Editorial Commentary

Remnant cholesterol: new outcomes highlight its potential as a clinically useful cardiovascular risk factor

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Introduction

Hypertriglyceridemia is a cardiovascular risk factor mainly thought to reflect increased plasma remnant lipoprotein particles, which contain a high proportion of cholesterol. This lipid readily accumulates during atherosclerosis and is the lipid usually measured as representative of blood remnant lipoproteins (1).

The concept of remnant lipoproteins (*Figure 1*) is indicative that lipoprotein particles originated during lipoprotein lipase (LPL)-mediated lipolysis of mature chylomicrons (generating smaller particles known as remnant chylomicrons) and very-low density lipoproteins (VLDL) generated remnant VLDL, also known as intermediate-density lipoproteins (IDL). IDL are at an intermediate stage, both in size and lipid content, between VLDL and low-density lipoproteins (LDL). The term "remnant cholesterol" has been also used as equivalent to VLDL cholesterol (VLDL-C), which is currently calculated or measured in the clinical laboratory (2,3).

Remnant lipoproteins can be detected in fasting and, especially, in postprandial conditions (1-3). Classically, it has been thought that human lipoprotein particles originating from chylomicrons contain apolipoprotein (apo) B-48, whereas VLDL and IDL only contain the complete form of apoB (apoB-100). However, in recent years, it has been shown that the intestines secrete apoB48-containing particles not only as chylomicrons but also as VLDL, both in fasting and postprandial states. ApoB48-containing particles represent around 20–25% of VLDL and, especially in patients with hypertriglyceridemia, are slowly catabolized (4).

The hypothesis that increased remnant cholesterol (*Figure 1*) represents a risk factor for cardiovascular disease was first proposed by Donald B. Zilversmit in the 1970s (5). Even though type III hyperlipoproteinemia (a condition characterized by increased IDL concentration) was widely accepted as a highly proatherogenic disease long ago (6), the importance of remnant lipoprotein research was somewhat overshadowed by LDL and the consequent development of statins. However, in the last decade, and especially in the last few years, the hypothesis that remnant lipoprotein cholesterol is a risk factor for cardiovascular disease has been supported with novel results. In this editorial comment, we review only these recent findings as demonstrated by two papers published concomitantly in 2020 (2,3).

Clinical, epidemiological and mendelian randomization studies

As recently noted in a comprehensive review (7), levels of remnant cholesterol were associated with cardiovascular

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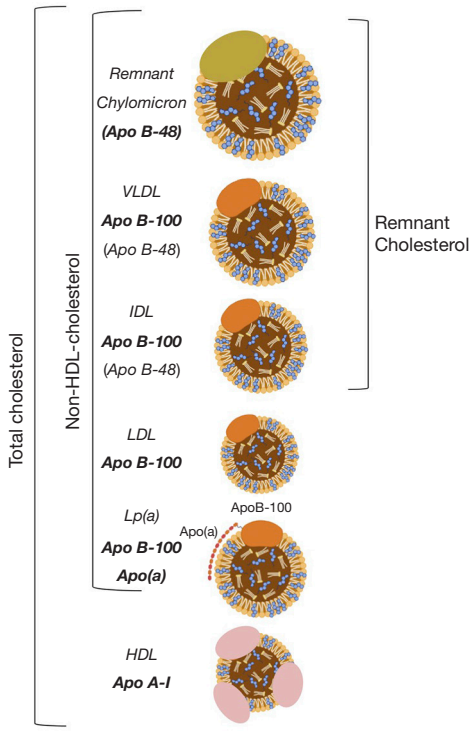

Figure 1 Spectrum of plasma lipoproteins that contribute, respectively, to total cholesterol, non-HDL-cholesterol and remnant cholesterol measurement, with indication of their major, definitory apolipoprotein. Apo, apolipoprotein; HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; Lp(a), lipoprotein (a); VLDL, very-low-density lipoproteins.

risk in older participants in the Atherosclerosis Risk in Communities Study and in a cohort from the Jackson Heart Study and the Framingham Offspring Cohort Study. Furthermore, it has been demonstrated that the cholesterol in triglyceride-rich lipoproteins is associated with peripheral artery disease risk (7). Moreover, different Mendelian randomization analyses have demonstrated that genetic variants that regulate remnant cholesterol plasma levels [either by codifying for apolipoproteins, such as *APOC3*; enzymes, such as LPL; or proteins that control LPL catabolism, such as angiopoietin protein-like 3 (*ANGPLT3*)] are causally associated with cardiovascular risk (7).

Primary prevention

Plasma cholesterol and triglycerides were measured using nuclear magnetic resonance (NMR) in VLDL, IDL, and LDL in about 25% of the 4-hour fasted samples of individuals that participated in the Copenhagen General Population Study (CGPS). The study therefore included 25,480 individuals with a mean age of 60 years who did not have experienced myocardial infarction or undergone lipid-lowering therapy at the beginning of the study. At the median follow-up of 11 years, 1,816 subjects were diagnosed with myocardial infarction (3). VLDL-C, which, as previously stated, was considered remnant cholesterol by the authors, explained 50% of the risk of myocardial infarction associated with apoB-containing lipoproteins, whereas IDL + LDL cholesterol explained 29%. The high association of LDL cholesterol (LDL-C) and IDL cholesterol (IDL-C) concentrations in this study explained its consideration as a unique variable. VLDL triglycerides, in contrast, were not associated with cardiovascular risk (3). Interestingly, the multivariable-adjusted hazard ratio (HR) of myocardial infarction obtained by increasing 1 mmol/L of VLDL-C (×38.61 to obtain cholesterol in mg/dL) was 1.71 and ranked first with respect to increasing 1 mmol/L of IDL + LDL-C (HR 1.32), smoking (yes *vs.* no, HR 1.31), and increasing 10 mmHg of systolic blood pressure (HR 1.11) (3). This does not necessarily have to be interpreted as remnant cholesterol being more important than LDL-C in inducing cardiovascular disease, as usually, LDL is the major cholesterol carrier in plasma.

In addition, in the context of the CGPS study, another investigation performed with 16,207 individuals directly explored whereas 4-hour fast measured remnant cholesterol was superior to calculated remnant cholesterol in predicting coronary heart disease (8). The calculated remnant cholesterol was, in fact, VLDL-C [remnant cholesterol = total cholesterol – high-density lipoprotein (HDL) cholesterol – LDL-C], with LDL-C calculated by the Martin-Hopkins method (9) rather than by the Friedewald equation. Remnant cholesterol was measured as the cholesterol in all triglyceride-rich lipoproteins using a recently developed, automated direct assay from Denka Seiken Co. Ltd. (8), which is traceable to the lipoproteins with density ≤1.019 g/mL and differs from a previous remnant assay by the same company (10). Directly measured remnant cholesterol identified 5% more of cases at risk than calculated remnant cholesterol (8). Importantly, in the CGPS, the inclusion of elevated remnant cholesterol levels improved heart disease risk prediction by 10% for myocardial infarction and by 5% for ischemic heart disease (11).

Step-wise higher remnant cholesterol concentrations

were also associated with higher ischemic stroke risk in the CGPS and in the Copenhagen City Heart Study, with a multivariable adjusted HR of up to 1.99 for individuals with remnant cholesterol concentrations ≥1.5 mmol/L (~58 mg/dL) with respect to individuals with remnant cholesterol <0.5 mmol/L (~19 mg/dL). In this case, remnant cholesterol was calculated as the difference between total cholesterol minus LDL-C minus HDL-C (LDL-C was measured by direct methods when triglycerides >4 mmol/L; to obtain mg/dL, this value was multiplied by 88.5) (12).

Elevated remnant cholesterol in the CGPS and in the Copenhagen Heart City Study was associated with a five-fold increased risk of peripheral artery disease in the general population, which was more than twice that of myocardial infarction and ischemic stroke (13). Remnant cholesterol was calculated using LDL-C obtained by the Friedewald equation. Others formulas for calculating LDL-C, such as Martin-Hopkins or Sampson-NIH, provided very similar results (13).

In pooled data from 17,532 cardiovascular event-free individuals from the Atherosclerosis Risk in Communities study, the Multi-Ethnic Study of Atherosclerosis, and the Coronary Artery Risk Development in Young Adults, plasma remnant cholesterol was independently associated with atherothrombotic cardiovascular disease (14). Interestingly, the discordant high remnant cholesterol/low LDL-C group, but not the low remnant cholesterol/high LDL-C group, was associated with disease (14). In this study, the levels of remnant cholesterol were estimated as total cholesterol minus HDL cholesterol (HDL-C) minus calculated LDL-C using the Martin-Hopkins equation (14).

Secondary prevention or equivalent high cardiovascular risk

In the Spanish Predimed Trial, fasting remnant cholesterol (which was considered VLDL-C) calculated as triglycerides (mg/dL)/5 when the concentration of plasma triglycerides was <300 mg/dL, was also associated with major cardiovascular events, namely myocardial infarction, stroke, or cardiovascular death. The Predimed study included 6,901 men and women with a mean age of 67 years and a mean body mass index of 30 kg/m^2 presenting with diabetes mellitus (48%) or three or more cardiovascular risk factors. The main goal of the study was to assess the effects of extra virgin olive oil and mixed nuts. There was a median follow-up of 4.8 years in which 263 events were detected (3.8%) (2). In a multivariable-adjusted analysis, an increase in 10 mg/dL (~0.25 mmol/L) of fasting remnant cholesterol was associated with an increased cardiovascular risk (HR of 1.21), similarly to non-HDL-C (HR 1.05) or triglycerides (HR 1.04), whereas no differences were observed for LDL-C and HDL-C (2). Fasting remnant cholesterol (or VLDL-C >30 mg/dL or 0.77 mmol/L) differentiated subjects at high risk of major cardiovascular events regardless of LDL-C being higher or lower than 100 mg/dL (2).

Direct measurement of remnant cholesterol using an automated assay (Denka Seiken Co. Ltd., Seiken) was performed in 4,355 patients from China with angiographically confirmed coronary artery disease during a median follow-up of 5.1 years. Adding this information resulted in better prediction of the 543 events that occurred during this period (10). In another study from the same country, 19.2% of the 94,869 Chinese patients hospitalized for acute coronary syndrome presented elevated remnant cholesterol (>1 mmol/L) (15).

A *post hoc* analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which included around 10,000 participants followed for a median of 8.8 years, assessed the associations between remnant cholesterol and cardiovascular outcomes in patients with type 2 diabetes. After adjusting for traditional cardiovascular risk factors, each unit of standard deviation (SD) increase in remnant cholesterol was associated with a 7% higher risk of major adverse cardiovascular events. In addition, remnant cholesterol ≥31 mg/dL identified individuals at a higher major adverse coronary event risk, regardless of LDL-C concentration (16).

In patients with type 2 diabetes, chronic kidney disease, and incident diabetic nephropathy, remnant cholesterol was associated with a higher risk of cardiovascular-related death (17). Similar results were also observed in long-term kidney transplant recipients (18).

Remnant cholesterol was independently associated with the risk of metabolic dysfunction-associated fatty liver disease and predicted all-cause, cardiovascular, and cancer-related mortalities in the NHANES III study (odds ratio of 1.71) (19). Remnant cholesterol concentration has also been independently linked to several cardiometabolic risk factors, even though it remains to be established whether this relationship is causal. For instance, remnant cholesterol has been shown to have a strong positive correlation with diabetes and with the risk of complications such as neuropathy and nephropathy (20,21), as well as with diabetes and fatty liver disease occurrence and severity (22).

Laboratory tests for clinical practice

The most frequently used method to establish the concentration of plasma remnant cholesterol (or VLDL-C) is calculating total cholesterol minus HDL-C and LDL-C. This follows the Friedewald equation, which is used in clinical assistance since the results resemble (in the absence of lipoprotein disorders) those obtained by measuring cholesterol in VLDL isolated by sequential ultracentrifugation (density ≤1.006 g/mL), a context in which IDL-C is usually included within LDL-C. Calculating remnant (or VLDL) cholesterol would involve the same imprecision as the measurement needed for calculation, namely triglycerides in the case of the Friedewald equation. Direct LDL-C determination or application of other formulas (Martin-Hopkins, Sampson-NIH) are also options to measure LDL-C and, afterwards, calculate remnant (or VLDL) cholesterol as total cholesterol – (LDL-C + HDL-C). In the latter case, remnant (VLDL) cholesterol calculation would be impacted by the imprecision of all the components used of the formula.

A second option is the use of a test from Denka Seiken Co. Ltd. (to our knowledge, not still commercially available), a direct automated method for measuring cholesterol from chylomicrons, VLDL, and IDL, which can be added up to obtain the remnant cholesterol. This method has been used in some of the studies reviewed in the present comment, but direct comparison with calculated remnant cholesterol only allowed for the identification of 5% more patients with increased concentration with respect to the calculation (8). A third option, used by some of the studies reviewed in this report, was NMR, a method that at this time remains unavailable to most clinical laboratories. Finally, and despite not being widely available (e.g., none of the studies reviewed here used it), measuring cholesterol in triglyceride-rich lipoproteins isolated by sequential ultracentrifugation (density ≤1.019 g/mL) may also be an option.

In *Table 1*, one can observe that there are differences between studies, both in the methodologies for measuring or calculating remnant (or VLDL) cholesterol and in the fasting period, which contrast with the quite consistent results showing, as explained, that remnant cholesterol concentration is associated with cardiometabolic risk. Thus, overall, remnant cholesterol information lent value to several studies compared to the more traditional parameters used in a clinical laboratory setting, including LDL-C, non-HDL-C, triglycerides, or apoB-100. It is, however, unclear yet whether remnant cholesterol is superior to other parameters that may provide (at least partly) similar information, such as apoC-III, LDL triglyceride, or ANGPTL3 concentrations (7,10,23,24). Certainly, the calculation of remnant cholesterol rather than experimental determination of the other biomarkers might provide an advantage through its simplicity and lack of cost, but some of these other biomarkers (i.e., apoC-III or ANGPTL3) are directly targeted by drugs in current development, which could favor their use in the future.

Conclusions and perspectives

Consistent results indicate that increased plasma remnant cholesterol is a risk factor for cardiovascular disease both in primary and secondary prevention and seems particularly indicative of peripheral artery disease risk. Mendelian randomization analysis suggests causality. There are indications that remnant cholesterol might improve patient risk classification. Large, randomized trials of triglyceride- and remnant cholesterol-lowering treatment are needed in order to know whether they can further reduce cardiovascular disease risk with respect to the current standard of care. The results of these interventional studies will likely determine whether and which specific laboratory tests (calculated or measured remnant cholesterol, apoC-III, or ANGPTL3), in addition to the standard lipid profile, are best suited for clinical practice and under which circumstances (overnight or 4-h) of fasting should be used. Further studies are also needed to understand the role of remnant lipoproteins in the development and prognosis of high cardiovascular risk in illnesses such as diabetes mellitus, obesity, and renal disease.

Table 1 Design and methodology characteristics of some recent clinical and epidemiological studies focused on remnant cholesterol

Author, country (studied population), reference	Context	Individuals/ patients	Fasted plasma	Measurement method
Balling *et al.*, Denmark (3)	Primary prevention, 11-year follow-up	25,480	4-hour fast	NMR Remnant cholesterol (VLDL-C) calculated as TG/2.2 (when TG <4 mmol/L), or calculated after direct LDL-C measurement (when TG >4 mmol/L) as Remnant cholesterol = TC – (LDL-C + HDL-C)
Varbo *et al.*, Denmark (8)	Primary prevention, 4-year follow-up	16,207	4-hour fast	Not commercially available Denka Seiken method, RLP-C Remnant cholesterol (VLDL-C) = TG/2.2 (when TG <4 mmol/L), or calculated (when TG >4 mmol/L) as Remnant cholesterol = TC – (LDL-C + HDL-C) with LDL-C estimated with the Martin-Hopkins formula
Varbo *et al.*, Denmark (12)	Primary prevention, 14-year follow-up	102,964, reconfirmed in 9,548 more	4-hour fast	Remnant cholesterol (VLDL-C) calculated as TG/2.2 (when TG <4 mmol/L, or calculated after direct LDL-C measurement (when TG >4 mmol/L) as Remnant cholesterol = TC – (LDL-C + HDL-C)
Doi *et al.*, Denmark (11)	Primary prevention, 10-year follow-up	41,928	4-hour fast	Remnant cholesterol (VLDL-C) calculated as TG/2.2 (when TG <4 mmol/L, or calculated after direct LDL-C measurement (when TG >4 mmol/L) as Remnant cholesterol = TC – (LDL-C + HDL-C) LDL-C was also calculated by the Martin-Hopkins or the Sampson-NIH formula
Wadström *et al.*, Denmark (13)	Primary prevention	106,397	4-hour fast	Remnant cholesterol (VLDL-C) as TG/2.2 (when TG <4 mmol/L), or calculated after LDL-C measurement (when TG >4 mmol/L) as Remnant cholesterol = TC – (LDL-C + HDL-C). LDL-C was also calculated by the Martin-Hopkins or the Sampson-NIH formula
Quispe *et al.*, USA (14)	Primary prevention, 18.7-year follow-up	17,532	Overnight	Remnant cholesterol (VLDL-C) = non-HDL-C – Martin-Hopkins calculated LDL-C
Castañer *et al.*, Spain (2)	High CVD risk, 4.8-year follow-up	6,901	Overnight	Remnant cholesterol (VLDL-C) as TG/2.2 (when TG <3.39 mmol/L)
Cao *et al.*, China (10)	High CVD risk, 5.1-year follow-up	4,355	Overnight	Not commercially available Denka Seiken method, RLP-C
Fu *et al.*, USA and Canada (16)	High CVD risk, 8.8-year follow-up	10,196	Overnight	Remnant (VLDL) cholesterol = non-HDL-C – LDL-C
Yu *et al.*, China (17)	High CVD risk, 2-year follow-up	2,282	Overnight?	Remnant cholesterol (VLDL-C) as TG/2.2
Jansson Sigfrids *et al.*, Finland (21)	High CVD risk, up to 17-year follow-up	5,150	Light fasting	Remnant cholesterol (VLDL-C) = TC – (Sampson-NIH formula calculated LDL-C + HDL-C)
Hussain *et al.*, USA (23)	High CVD risk, up to 6-year follow-up	6,359	Overnight	Not commercially available Denka Seiken method, RLP-C

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; NIH, National Institutes of Health; NMR, nuclear magnetic resonance; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; RLP-C, remnant lipoprotein particle-cholesterol; VLDL-C, very-low-density lipoprotein cholesterol.

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Footnote

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