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High Antifibrinolytic Activity of Lipoprotein(a) Containing Small Apolipoprotein(a) Isoforms
To the Editor:

Small apolipoprotein(a) [apo(a)] isoforms are frequently found in patients with coronary heart disease. However, the question remains regarding whether short apo(a) isoforms are themselves an atherothrombotic risk factor or if they favor atherogenesis by increasing the concentration of lipoprotein(a) [Lp(a)]. An antifibrinolytic mechanism may explain the pathophysiological effects of Lp(a) through its relationship with both high concentrations of Lp(a) and small apo(a) isoforms. My colleagues and I clearly showed that the higher antifibrinolytic activity of small apo(a) isoforms remains to be tested.

I would like to add the following fact to their careful editorial on the stimulating study by Kronenberg et al on the role of Lp(a) and apo(a) phenotype in atherogenesis: the existence of apo(a) functional heterogeneity with regard to antifibrinolytic activity has been demonstrated. This fact was also clearly indicated by Kronenberg et al in the following statement: “Lp(a) particles containing low molecular weight apo(a) isoforms have the most profound influence on fibrinolysis by acting as a prominent competitive antagonist of plasminogen. This mechanism is in agreement with the emergence of low-molecular-weight apo(a) phenotypes as a leading risk condition of advanced stenotic atherosclerosis.”

In addition, my colleagues and I recently provided the first quantitative evidence that individual modifications in the concentration of small apo(a) isoforms in vivo efficiently compete with plasminogen and inhibit plasmin formation on fibrin. These studies suggest that high Lp(a) concentrations may be associated with markedly different atherothrombotic risks depending on the apo(a) isoform, and they add a new qualitative functional notion to the quantitative concept of Lp(a) as a cardiovascular risk factor.

E. Anglés-Cano, MD, DSc
INSERM U.143
Hemostasis and Vascular Biology
Hôpital de Bicêtre
84 rue du General-Léclerc
F-94276-Cedex, Bicêtre, France
angles@infobiogen.fr


Response
We gladly acknowledge the contribution of Dr Anglés-Cano’s group on the role of lipoprotein(a) [Lp(a)] in the fibrinolytic process. This group reported that Lp(a) containing differently-sized apolipoprotein(a) isoforms exhibited differences with respect to binding to fibrin surfaces in vitro and to the tissue plasminogen activator–mediated plasmin formation stimulated by these surfaces. However, on the basis of the limited number of Lp(a) variants examined in these studies and considering the known heterogeneity of Lp(a) in plasma with respect to binding to lysine or to fibrin, it remains to be definitively demonstrated that variably-sized Lp(a) isoforms possess inherent differences in their ability to bind to fibrin or to inhibit plasmin generation.

Furthermore, as we stated in our editorial, the effect of Lp(a) isoform size on the process of fibrinolysis itself has yet to be directly examined experimentally.

It is important to note that many plausible mechanisms by which Lp(a) may promote thrombosis have been reported in addition to the well-documented ability of Lp(a) to inhibit fibrin-dependent tissue plasminogen activator–mediated plasminogen activation. These possible mechanisms include the inhibition of plasminogen activation on platelets and on the surface of endothelial cells, the potentiation of platelet responses, and the stimulation of plasminogen activator inhibitor secretion by endothelial cells. Indeed, it could readily be argued that the binding of Lp(a) to fibrin and the resultant competition for plasminogen binding do not constitute the only mechanism by which Lp(a) inhibits plasminogen activation; we have shown that apolipoprotein(a) and plasminogen can bind in solution and that this complex seems to bind very poorly to fibrin. Overall, on the basis of the clinically suggestive results of Kronenberg et al., it is tempting to speculate that smaller apolipoprotein(a) isoforms possess a greater thrombogenic/antifibrinolytic potential.

E. Anglés-Cano, MD, DSc
INSERM U.143
Hemostasis and Vascular Biology
Hôpital de Bicêtre
84 rue du General-Léclerc
F-94276-Cedex, Bicêtre, France
angles@infobiogen.fr

Santica M. Marcovina, PhD, ScD
University of Washington
Northwest Lipid Research Laboratories
2121 North 35th Street
Seattle, WA 98103
smm@u.washington.edu


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Isoforms
E. Anglés-Cano

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