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The Current Landscape of Lipoprotein(a) in Calcific Aortic Valvular Disease

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Abstract

Purpose of review——Calcific aortic stenosis (CAVS) is the most common form of valvular heart disease in developed countries, increasing in prevalence with the aging population. Surgical or transcatheter aortic valve replacement is the only treatment available for CAVS. However, these interventions are typically reserved for severe symptomatic AS. The purpose of this review is to summarize the recent literature in uncovering the underlying pathophysiology of CAVS in the setting of lipoprotein (a) [Lp(a)} and emerging therapies targeting Lp(a) which may help halt disease progression in CAVS.

Recent findings——Pathophysiologic, epidemiological, and genetic studies over the past two decades have provided strong evidence that Lp(a) is an important mediator of calcific aortic valvular disease (CAVD). Studies suggest that Lp(a) is a key carrier of pro-calcifying oxidized phospholipids (OxPL). The metabolism of OxPL results in a pro-inflammatory state and subsequent valvular thickening and mineralization through pro-osteogenic signaling. The identification of Lp(a) as a causal mediator of CAVD has allowed for opportunities for emerging therapeutic agents which may slow the progression of CAVD (Figure 1).

Summary——This review summarizes the current knowledge on the association of Lp(a) with CAVD and ongoing studies of potential Lp(a)-lowering therapies. Based on the rate-limiting and causal role of Lp(a) in progression of CAVS, these therapies may represent novel pharmacotherapies in AS and inform the developing role of Lp(a) in the clinical management of CAVD.

Keywords

Calcific aortic valvular disease; Calcific aortic stenosis; Elevated lipoprotein(a)

Introduction

Calcific aortic valve disease (CAVD), including calcific aortic valve stenosis (CAVS), is the most prevalent form of valvular heart disease in the Western World and is the leading cause

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of valve-related mortality in the United States[1,2]. CAVS affects nearly 3% of the population greater than 65 years of age with projections that the prevalence of CAVS is expected to triple in the next 40 years. CAVD is marked by thickening of the aortic valve leaflets with resultant progressive stenosis of the aortic valve. CAVD is an insidious disorder as the early stages of CAVD are predominantly asymptomatic. However, the eventual development of restricted aortic valve leaflet mobility ultimately leads to significant left ventricular outflow obstruction and subsequent symptoms of angina, heart failure, and syncope. Among those individuals who develop severe CAVS, the 2-year survival rate without surgical intervention approaches 50%[3]. At present, surgical or transcatheter aortic valve replacement (AVR) is the only treatment available for severe symptomatic CAVS. The number of individuals requiring surgical or transcatheter aortic valve replacement (AVR) is expected to double by 2050[4,5]. Given the high cost and significant periprocedural and long-term morbidity and mortality associated with these procedures, there is a need for a better understanding of the pathogenesis of CAVD and for the development of effective pharmacologic therapies.

Pathogenesis of CAVS

Because its incidence increases with age, CAVD was traditionally considered a passive and degenerative disease caused by continuous wear and tear of the aortic valve leaflets. However, it is now well established that that CAVD is actually a multifactorial phenomenon characterized by active inflammation followed by highly regulated fibro-calcific remodeling of the valve[6,7].

The pathogenesis of CAVD can be divided into two distinct phases: an early initiation phase marked by valvular endothelial injury, lipid deposition, and inflammation, and a later propagation phase driven by pro-calcific and pro-osteogenic factors[8]. The initiation phase is similar to the development of atherosclerosis, with both conditions sharing similar key risk factors of age, male sex, dyslipidemia, metabolic syndrome, hypertension, metabolic syndrome, diabetes mellitus[9]. This early stage is triggered by endothelial injury to the outer layer of valve endothelial cells (VECs) due to mechanical shear stress. Impaired integrity and activation of VECs ensues and allows for the infiltration of the same lipids implicated in atherosclerosis, in particular low density protein [LDL] and lipoprotein(a) [Lp(a)][10–12]. Progressive endothelial injury and oxidation of these lipids stimulate an inflammatory response driven by macrophages, mast cells, and T cells which release pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α.

This inflammatory milieu induces the normally quiescent valvular interstitial cells (VICs) to undergo osteogenic differentiation during the propagation phase of CAVD. These activated VICs gain a myofibroblast-like phenotype and lay down a disorganized collagen matrix and release other bone-related proteins, such as bone morphogenetic protein 2 (BMP2) and Runt-related transcription factor 2 (RUNX2). These osteogenic markers lead to release of calcium- and phosphate-rich extracellular vesicles which aggregate and provide a disorganized scaffold upon which progressive dystrophic calcification of the aortic valve can develop[13,14]. Apoptosis of VICs also results in microcalcifications at sites of endothelial injury and lipid deposition[15,16]. Cell death and release of apoptotic bodies facilitates the formation of hydroxyapatite crystals which form nucleation sites for further

calcium deposition. Hydroxyapatite deposition prompts further pro-inflammatory responses from macrophages, creating a positive feedback loop of calcification and inflammation[13]. The fibrotic remodeling, dystrophic calcification, and biomineralization of the valvular extracellular matrix during this propagation phase ultimately results in progressive fibrosis, thickening, and dysfunction of the aortic valve leaflets. Therefore, the self-perpetuating cycle of calcification and valvular injury is an important driver of disease progression in CAVD.

Lp(a) is a risk factor for CAVS

The pathogenesis of CAVS demonstrates an important link between lipid deposition, inflammation, and calcification. An improved understanding of the biology of CAVS has highlighted potential therapeutic targets to slow the progression of CAVD and possibly avoid or delay the need for valve replacement. In particular, the emergence of epidemiological and genetic studies over the past two decades has identified elevated plasma Lp(a) levels as an important mediator of CAVS and a predictor for faster CAVS disease progression.

Lp(a) is a low-density-like-lipoprotein-like particle which is covalently bound to an apolipoprotein(a) [apo(a)] tail, encoded by the LPA gene. Apo(a) is comprised of 10 unique subtypes of kringle 4 (KIV) domains, followed by a kringle 5-like (KV) domains, and an inactive protease domain. Of these KIV subtypes, only KIV_2 is present at different copy numbers ranging from 1 to more than 40 on each allele. Only one copy of KIV1 and $KIV_{3–10}$ are present, but the number of KIV_2 repeats determines the apo(a) isoform size as well as the variability in plasma Lp(a) concentration between individuals[21]. In general, there is an inverse relationship between the number of KIV_2 copies in apo(a) and plasma Lp(a) concentrations.

Elevated Lp(a) is highly prevalent, affecting at least 20% of the global population with likely an even higher incidence among individuals with atherosclerosis and CAVD[17]. A strong association between Lp(a) and CAVS was first described in 1995 by Gotoh et al. Amongst 748 men and women in a rural Japan, the prevalence of aortic valvular sclerosis on echocardiography was nearly threefold higher among individuals with Lp(a) levels greater than 30 mg/L compared with individuals who had lower Lp(a) levels, independent of other risk factors[18].

Lp(a) levels have high heritability with an autosomal co-dominant pattern[22]. The study of Lp(a) genetics has been instrumental in establishing potential causality for Lp(a) in calcific AS. In 2013, the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium) Consortium group published a landmark genome-wide association study which showed that the rs10455872 LPA single-nucleotide polymorphism is associated with CAVD. In addition, LPA genotype is also associated with increased incidence of aortic valve calcification and need for aortic valve replacement across multiple diverse cohorts and racial/ethnic groups[19]. No similar genome-wide associations have been noted in mitral valve calcification, highlighting the distinct specificity of this association with aortic valvular disease. Multiple studies, including the Copenhagen City Heart Study and the Copenhagen General Population Study, have corroborated these key findings,

showing that LPA genotypes predicted elevated Lp(a) levels, and that elevated Lp(a) levels >90 mg/dL was associated with a 3-fold increased risk of AS[20]. These genetic studies have complemented prior observational studies in providing strong evidence of Lp(a) as a genetically determined and likely important causal risk factor for calcific AS.

Lp(a) mediates calcification in CAVS

At present, molecular studies have shown that Lp(a), not LDL, is the preferential lipoprotein carrier of oxidized phospholipids (OxPL). Lp(a) can infiltrate denuded valvular endothelium, accumulate in the valve, and subsequently deliver its cargo of OxPL[24]. OxPL transported by Lp(a) acts as a substrate for lipoprotein-associated phospholipase A2 (PLA-2), secreted largely by macrophages, to generate lysophophatidylcholine (LPC). LPC is a highly reactive metabolite with pro-osteogenic properties present in mineralized aortic valves. Autotaxin (ATX), a lysophopholipase D enzyme transported into the valvular endothelium by Lp(a), uses LPC as a substrate for the generation of lysophosphatidic acid (LPA) which has been shown to promote the microcalcification of the aortic valve through activation of NF-kB[21]. This induces the upregulation of genes involved in osteogenic differentiation including IL-6, BMP2, and RUNX2[22]. ATX transported by Lp(a) can additionally induce ATX expression by VICs in a feed forward cycle. More recent research has additionally demonstrated that the protein apolipoprotein C-III (apoC-III) binds to Lp(a) to form ApoCIII-Lp(a) complexes which associate with progression of calcific aortic valve stenosis and are found in proximity to calcified regions of stenotic aortic valves[23–25].

There are also ongoing animal studies to help further understand the mechanistic role of Lp(a) in CAVS. In an atherogenic mouse model ($Ldlr^{-/-}$E06-scFv) that expressed a natural E06-derived antibody which binds to OxPL and thereby inhibits its pro-inflammatory properties, echocardiographic evaluation showed significant attenuation of transaortic mean gradients and histology showed decreased calcium content of the aortic valve when compared to $Ldlr^{-/-}$ mice[26]. In a transgenic mouse model of CAVD ($Ldlr^{-/-}$/$Apob^{100/100}$) fed a diet high in lysophosphatidic acid (the enzymatic product of ATX), findings demonstrated overexpression of ATX and lysophosphatidic acid-mediated promotion and acceleration of CAVS[23]. Though a Lp(a) mouse model does not yet exist, these current animal studies provide evidence for the central role of Lp(a)-associated OxPL and ATX in the progression of CAVD.

The findings from these in vitro and animal studies have been borne out in clinical investigations as well. In recent years, ^{18}F-sodium fluoride (NaF) uptake on positron emission tomography computed tomography (PET/CT) has emerged as an important measure of micro-calcification predictive of CAVS progression. Studies have shown that individuals with elevated Lp(a) > 75 nmol/L or > 35 mg/dL develop increased aortic valve micro-calcifications on ^{18}F-NaF PET/CT imaging; these micro-calcifications are predictive of developing CAVD, manifesting before the development of clinically significant CAVS[28,29]. Compared with persons with Lp(a) < 35 mg/dL, those with elevated Lp(a) > 35 mg/dL additionally experienced increased progression on serial valvular computed tomography calcium score and faster hemodynamic progression on serial echocardiography based on peak transaortic velocity when compared with persons with Lp(a) levels < 35

mg/dL. Moreover, individuals with elevated OxPL-apoB levels, the predominant contributor to OxPL content of Lp(a) and reflective of the biological activity of Lp(a), also had increased valvular ^{18}F-NaF uptake[29]. In a secondary analysis of the ASTRONOMER study, patients with preexisting mild to moderate CAVS with elevated Lp(a) levels in the top tertile exhibited faster disease progression of CAVD with a linear relationship between Lp(a) levels and the annual rate of peak transaortic velocity[29]. More importantly, elevated Lp(a) levels were associated with increased risk for aortic valve replacement or cardiovascular death in the ASTRONOMER, SALTIRE, Ring of Fire, and SAFEHEART studies[29,31,32]. Overall, these basic, translational and clinical studies support the important roles that Lp(a) and its associated OxPL play in the development of CAVS.

Emerging Lp(a) lowering therapies

The current data present important clinical implications regarding the monitoring and management of patients with CAVD. First, for patients with severe asymptomatic CAVS, Lp(a) and OxPL-apoB might serve as biomarkers to help guide timing of valve intervention and timing of imaging surveillance. Second, in the absence of any pharmacologic treatments for CAVD, Lp(a)-lowering therapeutics are an attractive strategy to halt the progression of CAVD.

Several existing lipid-lowering therapies and their potential in attenuating Lp(a) levels and CAVD have been studied. Statins have been widely investigated in CAVS with several clinical trials showing that statins are not only unable to reduce progression or induce regression of CAVS in patients with mild to moderate disease, but actually also increase Lp(a) levels by ~20%[33–36]. The mechanism by which this occurs is not understood but is felt to be attributed to increased apo(a) expression.

Niacin therapy lowers Lp(a) by ~ 20% to 30%[37–39]. Despite studies showing favorable reduction in Lp(a) with niacin treatment, niacin is not included in current guidelines due to the lack of clinical benefit in patients with atherosclerotic cardiovascular disease and increased risk of serious adverse events[39]. However, niacin therapy in patients with early CAVD and high Lp(a) ≥ 50 mg/dL is under ongoing investigation in the Early Aortic Valve Lipoprotein(a) Lowering (EAVaLL) randomized trial[40].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors can similarly lower Lp(a) levels by ~20–30% though the mechanism is currently unclear[41,42]. Nevertheless, there is growing evidence that PCSK9 may be involved in CAVD. In one prospective study, increased plasma PCSK9 levels were a predictor of CAVD; however, unlike Lp(a), PCSK9 levels positively correlated with the presence of CAVD, but not its severity[43]. From a large cohort of Danish patients, PCSK9 loss of function mutation R46L was associated with lower levels of Lp(a) as well as reduced risk of CAVS[44]. One study of a PCSK9 knockout mouse model has shown that PCSK9 deficient mice had lower aortic valve calcification compared to wildtype mice[45]. In vitro data from this study additionally showed that PCSK9 is highly expressed in calcified aortic valves and that aortic valve calcification might be caused by VIC-related PCSK9 expression. Sub-analyses of cardiovascular outcomes of studies of evolocumab (FOURIER trial) and alirocumab (ODYSSEY OUTCOMES) showed that the

greatest absolute Lp(a) reductions were observed in those patients in the high quartile of baseline Lp(a) values. These patients additionally derived greater cardiovascular benefit from PCSK9 inhibitor treatment. An exploratory analysis of PCSK9 inhibition and aortic stenosis in the FOURIER trial revealed Lp(a) concentration was associated with future AS events of new or worsening CAVS or aortic valve replacement. More interestingly, this study showed that long-term therapy with evolocumab beyond 1 year may reduce AS events[46]. However, this post hoc analysis only encompassed a small number of patients and AS events, and similarly to the ODYSSEY OUTCOMES trial, the FOURIER trial was not designed to evaluate the effect of PCSK9 inhibitors on CAVD or the impact of Lp(a) on this disease. Furthermore, the modest reduction in Lp(a) levels brought about by niacin or PCSK9 inhibitor treatment may be inadequate to provide a clinically meaningful impact on the pathogenesis of CAVD[47,48].

Two pivotal clinical trials investigating novel Lp(a)-lowering therapies are currently underway. The HORIZON phase 3 study is investigating the benefit of Lp(a)-lowering with pelacarsen (also termed IONIS-APO(a)-LRx, AKCEA-APO(a)-LRx, and TQJ230) on major cardiovascular outcomes of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent coronary re-vascularization requiring hospitalization among individuals with established cardiovascular disease and elevated Lp(a) levels. Pelacarsen is a highly potent hepatocyte-directed antisense oligonucleotide targeting the LPA gene messenger RNA, inhibiting its transcription to apolipoprotein(a)[49]. Phase 2 study data showed that Pelacarsen safely and dose-dependently decreases Lp(a) and its associated OxPL levels by up to 80%; approximately 98% of patients treated with the highest-dose regimen achieved Lp(a) levels below 125 nmol/L (~50 mg/dL), the established threshold for Lp(a)-driven cardiovascular disease for individuals already on statin therapy[50–52]. A separate phase 2 randomized study is currently being conducted to evaluate the efficacy, safety, and tolerability of olpasiran (also known as AMG 890) in individuals with elevated levels of Lp(a). Olpasiran is a small interfering RNA (siRNA) molecule targeting hepatic expression of apolipoprotein(a). Phase 1 study outcomes showed that 90% reduction in Lp(a) levels could be observed with olpasiran treatment. Although no pre-specified CAVD endpoints have been assessed as part of trial designs for both pelacarsen and olpasiran, these investigations represent landmark trials In the Lp(a) field and may ultimately lead to novel therapeutics for the management of CAVD.

Conclusions

Although Lp(a) has been accepted as an important independent risk factor for both cardiovascular disease and CAVD, there are challenges to integration of Lp(a) levels into clinical decision making. One obstacle is that the measurement of Lp(a) is not yet standardized. The most common method for measuring Lp(a) are immunoassays which utilize polyclonal antibodies to target the apo(a) molecule. However, the large heterogeneity in apo(a) size between, as well as within individuals because of the heterozygosity of the apo(a) gene, can lead to inaccurate determination of Lp(a) plasma concentration. Because these polyclonal antibodies cross-react with the multiple KIV_2 repeats, these assays can result in an overestimation of Lp(a) plasma concentrations in individuals with large isoforms and underestimation of Lp(a) levels in those with small isoforms[53,54]. For this reason, there

may be a benefit in switching from the most commonly used total mass assays which report Lp(a) levels in mg/dL to measuring Lp(a) concentration in nmol/L[17].

In addition, an important challenge in using Lp(a) as a biomarker to identify patients at higher risk for atherosclerotic cardiovascular disease (ASCVD) and CAVD is the lack of consensus on the target level of Lp(a). Based on the available studies, the National Lipid Association suggests using a universal cut point of ≥ 100 nmol/L, which approximates the 80th percentile in the Caucasian United States populations[55]. However, the 2019 American College of Cardiology (ACC)/American Heart Association (AHA) Cholesterol Guidelines recommend using Lp(a) concentration ≥ 125 nmol/L (> 50 mg/dL)[56]. These guidelines are likely to change as future studies take into account epidemiological differences based on risk, ethnicity, and comorbidities to determine the optimal cut-off levels.

Finally, integrating assessment of Lp(a) into current clinical care is not yet common practice. Measuring Lp(a) may be reasonable in patients at high risk for ASCVD, those with a family history of premature ASCVD, and for reclassification purposes in patients at borderline risk for ASCVD. However, current European and ACC/AHA recommendations offer less guidance in the assessment of Lp(a) among patients with known CAVD, with or without concurrent ASCVD[56,57]. Additionally, it remains unclear how Lp(a) might be used to identify those individuals at greater risk for CAVD and whether such information may guide timing of valvular intervention and imaging surveillance. Ultimately, clinical trials will be required to determine if new Lp(a)-lowering agents can slow the progression of CAVD. Such trials will require careful design with respect to enrolling patients who have elevated Lp(a) and aortic valve disease. However, it will also be important to identify patients who do not yet have severe disease, where the disease may still be modifiable. While there will be much more to learn, it is thought-provoking to know that Lp(a)-lowering agents may prove to be the first medical therapy that can modify the progression of CAVD.

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Conflicts of interest

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Key Points:

- Lp(a) is associated with increased severity and increased progression of CAVD.
- Lp(a) is a key mediator of calcific aortic stenosis via its delivery of OxPL to aortic valvular interstitial cells.
- There are no approved therapies to lower Lp(a), but several agents are being evaluated in clinical trials.
- Niacin and PCSK9 inhibitors can lower Lp(a), but the resulting modest reductions in Lp(a) may be insufficient to halt progression of CAVD.
- Future studies will be required to determine whether emerging RNA-targeted therapeutics to lower Lp(a) may impact the progression of CAVD.

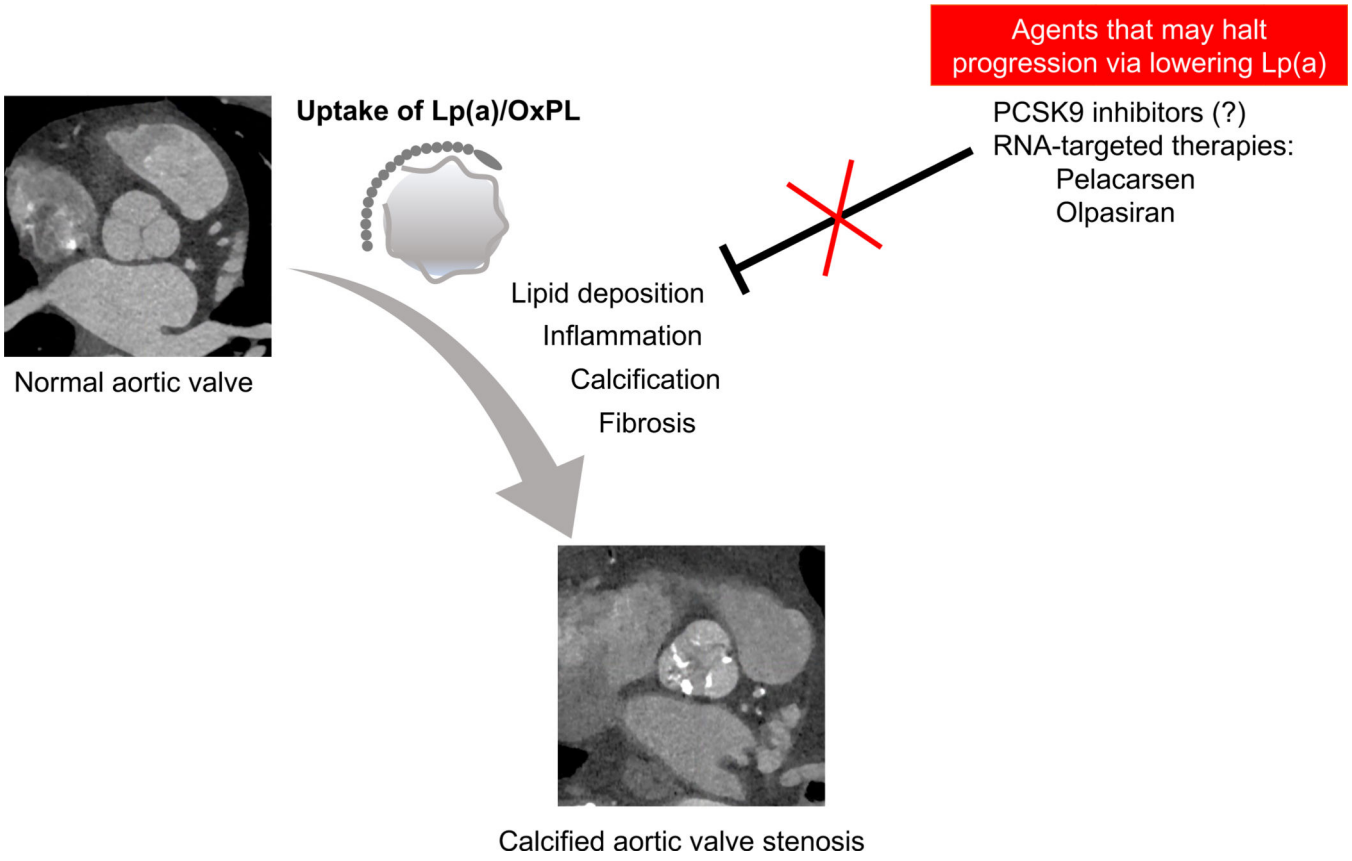

Figure 1.

Lipoprotein (a) mediates the progression of calcific aortic valvular disease. Upon endothelial damage, lipoprotein(a) and oxidized phospholipids (OxPL) accumulate within the valvular tissue, driving a feed-forward cycle of inflammation, calcification, and fibrosis. This ultimately results in calcified aortic valve stenosis. Currently, there are no approved medical therapies for aortic stenosis. However, emerging therapies to target Lp(a), including PCSK9 inhibitors and RNA-based therapeutics, may halt disease progression in aortic stenosis.