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Oxidized Phospholipids, Lipoprotein(a), and Cardiovascular Outcomes after Acute Coronary Syndrome

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BACKGROUND: Oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) reflect pro-inflammatory properties of Lp(a) (lipoprotein(a)). The effect of OxPL-apoB on major adverse cardiovascular events (MACE) in patients with acute coronary syndrome in recent the era is not known.

METHODS: OxPL-apoB levels and Lp(a) were measured in 11 630 participants before and 5185 participants 4 months after randomization to alirocumab or placebo in the ODYSSEY OUTCOMES trial. Proportional hazards models adjusted for baseline covariates evaluated associations between $\log_2$-transformed OxPL-apoB and Lp(a) with MACEs. Interactions between the 2 biomarkers and treatment were also evaluated.

RESULTS: Participants were followed for a median 2.9 years; the median age was 58 years, and 23.9% were female. Alirocumab reduced median placebo-adjusted OxPL-apoB by 13.0% and Lp(a) by 26.2% (both $P<0.0001$). In the placebo group, a doubling of baseline OxPL-apoB was associated with a hazard ratio (HR) of 1.081 (95% CI, 1.026–1.139; $P=0.0034$) for MACEs. Addition of Lp(a) to the model relegated the relationship of OxPL-apoB insignificant. In the alirocumab group, neither OxPL-apoB nor Lp(a) remained significantly associated with MACEs. A significant 3-way interaction was present among continuous $\log_2$ OxPL-apoB, Lp(a) stratified at the median, and treatment group on MACEs ($P_{interaction}=0.0023$) so that, in the placebo group, increasing OxPL-apoB was associated with higher risk of MACEs when Lp(a) was below the median concentration but not above. In the alirocumab group, OxPL-apoB was not related to MACE risk irrespective of Lp(a) concentration.

CONCLUSIONS: In patients with recent acute coronary syndrome receiving optimized statin treatment, elevated OxPL-apoB levels predicted MACEs, a relationship abrogated by alirocumab. The interaction of OxPL-apoB and Lp(a) in the placebo group indicates that OxPL-apoB independently predicts MACEs when Lp(a) levels are relatively low.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT001747 and NCT01663402.

Key Words: acute coronary syndrome ■ alirocumab ■ lipoprotein(a) ■ oxidation ■ oxidized phospholipids ■ PCSK9 inhibitors

PCSK9 (proprotein convertase subtilisin/kexin type 9) is a major regulator of the LDL (low-density lipoprotein) receptor[1] and plasma LDL cholesterol (LDL-C) levels.[2] The development of PCSK9 inhibitor has expanded the therapeutic armamentarium of cardiovascular disease by potently lowering plasma LDL-C levels when added to statins and other oral hypolipidemic agents. In phase 3 clinical trials, monoclonal

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Clinical Perspective

What Is New?

- Oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) are independently associated with major adverse cardiovascular events in statin-treated patients with recent acute coronary syndrome when lipoprotein (a) levels are low.
- Alirocumab treatment significantly reduces both OxPL-apoB and lipoprotein (a) levels and mitigates OxPL-apoB–associated cardiovascular risk.
- A novel automated OxPL-apoB assay demonstrated prognostic utility and enables large-scale biomarker evaluation.

What Are the Clinical Implications?

- OxPL-apoB may serve as an independent biomarker of residual cardiovascular risk in patients after acute coronary syndrome with low lipoprotein(a) levels, even on optimized statin therapy.
- PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition with alirocumab may attenuate OxPL-apoB–related risk, supporting its broader use in high-risk patients beyond low-density lipoprotein cholesterol reduction.
- Automated measurement of OxPL-apoB offers a scalable tool for cardiovascular risk stratification.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
HDL-C	high-density lipoprotein cholesterol
IDL	intermediate-density lipoprotein
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MACE	major adverse cardiac event
OxPL-apoB	oxidized phospholipids on apolipoprotein B100
VLDL	very-low-density lipoprotein

antibodies directed against PCSK9 reduced cardiovascular events in secondary prevention subjects optimized on statin therapy.[3,4] The clinical benefit of PCSK9 inhibitors for major adverse cardiovascular events (MACE) is modified by baseline Lp(a) (lipoprotein(a)) levels[5–8] so that elevated Lp(a) is associated with both greater relative and absolute benefit of treatment.[9]

Recent studies indicate that, at equimolar concentrations, Lp(a) particles are approximately 6 times more atherogenic than LDL particles, indicating that elevated Lp(a) imparts a substantial contribution to cardiovascular risk.[10–12] This suggests that apolipoprotein B-100, common to both LDL and Lp(a), may not drive this additional increased atherogenicity of Lp(a).[13] Among lipoproteins, Lp(a) is the predominant carrier of oxidized phospholipids (OxPLs) in plasma.[14,15] Multiple studies have shown that a major contributor to Lp(a)-mediated cardiovascular disease risk is its content of proinflammatory OxPL.[16–20] In this study, we determined the effects of the PCSK9 inhibitor alirocumab on OxPLs of apolipoprotein B-100 (OxPL-apoB), evaluated the relationship of OxPL-apoB levels to MACEs in the placebo and alirocumab groups, and assessed the interrelationships of OxPL-apoB and Lp(a) with MACE in the ODYSSEY OUTCOMES trial.

METHODS

Requests from qualified investigators for data from the ODYSSEY OUTCOMES trial will be considered by its executive steering committee and the sponsor and should be submitted to odysseyoutcomesesc@gmail.com.

Analysis Cohort

The ODYSSEY OUTCOMES trial was approved by the institutional review board of each site, and all patients provided informed consent. The design and principal results of the trial have been published.[4] The ODYSSEY OUTCOMES trial included 18 924 patients with recent acute coronary syndrome (ACS; acute myocardial infarction or unstable angina) at 1315 sites in 57 countries who were followed for a median of 2.9 (maximum 5.0) years. Patients were required to have an LDL-C level ≥70 mg/dL (1.81 mmol/L), or a non–high-density lipoprotein cholesterol level ≥100 mg/dL (2.59 mmol/L), or apolipoprotein B ≥80 mg/dL during stable treatment with 40 to 80 mg of atorvastatin daily, 20 to 40 mg of rosuvastatin daily, or the maximum tolerated dose of either statin. Between 1 and 12 months after the index ACS, patients were randomized at a 1:1 ratio to receive alirocumab or matching placebo subcutaneously every 2 weeks.

For the present post hoc analysis, all available stored serum samples were used for measurement of OxPL-apoB. Of the intention-to-treat cohort, 5804 of 9462 patients in the alirocumab group and 5826 of 9462 in the placebo group had biomarker samples for analysis of OxPL-apoB at baseline. The sample set included 11 630 trial participants at baseline (5804 randomized to alirocumab and 5826 to placebo). Additionally, there were 5185 stored samples at the month-4 time point (2589 randomized to alirocumab and 2596 to placebo). This article adheres to the CONSORT reporting checklist.

Cardiovascular Outcomes

The primary efficacy outcome of the trial and the current analysis was time to first occurrence of a MACE, consisting of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. We also analyzed all-cause death as a secondary efficacy outcome. All events included in the analyses were adjudicated by an independent committee blinded to treatment assignment.

Measurement of Lp(a)

Serum Lp(a) values from these blood samples and time points were provided in molar concentration by a Roche Cobas C 502 analyzer using an immunoturbidimetric assay with rabbit polyclonal anti-Lp(a) detection (Roche Tina-Quant Lipoprotein(a) Gen.2). Bilevel internal quality control samples were measured at the start and end of every analysis day. Three high-Lp(a) internal quality control sample lots had mean (SD) values of 106.6 (2.8) nmol/L, 112.5 (3.6) nmol/L, and 111.2 (3.0) nmol/L with an overall interassay coefficient of variation of 2.9%.[21]

Measurement of OxPL-apoB With a Novel Automated Method

This is the first analysis to use an automated method to measure OxPL-apoB (Diazyme, Inc; Poway, CA) to validate its prognostic information for cardiovascular events. OxPL as measured with this method reflects the cumulative amount of OxPL carried by all apoB-100 particles, which include Lp(a), LDL, VLDL (very low-density lipoprotein), and IDL (intermediate-density lipoprotein). The majority of OxPLs among these lipoproteins are carried by Lp(a), but the proportion relative to other lipoprotein carriers may vary from approximately 20% to 80% depending on clinical scenario and other factors.[16]

A detailed description of the methods is provided in the Supplemental Appendix. In brief, OxPL-apoB was measured in serum samples using an automated magnetic bead chemiluminescence immunoassay by capturing a fixed amount of human apoB-100 on magnetic beads and then detecting the OxPL content with the IgM murine monoclonal antibody E06.[16] This method replicates the OxPL-apoB ELISA methodology[16] but uses MS160-carboxyl magnetic beads (Magnosphere, MBL, Schaumburg, IL) coated with the murine monoclonal antibody MB47, which recognizes all apoB-100 particles (very low-density lipoprotein, IDL, LDL, and Lp(a)) equally. The conditions are designed to capture an equal and saturating amount of apoB-100 from each sample. This allows the determination of the carrying capacity for OxPLs, thereby making the measurement independent of total plasma apoB-100 or LDL-C. The content of OxPLs on apoB-100 is measured by the murine IgM antibody monoclonal antibody E06, which recognizes OxPL but not native phospholipids.[16] The signal reflecting OxPL-apoB concentration is reported in molar concentration (nanomoles per liter) of phosphocholine molar equivalents.[22]

Validation of the OxPL-apoB assay was performed according to the Clinical and Laboratory Standards Institute. The assay was based on and traceable to the predicate gold-standard ELISA method developed at the University of California San Diego.[16] The assay has a limit of quantitation of 0.57 nmol/L, is linear up to 50 nmol/L, and has a value coefficient of variation of low values of 5.6% and high values of 3.0%. The assay is fully automated with the DZ-Lite Meglumi 3000 chemiluminescent immunoanalyzer. For the current analysis, OxPL-apoB was measured at the Department of Clinical Chemistry and Laboratory Medicine, Leiden University Medical Center, Leiden, the Netherlands.

Statistical Analysis

Concentrations below the lower limit of quantification for OxPL-apoB (0.57 nmol/L) and Lp(a) (7.0 nmol/L) were set to the midpoint between 0 and the respective limit. Continuous variables are described by median (quartile 1 and quartile 3), whereas categorical variables are presented as counts and percentages. In all analyses, there was no imputation of missing data. Quantile regression was used to calculate CIs for medians and *P* values for differences in medians. For modeling purposes, baseline OxPL-apoB and Lp(a) were $\log_2$ transformed, and their relationships with MACEs were analyzed in proportional hazards models. Models included adjustment for baseline characteristics of age, sex, race, systolic blood pressure, LDL-C, high-density lipoprotein cholesterol (HDL-C), triglyceride, $\log_2$[high-sensitivity C-reactive protein], body mass index, history of diabetes (yes or no), current smoker (yes or no), estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (yes or no), and high-intensity statin (yes or no).

The 3-way interaction between continuous baseline $\log_2$ OxPL-apoB, continuous baseline $\log_2$ Lp(a), and treatment group for risk of MACE was determined in a proportional hazards model. To further illustrate the nature of this interaction, 3-way interactions between continuous $\log_2$-transformed values of one biomarker, stratification at the median concentration of the other biomarker, and treatment group were assessed. Proportional hazards models for subgroups defined by the median stratified biomarker and treatment group were applied to illustrate these interactions; the models also included adjustment for continuous $\log_2$-transformed values of the biomarker that was stratified at the median. Two-way interactions between baseline OxPL-apoB and Lp(a) within each treatment group were also estimated as sensitivity analyses. Finally, the continuous relationships of one biomarker with estimated 4-year cumulative incidence of MACE, stratified by median concentration of the other biomarker and treatment group, were estimated by restricted cubic splines from proportional hazards models with knots at the 25th, 50th, and 75th percentiles of the continuous biomarker, and plotted from the first to 99th percentiles. Analyses were performed by an independent academic statistician (M.S.) using SAS version 9.4.

RESULTS

Baseline Patient Characteristics

The baseline characteristics of the study participants are shown in Table 1. The median age of the participants was 58, and >75% were male and White, which is generally reflective of the overall ODYSSEY OUTCOMES trial population.[4] A comparison of baseline characteristics of included versus excluded participants is shown in Table S1, and MACE treatment group comparisons are shown in Table S2. Although there were some differences between the analysis cohort and those excluded, these were likely attributable to the large sample sizes rather than meaningful group differences. The small size of the differences suggests that the findings should still apply to the full study population.

Baseline and Month-4 Changes in OxPL-apoB and Lp(a) Levels

The distribution of OxPL-apoB and Lp(a) in the overall cohort is shown in Figure 1 and displays a right skew

Table 1. Baseline Characteristics of the Analysis Cohort

	Alirocumab (n=5804)	Placebo (n=5826)
Median age, years IQR (Q1, Q3)	58 (51, 65)	58 (52, 65)
Female sex	1377 (23.7)	1405 (24.1)
Race and ethnicity		
White	4655 (80.2)	4720 (81.0)
Asian	712 (12.3)	710 (12.2)
Black	162 (2.8)	150 (2.6)
Other*	275 (4.7)	246 (4.2)
Region of enrollment		
Central and eastern Europe	1114 (19.2)	1126 (19.3)
Western Europe	1375 (23.7)	1384 (23.8)
Canada or United States	1373 (23.7)	1382 (23.7)
Latin America	753 (13.0)	747 (12.8)
Asia	684 (11.8)	680 (11.7)
Rest of world	505 (8.7)	507 (8.7)
Index ACS		
STEMI	2103 (36.2)	2084 (35.8)
Non-STEMI	2790 (47.9)	2766 (47.7)
Unstable angina	943 (16.2)	925 (15.9)
Missing	9 (0.2)	10 (0.2)
Revascularization for index ACS	4230 (72.9)	4324 (74.2)
Diabetes	1699 (29.3)	1746 (30.0)
Current smoker	1388 (23.9)	1418 (24.3)
Hypertension	3694 (63.4)	3643 (62.5)
eGFR <60, mL/min per 1.73 m^2	778 (13.4)	802 (13.8)
High intensity statin	5137 (88.5)	5208 (89.4)
BMI, kg/m^2	28.0 (25.4, 31.2)	28.0 (25.2, 31.2)
Systolic BP, mm Hg	127 (118, 138)	126 (116, 138)
LDL-C, mg/dL	86.0 (72.6, 103.5)	86.5 (73.0, 105.0)
HDL-C, mg/dL	42.1 (36.0, 50.0)	42.1 (36.0, 49.8)
Triglyceride, mg/dL	130.1 (94.7, 182.0)	131.9 (95.0, 185.0)
ApoB, mg/dL	79.0 (69.0, 93.0)	80.0 (69.0, 94.0)
hsCRP, mg/L	1.7 (0.8, 3.7)	1.7 (0.8, 4.0)

Values in table are median (Q1, Q3) or n (%). ACS indicates acute coronary syndrome; apoB, apolipoprotein B; BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; and STEMI, ST-segment–elevation myocardial infarction.

*Other indicates anything other than White, Asian, or Black.

pattern typical of these variables. The baseline and absolute change in OxPL-apoB and Lp(a) levels are shown in Table 2. The Spearman rho coefficient between baseline OxPL-apoB and Lp(a) was 0.665 ($P<0.0001$), and the 4-month rho coefficients were 0.656 and 0.663 in the alirocumab and placebo groups, respectively (both $P<0.0001$).

The baseline mean and median levels of OxPL-apoB were similar in the alirocumab and placebo groups. At 4 months of assigned randomized treatment, the absolute median change of OxPL-apoB in the alirocumab group was −0.19 mmol/L and 0 nmol/L in the placebo group, resulting in a median placebo-corrected difference in OxPL-apoB of −13.0% ($P<0.0001$). The changes in Lp(a) at 4 months were −26.2% and 0.0% ($P<0.0001$) in the alirocumab and placebo groups, respectively.

Baseline OxPL-apoB and Lp(a) and Risk of MACEs in the Placebo Group

In separate, unadjusted models in the placebo group, the risk of MACE was associated with baseline log_2-transformed OxPL-apoB and with baseline log_2-transformed Lp(a) (Table 3). Significant associations with MACE persisted for both predictor variables in separate models adjusted for demographic and clinical covariates, with hazard ratios (HRs) for MACE for a doubling of baseline OxPL-apoB of 1.093 (95% CI, 1.034–1.155; $P=0.0016$), and for a doubling of baseline Lp(a) (HR, 1.080; 95% CI, 1.041–1.120; $P<0.0001$). When OxPL-apoB and Lp(a) were included together in an adjusted model, OxPL-apoB was no longer significantly associated with MACE (HR, 1.029 [95% CI, 0.961–1.103]; $P=0.41$), whereas Lp(a) remained significantly associated with MACE (HR, 1.067 [95% CI, 1.019–1.117]; $P=0.0056$).

Baseline OxPL-apoB and Lp(a) and Risk of MACEs in the Alirocumab Group

Assignment to treatment with alirocumab mitigated the risk associated with elevated OxPL-apoB or elevated Lp(a). In an adjusted model using both log_2-transformed OxPL-apoB and Lp(a) as predictor variables, neither predictor was significantly associated with MACE, with HRs for doubling of 1.039 (95% CI, 0.961–1.124; $P=0.33$) and 1.037 (95% CI, 0.983–1.094; $P=0.18$), respectively (Table 4).

Three-Way Interrelationship Among Baseline OxPL-apoB, Baseline Lp(a), and Treatment Group on Risk of MACEs

There was a significant 3-way interaction among continuous baseline log_2 OxPL-apoB, continuous baseline log_2 Lp(a), and treatment group on MACE ($P_{interaction}=0.0079$); the interactions among: (1) Lp(a) dichotomized at median, continuous log_2 OxPL-apoB, and treatment ($P_{interaction}=0.0041$), and (2) OxPL-apoB dichotomized at median, continuous log_2 Lp(a), and treatment ($P_{interaction}=0.0091$) were also significant. In the placebo group, a higher

continuous OxPL-apoB concentration was associated with higher MACE risk in patients with Lp(a) below the median concentration (HR for doubling of OxPL-apoB concentration, 1.176 [95% CI, 1.054–1.313]; *P*=0.0038) but not in patients with Lp(a) at or above the median concentration (Table 5). In contrast, in the alirocumab group, there was no significant relationship between OxPL-apoB and risk of MACE either below or at or above the median Lp(a) concentration. Splines of OxPL-apoB versus estimated 4-year cumulative incidence of MACE illustrate these findings, in which increasing OxPL-apoB concentration was associated with increasing risk of MACE only in the placebo group when baseline Lp(a) was below the median concentration (Figure 2A and 2B).

When stratifying by baseline OxPL-apoB concentration in the placebo group, a higher Lp(a) concentration was associated with a higher MACE risk among those with an OxPL-apoB concentration below the median

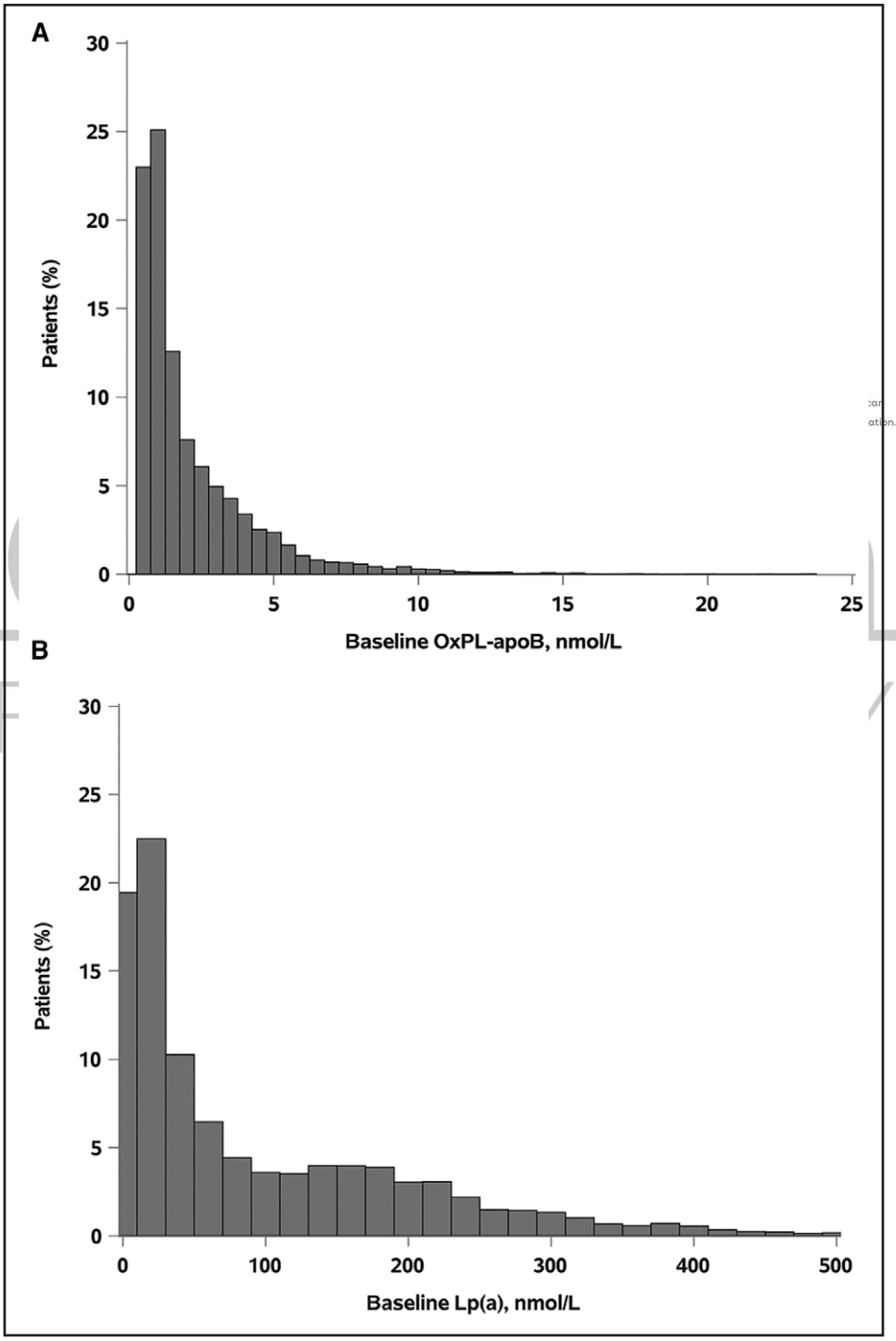

Figure 1. Distribution of oxidized phospholipids on apolipoprotein B100 (OxPL-apoB; A) and lipoprotein(a) (Lp(a); B) plasma levels in the placebo group.

Table 2. Changes in OxPL-apoB and Lp(a) Levels From Baseline to Month 4

	Alirocumab	Placebo	Alirocumab vs placebo *P* value
Baseline OxPL-apoB, nmol/L			
n	5804	5826	1.0000
Mean (SD)	2.11 (2.18)	2.19 (2.26)	
Median (95% CI)	1.30 (1.26–1.34)	1.30 (1.26–1.34)	
[Q1, Q3]	[0.78, 2.74]	[0.80, 2.87]	
Range	[0.285, 23.71]	[0.285, 23.26]	
Baseline OxPL-apoB among those with baseline and month-4 values, nmol/L			
n	2589	2598	0.3238
Mean (SD)	2.16 (2.24)	2.19 (2.25)	
Median (95% CI)	1.30 (1.24–1.36)	1.34 (1.28–1.40)	
[Q1, Q3]	[0.78, 2.83]	[0.80, 2.87]	
Range	[0.285, 23.71]	[0.285, 20.10]	
Month-4 OxPL-apoB among those with baseline and month-4 values, nmol/L			
n	2589	2596	<0.0001
Mean (SD)	1.84 (1.98)	2.20 (2.35)	
Median (95% CI)	1.10 (1.06–1.14)	1.31 (1.25–1.37)	
[Q1, Q3]	[0.70, 2.36]	[0.8, 2.87]	
Range	[0.285, 20.03]	[0.285, 27.79]	
Absolute change baseline to month-4 OxPL-apoB, nmol/L			
n	2589	2596	<0.0001
Mean (SD)	−0.32 (1.80)	0.01 (1.84)	
Median (95% CI)	−0.19 (−0.22 to −0.16)	0.01 (−0.02 to 0.04)	
[Q1, Q3]	[−0.80, 0.29]	[−0.54, 0.58]	
Percent change baseline to month-4 OxPL-apoB, nmol/L			
n	2589	2596	<0.0001
Mean (SD)	77.6 (965.1)	128.6 (1502.9)	
Median (95% CI)	−15.7 (−17.9 to −13.4)	0.4 (−2.1 to 2.7)	
[Q1, Q3]	[−43.6, 27.0]	[−31.4, 46.4]	
Baseline Lp(a), nmol/L			
n	5804	5826	0.5831
Mean (SD)	93.5 (109.3)	96.7 (112.4)	
Median (95% CI)	44.3 (41.0–47.6)	45.4 (42.5–48.3)	
[Q1, Q3]	[13.3, 150.6]	[13.1, 157.3]	
Baseline Lp(a) Among those with baseline and month-4 values, nmol/L			
n	2589	2596	0.9325
Mean (SD)	94.5 (109.3)	99.7 (116.1)	
Median (95% CI)	46.1 (41.5–50.7)	45.7 (41.3–50.1)	
[Q1, Q3]	[12.9, 149.6]	[13.1, 161.7]	
Month-4 Lp(a) among those with baseline and month-4 values, nmol/L			
n	2589	2596	<0.0001
Mean (SD)	72.9 (91.8)	96.2 (112.6)	
Median (95% CI)	27.4 (23.7–30.9)	43.3 (38.8–47.8)	
[Q1, Q3]	[3.5, 118.6]	[12.3, 158.1]	
Absolute change baseline to month-4 Lp(a), nmol/L			
n	2589	2596	<0.0001
Mean (SD)	−21.6 (37.1)	−3.5 (31.1)	
Median (95% CI)	−12.0 (−13.0 to −11.0)	0.0 (−0.24 to 0.24)	
[Q1, Q3]	[−32.3, −2.1]	[−9.3, 4.3]	
Percent change baseline to month-4 Lp(a), nmol/L			
n	2589	2596	<0.0001
Mean (SD)	−21.8 (140.1)	3.3 (128.7)	
Median (95% CI)	−26.2 (−27.6 to −24.7)	0.0 (−0.48 to 0.48)	
[Q1, Q3]	[−49.2, −4.8]	[−15.0, 9.6]	

The minimum OxPL-apoB values (0.285 nmol/L) represent the midpoint between 0 and the lower limit of quantification (0.57 nmol/L). Lp(a) indicates lipoprotein(a) and OxPL-apoB, oxidized phospholipids on apolipoprotein B_{100}.

Table 3. Hazard Ratios for Major Adverse Cardiovascular Events With Doubling of Baseline OxPL-apoB and Lp(a) in the Placebo Group (n=5826, 708 events)

Model	HR (95% CI) for doubling of parameter	*P* value
Unadjusted (separate univariable models)		
OxPL-apoB	1.068 (1.013, 1.125)	0.0141
Lp(a)	1.084 (1.046, 1.123)	<0.0001
Adjusted for baseline characteristics* (separate multivariable models)		
OxPL-apoB	1.081 (1.026, 1.139)	0.0034
Lp(a)	1.080 (1.041, 1.120)	<0.0001
Unadjusted (single model with both OxPL-apoB and Lp(a))		
OxPL-apoB	0.987 (0.925, 1.052)	0.68
Lp(a)	1.090 (1.042, 1.141)	0.0002
Adjusted for baseline characteristics* (single model with both OxPL-apoB and Lp(a))		
OxPL-apoB	1.023 (0.962, 1.088)	0.47
Lp(a)	1.069 (1.023, 1.118)	0.0032

Lp(a) indicates lipoprotein(a) and OxPL-apoB, oxidized phospholipids on apolipoprotein B_{100}.

*Age, sex, race, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, $\log_2$(high-sensitivity C-reactive protein), body mass index, history of diabetes (yes or no), current smoker (yes or no), estimated glomerular filtration rate<60 (yes or no), and intense statin (yes or no).

Table 4. Hazard Ratios for Major Adverse Cardiac Events With Doubling of Baseline OxPL-apoB and Lp(a) in the Alirocumab Group (n=5804, 582 events)

Model	HR (95% CI) for doubling of parameter	*P* value
Unadjusted (separate univariable models)		
OxPL-apoB	1.050 (0.989, 1.114)	0.11
Lp(a)	1.043 (1.003, 1.084)	0.0349
Adjusted for baseline characteristics* (separate multivariable models)		
OxPL-apoB	1.061 (0.999, 1.127)	0.0533
Lp(a)	1.055 (1.013, 1.099)	0.0101
Unadjusted (single model with both OxPL-apoB and Lp(a))		
OxPL-apoB	1.015 (0.941, 1.094)	0.70
Lp(a)	1.037 (0.986, 1.090)	0.16
Adjusted for baseline characteristics* (single model with both OxPL-apoB and Lp(a))		
OxPL-apoB	1.016 (0.942, 1.097)	0.68
Lp(a)	1.048 (0.994, 1.104)	0.08

Lp(a) indicates lipoprotein(a) and OxPL-apoB, oxidized phospholipids on apolipoprotein B_{100}.

*Age, sex, race, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, $\log_2$(high-sensitivity C-reactive protein), body mass index, history of diabetes (yes or no), current smoker (yes or no), estimated glomerular filtration rate<60 (yes or no), and intense statin (yes or no).

(HR for doubling of Lp(a) concentration, 1.126 [95% CI, 1.055–1.201]; *P*=0.0003) but not with an OxPL-apoB concentration at or above the median (Table 6). The opposite was observed in the alirocumab group, in which a higher Lp(a) concentration was associated with a higher MACE risk among those with OxPL-apoB at or above the median concentration (HR for doubling of Lp(a) concentration, 1.126 [95% CI, 1.055–1.201]; *P*=0.0003), but not among those with OxPL-apoB below the median concentration. These findings were confirmed by splines depicting the risk of MACE by Lp(a) concentration in subgroups dichotomized at the median OxPL-apoB concentration (Figure 3A and 3B).

Relationships between baseline OxPL-apoB, Lp(a), and MACE were similar when estimated from models reflecting 2-way interactions between these biomarkers within each treatment group, in which the interactions were only significant in the placebo group (Tables S3 and S4).

DISCUSSION

This analysis provides novel observations about the interplay of OxPL-apoB and Lp(a) as biomarkers of cardiovascular risk in patients enrolled within 1 year after recent ACS on optimized statin treatment, randomized to placebo or alirocumab. First, continuous OxPL-apoB as a single predictor was associated with MACE in the placebo group. When continuous Lp(a) was added as a second predictor variable, Lp(a), but not OxPL-apoB, remained an independent predictor of MACE. Second, there was a 3-way interaction among OxPL-apoB, Lp(a), and treatment group so that the relationship of OxPL-apoB to MACE in the placebo group was strongest in patients with Lp(a) levels approximately <44 nmol/L. Third, OxPL-apoB was not predictive of risk in the group assigned to alirocumab, indicating that alirocumab attenuated OxPL-apoB–associated risk. These observations suggest that, in post-ACS settings with optimized statin therapy, OxPL-apoB may provide additional prognostic information in patients with Lp(a) in the normal range.

The large sample size of the current analysis allowed interrelationships between OxPL-apoB and Lp(a) to be explored in both continuous and dichotomous analyses. In continuous analysis in the placebo group following multivariable adjustment, the addition of Lp(a) relegated the MACE effect of OxPL-apoB overall nonsignificant. However, visually in spline analyses and quantitatively in the 3-way interaction tests, the findings indicate that the relationship is not static across all Lp(a) values; rather, OxPL-apoB may provide additional predictive information when the Lp(a) concentration is in a lower range (<44 nmol/L) but is not informative beyond Lp(a) when the Lp(a) concentration is at or above 44 nmol/L.

In previous studies that did not include statin-stabilized patients, OxPL-apoB/Lp(a) interrelationships with MACE have been variable. Several studies have documented that OxPL-apoB is independently predictive of anatomical coronary disease,[23] MACE,[24] and aortic stenosis[25] or that risk prediction is additive to Lp(a).[26,27] In other studies, the risk associated with OxPL-apoB could be explained by concurrent Lp(a) levels.[28,29] The variability noted in these interrelationships may reflect the fact that Lp(a) and OxPL-apoB may mediate risk through

Table 5. Hazard Ratios for Major Adverse Cardiac Events With Doubling of Baseline OxPL-apoB Stratified by Median Lp(a) and Treatment Group From a Single Model

Treatment group	Lp(a) strata	Median (Q1, Q3) OxPL-ApoB (nmol/L)	HR (95% CI) for doubling of OxPL-apoB	*P* value
Placebo				
	< Median (<44.9 nmol/L)	0.87 (0.57, 1.19)	1.176 (1.054–1.313)	0.0038
	≥ Median (≥44.9 nmol/L)	2.60 (1.47, 4.40)	0.933 (0.858–1.015)	0.10
Alirocumab				
	< Median (<44.9 nmol/L)	0.87 (0.56, 1.20)	0.975 (0.867–1.096)	0.67
	≥ Median (≥44.9 nmol/L)	2.51 (1.48, 4.17)	1.042 (0.944–1.150)	0.42

The interaction *P* value between Lp(a) strata, continuous $\log_2$ OxPL-apoB, and treatment is 0.0041. Lp(a) indicates lipoprotein(a) and OxPL-apoB, oxidized phospholipids on apolipoprotein B_{100}.

different pathways. Elevated plasma Lp(a) is primarily genetically determined with small effects by dietary and environmental influences. In contrast, OxPLs are generated independent of Lp(a) and reflect the increased propensity of cell membranes, apoptotic cells, hepatocytes, lipids, and lipoproteins to oxidize or generate OxPLs, which may then accumulate on apoB-containing lipoproteins.[17,24] A potential explanation for these data is that, when the Lp(a) concentration is elevated, Lp(a) subsumes the risk of OxPL-apoB. However, when the Lp(a) concentration is lower, it does not serve as the major carrier of OxPLs, and OxPL-apoB then becomes an independent risk predictor. This is supported by data analyzing the presence of OxPLs and Lp(a) in 24 fine-density fractions isolated by ultracentrifugation from patients with low (≈10 mg/dL), intermediate (≈50 mg/dL), and high (≈136 mg/dL) Lp(a). In whole fractions, OxPLs were primarily detected in the Lp(a)-containing fractions, and OxPL/apoB was very low in the low-Lp(a) group but increased proportionally with increasing Lp(a) levels.[30]

The data in the placebo group of this study build upon previous findings demonstrating that, although statin treatment mitigates LDL-C–attributable cardiovascular risk, statins do not necessarily affect risk attributable to OxPL-apoB or Lp(a). For example, elevated OxPL-apoB levels remained independently predictive of MACE in patients treated with atorvastatin (80 mg daily) in the TNT[31] and SPARCL[32] trials, with HRs of 1.98 and 4.60 in the highest versus lowest quantile, respectively. In an individual-patient data meta-analysis comprising 29 069 patients enrolled in several landmark statin trials, both baseline and on-statin Lp(a) levels were directly associated with cardiovascular disease risk.[33]

Statin treatment may increase concentrations of Lp(a) and OxPL-apoB by 10% to 20%.[34,35] The mechanism underlying this effect has not been fully elucidated, but in cell culture studies, atorvastatin increases production of both PCSK9 protein and apolipoprotein(a).[34] Conversely, kinetic studies suggest that alirocumab reduces the production and increases the catabolic rate of Lp(a)[36] and that binding of PCSK9 protein by alirocumab may reduce synthesis of apolipoprotein(a) and, subsequently, assembly of Lp(a). Because Lp(a) is the main carrier of OxPLs by lipoproteins in plasma, statins may also increase OxPL-apoB, which reflects the content of OxPLs among circulating Lp(a) levels.[35] Whereas statins lower apoB, and adjustment for apoB completely abrogates LDL-C–mediated risk, Lp(a)-mediated risk persists despite adjustment for apoB[13] and therefore must reflect other components of the Lp(a) particle.

Alirocumab produced a 13.0% placebo-adjusted median reduction in OxPL-apoB and a 26.2% reduction in Lp(a), both statistically significant. A decrease in OxPL-apoB with alirocumab was suggested in a previous small study[37] and may be secondary to decreased OxPL-carrying capacity from the reduction in Lp(a). Although the reduction in OxPL-apoB may appear modest, previous studies suggest that OxPLs on Lp(a) may mediate a substantial proportion of Lp(a)-associated cardiovascular risk.[16] Therefore, even small changes in OxPL-apoB levels could have outsized clinical implications, particularly in subgroups in which OxPL burden is disproportionately high. However, the attenuation of OxPL-apoB–associated risk by alirocumab is likely multifactorial. Beyond lowering OxPL-apoB and Lp(a), alirocumab profoundly reduces LDL-C and may exert additional anti-inflammatory or vascular effects. However, in the lowest versus highest quantiles of Lp(a) and OxPL-apoB, LDL-C reductions were similar, but there was very little CV risk reduction in the lowest quantiles. Similar findings were observed in the FOURIER study.[6] Thus, the apparent loss of predictive value for OxPL-apoB with alirocumab treatment may not be solely attributable to biomarker reduction but could reflect broader therapeutic effects. Given the observational, post hoc nature of this analysis, these findings should be interpreted as hypothesis generating, and future studies are needed to disentangle the specific mechanistic contributions of OxPL-apoB lowering to cardiovascular risk reduction.

Measurement of OxPL-apoB with traditional manual ELISA techniques is labor intensive and impractical for large-scale clinical use. In the current analysis, OxPL-apoB was measured with a conceptually similar method to the predicate[22] but with an automated system using magnetic bead methodology. The absolute mean values in this study (≈2.2 nmol/L) are lower than with ELISA

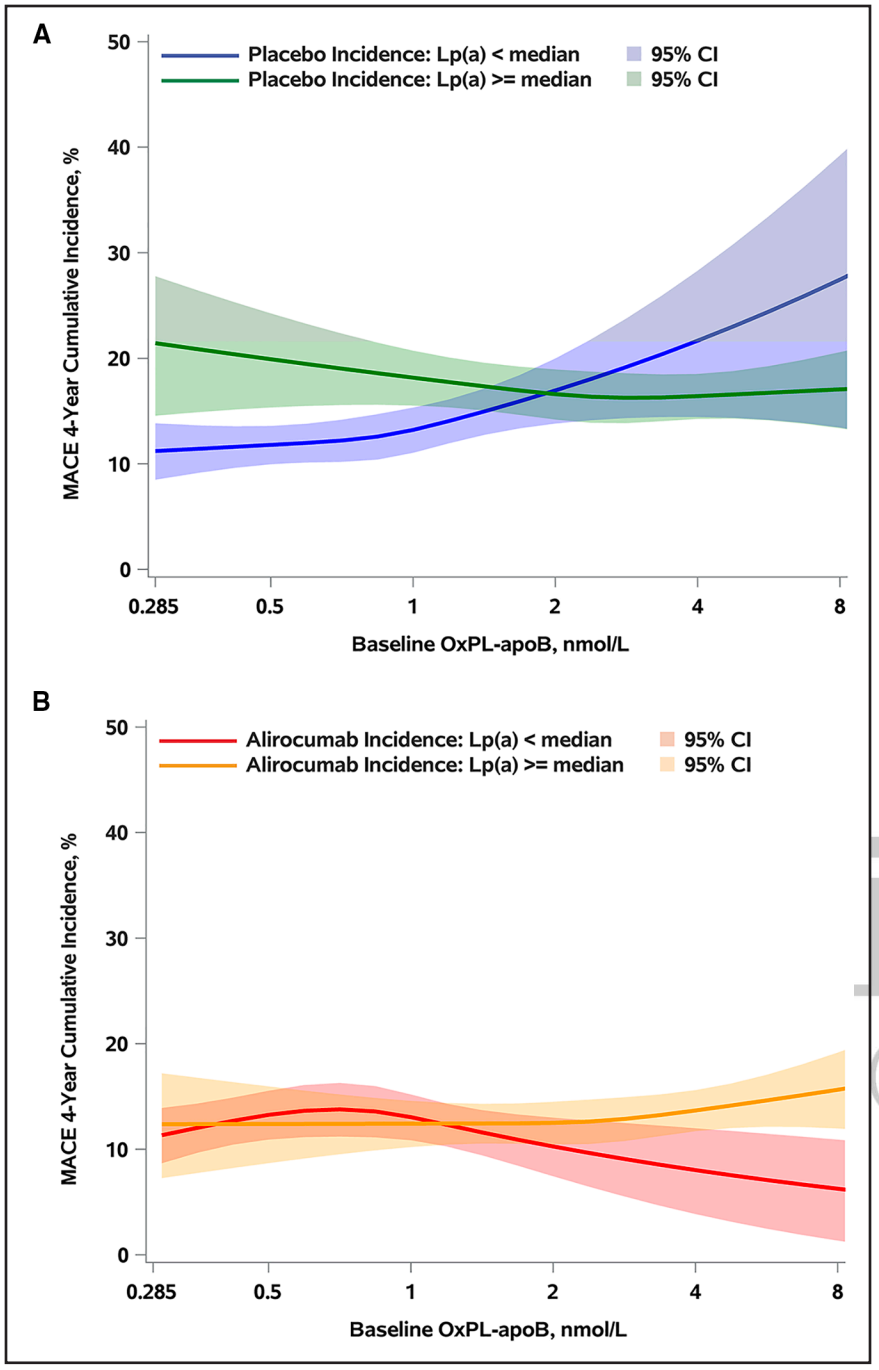

Figure 2. Spline of continuous baseline oxidized phospholipids on apolipoprotein B100 (OxPL-apoB) vs estimated cumulative incidence of major adverse cardiac events (MACEs) through 4 years, stratified by baseline lipoprotein(a) (Lp(a)) within the placebo group (A) and within the alirocumab group (B).
Spline *P*=0.0031, 0.33, 0.13, and 0.25 for placebo group less than median Lp(a), placebo group median Lp(a) or greater, alirocumab group less than median Lp(a), and alirocumab group median Lp(a) or greater, respectively. Splines are restricted cubic with knots at the 25th, 50th, and 75th percentiles of OxPL-apoB and span the approximate first to 99th percentiles, estimated in proportional hazards models. A solid line indicates the estimated 4-year cumulative incidence of MACE, and the shaded area indicates 95% CI *x* axes are $\log_2$ scale. The estimated 4-year cumulative incidences (95% CIs) of MACE for OxPL-apoB of 0.5, 1, 2, and 4 nmol/L are 11.8% (10.0–13.6%), 13.2% (11.1–15.3%), 17.0% (13.8–20.0%), and 21.7% (14.5–28.3%) for the placebo group less than median Lp(a); 19.9% (15.4–24.2%), 18.2% (15.5–20.7%), 16.6% (14.2–18.9%), and 16.4% (14.3–18.5%) for the placebo group median Lp(a) or greater; 13.3% (10.9–15.5%), 13.0% (10.9–15.2%), 10.3% (7.5–13.0%), and 8.0% (3.9–12.0%) for the alirocumab group less than median Lp(a); and 12.4% (10.9–15.5%), 12.4% (10.2–14.6%), 12.5% (10.5–14.5%), and 13.7% (11.7–15.6%) for the alirocumab group median Lp(a) or greater.

in other cohorts with coronary heart disease (3.2 nmol/L in TNT[31] and 3.8 nmol/L in Casablanca[38]). Differences in cohort characteristics as well as analytical methods prevent direct comparisons of absolute OxPL-apoB values from previous and current studies. Nonetheless, the predictive value of the current automated and established ELISA methods provides reassurance that both properly reflect the pathophysiology of OxPL-apoB.

Among the limitations is that this was a post hoc analysis and therefore must be considered exploratory. Because of sample availability, baseline OxPL-apoB was measured in approximately 62% of all ODYSSEY OUTCOMES participants and in approximately half of those at the month-4 time point, which diminished power. Nonetheless, the sample was sufficient to draw several statistically significant inferences. The analysis cohort was a stabilized post-ACS cohort, and the findings may not necessarily apply to other clinical contexts or studies in ongoing Lp(a)-lowering studies. The patient population was also primarily male and White.

In conclusion, OxPL-apoB-mediated residual risk persists in patients with recent ACS on optimized statin treatment, but it can be significantly attenuated by alirocumab. Among statin-treated patients with recent ACS and low levels of Lp(a), elevated OxPL-apoB may be a useful independent biomarker of ongoing cardiovascular risk.

Table 6. Hazard Ratios for Major Adverse Cardiac Events With a Doubling of Baseline Lp(a) Stratified by Median OxPL-apoB and Treatment Group From a Single Model

Treatment group	OxPL-apoB strata	Median (Q1, Q3) Lp(a) (nmol/L)	HR (95% CI) for doubling of Lp(a)	*P* value
Placebo				
	< Median (<1.30 nmol/L)	17.0 (7.7, 38.2)	1.125 (1.054–1.200)	0.0004
	≥ Median (≥1.30 nmol/L)	142.9 (6.03, 220.8)	1.015 (0.955–1.078)	0.64
Alirocumab				
	< Median (<1.30 nmol/L)	17.0 (7.7, 36.2)	1.009 (0.941–1.083)	0.79
	≥ Median (≥1.30 nmol/L)	140.6 (58.7, 216.0)	1.087 (1.009–1.171)	0.0280

The interaction *P* value between Ox-PL-apoB strata, continuous $\log_2$ Lp(a), and treatment is 0.0091. Lp(a) indicates lipoprotein(a) and OxPL-apoB, oxidized phospholipids on apolipoprotein B_{100}.

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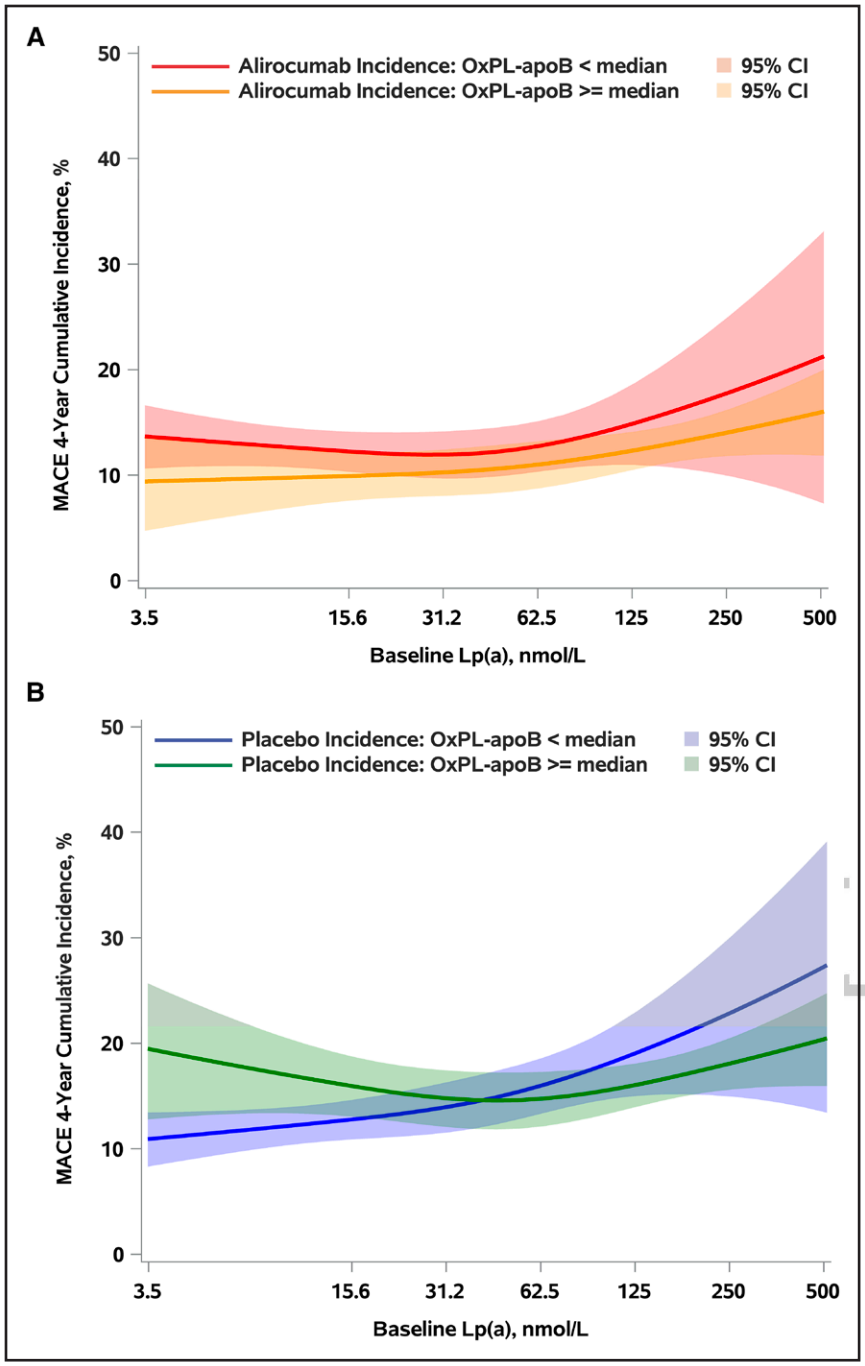

Figure 3. Spline of continuous baseline lipoprotein(a) (Lp(a)) vs estimated cumulative incidence of major adverse cardiac events (MACE) through 4 years, stratified by baseline oxidized phospholipids on apolipoprotein B-100 (OxPL-apoB) within the placebo group (A) and within the alirocumab group (B). Spline *P*=0.0006, 0.11, 0.25, and 0.0354 for placebo group less than median OxPL-apoB, placebo group median OxPL-apoB or greater, alirocumab group less than median OxPL-apoB, and alirocumab group median OxPL-apoB or greater, respectively. Splines are restricted cubic with knots at the 25th, 50th, and 75th percentiles of OxPL-apoB and span the approximate first to 99th percentiles, estimated in proportional hazards models. A solid line indicates the estimated 4-year cumulative incidence of MACEs, and the shaded area indicates 95% CI. *x* axes are $\log_2$ scale. The estimated 4-year cumulative incidences of MACE for Lp(a) of 16, 32, 64, and 128 nmol/L are 12.8% (10.9–14.7%), 14.0% (11.6–16.4%), 16.1% (13.4–18.6%), and 19.2% (15.0–23.1%) for the placebo group less than median OxPL-apoB; 15.9% (13.0–18.7%), 14.8% (12.0–17.4%), 14.8% (12.2–17.3%), and 16.1% (14.0–18.1%) for the placebo group median OxPL-apoB or greater; 12.2% (10.3–14.1%), 11.9% (9.7–14.1%), 12.8% (10.4–15.2%), and 14.9% (11.0–18.7%) for the alirocumab group less than median OxPL-apoB; and 9.9% (7.6–12.2%), 10.3% (8.1–12.4%), 11.0% (8.8–13.2%), and 12.4% (10.6–14.1%) for the alirocumab group median OxPL-apoB or greater.

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Supplemental Material

Supplemental Methods

Tables S1–S4

Figure S1

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