ORIGINAL RESEARCH

Association Between Plasma Lipoprotein Levels and Aortic Valve Calcification Among Patients with Aortic Valve Replacement Surgery: A Retrospective Study

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Objective: Calcific aortic valve disease (CAVD) is a prevalent type of valvular heart disease, its association with dyslipidemia remains controversial.

Methods: Of 449 CAVD patients who underwent aortic valve replacement, 228 formed the aortic valve calcification (AVC) group, and 221 were the non-calcification group. We retrospectively reviewed the preoperative and one-year postoperative plasma lipoprotein levels of both and performed a logistic regression to evaluate the factors associated with AVC.

Results: Preoperatively, AVC patients had significantly higher coronary heart disease (43.0% vs 24.9%, p<0.001), peripheral vascular disease (41.7% vs 26.2%, p<0.001), and heart failure rates (63.6% vs 47.1%, p<0.001), and a higher level of total cholesterol (4.1±0.9 vs 3.9±0.8 mmol/L, p=0.032) and very low-density cholesterol (0.6 (0.4–0.7) vs 0.5 (0.3–0.7) mmol/L, p=0.054). Echocardiography revealed a significant difference of aortic stenosis in both AVC and non-AVC groups (p<0.05), and also identified aortic regurgitation (AR) with a significant difference between these two groups (p=0.003). The peak transaortic jet velocity, peak transaortic gradient, and mean transaortic gradient were significantly higher in the calcification group (all p<0.001), but the aortic valve area (0.7 (0.5–1.0) vs 4 (0.9–4.5) cm^2; p<0.001) was smaller. Age (OR=1.023), total cholesterol (OR=1.272), and mean transaortic gradient (OR=1.182) were AVC risk factors. A larger aortic valve area (OR=0.010) were protective factors. The one-year mortality and perivalvular leakage rates were significantly higher in the calcification group.

Conclusion: Total cholesterol was significantly higher in AVC patients and may be an AVC risk factor along with age and mean transaortic gradient. AVC patients had a relatively poorer outcome within one year.

Keywords: aortic valve calcification, total cholesterol, plasma lipoprotein levels, low-density lipoprotein, aortic valve replacement

Introduction

Calcific aortic valve disease (CAVD) is a prevalent type of valvular heart disease, which can ultimately result in chronic heart failure. Different types of cardiovascular diseases (CVDs) share similar etiological pathways,[1,2] and the process of calcific aortic valve stenosis (CAVS) is highly akin to that of atherosclerosis.[3–5] Evidence has shown that dyslipidemia may contribute to atherosclerotic-related diseases.[6,7] However, recent findings about the association between plasma lipoprotein levels and aortic valve calcification (AVC) have demonstrated inconsistent results,[2,5,8,9] and no convincing randomized controlled trials (RCTs) have confirmed the effect of statin therapy on the progression of aortic stenosis (AS).[10–12] Despite some disappointing results from prospective treatment trials, the retrospective analyses continue to suggest that there may be a positive association between lipid-lowering therapy and AVC,[13,14] some lipid-lowering therapies may influence the progression of CAVD.[7,14]

In this clinical retrospective study, we aimed to analyze the association between plasma lipoprotein levels and AVC severity among patients who underwent aortic valve replacement (AVR) surgery. We explored factors associated with AVC and hope the present study will contribute to the therapy for CAVD patients.

Materials and Methods
Study Design and Patient Data Collection

We consecutively enrolled 1608 patients who underwent isolated or concomitant AVR surgery from January 1st, 2015, to January 1st, 2020, at the Department of Cardiovascular Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine. We excluded 1146 patients due to reasons shown in Figure 1. Finally, 449 patients with complete clinical data were included and were separated into two groups according to whether their aortic valve was obviously calcified.

We collected and evaluated general data from all patients, which included age, sex, medical history, comorbidities (hypertension, diabetes, coronary artery disease (CAD), peripheral artery disease (PAD), stroke, and atrial fibrillation (AF)). We analyzed the plasma lipoprotein levels of these patients using low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and total cholesterol levels, and also included triglyceride and C-reactive protein levels. The parameters relevant to valvular disease were all determined by two types of echocardiography: transthoracic echocardiography (TTE) and transesophageal echocardiography.

This study was reviewed and approved by the Research Ethics Committees of the First Affiliated Hospital of Zhejiang University School of Medicine, under the Reference Number IIT20210002A. The need for individual informed consent
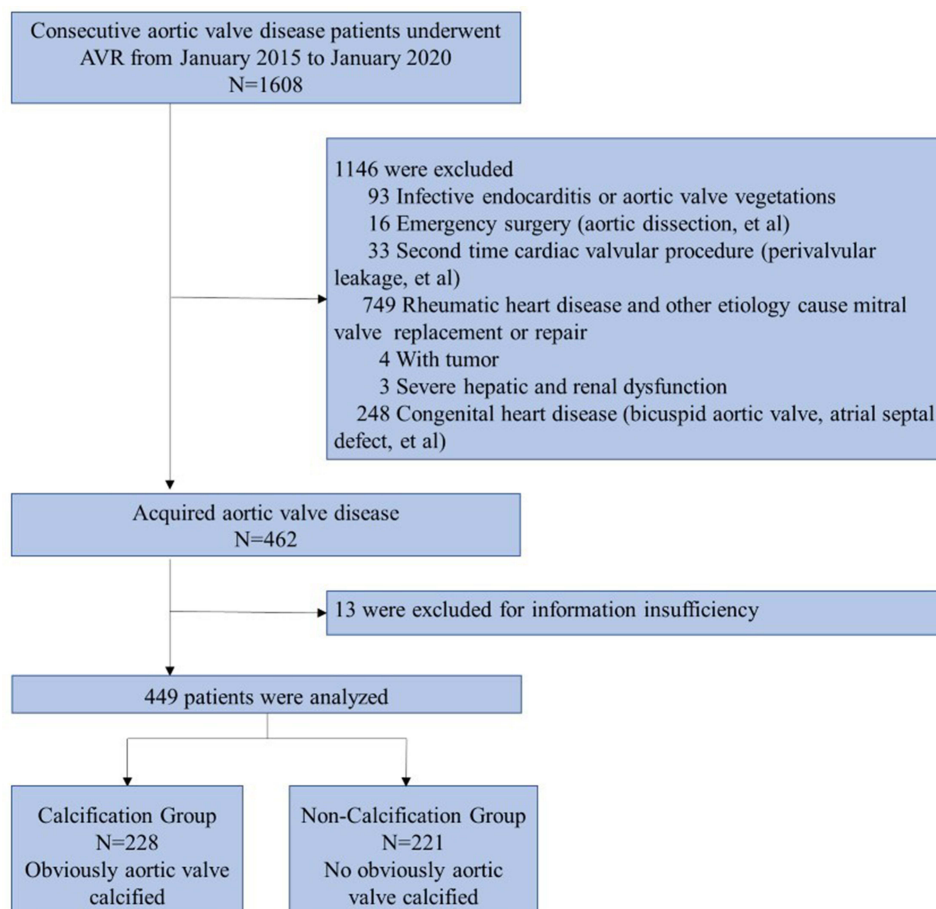
Figure 1 This study flow demonstrated the progress of our enrollment. A total of 449 patients were included in the final analysis, which were later separated into two groups, calcification group (N=228) and non-calcification group (N=221). A total of 1146 patients were met the exclusion criteria and other 13 patients for information insufficiency were also excluded.

was waived by the ethics committee due to the study's retrospective nature. All the procedures were performed under principles of the local law and the Declaration of Helsinki.

Definitions

We analyzed all consecutive patients over 18 years of age who underwent first-time selective AVR. Patients with concomitant mitral valve replacement (MVR), emergency procedures, rheumatic heart disease (RHD), infective endocarditis, active malignant tumors, or severe hepatic and renal dysfunctions were excluded.

The calcification group and the non-calcification group were separated based on the calcification condition of the aortic valve, which was confirmed by imageology data preoperatively and reconfirmed by the surgeons during the operation.

Coronary artery disease is typically confirmed according to evidence on invasive coronary angiography or computed tomography angiography.

Heart failure is defined as Classification III and IV of the New York Heart Association (NYHA). Patients with an ejection fraction (EF) lower than 30% were excluded from our study.

Medication use indicates that the medication taking condition of patients upon admission.

The stroke classification system used in this study was based on a statement issued by the American Heart Association/American Stroke Association in 2013,[15] the occurrence of stroke was counted when it was specifically accompanied by overt symptoms. In addition, the presence of a perivalvular leak within one year postoperatively was defined by all degrees that can be detected by echocardiography.

Patients in hypercholesterolemia group were defined as the receipt of treatment with cholesterol-lowering medication or an elevated level of total cholesterol (>200 mg per deciliter [5.2 mmol per liter]).[16]

Surgical Procedure

The procedures were performed via either median sternotomy or minimally invasive incision. Isolated or concomitant AVR was carried out in all patients with the implantation of either a bioprosthetic or mechanical prosthesis. Concomitant operations in some of the patients included coronary artery bypass grafting (CABG) and tricuspid valvuloplasty (TVP). Standard general anesthesia, extracorporeal circulation, and myocardial protection methods were used for all participants. All the procedures were performed under principles of the local law and the Declaration of Helsinki.

Statistical Analysis

Continuous variables were presented as the mean ± standard deviation (SD) or the median and interquartile range (IQR) for Gaussian and non-Gaussian distributed data, respectively. Categorical variables were expressed as numbers and percentages (n%). Pearson's χ^2 test was used for descriptive, univariate statistics. Student's unpaired t-test was carried out to compare normally distributed data. The Mann–Whitney U-test was used for the group comparison of continuous, non-Gaussian distributed variables. Regression and correlation analyses were performed using logistics regression analysis. Any horizontal pleiotropy was balanced.

All statistical analyses were performed with the Statistical Package for the Social Sciences software, version 23 (Armonk, New York). A p-value of less than 0.05 (p<0.05) was considered statistically significant for all included statistical tests.

Results

Demographics, Preoperative Plasma Lipid Levels and AVC

Baseline clinical characteristics are shown in Table 1. Of the 449 patients we reviewed, calcification was detected in 50.8% (228/449) of the patients (calcification group); the remaining participants were placed in the non-calcification group. The median age (63 vs 62 years old) and percentages of males (69.7% vs 67.9%), current smokers (27.2% vs 26.7%), hypertension (44.3% vs 53.4%), diabetes (6.6% vs 5%), stroke (3.9% vs 5%), and AF (7.5% vs 7.2%) were similar in the calcification and non-calcification groups, respectively. Patients with AVC had significantly higher rates of coronary heart

Table 1 Baseline Clinical Characteristics

	Calcification Group (N=228)	**Non-Calcification Group (N=221)**	**p valve**
Demographic variables			
Age (yrs)	63 (56–69)	62 (53.5–68)	0.085
Male	159 (69.7)	150 (67.9)	0.670
Current smoker	62 (27.2)	59 (26.7)	0.620
Hypertension	101 (44.3)	118 (53.4)	0.054
Diabetes	15 (6.6)	11 (5)	0.470
Coronary heart disease	98 (43.0)	55 (24.9)	**<0.001**
Peripheral vascular disease	95 (41.7)	58 (26.2)	**<0.001**
Stroke	9 (3.9)	11 (5)	0.600
Atrial fibrillation	17 (7.5)	16 (7.2)	0.560
Heart failure	145 (63.6)	104 (47.1)	**<0.001**
Medication use			
Aspirin and or clopidogrel	30 (13.2)	32 (14.5)	0.690
β-blocker	32 (14.0)	33 (14.9)	0.790
CCB	41 (18.0)	56 (25.3)	0.058
Statins	40 (17.5)	29 (13.1)	0.190
Warfarin	6 (2.6)	3 (1.4)	0.340
Initial blood laboratory test			
Creatinine (μmol/L)	83.4±70.3	82.9±46.7	0.250
UA (μmol/L)	359.3±96.5	370.3±106.2	0.250
BUN (mmol/L)	6.5±2.3	6.5±2.6	0.930
ALT (U/L)	20.4±19.2	18.6±12.7	0.240
AST (U/L)	22.3±15.2	20.1±7.2	0.060
Lipid profile components			
Triglycerides (mmol/L)	1.2 (0.8–1.6)	1.1 (0.8–1.7)	0.280
Total cholesterol (mmol/L)	4.1±0.9	3.9±0.8	**0.032**
LDL cholesterol (mmol/L)	2.3±0.8	2.2+0.7	0.110
HDL cholesterol (mmol/L)	1.2±0.3	1.2±0.3	0.620
VLDL cholesterol (mmol/L)	0.6 (0.4–0.7)	0.5 (0.3–0.7)	**0.054**

Notes: Data are expressed as mean±SD, median (interquartile range) or as percentages. The bold values indicate statistical significance.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CCB, calcium channel blocker; UA, uric acid.

disease (43.0% vs 24.9%, p<0.001), peripheral vascular disease (41.7% vs 26.2%, p<0.001), and heart failure (63.6% vs 47.1%, p<0.001). They also had higher total cholesterol (4.1±0.9 vs 3.9±0.8 mmol/L, p=0.032) and VLDL cholesterol (0.6 (0.4–0.7) vs 0.5 (0.3–0.7) mmol/L, p=0.054) levels. Other results of lipid profile components were similar (Table 1).

Echocardiographic Data

The pre-operative echocardiographic findings are shown in Table 2. AS was detected in 86% (196/228) patients with AVC and in only 24% (53/221) of participants without AVC (p<0.001). Echocardiography identified 210 (92.1%) aortic regurgitation (AR) patients with AVC and 217 (98.2%) in patients without AVC, with a significant difference between the two groups (p=0.003). The peak transaortic jet velocity, peak transaortic gradient, and mean transaortic gradient were significantly higher in patients with AVC (p<0.001 for all), while the aortic valve area was significantly smaller in this group of patients (0.7 (0.5–1.0) vs 4 (3.9–4.5) cm^2, p<0.001).

Logistic Regression Analysis of Lipids Associated with AVC

The final results of our multivariate logistic regression analysis are shown in Table 3. Age, total cholesterol, and mean transaortic gradient were significant risk factors for AVC in these AVR patients, with an odds ratio (OR) of 1.023 (95%

Table 2 Pre-Operative Echocardiographic Findings

	Calcification Group (N=228)	Non-Calcification Group (N=221)	p valve
Aortic stenosis	196 (86)	53 (24)	**<0.001**
Aortic regurgitation	210 (92.1)	217 (98.2)	**0.003**
AS & AR	178 (78.1)	49 (22.2)	NA
EF (%)	61.7±9.7	61.4±8.5	0.650
Aortic valve annulus diameters (mm)	23 (22–25)	23 (22–25)	0.680
Peak transaortic jet velocity (m/s)	4 (3.1–4.8)	1.9 (1.6–2.4)	**<0.001**
Peak transaortic gradient (mmHg)	64 (37.5–92.2)	14.3 (9.8–22.1)	**<0.001**
Mean transaortic gradient (mmHg)	43 (33–58.5)	23 (17.8–31)	**<0.001**
Aortic valve area (cm^2)	0.7 (0.5–1.0)	4 (3.9–4.5)	**<0.001**

Notes: Data are expressed as mean±SD, median (interquartile range) or as percentages. The bold values indicate statistical significance.
Abbreviations: AR, aortic regurgitation; AS, aortic stenosis; EF, ejection fraction; NA, not applicable.

Table 3 Multivariate Logistic Regression Analysis of Lipids Associated with Aortic Valve Calcification (r^2=0.594)

Variable	B	SE (b)	Wald χ^2	p valve	95% CI	OR
Age (yrs)	0.023	0.009	6.491	0.011	1.005–1.041	1.023
Total cholesterol (mmol/L)	0.241	0.112	4.605	0.032	1.021–1.585	1.272
Mean transaortic gradient (mmHg)	0.167	0.029	32.307	<0.001	1.116–1.252	1.182
HDL cholesterol (mmol/L)	−4.086	2.225	3.373	0.066	0.000–1.316	0.017
Aortic valve area (cm^2)	−8.175	3.251	6.323	0.006	0.000–0.265	0.010

Abbreviations: CI, confidence interval; OR, odds ratio.

CI: 1.005–1.041, p=0.011), 1.272 (95% CI: 1.021–1.585, p=0.032), and 1.182 (95% CI: 1.116–1.252, p<0.001), respectively. The analysis revealed a protective effect of larger aortic valve area (OR=0.010, 95% CI: 0.000–0.265, p=0.006) on AVC. The factor of HDL cholesterol may be associated with AVC, but statistically insignificant (OR=0.017, 95% CI: 0.000–1.316, p=0.066).

One-Year Outcomes

The one-year mortality was significantly higher in the calcification group (1.8%) compared to 0% in the non-calcification group (p=0.048). AVC patients also had significantly higher rates of perivalvular leakage (10.5% vs 4.5%, p=0.016). Other aspects of one-year outcomes, including the incidence of valvular vegetation, revision cardiac surgery, new onset stroke, new onset heart failure, re-entering the intensive care unit (ICU), or new AF after surgery were roughly the same in this study (p>0.05; Table 4).

Patients with High Cholesterol

Since patients with AVC had a higher level of total cholesterol, we regrouped them based on an elevated level of total cholesterol (>200 mg per deciliter [5.2 mmol per liter]), the results are shown in Table 5. Patients in hypercholesterolemia group (n=41) also had higher rate with AVC (70.7%, p=0.005) comparing to the rest patients in non-hypercholesterolemia group (n=408), and they significantly tended to suffer AS (70.7% vs 53.9%, p=0.027). The prognosis of patients with higher cholesterol was relatively poor as far as the significantly high rate of new AF after surgery (9.8% vs 1.5%, p=0.008).

Table 4 Outcomes Within 1 Year

	Calcification Group (N=228)	Non-Calcification Group (N=221)	p valve
Mortality	4 (1.8)	0 (0)	**0.048**
Perivalvular leakage	24 (10.5)	10 (4.5)	**0.016**
Valvular vegetation	2 (0.9)	2 (0.9)	0.975
Re-do cardiac surgery	9 (3.9)	3 (1.4)	0.089
New onset stroke	1 (0.4)	0 (0)	0.324
New onset heart failure	8 (3.5)	3 (1.4)	0.140
Re-entering ICU	9 (3.9)	10 (4.5)	0.761
New AF after surgery	7 (3.1)	3 (1.4)	0.219

Notes: Data are expressed as percentages. The bold values indicate statistical significance.
Abbreviations: AF, atrial fibrillation; ICU, intensive care unit.

Table 5 Patients with High Cholesterol

	Hypercholesterolemia Group (n=41)	Non Hypercholesterolemia Group (n=408)	P valve
AVC	29 (70.7)	199 (48.8)	**0.005**
Aortic stenosis	29 (70.7)	220 (53.9)	**0.027**
Aortic regurgitation	39 (95.1)	388 (95.1)	0.675
Mortality	0 (0)	3 (0.7)	0.750
Perivalvular leakage	4 (9.8)	30 (7.4)	0.377
Valvular vegetation	0 (0)	4 (1.0)	0.681
Re-do cardiac surgery	2 (4.9)	10 (2.5)	0.301
New onset stroke	0 (0)	1 (0.2)	0.909
New onset heart failure	3 (7.4)	8 (2.0)	0.070
Re-entering ICU	2 (4.9)	17 (4.2)	0.533
New AF after surgery	4 (9.8)	6 (1.5)	**0.008**

Notes: Data are expressed as percentages. The bold values indicate statistical significance.
Abbreviations: AVC, aortic valve calcification; AF, atrial fibrillation; ICU, intensive care unit.

Discussion

CAVD is a relatively prevalent valvular heart disease in western societies.[3,4,8] With the recent rise in life expectancy and decline in RHD, age-related diseases like CAVD have also increased in China.[17] CAVD has been considered as an age-related benign degenerative condition for a long time.[9] Many recent studies have shown a link between the process of this disease and lipidic accumulation,[18] calcium deposition,[4] and chronic inflammation.[19] However, the exact causal factors that lead to AVC remain unknown.[8] Therefore, there is currently limited medical treatment to prevent the progression of CAVD.[20,21] When the disease progresses to a severe stage, the only available option is surgical,[22] including open-heart AVR or transcatheter aortic valve implantation.[5] Approximately 50% of these patients will die within the next 12–18 months[19] without surgery or interventional treatment.

Studies on CVDs have disclosed that different types CVDs can share similar aetiological pathways[1,2] and substantial evidence show that elevated lipoprotein levels contribute to CVD and CAVS.[12] At the early stage of AVC, valvular endothelial cells are dysfunctional, leading to amplified mechanical stress and diminished shear stress, which inevitably resulted in adhesion, deposition, proliferation, a transition of microcalcification.[21] This series of process is highly akin to atherosclerosis, like CAD and PAD,[3] and 50% of CAVS patients have comorbid CAD,[4] which is consistent with our findings that a significant number of patients had a history of CAD or PAD. However, although lipid-lowering therapies have been widely applied to CAD and PAD patients, the findings about the association between plasma lipoprotein levels and AVC are still inconsistent.[2,5,8] In addition, no convincing RCTs have confirmed the effect of statin therapy on the progression of AS.[10–12] Recently, several researchers have turned their attention to lipoprotein(a) lowering therapy.[23,24]

AVC assessment presents quite a challenge. Doppler echocardiography, the commonly preferred method, relies on the combined results of the valve area and mean transvalvular gradients, which can be unclear, particularly in patients with a poor EF.[25,26] Studies on computed tomography (CT) calcium scoring suggest that this modality can aid in the diagnosis and also demonstrates close correlations between AVC and CAVS severity.[18,25] The recent electron beam computed tomography (EBCT) and multidetector row computed tomography (MDCT) technologies have validated for the quantification and assessment of AVC load.[26,27] In this study, cardiac surgeons reconfirmed the AVC severity based on the grading of AVC that Warren BA and Yong JL proposed in 1997,[28] which is in addition to the TTE preoperative assessment.

AVC is considered a possible source of embolism for CAVD patients. Even after undergoing TAVR, they risk having a shorter long-term survival rate,[29] which emphasizes the need to prevent or reduce to the progress of calcification and therefore improve the prognosis of CAVD patients.[30]

In this retrospective study, we screened patients who underwent isolated or concomitant AVR surgery at our institution from January 2015 to January 2020. After we analyzed the association between plasma lipoprotein levels and AVC severity, we found that patients with AVC had a significantly higher total cholesterol level, and the later logistics regression analysis revealed this valve to be a risk factor associated with AVC, along with age and mean transaortic gradient. AVC patients also showed a high level of VLDL cholesterol (0.6 (0.4–0.7) vs 0.5 (0.3–0.7) mmol/L, p=0.054), but other lipid profile components were rather similar in this study, which may have been caused by the limitations of this investigation as a single center study. The total cholesterol findings support the notion that higher triglycerides and remnant cholesterol may be factors that facilitate the evolution of AS.[20] In addition, our logistic regression analysis also suggested a large aortic valve area may have a protective effect on AVC. We also found the one-year mortality and the incidence of perivalvular leakage to be significantly higher in the calcification group, which implied patients with AVC might experience a poorer outcome.

The limitations of this research include it being a single-center study and having a relatively small sample size, a short study length, and a short follow-up period. The mortality rate may be underestimated, since only hospital-reported mortality was recorded. In addition, the criterion of calcification is a qualitative indicator that mainly relies on imageology data and cardiac surgeons' intraoperative reconfirmation. As a result, the lack of quantitative indicators may add bias to our findings. We hope to contribute evidence in support of lipid-lowering therapy to aid in the treatment of CAVD at the early initiation phase.[22] A larger sample analysis and future experimental studies will be required to further explore the mechanism of action of cholesterol on the progression of AVC.

Conclusion

In summary, we concluded that the association between plasma lipoprotein levels and AVC with the total cholesterol level was significant in patients with AVC, and it could be one important risk factor in the progress of CAVD.

Abbreviations

AF, atrial fibrillation; ALT, alanine transaminase; AR, aortic regurgitation; AS, aortic stenosis; AST, aspartate amino-transferase; AVC, aortic valve calcification; AVR, aortic valve replacement; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CAVD, calcific aortic valve disease; CAVS, calcific aortic valve stenosis; CCB, calcium channel blocker; CT, computed tomography; EBCT, electron beam computed tomography; EF, ejection fraction; HDL, high density lipoprotein; ICU, intensive care unit; IQR, interquartile range; LDL, low-density lipoprotein; MDCT, multi-detector row computed tomography; MVR, mitral valve replacement; NYHA, New York Heart Association; OR, odds ratio; RCT, randomized controlled trial; RHD, rheumatic heart disease; SD, standard deviation; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; TVP, tricuspid valvuloplasty; UA, uric acid; VHD, valvular heart disease; VLDL, very low-density lipoprotein.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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