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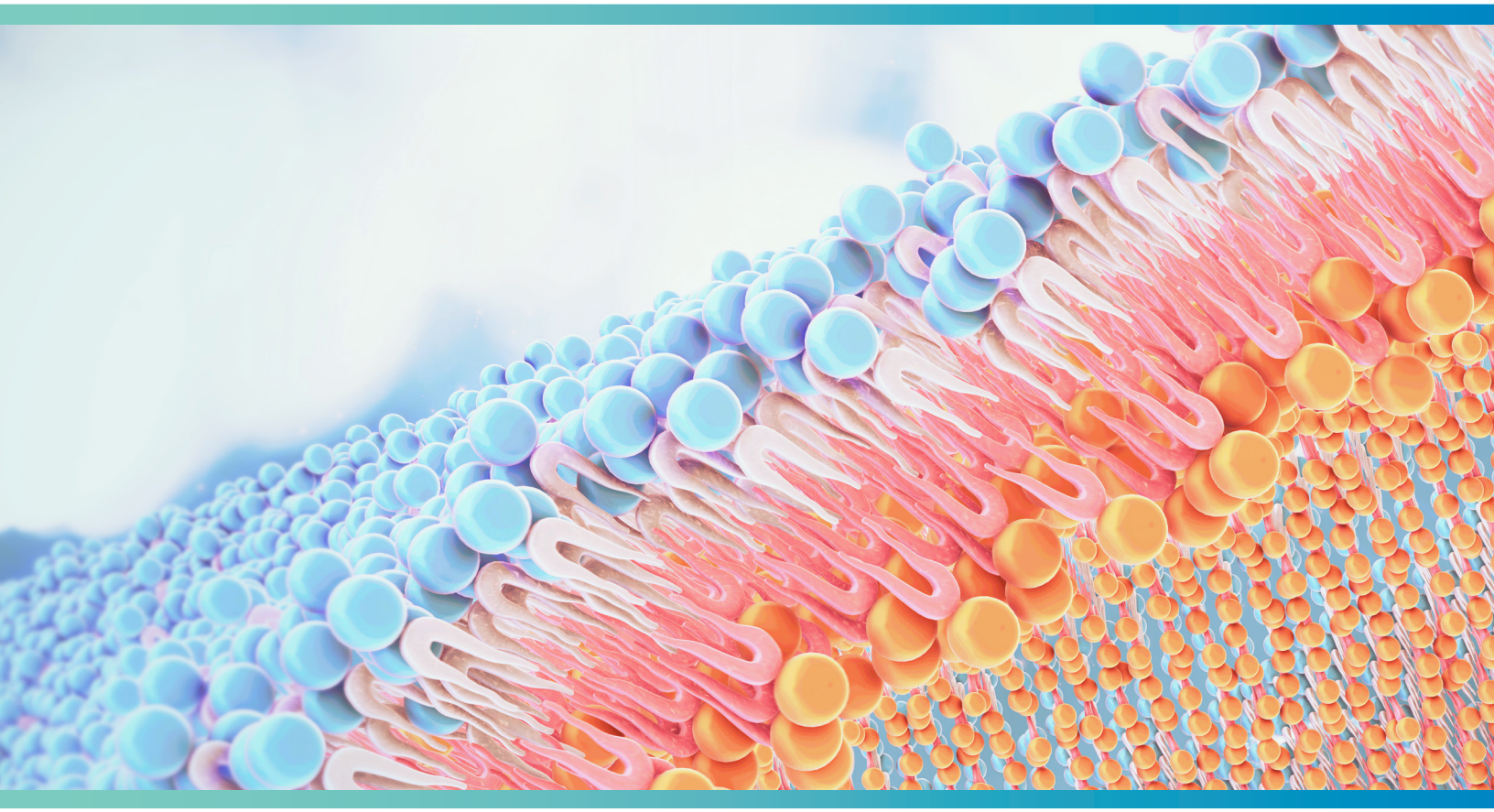

OxPL-apoB and OxPL-apo(a):

Oxidized Phospholipid Biomarkers for Therapeutic Monitoring

Santica Marcovina, PhD and Sotirios Tsimikas, MD

Overview

Phosphocholine-containing oxidized phospholipids (OxPLs) are key mediators of chronic inflammation[1], particularly within atherosclerotic lesions. In plasma, OxPLs are primarily detected on apolipoprotein B-100 (apoB-100)-containing lipoproteins, with lipoprotein(a) [Lp(a)] serving as the predominant carrier. Validated methods now allow for quantification of phosphocholine-containing OxPLs on all apoB-containing lipoprotein particles (OxPL-apoB) or on Lp(a) particles [OxPL-apo(a)]. OxPLs are measured using the natural IgM murine monoclonal antibody E06 that specifically binds oxidized, but not native, phospholipids via their phosphocholine headgroup[2,3]. Results are normalized to apoB or Lp(a) to ensure accurate across-sample comparison.

OxPL-apoB and OxPL-apo(a) serve as biomarkers of oxidative stress and vascular inflammation, central to the pathogenesis of atherosclerotic cardiovascular disease (ASCVD)[1]. These biomarkers are valuable tools for cardiovascular risk stratification and as pharmacodynamic endpoints in Lp(a)-lowering and anti-inflammatory drug development.

Introduction

Despite advances in lipid-lowering therapies, a considerable residual ASCVD risk persists, prompting a focus on non-traditional factors such as oxidation and inflammation. Oxidation plays a critical role in atherosclerosis by modifying lipoproteins and promoting inflammation.

All apoB-100-containing lipoprotein particles are causally linked to the risk of CVD due to their capacity to enter the arterial subintimal space, become trapped and deliver cholesterol, cholesteryl ester and phospholipids to the vessel wall. These particles are then susceptible to oxidative modifications, resulting in the formation of oxidation-specific epitopes recognized as damage-associated molecular patterns by the immune system[4], which trigger chronic inflammation. OxPLs, a subset of these oxidation-specific epitopes, are bioactive lipids generated through the oxidative modification of polyunsaturated fatty acids on phospholipids[5].

OxPLs are abundant in atherosclerotic lesions where they promote endothelial dysfunction, immune system activation, and foam cell formation. Their presence is mechanistically and clinically linked to the initiation, progression, and destabilization of atherosclerotic plaques[6].

OxPLs are also present on circulating apoB-100-containing lipoprotein particles, especially Lp(a). Measurement of OxPL-apoB reflects the total burden of OxPLs carried on all apoB-containing lipoproteins, including, VLDL, IDL, LDL, and Lp(a). Measurement of OxPLs on apo(a), the distinctive protein component of Lp(a), specifically quantify OxPLs carried by Lp(a)[7] [OxPL-apo(a)], an independent risk factor for ASCVD.

These markers offer mechanistic insights and add granularity to inflammation and oxidation assessment beyond traditional measures like LDL-C, apoB, and hsCRP.

Mechanistic Role of OxPLs in Atherosclerosis

OxPLs are primarily generated when native phospholipids on apoB-containing lipoproteins undergo oxidative modifications. These oxidized products bind to scavenger receptors such as CD36 and Toll-like receptors, promoting macrophage uptake and foam cell formation, which are central processes to plaque development. OxPLs also upregulate inflammatory cytokines such as IL-1β, IL-6, and TNF, perpetuating a cycle of inflammation and oxidative stress[4,5].

Human Atherosclerotic Lesions and OxPLs

Histological studies in human coronary and carotid arteries reveal that OxPLs and apo(a) are much more prevalent than apoB-100 in advanced plaques, particularly in fibrous caps and necrotic cores[6]. This distribution pattern suggests that while apoB-100 may initiate lesion formation, OxPLs and Lp(a) are more involved in plaque progression and instability. OxPLs have also been found in debris collected during vascular interventions, confirming their clinical relevance[8].

Lp(a): The Main Lipoprotein Carrier of OxPLs

Among all apoB-containing lipoproteins, Lp(a) carries the largest OxPL burden[9,10]. This is due to both the covalent attachment of OxPLs to apo(a) and their presence in the lipid phase of the LDL-like component of Lp(a). Experimental evidence shows that OxPLs preferentially transfer to Lp(a) from other lipoproteins, and OxPL-apoB levels correlate closely with plasma Lp(a) concentration[9]. However, OxPLs contribute additional predictive value beyond Lp(a) alone by reflecting inflammatory and oxidative stress[11].

Pathophysiological Role of OxPL-Lp(a) Interaction

The binding of OxPLs to the KIV_{10} domain of apo(a), through a lysine binding pocket (LBS), is essential for their accumulation on Lp(a)[10]. Transgenic mice expressing Lp(a) with mutated LBS show markedly reduced OxPL accumulation[10,13]. The source of OxPLs is likely systemic, transferred from inflamed or apoptotic cells such as hepatocytes in steatohepatitis or immune cells in autoimmune conditions. Interestingly, while plasminogen also carries OxPLs, its clinical significance in ASCVD is less defined than that of Lp(a)[14].

Inflammation and Monocyte Priming

High Lp(a) levels are associated with increased arterial inflammation and monocyte activation[15-20]. In vitro studies, show that these inflammatory responses are mitigated by blocking OxPLs using monoclonal antibody E06. Lp(a)-stimulated endothelial cells exhibit upregulated glycolysis and enhanced monocyte adhesion, underscoring its role in vascular inflammation.

Evolutionary Insights

The human *LPA* gene, encoding apo(a), is a derivative of the plasminogen gene (*PLG*) and is unique to primates, African monkeys and hedgehogs[12]. Only human apo(a) retains a LBS in kringle IV type 10 (KIV_{10}) capable of binding OxPLs, a property absent in other species[10]. The evolutionary advantage of Lp(a) remains uncertain, though hypotheses include potential roles in wound healing, parasitic defense, or hemostasis during childbirth.

Methodologies for Measuring OxPL-apoB and OxPL-apo(a)

Both assays use a proprietary ELISA platform based on the use of monoclonal antibody E06 to detect OxPLs. OxPL-apoB is measured on all apoB-containing particles captured on microtiter well plates by an apoB-specific monoclonal antibody (MB47), while OxPL-apo(a) is measured on Lp(a) particles captured by an apo(a)-specific monoclonal antibody (LPA4).

This specificity to OxPL has enabled the development of the OxPL-apoB and the OxPL-apo(a) assays Results are normalized to apoB or to Lp(a) mass captured on the microtiter well plates to ensure accurate cross-sample comparisons.

Summary of Assay Methodology: OxPL-apoB

- Capture: MB47 antibody (5 µg/mL) coats the plate, binding apoB-100 from plasma (1:50 dilution).
- Detection: Biotinylated E06 (1 µg/mL) binds to OxPLs; streptavidin-alkaline phosphatase links detection to chemiluminescent readout.
- Output: Relative light units (RLU) proportional to OxPL levels, converted to nmol/L using a PC equivalent standard curve.
- Note: MB47 captures apoB equally across LDL, IDL, VLDL, and Lp(a), reflecting total apoB-containing particles.

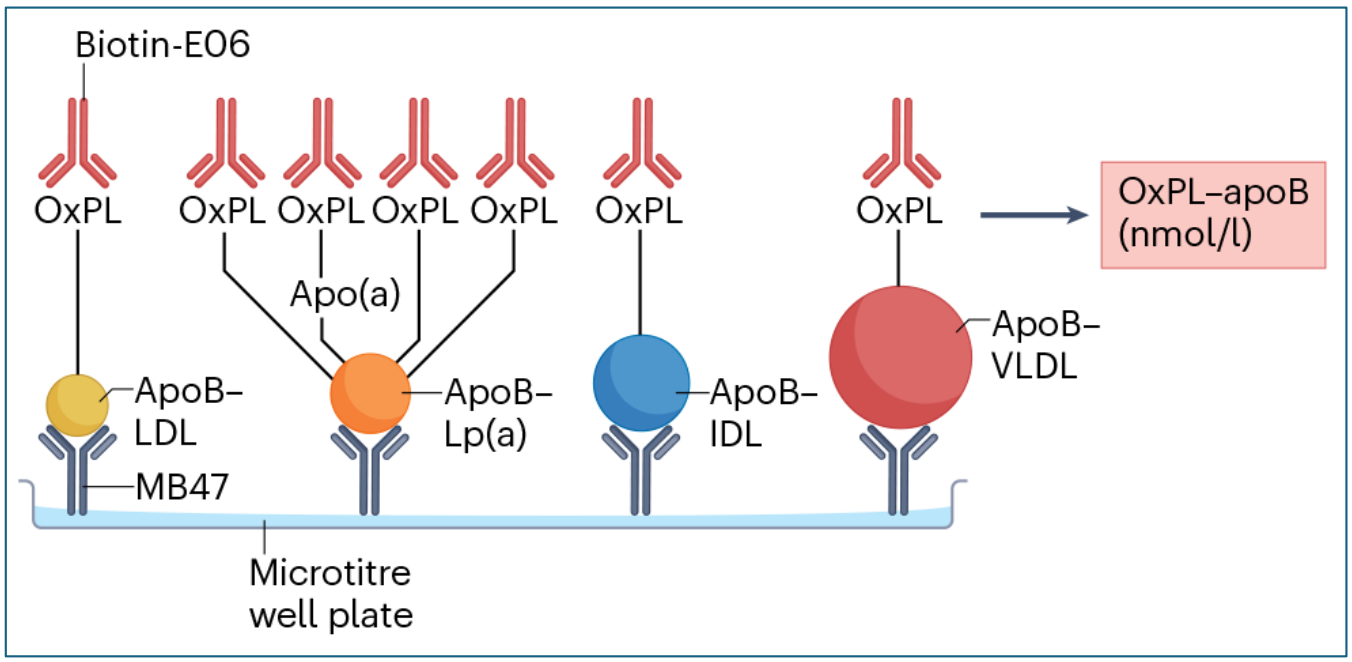

Figure 1. To quantify OxPL-apoB, the MB47 antibody is plated overnight at 5 µg/ml to bind apoB-100 on the microtiter plate; the excess material is then washed off and the plasma sample is added at a 1:50 dilution to allow apoB-100 to bind to the immobilized MB47. Because MB47 recognizes all apoB-100-containing particles with similar specificity, the apoB-100 captured on the plate will reflect the proportion of apoB-100-containing particles that are present in the plasma sample. For example, if Lp(a) levels are elevated, a higher proportion of apoB-100 from Lp(a) will be captured on the microtiter well plate. Biotin-modified E06 (1 µg/ml) is then added to the plate to bind to the OxPLs present on apoB-100-containing lipoproteins, and streptavidin modified with alkaline phosphatase is added to bind to the biotin–E06 in a 1:1 ratio. A chemiluminescent substrate for alkaline phosphatase (Lumi-Phos) is then added to generate light, which is directly proportional to the amount of phosphocholine-containing OxPLs present in the microtiter well plate and reported as RLU emitted per 100 ms. RLUs are then converted to nanomoles per liter using a standard curve of phosphocholine (PC) equivalents[1].

Summary of Assay Methodology: OxPL-apo(a)

- Capture: LPA4 antibody (5 µg/mL) selectively binds Lp(a)/apo(a).
- Detection and readout: Follows the same procedure as OxPL-apoB using biotin-E06 and chemiluminescence.
- Specificity: Reflects the OxPL load specifically on Lp(a).

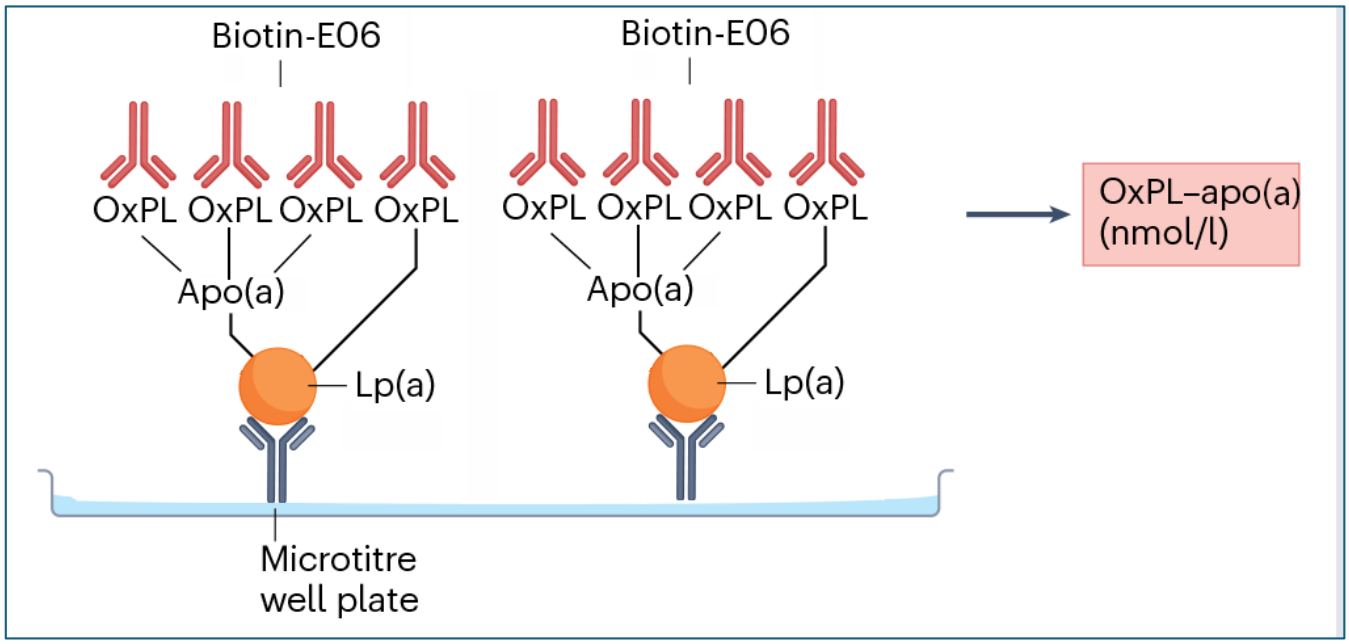

Figure 2. To quantify OxPL-apo(a), the LPA4 antibody is plated overnight at 5 µg/ml to bind apo(a) on the microtiter plate; the excess material is then washed off and the plasma sample is added at a 1:50 dilution to allow Lp(a)/apo(a) to bind to the immobilized LPA4. Biotin-modified E06 (1 µg/ml) is then added to the plate to bind to the OxPLs present on Lp(a)/apo(a)-containing lipoproteins, and streptavidin modified with alkaline phosphatase is added to bind to the biotin–E06 in a 1:1 ratio. A chemiluminescent substrate for alkaline phosphatase (Lumi-Phos) is then added to generate light, which is directly proportional to the amount of PC-containing OxPLs present in the microtiter well plate and reported as RLU emitted per 100 ms. RLUs are then converted to nanomoles per liter using a standard curve of PC equivalents[1].

Differences in OxPL-apoB and OxPL-apo(a) Levels

The OxPL-apoB assay measures oxidized phospholipids on all apoB-containing lipoproteins, including LDL, VLDL, IDL, and Lp(a). It is performed using EDTA plasma or serum. Levels above 5 nmol/L (>75th percentile are associated with increased systemic oxidative stress and inflammation related to atherogenesis.

This assay employs the MB47 antibody to capture apoB-100–containing particles, so the assay reflects the distribution of these particles in plasma. LDL particles, which make up most of apoB-100 lipoproteins, predominate on the assay plate, but Lp(a) carries the highest OxPL content. Thus, OxPL-apoB reflects the total mass of OxPL per fixed amount of captured apoB-100, with LDL being most abundant and Lp(a) disproportionately enriched in OxPL.

In contrast, the OxPL-apo(a) assay is specific to OxPL on Lp(a) particles. Like OxPL-apoB, it uses EDTA plasma or serum and typically yields higher values, as only Lp(a) particles are bound to the plate, excluding other apoB-containing lipoproteins. Because Lp(a) carries most of the OxPL found on lipoproteins in plasma, the absolute OxPL levels measured in this assay are higher than those in the OxPL-apoB assay if measured in the same sample.

OxPL-apoB is a composite marker reflecting oxidative modification of all apoB-containing lipoproteins (primarily LDL and Lp(a)), while OxPL-apo(a) is a more specific measure of the OxPL on Lp(a) alone. The OxPL-apo(a) assay is particularly useful for monitoring the biochemical effect of Lp(a)-lowering therapies in individuals with elevated Lp(a), especially since Lp(a) carries the majority of OxPLs in plasma. Notably, in clinical trials, reductions in Lp(a) levels via pelacarsen were paralleled by marked reductions in OxPL apo(a), further supporting the potential utility of this biomarker in monitoring the therapeutic response.

These assays provide complementary information: OxPL-apoB reflects the overall oxidative burden across all atherogenic apoB-containing lipoproteins, whereas OxPL-apo(a) offers measures Lp(a)-specific proatherogenic and prothrombotic risk (Table 1).

Table 1. Summary of key characteristics of OxPL-apoB and OxPL-apo(a) assays

Biomarker	Target Lipoproteins	Sample Type	Analytical range	Population >75th percentile	Key Clinical Utility
OxPL-apoB	ApoB-containing lipoproteins (LDL, VLDL, IDL, Lp[a])	Serum/ EDTA plasma	1.48 to 148.8 nmol/L	>5 nmol/L	Systemic Lipoprotein-associated oxidative stress and inflammation
OxPL-apo(a)	Lp(a)	Serum/ EDTA plasma	1.48 to 148.8 nmol/L	>25 nmol/L	Lp(a)-mediated atherothrombotic risk

Clinical Applications of OxPL-apoB and OxPL-apo(a) Measurement

The OxPL-apoB assay provides a powerful cardiovascular risk marker, independent of LDL-C or apoB concentrations[1]. It detects the number of OxPLs per unit of apoB-100 using MB47 (for capture) and biotin-E06 (for detection). Notably, OxPL-apoB levels are a more specific indicator than commonly used OxLDL assays, which lack specificity and are confounded by native LDL cross-reactivity.

Predictive Value in Cardiovascular Events

Over 50 clinical studies using OxPL-apoB assay have demonstrated its utility in predicting:

- Extent of anatomical atherosclerosis
- First and recurrent myocardial infarction (MI)
- Ischemic stroke
- Peripheral artery disease (PAD)

In many cohorts, OxPL–apoB was a stronger or independent predictor compared to Lp(a), especially in the context of systemic inflammation (e.g., acute coronary syndromes)[1,11]. Importantly, elevated OxPL-apoB improves risk reclassification, particularly in intermediate-risk individuals – a key demographic for preventive interventions[21].

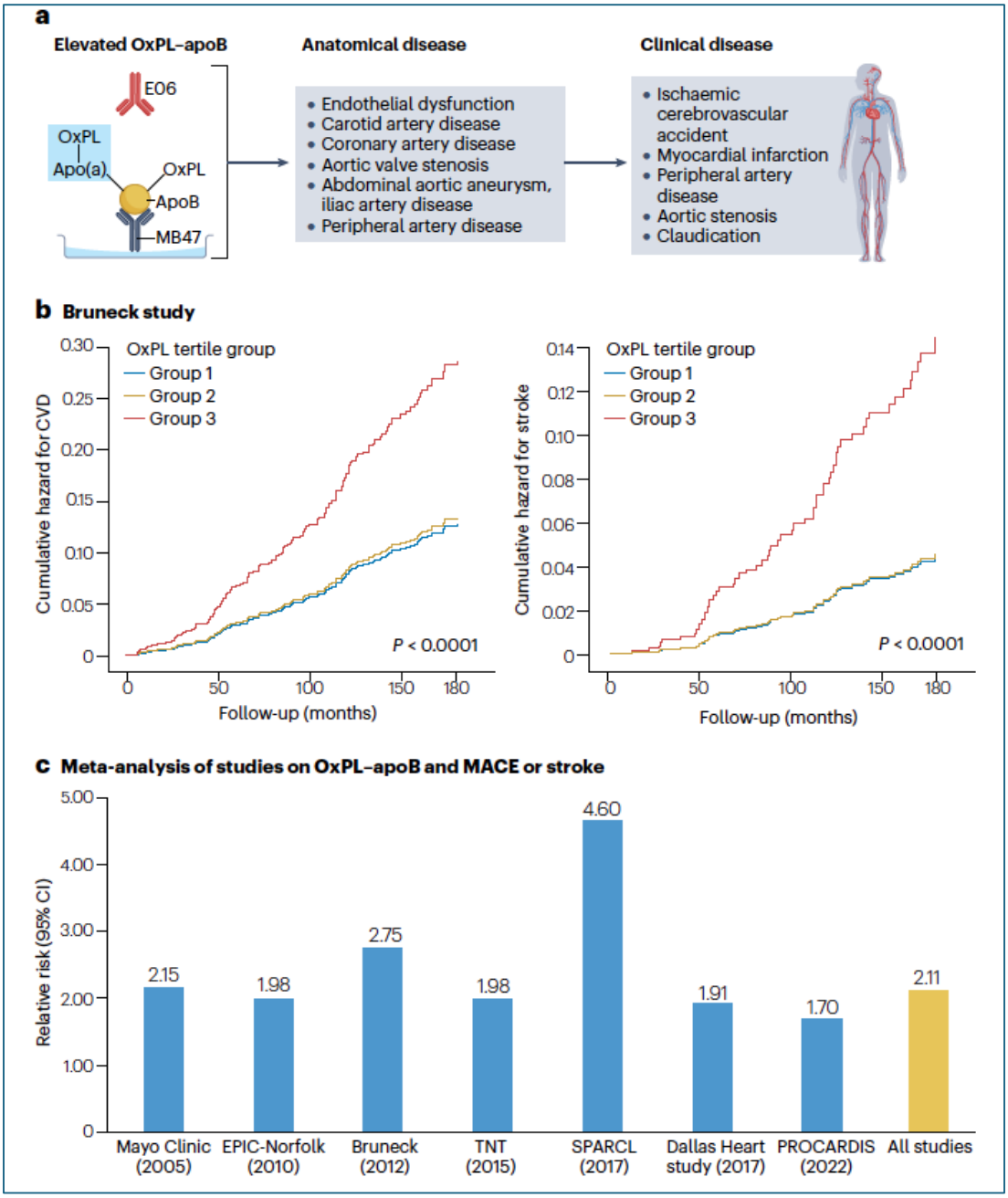

Figure 3. Association of OxPL-apoB with anatomical pan-arterial disease and cardiovascular events. **a-** Schematic of the oxidized phospholipid (OxPL)-apolipoprotein B (apoB) assay and the association between elevated OxPL-apoB levels and endothelial dysfunction, carotid, coronary and peripheral artery disease, and aortic stenosis. The evidence for these studies is summarized in the main text. **b-** Cumulative hazard curves for the incidence of cardiovascular disease (CVD) or stroke by OxPL-apoB tertile groups over 15 years of prospective follow-up. **c-** Association between OxPL–apoB and the risk of major adverse cardiovascular events (MACE) or stroke in a meta-analysis of seven published studies. The values represent the relative risk (95% CI) of MACE or stroke for the top versus bottom fifths of plasma OxPL-apoB level after adjusting for established risk factors for CVD. Adapted with permission from publisher[1].

Therapies that Lower OxPL-apoB and OxPL-apo(a):

1. **Antisense oligonucleotides (ASOs) and siRNA:** These include agents such as pelacarsen[22] and olpasiran[23] which target the *LPA* mRNA, effectively reducing the synthesis of apolipoprotein(a), and thus Lp(a) itself. Since Lp(a) is the main carrier of OxPLs among apoB-containing lipoproteins, lowering Lp(a) with ASOs and siRNAs substantially reduces both OxPL-apoB (88-92%) and pelacarsen lowered OxPL-apo(a) levels by 70%[22].
2. **Muvalaplin:** An oral small molecule inhibitor that disrupts apo(a)-apoB interaction, was shown to significantly lower plasma Lp(a) concentrations in a dose-dependent manner. At the highest doses of muvalaplin (60 and 240 mg/day), OxPL-apo(a) levels were reduced by 70.9% and 73.0%, and OxPL-apoB levels by 67.2% and 58.8%, respectively[24].
3. **Lipoprotein apheresis:** This extracorporeal therapy physically removes Lp(a) and other apoB-containing lipoproteins from the circulation, leading to an acute and often sustained reduction in OxPL-apoB levels[25]. It is particularly useful in patients with extremely elevated Lp(a) and high cardiovascular risk.
4. **Niacin (vitamin B3):** While not widely used today due to side effects and modest outcome benefit, niacin has been shown to reduce plasma Lp(a) levels and, consequently, OxPL-apoB concentrations[26].
5. **Bariatric surgery:** In individuals with obesity, bariatric surgery not only improves traditional lipid profiles and metabolic markers but also reduces systemic inflammation and OxPL-apoB levels, likely by altering lipoprotein metabolism and oxidative stress burden[27].
6. **Experimental antibody therapy (E06-based):** Although not yet clinically available, preclinical studies using the IgM monoclonal antibody E06 or its single-chain variable fragment, scFv, demonstrate potent binding and neutralization of OxPLs. Expression of E06 in animal models has shown significant reductions in OxPL levels, inflammatory cytokines, inflammatory gene expression[1,14,15]. E06 has also been shown in mouse models to ameliorate a variety of OxPL-driven pathologies, including atherosclerosis and steatohepatitis, by neutralizing OxPLs[28,29].

These therapies provide complementary strategies — either directly reducing Lp(a), the carrier of most OxPL, or removing/inactivating OxPLs themselves — to mitigate the atherogenic and inflammatory burden attributed to oxidized phospholipids.

Statins are not effective for reducing OxPL-apoB or OxPL-apo(a) levels. In fact, statins can increase Lp(a) levels and associated OxPL content by approximately 10–20% in some individuals[30]. Given that Lp(a) is the primary carrier of OxPL among apoB-containing lipoproteins, this increase may lead to higher levels of OxPL-apo(a) and contribute to a paradoxical rise in OxPL-apoB as well. This finding emphasizes that while statins are effective for lowering LDL-C, they may have limited or even adverse effects on Lp(a)- and OxPL associated cardiovascular risk markers[31]. Therefore, in patients with elevated Lp(a) or OxPL, additional therapies beyond statins may be required to address this residual risk.

Table 2. Therapies that modify OxPL-apoB and OxPL-apo(a) levels.

Drug/Device	% Change in OxPL-apoB	% Change in OxPL-ap(a)
Statins	+20-30	N/A
Apheresis	-20-60	-65-75
Niacin	-15	N/A
PCSK9i	-15	N/A
Pelacarsen, 80 mg	-88	70
Olpasiran, 75 mg	-90	N/A
Olpasiran, 225 mg	-92	N/A
Muvalaplin, 60 mg	-67	-59
Muvalaplin, 240 mg	-71	73
Lepodisiran	N/A	N/A
Zerlasiran	N/A	N/A

Research Applications of OxPL-apoB and OxPL-apo(a)

1. Cardiovascular Risk Stratification

- Elevated OxPL-apoB and OxPL-apo(a) are independently associated with ASCVD events, vulnerable plaque, and coronary calcification.
- OxPL-apo(a) levels correlate with Lp(a) levels but also reflecting the inflammatory potential of Lp(a), offer added prognostic value.

2. Monitoring Lp(a)-Lowering Therapies

- In clinical trials of pelacarsen (antisense oligonucleotide), siRNA therapies such as olpasiran, or assembly inhibitors such as muvalaplin, OxPL-apoB and OxPL-apo(a) levels decline 60-90%, supporting their role as sensitive pharmacodynamic markers.
- These reductions reflect meaningful improvements in oxidative lipoprotein burden and vascular inflammation.

3. Residual Inflammatory Risk Assessment

- Patients with controlled LDL-C but elevated Lp(a) may harbor high OxPL-apoB or OxPL-apo(a) levels, indicating persistent atherothrombotic risk
- Because these measures are independent of most cardiovascular risk factors, they may be used alongside hsCRP and IL-6 to complement inflammatory risk panels.

4. Drug Development and Mechanistic Studies

- Both biomarkers can serve as mechanistic endpoints in early- and late-phase clinical trials targeting lipoprotein oxidation, immune modulation, or Lp(a)-lowering.
- Applications include cardiovascular outcome studies, atherosclerosis regression trials, and imaging biomarker substudies.

Conclusions

OxPLs are potent mediators of inflammation and atherosclerosis. Their presence on apoB-containing lipoproteins—especially Lp(a)—provides a robust biomarker for cardiovascular risk. OxPL-apoB integrates genetic, inflammatory, and oxidative information, offering a comprehensive perspective on risk prediction. Measurement of these biomarkers can refine clinical risk stratification and guide therapeutic interventions, advancing personalized cardiovascular care.

Why Partner with Medpace?

Medpace's central laboratories offers a unique advantage for Sponsors seeking advanced biomarker analysis through its exclusive research rights from Kleanthi Diagnostics for OxPL-apoB and OxPL-apo(a). These assays are derived from and validated against the original gold-standard methods developed in Dr. Sotirios Tsimikas' laboratory, ensuring scientific rigor and reliability. As the only reference lab to offer both OxPL-apoB and OxPL-apo(a) testing, Medpace also provides optional panels including Lp(a), Lp(a)-cholesterol, apoB, and inflammatory markers for comprehensive lipid and inflammatory profiling. Developed in collaboration with leading experts in Lp(a), oxidized lipids, and lipoprotein biology, these assays are fully suited for both GCP-aligned clinical trials and observational research.

About the Authors

Santica M. Marcovina, ScD, PhD, FAHA

Dr. Marcovina, is presently Sr. Director of Clinical Laboratory Sciences at Medpace Reference Laboratories. In this capacity, she oversees the validation and implementation of complex lipid and metabolic biomarkers, providing scientific and technical support to a team of laboratory scientists and medical technologists to ensure excellence in key parameters for endpoint and exploratory analyses in clinical trials. Before joining Medpace, she was for 30 years Research Professor of Medicine at the University of Washington and Director of the Northwest Lipid Research Laboratories where she has been the Principal Investigator in >60 NIH-funded clinical trials primarily in diabetes and its complications. Throughout her career, Dr. Marcovina's major field of research has been focused on Lp(a). Under NHLBI research grants, she developed high affinity monoclonal antibodies with well-defined epitope specificity on apo(a) kringle IV domains. These antibodies, and particularly one directed to a unique epitope present in apo(a) KIV9, were used to study the structure-function of Lp(a), and to demonstrate the impact of apo(a) KIV2 repeated domains on the accuracy of the immunochemical measurements of Lp(a). They were additionally used to develop an Lp(a) gold standard ELISA method and to develop a high-sensitivity agarose gel electrophoresis that first evidenced the existence of >35 apo(a) isoform size. Dr. Marcovina has published her work in major medical journals, including NEJM, Diabetes Care, EHJ, Nature, JAMA, JACC, Circulation, and has over 600 original papers, review articles, and book chapters.

Sotirios (Sam) Tsimikas, MD, FACC, FAHA

Dr. Tsimikas is a practicing Board-Certified Cardiologist and Professor of Medicine and the Director of Vascular Medicine at the University of California San Diego School of Medicine. His obtained his Medical Degree from the University of Massachusetts Medical School, Internal Medicine training at the University of Massachusetts Medical Center, and separate fellowships in Cardiovascular Medicine, Atherosclerosis and Molecular Medicine and Interventional Cardiology at the University of California San Diego (UCSD) Medical Center. He directs a basic and translational research laboratory focused on Lp(a) and their content of oxidized phospholipids as pro-inflammatory mediators of cardiovascular disease, with NIH-R01 funded research. He is the Founding Director of the Vascular Medicine Program within the Cardiovascular Medicine Division. He founded the UCSD "Lp(a) Clinic" as a novel paradigm to diagnose, manage and follow patients with elevated Lp(a). He has published his work in major medical journals, including NEJM, Lancet, Nature, Cell, JACC, Circulation, EHJ, and has over 400 original manuscripts, review articles and book chapters. In partnership with Dr Joseph Witztum, they defined the role of oxidized phospholipids (OxPLs) in atherosclerosis and vascular inflammation. In translational studies, they demonstrated that OxPL-apoB levels are elevated in individuals at risk for cardiovascular events and serve as both biomarkers and potential causal factors in atherogenesis. Through the development of specific assays and translational studies, they have established OxPL-apoB and OxPL-apo(a) as a mechanistically relevant and clinically actionable target in lipid-driven cardiovascular disease.

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