Editorial

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Apolipoprotein B, Non-HDL Cholesterol, and LDL Cholesterol as Markers for Atherosclerotic Cardiovascular Disease Risk Assessment

Despite evidence for the superiority of non-HDL cholesterol (HDL-C) and apolipoprotein B (Apo B) in the accurate estimation of atherosclerotic cardiovascular disease (ASCVD) risk [1-4], LDL cholesterol (LDL-C) remains the primary marker recommended in major lipid guidelines to judge treatment adequacy [5, 6]. Non-HDL-C values are calculated by subtracting the HDL-C level from the total cholesterol level, which can reflect LDL-C levels as well as very low-density lipoprotein cholesterol (VLDL-C), intermediate-density lipoprotein cholesterol (IDL-C), remnant parts, and lipoprotein (a) [Lp (a)] levels [7]. Apo B is the main protein that makes up LDL-C, VLDL-C, IDL-C, and Lp (a). All lipoprotein particles have a single Apo B molecule; therefore, when Apo B is measured, it is possible to check the number of VLDL-C, IDL-C, and Lp (a) particles, including LDL-C, as ASCVD risk factors [2]. Trapping of Apo B in the arterial wall is the main cause of ASCVD, and cholesterol is the only proatherogenic element deposited after Apo B is trapped in the arterial wall. Oxidized phospholipids and Apo B are powerful inducers of inflammation, damage, and angiogenesis, and Apo B particles are fundamental factors in arterial wall injury [2, 4]. Since VLDL particles are also atherogenic and Apo B levels can reflect the number of VLDL particles as well as LDL, the Apo B level can be used to more accurately assess ASCVD risk than LDL-C and non-HDL-C levels [1, 2, 4, 6].

The 2019 European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) guidelines suggest that Apo B can more accurately measure ASCVD risk and the adequacy of lipid-lowering treatment than LDL-C or non-HDL-C and that Apo B can also be measured more accurately than LDL-C and non-HDL-C [6]. However, owing to the very high correlations among LDL-C, non-HDL-C, and Apo B, it has been suggested that Apo B may in fact not be superior to non-HDL-C and LDL-C for risk assessment [8, 9].

In this issue of *Annals of Laboratory Medicine*, Yun, *et al.* [10] report that the Apo B level can serve a useful marker for ASCVD risk assessment in patients with ASCVD risk factors, even those presenting normal LDL-C levels. Because LDL-C, non-HDL-C, and Apo B are highly correlated, it is very difficult to distinguish their individual relationships with ASCVD risk using a general statistical analysis method. Discordance analysis can be used to compare highly correlated variables, which could enable comparison between patients with average and discordant (higher or lower than average) cholesterol mass per Apo B particle [2, 11]. Johannesen, *et al.* [1] conducted the first discordance analysis in patients treated with a statin for myocardial infarction and assessed death risk according to discordant Apo B, non-HDL-C, and LDL-C levels. They found that high Apo B or non-HDL-C but low LDL-C levels were associated with an increased risk of ASCVD and mortality, whereas high LDL-C but low Apo B or non-HDL-C levels did not show an association. High Apo B/low non-HDL-C was associated with a higher all-cause risk than low

Apo B/high non-HDL-C. In conclusion, Johannesen, *et al.* [1] suggested that Apo B is a more accurate ASCVD risk marker than LDL-C and non-HDL-C in statin-treated patients.

Yun, *et al.* [10] conducted the first discordance analysis study for ASCVD risk in adults using Apo B, non-HDL-C, and LDL-C levels based on Korean Genome and Epidemiology Study data. They divided patients according to median Apo B, non-HDL-C, and LDL-C levels and compared the ASCVD risk between the four discordant groups (high Apo B/low LDL-C, high Apo B/low LDL-C, high non-HDL-C/low LDL-C, and low non-HDL-C/high LDL-C) and the four concordant groups (low Apo B/low LDL-C, high Apo B/high LDL-C, low non-HDL-C/low LDL-C, and high non-HDL-C/high LDL-C) [10]. The high Apo B/low LDL-C patient group showed the highest adjusted hazard ratio (aHR) per 1-SD ASCVD compared to the low Apo B/low LDL-C patient group, and an increased ASCVD risk was found in patients with high Apo B and low LDL-C levels [10].

Despite recent reports on the superiority of Apo B for accurate ASCVD risk and treatment target assessment, current guidelines still recommend using LDL-C as the primary marker for ASCVD risk assessment and lipid-lowering therapy [5, 6]. In 2012, Sniderman, *et al.* [3] estimated that using non-HDL-C rather than LDL-C as a treatment target indicator would prevent 300,000 more cardiovascular events over 10 yrs in adults in the United States and using Apo B rather than LDL-C would prevent 500,000 more events. The Apo B level can be conveniently measured at low cost in routine clinical laboratories and the measurements are more accurate than those of LDL-C or non-HDL-C [6]. Further in-depth study and evaluation are required to validate the recently proposed candidate primary markers for accurate ASCVD risk assessment [12, 13]. Continuous efforts to determine the best way for ASCVD risk assessment and treatment target are required.

AUTHOR CONTRIBUTIONS

Yun YM contributed to the manuscript writing.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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