Original research

Role of lipoprotein(a) concentrations in bioprosthetic aortic valve degeneration

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ABSTRACT

Objectives Lipoprotein(a) (Lp(a)) is associated with an increased incidence of native aortic stenosis, which shares similar pathological mechanisms with bioprosthetic aortic valve (bAV) degeneration. However, evidence regarding the role of Lp(a) concentrations in bAV degeneration is lacking. This study aims to evaluate the association between Lp(a) concentrations and bAV degeneration.

Methods In this retrospective multicentre study, patients who underwent a bAV replacement between 1 January 2010 and 31 December 2020 and had a Lp(a) measurement were included. Echocardiography follow-up was performed to determine the presence of bioprosthetic valve degeneration, which was defined as an increase >10 mm Hg in mean gradient from baseline with concomitant decrease in effective orifice area and Doppler Velocity Index, or new moderate/severe prosthetic regurgitation. Levels of Lp(a) were compared between patients with and without degeneration and Cox regression analysis was performed to investigate the association between Lp(a) levels and bioprosthetic valve degeneration.

Results In total, 210 cases were included (mean age 74.1±9.4 years, 72.4% males). Median time between baseline and follow-up echocardiography was 4.4 (IQR 3.7) years. Bioprostheses degeneration was observed in 33 (15.7%) patients at follow-up. Median serum levels of Lp(a) were significantly higher in patients affected by degeneration versus non-affected cases: 50.0 (IQR 72.0) vs 15.6 (IQR 48.6) mg/dL, p=0.002. In the regression analysis, high Lp(a) levels (≥30 mg/dL) were associated with degeneration both in a univariable analysis (HR 3.6, 95% CI 1.7 to 7.6, p=0.001) and multivariable analysis adjusted by other risk factors for bioprostheses degeneration (HR 4.4, 95% CI 1.9 to 10.4, p=0.001).

Conclusions High serum Lp(a) is associated with bAV degeneration. Prospective studies are needed to confirm these findings and to investigate whether lowering Lp(a) levels could slow bioprostheses degradation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ It is well established that elevated serum levels of Lp(a) are associated with an increased incidence of native aortic stenosis and calcification.
⇒ However, information regarding the role of Lp(a) in bioprosthetic aortic valve (bAV) degeneration is lacking.

WHAT THIS STUDY ADDS

⇒ High concentrations of Lp(a) are associated with structural bAV degeneration.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients undergoing a bAV replacement, Lp(a) levels could help predict the onset of structural valve degeneration.
⇒ Larger prospective studies are needed to confirm these findings and to investigate whether new therapeutics targeting Lp(a) could increase bioprostheses durability.

INTRODUCTION

The incidence of aortic stenosis (AS) is rising, mainly because of the rapid ageing of populations worldwide.[1] Bioprosthetic aortic valves (bAVs) are increasingly used for management of AS due to several reasons, including lower thrombogenicity, lack of obligatory long-term anticoagulation and the expansion of transcatheter aortic valve replacement (TAVR) indications.[2–4]

On the other hand, bAVs are susceptible to structural valve degeneration (SVD), which can limit their durability and expose patients to redo valve replacements. While the mechanisms underlying SVD are not completely understood, they could share similar pathophysiological ground with native AS, including atherosclerotic and inflammatory processes, which leads to progressive valve calcification.[4 5] These facts support the theory of a potential lipid-mediated mechanism accelerating SVD.[5]

Lipoprotein(a) (Lp(a)) is a low-density lipoprotein with an added apolipoprotein(a) which has proatherosclerotic, prothrombotic and pro-inflammatory effects.[6] It is well recognised that elevated serum levels of Lp(a) are associated with an increased incidence of AS and the need for aortic valve replacement.[7 8] However, information regarding the role of Lp(a) in SVD is lacking, with one recent publication reporting no association between serum Lp(a) concentrations and bAV degeneration over a 24-month follow-up period.[2] Considering the rapidly evolving development of

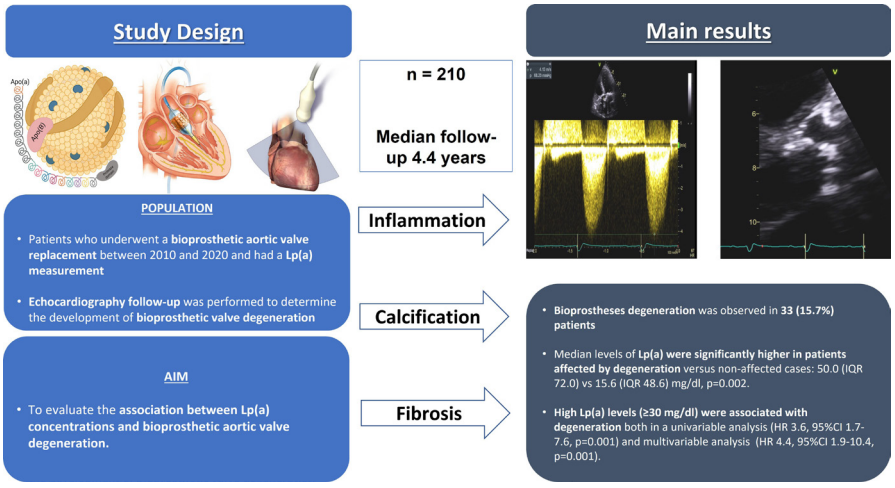

Figure 1 Graphical overview of the present study, with emphasis on study design and main findings. Lp(a), lipoprotein(a).

treatment options to lower Lp(a) levels,[9] a deeper understanding of its role as a predictor of SVD could be crucial to improve the therapeutics to increase bAV durability.

METHODS

Population

A retrospective cohort study was performed including patients identified in an electronic database at the three Mayo Clinic campuses (Rochester, Minnesota; Phoenix, Arizona; Jacksonville, Florida, USA). Patients who underwent a bAV replacement (both surgical and transcatheter) between January 2010 and December 2020 and also had a Lp(a) measurement were included (figure 1). Included patients must have had a baseline transthoracic echocardiography (TTE) performed during the first year after the aortic valve replacement and a follow-up TTE performed at least 24 months after the baseline test. If more than one follow-up TTE was performed during the considered time period, the most recent test was included for analysis. If the patient underwent a reintervention during follow-up due to SVD, the last TTE before reintervention was used. Patients with evidence of significant bAV abnormal function in the baseline TTE (Doppler Velocity Index (DVI) <0.25 or mean gradient >35 mm Hg or peak velocity >4 m/s, or severe prosthetic regurgitation) were excluded.[10]

Patient involvement

Patients were not involved in the design of this study, the recruitment and conduct of this research. Considering the retrospective nature of this research and the lack of an intervention, patients were not asked to assess the burden of the intervention and time required to participate in the research.

Echocardiography

TTE with 2D imaging and Doppler were performed using commercially available ultrasound scanners (ie, 33 or EPIQ (Philips Medical Systems) or Vivid E9 (GE Healthcare)). Tests were interpreted by cardiologists with a level III American Society of Echocardiography certification for competency in echocardiography.

Both baseline and follow-up TTE must have included measurement of aortic valve mean gradient, effective orifice area (EOA) and DVI to determine SVD. Significant SVD at follow-up was defined as follows:

a. An increase >10 mm Hg in mean bAV gradient from baseline status+a decrease in EOA+a decrease in DVI+exclusion of clinically thrombotic leaflet thickening.[11]
b. New moderate or severe prosthetic aortic regurgitation (if the main component was periprosthetic aortic regurgitation, then it was not considered).

Patient-prosthesis mismatch was defined as a baseline EOA index <0.65.[12]

Lp(a) concentrations

Electronic medical records were used to collect demographic characteristics, aortic valve replacement procedure information, therapeutics and laboratory test information, including serum levels of Lp(a). Serum Lp(a) levels were measured by immunoturbidimetric assay during the whole study period and were considered abnormally high when ≥30 mg/dL.[8]

Statistical analysis

Statistical comparisons between patients with and without SVD were performed using independent-samples t-test or independent-samples Mann-Whitney U test for continuous variables (according to distribution) and χ^2 for categorical variables. Cox regression was performed to evaluate the association between baseline Lp(a) levels and a binary SVD endpoint. For the Cox regression analysis, both a univariable and a multivariable analysis adjusted by risk factors for SVD identified by previous investigations (age, male sex, hypertension, smoking, patient-prosthesis mismatch, creatinine levels, low-density lipoprotein (LDL) levels and body surface area) were performed.[5 13 14] For this specific analysis, all the prespecified risk factors and Lp(a) were first analysed with a univariable approach, and a forward selection method was used to build the multivariable analysis with an entry criterion of p<0.05. Cox regression was also performed for mortality and clinical endpoints analysis to compare differences between groups according to Lp(a) concentrations. Time zero in the Cox models was set at the time of baseline TTE. The Kaplan-Meier estimator was used to show survival curves. Statistical analyses were conducted using IBM SPSS Statistics, V.28.0 (IBM Corporation, Armonk, New York, USA). Data were presented as means with SDs (mean±SD) or median and IQR (median (IQR)) for continuous variables and frequencies and percentages for categorical variables; p values <0.05 were considered statistically significant for all analyses.

Table 1 Baseline characteristics of the included population (N=210)

Age, years	74.1±9.4
Sex, n (%)	
Male	152 (72.4%)
Female	58 (27.6%)
Type of surgery, n (%)	
SAVR	147 (70.0%)
TAVR	63 (30.0%)
Body surface area, m^2	1.99±0.3
Body mass index, kg/m^2	29.5±5.9
Comorbidities, n (%)	
Hypertension	146 (69.5%)
Dyslipidaemia	183 (87.1%)
Smoking	11 (5.2%)
Medications, n (%)	
Aspirin	205 (97.6%)
Clopidogrel	85 (40.5%)
Warfarin	63 (30.0%)
DOACS	31 (14.8%)
ACEIs/ARB	146 (69.5%)
Beta-blockers	193 (91.9%)
Calcium channel blockers	66 (31.4%)
Statins	183 (87.1%)
Laboratory tests	
Creatinine levels, mg/dL	1.1±0.7
Lp(a) levels, mg/dlL	18.0 (IQR 58.7)
LDL-cholesterol, mg/dL	83.0 (IQR 34.5)
HDL-cholesterol, mg/dL	49.0 (IQR 20.0)
Triglycerides, mg/dL	114.0 (IQR 69.75)
Baseline TTE	
IVSd, mm	12.3±2.0
LVPW, mm	11.2±1.8
End-diastolic diameter, mm	48.4±5.9
Ejection fraction, %	60.4±9.5
Mean gradient, mm Hg	11.1±4.9
EOA, cm^2	2.3±0.7
EOA index, cm^2/m^2	1.1±0.4
LVOT velocity, m/s	1.2±0.2
AV velocity, m/s	2.3±0.5
Doppler Velocity Index	0.5±0.1
Aortic regurgitation	
None	178 (84.8%)
Mild	29 (13.8%)
Moderate	3 (1.4%)
Severe	0 (0.0%)
Mitral regurgitation	
None	108 (51.4%)
Mild	79 (37.6%)
Moderate	23 (11.0%)
Severe	0 (0.0%)
Patient-prosthesis mismatch, n (%)	8 (3.8%)

ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; AV, aortic valve; DOACs, direct oral anticoagulants; EOA, effective orifice area; HDL, high-density lipoprotein; IVS, interventricular septum; LDL, low-density lipoprotein; LVOT, left ventricular outflow tract; LVPW, left ventricular posterior wall; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

RESULTS

In total, 210 cases were included (mean age 74.1±9.4 years, 72.4% males, 30.0% of the procedures were TAVR). Median time between aortic valve replacement and baseline TTE was 5.0 (IQR 30.0) days. Median time between baseline TTE and the most recent follow-up TTE was 4.4 (IQR 3.7) years. Overall median time between the measurements of the Lp(a) levels and the aortic valve replacement was 5.2 (IQR 9.8) years; during this period, 39 patients (18.6%) had repeated Lp(a) measurements with no significant variation in Lp(a) concentrations: 26.0 (IQR 66.0) vs 25.0 (IQR 68.0) mg/dL, p=0.782. Median time between repeated tests was 2.2 (IQR 2.1) years.

Across all the cohort, median Lp(a) levels were 18.0 (IQR 58.7), with 79 patients (37.6%) having high (≥30 mg/dL) Lp(a) serum

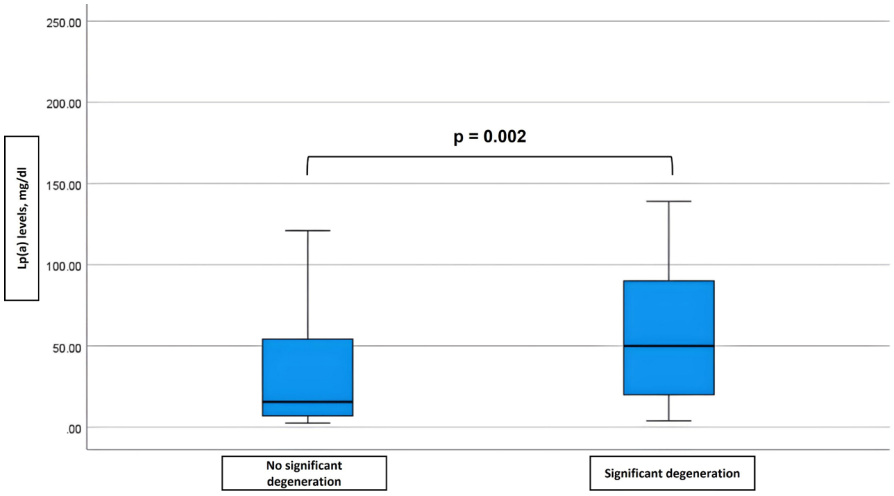

Figure 2 Box plot graph showing that lipoprotein(a) (Lp(a)) levels were higher in patients with significant bioprosthetic aortic valve degeneration.

concentrations. Patient-prosthesis mismatch at baseline TTE was present in eight (3.8%) patients. The baseline characteristics of the study population are shown in table 1.

SVD was observed in 33 (15.7%) patients at follow-up TTE. Median serum levels of Lp(a) were significantly higher in patients affected by SVD versus non-affected cases: 50.0 (IQR 72.0) vs 15.6 (IQR 48.6) mg/dL, p=0.002 (figure 2). In the Cox regression analysis, Lp(a) levels ≥30 mg/dL were associated with SVD both in the univariable analysis (HR 3.57, 95% CI 1.67 to 7.64, p=0.001) and multivariable analysis adjusted for other risk factors for SVD (HR 4.44 95%, CI 1.89 to 10.42, p=0.001) (table 2) (figure 3). This last finding was also consistent when evaluating Lp(a) levels as a continuous variable (per unit increase), both in the univariable analysis (HR 1.01, 95% CI 1.01 to 1.02, p=0.004) and multivariable analysis (HR 1.01, 95% CI 1.01 to 1.02, p=0.001) (table 3). Considering that the distribution of Lp(a) variable was positively skewed, an additional Cox regression analysis after a log10 transformation of Lp(a) was performed; the significant association between Lp(a) levels and SVD remains after the log transformation (online supplemental table S1).

In total, 57 (27.1%) patients died and 14 (6.7%) required an aortic valve reintervention during follow-up. No significant differences were seen when analysing survival probabilities or freedom from aortic valve reintervention according to the levels of Lp(a) (≥30 mg/dL vs <30 mg/dL) (figure 4).

Table 2 Association between high Lp(a) levels (≥30 mg/dL) and bioprosthetic aortic valve degeneration

Variable	P value	HR	95% CI for HR
Univariable analysis			
Lp(a) ≥30 mg/dL	0.001	3.57	1.67–7.64
Smoking	0.167	2.12	0.73–6.17
Body surface area, per unit increase	0.075	0.25	0.54–1.15
Male sex	0.267	1.56	0.71–3.44
LDL-C, per unit increase	0.669	1.00	0.99–1.01
Hypertension	0.284	1.51	0.71–3.18
Age, per unit increase	0.661	0.99	0.95–1.03
Patient-prosthesis mismatch	0.748	0.72	0.10–5.35
Creatinine levels, per unit increase	0.837	1.05	0.65–1.71
Multivariable analysis			
Lp(a) ≥30 mg/dL	0.001	4.44	1.89–10.42
Smoking	0.016	4.08	1.30–12.84

LDL-C, low-density lipoprotein-cholesterol.; Lp(a), lipoprotein (a).

DISCUSSION

In this retrospective cohort study including 210 patients, high serum concentrations of Lp(a) were associated with a higher risk of SVD after aortic valve replacement at a median follow-up of 4.4 years. The results were consistent in the univariable analysis and in the multivariable analysis after adjusting by risk factors that have been associated with SVD such as young patient age, smoking, hypertension, renal failure, increased body surface area, LDL levels and patient-prosthesis mismatch of the implanted valve. [13 14] To the best of our knowledge, this is the first report demonstrating an association between Lp(a) and SVD.

Although Lp(a) has received less attention compared with other cardiovascular disease treatment targets, emerging medications to lower Lp(a) levels are being developed.[9] Therefore, a deeper understanding of its role as predictor of cardiovascular conditions could be crucial. Lp(a) is a well-recognised risk factor for cardiovascular disease, including myocardial infarction, ischaemic stroke and calcific AS,[15] but its association with SVD was not clear in the literature.

As mentioned, there is consistent epidemiological and genetic evidence that high Lp(a) concentrations are associated with the development of native AS. [16–18] A strong and consistent association between a genetic variant affecting Lp(a) levels (rs10455872) and AS risk was indeed confirmed recently by genome-wide association studies and cohort studies, thus providing support for Lp(a) as a therapeutic target for AS prevention.[19 20] Lp(a) is an important carrier of oxidised phospholipids which are considered key culprits for the development of aortic valve calcification.[16 18] Moreover, the pathophysiological role of Lp(a) in aortic valve disease could be attributable, at least in part, to the role of autotaxin. Autotaxin is a key enzyme that catalyses oxidised phospholipids to produce lysophosphatidic acid, a process that promotes valve calcification. A recent study demonstrated that autotaxin activity and lysophosphatidic acid contents are high in Lp(a).[21]

Mechanisms underlying SVD are still incompletely understood, with recent studies providing evidence that multiple active processes are involved in its pathogenesis, including

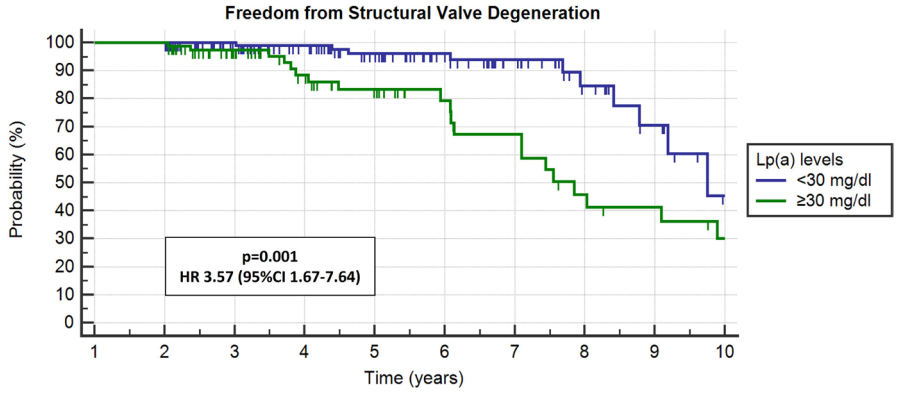

Figure 3 Freedom from structural valve degeneration after a bioprosthetic aortic valve replacement according to the levels of lipoprotein(a) (Lp(a)).

similarities with native AS such as inflammation (explained in part by long-term immune rejection) and atherosclerosis-like tissue remodelling.[22] Therefore, studying the association between Lp(a) levels and SVD seems to have solid pathophysiological bases.

Although not analysing specifically Lp(a) levels, one prospective study demonstrated that a dysmetabolic profile characterised by elevated plasma lipoprotein-associated phospholipase A2 activity and proprotein convertase subtilisin/kexin 9 was associated with increased risk of SVD.[3] On the other hand, and despite the above-mentioned pathological similarities between AS and SVD, a recent post hoc analysis from a prospective multimodality imaging study suggested that serum Lp(a) concentrations were not associated with imaging or haemodynamic SVD at baseline (1 month, 2, 5 or 10 years after the intervention) or over 24 months of follow-up.[2]

Apart from the larger sample size of our study, other reasons could contribute to our different findings in comparison with prior negative reports.[2] Our study included only patients with a baseline TTE close to the date of the valve replacement (median time: 5 days) when other studies included patients at different timepoints after the valve intervention, potentially increasing the heterogeneity of the sample. Specifically, without a close baseline TTE, the data could reflect the disease progression rather than the incidence/onset of the SVD. It has been theorised by some studies that Lp(a) is associated with baseline and new-onset aortic valve calcification, but not with the disease progression, suggesting that Lp(a) mainly drives the initiation, but not the propagation of aortic valve disease, which can be highly influenced by other factors.[23] Additionally, the relatively short follow-up duration in prior studies may not completely catch SVD events, which is commonly considered a progress of 5 years or more.[11 24] Selecting patients without first aortic valve calcifications (close to the aortic valve replacement) and deciding on the best definition of high Lp(a) concentrations could also have influenced the results.

SVD is a rising concern, considering that bAV implantation is increasingly becoming the treatment of choice for AS and valve replacement interventions are predicted to steadily increase in the future decades.[25] Although it is difficult to precisely estimate the overall incidence of SVD considering the heterogeneity of host factors and the rapid evolvement of bioprostheses and interventional procedures, rates of SVD can be as high as 50% at 8 years post-implantation, with higher rates with longer follow-up periods.[4 11 26]

Considering the above-mentioned factors, there is an increasing need to accurately predict SVD and to develop novel methods and treatments to increase bAV durability. Therefore, evaluation of Lp(a) as a therapeutic target to fight against AS and SVD could be a future field of study. This is even more important, given the fact that up to now, no medical therapy has been shown to be capable of slowing disease onset and progression of either entity, beyond surgical or transcatheter interventions.[16] However, ahead of therapeutic trials, the role of Lp(a) in SVD should be investigated in larger prospective studies.

Table 3 Association between Lp(a) levels (per unit increase) and bioprosthetic aortic valve degeneration

Variable	P value	HR	95% CI for HR
Univariable analysis			
Lp(a) levels, per unit increase	0.004	1.01	1.01–1.02
Multivariable analysis			
Lp(a) levels, per unit increase	0.001	1.01	1.01–1.02
Smoking	0.044	3.11	1.03–9.39

Lp(a), lipoprotein (a).

LIMITATIONS

The limitations of this study include its retrospective nature. Even when the sample size represents a small portion of patients, this is to our knowledge the largest study performed up to date regarding this topic. Our cohort was mainly composed of elderly patients with calcific degenerative AS, thus the results of this study may not apply to younger patients with aortic valve disease of different aetiologies. It was not standardised practice to measure Lp(a) in all patients undergoing aortic valve replacement, thus introducing potential selection bias. A relatively small number of primary endpoint cases (SVD) were noted in this cohort, thus implying a potential risk of overfitting in the multivariable analysis. The difference in time between the baseline and follow-up TTEs was heterogeneous to some extent, so it is hard to make recommendations about when to ideally perform the assessment for SVD. This study used only TTE for the assessment of SVD, thus a haemodynamic definition of SVD was used; a comprehensive multimodality imaging strategy could be more accurate to better define SVD.

Even when a trend to an increase in aortic reinterventions procedures was seen in the group with higher Lp(a) levels, no significant differences were seen when analysing survival

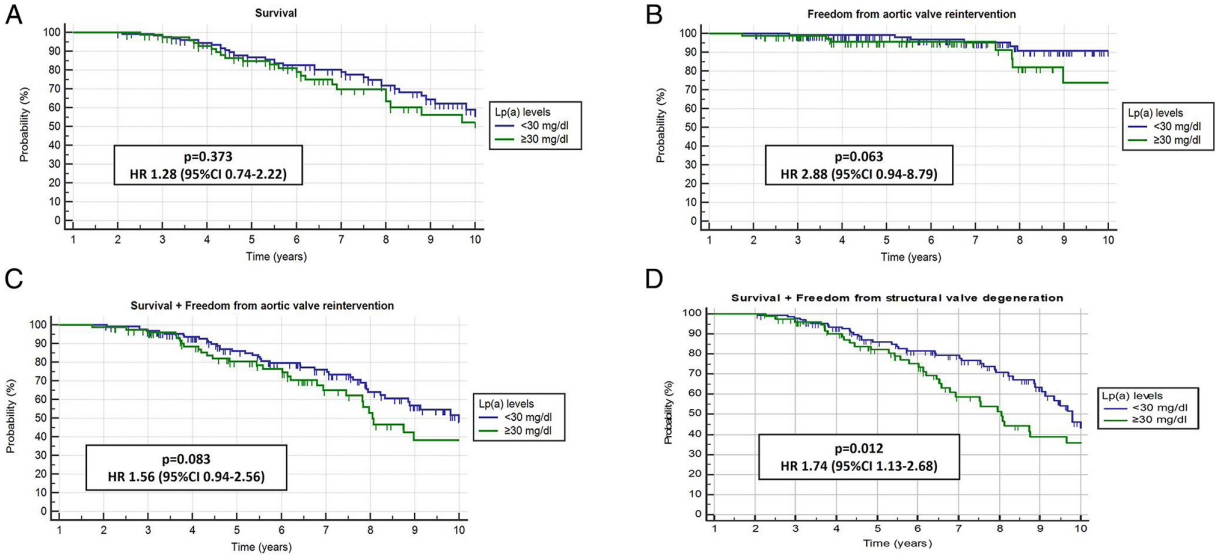

Figure 4 A. Survival probability after a bioprosthetic aortic valve replacement according to the levels of lipoprotein(a) (Lp(a)). (B) Freedom from aortic valve reintervention after a bioprosthetic aortic valve replacement according to the levels of Lp(a). (C) Survival probability+freedom from aortic valve reintervention after a bioprosthetic aortic valve replacement according to the levels of Lp(a). (D) Survival probability+freedom from bioprosthetic aortic valve degeneration according to the levels of Lp(a).

probabilities or freedom from aortic valve reintervention according to the levels of Lp(a). This fact could be related to several factors, including the small sample size of the study, the small rate of reintervention procedures in this cohort (6.7%) and the relative short median follow-up for clinical endpoints in this study. The time between the development of subclinical SVD and clinically relevant SVD is difficult to predict and can be affected by several variables, thus a longer follow-up period could help detect higher rates of clinical events in this population.[27]

CONCLUSION

High serum Lp(a) concentration is independently associated with SVD according to this retrospective study. Prospective studies are needed to confirm these findings and to investigate whether lowering Lp(a) could increase bioprostheses durability. This is timely considering the new therapeutics that are being developed to target this molecule.

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Contributors RA is responsible for the overall content as guarantor. JMF, CJC, MP, MR, RA and FM contributed to study design. MP, MR, EFS and TB collected and cleaned data. JMF, MP and MR performed analyses with statistical supervision by CJC, CA, RA and FM. JMF, CJC, TB, SA, KSD, JPS, DFF, CA, SJL and JKO drafted the manuscript including tables and figures. All coauthors interpreted results, generated content for discussion, critically reviewed manuscript and contributed to revisions.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by Mayo Clinic institutional review board, protocol number 20-010249.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data that support the findings of this study are available from the corresponding author on reasonable request.

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