Relation of Oxidized Phospholipids and Lp(a) to Outcomes after Acute Coronary Syndrome:

A post hoc analysis of the ODYSSEY OUTCOMES trial

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Disclosures

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- Sanofi provided support to the Leiden University Medical Center to perform the measurement of OxPL-apoB. Diazyme Inc provided the instrument and assay cartridges for OxPL-apoB to Leiden University Medical Center
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- Dr Fazio is an employee and stockholder of Regeneron Pharmaceuticals
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Background and objectives

Background

Oxidized phospholipids contribute to pro-inflammatory properties of lipoprotein(a) [Lp(a)] and can be quantitated on apolipoprotein B-100-containing lipoproteins (OxPL-apoB)

Objective

To assess the individual and joint relationships of OxPL-apoB and Lp(a) on MACE* in patients with recent acute coronary syndrome on optimized statin treatment, randomized to treatment with PCSK9 inhibitor alirocumab or placebo

*Major adverse cardiovascular events (coronary heart disease death, non-fatal MI, fatal and non-fatal ischemic stroke, and hospitalized unstable angina)

Study design and methods

- ODYSSEY OUTCOMES trial: 18,924 patients with ACS* 1–12 months prior to randomization
- LDL-C ≥70 mg/dL (1.81 mmol/L), non-HDL-C ≥100 mg/dL (2.59 mmol/L), or apoB ≥80 mg/dL on optimized statin (atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily, or maximum tolerated dose of either
- Randomized 1:1 to receive alirocumab or matching placebo subcutaneously every 2 weeks
- OxPL-apoB and Lp(a) measured in 11,630 participants at randomization and 5185 participants 4 months after randomization
- Primary MACE† outcome: coronary heart disease death, non-fatal MI, ischemic stroke, hospitalized unstable angina
- Proportional hazards models adjusted for baseline covariates including LDL-C evaluated associations of OxPL-apoB and lipoprotein(a) with MACE, with hazard ratios for doubling of predictor variables

*Acute coronary syndrome, including myocardial infarction and unstable angina; † MACE, major adverse cardiovascular events

Serum Lp(a) and OxPL-apoB measurement

OxPL-apoB

- Detects OxPL on all apoB-100 particles (Lp(a), LDL, VLDL and IDL)
- Lp(a) is the predominant lipoprotein carrier of OxPL
- Automated measurement (Diazyme, Inc, Poway, CA, USA)
- Value coefficient of variation of 5.6% for low values and 3.0% for high values

Lp(a)

- Molar concentration by immunoturbidimetric assay (Roche Diagnostics Tina-Quant Gen. 2) with rabbit polyclonal anti-Lp(a) detection
- Interassay coefficient of variation of 2.9%

Baseline and month 4 OxPL-apoB levels

		Alirocumab	Placebo	Alirocumab versus Placebo p-value
Baseline OxPL-apoB, nmol/L	N Mean (SD) Median (95% CI) [Q1, Q3]	5804 2.11 (2.18) 1.30 (1.26, 1.34) [0.78, 2.74]	5826 2.19 (2.26) 1.30 (1.26, 1.34) [0.80, 2.87]	1.0000
Month 4 OxPL-apoB, nmol/L	N Mean (SD) Median (95% CI) [Q1, Q3]	2643 1.84 (1.97) 1.11 (1.07, 1.15) [0.71, 2.36]	2652 2.20 (2.34) 1.31 (1.24, 1.36) [0.81, 2.85]	<0.0001
Percent Change Baseline to Month 4 OxPL-apoB, nmol/L	N Mean (SD) Median (95% CI) [Q1, Q3]	2589 77.6 (965.1) -15.7 (-17.9, -13.4) [-43.6, 27.0]	2596 128.6 (1502.9) 0.4 (-2.1, 2.7) [-31.4, 46.4]	<0.0001

Relation between log_2-transformed baseline OxPL-apoB and Lp(a) with first MACE

Model	HR (95% CI) for Doubling of Parameter	p-value
Adjusted for baseline characteristics (separate multivariate models)**		
OxPL-apoB	1.075 (1.020, 1.132)	0.0067
Lp(a)	1.082 (1.043, 1.123)	<0.0001
Adjusted for baseline characteristics (single model containing both OxPL-apoB and Lp(a))**		
OxPL-apoB	1.023 (0.962, 1.088)	0.4687
Lp(a)	1.069 (1.023, 1.118)	0.0032

**Age, sex, race, systolic BP, LDL-C, HDL-C, triglycerides, hsCRP, BMI, history of diabetes, current smoker, eGFR <60, high-intensity statin treatment.

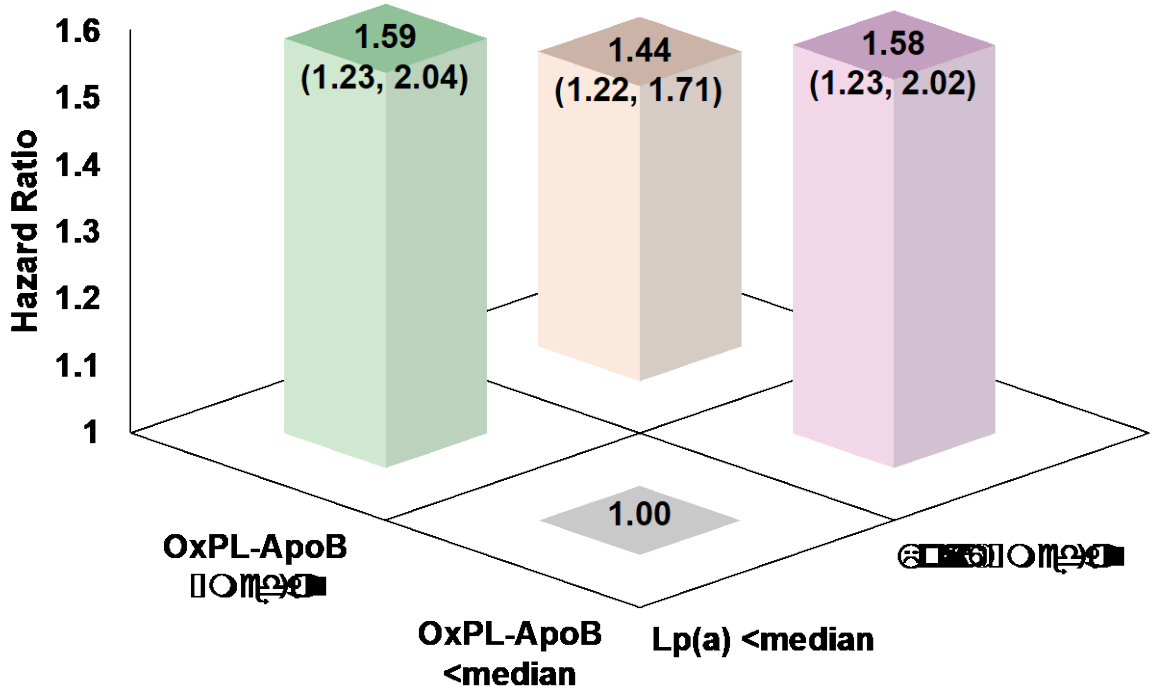
Association between quartile of baseline OxPL-apoB and MACE in placebo and alirocumab groups

In the **placebo group**, increasing quartiles of OxPL-apoB were associated with higher incidence of MACE (P=0.0007).
In the **alirocumab group**, the absolute reduction in risk of MACE was generally greater with higher baseline OxPL-apoB.
Therefore, the risk of MACE was no longer associated with baseline quartile of OxPL-apoB.

Association between quartile of Lp(a) and cardiovascular events in placebo and alirocumab groups

Findings qualitatively similar as with OxPL-apoB, although relationship between quartile of Lp(a) and risk of MACE remained significant in the alirocumab group

Relative risk of MACE in placebo group according to OxPL-apoB and Lp(a) dichotomized at median



Conclusions

- Alirocumab significantly reduced circulating OxPL-apoB levels
- In the placebo group, elevated OxPL-apoB was associated with increased risk of MACE in statin-treated patients with recent ACS. This effect was contingent on elevated Lp(a), suggesting the OxPL on Lp(a) is a key determinant of Lp(a)-mediated risk
- Alirocumab abrogated risk associated with elevated OxPL-apoB, providing an additional potential mechanism for the benefit of PCSK9 inhibitors