



The Role of Lipoprotein (a) as a Marker of Residual Risk in Patients With Diabetes and Established Cardiovascular Disease on Optimal Medical Therapy: Post-Hoc Analysis of ACCELERATE

<https://doi.org/10.2337/dc19-1117>

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Despite optimal medical treatment, patients with diabetes and established atherosclerotic disease remain at high risk for recurrent cardiovascular events. Consequently, identification and modification of novel risk factors that mediate residual risk remain an important clinical priority. Lipoprotein (a) [Lp(a)] is an LDL-like particle in which apolipoprotein B is covalently bound by a single disulfide bond to apolipoprotein A, and it has both thrombotic and proinflammatory characteristics (1). There is also a growing body of evidence showing causality of atherosclerotic disease with elevated Lp(a) (1). However, little is known about the predictive role of Lp(a) in patients with diabetes and established cardiovascular disease receiving optimal medical treatment. Thus, given that Lp(a) is an established marker of cardiovascular disease with targeted therapies currently in clinical trials (NCT03070782), we sought to see the impact of elevated Lp(a) in a high-risk secondary prevention cohort of patients with diabetes on optimal medical treatment enrolled in the ACCELERATE trial to identify patients who could potentially benefit from Lp(a)-targeted treatment (2).

In our post hoc analysis, participants who met eligibility to enroll in the trial

were divided into patients with and without diabetes to assess the impact of Lp(a) tertiles in each group. Baseline Lp(a) levels (in nmol/L) were measured by a central laboratory, using the commercially available Randox assay that employs the Denka Seiken method. Participants were chosen from the placebo arm of the trial to limit any potential drug effect on the outcomes. The following comparisons were made:

1. Highest versus lowest tertile of baseline Lp(a) among all placebo treatment patients.
2. Highest versus lowest tertile of baseline Lp(a) among placebo patients with and without diabetes.
3. Tertiles of baseline Lp(a) in all placebo patients.

The primary end point for this analysis was the first occurrence of any component of the composite cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Patients were followed every 3 months after randomization as specified in the study protocol, with a median duration of 28 months. Data were censored from event-free patients after 915 days in the

intention-to-treat population. All events were centrally adjudicated by a blinded clinical endpoint committee utilizing pre-specified definitions.

Overall, 5,121 patients (3,482 patients with diabetes, 1,639 without diabetes) in the placebo arm of ACCELERATE had baseline Lp(a) levels evaluated. A total of 3,426 had a diagnosis of type 2 diabetes, and 56 had a diagnosis of type 1 diabetes. A majority of patients were Caucasian males, and the average age of the entire study population was 64 ± 10 years. Baseline mean LDL cholesterol, mean HDL cholesterol, and median triglyceride levels were 81.6 ± 27.9 mg/dL, 45.6 ± 11.8 mg/dL, and 128.0 (93.0, 178.0) mg/dL, respectively. The median Lp(a) was 29.1 (10.8, 108.1) nmol/L. African Americans had a higher median Lp(a) compared with Caucasians and Asians (118.4 vs. 28.9 vs. 26.0 nmol/L, respectively; $P < 0.01$). Participants without diabetes had higher median Lp(a) values compared with their counterparts with diabetes (31.3 nmol/L vs. 27.6 nmol/L; $P = 0.03$). Event rates for the composite end point were significantly higher in the highest tertile of Lp(a) (64.6–816 nmol/L) compared with the lowest tertile [adjusted hazard ratio (HR) 1.29 (95% CI 1.06–1.56); $P = 0.02$]. Among

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Received 4 June 2019 and accepted 9 November 2019

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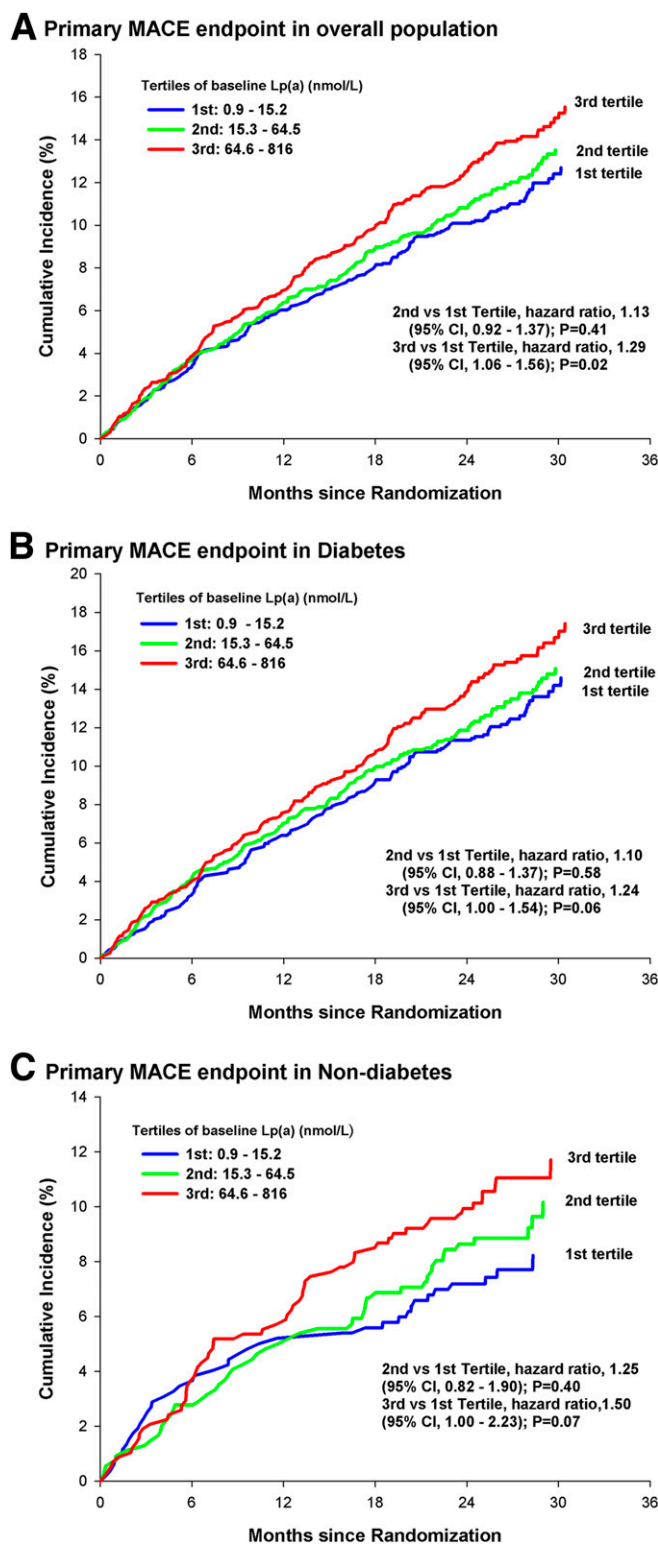


Figure 1—Kaplan-Meier curves for the cumulative incidence of primary MACE end point, stratified by the tertiles of baseline Lp(a) levels.

patients with diabetes, the adjusted HR was 1.24 (95% CI 1.00–1.54) ($P = 0.06$), and among patients without diabetes, the adjusted HR was 1.50 (95% CI 1.00–

2.23) ($P = 0.07$; interaction $P = 0.43$). Kaplan-Meier curves for the cumulative incidence of primary major adverse cardiovascular event (MACE) end points

stratified by Lp(a) tertiles for the study population are shown in Fig. 1. There was a significant increase in primary MACE at the 3rd tertile in the overall population. Only a borderline significance was seen at the 3rd tertile in patients both with and without diabetes, likely a function of the smaller numbers in the respective subgroups.

Thus, in a contemporary population of patients with high-risk established cardiovascular disease on optimal medical treatment, higher tertiles of Lp(a) were associated with increased cardiovascular events. This relationship of cardiovascular events was similar in patients with and without diabetes. Our results are consistent with prior literature that suggests Lp(a) to be a potent harbinger of clinical cardiovascular disease (3,4) but are strengthened by the fact that these results from ACCELERATE were obtained in the context of a robust randomized clinical trial with central blinded adjudication of clinical end points. Furthermore, based on our findings, at least a third of contemporary high-risk patients with diabetes on optimal medical treatment have high Lp(a) levels (≥ 64.6 nmol/L) and increased risk for new cardiovascular events and might benefit from pharmacological intervention aiming at significantly reducing Lp(a) levels (5).

Acknowledgments. The authors thank all staff, coordinators, and participants of the ACCELERATE clinical trial.

Duality of Interest. This study was funded by Eli Lilly and Company. L.C. is a research consultant to Amgen, Esperion, Novartis, and AstraZeneca. G.R., G.W., and J.S.R. are a full-time employees of Eli Lilly and Company, a company that develops drugs to treat diabetes and lipid disorders. S.J.N. has received funding from AstraZeneca, Amgen, Anthera, Eli Lilly and Company, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience. Additionally, he is an inventor of a patent focused on PCSK9 inhibition. A.M.L. has research contracts with AstraZeneca, CSL, Esperion, Eli Lilly and Company, and Novartis and serves as a consultant for Novo Nordisk and Eli Lilly and Company. The Cleveland Clinic Center for Clinical Research (C5Research) has received funding to perform clinical trials from AbbVie, AstraZeneca, Amgen, Cerenis, Eli Lilly and Company, Esperion, Medtronic, MyoKardia, Novartis, Pfizer, The Medicines Company, Silence Therapeutics, Takeda, and Orexigen; S.E.N. is involved in these clinical trials but receives no personal remuneration for his participation. S.E.N. consults for many pharmaceutical companies but

requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. N.P.S. wrote the manuscript, researched data, and edited the manuscript. Q.W. researched data, performed analysis, wrote methods, and edited the manuscript. K.E.W. researched data, performed analysis, and reviewed and edited the manuscript. L.C., E.M., G.R., G.W., J.S.R., S.J.N., A.M.L., and S.E.N. reviewed and edited the manuscript. V.M. supervised project development and reviewed and edited the manuscript. N.P.S. and V.M. are

the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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