

High Lipoprotein(a) Levels and Risk of Aortic Valve Stenosis Related Clinical Events: A Systematic Review

Niveles elevados de lipoproteína(a) y riesgo de eventos clínicos relacionados con la estenosis valvular aórtica: una revisión sistemática

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ABSTRACT

Background: Several studies have evaluated the association between lipoprotein(a) plasma levels [Lp(a)] and the occurrence of aortic valve stenosis related events, with contradictory results.

Objective: The main objective of this systematic review was to analyze the predictive capacity of elevated Lp(a) levels on major clinical events associated with aortic valve stenosis.

Methods: This systematic review was conducted in accordance with PRISMA and STROBE recommendations. A search was carried out in order to identify studies with a cohort design evaluating the association between Lp(a) levels and the events of interest. The primary endpoint was the incidence of clinical events related with aortic valve stenosis (aortic valve replacement, death or hospitalization). This review was registered in PROSPERO.

Results: Seven observational studies with a total of 58 783 patients were eligible for analysis. Our findings showed that the presence of elevated Lp(a) levels was associated with an increased risk of events related with aortic valve stenosis in most of the studies evaluated (between 70% and approximately 3-fold higher risk), despite adjusting for other risk factors.

Conclusion: This review suggests that elevated Lp(a) levels are associated with a higher incidence of aortic valve stenosis related clinical events. However, considering the limitations of this study, the clinical usefulness of Lp(a) as a prognostic marker in aortic valve disease should be confirmed in future investigations.

Keywords: Lipoprotein (a) - Aortic valve stenosis - Aortic valve replacement - Mortality - Systematic review.

RESUMEN

Introducción: Varios estudios han evaluado la asociación entre los niveles plasmáticos de lipoproteína (a) [Lp(a)] y la aparición de eventos relacionados con la estenosis valvular aórtica, aunque los resultados fueron contradictorios.

Objetivo: El objetivo de esta revisión fue analizar la capacidad predictiva de los niveles elevados de Lp(a) sobre los eventos clínicos relacionados con la estenosis valvular aórtica.

Material y métodos: Esta revisión sistemática se realizó de acuerdo con las recomendaciones PRISMA y STROBE. Se realizó una búsqueda en diferentes bases de datos con el objetivo de identificar estudios de cohorte que evaluaran la asociación entre los niveles de Lp(a) y los eventos de interés. El punto final primario fue la incidencia de eventos clínicos relacionados con la estenosis aórtica (reemplazo valvular aórtico, muerte u hospitalización). Esta revisión fue registrada en PROSPERO.

Resultados: Se consideraron elegibles para el análisis siete estudios observacionales con un total de 58 783 pacientes. Los valores elevados de Lp(a) se asociaron con un mayor riesgo de eventos relacionados con la estenosis valvular aórtica en la mayoría de los estudios evaluados (entre un 70% y aproximadamente 3 veces más riesgo), a pesar de ajustar por otros factores de riesgo.

Conclusión: Esta revisión sugiere que los niveles elevados de Lp(a) se asocian con una mayor incidencia de eventos clínicos relacionados con la estenosis valvular aórtica. Sin embargo, y considerando las limitaciones de este estudio, la utilidad clínica de la Lp(a) como marcador pronóstico en la enfermedad valvular aórtica deberá confirmarse en futuras investigaciones.

Palabras clave: Lipoproteína (a) - Estenosis valvular aórtica - Reemplazo valvular aórtico - Mortalidad - Revisión sistemática

INTRODUCTION

Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL) variant containing an apolipoprotein B molecule, covalently bonded to a glycoprotein of vari-

able molecular weight, apolipoprotein(a), through a disulfide bond. (1,2) Based on current evidence, it is well established that high Lp(a) levels confer greater risk of cardiovascular disease (mainly coronary heart

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disease). Epidemiological and genetic studies indicate an association between high Lp(a) levels and increased cardiovascular risk. (3-5)

Aortic valve stenosis is associated with the progressive reduction of the aortic valve orifice and impaired leaflet motion. It is the most common type of valvular disease and the most prevalent in the elderly population, with degenerative calcification being the most frequent acquired cause. (6)

Interestingly, lipoprotein or lipidic precursor accumulation has been observed within the stenotic aortic valves, including conventional LDL, oxidized LDL and oxidized phospholipid particles. (7,8) In addition, several observational studies have evaluated the relationship between Lp(a) levels and calcific aortic valve. (9) Moreover, various reports, mostly from cohort studies, have analyzed whether high Lp(a) levels are an independent risk factor for the progression of aortic valve stenosis or the occurrence of clinical events, though with contradictory results. (10-17) The identification of Lp(a) as a potential risk factor to develop cardiovascular disease (including aortic valve disease) has awakened the interest to develop pharmacological therapies specifically targeting the reduction of its levels.

Consequently, the main purpose of the present systematic review was to analyze the ability of high Lp(a) levels to predict the occurrence of clinical events related with aortic valve disease.

METHODS

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations developed to steer the performance of systematic reviews and analyze observational studies in epidemiology, respectively. (18,19)

A systematic bibliographic search was carried out to identify studies evaluating the association between Lp(a) levels and clinical events related with aortic valve stenosis. Two independent reviewers performed the search in PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar and Cochrane Controlled Trials electronic databases, using the term "lipoprotein(a)", alone or combined with the following terms: "aortic valve stenosis", "aortic valve replacement", "aortic stenosis mortality", "aortic stenosis hospitalization", "aortic valvulopathy" and "aortic valve calcification".

The following inclusion criteria were used to select the studies:

- 1) Observational cohort design studies (prospective or retrospective). No case series, cross-sectional or case control studies were included.
- 2) Studies comparing patients with or without high Lp(a) levels. No specific cut-off point was established; some studies used the highest Lp(a) tertile, and others analyzed preestablished cut-off points (e.g.: 50 mg/dL).
- 3) Studies evaluating the relationship between Lp(a) levels and risk of clinical events associated with valvular disease.

The primary endpoint of the study was the incidence of events related with aortic valve stenosis. This endpoint, defined according to the events reported in each selected study,

was a composite of clinically relevant events, as aortic valve replacement, death or hospitalization associated with valvular disease. The hazard ratio (HR) was the measure of association used, with its corresponding 95% confidence interval (95% CI).

Two independent reviewers assessed the quality of the studies included, using the QUIPS (Quality in Prognostic Studies) tool criteria. (20) Any discrepancy between the two reviewers was solved through the participation of a third reviewer.

This systematic review was registered in PROSPERO.

The performance of a quantitative analysis (meta-analysis) was not possible due to the heterogeneity of the populations included, the different Lp(a) cut-off points and diagnostic methods used, and the type of clinical events reported.

RESULTS

A total of 7 studies, including 58 783 patients, were identified and considered eligible for the qualitative analysis. Figure 1 shows the flow diagram of the studies' selection process.

All included studies were observational cohort studies (prospective or retrospective). The risk of bias was evaluated in all studies. Only one study was identified as low risk of bias, and in the remaining 6 studies a moderate risk was observed. These studies had methodological issues more frequently related with study discontinuation and statistical analysis or reporting. The quality of the assessed studies is shown in Figure 2.

Mean age and the proportion of women ranged between 58 and 70.3 years and between 31.7% and 72.7%, respectively. Three studies included patients with mild to moderate aortic valve stenosis, (10-12) one study analyzed subjects with familial hypercholesterolemia (13) and three studies evaluated individuals belonging to the general population. (14-16) Mean follow-up ranged between 3.2 and 19.8 years.

Three studies considered the highest Lp(a) tertile as cut-off point, (10-12) and another three analyzed a preestablished Lp(a) level of 50 mg/dL as their cut-off point. (13-15) In the case of the study published by Kamstrup et al., the subgroup of patients with Lp(a) levels between 67 and 89 mg/dL was selected for this analysis and compared with reference values (<22 mg/dL). (16) Table 1 depicts the characteristics of the studies included.

The qualitative analysis showed that two studies did not report a significant association between high Lp(a) levels and the primary endpoint, although the trend was markedly in favor of the association in one of them. Conversely, the remaining five studies reported a greater risk of events associated with aortic valve stenosis in those patients with elevated Lp(a) levels, ranging between 70% and approximately 3-fold higher risk, despite adjusting for traditional risk factors (Figure 3).

DISCUSSION

In this systematic review, high compared with lower Lp(a) levels were associated with greater incidence of

Fig. 1. Flow diagram of studies' selection process.

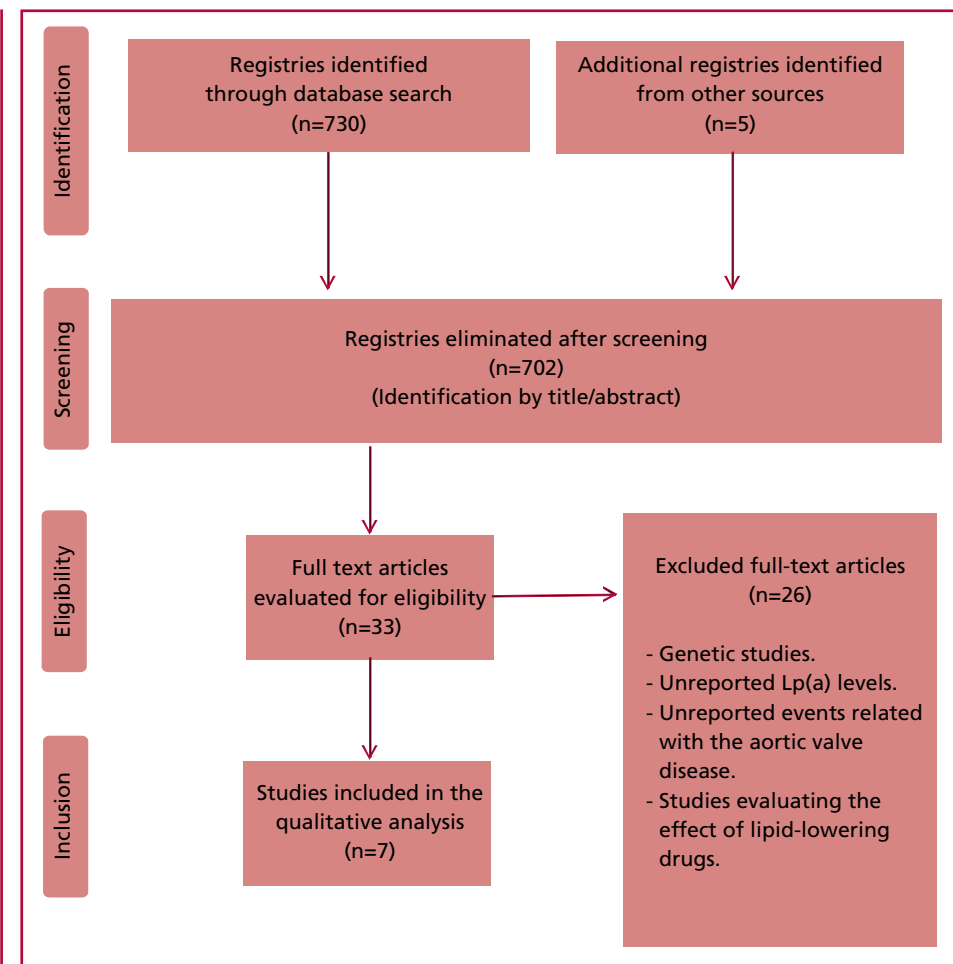


Fig. 2. Bias assessment in the included studies.

Domains for bias risk assessment

	D1	D2	D3	D4	D5	D6	General
Liu et al. 10	+	-	+	+	-	+	-
Capoulade et al. 11	+	+	+	+	+	-	-
Zheng et al. 12	+	-	+	-	+	+	-
Pérez de Isla et al. 13	+	+	+	+	+	+	+
Zheng et al. 14	+	+	-	+	-	+	-
Arsenault et al. 15	+	+	+	-	+	-	-
Kamstrup et al. 16	+	-	+	+	+	-	-

Domains

D1: Bias due to participation.
D2: Bias due to discontinuation.
D3: Bias due to prognostic factor assessment.
D4: Bias due to endpoint assessment.
D5: Bias due to confounders.
D6: Bias due to statistical analysis and reporting.

Evaluation

⊗ High
 - Moderate
 + Low

Table 1. Characteristics of the studies analyzed

Study	N	Population	Lp(a) groups evaluated (mg/dL)	Study methodology	Events evaluated related with aortic valve stenosis	Follow-up (years)
Liu et al. ¹⁰	359	>18 years. Mild to moderate aortic valve stenosis (peak velocity >2.5 and <4m/s). Men: 58.3%	>38.15 vs. ≤38.15	Cox regression analysis. Adjusted for age, sex and traditional risk factors.	AVR or cardiac death.	3.2
Capoulade et al. ¹¹	219	>18 years. Mild to moderate aortic valve stenosis (peak velocity >2.5 and <4m/s). Men: 60%	>58.5 vs. ≤58.5	Cox regression analysis. Adjusted for age, sex and baseline aortic stenosis severity.	AVR or cardiac death.	3.5
Zheng et al. ¹²	145	> 50 years. Aortic valve stenosis with peak velocity > 2.5 m/s and aortic calcification. Men: 68.3%	>35 vs. ≤35	Cox regression analysis. Adjusted for age, sex, traditional risk factors, history of CVD and baseline aortic stenosis severity.	AVR or death.	5
Pérez de Isla et al. ¹³	3712	>18 years. Familial hypercholesterolemia Men: 65.7%.	>50 vs. ≤50	Cox regression analysis. Adjusted for age, sex, history of CVD and traditional risk factors.	AVR	7.5
Zheng et al. ¹⁴	17 745	General population 39 -79 years. Men: 55.1%.	>50 vs. ≤50	Cox regression analysis. Adjusted for age, sex, history of CVD and LDL-C.	Death or hospitalization	19.8
Arsenault et al. ¹⁵	17 553	General population between 39 and 79 years. Men: 44%.	≥50 vs. <50	Cox regression analysis. Adjusted for age, sex, smoking and LDL-C.	Death or hospitalization	11.7
Kamstrup et al. ¹⁶	19050	General population >20 years. Men: 44%.	67-89 vs. <22	Cox regression analysis. Adjusted for age, sex and traditional risk factors.	AVR	5

LDL-C: Low-density lipoprotein cholesterol; CVD: Cardiovascular disease; AVR: Aortic valve replacement

clinical events related with aortic valve stenosis in almost all the studies evaluated.

Growing information suggests that lipids could play a role in the pathophysiology of aortic valve stenosis. (6) Furthermore, a genomic study revealed that certain polymorphisms in the Lp(a) gene locus are associated with greater risk of valvular calcification. (21)

The main blood transporter of oxidized phospho-

lipids is Lp(a). It has been shown that these modified phospholipids promote valvular mineralization and calcification through the positive regulation of reactive oxygen species and inflammatory cytokines released by macrophages. (6,22) Also, within the valve, lipoprotein-associated phospholipase A2 uses oxidized phospholipids to generate lysophosphatidylcholine, an enzyme which has demonstrated in vitro an effect on mineralization. (23,24) Conversely, other mechanisms

not related with oxidized phospholipids have been proposed: Lp(a) significantly increases the activity of alkaline phosphatase, phosphate release, calcium deposits, hydroxyapatite, cellular apoptosis, vesicle formation in the extracellular matrix and phosphorylation of certain proteins involved in signal transduction. (22)

Calcification is one of the most relevant processes which determine the progression of aortic stenosis. Previously published reports showed that the presence of valvular calcification has significant prognostic value. (25-27) In this sense, high Lp(a) values could favor valvular calcification and, consequently, increase the risk of clinical events related with valvular disease. In line with previously mentioned pathophysiological findings, most studies evaluated in this review showed a positive and significant association between Lp(a) levels and clinical events related with aortic valve disease.

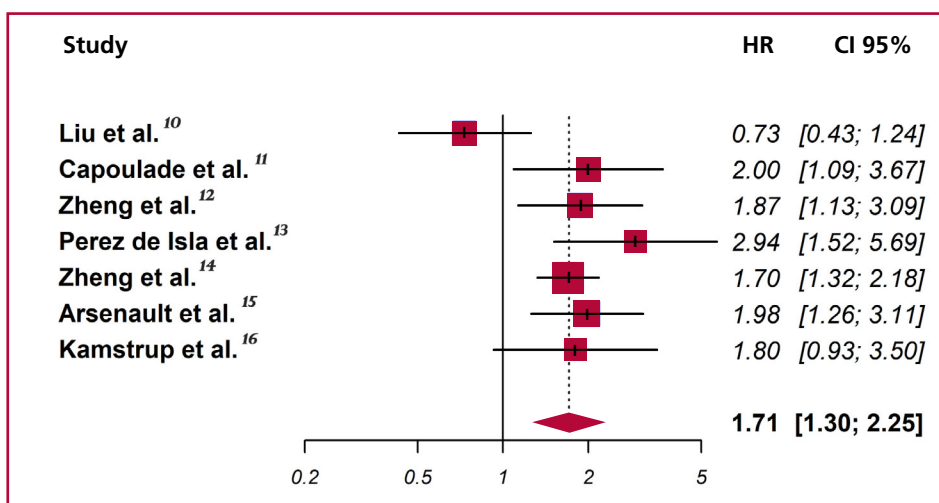
The individual analysis of the studies included in this systematic review revealed that they did not always concur. On the one hand, the analysis of two studies evaluating populations with a previous degree of aortic stenosis showed a significant association between high Lp(a) levels and the primary endpoint, (11,12) whereas a third study did not. (10) In the latter case, the study only included Chinese patients [potential ethnic variation of the Lp(a) effect], the Lp(a) cut-off point was low and the follow-up time was lower compared with the other two studies. On the other hand, two of the studies evaluating the same association in the general population found a significant relationship (14,15), but not a third study. The result of this last case showed a clear trend in favor of the association, and it should be considered that the follow-up time was markedly shorter in this study compared with the other two. (16) The only study evaluating patients with familial hypercholesterolemia showed a significant association between elevated Lp(a) levels and valvular events. A previously published review

showed similar findings to those of our investigation. (9) However, this review mostly included studies with a cross-sectional or case-control design. Also, a meta-analysis evaluated the association between aortic stenosis and the different genetic Lp(a) variants. (28) Consequently, to the best of our knowledge, this is the first systematic review based on observational cohort studies, specifically examining the Lp(a) effect on clinical events related with aortic valve stenosis.

Lp(a) concentrations vary widely among individuals within the same population, as well as between different ethnic groups. (29) This variation complicates establishing a universal clinical risk threshold, which is currently considered >50 mg/dL. The studies included in our analysis considered different cut-off points for this lipidic marker. Therefore, we cannot ascertain, from this review, which would be the Lp(a) cut-off point with greatest predictive power. In addition, and taking into account the variations of this marker in the different populations, it would be good practice to have local investigations and not extrapolate results obtained in other regions.

To date, there are no effective medical treatments for aortic valve stenosis. The evidence from randomized controlled trials showed that statin-based lipid-lowering therapy was not associated with a reduction of events related with calcific aortic stenosis. (30) As is well known, statins are inefficient or may even increase Lp(a) serum levels. (31,32) Niacin reduces Lp(a) between 20% and 25%. However, clinical trials with these agents did not evidence a reduction of major cardiovascular events and currently their use is not recommended. (33) Different from niacin, PCSK9 inhibitors have been demonstrated to decrease Lp(a) levels and reduce cardiovascular events. Moreover, a recent study with these drugs has shown promising results regarding a decreased rate of aortic stenosis progression. (34) The greater reduction of Lp(a) levels with PCSK9 inhibitors, compared with statins, would explain the benefit of these drugs

Fig. 3. Effect of high Lp(a) levels on events related with aortic valve stenosis. Hazard ratios (HR) and 95% confidence intervals (CI).



in aortic stenosis. (35) New therapies are being developed to reduce Lp(a) levels, including an antisense oligonucleotide that selectively binds to the messenger RNA that codifies the Lp(a). (36) Nevertheless, future clinical trials should demonstrate its potential role in the treatment of aortic stenosis.

This systematic review presents some limitations. Firstly, we were unable to perform a quantitative analysis (meta-analysis) due to the clinical heterogeneity (population characteristics, different Lp(a) cut-off points, aortic events reported and follow-up times). Secondly, although the number of patients in the studies published by Zheng et al. (14) and Arsenaault et al. (15) were not exactly the same and the follow-up time was different, they were probably obtained from the same database. Consequently, we cannot rule out some degree of overlap in the events identified in the first follow-up years. Thirdly, our review included only observational studies. Therefore, there are probably biases and confounding factors related with this type of design. Finally, the review included few studies. However, until more and better-quality studies are developed, our review analyzed the best available evidence so far.

CONCLUSION

Our data suggest that high Lp(a) levels are associated with greater incidence of aortic valve stenosis related clinical events. However, and considering the limitations of this review, the clinical usefulness of Lp(a) as a prognostic marker in aortic valve disease should be confirmed in future investigations.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

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