Key Points

- Epidemiological studies have shown that a large percentage of the variation within and between countries in coronary heart disease (CHD) incidence can be accounted for by lipid-associated risk factors.

- More than 90% of the population-attributable risk for CHD can be explained by potentially modifiable risk factors (lipids, blood pressure, body weight, diabetes, psychosocial factors, diet, and physical activity).

- Clinical trials have shown that each 1% reduction in low-density lipoprotein cholesterol (LDL-C) is associated with a reduction of approximately 1% in CHD risk. However, observational data suggest that the benefit may be as much as 3% CHD risk reduction per 1% decrement in LDL-C if maintained for many years.

- The non-high-density lipoprotein cholesterol (non-HDL-C) level is highly correlated with the level of apolipoprotein B and is a better predictor of CHD risk than LDL-C in patients with elevated triglycerides (≥200 mg dl⁻¹); therefore non-HDL-C goals have been established by the National Cholesterol Education Program (NCEP) as secondary targets for patients with elevated triglycerides.

- National surveys indicate that cholesterol management in clinical practice has improved dramatically since 1997, although recent research shows some groups are at increased risk for not achieving their
treatment targets, including patients with elevated triglycerides, women, minorities, current smokers, and those with CHD risk equivalents.

- Based on recently published evidence that reducing LDL-C to levels well below 100 mg dl$^{-1}$ is associated with further reductions in risk, the NCEP has issued optional treatment targets for patients at very high risk, including LDL-C < 70 mg dl$^{-1}$.

- It is likely that use of high-dose statin and multidrug therapy will need to expand in order to achieve these more aggressive goals.

1.1 EARLY HISTORY OF CARDIOVASCULAR EPIDEMIOLOGY

As recently as 1950, the prevailing view in the medical community was that atherosclerosis was a degenerative condition that was an inevitable result of aging. In the early 1950s, Ancel Keys and colleagues documented that mortality from CHD varied enormously between countries [1]. The results of the Seven Countries Study showed that coronary mortality differed by roughly 10-fold between countries and that the average circulating cholesterol level was strongly associated with coronary death [1, 2]. Later studies showed that when groups of people migrated from developing countries to more developed western countries, and adopted lifestyle features of their new home, their blood cholesterol levels rose and this was accompanied by an increase in CHD [3]. These findings were supported by results from early autopsy studies that showed marked variation in cholesterol levels and coronary atherosclerosis between countries [1].

The Framingham Heart Study was initiated in 1948 and provided the foundation for the idea that variation in CHD rates within a population could be predicted by several “risk factors”. In fact, the term risk factor was first used in 1961 in a publication from this landmark investigation, which measured various characteristics of a group of roughly 5000 residents in the town of Framingham, Massachusetts and followed them over decades to determine what features were associated with CHD and other cardiovascular events.

Epidemiology is the study of the distribution and determinants of disease in human populations. Before the middle of the twentieth century, epidemiological methods had mainly been employed in the study of infectious diseases (“epidemics”). The Framingham Heart Study has contributed hundreds of papers to the scientific literature that helped to establish the risk factors that were associated with the development of CHD. Many of these were identifiable years or decades before clinical events, suggesting the potential for prevention through risk factor modification.
Thus, the foundation laid by the study of risk factors associated with variations in CHD incidence between and within populations has allowed the development of clinical tools for risk stratification, such as the Framingham Risk Score, that has been incorporated into the NCEP guidelines [4]. A central feature of the approach advocated by the NCEP is matching the intensity of lipid modification with the level of CHD risk. The NCEP method entails use of major CHD risk factors (sex, age, HDL-C, smoking status, blood pressure, diabetes) and the presence or absence of clinical atherosclerosis to stratify subjects according to 10-year CHD risk. Specific treatment goals for LDL-C are recommended, with those at the highest risk (known CHD or risk equivalents) having the most aggressive goals.

1.2 LIPID RISK FACTORS ARE CENTRAL TO EFFORTS AT CHD PREVENTION

Recently, the INTERHEART study evaluated the relationships between major risk factors identified in earlier epidemiologic investigations and CHD in 52 countries [5]. This global investigation showed that nine potentially modifiable risk factors could explain more than 90% of the variation in acute myocardial infarction among men and women (Table 1.1).

The results from INTERHEART illustrate the importance of lipid-related risk factors. Because of its strong association with CHD risk and high prevalence, an elevated ratio of apolipoprotein B to AI explains nearly half (49.2%) of the global population-attributable risk for CHD. Apolipoprotein B is the main protein constituent of atherogenic lipoproteins (LDL, very low-density lipoprotein (VLDL), and remnants of triglyceride-rich particles), whereas apolipoprotein AI is the main protein constituent of HDL, which is inversely associated with CHD risk. Accordingly, these apolipoprotein concentrations indicate the number of circulating atherogenic (apolipoprotein B) and protective (apolipoprotein AI) lipoprotein particles.

Clinically, lipoprotein cholesterol levels are more commonly measured than apolipoproteins. Many studies have shown that levels of non-HDL-C and HDL-C are highly correlated with apolipoprotein B and AI levels, respectively, and have predictive values that are only slightly less robust than those of apolipoproteins [6]. The NCEP ATP III guidelines have recommended the use of lipoprotein cholesterol (LDL, non-HDL and HDL) and triglyceride concentrations for assessment of CHD risk status. Treatment goals have been recommended for LDL-C as the primary target of lipid management, and non-HDL-C as a secondary target for patients with elevated triglycerides (≥200 mg dl⁻¹). Treatment targets are discussed in detail in Chapter 3.
Table 1.1 Potentially modifiable risk factors, their association with coronary heart disease case status and estimated population-attributable risk in the INTERHEART study.

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Odds ratio$^a$</th>
<th>Population-attributable risk (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lipids</td>
<td>Apo B/Apo AI ratio</td>
<td>3.25</td>
<td>49.2</td>
</tr>
<tr>
<td>2. Smoking</td>
<td>Current, past, never</td>
<td>2.87</td>
<td>35.7</td>
</tr>
<tr>
<td>3. Psychosocial factors</td>
<td>Composite</td>
<td>2.67</td>
<td>32.5</td>
</tr>
<tr>
<td>4. Abdominal obesity</td>
<td>Waist hip ratio</td>
<td>1.62</td>
<td>20.1</td>
</tr>
<tr>
<td>5. History of hypertension</td>
<td>Yes, no</td>
<td>1.91</td>
<td>17.9</td>
</tr>
<tr>
<td>6. Fruit and vegetable intake</td>
<td>Frequency</td>
<td>0.70</td>
<td>13.7</td>
</tr>
<tr>
<td>7. Physical activity</td>
<td>Frequency</td>
<td>0.86</td>
<td>12.2</td>
</tr>
<tr>
<td>8. Diabetes mellitus</td>
<td>Yes, no</td>
<td>2.37</td>
<td>9.9</td>
</tr>
<tr>
<td>9. Alcohol intake</td>
<td>Frequency</td>
<td>0.91</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>90.4</strong></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Estimated from a logistic regression model adjusted for age, sex and all other variables. Comparisons for odds ratios were as follows: apolipoprotein B/AI ratio, top versus lowest quintile; smoking, current versus never; psychosocial factors, index for depression, general stress, low locus of control, major life events, versus nonexposure to all five factors; abdominal obesity, top versus bottom tertile; hypertension and diabetes history, yes versus no; physical activity, ≥4 hours per week versus <4 hours per week; alcohol consumption ≥3 times per week versus <3 times per week; daily fruit and vegetable intake versus none or irregular.

$^b$Population-attributable risk is the percentage of cases that can be attributed to this risk factor given the probability of exposure in the population and the increase or decrease in relative risk (or relative odds) associated with the risk factor.

$^c$Apo, apolipoprotein.


1.3 LDL-C AND CHD RISK

LDL particles typically carry a majority of the circulating cholesterol and evidence from population, laboratory and intervention studies has clearly shown that these particles are atherogenic. Populations that maintain LDL-C <100 mg dl$^{-1}$ have very low rates of CHD. The average LDL-C concentration among adults in the United States of America (USA) is ~123 mg dl$^{-1}$ [7]. Therefore, a majority of the population can be considered to have some increase in CHD risk due to elevation in LDL-C, which accounts, in part, for the high lifetime risk for clinical CHD in the USA: 49% for men and 32% for women [8]. When other consequences of atherosclerotic disease (e.g. stroke, peripheral arterial disease, and revascularization procedures) are considered, it becomes evident that a majority of Americans can be expected to suffer from clinical atherosclerotic disease at some time in their lives. Lifetime risk for cardiovascular disease is approximately two in three for men and one in two for women in the USA [9].
A strong linear relationship exists between the level of LDL-C and CHD risk that is independent of other major CHD risk factors. Clinical trials of interventions for lowering LDL-C have consistently shown reduced CHD events after various treatments to lower LDL-C including diet, ileal bypass surgery, and drug therapy with bile acid sequestrant and statin drugs [4]. Meta-analyses [4, 10, 11] indicate that benefits are observed in all subgroups studied, including those with or without prior evidence of atherosclerotic disease, in the presence or absence of other risk factors such as diabetes or hypertension, and at all baseline levels of lipids and lipoproteins. Recent studies suggest that the relationship between LDL-C and CHD event rate extends to LDL-C levels well below 100 mg dl$^{-1}$ (Figure 1.1), which prompted the NCEP to recommend an optional LDL-C treatment goal of $<70$ mg dl$^{-1}$ for patients at “very high risk” [12, 13].

![Figure 1.1](image)

**Figure 1.1** Low-density lipoprotein cholesterol levels and proportion of subjects with coronary heart disease events in secondary prevention trials. 4S, scandinavian simvastatin survival study; ALLIANCE, aggressive lipid-lowering initiation abates new cardiac events trial; AT, atorvastatin (10 or 80 mg); CARE, cholesterol and recurrent events trial; HPS, heart protection study; LIPID, long-term intervention with pravastatin in ischemic disease trial; P, placebo; PR, pravastatin; PROSPER, prospective study of pravastatin in the elderly at risk; PROVE-IT, pravastatin or atorvastatin evaluation and infection therapy trial; $R^2$, coefficient of determination; S, simvastatin; TNT, treating to new targets trial; UC, usual care. From Maki, K.C. et al. (2005) *The American Journal of Cardiology*, 96 (suppl 9A), 59K–64K, [13] with permission from Elsevier.
1.4 LDL-C LOWERING AND CHD RISK REDUCTION

Clinical trial results have shown that each 1% reduction in LDL-C reduces CHD event risk by roughly 1% over a period of five years. However, atherosclerotic disease develops and progresses over decades. Accordingly, trials of three to six years may be insufficient to demonstrate the full benefit of LDL-C lowering. Evidence from observational studies suggests that the benefits may be larger if reduced LDL-C concentrations are maintained over an extended period. For example, Cohen et al. [14] studied the effects of mutations in a protease gene involved in LDL receptor degradation on LDL-C levels and CHD events in the Atherosclerosis Risk in Communities study. They found that a version of the mutation that was associated with a 28% lower LDL-C level was also associated with a remarkable 88% reduction in the incidence of CHD. Another mutation that was associated with a 15% lower level of LDL-C was associated with a 47% reduction in the incidence of CHD. These findings, as well as inter-country comparisons,

![Figure 1.2](image)

**Figure 1.2** Effects of low-density lipoprotein cholesterol (LDL-C) reduction and length of treatment on the difference from placebo in ischemic heart disease events based on a meta-analysis of 50 trials of lipid modification with at least one year of treatment. Adapted from Law, M.R. et al. (2003) *British Medical Journal*, 326, 1423–30 [10] with permission from BMJ Publishing Group.
OTHER ATHEROGENIC LIPOPROTEINS

suggest that each 1% lowering of LDL-C might produce a 2–3% reduction in CHD risk if maintained over an extended period [2]. Clinical trial results provide some support for this concept, in that they have generally shown greater risk reduction with longer treatment (Figure 1.2), although few trials have extended beyond six years, limiting the conclusions that can be drawn from the available data.

In the past a great deal of debate has surrounded the question of how aggressively LDL-C should be managed in elderly patients. One reason for this was that the relative risk increase for an elevated level of LDL cholesterol in epidemiological studies was smaller in the elderly than in younger subjects. However, the benefits of preventive therapies depend not only on the relative risk reduction that can be achieved, but also on the absolute risk of the individual for the event. For example, if the relative risk reduction associated with a 30% lowering of LDL-C in a younger individual is 30%, but only two-thirds of that (20%) in an elderly individual, the absolute risk reduction is larger for the older patient because of the higher baseline risk. Average 10-year risk for a 72-year-old man in the USA is ~25%, whereas that for a 45-year-old man is ~6%. A 20% reduction for the older man reduces event risk by 5%, whereas a 30% reduction for the younger man reduces absolute event risk by only 1.8%. Therefore, the NCEP treatment goals for LDL-C apply across the age spectrum in adults.

1.5 OTHER ATHEROGENIC LIPOPROTEINS:
ATHEROGENIC REMNANTS

While the data supporting the relationship between increased LDL-C and CHD risk are extremely well established, other atherogenic lipoproteins also appear to contribute to CHD risk. For years it has been recognized that elevated levels of triglycerides were associated with increased CHD incidence. However, because the triglyceride concentration varies substantially from day-to-day and hypertriglyceridemia is associated with a number of other risk factors including depressed levels of HDL-C; small, dense LDL particles; and increased levels of inflammatory and hemostatic markers, determining the independent contribution of elevated triglycerides to CHD risk was difficult. In recent years it has become clear that remnants of triglyceride-rich lipoproteins, including VLDL, intermediate-density lipoprotein (IDL), and chylomicron remnant particles, are atherogenic. Although technology exists to measure remnant particles, or the lipids carried by such particles, these are mainly research tools. In clinical practice, the VLDL-C concentration may be used as an indicator of the circulating level of atherogenic remnants and a target for modification.
In patients with triglyceride levels $<200 \text{ mg dL}^{-1}$, a large majority of the cholesterol carried by atherogenic particles is carried by LDL particles. Therefore, the primary therapeutic strategy is to maintain LDL-C at an acceptable level for the patient’s CHD risk status. However, when the triglyceride level is elevated ($\geq 200 \text{ mg dL}^{-1}$), levels of atherogenic remnants are also increased, thus the LDL-C level alone does not fully account for the burden of circulating atherogenic particles.

Non-HDL-C is calculated as the difference between the total and HDL-C concentrations. It represents all of the cholesterol carried by potentially atherogenic particles containing apolipoprotein B, including LDL, VLDL,
LDL, lipoprotein(a), and chylomicron remnant particles. The level of non-HDL-C is highly correlated with the apolipoprotein B concentration, and, like apolipoprotein B, has been found to be a better predictor of cardiovascular mortality than LDL-C (Figure 1.3) [15]. Accordingly, the NCEP ATP III recommended non-HDL-C goals as secondary targets for treatment in patients with elevated triglycerides (≥200 mg dl\(^{-1}\)). As discussed in Chapter 3, the non-HDL-C goal is 30 mg dl\(^{-1}\) above the LDL-C goal for each risk category. Thus, although the triglyceride level is used for classification, treatment goals focus on reductions in lipoprotein cholesterol levels (LDL-C and VLDL-C) rather than on triglycerides per se.

### 1.6 HDL-C AND CHD RISK

Population studies have consistently shown a strong inverse correlation between HDL-C and CHD risk. Each decrement of 1% in HDL-C is associated with an increase of 2–3% in CHD event rate. Evidence from animal studies and from genetic conditions associated with low or high circulating levels of HDL or HDL-C suggests that these particles may play a direct role in atherogenesis. HDL particles are involved in “reverse cholesterol transport,” acting to remove cholesterol from peripheral tissues, including foam cells in the arterial wall, and delivering it to the liver for excretion, either directly or via transfer to other lipoproteins (VLDL and LDL).

Although the weight of the evidence suggests that HDL particles are directly antiatherogenic, the mechanisms by which they exert their effects are only partially understood (see Chapter 7 for further discussion). Unlike LDL, no drugs have been tested in outcomes studies that markedly alter the HDL concentration without concomitant effects on other lipoproteins (VLDL and LDL). However, multivariate statistical analyses of results from clinical trials suggest that increases in HDL-C induced by some lipid drugs such as statins and fibrates do contribute to the observed reductions in cardiovascular event rates [4].

Several mechanisms exist through which the HDL-C or HDL particle concentration can be increased, but it is not certain that all will be beneficial. Moreover, the HDL-C concentration is strongly associated with levels of other risk factors such as triglycerides, remnant lipoproteins and small, dense LDL particles. Therefore, the degree to which a reduced HDL or HDL-C level is contributing directly to CHD risk still remains unclear. A low HDL-C concentration (<40 mg dl\(^{-1}\)) is counted as a major CHD risk factor for risk stratification, and as a component of the Metabolic Syndrome (<40 mg dl\(^{-1}\) for men, <50 mg dl\(^{-1}\)L for women) in the NCEP recommendations. Therapeutic efforts to raise HDL-C are via non-drug and drug therapies are advocated for those with low levels, particularly weight loss, increased physical activity, and smoking cessation, where appropriate.
However, the ATP III did not establish HDL-C treatment goals. Risk stratification and identification is covered in detail in Chapter 4.

1.7 TRENDS IN LIPIDS AND LIPID MANAGEMENT IN THE USA

The results of the Lipid Research Clinics Coronary Primary Prevention Trial were published in 1984, which provided the first clear evidence from a randomized clinical trial that lowering the circulating cholesterol level results in a reduction in CHD events [16]. The ATP I recommendations from the NCEP were published in 1988, followed by ATP II in 1993 and ATP III in 2001. A national survey of lipid management in clinical practice called the Lipid Treatment Assessment Program was conducted in 1996 and 1997. Despite the fact that the survey focused on physicians who were high prescribers of lipid-altering drug therapies, the results showed that only 38% of patients overall had achieved their target LDL-C concentration and that only 18% of those with CHD had an LDL-C concentration of 100 mg dl$^{-1}$ or less, as recommended by the ATP II guidelines [17].

Data from the National Health and Nutrition Examination Surveys show that the average serum cholesterol level among men and women 60–74 years of age in the USA declined by more than 9% between the 1976–1980 and 1999–2002 surveys [7]. The fall in average cholesterol level was much larger during this period among older individuals than among younger participants (<40 years), who showed declines of 2–4%. This decline was likely due to a combination of lifestyle changes (e.g. less consumption of saturated fat and cholesterol) and greater use of cholesterol-lowering drug therapies. Between the 1988–1994 and 1999–2002 surveys, the fraction of men 60–74 years of age who reported use of a cholesterol-lowering medication increased from 6.8 to 24.3%. The corresponding numbers for women were 8.7 and 21.6%, respectively. The expanded use of cholesterol-lowering drug therapy corresponded with a period when data from large, randomized clinical trials of lipid-altering interventions, particularly statin drugs, were rapidly accumulating.

1.8 THE NATIONAL CHOLESTEROL EDUCATION PROGRAM EVALUATION PROJECT USING NOVEL E-TECHNOLOGY (NEPTUNE) II SURVEY

In 2003, the NEPTUNE II survey was conducted as a follow-up to the Lipid Treatment Assessment Program. This national survey of patients receiv-
ing lipid management from physicians who were high prescribers of lipid-altering drugs showed that 67% of the 4885 subjects had achieved their LDL-C treatment goal, including 62% of those with CHD [18]. These rates of treatment success compared favorably with those from 1997 (38 and 18%, respectively) [17]. However, despite the fact that the survey only included patients of physicians who were high prescribers of lipid-altering medications, and therefore likely to have been managing lipids more effectively than average, several gaps existed between the NCEP ATP III recommendations and what was achieved in practice.

Treatment success was strongly related to risk category (Figure 1.4) [18]. Most subjects (89%) with 0–1 risk factor (LDL-C goal <160 mg dl\(^{-1}\)) had achieved their LDL-C goal, whereas only 57% of those with CHD or risk equivalents had achieved their treatment target (LDL-C <100 mg dl\(^{-1}\)). Subjects with triglycerides ≥200 mg dl\(^{-1}\) were less likely to have achieved their LDL-C target in each risk category. The percentage of subjects who had achieved both their LDL-C and non-HDL-C targets was lower still.

![Figure 1.4](image.png)

**Figure 1.4** Percentage of subjects at their National Cholesterol Education Program Adult Treatment Panel III treatment goals according to risk category for all subjects and the subset with triglycerides >200 mg dl\(^{-1}\) in the National Cholesterol Education Program Evaluation Project Utilizing Novel E-technology (NEPTUNE) II survey. LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; RE, risk equivalent. Adapted from Davidson, M.H. *et al.* (2005) *The American Journal of Cardiology*, 96, 556–63 [18] with permission of Elsevier.
Notably, only 27% of those with CHD and risk equivalents had achieved their LDL-C and non-HDL-C targets.

Factors associated with a greater likelihood of goal achievement included older age, a greater number of major CHD risk factors, use of drug therapy, use of a high efficacy statin (simvastatin or atorvastatin) and treatment by a subspecialist (cardiology or endocrinology) [18]. In contrast, minority ethnicity, female sex (CHD and risk equivalents category only), current smoking and presence of a non-CHD risk equivalent (diabetes, non-CHD atherosclerosis, or multiple risk factors producing an estimated 10-year CHD risk >20%) were associated with a lower likelihood of goal achievement [18–20]. In addition, fewer than 10% of subjects were taking more than one lipid medication (70% of subjects were on statin monotherapy), which is nearly identical to the prevalence of combination drug use in the Lipid Treatment Assessment Program.

These findings suggest that aspects of the NCEP recommendations that are new to ATP III have not been fully assimilated into clinical practice (e.g. non-HDL-C goals and CHD risk equivalents). They also indicate that women, minorities and smokers are at increased risk for insufficient lipid management and clinicians should target these groups for more aggressive therapy. Furthermore, in light of new evidence showing that the benefits of lipid therapy extend to levels of LDL-C <100 mg dl\(^{-1}\), the NCEP has issued new, more aggressive (but optional) treatment targets [12]. It appears likely that use of high-dose statin and multi-drug therapy will need to expand in order to achieve these more aggressive goals. It is notable that 75% of subjects in the NEPTUNE II study who were in the CHD and risk equivalents category would qualify as “very high risk” and thus be eligible for an optional LDL-C treatment target of <70 mg dl\(^{-1}\).^1

**CONTROVERSY**

**SHOULD A MEASURE OF ATHEROGENIC LIPOPROTEIN PARTICLE NUMBER BE USED IN RISK ASSESSMENT AND/OR TO EVALUATE THE RESPONSE TO LIPID THERAPY?**

In recent years it has become apparent that lipoproteins other than LDL have atherogenic potential. Triglyceride-rich lipoproteins such as VLDL, IDL, and chylomicron remnants have been found to contribute to the development and progression of atherosclerotic plaques in animal models. Furthermore, conditions associated with elevated levels of remnant lipoproteins in the absence of increased LDL-C
(e.g. familial dysbetalipoproteinemia) are associated with increased risk for CHD. These findings prompted the NCEP ATP III to establish non-HDL-C as a secondary target for treatment. Non-HDL-C correlates strongly with the circulating concentration of Apo B and represents the cholesterol carried by all types of potentially atherogenic particles, including LDL, lipoprotein(a), and triglyceride-rich lipoproteins.

Since each potentially atherogenic particle contains only one molecule of Apo B, the Apo B concentration provides a measure of the number of circulating particles with atherogenic potential. Some Apo B-containing particles may be more atherogenic than others. For example, LDL particles may be more atherogenic than VLDL particles and smaller, denser LDL particles may be more atherogenic than larger, more buoyant LDL particles. However, the gradient of atherogenicity of Apo B containing particles has not been fully quantified and is the subject of considerable debate (see Chapter 6 for more detail regarding this issue). Nevertheless, several studies have shown that Apo B or non-HDL-C predict CHD events better than LDL-C, particularly when the triglyceride concentration is elevated, lending support to the concept that the number of circulating atherogenic particles is a more precise indicator of dyslipidemia-associated CHD risk than LDL-C [1].

An additional consideration is the influence of drug therapy on lipoprotein cholesterol levels, as compared to the number of circulating atherogenic particles. Figure 1 shows the effects of statin therapy on LDL-C, non-HDL-C, and Apo B concentrations during a large clinical trial, expressed as population percentiles [2]. All three variables had baseline values above the 85th percentile. During statin treatment the mean values for LDL-C and non-HDL-C dropped to roughly the 25th percentile. However, the mean Apo B level was still above the 50th percentile. Thus, statin therapy lowered cholesterol levels relatively more than it lowered the number of atherogenic particles.

A similar conclusion has been reached when the number of LDL particles (LDL-P) was examined with nuclear magnetic resonance in subjects with type 2 diabetes who had LDL-C <100 mg dl$^{-1}$ (most of whom were likely receiving lipid drug therapy). An LDL-C value of 100 mg dl$^{-1}$ represents approximately the 25th percentile in the US population. Nearly one-quarter (23.7%) of these individuals with LDL-C in the bottom quartile for the population had an LDL-P concentration that was above the 50th percentile (1300 nmol l$^{-1}$) [3].
Figure 1 Effects of statin therapy on low density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apo B) concentrations, expressed as population percentiles in the Atorvastatin Comparative Cholesterol Efficacy and Safety Study. Reprinted from Sniderman, A.D. et al. (2003) Lancet, 361, 777–80 [2] with kind permission of Elsevier.

Taken together, these results suggest that using non-HDL-C and LDL-C levels to evaluate the effects of treatment can lead to an over-estimation of the degree to which atherogenic particle concentration has been reduced. This raises the possibility that using Apo B or LDL-P responses would provide the clinician with a better indication of the degree of risk reduction than relying on lipoprotein cholesterol levels (LDL-C and non-HDL-C). Of course, using either of these tests entails added expense and complexity.

The questions of whether use of apolipoproteins or measurements of particle concentrations add predictive value to risk assessment has been addressed in several recent studies [4–6]. The results have uniformly supported greater predictive ability of measures of particle number compared with lipoprotein levels. However, the degree to
which these tests add discriminatory value to the recommended methods of risk assessment (e.g. the Framingham risk score) is minimal, suggesting that the additional cost associated with these tests cannot currently be justified with regard to risk stratification [7]. Whether greater treatment efficacy can be achieved by using indicators of atherogenic particle number rather than cholesterol levels to guide treatment decisions remains an open question. Clinical trials to test this hypothesis are urgently needed. The authors are optimistic that using Apo B or LDL-P responses to guide treatment might prove superior to using lipoprotein cholesterol targets. If so, this would have important implications for clinical lipid management.

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