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Editorial

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Personalized Medicine beyond Low-Density Lipoprotein Cholesterol to Combat Residual Risk for Coronary Artery Disease

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Assessing Residual Risks for Coronary Artery Disease

There are many biomarkers that have been shown as residual risks for coronary artery disease (CAD). Among them, serum lipids, including triglycerides (triglyceride-rich lipoproteins), lipoprotein (a) [Lp(a)], and small dense low-density lipoprotein (LDL) cholesterol (sd-LDL-C) can be considered as "established" residual risks, as not only observational studies but also post-hoc analysis of randomized controlled trial using statins, as well as Mendelian randomization studies suggested that these lipids appear to be associated with CAD, independent of LDL-C[1-5]. We need to keep in mind the simple fact that cholesterol is one of the major causes of atherosclerosis. In this sense, it is not surprising that these lipids containing cholesterol that are not cleared sufficiently from blood using statins are one of the major residual risks. Additionally, it is of note that there is some difference among these lipids regarding the effects on atherosclerosis. For example, triglyceride-rich lipoproteins is associated with myocardial infarction and peripheral artery disease, whereas, sd-LDL-C is associated with MI alone[6]. In this issue, Sekimoto *et al.* showed that the sd-LDL-C level was a residual risk for CAD in this statin era among patients with acute coronary syndrome[7]. The assessment of sd-LDL-C appears to be useful for the risk stratification beyond LDL-C because the total volume of LDL-C may not be reflecting accurate cardiovascular risk **(Fig. 1)**. This information can be used as personalized medicine, at least for the risk prediction of various types of atherosclerotic disease.

Apolipoprotein B, "B" for Bad

Recent Mendelian randomization studies have suggested the causal relationships between these lipids and CAD. Although triglyceride-rich lipoproteins, Lp(a), and sd-LDL-C are all considered as lipids, we usually regard them as different properties. However, Ference *et al.* have shown that Mendelian randomization studies for LDL-C and triglycerides can be combined in one axis when we focus on apolipoprotein B, rather than triglycerides or LDL-C[8]. Regardless of the difference of the content, apolipoprotein B-containing lipoproteins are atherogenic, suggesting that "B" of apolipoprotein B stands for "bad" for atherosclerosis. In fact, we have shown that individuals with a protein-truncating mutation in *APOB* whose apolipoprotein B level is quite low exhibit extremely cardio-protective phenotype[9].

Do not be Satisfied with the Assessments of LDL-C Alone

In our clinic, we typically assess LDL-C using the Friedwald's formula. However, it has been shown that there are substantial differences regarding atherogenic properties among different sizes/densities of lipoproteins, even among "LDL" particles. We cannot differentiate clearly the atherogenic properties of LDL particles through the standard measurements of LDL-C. The assessments of sd-LCL-C should be considered, especially in the patients with metabolic syndrome, insulin resistance, and those who eat high-carbohydrate diet where the associations with

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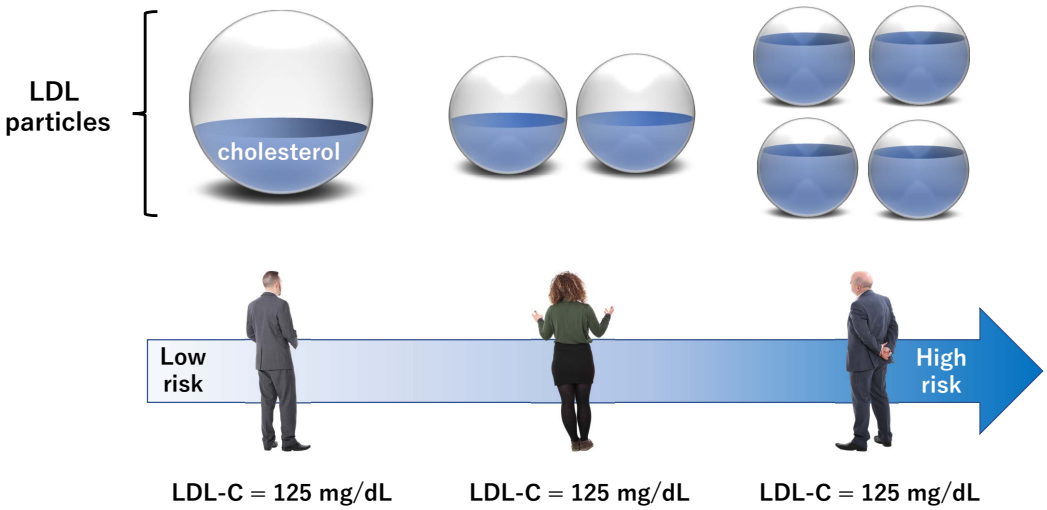

Fig. 1. Risk stratification among individuals whose LDL-C are the same

Even among the individuals whose LDL-C are the same, the atherogenicity of the LDL particles are different.

sd-LDL-C are observed[10].

Toward Personalized Medicine to Combat Residual Risks

Based on the notion that sd-LDL-C appears to be causally associated with CAD, it can be used as an useful tool for personalized medicine, especially to combat the residual risk. Now, there are many agents to lower apolipoprotein B-containing lipoproteins on top of statins, including ezetimibe, resins, fibrates, proprotein convertase subtilisin/kexin type 9 inhibitors, polyunsaturated fatty acids, microsomal triglyceride transfer protein inhibitors, and bempedoic acids. Several more agents such as angiopoietin-like 3 inhibitor, antisense oligonucleotide for Lp(a), and apolipoprotein C3 inhibitor will be coming soon. We need more detailed data as to which agents are better for whom and for what reasons, including the effects on sd-LDL-C, and triglyceride-rich lipoproteins. This information should collectively lead to our more advanced personalized medicine to combat residual risk for CAD.

Conclusion

Apolipoprotein B-containing lipoproteins, including sd-LDL-C, are one of the established residual risk factors for CAD. We need to be much more careful for this variable, especially in the patients with metabolic syndrome, insulin resistance, and those who eat a high-carbohydrate diet.

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Conflict of Interest

None.

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