Panel III guidelines in 2002, has long been puzzling, because blacks. This observation, included in the Adult Treatment coronary heart disease in white populations, but not among elevated levels of lipoprotein(a) \([\text{Lp(a)}]\) are a risk marker for 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. For >20 years, textbooks of medicine and guidelines for cardiovascular risk screening have suggested that elevated levels of lipoprotein(a) \([\text{Lp(a)}]\) 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. This 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)]=1.14, 95% confidence interval 1.09–1.19], a null finding for Lp(a) was reported for individuals of African origin based on 7540 incident 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-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association. From the Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital Harvard Medical School, Boston, MA. Correspondence to Paul M Ridker, MD, MPH, Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, 900 Commonwealth Ave East, Boston MA 02215. E-mail pridker@partners.org (Circulation. 2012;125:207-209.) © 2011 American Heart Association, Inc. Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIRCULATIONAHA.111.077354

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

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that Lp(a) binds and transports proinflammatory oxidized phospholipids, a process that might directly result in the promotion of coronary artery disease.\textsuperscript{12} Similarly, the liver, reduces Lp(a) by 15\% to 25\% when given in weekly doses of between 100 and 300 mg per week.\textsuperscript{13} 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.\textsuperscript{14} 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.\textsuperscript{15} The well-powered ethnicity-stratified data from Virani et al\textsuperscript{2} 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


**Key Words:** Editorials | atherosclerosis | biomarkers | risk factors | ethnicity | lipoprotein(a)
Lipoprotein(a), Ethnicity, and Cardiovascular Risk: Erasing a Paradox and Filling a Clinical Gap
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Circulation. 2012;125:207-209; originally published online November 29, 2011;
doi: 10.1161/CIRCULATIONAHA.111.077354

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