EDITORIAL

The Evolving Story of Triglycerides and Coronary Heart Disease Risk

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While elevated low-density lipoprotein cholesterol (LDL-C) is an established risk factor for coronary heart disease (CHD), the association between elevated triglyceride (TG) levels and CHD has been less well-defined. Many analyses have shown that adults with elevated TG levels have higher CHD risk, yet it is unclear whether TGs alone cause CHD or whether they are a surrogate for other concomitant metabolic derangements (obesity, diabetes, or other lipoprotein elements) that confer actual risk.[1,2] Some genetic variants associated with isolated lifetime increases in TGs are associated with increased CHD risk, but the degree to which this is due to TGs or other lipid-related changes, such as elevations in apolipoprotein B (ApoB) or very-low-density lipoprotein (VLDL) particles remains unknown.[3] Furthermore, clinical trials of TG lowering with fibrates have shown mixed results.[4,5]

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The apparent inconsistency in the association between TGs and CHD should not be unexpected given the complexities of TG metabolism. TGs are mostly found in chylomicrons, which transport dietary fatty acids and cholesterol from the intestine, and VLDL particles, which transport TGs from the liver. Serum TG measurements assess the total mass of TGs, not the number or type of particles carrying those TGs. When TG levels are elevated due to isolated elevations in chylomicrons, which are too large to enter the arterial wall, atherosclerotic risk is not increased. Beyond chylomicrons, measured TG levels can also be elevated with either an increase in the TG content of VLDL particles or an increase in the total number of VLDL particles. Thus, hypertriglyceridemia should not be considered a single disease, but rather a heterogeneous collection of disorders, with potentially different degrees of cardiovascular risk.

The importance of particle number and composition has previously been shown for LDL-C. The atherosclerotic risk conferred by a large number of small LDL particles is much higher than the risk conferred by a smaller number of large, cholesterol-enriched particles. That is, given the same overall mass cholesterol within LDL particles (measured LDL-C), a higher particle number confers greater risk. Whether the same is true for the mass of TGs and the number of VLDL particles is unclear.

In this issue of *JAMA*, Ference and colleagues[6] report findings from a series of elegant mendelian randomization analyses that help answer this and several other important questions regarding the association between TGs and CHD. The authors evaluated genetic mutations in lipoprotein lipase (LPL), a critical enzyme in TG metabolism and a target for TG-lowering therapies such as fibrates and several new drugs under development.[7,8] Genetic mutations that decrease LPL activity and increase TG levels have been associated with increased CHD risk, but the factors mediating that association have not been fully described.[9] To understand the relative association of these lipoprotein constituents and CHD risk, the authors created genetic scores for *LPL* genetic variants. For comparison, they also created genetic scores for variants in the LDL receptor (LDLR), which are associated with higher LDL-C levels and CHD risk. Medications targeting the LDLR pathway include statins and proprotein convertase subtilisin/kexin type 9 inhibitors.

In their analyses of 654 783 participants, including 91 129 cases of CHD, Ference and colleagues[6] found that *LPL* variants and *LDLR* variants were both associated with lower CHD risk. To understand how these variants affected the number and composition of lipoprotein particles, the authors also assessed their associations with ApoB levels. ApoB, a measure of particle number, is a surface molecule present in a 1:1 ratio on each VLDL and LDL particle. The LDLR pathway, associated with changes in LDL-C, lowers ApoB levels predominately via reductions in the number of LDL particles. The LPL pathway, associated with reduced TGs, lowers ApoB primarily via VLDL lowering. To compare "apples to apples," the authors evaluated the association between *LPL* and *LDLR* genetic scores and CHD risk per unit of lower ApoB. After standardizing per unit lower increment of ApoB, the associations between CHD risk and genetic variants that affected either LDLR or LPL were similar. Given the different ApoB-containing particles affected by LDLR and LPL, this finding provides some of the first evidence that VLDL particles are as atherogenic as LDL particles.

The authors extended their analysis beyond LPL and LDLR pathways by identifying a total of 168 genetic variants associated with either LDL-C or TGs. Similar to the analysis of LDLR and LPL, the relative risk reductions for CHD for these variants were similar when standardized to the degree of lower ApoB, regardless of whether the variants were associated with LDL-C levels, TG levels, or both. The authors then examined the degree to which differences in individual lipid parameters were most closely associated with CHD risk. For genetic variants associated with LDL-C, every 10-mg/dL lower level of LDL-C was associated with a 15% lower CHD risk. For TG variants, every 50-mg/dL lower level was associated with an 18% lower risk of CHD. However, after adjusting for differences in ApoB, neither LDL-C nor TGs remained

independently related to CHD risk. Thus, differences in ApoB, not changes in LDL-C or TG levels, appeared to account for the observed lower risk of CHD.

The use of ApoB as a lens through which to examine the benefit of genetic variants associated with lower LDL-C or TG levels is a biologically informed approach that helps simplify the complexity of lipid biology. This is particularly relevant for understanding TGs. Unlike LDL-C and ApoB, which are tightly correlated, many of the genetic variants identified by Ference et al[6] that were related to lower TGs had no apparent relationship with ApoB. Variants associated with TG lowering, but not ApoB lowering, likely led to either decreases in chylomicrons or the TG content of VLDL particles, rather than increases in the number of VLDL particles. Thus, ApoB appears to act as an elegant filter to identify variants that affect particle number and subsequent CHD risk.

This work helps improve understanding of why results have been mixed for trials involving TG-lowering therapies. For genetic variants associated with the LPL pathway, the magnitude of TG lowering needed to reduce ApoB was relatively large. To achieve a 10-mg/dL reduction in ApoB, the TG level must be reduced by 70 mg/dL. In comparison, the same ApoB reduction could be achieved with only a 14-mg/dL reduction in LDL-C level via LDLR. Although ApoB levels in fibrate trials have not been systematically examined, prior reviews have suggested that the variability in effects seen in fibrate trials are proportional to the degree of ApoB lowering.[10] Similarly, a meta-analysis of randomized trials of LDL-C lowering has shown that the degree of ApoB lowering most closely correlates with cardiovascular risk reduction.[11]

However, there are important limitations to the approach of Ference et al, particularly as it relates to extrapolation to treatment effects. Mendelian randomization studies examine the potential causal relationship of genetically altered exposure to lipids from birth. In contrast, individuals who are treated in a clinical trial are exposed to therapy for a significantly shorter period and often only after atherosclerotic disease has developed. As such, the magnitude of risk reduction expected in clinical trials is generally much less than observed in genetic studies. Furthermore, mendelian randomization does not account for pleiotropic, non-lipid-related effects. This is likely the case for the REDUCE-IT trial, in which adults with diabetes or cardiovascular disease and elevated TG levels on statin therapy were randomized to placebo or high-dose ω-3 oil eicosapentaenoic acid (EPA).[12] In this trial, EPA reduced the relative risk of the primary end point of cardiovascular events by 25% (absolute rates of 17.8% in the EPA group vs 22% in the placebo group). However, while EPA did lower TG levels, it had a negligible effect on ApoB (decreased by 2 mg/dL in the treatment group vs a 4-mg/dL increase in the placebo group). Thus, EPA benefits were likely due to non-TG-, non-ApoB-related, off-target effects.[12]

An additional limitation is that the authors did not investigate all potential interactions between the LDLR and LPL pathways and CHD risk, including interactions between different genetic variants and interactions by key clinical variables. For example, evidence from the FIELD trial suggested a possible interaction in TG lowering for fibrates by sex, with women achieving greater reductions in ApoB compared with men.[13] Additionally, even though the analysis by Ference et al[6] supports an association between TGs and CHD risk, particularly as it relates to changes in ApoB, the findings do not prove a direct causal link between TGs and CHD risk. When an ApoB-containing particle is trapped in the arterial wall, all of the contents of that particle, including TGs, ApoB, phospholipids, and cholesterol esters, are present.[14,15] Whether the TGs alone cause atherosclerosis, or are inert bystanders in that process, still remains to be determined.

Despite these limitations, the study by Ference et al has several important messages for scientists and clinicians. Hypertriglyceridemia should not be considered as a single entity but rather multiple conditions that vary in CHD risk based on overall particle number and composition. A simple diagnostic algorithm using total cholesterol level, TG level, and ApoB, a measure of the number of VLDL and LDL particles in circulation, can be used to categorize phenotypes of hypertriglyceridemia.[16] Elevations in TG levels that are associated with greater particle number are associated with greater CHD risk, and the relative potential benefits of TG lowering and LDL-C lowering (via genetics at least) are similar when standardized for their effects on ApoB. Barring off-target effects, treatments that lower LDL-C or TG levels should lead to reductions in CHD risk proportional to their reduction in ApoB. Given the growing body of evidence supporting the importance of ApoB, the guidelines should consider including broader measurement of ApoB as part of routine clinical care.

ARTICLE INFORMATION

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