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ORIGINAL RESEARCH

Lipoprotein(a) Levels in Severe Aortic Stenosis Referred for Transcatheter Aortic Valve Implantation Compared to Controls

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ABSTRACT

BACKGROUND Limited observational reports link elevated lipoprotein(a) (Lp[a]) levels to aortic stenosis (AS) or to disease progression. Data on large cohorts of verified severe AS patients are lacking.

OBJECTIVES The purpose of the study was to characterize Lp(a) levels of severe AS patients referred to transcatheter aortic valve implantation (TAVI) and compare them to a large cohort of Lp(a) samples derived from the general population.

METHODS Lp(a) levels obtained from frozen serum samples of TAVI patients between 2012 and 2017 were compared to a control group for whom Lp(a) levels were obtained for any reason and stratified by gender. Multivariable binary logistic regression analyses were conducted to investigate associations between younger age at TAVI and an Lp(a) cutoff of 50 mg/dL.

RESULTS Lp(a) levels of 503 TAVI were compared to 25,343 controls. Patients in the AS group had mildly higher median Lp(a) levels compared to controls (20.5 vs 18.7 mg/dL, $P = 0.04$). Lp(a) levels in males with severe AS were higher than controls (19.9 vs 16.6 mg/dL, $P = 0.04$). Females had a nonsignificant difference (22.1 vs 21.3 mg/dL, $P = 0.87$). In multivariable analysis, an Lp(a) cutoff of above 50 mg/dL was not associated with an earlier age at TAVI (beta: 1.04; 95% CI: 0.42-2.57; $P = 0.94$).

CONCLUSIONS Median Lp(a) levels were only mildly higher in severe AS patients undergoing TAVI in comparison to a large control group, mainly driven by higher Lp(a) levels in males. Higher Lp(a) levels were not associated with an earlier age at TAVI, rejecting its association with an accelerated disease progression. (JACC Adv. 2024;3:101264)

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ABBREVIATIONS AND ACRONYMS

AC = all-comers

AS = aortic stenosis

CVD = cardiovascular disease

LDL = low-density lipoprotein

TAVI = transcatheter aortic valve implantation

Aortic stenosis (AS) incidence is projected to dramatically increase (>300%) by 2050.[1] Despite effective interventional options for aortic valve replacement, their capacity currently does not meet the high demand, a deficit anticipated to escalate with the aging population.[2,3]

Calcific AS, by far the most common cause of AS worldwide, and in the western world specifically,[4] shares a common pathophysiology with cardiovascular disease (CVD), including atherosclerosis, calcification, and inflammation. In contrast to other CVDs, there are no pharmacologic treatment options that effectively counteract AS progression.[1]

Lipoprotein a (Lp[a]) is a low-density lipoprotein (LDL)-like particle containing apolipoprotein B100. As opposed to LDL, Lp(a) concentration levels are genetically determined, and levels remain relatively stable over a lifetime without significant dietary or environmental influences.[1] High Lp(a) levels and genetic variants have been proven to promote valvular calcification with a causal association to AS,[5-7] but recent studies[8,9] have called into question the previously established correlation between increased disease activity and accelerated disease progression.[10-12]

Our aim was to characterize the distribution of Lp(a) levels of patients with severe AS and compare them to a large cohort of patients in the general population. We questioned whether consecutive patients with documented severe AS who were referred to transcatheter aortic valve implantation (TAVI) have higher levels of Lp(a) as compared to a very large all-comer cohort of patients from whom Lp(a) samples were obtained for any reason. We also analyzed the association of earlier age with an earlier referral for intervention as a possible marker for accelerated disease progression.

METHODS

We conducted an observational analysis on laboratory data obtained from the electronic medical records of a university-affiliated tertiary referral center, as well as on data obtained from frozen serum samples of a large registry of consecutive patients referred to TAVI between the years 2012 and 2017. Laboratory analyses were supported using a grant from the Novartis external grants program. Specifically, the funding was entirely allocated to laboratory testing performed on the frozen serum samples. The funder had no part in the design and interpretation of study outcomes.

STUDY POPULATION. We compared two groups: severe AS group (AS) and control group. Lp(a) levels of persons in the control group were extracted from the institutional MDCLONE database, a system designed to ease data extraction from electronic medical record.[13,14] The control group Lp(a) tests were conducted mainly as an outsourced laboratory test provided as a service to health care maintenance corporations, or in the minority of cases (<10%), for patients at the medical center's outpatient clinics or for hospitalized patients. Although Lp(a) levels are genetically determined and generally stable throughout an individual's life, this study excluded individuals under 18 years old due to potential increases in Lp(a) levels into adulthood.[1] Additionally, the exclusion mitigated confounding from early manifestations of genetic diseases in which Lp(a) levels were assessed for diagnostic purposes.

All patients undergoing TAVI had symptomatic and severe AS. The diagnosis of severe symptomatic AS conformed to published guidelines,[15] utilizing clinical, echocardiographic, and hemodynamic criteria. As detailed in a previous study,[16] severe AS was defined by an aortic valve area less than 1 cm^2, an aortic valve mean gradient exceeding 40 mm Hg, and a peak jet velocity greater than 4 m per second. Each patient was assessed by our institutional heart team and classified as intermediate or high-risk for conventional valve surgery. Baseline patient, procedural, and echocardiographic characteristics, as well as outcomes, were described previously in detail.[17,18]

This study received authorization from the institutional review board, including a waiver of informed consent for accessing information from the institutional database within the MDCLONE system. All TAVI patients gave informed consent for additional laboratory testing as part of their participation in our TAVI registry.[17,19]

LABORATORY METHODS. Severe AS patient Lp(a) levels were obtained from frozen serum samples of consecutive TAVI patients, originally obtained as part of the TAVI index hospitalization, and immediately processed and frozen at −80 °C. For quality control in the TAVI group, we compared known values of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and LDL cholesterol levels obtained from routine preprocedural workup during the index TAVI hospitalization. A 10% cutoff was determined as plausible a priori. The 503 frozen samples were therefore also tested for cholesterol, triglycerides, and high-density lipoprotein cholesterol, analyzed using a Siemens chemistry system (SIEMENS

Healthcare Diagnostics Inc). LDL cholesterol levels extrapolated were calculated using the Friedewald formula. Lp(a) levels were measured by a quantitative immunoassay method using an ADVIA Chemistry system (SIEMENS Healthcare Diagnostics Inc) with a reference range <30 mg/dL. All Lp(a) measurements were conducted with an identical method, and Lp(a) assays are traceable to an internal standard.

STATISTICAL ANALYSIS. Continuous variables for Lp(a) right-skewed distributions are reported as medians and interquartile ranges and compared using the Mann-Whitney U tests, and continuous variables with normal distribution are reported as mean ± SD and compared using the student's t test. Categorical variables are reported as numbers (percentage) and compared using Pearson's chi-test or Fisher's exact test. The normal distribution of continuous variables was assessed using histograms and Q-Q plots. A two-tailed P value <0.05 was considered statistically significant. Subgroup analyses of persons over 65 years old and persons with diabetes were also conducted. For patients with severe AS admitted for TAVI, multivariable binary logistic regression models were used to estimate the association of an Lp(a) cutoff of 50 mg/dL with a younger age requirement for TAVI with different age cutoffs of 70, 75, and 80 years. A similar linear regression model was performed for age as a continuous variable. An Lp(a) cutoff of above 50 mg/dL was chosen due to its association with enhanced CVD risk in patients with and without baseline CVD.[20] Multivariable analyses for the young age cutoffs were adjusted for baseline characteristics associated with cardiovascular risk (body mass index, diabetes, hypertension, coronary artery disease, history of stroke or transient ischemic attack, smoking history, LDL cholesterol, glomerular filtration rate, and Society of Thoracic Surgeons score). A 1:1 propensity-matched analysis based on gender, age, and baseline diabetes, hypertension, and ischemic heart disease were also conducted, with a match tolerance of 0.1. Statistical analyses were conducted using IBM SPSS for Windows, Version 29.0 (released in 2022).

RESULTS

STUDY POPULATION. The control group comprised a total of 27,451 Lp(a) samples that were collected between 2007 and 2023 for various reasons. After exclusion of patients under 18 years old, 25,343 patients remained in the control group. The AS group comprised samples of 503 patients with severe AS referred to TAVI at our institution. Overall, 25,846 Lp(a) measurements were available. Quality control yielded differences under 10% (Supplemental Table 1). Baseline characteristics of both study groups can be seen in **Table 1**. The control group had a mean age of 54.3 years and comprised 45.1% females. AS patients had a mean age of 83.1 years and comprised 55.5% females. Body mass index and body surface area did not differ significantly between groups; however, comorbidities were more commonly observed in the AS group. Lipid parameters were generally elevated in the control group, with the exception of high-density lipoprotein cholesterol, which was comparable across both groups.

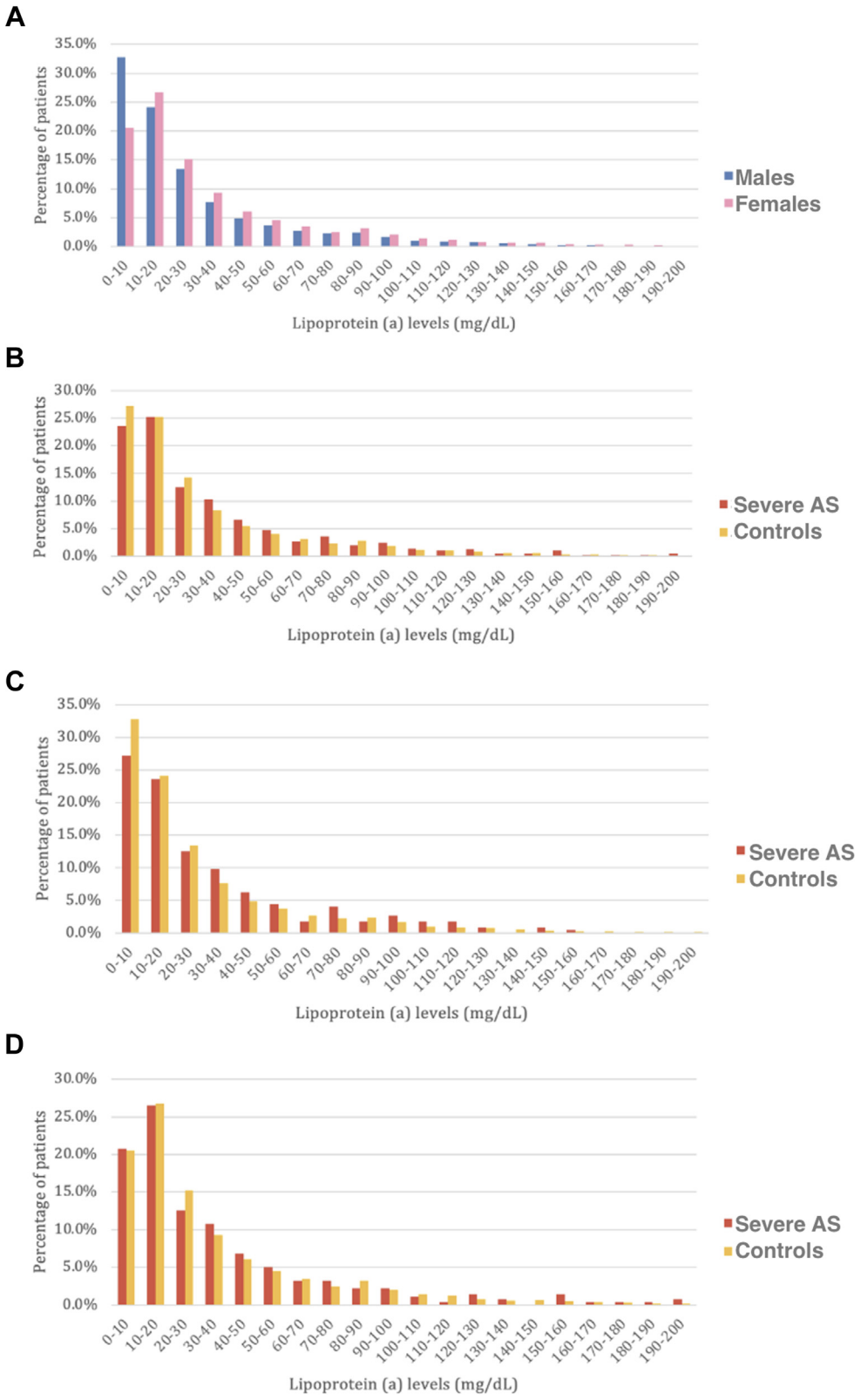
TABLE 1 Baseline Characteristics of Severe Aortic Stenosis Patients and Controls

	Severe Aortic Stenosis (n = 503)	Controls (n = 25,343)
Age (y)	83.1 ± 6.2	54.3 ± 13.1
Female	279 (55.5%)	11,419 (45.1%)
Height (cm)	163.0 ± 9.1	168.6 ± 14.3
Weight (kg)	72.5 ± 13.6	77.1 ± 17.1
Body mass index (kg/m^2)	27.3 ± 4.7	27.0 ± 12.0
Body surface area (m^2)	1.81 ± 0.19	1.88 ± 0.25
Hypertension	433 (87.5%)	2,291 (8.6%)
Diabetes	191 (38.6%)	1,041 (3.9%)
Chronic kidney disease	172 (34.2%)	335 (1.2%)
Ischemic heart disease	275 (55.7%)	2,124 (7.9%)
Total cholesterol (mg/dL)	144 (123-168)	174 (143-207)
LDL cholesterol (mg/dL)	77 (61-94)	102 (75-129)
HDL cholesterol (mg/dL)	45 (36-55)	46 (37-57)
Triglycerides (mg/dL)	91 (67-136)	102 (73-146)
Total cholesterol (mg/dL)	147.3 ± 34.8	175.3 ± 51.9
LDL cholesterol (mg/dL)	80.1 ± 26.1	103.6 ± 39.7
HDL cholesterol (mg/dL)	46.7 ± 15.1	47.7 ± 16.4
Triglycerides (mg/dL)	107.7 ± 59.5	125.6 ± 90.1
Hemoglobin (g/dL)	13.5 ± 1.7	11.9 ± 1.4
C-reactive protein (mg/L)	4.99 (1.26-17.66)	3.61 (0.89-12.62)
C-reactive protein (mg/L)	12.1 ± 17.3	17.2 ± 38.4
Creatinine (mg/dL)	1.28 ± 0.88	0.95 ± 0.44
Glomerular filtration rate (mL/min/1.73 m^2)	57.7 ± 20.4	82.7 ± 24.4

Values are mean ± SD, n (%), or median (IQR).
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

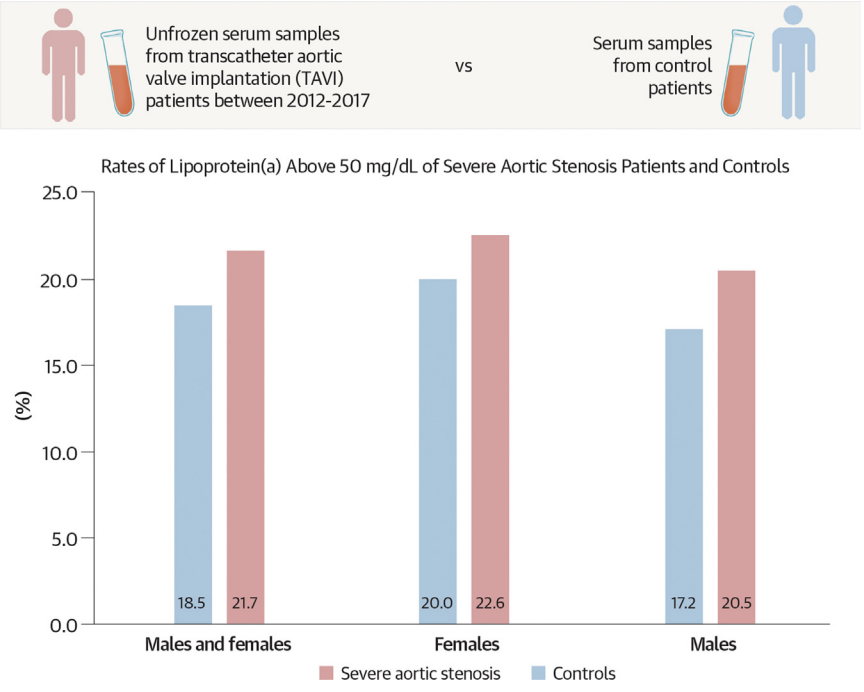
LIPOPROTEIN(A) LEVELS. Lp(a) levels in all groups showed right-skewed distribution curves (**Figure 1**). The median level of all Lp(a) samples was 18.7 (IQR: 9.2-39.7) mg/dL, with a range of 0 to 406.9 mg/dL. Lp(a) levels at 75%, 90%, 95%, 99%, and 99.9% percentiles were >39.7, >79.7, >102.5, >162.1, and >259.1 mg/dL, respectively. For all patients, females had higher Lp(a) levels than males (21.3 [IQR: 11.2-44.7] vs 16.7 [IQR: 7.6-35.8], $P < 0.001$). Lp(a) concentrations >30 mg/dL were found in 33.1% and 38.6% ($P = 0.01$) in the control group vs the AS group, respectively. Lp(a) concentrations >50 mg/dL were

FIGURE 1 Lipoprotein(a) Level Distributions of the Different Study Populations



Lipoprotein(a) showed right-skewed distribution curves in all groups. (A) Lipoprotein(a) levels in females vs males in the entire cohort; (B) lipoprotein(a) levels of patients with severe aortic stenosis vs controls for the entire cohort; (C) lipoprotein(a) levels of males with severe aortic stenosis vs controls; (D) lipoprotein(a) levels of females with severe aortic stenosis vs controls.

CENTRAL ILLUSTRATION **Rates of Lipoprotein(a) Above 50 mg/dL of Severe Aortic Stenosis Patients and Controls**



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found in 18.5% and 21.7% ($P = 0.07$) in the control group vs the AS group, respectively, with similarly higher but not statistically significant differences between males and females in the control group or AS group (Central Illustration).

Median levels of Lp(a) comparisons are displayed in Table 2. Patients with severe AS had higher Lp(a) levels (20.5 [IQR: 10.8-46.1] mg/dL) in comparison to the control group (18.7 [IQR: 9.7-39.5] mg/dL). Male patients with severe AS had higher Lp(a) levels (19.9 [IQR: 9.3-42.7] mg/dL) in comparison to those of the control group (16.6 [IQR: 7.6-35.7] mg/dL). Differences between female patients with severe AS (22.1 [IQR: 11.8-47.3] mg/dL) and females in the control group (21.3 [IQR: 11.2-44.6] mg/dL) were not statistically significant. When comparing Lp(a) levels of persons above 65 years old (n = 7,479), severe AS patients (n = 498) had a nonsignificantly ($P = 0.16$) higher median Lp(a) levels (20.4 [IQR: 10.7-46.1] mg/dL) than control group patients (19.3 [IQR: 9.2-40.4] mg/dL). Similarly, patients with severe AS and diabetes had higher median Lp(a) levels (23.2 [IQR: 10.3-47.5]) compared to those of control group patients with diabetes (19.5 [IQR: 7.6-40.4]). This difference did not reach statistical significance ($P = 0.16$), also when stratified for gender, with P values of 0.52 for males and $P = 0.17$ for females. In a propensity-matched analysis, Lp(a) levels were similarly nonsignificantly higher for AS patients (Supplemental Table 2).

AGE REQUIREMENT FOR TAVI AND LP(A) LEVELS.

We found no association between earlier age during the TAVI procedure and Lp(a) levels in all univariable (Supplemental Table 3) and multivariable analyses performed. A multivariable logistic regression analysis examining an association between TAVI before or after the age of 75 and having an Lp(a) level exceeding 50 mg/dL, while adjusting for CVD risk factors (Table 3), revealed no significant association with the age at which TAVI was performed (beta: 1.04; 95% CI: 0.42-2.57; $P = 0.94$). Age cutoffs of 70 years (beta: 4.14; 95% CI: 0.49-14.9; $P = 0.19$) and 80 years (beta: 0.98; 95% CI: 0.54-1.79; $P = 0.94$), yielded similarly nonsignificant associations.

DISCUSSION

Lp(a) levels are predominantly genetically determined, mainly by Kringle-IV repeat polymorphisms, and remain relatively stable over a lifetime without

TABLE 2 Median Lipoprotein(a) Levels of Severe Aortic Stenosis Patients vs Controls, Stratified by Gender

	Severe Aortic Stenosis	All-Comers	*P* Value
All patients	(n = 503)	(n = 25,343)	
Lp(a)	20.5 (10.8,46.1)	18.7 (9.1,39.5)	0.04
>30 mg/dL	194 (38.6%)	8,392 (33.1%)	0.01
>50 mg/dL	109 (21.7%)	4,902 (19.3%)	0.19
Females	(n = 279)	(n = 11,419)	
Lp(a)	22.1 (11.8,47.3)	21.3 (11.2,44.6)	0.87
>30 mg/dL	112 (40.1%)	4,280 (37.5%)	0.38
>50 mg/dL	63 (22.6%)	2,528 (22.1%)	0.89
Males	(n = 224)	(n = 13,924)	
Lp(a)	19.9 (9.3,42.7)	16.6 (7.6,35.7)	0.04
>30 mg/dL	82 (36.6%)	4,112 (29.5%)	0.03
>50 mg/dL	46 (20.5%)	2,374 (17.0%)	0.18

Values are median (IQR) or n (%).
Lp(a) = lipoprotein(a).

significant dietary or environmental influences.[1] Lp(a) accumulates and promotes inflammation in vascular tissues and aortic valve leaflets[1,21,22] and is strongly associated with CVD risk,[23,24] independent of other CVD risk factors. Sharing a mutual pathophysiology with CVD, AS disease activity and progression are directly related to Lp(a) levels, and a causal relationship with Lp(a) has also been established,[1,5,11,12] due to the atherogenicity of the LDL-like moiety causing plaque deposition and calcification, as well as antifibrinolytic and proinflammatory effects.

We examined the median levels and distribution of Lp(a) of patients with severe AS in comparison to those of random adult persons undergoing Lp(a) testing for various reasons. In concordance with current literature,[1,25] Lp(a) levels of women in our entire cohort were higher than those of men in the whole study population. We found that patients with severe AS had significantly higher median Lp(a) levels in comparison to Lp(a) levels of the general population. This was mainly driven by higher Lp(a) levels in males with severe AS. When comparing Lp(a) levels of women with severe AS to those in the general population, median levels were higher, but the difference was not statistically significant. As previously known, Lp(a) levels were skewed rightward in all groups.

Lp(a) levels differ widely across published studies, mostly due to genetic variance across racial and ethnic groups.[1] Yet a variance can also be explained, at least in part, by the variation in laboratory measurements of Lp(a), which is complex, not optimally standardized, and the unreliable conversion between molar and mass concentration units.[1,26,27] Having said that, median Lp(a) levels of 18.7 mg/dL in the control group in our study are generally similar to known literature regarding Lp(a) levels in generally healthy patients.[21,24,28] Patients with severe AS in our study had a median Lp(a) of 20.5 mg/dL, which was higher in comparison to controls. Bhatia et al[29] found median Lp(a) levels of 17 mg/dL for patients with AS, which was nonsignificantly higher than persons without AS, as opposed to our findings that were significantly different. It is conceivable that the substantial cohort size may have revealed significant differences in Lp(a) levels between groups that were not apparent in a smaller-scale study. Nissen et al[25] found Lp(a) levels of 18 mg/dL for patients with CVD, which is also lower in comparison to patients with severe AS in our analysis. Yet their inclusion of a low percentage of female patients (approximately 25%), which are known to have higher Lp(a) levels, may have caused underestimation of true Lp(a) levels. Notably, previous studies, including a previous study of an Israeli population published in 2022, generally reported slightly higher rates of median Lp(a) levels above a cutoff of 50 mg/dL.[30-33]

Due to the associations between aging, diabetes,[34] and the development of atherosclerosis and AS, we conducted subgroup analyses of Lp(a) levels in individuals over 65 years of age and those diagnosed with diabetes. In both subgroups, Lp(a) levels were higher in AS patients compared to the control group. Notably, although the differences observed in both comparisons were not statistically significant, it is important to note that the subgroups analyzed were considerably smaller. Presumably, larger sample sizes might yield statistically significant outcomes.

Despite the similar pathophysiology of AS and CVD,[1,35] lipid-lowering agents proven to change the natural course of CVD do not slow or stop disease

TABLE 3 Multivariable Logistic Regression Analysis Examining an Association Between TAVI Before or After the Age of 75, and Having an Lp(a) Level Exceeding 50 mg/dL, Adjusted for CVD Risk Factors

	HR	95% CI	*P* Value
Lipoprotein(a) >50 mg/dL	1.04	0.42-2.57	0.94
Diabetes mellitus	1.94	0.88-1.04	0.32
Hypertension	0.96	0.23-1.16	0.11
Body mass index	1.04	0.28-3.92	0.95
Coronary artery disease	1.94	0.22-1.20	0.12
Stroke or transient ischemic attack	1.06	0.30-2.94	0.92
Smoking history	1.11	0.28-2.89	0.86
Low-density lipoprotein cholesterol	1.00	0.98-1.02	0.86
Society of thoracic surgeons score	0.78	0.99-1.65	0.06
Glomerular filtration rate	0.98	0.99-1.04	0.16

Multivariable binary logistic regression analysis.
CVD = cardiovascular disease; Lp(a) = lipoprotein(a); TAVI = transcatheter aortic valve implantation.

progression in AS.[36] Because standard laboratory assessments of LDL-cholesterol reflect the cholesterol content of both LDL and Lp(a),[26,37] and as Lp(a) is not reduced by statins, dietary, or environmental factors, patients with elevated Lp(a) may better respond to specific Lp(a)-lowering therapy. New pharmacologic RNA-based agents targeting Lp(a) reduction have been shown to reduce Lp(a) levels dramatically[38,39] and can hypothetically improve outcomes for patients with symptomatic or significant AS.[1] Lp(a)-lowering drugs are currently the focus of several Phase 3 clinical trials assessing cardiovascular outcomes related to Lp(a)-targeted therapies.

Current literature is conflicting regarding the association of Lp(a) and severe AS. While Lp(a) has been consistently correlated with AS incidence, previous research has shown inconsistent results regarding the correlation between Lp(a) levels and the progression of AS.[9] A proven correlation with AS progression or severity suggests that patients with elevated Lp(a) might benefit from early intervention or from pharmacological strategies aimed at reducing Lp(a) levels. A recent study by Kaiser et al,[8] which utilized computed tomography to analyze AS calcification, contradicted the previously established link between high Lp(a) levels and AS progression, as reported in studies by Després et al,[40] Zheng et al,[11] and a subanalysis of the ASTRONOMER study.[12] In our analysis, higher Lp(a) levels were not predictive of an earlier requirement for valve intervention, contradicting the aforementioned hypothesis and strengthening results of Kaiser et al.[8]

STUDY LIMITATIONS. This is an observational study, exposed to inherent flaws. This is a single-center study, and therefore generalizability of its results is limited. Data regarding the reasons for attainment of control group Lp(a) levels are missing, and inherent biases cannot be excluded. Consequently, the inclusion of individuals with severe AS in the control group cannot be ruled out. Nonetheless, analyses across comparable age groups yielded consistent results. The validity of laboratory measurement of frozen samples has not been proven, although we conducted quality control measurements without significant differences between frozen samples and values obtained at admission for TAVI. Substantial differences in baseline characteristics were noted between the two study groups. Nevertheless, most of these differences do not affect Lp(a) levels. Notably, age differences existed between the groups, but given that Lp(a) levels are generally stable throughout life and individuals under 18 years old were excluded from the study to mitigate confounding factors, these age disparities are unlikely to affect the study outcomes. Finally, clinical outcomes have not been evaluated in this study.

CONCLUSIONS

Lp(a) levels of patients with severe AS were mildly higher in comparison to persons in the control group. This was mainly driven by higher Lp(a) levels in males with severe AS. Lp(a) levels were not predictive of severe AS requiring earlier intervention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Lp(a) has been associated with AS and disease progression. Currently available pharmacologic treatment is ineffective for treatment and prevention of severe AS.

COMPETENCY IN PATIENT CARE: Patients with high Lp(a) levels may potentially be offered either earlier intervention or pharmacologic treatment that lowers Lp(a) levels.

TRANSLATIONAL OUTLOOK: Whether treating patients with severe AS and elevated Lp(a) levels with Lp(a)-lowering therapies currently investigated can potentially reverse damage or slow disease progression remains to be evaluated.

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APPENDIX For supplemental tables, please see the online version of this paper.