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Editorial

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Is Non-High-Density Lipoprotein Cholesterol Evaluation Perfect? From the High-Density Lipoprotein Function Viewpoint

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Low-density lipoprotein cholesterol (LDL-C) is one of the established risk factors for atherosclerotic cardiovascular disease (ASCVD). Serum LDL-C levels are measured directly or calculated using Friedewald equation; however, the accuracy of LDL-C values reduces under the presence of extremely high triglycerides levels in both methods. Furthermore, atherogenic remnant lipoproteins, such as intermediate metabolites of chylomicron and very-low-density lipoprotein, are not evaluated during LDL-C measurement. To overcome these limitations, estimation of non-high-density lipoprotein cholesterol (non-HDL-C) has emerged as a simple and comprehensive evaluation of atherogenic lipoprotein profile, including low-density and remnant lipoproteins.

In the recent issue of JAT, Hu *et al.* reported[1] that elevated non-HDL-C levels increased cardiovascular risk in a contemporary Japanese worksite-based cohort. Intriguingly, a decrease in non-HDL-C levels also showed a trend toward increase in total cardiovascular risk, specifically the risk of stroke. One possible explanation for this U-shaped relationship is the presence of individual variations of HDL function. Although HDL-C is considered to have anti-atherogenic function, a previous cohort study[2] indicated that extremely high HDL-C levels increased the prevalence of ischemic ST-segment changes on electrocardiography. These findings suggest that HDL-C does not necessarily function as anti-atherogenic. Among the several anti-atherogenic functions of HDL, one of its vital actions is cholesterol efflux capacity, which is the ability of HDL to accept cholesterol from macrophages in the arterial wall. A recent population-based cohort study conducted in the United States of America[3] reported only a weak correlation between cholesterol efflux capacity of HDL and serum HDL-C concentrations (correlation coefficients=0.07). Moreover, serum HDL-C levels did not indicate any predictive value for future ASCVD onset after adjusting for traditional risk factors, while reduced cholesterol efflux capacity of HDL significantly increased the risk of ASCVD even after adjusting for traditional risk factors including HDL-C levels. These results indicate that HDL function, rather than HDL-C levels, is a real risk factor for ASCVD. The low non-HDL-C levels result from low total cholesterol levels, high HDL-C levels, or both. Therefore, the recent findings by Hu *et al.*[1] regarding the relationship between low non-HDL-C and increased cardiovascular risk may be partially explained by the presence of individuals with high HDL-C but reduced HDL function in this cohort.

The conventional procedure for evaluation of cholesterol efflux capacity of HDL requires preparation of incubated macrophages with radio- or fluorescence-labeled cholesterol, and is extremely time-consuming. This complex and inefficient procedure hinders the HDL function estimation in a high-throughput environment including daily clinical settings. Recently, a plate-assay system without using radioisotopes or cells has been developed for easy assessment of cholesterol uptake capacity (CUC) of HDL[4], which is considered substantially identical to cholesterol efflux capacity of HDL. A clinical study[5] demonstrated the usefulness of measuring CUC of HDL for the prediction of long-term coronary stent failure after coronary percutaneous intervention. However, there is no clear evidence of CUC of HDL as an independent risk factor for ASCVD in epidemiological settings so far.

Possible strengths and limitations of non-HDL-C

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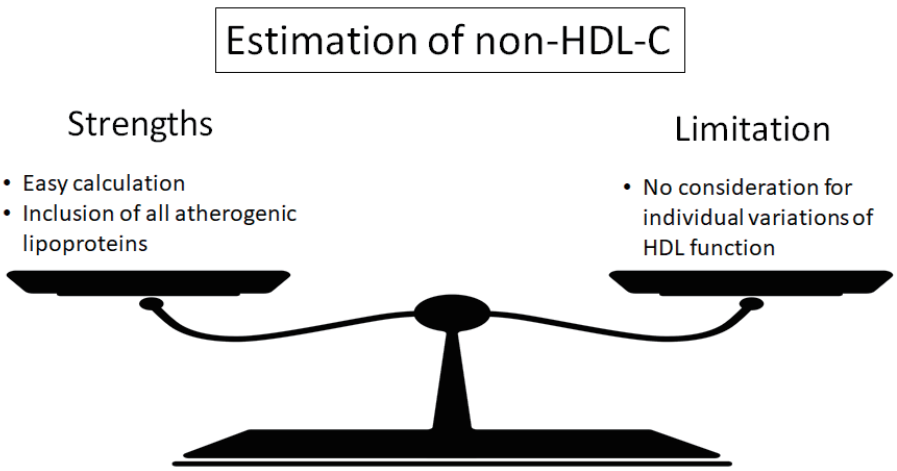

Fig. 1. Strengths and limitation of the estimation of non-HDL-C
HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol

measurement are summarized in **Fig. 1**. Further epidemiological studies are anticipated to clarify the usefulness of the CUC of HDL, such as an improved ability for predicting future risk of ASCVD by combined assessment of non-HDL-C and CUC of HDL within the general population.

Conflicts of Interest

None.

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