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EAS Updates

Triglycerides and cardiovascular risk: Apolipoprotein B holds the key

Jane Stock

European Atherosclerosis Society, World Trade Center Göteborg, Mässans Gata 18, SE-41251, Göteborg, Sweden

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Low-density lipoprotein (LDL) is clearly causal in atherosclerotic cardiovascular disease (ASCVD) [1]. Landmark studies using PCSK9 inhibitors, FOURIER with evolocumab [2] and ODYSSEY OUTCOMES with alirocumab [3] have provided 'icing on the cake' proof that lowering LDL cholesterol (LDL-C) beyond current guideline goals, reduces ASCVD events [2,3]. The case for triglyceride (TG)-rich lipoproteins and their remnants as causal cardiovascular risk factors has, however, been more contentious. While there is accumulating evidence from mechanistic, epidemiologic and genetic studies supporting the atherogenicity of TG-rich lipoproteins [4], cardiovascular outcomes studies using fibrates or omega-3 fatty acids have had mixed results [5,6]. Moreover, plasma TG levels assess total TG mass and do not provide insights into the number or composition of TG-rich lipoproteins, both of which are important considerations for atherosclerotic risk, as previously shown for LDL-C.

Do Mendelian randomization approaches offer a means to address this controversy? Apolipoprotein B (apoB) is the main apolipoprotein constituent of LDL and TG-rich lipoproteins and their remnants. As each apoB-containing lipoprotein contains a single molecule of apoB, concentrations of apoB are considered to be a direct measure of the total number of atherogenic lipoproteins in the circulation. This therefore provides a rationale for standardizing comparison of the effects of TG or LDL-C lowering on cardiovascular risk.

This was the approach taken by Ference and colleagues in a recent study [7]. Briefly, this analysis included data from 654,783 subjects enrolled in the UK Biobank study to identify TG-lowering variants in the lipoprotein lipase (*LPL*) gene and LDL-C–lowering variants in the LDL receptor gene (*LDLR*) that were associated with reduction in cardiovascular risk. The *LPL* gene was selected as LPL has a key role in the metabolism of TG-rich lipoproteins, by hydrolysing the TG core of circulating TG-rich lipoproteins such as chylomicrons and very low density lipoproteins (VLDL). Thus, the LPL pathway lowers apoB mainly by lowering VLDL. On the other hand, the LDL receptor, which is critical to regulation of circulating LDL-C levels, mainly lowers apoB by reducing the number of LDL particles in the circulation.

The genetic variant data were used to construct genetic scores for *LPL* (including five independently inherited variants) and *LDLR* (including three independently inherited variants) that were associated with coronary heart disease (CHD) risk. For each 10 mg/dL decrease in apoB-containing lipoproteins, the *LPL* score was associated with 69.9 mg/dL (95% confidence interval [CI] 68.1–71.6) lower TG levels and the *LDLR* score was associated with 14.2 mg/dL (95% CI, 13.6–14.8) lower LDL-C levels. Both scores were associated with similar reduction (by 23%) in CHD risk per 10 mg/dL lower levels of apoB-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively). If the atherogenicity of all apoB-containing particles is the same, these findings indicate that for a similar reduction in cardiovascular risk, the reduction in plasma TG needs to be 5-fold that of LDL-C.

There are, however, a number of limitations to bear in mind. First, as the data for genetic variants relate to the lifelong effects of exposure to these variants, the magnitude of reduction in cardiovascular risk is substantially greater than observed from relatively short-term exposure to pharmacotherapy targeting LDL-C or TG. Second, the study fails to take account of potential pleiotropic effects that such treatments may have on cardiovascular risk. An example of this may be the recent REDUCE-IT trial, in which the reduction in cardiovascular risk observed with treatment with the omega-3 fatty acid eicosapentaenoic acid was substantially greater than that predicted from the extent of TG-lowering, implying the involvement of non-lipid related effects [8]. Furthermore, the findings from the study by Ference and colleagues provide one explanation for the mixed results observed in the previous major fibrate trials, with the variability in treatment effect in part

E-mail address: office@eas-society.org.

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potentially due to the magnitude of apoB lowering, although there were also other issues, such as patient selection and level of baseline TG [9].

Irrespective of these caveats, the take home message from this study is that the clinical benefit from treatments that lower LDL-C or TG is proportional to the absolute reduction in apoB-lipoprotein particles (whether contained in LDL or VLDL particles), irrespective of changes in plasma levels of LDL-C or TG.

1. Why are these findings important?

Plasma TG measurement reflects the total mass of TG, not the number or composition of particles that carry TG. Therefore, beyond the setting of familial chylomicronaemia, elevated plasma TG may be due to an increase in the total number of TG-rich particles (notably, VLDL) or the TG content of these particles. Thus, hypertriglyceridemia may be due to increased secretion, conversion, or catabolism of lipoprotein particles of TG-rich lipoproteins, which may confound the interpretation of clinical trials that have investigated the effect of different TG-lowering therapies [10,11].

These considerations are highly pertinent given that interest in the therapeutic potential of key targets that regulate TG metabolism, including apo C—III, and the angiopoietin-like proteins 3 and 4, has increased in the light of evidence from studies that loss-of-function variants in genes encoding these targets were associated with lifelong lower TG and reduced coronary artery disease risk [12–16]. There are also two ongoing major trials evaluating therapeutic approaches to lowering plasma TG - STRENGTH (Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia), using omega3 fatty acids [17], and PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) using a selective peroxisome proliferator activated receptor alpha modulator (SPPARMα) [18] – for which the findings from this analysis may be relevant.

Consequently, apoB measurement will have benefit not only in the interpretation of results (as seen with REDUCE-IT), but also in the design of cardiovascular outcomes studies. Indeed, the findings by Ference colleagues imply that trial design should consider the magnitude of the reduction in apoB-containing lipoproteins, rather than the changes in TG or LDL-C, needed to attain the calculated reduction in cardiovascular events.

2. Do we need to change routine practice?

The Joint European Society of Cardiology/European Atherosclerosis Society (EAS) already recommend apoB as an alternative risk marker, and as a secondary target when available, especially in subjects with high TG levels [19]. More recently, a Joint Consensus Initiative from the EAS and the European Federation of Clinical Chemistry and Laboratory Medicine reaffirmed that while LDL-C remains the primary target of lipid-lowering therapy, after attainment of LDL-C goal, apoB (or non-HDL-C) are preferred as secondary treatment targets in patients with moderately elevated TG (2–10 mmol/L OR 175–880 mg/dL), or in those with obesity, metabolic syndrome, or type 2 diabetes [20]. As the population prevalence of hypertriglyceridemia increases, tracking the parallel pandemics of visceral obesity and type 2 diabetes, clinical practice may need to consider broader lipid measurement in such patients. ApoB may be one candidate for inclusion in diagnostic algorithms that may help in categorizing the hypertriglyceridemia phenotype and its associated cardiovascular risk.

Conflicts of interest

The author declared she does not have anything to disclose regarding conflict of interest with respect to this manuscript.

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