Circ J 2017; **81:** 1098–1099
doi:10.1253/circj.CJ-17-0586

EDITORIAL

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 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 al[8] 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.

Article p1150

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

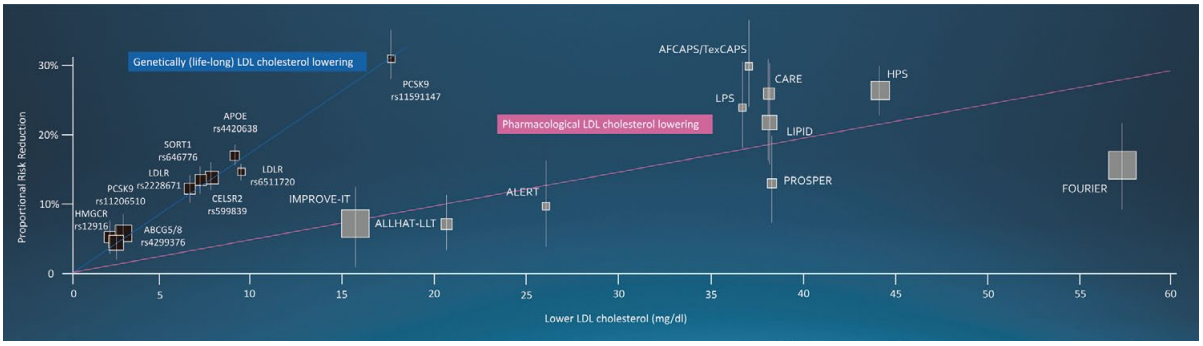

Figure. Linear relationship between coronary artery disease (CAD) risk reduction and lowering of low-density lipoprotein (LDL) cholesterol. Blue line indicates the relationship between CAD risk reduction and genetic (lifelong) LDL-cholesterol lowering. Pink line indicates the relationship between CAD risk reduction and pharmacological lowering of LDL-cholesterol.

Received June 12, 2017; accepted June 13, 2017; released online July 1, 2017
Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Japan
Mailing address: Hayato Tada, MD, Division of Cardiovascular Medicine, Kanazawa University Graduate School of Medicine, 13-1 Takara-machi, Kanazawa 920-8641, Japan. E-mail: ht240z@sa3.so-net.ne.jp
ISSN-1346-9843

genetic variants (**Figure**). 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]

Acknowledgments / Sources of Funding / Conflict of Interest

None.

References

1. Steg PG, Ducrocq G. Future of the prevention and treatment of coronary artery disease. *Circ J* 2016; **80:** 1067–1072.
2. Tada H, Kawashiri MA, Nohara A, Inazu A, Mabuchi H, Yamagishi M. Impact of clinical signs and genetic diagnosis of familial hypercholesterolaemia on the prevalence of coronary artery disease in patients with severe hypercholesterolaemia. *Eur Heart J* 2017; **38:** 1573–1579.
3. Mabuchi H, Nohara A, Noguchi T, Kobayashi J, Kawashiri MA, Inoue T, et al. Genotypic and phenotypic features in homozygous familial hypercholesterolemia caused by proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutation. *Atherosclerosis* 2014; **236:** 54–61.
4. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; **376:** 1713–1722.
5. Leander K, Mälarstig A, Van't Hooft FM, Hyde C, Hellénius ML, Troutt JS, et al. Circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) predicts future risk of cardiovascular events independently of established risk factors. *Circulation* 2016; **133:** 1230–1239.
6. Ridker PM, Rifai N, Bradwin G, Rose L. Plasma proprotein convertase subtilisin/kexin type 9 levels and the risk of first cardiovascular events. *Eur Heart J* 2016; **37:** 554–560.
7. Zhu YM, Anderson TJ, Sikdar K, Fung M, McQueen MJ, Lonn EM, et al. Association of proprotein convertase subtilisin/kexin type 9 (PCSK9) with cardiovascular risk in primary prevention. *Arterioscler Thromb Vasc Biol* 2015; **35:** 2254–2259.
8. Xiao Y, Peng C, Huang W, Zhang J, Gao Y, Kim JH, et al. Proprotein convertase subtilisin/kexin type 9 (PCSK9) concentration and risk of cardiovascular events: Systematic review and meta-analysis of prospective studies. *Circ J* 2017; **81:** 1150–1157.
9. Tada H, Kawashiri MA, Yamagishi M. Comprehensive genotyping in dyslipidemia: Mendelian dyslipidemias caused by rare variants and Mendelian randomization studies using common variants. *J Hum Genet* 2017; **62:** 453–458.
10. Laugsand LE, Åsvold BO, Vatten LJ, Janszky I, Platou CG, Michelsen AE, et al. Circulating PCSK9 and risk of myocardial infarction. *JACC Basic Transl Sci* 2016; **1:** 568–575.
11. Tada H, Kawashiri MA, Yoshida T, Teramoto R, Nohara A, Konno T, et al. Lipoprotein(a) in familial hypercholesterolemia with proprotein convertase subtilisin/kexin type 9 (PCSK9) gain-of-function mutations. *Circ J* 2016; **80:** 512–518.