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Lipoprotein(a) and aortic stenosis: Practical insights

Kyriakos Dimitriadis [a,*], Konstantinos G. Kyriakoulis [a], Nikolaos Pyrpyris [a], Eirini Beneki [a], Vasileios Kamperidis [b], Anastasios Kollias [c], Edina Cenko [d], Konstantinos Aznaouridis [a], Konstantina Aggeli [a], Konstantinos Tsioufis [a]

[a] First Department of Cardiology, School of Medicine, National and Kapodistrian University of Athens, Hippokration General Hospital, Athens, Greece
[b] First Cardiology Department, Medical School, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece
[c] Hypertension Center STRIDE-7, School of Medicine, Third Department of Medicine, Sotiria Hospital, National and Kapodistrian University of Athens, Athens, Greece
[d] Laboratory of Epidemiological and Clinical Cardiology, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

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ABSTRACT

Aims: The role of Lp(a) in cardiovascular diseases is increasingly recognized, with high Lp(a) levels shown to be associated with worse outcomes. In this review, we aim to summarize the literature and the current research status regarding AS and Lp(a) with a comprehensive approach, in order to inform basic and clinical scientists with the most up-to-date data and insights.

Data synthesis: Lp(a) is significantly involved in the pathogenesis of aortic stenosis (AS), with the interplay between AS and Lp(a) being documented in observational studies and a causal association being proposed based on genetic studies. Patients with AS have generally higher levels of Lp(a) and increased Lp(a) levels are associated with higher risk of AS development. The above observations offer opportunities for further research, mainly regarding potential therapeutic implications, particularly considering the Lp(*a*)-specific lowering therapies that are awaited to influence the prevention and treatment strategies for AS.

Conclusion: Increased Lp(a) levels can be predictive of the presence, development and progression of AS, as well as could offer novel insights in the pathophysiology of bioprosthetic valve function. Further research, focusing on Lp(*a*)-lowering agents, is key in order to identify any benefit in such patient phenotypes.

1. Introduction

Aortic stenosis (AS) is one of the commonest valvulopathies, with higher rates in older adults and an increasing prevalence due to the aging population [1], with data from the European Society of Cardiology (ESC) Atlas showing that the prevalence of calcific AS in Europe is 357.9 cases per 100,000 individuals [2]. The pathophysiology of AS has been largely investigated, with many mechanisms contributing to its pathogenesis [3]. Several of these links are shared between calcific AS and atherosclerotic coronary artery disease (CAD) [4]. However, the aim to identify modifiable risk factors that could be used therapeutically to slow the progression of AS has fallen short, with no pharmacotherapy options currently available. Therefore, besides symptom management, the remaining option for patients is valve replacement, either transcatheter or surgical. Transcatheter aortic valve implantation (TAVI) is indicated in patients with severe AS and high surgical risk (IA recommendation) [5]. However, recent efforts have established the safety and feasibility of TAVI in lower risk and younger patients with severe AS, as well as in asymptomatic ones [6–9]. Considering the expansion of TAVI indications delaying the progression of AS, and subsequently the timing of intervention, could alter clinical practice.

Lipoprotein-a [Lp(a)] is a relatively novel risk factor for cardiovascular disease, originally recognized as a key molecule participating in the pathogenesis of atherosclerotic CAD [10]. A large number of observational and genetic studies have established the association of increased Lp(a) levels with increased risk for cardiovascular mortality, myocardial infarction and stroke [11–13]. More recently, increased Lp (a) has been recognized as an independent risk factor for heart failure (HF) progression and cardiovascular death, in patients with early-stage HF [14]. Considering shared pathogenetic implications between AS and atherosclerosis, further investigations revealed an important role of elevated Lp(a) levels with AS. Given that Lp(a) levels are majorly determined by genetics [15], identifying a link between its elevation and AS development and/or progression could offer a significant therapeutic target. Therefore, the aim of this review is to provide the

* Corresponding author. Vasilissis Sofias 114 Athens, 11527, Greece.
E-mail address: dimitriadiskyr@yahoo.gr (K. Dimitriadis).

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Abbreviations

ACS	Acute Coronary Syndrome
AS	Aortic Stenosis
BAV	Bicuspid Aortic Valve
BVD	Bioprosthetic Valve Degeneration
CAD	Coronary Artery Disease
ESC	European Society of Cardiology
EPIC	European Prospective Investigation into Cancer
HALT	Hypoattenuating Leaflet Thickening
HF	Heart Failure
hsCRP	High-Sensitivity C-Reactive Protein
LDL	Low-Density Lipoprotein
Lp(a)	Lipoprotein(a)
MAC	Mitral Annulus Calcification
PET/CT	Positron Emission Tomography/Computed Tomography
PCSK9i	Proprotein Convertase Subtilisin/Kexin type 9 inhibitors
SAVR	Surgical Aortic Valve Replacement
siRNA	small interfering RNA
SNP	Single Nucleotide Polymorphism
TAVI	Transcatheter Aortic Valve Implantation
VEC	Valvular Endothelial Cells
VIC	Valvular Interstitial Cells
ViV	Valve in Valve

pathophysiologic relationship between AS and Lp(a), describe the studies associating Lp(a) with AS and TAVI, as well as analyze current and novel therapeutic interventions and discuss future perspectives.

2. Pathophysiology

Lp(a) is a lipid particle found in plasma and much resembling to the LDL-cholesterol particles; however, with the addition of a unique apolipoprotein(a) component that is bound to the apolipoprotein B part of LDL-cholesterol [16] (Fig. 1). The coding gene for apolipoprotein(a) presents similarities and evolutionary relationship with the coding gene for plasminogen [16,17]. In this respect, it could be expected that apolipoprotein(a) and subsequently Lp(a) would have fibrinolytic and anti-coagulant properties [16]. Nevertheless, Lp(a) presents a completely opposite function, inhibiting plasminogen to plasmin conversion, promoting plasmin production, and eventually acting as a prothrombotic factor [16,18]. The role and significance of Lp(a) in the physiological human homeostasis has not been totally clarified; however, it has been argued that during evolution it has been offering a survival advantage, contributing to the adequate wound healing [16,19]. Considering the main function and molecular form of Lp(a), it is not surprising that high levels of Lp(a) are accompanied by increased risk of thrombotic events and subsequent cardiovascular disease [18,20], with both the biological and pathophysiological background of Lp(a), but also genetic and epidemiological studies having demonstrated the causal relationship of high Lp(a) levels and cardiovascular morbidity and mortality [18,21].

From a pathophysiological point of view, the contribution of Lp(a) in the pathogenesis of AS begins during the "Initiation Phase" (Fig. 2) in the context of the lipid infiltration and accumulation in the aortic valve cusps' inner layers after the initial endothelial damage due to significant shear stress [22]. Lp(a) (as well as other lipids e.g., LDL-cholesterol) are then oxidized and act as triggers for the transition to the "Propagation Phase" (Fig. 2) by activation of the inflammatory process and induction of VICs apoptosis [22]. Lp(a) does not act only as a pro-inflammatory factor, but also as a pro-thrombotic factor inducing microthrombi formation and further enhancing inflammation and valve degeneration [16]. It has been also shown that increased Lp(a) levels regulate and promote the activation of inflammation- and calcification-related genes in cells found in vascular and valvular structures [18]. This molecular cascade eventually leads to osteoblastic differentiation of VICs and calcium accumulation. Aortic valve microcalcification represents an early phase and a precursor of aortic valve calcification and subsequent stenosis, and its potentially causal association with increased Lp(a) levels has been shown and supported by observational but most importantly by genetic studies [23–25]. Aortic valve sclerosis, an intermediate step before the development of clinically important AS, has also been found to be more prevalent in individuals with increased Lp(a) levels [26]; thus, enhancing and reassuring the pathophysiological link between Lp(a) levels and AS disease spectrum and natural history.

3. Role of Lp(a) in native aortic stenosis

Having established the potential role of Lp(a) levels in the pathophysiology of AS, there was a need to confirm whether patients with higher Lp(a) levels have increased risk for aortic valve calcification, AS and progression of the disease. The first notion of a potential relationship came from a study conducted in 1995 [26], reporting that aortic

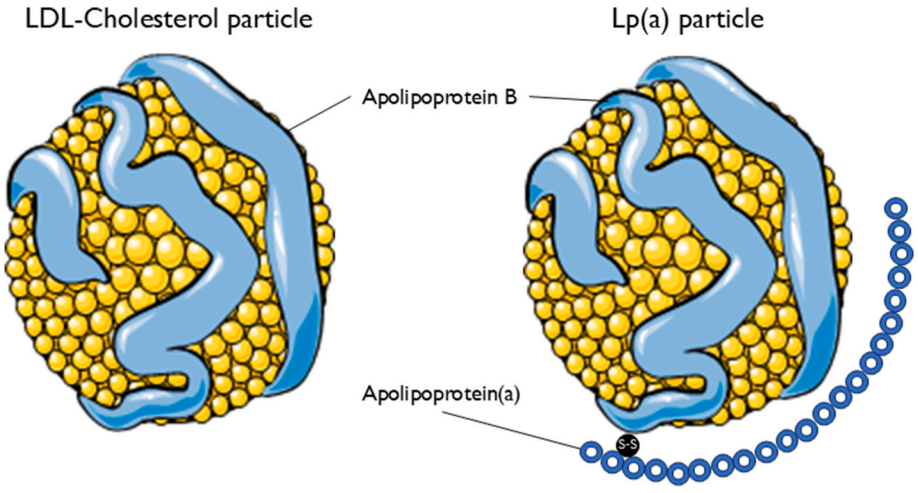

Fig. 1. Principles of Lp(a) structure and resemblance to LDL-cholesterol particles. Apolipoprotein(a) is linked to Apolipoprotein B through a disulfide bridge (S–S).

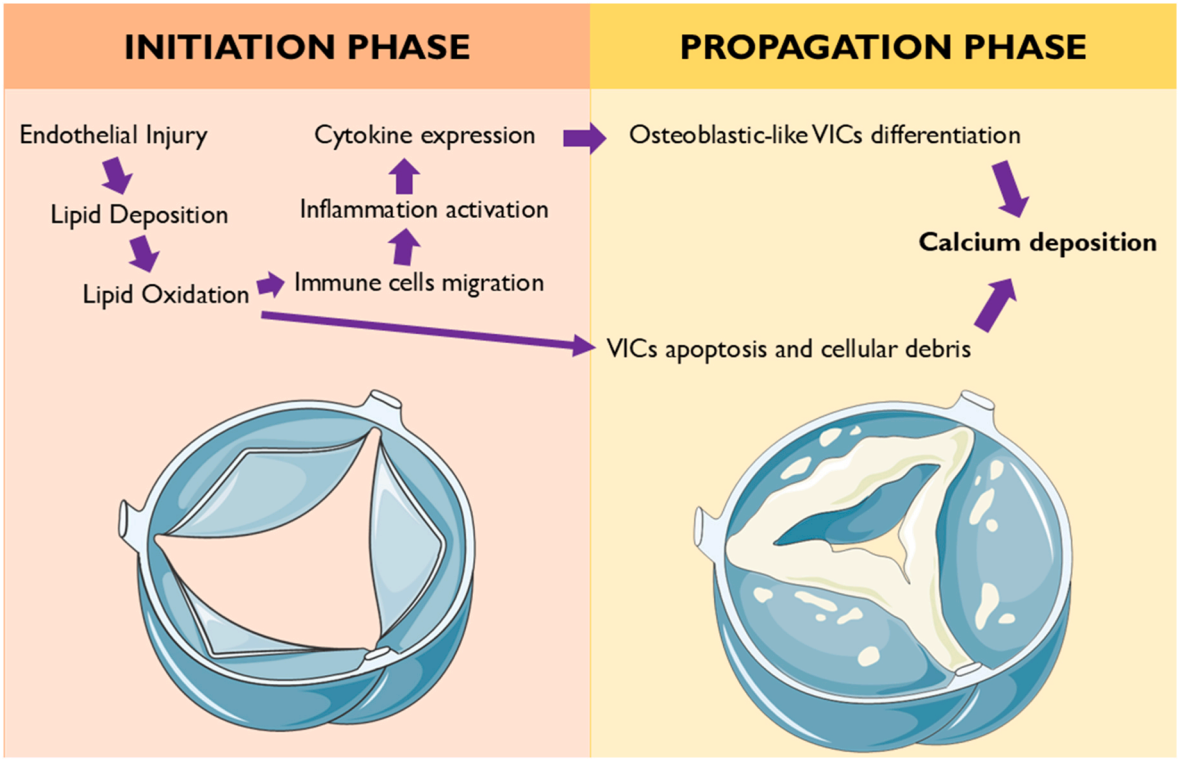

Fig. 2. Graphical summary of the pathophysiological process leading to aortic valve calcium deposition and subsequent aortic valve stenosis.

valve sclerosis was more prevalent among participants with Lp(a) ≥30 mg/dl. Later in 1997, Stewart et al. [27] identified, among other factors, Lp(a) levels as a significant risk factor for AS or aortic sclerosis, with an odds ratio of 1.23 (95 % CI: 1.14–1.32). The first longitudinal prospective analysis on this context was performed by Arsenault et al. [28], including 17,553 participants of the European Prospective Investigation into Cancer (EPIC)-Norfolk study. The investigators showed that individuals in the top tertile of Lp(a) levels had a significantly higher risk for AS development (hazard ratio 1.57; 95 % CI: 1.02–2.42) after multivariate adjustment for demographics. These findings were further supported by analysis of two prospective general population studies by Kamstrup et al. [29], showing that the risk for AS was almost 3-fold in those with levels greater than the 95th percentile.

Besides establishing the link of Lp(a) serum levels with the risk for AS, all of the aforementioned prospective trials also reported genetic associations in regards to the LPA locum. Thanassoulis et al. [30], aiming to determine genomewide associations with the presence of calcification of the aortic valve, among 6942 individuals, identified a single nucleotide polymorphism (SNP) in the locus of the LPA gene, namely rs10455872, that was significantly associated with the presence of AS in all tested ethnicities and in the overall cohort. Furthermore, the study reported that LPA genotype was associated with incident AS (hazard ratio per allele, 1.68; 95 % CI: 1.32–2.15), as well as future aortic valve replacement (hazard ratio, 1.54; 95 % CI: 1.05–2.27). Further efforts, in the context of the aforementioned population prospective studies, discovered another LPA allele related with AS. In particular, Kamstrup et al. [29] identified increased Lp(a) levels among carriers of both rs10455872 as well as rs3798220 alleles, along with individuals with low number of KIV-2 repeats ($p < 0.001$ for all), whilst also establishing that this genotype was associated with an increased risk for AS. These findings were confirmed by future analyses. Chen et al. [31], beyond establishing the statistical significance of the two alleles with the risk for AS, also showed that individuals carrying two high risk alleles are at even greater risk, which was approximately 2-fold for homozygous rs10455872 phenotypes, 4-fold for homozygous rs3798220 and 2-fold for heterozygous rs10455872 and rs3798220. Moreover, they showed that risk for AS was greatest for individuals between 55 and 64 years old (only for the rs10455872 allele), showing that the risk of increased Lp(a) may be more clinically relevant in younger patients. Interestingly, these findings are significant regardless of CAD presence, as Perrot et al. [32] showed that the Lp(a) genetic risk was independently associated with an increased risk for AS. Finally, regarding the role of sex, original studies reported an association of only rs3798220 with a greater risk for AS in male patients [31]; however, more recent analyses indicate no sex differences [33].

Aiming to summarize the available evidence from both epidemiology and genetic studies, a meta-analysis by Pantelidis et al. [24] was recently performed, including a total of 44 studies and 163,139 individuals. This analysis confirms the relationship among Lp(a) levels and calcific AS, especially in younger individuals. In particular, patients with AS had higher mean Lp(a) levels by 22.63 nmol/L (95 % CI: 9.98–35.27), with smaller differences in Lp(a) levels of normal and AS individuals of older age. In terms of genetic associations, the meta-analysis demonstrated that both aforementioned alleles were significantly associated with an increased risk for AS presence and development (pooled odds ratio 1.42; 95 % CI: 1.34–1.50 and 1.27; 95 % CI: 1.09–1.48, respectively). Lastly, patients with high Lp(a) had a higher risk for mortality (pooled hazard ratio 1.39; 95 % CI: 1.01–1.90). Therefore, this cumulative synthesis further expands the evidence regarding the significant association of Lp(a) levels and calcific AS, also reflecting an increase in adverse events. Finally, studies including patients with bicuspid aortic valve (BAV) offer a unique model of fast valve degeneration and have also settled a link between AS and Lp(a) [34–37]. R epresentative studies are summarized in Table 1.

While it has been well established that increased Lp(a) levels and specific LPA alleles are related with increased incidence of AS and development of this entity, evidence is less robust for the role of Lp(a) levels in AS progression. Capoulade et al. [38] in a secondary analysis of the ASTRONOMER trial including 220 patients with mild to moderate AS being echocardiographically followed up for 3–5 years, found a

Table 1
Studies investigating Lp(a) and aortic stenosis in patients with bicuspid aortic valve.

Study	Study Design Country	N	Age (years)	Males (n, %)	Main Findings
Krzesinska 2023[48]	Retrospective Poland	75	54	21 (28)	• Lp(a) > 50 mg/dl more frequently in AS patients • Lp(a) > 50 mg/dl associated with aortic valve replacement in younger age
Sticchi 2018[50]	Cross-sectional Italy	69	45	55 (80)	• Higher Lp(a) in higher degree of aortic valve calcification • Higher Lp(a) in AS patients
Ker 2013[49]	Case series/ Cross-sectional South Africa	10	41	9 (90)	• Normal Lp(a) in all cases without aortic valve calcification (6 out of 6) • Elevated Lp(a) in most cases with aortic valve calcification (3 out of 4)

AS, aortic stenosis; BAV, bicuspid aortic valve; Lp(a), lipoprotein(a).

linear association between Lp(a) serum levels and progression of AS, with an odds ratio of 1.10 per 10 mg/dL increase in Lp(a) (95 % CI: 1.03–1.19). This association remained statistically significant after multivariate adjustment, while it was more marked in younger individuals (odds ratio for Lp(a) 1.19 per 10 mg/dL increase; 95 % CI: 1.07–1.33). Similar results have been reported by Zheng et al. [39], indicating increased progression of valvular calcium score during follow-up. However, a study by Kaiser et al. [40], including 922 individuals from a population-based study, showed that Lp(a) levels, despite being correlated with baseline aortic valve calcium and new-onset aortic valve calcium, were not related with the progression of aortic valve calcium. This finding supported the analysis of the MESA study, which found that only baseline aortic valve calcium and not Lp(a) is associated with disease progression [41]. The different definitions of AS progression could account for the lack of consistent results between studies. Noteworthy, the meta-analysis of Pantelidis et al. [24], using only peak aortic velocity change as a surrogate for disease progression, showed a significant association with Lp(a), including, however, only 2 studies [38,39] and a limited number of participants. In another recent individual patient data meta-analysis including data from 757 individuals [42], those in the highest tertile of Lp(a) distribution were found to present a faster progression of peak aortic jet velocity and mean transvalvular gradient [42]. Additional systematic reviews and meta-analyses have confirmed these findings [43,44]. As the importance of increased Lp(a) is increasingly established, further evaluation of the role of Lp(a) in hemodynamic and structural valve changes, especially in patients with mild or moderate disease, are of key importance into understanding the role of Lp(a) lowering strategies in such patient phenotypes.

4. Role of Lp(a) in transcatheter aortic valve implantation

Data regarding the role of Lp(a) in the setting of TAVI are profoundly more limited (Table 2). The increasing interest regarding the interplay between Lp(a) and TAVI is depicted by increase of Lp(a) testing during recent years. In a relevant cohort study, where Lp(a) testing in cardiology and internal medicine clinics has been promoted with educational approaches [45], a five-fold increase in the testing of Lp(a) over a

Table 2
Studies investigating the role of Lp(a) in patients undergoing transcatheter aortic valve implantation.

Study	Study Design Country	N	Age (years)	Males (n, %)	Main Findings
Loewenstein 2024[61]	Retrospective Israel	503	83	224 (45)	• TAVI patients had slightly higher median Lp(a) compared to controls • Lp(a) > 50 mg/dl not associated with TAVI in younger age
Shi 2024[62]	Retrospective China	307	74	167 (54)	• Incidence of HALT 1year post-TAVI was 36 % • Risk of HALT associated with increasing levels of Lp(a)
Sorysz 2024[63]	Prospective Poland	31	84	NR	• Weak or no-significant associations of Lp(a) with valve degeneration • Lp(a) levels before vs after TAVI remined stable
Ma 2019[60]	Retrospective USA	131	81	76 (58)	• Prevalence of Lp (a) > 30 mg/dl was 35 % • Patients with Lp (a) > 30 mg/dl had higher incidence of CAD requiring revascularization • Patients with Lp (a) > 30 mg/dl had higher incidence of paravalvular leak

AS, aortic stenosis; CAD, coronary artery disease; HALT, hypoattenuating leaflet thickening; Lp(a), lipoprotein(a); NR, not reported; TAVI, transcatheter aortic valve implantation.

10-year time period was observed with a peak of 24.2 % of AS and 88.5 % of TAVI patients being tested for Lp(a) [45]. Importantly, 35 % and 26 % of TAVI patients had increased Lp(a) levels (Lp(a) > 30 mg/dl and 50 mg/dl, respectively) [45]. In a further analysis performed by the same research group, it was shown that increased levels of Lp(a) in TAVI patients is associated with increased incidence of CAD requiring revascularization (65 % vs 47 %) [46]. Notably, TAVI patients with high levels of Lp(a) presented a higher incidence of paravalvular leak (13 % vs 4 %) [46]. A hypothesis explaining this observation could be that the relationship between high levels of Lp(a) and procedural complications is mediated by a potential increased aortic cusp and annulus calcification [46]. These observations suggest potential therapeutic implications, since effective Lp(a) lowering could enhance procedural outcomes. In another cohort study including 503 patients with severe AS undergoing TAVI, Lp(a) levels were found to be only slightly higher in TAVI patients compared to controls and this difference was mainly driven by increased Lp(a) levels in males [47]. Unexpectedly, Lp(a) levels were not found to be predictive of early TAVI intervention in a multivariable logistic regression analysis evaluating determinants of TAVI before vs after the age of 75 years [47]. In this analysis, age was inserted in the model as a dependent categorical variable with a cut-off limit at 75 years [47] and an analysis with age as a continuous variable or a survival analysis approach could potentially provide different results. In this respect, in a study including patients with bicuspid aortic valve and AS undergoing

surgical aortic valve replacement (SAVR) (mean age 54 years), an association of increased Lp(a) level with earlier surgery (in younger age) was demonstrated by employing survival analysis [34]. It could be hypothesized that the prognostic impact of Lp(a) is more profound in younger compared to older patients, in whom accumulation of many different cardiovascular risk factors concomitantly leads in the pathogenesis of cardiovascular disorders and AS.

Only a few studies have investigated the role of Lp(a) postoperatively after TAVI in terms of hypoattenuating leaflet thickening (HALT) and bioprosthetic valve degeneration (BVD). Shi et al. evaluated the risk of HALT in 307 TAVI patients and demonstrated that increasing levels of Lp(a) was a predictor of HALT, with an odds ratio of 1.18 (95 % CI: 1.09–1.29) for every 10 mg/dl increase of Lp(a) [48]. This association has a clear pathophysiological basis, since HALT represents a condition of subclinical valve leaflet thrombosis and Lp(a) has significant prothrombotic properties [16]. In another approach evaluating post-TAVI BVD using positron emission tomography/computed tomography (PET/CT) and echocardiography, weak or no-significant associations with Lp(a) were observed during a follow-up period of 12 months [49]. However, the sample size of the study was relatively low and included elderly patients (median age 84 years), who may be not the optimal cohort for these evaluations, as aforementioned. Interestingly, the investigators of this study also obtained serial Lp(a) measurements both before and after TAVI [49], showing that Lp(a) levels did not present any significant difference and supporting the evidence of relatively stable Lp(a) levels during one's life due to genetic determination [16,18]. In another prospective study, including 97 patients (mean age 75 years) with the majority (78 %) undergoing SAVR [50], Lp(a) levels were not significantly different in the presence or not of any valve degeneration stage and were not correlated with indices of incident BVD at 2 years [50]. In contrast, Farina et al., assessing BVD using echocardiography after a median period of 4.4 years in a mixed cohort (SAVR 70 %) [51] and using a survival analysis, concluded in favor of the association of Lp(a) > 30 mg/dl with BVD [51]. The findings of the present study are relatively contradictory to those of the above-mentioned studies; however, various sources of heterogeneity should be considered. On the other hand, it is the study with the largest sample size and with the longest follow-up period. Thus, safe and robust conclusions cannot be drawn and properly designed prospective studies are needed in the future.

5. Management of increased Lp(a) levels

Timely and efficient recognition of increased Lp(a) levels, especially in high-risk individuals, could reduce major adverse cardiovascular events. Considering the metabolism of Lp(a), several lipid-lowering agents have been tested, while more recently, targeted therapies have emerged, with promising results (Table 3).

Statins are the most used lipid-lowering therapy worldwide, with recent evidence showing that more than 50 million Americans are eligible for statin prescription [52]. The levels of Lp(a) have been found to be significantly associated with adverse events, even in those receiving statin treatment [53]. However, the effect of statins in Lp(a) levels are conflicting, with studies showcasing an increase of Lp(a) in

Table 3
Agents of potential use for the management of increased Lp(a) levels.

Agent	Lp(a) Reduction Mechanism	Administration and Dosing	Lp(a) Reduction (%)	Available Studies	Key Findings
Statins	Non Lp(*a*)-Specific	Oral, dosing depends on agent used	Conflicted	Meta-Analysis	• Conflicting studies showing either increase, no benefit or small decrease in the levels of Lp(a) • Despite the unclear effect (including potential increase), there is no suggestion of statin interruption in patients with increased Lp(a) due to the absence of supporting evidence
Ezetimibe	Non Lp(*a*)-Specific	Oral, 10 mg	Conflicted	Meta-Analysis	• Conflicting results of available analyses, showing no benefit or small reductions
Bempedoic Acid	Non Lp(*a*)-Specific	Oral, 180 mg	No effect	Meta-Analysis	• Studies show no benefit of the addition of bempedoic acid on Lp(a) levels
PCSK9 Inhibitors	Non Lp(*a*)-Specific	Subcutaneous, dosing depends on agent used	20–27 %	Sub-Analysis of Phase III studies	• Sub-analyses of randomized studies evaluating the safety and efficacy of alirocumab and evolocumab show reduction of Lp(a) levels with both drugs • An analysis of the FOURIER trial (evolocumab) showed a greater reduction of adverse events in those with higher baseline Lp(a)
Inclisiran	Non Lp(*a*)-Specific	Subcutaneous, 284 mg/ 1.5 mL	13–19 %	Sub-Analysis of Phase III studies	• Analyses of the ORION studies show a significant reduction of Lp(a) levels • More data comparing baseline with follow-up values are needed for robust conclusions
Pelacarsen	Lp(*a*)-Specific (siRNA)	Subcutaneous, 80 mg	80 %	Phase III trial ongoing	• In a dose-dependent manner, pelacarsen reduced Lp(a) from 35 to 80 % at 14 weeks follow • 98 % of individuals under the 80 mg monthly dose achieved an Lp (a) < 50 mg/dL • Phase III trial with pelacarsen 80 mg (once a month) is ongoing
Olpasiran	Lp(*a*)-Specific (ASO)	Subcutaneous	70.5–101.1 %	Phase III trial (enrollment complete)	• At 36 weeks follow-up, a significant reduction of Lp(a) was reported in a dose-dependent manner, ranging from 70.5 to 100.5 % • The phase III trial OCEAN(*a*)-Outcomes (NCT05581303) has completed patient enrollment and study completion is awaited in 2026
Lepodisiran	Lp(*a*)-Specific (ASO)	Subcutaneous	41–97 %	Phase III ongoing	• Significant reduction of Lp(a) was noted with all administered doses, ranging from 41 to 97 % at 48 weeks follow-up • The phase III trial ACCLAIM (NCT05581303) is enrolling patients, with an estimated completion date in 2029
SLN360 (zerlasiran)	Lp(*a*)-Specific (ASO)	Subcutaneous	81–86 %	Phase III awaited	• Lp(a) was significantly reduced by more than 80 % in all administered doses, ranging from 81 to 86 % • Phase III trial is awaited
CRISPR-Cas 9	Lp(*a*)-Specific (gene editing)	No available human studies	Preclinical Studies	Not Applicable	• Animal studies show that gene editing of the LPA gene results in complete elimination of apo(a) from the circulation within a week • More extensive research and human studies are needed

apo(a): Apolipoprotein-a; ASO: Antisense Oligonucleotide; Lp(a): Lipoprotein-a; PCSK9: Proprotein Convertase Subtilisin/Kexin type 9; siRNA: Small Interference Ribonucleic Acid.

those receiving statin treatment [54] and, therefore, a potential increase in cardiovascular risk [53]. Contrary, other studies report a reduction of Lp(a) levels in individuals treated with atorvastatin or simvastatin, in the presence of heterozygous familial hypercholesterolemia [55]. Meta-analysis data do not provide any more clarity. In specific, de Boer et al. [56] showed no significantly increased Lp(a) levels in patients receiving statins, with similar results were reported by Wang et al. [57]. Contrary, a meta-analysis by Tsimikas et al. [58], including independent patient data from 6 randomized controlled studies, showed a mean percent change from baseline ranging from 8.5 % to 19.6 % in those treated with statins and −0.4 % to −2.3 % in the placebo arm, with greater increase of Lp(a) in those receiving atorvastatin. Furthermore, they report that after incubation of HepG2 hepatocytes with atorvastatin, there is an increase of the expression of LPA mRNA as well as apolipoprotein(a) protein, which may explain the reason behind the neutral or negative effects of statin on Lp(a) levels, despite the upregulation of LDL receptors. Despite the aforementioned evidence, current consensus documents do not support statin discontinuation in those with increased Lp(a), as the benefits outweigh the risks. However, more research is needed on whether lipid-lowering agents reducing both LDL and Lp(a) are more suitable in those patient phenotypes. Similarly, the effect of ezetimibe, that prevents cholesterol absorption from the small intestine, in Lp(a) levels is also unclear, with a meta-analysis by Awad et al. [59] reporting significantly reduced Lp(a) by 7.06 % (95 % CI: 11.95, −2.18), regardless of baseline LDL and Lp(a) concentration, while other meta-analyses [60] show no effect on Lp(a) levels. No particular effect on Lp(a) levels is also shown for bempedoic acid, despite reducing LDL, total cholesterol and apolipoprotein B levels [61].

Contrary, the use of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) showed a notion of positive results on the levels of Lp(a), reducing its levels by approximately 20–25 % [62,63]. In specific, O'Donoghue et al., analyzing the FOURIER trial, reported that evolocumab reduced Lp(a) by a mean of 26.9 % (95 % CI: 6.2–46.7 %), while it also reduced the risk of CAD death, myocardial infarction, or urgent revascularization by 23 % in those with Lp(a) greater than the median and by 7 % in those with Lp(a) lower than the median [64]. A similar benefit has been also reported for alirocumab [65]. These results have been replicated in a real-world setting [66] as well as in the setting of acute coronary syndromes (ACS), showing a benefit even when considering early post-ACS PCSK9i administration [67–69]. These effects could be related to the increased catabolism and decreased production of Lp(a) particles potentially initiated by PCSK9i [70], however the exact mechanism has yet to be determined.

Similarly to PCSK9i, inclisiran, a siRNA targeting hepatic PCSK9 production, could be another agent of promise. The ORION 9, 10 and 11 trials showed that inclisiran reduced Lp(a) concentrations (−13.5 %, −21.9 % and −18.6 %, respectively), without providing p-values for statistical significance [71,72]. However, a subsequent analysis of the ORION-11 trial [73], including patients without history of cardiovascular events and LDL >100 mg/dL, showed a reduction of Lp(a) by 12.1 % in the inclisiran arm, with the least squares mean difference being −28.9 % (95 %CI: 40.9, −16.9; $p < 0.0001$). It has to be noted that the increase of Lp(a) by 16.8 % in the placebo arm could have resulted in the aforementioned statistically significant result, therefore necessitating more research in this context.

Moving beyond traditional lipid lowering treatment, novel agents that could potentially not only lower the serum Lp(a), but also reduce the risk for cardiovascular events have been developed. Anti-sense oligonucelotides, which act via binding to the apo(a) mRNA, lead to inhibition of its synthesis in the liver. First phase I and II studies (IONIS-APO(*a*)Rx) showed that the tested molecule substantially reduced the serum levels of Lp(a), as well as oxidized phospholipids, and particularly in those with higher baseline Lp(a) [74,75]. Modification of the molecule, including conjugation with GalNac3 in order to be more liver-specific, led to the development of pelacarsen [75]. A phase IIb trial with pelacarsen showed a dose-dependent reduction of Lp(a), ranging from 35 to 80 % at 14 weeks follow up, while 98 % of individuals under the 80 mg monthly dose achieved an Lp(a) < 50 mg/dL. As with previous molecules, pelacarsen also reduced oxidized phospholipids, apoB and LDL-C [76]. Given the positive results from phase I and II studies, the currently ongoing phase III HORIZON trial (NCT04023552) will address whether pelacarsen 80 mg injected monthly, in patients with an Lp (a) > 70 mg/dL and a previous ischemic event, could reduce major adverse cardiovascular events. The primary results of the study are expected in 2025. Finally, it is important to note the ongoing Lp(*a*)FRONTIERS CAVS study (NCT05646381), which is a Phase II study that is going to evaluate the effect of Lp(*a*)-lowering with pelacarsen, compared to placebo, on the progression of AS. The trial is estimated to include approximately 500 patients, aged between 50 and 80 years of age with and Lp(a) ≥175 nmol/L at baseline and mild or moderate AS. These patients, which will be optimally treated at baseline for all cardiovascular risk factors, with either receive pelacarsen on placebo and will be followed up for up to 36 months. The primary outcomes of the study will be changes in peak aortic valve velocity and aortic calcium score between baseline and 36 months. The study is estimated to be completed in 2030 and will give significant novel insights on the role of Lp(a) lowering in AS progression.

Except from anti-sense oligonucleotides, other researchers have focused in a similar concept of targeting Lp(a) in the molecular level, via creating small interfering RNA (siRNA), that acts by inhibiting mRNA translation and therefore limiting the production of Lp(a) [77]. There are several siRNAs currently being tested, including olpasiran, lepodisiran, SLN360 (zerlasiran). Most studies to date have examined the safety of these agents, as well as their efficacy in reducing Lp(a) levels. In particular, the OCEAN(*a*)-Dose trial [78] included 281 patients with a median Lp(a) concentration at baseline of 260.3 nmol/L, that were administered increasing doses of olpasiran. At 36 weeks follow-up, Lp(a) had increased by a mean of 3.6 % in the placebo group, while it was significantly reduced in a dose-dependent manner following olpasiran treatment. Regarding adverse effects, the most common was injection site pain [78]. Similar results have been described for leposidiran [79] and zerlasiran [80]. Currently, ongoing trials aim to address the effect of these novel Lp(a) lowering drugs on cardiovascular outcomes, including the OCEAN(*a*)-Outcomes (NCT05581303) study, evaluating olpasiran, which has completed patient enrollment and is expected to be completed at the end of 2026. Moreover, the ACCLAIM (NCT06292013) study, which is evaluating the safety and efficacy of lepodisiran, is currently enrolling patients with an estimated study completion at the start of 2029, while the phase III study of zerlasiran is also being awaited. Finally, the technology of gene editing with CRISPR-Cas9 has been introduced as a potential intervention for lowering Lp(a) levels in preclinical models [81]. Further animal and subsequently human studies could provide a genetic therapy alternative, lowering the genetically mediated cardiovascular risk in those with increased Lp(a) levels.

6. Future perspectives

The role of Lp(a) and Lp(a) therapeutics in the future are awaited to be game-changing in AS and AS-related interventions. In the setting of disease prevention, detection of increased Lp(a) and effective Lp(a) lowering with appropriate drugs may radically change the natural history of AS. Lp(a) levels could also provide useful information regarding the TAVI procedure itself. High Lp(a) levels could imply an increased risk for faster HALT or BVD. This information could influence and guide the individualized strategy for the selection of the optimal aortic valve system to be used in the TAVI procedure or could offer useful information for a future valve-in-valve (ViV) TAVI intervention. Following the paradigm of aortic valve, Lp(a) could play a significant role in the pathogenesis and management of other entities and valvulopathies; e.g., mitral annulus calcification (MAC). Interestingly, accumulating evidence is in favor of a close relationship between Lp(a) and MAC and future studies will address this role and clarify its significance [23,82,

83].

In the future, significant gaps in knowledge are awaited to be addressed and shed light on various Lp(a) and AS-related aspects. The genetic background and respective clinical implications are awaited to be better determined, whilst the correct and most reproducible Lp(a) measurement methodology will hopefully be standardized. Studies in heterogeneous and diverse populations are needed and the true role and impact of Lp(a) lowering pharmaceutical interventions will be investigated for the prevention and/or treatment of AS. In this context, practical clinical questions will emerge and further studies with appropriate design will be needed.

7. Conclusions

Measuring Lp(a) in patients with AS may offer prognostic information regarding the progression of the disease, bioprosthetic valve durability and post-procedural complications in patients undergoing TAVI. Further research, investigating the role of Lp(*a*)-lowering agents, will provide further guidance regarding any significant decrease of adverse outcomes, whilst evaluating their efficacy in halting AS progression, providing an intervention directly targeting its pathophysiological development.

Author contributions

Conceptualization: K.D.; Investigations: K.G.K. and N.P.; Data Curation: K.G.K. and N.P.; Writing-Original Draft: K.G.K., K.D. and N.P.; Writing-Review and Editing: K.G.K., K.D., N.P., E.B., P.T., V.K., A.K., E. C., K.A.(Konstantinos Aznaouridis)., K.A.(Konstantina Aggeli) and K.T.; Supervision: K.D. and K.T. All authors have reviewed and agree with the final version of this manuscript.

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Declaration of competing interest

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