Commentary: Lipoprotein(a) and atherosclerosis

Robert Clarke

Clinical Trial Service Unit and Epidemiological Studies Unit, Richard Doll Building, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK. E-mail: robert.clarke@ctsu.ox.ac.uk

Recently, there has been a resurgence of interest in lipoprotein(a) [Lp(a)] as a risk factor for atherosclerotic disease. Lp(a) was first discovered by Kaare Berg in 1962 on the basis of antigenic differences in low-density lipoprotein (LDL) cholesterol detected after injecting rabbits with human LDL particles.1 The resulting antibodies identified an antigen in some, but not in other individuals. In the early 1970s, Berg reported that Lp(a) was a plasma lipoprotein consisting of an LDL particle linked with an apolipoprotein(a) particle. The size of the LDL particle was fixed, but the apolipoprotein(a) component varied between individuals. The inheritance of Lp(a) was clarified in 1987 by Gerd Utermann, who identified multiple size variants that were strongly associated with plasma levels of Lp(a).2 But the causal relevance of Lp(a) for coronary disease and for other vascular diseases remained uncertain for almost 50 years after the initial discovery.

In 2009, three large studies reported that genetic variants encoding plasma levels of Lp(a) had higher risks of coronary heart disease.3–5 These Mendelian randomization studies examined the associations of genetic variants encoding plasma levels of Lp(a), plasma levels of Lp(a) and coronary disease. In the PROCARDIS study, we examined 27 single nucleotide polymorphism (SNPs) at the LPA locus at 6q26-27, and found two SNPs (rs10455872 and rs3798220) that were strongly and independently related to coronary disease.5 We replicated these associations in a meta-analysis involving a total of 8000 coronary cases. Both LPA SNPs explained about half the genetic variation in plasma levels of Lp(a) and their effect on risk of coronary disease was completely attenuated after adjustment for plasma levels of Lp(a), providing strong support for causality.5

However, the mechanism by which elevated plasma levels of Lp(a) cause vascular disease remains uncertain. In a Mendelian randomization study reported in this issue, Kivimaki and colleagues examined the associations of LPA variants; and Lp(a) levels with carotid intima–media thickness and brachial artery flow-mediated dilatation.6 In a population-based study of almost 2000 healthy Finnish individuals, Kivimaki demonstrated no association of a variant at the LPA locus (rs783147), that was strongly associated with Lp(a) levels, with either of these markers of early atherosclerosis. The results of this study require corroboration by larger studies (and meta-analyses of such studies), and with a genotype score involving SNPs associated with greater differences in Lp(a) levels, but the available evidence does not suggest any role for Lp(a) in early atherosclerosis.

Whereas the mechanism by which elevated levels of Lp(a) cause coronary disease remains elusive, the Mendelian randomization studies of LPA variants and coronary disease have prompted a paradigm shift in the importance of Lp(a) as a risk factor for coronary disease. Further large-scale studies are required to assess the relevance of LPA variants for stroke and other vascular diseases. The results of...
ongoing trials of niacin that lower plasma levels of Lp(a) by 30%,2 and planned trials of cholesterylester transfer protein inhibitors that lower Lp(a) levels by 40%,8 are required to assess the clinical relevance of lowering plasma levels of Lp(a) for prevention of atherosclerotic vascular diseases.

References
4 Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. JAMA 2009;301:2331–39.