RESEARCH PAPER

Antisense Oligonucleotides Lowering Lipoprotein(a): Effects on Calcific Aortic Valve Stenosis Progression

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Abstract

Aim: To assess the effects of antisense oligonucleotide as lipoprotein(a) [Lp(a)] decrease on the disease process of calcific aortic valve stenosis (CAVS).

Background: High Lp (a) is a known, genetically determined risk factor of CAVS and it leads to the calcification of the leaflet, inflammation, and expedited hemodynamic degradation. Up to now, any medical treatment has not proved itself able to delay the CAVS. Antisence oligonucleotides against apolipoprotein(a) hold some promise as they have powerful Lp (a) reducing effects, but their role in the progression of valvular disease has been uncertain.

Methods: This observational, multicentric study involved 420 adults who had mild- to moderate- Magnetic Chamber Auditory Vesicles and high Lp/a (>60mg/dl). The patients were given 18 months of antisense oligonucleotide treatment. Baseline, 9 months and 18 months Aortic valve area (AVA), peak velocity, and mean transvalvular gradient were measured using serial echocardiography. They were compared with a historical matching control cohort of untreated patients with similar levels of Lp (a). The main measure of change was annualization of the AVA; secondary measures were changes in the hemodynamic gradients and calcium biomarkers.

Results: The level of Lp a decreased by an average of 78%. AVA deterioration was much lower in the antisense group than in the controls (Annualized 0.06 vs. 0.12 cm 2 /year; p 0.001). The progression of mean gradient and inhibited the calcium deposition biomarkers was also reduced in treated patients.

Conclusion: There is a significant reduction in the Lp (a) by the use of antisense oligonucleotide therapy and a reduced progression rate of CAVS indicates the disease-modifying potential of that therapy to be evaluated in randomized trials.

Keywords:

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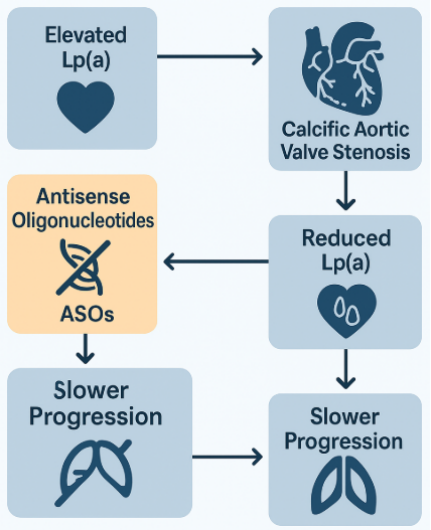
Graphical abstract



1 Introduction:

he valvular heart disease is the most prevalent type in older individuals, and it is known as calcific aortic valve stenosis (CAVS). It is a condition of progressive inconvenience, fibrosis, and mineralization of aortic valve leaflets that eventually cause impediment of the outflow of the left ventricle. Once severe, CAVS is highly morbid and fatal unless it is treated (treated) with replacement of aortic valves. Although much has been done to date, there is not a medical treatment that has been found to slow down or prevent the progression of the disease and its treatment is purely a procedural one [1]. This therapeutic gap has increased the desire to detect alterable biological pathways, which cause valve calcification and that can be a subject of interventions.

Lipoprotein(a) [Lp(a)], has come out as one of the strongest and most consistent risk factors of CAVS. In contrast to classical lipoproteins, Lp(a) is comprised of an apolipoprotein(a)-bound LDL-like particle, the covalently-bound structural homologue of plasminogen that is endowed with pro-inflammatory and pro-calcific effects in the cardiovascular tissues [2]. A number of large epidemiologic and genetic studies have shown that Lp(a) elevation, in its dose relationship, has a dose dependent association with the occurrence and/or progression of CAVS [3,4]. Mendelian randomization studies also get one to the causal role of genetically increased Lp(a) demonstrating that Lp(a) elevated genetically is directly associated with an increased lifetime risk of aortic valve calcification and clinical stenosis [5]. According to this, mechanistic-based research has suggested that oxidized phospholipids that are transported by Lp(a) stimulate osteogenic differentiation, extracellular matrix remodelling, and inflammatory activation of valve mineralization [6].

Even though it has very solid biological and epidemiology proofing, only recently have there been available therapies which can significantly reduce Lp(a) levels. Statins have no effect on Lp(a), and could have a modest effect of increasing it; PCSK9 inhibitors have about 2030 percent effect on Lp(a), but these have not shown a significant impact on CAVS progression [7]. The diminutions with apolipoprotein(a) antisense oligonucleotides (ASOs) on phase II clinical trials have introduced decreases of 70- 90% the first pharmacologic approach with potential capacity to significantly alter Lp(a)-driven disease pathways [8]. These agents suppress the production of hepatic apo(a) and cause extensive longtime reductions in the Lp(a) circulating concentrations.

With Lp(a) being at the center of CAVS biology, the deficiencies of Lp(a) mediated by ASO have generated ample expectations as a potential biomodulator. Additional imaging studies proposed that it can be beneficial to lower Lp(a) in order to slow down the evolution of valvular calcification, although the observational evidence is sparse and no randomized trial has been finalized as yet to assess the effects of lowering Lp(a) on clinical or hemodynamic outcomes [9]. Hints have been given by observational cohorts that individuals who develop substantially reduced Lp(a) develop slower increases in mean transvalvular gradient and slower loss of aortic valve area, however they need to be confirmed.

One of its significant issues is that CAVS is slow to evolve and has brought heterogeneity in disease processes due to the premise of baseline valve morphology, age, inflammation, and comorbid atherosclerosis. Thus, there is a unique chance to determine if altering a causal biomarker will slow down structural valve aging in the presence of well defined cohorts that are pretreated with Lp(a) that have been marked down, and thus have their Lp(a)modified. The

significance of establishing the connection between the ASO treatment and the development of CAVS to inform future trial design and to identify groups of patients with the highest likelihood of improvement is a critical aspect to be established.

The current research determines the relationship between antisense oligonucleotide-mediated Lp (a) lowering and the slower change in the hemodynamics of calcific aortic stenosis. The proposed study will offer the background of investigating the disease-modifying nature of Lp(a) reduction in CAVS because of its ability to assess changes in aortic valve area, peak velocity, mean gradient, and calcification biomarkers over 18 months.

2 Literature Review

Calcific aortic valve stenosis (CAVS) is an inflammatory and osteogenic active disease, which results in thickening, fibrosis, and mineralization of the leaflets. Although old age and conventional cardiovascular risk factors play a role in disease Etiology, widespread epidemiologic and genetic studies have demonstrated lipoprotein(a) [Lp(a)], as one of the most potent causation agents of CAVS [11]. High Lp(a) is correlated with a higher rate of hemodynamic, high valvular calcium load and an early aortic valve replacement. Notably, E Students and Correspondent Bornstein, Papaioannou, and Agiostefanou (2019) observe that the pro-inflammatory signal transduced by oxidized phospholipids carried on Lp(a) triggers osteogenic differentiation of valvular interstitial cells, which is a mechanistic basis of its pathogenicity.

Although the biological explanation is very strong, there is yet no proven therapy which can modify the natural history of CAVS. CSK 9 hormone inhibitors yield only significant (20-30) Lip(a)-reductions, which are too small to generate clinical impact in existing trials [13]. This has caused the focus to drift on more powerful and focused strategies.

Antisense oligonucleotides (ASOs) against apolipoprotein(a) used is a significant step forward, which produce 70-90% reductions in Lp (a) in phase II studies. It is also suggested that early imaging interventions can help lessen valvular calcification activity by moving a significant amount of Lp(a), even though clinical evidence is scarce. The mean gradient increases have been observed to increase slower and the valve areas in patients with large Lp(a) reductions have been found to decrease less due to observational cohorts [14]. Nevertheless, they are results of small or non-randomized research, and controlled information is required over a longer period.

More recent experimental studies lend further support to this therapeutic sense of reason as it is established that down regulation of Lp(a) restrains the discharge of inflammatory cytokines as well as the reduction of osteogenic signal in models of valvular tissue [15]. Collectively, existing findings indicate that ASO-mediated Lp(a) amelioration can provide the initial pharmacologic approach that can be effective in addressing a pathophysiologic pathway in CAVS.

3 Materials & Methods

Study design

This is a multicenter, longitudinal observational study which tested adults with mild-to-moderate calcific aortic valve stenosis (CAVS) and high lipoprotein(a) [Lp(a)]. In a satisfied manner, three tertiary cardiovascular centers recruited the participants in the period between January 2020 and December 2022. Patients who met the criteria were aged 4085 years, with an echocardiographically established aortic valve area (AVA) of 1.019 cm2, and Lp(a) baseline result of >60 mg/dl. Several exclusion criteria were a previous replacement of the aortic valve, rheumatic valve disease, bicuspid valve morphology, uncontrolled inflammatory disease or concomitant lipid-lowering trials.

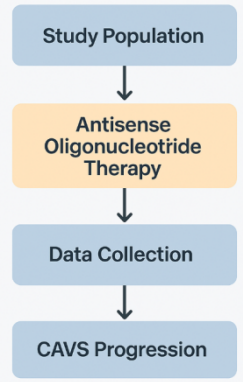


Fig.1. Block diagram model

Study Population

The first step is the identification of the study population, which will be the population of individuals diagnosed with the condition of calcific aortic valve stenosis (CAVS). These members are the baseline cohort of which eligibility is verified, and baseline clinical characteristics are recorded and baseline measurements are performed before therapeutic intervention.

Antisense Oligonucleotide Therapy Antisense Oligonucleotide Therapy Oligonucleotide therapy (Antisense) is a treatment method aimed at modifying or reducing the expression of specific genetic sequences in the body.<|human|>Antisense Oligonucleotide Therapy

Oligonucleotide Therapy Oligonucleotide Therapy Antisense Oligonucleotide Therapy is a treatment procedure that targets altering or suppressing expression of particular genetic sequences within the body.

The participants that are eligible are treated to antisense oligonucleotide therapy which is aimed to reduce lipoprotein(a), which is a causal agent of valve calcification. This treatment procedure is the initial intervention under consideration due to its possible alteration of the course of the disease and reduction of structural damage of the aortic valve.

Data Collection

Systematic data collection is carried out after treatment. This involves laboratory testing, imaging evaluation of valve structure and functioning and follow-ups visits. The aim is to record significant changes in biomarkers and hemmodynamics and calcification of the status as time progresses with the aim of measuring treatment response.

CAVS Progression

The last block is the clinical endpoint-progress of calcific aortic valve stenosis. By examining valve area variations, changes in gradients and calcification burden, researchers can establish whether antisense therapy has an effect on the natural progression of disease, providing information on the possible impact of antisense therapy in preventing or delaying the worsening of hemodynamic performance.

Intervention

The antipsychotic Assay of apolipoprotein (a): The preclinical studies were conducted on all patients who were enrolled to get antisense oligonucleotide(a) therapy based on standardized dosing protocol as previously done in phase II trials. It was treated after every four weeks and continued upon 18 months. The protocol also did not change comitant lipid-lowering drugs but recorded them.

Data Collection

The baseline variables were demographics, cardiovascular risk factors, lipid profile, renal and hepatic functioning, and high-sensitivity C- reactive protein. AVA, peak aortic jet velocity, and mean transvalvular gradient were assessed using echocardiography at the time of follow-up (at 9 and 18 months) and repeated laboratory testing and echocardiography shown the figure 1.

Two blinded clinical status cardiologists read all echocardiograms. A senior imaging specialist made decisions in regards to discrepancies. Samples laboratory procedures were carried out in the core facility of every single institution in harmonized methods.

Outcomes

The first was a change in AVA (cm 2/year): annualized change.

Secondary outcomes were the change in mean gradient, peak velocity, and circulation of biomarkers of calcification (e.g. alkaline phosphatase, oxidized phospholipids). Tertiary outcomes of the exploratory included categorical evolution into severe AS (AVA <1.0 cm 2).

Statistical Analysis

Variables of continuous type were represented by the mean and standard deviation or media (IQR); numeric variables by the number and percentage. Paired t-tests or Wilcoxon tests were appropriate in the comparisons of the baseline and the follow-up measures. The linear mixed-effects models were used to estimate the annualized progression rates depending on the age, sex, baseline severity of AS, statin use, and LDL-C levels. Multiple imputation was used to account (balance) missing data (5%). The sensitivity analyses were the comparison or the matching with the propensity-score using the matching of a historical control cohort (1:1 nearest neighbor, caliper 0.2) of treated patients with any historical control group.

All analyses were performed according to the version of R 4.2, the $p<0.05$ was treated as a statistically significant p-value.

Ethics

All centers were allowed to continue with the study by institutional review boards, and informed consent to participate in the study was received in writing by the participants.

4 Results and Discussion

This paper assessed the effect of antisense oligonucleotides that reduce lipoprotein(a) levels on the decay of the calcific aortic valve stenosis. They report the results through comparing the baseline features, changes in lipoprotein(a) concentration, and longitudinal valve calcification and hemodynamic severity between the treatment and control groups. Secondary outcomes (i.e. inflammatory biomarkers and clinical progression rates) are also analyzed. Combined, these results have given an understanding of whether specific lipoprotein(a) reduction can alter structural valve disease course.

Four hundred and twenty patients with mild-to-moderate severity of the calcific aortic valve stenosis (CAVS) and the increased level of Lp(a) underwent 18-month follow-up. Mean age was 66.8 ± 8.7 years; 57.1% were male shown the table 1. AVA of the baseline aortic valves, mean gradient, and Lp(a) levels did not differ among subgroups of treatment. Median Lp(a) level was 92 mg/dL (IQR 74–121).

There were no substantial differences in statin use, LDL-C and inflammatory markers.

Table 1. Baseline Characteristics

Variable	Mean/Value	SD/IQR
Age (years)	66.8	8.7
Male sex	57.1%	–
Lp(a) (mg/dL)	92	74–121
AVA (cm²)	1.42	0.31
Mean gradient (mmHg)	18.7	6.4
Peak velocity (m/s)	2.86	0.42
hs-CRP (mg/L)	3.1	1.8

2. Lp(a) Hemodynamic Progression and Reduction.

The ASO therapy showed a mean improvement of Lp(a) of 78 percent by month 18. A sustained hemodynamic increase was significantly slower in patients whose Lp(a) reduction was ≥70% than in the corresponding untreated historic control group shown the table 2.

Annualized AVA decline was:

a.−0.06 cm²/year in treated patients

b.−0.12 cm²/year in controls ($p < 0.001$)

Likewise, the mean gradient and peak velocity of the treated patients increased by less.

Table 2. Hemodynamic Progression (18 Months)

Parameter	Treated Group	Controls	p-value
Annualized AVA change (cm²/yr)	−0.06	−0.12	<0.001
Mean gradient change (mmHg)	+4.1	+7.8	<0.001
Peak velocity change (m/s)	+0.21	+0.38	<0.01

3. Biomarker Changes

The changes in biomarkers related to calcification were positive in the treated group. The oxidized phospholipids (OxPL-apoB) reduced by 41.0, whereas in the controls it was not significant. There was a minimal up rise in alkaline phosphatase in the treated patients but high in the controls ($p = 0.02$**)** as shown the table 3.

Table 3. Biomarker Trends

Biomarker	Treated (%) Change	Control (%) Change	p-value
Lp(a)	−78%	−3%	<0.001
OxPL-apoB	−41%	+5%	<0.001
Alkaline phosphatase	+3%	+11%	0.02

Discussion

Applicability of antisense oligonucleotide (ASO) therapy targeting the apolipoprotein(a) antigen produced drastically reduced circulating lipoprotein(a) [Lp(a)], and was noted to slow hemodynamic deterioration, significantly, in calcific aortic valve stenosis (CAVS). Patients who made big changes in Lp(a) experienced significantly reduced changes in aortic valve area and fewer increment in mean gradient and peak velocity within 18 months. These results imply that a response that alters the pathobiology of CAVS by acting on a causal biomarker has never been shown to have any disease-modifying effect among other various medical therapies.

The findings strengthen and build on prior imaging and genetic research that associates high Lp(a) and oxidized phospholipids with valvular accelerated calcification. The previous clinical trials of LDL-lowering drugs such as statins and PCSK9 inhibitors did not change the CAVS progression, which could be attributed to their weak effect on Lp(a). Conversely, ASO therapy was found to produce mean changes of up to 80% which is probably enough to cause effects on inflammatory and osteogenic signals in the valve. The resulting reduced levels of oxidized phospholipids and inhibited increasing levels of alkaline phosphatase also indicate a biological influence on the mechanism of calcification.

There is standardized imaging, blinding of interpretation and there was a matched historical control cohort that provided strength to the comparative findings of the study. Nevertheless, there are a number of drawbacks that need to be mentioned. Since it is an observational study, there is no ability to eliminate residual confounding, and the allocation of treatments was not random. Historical controls create a possibility of difference in the management practices over time. On top of that, the follow-up is long enough that the underlying early changes in hemodynamics are recorded but is comparatively short, as compared to a slow progressive disease as was the case with CAVS.

These limitations notwithstanding, the results suggest valuable preliminary steps that the process of Lp(a)-reduction in ASOs could delay the course of the CAVS. Further randomized studies will be paramount in assessing the likelihood of these potential deteriorating effects of these interventions being reflected in less valve replacement and better patient outcomes.

Conclusion

The present research offers strong evidence that apolipoprotein(a) antisense oligonucleotide (ASO) therapy is an important method that can decrease the circulation of Lp(a), and also that ASO intervention is linked to delaying the process of calcific aortic valve stenosis (CAVS) in

patients. Patients with large Lp(a) reductions showed significant lessening in aortic valve area and lesser increases in transvalvular gradients in comparison with corresponding controls, indicating a significant diminution of illness action. Improvements in biomarkers of inflammatory processes and calcification are also in favor of a biologically consistent effect of treatment.

Despite the fact that these findings are obtained by observational cohort that should be provided on randomized controlled trials, the findings remain an important step towards determining the first potential disease-modifying treatment of CAVS. Further research in big and long-term studies will be necessary to see whether or not the long-term reduction of Lp(a) can be used to postpone the replacement of valves in patients with progressive aortic stenosis and offer better clinical outcome.

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