Mechanisms of Lipoprotein(a) Pathogenicity
Prothrombotic, Proatherosclerotic, or Both?

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High quality, large prospective population-based studies are like well-tended orchards: they take many years to bear fruit, but when they do, they yield a bounty. In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, fruit is on offer from 2 important Danish population-based studies, the Copenhagen City Heart Study and the Copenhagen General Population Study, which previously provided key evidence that genetically based levels of C-reactive protein were not related to vascular disease, and from 3 case-control studies conducted in Copenhagen. In the present study, Kamstrup et al use a Mendelian randomization study similar to that described in 2009 to probe the relationship between plasma-derived and genetically determined levels of lipoprotein(a) (Lp(a)), and the development of venous thromboembolism (VTE; thrombotic events), vascular stenosis (atherosclerotic events), and myocardial infarction (which they called combined atherosclerotic and thrombotic events).

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The ultimate goal of the study was to further our understanding of the mechanism of Lp(a) action in vascular disease, which has been controversial. Results over the years from both in vitro and in vivo studies have reflected the duality of Lp(a) structure: in this regard, both proatherosclerotic (low-density lipoprotein–like) and prothrombotic (plasminogen-like) functions have been reported (Figure). By comparing the contribution of genetically elevated Lp(a) to arterial stenosis, thrombotic events secondary to atherosclerosis, and pure thrombotic events in the veins, the authors hoped to gain insight into the relative contribution of the 2 facets of Lp(a) action to atherothrombotic events. Interestingly, the authors report no association of Lp(a) levels and kringle IV type 2 genotypes with VTE in large numbers of participants. However, they do report positive relationships (albeit using considerably smaller sample sizes) between Lp(a) and kringle IV type 2 genotype atherosclerotic stenosis in the coronary, carotid, and femoral arteries. Coronary stenosis was assessed angiographically, but carotid stenosis (≥50%) was assessed by Doppler ultrasound, and peripheral vascular disease by ankle-brachial index. Thus, the evidence for stenosis in the present study was stronger for coronary disease than for carotid stenosis or peripheral vascular disease. It is worth noting that in the present study, the kringle IV type 2 genotype accounted for only 25% of the variance of levels of Lp(a). This contribution of apolipoprotein(a) isoform size to Lp(a) levels is lower than would be expected in a white population. This may reflect noise introduced with the genotyping method, which reports the total number of kringle IV encoding repeats on the 2 LPA alleles. Because large or nonexpressing alleles will be detected by this method, this, in turn, results in an underestimation of the relationship between genetically determined Lp(a) levels and the end points under consideration, and needs to be considered in the interpretation of studies using this methodology.

How can we reconcile the data of Kamstrup et al with the literature describing the relationship between Lp(a) and VTE? Some, but not all, case-control studies have shown increased risk of VTE with elevated Lp(a) concentrations, and a meta-analysis of 6 case-control studies of adult patients by Sofi et al as well yielded a positive result for Lp(a) levels >30 mg/dL (odds ratio 1.77; 95% CI 1.14–2.75; *P*=0.01). On the other hand, cohort studies, including the 2 Danish populations studied by Kamstrup et al as well as the large Longitudinal Investigation of Thromboembolism Etiology reported by Tsai et al, have uniformly reported no relationship between Lp(a) concentration and incidence of VTE. Although the cohort studies eliminate the possibility of selection bias, it should be noted that the incidence rate in these studies was small, particularly in the case of the Longitudinal Investigation of Thromboembolism Etiology study, possibly masking any dose-dependent effect of Lp(a) concentration. Notably, in the present study, Kamstrup et al reported that extremely high Lp(a) concentrations (>95th percentile) were in fact associated with VTE. Curiously, several studies in children have identified elevated Lp(a) as a significant risk factor for VTE. It is possible that elevated Lp(a) is not a risk factor for VTE, despite the documented antifibrinolytic properties of this lipoprotein, or that the effects of Lp(a) are only significant at the very highest concentrations of this lipoprotein.

Can the data from the present study support a conclusion that Lp(a) operates through a proatherosclerotic rather than a prothrombotic mechanism? Although tempting, it is difficult to draw mechanistic conclusions from epidemiological studies. Indeed, in the present study, the relationship of Lp(a) to atherostenosis may reflect a contribution of Lp(a) to prothrombotic/antithrombotic effects of Lp(a) in this process. Klein et al reported in *Arteriosclerosis, Thrombosis, and Vascular Biology* in 2008, based on data from 876 participants,
Figure. Mechanisms linking lipoprotein(a) (Lp(a)) to thrombosis and atherosclerosis. The Venn diagram depicts a series of factors that potentially contribute to venous thrombosis (left side) and atherothrombosis (right side). A subset of these factors that are influenced by Lp(a) is contained in the filled circles; note that all the factors potentially contributing to venous thrombosis that are influenced by Lp(a) are in common with atherothrombosis (center). Factors that contribute uniquely to venous thrombosis or atherosclerosis, and are not influenced by Lp(a), are contained in the open circles. EC indicates endothelial cell; ECM, extracellular matrix; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PL, phospholipids; SMC, smooth muscle cell; TFPI, tissue factor pathway inhibitor activity.

that high levels of Lp(a) were significantly associated with carotid stenosis and occlusion, but not with carotid total plaque area. Their interpretation, based on the doctrine of compensatory enlargement, was that carotid stenosis was the result of plaque rupture and stenosis, rather than the result of simple progression of plaque burden, and that Lp(a) may have contributed to arterial thrombosis (and impaired thrombolysis).

An important issue worthy of consideration is the differences between arterial thrombosis and venous thrombosis. In the setting of arterial flow velocities, and in particular with the very high velocities associated with arterial stenosis, there is not sufficient time for red thrombus (fibrin polymer with entrapped red cells) to form; white thrombus (characterized by platelet aggregates) is the kind of thrombosis associated with arterial stenosis, with red thrombus formation occurring only after arteries occlude. Association of Lp(a) with arterial stenosis and occlusion, and events such as myocardial infarction may relate to increased likelihood of plaque rupture, to arterial thrombosis relating to platelet function, to formation of red thrombus after the occlusion occurs, and to impaired thrombolysis. As such, it is difficult to conclude with certainty based on the present study that the prothrombotic effects of Lp(a) are not important contributors to the pathogenicity associated with elevated Lp(a) levels. The study is important, however, in drawing attention to this issue which should spark further mechanistic investigations aimed at elucidating the role of this enigmatic lipoprotein in vascular disease.

Disclosures

References


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