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(Stroke. 2006;37:1350-1351.)
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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000222979.34697.bf

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In this issue of Stroke, the Atherosclerosis Risk in Communities (ARIC) study provides evidence that lipoprotein(a) [Lp(a)] is a significant predictor of stroke.1 This is an important finding, because ARIC is both large and prospective. Over 14 000 patients were enrolled in 1987 to 1989, and during 13.5 years of follow-up, they experienced 496 ischemic strokes. Lp(a) remained a significant predictor of stroke after adjustment for age, race, systolic blood pressure, antihypertensive medication, smoking status, use of postmenopausal hormone therapy, diabetes, LDL cholesterol, HDL cholesterol, fibrinogen, and von Willebrand factor. It thus seems likely that Lp(a) is potentially an important treatable risk factor.

But what is Lp(a), and how does it relate to atherosclerosis and cardiovascular events? A meta-analysis of prospective studies of coronary events2 seems to establish that Lp(a) is also a predictor of myocardial infarction, but numerous studies indicate that it does not seem to predict the burden of atherosclerosis as assessed by intima-media thickness,3,4 except perhaps in patients with renal failure.5 Rossel et al6 found that Lp(a) was not associated with IMT or plaque but was associated with stenosis of carotid arteries.

We have previously shown that carotid plaque area more strongly predicts vascular outcomes than does stenosis assessed by carotid Doppler velocities7,8; an analysis of that database prompted by this commentary (previously unpublished) showed that in multiple regression adjusted for age, sex, systolic blood pressure and pack-years of smoking, Lp(a) was not associated with baseline plaque area (P=0.59), but was associated with baseline carotid stenosis (P=0.049). How can this be? It happens because phenotypes of atherosclerosis assessed by ultrasound, angiography and coronary calcification by computed tomography are biologically and genetically distinct.9,10

Because of compensatory enlargement,11,12 stenosis is probably not the consequence of plaque progression but the consequence of plaque rupture. Plaque area, which represents the burden of atherosclerosis at a point in time, reflects the effects over a lifetime of the traditional risk factors of atherosclerosis, but stenosis probably reflects the effects of factors affecting plaque rupture, such as inflammatory cytokines, matrix metalloproteinases and possibly infection, as well as the effects of factors affecting thrombosis and fibrinolysis.9

It seems likely that Lp(a) is involved in thrombosis and fibrinolysis. Two recent reviews help in the understanding of its mechanism of action and its role in atherosclerosis. Koschinsky13 emphasized the mechanism of action of Lp(a):

Lp(a) is a challenging lipoprotein to study because it has a complex structure consisting of a low-density lipoprotein-like moiety to which is covalently attached the unique glycoprotein apolipoprotein(a) (apo(a)). Apo(a) contains multiply repeated kringle domains that are similar to a sequence found in the fibrinolytic proenzyme plasminogen; differing numbers of kringle sequences in apo(a) give rise to Lp(a) isoform size heterogeneity. In addition to elevated plasma concentrations of Lp(a), apo(a) isoform size has been identified as a risk factor for coronary heart disease, although studies addressing this relationship have been limited. The similarity of Lp(a) to low-density lipoprotein and plasminogen provides an enticing link between the processes of atherosclerosis and thrombosis, although a clear demonstration of this association in vivo has not been provided. Clearly, Lp(a) is a risk factor for both atherothrombotic and purely thrombotic events; a plethora of mechanisms to explain these clinical findings has been provided by both in vitro studies as well as animal models for Lp(a).

Berglund and Ramakrishnan14 emphasized population differences (higher levels in blacks, possibly related to the finding that Lp(a) was most strongly predictive of stroke in blacks in ARIC) and the role of variation in the size of the apo(a) moiety of Lp(a). Lp(a) is subject to oxidation, and proinflammatory oxidized phospholipids are preferentially bound to Lp(a) and taken up by macrophages,14 contributing to foam cell formation, and possibly to plaque rupture. Does any of this matter? It may, particularly for patients with renal failure.15 Naruzevic et al showed that vitamin therapy reduced Lp(a) along with fibrinogen and total homocysteine in patients with renal failure;16 his group has also shown that antioxidant vitamins17,18 and probucol16 reduce oxidation of Lp(a).

It also matters because levels of Lp(a) can be reduced by therapy. Although statins are not very effective in reducing levels of Lp(a), and fibrates are only slightly effective, there is a moderate effect of niacin, which is now more accessible with the recent availability of slow-release preparations that reduce flushing while maintaining efficacy and avoiding hepatotoxicity19 (features that were not true of older slow-release preparations20). Recently, a more promising therapy for
lowering of Lp(a) has appeared on the horizon: Meinertz et al found that alcohol-extracted soy protein reduced Lp(a) by 60% compared with a diet containing unextracted soy protein.21 If that finding is replicated, it suggests a therapeutic approach to lowering of Lp(a) that should be further tested in clinical trials.

References


Key Words: artery plaques, carotid cerebrovascular disorders intima-media thickness Lp(a) lipoprotein(a) thrombosis
Lipoprotein(a): Involved in Events, but Not Burden of Atherosclerotic Disease?
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Stroke. 2006;37:1350-1351; originally published online May 4, 2006;
doi: 10.1161/01.STR.0000222979.34697.bf
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/37/6/1350

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