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Atherosclerosis and cholesterol: What we should know

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ABSTRACT

Epidemiological studies consistently link high low-density lipoprotein cholesterol (LDL-C) levels with an increased risk in cardiovascular disease. This correlation remains strong across various populations. LDL-C plays a key role in atherosclerosis by transporting cholesterol to arterial walls, where it induces plaque formation. Lowering LDL-C levels has proven to reduce the risk of coronary heart disease, regardless of the drug used. Although high-density lipoprotein cholesterol (HDL-C) has long been considered protective, recent studies have suggested that increasing HDL-C alone may not reduce cardiovascular risk and that the function of HDL may be relevant, rather than the HDL-C plasma level. Genetic studies, such as Mendelian randomisation, have confirmed that LDL-C is a causal factor for heart disease. Triglyceride levels, which are transported by lipoproteins, also contribute to cardiovascular risk, although lowering apolipoprotein B is considered more crucial for reducing cardiovascular events. Overall, lowering LDL-C levels remains the cornerstone of cardiovascular disease prevention and treatment.

Keywords
Cholesterol; atherosclerosis; low-density lipoprotein; lipid-lowering

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Epidemiological studies have consistently shown a strong association between elevated LDL-C levels and increased cardiovascular risk. The well-established relationship between plasma cholesterol levels and the risk of cardiovascular events is continuous, regardless of whether total cholesterol or its fractions, such as LDL-C, are considered.

When analysing plasma cholesterol levels and integrating data from several studies, including the Pooling Project, the Framingham Heart Study and the Israeli Perspective Study, a consistent association between serum cholesterol levels and coronary events was confirmed worldwide [1]. This pattern was particularly clear in the Seven Countries Study, in which the relative risks of coronary heart disease (CHD) mortality as a function of serum cholesterol levels were similar in the different cohorts studied, although the absolute risks were different [2]. The observed differences in risk between different populations are largely attributable to baseline risk values, suggesting that other factors, such as diet, may play an important role. The Framingham Heart Study has shown that its results are applicable in any country when adjusted for baseline risk, suggesting a universal pattern in the relationship between cholesterol levels and cardiovascular risk. This has led to debate because the relationship has been oversimplified and presented as linear when it is not so in absolute terms. For example, a 0.5 mmol/L (about 20 mg/dL) increase in total cholesterol correlates with a 12% relative increase in CHD mortality risk. Consistent with this observation, data from the Cholesterol Treatment Trialists' (CTT) Collaboration showed that lowering low-density lipoprotein cholesterol (LDL-C) by 1 mmol/L reduces the risk of coronary heart disease by 22-23%, which is consistent with data from clinical trials [3]. A collaborative meta-analysis of ~900,000 individuals in 61 prospective observational studies has shown that age significantly attenuates the proportional (relative) relationship between ischemic heart disease (IHD) mortality and cholesterol levels. However, cholesterol level is a strong positive risk factor for IHD mortality not only in early middle age but also in old age. Although the proportional differences in risk decrease with age, the absolute impact of cholesterol levels on annual mortality from IHD is much greater at older ages than at younger ages [4].

In summary, extensive research confirms that cholesterol is a determinant of cardiovascular risk that is consistently observed in different populations and age groups. This understanding is crucial for the development of public health strategies and individualised treatment plans.

Cholesterol is essential for cell function, as it is an essential component of all cell membranes. It co-operates with fatty acids and phospholipids to regulate membrane fluidity. Cholesterol clusters in the membranes are crucial for the localisation of receptors, including

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the LDL receptor (LDLR), in specific regions (coated pits). These areas of the cell surface are crucial for the recruitment of receptors, their ability to interact and cellular responses. Cholesterol is also crucial for the function of internal membranes, such as those of mitochondria, endosomes, and lysosomes. The body's need for cholesterol is emphasised by its ability to acquire it either from the outside, via the LDLR on hepatocytes and enterocytes, or from the inside via the mevalonate pathway. These pathways are interconnected; increased dietary cholesterol intake reduces endogenous synthesis, and vice versa. Contrary to popular belief, lowering plasma cholesterol to very low levels does not pose a biological risk, as the body can synthesise sufficient cholesterol for cell division and brain development.

When referring to plasma cholesterol, we are talking about the lipoproteins that transport cholesterol mainly in esterified form and not free cholesterol molecules. Lipoproteins carrying cholesterol, especially apoB-containing lipoproteins, are atherogenic (5). Their ability to penetrate and become trapped within the arterial wall initiates a cascade of atherosclerotic processes. Lowering LDL-C levels decreases the number of these lipoproteins and thus lowers the risk of plaque formation and progression. Remnants of lipoproteins, including very low-density lipoproteins (VLDL) and chylomicrons, also play a role in cholesterol transport and metabolism, with VLDL remnants eventually transforming into LDL.

The formation of foam cells by accumulation of excess cholesteryl esters is a key process in the initial stage of lesion development, particularly related to vascular permeability [6]. This early stage does not necessarily lead to immediate progression of the lesion. Studies conducted on young American soldiers who died in Vietnam showed numerous fatty streaks that do not always correspond to later plaque development sites. This suggests a dynamic process in the early stages, where plaques do not necessarily form at the sites of initial lipid deposition, allowing for possible damage reversal. Lowering LDL-C levels has been shown to induce plaque regression, a process in which there are significant changes in plaque composition, including a marked decrease in lipid content and an increase in the thickness of the fibrous cap (which is considered inert with respect to inflammatory activity).

LDL is a causal factor in atherosclerosis, not cholesterol itself [7]. This distinction is crucial because the role of LDL in transporting cholesterol to the arterial walls is what initiates the damage. In contrast, HDL (high-density lipoprotein), which also transports cholesterol, is not causal. Conversely, a low level of HDL-C is associated with a higher risk of cardiovascular events. However, the causal relationship between HDL-C and cardiovascular risk is more complex and less well understood than that for LDL-C. Genetic studies and clinical trials have challenged the notion that simply increasing HDL-C levels pharmacologically reduces cardiovascular risk, suggesting that HDL functionality may be more important than HDL-C levels alone [8]. Surprisingly, extremely high HDL-C levels have been associated with higher cardiovascular risk [8] casting several doubts on the antiatherogenic role of HDL and determined by the measurement of HDL cholesterol or apo A-I.

Genetic studies, including Mendelian randomisation analyses, have provided compelling evidence for the causal role of LDL-C in atherosclerosis and cardiovascular disease [7]. Individuals with genetic mutations that result in lower lifelong LDL-C levels, such as those affecting the *PCSK9* or *HMGCR* genes, have a significantly lower risk of CAD, supporting the concept that LDL-C is a causal factor in the development of atherosclerotic disease. Different genetic scores predicting a 10 mg/dL reduction in LDL-C show consistent lifelong benefits [9]. This suggests that the mechanism of LDL-C lowering, whether by statins or PCSK9 inhibitors, leads to similar outcomes. Therefore, it is the lowering of LDL-C levels that is crucial, regardless of the method used. These findings are confirmed by clinical trials of LDL-C-lowering therapies, which consistently show that reducing LDL-C levels reduces the incidence of cardiovascular events. To date, clinical trials have shown that lowering LDL-C to very low levels is associated with a further CV risk reduction with no association with excess adverse events [10].

Genetic studies, Mendelian randomisation, and clinical trials involving patients with familial hypercholesterolemia (FH) have demonstrated that cholesterol trajectories can be altered [11]. In a typical population, average cholesterol levels eventually reach a threshold where clinical disease manifests. Not surprisingly, in individuals with heterozygous FH, higher cholesterol levels from birth accelerate the progression of the disease. Early intervention to reduce LDL-C can significantly alter this trajectory, suggesting that early and sustained LDL-C reduction has a profound impact on delaying disease onset. This concept is clearly illustrated in homozygous FH, where lowering LDL-C can extend life expectancy by approximately 25 years [11]. Randomised clinical trials, observational studies, and Mendelian randomisation studies all support the notion that prolonged exposure to lower LDL-C levels accrues greater cardiovascular benefits. For instance, a lifelong LDL-C reduction of 0.3 mmol/L (10-12 mg/dL) can achieve the same cardiovascular risk reduction seen in five years of statin therapy, and this can be obtained through moderate lifestyle changes.

Triglycerides (TG) have been identified as an independent risk factor for cardiovascular disease. TG are transported by lipoproteins, mainly chylomicrons and very low-density lipoproteins (VLDL) as well as their remnants. Remnant lipoproteins are considered atherogenic, functioning similarly to LDL in terms of their pathological impact [12]. The distribution of the so-called "remnant cholesterol" is closely linked to TG levels, which makes its use as an independent marker difficult.

Mendelian randomisation studies support the causal role of remnant cholesterol in cardiovascular disease [13]. However, intervention studies specifically targeting triglycerides are limited. Lowering TG through LPL-targeted pathways, including ANGPTL3, APOC2, APOC3, and APOE, however has shown potential in observational and genetic studies. Despite numerous trials with fibrates (drugs that reduce mainly plasma TG) showing overall negative results, subgroups with high TG and low HDL-C had benefits, suggesting that targeting this subgroup may be effective. The debate on whether apoB is a more meaningful marker than TG continues. In a study that assessed the impact of genetic scores for LPL and LDL, the association of different genetic variants with apoB concentrations resulted in a log-linear relationship with the risk of coronary heart disease, establishing apoB as a reliable indicator that includes the contributions of both LDL-C and TG [9]. This suggests that the number of particles is the most accurate proxy for measuring disease causation.

This hypothesis is supported by the PROMINENT trial of pemafibrate in an ideal population (high TG, low HDL, diabetes, cardiovascular disease) [14]. Despite reductions in remnant cholesterol and TG, there was no change in apoB levels, suggesting that apoB is the primary driver of the clinical benefit. This highlights the importance of lowering apoB as opposed to simply lowering other lipid parameters. This concept is further reinforced by comparing the results of the STRENGTH and REDUCE-IT trials with omega-3 fatty acids [15, 16]. Although both trials showed a decrease in TG, only the REDUCE-IT trial showed a reduction in apoB, suggesting that the therapeutic benefit is related to apoB reduction.

In summary, apoB-containing lipoproteins fulfil the criteria for causal involvement in atherosclerosis. Lowering apoB levels is critical

even with delayed intervention, although the effects may not be fully reversible.

Conclusion

The relationship between LDL-C and cardiovascular risk is well-established and supported by a wealth of epidemiological, genetic, and clinical trial data (**Figure 1**). Elevated LDL-C is a major causal factor in the development of atherosclerosis and cardiovascular disease, and interventions that lower LDL-C levels consistently reduce the risk of cardiovascular events. While the role of HDL-C in cardiovascular risk remains less clear, lowering LDL-C levels remains a cornerstone of cardiovascular disease prevention and treatment. As research advances, further insights into cholesterol metabolism and its impact on cardiovascular health may lead to new strategies for reducing the burden of cardiovascular diseases globally.

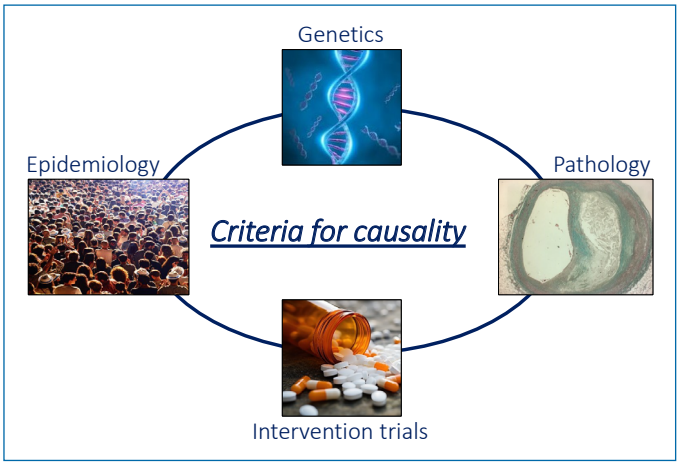

Figure 1 | LDL and atherosclerosis: Criteria for causality.

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Conflicts of interest

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