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Editorial

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Contribution of Remnant Cholesterol to Coronary Atherosclerosis

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Recently, genetic studies have identified elevated serum levels of triglyceride (TG) as causal factors for atherosclerosis and atherosclerotic cardiovascular disease (ASCVD)[1]. TGs are major components of TG-rich lipoproteins (TRLs), such as chylomicrons (CM) and very low-density lipoproteins (VLDLs), and are rapidly catabolized in circulating blood by lipoprotein lipase (LPL) on the blood vessel walls, producing respective remnant lipoproteins (remnants), which are rich in cholesterol relative to TGs. Although serum TGs accumulate much less than cholesterol in atherosclerotic plaques and are unlikely to directly cause atherosclerosis, elevated serum TG levels reflect increased levels of TRLs and may serve as biomarkers of elevated levels of cholesterol in RLPs and as causal factors for ASCVD.

Shao *et al.* investigated the association between elevated remnant cholesterol (RC) levels and cardiovascular outcomes in patients with acute coronary syndrome (ACS) with or without diabetes[2]. RC was calculated as total cholesterol minus high-density lipoprotein-cholesterol (HDL-C) minus low-density lipoprotein-cholesterol (LDL-C). During a median follow-up of 927 days, patients with abnormally elevated RC (>0.79 mmol/L) had significantly higher recurrent major adverse cardiovascular events (MACEs) than those with RC ≤ 0.79 mmol/L even if serum LDL-C levels were controlled under the target levels, especially in patients with diabetes. RC demonstrated a significantly higher risk of MACEs after adjustments for potential confounders in patients with or without diabetes (hazard ratio [95% confidence interval]: 1.667 [1.222–2.276] and 1.501 [1.060–2.125], respectively). In patients with diabetes, RC significantly improved the predictive ability of the baseline models for MACEs, but not in patients without diabetes.

Most guidelines propose that non-HDL-C is a secondary therapeutic target after achieving target LDL-C levels. In this study, plasma LDL-C and non-HDL-C levels were below the therapeutic target goals; however, RC remained a significant residual risk factor for ASCVD events, especially in patients with diabetes. Patients with diabetes have more ASCVD events than those without diabetes, despite a marked reduction in LDL-C levels, which indicates a significant residual ASCD risk. There are several reasons why LDL-C-lowering therapy in patients with diabetes cannot reduce ASCVD events to the same levels as found in patients without diabetes. First, the atherogenic lipid profile in patients with diabetes is characterized not only by increased TG levels and decreased HDL-C levels, but also by increased small-dense LDL particles and RC levels. In patients with diabetes, insulin resistance increases hepatic VLDL production and decreases the clearance of TRLs. Elevated VLDL-TGs further activate cholesteryl ester transfer protein (CETP), which causes TG enrichment in LDLs and HDLs. The TG content of these particles is hydrolyzed by hepatic triglyceride lipase, resulting in the formation of small-dense LDL and HDL particles. Studies have reported that small-dense LDL is positively associated with coronary artery disease (CAD) and is a risk marker for the condition[3]. Second, a previous study demonstrated that an increased RC level is an independent risk factor for CAD and a predictor of future coronary events in patients with CAD and type 2 diabetes[4, 5]. Fujihara *et al.* also demonstrated that remnant-like lipoprotein particle cholesterol (RLP-C) measured by the immune-separation method was a significant predictor of future ASCVD events in patients with stable CAD and controlled LDL-C levels (<70 mg/dL) receiving

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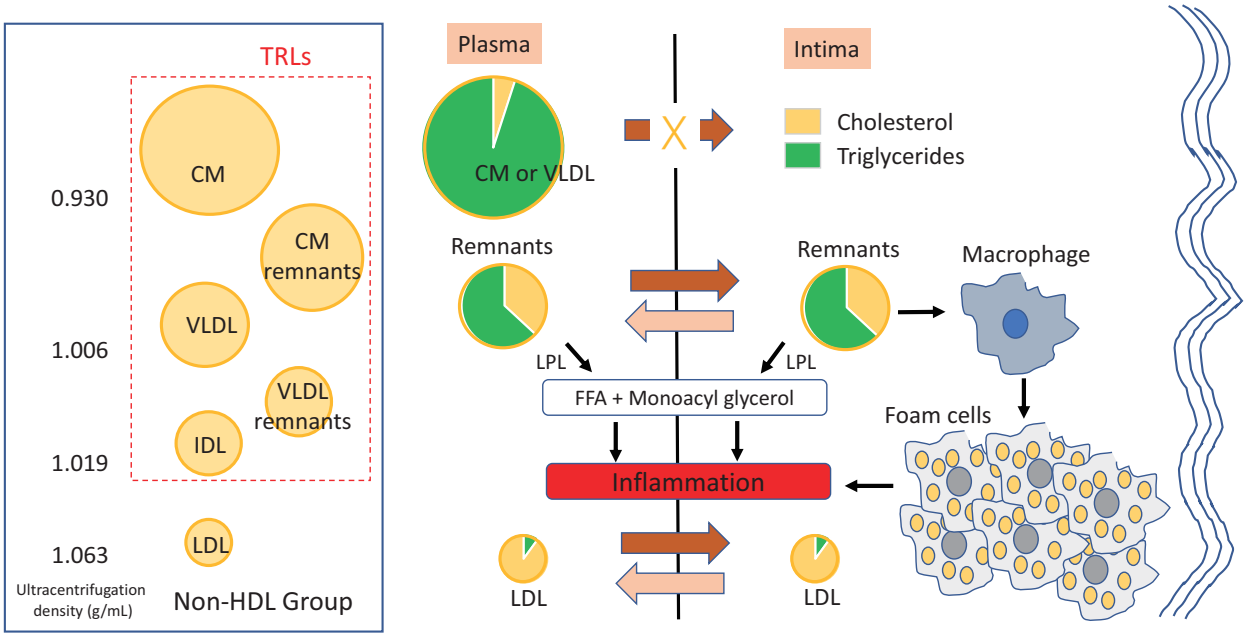

TRL: triglyceride-rich lipoprotein, CM: chylomicron, VLDL: very low-density lipoprotein, IDL: intermediate-density lipoprotein, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FFA: free fatty acid, LPL: lipoprotein lipase

Modified construction from Nordestgaard BG, and Varbo A. Lancet 2014; 384: 626–635.

Fig. 1. Stratification of lipoproteins, and raised plasma remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis. RLPs constitute a diverse population of particles, which cannot be effectively separated from other lipoproteins.

statin[6]. Atherosclerotic lesions in patients with diabetes have a greater number of macrophages and tend to be more inflammatory[7]. This phenomenon may be at least partly linked to elevated plasma levels of TRLs. Unlike LDL particles, remnants can penetrate the arterial intima and can be directly taken up by macrophages without undergoing oxidative modification[8]. Moreover, LPL on the endothelial surface or within the arterial intima degrades TGs in VLDL and VLDL remnants, with liberation of free fatty acids and monoacylglycerols, both of which cause tissue toxicity, such as endothelial dysfunction, and precipitate local inflammation[9]. Therefore, it is presumed that elevated remnants are associated with low-grade inflammation and accelerate foam cell formation via macrophage uptake directly at the arterial wall, followed by the development of atherosclerosis (Fig. 1)[1]. Thus, RLP-C or calculated RC (clinically estimated as remnants) might be promising therapeutic targets to prevent the development of atherosclerosis and ASCVD events, especially in very high-risk patients such as those with ACS and/or those with diabetes after ACS.

However, some issues remain to be resolved. First, there is no established method for measuring the cholesterol content of TRLs or remnants. Most CM-derived remnants are cleared by the liver, and VLDL-derived remnants undergo additional lipolysis by LPL, followed by conversion to LDL. Remnants consist of a heterogeneous population of lipoprotein particles, varying in size and composition because remnants are dynamic products of the ongoing lipolysis of CMs and VLDLs (Fig. 1). Therefore, remnants cannot be clearly separated from other lipoproteins, although they are classified by ultracentrifugation density and particle size. From this point of view, it is reasonable to calculate RC using the serum total cholesterol minus HDL-C minus LDL-C. Second, further studies are needed to clarify whether RC or non-HDL-C is a better therapeutic target to effectively reduce the residual risk. Third, it should be clarified whether RC-lowering therapy can reduce the residual risk of ASCVD events. Post-hoc analysis in the Treating to New Targets (TNT) trial demonstrated that a reduction in TRL-cholesterol (TRL-C) with statins resulted in a significantly lower risk of MACEs, independent of the reduction in LDL-C among patients with CAD and elevated levels of TRL-C[10]. Considering the above and a report from Japan[6], more intensive LDL-C-lowering therapy for achieving far less than 70 mg/dL by high-intensity statins may reduce the residual risk in those with higher RC levels. However, further research is required to determine whether combination therapy with high-

intensity statins and ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors leads to further benefits in cardiovascular risk reduction. On the other hand, there are no data on whether altering TRLs or RC via the LPL pathway by TG-lowering therapy can reduce cardiovascular events. The results of ongoing clinical trials should help to answer this question. The PROMINENT trial was designed to the target residual cardiovascular risk remaining after treatment in order to reduce LDL-C in individuals with dyslipidemia in type 2 diabetes using pemafibrate, which is a selective peroxisome proliferator-activated receptor alpha modulator (SPPARM-α)[11]. A phase II trial using vupanorsen, which selectively inhibits angiopoietin-like 3 (ANGPTL3) protein synthesis, demonstrated a favorable lipid/lipoprotein profile, including reduced serum levels of TG, remnant cholesterol, non-HDL-C, and apolipoprotein B, and increased serum levels of HDL-C, and provides a potential strategy for reducing residual cardiovascular risk[12]. These trials may provide further insights into the cardiovascular benefits of TRL-C-lowering therapy.

Conflicts of Interest

None.

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