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Review Articles

A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality

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Abstract: Cardiovascular (CV) disease is a leading cause of death worldwide, accounting for approximately 31.4% of deaths globally in 2012. It is estimated that, from 1980 to 2000, reduction in total cholesterol accounted for a 33% decrease in coronary heart disease (CHD) deaths in the United States. In other developed countries, similar decreases in CHD deaths (ranging from 19%–46%) have been attributed to reduction in total cholesterol. Low-density lipoprotein cholesterol (LDL-C) has now largely replaced total cholesterol as a risk marker and the primary treatment target for hyperlipidemia. Reduction in LDL-C levels by statin-based therapies has been demonstrated to result in a reduction in the risk of nonfatal CV events and mortality in a continuous and graded manner over a wide range of baseline risk and LDL-C levels. This article provides a review of (1) the relationship between LDL-C and CV risk from a biologic, epidemiologic, and genetic standpoint; (2) evidence-based strategies for LDL-C lowering; (3) lipid-management guidelines; (4) new strategies to further reduce CV risk through LDL-C lowering; and (5) population-level and health-system initiatives aimed at identifying, treating, and lowering lifetime LDL-C exposure.

Introduction

Cardiovascular (CV) disease is the leading cause of mortality worldwide, accounting for 31.4% of deaths in 2012.[1] In developed countries, age-adjusted CV mortality rates are declining, but CV disease remains the leading cause of mortality due to rapid aging of the population. In low-income to middle-income countries, both age-adjusted CV mortality rates and aging of these populations are contributing to a rapid increase in CV mortality.[2] Data from 2010 demonstrate that CV disease accounted for 31.9% of US deaths, with ischemic heart disease and stroke accounting for the vast majority (total 27.6%; 21.1%, and 6.5%, respectively). In the United States, the resultant direct and indirect annual costs were estimated to be $240.9 billion.[3,4]

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The global cost of CV disease was estimated to be $863 billion in 2010, with a 22% increase expected by 2030.[5]

A large, worldwide study found that among all modifiable risk factors, abnormal lipid levels were associated with the highest population attributable risk (approximately 50%) for the occurrence of myocardial infarction (MI; Table 1).[6]

This is due to their prevalence and strong, independent association with the risk of MI. In western countries, lifestyle interventions and evidence-based therapies, including those focused on hypercholesterolemia, have led to a reduction in CV risk on a population level. In a series of studies covering the 1980 to 2010 time period in the United States, Canada, and Europe (Table 2), it was estimated that 19%–46% of the total reduction in the rate of coronary heart disease (CHD) mortality was explained by a reduction in total cholesterol levels attributed to lifestyle changes and pharmacologic treatment.[7–16]

Low-density lipoprotein cholesterol (LDL-C) has now largely replaced total cholesterol as the primary lipid measurement for evaluation of risk due to atherogenic lipoproteins. LDL-C is a measure of the total cholesterol content of LDL particles, reflecting both the number of LDL particles and their individual cholesterol content. Most current guidelines include LDL-C as a primary target for initiating and adjusting lipid-lowering interventions.[17–20]

In addition, more effective and/or scalable LDL-C reduction strategies are under investigation for risk reduction in both primary and secondary prevention. This article provides a review of (1) the relationship between LDL-C and CV risk from a biologic, epidemiologic, and genetic standpoint; (2) evidence-based strategies for LDL-C lowering; (3) lipid-management guidelines; (4) new strategies to further reduce CV risk through LDL-C lowering; and (5) population level and health-system initiatives aimed at identifying, treating, and lowering lifetime LDL-C exposure.

Table 1 Population attributable risk for the incidence of acute MI for modifiable risk factors*

Risk factor	Population attributable risk (%)‡
Abnormal lipids†	49.2
Tobacco consumption (current smoker)	35.7
Psychosocial	32.5
Abdominal obesity	20.1
Hypertension	17.9
Diet (lack of daily vegetable and fruits)	13.7
Physical activity	12.2
Diabetes	9.9
Alcohol intake	6.7

Apo, apolipoprotein.
*Based on the INTERHEART study by Yusuf et al., 2004.[6]
†Estimated by apoB/apoA1 ratio (fifth quintile compared to first).
‡Population attributable risk percentages do not add up to 100% for a combination of risk factors, because an MI can be simultaneously attributed to >1 risk factor and thus be counted twice.

Relationship between LDL and CV risk

Cholesterol is circulated in the body's aqueous extracellular environment by 5 major types of lipoprotein (chylomicrons, very low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL], LDL, and high-density lipoprotein [HDL]). The liver serves as the key organ for cholesterol metabolism and regulation of plasma levels of cholesterol. The process of LDL formation begins when intrahepatic cholesterol, either from gut absorption or *de novo* synthesis, is repackaged by the liver (along with proteins, triglycerides, and phospholipids) into VLDL. VLDL then enters the circulation and is converted by lipoprotein lipase and cholesteryl ester transfer protein (CETP) into more cholesterol-enriched species, first IDL and then LDL. The liver regulates the concentration of these circulating lipoprotein species primarily by their clearance through LDL receptors on the hepatic surface.[21]

Circulating LDL particles are able to penetrate the endothelium of arterial walls and become oxidized, promote inflammation, and drive injury to the overlying endothelium and surrounding smooth muscle cells.[22] Persistent elevations in circulating LDL-C have been directly linked to progression from early-stage fatty streaks to advanced-stage, lipid-rich plaques. For example, LDL receptor-deficient mice (i.e., unable to clear LDL from the circulation) have elevated LDL-C and consequently develop severe atherosclerosis.[23] Conversely, mice with virtually no LDL-C do not develop atherosclerosis irrespective of diet and other CHD risk factors.[24]

Epidemiologic investigations have validated LDL-C as an independent predictor of CV risk. The Framingham Heart Study demonstrated that men and women were >1.5 times more likely to develop clinically significant CHD if their LDL-C was >160 mg/dL compared to a reference population with LDL-C <130 mg/dL.[25] In the Atherosclerosis Risk in Communities (ARIC) study, the risk of an incident CHD event was elevated by approximately 40% for every 39 mg/dL incremental increase in LDL-C.[26]

Genetic analyses have demonstrated that a number of single-nucleotide polymorphisms (SNPs) are associated with LDL-C and CV risk. A study by Willer et al. demonstrated that SNPs of genes such as *PCSK9*, *APOE*, *APOB*, and *LDLR* that result in elevated LDL-C are also associated with elevated CV risk.[27] Another study by Kathiresan et al. demonstrated that specific SNPs of genes such as *PCSK9, APOE, APOB, HMGCR,* and *LDLR* result in decreased LDL-C and are associated with decreased CV risk.[28] These associations have been validated in other investigations.[29–32]

Genetic studies suggest that CV risk is associated not just with the absolute concentration of LDL-C but also with the duration of exposure. Certain genetic mutations