Transcatheter Aortic Valve Implantation in Patients with Rheumatic Aortic Stenosis

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ABSTRACT

Background: Rheumatic heart disease (RHD) accounts for the highest number of deaths from valvular heart disease globally. Yet, rheumatic aortic stenosis (AS) was excluded from landmark studies investigating the safety and efficacy of transcatheter aortic valve implantation (TAVI). We aimed to describe clinical and anatomical characteristics of patients with rheumatic AS undergoing TAVI, and to compare procedural and clinical outcomes to patients undergoing TAVI for degenerative AS.

Methods: In a prospective TAVI registry, patients with rheumatic AS were identified based on ICD-10 codes and/or a documented history of acute rheumatic fever and/or the World Heart Federation criteria for echocardiographic diagnosis of RHD, and propensity score-matched in a 1:4 ratio to patients with degenerative AS.

Results: Among 2,329 patients undergoing TAVI, 105 patients (4.5%) had rheumatic AS. Compared to patients with degenerative AS, patients with rheumatic AS were more commonly female, older, had a higher surgical-risk, and more commonly suffered from multivalvular heart disease. In the unmatched cohort, both technical success (85.7% vs 85.9%; P = 0.887) and 1-year cardiovascular mortality (10.0% vs. 8.6%; HR 1.16; 95%

CI 0.61-2.18; P=0.656) were comparable between patients with rheumatic and degenerative AS. In contrast, patients with rheumatic AS had lower rates of 30-day and 1-year cardiovascular mortality compared to matched patients with degenerative AS (1.9% vs. 8.9%; HR_{adj} 0.18; 95% CI 0.04-0.80; P=0.024, and 10.0% vs. 20.3%; HR_{adj} 0.44; 95% CI 0.24-0.84; P=0.012, respectively).

Conclusion: TAVI may be a safe and effective treatment strategy for selected elderly patients with rheumatic AS.

Keywords: rheumatic heart disease, aortic stenosis, transcatheter aortic valve implantation.

Key Messages

What is already known about this subject?

Patients with rheumatic AS were excluded from landmark trials, and the available evidence was limited to small case series and administrative data without granularity on imaging features and concomitant valvular disease.

What does this study add?

In this registry-based study of patients undergoing TAVI for native severe AS, patients with rheumatic AS had comparable procedural and 1-year and 5-year clinical outcomes to patients with degenerative AS despite higher surgical risk and higher prevalence of multivalvular heart disease. Furthermore, cardiovascular mortality up to 1 year was substantially lower in patients with rheumatic AS compared to propensity-score matched patients with degenerative AS.

How might this impact on clinical practice?

TAVI may be offered as a safe and effective treatment strategy for elderly patients with rheumatic AS. Further studies are warranted to explore TAVI in regions of the world where an endemic pattern of RHD prevails.

Introduction

Rheumatic heart disease (RHD) results from a chronic inflammatory response to repeated episodes of untreated streptococcal pharyngitis and accounts for two out of three deaths from valvular heart disease worldwide[1 2]. A steady decline in prevalence of RHD in high-income countries over recent decades contrasts with a continuously high burden of disease in low- and middle-income countries.

Mitral regurgitation (MR), mitral stenosis (MS) and aortic regurgitation (AR) are the typical manifestations of RHD, while rheumatic aortic stenosis (AS) is comparably less common and frequently combined with other valvular lesions[3-5]. Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of patients with symptomatic severe AS. Patients with rheumatic AS were, however, excluded from landmark trials, and the available evidence is limited to small case series and data from insurance claims without granularity on imaging features and concomitant valvular disease[6-10]. Primary concerns to expand TAVI to patients with rheumatic AS relate to the typical morphological features of RHD with fibrinous thickening of the leaflets, commissural fusion, limited calcification, and the frequent

87 combination of AS with other valvular lesions less amenable to transcatheter
88 interventions[3-5 7 8 11 12].
89 The aim of the present analysis was to describe clinical and anatomical
90 characteristics of patients with rheumatic AS undergoing TAVI, and to compare
91 procedural and clinical outcomes to patients undergoing TAVI for degenerative AS.
92
93 # Methods
94 **Study design and population**
95 The study cohort for this retrospective analysis comprised consecutive patients
96 undergoing TAVI at Bern University Hospital from August 2007 to December 2019,
97 who were prospectively enrolled into the Bern TAVI registry, which forms part of the
98 nationwide Swiss TAVI registry (NCT01368250). For the purpose of the present study,
99 patients who underwent TAVI for a degenerated surgical or transcatheter aortic
100 bioprosthesis, patients who underwent TAVI for pure native aortic valve regurgitation,
101 and those without comprehensive data for the diagnosis of RHD were excluded. The
102 registry was approved by the Bern cantonal ethics committee and all participants

provided written informed consent prior to inclusion. The study was conducted in compliance with the Declaration of Helsinki.

Diagnosis of RHD

Diagnoses of RHD were based on a clinical diagnosis of RHD according to ICD-10 codes (I05, I06, I07, I08, and I09) and/or a documented history of acute rheumatic fever and/or functional and morphological features of RHD as defined by the criteria of the World Heart Federation (WHF) for echocardiographic diagnosis of RHD in individuals >40 years [13]. Patients with 1) moderate or greater MR, 2) mean mitral gradient ≥4 mmHg, or 3) moderate or greater AR were retrieved for further analysis of morphological features consistent with RHD. A diagnosis of RHD was made in the presence of at least two of the following morphological features of RHD of the mitral valve: 1) anterior mitral valve leaflet thickening ≥5 mm, 2) chordal thickening, and 3) restricted leaflet motion (**Figure 1, Online Supplement 1**). There is no definition of morphological features of the aortic valve for individuals ≥35 years. A clinical diagnosis of RHD according to ICD-10 codes was further confirmed by the presence of

a documented history of acute rheumatic fever or the presence of echocardiographic features of RHD.

The assessment of the morphological criteria of RHD was individually performed by two assessors (T.O. and D.T.). In case of discrepant diagnosis between the two investigators, the diagnosis was determined by a third investigator (E.B.). Interobserver agreement was excellent between the two primary investigators (Kappa = 0.85, $p<0.001$).

Data collection and clinical endpoints

A web-based database with standardized case report forms is used for prospective data collection. Baseline echocardiographic and computed tomographic (CT) imaging data were independently re-evaluated by dedicated imaging specialists, and integrated into the database. Valve dysfunction (regurgitation and stenosis) was graded according to integrative criteria described by current guidelines[14 15]. Aortic valvular complex calcium volume (mm^3) was quantified as previously validated[16]. Clinical follow-up data at 30 days, 1 year and 5 years were obtained by the use of standardized interviews, documentation from referring physicians, and hospital

discharge summaries. Adverse events were reviewed by a dedicated clinical event committee and adjudicated according to the standardized endpoint definitions proposed by the Valve Academic Research Consortium (VARC)[17]. An independent Clinical Trials Unit is responsible for central data monitoring to verify completeness and accuracy of data and independent statistical analysis.

Statistical analysis

Categorical variables are reported as frequencies and percentages and compared using the Chi-square test or two-tailed Fisher's exact test. Continuous variables are presented as mean values ± standard deviation (SD) and compared between groups using two-sample t-test. Time-to-event curves were depicted using the Kaplan-Meier method. Conditional Poisson regression analysis for binary outcome and conditional Cox regression with Breslow method for time time-to-event outcome were used to calculate rate ratios (RR) and hazard ratios (HR), respectively, and 95% confidence intervals (CI). In all time-to-event analyses, data for a patient were censored at the time of the first event that occurred in that patient. All p-values were two-sided, and a p-value < 0.05 was considered significant for all tests.

It was anticipated that patients with rheumatic AS and degenerative AS would have significantly different patient baseline demographics. To adjust confounding due to these differences, 1:4 propensity-score matching was used (**Online Supplement 2**). Absolute standardized differences (ASD) were estimated to assess the balance in baseline demographics. ASD < 0.10 was considered to indicate good balance. Multivariable adjustment was further performed with Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), chronic kidney disease (CKD), body mass index (BMI), chronic obstructive pulmonary disease (COPD), and history of coronary artery bypass graft (CABG) in view of residual imbalances between groups. All statistical analyses were performed with the use of Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Baseline clinical characteristics

Among 2,329 patients undergoing TAVI between August 2007 and December 2019, 105 patients (4.5%) were identified to have rheumatic AS (**Figure 2**). Out of 85

patients with a clinical diagnosis of RHD according to ICD-10 codes, 59 did not fulfil the WHF criteria and had no documented history of acute rheumatic fever; thus, they were not included in the rheumatic AS cohort.

Baseline characteristics of the unmatched and the matched populations are shown in **Table 1**. Before propensity-score matching, patients with rheumatic AS were more commonly female (74.3% vs. 50.5%; P <0.001), older (84.2±6.1years vs. 82.1±6.1years; P<0.001), had a lower BMI (24.4±5.50kg/m^2 vs. 26.7±5.22kg/m^2; P<0.001), an increased surgical risk (STS-PROM: 7.1 ± 4.5 vs. 5.3 ± 4.0; P<0.001), and more advanced heart failure symptoms (NYHA III/IV: 81.0% vs. 68.1%; P=0.005) than patients with degenerative AS. While dyslipidaemia (50.5% vs. 66.3%; P=0.001) and coronary artery disease (48.6% vs. 61.9; P=0.007) were less frequent in patients with rheumatic as compared to degenerative AS, atrial fibrillation (50.5% vs 33.4%; P<0.001), CKD (83.8% vs. 67.6%; P<0.001), and a history of mitral valve surgery (4.8% vs. 1.2%; P=0.013) were recorded more frequently among patients with rheumatic AS. Patients with rheumatic AS were more likely to be treated with oral anticoagulation, particularly with vitamin K antagonists (VKA), than those with

degenerative AS (Aspirin: 47.6% vs. 59.9%; P=0.014; VKA: 30.5% vs. 17.2%; P=0.001).

Imaging characteristics

Imaging characteristics of the unmatched and the matched populations are shown in **Table 2**. Multivalvular heart disease was more common among patients with rheumatic AS than patients with degenerative AS. Patients with rheumatic AS had higher prevalence of ≥moderate AR (19.0% vs 8.5%; P=0.001), MR (59.4% vs 21.7%; P<0.001), MS (21.9% vs 1.9%; P<0.001), and tricuspid regurgitation (37.4% vs. 15.8%; P<0.001) than patients with degenerative AS.

In echocardiographic assessment, patients with rheumatic AS had a smaller aortic valve area (0.58±0.22cm^2 vs. 0.67±0.24cm^2; P<0.001) and higher pulmonary artery systolic pressures (53.1±15.5mmHg vs. 47.6±16.0mmHg; P=0.001) compared to patients with degenerative AS. Aortic valvular complex calcium volume was not different between groups (312.6 ± 337.1mm^2 vs. 333.9 ± 342.6mm^2; P = 0.556).

Propensity score matching

After propensity-score matching, patients with rheumatic and degenerative AS were well balanced with ASD <0.10 across all measured baseline characteristics, except for a larger BMI (ASD=0.135), lower rates of CKD (ASD=0.123) and prior CABG (ASD=0.100), and more frequent COPD (ASD=0.136) in patients with rheumatic AS than patients with degenerative AS.

Procedural characteristics and technical success

Procedural characteristics and outcomes in the unmatched and matched cohorts are shown in **Table 3**. There were no differences in the primary access site, type of valve implanted, and use of pre-/post-dilation between groups before and after propensity-score matching. Procedural complications were rare with no differences between groups with regards to valve dislocation/embolization, conversion to surgical aortic valve replacement, annular rupture/aortic dissection, cardiac tamponade/rupture, and coronary artery obstruction in both the unmatched and the matched population. VARC-3 technical success was achieved in more than 85% of patients without significant differences between groups both in the unmatched (P=0.887) and matched

cohorts (P=0.505). At discharge, there were no significant differences in valve hemodynamics and rates of paravalvular regurgitation between groups.

Clinical outcomes

Clinical follow-up at 1 year was complete in 2,300 patients (99.0%). Clinical outcomes at 30 days and 1 year in the unmatched and matched cohorts are shown in Table 4. In the unmatched population, there were no significant differences in 30-day cardiovascular mortality (1.9% vs. 2.7; HR 0.71; 95% CI 0.17-2.91; P=0.637) and 30-day stroke rates (2.9% vs. 3.6%; HR 0.80; 95% CI 0.25-2.52; P=0.699). After propensity-score matching, cardiovascular mortality at 30 days was significantly lower in patients with rheumatic AS compared to patients with degenerative AS (1.9% vs. 8.6%; HR_{adj} 0.18; 95% CI 0.04-0.80; P=0.024), while numerically lower rates of stroke did not reach conventional levels of statistical significance (2.9% vs. 6.3%; HR_{adj} 0.45; 95% CI 0.11-1.89; P=0.180).

Cumulative incidences for cardiovascular mortality and stroke in the unmatched and matched cohorts up to 1-year follow-up are depicted in Figure 3. In the unmatched population, there were no significant differences in 1-year cardiovascular mortality

(10.0% vs. 8.6%; HR 1.16; 95% CI 0.61-2.18; P=0.656) and 1-year stroke between groups. In the matched cohort, patients with rheumatic AS had lower cardiovascular mortality at 1 year than patients with degenerative AS (10.0% vs. 20.3%; HR_{adj} 0.44; 95% CI 0.24-0.84; P=0.012), while there was no significant difference in the 1-year stroke rate between groups (6.2% vs. 8.7%; HR_{adj} 0.66; 95% CI 0.28-1.58; P=0.353). There were no significant differences in the other clinical outcomes between groups both in unmatched and matched cohorts (**Table 4**).

Extended follow-up data until 5 years in the matched cohort are shown in **Figure 4**. Consistent with the 1-year analysis, patients with rheumatic AS had lower cardiovascular mortality at 5 years than those with degenerative AS. There were no significant differences in the occurrences of structural valve deterioration and repeat aortic valve intervention between groups.

Discussion

In this registry-based study of patients undergoing TAVI for native severe AS, rheumatic AS was identified in nearly 5% of patients. Compared to patients with

degenerative AS, patients with rheumatic AS were more commonly female, older, and had a higher surgical risk and higher prevalence of multivalvular heart disease. Nevertheless, patients with rheumatic AS were found to have comparable rates of technical success as patients with degenerative AS. Furthermore, cardiovascular mortality was substantially lower in patients with rheumatic AS compared to propensity-score matched patients with degenerative AS.

The prevalence of rheumatic AS documented in our cohort is consistent with data from the Euro Heart Survey on valvular heart disease. Among 5,001 patients from 92 centers in 25 European countries, RHD accounted for approximately 10% of patients with AS and peaked during the sixth decade of life[18]. In contrast, Medicare data from the United States indicate that less than 1% of patients underwent TAVI for rheumatic AS[8]. Several factors need to be considered in the interpretation of the reported prevalence of RHD. First, the methods used for the identification of patients with RHD were different across studies. While diagnosis was based on a combination of clinical context, echocardiographic findings and surgical presentation in the Euro Heart Survery[18], the study from the United States relied on ICD-10 codes[8]. In the present

study, ICD-10 codes were also considered; however, the final diagnosis was based on a documented history of acute rheumatic fever and/or the standardized WHF criteria for echocardiographic diagnosis of RHD[13]. Second, RHD typically presents with MR, MS or AR in middle age. Manifestation of isolated rheumatic AS in octogenarians is comparably rare. Furthermore, rheumatic AS commonly presents with multivalvular heart disease qualifying for surgical valve replacement rather than transcatheter intervention[4 5 19]. In the present study of selected patients undergoing TAVI, concomitant clinically relevant AR was documented in 20%, MR in 60%, MS in 20%, and tricuspid regurgitation in 40% of patients with rheumatic AS. And third, although the prevalence of RHD in Switzerland was substantially higher in the first half of the 20th century when current TAVI candidates were children, RHD is now comparably rare in affluent regions of the world. However, RHD among TAVI candidates may increase in significance in the forthcoming years as a consequence of expansion of TAVI to younger patients and immigration from low-and middle income countries[20]; most importantly however, RHD will come to the spotlight with dissemination of TAVI to middle-income countries[21]. Affordable transcatheter heart valves (THV) developed in

276 emerging countries[22 23] may open the door to this technology for the rest of the world[24]
277 and catalyse the expansion of TAVI to patients with RHD.

278 In the present study, procedural outcomes including technical success and valve
279 performance were similar in patients with rheumatic and degenerative AS. Post-
280 inflammatory commissural fusion and fibrinous thickening of the aortic valve with
281 limited calcification[12 25] raised concerns about adequate anchoring of THVs, and was
282 one of the reasons why this population has been excluded from major randomized trials[9]
283 [10 12]. However, in the present study, patients with rheumatic AS had a similar amount of
284 aortic valvular complex calcification compared to patients with degenerative AS. This
285 observation is consistent with the results of a previous case series of rheumatic AS
286 reporting a mean Agatston score of the aortic valvular complex of 2061 ± 864[7], and is
287 also corroborated by the findings of a histopathological study that found no significant
288 differences in the severity and localization of calcification between cases of rheumatic
289 and degenerative AS[26]. While patients identified to have RHD in our cohort were safely
290 and effectively treated with conventional THV systems, it is important to note that they
291 are not representative for the majority of young patients with RHD. Dedicated devices

292 may need to address higher prevalence of AR in patients with RHD. A THV system
293 with self-locating inflatable balloon trunks and antigen-depleted and antigen-masked
294 bioprosthetic leaflets specifically designed for patients with RHD showed promising
295 results in a preclinical study[27].

296 In the unmatched cohort, rates of cardiovascular mortality and disabling stroke
297 were comparable in patients with rheumatic and degenerative AS despite a higher
298 surgical risk and higher prevalence of multivalvular disease in patients with RHD.
299 Similarly, in an analysis from the Medicare health claims database, rheumatic AS
300 patients had comparable mortality at a median follow-up of 17 months as degenerative
301 AS patients despite higher prevalence of heart failure, prior ischemic stroke, atrial
302 fibrillation and lung disease. Of note, the latter study lacks detailed imaging data on
303 multivalvular disease, which significantly affects patient outcomes following TAVI[11].
304 In previous analyses, we demonstrated an increased risk of cardiovascular mortality in
305 TAVI patients with concomitant primary MR as compared to patients with no or
306 functional MR[28], in patients with degenerative or rheumatic MS as compared to patients
307 with no MS[29], and in patients with valvular atrial fibrillation as compared to patients

with non-valvular atrial fibrillation and no atrial fibrillation[30]. Nevertheless, patients with rheumatic AS, who frequently presented with multivalvular disease, had comparable clinical outcomes as patients with degenerative AS. Furthermore, when propensity-score matched to degenerative AS patients with similar prevalence of multivalvular heart disease, patients with rheumatic AS had significantly lower cardiovascular mortality. The reason for this finding resorts to speculation. A selection of patients with slower progression of RHD may explain both the late presentation in their eighties and the lower impact of multivalvular disease on overall prognosis compared to patients with degenerative aetiology.

Study Limitations

The findings of our cohort study are exploratory and need to be interpreted in light of several limitations. First, the diagnosis of RHD was carefully verified based on established criteria; however, the criteria were not designed to differentiate between degenerative and rheumatic aetiology in this elderly population. The validity of using the criteria in TAVI populations needs to be further examined. Although commissural fusion, the most typical manifestation of rheumatic mitral stenosis, was observed in all

RHD patients with assessable short-axis views (n=37), the assessment was frequently impossible due to unavailability or poor quality of images. The assessment of commissural fusion of the aortic valve is further compromised due to the presence of degenerative changes and severe stenosis (**Online Supplement 3**). Although commissural fusion of the aortic valve was observed in all but one of assessable cases (n= 48/49), a typical less-calcified triangular orifice with commissural fusion was observed in only one in five of the cases. Patients identified to have RHD in our TAVI registry are, thus, highly selected individuals and not representative for RHD patients in other regions of the world. The findings of octogenarians with rheumatic AS undergoing TAVI are therefore not generalizable to younger RHD patients with non-calcified fibrotic AS. Second, the number of patients with rheumatic AS in our cohort was modest. Conversely, our registry yields detailed imaging data and granularity in terms of procedural success and long-tern clinical outcome. The robustness of the findings is furthermore underscored by the prospective data collection, completeness of 1-year follow-up in 99% of the patients, independent event adjudication, and rigorous statistical analysis by an independent statistical unit. Third, while we used propensity

score matching, unmeasured confounding may have affected our findings and cannot be ruled out.

Conclusion

TAVI may be a safe and effective treatment strategy for selected elderly patients with rheumatic AS. Further studies are warranted to explore TAVI in regions of the world where an endemic pattern of RHD prevails.

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Figure Legends

Figure 1. Echocardiographic assessment of morphological features of rheumatic heart disease.

(Left) Parasternal long axis views showing thickening of the AMVL (upper) compared to a normal anterior mitral leaflet (lower). (Middle) Parasternal long axis views showing restricted leaflet motion with classic dog-leg deformity of the anterior mitral leaflet (upper) and non-restricted leaflet motion (lower). (Right) Apical views with chordal thickening (upper) and normal chordal morphology (lower). Videos of the echocardiography of the RHD case are provided in **Online Supplement 1.**

AMVL = anterior mitral valve leaflet; RHD = rheumatic heart disease.

Figure 2. A flowchart of patients included in the present analysis.

AR = aortic regurgitation; ARF = acute rheumatic fever; AS = aortic stenosis; ICD-10 = International Classification of Diseases Version 10; MR = mitral regurgitation; MV = mitral valve; RHD = rheumatic heart disease; TAVI = transcatheter aortic valve implantation.

Figure 3. Kaplan-Meier curves for cardiovascular death and stroke in the entire cohort and PS-matched cohort.

Hazard ratios and p-values were calculated with the use of Cox proportional hazards models. Abbreviations as in **Figure 1**.

Figure 4. Kaplan-Meier curves for cardiovascular death, structural valve deterioration, and unplanned repeat aortic valve intervention up to 5 years in the PS-matched cohort.

Structural valve deterioration was defined according to the Valve Academic Research Consortium-2 criteria[17]. Unplanned repeat aortic valve intervention was defined as a composite endpoint including valve-in-valve procedure, balloon valvuloplasty, surgical revision, or paravalvular leak closure.

Hazard ratios and p-values were calculated with the use of Cox proportional hazards models. Abbreviations as in **Figure 1**.

543 **Table 1.** Baseline characteristics of the unmatched and matched population

	Unadjusted Cohort				**Propensity Score Matched Cohort**			
	Non-RHD (N = 2,224)	**RHD (N = 105)**	**P value**	**ASD**	**Non-RHD (N = 420)**	**RHD (N = 105)**	**P value**	**ASD**
Age, years	82.1 ± 6.1	84.2 ± 6.1	<0.001	-0.352	84.2 ± 5.3	84.2 ± 6.1	0.984	-0.002
Female, n (%)	1,123 (50.5%)	78 (74.3%)	<0.001	-0.506	322 (76.7%)	78 (74.3%)	0.610	0.055
Body mass index, kg/cm²	26.7 ± 5.22	24.4 ± 5.50	<0.001	0.419	23.8 ± 4.26	24.4 ± 5.50	0.180	-0.135
STS-PROM, %	5.31 ± 4.0	7.13 ± 4.53	<0.001	-0.424	7.21 ± 4.90	7.13 ± 4.53	0.876	0.017
NYHA functional class III or IV, n (%)	1,513 (68.1%)	85 (81.0%)	0.005	-0.297	346 (82.4%)	85 (81.0%)	0.776	0.037
Comorbidities								
Hypertension, n (%)	1,916 (86.2%)	85 (81.0%)	0.150	0.140	355 (84.5%)	85 (81.0%)	0.376	0.094
Diabetes mellitus, n (%)	595 (26.8%)	25 (23.8%)	0.573	0.068	89 (21.2%)	25 (23.8%)	0.597	-0.063
Dyslipedemia, n (%)	1,475 (66.3%)	53 (50.5%)	0.001	0.325	210 (50.0%)	53 (50.5%)	1.00	-0.009
CKD (eGFR <60 mL/min/1.73 m^2), n (%)	1,502 (67.6%)	88 (83.8%)	<0.001	-0.384	370 (88.1%)	88 (83.8%)	0.253	0.123
COPD, n (%)	272 (12.2%)	11 (10.5%)	0.759	0.056	28 (6.7%)	11 (10.5%)	0.210	-0.136
Atrial fibrillation, n (%)	743 (33.4%)	53 (50.5%)	<0.001	-0.350	222 (52.9%)	53 (50.5%)	0.664	0.048
Coronary artery disease, n (%)	1,377 (61.9%)	51 (48.6%)	0.007	0.270	213 (50.7%)	51 (48.6%)	0.744	0.043

History of PCI, n (%)	606 (27.2%)	24 (22.9%)	0.369	0.101	91 (21.7%)	24 (22.9%)	0.793	-0.029
History of CABG, n (%)	242 (10.9%)	5 (4.8%)	0.050	0.229	30 (7.1%)	5 (4.8%)	0.513	0.100
History of MI, n (%)	332 (14.9%)	13 (12.4%)	0.574	0.074	61 (14.5%)	13 (12.4%)	0.641	0.063
Previous Mitral valve replacement/repair, n (%)	27 (1.2%)	5 (4.8%)	0.013	-0.209	23 (5.5%)	5 (4.8%)	1.000	0.032
History of cerebrovascular accident, n (%)	251 (11.3%)	16 (15.2%)	0.210	-0.116	68 (16.2%)	16 (15.2%)	0.883	0.026
Peripheral artery disease, n (%)	300 (13.5%)	16 (15.2%)	0.562	-0.050	63 (15.0%)	16 (15.2%)	1.000	-0.007
Previous pacemaker implantation, n (%)	182 (8.2%)	14 (13.3%)	0.071	-0.166	62 (14.8%)	14 (13.3%)	0.877	0.041
Medications at baseline								
Aspirin, n (%)	1,329 (59.9%)	50 (47.6%)	0.014	0.247	180 (42.9%)	50 (47.6%)	0.382	-0.095
P2Y12 antagonist, n (%)	424 (19.1%)	18 (17.1%)	0.703	0.051	57 (13.6%)	18 (17.1%)	0.352	-0.099
VKA, n (%)	381 (17.2%)	32 (30.5%)	0.001	-0.315	136 (32.4%)	32 (30.5%)	0.815	0.041
NOAC, n (%)	271 (12.2%)	17 (16.2%)	0.225	-0.114	68 (16.2%)	17 (16.2%)	1.000	<0.001

Depicted are means with standard deviations (± SD), or counts with percentages (%). ASD = absolute standardized difference; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NOAC = non vitamin K antagonist oral anticoagulant agent; NYHA = New York Heart Association; OAC = oral anticoagulant agent; PCI = percutaneous coronary intervention; RHD = rheumatic heart disease; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; VKA = vitamin K antagonist.

544

545 **Table 2.** Imaging characteristics of the unmatched and matched population

	Unadjusted Cohort				**Propensity Score Matched Cohort**			
	Non-RHD (N = 2,224)	**RHD (N = 105)**	**P value**	**ASD**	**Non-RHD (N = 420)**	**RHD (N = 105)**	**P value**	**ASD**
Echocardiography								
Aortic valve area, cm^2	0.67 ± 0.24	0.58 ± 0.22	<0.001	0.379	0.58 ± 0.24	0.58 ± 0.22	0.931	-0.010
Aortic valve mean gradient, mmHg	40.0 ± 17.3	40.5 ± 16.9	0.741	-0.033	41.3 ± 20.1	40.5 ± 16.9	0.708	0.043
LVEF, %	54.6 ± 14.5	54.4 ± 14.8	0.917	0.010	53.5 ± 14.7	54.44± 14.8	0.563	-0.063
Moderate/severe AR, n (%)	188 (8.5%)	20 (19.0%)	0.001	-0.310	84 (20.0%)	20 (19.0%)	0.892	0.024
Moderate/severe MR, n (%)	419 (21.7%)	60 (59.4%)	<0.001	-0.830	256 (61.4%)	60 (59.4%)	0.734	0.040
Moderate/severe MS, n (%)	42 (1.9%)	23 (21.9%)	<0.001	-0.647	81 (19.3%)	23 (21.9%)	0.584	-0.065
Moderate/severe TR, n (%)	299 (15.8%)	37 (37.4%)	<0.001	-0.501	157 (37.7%)	37 (37.4%)	1.00	0.008
PASP, mmHg	47.6 ± 16.08	53.1 ± 15.5	0.001	-0.350	53.8 ± 17.2	53.1 ± 15.5	0.738	0.038
Computed tomography								
Aortic valve complex calcium, mm^3	312.6 ± 337.1	333.9 ± 342.6	0.556	-0.062	354.2 ± 363.3	333.9 ± 342.6	0.631	0.057

Depicted are means with standard deviations (± SD), or counts with percentages (%).

AR = aortic regurgitation; ASD = absolute standardized difference; LVEF = left ventricular ejection fraction; MR = mitral valve regurgitation; MS = mitral stenosis; PASP = pulmonary artery systolic pressure; RHD = rheumatic heart disease.

546

547 **Table 3.** Procedural characteristics and complications of the unmatched and matched population

	Unadjusted Cohort			**Propensity Score Matched Cohort**		
	Non-RHD (N = 2,224)	**RHD (N = 105)**	**P value**	**Non-RHD (N = 420)**	**RHD (N = 105)**	**P value**
Procedural characteristics						
Femoral main access site, n (%)	2,015 (90.6%)	97 (92.4%)	0.730	390 (92.9%)	97 (92.4%)	0.835
Type of valve, n (%)			0.336			0.530
Balloon-expandable	1,113 (50.1%)	46 (43.8%)	0.231	160 (38.1%)	46 (43.8%)	0.315
Self-expandable	980 (44.1%)	54 (51.4%)	0.159	234 (55.7%)	54 (51.4%)	0.444
Mechanical-expandable	128 (5.8%)	5 (4.8%)	0.831	26 (6.2%)	5 (4.8%)	0.817
Pre-dilation, n (%)	1,567 (70.6%)	70 (66.7%)	0.384	305 (72.6%)	70 (66.7%)	0.229
Post-dilation, n (%)	568 (25.6%)	33 (31.4%)	0.209	120 (28.6%)	33 (31.4%)	0.551
Procedural complications						
Valve in series, n (%)	29 (1.3%)	2 (1.9%)	0.648	9 (2.1%)	2 (1.9%)	1.00
Valve dislocation/embolization, n (%)	36 (1.6%)	1 (1.0%)	1.00	11 (2.6%)	1 (1.0%)	0.475

Conversion to SAVR, n (%)	12 (0.5%)	1 (1.0%)	0.452	6 (1.4%)	1 (1.0%)	1.00
Annulus rupture/aortic dissection, n (%)	12 (0.5%)	1 (1.0%)	0.456	0 (0.0%)	1 (1.0%)	0.202
Cardiac tamponade/rupture, n (%)	15 (0.7%)	1 (1.0%)	0.523	5 (1.2%)	1 (1.0%)	1.00
Coronary artery occlusion, n (%)	9 (0.4%)	0 (0.0%)	1.00	1 (0.2%)	0 (0.0%)	1.00
VARC-3 technical success	1,911 (85.9%)	90 (85.7%)	0.887	371 (88.3%)	90 (85.7%)	0.505
Echocardiographic outcomes at discharge*						
Aortic valve area, mm	1.74 ± 0.50	1.68 ± 0.52	0.345	1.60 ± 0.39	1.68 ± 0.52	0.109
Prosthetic valve mean gradient at discharge, mmHg**	9.53 ± 4.44	8.38 ± 4.21	0.010	8.89 ± 4.52	8.38 ± 4.21	0.296
Aortic regurgitation grade at discharge, n (%)**			0.614			0.092
none	854 (38.5%)	38 (36.2%)		107 (25.5%)	38 (36.2%)	
mild	1228 (55.3%)	58 (55.2%)		271 (64.7%)	58 (55.2%)	
moderate or severe	139 (6.3%)	9 (8.6%)		41 (9.8%)	9 (8.6%)	

Depicted are means with standard deviations (±SD), or counts with percentages (%).

* if missing, post-procedure data were used.

548

549 **Table 4.** Clinical outcomes of the unmatched and matched population

	Unadjusted cohort				**Propensity Score Matched Cohort***			
	Non-RHD (N = 2,224)	**RHD (N = 105)**	**HR/RR (95% CI)**	**P value**	**Non-RHD (N = 420)**	**RHD (N = 105)**	**HR/RR (95% CI)**	**P value**
At 30 days								
Cardiovascular mortality, n (%)	59 (2.7%)	2 (1.9%)	0.71 (0.17-2.91)	0.637	36 (8.6%)	2 (1.9%)	0.18 (0.04-0.80)	0.024
Stroke, n (%)	79 (3.6%)	3 (2.9%)	0.80 (0.25-2.52)	0.699	26 (6.3%)	3 (2.9%)	0.45 (0.14-1.45)	0.181
Disabling stroke, n (%)	53 (2.4%)	2 (1.9%)	0.79 (0.19-3.26)	0.750	18 (4.4%)	2 (1.9%)	0.43 (0.11-1.89)	0.277
New permanent pacemaker implantation, n (%)	426 (19.3%)	21 (20.0%)	1.05 (0.68-1.63)	0.819	99 (24.0%)	21 (20.0%)	0.83 (0.53-1.32)	0.442
NYHA III or IV, n/N (%)	185/2014 (9.2%)	13/95 (13.7%)	1.49 (0.88-2.51)	0.136	46/365 (12.6%)	13/95 (13.7%)	1.05 (0.59-1.87)	0.875
At 1 year								
Cardiovascular mortality, n (%)	185 (8.6%)	10 (10.0%)	1.16 (0.61-2.18)	0.656	84 (20.3%)	10 (10.0%)	0.44 (0.24-0.84)	0.012
Stroke, n (%)	110 (5.1%)	6 (6.2%)	1.15 (0.51-2.62)	0.735	34 (8.7%)	6 (6.2%)	0.66 (0.28-1.58)	0.353

Disabling stroke, n (%)	75 (3.5%)	4 (4.2%)	1.13 (0.41-3.09)	0.811	20 (5.0%)	4 (4.2%)	0.82 (0.30-2.25)	0.697
Myocardial infarction, n (%)	38 (1.8%)	1 (1.1%)	0.56 (0.08-4.10)	0.571	4 (1.1%)	1 (1.1%)	0.88 (0.10-8.05)	0.906
Major or life-threatening bleeding, n (%)	474 (21.6%)	27 (26.0%)	1.22 (0.83-1.80)	0.307	104 (25.0%)	27 (26.0%)	1.04 (0.70-1.54)	0.853
NYHA III or IV, n/N (%)	210/1854 (11.3%)	11/85 (12.9%)	1.14 (0.65-2.01)	0.645	23/302 (7.6%)	11/85 (12.9%)	1.69 (0.90-3.19)	0.104

Depicted are number of events (counting first event per patient only), with Kaplan-Meier cumulative incidences in percentages in brackets and hazard ratios HR with 95% CI in brackets. NYHA III or IV is provided as numbers/assessed patients (%) with rate ratio from robustified Poisson regression with 95% confidence intervals in brackets.

*The Matched cohort is cluster-robustified for the matched sets (105 sets: each set contains one RHD and four non-RHD patients). Adjusted for STS-PROM, BMI, CKD, COPD, and history of CABG in view of residual imbalances.

CI = confidence intervals; HR = hazard ratio; RR = rate ratio; RHD = rheumatic heart disease; NYHA = New York Heart Association.

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