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RESEARCH LETTER
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Comparison of change in lipoprotein(a) mass and molar concentrations by alirocumab and risk of subsequent cardiovascular events in ODYSSEY OUTCOMES

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Lipoprotein(a) [Lp(a)] is a genetically determined risk factor for incident and recurrent atherosclerotic cardiovascular disease events.[1–6] PCSK9 inhibitors produce moderate reductions in Lp(a) concentration, with greater absolute reductions among individuals with higher baseline levels. Moreover, Lp(a) appears to be an effect modifier for the cardiovascular benefits of PCSK9 inhibitors, such that patients with higher baseline Lp(a) concentrations not only derive greater reductions in Lp(a) with treatment, but also greater relative and absolute reductions in cardiovascular risk.[4,5,7]

Competing methods to measure Lp(a) have challenged clinicians in the interpretation of Lp(a) levels and their changes with treatment. Existing tests of Lp(a) concentration include immunoassays (IAs) reporting in mass or molar units that may be susceptible to error from variable Lp(a) isoform size, and mass spectrometry (MS) reporting molar concentration without isoform dependence.[8] Baseline Lp(a) concentration is similarly related to cardiovascular risk when measured by any of the above methods.[8] However, it has not been determined whether the assay method influences the relationship between change in Lp(a) concentration and reduction of cardiovascular events under treatment with a PCSK9 inhibitor.

We addressed this unresolved question with data from ODYSSEY OUTCOMES, a trial that compared the PCSK9 inhibitor alirocumab with placebo in patients with recent acute coronary syndrome.[9] In a subgroup of trial participants, Lp(a) concentration was measured at baseline and Month 4 by IA reporting in mass units (Siemens), IA reporting in molar units (Roche), and MS reporting in molar units. Details of each assay have been previously described.[8] Relationships between changes in Lp(a) by the three tests within the alirocumab group were estimated by Spearman correlations. In the alirocumab group, proportional hazards models related changes in Lp(a) from baseline to Month 4 to the subsequent risk of the primary efficacy outcome of the study, first major adverse cardiovascular event (MACE; coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina hospitalization). Models were adjusted for baseline Lp(a), baseline LDL cholesterol (LDL-C) and its change from baseline to Month 4, and other baseline patient characteristics that are related to risk of MACE (age, sex, geographic region, estimated glomerular filtration rate, log-transformed high-sensitivity C-reactive protein, and history of diabetes and heart failure). Hazard ratios (HRs) and associated 95% confidence intervals were calculated

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Table 1 Lipoprotein(a) descriptives for participants included in analyses

	Baseline	Change baseline to Month 4	Percent change baseline to Month 4
IA-mass, mg/dL			
All patients ($n = 5500$)	20.9 (6.8, 58.5)	−5.1 (−13.4, 0)	−23.8 (−46.5, 0)
Patients ≥50 mg/dL ($n = 1636$)	81.5 (63.6, 111.0)	−17.6 (−30.9, −7.2)	−21.7 (−33.5, −9.4)
Patients <50 mg/dL ($n = 3864$)	11.2 (4.7, 24.0)	−3.2 (−8.0, 0)	−25.6 (−54.6, 0)
IA-molar, nmol/L			
All patients ($n = 5500$)	43.5 (13.2, 149.7)	−11.9 (−31.7, −2.1)	−26.9 (−49.1, −5.0)
Patients ≥125 nmol/L ($n = 1654$)	206.3 (163.1, 276.1)	−44.7 (−72.8, −18.7)	−21.4 (−31.9, −9.4)
Patients <125 nmol/L ($n = 3846$)	20.4 (9.0, 49.3)	−7.3 (−17.7, 0)	−33.2 (−56.8, 0)
MS-molar, nmol/L			
All patients ($n = 5500$)	40.9 (14.3, 138.8)	−10.4 (−28.1, −2.7)	−27.5 (−46.6, −9.6)
Patients ≥125 nmol/L ($n = 1536$)	200.5 (157.0, 270.2)	−40.9 (−67.6, −16.4)	−20.4 (−30.7, −8.6)
Patients <125 nmol/L ($n = 3964$)	22.3 (10.2, 50.0)	−7.1 (−16.0, −2.0)	−33.2 (−52.7, −10.1)

Values in table are median (Q1, Q3).

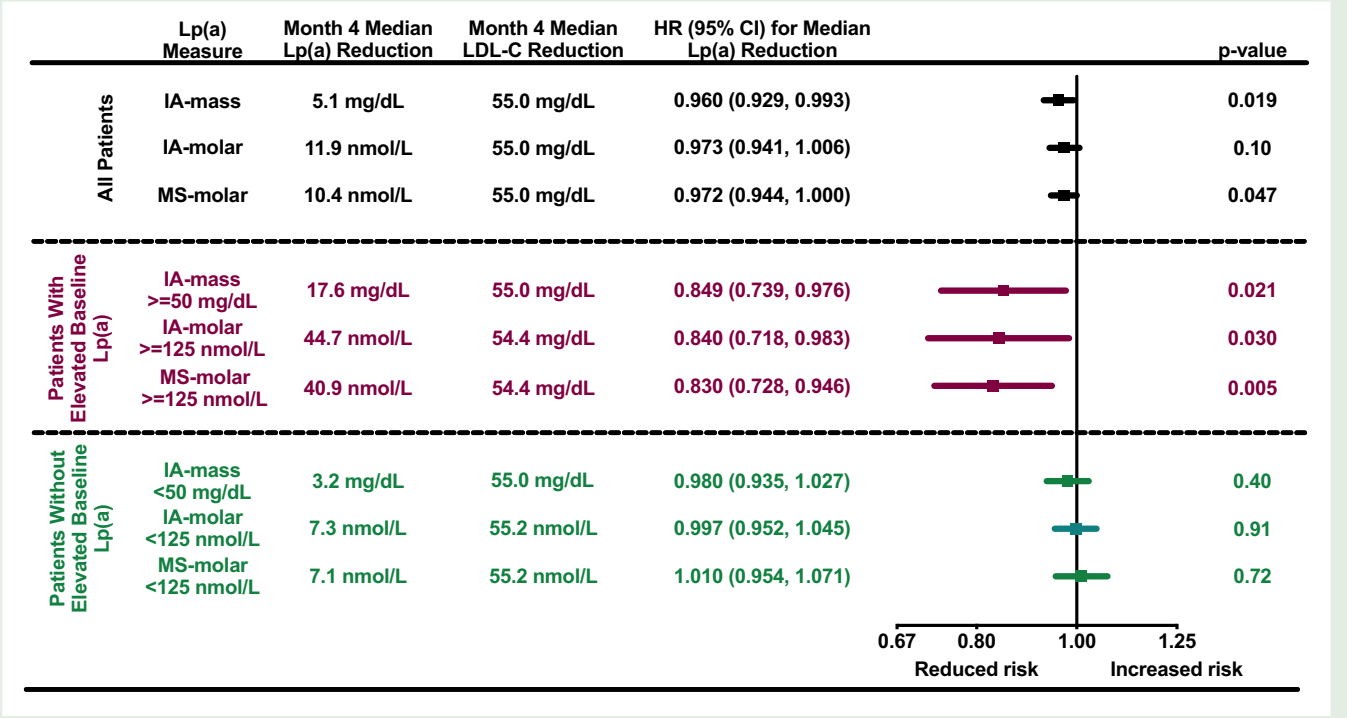

Figure 1 Relationship between reduction in lipoprotein(a) concentration from baseline to Month 4 and first major adverse cardiovascular event after Month 4 in the alirocumab group by lipoprotein(a) measurement method. Hazard ratios, confidence intervals, and *P*-values reflect adjustment for baseline lipoprotein(a), baseline LDL cholesterol, change from baseline to Month 4 in LDL cholesterol, age, sex, geographic region, estimated glomerular filtration rate, log-transformed high-sensitivity C-reactive protein, and history of diabetes and heart failure.

for the median Lp(a) change by each assay. All analyses were by intention-to-treat.

Among 5500 participants randomized to alirocumab with available data from all three Lp(a) assays, 443 experienced a MACE after their Month 4 assessments during a median 2.4 years of follow-up. Median (Q1, Q3) baseline, change, and percent change from baseline to Month 4 in Lp(a) IA-mass, IA-molar, and MS concentrations are summarized in *Table 1* for all evaluable participants and for subsets with levels above or below clinically relevant thresholds.[10] As expected, those with higher baseline concentrations had more substantial absolute reductions with alirocumab treatment. Change in Lp(a) IA-mass, IA-molar, and MS concentrations were correlated, with the strongest correlation between IA-molar and MS ($r = 0.834$; $P < 0.0001$) and somewhat weaker correlations between IA-mass and MS ($r = 0.693$; $P < 0.0001$) and IA-mass and IA-molar ($r = 0.690$; $P < 0.0001$).

Among all evaluable participants, reductions in Lp(a) IA-mass and MS-molar concentration were significantly associated with reductions in first MACE risk, while this association for IA-molar was marginally

significant (*Figure 1*). When LDL-C was replaced in the models with a measure that incorporated an approximation of cholesterol content in Lp(a) measured as LDL-C (i.e. 'corrected' LDL-C = LDL-C − 0.3 × IA-mass), results were essentially identical. Importantly, MACE HRs for median Lp(a) change were of similar magnitude across tests. These relationships were more evident in analyses restricted to participants with Lp(a) ≥ 50 mg/dL or ≥125 nmol/L, representing untreated concentration thresholds that denote enhanced cardiovascular risk[10] and where future use of Lp(a)-lowering therapies may be clinically appropriate. Additionally, LDL-C reductions with alirocumab did not depend on baseline Lp(a) concentration.

With caveats of a relatively modest number of MACE available for analysis, moderately elevated Lp(a) levels, and intra-patient variability in serial values, each of the three Lp(a) assay methods was similarly predictive of MACE reductions with alirocumab, independent of LDL-C reductions. Regardless of the measurement method, in unselected populations relatively modest Lp(a) reductions under treatment with a PCSK9 inhibitor should translate to modest clinical benefit on cardiovascular events. Among those with higher untreated concentrations, Lp(a) reductions in the range of 18 mg/dL or 45 nmol/L with PCSK9 inhibition would be expected to result in a ≥15% relative reduction in the risk of cardiovascular events. With the emergence of new potent Lp(a)-lowering agents, greater clinical benefits might be observed.

Author contributions

P.G.S. and G.G.S. contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. M.S. drafted the manuscript. All authors critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of their work, ensuring integrity and accuracy.

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Data availability

Requests from qualified investigators for data from the ODYSSEY OUTCOMES trial will be considered by its Executive Steering Committee at odysseyoutcomesESC@gmail.com.

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