Lipoprotein(a), Ethnicity, and Cardiovascular Risk
Erasing a Paradox and Filling a Clinical Gap

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For >20 years, textbooks of medicine and guidelines for cardiovascular risk screening have suggested that elevated levels of lipoprotein(a) [Lp(a)] are a risk marker for coronary heart disease in white populations, but not among blacks. This observation, included in the Adult Treatment Panel III guidelines in 2002, has long been puzzling, because blacks have both higher Lp(a) levels and higher absolute cardiovascular event rates than age- and sex-matched whites. Many explanations for this assumed ethnicity-based Lp(a) paradox have been described in the cardiovascular literature, including effect modification on the basis of diverse environmental and social influences, as well as genetic differences related to variation in kringle IV type 2 copy number. In retrospect, however, this embedded piece of preventive cardiology wisdom may prove to be a faux clinical pearl that entered the literature because of little more than poor statistical power.

In this issue of Circulation, Virani and colleagues use data from the National Heart, Lung, and Blood Institute–funded Atherosclerosis Risk in Communities (ARIC) Study to perform an updated prospective evaluation of Lp(a) and subsequent vascular risk in a biracial cohort that included 3467 blacks and 9851 whites. As anticipated, and consistent with prior data, Lp(a) levels in ARIC were significantly higher among the black group than the white group, and in both populations, increasing Lp(a) levels tended to correlate positively with low-density lipoprotein cholesterol and negatively with triglycerides. However, in apparent contradiction to almost all earlier work (including prior data from ARIC itself), increasing quintiles of Lp(a) in this updated analysis were just as predictive of future cardiovascular disease in the black population as in the white population. This was true in analyses in which ethnic-specific quintiles were used, in analyses based on a 1-SD log transformation of Lp(a), and in analyses based on a series of predetermined 10-mg/dL cutoff points for Lp(a). Thus, at least within this updated ARIC cohort analysis, the relationship between Lp(a) and subsequent vascular risk in black and white groups is far more similar than different (Figure).

Why do the present data from ARIC differ from those of the past? The most likely reason is power. In the 20-year prospective follow-up reported by Virani et al, 676 incident cardiovascular events accrued in the black component of ARIC (481 coronary heart disease events, 283 stroke events). By comparison, in the prior null study from ARIC published in 2001, the total number of coronary events was 68 among black women and 90 among black men. Furthermore, in an otherwise comprehensive 2009 meta-analysis conducted by the Emerging Risk Factors Collaboration in which Lp(a) was associated with risk among whites on the basis of 7540 incident vascular events [relative risk per SD increase in Lp(a)=1.14, 95% confidence interval 1.09–1.19], a null finding for Lp(a) was reported for individuals of African origin based on 261 total vascular events [relative risk per SD increase in Lp(a)=1.05, 95% confidence interval 0.90–1.23]. The current positive finding may reflect in part a more consistent pattern between Lp(a) and stroke, a finding also reported by other investigators. Although assay issues have long hampered the Lp(a) field based on whether or not the particular method used is affected by apolipoprotein(a) isoform variation, this is an unlikely explanation for the present data, because Virani and colleagues were careful to show that the assay used in ARIC was highly concordant with that of Marcovina et al.

Where then does the epidemiology of Lp(a) stand? First, if the ARIC data are correct, we can remove the paradox for blacks and take pathophysiological comfort from the fact that almost all populations with elevated Lp(a) indeed have elevated risk. In this respect, the data of Virani et al do more than fill a clinical gap for our black patients; the present data also remove an improper level of uncertainty among investigators as to why a population with genetically high levels of Lp(a) did not have an anticipated increase in event rates. Second, a series of recent Lp(a) studies has greatly expanded our understanding of this unique lipoprotein fraction. Mendelian randomization studies, which can be helpful when positive, appear to support Lp(a) as a potential causal agent in atherothrombosis. Other randomized pharmacogenetic data have found that the antithrombotic benefit of prophylactic aspirin is closely linked to specific genetic polymorphisms associated with Lp(a) expression, an intriguing observation given the long-recognized homology between plasminogen and Lp(a). In addition, very recent prospective cohort data have found an inverse relationship between Lp(a) and type 2 diabetes mellitus, which suggests that unlike inflammatory path-
ways, Lp(a) has divergent effects on atherothrombosis and glucose metabolism. Finally, translational work suggests that Lp(a) binds and transports proinflammatory oxidized phospholipids, a process that might directly result in the promotion of coronary artery disease.

Despite these advances, there remain reasons to be skeptical about screening for Lp(a) outside of situations with a strong family history of premature atherothrombosis. In general, clinicians should not measure a biomarker simply because it is associated with an increase in vascular risk. Rather, for a biomarker to be used in clinical practice, we additionally need clear evidence (preferably from randomized trials) that those identified by the biomarker of interest benefit from a specific therapy the patient otherwise would not have received. Discrimination, recalibration, and reclassification also need to be addressed carefully for Lp(a) before any general screening program is considered. Because all individuals in primary prevention should receive advice on diet, exercise, and smoking cessation, what we need for Lp(a) is evidence that those identified as being at high risk because of elevated levels benefit from a specific therapy.

Unfortunately, few such data currently exist. Although aspirin and statin therapy are often recommended for those with marked elevations of Lp(a), data supporting these interventions among those who do not already have an indication for prophylactic care are scarce. Niacin and estrogen are the most commonly used agents that reduce Lp(a) levels, yet randomized trials of these agents in cardiovascular prevention have been disappointing.

Several lipid-lowering agents in development significantly reduce Lp(a). Mipomersen, an antisense oligonucleotide designed to inhibit synthesis of human apolipoprotein B100 in the liver, reduces Lp(a) by 15% to 25% when given in weekly doses of between 100 and 300 mg per week. Similarly, inhibitors of cholesteryl ester transfer protein (CETP) reduce Lp(a); in a recent report for anacetrapib 100 mg daily compared with placebo, a 36% reduction in Lp(a) was observed at 24 weeks. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK-9) also result in lower Lp(a) levels concomitant with low-density lipoprotein cholesterol and apolipoprotein B reduction. All of these agents, however, have profound effects on other lipid fractions. Thus, as outcomes trials based on these novel agents are conducted, it will be difficult to ascribe any potential beneficial effects to changes in Lp(a) alone.

These limitations aside, our understanding of Lp(a) has come a very long way since its initial description by Kare Berg in 1963. The well-powered ethnicity-stratified data from Virani et al in the current issue of Circulation provide closure for one longstanding debate in the Lp(a) field, as well as a reminder as to why population studies of underrepresented minorities continue to matter.

Disclosures
None.

References


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