

EDITORIAL COMMENT

Remnant Cholesterol and Atherosclerotic Cardiovascular Disease Risk*



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A striking recent development in lipidology has been the renaissance of plasma triglycerides (TG) as a risk factor and likely causal agent for atherosclerotic cardiovascular disease (ASCVD) (1). Concurrently, a consensus opinion has emerged that high-density lipoprotein (HDL) cholesterol is no longer an independent direct actor in ASCVD, although it remains a clinically valuable predictor of risk (2). The reprioritization of TG ahead of HDL cholesterol followed from genetic epidemiology studies and clinical trial evidence (3). Analogous data reaffirm the pre-eminence of low-density lipoprotein (LDL) cholesterol in ASCVD causation (4,5). Yet, while LDL is relatively well understood by both lipid insiders and those in the general cardiology world, TG is a fuzzier and more enigmatic entity.

Conceptualizing TG is challenging, because this lipid is carried in the core of a diverse population of spherical lipoprotein particles (6). These range from enormous and buoyant but short-lived intestinally derived chylomicrons and their smaller denser remnants through to liver-derived very-low-density lipoprotein (VLDL) and even smaller denser remnants, which are called intermediate-density lipoprotein (IDL) (7). Collectively, this mini-solar system of

particles is referred to as “TG-rich lipoproteins” (Figure 1). Importantly, they all carry cholesterol in addition to TG (8). The cholesterol within TG-rich lipoproteins is considered to be the predominant atherogenic agent that feeds the development of arterial wall plaques (9). In contrast, the TG inside this family of particles are less directly toxic to the artery (10).

A technical challenge arising from the existence of these various species is that there is no simple, widely available assay to measure the cholesterol content of TG-rich lipoproteins and remnants. TG levels themselves provide a first approximation, but mechanistically and clinically it is more important to quantify the cholesterol component of these particles (11). A potential distinguishing feature is full-length carrier molecule apolipoprotein (apo) B-100, which is absent from chylomicrons and their remnants, but is present on VLDL and IDL (12). Apo B is becoming a popular clinical biomarker, but because it is also present on LDL and lipoprotein(a), it does not allow for a pure measurement of cholesterol in TG-rich remnant lipoproteins. In the past, remnant cholesterol content was estimated by plugging standard lipid variables into a mathematical equation (13). Direct laboratory methods, for example, nuclear magnetic resonance (NMR) analysis of blood samples (14), can also determine the breakdown of cholesterol and TG carried within lipoprotein species, including TG-rich remnants.

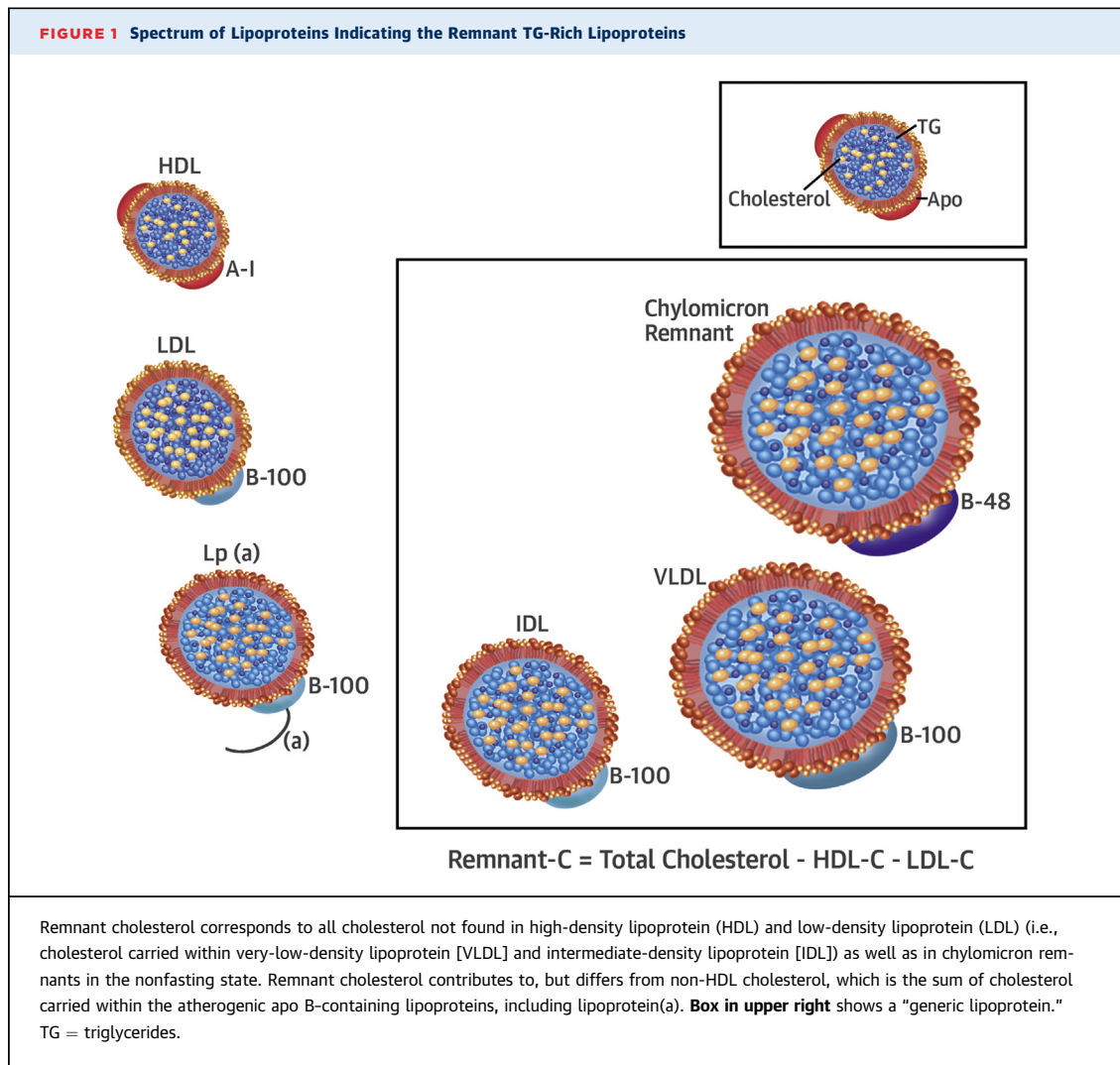
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In this issue of the *Journal*, 2 papers have evaluated ASCVD risk attributable to cholesterol within TG-rich lipoproteins and remnant particles. In the first paper, Castañer et al. (15) have used observational data from the PREDIMED (PREvención con Dieta MEDiterránea) study, an intervention trial of the effects of a Mediterranean diet on ASCVD prevention,

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to explore the relationship between TG and remnant cholesterol with cardiovascular outcomes (15). A total of 6,901 older (mean age 67 years, 57% women, mean body mass index 30 kg/m²) community-dwelling Spanish participants at high cardiovascular risk, but with no prior ASCVD, who had a diagnosis of type 2 diabetes (48%) or 3 or more other risk factors, had been randomized to 1 of 3 dietary arms, and followed for a median of 4.8 years. Fasting lipid profiles were performed on frozen samples taken at baseline, with LDL cholesterol calculated according to the Friedewald formula when TG was <300 mg/dl (<3.4 mmol/l), remnant cholesterol by subtracting HDL cholesterol and LDL cholesterol from total cholesterol, and non-HDL cholesterol by subtracting HDL cholesterol from total cholesterol.

The primary endpoint was a composite of major adverse cardiovascular events (MACE), namely

myocardial infarction (MI), stroke, or cardiovascular death. A MACE event occurred in 263 participants (3.8%). In a multivariable-adjusted Cox model, Castañer et al. (15) found that for every 10-mg/dl increment in TG, the risk of incident MACE was higher (hazard ratio: 1.04; 95% confidence interval [CI]: 1.02 to 1.06); it was similar for non-HDL cholesterol (hazard ratio: 1.05; 95% CI: 1.01 to 1.10) and, to a greater magnitude, for remnant cholesterol (hazard ratio: 1.21; 95% CI: 1.10 to 1.33). A baseline remnant cholesterol level ≥ 30 mg/dl (75th percentile of the cohort) was able to identify individuals at high risk of MACE independent of LDL cholesterol. Somewhat unexpectedly, neither LDL cholesterol nor HDL cholesterol was associated with MACE.

In the second paper, Balling et al. (16) studied a subset of 25,480 individuals from the CGPS (Copenhagen General Population Study) who were not on

lipid-lowering therapy and did not have a history of MI at study entry. Over the 11 years of follow-up, 1,816 individuals were subsequently diagnosed with MI. The baseline cholesterol and TG content of VLDL, IDL, and LDL were measured using NMR spectroscopy.

The authors reported that for each 1 mmol/l (39 mg/dl) higher cholesterol content, the multivariable adjusted MI hazard ratio was 2.07 (95% CI: 1.81 to 2.36) for VLDL. Interestingly, for VLDL TG (hazard ratio: 1.19; 95% CI: 1.14 to 1.25) the risk estimates reached a plateau at 2 mmol/l (177 mg/dl). The hazard ratio for MI per 1 mmol/l (39 mg/dl) increase was 1.86 (95% CI: 1.62 to 2.14) for LDL cholesterol and 5.38 (95% CI: 3.73 to 7.75) for IDL cholesterol. The authors concluded that VLDL cholesterol explains 46% of MI risk from apo B-containing lipoproteins, IDL + LDL cholesterol explained 25%, whereas VLDL TG was not associated with risk. In a corresponding model, calculated remnant cholesterol explained only 10% (95% CI: 0% to 24%) of MI risk. Thus, in CGPS, directly measured VLDL cholesterol emerged as the most important MI risk factor, ahead of systolic blood pressure, smoking, and IDL + LDL cholesterol.

So, PREDIMED and CGPS, although distinct in design and analytical methods, yielded complementary results. In PREDIMED, lipid-associated risk came from TG and calculated remnant cholesterol, with a negligible role for LDL cholesterol. Meanwhile, the CGPS data showed that directly measured cholesterol within VLDL particles explains one-half of the MI risk attributable to apo B-containing lipoproteins. Notably, TG within VLDL was not associated with ASCVD events. Thus, in contrast to PREDIMED, CGPS gives LDL some credit, even if it seems dwarfed by the effect of VLDL cholesterol.

What do these studies mean for the clinical cardiologist? For example, should we now shelve LDL cholesterol and embrace VLDL and remnant cholesterol as the new oracles of ASCVD risk (17)? Not so

fast. It would be premature to discard LDL cholesterol based on PREDIMED, which was a 4.8-year study with only 263 total MACE events. This is insufficient to offset the mountain of literally hundreds of studies and independent types of experiments that uphold the value of LDL cholesterol in prediction and intervention of ASCVD (4,5). In contrast, CGPS indicates that although VLDL cholesterol is the new kid in town for prediction, LDL cholesterol retains predictive power. Replication of the CGPS results would be desirable. The NMR methodology, although promising, is relatively new, expensive, and not widely available, and it needs to be further field tested and validated. However, if these results can be replicated, they represent a potential advance for diagnosis and prevention of ASCVD endpoints. One could envision a future where in addition to the routine lipid profile, newer analytes such as remnant cholesterol as well as lipoprotein(a) and apo B are reported to improve prognostication and help guide preventive treatments (18).

AUTHOR DISCLOSURES

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