Lipoprotein(a) and calcific aortic valve disease: current evidence and future directions

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Purpose of review
Calcific aortic valve disease (CAVD), the most common cause of aortic stenosis (AS), is characterized by slowly progressive fibrocalcific remodelling of the valve cusps. Once symptomatic, severe AS is associated with poor survival unless surgical or transcatheter valve replacement is performed. Unfortunately, no pharmacological interventions have been demonstrated to alter the natural history of CAVD. Lipoprotein(a) [Lp(a)], a low-density lipoprotein-like particle, has been implicated in the pathophysiology of CAVD.

Recent findings
The mechanisms by which Lp(a) results in CAVD are not well understood. However, the oxidized phospholipids carried by Lp(a) are considered a crucial mediator of the disease process. An increasing number of studies demonstrate a causal association between plasma Lp(a) levels and frequency of AS and need for aortic valve replacement, which is independent of inflammation, as measured by plasma C-reactive protein levels. However, not all studies show an association between Lp(a) and increased progression of calcification in individuals with established CAVD.

Summary
Epidemiologic, genetic, and Mendelian randomization studies have collectively suggested that Lp(a) is a causal risk factor for CAVD. Whether Lp(a)-lowering can prevent initiation or slow progression of CAVD remains to be demonstrated.

Keywords
aortic stenosis, aortic valve, calcification, cardiovascular diseases, lipids, lipoprotein(a), risk factors

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a hepatically-synthesized low-density lipoprotein (LDL)-like particle, in which apolipoprotein(a) [apo(a)] is covalently bound to apolipoprotein B (apoB) [1▪]. Lp(a) levels are predominantly genetically determined and do not change substantially over an individual's lifetime [2]. Approximately 20–30% of individuals have elevated Lp(a) (>50 mg/dl or 125 nmol/l), with a varying prevalence among ethnicities [3]. Epidemiologic, genetic, and Mendelian randomization studies have demonstrated that Lp(a) is a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) [4▪]. Increasing evidence suggests that Lp(a) is also a causal risk factor for aortic valve (AV) calcification and aortic stenosis (AS) [5]. Indeed, individuals with loss-of-function *LPA* gene variants have lower risk of AS, as well as ASCVD [6].

Calcific aortic valve disease (CAVD) is characterized by progressive fibrocalcific remodelling of the valve cusps [7▪]. Thickening and calcification of the cusps results in AV sclerosis, which affects ~25% of individuals aged ≥65 years and confers an increased risk of death [7▪]. Severe calcification, impaired cusp motion, and reduction in AV area occurs gradually, resulting in AS [7▪]. Untreated, moderate-to-severe AS is associated with poor survival, with a 5-year mortality >50% [8]. Unfortunately, no pharmacological therapies have been shown to alter the progression of AS [9▪,10▪]. The only effective treatments for severe AS are transcatheter/surgical AV replacement, but these address the late stages of the disease, are costly, are not appropriate for some patients and carry procedural risks [9▪,11,12].

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KEY POINTS

- The mechanisms by which lipoprotein(a) [Lp(a)] results in calcific aortic valve disease (CAVD) remains poorly understood, but oxidized phospholipids carried by Lp (a) may play a crucial role.
- Epidemiologic, genetic, and Mendelian randomization studies suggest that Lp(a) is a causal risk factor for development and progression of CAVD.
- Recent observational studies have found that Lp(a) may not be associated with progression of calcification in individuals with established CAVD.
- There is also evidence that the association between Lp (a) and CAVD is independent of inflammation, measured by plasma C-reactive protein levels.
- Whether Lp(a)-lowering can slow or halt the progression of CAVD remains to be elucidated, with few trials of Lp (a)-lowering therapies currently underway.

This review provides an overview of the pathophysiology linking Lp(a) and CAVD, summarizes recent studies evaluating the association between Lp(a) and CAVD/AS, and discusses trials of Lp(a)-lowering therapies for the prevention of AS.

REVIEW

Pathophysiology of lipoprotein(a) in calcific aortic valve disease

The AV is typically tricuspid, with cusps less than a millimetre thick and covered by valvular endothelial cells, beneath which lies valvular interstitial cells (VICs) [7▪,10▪]. CAVD was previously considered a degenerative process, related to ''wear and tear'' of the cusps and passive deposition of calcium [10▪]. However, CAVD is now considered a metabolically active process regulated by several mechanisms (Fig. 1), influenced by genetic and environmental

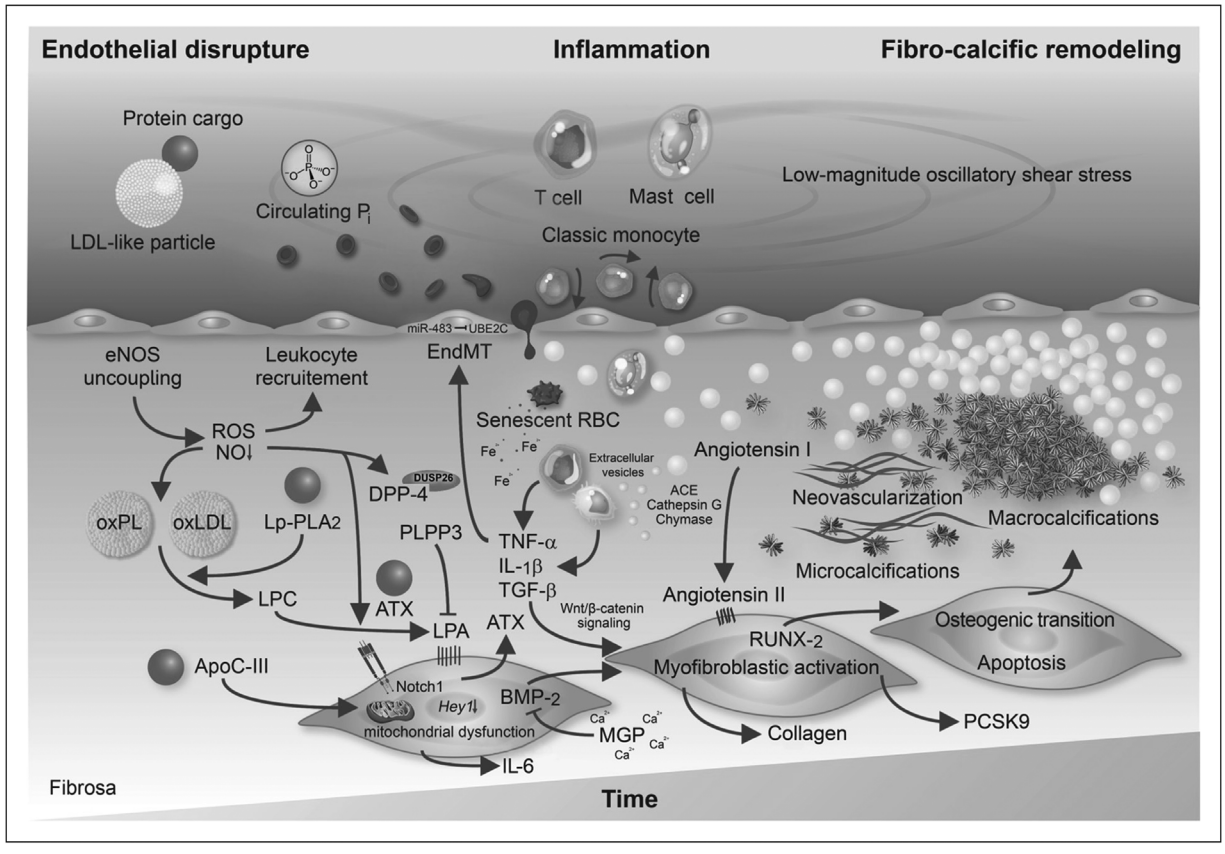

FIGURE 1. Pathogenesis of CAVD [9▪]. The pathogenesis of CAVD is complex and has been reviewed in detail. In brief, endothelial injury results in the vascular infiltration of immune cells, red blood cells and low-density lipoprotein-like particles. Multiple pathways are activated, leading to reactive oxygen species formation, endothelial immune-cell trafficking, apoptosis of VICs and inflammation, with resultant deposition of calcium. Expression of pro-osteogenic transcription factors results in osteogenic differentiation of VICs, further promoting calcification. There is also disruption of extracellular matrix homeostasis and production of collagen which promotes stiffening of the AV cusps. AV, aortic valve; CAVD, calcific aortic valve disease; VIC, valvular interstitial cell. To be reproduced with permission from: Kraler S, Blaser MC, Aikawa E, *et al*. Calcific aortic valve disease: from molecular and cellular mechanisms to medical therapy. Eur Heart J. 2022;43(7):683–697 (Fig. 2).

factors [9▪]. The initiation phase of CAVD shares many similarities to atherosclerosis including endothelial injury/activation and inflammation, whereas the propagation phase is characterized by progressive fibrosis and accelerated calcification [7▪,13]. After the inception of calcification, the decreased compliance of the cusps leads to further mechanical stress, inducing a cycle whereby ''calcium begets calcium'' [14▪▪]. Permissive risk factors for CAVD include age, male sex, hypertension, smoking, obesity, congenital bicuspid morphology, genetic variants, LDL-cholesterol, Lp(a) and other apoB-containing lipoproteins [13,15▪▪,16▪▪,17▪].

The mechanisms by which Lp(a) results in AV calcification are not well understood. Lp(a) binds to proteoglycans and fibronectin on the subendothelial matrix and infiltrates the AV to act on VICs [18]. Lp(a) carries >85% of circulating oxidized phospholipids (OxPLs) which bind to lipoprotein-associated phospholipase A2, resulting in lysophosphatidylcholine production [19,20]. Autotaxin, an enzyme present on Lp(a) and overexpressed in mineralized VICs, converts lysophosphatidylcholine to lysophosphatidic acid [21]. This leads to activation of nuclear factor kappa-light-chain-enhancer of activated B cells and osteogenic differentiation of VICs into osteoblastic phenotypes, which promote calcification [21].

Innate immune cells recognize OxPLs as damage-associated molecular patterns, which results in inflammation and oxidative stress [19,20]. Exposure of VICs to Lp(a) induces expression of the inflammatory mediator interleukin-6, and osteogenic regulators including bone morphogenetic protein 2, Runt-related transcription factor 2, osteocalcin, osterix and Wnts, which favour the differentiation of VICs into osteoblasts-like cells [20,22]. Lp(a) increases alkaline phosphatase activity, phosphate and calcium content, and matrix vesicle formation in VICs, and increases phosphorylation of transduction kinases involved in cellular remodelling and apoptosis [22]. Lp(a) increases expression of LOX-1, which may trigger early apoptosis [22]. Release of apoptotic bodies triggers pro-inflammatory cytokine secretion; the pro-inflammatory phenotype contributes to stiffening of the AV due to recruitment of immune cells, deposition of extracellular matrix proteins and proliferation of fibroblasts [20,22].

Lp(a) is prothrombotic, the apo(a) moiety having a high degree of homology with plasminogen [23▪]. Accordingly, Lp(a) may play a role in arterial thrombosis [24]. By competing with plasminogen for fibrin binding sites, Lp(a) inhibits the action of plasmin in dissolving fibrin clots, which leads to fibrin retention [23▪]. Lp(a) promotes platelet aggregation, inhibits synthesis of tissue factor pathway inhibitor and stimulates plasminogen activator inhibitor, thereby potentially resulting in microvascular thrombosis within the AV [23▪].

Lipoprotein(a) and frequency of calcific aortic valve disease/aortic stenosis

Individuals with CAVD are often asymptomatic and physical examination may not be accurate for diagnosing/assessing AS [25]. Echocardiography is the mainstay investigation for assessing AV anatomy and area, and transvalvular velocity/gradients [11,12]. However, haemodynamic assessment is not an ideal measure of CAVD, since AS occurs late in the disease. Cardiac computed tomography (CT) is more sensitive in detecting CAVD prior to the development of AS by several years [14▪▪,26]. CAVD can be quantified by CT using Agatston units [26]. Furthermore, 18F-fluorodeoxyglucose (18F-FDG) or 18F-sodium fluoride (18F-NaF) positron emission tomography (PET) can detect microcalcifications, inflammation, mineralization, and progression of disease [27,28].

Recent studies of association between Lp(a) and CAVD/AS are shown in Table 1 [15▪▪,16▪▪,29▪▪,30▪▪–36▪▪]. Many prior studies have reported Lp(a) concentration in mg/dl. Current guidelines recommend the use of assays that are ideally apo(a) isoform-insensitive and the preferred unit of measure as nmol/l. Converting between mg/dl and nmol/l is not generally recommended. However, to convert mg/dl to nmol/l, a conversion factor of between 2 and 2.5 has been proposed [1▪].

The association between Lp(a) and CAVD/AS appears similar between sexes and has been reported in individuals with bicuspid AV, and individuals with familial hypercholesterolaemia (FH) [32▪▪,37,38▪]. However, there may be differences among ethnicities; an association between Lp(a) and CAVD has been demonstrated in White and Black individuals but not in South Asians, Hispanic or Chinese individuals [32▪▪,39]. The ASCVD risk associated with Lp(a) may be modulated by inflammation, whereby Lp(a) is associated with ASCVD in individuals with elevated high-sensitivity C-reactive protein (CRP) levels ($\geq$2 mg/l) [40▪]. In contrast, Lp(a) is associated with AS independent of CRP, highlighting a key difference [34▪▪,35▪▪]. Individuals with extremely high Lp(a) levels and body mass index also have increased risk of CAVD [31▪▪]. Absolute 10-year risk charts for CAVD/AS accounting for age, sex, Lp(a), and CRP or body mass index have been created, but these require further research [31▪▪,35▪▪].

Lipoprotein(a) and progression of calcific aortic valve disease/aortic stenosis

Higher Lp(a), OxPL-apoB and OxPL-apo(a) levels are associated with faster progression of AS in

Table 1. Recent studies investigating the association between Lp(a) and CAVD or AS

Author and Year Published	Population[a]	Imaging	Main Finding(s)
Kaiser Y, *et al.* (2022) [30▪▪]	52 individuals (26 matched pairs) with mild-to-moderate AS; age 66.4 ± 5.5 years	PET/CT	• No difference in AV ^{18}F-NaF uptake between the high and low Lp(a) (<50 mg/dl) groups ($P = 0.902$) • Lp(a) was not associated with AV ^{18}F-NaF uptake in those with high Lp(a) ($P = 0.305$) • Regression analysis showed AV calcium score to be the only significant determinant of 18F-NaF uptake ($P < 0.001$)
Kaiser Y, *et al.* (2022) [29▪▪]	922 individuals from the Rotterdam Study; age 66.0 ± 4.2 years	CT	• Lp(a) was associated with baseline AV calcification (OR 1.43 for each 50 mg/dl higher Lp(a); 95% CI 1.15–1.79) and new-onset CAVD (OR 1.30 for each 50 mg/dl higher Lp(a); 95% CI 1.02–1.65) • Lp(a) was not associated with progression of CAVD, only baseline AV calcium score was associated with CAVD progression ($P < 0.001$)
Kaltoft M, *et al.* (2022) [36▪▪]	12 006 individuals from the CGPS who underwent cardiac CT [age 59.2 (51.1–67.0) years] and 85 884 individuals with Lp(a) measurement [61.9 (52.0–70.6) years]	CT and registries	• For 10-fold higher Lp(a) level, the adjusted OR for AV calcification was 1.62 (95% CI 1.48–1.77) and HR for AV stenosis was 1.54 (95% CI 1.38–1.71) • For ≤23 vs. ≥36 KIV2 repeats, the age- and sex-adjusted OR for AV calcification was 2.23 (95% CI 1.81–2.76) and for carriers vs. noncarriers of *LPA* rs10455872, the OR for AV calcification was 1.86 (95% CI 1.64–2.13) • 31% (95% CI 16–76%) of the effect of Lp(a) on AS was mediated through calcification
Kaltoft M, *et al.* (2022) [31▪▪]	69 988 individuals from the CGPS; median age 60 years	N/A: registries	• High Lp(a) and body mass index (90–100th percentiles for both) conferred a 3.5-fold increased risk of CAVD compared to 1–49th percentiles for both.
Obisesan O, *et al.* (2022) [32▪▪]	2083 individuals from the ARIC study; age 59.2 ± 4.3 years	CT	• In multivariable analyses, Lp(a) >50 mg/dl was associated with presence of AV calcium (OR 1.82; 95% CI 1.34–2.47) and AV ring calcium (OR, 1.36; 95% CI 1.07–1.73)
Bhatia H, *et al.* (2023) [33▪▪]	6699 individuals from the MESA study; age not specified	CT	• Prevalence of CAVD was higher in the top Lp(a) quartile (>40.6 mg/dl) compared with the bottom (2.0–7.5 mg/dl) quartile (4.4% vs. 3.2%; $P < 0.001$) • Among those without CAVD, the top Lp(a) quartile was associated with incident AV calcification at first (OR 2.49; 95% CI 1.59–3.88) and second (OR 1.72; 95% CI 1.17–2.54) follow-up • Among those with AV calcification at first follow-up, the top Lp(a) quartile was associated with greater annual progression ($P = 0.021$)
Girard A, *et al.* (2023) [34▪▪]	18 226 individuals from the EPIC-Norfolk study (age 59.1 ± 9.2 years), 438 260 from the UK Biobank (56.4 ± 8.1 years) and 220 from the ASTRONOMER trial (57.7 ± 13.1 years)	N/A: registries	• In EPIC-Norfolk, those with elevated Lp(a) (>50 mg/dl) and low CRP and those with elevated Lp (a) and elevated CRP (>2.0 mg/l) had higher risk of AS compared to those with low Lp(a) and low CRP (HR 1.86; 95% CI 1.30–2.67 and HR 2.08; 95% CI 1.44–2.99 respectively) • Similar findings in the UK Biobank and ASTRONOMER cohorts

Table 1 (*Continued*)

Author and Year Published	Population[a]	Imaging	Main Finding(s)
Thomas P, *et al.* (2023) [35▪▪]	68 090 individuals from the CGPS; median age 60 years	N/A: registries	• In individuals with Lp(a) in the 91–100th percentiles (≥70 mg/dl, ≥147 nmol/l) vs. 1–33rd percentiles (≤6 mg/dl, ≤9 nmol/l), the adjusted HR for AS in those with CRP < 2 mg/l was 2.01 (95% CI 1.59–2.55) and in those with CRP ≥2 mg/l it was 1.73 (95% CI 1.31–2.27)
Small A, *et al.* (2023) [15▪▪]	14 451 individuals with AS and 398 544 controls in the Million Veteran Program with replication performed in the Million Veteran Program, Penn Medicine Biobank, Mass General Brigham Biobank, BioVU, and BioMe, totalling 12 889 cases and 348 094 controls; mean age between 54.5 and 73.2 years	N/A: registries	• Multivariable Mendelian randomization demonstrated independent associations between LDL-cholesterol (OR 1.14; 95% CI 1.05–1.46) and Lp(a) (OR 1.27; 95% CI 1.23–1.32) with AS, but not for triglycerides or HDL-cholesterol • rs10455872 was significantly associated with AS (discovery OR 1.42; 95% CI 1.35–1.48 and replication OR 1.37; 95% CI 1.30–1.44)
Yu Chen H, *et al.* (2023) [16▪▪]	11.6 million variants in 10 cohorts involving 653 867 European ancestry participants (13 765 cases); median age between 58 and 77 years	N/A: registries	• Mendelian randomization supported a causal role for apoB-containing lipoproteins in AS (OR per g/l of apoB 3.85; 95% CI 2.90–5.12) and Lp(a) (OR per natural logarithm 1.20; 95% CI 1.17–1.23)

[a]Age is presented as mean±standard deviation or median (interquartile range) unless otherwise specified.
^{18}F-NaF, ^{18}F-sodium fluoride; ApoB, apolipoprotein B; ARIC, Atherosclerosis Risk in Communities Study; AS, aortic stenosis; ASTRONOMER, Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; AV, aortic valve; CAVD, calcific aortic valve disease; CGPS, Copenhagen General Population Study; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; EPIC-Norfolk, European Prospective Investigation into Cancer in Norfolk Prospective Population Study; FH, familial hypercholesterolaemia; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HDL, high-density lipoprotein; HR, hazard ratio; KIV2, kringle IV type 2; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); MASALA, Mediators of Atherosclerosis in South Asians Living in America; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio; PET, positron emission tomography; SAFEHEART, Spanish Familial Hypercholesterolemia Cohort Study; SD, standard deviation; UK, United Kingdom.

individuals with AS; this association appears linear (28% greater odds of progression of AS per 10 mg/dl increase in Lp(a) level), and was demonstrated in individuals aged ≤57 years (median age) but not >57 years [20,41]. Whether the effects of OxPLs were independent of Lp(a) was not reported [20,41]. Increased progression of AV calcification with higher Lp(a) levels is supported by another study that included those without AS; the highest Lp(a) quartile was associated with incident AV calcification among those without CAVD and greater progression of AV calcification among those with AV calcification [33▪▪].

However, two recent studies suggest that Lp(a) levels may not be associated with progression of CAVD [29▪▪,30▪▪]. In a matched case-control study of 52 individuals with mild-to-moderate AS, no difference in valvular 18F-NaF uptake on PET was observed between the high and low Lp(a) groups [30▪▪]. In 922 healthy individuals, Lp(a) levels were associated with baseline and new-onset AV calcification on CT [29▪▪]. However, Lp(a) levels were not associated with progression of CAVD after a median follow-up of 14 years [29▪▪]. For both studies, the baseline AV calcium score was the only significant predictor of disease progression, suggesting that initiating factors may lose their importance once calcification ensues and that propagation is driven by calcification (i.e., ''calcium begets calcium'') [29▪▪,30▪▪].

Genetic studies of lipoprotein(a)/calcific aortic valve disease

Lp(a) is the only monogenic cause of AS [20,41]. Since >90% of variation in plasma Lp(a) levels is explained by genetic variations in, and around, the *LPA* gene, and because elevated levels are present from birth, Lp(a) is an ideal candidate for Mendelian randomization studies [42▪]. Copy number variation at the *LPA* gene encoding kringle IV–type 2 repeats (KIV2) determines the apo(a) isoform size and explains most of the variability in Lp(a) levels [43]. Moreover, two single nucleotide polymorphisms (SNPs), rs10455872 and rs3798220, are associated with Lp(a) levels [43]. Recent genetic studies support a causal role of Lp(a) in the development of CAVD/AS [15▪▪,16▪▪,36▪▪].

Both rs10455872 and rs3798220 have been associated with AS (Fig. 2) [36▪▪,44]. Individuals with 2 risk alleles (homozygous or compound heterozygous for rs10455872 and rs3798220) may have >2-fold

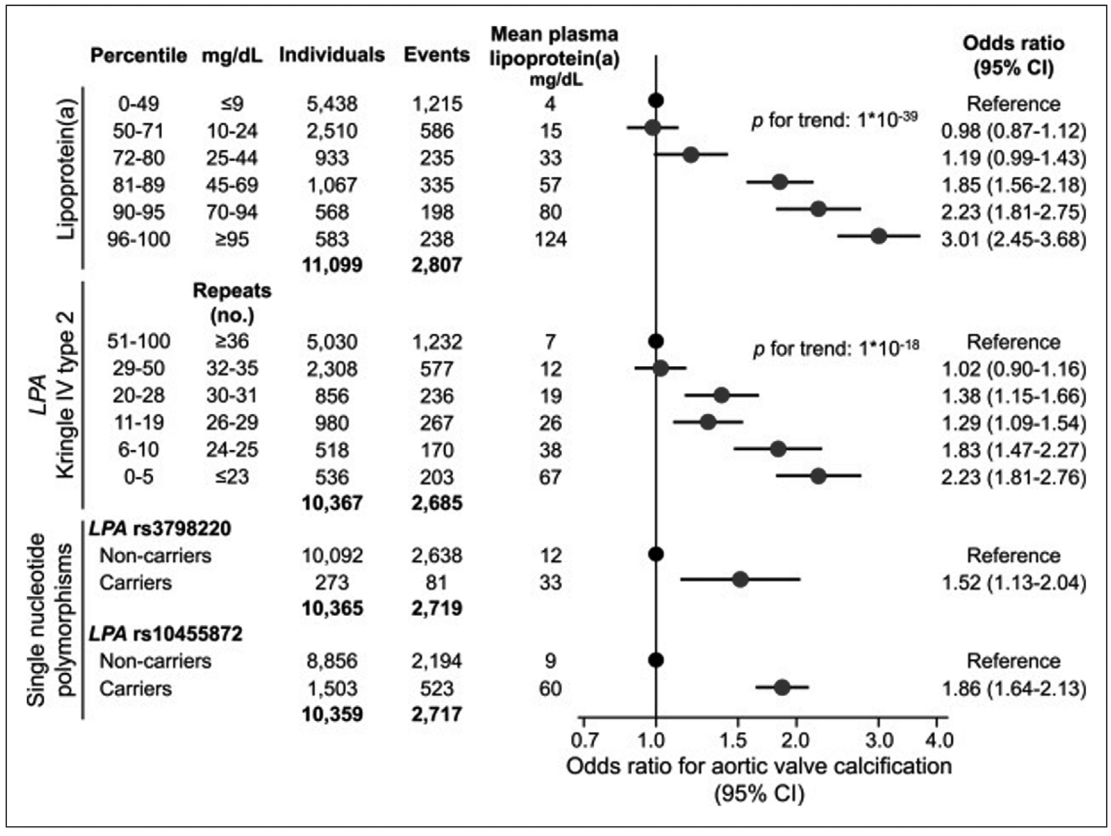

FIGURE 2. Risk of CAVD by categories of Lp(a), KIV2 repeats and *LPA* SNPs [36▪▪]. Lp(a), KIV2 repeats and *LPA* rs10455872 or rs3798220 single nucleotide polymorphism carrier status were associated with increased risk of AV calcification in a large study, with data presented as odds ratio and 95% confidence intervals (CI). AV, aortic valve; CAVD, calcific aortic valve disease; Lp(a), lipoprotein(a). To be reproduced with permission from: Kaltoft M, Sigvardsen PE, Afzal S, *et al.* Elevated lipoprotein(a) in mitral and aortic valve calcification and disease: The Copenhagen General Population Study. Atherosclerosis. 2022;349:166–174 (Fig. 1).

greater odds of developing AS compared with those with no risk alleles [44]. For rs10455872, the odds ratio for AS was greatest in those aged 55–64 years, and declined with age, suggesting that age modifies the association [44]. A weighted Lp(a) genetic risk score based on rs10455872, rs3798220 and rs41272114 is also associated with increased risk of AS [45]. However, a Mendelian randomization study found that elevated Lp(a) does not cause low-grade inflammation, as measured through CRP, despite a causal association with AS [5]. Furthermore, Lp(a) is observationally and genetically associated with mitral valve calcification, which is reviewed elsewhere [36▪▪,46▪▪].

Lipoprotein(a)-lowering and prevention of aortic stenosis

Initial efforts at preventing AS focused on reducing atherogenic lipoproteins, particularly LDL-cholesterol [47]. Additionally, individuals with homozygous FH have a high prevalence of supravalvular and valvular AS [48,49]. However, statins have not been demonstrated to slow the progression of AS [10▪,13]. The lack of benefits may be because statins increase Lp(a) by 10–20% and have pro-osteogenic effects, or because the trials had a relatively short duration of follow-up and enrolled individuals with established CAVD [50,51]. Interest has thus turned to therapeutic modulation of Lp(a) [3]. Importantly, elevated Lp(a) levels are common in individuals with AS [52]. For each standard deviation of genetically lowered Lp(a) level, the risk of AS decreases by 37% [6]. Furthermore, marked Lp(a)-lowering in individuals with Lp(a) levels ≥50 mg/dl may prevent 1 in 7 cases of AS [53]. Studies assessing Lp(a)-lowering for the prevention of AS are underway (Table 2).

Extended-release niacin lowers Lp(a) levels by ~20–30% and its effects on progression of AS are being studied (NCT02109614). Monoclonal antibodies targeting PCSK9 lower Lp(a) levels by ~20–30% and an exploratory analysis demonstrated that evolocumab may reduce the incidence of AS events (new or worsening AS or AV replacement) [54,55].

Table 2. Ongoing trials evaluating Lp(a)-lowering therapies and progression of CAVD

Study name	NCT number	Population	Intervention and comparison	Primary endpoint(s)	Secondary endpoint(s)
Early Aortic Valve Lipoprotein(a) Lowering Trial (EAVaLL)	02109614	238 adults with AV sclerosis or mild AS and elevated Lp(a) (>50 mg/dl)	Randomized, double-blind extended-release niacin 1500–2000 mg daily versus placebo	AV calcium score progression by cardiac CT at 2 years	Change in Lp(a) levels at 2 years and AV disease progression by echocardiography at 1 and 2 years
PCSK9 Inhibitors in the Progression of Aortic Stenosis	03051360	140 adults with a working diagnosis of mild-to-moderate AS	Randomized, double-blind bi-weekly PCSK9 inhibitor vs. bi-weekly placebo injection	AV calcium score progression by cardiac CT and sodium fluoride PET at 2 years	Change in calcium score based on Lp(a) SNPs, change in Lp(a) levels, AV disease progression by echocardiography and incidence of coronary heart disease events/mortality at 2 years
Effect of PCSK9 InhibitorS On Calcific Aortic Valve DiseasE (EPISODE)	04968509	160 adults with calcific AS detected by echocardiography, requiring long-term statin with LDL-cholesterol still ≥1.8 mmol/l and/or Lp (a) >50 mg/dl	Randomized, double-blind PCSK9 inhibitor injection plus statin versus statin only	Annual change in AV velocity by echocardiography	Annual change in AV calcium score by cardiac CT, change in Lp(a) levels and incidence of major adverse cardiovascular events up to 2 years
A Multicenter Trial Assessing the Impact of Lipoprotein(a) Lowering With Pelacarsen (TQJ230) on the Progression of Calcific Aortic Valve Stenosis (Lp(a) FRONTIERS CAVS)	05646381	502 adults age ≥50 years with Lp(a) ≥125 nmol/l and mild or moderate AS	Randomized, double-blind pelacarsen versus monthly placebo injection	Change in peak AV velocity by echocardiography and AV calcium score by cardiac CT at 36 months	Change in Lp(a) levels at 12 months, fibrocalcific thickening of the AV by cardiac CT at 36 months and time to first occurrence of composite clinical endpoint event (hospitalization due to calcific AV stenosis, requirement for AV replacement or death related to calcific AV stenosis) up to 36 months

AS, aortic stenosis; AV, aortic valve; CAVD, calcific aortic valve disease; CT, computed tomography; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); NCT, national clinical trial; PCSK9, proprotein convertase subtilisin/kexin type 9; SNP, single nucleotide polymorphism.

Whether PCSK9 monoclonal antibodies can slow the progression of AS is being studied (NCT03051360, NCT04968509). Inclisiran, a small interfering RNA that inhibits hepatic synthesis of PCSK9, is being evaluated in ASCVD outcome trials (NCT03705234, NCT05030428) but not in the prevention of AS [56]. The impact of lipoprotein apheresis on CAVD is unclear; current data are limited to observational studies of individuals with homozygous FH [48].

Pelacarsen is a hepatocyte-directed antisense oligonucleotide targeting the synthesis of apo(a) [57]. In individuals with Lp(a) level ≥60 mg/dl (or 150 nmol/l) and ASCVD, pelacarsen safely lowered Lp(a) by up to 80% [57]. Furthermore, a small interfering RNA, olpasiran, safely lowered Lp(a) by >90% in individuals with Lp(a) level >150 nmol/l (or approximately 70 mg/dl) and ASCVD [58▪▪]. ASCVD outcome trials of these therapies are ongoing to determine whether Lp(a)-lowering reduces ASCVD risk (NCT04023552, NCT05581303); notably, AS-related events are not secondary endpoints [57,58▪▪]. Whether pelacarsen can slow the progression of AS in adults ≥50 years with Lp(a) level ≥125 nmol/l and mild or moderate AS is being studied (NCT05646381).

Randomized trials of Lp(a)-lowering may need to target younger individuals with elevated Lp(a) levels and early CAVD, where disease progression may be highest and more likely due to Lp(a) than other factors [41]. Such trials could target individuals with genetic variants resulting in elevated Lp(a) levels, as genetically determined Lp(a) reflects greater lifelong cumulative exposure [44]. However, if Lp(a) is associated with initiation but not progression of CAVD, then Lp(a)-lowering trials may need to enrol individuals without CAVD, but who are at high risk of CAVD [29▪▪,30▪▪,59]. Thus, the optimal population (no CAVD, mild CAVD, AV sclerosis or AS), Lp(a) thresholds (50 mg/dl or 125 nmol/l, or higher) and outcomes (onset of CAVD, progression of calcification, haemodynamic progression of AS, or AV replacement) require careful consideration. Lp(a)-lowering trials may be needed in individuals with no CAVD but with very high Lp(a) levels (e.g., >90th percentile), but would be costly, require a large sample size, PET/CT imaging to detect early CAVD, and a long duration of follow-up [59].

The proportion of Lp(a)-attributable risk for CAVD accounted for by OxPLs remains unclear, for it is difficult to statistically unbundle the effects of Lp(a) from OxPLs [19,20,41]. There is a strong correlation between OxPL-apoB and OxPL-apo(a) levels with Lp(a) levels, and the association between OxPLs and risk of CAVD may be ascribed to association with Lp(a) [19,41]. Interventions that lower Lp(a) levels also lower OxPL levels [60]. However, Lp(a)-induced osteogenic differentiation of VICs can be attenuated by an E06 monoclonal antibody that binds and inactivates OxPLs, offering the opportunity that selective modulation of OxPLs may be useful in the prevention AS, a notion that merits further investigation [20].

Current guidelines

The European Atherosclerosis Society recommends measurement of Lp(a) at least once in an adult's lifetime to identify those with levels >180 mg/dl (or 430 nmol/l) who may have a risk of ASCVD equivalent to having heterozygous FH [1▪]. The Canadian Cardiovascular Society also recommends measurement of Lp(a) at least once in a person's lifetime [61▪]. The role of Lp(a) in ASCVD risk-stratification is highlighted in multiple guidelines [1▪,4▪,61▪,62,63]. In individuals with calcific AS, measurement of Lp(a) can be considered according to the Heart UK and the National Lipid Association [62,63]. Similarly, the Australian Atherosclerosis Society recommends measurement of Lp(a) in individuals with premature or rapidly progressive calcific AS [64▪]. Although there are recommendations on the frequency of surveillance in individuals with AS, this does not account for those with elevated Lp(a) levels, who may have more rapid progression of disease [11,12]. There are at present no specific recommendations on screening for CAVD in individuals with elevated Lp(a) levels, perhaps driven by the lack of evidence for benefit from therapeutic lowering of Lp(a) [1▪,4▪,61▪,62,63].

CONCLUSION

Epidemiologic, genetic, and Mendelian randomization studies suggest that Lp(a) is causally associated with AS, a condition for which there are no medical therapies proven to slow disease progression. The pathophysiology of Lp(a) in CAVD is not well understood, but OxPLs are a crucial mediator. Progression from subclinical calcification to clinical AS typically occurs over a decade or more, highlighting ample opportunity to intervene with preventive therapies. Whether Lp(a)-lowering can prevent initiation or slow progression of CAVD remains to be demonstrated.

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Conflicts of interest

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