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Beyond LDL-C levels, does remnant cholesterol estimation matter?

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Clinical evidence suggests that the residual cardiovascular (CV) risk observed in patients with well-controlled low-density lipoprotein cholesterol (LDL-C) levels can be, in part, explained by residual lipid risk factors, among which the cholesterol content of remnants of triglyceride (TG)-rich lipoproteins (TRLs) appears to play a key role.[1] Observational and genetic studies have shown that remnant cholesterol (RC) is a causal risk factor for ischemic heart disease,[2] and more recently it has been associated also with an increased risk of ischemic stroke.[3] Indeed, several studies have shown that non-high-density lipoprotein cholesterol (non-HDL-C) levels, which recapitulate the cholesterol content of all atherogenic apolipoprotein B (apoB)-containing lipoproteins including remnants, are a better predictor of CV risk than LDL-C levels alone.[4,5] In agreement with these observations, Mendelian randomization studies have suggested that the clinical benefit of lowering LDL-C may be better explained by the absolute reduction in apoB-containing lipoproteins.[6,7]

In their study, Elshazly et al. have evaluated whether RC associates with coronary atheroma progression and clinical events independently of LDL-C values in 5754 patients from 10 interventional trials.[8] Despite an overall effective treatment resulting in robust reductions of plasma lipids (including LDL-C, RC, TG, non-HDL-C) and apoB levels, a variability in the response for changes in the percent atheroma volume (PAV) was observed.[8] Of note, higher on-treatment RC levels were significantly associated with a greater progression of coronary atheroma, and also with an increased cumulative incidence of major adverse CV events at 24 months.[8] Atheroma progression occurred when on-treatment RC levels were higher than 25–30 mg/dL (depending on the method used for LDL-C level estimation), and was more strongly associated with changes in RC than LDL-C or apoB levels.[8] These results seem to be in agreement with a recent study demonstrating a relationship between RC and total coronary atherosclerotic plaque burden (evaluated by computed tomography coronary angiography) in a population of patients with optimal LDL-C levels (mostly treated with statins), in which RC levels remained an independent predictor of coronary atherosclerotic burden after adjusting for traditional risk factors.[9] In the GLAGOV study (included in the analysis of Elshazly et al.), only about two-thirds of Evolocumab-treated patients achieved plaque regression, despite reaching very low levels of LDL-C.[10] Although the possibility that the limited length of this trial (78 weeks) explains this result, as the reduction of plasma LDL-C levels does not immediately translate into an effective decrease of cholesterol load within the arteries, it also suggests that factors other than LDL-C might contribute to the disease (and to the residual CV risk), including RC. In addition, the composition of atherosclerotic plaque, and more specifically its lipid content, is a major determinant of the regression process potentially induced by a lipid-lowering treatment; indeed, a meta-analysis showed that high-intensity statin therapy promotes coronary plaque calcification rather than overall atheroma volume regression.[11]

The mechanisms by which TRL remnants contribute to the atherogenic process are not fully understood. Due to their size, remnants can enter the subendothelial space, where they are retained; of note, remnant lipoproteins carry significantly more cholesterol per particle than LDL and do not require oxidation to be taken up by macrophages; within the subendothelial space, remnants induce a local low-grade inflammation,

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endothelial dysfunction, and foam cell formation, as it occurs for LDL.[1,12,13]

The study by Elshazly et al. presents with some limitations. The first is of methodological nature, as the definition of RC is at the best approximate, since it recapitulates the cholesterol present in circulating TG-rich particles, mainly very low-density lipoprotein (VLDL). Measuring remnants of chylomicrons and VLDL (which represent variable fractions of the total VLDL-cholesterol) is not something that is easily done and certainly was not performed in the studies analysed by the authors. Further, the observation that apoB is outperformed by the cholesterol content of VLDL (as in all trials patients with elevated TG were excluded and samples were obtained in fasting conditions) is rather surprising and may be related to the relatively poor standardization of apoB determination versus cholesterol evaluation.

That said, other points require further analyses: for instance, whether subjects who had higher on-treatment RC levels benefited differently from lipid-lowering. Moreover, this analysis included studies evaluating drugs targeting different CV risk factors, including not only lipid-modifying drugs (statins, a cholesteryl ester transfer protein (CETP) inhibitor and a proprotein convertase subtilisin/kexin type 9 inhibitor), but also anti-hypertensive or anti-diabetics agents (which are not reported to have significant effects on lipid levels). All the studies testing the effect of non-statin therapies on PAV progression had an elevated percentage of patients (>80%) on a background statin treatment, and this could have affected the possibility to appreciate changes in lipoprotein catabolism. Indeed, while the emerging key message from the study is that the reduction of LDL-C levels (~23%) does not translate in RC reduction (~3%), the possibility that specific trials might diverge from this picture and perhaps drive the overall result is not discussed. In addition, for the calculation of RC, in their analysis the authors estimated LDL-C using the Hopkins–Martin equation, instead of Friedewald's[8] (when TG levels were <400 mg/dL) – a comparison between these two approaches would have been useful.

Taking into account these limitations, the multivariate analysis showed that, after adjusting for several factors, including trial duration, baseline plaque atheroma volume, C-reactive protein (CRP), on-treatment LDL-C, and apoB levels, differences in on-treatment RC surprisingly remained significantly associated to atheroma progression.[8] This is an unexpected finding as apoB, per se, should better mirror the totality of atherogenic lipoproteins. Indeed, a recent Mendelian randomization study showed that TG-lowering variants in the lipoprotein lipase gene and LDL-C-lowering variants in the LDL receptor gene were associated with comparable coronary heart disease (CHD) risk reduction per 10-mg/dL lower level of apoB-containing lipoproteins.[7] The multivariable Mendelian randomization analysis showed that the significant direct association of TG and of LDL-C levels with CHD became null after adjusting for apoB levels, suggesting that the clinical benefit of lowering TG levels or LDL-C levels are similar per unit change in apoB levels and likely associated to the absolute reduction in apoB-containing lipoprotein particles.[7] On this premise, the data by Elshazly et al. raise the question of whether measuring RC levels provides superior information on the atherogenic load of remnant particles beyond apoB determination. Changes in plaque composition and size may not be, overall, related to the clinical events and this may also explain the apparent divergent results.

Another point of discussion is the observation that, in contrast with previous studies proposing that remnant particles contribute to atherogenesis by inducing low-grade inflammation,[12,14] as well as endothelial dysfunction by promoting endothelial pro-inflammatory activation and a reduced flow-mediated dilatation both under fasting and post-prandial response,[13,15] the study by Elshazly et al. showed that RC remains an independent predictor of PAV progression even after adjusting for CRP. This seems to suggest that the deleterious effect of RC is independent of the systemic inflammatory response as determined by CRP (as observed also for LDL) and further raises questions on the pathophysiological mechanisms triggered by remnant particles. Are they supporting atherosclerosis progression and vascular damage without activating the inflammatory response via the classical inflammasome/IL-1ß/IL-18 pathway as it happens when cholesterol crystals accumulate within macrophages? If this is the case, is cholesterol carried by remnant particles handled differently from that deriving from LDL particles within vascular wall cells? While further ad hoc studies are needed to answer these questions, the work by Elshazly et al. clearly represents a good example on how the analysis of clinical data generates novel hypotheses to be tested at the molecular and cellular levels.

In conclusion, this work highlights how a residual risk related to lipoprotein classes other than LDL persists also in patients with baseline values for non-LDL-C lipid variables, including plasma TG and HDL-C, within what is regarded as a normal range; however, it does not detract, as also stated by the authors, from the benefits of lowering LDL-C.

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