myopathy and rhabdomyolysis when used in combination with statins in elderly patients and should be avoided unless treatment of severe hypertriglyceridemia (triglycerides >500 mg/dl) is required to prevent pancreatitis. In an analysis of patients hospitalized for rhabdomyolysis, a patient ≥ 65 years with diabetes treated with both a statin and a fibrate had a 48-fold greater risk than younger patients, translating into a number needed to harm of 484 [53]. Niacin raises HDL-c by 15–35%, making it the most effective HDL-c- raising drug currently available [54]. However, drug treatment targeting HDL-c levels is not indicated since the incremental benefit of raising HDL-c in the background of statin therapy has yet to be established in the elderly, although such a trial is underway [55].

SAFETY

In analyses of manufacturer's clinical databases, muscle and hepatic safety were similar across the dose range for all currently marketed statins and simvastatin/ezetimibe in properly selected subjects above or below the age of 65 years [37–44]. It should be noted, however, that participants in clinical trials are carefully selected to minimize the potential for toxicity. Much higher rates of the most severe form of statin myotoxicty, rhabdomyolysis, have been found when statins were used in patients with multiple risk factors for myopathy, including concomitant use of gemfibrozil, other inhibitors of statin metabolism such as those inhibiting cytochrome P450 CYP3A4, advanced age, underweight or small patients, impaired renal function, and serious comorbid conditions such as alcoholism, infection, or trauma [53]. Strategies to enhance the use of statins in the elderly are outlined in Table 20.3.

Although muscle and liver adverse effects are uncommon, there is evidence of a dose relationship with some statins. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYP3A4 and concomitant use with potent inhibitors of this pathway should be avoided (Table 20.3). Lower doses of simvastatin ≤ 20 mg and lovastatin ≤ 40 mg are indicated if used concomitantly with weak inhibitors of CYP3A4, such as verapamil or diltiazem, as well as with amiodarone [56, 57]. Fluvastatin is metabolized *via* CYP 2C9 and pravastatin is primarily metabolized *via* glucuronidation [58, 59]. Rosuvastatin is minimally metabolized and has no significant cytochrome P450 interactions [60]. Extreme caution and lower starting doses are recommended for simvastatin (5 mg) and lovastatin (20 mg) in patients with severe renal impairment (glomerular filtration rate [GFR] <30 ml/min/1.73 m^2)

[44, 57]. In the clinical database for simvastatin, the risk of myopathy and rhabdomyolysis was 0.02% for 20 mg, 0.08% for 40 mg, and 0.53% for 80 mg [57].

In a small study of 70–78-year-old subjects, simvastatin levels were 45% higher than in 18–30-year-old subjects comparably dosed, suggesting that elderly persons may be at somewhat increased myopathy risk with the highest dose of simvastatin [57]. In HPS, which included subjects as old as 80 years, there were ten cases of myopathy/rhabdomyolysis in the 10 269 subjects allocated to simvastatin 40 mg (0.1%), four of whom were >65 years; four cases of myopathy occurred in the placebo group (0.04%) [9, 57]. Safety data on simvastatin 80 mg in the elderly is expected from the ongoing Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), a 5-year trial in the UK comparing an 80 mg to a 20 mg dose of simvastatin on the incidence of CHD events in 12 000 subjects with a history of myocardial infarction [61].

No evidence of myotoxicity with atorvastatin 80 mg emerged in either the Treating to New Targets (TNT) or the IDEAL study [46, 47]. Since the risk of myopathy increases with advancing age, as well as declining renal and hepatic function, statins at the highest doses should be considered only for elderly subjects with GFR >60 ml/min/1.73 m^2 who do not have other conditions that could compromise renal function, including chronic use of nonsteroidal anti-inflammatory agents (NSAIDS), high doses of diuretics, or advanced heart failure.

Atorvastatin 80 mg had higher rates of persistent hepatic transaminase elevations >3 times the upper limit of normal (ULN) in TNT and IDEAL than did the comparator treatments, although still at a rate of only approximately 1% over 5 years of treatment. Some evidence of a a dose response for transaminase elevations is also present with simvastatin 40 mg and 80 mg, although rates were again quite low at <1% [28]. There was no evidence of liver or muscle toxicity with pravastatin 40 mg in those participants >65 years in the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial [37].

The safety of rosuvastatin and simvastatin/ezetimibe is not yet established in long-term event trials. The pharmacokinetics of rosuvastatin are unchanged in those ≥65 years although Asian subjects appear to have 2-fold higher blood levels than other racial groups. As such, the recommended starting dose of rosuvastatin is 5 mg for Asian patients. The rate of adverse muscle effects when ezetimibe is used in combination with a statin appears to be no higher than when a statin is used alone [62]. Rates of persistent hepatic transaminase elevation, with ezetimibe, however, are slightly higher (3% vs 1%) although these elevations are reversible [63].

Concomitant use of a fibrate with a statin should be avoided in the elderly unless severe hypertriglyceridemia is present and the benefit is estimated to outweigh the risk. Gemfibrozil increases blood levels of all the statins so its concomitant use with statins should be avoided in elderly subjects [63,64]. The large majority of statin-related rhabdomyolysis cases in the US Food and Drug Administration adverse drug experience database occurred in patients receiving concomitant gemfibrozil therapy, many of whom were over age 65 or had serious comorbidites [65]. In a review of patients hospitalized with rhabdomyolysis, the rate was >45-fold higher in those aged >65 with diabetes who received a statin in combination with a fibrate, a group at very high CV risk in whom combination therapy may otherwise be considered [25, 53]. Fenofibrate has weaker effects on statin blood levels [66], but it should still be used with caution in the elderly. The rate of rhabdomyolysis is about 15 times lower for fenofibrate–statin use than for gemfibrozil–statin use, but still substantially higher than for statin monotherapy [67]. Concomitant fenofibrate and statin use should be completely avoided in elderly patients if there is evidence of renal insufficiency since fenofibrate undergoes significant renal elimination (≈60%) [68]. Until the incremental benefit of a fibrate added to statin therapy has been established, omega-3 fish oil in doses sufficient to provide 3.5 g of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) may be considered as a suitable alternative to fibrate therapy for the treatment of severe hypertriglyceridemia [69].

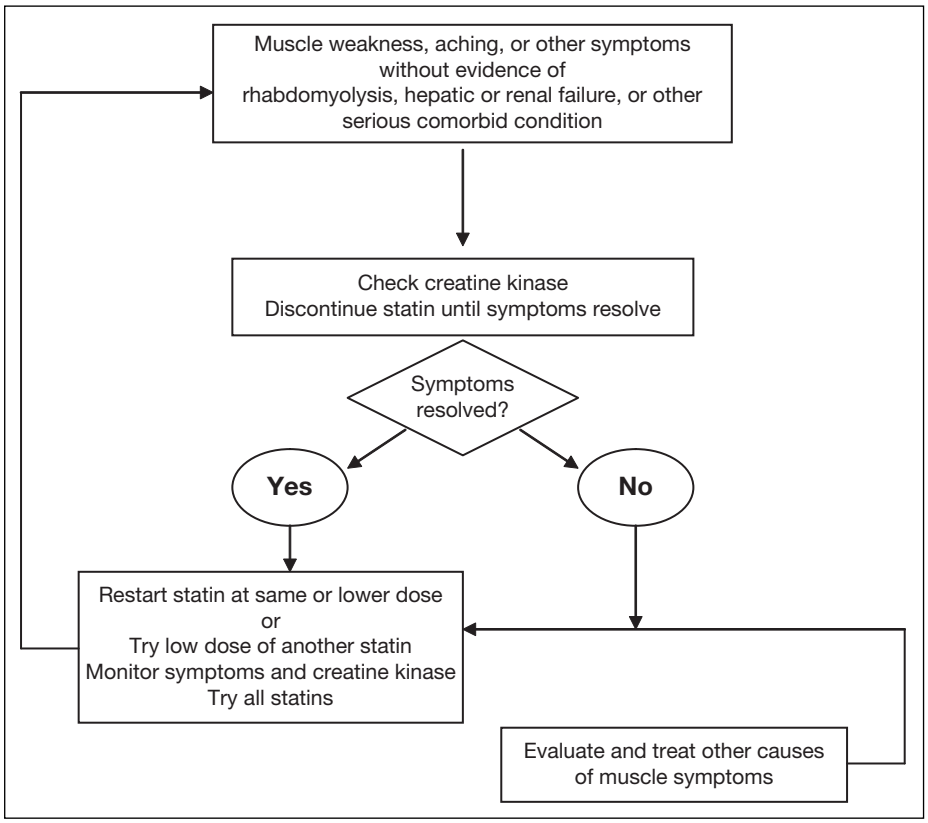

Figure 20.2 Clinical approach to mild to moderate muscle and other symptoms in patients receiving cholesterol-lowering drug therapy.

MUSCLE SYMPTOMS IN THE ELDERLY

Musculoskeletal symptoms are extremely common in patients of all ages. Routine monitoring of creatine kinase (CK) is not recommended in statin-treated patients but may be considered as part of the evaluation of patients with muscle symptoms [49]. Adverse muscle effects in the elderly are often manifested as progressive, sometimes profound, weakness rather than pain or tenderness. Determining whether muscle symptoms are due to a statin requires a systematic approach including discontinuing the statin, measuring CK levels, waiting until muscle symptoms resolve, and rechallenging with the same or a different statin (Figure 20.2) [49]. Often, patients will have no muscle symptoms upon rechallenge at an unchanged dose of the same statin. If necessary, the patient should be rechallenged with very low doses of the remaining statins with careful symptom and CK monitoring. Successful creative dosing strategies include half of the lowest dose every other day, and 1- or 2-week drug holidays for patients who develop muscle symptoms after a predictable time interval (e.g., in patients with myalgias after 3 months, stop the statin after 2½ months and then resume treatment). Ezetimibe can often be added to a low-dose statin without exacerbating muscle symptoms. An elderly patient who experiences myopathy (muscle symptoms with CK >10 times ULN) or clinical rhabdomyolysis (muscle symptoms with CK

>10 times ULN and renal impairment) on a statin should only be rechallenged with the greatest caution, if at all. If muscle symptoms do not resolve within 2 months of statin discontinuation, the patient should be evaluated for other disorders affecting muscle, including hypothyroidism, polymyalgia rheumatica and other rheumatologic diseases, and disturbed sleep due to sleep apnea or other sleep disturbances (in the patient or partner).

TRANSAMINASE ELEVATIONS IN THE ELDERLY

Hepatic transaminase elevations are common but rarely due to statin therapy. Hepatic transaminase levels should typically be evaluated at baseline. Monitoring thereafter should occur according to the manufacturer's instructions although recent expert recommendations question the value of routine monitoring [70]. Baseline elevations of hepatic transaminases <3 times ULN are not a contraindication to statin therapy. Transaminase levels fluctuate between 1.5 and 3 times ULN in many patients with diabetes, metabolic syndrome or obesity who have non-alcoholic fatty liver disease, or non-alcoholic steatohepatitis [71]. Transaminase level elevations due to fatty liver often improve in the face of long-term statin therapy [70].

After establishing that no other etiology is responsible for transaminase elevations, low- to moderate-dose statin therapy can be started with close monitoring of alanine aminotransferase levels. The dose can be carefully titrated upward and additional LDL-c- lowering therapies can be added as tolerated. Since few data are available for the use of niacin in those >65 years of age, niacin should probably be avoided in these patients due to drug-specific concerns about hepatotoxitity.

For patients with a transaminase level >3 times ULN, the first step is to have the patient discontinue all potential hepatotoxic agents, including alcohol, non-steroidal anti-inflammatory agents, acetaminophen, H_2-blockers, muscle relaxants, herbal remedies, and other over-the-counter agents. If transaminase levels remain elevated >3 times ULN on 2 consecutive occasions more than 2 weeks apart, the statin should be discontinued until transaminase levels return to the patient's baseline (which may not be a normal range value). At this point, the patient can be rechallenged with the same statin at a lower dose and carefully titrated upward, or started on a low dose of a different statin. If transaminase levels remain persistently elevated after at least 1 month off the statin, then other causes should be pursued. Statins can be used safely in the setting of chronic liver disease and compensated cirrhosis with the proviso that such patients are carefully instructed on the risk of myopathy. Decompensated cirrhosis and acute liver failure, however, are contraindications to statin therapy [70].

OTHER SAFETY ISSUES

No consistent evidence of increased cancer incidence or mortality has emerged in the statin trials [6]. Although patients are occasionally concerned about impairments in cognitive function with statin therapy, simvastatin 40 mg had no effect, either beneficial or harmful, on cognitive functioning in HPS in subjects as old as 80 years. Stroke becomes increasingly important with advancing age, and in women surpasses the rate of acute myocardial infarction and CHD death after age 75 [72]. Stroke was not reduced in either the secondary or primary prevention groups in PROSPER where the mean BP was 154/85 mmHg; however, this failure to reduce stroke rate may have reflected an excess of hemorrhagic stroke due to poorly controlled hypertension. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, an excess of hemorrhagic stroke occurred in those receiving atorvastatin 80 mg who had poorly controlled hypertension or a history of hemorrhagic stroke [73, 74]. These data further emphasize the importance of adequate BP control in elderly patients who are receiving cholesterol-lowering dug therapy.

SUMMARY

Evidence supports lowering LDL-c to <100 mg/dl to reduce the CV risk in high-risk patients over the age of 65. Treatment should be initiated with both lifestyle changes and a moderate dose of a drug such that a 30–40% reduction in LDL-c level is achieved. The efficacy and safety of moderate-dose statin therapy is well established in older patients without risk factors for myopathy. The risk of serious muscle and hepatic adverse effects is dose-related, and risk increases with advancing age, impaired renal and hepatic function, and the presence of other comorbidities and medications. Although many patients may need higher doses of the more efficacious statins to achieve an LDL-c level <100 mg/dl, the highest doses should be used with caution in those aged >80 years, evidence of severe renal impairment, or other conditions increasing the risk of myopathy. The benefit of cholesterol treatment should be carefully considered in patients aged >80 years, although those who are in good to excellent health are likely to live at least 5 more years, a time period over which a benefit is expected. In primary prevention, the highest priority is to perform a properly designed trial of cholesterol-lowering therapy in patients >70 years of age so that evidence-based treatment guidelines can be developed. Until these data are available, it is reasonable to treat elderly patients without clinical evidence of CV disease or diabetes according to current guidelines.

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Abbreviations

4S	Scandinavian Simvastatin Survival Study
A to Z	Aggrastat to Zocor study
AAA	abdominal aortic aneurysm
ABC	adenosine triphosphate-binding cassette
ABCA1	ATP binding cassette A1
ABI	ankle–brachial index
ACAT	acyl-coenzyme A cholesterol acyltransferase
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ADA	American Diabetes Association
AERS	adverse events reporting system
AF	atrial fibrillation
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AFREGS	Armed Forces Regression Study
AHA	American Heart Association
AIH	autoimmune hepatitis
AIM HIGH	Atherosclerosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (study)
ALLHAT-LLT	Antihypertensive and Lipid Lowering Heart Attack – Lipid Lowering Trial
ALT	alanine aminotransferase
ANA	antinuclear antibody
Ang	angiotensin
anti-LC1	antibody to liver cytosol type 1
anti-LKM1	antibodies to liver kidney microsome type 1
anti-SLA/LP	antibodies to soluble liver antigen/liver pancreas
AP	alkaline phophatase
apo(a)	apolipoprotein (a)
apoB	apolipoprotein B
ARB	angiotensin receptor blocker
ARBITER	Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol trial
ARIC	Atherosclerosis Risk in Communities (study)
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ASCOT–LLA	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AT_1	angiotensin receptor subtype 1

ATP III	Third Adult Treatment Panel of the NCEP
ATP	adenosine triphosphate
AUC	area under the curve
BAS	bile acid sequestrant
BIP	Bezafibrate Intervention Prevention
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CACS	coronary artery calcium score
CAD	coronary artery disease
CARDS	Collaborative Atorvastatin Diabetes Study
CARE	Cholesterol and Recurrent Events Study
CASANOVA	Carotid Artery Surgery Asymptomatic Narrowing Operation Versus Aspirin
CDC	Centers for Disease Control and Prevention
cdk	cyclin dependent kinase
CDP	Coronary Drug Project
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CI	confidence interval
CIMT	carotid intima–media thickness
CK	creatine kinase
CKD	chronic kidney disease
CLAS	Cholesterol-Lowering Atherosclerosis Study
C_{max}	serum concentration
COMPELL	COMParative Effects on Lipid Levels of *Niaspan*
CoQ10	co-enzyme Q10
CRP	C-reactive protein
CT	computed tomography
CTT	Cholesterol Treatment Trialists
CV	cardiovascular
CVD	cardiovascular disease
DAIS	Diabetes Atherosclerosis Intervention Study
DART	Diet and Reinfarction Trial
DGAT2	diacyl glycerol acyl transferase-2
DGU	density gradient ultracentrifugation
DHA	docosahexaenoic acid
DIAD	Detection of Silent Myocardia Ischaemia in Asymptomatic Diabetes (study)
DIH	drug-induced hepatotoxicity
DM	diabetes mellitus
DP1	D_2 receptor subtype 1
DPP	Diabetes Prevention Program
DREAM	Diabetes REduction Assessment with ramipril and rosiglitazone Medication trial
EAS	European Atherosclerosis Society
ECG	electrocardiogram
ECST	European Carotid Surgery Trial
ELISA	enzyme-linked immunosorbent assay
eNOS	endothelial nitric oxide synthase
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition

ER	extended-release
ESC	European Society of Cardiology
ET	endothelin
EXCEL	EXpanded Clinical Evaluation of Lovastatin
FA	fatty acid
FAAT	Fatty Acid Antiarrhythmia Trial
FATS	Familial Atherosclerosis Treatment Study
FDB	familial defective apoB-100
FFA	free fatty acid
FH	familial hypercholesterolemia
FHS	Framingham Heart Study
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FLORIDA	Fluvastatin On Risk Diminishment After Acute Myocardial Infarction
FPP	farnesyl pyrophosphate
FRS	Framingham risk score
GFR	glomerular filtration rate
GGE	gradient gel electrophoresis
GGPP	geranylgeranylpyrophosphate
GISSI	Gruppo Italiano por lo Studio della Streptochinasi nell'Infarto Miocardico
GLP-1	glucagon-like peptide-1
GTP	guanine nucleotide-binding proteins
HARP	Harvard Atherosclerosis Reversibility Project
HATS	HDL Atherosclerosis Treatment Study
HDL	high-density lipoprotein
HDL-c	high-density lipoprotein cholesterol
HHS	Helsinki Heart Study
HIT	High-Density Lipoprotein Cholesterol Intervention Trial
HMG-CoA	3-hydroxyl-3-methyglutaryl coenzyme A
HOPE	Heart Outcomes Prevention Evaluation (study)
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection 2-Treatment of HDL to Reduce the Incidence of Vascular Events
HR	hazard ratio
HRT	hormone replacement therapy
hs-CRP	high sensitivity C-reactive protein
ICAM-1	intercellular adhesion molecule-1
ICD	implantable cardioverter defibrillators
IDEAL	Incremental Decrease in End Points Through Aggressive Lipid Lowering (trial)
IDF	International Diabetes Federation
IDL	intermediate-density lipoprotein
IDL-P	intermediate-density lipoprotein particle concentration
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IHD	ischemic heart disease
IL	interleukin
IMPROVE IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IOTF	International Obesity Task Force
IR	immediate-release

JELIS	Japan EPA Lipid Intervention Study
JNC7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JUPITER	Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin
LASA	Longitudinal Aging Study Amsterdam
LBS	lysine-binding site
LDL	low-density lipoprotein
LDL-c	low-density lipoprotein cholesterol
LDL-P	LDL particle concentration
LFT	liver function test
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease Study
Lp(a)	lipoprotein (a)
LPL	lipoprotein lipase
$LpPLA_2$	lipoprotein associated phospholipase A_2
LRC	Lipid Research Clinic
LRC-CPPT	Lipid Research Clinic – Coronary Primary Prevention Trial
MEDPED	Make Early Diagnosis to Prevent Early Deaths
MESA	Multi-Ethnic Study of Atherosclerosis
MHC-1	major histocompatibility complex-1
MI	myocardial infarction
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
MRFIT	Multiple Risk Factor Intervention Trial
mRNA	messenger ribonucleic acid
MS	metabolic syndrome
MTP	microsomal triglyceride transfer protein
NAFLD	non-alcoholic fatty liver disease
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NCEP	National Cholesterol Education Program
NF-κB	nuclear factor kappa B
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NLA	National Lipid Association
NMR	nuclear magnetic resonance
NO	nitric oxide
NORVIT	Norwegian Vitamin Trial
NSAID	non-steroidal anti-inflammatory drug
OASIS	Organization to Assess Strategies in Acute Ischemic Syndromes
OATP1B1	organic anion transporter 1B1
oxLDL	oxidized low-density lipoprotein
PACT	Pravastatin Acute Coronary Treatment
PAI-1	plasminogen activator inhibitor 1
pANCA	perinuclear anti-neutrophil cytoplasmic antibodies
PCSK9	proprotein convertase subtilisin/kexin type 9
PDGF	platelet-derived growth factor
POSCH	Program on the Surgical Control of the Hyperlipidemias
PPAR	peroxisome proliferators receptor
PPRE	peroxisomal proliferators response element
PR	prolonged-release
PRIME	Prospective Epidemiological Study of Myocardial Infarction

PRIMO	Prediction of Muscular Risk in Observational Conditions (study)
PRINCESS	Prevention of Ischemic Events by Early Treatment with Cerivastatin
PROCAM	Prospective Cardiovascular Münster
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE IT-TIMI 22	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PTCA	percutaneous transluminal coronary angioplasty
PUMA-G	protein upregulated in macrophages by interferon-gamma
RCT	reverse cholesterol transport
RDA	recommended daily allowance
REVERSAL	Reversal of Atherosclerosis with Aggressive Lipid Lowering (trial)
ROS	reactive oxygen species
RR	relative risk
RXR	retinoid X receptor
SAGE	Study Assessing Goals in the Elderly
SCORE	Systematic Coronary Risk Evaluation System
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SHAPE	Screening for Heart Attack Prevention and Education
SMA	smooth muscle antibody
SMC	smooth muscle cell
SOFA	Study on Omega-3 Fatty acids and ventricular Arrhythmia
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SR	sustained-release
SR-B1	scavenger receptor 1
SREBP-1c	sterol regulatory element binding protein 1c
SSRI	selective serotonin reuptake inhibitor
TC	total cholesterol
TFPI	tissue factor pathway inhibitor
TG	triglyceride
TGF-β	transforming growth factor β
tHcy	total homocysteine
TIA	transient ischemic attack
TLC	therapeutic lifestyle changes
TNFα	tumor necrosis factor-α
TNT	Treating to New Targets (study)
t-PA	tissue plasminogen activator
TSH	thyroid-stimulating hormone
TZD	thiazolidinedione
UGT	uridine diphosphate glucuronosyl transferase
UKPDS	UK Prospective Diabetes Study
ULN	upper limit of normal
VA-HIT	Veterans Affairs High-Density Lipoprotein Intervention Trial
VCAM-1	vascular cell adhesion molecule-1
VF	ventricular fibrillation
VISP	Vitamin Intervention for Stroke Prevention Study
VLDL	very-low-density liopoprotein
VLDL-c	very-low-density lipoprotein cholesterol
VLDL-P	very-low-density lipoprotein particle concentration
VT	ventricular tachycardia
WACS	Women's Antioxidant Cardiovascular Study

WHHL	Watanabe Heritable Hyperlipidemic
WHI	Women's Health Initiative
WHO	World Health Organization
WOSCOPS	West of Scotland Coronary Prevention Study

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