British Cardiovascular Society

Lp (a) – The forgotten lipoprotein

Patrick Savage MB BCh BAO BSc (Hons)

Cardiology Research Fellow

Royal Victoria Hospital, Belfast, UK

What is Lp (a)?

Take Home Messages

- Lp (a) is an underappreciated cardiovascular risk factor with a casual association for the development of atherosclerotic cardiovascular disease.
- Lp (a) is also associated with other cardiovascular conditions including the development of aortic valve calcification and abdominal aortic aneurysms.
- Lp (a) testing may have clinical utility in selecting patients who stand to gain enhanced benefit from aspirin for primary prevention.
- Important new treatments, targeting Lp(a) directly, are under development which may dramatically change the future landscape of preventive cardiology.

Lipoprotein (Lp) [a] consists of a low-density lipoprotein (LDL) like moiety bound to a highly glycosylated apolipoprotein (a) particle and an apolipoprotein B-100 particle linked via a single disulfide bond (*Figure 1*). Since its discovery in 1963 by Kare Berg, Lp(a) has gone relatively unnoticed in cardiovascular (CV) risk reduction algorithms (1). More recently, greater attention has been afforded to Lp(a) with growing evidence suggesting its causality in the development of atherosclerotic cardiovascular disease (ASCVD), culminating in a recent consensus statement published by the ESC (2).

The clinical impact of Lp (a) on CV risk

Elevated Lp(a) has been implicated in several cardiac conditions, including ASCVD, aortic stenosis (AS), abdominal aortic aneurysm (AAA)'s and heart failure (HF) (3–6) (*Figure 2*). Strikingly, there appears to be a dose-dependent relationship with Lp(a) levels and risk of both CV and all-causes mortality (2). In a meta-analysis of prospective observational studies evaluating the association of Lp(a) and mortality conducted by Amiri *et al*, involving nearly one million patients, found a linear dose-response for each 50 mg/dL increase in Lp(a) with an associated 31% greater risk of CV death (HR 1.31: 95% CI 1.21-1.42) (7). Additionally, a non-

linear dose-response association was observed between Lp(a) levels and risk of all-cause or CV mortality (8,9).

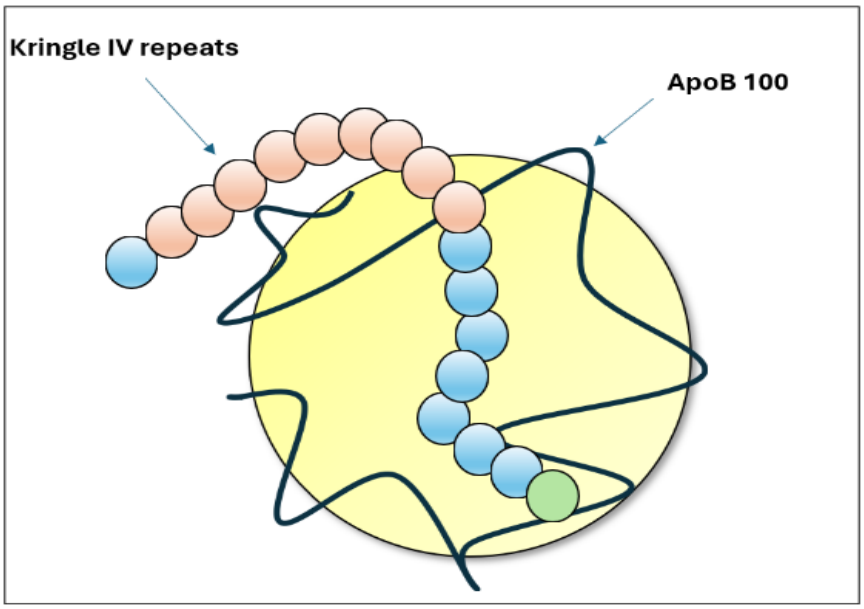

Figure 1. Molecular structure of the lipoprotein a [lp(a)] particle. A single apo (a) molecule is attached to an apoB 100 polypeptide (blue line) which surrounds the cholesteryl-ester core of the LDL component of the particle. A variable number of Kringle repeats may be present which reflects inherited heterogeneity of the molecule.

Valuable data from the UK Biobank study has shed more light on the association of serum Lp(a) with ASCVD risk - with high levels of Lp(a) (defined as >100mg/dL (250nmol/L)) almost doubling the risk of ASCVD (ten-year risk of ASCVD event 4.2% vs 2.8%), regardless of baseline risk. Indeed, very high levels (>180 mg/dL or >430 nmol/L) confer a risk of ASCVD similar to that of untreated heterozygous familial hypercholesterolaemia (FH) (3).

Interestingly, strong evidence from mendelian randomisation studies supports a causal link between Lp(a) and AS. Indeed, high Lp(a) levels have been associated with accelerated valvular macrocalcification with a Lp(a) >80th percentile conferring a threefold higher risk of AS, particularly notable in younger patients (8,9). Furthermore Lp(a) has been linked to incident risk of HF with a 10-fold increment in Lp(a) level associated with an odds ratio for HF of 1.44 (95%

CI:1.23 – 1.69) (10). Additionally, after adjusting for age, sex, and race, Kubota et al demonstrated that individuals in the highest quintile of plasma Lp(a) had a 1.63-fold greater risk of AAA's relative to those in the lowest quintile (6). Furthermore, elevated Lp(a) seems to be implicated in stroke risk also, particularly those <60 years without atrial fibrillation (AF) (4).

What is the function of Lp(a)?

Lp(a) has several key physiological roles. It has been implicated in several pro-inflammatory pathways, mediating endothelial function and cascade activation of pro-inflammatory cytokines. Interestingly, Lp(a) has also been shown to exert inhibitory effects on the athero-protective protein transforming growth factor-β (TGF-β) and pro-inflammatory monocyte chemoattractant protein 1 (MCP-1) demonstrating a bi-directional functionality (1). Furthermore, Lp(a) has a demonstrable role in promoting wound healing and repair, with in vitro studies demonstrating an interaction between Lp(a) and components of the vascular wall and extra cellular matrix such as fibrin, fibronectin, glycosaminoglycans and proteoglycans (11). Related to this, it has been shown to promote platelet aggregation and tissue factor pathway inhibitor (TFPI) binding. Indeed, given its high homology with plasminogen, it was previously postulated it may be a risk factor for thromboembolic events; however, this data is not strongly supported by clinical data and indeed not supported by mendelian randomised data (10,12).

What determines plasma Lp(a)?

Lp(a) concentration ranges between <0.1 mg/dL and >300 mg/dL (<0.2–750 nmol/L) and are largely genetically determined with peak levels usually attained by 5 years of age (2,13). Interestingly these levels have been shown to not vary throughout the course of life. A hypervariable coding copy number variation, the Kringle-IV (K-IV) repeat, has been implicated in the inheritability of high levels of Lp(a) however, it is likely that other genetic and regulatory effects are involved. Amongst different ethnicities, Black and South Asian populations have, on average higher median values of Lp(a) compared to white or east Asian individuals (3).

When should we measure Lp(a)?

Current ESC guidance suggests that all patients should have their Lp(a) levels measured at least once in their lifetime, to appropriately stratify their cardiac risk (2). Additionally, it is

recommended for evaluation of relatively young patients presenting with ischaemic stroke or a family history of premature ASCVD (2). Testing poses many challenges, indeed, one must note that there isn't yet a standardised assay for laboratory measurement of Lp(a) which may lead to issues regarding interpretation (14). Additionally, due to the molecular nature of Lp(a) and natural variation in isoform size, aberrancies in measurement may become apparent when levels reach a threshold value, i.e. potentially misclassifying a patients risk as low/medium or medium/high (15). Timing of measurement is also a factor, give the implication that Lp(a) may be an acute phase reactant and thus falsely elevated in pro-inflammatory states, such as myocardial infarction (MI) which may limit its utility in the hospital setting (1).

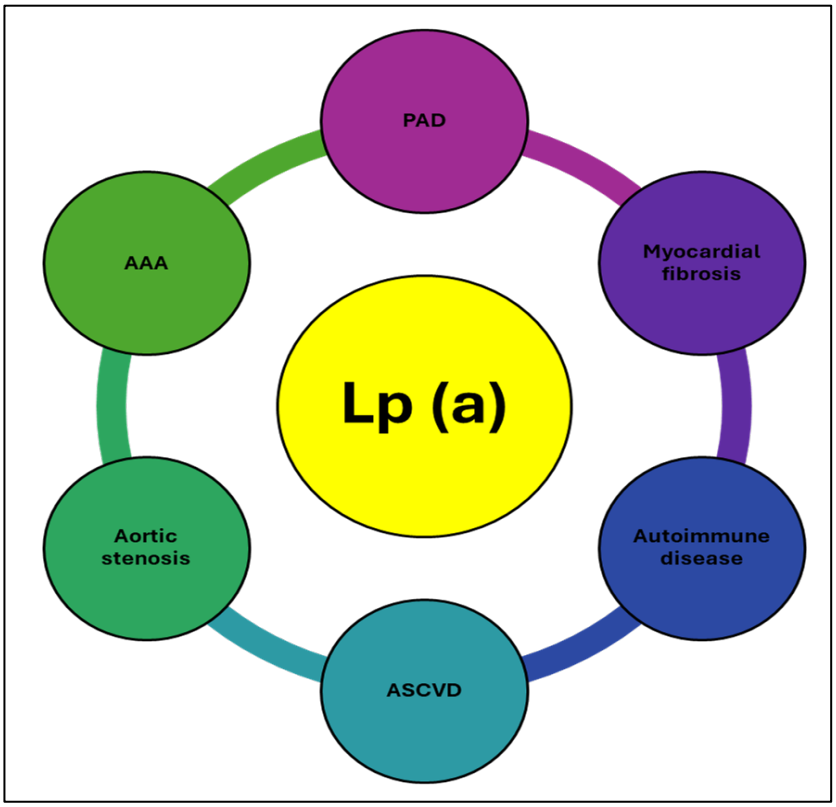

Figure 2. Schematic detailing various pathologies associated with elevated Lp (a).

Lp (a): Lipoprotein a, ASCVD: Atherosclerotic cardiovascular disease, AAA: Abdominal aortic aneurysm: PAD: peripheral arterial disease

Current treatments and effects on Lp(a) levels

There are currently no approved treatments for lowering of Lp(a) levels. In extreme cases, lipoprotein apheresis may be used however this is not widely available and has limited data to support benefit (13). Although statin therapy can slightly increase Lp (a) levels, this effect is minimal and offset by its net CV benefit as evidenced in a recent meta-analysis (16). PCSK-9 inhibitors can lower Lp(a) by approximately 20% however they are not licensed for this indication. Although a low carbohydrate diet may lower Lp(a) by approximately 10-15%, exercise and general lifestyle measures appear to have no effect, however, it must be noted that these measures do serve to reduce CV risk in general (2).

What to do with a high Lp(a)?

Currently, treatment for high Lp(a) is much the same as that of general CV risk reduction encompassing lifestyle management, blood pressure, glucose, and LDL control, albeit with perhaps greater tenacity (2,17). One could argue against the measurement of Lp(a) given the lack of interventions catering to its treatment in the UK however its measurement may also serve as valuable additional input in CV risk assessment especially in the context of otherwise borderline cases i.e a patient with borderline risk of CV disease who has a high Lp(a) and is thus motivated to start lipid lowering therapy.

Interesting data has also been yielded from the primary prevention trial ASPREE (ASPirin in Reducing Events in the Elderly), with respect to Lp(a) (18). The original results demonstrated the reduction in major adverse cardiovascular events (MACE) conferred by aspirin was offset by the increased risk of bleeding, however in a post-hoc analysis of patients with a high Lp(a)-genomic risk aspirin reduced MACE by 11.4 and 3.3 events per 1000 person-years respectively, without significantly increased bleeding risk. This poses interesting questions and could justify a randomised controlled trial (RCT) to formally answer this question. Indeed, post-hoc data from FOURIER has suggested that lowering Lp(a) may present a novel treatment option for aortic stenosis, however this data is only hypothesis generating and is yet to be tested in a formal clinical trial (19).

Several trials concerning Lp(a) specific lowering therapies are underway and are detailed in *table 1* (20–25). Although genetic evidence suggests that Lp(a) lowering will confer CV benefit,

clinical outcome data from RCT's are needed to clarify this hypothesis and the results of these studies are eagerly awaited. Indeed, if these studies collectively prove to be positive, Lp(a) targeted therapies may prove to be the next frontier in CV medicine and Lp(a) will no longer be a forgotten lipoprotein.

Drug development focusing on lp (a)											
Study	**Trial registration**	**Drug**	**Company**	**Phase**	**Design**	**Mechanism**	**Lp (a) level**	**Route administration**	**Follow up**	**Primary Endpoint**	**Completion date**
APOLLO	NCT04606602	SLN360	Silence Therapeutics	1	Doubled blind RCT	short-interfering RNA which prevents Lp (a) assembly	Lp(a) concentrations ≥ 150 nmol/L	SC injection of 30, 100, 300, or 600 mg	Five months	Safety, tolerability, pharmacokinetics	Completed
AKCEA-APO (a) - LRx	NCT03070782	ISIS 681257	Akcea Therapeutics	2	Doubled blind RCT	hepatocyte-directed antisense oligonucleotide	Lp(a) level ≥60 mg/dL	SC injection of varying doses (2 weekly and 4 weekly intervals)	6 months	Safety, tolerability, pharmacokinetics	Completed
KRAKEN	NCT04472676	Muvalapin	Eli Lilly	2	Doubled blind RCT	short-interfering RNA which prevents Lp (a) assembly	Lp(a) level ≥175 nmol/L	Daily PO dose	22 weeks	Safety, tolerability, pharmacokinetics	Mar-24
LY3819469	NCT05565742	LY3819469	Eli Lilly	2	Doubled blind RCT	short-interfering RNA which prevents Lp (a) assembly	Lp(a) ≥175 nmol/L	Varying SC doses	20 months	Safety, tolerability, pharmacokinetics	Oct-24
Lp (a) HORIZON	NCT04023552	Pelacarsen	Novartis	3	Doubled blind RCT	hepatocyte-directed antisense oligonucleotide targeting the mRNA transcribed from the LPA gene	Patients with Lp (a) ≥70mg/Dl	80mg SC monthly	Four years	MACE	May-25
OCEAN (a) - Outcomes	NCT05581303	Olpasiran	Amgen	3	Doubled blind RCT	short-interfering RNA which prevents Lp (a) assembly	Lp(a)≥ 200 nmol/L	SC 12 weekly	Four years	CV death , MI, urgent revascularisation	Dec-26

Table 1: Table demonstrating trials evaluating Lpa specific lowering therapies which are either underway or completed.
RCT: Randomised controlled trial, RNA: Ribonucleic acid, Lp(a): Lipoprotein (a), SC: Subcutaneous, CV: Cardiovascular, MI: Myocardial infarction, MACE: Major adverse cardiovascular event.

Disclosures

Nothing to disclose.

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