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EDITORIAL

What is 'remnant cholesterol'?

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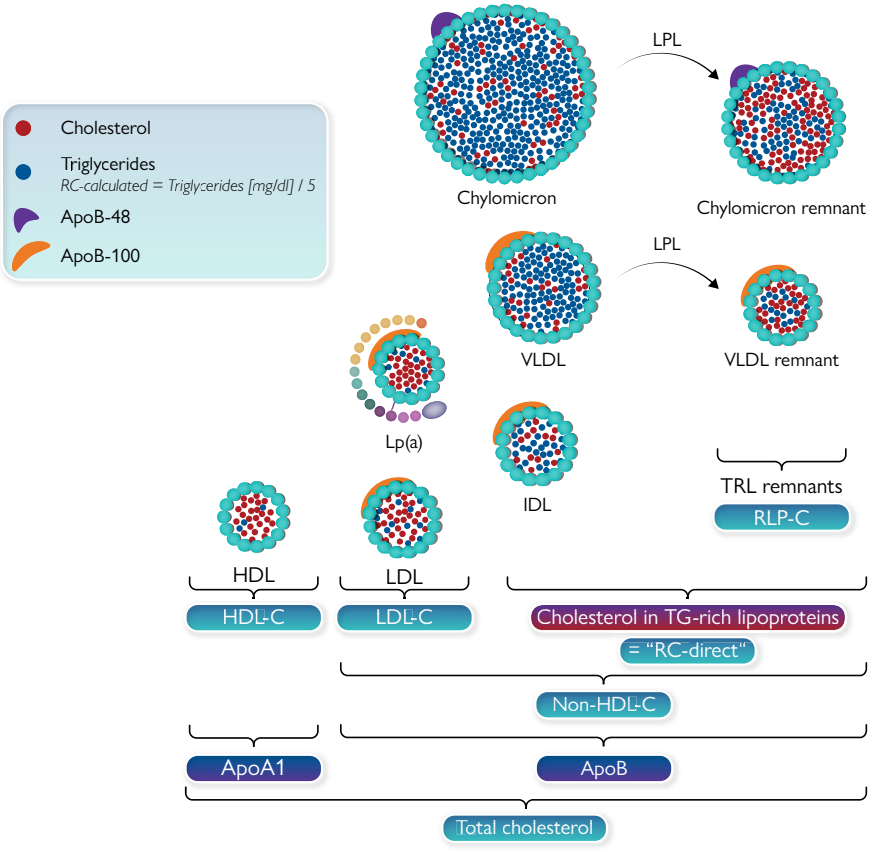
This editorial refers to 'Elevated remnant cholesterol, plasma triglycerides, and cardiovascular and non-cardiovascular mortality', by B.N. Wadström *et al.*, https://doi.org/10.1093/eurheartj/ehac822.

Graphical Abstract



Lipoproteins and definitions of 'remnants. The serum cholesterol and triglycerides are transported in lipoproteins of different size and composition. Triglycerides of exogenous origin are carried in apoB-48-containing chylomicrons, while the triglycerides synthesized in the liver are mainly released in VLDL particles. Chylomicrons and VLDL undergo hydrolysis by lipoprotein lipase, and thus reducing the triglyceride content, and forming chylomicron and VLDL remnants, respectively. Both are also referred to as 'triglyceride-rich lipoprotein (TRL) remnants', and their cholesterol content is denoted 'remnant lipoprotein particle cholesterol' (RLP-C). Another definition of remnants used by the group of Nordestgaard, the 'remnant cholesterol' (RC), additionally encompasses the cholesterol content of VLDL, chylomicrons, and IDL, and therefore the cholesterol carried by all TRL. This 'remnant cholesterol' can either be measured ('RC-direct') or approximated by dividing total serum triglycerides in mg/dL by 5 or in mmol/L by 2.2 ('RC-calculated').

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Triglycerides (TGs), the main constituents of fat in vertebrates, are carried within the hydrophobic core of a very diverse population of serum lipoprotein particles that are collectively called 'TG-rich lipoproteins'. All of these lipoprotein particles contain cholesterol, phospholipids, and protein components in addition to TGs. The composition, size, and the content of TGs and cholesterol in lipoproteins are dynamic. Important regulators include the lipoprotein lipase (LPL) on the surface of endothelial cells that hydrolyses TGs in lipoproteins.[1] Partial lipolysis can prolong the residence time of a lipoprotein in the circulation and reduce delipidation. For example, remnants of VLDLs are enriched in cholesteryl esters, and are believed to be at least as atherogenic as LDL-cholesterol on a per particle basis. Lipoproteins are stabilized and distinguished by apolipoproteins. TGs are primarily transported by apolipoprotein B (apoB)-containing lipoproteins. The intestine makes a short form of apoB (B-48), whereas the liver produces full-length apo B100, which allows tracking TG-rich particles from these two tissue sources. Historically, the term 'remnant' has been used to describe partially metabolized lipoproteins. The 'remnant' lipoproteins are a very diverse subset of the spectrum of TG-transporting lipoproteins that is subject to several regulatory mechanisms. Increasing evidence shows that the cholesterol content of TG-transporting lipoproteins is associated with impaired clinical outcomes independent from LDL-C and HDL-C.[1] Therefore, it is important to assess this risk. However, in the current literature, at least eight different definitions of the term 'remnant' in relation to lipoprotein particles and their contents are used. The in part overlapping definitions do not make the life easy for non-lipidologists (*Graphical Abstract*).

(i) Remnants of triglyceride-rich lipoproteins (TRLs), (ii) chylomicron remnants, and (iii) VLDL remnants

'TRLs' are metabolic intermediates formed when apoB-48-containing chylomicrons (CMs) of intestinal origin and apoB-100-containing VLDLs of hepatic origin are hydrolysed by lipoprotein lipase. They are also referred to as CM remnants and VLDL remnants, respectively.[2]

(iv) Remnant lipoprotein particles (RLPs) and (v) their cholesterol content (RLP-C)

'RLPs' is used as an alternative term to describe remnant intermediates of chylomicrons and VLDLs. RLP cholesterol (RLP-C) is the cholesterol content of this subfraction.[3] 'RLPs' have been reported to be one of the most atherogenic TRL remnants.[4,5] RLP-C is an independent risk factor for CVD in women.[3] 'RLPs' can be quantified by immunoseparation using monoclonal antibodies to apoA-I and apoB-100 to remove 'non-remnant' lipoproteins and quantification of cholesterol in the remaining (='remnant') apoE-rich fraction (RLP-C).[6]

(vi) Remnant cholesterol according to Nordestgaard *et al.* (RC), (vii) RC directly measured (RC-direct), and (viii) RC calculated based on Friedewald (RC-calculated)

'RC' is a term introduced by the group of Nordestgaard to describe the cholesterol content of all TG-rich lipoproteins, e.g. the plasma cholesterol outside of LDL and HDL. In this definition, and this may be the reason for some ongoing confusion, all TG-rich lipoproteins are called 'remnants'—irrespective of whether they have been metabolized or newly synthesized. 'RC-N' is the cholesterol contained in the CMs, VLDLs, and intermediate-density lipoproteins (IDLs). Two principal methods to determine 'RC'—direct measurement and calculation—have been used in clinical studies that describe overlapping but distinct entities.

Quantification of 'RC-direct', the cholesterol outside of LDL and HDL, can be achieved by ultracentrifugation or nuclear magnetic resonance spectroscopy. In addition, automated two-step assays are available that use enzymes and surfactants to remove cholesterol in 'other' lipoproteins. In a second step, cholesterol is quantitated in the remaining remnant lipoprotein particles. The automated assay allows assessing RC-direct in large cohort studies.[7,8]

'RC-calculated' is neither cholesterol nor a group of lipoproteins but another term for serum TGs. As defined by Nordestgaard and Varbo, remnant cholesterol is total cholesterol minus LDL-C minus HDL-cholesterol.[9] According to the widely used Friedewald equation, LDL-C is assessed as total cholesterol minus HDL-C minus triglycerides in mg/dL divided by 5. Therefore, RC-calculated = total cholesterol − HDL-C − (total cholesterol − (TG in mg/dL)/5 − HDL-C) which is TGs divided by 5. Simply put, 'remnant cholesterol' according to this definition is serum TGs in mg/dL divided by 5 (or TG in mmol/L divided by 2.2).[9]

'RC-calculated' has strengths and limitations. 'RC-calculated' is readily available when TGs are measured without extra cost. 'RC-calculated' compares with 'RC-direct' in very large populations but has significant limitation for individual patient care. The Friedewald equation assumes a fixed ratio between TGs and VLDL-C of 5:1. However, the ratio between TGs and cholesterol in remnant particles is not constant but differs significantly inter- and intraindividually, e.g. after food intake. This can be partly avoided by calculating 'RC-calculated' using LDL-C that is estimated with the Martin–Hopkins equation that is based on strata for the ratios of TG to VLDL-C.[10] As the group of Nordestgaard has elegantly shown, 'measured remnant cholesterol made up only 9% of calculated remnant cholesterol at non-fasting triglyceride concentrations <1 mmol/L (89 mg/dL) and only 43% at triglycerides >5 mmol/L (443 mg/dL)'.[10] 'Directly measured vs. calculated remnant cholesterol identifies 5% overlooked individuals in the general population with cholesterol-rich, triglyceride-poor remnants and 1.8-fold increased risk of MI'.[11] Indeed, the positive correlation between 'RC-calculated' and 'RC-direct' using the Denka-assay in the Copenhagen General Population Study only shows an r^2 of 0.68, i.e. large discrepancies for individual samples.[12]

In this issue of the *European Heart Journal*, Wadström and colleagues show that calculated 'remnant' 'cholesterol above 1 mmol/L (39 mg/dL), present in 22% of the population, is associated with two-fold mortality from cardiovascular and other causes but not from cancer.[12] Another way of presenting these important findings is to translate the calculated 'remnant cholesterol' back to serum triglycerides: the study shows that TG > 2.2 mmol/L or > 200 mg/dL identifies persons at risk of atherosclerotic cardiovascular disease (ASCVD) and death. The data are obtained from >87 000 very well characterized contemporary persons in the Copenhagen General Population Study with up to 13 years of follow-up. The endpoints are derived from the national Danish Causes of Death Registry.[12] The data provide important confirmation of several very large prospective studies that have shown that serum TG levels are associated with increased risk of future cardiovascular events (e.g. the Women's Health Study;[13] PREDIMED;[14] and the Copenhagen General Population Study and the Copenhagen City Heart Study[15,16]).[1] An important novel finding of the study relates to the association of serum TG with total mortality. The relationship between calculated 'remnant' cholesterol and other mortality was attenuated after adjustment for body mass index, waist circumference, and diabetes, because these conditions are associated with higher serum TG. The relationship was 'nominally attributed to increased mortality from all other mortality subcategories, except for mental disorders and respiratory diseases, and especially to infectious and endocrinological diseases'.[12] Interestingly, there was no association of TG with

cancer mortality. The observations are not yet mechanistically explained and set the stage for further studies to understand the relationship of serum TG with different non-cardiovascular diseases. With emerging therapeutic options to reduce TG-rich lipoproteins, this field of research is likely to become increasingly important.

The elegant paper by Wadström and colleagues stresses the importance of basing clinical decisions on serum TGs in addition to LDL-C. In epidemiological studies, non-HDL-C or apo-B are better predictors of ASCVD compared with LDL-C alone because they include the cholesterol contained in TG-rich particles including 'remnants' of all definitions. The majority of patients with elevated TGs (and elevated remnants) show metabolic alterations such as impaired glucose tolerance, high body weight, or fatty liver disease. When these conditions are taken into consideration in individual patient assessment, 'remnants' provide relatively little clinically important additional information on top of LDL-C and TGs. As demonstrated again by the PROMINENT study, reduction of calculated RC without reduction of LDL-C does not reduce ASCVD.[17] As we still struggle within the medical community to communicate the causality of cholesterol for ASCVD and in the light of very poor achievement of LDL-C treatment goals, it is important not to overcomplicate lipid treatment. At the same time, TG-rich lipoproteins are relevant for lipid specialists and clinical research with novel therapeutic options on the horizon.[1]

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Data availability

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