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Citation

Szarek, M., Reijnders, E., Steg, P. G., Jukema, J. W., Schwertfeger, M., Bhatt, D. L., ... Schwartz, G. G. (2024). Comparison of change in lipoprotein(a) mass and molar concentrations by alirocumab and risk of subsequent cardiovascular events in ODYSSEY OUTCOMES. *European Journal Of Preventive Cardiology*, 31(10), e75-e78.
doi:10.1093/eurjpc/zwae110

Version: Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

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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Received 25 October 2023; revised 19 February 2024; accepted 11 March 2024; online publish-ahead-of-print 19 March 2024

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).

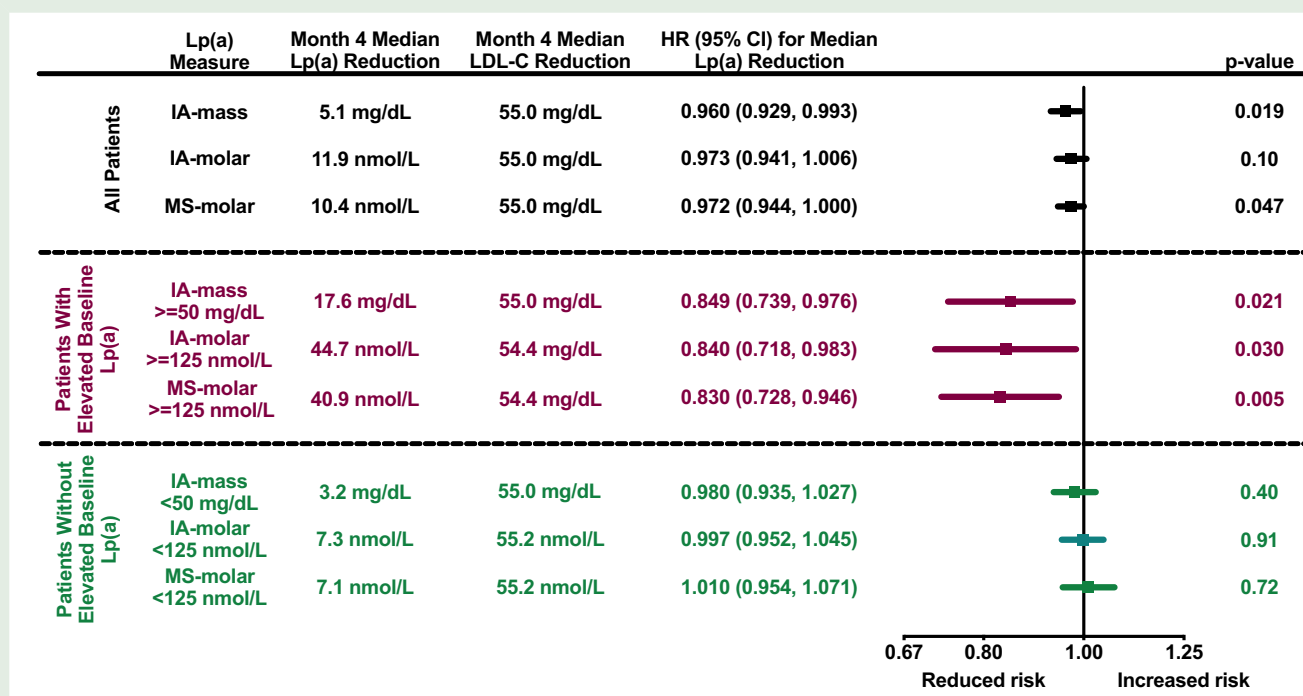


Figure 1 Relationship between reduction in lipoprotein(a) concentration from baseline to Month 4 and first major adverse cardiovascular event after Month 4 in the alirocumab group by lipoprotein(a) measurement method. Hazard ratios, confidence intervals, and *P*-values reflect adjustment for baseline 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 risk¹⁰ 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.

Funding

This work was supported by Sanofi and Roche Diagnostics.

Conflict of interest: M.S. reports serving as a consultant or research support (or both) from CiVi, Resverlogix, Lexicon, Baxter, Esperion, Amarin, New Amsterdam, Tourmaline, Sanofi, and Regeneron Pharmaceuticals, Inc. E.R.: No disclosures. P.G.S. reports grants, personal fees, and non-financial support from Sanofi; grants and personal fees from Amarin, Servier, and Bayer; personal fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Idorsia, Pfizer, and Novartis. J.W.J. receives research grants from The Netherlands Heart Foundation, the Interuniversity Cardiology Institute of The Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi Sankyo, Lilly, Merck-Schering-Plough, Novartis, Pfizer, Roche, and Sanofi. M.Sc. is an employee of Roche and may hold shares in the company. D.L.B. discloses the following relationships: Advisory Board: Angiowave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; Board of Directors: Angiowave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures, Hims; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair,

PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), CSL Behring (AHA lecture), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); Other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Alnylam, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Otsuka, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, *Braunwald's Heart Disease*); Site Co-Investigator: Author contributions Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solut.

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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