Title

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Author

Tsimikas, Sotirios

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Potential causality and emerging medical therapies for lipoprotein(a) and its associated oxidized phospholipids in calcific aortic valve stenosis

Sotirios Tsimikas, MD

Division of Cardiovascular Medicine, Sulpizio Cardiovascular Center, University of California San Diego, La Jolla, CA.

Abstract

The prevalence of calcific aortic valve disease (CAVD) is increasing with aging of the population. Current treatment options for advanced or symptomatic aortic stenosis (AS) are limited to traditional surgical or percutaneous aortic valve replacement (AVR). Medical therapies that impact the progression of CAVD do not currently exist. New pathophysiological insights suggest that the processes leading to CAVD are metabolically active for many years before and during the clinical expression of disease. The identification of genetic and potentially causal mediators of CAVD allows opportunities for therapies that may slow progression to the point where AVR can be avoided. Recent studies suggest that approximately one third of AS cases are associated with either highly elevated Lp(a) and/or pathways related to the metabolism of pro-calcifying oxidized phospholipids (OxPL). OxPL can be carried by Lp(a) into valve leaflets but can also be formed in situ from cell membranes, lipoproteins and apoptotic cells. This review will summarize the clinical data implicating the potential causality of Lp(a)/OxPL, describe emerging therapeutic agents and propose clinical trial designs to test the hypothesis that lowering Lp(a) will reduce progression AS and the need for AVR.

Keywords

aortic stenosis; aortic valve; lipoprotein(a); oxidation; Atherosclerosis; Thrombosis; Pharmacology

Introduction

Calcific aortic valve disease (CAVD) is a prevalent disorder that affects patients starting at middle-age but whose incidence accelerates rapidly as individuals age beyond >80 years old.[1,2] It is estimated that >4.5 million cases of clinically-evident aortic stenosis (AS) will be present globally by 2030.[3] The relatively poor outcomes of aortic valve replacement (AVR) in the elderly has led to the development and rapid implementation of transvalvular aortic valve replacement (TAVR).[4] Although TAVR provides an excellent option for inoperable or moderate-high risk disease, patients with advanced AS continue to have poor prognosis due to advanced age and co-morbidities that limit overall survival despite optimal technical

Address for correspondence: Sotirios Tsimikas, Vascular Medicine Program, University of California San Diego, 9500 Gilman Drive, La Jolla, California 92093-0682. stsimikas@ucsd.edu.

results.[5] AS, unlike unstable atherosclerosis mediated vascular disease, does not occur in episodic catastrophes of acute presentations, but in a slower and relatively linear progression of valvular orifice narrowing for several years prior to the need of AVR/TAVR. Therefore, opportunities for earlier intervention in the disease process may become more realistic as the molecular mechanisms leading to AS are better understood. Although many potential pathways can be proposed,[6] this review will focus on lipoprotein(a) [Lp(a)] and oxidized phospholipids (OxPL) as potential etiological agents and targets of therapy for AS.

Risk factors for AS

The contributors to AS are not fully defined, but broadly include pathways in lipid disorders, oxidative stress, the renin-angiotensin aldosterone system, calcification and bone metabolism, renal disease, metabolic syndrome and intrinsic valve disease such as bicuspid aortic valve disease with attendant abnormal hemodynamic stresses.[3,7,8] In addition, age, which is the strongest risk factor in most cardiovascular phenotypes due to summation of all known and unknown risk factors, is a very prominent risk factor for advanced AS. Initial interest in elevated low-density lipoprotein cholesterol (LDL-C) as a causal mediator waned when four randomized controlled trials with statins alone or statin/ezetimibe combination showed nearly identical echocardiographically-determined progression rates between groups, despite 40–50% reductions in LDL-C versus placebo.[9–12] Although the mechanisms behind the failure of these trials are not definitively known, it likely reflects the fact that LDL-C and/or statin/ezetimibe therapy do not fully address the underlying pathophysiological mechanisms leading to CAVD. A recent study suggested a weighted genetic risk score of LDL-C variants was predictive of aortic valve calcification and incident AS.[13] In this study, although Lp(a) levels were balanced across groups, since LDL-C contains the Lp(a)-cholesterol content which can be substantial contribution to high LDL-C and high Lp(a) patients,[14,15] it is not clear if these relationships would have been attenuated if the corrected LDL-C was used instead of measured LDL-C.

Genetic and potentially causal pathways for AS

Relevant to the current topic, elevated Lp(a) has been shown to be a risk factor for AS since the 1990s, but had not been fully appreciated (Reviewed in Yeang et al[16]), In 2013, the CHARGE Consortium group first showed that the *LPA* gene, as reflected by a single nucleotide polymorphisms (SNP) that were associated with highly elevated Lp(a) levels, was associated with aortic valve calcification and need for AVR in multiple diverse cohorts and racial/ethnic groups.[17] Remarkably, of 2.5 million SNPs measured or imputed, only *LPA* SN: rs10455872, present in up to 15% of individuals of European descent, reached genome-wide significance in this association. Interestingly, no replicated, genome-wide associations were noted in mitral valve calcification, suggesting this association is unique to aortic valve disease and the physiological and hemodynamic factors that affect aortic valve leaflets. In the last 5 years, multiple studies have replicated these findings.[18–25] The totality of evidence now includes over 10,000 patients that point to the *LPA* gene, which is responsible for >90% of circulating Lp(a) levels,[26] as a likely causal mediator of clinically-relevant AS (Table 1). More recently, a gene in the vicinity of rs7543130, possibly the PALMD gene, which

expresses a protein localized predominantly in actin filaments, has also been implicated in GWAS studies as a potential causal mediator.[24,25]

Potential mechanisms of Lp(a) and oxidized phospholipids contributing to AS

The *LPA* gene is evolutionarily derived from and highly homologous to the plasminogen (*PLG*) gene.[27,28] The PLG gene encodes 5 unique kringle domains and an active protease domain that is activated to plasmin by tissue plasminogen activators. The *LPA* gene, and therefore apolipoprotein(a), differs from *PLG* in that it does not contain kringles I-II, but does contain KIV, KV but an inactive protease domain that contains the catalytic triad of plasminogen, but cannot be converted to a plasmin-like molecule due to amino acid substitutions at the site of cleavage of plasminogen activators. Furthermore, due to multiple duplication events during evolution, the *LPA* gene it has accumulated 10 copies of KIV that are each unique in amino acid sequence except for KIV_2. KIV contains one copy of each KIV_1 and $KIV_{3–10}$, but variable copies of KIV_2, ranging from 1 to >40 on each allele among individuals and populations. KIV2 repeats may differ in nucleic acid sequence but are identical in amino acid sequence (Figure 1).[26]

Lp(a) is a unique lipoprotein that is composed of apolipoprotein B-100 of an LDL-like particle to which is covalently attached apolipoprotein(a). The apolipoprotein(a) component of Lp(a) is not a lipoprotein per se since it has no traditional lipid binding domains. Apolipoprotein(a), unlike lipid-laden apolipoprotein B-100, is hydrophilic and sweeps out into the aqueous phase and may interact with vascular endothelium, as well as cellular receptors, to mediate pathophysiologic effects. This allows Lp(a) to have divergent effects on vascular phenotypes that include atherosclerosis and AS.[27,29]

Lipoproteins such as LDL and VLDL can passively diffuse through endothelial surfaces via concentration gradients, accumulate in subendothelial spaces, become oxidized, promote pro-inflammation and mediate atherogenesis.[30] In a similar way, Lp(a) may permeate through vascular endothelium and provide a substrate for lipid peroxidation and inflammation.[31] However, the apolipoprotein(a) component has an additional mechanism to allow Lp(a) to accumulate in vascular tissue and also be retained to sub-endothelial surfaces. It contains at least one potent lysine binding pocket composed of 7 amino acids present on KIV_{10} that allows it to bind to exposed lysine on denuded endothelial surfaces and in the subendothelial matrix of vascular tissue.[32] A theoretical construct is proposed how Lp(a) may be taken up, retained and induce calcification of aortic valve leaflets (Figure 1). Lp(a) along with its associated OxPL bind to denuded aortic valve leaflet endothelium, become internalized and further bind tightly to proteoglycans and other subendothelial structures, are permanently retained and subsequently mediate pro inflammatory and pro-calcifying effects.

OxPL are present on Lp(a), oxidized LDL, apoptotic cells, oxidized cell membranes and sites of inflammation. Lp(a) has also been shown to be the preferential lipoprotein carrier of certain species of oxidized phospholipids (OxPL),[33,34] which may impart additional and potent pro-inflammatory properties to Lp(a).[35,36] OxPL are present in both the lipid phase of the LDL-moiety as well as covalently attached to an unidentified amino acid in the KIV_{10}/V

region of apolipoprotein(a). Additionally, such OxPL have been shown to regulate over 1000 genes in aortic endothelial cells, many in inflammatory gene modules, as well as promote pro-inflammatory responses in macrophages, smooth muscle cells, dendritic cells, platelets and monocytes, that may link Lp(a)/OxPL to AS pathophysiology.[37–41]

As an analogy of the pro-inflammatory effects of Lp(a) that may be occurring in the aortic valve, recent clinical data has shown that patients with elevated have increased arterial inflammation and enhanced peripheral blood mononuclear cells trafficking to the arterial wall as evidenced by an increased capacity to transmigrate and produce proinflammatory cytokines on stimulation versus patients with low Lp(a).[40] In addition, exposure of monocytes derived from healthy donors could be shown to generate pro-inflammatory responses that could be inhibited by using apolipoprotein(a) constructs lacking OxPL, or by co-incubation of Lp(a) with the antibody E06, which prevented release on monocyte-derived IL-6, IL1beta and TNFalpha by 50–75%. Although such studies have not yet been carried out in valvular interstitial cells, it suggests a paradigm through which a similar mechanism may be responsible for aortic valve leaflet inflammation. OxPL can be measured in plasma on apoB-containing lipoproteins and an extensive database of approximately 50 original studies demonstrate that levels of OxPL carried by apoB-containing lipoproteins, and primarily by Lp(a) [measured as OxPL-apoB and OxPL-apo(a)], are robust predictors of a variety of CVD phenotypes and CVD events,[42–44] and more recently in predicting development and progression of AS.[22,45–47] In further proof of their association with AS, both Lp(a) and OxPL are strongly present immunologically in surgically removed, pathologically advanced, aortic valve leaflets (Figure 2).[47,48] Additionally, elution of lipids from aortic valve leaflets and detection by LC/MS-MS shows direct evidence of the presence of a variety of distinct species of phosphocholine-containing OxPL known to be pro-inflammatory.[47]

Besides pro-inflammatory effects, OxPL are known to be influence microcalcification pathways in valve interstitial cells.[3] Hypotheses have been proposed that atherosclerotic calcification in humans arises from chronic inflammation, and that the most common source of chronic vascular inflammation is atherosclerosis, and its underlying contributing factor is accumulation of oxidized lipids. Although this is a highly complex area with multiple potential contributors to CAVD,[6] work in cell culture systems provide a rationale how oxidized lipids may partly mediate microcalcification pathways.[49] These include downregulation of osteoprotegerin that normally inhibits calcification by suppressing osteoclastic bone resorptive activity through the nuclear factor-κB ligand (RANKL) and by stimulating extracellular matrix calcium deposition and upregulation of alkaline phosphatase leading to enhanced calcification.[3] OxPL may also act as substrates for the generation of lysophosphatidic acid by the enzyme autotaxin, which has been shown to promote the microcalcification of the aortic valve through a nuclear factor κB/interleukin 6/bone morphogenetic protein pathway.[48] Human aortic valve interstitial cells exposed to purified Lp(a) from normal donors have recently been shown to significantly increased alkaline phosphatase activity, release of phosphate, calcium deposition, hydroxyapatite, cell apoptosis, matrix vesicle formation, an important mechanism in the initiation of microcalcification,[50] and phosphorylation of signal transduction.[51] proteins; increased expression of chondro-osteogenic mediators; and decreased SOX9 and matrix Gla protein.[51]

Evidence from clinical studies on relationship of Lp(a) and oxidized phospholipids in patients with pre-existing AS

Although the genetic data point to causality of Lp(a) in mediating AS, they are limited in that they study incident AS, i.e. the development of AS in patients without pre-existing disease. At the bedside, the practicing cardiologist is faced with patients with pre-existing AS in trying to ascertain prognosis and potential timing of surgery. In the ASTRONOMER trial, which randomized patients to rosuvastatin 40 mg daily versus placebo, rosuvastatin showed no differences in echocardiographically-determined annualized progression rate by peak aortic jet velocity (V_{peak}).[12] In a follow-up study from ASTRONOMER that addressed the Lp(a) hypothesis of AS, it was demonstrated that elevated Lp(a) (>58.5 mg/dL, ~150 nmol/L) and OxPL-apoB and OxPL-apo(a) levels at or above the highest tertile were strong predictors of the annualized progression rate and need for AVR over a median 3.5-year follow-up (Figure 3A and 3B).[45] Furthermore, and perhaps in further support of the Lp(a) hypotheses and failure of statin/ezetimibe therapy, rosuvastatin increased Lp(a) levels by 20% (mean ~45 mg/dL to 55 mg/dL) and OxPL-apoB by 46% from baseline to year one (Figure 3C and 3D), which may also have mitigated any potential beneficial effect of LDL-C lowering. In another case-control study in 300 patients with AS plus coronary artery disease (CAD) versus CAD alone, autotaxin, which generates lysophosphatidic acid from lysophophatidylcholine, showed strong interactions with Lp(a), OxPL-apoB and OxPL-apo(a), with patients with the highest autotaxin activity and Lp(a) or OxPL-apoB/OxPL-apo(a) having an elevated risk of AS with odds ratio of >5.[46]

To further define the genetic contribution of OxPL, a nested case-control study was performed within the Copenhagen General Population Study (N=87980) in 725 cases of AS and 1413 controls free of cardiovascular disease to test the hypothesis that risk is mediated by the content of OxPL on Lp(a).[22] OxPL-apoB and OxPL-apo(a) levels were highest in individuals with low number or percentage of KIV_2 repeats, as well as those that carried the rs10455872 risk allele (Figure 4A), reaching an odds ratio 3.4 for levels >95th percentile, versus levels <34th percentile. *LPA* genotypes explained 34% and 39% of the total variation in OxPL-apoB and Lp(a) levels. Furthermore, OxPL-apoB and Lp(a) levels were comparable mediators of risk between *LPA* genotype and AS (Figure 4B).

Overall, these basic, translational and clinical data support the hypothesis that a pathophysiological link through which Lp(a) may mediate CVAS is by delivering its content of lipids to the aortic valve and by mediating pro-inflammatory, pro-apoptotic and pro-calcifying effects via its content of OxPL and their breakdown products. In turn, inflammation induces fibrosis which further accelerates aortic valve thickening and loss of pliability, stenosis and systolic orifice area reduction. These data further suggest several viable approaches to test the hypothesis of reducing risk of development or progression of CAVD through these pathophysiologically-linked pathways, including lowering plasma levels of Lp(a) and OxPL, inactivating the pro-inflammatory effects of OxPL, or reducing the local generation of lysophosphatidic acid.

Emerging therapies to lower Lp(a)

Currently, there are no approved specific therapies to lower Lp(a). Niacin[52] and PCSK9 inhibitors can lower Lp(a) ~20–30%,[53,54] but PCSK9 inhibitors which appear to have smaller effects (~18% reduction) in patients with elevated Lp(a).[54] These modest reductions in Lp(a) are unlikely to be of sufficient robustness to impact the disease process, particularly in patients who may need >50% reduction in Lp(a) levels.[55,56]

Traditional drug therapies generally include small molecules that inhibit enzyme activity or receptor function, such as HMG-CoA reductase inhibitors, or antibodies that bind to and inactivate proteins, such as PCSK9 inhibitors (Figure 5A). These approaches are not likely feasible in treating elevated Lp(a) levels, because Lp(a) has neither enzyme activity or receptor functions, or practical as the plasma concertation of Lp(a) is very high for antibody-based approaches to be considered safe in clearing the large mass of immune complexes that will be generated or cost-effective in requiring very large amounts of antibody. For example, apolipoprotein(a) levels are 20 – 150-fold higher than PCSK9 levels (~125–1000 nM vs. ~6 nM). A fundamentally novel approach is to use RNA targeted therapeutics, and specifically antisense oligonucleotides, to inhibit apolipoprotein(a) mRNA production in the hepatocyte, [57] which is responsible for >99% of plasma apolipoprotein(a) levels. This concept was first documented with the use of an apoB-100 mRNA inhibitor, mipomersen, that lowered Lp(a) by ~75% in Lp(a)-transgenic Lp(a) mice by limiting availability of apoB to assemble Lp(a). [58] The Lp(a) lowering effect of mipomersen was subsequently confirmed in humans,[59] with~25% reduction in Lp(a), but at lower equivalent doses compared to mice. However, this approach did not affect apolipoprotein(a) levels which now circulated free without being bound to available apoB-100. Further refinements were made by specifically targeting of apolipoprotein(a) mRNA in transgenic Lp(a) mice.[60]

This approach has been subsequently translated to humans in 3 trials.[61,62] Following a successful phase 1 study in volunteers using IONIS-APO(a)$_{Rx}$,[61] a phase 2 study in subjects with highly elevated Lp(a) levels (one group with Lp(a) 50–175 mg/dL and a second group with >175 mg/dL) showed a mean 72% reduction in Lp(a) levels in both groups (Figure 5B), along with a modest reduction (25–50%) reduction in OxPL-apoB and OxPL-apo(a) (Figure 5C–D).[33,34,63] This molecule has been supplanted by IONIS-APO(a)-L$_{Rx}$ which has the same nucleic acid sequences but differences in the backbone structure.[62] One additional important difference is that IONIS-APO(a)-L$_{Rx}$ contains a specific hepatocyte targeting moiety, triantennary N-acetyl galactosamine (GalNAc), targeting the asialoglycoprotein receptor.[64] This results in ~30-fold higher potency, allowing similar or greater efficacy with significantly lower doses, thus potentially improving the tolerability and side effect profile.[62] In a phase 1 trial in otherwise healthy volunteers with elevated Lp(a) levels given a dosing regimen that is equivalent of 10 mg, 20 mg and 40 mg weekly, IONIS-APO(a)-L$_{Rx}$ resulted in mean 68%, 80% and 92% reductions in Lp(a), as well as a decline in OxPL-apoB (Figure 5E–F). This robust potency suggests that most patients may be able to attain normal Lp(a) levels post therapy, even if starting with highly elevated levels. A phase 2 safety and dose-ranging study (NCT03070782-Phase 2 Study of ISIS 681257 (AKCEA-APO(a)-L$_{Rx}$) in Patients With Hyperlipoproteinemia(a) and Cardiovascular Disease) is currently ongoing.

Ongoing trials of medical therapies for native AS

Only 3 trials are listed in clinicaltrials.gov evaluating medical therapies for AS with valvular endpoints (Table 2). These include SALTIRE II which is testing the calcification hypothesis with denosumab, alendronic acid or placebo in mild-moderate AS, EAVaLL describing the use of niacin versus placebo that is recruiting very slowly and is unlikely to be completed, and a study of PCSK9 inhibitors that has not yet begun recruitment. These trials are primarily assessing changes in aortic valve calcium or ^{18}F-NaF PET imaging.[65]

Potential trial design of a medical therapy for AS targeting Lp(a)

The prevalence of AS, excluding aortic sclerosis, in the general community is estimated to be 2.5%, and ranges from 0.3% in subjects 18–44 years of age to 11.7% in subjects ≥75 years old, using data from several well-characterized cohorts of >28,000 subjects undergoing echocardiography.[66] Incident AS, which excludes subjects with prior diagnosis of AS and is therefore lower numerically than prevalent AS. In the large Copenhagen studies incident AS was present in 1.3%, 1.6% and 2.1% of patients with Lp(a) >40 mg/dL, >80 mg/dL and >120 mg/dL, respectively, followed for up to 20 years.[19] In patients with AS where data is relatively limited, elevated Lp(a) (>50 mg/dL) is present in approximately 30% of subjects with AS.[45,67,68] Therefore, only a minority of AS patients will be eligible for trials of Lp(a) lowering therapies.

In this group, there are 2 potential approaches that could be used, prevention of development of the disease or reduction in the progression of pre-existing disease. Although prevention of disease is ideal, reduction in the progression of pre-existing disease is a more realistic and nearer term goal. One potential trial design, from several possibilities, includes a trial with an Lp(a) lowering therapy versus placebo (Figure 6). As new data merges, the trial design may be altered, but an early attempt to conceptualize such a trial would include patients with mild-moderate aortic stenosis, defined as maximal aortic jet valve velocity 2.0–3.9 meters/second (V_{peak}),[69] where opportunity for affecting the disease process is more likely. More advanced levels of disease, such as severe aortic stenosis with heavy calcification and fixed, severe, obstruction are less likely to respond to medical therapy as best as can be predicted currently. Based on recent epidemiological data, an entry Lp(a) level >60 mg/dL, which will result in median levels 90–100 mg/dL in the trial based on epidemiologic prevalence data from laboratory databases,[70] appear to be most appropriate based on current knowledge of risk thresholds.[19,45] However, this area is in need of additional epidemiological data in AS patients to fine-tune the association of Lp(a) levels and risk thresholds where that most benefit may accrue.[67]

Unlike traditional cardiovascular outcomes trials that use cardiac death, myocardial infarction and revascularization as the main endpoints, such composite endpoints are not entirely relevant to the pathophysiology of AS. In patients with mild-moderate AS, all of these endpoints would be expected to be rare, as suggested by prior statin trials in AS. Therefore, pathophysiologically-relevant endpoints specific to AS are required to test the Lp(a) hypothesis. A composite endpoint of change in annualized V_{peak}, the rate of AVR and cardiac death seem the most appropriate endpoints for such a trial. V_{peak} is a robust endpoint

as it directly measures valve function and reflects reduced systolic opening of the aortic valve (i.e. it is not a surrogate endpoint) and from which aortic valve orifice area (AVA) is derived. V_{peak} has been used previously in statin trials as well as in current TAVR trials to assess short and long-term valve function.[71] Based on natural history studies of unoperated AS and additional clinical data, changes in V_{peak} correspond to mortality, symptoms and functioning of patients with AS, suggesting it would be acceptable from a regulatory standpoint for trial registration.[1,69,72–74] Patients with mild-moderate AS would be anticipated to have an AVR rate of 20–30% over a median of 3–4 years, as shown in the statin AS trials. It is not anticipated that these rates would be different today as the natural history of AS has not been significantly impacted by current medical therapies. The emergence of calcium imaging of the aortic valve suggests they it may be viable secondary endpoint, as it correlates with echocardiographically-determined progression rates.[65]^{18}F-NaF PET imaging detects early changes in microcalcification that may also be a sensitive and complementary measure to echocardiography.[75] Preliminary power analysis using the above composite endpoint suggests that <1000 patients would need to be enrolled to adequately test the hypothesis over a median of 4-year follow-up.

In conclusion, recent developments in the understanding of AS suggests that a significant subset of patients have elevated Lp(a)/OxPL as a potential etiology. The strength of the genetic data suggesting causally, the epidemiological studies and post-hoc trial data, along with an emerging and potent therapy that can lower Lp(a) substantially in most patients, provides a rationale for testing the Lp(a)/OxPL lowering hypothesis in patients with mild-moderate AS.

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Non-standard Abbreviations and Acronyms

CAVD	calcific aortic valve disease
AS	aortic stenosis
AVR	aortic valve replacement
AVA	aortic valve area
OxPL	oxidized phospholipids
Lp(a)	lipoprotein(a)
LPA	LPA gene
PCSK9	proprotein convertase subtilisin type 9

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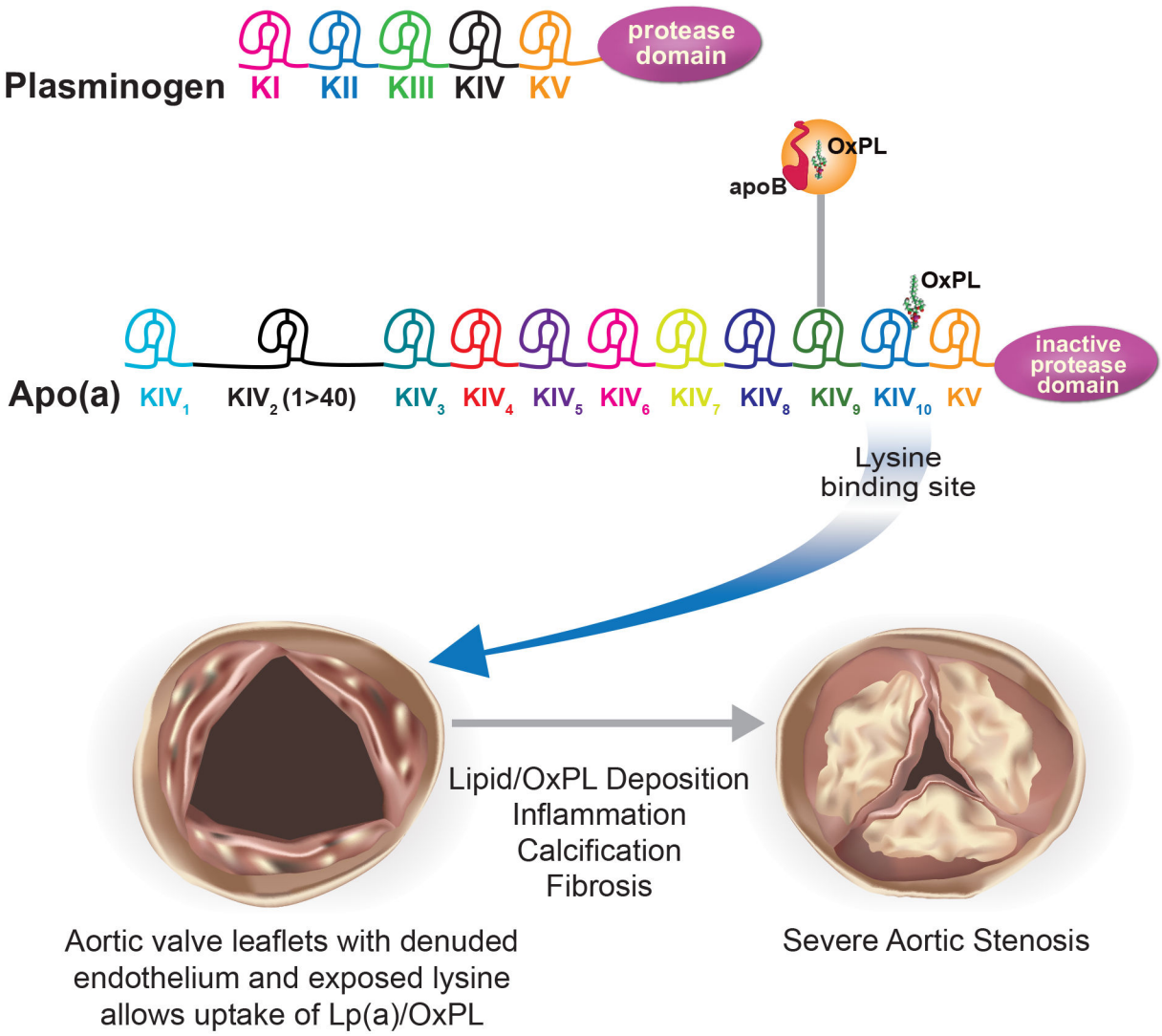

Figure 1.

Cartoon of the physical characteristics of apolipoprotein(a) and proposed mechanism through which it is bound to and retained in aortic valve leaflets. Plasminogen is composed of 5 unique kringles (protein unit with 3 disulfide bonds) and an active protease domain. In contrast, apolipoprotein(a) has 10 unique copies of KIV, of which KIV_2 is present in 1 to >40 copies, KV and an inactive protease domain. It further contains OxPL covalently attached to a yet to be identified amino acid near KIV-V as well as variable amounts of OxPL in the LDL-like particle. The lysine binding site of KIV_{10} allows attachment of apolipoprotein(a) to exposed lysine on denuded vascular endothelium. This facilitates further uptake and retention of the entire Lp(a) particle to the subendothelial spaces that can them mediate inflammation and calcification. Accumulation of OxPL mediates inflammation, calcification and fibrosis.

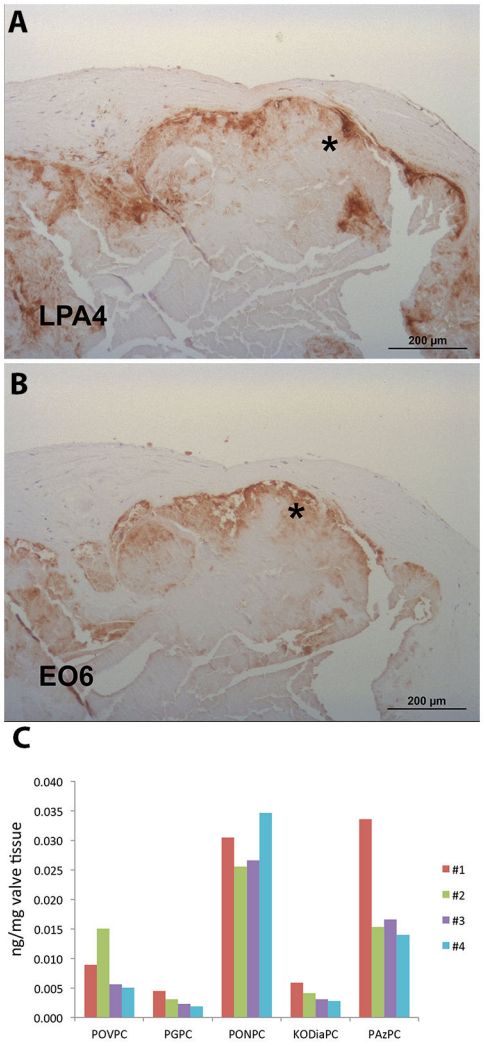

Figure 2.

Histological and mass spectrometry presence of Lp(a) and OxPL in aortic valve leaflets removed surgically. A and B- Sequential sections stained for apolipoprotein(a) (antibody LPA4) and OxPL (antibody EO6). Note the co-localization of Lp(a)/OxPL and within heavily calcified areas (*). The aortic side of the valve is at the top panels. C- shows reverse phase separation coupled with tandem mass spectrometry of the most abundant fragmented phosphocholine-containing oxidized phospholipid (PC-OxPL) compounds extracted from 4 human aortic valve leaflets. POVPC (1-palmitoyl-2-[5'-oxo-valeroyl]-sn-glycero-3-phosphocholine), PGPC (1-palmitoyl-2-glutaryl-sn-glycero-3-phosphocholine), PONPC (1-palmitoyl-2-[9'-oxononanoyl]-sn-glycero-3-phosphocholine), KODiA-PC (1-[palmitoyl]-2-[5-keto-6-octene-dioyl]-snglycero-3-phosphocholine), and PAzPC (1-palmitoyl-2-azelaoyl-sn-glycero-3-phosphocholine). Reprinted with permission from Torzewski et al.[47]

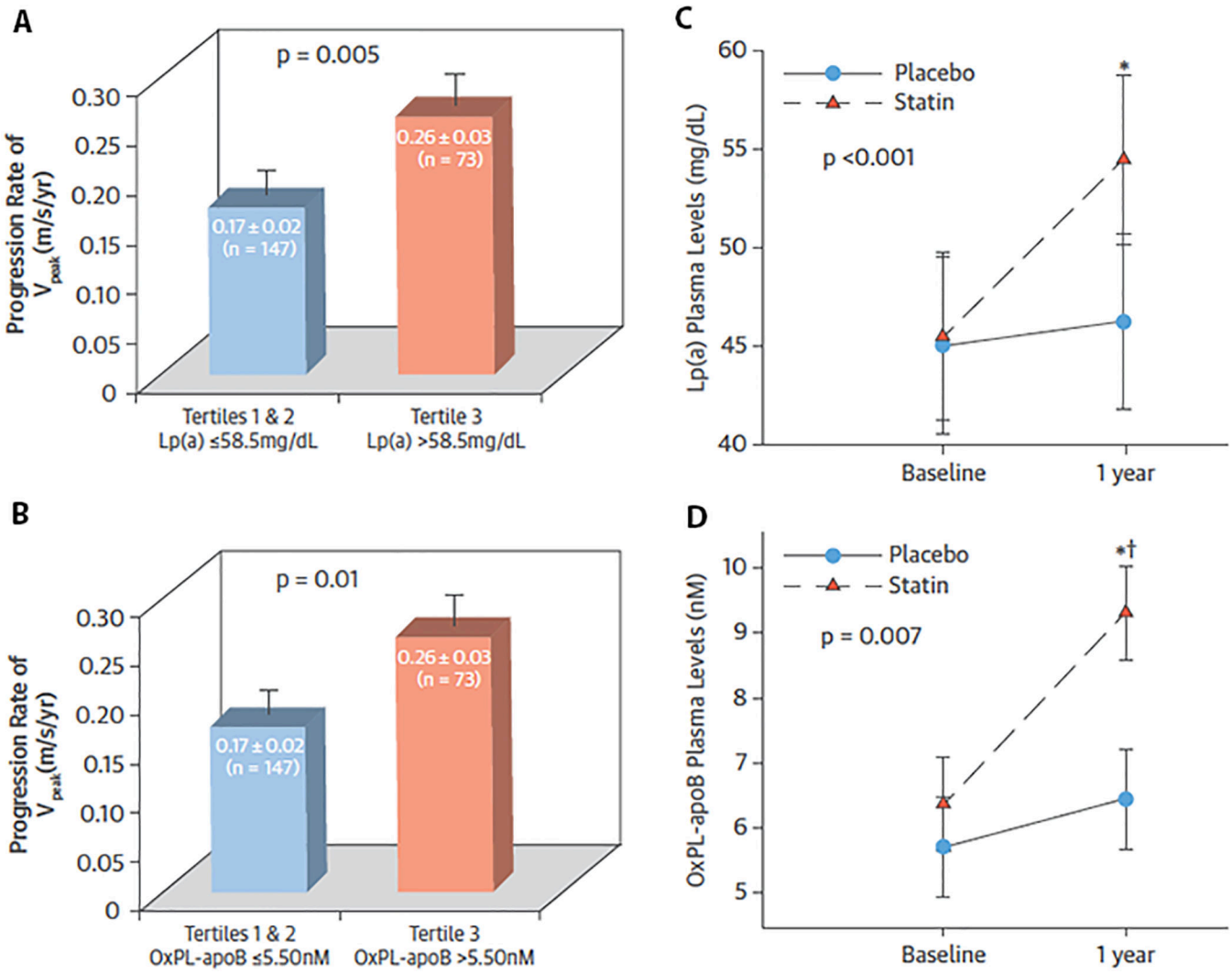

Figure 3.

Annualized progression rates according to Lp(a) and OxPL-apoB and effect of rosuvastatin on Lp(a) and OxPL-apoB levels. Annualized progression rate of V_{peak} is compared by tertiles for Lp(a) (A) and OxPL-apoB (B). Change in plasma levels of Lp(a) (C) and OxPL-apoB (B) in patients randomized to statin versus those randomized to placebo during the first year of the study (i.e., from baseline to 1 year). p values are for the 2-way ANOVAs. *p<0.05 compared to baseline; †p<0.05 compared to placebo. Error bars represent the SEM. ANOVA - analysis of variance. Modified and reprinted with permission from Capoulade et al.[45]

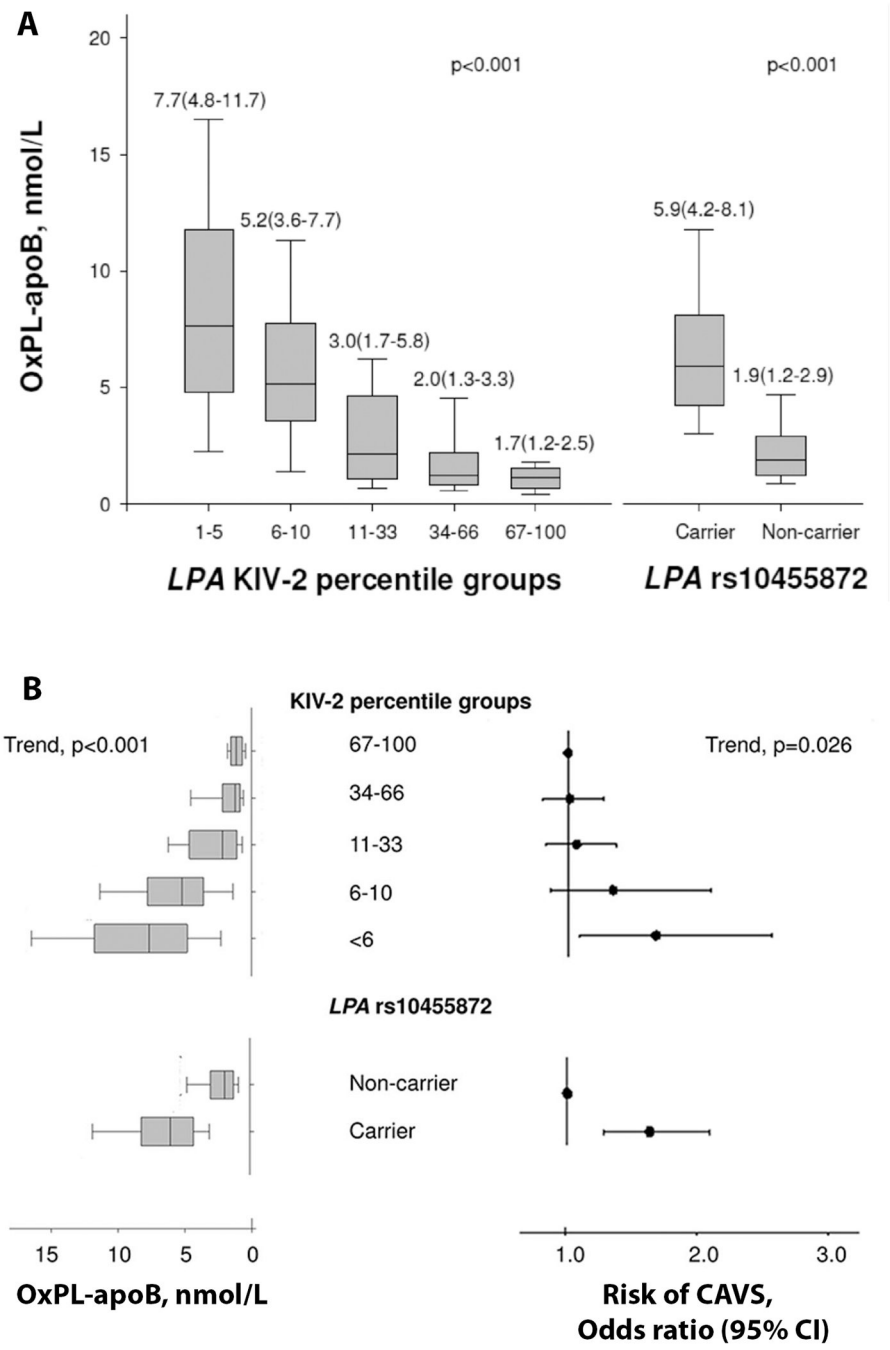

Figure 4.

Relationship of OxPL-apoB with KIV_2 repeats and LPA SNP rs10455872. Panel A depicts percentile of KIV_2 repeats and carriers and non-carriers of *LPA* SNP rs10455872. Panel B depicts the LPA genotype as reflected as either KIV_2 repeats or *LPA* SNP rs10455872. Both of these instruments are associated with elevated OxPL-apoB levels which are in turn associated with higher risk of AS. Modified and reprinted with permission from Kamstrup et al.[22]

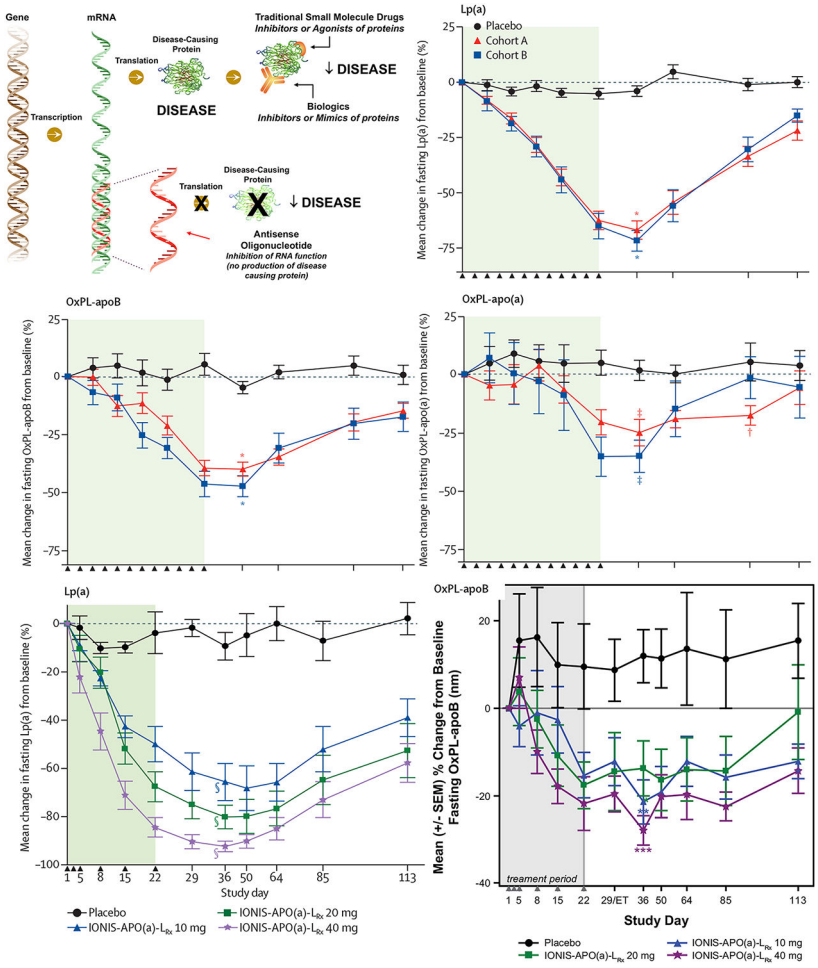

Figure 5.

Mechanism of antisense oligonucleotides in reducing protein synthesis and effect on Lp(a) and OxPL-apoB, and OxPL-apo(a) in clinical trials. A- Small molecules, antibodies and antisense oligonucleotides as therapeutic entities in clinical medicine. B- reduction in Lp(a) with IONIS-APO(a)$_{Rx}$. C- reduction in OxPL-apoB with IONIS-APO(a)$_{Rx}$. D- reduction in OxPL-apo(a) with IONIS-APO(a)$_{Rx}$. E- reduction in Lp(a) with IONIS-APO-L(a)$_{Rx}$. F- reduction in OxPL-apoB with IONIS-APO(a)-L$_{Rx}$.

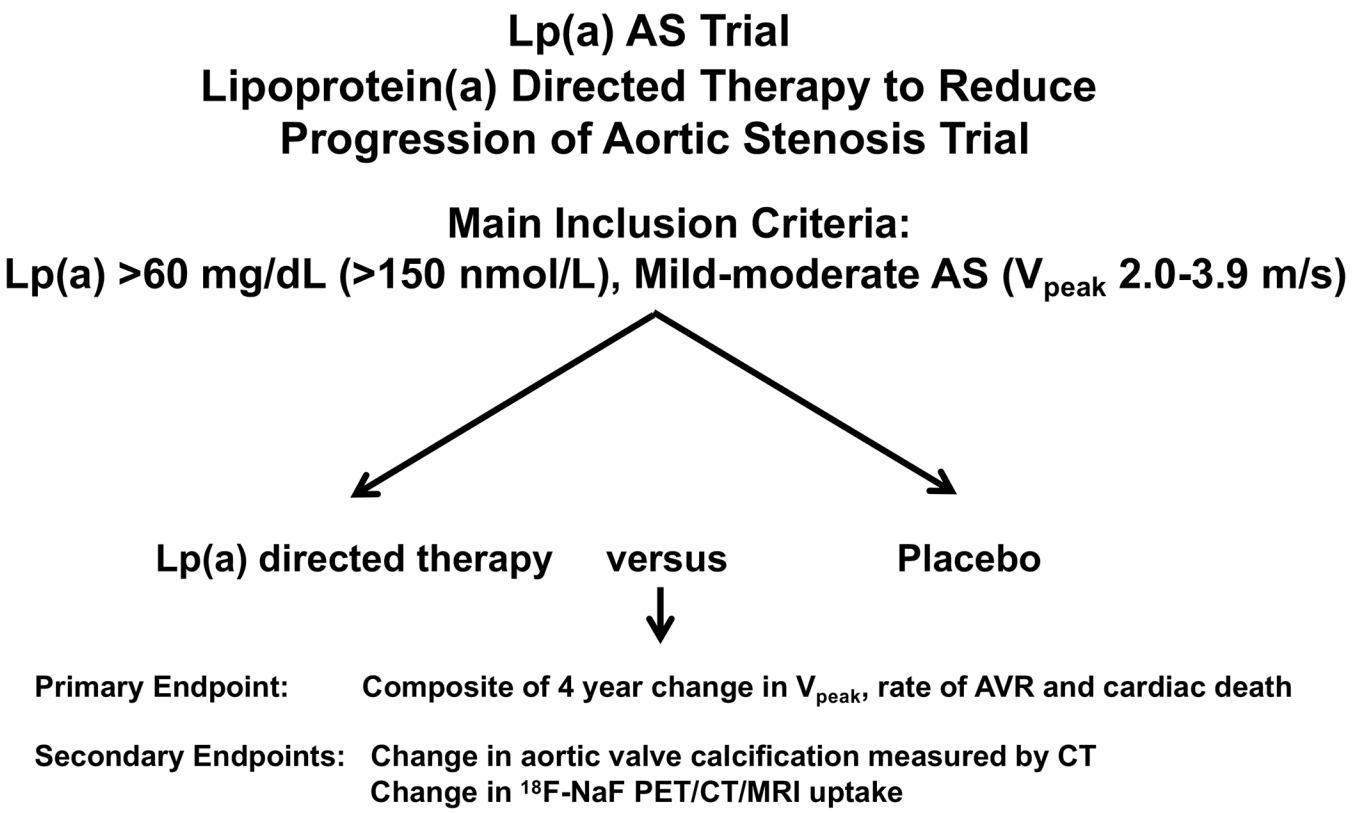

Figure 6.
Potential design of an Lp(a) lowering trial in mild-moderate AS.

Table 1.

Studies suggesting genetic causality of Lp(a)/OxPL in AS.

Study	Year	# AS cases	Genetic instrument	Key Findings
Thanassoulis et al[17]	2013	500	LPA SNP rs10455872	Per allele, OR 2.05 for AV calcification, HR 1.68 for incident AS and 1.54 for AVR
Kamstrup et al[19]	2014	454	LPA SNP rs10455872 and rs3798220 and KIV2 repeats	RR 1.6 for carriers of combined genotype vs non-carriers for incident AS OR 2.9 for Lp(a) 95th percentile vs <22nd percentile
Arsenault et al[76]	2014	497	LPA SNP rs10455872	Carriers HR 1.78 vs. non-carriers Q5 vs. Q1) for incident AS
Langsted et al[20]	2016	1437	PCSK9 R46L loss-of-function mutation	OR 0.64 for PCSK9 R46L for carriers vs. non-carriers
Kamstrup et al[22]	2017	725	LPA SNPs rs10455872 and rs3798220 and KIV2 repeats	OR 3.2 for OPL-apoB and 2.9 for OxPL-apo(a) for 95th percentile vs <34th percentile
Cairns[21]	2017	535	LPA SNPs rs10455872 and rs3798220	RR per minor allele: rs10455872 1.69, rs2798220 1.66
Chen[23]	2018	3469	LPA SNPs rs10455872 and rs3798220	RR per minor allele: rs10455872 1.34, rs2798220 1.31
Helgadottir et al[24]	2018	6886	LPA SNP rs10455872	Meta-analysis of 6 studies (Iceland, Sweden MDCS, Sweden Stockholm, UK biobank, Norway HUNT, USA Michigan) OR 1.46 for carriers vs. non-carriers

Table 2.

Ongoing trials of medical therapy for treatment of native AS with valve endpoints.

Study	NCT #	Intervention	Phase / # of patients	Main Inclusion Criteria	Main Primary Endpoint	Main Secondary Endpoint
SALTIRE II	NCT02132026	Denosumab, alendronic acid or placebo	II / 150	Age > 50 years, peak aortic jet velocity of >2.5 m/s, grade 2–4 calcification of the aortic valve on echocardiography	Change in aortic valve calcium score at 6 months and 2 years.	Change in aortic valve ^{18}F-NaF uptake at 6 months
EAVaLL	NCT02109614	Niacin 1500–2000 vs. placebo	II / 238	Aortic sclerosis or mild aortic stenosis (aortic valve area [AVA] >1.5 cm^2, mean gradient [MG] < 25 mmHg) and high Lp(a), Lp(a) >50 mg/dL	Calcium score progression by cardiac CT over 2 years	Change in peak velocity (in m/s); Change in mean gradient (in mm Hg); Change in AV area (in cm^2)
PCSK9 Inhibitors in the Progression of Aortic Stenosis	NCT03051360	PCSK9i vs placebo	II / 140	Mild-moderate AS, LDL-C >70 mg/dL	Progression of the calcium score measured by cardiac CT and by ^{18}F NaF PET over 2 years	Efficacy of inhibition in calcium score progression by the presence of Lp(a) SNPs
Bicuspid Aortic Valve Stenosis and the Effect of vitamin K2 on Calcium Metabolism on ^{18}F-NaF PET/MRI (BASIK2): a Pilot Study	NCT02917525	Vitamin K2 versus placebo	II / 44	Bicuspid aortic valve with mild-moderate aortic stenosis	Change in calcium metabolism, measured as uptake of the 18F-NaF tracer on a ^{18}F-NaF PET/CMR scan	Change in aortic valve calcium score, measured on CT.

SALTIRE = SALTIRE II and RANKL Inhibition in Aortic Stenosis

EAVaLL = A Pilot, Randomized Controlled-Trial of Lipoprotein(a) Lowering for the Prevention of Aortic Valve Disease- Translating Genomic Knowledge for Cardiovascular Prevention