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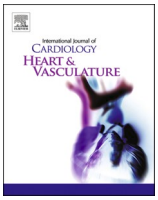

Role of Lipoprotein (A) in aortic valve stenosis: Novel disease mechanisms and emerging pharmacotherapeutic approaches☆

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ABSTRACT

Lipoprotein(a) (Lp(a)) has garnered increasing attention as a significant contributor to the pathogenesis of aortic stenosis (AS), prompting a focused investigation into innovative pharmacological strategies to target this lipoprotein and its associated risks. Despite its recognized role in AS progression, Lp(a) often remains overlooked in clinical assessments, mirroring the broader challenges observed in holistic disease management. This review delves into the mechanistic intricacies of Lp(a) involvement in AS pathophysiology and its potential as a therapeutic target. Drawing parallels with the imperative for healthcare providers to proactively engage with patients regarding treatment regimens, this review underscores the essential role of cardiologists and physicians in recognizing and addressing Lp(a) as a modifiable risk factor in AS management. Furthermore, it explores promising avenues of novel drug approaches, including emerging pharmacotherapies and targeted interventions, aimed at modulating Lp(a) levels and attenuating AS progression. By navigating the complexities of Lp(a) modulation and its implications for AS management, this review aims to bridge critical gaps in understanding and clinical practice, ultimately optimizing treatment strategies and improving patient outcomes in the realm of AS therapeutics.

1. Introduction

Aortic valve stenosis (AVS) is the most common valvular heart disease (VHD) in developed countries with prevalence of aortic sclerosis in individuals over 75 years around 40 % with a slow degenerative process of only 2 % developing progressive symptomatic AVS [1]. If left untreated, patients with symptomatic severe AVS exhibit poor outcomes with mean survival rates of 5 years, 3 years and 1 year when developing angina pectoris, syncope and dyspnea respectively [2]. Calcific degenerative AVS is mainly characterized by passive age-related mechanical stress-induced wear and tear process [3]. However, recent research has shed light on an active process of aortic valve atherosclerosis linked to similar pathways in atherosclerosis development. This process is regulated by lipid deposition, osteoblastosis of valve interstitial cells (VICs) as well as macrophage infiltration causing active inflammation in aortic valve calcification [4,5]. Both transcatheter aortic valve implantation (TAVI) as well as surgical aortic valve replacement (SAVR) remain as standard of care interventions receiving Class IA recommendation for patients with severe and symptomatic AVS. Nevertheless, such procedures hold potential risks including bleeding complications, paravalvular leak, conduction disturbances eventually requiring permanent pacemaker implantation, stroke and even cardiac death [6]. Unfortunately, no pharmacological interventions have demonstrated promising results in halting the progression of AVS. In addition, aortic valve degeneration has been associated in patients under anticoagulation with vitamin-K antagonists (VKA) due to several mechanisms which we will further elaborate in this manuscript [7]. Nevertheless, the emergence of novel research connecting lipoprotein (a) [Lp(a)] to the pathogenesis of AVS has brought forth a range of promising novel therapeutic agents that may potentially alleviate the advancement of aortic valve calcification,

☆ All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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consequently preventing its progression into symptomatic AVS.

The primary objective of this comprehensive review is fourfold: a) to scrutinize the pathogenesis of calcific aortic valve stenosis in relation to Lp(a), b) to delineate the current recommendations of professional societies regarding the assessment of Lp(a) levels, c) to explore emerging pharmacotherapeutic strategies, exercise and nutritional interventions aiming at reducing Lp (a) levels and how these approaches could affect regression of aortic valve calcification and d) to discuss the unmet needs in AVS pharmacologic interventions as well as the challenges and future directions for further clinical trials and research on this concept.

2. Lipoprotein (a)

2.1. Biochemical structure & Genetics

Lipoprotein (a) is a highly proatherogenic, pro-inflammatory, and potentially thrombogenic constituent of lipid molecules which is largely genetically determined and minimally responsive to lifestyle or behavioral modifications. Lipoprotein (a) is a low-density lipoprotein (LDL)-like lipid fraction consisting of two subunits – a single apolipoprotein a [apo (a)] molecule, which is a lipid enriched fraction produced by the liver; and apolipoprotein B-100 (apo B-100), which has a LDL receptor and is also a constituent of very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and LDL [8]. Lipoprotein (a) contains apo(a) and apo(b) in 1:1 M ratio and covalently bound by a disulfide bridge (Central illustration). Lipoprotein (a) molecules consist of protein (30 %), cholesterol esters (35 %), phospholipids (20 %), free cholesterol (8 %), cholesterol (5 %), and triglycerides (2 %) [9]. The *LPA* gene is responsible for regulating Lp(a) synthesis with dominant inheritance in the liver, with minimal or no influence of dietary or environmental factors. The *LPA* gene is located at positions 26 and 27 on the long arm of chromosome 6 (6q26-27) and it mutates through replication and modification of the plasminogen gene. A study done by Perrot et al. demonstrated that genetic variation at the *LPA* locus associated with elevated Lp(a) level correlated with AVS independently of the presence of coronary artery disease (CAD) in patients undergoing cardiac surgery [10]. Apolipoprotein (a) is connected to a protein domain called "kringle" five or four domains (KV or KIV). Apolipoprotein (a) is composed of a single KV and serine protease-like domain and it contains 10 subtypes of KIV (KIV1-KIV10) due to different amino acid replacements with a predominance of the KIV2 subtype repeated in multiple copies. High concentrations of the smaller Lp(a) isoform with few copies of KIV2 are strongly associated with increased cardiovascular risk [11]. The assembly of the Lp(a) particle occurs in two steps: first, noncovalent docking of the KIV-5 to KIV-8 domains to the N-terminus of apoB-100; secondly, covalent bonding of apo(a) to apo(B) occurs through the formation of a disulfide bond between the only unpaired cysteine in apo(a) in KIV-9 with Cys4326 in apo(B) [12,13].

2.2. Lipoprotein (a) and familial hypercholesterolemia

Familial hypercholesterolemia (FH) poses a substantial public health burden, with a global prevalence of heterozygous FH estimated at approximately 1 in 300 individuals across most populations. The worldwide prevalence of hyperlipoproteinemia (a) (> 100–125 nmol/L) is estimated to be around 1.5 billion. Even in patients undergoing statin therapy, including those achieving LDL-C levels below 70 mg/dL, the residual risk of atherosclerotic cardiovascular disease (ASCVD) is, in part, attributed to elevated levels of Lp(a) [14]. Notably, Lp(a) levels reaching 180 mg/dL (389 nmol/L) have been identified as equivalent to the heightened risk of myocardial infarction observed in genetic FH cases [15–17]. The latest European Society of Cardiology (ESC) Guidelines on the management of the dyslipidemias suggest that Lp(a) should be measured at least once in a person's lifetime because patients with extremely high levels (>180 mg/dL) of Lp(a) carry equivalent risk factors for major cardiovascular diseases as patients with heterozygous familial hypercholesterolemia [18]. A study done by Raitakari et al. [19] demonstrated that in a multivariable model for pooled data from YFS (Cardiovascular Risk in Young Finns Study) and BHS (Bogalusa Heart Study), individuals exposed to high Lp(a) were twice at risk (95 % CI, 1.0–3.7) for developing adult ASCVD compared with non-exposed individuals. This review will expound upon and provide detailed insights into recommendations from diverse professional societies, offering a nuanced exploration of their respective perspectives.

2.3. Aortic valve and its atherosclerosis into calcific aortic valve stenosis pathogenesis

Lipoprotein (a) is considered to mediate vascular and systemic inflammation via endothelial activation, monocyte and macrophage stimulation, *trans*-endothelial migration, and lipid deposition [20]. The aortic valve is characterized by a trilaminar structure consisting of three leaflets. The outer layer, oriented towards the aorta, exhibits a "fibrous" composition comprising circumferentially oriented type I and III collagen fibers. Conversely, the outer layer facing the left ventricle is composed of radially oriented elastic fibers, allowing for expansion under pressure and stress, thereby enhancing compliance. Both outer layers are lined by endothelial cells, serving as the interface between blood and the valve. The inner layer, known as "spongiosa," predominantly consists of valve interstitial cells (VICs), which play a pivotal role in phenotypic switching to osteogenic cells. The reprogramming of VICs is implicated in the mineralization of the aortic valve and the progression to AVS [21–23]. The pathogenetic mechanism of AVS is intricately regulated by dyslipidemia, inflammation, and calcification (Fig. 1). Analogous to vascular cells, the aortic valve is layered with endothelium. Fibrosis and calcification processes alter the biomechanical properties of aortic valve leaflets. The preclinical manifestation of this condition is aortic sclerosis, affecting a quarter of individuals over 65 years and half of those over 85 years of age. Initial lesions involve focal calcifications and leaflet thickening without alterations in gradients and velocity however, this is the initial hallmark for AVS development.

2.4. Inflammation and lipid oxidation

The primary cascade leading to AVS emanates from endothelial damage or shear stress, resulting in lipid infiltration as demonstrated in a study conducted by Kanno et al. [24]. Their study demonstrated that nitric oxide (NO) prevents differentiation of vascular smooth muscle cells (VSMCs) into osteoblastic cells by inhibiting TGF-beta signaling through a cGMP-dependent pathway which prevents vascular calcification in aortic valves. The ensuing inflammatory process disrupts the endothelial nitric oxide synthase (eNOS) pathway, contributing to the progression of the disease. This process initiates lipid oxidation, leading to the transformation of Lp(a) into Oxidized Lp(a) (Ox-LP) and Low-Density Lipoprotein (LDL) into Oxidized LDL (OxLDL). Within the lipid-laden environment of the valve, enzymes such as Lipoprotein-associated phospholipase A2 (LpPLA2), carried by LDL, and autotaxin (ATX), transported by Lp(a), play critical roles [25–28]. These enzymes contribute to the production of lysophospholipid derivatives, which are bioactive lipid compounds. LpPLA2 transforms Ox-LP into lysophosphatidylcholine (LysoPC), initiating the apoptotic process in Valve Interstitial Cells (VICs)[29]. Additionally, LpPLA2 generates arachidonic acid (AA), fostering the formation of inflammatory molecules through the cyclooxygenase-2 (Cox2) and 5- lipoxygenase (5-LO) pathways [30]. These proinflammatory molecules, in turn, enhance mineralization by upregulating the expression of bone morphogenetic proteins 2 and 6 (BMP2 and BMP6). The LysoPC gets converted into lysophosphatidic acid (LysoPA) which stimulates complex intracellular signaling pathways through its G-coupled receptor. The administration of LysoPA increased aortic valve mineralization in vivo models. Hence, the correlation between autotaxin and LysoPA could explain the association between AVS and Lp(a)[31].

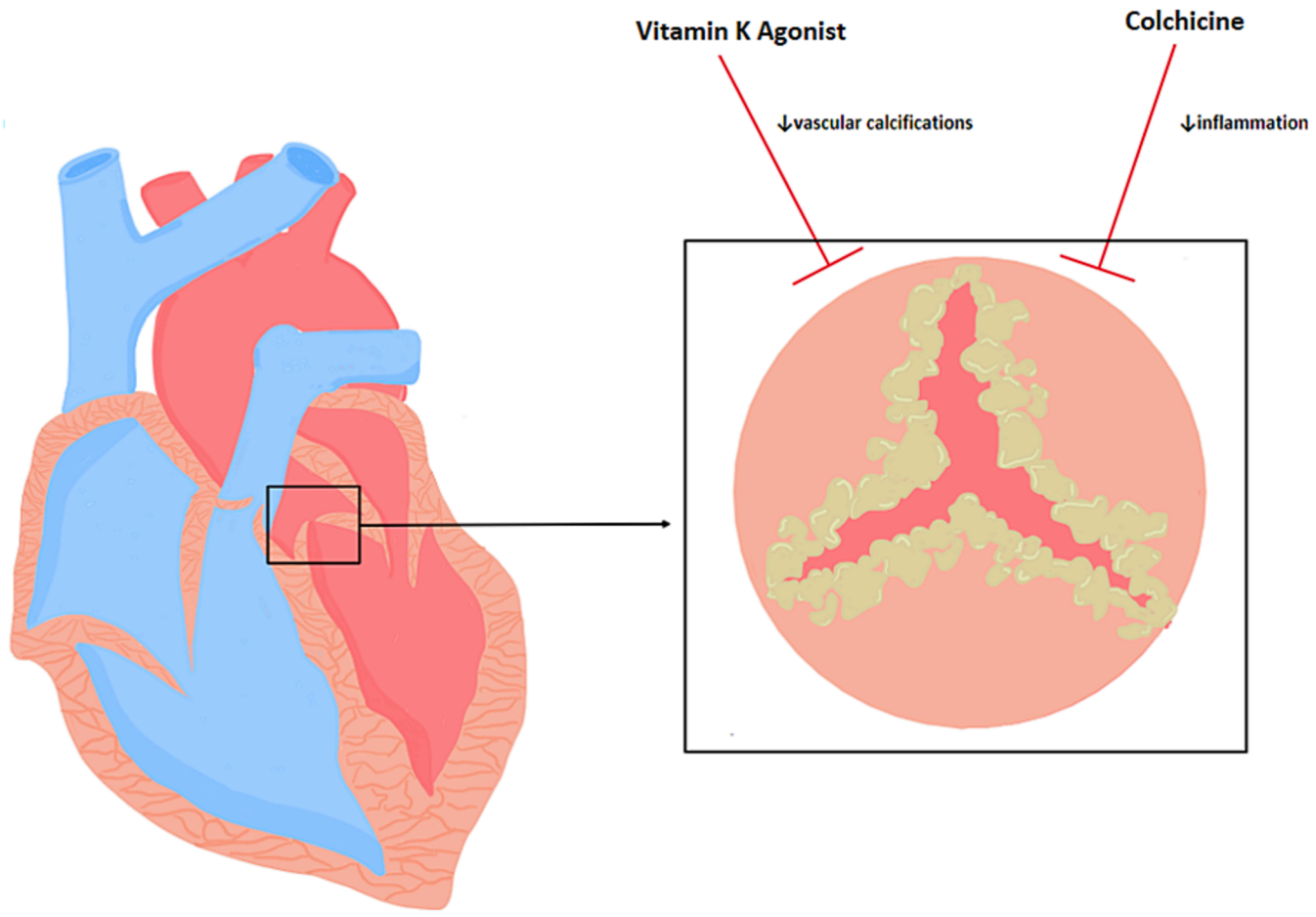

Fig. 1. Diseased aortic valve (stenotic) pre-Lp(a) reduction treatment. Cross-section of an open (diseased) aortic valve with inflammation and calcification before Lp (a) reduction treatment. Calcific valvular disease (CVD) is associated with increased Lp(a) and decreased KIV2 subunits in the Apo(a) domain. Both colchicine and Vitamin K antagonists could reduce progression of CVD.

In the clinical arena, ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial analysis demonstrated that both elevated levels of Lp(a) as well as oxidized phospholipids to apolipoprotein B ratio (OxPL/apoB) are independently associated with an augmented risk of AVS progression rate [32]. Consistently, additional investigations have underscored that heightened Lp(a) and OxPL/ApoB levels are independently associated with increased calcification of the aortic valve, progression of AVS, and an elevated incidence of aortic valve replacement and mortality [33–35]. In addition, the interplay between inflammation, Lp(a) and risk of aortic valve calcification was recently evaluated in a subgroup of patients from the MESA (Multi-Ethnic Study for Atherosclerosis) study. The authors included a total of 6,676 participants and evaluated at baseline levels of Lp(a), high-sensitivity C-reactive protein (hs-CRP) and aortic valve calcification (AVC) in patients with prior non-contrast cardiac computed tomography. Notably, higher Lp(a) levels were independently associated with AVC and patients with both higher Lp(a) and elevated hs-CRP $>$ 2 mg/dl had the greatest risk for incident AVC [36].

Collectively, Lp(a) and its associated OxPL, autotaxin (ATX), and lysophosphatidic acid (LysoPA) assume crucial roles in the pathogenesis of ASCVD and AVS. These findings provide a rationale for therapeutic strategies aimed at mitigating the risk associated with these chronic disorders.

The inflammatory infiltrate within the calcific aortic valve comprises macrophages, monocytes, mast cells, and T cells, collectively exerting a pivotal role in the remodeling of the valve leaflets [37–39]. It was noted that angiotensin-converting enzyme (ACE) exhibits heightened expression in calcific aortic valves [40]. ACE catalyzes the conversion of angiotensin I into angiotensin II which is a potent activation of nuclear factor-kappa B (NfKB). The activation of NfKB is implicated in the elevated levels of IL-6 and tumor necrosis factor-alpha (TNF-a) as well as increased collagen production in VICs [41,42].

Macrophages contribute to the secretion of vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), TNFα, and interleukin-1 (IL1). The heightened production of MMPs and reduced production of tissue inhibitors of metalloproteinases (TIMPs) lead to the accumulation of collagen, secreted by VICs, in the aortic valve, resulting in the formation of disorganized fibrous tissue. The secretion of VEGF and neo- angiogenesis play a role that is not fully understood but is believed to contribute to the recruitment of inflammatory and osteoprogenitor cells [43].

In a large longitudinal cohort of patients with CAD undergoing percutaneous coronary intervention (PCI), elevated Lp(a) levels were independently associated with increased long-term mortality [44]. The study suggests that effective LDL cholesterol control may mitigate the additional risk posed by elevated Lp(a) levels. However, the study carried some limitations, including limited generalizability to non-Caucasian ethnic groups as well as observational retrospective analysis without subgroup analysis according to lipid lowering strategies based on Lp(a) levels. Additionally, patients might have modified their lipid-

lowering therapy following PCI during the follow-up period which could influence clinical outcomes.

In addition, within a large cohort of patients > 70 years of age, Lp(a) was associated with clinical manifestations of CAD but not with AVS. The study suggested that in patients > 70 years old, the development of AVS is primarily an age-related process rather than linked to elevated Lp (a) levels. However, further studies are necessary to explore the relationship between Lp(a) and AVS in patients > 70 years old [45]. In contrast to this, a recent systematic review and *meta*-analysis by Arsenault et. al. [46] including a total of 757 patients from 5 longitudinal clinical studies conducted from March 2001 to March 2023 in Canada and the UK demonstrated that elevated levels of plasma Lp(a) concentrations were associated with accelerated rates of hemodynamic progression in AVS whose mean age was 65 years especially those in the higher Lp(a) tertile with 41 % of them showing faster progression of peak aortic jet velocity as well as 57 % faster progression of mean transvalvular gradient compared to patients in the lowest tertile.

It is important to consider that when present AVC is a stronger predictor of hemodynamic progression of AVS regardless of levels of LDL and Lp(a) according to a recent sub-analysis from the MESA study. The authors included a total of 6792 participants and notably, over a median follow-up of 16.7 years patients with AVC > 0 at baseline had the strongest association with severe AVS when Lp(a) was low (HR 33.8, 95 % CI 16.4–70) or high (HR 61.5, 95 % CI 7.7–494.2) with a cut-off of Lp (a) of 50 mg/dl and when LDL-C < 130 mg/dL HR of 31.1 (95 % CI, 14.4–67.1) or ≥ 130 mg/dL HR of 50.2 (95 % CI, 13.2–191.9) [47].

2.5. Calcific laden mineralization

Mineralization within the aortic valve is intricately associated with a conjoined process involving osteogenesis and apoptosis. The apoptosis process of valve interstitial cells (VICs) is triggered by reactive oxygen species, cytokines, and alterations in the purinergic signaling pathway such as ATP [48]. ATP plays a crucial role in preventing mineralization by binding it to the purine receptor P2Y2; and such an interaction between ATP and P2Y2 prevents apoptosis and enhances the production of carbonic anhydrase 12 (CA12). CA12 then acidifies the extracellular space which retards the deposition of amorphous calcium and phosphorous crystals [49]. Conversely, the osteogenesis process is activated through the ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase I), NT5E (ecto-5′– nucleotidase), and ALP (alkaline phosphatase) pathways. ENPP1 hydrolyzes ATP into AMP and pyrophosphate (PPi). ALP converts PPi into inorganic phosphate (Pi), where PPi inhibits mineralization, whereas Pi acts as a potent inducer. NT5E transforms AMP into adenosine and Pi, subsequently reducing ATP levels and elevating Pi levels, resulting in the formation of calcium and phosphorus-rich vessels. Consequently, apoptotic VIC bodies serve as deposition sites for amorphous calcium and phosphorous crystals [50]. A study designed by Yu et al. [51] investigated the effects of Lp(a) on aortic valve interstitial cells and identified apolipoproteins within diseased aortic valves. In this study, valve interstitial cells incubated with Lp(a) had remarkably higher calcium deposition and vesicle biogenesis when compared to the control group ($p < 0.001$).

Under normal conditions, the process of valve osteogenesis is prevented due to the expression of several anti-osteogenic genes (such as chordin and OPG) by the endothelium of the aortic valve. However, shearing stress and dysregulation of regulatory genes on the aortic side can lead to a switch in pathology, dependent on different hemodynamic conditions. Specifically, the ventricular side experiences unidirectional, pulsatile shear stress, while the aortic side encounters oscillatory shear stress, correlating with increased expression of inflammatory markers (VCAM-1, ICAM-1, TGFβ-1, and BMP-4) and miRNAs. This may be attributed to distinct gene expression patterns, lower expression of negative regulators, higher expression of miRNAs, and mRNAs capable of inducing disease progression [52,53]. Various miRNAs have been implicated in AVS development, with protective molecules such as miR-141 blocking the BMP2 pathway, while miR-34a, miR-486, miR-137, and miR-155 promote osteogenesis and mineralization. Inhibition of these miRNAs holds promise as a future therapeutic strategy [54].

In summary, recent studies have elucidated that the pathogenetic process is intricately linked to lipid infiltration, inflammation and osteogenetic response. Endothelial damage serves as the initiating event, triggering lipid infiltration into the valve and generating bioactive lipid species that attract inflammatory mediators. Dysregulation of various signal transduction pathways induces a phenotypic switch in VICs to an osteo-genetic phenotype, thereby fostering fibrocalcific remodeling of aortic valve leaflets.

2.6. Measurement Assays and professional Societies' Screening recommendations for Lipoprotein (a)

Lipoprotein (a), when expressed in mass units (mg/dl), encapsulates the mass of the entire particle, constituting apo(a), apoB-100, cholesterol, cholesteryl esters, phospholipids, and triglycerides. The inherent heterogeneity in apo(a) size, coupled with the prevalence of two distinct, genetically determined apo(a) isoform sizes in most individuals, renders standardization using a single calibrant material unfeasible (Table 1).

The presence of variable numbers of repeated KIV2 units in Lp(a) serves as multiple epitopes in immunoassays. The challenge arises when calibrants do not mirror the same range of isoforms as the test samples; this discrepancy leads to overestimation of serum levels in individuals with higher numbers of KIV2 repeats and underestimation in those with fewer repeats. Given that smaller isoforms exhibit a robust association with higher serum concentrations, the underestimation of Lp(a) is more pronounced at higher concentrations than at lower ones. Therefore, values for Lp(a) should be expressed in nmol/L and measured using isoform insensitive methods employing appropriate antibodies with calibrators traceable to WHO/IFCC reference material [55]. The assay relying on antibodies binding to KIV9 (ELISA), the unique non-repeating Kringle IV subtype, is acknowledged as the gold standard and is preferable for evaluating Lp(a) [9]. Recently, a method based on mass spectrometry has been validated to standardize Lp(a) measurement. This approach circumvents issues related to size polymorphisms by quantifying specific peptides not present in the KIV2 region [56]. Lipoprotein (a) exhibits an asymmetric distribution among different racial groups, emphasizing the necessity to establish appropriate cutoff values tailored to specific populations [57].

2.7. Emerging therapeutics for reducing Lipoprotein (a) and atherosclerotic burden

Despite the absence of an approved therapy specifically for calcific aortic valve stenosis (CAVS), noteworthy progress has been made in exploring therapeutic interventions aim at reducing Lp(a) levels. Presently available treatments primarily target dyslipidemia, addressing inflammation and calcification mechanisms, with the consequential reduction of Lp(a) levels. Various pharmacological strategies have been investigated to lower circulating levels of Lp(a) and counteract procalcifying substances and inflammation, factors potentially contributing to aortic valve calcification.

2.8. Current FDA approved lipid lowering agents' effects on Lipoprotein (a)

Several FDA-approved lipid-lowering therapies currently demonstrate significant effects on Lp(a). Statin usage, for instance, has been associated with an increase in Lp(a) levels ranging from 8 % to 24 % [58]. Conversely, niacin use exhibits a reduction in Lp(a) levels by 20 % to 30 %, though clinical benefits have not been consistently demonstrated [59].

Notably, PCSK9 inhibitors have proven effective in reducing Lp(a)

Table 1
Professional Societies' Recommendations on Lipoprotein (a) Screening.

Professional Society	Year	Current Screening Guidelines	Lp(a) Risk Threshold
European Society of Cardiology/ European Atherosclerosis Society [77]	2022	• Lp(a) should be measured at least once in adults to identify individuals at high cardiovascular risk • Screening is also advisable for young individuals with a history of ischemic stroke or a family history of premature ASCVD, especially if high Lp (a) is present without other identifiable risk factors • Cascade testing for high Lp(a) is recommended in specific scenarios, including familial hypercholesterolemia (FH), a family history of (very) high Lp(a), and a personal or family history of ASCVD	*Normal:* <30 mg/dL (or < 75 nmol/ L) *Intermediate:* 30–50 mg/dL (or 50–125 nmol/L) *Abnormal:* >50 mg/dL (or > 125 nmol/L)
Canadian Cardiovascular Society [78]	2021	• Lp(a) measurement once in a person's lifetime as a part of the initial lipid screening	≥50 mg/dL (or ≥ 100 nmol/L)
HEART UK Consensus Statement [55]	2019	• Calcific aortic valve stenosis Familial hypercholesterolemia or other genetic forms of dyslipidemiaFirst degree relatives with elevated serum Lp(a) levels (>200 nmol/L)Personal or family history of premature ASCVD (<60 years of age)A borderline increased (but < 15 %) 10-year risk of a cardiovascular event (reclassification)	
National Lipid Association [79]	2019	• Lp(a) measurement in patients with premature ASCVD, LDL-C level ≥ 190 mg/dL, men < 55 years of age, and women < 65 years of age • Recurrent or progressive ASCVD despite optimal lipid-lowering therapy • Lp(a) measurement if less-than-expected LDL-C lowering response, despite good adherence • Calcific aortic valve stenosis • Family history of elevated Lp (a) levels	>50 mg/dL (or > 100 nmol/L)
American College of Cardiology/ American Heart Association [80]	2018	• Lp(a) measurement in patients with family history of premature CVD • Lp(a) measurement is useful in adults 40–75 years old with no diabetes mellitus and with 10-year ASCVD risk of > 5–19.9 % • Lp(a) > 50 mg/dL or 125 nmol/L is regarded as a "risk enhancing" factor	≥50 mg/dL (or ≥ 125 nmol/L)

levels by 14 % to 35 %, with observed cardiovascular benefits for patients with elevated Lp(a) [60].

Lipoprotein apheresis, employing extracorporeal binding of Lp(a) and LDL via a filtration system, achieves a remarkable 64 % reduction in Lp(a) levels. Ongoing phase 3 clinical trials are assessing the outcomes of lipoprotein apheresis in individuals with elevated Lp(a) [61]. A post-hoc analysis of the FOURIER trial indicates that PCSK9 inhibitors not only reduce Lp(a) levels but also correlate with a decreased incidence of new diagnoses of aortic stenosis and valve replacement surgery [62,63].

Additional insight from a study by Langsted et al. [64] suggests that individuals with PCSK9 R46L mutation leading to a loss of PCSK9 function experience a reduced risk of ischemic cardiovascular disease as well as progression to AVS. While the established effects of these drugs on Lp(a) are evident, their direct impact on the progression of AVS is yet to be conclusively determined. Nevertheless, mounting evidence strongly links elevated Lp(a) levels with the advancement of aortic valve calcifications.

2.9. Current non-lipid lowering agents' potential effects on aortic stenosis

Numerous non-lipid lowering agents have been theorized as potential interventions to impede the progression or advancement of AVS. The following tabular representation aims to provide a succinct overview of the diverse non-lipid lowering agents under consideration, shedding light on their potential roles in mitigating the progression of aortic stenosis (Table 2).

In contrast to Vitamin K antagonists, the study done by Schultz et al. [65] has illuminated a noteworthy association, showcasing that a substantial dietary intake of vitamin K1–enriched foods is associated to a decreased occurrence of AVS and its ensuing complications.

The study posits a compelling hypothesis: an augmented consumption of vitamin K1–rich foods, particularly those abundant in green leafy vegetables, could potentially contribute to the mitigation of CAVS.

3. Novel potential therapeutics for reducing Lipoprotein (a) and halting calcific aortic valve Stenosis

Antisense oligonucleotides (ASOs) such as Pelacarsen (Fig. 2A), and small-interfering RNA (siRNA) therapies including Olpasiran, SLN360, and LY3819469 (Fig. 2B) have been crafted to meticulously target the expression of *LPA* mRNA. These innovative therapeutic interventions signify a targeted approach aimed at modulating Lp(a) expression, presenting promising avenues in the pursuit of precise and effective control over Lp(a) levels.

3.1. Antisense oligonucleotide therapy (ASOs)

3.1.1. Pelacarsen

ASOs, comprising 16 to 20 nucleic acid-long complementary DNA fragments to *LPA* mRNA, represent a refined therapeutic approach. These ASOs are strategically conjugated with N-acetylgalactosamine (GalNAc), with the GalNAc moiety binding to asialoglycoprotein, triggering the degradation of apo(a) mRNA. Administered via subcutaneous injection, ASOs traverse into hepatocytes, where ribonuclease H1 cleaves the ASO-mRNA complex, resulting in reduced *LPA* mRNA. This, in turn, decreases Lp(a) levels, as the availability of apo(a) to bind apo B-100 diminishes [66].

Beyond its impact on Lp(a) levels, ASOs have been demonstrated to influence oxidized phospholipids (OxPL-apo(a) and OxPL-apoB) by reducing their lipoprotein transporter, Lp(a) [67]. The resilient nature of the antisense strand confers extended half-lives of approximately 3–4 weeks. Pelacarsen, a second-generation ASO, showcased significant efficacy in reducing Lp(a) levels by 35–80 % in a dose-dependent manner, with maximum effects observed at 14 weeks of treatment. Notably, the study revealed that 98 % of patients receiving a monthly subcutaneous injection of 80 mg Pelacarsen achieved Lp(a) levels below 50 mg/dL, a target threshold endorsed by numerous professional societies [18]. Pelacarsen is currently undergoing evaluation in the Lp(a) HORIZON Phase III clinical trial (NCT04023552) enrolling 7680 patients with elevated Lp(a) levels (>70 mg/dL) sponsored by Novartis Pharmaceuticals. This trial assesses the impact of 80 mg Pelacarsen subcutaneous injections on cardiovascular events associated with high Lp(a) levels, with an expected completion date of May 30, 2025. These advancements underscore the potential of Pelacarsen as a pivotal therapeutic agent in

Table 2
Effects of non-lipid lowering agents on aortic valve calcification.

Drug	Mechanism of Action	Effects on Aortic Valve Calcification	Clinical Benefits	Study
Bisphosphonates	Bind to and inhibit the activity of farnesyl pyrophosphate synthase, a key regulatory enzyme in the mevalonic acid pathway critical to the production of cholesterol, other sterols, and isoprenoid lipids	Reduction in valvular calcification in women age > 65 years but increased prevalence of valvular calcification in younger women.	Inhibit secretion of pro-inflammatory cytokines, IL-1b, IL-6, TNF-a, MMP and reduce valve injury by monocytes. Inhibit bone resorption and calcium-phosphate mineral complexes on valvular tissue.	MESA by Elmariah et al. (2010) [81]
Warfarin	Competitively inhibits the vitamin K epoxide reductase complex 1 (VKORC1)	Association with aortic stenosis is due to the inhibition of vitamin K dependent protein Gla (MGP). MGP inhibits valve calcification by blocking BMP2 pathway, which downregulates calcification of aortic valve.	Patients treated with vitamin K antagonists have documented an increase in valve calcium. In contrast, supplementation with vitamin K halted advancement of valve calcification [82,83].	Koos et al. (2005) [84]

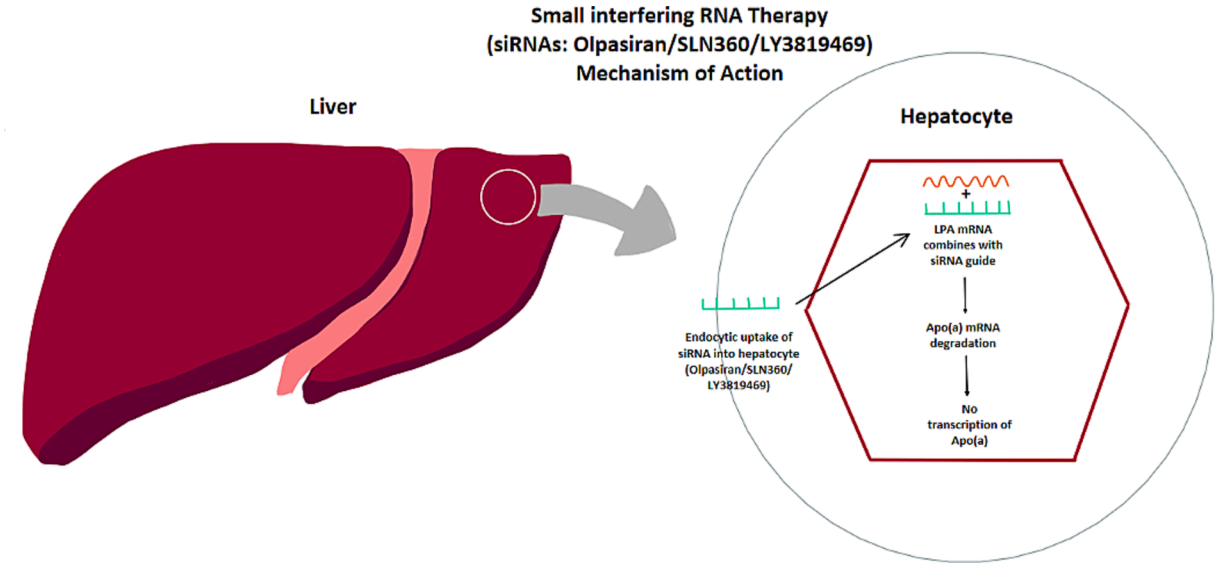

Fig. 2A. Pelacarsen is a GalNAc-conjugated antisense oligonucleotide (ASO) that targets apolipoprotein(a) [apo(a)] mRNA to reduce lipoprotein(a) [Lp(a)] levels. The GalNAc (N-acetylgalactosamine) ligand facilitates targeted delivery to hepatocytes by binding to the asialoglycoprotein receptor (ASGPR) on the liver cells, enhancing cellular uptake. Once internalized, pelacarsen binds to the complementary sequence of apo(a) mRNA, inducing degradation through the RNase H-mediated pathway. This cleavage of apo(a) mRNA prevents its translation, reducing the synthesis of apo(a) protein.

managing elevated Lp(a) levels, holding promise for cardiovascular health.

3.2. Small interfering RNA therapy (siRNAs)

3.2.1. Olpasiran

Olpasiran, a GalNac-conjugated small-interfering RNA (siRNA), exhibits a sophisticated mechanism upon entering hepatocytes, where it undergoes dissociation. One antisense strand engages the RNA-induced silencing complex (RISC), leading to the cleavage of target mRNA, while the other antisense strand binds to the target mRNA sequence, facilitating its degradation. Encouraging results from preclinical trials involving transgenic mice and cynomolgus monkeys paved the way for the Olpasiran Cardiovascular Events And lipoprotein(a) reduction-DOSE finding (OCEAN(a)-DOSE) trial [68] sponsored by Amgen. This Phase II multicenter study, characterized by its randomized, double-blind, and placebo-controlled design, enrolled 281 patients with elevated Lp(a) levels (>150 nmol/L). Subjects were randomly assigned to receive subcutaneous injections of Olpasiran or a matching placebo. The primary endpoint, a percent change in Lp(a) levels from baseline to week 36, revealed a noteworthy dose-dependent reduction (70.5 to 100.5 %) at the conclusion of the 36-week period. Notably, the reported adverse events were limited to injection site erythema and pain. The outcomes of Olpasiran in modulating Lp(a) levels prompted the initiation of a Phase III trial (NCT05581303). This ongoing investigation evaluates the effects of Olpasiran subcutaneous injections administered every 12 weeks in participants with ASCVD and Lp(a) levels ≥ 200 nmol/L. The anticipated completion of this trial is on December 2026. These findings collectively underscore Olpasiran's potential as a targeted therapeutic agent for mitigating elevated Lp(a) levels in the context of cardiovascular health.

3.2.2. SLN360

SLN360, a 19-mer GalNac-conjugated siRNA, offers a targeted approach by degrading apo(a) mRNA. In the initial phase of the APOLLO trial, sponsored by Silence Therapeutics pnc, a Phase I study, the safety and efficacy of SLN360 were scrutinized following a single dose administered to 32 participants with elevated Lp(a) levels (≥150 nmol/L). The primary endpoint of this trial focused on the plasma concentration of Lp(a) levels at the conclusion of the 21-week period.

Results from the APOLLO trial exhibited favorable outcomes, with SLN360 proving well- tolerated among participants. Notably, a dose-dependent reduction in Lp(a) levels was observed, reaching a maximum reduction of 98 % in the 600 mg SLN360 groups [69]. Building upon these encouraging findings, a Phase II clinical trial is underway (NCT05537571) which finished its enrolling phase (180 patients) by July 2024. This subsequent trial aims to delve deeper into the effects of SLN360 in patients with elevated Lp(a) levels at high risk of atherosclerotic CV events. The evolving research surrounding SLN360 positions it as a promising therapeutic candidate for addressing elevated

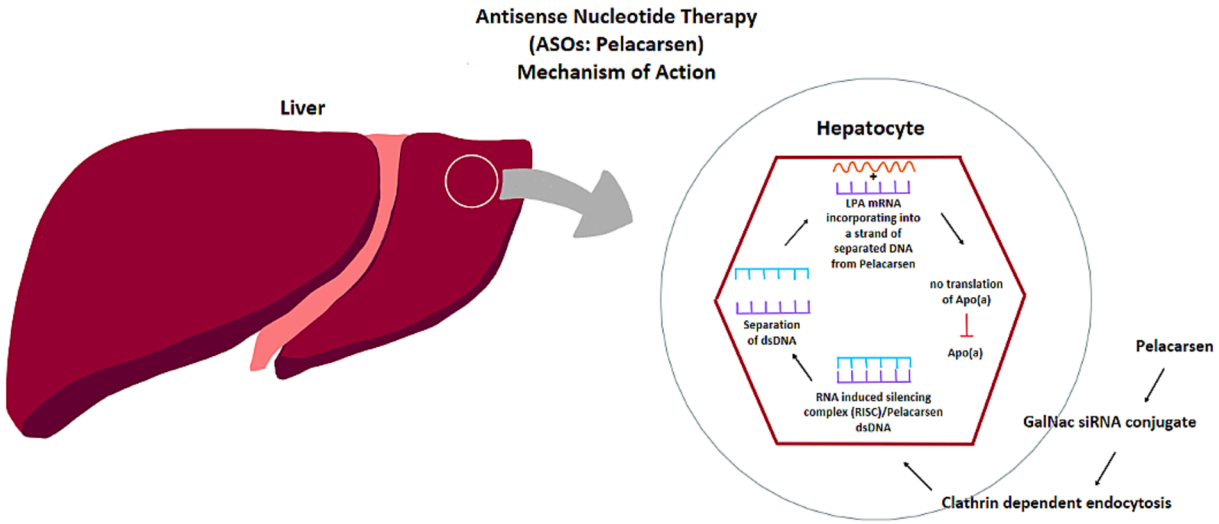

Fig. 2B. Mechanism of Action of siRNAs (Olpasiran, SLN360, LY3819469): These small interfering RNA (siRNA) therapeutics are designed to selectively reduce apolipoprotein(a) [apo(a)] synthesis, leading to a decrease in circulating lipoprotein(a) [Lp(a)] levels. Each siRNA (Olpasiran, SLN360, LY3819469) is conjugated with N-acetylgalactosamine (GalNAc), which binds to the asialoglycoprotein receptor (ASGPR) on hepatocytes, ensuring efficient and targeted delivery to the liver. Upon internalization into the hepatocytes, the siRNAs incorporate into the RNA-induced silencing complex (RISC). The activated RISC guides the siRNA to bind complementary apo(a) mRNA, leading to sequence-specific cleavage and degradation of the mRNA. This degradation prevents translation and synthesis of the apo(a) protein, ultimately reducing Lp(a) assembly, which consists of an LDL particle linked to apo(a).

Lp(a) levels.

3.2.3. LY3819469

LY3819469, the latest GalNac-conjugated siRNA therapeutic candidate crafted for lowering Lp(a), has emerged as a subject of keen interest. In its Phase I trial, meticulously designed to evaluate efficacy, 66 participants with elevated Lp(a) levels and CVD risk were enrolled [70]. While the specific outcomes of this trial are currently pending, the preliminary findings have demonstrated sufficient promise to warrant the registration of LY3819469 for a Phase II clinical trial. This progressive development underscores the commitment to advancing our understanding of LY3819469′s potential impact on reducing elevated Lp (a) levels and its implications for cardiovascular health.

3.3. CRISPR-Cas9

The Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR-associated 9 (CRISPR/Cas9) system stands as a remarkably powerful tool for precise double-stranded DNA breaks, offering unparalleled capabilities in targeted genome editing. Its potential for suppressing pro-atherogenic genes, notably *LPA*, has garnered significant attention.

Employing Adeno Associated Virus (AAV) vector delivery, successful silencing of the *LPA* gene in the hepatocytes of mice was achieved, resulting in the complete elimination of apo(a) from circulation within a remarkably short timeframe of one week [71].This breakthrough instills optimism for the in vivo targeting of the *LPA* gene.

The prospect of CRISPR-Cas9 to permanently eradicate Lp(a) in individuals with elevated residual CVD risk serves as a beacon of hope. However, the application of this exceptional tool in human contexts requires comprehensive investigations into safety and efficacy, leaving crucial aspects yet to be fully elucidated. The transformative potential of CRISPR/Cas9 in mitigating atherogenic risks underscores the need for meticulous exploration before its translation into practical clinical applications.

3.4. Immuno-modulatory drugs

Colchicine, acting as a β-tubulin inhibitor, exerts its anti-inflammatory effects by impeding neutrophil migration and degranulation. Notably, numerous studies have revealed a shared pathogenesis between aortic stenosis and coronary atherosclerosis. Building on the demonstrated efficacy of colchicine in attenuating inflammation in CAD [72], it is postulated that this anti-inflammatory agent may similarly prove effective in impeding the progression of CAVS.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) has provided encouraging findings [73], indicating reduced rates of MACE in individuals treated with colchicine compared to those in the placebo group. However, acknowledging the pleiotropic nature of colchicine, as underscored by Ciofani's study, it becomes apparent that the complete understanding of its role may elude current comprehension. Consequently, additional studies are imperative to delve deeper into the potential impact of anti-inflammatory agents, such as colchicine, in halting the progression of CAVS [74].

3.5. Role of exercise on aortic valve stenosis

While the impact of exercise training on aortic valve disease in humans remains to be fully elucidated, a study conducted by Matsumoto sheds light on the potential benefits observed in LDL receptor deficient mice [75]. The investigation explored the role of exercise training in halting the progression of degenerative aortic valve disease by addressing atherosclerosis, oxidative stress, and enhancing the bioavailability of nitric oxide.

The results revealed that the group undergoing regular exercise training exhibited noteworthy reductions in serum myeloperoxidase, accumulation of macrophages, oxidized LDL, and mineralization, in comparison to the cholesterol diet group that did not engage in exercise. The study's conclusion underscored the preventive effects of regular exercise training on aortic valve sclerosis, attributed to mechanisms such as the preservation of endothelial integrity, diminished inflammation, and inhibition of the osteogenic pathway in LDL receptor deficient mice.

These findings prompt the need for further investigations to discern the potential impact of exercise training on the progression of degenerative aortic valve disease in human subjects, contributing to a more comprehensive understanding of the role of physical activity in cardiovascular health.

3.6. Role of diet

Several studies have delved into the potential impact of nutrition on aortic stenosis. A study conducted by Janzi et al. sought to ascertain any association between dietary fiber intake and the incidence of aortic stenosis. The findings from this investigation revealed that there is no significant correlation between the intake of fiber, fruits, and vegetables, and the risk of developing aortic stenosis. However, a notable trend was observed, suggesting a potential link between the lowest intake of whole grains and a heightened risk of aortic stenosis, albeit not reaching statistical significance [76]. It is worth noting that this insight was derived from a specific study and further exploration is warranted. Prospective studies, encompassing diverse countries and exploring various ethnic food groups, should be meticulously designed to comprehensively investigate the potential nutritional role in the development of aortic stenosis. Such endeavors would contribute to a more nuanced understanding of the interplay between nutrition and the incidence of this cardiovascular condition.

4. Conclusion

In conclusion, the review of LPA and AVS progression underscores the complex interplay between genetics, hemodynamics, and inflammation in the pathogenesis of this condition. While significant advancements have been made in understanding the mechanisms driving disease progression, challenges remain in predicting individual patient outcomes and optimizing therapeutic strategies. Future research efforts focused on personalized medicine, incorporating multi-omics data, advanced imaging modalities, and innovative therapies, hold promise in improving outcomes and quality of life for patients with AVS. Ultimately, a comprehensive and multidisciplinary approach will be crucial in addressing the evolving landscape of aortic valve disease management.

CRediT authorship contribution statement

Mohammad Ishrak Khan: Writing – original draft, Project administration, Investigation, Conceptualization. **Raisa Subaita Zahir:** Writing – original draft, Methodology, Conceptualization. **Abel Casso Dominguez:** Writing – original draft, Supervision. **Francisco José Romeo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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