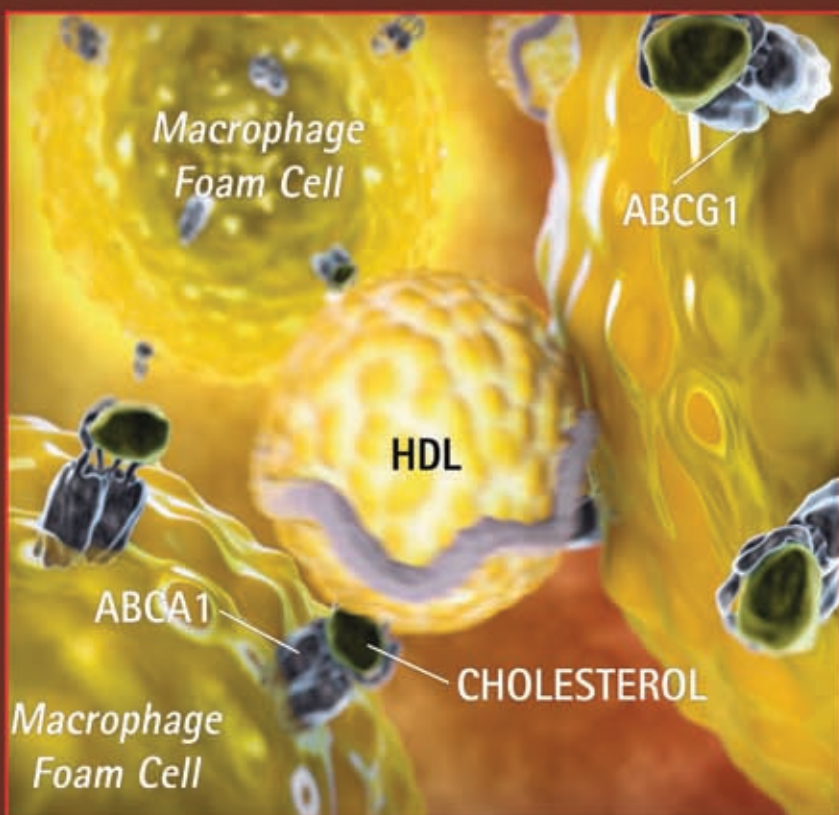


LIPID DISORDERS

Peter P. Toth • Domenic A. Sica



FOREWORD BY SCOTT M. GRUNDY

CLINICAL PUBLISHING

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 nutraceuticals 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
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1

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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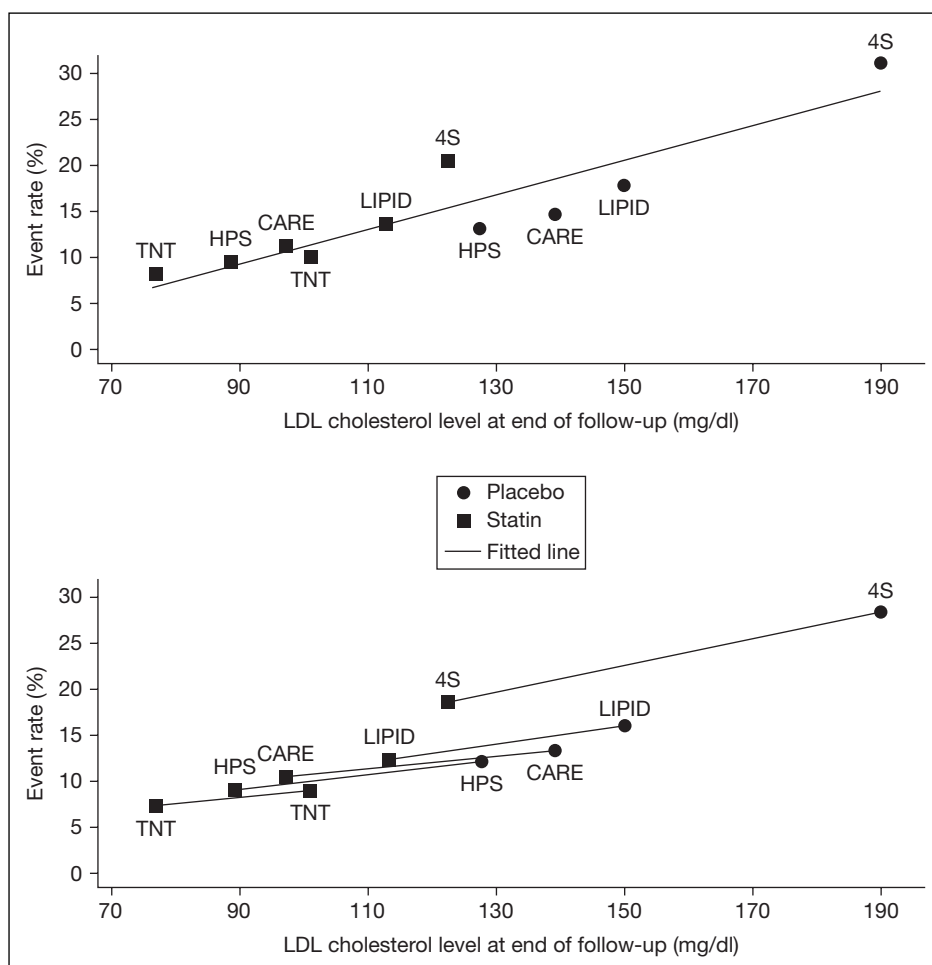


Figure 1.1 Top. Event rate assuming a single association between low-density lipoprotein cholesterol (LDL-c) and outcome across trials. **Bottom.** The LDL-c outcome associations found within each study. 4S = Scandinavian Simvastatin Survival Study; CARE = Cholesterol and Recurrent Events Study; HPS = 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.

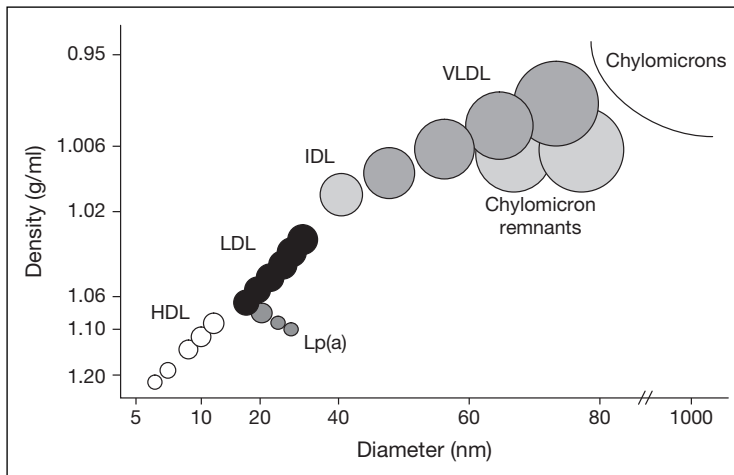


Figure 1.2 Relative sizes and densities of circulating lipoprotein particles. Adapted from [24]. Figure by courtesy of Dr James Otvos, LipiScience, Inc.

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

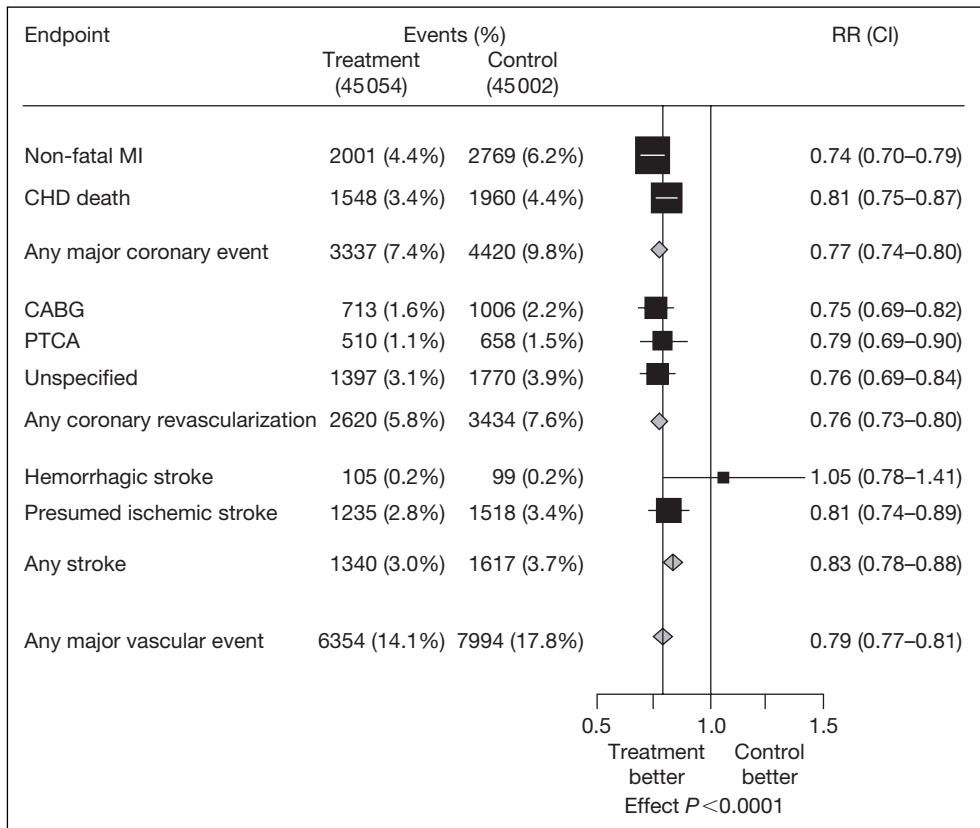


Figure 1.3 Proportional effects on major vascular events per mmol/l (38.7 mg/dl) LDL-c reduction in statin outcomes trials. CABG = coronary artery bypass graft; CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RR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

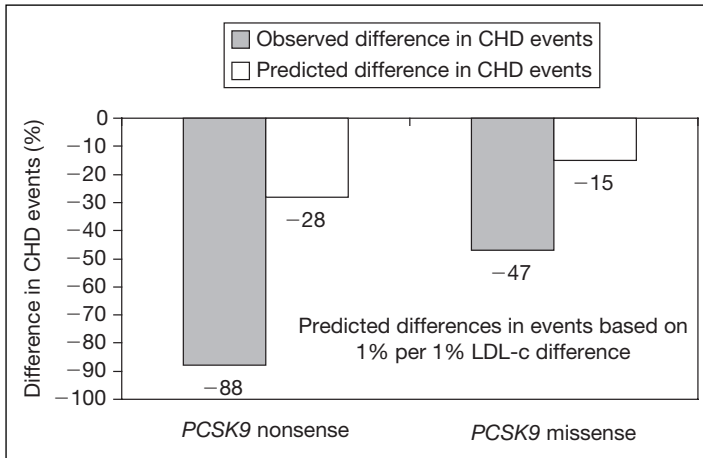


Figure 1.4 Predicted and observed differences in CHD events associated with sequence variations in *PCSK9* that result in chronically reduced levels of LDL-c. CHD = coronary heart disease; LDL-c = low-density lipoprotein cholesterol; *PCSK9* = pro-protein convertase subtilisin/kexin type 9 serine protease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

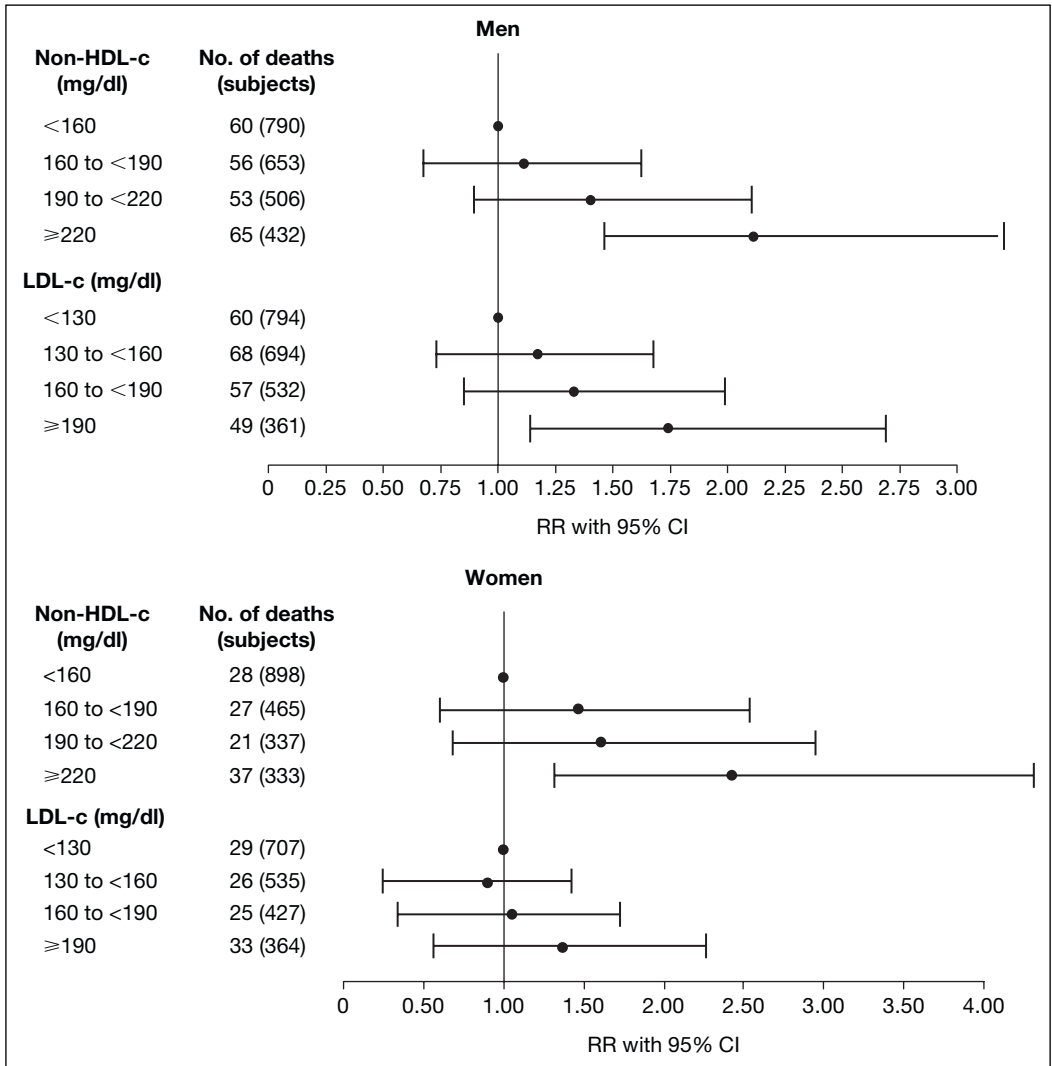


Figure 1.5 Cardiovascular disease mortality by non-HDL cholesterol and LDL cholesterol levels in men and women. CI = confidence interval; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; RR = relative risk. With permission from [33].

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 |

¹From 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

| <i>Parameter</i> | <i>Difference (SE) in IMT in μm per SD¹</i> | <i>P-value</i> |
|------------------|--|----------------|
| 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 |

¹Model 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-apoptotic, 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

| <i>Risk status¹</i> | <i>US guidelines</i> | <i>Canadian guidelines</i> |
|--|--------------------------------|---|
| 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 |

¹US 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.
²CHD 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%.
³Risk 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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