Causal Effect of Lipids and Lipoproteins on Atherosclerosis

Lessons from Genomic Studies

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KEYWORDS

• Genomics • Mendelian randomization • Lipids • LDL • Apolipoprotein B • VLDL • Triglycerides • HDL

KEY POINTS

- The causal effect of apolipoprotein B–containing lipoproteins on the risk of atherosclerotic cardiovascular disease (ASCVD) depends on both the absolute magnitude and total duration of exposure to those particles.
- The clinical benefit of lowering low-density lipoproteins (LDLs) is determined by the absolute reduction in circulating LDL particles (measured by apolipoprotein B [apoB]) rather than the reduction in cholesterol carried by those particles (measured by LDL cholesterol).
- The clinical benefit of lowering triglycerides is determined by the absolute reduction in circulating very low-density lipoproteins (VLDLs) and remnant particles (measured by apoB) rather than the reduction in triglycerides carried by those particles.
- Because atherosclerosis is caused by the retention of apoB-containing lipoproteins within the artery wall rather than the cholesterol content carried by those particles, high-density lipoprotein–mediated efflux of cholesterol from the artery wall may not reduce the risk of atherosclerosis.

INTRODUCTION

The apolipoprotein B (apoB)-100–containing lipoproteins, the vast majority of which are low-density lipoproteins (LDLs), carry cholesterol esters from the liver to the peripheral cells, whereas apolipoprotein A1-containing high-density lipoproteins (HDLs) carry excess cholesterol from the peripheral cells back to the liver.[1] The apoB-containing non-HDLs less than 70 nm in diameter freely flux across the arterial wall endothelial membrane, where they may interact with proteoglycans to become retained within the arterial wall, leading to the initiation and progression of atherosclerotic plaques.[2] By contrast, the apolipoprotein A1-containing HDL particles do not become retained but instead can efflux cholesterol from lipid-laden macrophages within the arterial wall and, therefore, can potentially decrease the progression of atherosclerosis and reduce the risk of atherosclerotic events.[3]

Consistent with this proposed mechanism for atherosclerosis, numerous epidemiologic studies have reported a strong, consistent, and dose-dependent association between increasing concentrations of plasma LDL cholesterol (LDL-C) and an increasing risk of atherosclerotic cardiovascular disease (ASCVD) and a similarly strong, consistent, and dose-dependent inverse association between increasing concentrations of plasma HDL cholesterol (HDL-C) and a decreasing risk of ASCVD.[4]

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Multiple randomized trials have demonstrated that lowering LDL-C by reducing LDL particles through up-regulation of hepatic LDL receptors with statins, ezetimibe, and PCSK9 inhibitors reduces the risk of atherosclerotic events proportional to the absolute reduction in LDL-C concentration.[5–7] By contrast, therapies that reduce LDL-C through mechanisms other than up-regulation of the LDL receptors have failed to consistently demonstrate a reduction in clinical events in randomized trials, thus raising the possibility that the clinical benefit of lowering LDL-C may depend on how LDL-C is lowered.[8,9] Similarly, therapies that predominantly lower triglyceride levels or increase HDL-C levels have also failed to consistently reduce the risk of cardiovascular events in randomized trials, thus raising the possibility that these lipids may not be causally related to the development of atherosclerosis.[10–15]

In this article, evidence from mendelian randomization studies is evaluated to assess the causal effect of various lipids and lipoproteins on the risk of ASCVD to help inform the interpretation of randomized trials and to make inferences about which therapies are most likely to reduce the risk of ASCVD events.

MENDELIAN RANDOMIZATION

A mendelian randomization study is an explicit attempt to introduce a randomization scheme into an observational study to assess whether an observed association between an exposure and an outcome is likely to be causal.[16] These studies use genetic variants that are associated with the exposure of interest as a proxy for higher or lower levels of the exposure. Because allocation of genetic variants is approximately random and occurs at conception, this study design should be less susceptible to confounding, reverse causation, and other forms of bias that can limit the validity of observational studies, thus permitting inferences to be made about causality.

Perhaps the most intuitive way to explain the concept of mendelian randomization is by way of analogy with a randomized trial. For example, numerous genetic variants are associated with lower LDL-C. Each of these variants is inherited approximately randomly at the time of conception in a process sometimes referred to as mendelian randomization. Therefore, inheriting an LDL-C–lowering allele is analogous to being randomly allocated to an LDL-C–lowering therapy whereas inheriting the other allele is analogous to being randomly allocated to usual care. If allocation is random and if the variant under study is associated only with LDL-C, but not with other pleiotropic effects, then the only difference between the groups being compared should be their plasma LDL-C level. Therefore, measuring the association between LDL-C–lowering variants and the risk of risk of cardiovascular disease should provide an unconfounded estimate of the causal effect of lifelong exposure to lower LDL-C on the risk of cardiovascular disease in a manner analogous to a long-term randomized trial.[17,18]

LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Numerous genetic variants are associated with lower LDL-C.[19] Nearly all these variants are also associated with a corresponding lower risk of ASCVD, thus providing powerful naturally randomized evidence that LDL is causally associated with the risk of ASCVD.[20] There is a dose-dependent log-linear relationship between the absolute magnitude of lifelong exposure to lower LDL-C and the corresponding risk of ASCVD. This relationship is similar to the dose-dependent log-linear relationship between the absolute reduction in LDL-C and the corresponding proportional reduction in cardiovascular events observed in the statin trials. The slope of these log-linear relationships, however, is much steeper for lifelong genetically determined exposure to lower LDL-C compared with short-term pharmacologically mediated lower LDL-C, thus implying that LDL has both causal and cumulative effects on the risk of ASCVD (**Fig. 1**).[21]

The magnitude of the cumulative effect of LDL-C on the risk of ASCVD can be estimated by adjusting the effect of each genetic variant on ASCVD for a standard decrement in LDL-C and then meta-analyzing the adjusted effect estimates, using the same methods for meta-analyzing a group of statin trials. Using this method of creating a genetic LDL score, long-term exposure to each unit lower LDL-C is associated with an approximately 3-fold greater reduction in the risk of ASCVD (on the log scale) compared with short-term exposure to LDL-C started later in life. More specifically, long-term exposure to each millimole per liter lower LDL-C is associated with up to a 55% reduction in the relative risk of ASCVD whereas each millimole per liter short-term reduction in LDL-C during treatment with a statin is associated with an approximately 20% reduction in risk.[21] This finding has important public health implications because it suggests that, for lowering LDL-C, both “lower is better” and “earlier is better.” The apparent reduced efficacy of short-term exposure compared with long-term exposure to lower LDL-C may explain much of the residual risk of ASCVD among persons treated with a statin or other lipid-lowering therapy. This observation implies that the