Fifty years ago, Dr Kare Berg described for the first time two main features of lipoprotein(a) or Lp(a), namely inheritance of its increased levels and the association with premature atherosclerotic cardiovascular diseases (ASCVD). Since then it has been regarded as an intriguing analog of low-density lipoprotein (LDL), present in plasma in much lower concentrations than LDL but lacking in proof of pathogenicity. However, recently published studies have unequivocally established Lp(a) as a causal and independent risk factor for ASCVD, even under maximal intensity statin treatment. Furthermore, a possible causal role of Lp(a) in aortic valve stenosis or heart failure development has been reported as well.

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Lp(a) consists of an LDL particle to which is attached a glycoprotein, apolipoprotein(a) (apo(a)), covalently linked to the apolipoprotein B (apoB) moiety of LDL by a disulfide bond (Figure 1). The presence of apo(a) increases the density of Lp(a) and greatly reduces its affinity for the LDL receptor (LDLR) (Figure 2). This could explain why raised Lp(a) levels in plasma are unaffected by statin treatment. Apo(a) has close structural similarity with plasminogen, which endows Lp(a) with antifibrinolytic properties via its competitive inhibition of tissue-type plasminogen activator. These attributes give Lp(a) the potential for promoting both atherosclerosis and thrombosis. Apo(a) consists of a number of pleated structures, Kringles, one of which, Kringle IV type 2, is repeated a variable number of times from 2 to >40; this results in considerable interindividual variation in the size and molecular weight of apo(a) (Figure 1). Based on this molecular background, Lp(a) levels are predominantly determined genetically, and are unaltered by other risk factors or by lifestyle.

The only evidence that lowering Lp(a) reduces risk has come from studies using lipoprotein apheresis. However, this costly procedure requires weekly or bi-weekly extracorporeal circulation on a long-term basis. One of the few drugs that has been shown to reduce Lp(a) levels significantly, niacin can reduce Lp(a) levels, but has failed to show benefit in outcome.
studies such as the AIM-HIGH trial.10 Cholesteryl-ester transfer protein inhibitor also reduces Lp(a) levels, but this class of drug has been stuck in development.10,11 In contrast, monoclonal antibodies to proprotein convertase subtilisin/kexin-9 (PCSK9), which has recently become available in the USA and Europe, and expected in Japan shortly, has been reported to lower Lp(a) by 40%.12 This could promptly raise an important clinical question as to whether Lp(a) levels in patients with gain-of-function mutation of PCSK9 (FH-PCSK9) might differ from those with impairment of the LDLR itself (FH-LDLR), both of which show genetically determined increased levels of LDL (ie, familial hypercholesterolemia [FH]). In other words, contrary to the circumstance in PCSK9 inhibition, opposite alterations in Lp(a) level would be expected in patients with a PCSK9 gain-of-function variant.

In this issue of the Journal, Tada and colleagues13 investigate this issue with molecular analyses in a large patient cohort. They report that Lp(a) levels in FH-LDLR patients were comparable to those in FH-PCSK9 patients, both of whom show significantly greater Lp(a) levels as compared with non-FH hospitalized subjects, using a propensity score-matching technique. It has already been reported that Lp(a) levels in heterozygous FH are 3-fold greater than in apo(a) phenotype-matched non-FH subjects in Western countries,14 but considerable ethnic variation in Lp(a) levels has also been described.15 Therefore, the study done by Tada et al advances our understanding of Lp(a) levels in Japanese FH and non-FH subjects. Despite this progress, some of their observations should be interpreted with great caution. Firstly, assay-dependent variability may exist in the influence of the number of Kringle IV domains of the apo(a) molecule,16 as the authors discuss them-

References
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