

LDL Not the Primary Culprit in ASCVD?

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Two new studies suggest that [low-density lipoprotein cholesterol](#) (LDL-C) may be not the main driver of [atherosclerotic cardiovascular disease](#) (ASCVD).

The findings instead implicate remnant cholesterol (remnant-C) and very low-density lipoprotein (VLDL) cholesterol in the development of cardiovascular disease (CVD) and [myocardial infarction](#) (MI).

The PREDIMED study, conducted in Spain, examined the association of triglycerides and remnant-C with major cardiovascular events (MACE) in older individuals with high CVD risk. It found that levels of triglycerides and remnant-C were associated with MACE [independently of other risk factors](#), but there was no similar association with LDL-C.

"These findings lead [clinicians] to consider in the clinical management of dyslipidemias a greater control of the lipid profiles as a whole, including remnant-cholesterol and/or triglycerides," Montserrat Fitó Colomer, MD, PhD, of the [Cardiovascular Risk](#) and Nutrition Research Group, Hospital del Mar Medical Research Institute, Barcelona, Spain, told [theheart.org](#) | [Medscape Cardiology](#).

In a [separate analysis](#), the Copenhagen General Population Study, which focused on 25,000 individuals who were not taking lipid-lowering therapy, looked at the role of VLDL and triglycerides in driving MI risk from [apolipoprotein B](#) (apoB)-containing lipoproteins.

"Elevated VLDL cholesterol explained a larger fraction of risk than did elevated LDL cholesterol, or elevated VLDL triglycerides," Børge G. Nordestgaard, MD, DMSc, professor, University of Copenhagen, Denmark, told [theheart.org](#) | [Medscape Cardiology](#).

Both studies were published online November 30 in the *Journal of the American College of Cardiology*.

But in an [editorial accompanying](#) both reports, John Burnett, MD, PhD, from the University of Western Australia in Perth, and colleagues cautioned that it would be "premature to discard LDL-C based on PREDIMED."

The findings are "insufficient to offset the mountain of literally hundreds of studies that uphold the value of LDL-C in prediction and intervention of ASCVD," Burnett and coauthors write.

Similarly, the editorialists cautioned that although the findings from the study by Nordestgaard and colleagues indicate that VLDL cholesterol is the "new kid in town for prediction, LDL cholesterol retains predictive power." Clinical cardiologists should not "shelve LDL cholesterol and embrace VLDL and remnant cholesterol as the new oracles of ASCVD risk."

Commenting for [theheart.org](#) | [Medscape Cardiology](#), Burnett said, "The take-home message for clinicians in both papers is that LDL-C is the main lipid measurement to guide clinical decisions; however, residual risk of atherosclerotic cardiovascular disease remains, even after LCL-C is treated.

"Assessment of residual ASCVD risk with nontraditional lipid biomarkers, including VLDL cholesterol and remnant cholesterol, as well as [lipoprotein \(a\)](#) and apoB, may improve prognostication and help guide preventive treatments," he added.

"Affordable and Inexpensive"

In their report, the PREDIMED study authors explain that atherogenic dyslipidemia is characterized by "an excess of serum triglycerides" contained in VLDL, intermediate-density lipoproteins, and their remnants, all of which are called "triglyceride-rich lipoproteins (TRLs)."

TRLs and remnant-C "have the capacity to cross the arterial wall," and may therefore play a causal role in [atherosclerosis](#) development, they write.

The [main PREDIMED trial](#) compared a low-fat diet with the Mediterranean Diet for the primary prevention of CVD in high-risk participants. Those enrolled in the trial "had a high prevalence of diabetes, obesity, and [metabolic syndrome](#), conditions that are associated with [insulin resistance](#), [hypertriglyceridemia](#), and atherogenic dyslipidemia," the current authors write. "Thus, this cohort of subjects at high cardiovascular risk was well suited to investigate the association of triglycerides and TRLs with cardiovascular outcomes."

The researchers investigated the role of triglycerides and remnant-C in incident CVD among these high-risk individuals, particularly those with chronic cardiometabolic disorders (pre-diabetes, type 2 diabetes, and poorly controlled diabetes); overweight and obesity; metabolic syndrome; and renal failure.

Their 6901 participants (42.6% male, mean age 67 years, mean BMI 30.0 kg/m²) had a diagnosis of type 2 diabetes or ≥3 CVD risk factors including current smoking, hypertension, elevated LDL-C levels, low HDL-C levels, elevated BMI, or family history of premature coronary heart disease.

The primary study endpoint was a composite of adverse cardiovascular events (MACE): MI, stroke, or cardiovascular death. Participants were followed for a mean of 4.8 years, during which there was a total of 263 MACE events.

Multivariable-adjusted analyses showed that levels of triglycerides and remnant-C were both associated with MACE independent of other risk factors (HR, 1.04; 95% CI, 1.02 - 1.06; and HR, 1.21; 95% CI, 1.10 - 1.33 per 10 mg/dl, respectively, both $P < .001$). Non-HDL-C was also associated with MACE (HR, 1.05; 95% CI, 1.01 - 1.10 per 10 mg/dl, $P = .026$).

In particular, elevated remnant-C (≥ 30 mg/dL), compared with lower concentrations, flagged subjects at a higher risk of MACE, even if their LDL-C levels were at target (defined as ≤ 100 mg/dL).

Levels of LDL-C and HDL-C were not associated with MACE.

"The indirect calculation of remnant-C is an affordable and inexpensive method, which could provide valuable data for clinical management," Fitó Colomer said.

"The results of this study suggest that, in individuals at high cardiovascular risk with well-controlled LDL-C, triglycerides and mainly remnant-C should be considered as a treatment target," she proposed.

New Oracles?

Evidence has pointed to triglyceride-rich remnants or VLDLs as contributing to atherosclerotic CVD, together with LDL-cholesterol, but it is "unclear which fraction of risk is explained by, respectively, cholesterol and triglycerides in VLDL," write the authors of the Copenhagen population study.

Nordestgaard said their study was motivated by an awareness that "in clinical practice, the focus for lipid-related risk is almost solely on reduction of LDL-C for prevention of ASCVD," so the current focus needs to be reevaluated because patients with low LDL-C but elevated VLDL-C and plasma triglycerides "may not be offered adequate preventive lipid-lowering therapy in order to prevent future MI and ASCVD."

His group therefore tested the hypothesis that VLDL-C and triglycerides may each explain part of the MI risk from apoB-containing lipoproteins.

They used measurements of plasma apoB and cholesterol and triglyceride content of VLDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and LDL-C in the study participants (N = 25,480, median age 61 years, 53% female), who were required to be free of MI and not receiving lipid-lowering therapy at baseline.

During a median 11-year follow-up period, 1816 participants experienced an MI. They tended to be older compared with those who did not experience an MI, and also more likely to be male, to smoke, and to have higher systolic blood pressure.

Each 39-mg/dL increase in lipid level was found to be associated with higher MI risk.

Table. Risk for myocardial infarction by lipid fraction

Lipid fraction	Adjusted HR (95% CI) with each 39 mg/dL increase
VLDL cholesterol	2.07 (1.81 - 2.36)
VLDL triglycerides	1.19 (1.14 - 1.25)
IDL cholesterol	5.38 (3.73 - 7.75)
LDL cholesterol	1.86 (1.62 - 2.14)

The researchers looked at MI-associated risk of specific subfractions of apoB-containing lipoproteins. "VLDL cholesterol explained half of the MI risk from elevated apoB-containing lipoproteins, and IDL and LDL-C together accounted for only 29% of the risk," Nordestgaard said.

"If LDL cholesterol is adequately reduced, clinicians need to evaluate possible elevated triglyceride-rich lipoproteins, either as elevated plasma triglycerides, remnant cholesterol, or elevated VLDL cholesterol; and, if elevated, consideration should also be given to reduction of triglyceride-rich lipoproteins," he advised.

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Full text [Remnant Cholesterol](#)

Full text [VLDL Cholesterol](#)

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