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Original Article

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Elevated Lipoprotein(a) Levels and Atrial Fibrillation: A Systematic Review

Walter Masson,[1] **Leandro Barbagelata**,[1] **Juan P Nogueira**,[2,3] **Pablo Corral**,[4] **Augusto Lavalle-Cobo**,[5] **Francisco J. Romeo**[6,7]

[1]Department of Cardiology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
[2]Department of Endocrinology, Nutrition and Metabolism Research Center, Faculty of Health Sciences, Universidad Nacional de Formosa, Formosa, Argentina
[3]International University of the Americas, San José, Costa Rica
[4]Faculty of Medicine, FASTA University, Mar del Plata, Argentina
[5]Department of Cardiology, Sanatorio Finochietto, Buenos Aires, Argentina
[6]Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Morningside & West, New York, NY, USA
[7]Department of Cardiology, University of Miami/Jackson Memorial Hospital, Miami, FL, USA

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Correspondence to
Leandro Barbagelata
Department of Cardiology, Hospital Italiano de Buenos Aires, Perón 4190, Buenos Aires C1199ABB, Argentina.
Email: leandro.barbagelata@hospitalitaliano.org.ar

ORCID iDs
Walter Masson
https://orcid.org/0000-0002-5620-6468
Leandro Barbagelata
https://orcid.org/0000-0003-3694-1083
Juan P Nogueira
https://orcid.org/0000-0002-8764-4700
Pablo Corral
https://orcid.org/0000-0003-0017-8725

ABSTRACT

Objective: The role of lipoprotein(a) (Lp[a]) as a possibly causal risk factor for atherosclerotic cardiovascular disease has been well established. However, the clinical evidence regarding the association between Lp(a) levels and atrial fibrillation (AF) remains limited and inconsistent. This study aimed to analyze the association between elevated Lp(a) levels or single-nucleotide polymorphisms (SNPs) related to high levels of Lp(a) and AF.
Methods: This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A literature search was performed to identify studies that evaluated the association between Lp(a) levels or SNPs related to high levels of Lp(a) and AF. Observational studies with a cross-sectional, case-control, or cohort design were included in this systematic review, without limitations according to language, country, or publication type.
Results: Eleven observational studies including 1,246,817 patients were eligible for this systematic review. Two cross-sectional studies, 5 prospective/retrospective cohort studies, and 4 Mendelian randomization studies were analyzed. Two cross-sectional studies that compared Lp(a) levels between patients with and without AF showed conflicting results. Cohort studies that evaluated the incidence of AF according to Lp(a) levels showed different results: no association (3 studies), a positive association (1 study), and an inverse relationship (1 study). Finally, Mendelian randomization studies also showed heterogeneous results (positive association: 2 studies; inverse association: 1 study; no association: 1 study).
Conclusion: Although there could be an association between Lp(a) levels and AF, the results of the studies published to date are contradictory and not yet definitive. Therefore, further research should clarify this issue.

Keywords: Lipoprotein(a); Atrial fibrillation; Systematic review; Dyslipidemia

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Augusto Lavalle-Cobo
https://orcid.org/0000-0002-1257-9211
Francisco J. Romeo
https://orcid.org/0000-0003-1261-5785

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Conflict of Interest
Walter Masson, Juan P. Nogueira, Pablo Corral, and Augusto Lavalle-Cobo are editors of *Journal of Lipid and Atherosclerosis*. However, they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement
The data underlying this article are available in the article and in its online supplementary material.

Author Contributions
Conceptualization: Masson W, Barbagelata L, Nogueira JP, Corral P, Lavalle-Cobo A, Romeo FJ; Formal analysis: Corral P; Writing - original draft: Masson W, Nogueira JP, Corral P, Lavalle-Cobo A, Romeo FJ; Writing - review & editing: Nogueira JP, Corral P, Romeo FJ.

INTRODUCTION

Atrial fibrillation (AF) is a major public health problem, linked to an aging population and an increasing prevalence of predisposing factors.[1] This type of arrhythmia is one of the most prevalent cardiovascular conditions, affecting millions of people worldwide.[2] Importantly, the increasing AF burden is associated with higher risks of both thromboembolic events and hospitalizations due to heart failure.[3]

During the last few decades, our understanding of the pathophysiology of AF has dramatically improved. The first episodes of AF (within hours) lead to changes in ion channels, promoting shortened atrial action potentials and decreasing the "wavelength" of re-entry circuits, which are paramount for the perpetuation of AF, triggering so-called "electrical remodeling" within the left atrium (LA). Furthermore, increased LA pressures and LA distention lead to structural changes within the atrial tissue, including interstitial fibrosis, which constitutes one of the key features linked to AF onset and recurrence.[4] In addition, preclinical and clinical studies have shown that the activation of inflammatory pathways may also play a key role in the pathogenesis of AF.[5]

Classic coronary risk factors such as high blood pressure, elevated body mass index, diabetes mellitus, and cigarette smoking have also been associated with an increased risk of AF.[6] Additionally, a meta-analysis of large cohort studies found inverse relationships between serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol levels and AF risk.[7]

Lipoprotein(a) (Lp[a]) is a lipid-carrying particle composed of an LDL-like particle containing apolipoprotein B-100 linked by a disulfide bond to apolipoprotein(a).[8] Lp(a) levels are fundamentally determined by genetic variability at the *LPA* locus.[9] Genetic and epidemiologic studies have shown that high levels of Lp(a) are an independent risk factor for atherosclerotic cardiovascular disease and aortic valve stenosis through mechanisms associated with increased atherogenesis, inflammation, and thrombosis.[10] Analyzing the association between Lp(a) and AF seems interesting given the fact that AF is an independent risk factor for stroke, as well as the demonstrated association between Lp(a) concentrations and the risk of cerebrovascular events.[11] Previous observational studies have evaluated the association between Lp(a) levels or single-nucleotide polymorphisms (SNPs) related to high levels of Lp(a) and the prevalence/incidence of AF.[12-22] However, the results were conflicting and heterogeneous. To the best of our knowledge, this is the first systematic review of studies investigating the association between Lp(a) and AF. Therefore, we sought to analyze the associations between elevated Lp(a) levels or SNPs related to high levels of Lp(a) and the risk of AF development.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations developed to steer the performance of systematic reviews.[23] This systematic review was registered in PROSPERO (CRD42023421398).

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A systematic bibliographic search was carried out to identify studies evaluating the association between Lp(a) levels and AF. Two independent reviewers performed the search in PubMed/MEDLINE, Embase, Science Direct, Scopus, Google Scholar, and Cochrane Controlled Trials electronic databases, using the terms "lipoprotein(a)" or "single nucleotide polymorphism" combined with the terms "atrial fibrillation" or "arrhythmia."

This systematic review included observational studies with a cross-sectional, case-control or cohort design (retrospective or prospective) with the aim of answering 3 questions: 1) Do patients with elevated Lp(a) levels have a higher prevalence of AF than patients with low Lp(a) levels?; 2) Among patients without AF, is a higher risk of incident AF associated with elevated Lp(a) levels compared to lower Lp(a) levels?; 3) Among patients without AF, is a higher risk of incident AF associated with the presence of genetic determinants related to elevated Lp(a) levels compared to the absence of those factors? No restrictions were applied in terms of language, country, or publication type.

The primary study endpoints were prevalent AF and incident AF, depending on the type of study evaluated (prevalence for cross-sectional studies; incidence for cohort studies). Data were extracted on the baseline population and effect sizes for the relationship between Lp(a) and outcomes. Effect sizes and 95% confidence intervals (CIs) for Lp(a) were reported as odds ratios (ORs) or hazard ratios (HRs), in accordance with how the data were reported in the original publications.

The risk of bias was assessed using the Cochrane Risk of Bias in Non-Randomized Studies of Interventions tool.[24] It evaluates 7 domains related to bias due to confounding, bias in the selection of participants into the study, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in the selection of the reported result. The categories for risk of bias judgments are "low risk," "moderate risk," "serious risk," and "critical risk" of bias. Discrepancies between reviewers were resolved by involving an additional third reviewer.

A meta-analysis was not possible due to the heterogeneity of the populations included, the different cut-off points and measurements of Lp(a) used, and the type of outcomes reported.

1. Ethical approval

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

The search included 108 potentially relevant articles after title/abstract screening, and 85 studies were excluded because they were duplicate publications or because they did not correspond to the purpose of this study. After a careful reading of the remaining articles, 12 studies were removed because they did not report the exposure/event of interest. A flow diagram of the study's screening process is shown in **Fig. 1**. Eleven observational studies including 1,246,817 patients were identified and considered eligible for this systematic review.[12-22] The quality of the selected studies is described in detail in **Fig. 2**. In total, 2 cross-sectional studies, 5 prospective/retrospective cohorts, and 4 Mendelian randomization studies were analyzed. The population characteristics of the studies are shown in **Table 1**.

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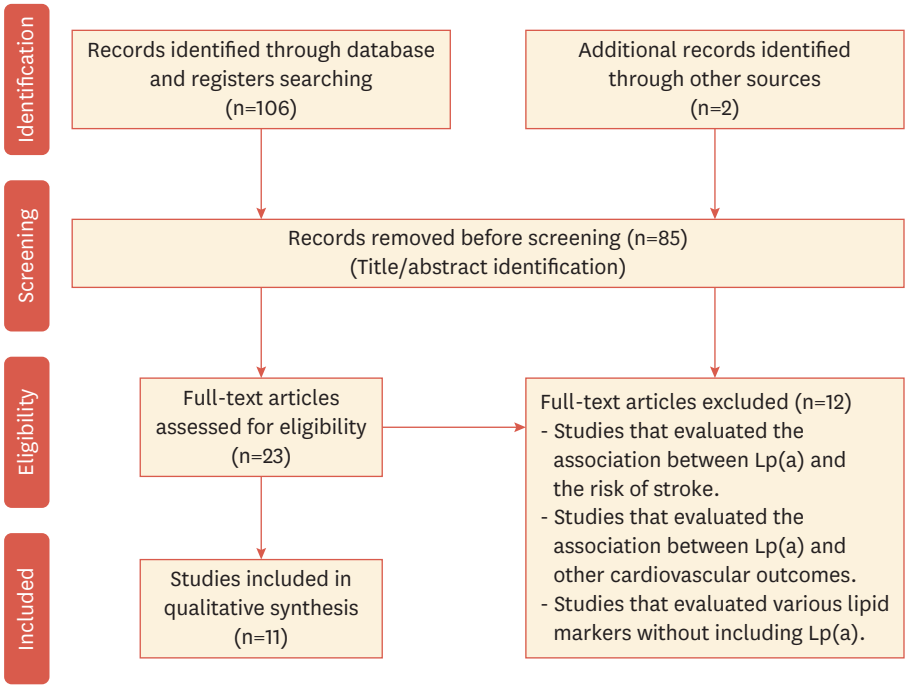

Fig. 1. Flow diagram of the study screening process.
LP(a), lipoprotein(a).

1. Studies comparing Lp(a) levels between patients with and without AF

A small study carried out in Galicia, Spain did not show a significant difference in Lp(a) levels between patients with or without AF (5.75±6.94 mg/dL vs. 7.3±8.71 mg/dL, p=0.16).[12] Another large study conducted in China showed a significant inverse association between Lp(a) levels and AF,[13] with the AF group exhibiting lower Lp(a) levels than the matched non-AF group (15.95 vs. 16.90 mg/dL; p<0.001). The AF prevalence decreased from 34.2% in quantile 1 (Lp[a] ≤8.71 mg/dL) to 30.9% in quantile 4 (Lp[a] >32.4 mg/dL) (p for trend <0.001). In the adjusted model, Lp(a) <32.4 mg/dL still showed a significant inverse association with AF (OR, 1.24; 95% CI, 1.12–1.38).

2. Studies that evaluated the incidence of AF according to Lp(a) levels.

A small study evaluated recurrent arrhythmia in a group of patients undergoing electrical cardioversion with a 2-year follow-up.[14] In the logistic regression model, Lp(a) did not show any statistically significant association with AF recurrence. Additionally, survival analysis showed a slightly higher AF recurrence rate in the group with higher Lp(a) levels (≥0.32 g/L), but the difference was not statistically significant (log-rank test, p=0.62).

During a median follow-up of 16.4 years, Mora et al.[15] did not find an association between Lp(a) levels and the incidence of AF in a large cohort. Comparing the top and bottom quintiles of Lp(a) levels in multivariate analysis, the HR for incident AF was 0.96 (95% CI, 0.76–1.20). Similarly, Aronis et al. reported that there was no association between Lp(a) levels and the incidence of AF in a large cohort with a median follow-up of 13.9 years.[16] The AF incidence rate was similar in participants with Lp(a) ≤10 mg/dL and those with >50 mg/dL (9.1 vs. 8.4 events per 1,000 person-years). In the adjusted model, the HR of AF for high Lp(a) levels (≥50 mg/dL) compared with <10 mg/dL was 0.98 (95% CI, 0.82–1.17).

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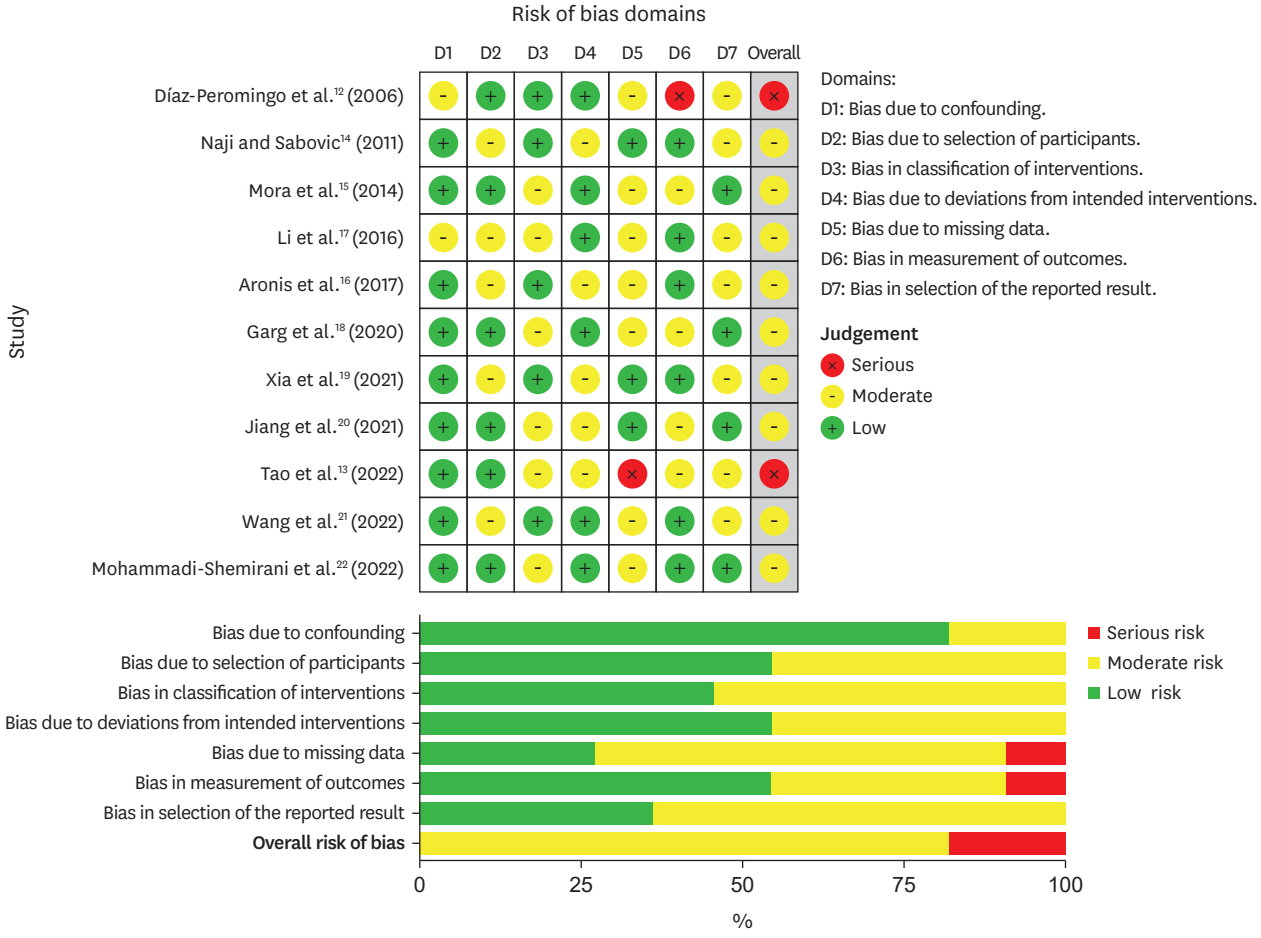

Fig. 2. Bias assessment of included studies.

Another study conducted in patients with chronic heart failure showed different results.[17] Compared to 534 patients without AF, patients with AF had a higher concentration of Lp(a) (mean±standard deviation [SD], 0.4±0.2 g/L, $p<0.05$). Of 534 patients without AF at enrollment, approximately 6.7% developed new-onset AF during the mean of 25 months follow-up. In multivariate analysis, Lp(a) showed a significant ability to predict new-onset AF (adjusted HR per 1-SD increase, 2.693; 95% CI, 1.005–7.22; $p<0.05$).

The Multi-Ethnic Study of Atherosclerosis recruited adults aged 45–84 years who were free of clinically recognized cardiovascular disease, with a median follow-up of 12.9 years.[18] That study showed that individuals with Lp(a) levels ≥30 mg/dL had a 16% reduced risk of incident AF (HR, 0.84; 95% CI, 0.71–0.99) compared to those with normal levels. Similarly, each log-transformed unit increase in Lp(a) was associated with a 9% decrease in AF risk.

3. Studies that analyzed the relationship between genetic determinants associated with Lp(a) and the incidence of AF (Mendelian randomization studies)

Several SNPs associated with Lp(a) levels in the Han Chinese population were analyzed in a study by Xia et al.[19] After adjusting for age and sex, 13 SNPs were significantly associated with Lp(a) levels ($p<0.05$): 4 SNPs in *SLC22A3*, 3 SNPs in *LPA*, 1 SNP in *APOE*, and 5 SNPs in

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Table 1. Population characteristics, design, and methodology used in the studies included in this review

Study	Year	No.	Design	Population	Lp(a) assay
Studies comparing Lp(a) levels between patients with and without AF					
Díaz-Peromingo et al.[12]	2006	202	Cross-sectional	Caucasian patients from Spain with long-term AF. Controls were patients without AF, matched for sex and age. AF group: median age 68 years, men 47.5%; control group: median age 66 years, men 45.5%	Enzyme-linked immunoabsorbent assay
Tao et al.[13]	2022	13,533	Cross-sectional	Chinese patients with AF and controls without AF, matched with the propensity score matching method Median age 69 years, women 46.9%	Latex-enhanced immunoturbidimetric method
Studies that evaluated the incidence of AF according to Lp(a) levels					
Naji and Sabovic[14]	2011	79	Retrospective cohort	Slovakian patients after successful electrical cardioversion. Mean age 62 years. Median age 62.7 years, 43.9% men and 21.6% Blacks	Not reported
Mora et al.[15]	2014	23,738	Prospective cohort	Apparently healthy female healthcare professionals, ages 45 years or older, and free of prior CVD and AF from the United States AF group: median age 52.6 years, White 95.5%; Control group: median age 58.7 years, White 97.9%	Immunoturbidimetric assay
Li et al.[17]	2016	679	Prospective cohort	Chinese patients with chronic heart failure. Mean age 70.4 years, 58.0% men. In total, 145 (21.4%) patients had AF at baseline	Enzyme-linked immunoabsorbent assay
Aronis et al.[16]	2017	9,908	Prospective cohort	Participants from the United States aged 45 to 64 years Mean age 62.7 years, 43.9% men and 21.6% Blacks	Latex-enhanced turbidimetric method
Garg et al.[18]	2020	6,593	Prospective cohort	Patients from the United States aged 45 to 84 years and free of clinically recognized cardiovascular disease. Mean age 62 years, 53% female	Latex-enhanced turbidimetric immunoassay
Studies that analyzed the relationship between genetic determinants associated with Lp(a) and the incidence of AF					
Xia et al.[19]	2021	1,256	Mendelian randomization study	Chinese patients with coronary heart diseases and matched controls who did not have cardiovascular disease. Median age 63 years, 81.8% women	Latex-enhanced turbidimetric immunoassay
Jiang et al.[20]	2021	377,660	Mendelian randomization study	European participants	Immunoturbidimetric assay
Wang et al.[21]	2022	377,590	Mendelian randomization study	European participants	Not reported
Mohammadi-Shemirani et al.[22]	2022	435,579	Mendelian randomization study	European participants	Immunoturbidimetric assay

Lp(a), lipoprotein(a); AF, atrial fibrillation; CVD, cardiovascular disease.

undefined pathways. Genetically elevated Lp(a) levels were inversely associated with the risk of AF (OR, 0.94; 95% CI, 0.90–0.98; p=0.012).

Another study published by Jiang et al. showed that genetically elevated levels of Lp(a) were significantly associated with an increased risk of AF.[20] In that study, summary estimations of genetic variants associated with Lp(a) levels yielded 30 SNPs. The OR for AF per SD increase was 1.001 (95% CI, 1.000–1.003; p=0.023). The individual SNP analysis assessed the causal effects of rs67302319 (OR, 1.015; 95% CI, 1.003–1.027) and rs141766382 (OR, 1.003; 95% CI, 1.000–1.006) on the risk of AF. Unlike the results of the 2 previously discussed studies, Wang et al.[21] reported that there was no causal association between genetic variants associated with Lp(a) (18 SNPs explored) and AF.

Finally, Mohammadi-Shemirani et al.[22] reported a study based on the UK Biobank (n=435,579 participants; 15 SNPs). After a median 11 years of follow-up, 20,432 participants developed incident AF, corresponding to a rate of 4.37 events per 1,000 person-years. After adjustment for common risk factors, the authors identified an increased incidence of AF by 3% per 50 nmol/L (23 mg/dL) increase in Lp(a) (HR, 1.03; 95% CI, 1.02–1.04). Moreover, each 50 nmol/L increase in genetically predicted Lp(a) levels was associated with an increased risk of incident AF (OR, 1.03; 95% CI, 1.02-1.05). Mendelian randomization analyses using independent data replicated the effect (OR, 1.04; 95% CI, 1.03–1.05 per 50 nmol/L Lp[a] increase).

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DISCUSSION

This systematic review included the full body of evidence on the relationship between Lp(a) levels and AF.

Previously, several mechanisms have been proposed to explain the potential association between Lp(a) and AF. A relationship between coronary heart disease (CHD) and AF has been observed in different scenarios.[25-27] However, elevated Lp(a) has been associated as an independent predictor of adverse coronary outcomes in the primary prevention setting.[28,29] Therefore, an important aspect to consider is the interplay between Lp(a) levels, CHD, and AF, as these interactions could partly explain the findings of this review. In the studies included in this systematic review, the CHD variable was not always analyzed in the same way. One of the studies that compared Lp(a) levels between patients with and without AF did not report the baseline prevalence of CHD and did not adjust the main outcome for this variable.[12] In contrast, approximately 27% of patients in another study had CHD, with both AF and non-AF control groups matched using the propensity score method for balancing covariates.[13] Meanwhile, 2 studies that evaluated the incidence of AF did not include patients with CHD,[15,18] whereas 2 others included a lower proportion of CHD patients and adjusted the main result for this variable.[14,16] The fifth study that analyzed this endpoint included all patients with congestive heart failure.[17] The proportion of patients with CHD was high but unbalanced between the AF and control groups. Furthermore, although the authors adjusted the main result for various echocardiographic variables, they did not do so for the etiology of heart failure (ischemic vs. non-ischemic). Similarly, Mendelian randomized studies have explored this issue in different ways. The study published by Xia et al.[19] included only patients with CHD, while another study did not provide information on this point.[21] CHD was used as a control outcome to verify the validity of instrumental variables in the study published by Jiang et al.,[20] although the association between Lp(a) and AF was not adjusted for the presence or absence of CAD. Finally, given the atherogenic properties of Lp(a) and role of atherosclerotic cardiovascular diseases as a risk factor for AF, Mohammadi-Shemirani et al.[22] sought to assess whether part of the effect of Lp(a) on AF was mediated independently of atherosclerotic cardiovascular disease. Mediation analysis determined that 62.2% of the effect of observed Lp(a) and 39.2% of the effect of genetically predicted Lp(a) on increased risk of AF was mediated through prevalent CHD and aortic valve stenosis considered together. However, after excluding participants with prevalent CHD, the relationship between Lp(a) and AF remained unchanged.

The other relevant point to analyze is the relationship between inflammation, Lp(a) levels, and AF. Inflammatory mediators can enhance AF by worsening the conductance of the electrical signal and by boosting the fibrogenesis and structural remodeling of the atria.[30] Likewise, patients with elevated levels of Lp(a) display increased arterial wall inflammation characterized by activation of the endothelium by Lp(a)-carried oxidized phospholipids and recruitment of circulating monocytes.[31] Moreover, Lp(a) promotes valvular calcification through the positive regulation of reactive oxygen species and inflammatory cytokines released by macrophages.[32] Accordingly, the possible relationship between Lp(a), inflammation, and the occurrence of AF is entirely plausible. In addition, one of the studies included in this review proposed that the association between Lp(a) and AF was not only due to atherosclerotic cardiovascular disease but also mediated by the direct action of Lp(a) on myocardial tissue.[22]

https://doi.org/10.12997/jla.2023.12.3.267

In addition to the previously mentioned mechanisms of atherosclerosis and inflammation, there are two additional factors to consider: Lp(a) infiltration into the aortic valve and changes in gene expression leading to cell death.[32,33] The oxidized phospholipids carried by Lp(a) promote inflammation and mineralization of the aortic valve and disease progression. Thus, aortic valve disease could represent an additional mechanism explaining the relationship between Lp(a) and AF.

The conflicting results of the studies included in this review preclude a definitive conclusion on this topic. It seems clear that the different sample sizes or the presence of different confounding factors can partly explain the heterogeneous results reported by the studies. Additionally, a frequent problem when analyzing studies that evaluated Lp(a) levels in different populations is the widely documented variation in Lp(a) levels according to ethnic groups.[34] The studies analyzed in this review included European, Asian, or American patients. However, conflicting results were observed even among studies that included patients from the same country, such as the US[15,16,18] or China.[17,19]

The conflicting results found in this review do not unequivocally establish the usefulness of Lp(a) as a marker of AF risk in clinical practice. It is mandatory to obtain more and better evidence, analyzing different ethnic groups and different clinical scenarios (presence or absence of CHD). Furthermore, future clinical trials that evaluate new therapies to lower Lp(a) levels should include the occurrence of AF as an additional endpoint.

This systematic review has some limitations. Firstly, relatively few studies were included. Secondly, performing a meta-analysis was impossible due to high clinical heterogeneity, the different Lp(a) cut-off points used, and the different endpoints reported. Finally, the studies included in this review were observational. Therefore, the presence of biases and confounders was highly expected. Despite these limitations, this systematic review analyzed all the current evidence published on this topic.

Although there could be an association between Lp(a) levels and AF, the results of the studies published up-to-date are contradictory and not definitive. Therefore, given the observational nature of the studies evaluated and the complex pathophysiological relationship between Lp(a) and AF, new studies should be conducted to shed light on this important issue.

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