Do We Expect Any Pleiotropic Effect of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition for Reducing Cardiovascular Events Beyond Low-Density Lipoprotein Cholesterol Reduction?

Hayato Tada, MD; Masa-aki Kawashiri, MD; Masakazu Yamagishi, MD

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been shown to play an important role in regulating low-density lipoprotein (LDL) cholesterol by binding to LDL receptors and targeting them for intracellular degradation.1-3 In addition, a recent clinical trial showed beneficial effects of PCSK9 inhibition on reducing not only LDL-cholesterol, but also cardiovascular disease (CVD).4

Although PCSK9 appears to play a crucial role in atherosclerosis, the usefulness of circulating PCSK9 as a biomarker for risk assessment of CVD in the general population remains unclear.5-7 In this issue of the Journal, Xiao et al8 investigate if circulating PCSK9 levels are associated with CVD using a schema of meta-analysis from prospective studies. The authors conclude that essentially no association was observed between circulating PCSK9 level and CVD. The prospective studies the authors included accounted for LDL-cholesterol levels. Accordingly, this critical question can be translated as, “Is there any pleiotropic effect in PCSK9 level (and PCSK9 inhibition) for reducing CVD events beyond LDL-cholesterol reduction?”

Regarding the issue of pleiotropic effect, considering the associations between genetic variations/pharmacological interventions and LDL-cholesterol/CVD is a good way of looking at this topic. Mendelian randomization studies have repeatedly shown that polymorphisms that are associated with lower LDL-cholesterol, including PCSK9 gene variations, are also associated with a lower risk of CVD. The magnitude of the reduction of the risk of CVD linearly correlates with the magnitude of the reduction of LDL-cholesterol as a result of polymorphisms, regardless of genes (Figure).9 This relationship between genetically mediated LDL-cholesterol and CVD risk reduction seems to be similar to that observed in randomized controlled trials using statins, ezetimibe, and PCSK9 inhibition, although the magnitude of the association is stronger in individuals with life-long exposure from...
If PCSK9 inhibition has any pleiotropic effect on reducing CVD events, the plots of genetic variations of the PCSK9 gene and those of randomized controlled trials should deviate to the upper side (of the Figure) compared with other plots comprising other targets. However, the linear relationship between magnitude of the reduction of the risk of CVD and that of the reduction of LDL-cholesterol, regardless of genes as well as drugs, suggests that there is no pleiotropic effect from such LDL-cholesterol-lowering genes and drugs, including PCSK9 inhibition. Consistent with this notion, a recent study showed that circulating PCSK9 does not contribute useful information in the assessment of myocardial infarction risk in the general population beyond the information provided by LDL-cholesterol measurement.10

Conclusions
In summary, the data collectively suggest that we cannot expect pleiotropic effects of PCSK9 inhibition for reducing CVD events beyond LDL-cholesterol reduction. Further studies focusing on the beneficial effects of reducing lipoprotein (a) [Lp(a)] by PCSK9 inhibition on Lp(a)-associated events such as aortic stenosis would be interesting, because PCSK9 inhibition could reduce Lp(a) levels substantially.11

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References