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Lipoprotein(a) for Risk Assessment in Patients With Established Coronary Artery Disease

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Objectives The purpose of this study was to assess the prognostic utility of lipoprotein(a) [Lp(a)] in individuals with coronary artery disease (CAD).

Background Data regarding an association between Lp(a) and cardiovascular (CV) risk in secondary prevention populations are sparse.

Methods Plasma Lp(a) was measured in 6,708 subjects with CAD from 3 studies; data were then combined with 8 previously published studies for a total of 18,978 subjects.

Results Across the 3 studies, increasing levels of Lp(a) were not associated with the risk of CV events when modeled as a continuous variable (odds ratio [OR]: 1.03 per log-transformed SD, 95% confidence interval [CI]: 0.96 to 1.11) or by quintile (Q5:Q1 OR: 1.05, 95% CI: 0.83 to 1.34). When data were combined with previously published studies of Lp(a) in secondary prevention, subjects with Lp(a) levels in the highest quantile were at increased risk of CV events (OR: 1.40, 95% CI: 1.15 to 1.71), but with significant between-study heterogeneity ($p = 0.001$). When stratified on the basis of low-density lipoprotein (LDL) cholesterol, the association between Lp(a) and CV events was significant in studies in which average LDL cholesterol was $\geq$130 mg/dl (OR: 1.46, 95% CI: 1.23 to 1.73, $p < 0.001$), whereas this relationship did not achieve statistical significance for studies with an average LDL cholesterol $<$130 mg/dl (OR: 1.20, 95% CI: 0.90 to 1.60, $p = 0.21$).

Conclusions Lp(a) is significantly associated with the risk of CV events in patients with established CAD; however, there exists marked heterogeneity across trials. In particular, the prognostic value of Lp(a) in patients with low cholesterol levels remains unclear. (J Am Coll Cardiol 2014;63:520–7) © 2014 by the American College of Cardiology Foundation

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Lipoprotein(a) [Lp(a)] consists of a cholesterol-rich low-density lipoprotein (LDL) moiety that is covalently linked to apolipoprotein(a). Evidence from genetic studies indicates that Lp(a) may play a causal role in the development of atherosclerosis (1). In the first of 2 large Mendelian randomization studies, genetic polymorphisms in the *LPA* gene were shown to influence Lp(a) levels and increase the risk of myocardial infarction (MI) in Danish subjects. In particular, a doubling of Lp(a) levels throughout life was associated with a 22% increase in the risk of MI (2,3). In a case-control study in 4 European countries, 2 common variants in the *LPA* gene were found to be strongly associated with Lp(a) levels, and individuals with these variants had more than a 50% increased risk of heart disease (2,3). Further, genetically determined Lp(a) levels, as determined by the *LPA* genotype, are associated with aortic valve calcification and incident clinical aortic stenosis (4).

Although Lp(a) may prove to be a causal risk factor for the development of ischemic heart disease, its clinical utility as a prognostic biomarker in secondary prevention remains a separate issue that is incompletely defined. Recently, a large pooled analysis in primary prevention populations confirmed that Lp(a) was an independent risk factor for coronary heart disease (CHD) death, nonfatal MI, and stroke, although the strength of the relationship appeared to be modest when Lp(a) was modeled as a continuous variable (5). In quantile analysis, the relationship appeared curvilinear (5), with significantly greater risk observed for those patients with Lp(a) levels in the highest quartile, consistent with prior reports from individual studies (6–8). As well, there was a trend toward a stronger association between Lp(a) and cardiovascular (CV) events for patients with higher non–high-density lipoprotein cholesterol levels (5), a finding that has been observed with LDL cholesterol in other analyses (7,9).

Although data in secondary prevention populations are limited, some professional societies have now endorsed routine 1-time screening for Lp(a) in individuals at intermediate or high risk of CV events, including selected patients with established coronary artery disease (CAD) (10,11). Moreover, it has been proposed that an Lp(a) level <50 mg/dl (~80th percentile in the general population) should be targeted with therapies that lower Lp(a), such as niacin (10).

Given that data regarding the prognostic value of Lp(a) in secondary prevention are sparse and new lipid-modifying therapies that reduce Lp(a) are in development (12–15), we assessed the independent prognostic utility of Lp(a) and evaluated proposed screening cut points in 3 large clinical trial populations of patients with either stable CAD or after an acute coronary syndrome (ACS). We further assessed the prognostic utility of Lp(a) by combining the new data with previously published secondary prevention studies, and assessed for effect modification by LDL or total cholesterol concentration.

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CAD = coronary artery disease
CHD = coronary heart disease
CI = confidence interval
CV = cardiovascular
HR = hazard ratio
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
MACE = major adverse cardiovascular event(s)
MI = myocardial infarction
OR = odds ratio

Methods

Study populations and design. The PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition) trial (16) enrolled patients with stable CAD and preserved left ventricular function. The CARE (Cholesterol and Recurrent Event) trial (17) randomized patients who had experienced an MI within the past 3 to 20 months to pravastatin 40 mg daily versus placebo. The PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (18) randomized patients following an ACS to atorvastatin 80 mg daily versus pravastatin 40 mg daily. Further details regarding the study designs are provided in the Appendix.

Based on prior data for Lp(a) (5), the clinical endpoint of interest for this analysis was major adverse cardiovascular events (MACE) defined as the composite of CV death, MI, or stroke, where available. Of note, in the CARE trial, Lp(a) was measured in an age-matched case-control population of subjects who had or had not experienced fatal CHD or recurrent MI. Endpoints were adjudicated by clinical events committees who were blinded to treatment assignment and to Lp(a) levels.

Blood sampling and analysis. As part of the study protocols, samples of venous blood were to be collected in EDTA-treated tubes from participating subjects in the PEACE, PROVE IT–TIMI 22, and CARE trials. The plasma component was frozen and shipped to a central laboratory where samples were stored at −70°C or colder. Details regarding the assays used to measure Lp(a) concentration in each trial are provided in the Online Appendix.

Statistical analysis. In order to evaluate its association with clinical outcomes, Lp(a) was first analyzed as a log-transformed continuous variable and was subsequently categorized into quintiles according to Lp(a) concentration. Given the previously demonstrated curvilinear relationship

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