Residual Risk Still Remains in Low-Density Lipoprotein

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The development of statins has significantly improved the prognosis of patients with coronary artery disease (CAD). Furthermore, the low-density lipoprotein (LDL)-cholesterol (C)-lowering effect of statins strongly suggests that LDL-C is the main cause of CAD. However, some patients have been reported to still develop CAD even after treatment with statin. Thus, the term “residual risk factor” has become a popular subject of discussion. Residual risk means a risk that cannot be reduced by statin therapy. It is also widely recognized as risk associated with hypertriglyceridemia and low high-density lipoprotein (HDL)-C. However, whether they really cause residual risk remains undetermined.

Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) is a large-scale secondary intervention study, which was conducted to examine if the high-dose pitavastatin therapy (4 mg/dL) can reduce the risk of major adverse cardiovascular events (MACE) in patients with stable CAD compared with the low-dose pitavastatin therapy (1 mg/dL). The results indicated that high-intensity statin therapy was beneficial for CAD patients compared with low-intensity statin therapy. The switching from low to high doses of pitavastatin resulted in a further reduction in LDL-C. This study demonstrated a significant reduction in the occurrence of MACE in the high-dose statin group. However, it remains unclear whether the reduction was entirely due to a decrease in LDL-C and who the responder to high-dose pitavastatin is.

In this study, the most attractive finding is that high-dose (relative to low-dose) pitavastatin therapy remarkably reduced the MACE risk by 46% in the study patients whose sdLDL-C level at baseline was in the top quartile (>34.3 mg/dL). However, this beneficial effect of high-dose pitavastatin was not observed in patients whose sdLDL-C levels were lower than 34.3 mg/dL at baseline. In contrast, there was no association between baseline LDL-C level and risk reduction of MACE by the high-dose pitavastatin therapy. Many large cohort studies have demonstrated the significant contribution of sdLDL-C to atherosclerotic cardiovascular disease (ASCVD) beyond LDL-C. However, little is known about the potentiality of sdLDL-C as a risk marker for ASCVD in secondary prevention studies.

This study by Ishii et al. provided additional evidence that sdLDL-C is strongly associated with the occurrence of cardiovascular events in CAD patients. Among the study population, the greatest reduction of sdLDL-C after treatment with high-dose pitavastatin was observed in patients who had higher levels of baseline sdLDL-C, and the same group of patients had the greatest risk reduction of MACE. This indicates that lowering sdLDL-C helps prevent the risk of MACE. Our group previously reported that in stable CAD patients, a higher sdLDL-C level (>35 mg/dL) was associated with worse prognosis, whereas a higher LDL-C level (>100 mg/dL) was not. Altogether, an sdLDL-C level greater than 35 mg/dL is considered to be dangerous for CAD patients even when the LDL-C levels are well-controlled.

Similar to sdLDL-C, the reduction of MACE risk by the high-dose pitavastatin therapy was prominent in patients whose triglyceride and TRL-C levels were in the top quartile. However, statin treatment did not reduce the triglyceride or TRL-C levels as it did for sdLDL-C. Many interventional studies using statins have demonstrated that statins significantly reduce the risk of MACE in...
subjects with hypertriglyceridemia without altering the triglyceride levels. These clinical evidences suggest that sdLDL-C, rather than triglyceride and TRL-C, is causally associated with MACE, whereas triglyceride and TRL-C are indirectly associated through enhanced sdLDL production pathway7).

The REAL-CAD study may justify the “Fire and Forget” strategy, the idea of which is that if the maximum amount of statin is given, the LDL-C levels do not need to be monitored. In contrast, this subanalysis of REAL-CAD reminds us of the need for the “Treat to Target” approach. The LDL-C goals of the ASCVD prevention guidelines are frequently revised. The main reason may be that LDL-C is not a sensitive risk marker for ASVCD. Current research suggests that sdLDL-C is a potential alternative to LDL-C as a new target for treatment. SdLDL-C may be a good indicator in determining the intensity of treatment that cannot be determined via LDL-C. Unfortunately, in this study, sdLDL-C was measured in only 13% of the subjects in the original REAL-CAD study, and there is no available lipid data at the later time of the follow-up duration. Therefore, accurate determination of the cutoff point for sdLDL-C that will prevent the occurrence of subsequent MACE is impossible. Nonetheless, this article by Ishii et al 2) strongly suggests the need for a “Target to Treat” strategy so as to efficiently select high-risk patients and evaluate the power of lipid-lowering agents. A number of non-statin lipid-lowering drugs, such as PCSK9 inhibitors, ezetimibe, and new fibrate, are currently available. The combination of statins and these drugs is expected to lower sdLDL-C more significantly than high-dose statins alone. With a variety of treatment options, “Fire and Forget” using statin alone is already becoming a thing of the past. Finally, the current study strongly suggests that LDL particles are not equally created 8) and that true residual risk still remains in LDL.

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References

8) Krauss RM: Low-density lipoprotein particles are not created equal. Arterioscler, Thromb, Vasc Biol, 2014; 34: 959-996