

29

ABSTRACT

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

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

40 **Results:** Among 2,329 patients undergoing TAVI, 105 patients (4.5%) had rheumatic
41 AS. Compared to patients with degenerative AS, patients with rheumatic AS were more
42 commonly female, older, had a higher surgical-risk, and more commonly suffered from
43 multivalvular heart disease. In the unmatched cohort, both technical success (85.7% vs
44 85.9%; $P = 0.887$) and 1-year cardiovascular mortality (10.0% vs. 8.6%; HR 1.16; 95%

45 CI 0.61-2.18; P=0.656) were comparable between patients with rheumatic and
46 degenerative AS. In contrast, patients with rheumatic AS had lower rates of 30-day and
47 1-year cardiovascular mortality compared to matched patients with degenerative AS
48 (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}
49 0.44; 95% CI 0.24-0.84; P=0.012, respectively).

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

52

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

55 **Key Messages**

56 **What is already known about this subject?**

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

60 **What does this study add?**

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

67 **How might this impact on clinical practice?**

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

Introduction

71

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

77 Mitral regurgitation (MR), mitral stenosis (MS) and aortic regurgitation (AR)
78 are the typical manifestations of RHD, while rheumatic aortic stenosis (AS) is
79 comparably less common and frequently combined with other valvular lesions³⁻⁵.
80 Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of
81 patients with symptomatic severe AS. Patients with rheumatic AS were, however,
82 excluded from landmark trials, and the available evidence is limited to small case series
83 and data from insurance claims without granularity on imaging features and
84 concomitant valvular disease⁶⁻¹⁰. Primary concerns to expand TAVI to patients with
85 rheumatic AS relate to the typical morphological features of RHD with fibrinous
86 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

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

105 **Diagnosis of RHD**

106 Diagnoses of RHD were based on a clinical diagnosis of RHD according to
107 ICD-10 codes (I05, I06, I07, I08, and I09) and/or a documented history of acute
108 rheumatic fever and/or functional and morphological features of RHD as defined by the
109 criteria of the World Heart Federation (WHF) for echocardiographic diagnosis of RHD
110 in individuals >40 years¹³. Patients with 1) moderate or greater MR, 2) mean mitral
111 gradient ≥ 4 mmHg, or 3) moderate or greater AR were retrieved for further analysis of
112 morphological features consistent with RHD. A diagnosis of RHD was made in the
113 presence of at least two of the following morphological features of RHD of the mitral
114 valve: 1) anterior mitral valve leaflet thickening ≥ 5 mm, 2) chordal thickening, and 3)
115 restricted leaflet motion (**Figure 1, Online Supplement 1**). There is no definition of
116 morphological features of the aortic valve for individuals ≥ 35 years. A clinical
117 diagnosis of RHD according to ICD-10 codes was further confirmed by the presence of

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

120 The assessment of the morphological criteria of RHD was individually
121 performed by two assessors (T.O. and D.T.). In case of discrepant diagnosis between
122 the two investigators, the diagnosis was determined by a third investigator (E.B.).
123 Interobserver agreement was excellent between the two primary investigators (Kappa =
124 0.85, $p < 0.001$).

125 **Data collection and clinical endpoints**

126 A web-based database with standardized case report forms is used for
127 prospective data collection. Baseline echocardiographic and computed tomographic
128 (CT) imaging data were independently re-evaluated by dedicated imaging specialists,
129 and integrated into the database. Valve dysfunction (regurgitation and stenosis) was
130 graded according to integrative criteria described by current guidelines^{14,15}. Aortic
131 valvular complex calcium volume (mm^3) was quantified as previously validated¹⁶.
132 Clinical follow-up data at 30 days, 1 year and 5 years were obtained by the use of
133 standardized interviews, documentation from referring physicians, and hospital

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

139 **Statistical analysis**

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

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

169 Baseline characteristics of the unmatched and the matched populations are
170 shown in **Table 1**. Before propensity-score matching, patients with rheumatic AS were
171 more commonly female (74.3% vs. 50.5%; $P < 0.001$), older (84.2 ± 6.1 years vs.
172 82.1 ± 6.1 years; $P < 0.001$), had a lower BMI ($24.4 \pm 5.50 \text{ kg/m}^2$ vs. $26.7 \pm 5.22 \text{ kg/m}^2$;
173 $P < 0.001$), an increased surgical risk (STS-PROM: 7.1 ± 4.5 vs. 5.3 ± 4.0 ; $P < 0.001$), and
174 more advanced heart failure symptoms (NYHA III/IV: 81.0% vs. 68.1%; $P = 0.005$) than
175 patients with degenerative AS. While dyslipidaemia (50.5% vs. 66.3%; $P = 0.001$) and
176 coronary artery disease (48.6% vs. 61.9%; $P = 0.007$) were less frequent in patients with
177 rheumatic as compared to degenerative AS, atrial fibrillation (50.5% vs 33.4%;
178 $P < 0.001$), CKD (83.8% vs. 67.6%; $P < 0.001$), and a history of mitral valve surgery
179 (4.8% vs. 1.2%; $P = 0.013$) were recorded more frequently among patients with
180 rheumatic AS. Patients with rheumatic AS were more likely to be treated with oral
181 anticoagulation, particularly with vitamin K antagonists (VKA), than those with

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

184 **Imaging characteristics**

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

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

196 **Propensity score matching**

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

202 **Procedural characteristics and technical success**

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

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

214 **Clinical outcomes**

215 Clinical follow-up at 1 year was complete in 2,300 patients (99.0%). Clinical
216 outcomes at 30 days and 1 year in the unmatched and matched cohorts are shown in
217 **Table 4**. In the unmatched population, there were no significant differences in 30-day
218 cardiovascular mortality (1.9% vs. 2.7; HR 0.71; 95% CI 0.17-2.91; P=0.637) and 30-
219 day stroke rates (2.9% vs. 3.6%; HR 0.80; 95% CI 0.25-2.52; P=0.699). After
220 propensity-score matching, cardiovascular mortality at 30 days was significantly lower
221 in patients with rheumatic AS compared to patients with degenerative AS (1.9% vs.
222 8.6%; HR_{adj} 0.18; 95% CI 0.04-0.80; P=0.024), while numerically lower rates of stroke
223 did not reach conventional levels of statistical significance (2.9% vs. 6.3%; HR_{adj} 0.45;
224 95% CI 0.11-1.89; P=0.180).

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

228 (10.0% vs. 8.6%; HR 1.16; 95% CI 0.61-2.18; P=0.656) and 1-year stroke between
229 groups. In the matched cohort, patients with rheumatic AS had lower cardiovascular
230 mortality at 1 year than patients with degenerative AS (10.0% vs. 20.3%; HR_{adj} 0.44;
231 95% CI 0.24-0.84; P=0.012), while there was no significant difference in the 1-year
232 stroke rate between groups (6.2% vs. 8.7%; HR_{adj} 0.66; 95% CI 0.28-1.58; P=0.353).
233 There were no significant differences in the other clinical outcomes between groups
234 both in unmatched and matched cohorts (**Table 4**).

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

240

241

Discussion

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243

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

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

250 The prevalence of rheumatic AS documented in our cohort is consistent with
251 data from the Euro Heart Survey on valvular heart disease. Among 5,001 patients from
252 92 centers in 25 European countries, RHD accounted for approximately 10% of patients
253 with AS and peaked during the sixth decade of life¹⁸. In contrast, Medicare data from
254 the United States indicate that less than 1% of patients underwent TAVI for rheumatic
255 AS⁸. Several factors need to be considered in the interpretation of the reported
256 prevalence of RHD. First, the methods used for the identification of patients with RHD
257 were different across studies. While diagnosis was based on a combination of clinical
258 context, echocardiographic findings and surgical presentation in the Euro Heart
259 Survey¹⁸, the study from the United States relied on ICD-10 codes⁸. In the present

260 study, ICD-10 codes were also considered; however, the final diagnosis was based on a
261 documented history of acute rheumatic fever and/or the standardized WHF criteria for
262 echocardiographic diagnosis of RHD¹³. Second, RHD typically presents with MR, MS
263 or AR in middle age. Manifestation of isolated rheumatic AS in octogenarians is
264 comparably rare. Furthermore, rheumatic AS commonly presents with multivalvular
265 heart disease qualifying for surgical valve replacement rather than transcatheter
266 intervention^{4 5 19}. In the present study of selected patients undergoing TAVI,
267 concomitant clinically relevant AR was documented in 20%, MR in 60%, MS in 20%,
268 and tricuspid regurgitation in 40% of patients with rheumatic AS. And third, although
269 the prevalence of RHD in Switzerland was substantially higher in the first half of the
270 20th century when current TAVI candidates were children, RHD is now comparably rare
271 in affluent regions of the world. However, RHD among TAVI candidates may increase
272 in significance in the forthcoming years as a consequence of expansion of TAVI to
273 younger patients and immigration from low-and middle income countries²⁰; most
274 importantly however, RHD will come to the spotlight with dissemination of TAVI to
275 middle-income countries²¹. Affordable transcatheter heart valves (THV) developed in

276 emerging countries^{22 23} may open the door to this technology for the rest of the world²⁴
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 trials⁹
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 AS²⁶. 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 study²⁷.

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 TAVI¹¹.

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 MR²⁸, in patients with degenerative or rheumatic MS as compared to patients
307 with no MS²⁹, and in patients with valvular atrial fibrillation as compared to patients

308 with non-valvular atrial fibrillation and no atrial fibrillation³⁰. Nevertheless, patients
309 with rheumatic AS, who frequently presented with multivalvular disease, had
310 comparable clinical outcomes as patients with degenerative AS. Furthermore, when
311 propensity-score matched to degenerative AS patients with similar prevalence of
312 multivalvular heart disease, patients with rheumatic AS had significantly lower
313 cardiovascular mortality. The reason for this finding resorts to speculation. A selection
314 of patients with slower progression of RHD may explain both the late presentation in
315 their eighties and the lower impact of multivalvular disease on overall prognosis
316 compared to patients with degenerative aetiology.

317 **Study Limitations**

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

324 RHD patients with assessable short-axis views (n=37), the assessment was frequently
325 impossible due to unavailability or poor quality of images. The assessment of
326 commissural fusion of the aortic valve is further compromised due to the presence of
327 degenerative changes and severe stenosis ([Online Supplement 3](#)). Although
328 commissural fusion of the aortic valve was observed in all but one of assessable cases
329 (n= 48/49), a typical less-calcified triangular orifice with commissural fusion was
330 observed in only one in five of the cases. Patients identified to have RHD in our TAVI
331 registry are, thus, highly selected individuals and not representative for RHD patients in
332 other regions of the world. The findings of octogenarians with rheumatic AS
333 undergoing TAVI are therefore not generalizable to younger RHD patients with non-
334 calcified fibrotic AS. Second, the number of patients with rheumatic AS in our cohort
335 was modest. Conversely, our registry yields detailed imaging data and granularity in
336 terms of procedural success and long-term clinical outcome. The robustness of the
337 findings is furthermore underscored by the prospective data collection, completeness of
338 1-year follow-up in 99% of the patients, independent event adjudication, and rigorous
339 statistical analysis by an independent statistical unit. Third, while we used propensity

340 score matching, unmeasured confounding may have affected our findings and cannot be

341 ruled out.

342 **Conclusion**

343 TAVI may be a safe and effective treatment strategy for selected elderly patients

344 with rheumatic AS. Further studies are warranted to explore TAVI in regions of the

345 world where an endemic pattern of RHD prevails.

346

347 **Contributors:** T.O., D.T., T.P. conceived the study. T.O., T.P. had responsibility for the
348 design of the study. T.O., D.T., T.P., E.B., J.L., C.R., C.D., S.H., D. Hagemeyer, A.P., D.
349 Heg, F.P., S.S., S.W. were responsible for the acquisition of data. D. Heg, T.O. did the
350 analysis and interpreted the results in collaboration with T.P., D.J. and all other authors.
351 T.O., D.T., T.P. wrote the first draft of the report. All authors critically revised the report
352 for important intellectual content and approved the final version.

353 **Acknowledgements:** None

354 **Sources of Funding:** None

355 **Competing interests:**

356 Dr. Windecker reports research and educational grants to the institution from Abbott,
357 Amgen, Astra Zeneca, BMS, Bayer, Biotronik, Boston Scientific, Cardinal Health,
358 CardioValve, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx,
359 Johnson & Johnson, Medicure, Medtronic, Novartis, Polares, OrPha Suisse, Pfizer,
360 Regeneron, Sanofi-Aventis, Sinomed, Terumo, V-Wave. Dr. Windecker serves as
361 unpaid advisory board member and/or unpaid member of the steering/executive group
362 of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, BMS, Boston Scientific,

363 Biotronik, Cardiovalve, Edwards Lifesciences, MedAlliance, Medtronic, Novartis,
364 Polares, Sinomed, V-Wave and Xeltis, but has not received personal payments by
365 pharmaceutical companies or device manufacturers. He is also member of the
366 steering/executive committee group of several investigator-initiated trials that receive
367 funding by industry without impact on his personal remuneration. Dr. Windecker is an
368 unpaid member of the Pfizer Research Award selection committee in Switzerland and
369 of the Women as One Awards Committee. Dr. Pilgrim reports research grants to the
370 institution from Edwards Lifesciences, Boston Scientific and Biotronik, personal fees
371 from Biotronik and Boston Scientific, and other from HighLife SAS. Dr. Praz reports
372 travel expenses from Abbott, Edwards Lifesciences, and Polares Medical. Dr. Stortecky
373 reports research grants to the institution from Edwards Lifesciences, Medtronic, Boston
374 Scientific and Abbott, as well as personal fees from Boston Scientific, Teleflex and
375 BTG. Dr. Okuno reports speaker fees from Abbott. Dr. Heg reports and with CTU Bern,
376 University of Bern, which has a staff policy of not accepting honoraria or consultancy
377 fees. However, CTU Bern is involved in design, conduct, or analysis of clinical studies
378 funded by not-for-profit and for-profit organizations. In particular, pharmaceutical and

379 medical device companies provide direct funding to some of these studies. For an up-to-

380 date list of CTU Bern's conflicts of interest see

381 http://www.ctu.unibe.ch/research/declaration_of_interest/index_eng.html. All other

382 authors have no relationships relevant to the contents of this article to disclose.

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Reference

- 386 1. Yadgir S, Johnson CO, Aboyans V, et al. Global, Regional, and National Burden of
387 Calcific Aortic Valve and Degenerative Mitral Valve Diseases, 1990-2017.
388 *Circulation* 2020;141(21):1670-80. doi:
389 10.1161/CIRCULATIONAHA.119.043391 [published Online First: 2020/04/01]
- 390 2. Marijon E, Mocumbi A, Narayanan K, et al. Persisting burden and challenges of
391 rheumatic heart disease. *Eur Heart J* 2021 doi: 10.1093/eurheartj/ehab407
392 [published Online First: 2021/07/16]
- 393 3. Sliwa K, Carrington M, Mayosi BM, et al. Incidence and characteristics of newly
394 diagnosed rheumatic heart disease in urban African adults: insights from the
395 heart of Soweto study. *Eur Heart J* 2010;31(6):719-27. doi:
396 10.1093/eurheartj/ehp530 [published Online First: 2009/12/10]
- 397 4. Zuhlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps
398 in evidence-based interventions in rheumatic heart disease: the Global
399 Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*
400 2015;36(18):1115-22a. doi: 10.1093/eurheartj/ehu449 [published Online First:

- 401 2014/11/27]
- 402 5. Shrestha NR, Pilgrim T, Karki P, et al. Rheumatic heart disease revisited: patterns of
403 valvular involvement from a consecutive cohort in eastern Nepal. *Journal of*
404 *cardiovascular medicine (Hagerstown, Md)* 2012;13(11):755-9. doi:
405 10.2459/JCM.0b013e32835854b6 [published Online First: 2012/08/24]
- 406 6. Daly MJ, Blair PH, Modine T, et al. Carotid-access transcatheter aortic valve
407 replacement in a patient with a previous mitral valve replacement. *Journal of*
408 *cardiac surgery* 2015;30(3):256-9. doi: 10.1111/jocs.12324 [published Online
409 First: 2014/03/13]
- 410 7. Saji M, Highchi R, Iguchi N, et al. Transcatheter aortic valve replacement in patients
411 with degenerative calcified rheumatic aortic stenosis: A 10-patient case series.
412 *International journal of cardiology* 2019;280:38-42. doi:
413 10.1016/j.ijcard.2018.11.090 [published Online First: 2018/12/07]
- 414 8. Mentias A, Saad M, Desai MY, et al. Transcatheter Versus Surgical Aortic Valve
415 Replacement in Patients With Rheumatic Aortic Stenosis. *J Am Coll Cardiol*
416 2021;77(14):1703-13. doi: 10.1016/j.jacc.2021.02.032 [published Online First:

- 417 2021/04/10]
- 418 9. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or Surgical Aortic-Valve
- 419 Replacement in Intermediate-Risk Patients. *The New England journal of*
- 420 *medicine* 2016;374(17):1609-20. doi: 10.1056/NEJMoa1514616 [published
- 421 Online First: 2016/04/05]
- 422 10. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or Transcatheter Aortic-
- 423 Valve Replacement in Intermediate-Risk Patients. *The New England journal of*
- 424 *medicine* 2017;376(14):1321-31. doi: 10.1056/NEJMoa1700456 [published
- 425 Online First: 2017/03/18]
- 426 11. Khan F, Okuno T, Malebranche D, et al. Transcatheter Aortic Valve Replacement in
- 427 Patients With Multivalvular Heart Disease. *JACC Cardiovascular interventions*
- 428 2020;13(13):1503-14. doi: 10.1016/j.jcin.2020.03.052 [published Online First:
- 429 2020/07/11]
- 430 12. Okor I, Bob-Manuel T, Garikapati K, et al. Transcatheter Aortic Valve Replacement
- 431 in Rheumatic Aortic Stenosis: A Comprehensive Review. *Curr Probl Cardiol*
- 432 2021;100843. doi: 10.1016/j.cpcardiol.2021.100843 [published Online First:

433 2021/05/18]

434 13. Remenyi B, Wilson N, Steer A, et al. World Heart Federation criteria for
435 echocardiographic diagnosis of rheumatic heart disease--an evidence-based
436 guideline. *Nat Rev Cardiol* 2012;9(5):297-309. doi: 10.1038/nrcardio.2012.7
437 [published Online First: 2012/03/01]

438 14. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the
439 echocardiographic assessment of native valvular regurgitation: an executive
440 summary from the European Association of Cardiovascular Imaging. *European*
441 *Heart Journal - Cardiovascular Imaging* 2013;14(7):611-44. doi:
442 10.1093/ehjci/jet105

443 15. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve
444 stenosis: EAE/ASE recommendations for clinical practice. *European journal of*
445 *echocardiography : the journal of the Working Group on Echocardiography of*
446 *the European Society of Cardiology* 2009;10(1):1-25. doi:
447 10.1093/ejechocard/jen303 [published Online First: 2008/12/10]

448 16. Okuno T, Asami M, Heg D, et al. Impact of Left Ventricular Outflow Tract

- 449 Calcification on Procedural Outcomes After Transcatheter Aortic Valve
450 Replacement. *JACC Cardiovascular interventions* 2020;13(15):1789-99. doi:
451 10.1016/j.jcin.2020.04.015 [published Online First: 2020/08/09]
- 452 17. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint
453 definitions for transcatheter aortic valve implantation: the Valve Academic
454 Research Consortium-2 consensus document (VARC-2). *European journal of*
455 *cardio-thoracic surgery : official journal of the European Association for*
456 *Cardio-thoracic Surgery* 2012;42(5):S45-60. doi: 10.1093/ejcts/ezs533
457 [published Online First: 2012/10/03]
- 458 18. Iung B, Baron G, Tornos P, et al. Valvular heart disease in the community: a
459 European experience. *Curr Probl Cardiol* 2007;32(11):609-61. doi:
460 10.1016/j.cpcardiol.2007.07.002 [published Online First: 2007/11/03]
- 461 19. Passos LSA, Nunes MCP, Aikawa E. Rheumatic Heart Valve Disease
462 Pathophysiology and Underlying Mechanisms. *Front Cardiovasc Med*
463 2020;7:612716. doi: 10.3389/fcvm.2020.612716 [published Online First:
464 2021/02/05]

- 465 20. Mutagaywa RK, Wind AM, Kamuhabwa A, et al. Rheumatic heart disease anno
466 2020: Impacts of gender and migration on epidemiology and management. *Eur J*
467 *Clin Invest* 2020;50(12):e13374. doi: 10.1111/eci.13374 [published Online First:
468 2020/08/14]
- 469 21. Pilgrim T, Windecker S. Expansion of transcatheter aortic valve implantation: new
470 indications and socio-economic considerations. *Eur Heart J* 2018;39(28):2643-
471 45. doi: 10.1093/eurheartj/ehy228 [published Online First: 2018/04/28]
- 472 22. Sharma SK, Rao RS, Chandra P, et al. First-in-human evaluation of a novel balloon-
473 expandable transcatheter heart valve in patients with severe symptomatic native
474 aortic stenosis: the MyVal-1 study. *EuroIntervention : journal of EuroPCR in*
475 *collaboration with the Working Group on Interventional Cardiology of the*
476 *European Society of Cardiology* 2020;16(5):421-29. doi: 10.4244/EIJ-D-19-
477 00413 [published Online First: 2019/10/01]
- 478 23. Chandra P, Jose J, Mattummal S, et al. Clinical evaluation of the Hydra self-
479 expanding transcatheter aortic valve: 6 month results from the GENESIS trial.
480 *Catheterization and cardiovascular interventions : official journal of the Society*

481 *for Cardiac Angiography & Interventions* 2021;98(2):371-79. doi:
482 10.1002/ccd.29733 [published Online First: 2021/04/21]

483 24. Zilla P, Williams DF, Bezuidenhout D. TAVR for Patients With Rheumatic Heart
484 Disease: Opening the Door for the Many? *J Am Coll Cardiol* 2021;77(14):1714-
485 16. doi: 10.1016/j.jacc.2021.02.044 [published Online First: 2021/04/10]

486 25. Remenyi B, ElGuindy A, Smith SC, Jr., et al. Valvular aspects of rheumatic heart
487 disease. *Lancet (London, England)* 2016;387(10025):1335-46. doi:
488 10.1016/S0140-6736(16)00547-X [published Online First: 2016/03/31]

489 26. Wallby L, Steffensen T, Jonasson L, et al. Inflammatory Characteristics of Stenotic
490 Aortic Valves: A Comparison between Rheumatic and Nonrheumatic Aortic
491 Stenosis. *Cardiol Res Pract* 2013;2013:895215. doi: 10.1155/2013/895215
492 [published Online First: 2013/03/12]

493 27. Scherman J, Ofoegbu C, Myburgh A, et al. Preclinical evaluation of a transcatheter
494 aortic valve replacement system for patients with rheumatic heart disease.
495 *EuroIntervention : journal of EuroPCR in collaboration with the Working Group*
496 *on Interventional Cardiology of the European Society of Cardiology*

497 2019;15(11):e975-e82. doi: 10.4244/EIJ-D-18-01052 [published Online First:
498 2019/08/14]

499 28. Vollenbroich R, Stortecky S, Praz F, et al. The impact of functional vs degenerative
500 mitral regurgitation on clinical outcomes among patients undergoing
501 transcatheter aortic valve implantation. *American heart journal* 2017;184:71-80.
502 doi: 10.1016/j.ahj.2016.10.015 [published Online First: 2016/11/29]

503 29. Asami M, Windecker S, Praz F, et al. Transcatheter aortic valve replacement in
504 patients with concomitant mitral stenosis. *Eur Heart J* 2019;40(17):1342-51.
505 doi: 10.1093/eurheartj/ehy834 [published Online First: 2019/01/01]

506 30. Okuno T, Hagemeyer D, Brugger N, et al. Valvular and Nonvalvular Atrial
507 Fibrillation in Patients Undergoing Transcatheter Aortic Valve Replacement.
508 *JACC Cardiovascular interventions* 2020;13(18):2124-33. doi:
509 10.1016/j.jcin.2020.05.049 [published Online First: 2020/09/26]
510

511

Figure Legends

512 **Figure 1. Echocardiographic assessment of morphological features of rheumatic**
513 **heart disease.**

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

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

521

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

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

527

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

530 Hazard ratios and p-values were calculated with the use of Cox proportional hazards
531 models. Abbreviations as in [Figure 1](#).

532

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

536 Structural valve deterioration was defined according to the Valve Academic Research
537 Consortium-2 criteria¹⁷. Unplanned repeat aortic valve intervention was defined as a
538 composite endpoint including valve-in-valve procedure, balloon valvuloplasty, surgical
539 revision, or paravalvular leak closure.

540 Hazard ratios and p-values were calculated with the use of Cox proportional hazards
541 models. Abbreviations as in [Figure 1](#).

542

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/cm ²	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
Dyslipidemia, 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 (\pm 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.

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 (\pm 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.