ORIGINAL RESEARCH

Association of Lipoprotein(a) With Severe Degenerative Aortic Valve Stenosis

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ABSTRACT

BACKGROUND Lipoprotein(a) (Lp[a]) is associated with the development of aortic valve calcification.

OBJECTIVES The aim of this study was to evaluate the association between the serum level of Lp(a) and the development of severe degenerative aortic stenosis (AS) and subsequent aortic valve replacement (AVR).

METHODS A total of 44,742 patients with Lp(a) measurements and echocardiography at baseline evaluation between 2000 and 2020 were included from a single tertiary heart center. The primary outcome was the development of severe degenerative AS, defined as a transaortic maximal velocity of ≥4.0 m/s.

RESULTS During a median follow-up period of 6.8 years (Q1-Q3: 2.3-12.4 years), severe degenerative AS was diagnosed in 472 patients (1.1%), and subsequent AVR was performed in 387 patients (0.9%). Lp(a) levels were associated with risk for severe degenerative AS, with levels of 30 to 50, 50 to 100, and >100 mg/dL demonstrating adjusted HRs of 1.02 (95% CI: 0.78-1.34; $P = 0.88$), 1.18 (95% CI: 0.91-1.53; $P = 0.22$), and 1.96 (95% CI: 1.31-2.94; $P = 0.001$) compared to <30 mg/dL. Similarly, the risk for AVR due to severe degenerative AS was significantly associated with higher levels of Lp(a) (>100 mg/dL) (adjusted HR: 2.05; 95% CI: 1.31-3.19; $P = 0.002$). Such associations were not observed in the development of severe bicuspid ($P = 0.63$) or rheumatic ($P = 0.96$) AS.

CONCLUSIONS Lp(a) levels >100 mg/dL were significantly associated with risk for severe degenerative AS and subsequent AVR, regardless of the baseline severity of AS. Such associations were not observed in other etiologies of severe AS. (JACC Asia. 2024;4:751-760) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

L ipoprotein(a) (Lp[a]) is a low-density lipoprotein-like particle composed of apolipoprotein(a) bound to apolipoprotein B. Since it was first described in 1963 by Kare Berg, Lp(a) has emerged as a risk factor for the development of atherosclerotic cardiovascular disease. In the current genetic era, Mendelian randomization studies have demonstrated possible causal relations between Lp(a) level and cardiovascular disease.[1,2] Since then, the significance of Lp(a) has continued to grow.

Increased levels of Lp(a) have been associated with atherosclerosis, inflammation, and thrombosis. Several studies have identified elevated Lp(a) as an independent, possibly causal, risk factor for atherosclerotic cardiovascular disease.[3,4]

Degenerative calcific aortic stenosis (AS) is the most common type of valvular disease in Western countries, representing a significant and growing burden in the aging population.[5] Given that AS shares common risk factors, such as Lp(a), with atherosclerotic cardiovascular diseases, small observational studies have reported that Lp(a) was significantly associated with aortic valve (AV) calcification, as well as the progression of AS.[6-8] Subsequent large Mendelian randomization studies have shown that elevated Lp(a) levels may be causally associated with a higher incidence of AV calcifications and an increased risk of AV replacement (AVR).[9-12] However, these studies were limited by their small sample sizes and cross-sectional study designs. Other studies were limited by the lack of echocardiographic data; therefore, the etiology of AS was not specified.[9-12] In addition, although there is evidence of ethnic heterogeneity in levels of Lp(a) and its impact on cardiovascular diseases,[13,14] most studies have focused on White populations.

In this study, we evaluated the association between Lp(a) and risk for the development of severe degenerative AS and AVR, including both transcatheter and surgical procedures. In addition, we also evaluated the associations between Lp(a) and other etiologies of severe AS, such as bicuspid AV or rheumatic valve disease, in a large set of Korean population.

METHODS

STUDY DESIGN AND POPULATION.
This study included all consecutive patients who underwent Lp(a) measurement and echocardiographic evaluation at baseline in Asan Medical Center, a tertiary, high-volume training hospital in Seoul, South Korea. Patient demographics, comorbidities, prescriptions, laboratory data, echocardiographic data, and outcomes were obtained from the Asan Biomedical Research Environment system, which is a deidentified clinical database of Asan Medical Center. The researchers who collected the data were blinded to the process of data analysis.[15] Patients who were diagnosed with severe AS during their initial hospital visits or had histories of previous AV surgery were excluded from this analysis. The Institutional Review Board of Asan Medical Center approved this study.

LP(A) MEASUREMENT AND GROUP CATEGORIZATION.
Lp(a) levels are routinely measured at our center for cardiovascular risk evaluation in patients admitted for coronary evaluation. For Lp(a) measurement, we used the immune-nephelometric assay BN II nephelometry (Siemens Healthcare Diagnostics), which is sensitive to the individual size heterogeneity of apolipoprotein(a) isoforms. The detection limit of the Lp(a) analysis in our study was 0.2 mg/dL. These measurements were taken for all patients prior to their index coronary angiographic examinations or percutaneous coronary interventions. Blood samples for all patients were routinely obtained in the morning on the day of the procedure and were directly sent to the laboratory. Lp(a) values were standardized using an internal reference preparation from Siemens Healthcare Diagnostics.

An agreed threshold for Lp(a) elevation has not been firmly established. In a previous South Korean percutaneous coronary intervention registry-based study,[16] patients with Lp(a) levels >30 mg/dL showed increased risk for recurrent ischemic events. In accordance with the previous studies,[13,16,17] patients were classified into 4 groups on the basis of their Lp(a) levels: <30, 30 to 50, 50 to 100, and >100 mg/dL.

Other lipid profiles, including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels were also measured simultaneously with Lp(a).

ECHOCARDIOGRAPHIC EVALUATION.
At baseline, all patients underwent comprehensive transthoracic echocardiographic evaluations conducted by expert cardiologists using commercially available echocardiographic systems.[18] The severity of AS was determined by measuring the trans-AV maximal velocity (V$_{max}$ using the apical, right parasternal, or suprasternal window that provided the highest velocity signal and was classified in accordance with the clinical guidelines[19] as follows: no stenosis (V$_{max}$ <2.0 m/s), mild (V$_{max}$ 2.0-2.9 m/s), moderate (V$_{max}$ 3.0-3.9 m/s), and severe (V$_{max}$ ≥4.0 m/s). On 2-dimensional imaging of the AV in the parasternal short-axis view, the etiology of AS was defined as degenerative if thickening and prominent calcification in the middle of the cusp tips were observed, bicuspid if there were 2 asymmetrical cusps with an ovoid valvular orifice, and rheumatic if commissural fusion combined with mitral valve pathologies were observed.[20]

OUTCOMES.
The primary outcome of the study was the development of severe degenerative AS, which was defined by a comprehensive echocardiographic

evaluation. The major secondary outcome was the occurrence of transcatheter or surgical AVR due to severe degenerative AS. Development of severe AS due to other etiologies, such as bicuspid AV or rheumatic AV disease, was not included as a component of the primary outcome and was reported separately. Death of any cause was considered as a competing risk. All event occurrences were adjudicated by an independent group of clinicians who were unaware of the baseline Lp(a) level and baseline echocardiographic data.

STATISTICAL ANALYSIS. Categorical variables are presented as frequencies with percentages, while continuous variables are presented as mean ± SD. Comparisons between groups were performed using analysis of variance for continuous variables and the chi-square test for categorical variables.

Survival curves were generated using the Kaplan-Meier method. Stratified Cox proportional hazards models were used to adjust for confounding factors, including age, sex, smoking status, body mass index, history of hypertension, history of diabetes, low-density lipoprotein cholesterol corrected for Lp(a), high-density lipoprotein cholesterol, statin therapy, serum creatinine, and concomitant coronary artery disease. The subjects were stratified into 3 subgroups on the basis of the severity of AS at baseline. To understand the effect of Lp(a) on clinical outcomes over its full range, we constructed restricted cubic spline regression models, adjusted using the same variables used in stratified Cox proportional hazards models. In addition, we conducted a competing-risks model analysis with all-cause death as the competing risk. For the missing variables, we assumed a possible missing-at-random pattern and used multiple imputations with a substantive model compatible with fully conditional specification.[21] All regressions were performed on the imputed data sets, and descriptive statistics were based on the original data.

All reported *P* values are 2-sided. *P* values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing).

RESULTS

STUDY POPULATION. Between January 2000 and December 2021, a total of 46,674 individuals had Lp(a) measurements and underwent echocardiographic evaluation at baseline. After excluding patients with severe AS at the initial echocardiographic

evaluation or histories of AVR at baseline, a total of 44,742 patients were included in the study.

Table 1 shows the baseline characteristics of the study population. In the overall population, the mean age was 61.4 ± 11.5 years, 66.8% were men, 53.9% had hypertension, and 30.4% had diabetes. Most patients (92.0%) did not have AS at baseline, and 0.6% had bicuspid AV disease. Median Lp(a) was 16.5 mg/dL (Q1-Q3: 7.0-34.0 mg/dL) (Supplemental Figure 1). According to the level of Lp(a), there were significant differences in cardiovascular risk factors; generally, those with higher Lp(a) levels had more risk factors. However, the incidence of bicuspid was not significantly different according to the Lp(a) levels.

DEGENERATIVE AS AND AVR. During the median follow-up period of 6.8 years (Q1-Q3: 2.3-12.4 years), 2,608 patients (5.8%) died. Severe degenerative AS was diagnosed in 472 patients (1.1%), and subsequent AVR was performed in 387 patients (0.9%). The risk for severe degenerative AS and subsequent AVR gradually increased as the serum level of Lp(a) increased (**Figure 1**). Restricted cubic spline models for the HR of Lp(a) levels also showed that the risk for severe degenerative AS and subsequent AVR increased as the Lp(a) level increased (**Figure 2**). The results of univariate Cox regression analysis of confounding factors are presented in Supplemental Table 1. After adjusting for baseline characteristics and accounting for the risk for death as a competing factor, there was a significant increase in the risk for developing severe degenerative AS for individuals with Lp(a) levels >100 mg/dL (competing HR: 1.96; 95% CI: 1.31-2.94; *P* = 0.001) compared with those with Lp(a) levels <30 mg/dL (**Table 2**). Similarly, the risk for AVR due to severe degenerative AS was significantly associated with higher levels of Lp(a) (>100 mg/dL) (competing HR: 2.05; 95% CI: 1.31-3.19; *P* = 0.002). Even without imputation for missing values, the risk for developing severe degenerative AS and AVR was associated with higher levels of Lp(a) (Supplemental Table 2). In addition, an Lp(a) level >100 mg/dL was significantly associated with higher risk for developing severe degenerative AS in patients with no AS, mild AS, or moderate AS at baseline evaluation (*P* = 0.63 for interaction) (**Figure 3**). However, the incidence rate of developing severe AS increased as the severity of AS at baseline worsened.

OTHER ETIOLOGIES OF SEVERE AS. During the follow-up periods, 87 patients were diagnosed with severe AS with bicuspid AV (75 patients underwent AVR), and 71 patients were diagnosed with severe

TABLE 1   Baseline Characteristics

	All (N = 44,742)	Lipoprotein(a)				P Value
		<30 mg/dL (n = 31,767)	30-50 mg/dL (n = 6,435)	50-100 mg/dL (n = 5,401)	>100 mg/dL (n = 1,139)	
Age, y	61.4 ± 11.5	61.0 ± 11.7	62.1 ± 11.1	62.4 ± 11.3	62.6 ± 10.6	<0.001
Male	29,891 (66.8)	21,611 (68.0)	4,244 (66.0)	3,383 (62.6)	653 (57.3)	<0.001
Body mass index, kg/m²	24.6 ± 3.3	24.7 ± 3.3	24.4 ± 3.3	24.4 ± 3.4	24.1 ± 3.2	<0.001
Hypertension	24,133 (53.9)	16,771 (52.8)	3,569 (55.5)	3,117 (57.7)	676 (59.4)	<0.001
Diabetes	13,621 (30.4)	9,432 (29.7)	1,989 (30.9)	1,752 (32.4)	448 (39.3)	<0.001
Smoking						<0.001
No	18,238 (40.8)	12,749 (40.2)	2,654 (41.2)	2,325 (43.0)	510 (44.8)	
Current	6,191 (13.8)	4,552 (14.3)	853 (13.3)	653 (12.1)	133 (11.7)	
Former	9,361 (20.9)	6,744 (21.2)	1,266 (19.7)	1,124 (20.8)	227 (19.9)	
Unknown	10,952 (24.5)	7,722 (24.3)	1,662 (25.8)	1,299 (24.1)	269 (23.6)	
Total cholesterol, mg/dL	168.7 ± 44.0	166.8 ± 43.4	172.0 ± 44.1	174.0 ± 46.1	179.7 ± 46.0	<0.001
LDL cholesterol, mg/dL	103.5 ± 37.1	101.7 ± 36.5	105.9 ± 37.8	108.8 ± 38.3	114.0 ± 38.9	<0.001
Corrected LDL cholesterol, mg/dL[a]	95.6 ± 37.4	97.9 ± 36.6	94.4 ± 37.8	88.0 ± 38.5	74.7 ± 39.4	<0.001
HDL cholesterol, mg/dL	42.6 ± 25.9	41.8 ± 25.6	44.9 ± 27.1	44.0 ± 26.2	45.5 ± 25.9	<0.001
Statin treatment	27,482 (61.4)	19,134 (60.2)	3,964 (61.6)	3,588 (66.4)	796 (69.9)	<0.001
Serum creatinine, mg/dL	1.2 ± 1.6	1.1 ± 1.4	1.3 ± 1.8	1.4 ± 2.0	1.8 ± 2.5	<0.001
Concomitant coronary artery disease	30,711 (68.6)	21,446 (67.5)	4,571 (71.0)	3,858 (71.4)	836 (73.4)	<0.001
Aortic stenosis at baseline						<0.001
No	41,170 (92.0)	29,365 (92.4)	5,911 (91.9)	4,880 (90.4)	1,025 (90.0)	
Mild	2,944 (6.6)	1,988 (6.3)	430 (6.7)	433 (8.0)	93 (8.2)	
Moderate	628 (1.4)	425 (1.3)	94 (1.5)	88 (1.6)	21 (1.8)	
Bicuspid aortic valve	273 (0.6)	208 (0.7)	28 (0.4)	30 (0.6)	7 (0.6)	0.21

Values are mean ± SD or n (%). [a]Corrected LDL cholesterol was calculated as: LDL cholesterol − 0.3 × Lp(a).

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

rheumatic AS (64 patients underwent AVR). There was no significant association between Lp(a) and the development of severe bicuspid or rheumatic AS (Supplemental Table 3).

DISCUSSION

From the large observational cohort including 44,742 patients with Lp(a) measurements who underwent echocardiographic evaluation at baseline, we demonstrated that Lp(a) was significantly associated with the development of severe degenerative AS and subsequent AVR (Central Illustration). This association remained consistent regardless of the severity of AS at baseline. In addition, the graphic inspection by spline plot showed a gradual association between Lp(a) level and risk for severe AS and for AVR; however, the risk was statistically significant only when Lp(a) level exceeded 100 mg/dL. Finally, such an association was not observed in other etiologies, including bicuspid or rheumatic severe AS.

Previous studies have suggested an association between Lp(a) and the development of severe AS.

Individuals with elevated levels of Lp(a) have an increased prevalence of AV calcification, as supported by animal studies indicating that Lp(a) may promote calcium deposition on the AV.[9-12,22] In addition, the severity of AS was significantly associated with the serum level of Lp(a).[6-8] Large genetic association studies have also demonstrated a significant association between high Lp(a) level and the development of severe AS and subsequent AVR.[9-12] In this study, we demonstrated an association between the development of severe degenerative AS and subsequent AVR in a large population with longitudinal follow-up, thereby reconfirming the significant association between Lp(a) and the development of severe degenerative AS through meticulous echocardiographic evaluations conducted at baseline and at the time of events.

This study also demonstrated several interesting findings. First, the study highlights a critical threshold of Lp(a) associated with the development of severe AS. A previous study showed a significant increase in the risk for AS between the 67th and 89th percentiles of Lp(a) (30-51 mg/dL) in the general

FIGURE 1 Cumulative Incidences of AS Development and Subsequent AVR According to Lp(a) Levels
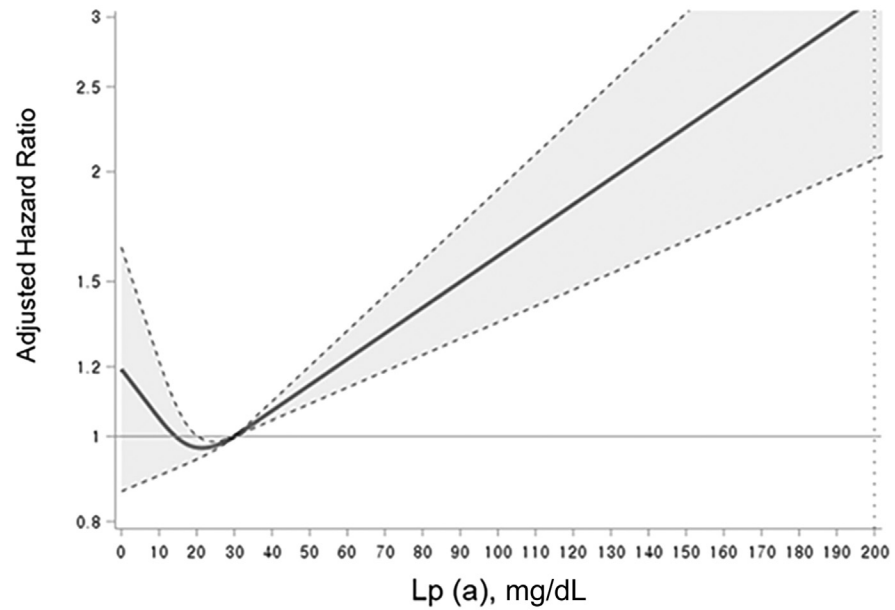
A Severe Degenerative Aortic Valve Stenosis
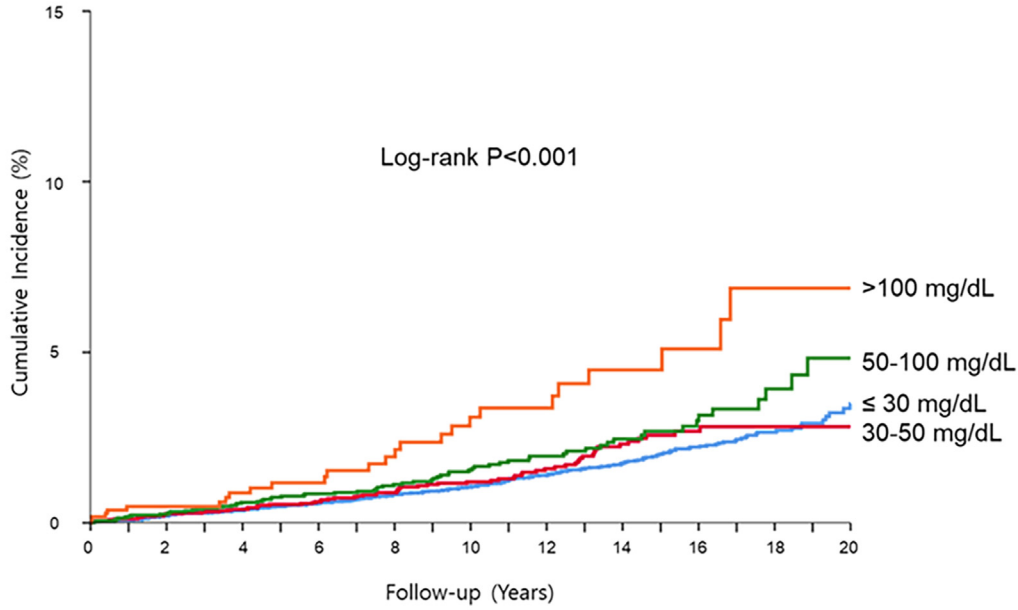
B Aortic Valve Replacement
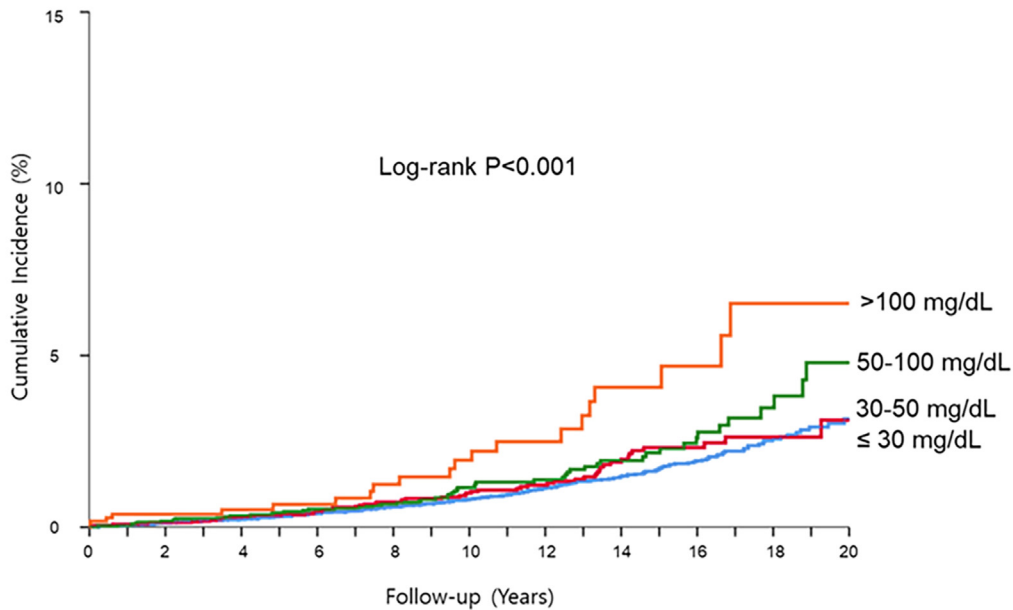
The study compared the cumulative incidences of severe degenerative aortic stenosis (AS) development and subsequent aortic valve replacement (AVR) on the basis of lipoprotein(a) (Lp[a]) levels. As the serum level of Lp(a) increases, there is a corresponding increase in the occurrence of severe AS development and subsequent AVR. Kaplan-Meier curves illustrate the cumulative incidence of (A) severe degenerative AS and (B) AVR.

FIGURE 2   Adjusted HRs According to Lp(a) Levels

A   Severe Degenerative Aortic Valve Stenosis

B   Aortic Valve Replacement
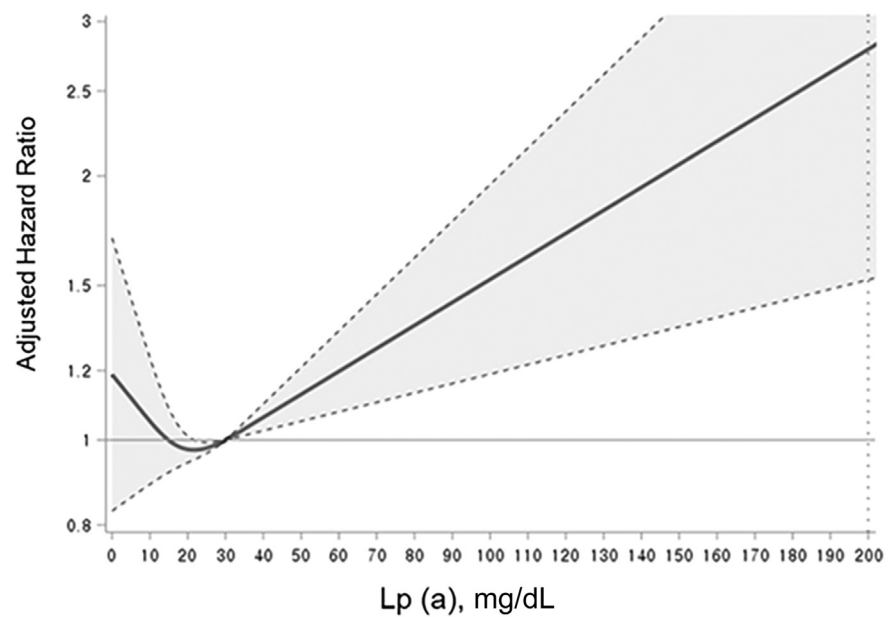
These curves depict the adjusted HRs for (A) the development of severe degenerative AS and (B) AVR. Restricted cubic spline regression models were used to adjust for confounding factors, including age, sex, smoking status, body mass index, history of hypertension, history of diabetes, total cholesterol, statin therapy, serum creatinine, and concomitant coronary artery disease. Solid lines indicate HRs, and shaded areas indicate 95% CIs. The risk for severe AS and subsequent AVR increased with increasing serum Lp(a) levels. Abbreviations as in **Figure 1**.

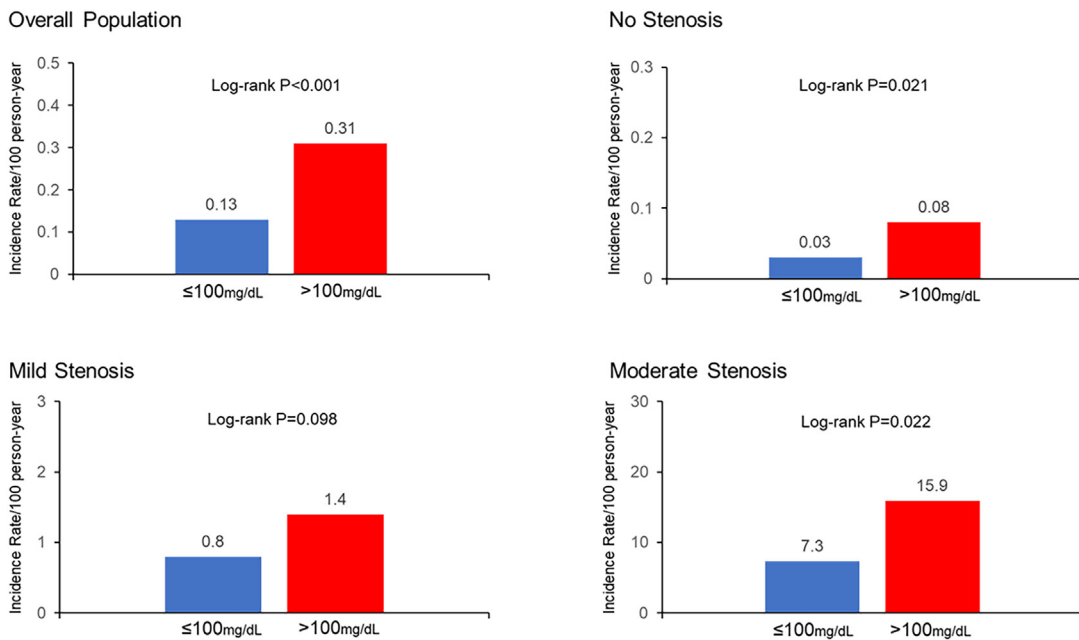**TABLE 2   Association of Lp(a) and Severe Degenerative Aortic Stenosis and Aortic Valve Replacement**

|	Crude HR	95% CI	P Value	Adjusted HR	95% CI	P Value	Competing HR	95% CI	P Value
Severe degenerative aortic stenosis									
			<0.001			0.015			0.009
Lp(a) < 30 mg/dL	1.000	(Reference)		1.000	(Reference)		1.000	(Reference)	
Lp(a) 30-50 mg/dL	1.101	0.850-1.426	0.464	1.067	0.811-1.378	0.677	1.021	0.778-1.338	0.883
Lp(a) 50-100 mg/dL	1.390	1.073-1.800	0.013	1.255	0.965-1.636	0.092	1.178	0.905-1.532	0.223
Lp(a) > 100 mg/dL	2.470	1.655-3.688	<0.001	1.855	1.235-2.788	0.003	1.963	1.311-2.939	0.001
Aortic valve replacement due to severe degenerative aortic stenosis									
			<0.001			0.022			0.016
Lp(a) < 30 mg/dL	1.000	(Reference)		1.000	(Reference)		1.000	(Reference)	
Lp(a) 30-50 mg/dL	1.132	0.853-1.500	0.391	1.115	0.826-1.486	0.476	1.054	0.789-1.409	0.721
Lp(a) 50-100 mg/dL	1.337	1.000-1.787	0.050	1.248	0.933-1.672	0.155	1.164	0.863-1.571	0.320
Lp(a) > 100 mg/dL	2.433	1.559-3.799	<0.001	1.932	1.232-3.022	0.004	2.045	1.311-3.188	0.002

Lp(a) = lipoprotein(a).

Danish population, which is just above the normal range;[10] in contrast, our study revealed a significant increase in risk starting at an Lp(a) concentration of 100 mg/dL in a categorical analysis in a multivariable adjustment model, while spline plot inspection showed a gradual increase even below this threshold. The discrepancy likely derived from the distinct study population. Our study included solely Korean

FIGURE 3   Incidence Rate Comparisons According to Baseline Severity

A high Lp(a) level (>100 mg/dL) was significantly associated with a higher risk for severe degenerative aortic stenosis (AS) development, irrespective of baseline AS severity (P = 0.63 for interaction).

CENTRAL ILLUSTRATION Association of Lp(a) With Severe Degenerative Aortic Stenosis Development and Aortic Valve Replacement
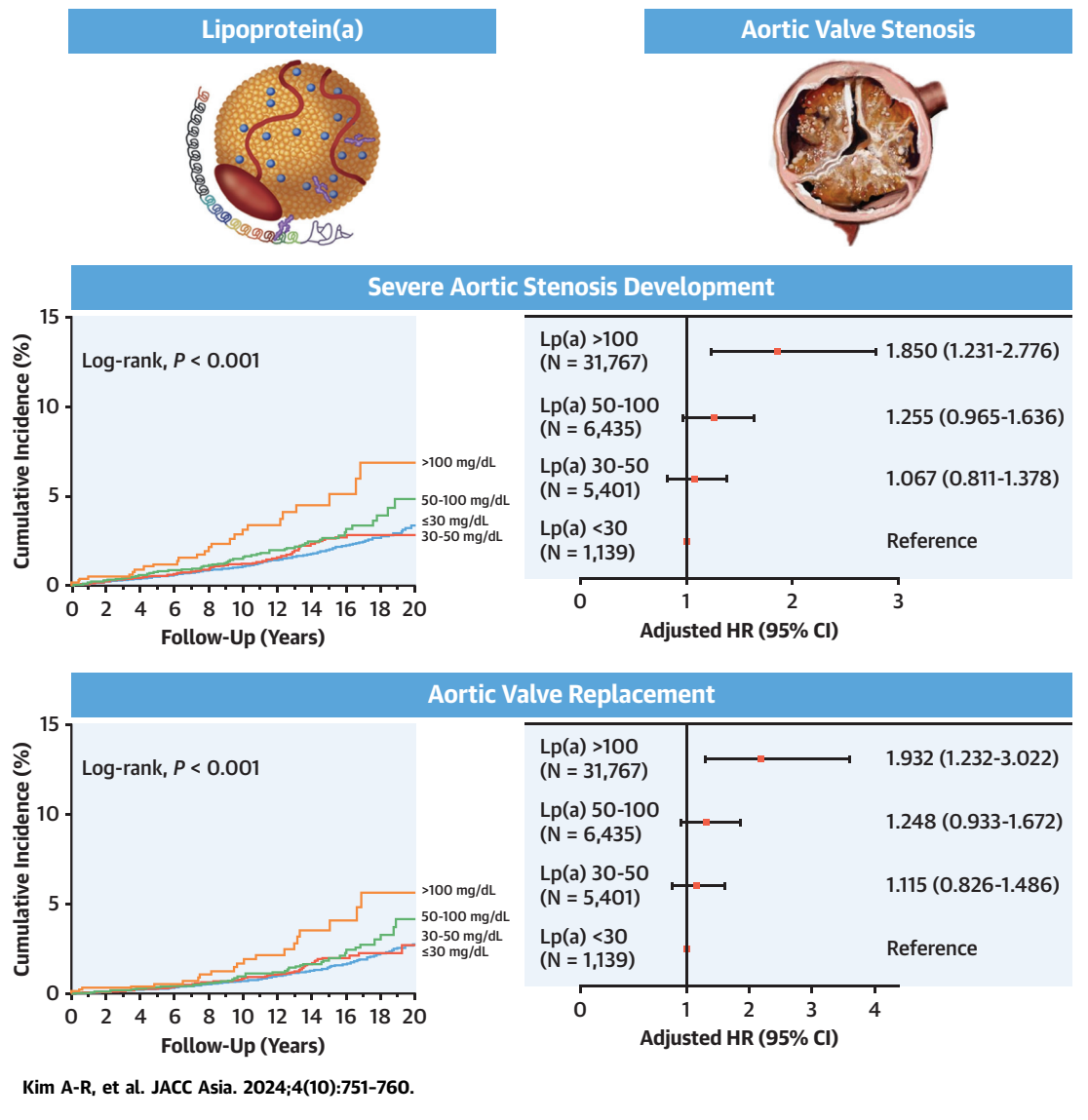
Lipoprotein(a) (Lp[a]) levels >100 mg/dL were significantly associated with risk for severe degenerative aortic stenosis and subsequent aortic valve replacement, even after adjusting for confounding factors, including age, sex, smoking status, body mass index, history of hypertension, history of diabetes, low-density lipoprotein corrected for Lp(a), high-density lipoprotein, statin therapy, serum creatinine, and concomitant coronary artery disease.

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subjects, in contrast to the aforementioned study on Lp(a), which was focused on Whites.[10] More important, our study included patients who were at high risk for developing coronary artery disease, making them more susceptible to severe AS

development, which could potentially increase the observed threshold.

Second, calcific AS has been divided into 2 distinctive phases: the initiation phase, mediated by an inflammatory response, and the propagation

phase, characterized by fibrosis and calcification.[23] Some studies have shown that Lp(a) is associated with the onset of AV calcification, but not with its progression,[24,25] while other studies have found an association between AS progression and Lp(a).[6-8] Therefore, there has been debate as to whether Lp(a) contributes solely to the initiation of AV calcification or influences the entire process of AS. Our study demonstrated the consistent impact of high Lp(a) on the development of severe AS, regardless of baseline AS severity, thereby further supporting the notion that Lp(a) may be involved in both the initiation and propagation of degenerative AS. However, it is noteworthy that the risk for severe AS doubles in patients with higher levels of Lp(a) compared with those with lower Lp(a), while the risk increases approximately 10-fold with increasing severity of AS. This observation implies that once AS is established, the impact of Lp(a) on its progression appears to be relatively weaker compared with structural changes and subsequent hemodynamic alterations.

Third, the contribution of high Lp(a) to other etiologies of severe AS, such as bicuspid AS, remains unclear. Some studies have proposed an association between Lp(a) and AV calcification, as well as early AVR, in patients with bicuspid AVs,[26-28] which would be plausible, as extensive calcification is a hallmark of bicuspid AS. However, such an association was not observed in this study, suggesting that continuous mechanical stress or inflammatory response might exert a more pronounced influence in these etiologies, possibly overshadowing the impact of high Lp(a). Nonetheless, it is important to note that the possibility of insufficient statistical power cannot be completely excluded.

To date, there is no established medical intervention to prevent the onset of AV stenosis or to halt or reverse its progression. Theoretically, Lp(a) has emerged as a drug target for AS prevention. An exploratory analysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial showed a significant association between elevated Lp(a) and AS events. Evolocumab, which is known to reduce Lp(a) by 20% to 30%, demonstrated a reduction in AS events during a median 2.2 years of follow-up.[29] Recently, potent Lp(a)-reducing RNA interference therapeutics, such as pelacarsen or olpasiran, have been developed and tested in clinical trials, revealing substantial reductions in Lp(a) levels of up to 80% to 90%.[30,31] Our study will have significant implications for the design and implementation of future trials aimed at preventing AS through Lp(a)-lowering therapy.

STUDY LIMITATIONS. First, caution should be exercised when applying our results to the general population, as this study specifically included patients who were at risk for coronary artery disease and also had a higher risk for developing degenerative AS.

Second, the patients were all from the Korean population and were treated at a single tertiary referral center. Given the heterogeneity of Lp(a) among different ethnicities, direct inferences cannot be made to other ethnicities and clinical circumstances.

Third, despite rigorous adjustment, unmeasured confounders could have influenced the observed findings. Fourth, the Lp(a) levels used in this study relied on a single measurement taken during the baseline echocardiographic evaluation; however, Lp(a) levels generally remain stable throughout a person's life.

Fifth, Lp(a) assays were reported in terms of Lp(a) mass (milligrams per deciliter) rather than molar (nanomoles per liter) concentration. Last, because of limitations in the data structure, we were unable to analyze the long-term effects of statins on Lp(a) levels, which is still controversial. Further studies on Lp(a)-lowering therapies are warranted.

CONCLUSIONS

This study demonstrated a significant association between elevated Lp(a) level and the development of severe degenerative AS, regardless of the severity of AS at baseline. Consequently, randomized trials exploring novel Lp(a)-lowering therapies to mitigate the risk for degenerative AS in patients with elevated Lp(a) are warranted.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: High levels of Lp(a) (>100 mg/dL) were significantly associated with risk for severe degenerative AS and the need for subsequent AVR.

TRANSLATIONAL OUTLOOK: Whether Lp(a) contributes to the initiation or entire progression of AS needs to be confirmed. Future trials to prevent AS using Lp(a)-lowering agents should be conducted.

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KEY WORDS aortic stenosis, lipids, lipoproteins, Lp(a)

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