Lipoprotein(a) Regulates Vascular Redox State and Predicts Adverse Cardiovascular Outcomes in Coronary Artery Disease

M. Polkinghorne[1*], C. Xie[1], J. Chauhan[1], A. Baragetti[4], P. Patel[1], E. de Araujo[1], E. Wahome[1], C. Kotanidis[1], I. Akoumianakis[1], G. Krasopoulos[2], N. Walcot[2], I. Badi[1], K.M. Channon[1], T. Guzik[3], G.D. Norata[4], C. Antoniades[1]

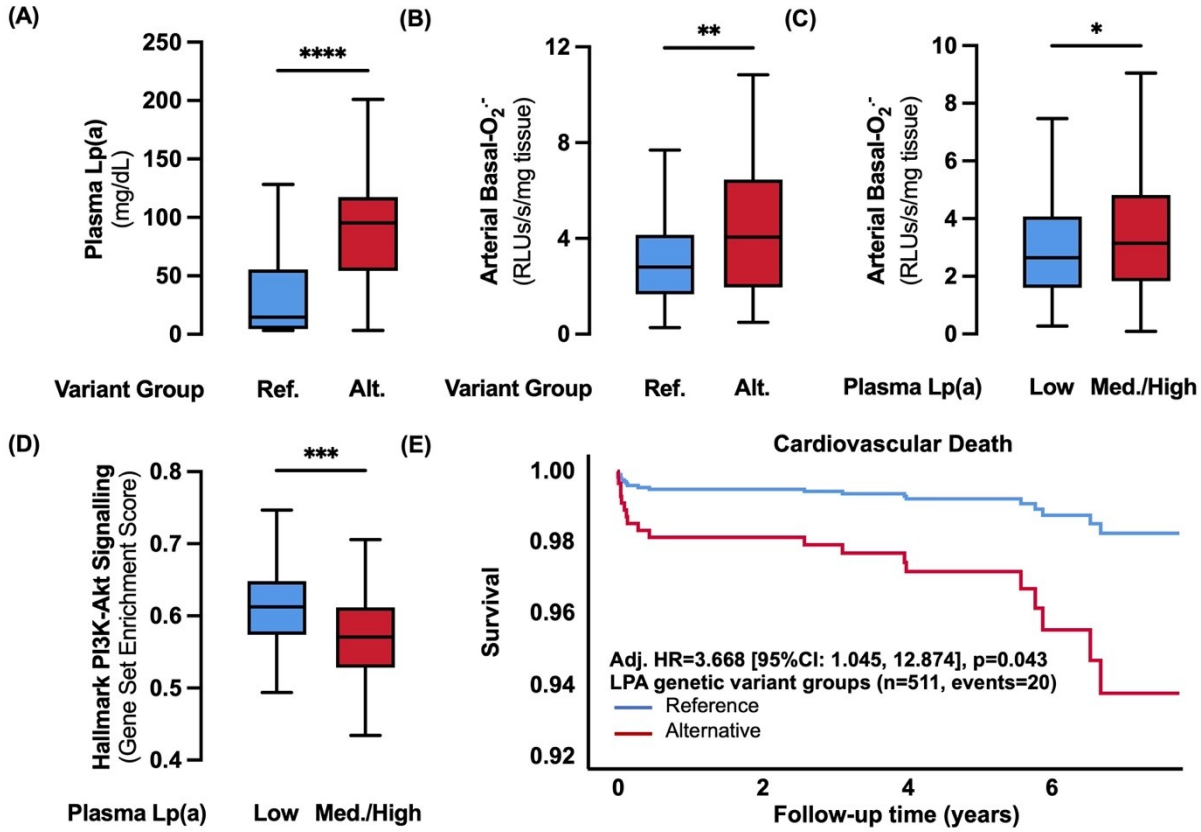
[1] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom
[2] John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom
[3] Institute of Cardiovascular & Medical Sciences, University of Glasgow, Glasgow, United Kingdom
[4] Department of Excellence of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

Background: Lipoprotein(a) [Lp(a)] has an established link with cardiovascular disease yet the underlying mechanisms are incompletely understood.

Methods: In 1472 cardiac surgery patients, we compared patients with any alternative allele from ≥3 of 7 Lp(a)-increasing SNPs (alternative variant group) to those with no alternative alleles in any of these SNPs (reference variant group). Plasma Lp(a) was measured using the Randox assay. The arterial redox state was measured using lucigenin chemiluminescence, where the contribution of NADPH-oxidases (NOX) and uncoupled nitric oxide synthases (eNOS) to superoxide ($O_2^{\cdot-}$) production was quantified. Arterial biopsies were used to perform RNA-sequencing. Patients were followed up for a median of 7.8 years.

Results: Alternative variant patients had significantly higher plasma Lp(a) (A), plasma apolipoprotein-B (ApoB) ($p<0.01$), and arterial basal-$O_2^{\cdot-}$ (B). Patients with medium/high vs low plasma Lp(a) had significantly increased plasma ApoB ($p<0.0001$) and arterial basal-$O_2^{\cdot-}$ (C) as well as reduced tetrahydrobiopterin bioavailability ($p<0.01$). The association between Lp(a) and arterial basal-$O_2^{\cdot-}$ was ApoB-independent. Non-diabetic patients in the alternative variant group and those with medium/high plasma Lp(a) had significantly increased arterial basal and eNOS-derived ($p<0.05$), but not NOX-derived, $O_2^{\cdot-}$. The transcriptomic profile of patients with high vs low plasma Lp(a) showed significantly downregulated PI3K-Akt signalling (D). Genetic tools revealed that Lp(a) is causally associated with an increased risk of cardiovascular death in an ApoB-independent manner (E). Patients with medium/high plasma Lp(a) also had a significantly increased risk of cardiovascular death (adj. HR=4.274 [95%CI: 1.227, 14.925], p=0.022).

Conclusions: We demonstrate that Lp(a) increases arterial $O_2^{\cdot-}$ through dysregulating vascular insulin signalling, mediating its association with cardiovascular disease.



Alternative variant patients had high plasma Lp(a) (A) and arterial basal-$O_2^{\cdot-}$ (B). Patients with medium/high plasma Lp(a) had increased arterial basal-$O_2^{\cdot-}$ (C) and downregulated PI3K-Akt signalling (D). Lp(a) independently increases CVD mortality risk (E).