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EDITORIAL COMMENT

Lp(a) and Accelerated Progression of Aortic Stenosis

A Rationale for Universal Measurement and Therapeutic Targeting

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Lipoprotein(a) (Lp[a]) has emerged at the forefront of clinical investigation. There are 3 ongoing cardiovascular outcomes trials testing the Lp(a) hypothesis, namely that potent lowering of plasma Lp(a) levels will reduce the risk of cardiovascular events.[1] This resurgence was begun by a confluence of pathophysiological, epidemiological, and genetic evidence for an association of cardiovascular disease and potentiated by the development of novel RNA-based therapeutics that are ideally suited to reduce plasma levels.[2] Elevated Lp(a) levels are associated with higher risk of most cardiovascular phenotypes, including myocardial infarction, stroke, peripheral arterial disease, calcific aortic valve disease, heart failure, cardiovascular and all-cause mortality, and possibly atrial fibrillation. Of these phenotypes, the strongest association is present with aortic stenosis.[3]

In this issue of *JACC: Asia*, Kim[4] provides convincing evidence to further support the association of Lp(a) with advanced calcific aortic stenosis and the need for aortic valve replacement. The investigators evaluated the records of 44,742 subjects derived from a single South Korean center from 2000 to 2020. All patients were being evaluated or treated for cardiovascular disease, had an Lp(a) level measured, and they were followed for a median of 6.8 years. The median Lp(a) levels were 16.5 mg/dL, which is typical of median general European populations but higher than general East Asian populations.[5] This likely reflects selection bias of higher-risk patients with cardiovascular disease that are known to have higher Lp(a) levels.[6] Over this time period, 1.1% of the subjects developed severe aortic stenosis, defined as V_{peak} >4 m/s across the aortic valve, and 0.9% required aortic valve replacement with percutaneous or surgical techniques. Compared with subjects with Lp(a) <30 mg/dL, a graded increase in the multivariable-adjusted HR was present with increasing Lp(a) categories of 30 to <50 mg/dL, 50 to 100 mg/dL, and >100 mg/dL with HR 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; $P = 0.001$), respectively. The corresponding HR (95% CI) for aortic valve replacement were HR 1.12 (95% CI: 0.83-1.49; $P = 0.48$), 1.25 (95% CI: 0.93-1.67; $P = 0.16$), and 1.93 (95% CI: 1.23-3.02; $P = 0.004$), respectively. Using restricted cubic spline regression models, the association of Lp(a) with aortic stenosis appeared to be linear from Lp(a) of 20 to 200 mg/dL with HRs up to 3. Interestingly, there also appeared to be a J curve at <20 mg/dL, but this was not likely statistically significant. Although of lower power, there did not seem to be an association of Lp(a) with either bicuspid or rheumatic aortic valve disease.

This study adds to the growing evidence base that elevated Lp(a), particularly highly elevated levels >100 mg/dL affecting ~10% of the general population,[7] is associated with aortic stenosis and need for aortic valve replacement (AVR). Although not entirely novel, the study has several unique features that further generalize the association of Lp(a) with aortic stenosis. These include a "big data" cohort of 44,742 patients, an extended median follow-up of 6.8 years, and the documentation in a Korean Asian population. The Lp(a) thresholds and HRs or risk of aortic stenosis are typical of what has been noted in other populations, suggesting that despite differences in population means of Lp(a) levels, the risk appears to be approximately similar when Lp(a) is elevated.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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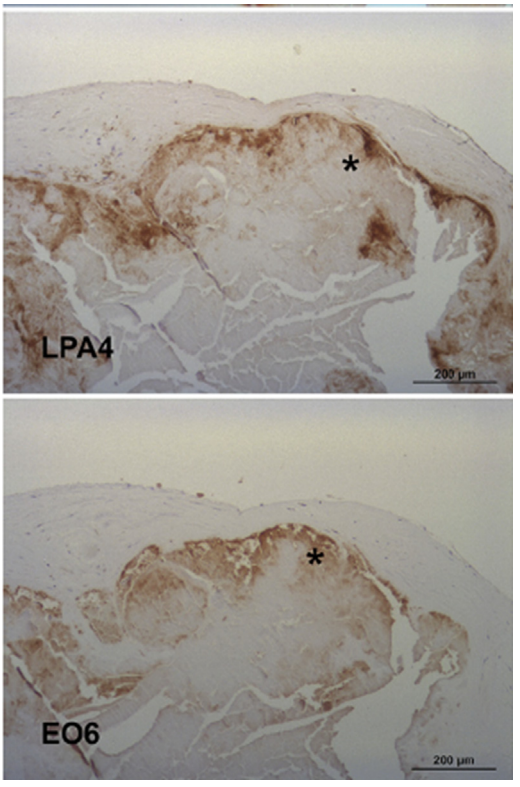
The study has several limitations, including the use of an Lp(a) assay that uses polyclonal antibodies to Lp(a), which is by definition isoform dependent and which may affect accuracy of Lp(a) levels, particularly at the high range.[8] It also reported Lp(a) in mg/dL rather than the preferred molar concentration in nmol/L. The patient cohort was primarily being evaluated for cardiovascular disease and because only approximately 50% of patients with aortic stenosis have cardiovascular disease, these findings may not be representative of all patients with aortic stenosis. Finally, inflammatory conditions and drugs that may affect baseline Lp(a) levels were not available.

The authors are to be commended for routinely measuring Lp(a) in such a large cohort. The European Atherosclerosis Society/European Society of Cardiology, Canadian, and National Lipid Association guidelines recommend measuring Lp(a) at least once in every adult. However, clinical practice lags significantly behind, and particularly in subjects with aortic stenosis. In the author's own institution, the prevalence of any Lp(a) measurement was 4.6% in patients with calcific aortic valve disease approximately 1 decade ago,[9] but this is rapidly increasing in the current era with significantly higher testing.[10] However, testing for elevated Lp(a) in general practice is likely to be <1%. The preponderance of evidence now suggests that measuring an Lp(a) level in a patient with calcific aortic valve disease allows the clinician to predict a significantly faster progression rate and need for AVR.[11-14] For example, patients with moderate aortic stenosis with V_{peak} 3.0 m/s and Lp(a) >100 mg/dL may progress to 4 m/s in 3 to 4 years vs subjects with low Lp(a) may progress to this stage in 7 to 10 years. This may allow more personalized monitoring and evaluation for specific patients at higher risk. The study by Kim[4] provides evidence that universal testing should be performed for all patients with calcific aortic valve disease to allow the detection of patients at highest risk for progression and need for AVR.

What is the potential mechanism that allows Lp(a) to be a uniquely potent risk factor for aortic stenosis? Immunohistological studies demonstrate that Lp(a) accumulates in aortic valve leaflets according to severity of the leaflet pathology and colocalizes with oxidized phospholipids (**Figure 1**).[15] Lp(a) is a preferential carrier of oxidized phospholipids that mediates pro-inflammatory and pro-calcifying responses in valvular interstitial cells.[16] Lp(a) also contains a potent lysine binding pocket that can bind to expose lysine on aortic valve endothelial cells. Lp(a) can then bind tightly and deliver its cargo of oxidized phospholipids that then mediate pro-calcifying responses.

FIGURE 1 The Presence of Lp(a) and OxPL in Advanced Aortic Valve Lesions



Sequential sections stained for apolipoprotein(a) and OxPLs with monoclonal antibodies LPA4 and EO6, respectively. *Colocalization of Lp(a) and OxPL around and within heavily calcified areas. Reprinted with permission from Torzewski et al.[15] Lp(a) = lipoprotein (a); OxPL = oxidized phospholipid.

There are no therapies currently to slow the progression of aortic stenosis. However, with the advent of potent Lp(a)-lowering agents, it can be hypothesized that a portion of calcific aortic valve disease may be ameliorated by lowering Lp(a). In prior studies, approximately 30% of patients with aortic stenosis have elevated Lp(a).[9,10] The Lp(a) FRONTIERS CAVS (A Multicenter Trial Assessing the Impact of Lipoprotein(a) Lowering With Pelacarsen (TQJ230) on the Progression of Calcific Aortic Valve Stenosis; NCT05646381) study is currently enrolling

approximately 502 patients with mild-moderate aortic stenosis and Lp(a) >175 nmol/L (~70 mg/dL) who will be randomized to pelacarsen 80 mg subcutaneously monthly vs placebo. The primary efficacy measures will be the 3-year rate of progression as measured by V_{peak} change in aortic valve calcification. Secondary measures will be a change in Lp(a) levels, change in fibrocalcific thickening of the aortic valve, and time from randomization to first occurrence of composite clinical endpoint event defined as unplanned calcific aortic valve stenosis-related hospital admission, aortic valve intervention, or death related to calcific aortic valve stenosis. The results of this study could pave the way for a medical therapy for calcific aortic valve stenosis.

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REFERENCES

1. Tsimikas S. Lipoprotein(a) in the year. 2024: A look back and a look ahead. *Arterioscler Thromb Vasc Biol*. 2024;44:1485–1490.

2. Tsimikas S, Moriarty PM, Stroes ES. Emerging RNA therapeutics to lower blood levels of lp(a): JACC focus seminar 2/4. *J Am Coll Cardiol*. 2021;77:1576–1589.

3. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med*. 2013;368:503–512.

4. Kim A-R, Ahn J-M, Kang D-Y, et al. Association of lipoprotein(a) with severe degenerative aortic valve stenosis. *JACC Asia*. 2024;4(10):751–760.

5. Tsimikas S, Fazio S, Ferdinand KC, et al. NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J Am Coll Cardiol*. 2018;71:177–192.

6. Nissen SE, Wolski K, Cho L, et al. Lipoprotein(a) levels in a global population with established atherosclerotic cardiovascular disease. *Open Heart*. 2022;9:e002060.

7. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated lp(a) mass levels and patient thresholds in 532 359 patients in the United States. *Arterioscler Thromb Vasc Biol*. 2016;36:2239–2245.

8. Scharnagl H, Stojakovic T, Dieplinger B, et al. Comparison of lipoprotein (a) serum concentrations measured by six commercially available immunoassays. *Atherosclerosis*. 2019;289:206–213.

9. Wilkinson MJ, Ma GS, Yeang C, et al. The prevalence of lipoprotein(a) measurement and degree of elevation among 2710 patients with calcific aortic valve stenosis in an academic echocardiography laboratory setting. *Angiology*. 2017;68:795–798.

10. Ma GS, Wilkinson MJ, Reeves RR, et al. Lipoprotein(a) in patients undergoing transcatheter aortic valve replacement. *Angiology*. 2019;70:332–336.

11. Capoulade R, Chan KL, Yeang C, et al. Oxidized phospholipids, lipoprotein(a), and progression of calcific aortic valve stenosis. *J Am Coll Cardiol*. 2015;66:1236–1246.

12. Capoulade R, Yeang C, Chan KL, Pibarot P, Tsimikas S. Association of mild to moderate aortic valve stenosis progression with higher lipoprotein(a) and oxidized phospholipid levels: Secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2018;3:1212–1217.

13. Nsaibia MJ, Mahmut A, Boulanger MC, et al. Autotaxin interacts with lipoprotein(a) and oxidized phospholipids in predicting the risk of calcific aortic valve stenosis in patients with coronary artery disease. *J Intern Med*. 2016;280:509–517.

14. Arsenault BJ, Loganath K, Girard A, et al. Lipoprotein(a) and calcific aortic valve stenosis progression: a systematic review and meta-analysis. *JAMA Cardiol*. 2024;9(9):835–842. https://doi.org/10.1001/jamacardio.2024.1882

15. Torzewski M, Ravandi A, Yeang C, et al. Lipoprotein(a) associated molecules are prominent components in plasma and valve leaflets in calcific aortic valve stenosis. *JACC Basic Transl Sci*. 2017;2:229–240.

16. Zheng KH, Tsimikas S, Pawade T, et al. Lipoprotein(a) and oxidized phospholipids promote valve calcification in patients with aortic stenosis. *J Am Coll Cardiol*. 2019;73:2150–2162.

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