Prosthesis-patient mismatch following transcatheter aortic valve replacement with supra-annular and intra-annular prostheses

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ABSTRACT

Objectives: To compare the frequency of PPM with self-expandable valves (SEV) to balloon-expandable valves (BEV).

Background: Prosthesis-patient mismatch (PPM) has been associated with increased mortality after transcatheter aortic valve replacement. Data on the frequency of PPM as a function of supra-annular or intra-annular position of transcatheter heart valves is insufficient.

Methods: A total of 757 patients treated with SEV (CoreValve, Evolut R) and BEV (SAPIEN THV/XT/3) were enrolled in the present analysis between August 2007 and June 2017. PPM was classified based on discharge prosthetic effective orifice area indexed to BSA as severe (<0.65 cm^2/m^2) or moderate (0.65 to 0.85 cm^2/m^2) in the general population, and as severe (<0.60 cm^2/m^2) or moderate (0.60 to 0.90 cm^2/m^2) in the obese population (BMI ≥ 30 kg/m^2).

Results: Propensity score matching resulted in 224 matched pairs. At discharge, SEV were associated with a lower incidence of PPM compared with BEV (PPM: 33.5% vs. 46.9%, p=0.004; severe PPM: 6.7% vs. 15.6%, p=0.003). The lower frequency of severe PPM in SEV was observed even in patients with larger annulus. While patients with BSA >1.83 m^2 had a significantly lower incidence of PPM with SEV compared to BEV, there was no significant difference in patients with BSA ≤ 1.83 m^2. We found no impact of PPM on cardiovascular mortality or NYHA functional class at 1 year.

Conclusions: SEV were associated with a lower frequency of PPM compared to BEV irrespective of annulus area. The difference was mainly driven by larger patients with BSA >1.83 m^2.

CONDENSED ABSTRACT

We performed a propensity score matched comparison of prosthesis-patient mismatch (PPM) between self-expandable valves (SEV) and balloon-expandable valves (BEV). SEV were significantly associated with a lower incidence of PPM compared with BEV (PPM: 33.5% vs. 46.9%, p=0.004; severe PPM: 6.7% vs. 15.6%, p=0.003; respectively). The difference was independent of annulus sizes or valve sizes, but was driven by larger patients with BSA > 1.83m^2 (PPM: 45.3% vs. 60.9%, p=0.021; severe PPM: 8.5% vs. 22.6%, p=0.004), while there was no significant difference in smaller patients with BSA ≤ 1.83 m^2 (PPM: 22.9% vs. 32.1%, p=0.120; severe PPM: 5.1% vs. 8.3%, p=0.341).

ABBREVIATION AND ACRONYMS

AVC = Aortic valvular complex

BSA = Body surface area

CT = Computed tomography

EOA = Effective orifice area

LVOT = Left ventricular outflow tract

PPM = Prosthesis-patient mismatch

SAVR = Surgical aortic valve replacement

STS PROM= Society of Thoracic Surgery-Predicted Risk Of Mortality

TAVR = Transcatheter aortic valve replacement

VARC = Valve Academic Research Consortium

Introduction

Prosthesis-patient mismatch (PPM) has been a topic of debate ever since it was first conceived by Rahimtoola in 1978(1). Recently, transcatheter aortic valve replacement (TAVR) has evolved as an alternative to surgical aortic valve replacement (SAVR) in various clinical settings and has been associated with superior hemodynamic performance and a lower incidence of PPM(2,3). A retrospective analysis of 62,125 patients enrolled in the STS (Society of Thoracic Surgeons)/ACC (American College of Cardiology) TVT (Transcatheter Valve Therapy) registry reported that the rate of severe PPM following TAVR was approximately 12% and was associated with higher mortality and heart failure rehospitalization at 1 year follow-up(4).

PPM occurs when the effective orifice area (EOA) of the prosthesis is too small relative to the patient's body size. Self-expandable transcatheter heart valves (SEV) are supra-annular in position allowing for a larger EOA and thereby potentially preventing PPM as compared to balloon-expandable valves (BEV) which have an intra-annular position(5). The aim of the present analysis is therefore to compare the frequency of PPM with SEV to BEV.

Methods

Study population

All patients undergoing TAVR at Bern University Hospital, Bern, Switzerland, are

consecutively enrolled into a prospective institutional registry that is a part of the Swiss

TAVI registry (NCT01368250). The registry has been approved by the local ethics

committee, and patients provide written informed consent to participate. For the purpose

of the present analysis, we analyzed all patients treated with SEV (CoreValve and Evolut

R, Medtronic, Minneapolis, MN, USA) and those treated with BEV (SAPIEN THV/XT

and SAPIEN 3, Edwards Lifesciences, Irvine, CA, USA). Patients without hemodynamic

assessment by post-procedural echocardiography or pre-procedural CT raw data adequate

for a comprehensive assessment of aortic valvular complex (AVC) were excluded from

the analysis.

Transcatheter aortic valve replacement

In the majority of cases, TAVR was performed by transfemoral access. In patients

who could not undergo transfemoral access due to calcified, tortuous or small caliber

vessels, transapical or transsubclavian access was used. Prosthesis selection was based on

CT anatomical assessment and clinical suitability of each patient. Post-procedural care

included rhythm monitoring for at least 48h after the intervention, laboratory testing, and

daily 12-lead electrocardiograms directly after the procedure and then on a daily basis.

Echocardiographic assessment

Standardized transthoracic echocardiography was performed before and after

TAVR by a board-certified cardiologist and assessed in accordance to the Valve Academic

Research Consortium (VARC-2) recommendations(6). EOA was assessed using the

continuity equation and indexed to the body surface area (BSA). The mean transaortic

valve gradient was measured using continuous-wave Doppler. Post-procedural

regurgitation severity was evaluated using a multiparametric approach and classified as

follows: none/trace, mild, moderate, and severe. PPM was classified based on discharge

prosthetic EOA indexed to BSA as severe (<0.65 cm^2/m^2) or moderate (0.65 to 0.85

cm^2/m^2) in the general population, and as severe (<0.60 cm^2/m^2) or moderate (0.60 to

0.90 cm^2/m^2) in the obese population (BMI $\geq$ 30 kg/m^2).

Data collection and clinical follow-up

Baseline clinical data, procedural characteristics, and follow-up data were entered

into a dedicated database, which is verified and maintained by the Clinical Trials Unit of

the University of Bern. Clinical follow-up was scheduled at 30 days and 1 year using

standardized interviews, documentation from referring physicians, and hospital discharge

summaries. All target events were systematically collected and adjudicated by a dedicated

clinical event committee, involving cardiologists and cardiac surgeons, according to the

VARC-2 criteria(6).

Statistical analysis

Categorical data are represented as frequencies and percentages and the

differences between groups are evaluated with the Chi-square test or Fisher's exact test.

Continuous variables are expressed as mean values ± standard deviation and compared

between groups using t tests.

Because the valve type and size selection was based on CT anatomical assessment

and clinical suitability of each patient, which could significantly affect the hemodynamic

result of the implanted valve, we applied a propensity score matching method to control

for these confounding baseline variables. Propensity score was modelled using a

multivariate logistic regression model based on the following baseline variables: age, sex,

BSA(cm^2), STS PROM(%), atrial fibrillation, peripheral artery disease, left ventricular

ejection fraction(%), moderate or severe mitral regurgitation (MR), moderate or severe

tricuspid regurgitation (TR), as well as CT measured variables: bicuspid valve, annulus

area (mm^2), AVC calcium volume (mm^3), left ventricular out flow tract (LVOT) calcium

volume (mm^3), aortic angulation, and annulus eccentricity (=minimum annulus

diameter/maximum annulus diameter). These variables were selected based on their

presumed association with prosthesis selection and hemodynamic outcome. We matched

patients treated with SEV and BEV using propensity score with a caliper of 0.2. All main

analyses presented are on this propensity score matched cohort.

Univariate logistic regression was used to estimate the effect of the valve type on

the incidence of PPM. Event-free survival curves were constructed using the Kaplan-

Meier method and Cox proportional hazards models were used to calculate crude hazard

ratios (HR) and 95% confidence intervals (95% CI). Pearson's correlation coefficients

and Spearman's rank correlation coefficients were used to measure associations between

variables. Fisher's tests, chi-square test or multinomial models were used to test

relationships between variables and PPM. A multinomial model was applied when the

response variables were categorical (valve sizes and PPM incidence). Odds ratios (OR

with 95% confidence interval) are given for effect sizes, where appropriate. Throughout

the present study, a p-value of <0.05 was considered significant. Statistical analyses were

performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Propensity score matching and patient populations

Among 1811 consecutive patients undergoing TAVR between August 2007 and

June 2017, a total of 757 patients met the inclusion criteria and were eligible for the

present analysis. Among them, 420 patients were treated with BEV (SAPIEN THV/XT

and SAPIEN 3) and 337 patients were treated with SEV (CoreValve and Evolut R).

Propensity score matching resulted in 224 matched pairs. The baseline characteristics of

the unmatched and matched population are shown in **Table 1**. Before propensity score

matching, there were significant differences in annulus area/perimeter, LVOT calcium

volume, and aortic angulation between the two groups. After propensity score matching,

baseline characteristics including the CT assessment data were well balanced between the

two groups.

Procedural characteristics and clinical outcomes

Procedural characteristics and clinical outcomes are summarized in **Table 2**. Pre-

dilatation rate was significantly lower, whereas post-dilatation rate was significantly

higher in the SEV group. Valve dislocation or embolization was observed in 5.5% in the

SEV group, which was significantly higher compared with 0.5% in the BEV group

(p=0.004). Clinical follow-up at 30 days was complete in all patients and the outcomes

were comparable between the two groups, except for a higher rate of new permanent

pacemaker implantation in the SEV group (31.7% vs. 13.8%, OR [95% CI]: 2.9 [1.8-4.6],

p<0.001).

Echocardiographic outcomes and PPM

Echocardiographic outcomes at discharge are shown in **Table 3**. The incidence of

moderate or severe post-procedural aortic regurgitation (AR) was significantly higher in

the SEV group (13% vs. 6%, OR [95% CI]: 2.2 [1.1-4.3], p =0.021). EOA and EOA

indexed to the BSA (iEOA) were significantly higher in the SEV group as compared to

the BEV group (1.80 ± 0.46 vs. 1.68 ± 0.52, p = 0.010; 0.99 ± 0.27 vs. 0.93 ± 0.31, p =

0.021; respectively), and mean transvalvular gradients were 8.28 ± 3.87 mmHg in the

SEV group and 10.68 ± 4.65 mmHg in the BEV group (p<0.001). Consequently, SEV

were significantly associated with a lower rate of PPM compared with BEV (PPM: 33.5%

vs. 46.9%, OR [95% CI]: 0.57 [0.39-0.84], p=0.004; severe PPM: 6.7% vs. 15.6%, OR

[95% CI]: 0.39 [0.21-0.73], p=0.003) as shown in **Central illustration**. Subgroup

analyses were performed to investigate the effect of annulus size and BSA on the

incidence of PPM (**Central illustration**). Subgroups based on annulus area and BSA

were divided into 2 groups using the specified cut-off values. The annulus area was

divided at 430 mm^2, which is a cut-off value between 23mm and 26mm of SAPIEN 3,

and the BSA was divided at the mean value of the analyzed population. Among patients

with small annuli (< 430 mm^2), PPM was more common (51.1% vs. 29.9%, p=0.003) and

severe PPM occurred numerically more frequently (13.6% vs. 8.6%, p=0.284) in the BEV

group. Among patients with larger annulus (≥ 430 mm^2), PPM was numerically more

common (44.1% vs. 36.6%, p=0.214) and severe PPM occurred significantly more often

(16.9% vs. 5.3%, p=0.004) in the BEV group. Both PPM and severe PPM occurred

significantly more often in the BEV group as compared to the SEV group in the subset of

larger BSA (60.9% vs. 45.3%, p=0.021; 22.6% vs. 8.5%, p=0.004; respectively), whereas

the rates of PPM and severe PPM were comparable in the subset of patients with smaller

BSA (32.1% vs. 22.9%, p=0.120; 8.3% vs. 5.1%, p=0.341; respectively). There were no

interaction effects both in annulus area divided at 430 mm^2 (p=0.117 for PPM, p=0.685

for severe PPM) and BSA divided at 1.83 m^2 (p=0.247 for PPM, p=0.358 for severe PPM).

EOAi and PPM rate according to the valve type and size are summarized in **Table 4**. As

shown, there was no increase in EOAi according to increased valve size. The effect of the

valve size on the incidence rates of moderate or severe PPM was examined by a

multinomial model and there was no significant effect (p=0.37).

Impact of PPM on clinical outcomes

Clinical outcome data was available in 446 patients (99.6%), 1 patient refused

follow-up and 1 patient was not traceable. Kaplan-Meier curves of cardiovascular

mortality according to PPM are shown in **Figure 1**. Cumulative mortality rate at 1 year

in patients with severe PPM was numerically higher as compared to patients with

moderate PPM and without PPM (10.3% vs. 6.3% vs. 6.6%; Severe PPM vs. No PPM

HR [95% CI]: 1.60 [0.59-4.34], p=0.355; Moderate PPM vs. No PPM HR [95% CI]: 0.96

[0.42-2.23], p=0.929; Severe PPM vs. No or Moderate PPM HR [95% CI]: 1.62 [0.62-

4.24], p=0.324). New York Heart Association functional class at 1 year did not differ

significantly between patients with no PPM, moderate PPM, and severe PPM (p=0.84,

Figure 2).

Discussion

The key findings of this propensity score matched analysis comparing SEV

(supra-annular valves) and BEV (intra-annular valves) are as follows: 1) The rate of PPM

was significantly lower in SEV as compared to BEV (PPM: 33.5% vs. 46.9%, p=0.004;

severe PPM: 6.7% vs. 15.6%, p=0.003); 2) The effect was consistent across different

annulus sizes and driven by larger patients with BSA >1.83 m^2. Previous analyses have

used an alternative definition of PPM without adjustment for BMI (2-4, 7-9, 13, 14). We

found consistent findings irrespective of which definition was used and provide an

analysis using an alternative definition of PPM in the Online Supplement (**Online Figure**

1).

The concept of PPM has originally been described in 1978(1), since then

numerous studies have investigated the incidence of PPM and the potential effects on

clinical outcomes. Although previous studies have shown a lower incidence of PPM in

TAVR compared to SAVR(2,3,7,8), moderate PPM and severe PPM still occurred in 9 to

36% and 1 to 28% of the patients, respectively(2-4,7-13). BEV are constrained by the

native valve area, whereas SEV can achieve a larger EOA by being situated above the

native valve allowing more space and have been suggested to be associated with less PPM.

However, there is limited data demonstrating a relationship between SEV and PPM.

Nombela-Franco et al. reported similar rates of severe PPM between CoreValve and

SAPIEN prostheses within patients receiving the same prosthesis size (26mm) in a

propensity score matched analysis(14). More recently, Mauri et al. demonstrated a lower

incidence of PPM in patients treated with ACURATE neo (Boston Scientific,

Marlborough, Massachusetts, USA), which is also a self-expandable and supra-annular

position valve, as compared to SAPIEN 3 in patients with small annulus area

($<400mm^2$)(11). In clinical practice, valve selection is based on CT assessment such as

annulus size, AVC calcium, and annulus eccentricity, which may directly influence the

prosthesis EOA after implantation. These potential confounding factors need to be taken

into account. We applied propensity score matching analysis adjusting for these

confounding factors to compare SEV and BEV, and found a significantly lower incidence

of PPM and severe PPM in SEV compared to BEV.

To date, patients with small aortic annuli have been considered to have a greater

risk of PPM and therefore previous studies focused on this population when investigating

PPM(11,15). However, in our data, BEV was associated with higher rate of PPM as

compared to SEV even in patients with relatively larger annulus area ($\geq$430 mm^2).

Moreover, the larger valve size did not result in a lower incidence of moderate or severe

PPM. This was likely due to patients treated with larger valve sizes tending to have larger

body sizes (r=0.277, p<0.001). Annulus area, which fundamentally determines valve size,

had a weak but positive correlation with BSA (r=0.356, p<0.001) (**Online Figure 2**). On

the other hand, the incidence of PPM was comparable between BEV and SEV in patients

with smaller BSA ($\leq$1.83m^2). Therefore, BSA seems to be the more important factor

indicating vulnerability to PPM rather than annulus size. It might be necessary to select

the valve type considering the risk of PPM in patients with relatively large body sizes

even if the annulus size is not too small, while keeping in mind higher possible risk of

valve dislocation or embolization, permanent pacemaker implantation, and post-

procedural AR.

There is conflicting evidence on the impact of PPM on clinical outcome, likely

due to methodological differences across the studies and the patient population being

studied(16-18). In the present study, neither moderate PPM nor severe PPM significantly

predicted cardiovascular mortality or NYHA functional class at 1 year. In contrast to a

previous study(2), severe PPM did not predict mortality in our cohort in a sensitivity

analysis excluding patients with significant post-procedural AR (**Online Figure 3a**).

Moreover, we found no effect of PPM on mortality after exclusion of patients with

moderate or severe MR (**Online Figure 3b**). This is in line with the results from some of

the previous studies in TAVR(7,9,11,12), whereas some other studies demonstrated

adverse effects of PPM on mortality or NYHA functional class(2,4,8,10). PPM increases

left ventricular (LV) afterload, which may impair coronary flow reserve(19). It also

impedes regression of LV hypertrophy and dysfunction(2,8,10,20), and attenuates

improvement of MR(21). PPM has also been suggested to be associated with other

adverse outcomes such as abnormalities of the Von Willebrand factor caused bleeding

complications(22), exercise-induced arrhythmias(23), and congestive heart failure(4,24).

Although there were inconsistent results regarding the association of PPM with mortality

in SAVR(16) as in TAVR, a large meta-analysis of 34 observational studies comprising

27,186 patients demonstrated an increased mortality in patients with PPM(17). Our study

included a modest number of patients with limited duration of follow-up and may

therefore be underpowered to demonstrate a clinical impact of PPM. Moreover, some

studies in SAVR have suggested that the impact of PPM on mortality was only observed

in younger patients (age < 60 or 70 years old) with a more active life style(25,26). This

may explain at least in part why we failed to demonstrate a clinical impact of PPM in our

cohort, in which the average age was over 80 years of age. PPM is also suggested to be

an important risk factor for early structural valve deterioration and re-intervention(18,27).

Therefore, further studies with a younger population and with longer follow-up are

needed to investigate the clinical importance of PPM as a modifiable risk factor for

mortality, heart failure, and valve deterioration.

Study Limitations

Our results should be interpreted in light of several limitations. We did not use an independent core laboratory. However, our measurements are consistent with previously reported core lab analyses for EOA(28). The EOA measurement by Doppler echocardiography may be affected by technical pitfalls or measurement errors and the accuracy and reproducibility could not be assessed. Although we applied propensity score matched analysis in order to adjust for important confounders including annulus size, which could significantly affect the hemodynamic results of the procedure, unknown confounders might be present. Finally, longer follow-up and inclusion of younger patients might be necessary to evaluate the impact of PPM on clinical outcomes more comprehensively.

Conclusion

SEV had a preventative effect on PPM as compared to BEV in general and even in patients with relatively larger annulus size. The difference was mainly driven by patients with larger body size. Although PPM did not affect clinical outcomes in the present analysis, further investigation is required to evaluate the clinical significance of

PPM.

PERSPECTIVES

WHAT IS KNOWN: The supra-annular position of self-expandable valves (SEV) may increase effective orifice area and prevent prosthesis-patient mismatch (PPM), a risk factor for adverse clinical outcomes. Moreover, patients with small aortic annuli are considered high risk for PPM and may particularly benefit from SEV. However, there were few direct comparison of SEV and balloon-expandable valves (BEV) with regard to the incidence of PPM in real clinical practice.

WHAT IS NEW: SEV are associated with a significantly lower incidence of PPM as compared to BEV in general and even in patients with relatively larger annuli. The difference was largely driven by patients with larger body sizes (BSA > 1.83 m^2).

WHAT IS NEXT: Future risk prediction models to identify patients at higher risk of PPM and may benefit from SEV are expected. Further studies with a younger population and with longer follow-up are needed to investigate the clinical importance of PPM as a modifiable risk factor for mortality, heart failure, and valve deterioration.

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Figure Legends

Central illustration. Prosthesis-patient mismatch (PPM) according to the valve

type.

A. The rate of PPM was significantly lower in self-expandable valves (SEV)

compared to balloon-expandable valves (BEV).

B. SEV were associated with a significantly lower rate of PPM and numerically

lower rate of severe PPM in the subset of smaller annulus area ($<430mm^2$). In the

subset of larger annulus area ($\geq430mm^2$), SEV were associated with numerically

lower incidence of PPM and significantly lower incidence of severe PPM. SEV were

associated with significantly lower incidences of PPM and severe PPM in the subset

of larger BSA ($>1.83m^2$), whereas the incidences were comparable between SEV and

BEV in the subset of smaller BSA ($\leq1.83m^2$). The p value for the interaction between

SEV use and annulus area for PPM and severe PPM was not significant (p=0.117,

p=0.685, respectively). The p value for the interaction between SEV use and BSA for

PPM and severe PPM was not significant either (p=0.247, p=0.358, respectively).

Figure 1. Kaplan-Meier curves of cardiovascular death according to the presence

of PPM.

Cumulative mortality rate at 1 year in patients with severe PPM was numerically

higher as compared to patients with moderate PPM and without PPM (10.3% vs.

6.3% vs. 6.6%; Severe PPM vs. No PPM HR [95% CI]: 1.60 [0.59-4.34], p=0.355;

Moderate PPM vs. No PPM HR [95% CI]: 0.96 [0.42-2.23], p=0.929; Severe PPM

vs. No or Moderate PPM HR [95% CI]: 1.62 [0.62-4.24], p=0.324). Blue line

indicates no PPM; orange line indicates moderate PPM; red line indicates severe

PPM.

Figure 2. New York Heart Association (NYHA) functional class at one year

according to the presence of moderate or severe PPM.

NYHA functional class at one year did not differ significantly among no PPM,

moderate PPM, and severe PPM (p=0.84).

Tables

Table 1. Baseline characteristics of the unmatched and matched population						
	Unmatched Cohort			Matched Cohort		
	Intra-annular valves (SAPIEN THV/XT/3) (n=420)	Supra-annular valves (CoreValve, Evolut R) (n=337)	p-value	Intra-annular valves (SAPIEN THV/XT/3) (n=224)	Supra-annular valves (CoreValve, Evolut R) (n=224)	p-value
Age (years)	82.3 ± 5.8	82.7 ± 5.6	0.417	82.9 ± 5.6	82.9 ± 5.4	0.999
Female gender (n, %)	201 (47.9%)	199 (59.1%)	0.003	116 (51.8%)	114 (50.9%)	0.925
Body mass index (kg/m^2)	27.0 ± 5.0	26.4 ± 5.5	0.125	26.8 ± 5.2	26.9 ± 5.8	0.885
Body surface area (m^2)	1.87 ± 0.23	1.81 ± 0.24	0.001	1.84 ± 0.24	1.84 ± 0.25	0.861
STS PROM (%)	5.02 ± 3.23	5.90 ± 3.91	0.001	5.65 ± 3.69	5.28 ± 3.22	0.258
NYHA functional class Ⅲ/Ⅳ (n, %)	289 (68.8%)	247 (73.3%)	0.198	157 (70.1%)	160 (71.4%)	0.835
Concomitant diseases						
Arterial hypertension (n, %)	358 (85.2%)	292 (86.6%)	0.601	198 (88.4%)	195 (87.1%)	0.774
Diabetes mellitus (n, %)	107 (25.5%)	84 (24.9%)	0.867	61 (27.2%)	58 (25.9%)	0.831

Dyslipidemia (n, %)	270 (64.3%)	210 (62.3%)	0.596	149 (66.5%)	143 (63.8%)	0.620
CKD (eGFR<60) (n, %)	261 (62.1%)	228 (67.7%)	0.126	148 (66.1%)	144 (64.3%)	0.766
COPD (n, %)	49 (11.7%)	49 (14.5%)	0.276	29 (12.9%)	31 (13.8%)	0.890
Atrio-ventricular block (n, %)	77 (20.9%)	63 (24.6%)	0.285	44 (22.7%)	39 (23.5%)	0.900
Atrial fibrillation (n, %)	131 (31.2%)	109 (32.3%)	0.754	72 (32.1%)	72 (32.1%)	1.000
Previous history						
Coronary artery disease (n, %)	267 (63.6%)	202 (59.9%)	0.328	143 (63.8%)	146 (65.2%)	0.843
History of cerebrovascular accident (n, %)	49 (11.7%)	36 (10.7%)	0.729	29 (12.9%)	20 (8.9%)	0.226
Peripheral artery disease (n, %)	30 (7.1%)	48 (14.2%)	0.002	22 (9.8%)	24 (10.7%)	0.876
Laboratory data						
Hemoglobin (g/dl)	122.5 ± 16.6	122.3 ± 16.9	0.851	122.2 ± 16.5	123.8 ± 16.9	0.295
BNP level (pg/ml)	510.1 ± 702.0	630.8 ± 863.2	0.054	584.9 ± 800.5	585.4 ± 809.8	0.996
Echocardiographic data						
Aortic valve area (cm^2)	0.68 ± 0.23	0.63 ± 0.26	0.008	0.66 ± 0.23	0.65 ± 0.26	0.740
Aortic valve mean gradient (mmHg)	42.0 ± 16.0	42.6 ± 18.5	0.667	40.8 ± 16.0	41.9 ± 17.1	0.493
LVEF (%)	55.8 ± 14.0	54.7 ± 14.6	0.259	54.5 ± 14.9	54.9 ± 13.7	0.750
Moderate/severe AR (n, %)	27 (7.1%)	32 (10.7%)	0.102	16 (7.8%)	15 (7.6%)	1.000
Moderate/severe MR (n, %)	51 (13.2%)	65 (21.0%)	0.008	31 (14.9%)	42 (20.5%)	0.156

Moderate/severe TR (n, %)	30 (8.4%)	35 (14.1%)	0.032	17 (8.8%)	18 (11.1%)	0.479
Computed tomography data						
Bicuspid valve (n, %)	33 (7.9%)	22 (6.5%)	0.573	15 (6.7%)	12 (5.4%)	0.692
Annulus area (mm²)	470.2 ± 84.0	446.7 ± 99.5	<0.001	459.5 ± 86.8	459.8 ± 85.7	0.963
Annulus perimeter (mm)	78.1 ± 6.9	76.1 ± 8.2	<0.001	77.3 ± 7.3	77.3 ± 7.1	0.968
AVC calcium (mm³)	348.4 ± 322.1	319.3 ± 332.6	0.223	338.1 ± 317.7	334.8 ± 356.8	0.918
LVOT calcium (mm³)	12.5 ± 32.3	20.3 ± 59.8	0.023	15.6 ± 34.5	17.0 ± 41.1	0.710
Porcelain Aorta (n, %)	17 (4.0%)	17 (5.1%)	0.597	7 (3.1%)	9 (4.0%)	0.800
Aortic Angulation (°)	50.5 ± 9.5	47.9 ± 10.1	<0.001	49.3 ± 9.1	49.1 ± 10.0	0.824
Eccentricity of annulus (0-1)	0.77 ± 0.06	0.76 ± 0.06	0.081	0.77 ± 0.06	0.76 ± 0.06	0.903

AR = Aortic regurgitation; AVC = Aortic valvular complex; BNP = Brain natriuretic peptide; COPD = Chronic obstructive pulmonary disease; CKD = Chronic kidney disease; LV = Left ventricle; LVEF = Left ventricular ejection fraction; LVOT = left ventricular outflow tract; MR = Mitral regurgitation; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TR = Tricuspid regurgitation.

Table 2. Procedural characteristics, complications, and clinical outcomes of the matched population			
	Intra-annular valves (SAPIEN THV/XT/3) (n=224)	**Supra-annular valves (CoreValve, Evolut R) (n=224)**	**p-value**
Procedural characteristics			
Pre-dilatation (n, %)	179 (79.9%)	153 (68.3%)	0.007
Post-dilatation (n, %)	40 (17.9%)	87 (38.8%)	<0.001
Procedural Complications			
Major Vascular complication	27 (12.1%)	24 (10.7%)	0.766
Valve in series (n, %)	1 (0.4%)	6 (2.7%)	0.122
Annulus rupture/aortic dissection (n, %)	0 (0.0%)	0 (0.0%)	
Valve dislocation/embolization (n, %)	1 (0.5%)	10 (5.5%)	0.004
Coronary artery occlusion (n, %)	3 (1.4%)	0 (0.0%)	0.252
Post-procedural Clinical outcomes (at 30 days)			
Mortality	6 (2.7%)	2 (0.9%)	0.285
Myocardial Infarction	3 (1.3%)	3 (1.3%)	1.000
Disabling stroke	3 (1.3%)	1 (0.4%)	0.623
Bleeding: Life-threatening	11 (4.9%)	12 (5.4%)	1.000

Bleeding: Major	23 (10.3%)	32 (14.3%)	0.249
Kidney injury Stage3	5 (2.2%)	8 (3.6%)	0.575
Permanent Pacemaker Implantation	31 (13.8%)	71 (31.7%)	<0.001

Table 3. Echocardiographic outcomes at discharge according to type of valve in the matched population			
	Intra-annular valves (SAPIEN THV/XT/3) (n=224)	**Supra-annular valves (CoreValve, Evolut R) (n=224)**	**p value**
Discharge			
EOA (cm^2)	1.68 ± 0.52	1.80 ± 0.46	0.010
indexed EOA (cm^2/m^2)	0.93 ± 0.31	0.99 ± 0.27	0.021
Transvalvular mean gradient (mmHg)	10.7 ± 4.7	8.3 ± 3.9	<0.001
LVEF (%)	56.5 ± 11.5	56.5 ± 10.8	0.959
PPM (n, %)	105 (46.9%)	75 (33.5%)	0.004
Moderate PPM (n, %)	70 (31.3%)	60 (26.8%)	0.298
Severe PPM (n, %)	35 (15.6%)	15 (6.7%)	0.003
≥ moderate AR (n, %)	14 (6.4%)	29 (13.0%)	0.021
≥ moderate MR (n, %)	25 (11.6%)	23 (12.5%)	0.775
≥ moderate TR (n, %)	20 (9.4%)	23 (12.8%)	0.289
AR = Aortic regurgitation; EOA = Effective orifice area index; LVEF = Left ventricular ejection fraction; MR = Mitral regurgitation; PPM = prosthesis-patient mismatch; TR = tricuspid regurgitation.			

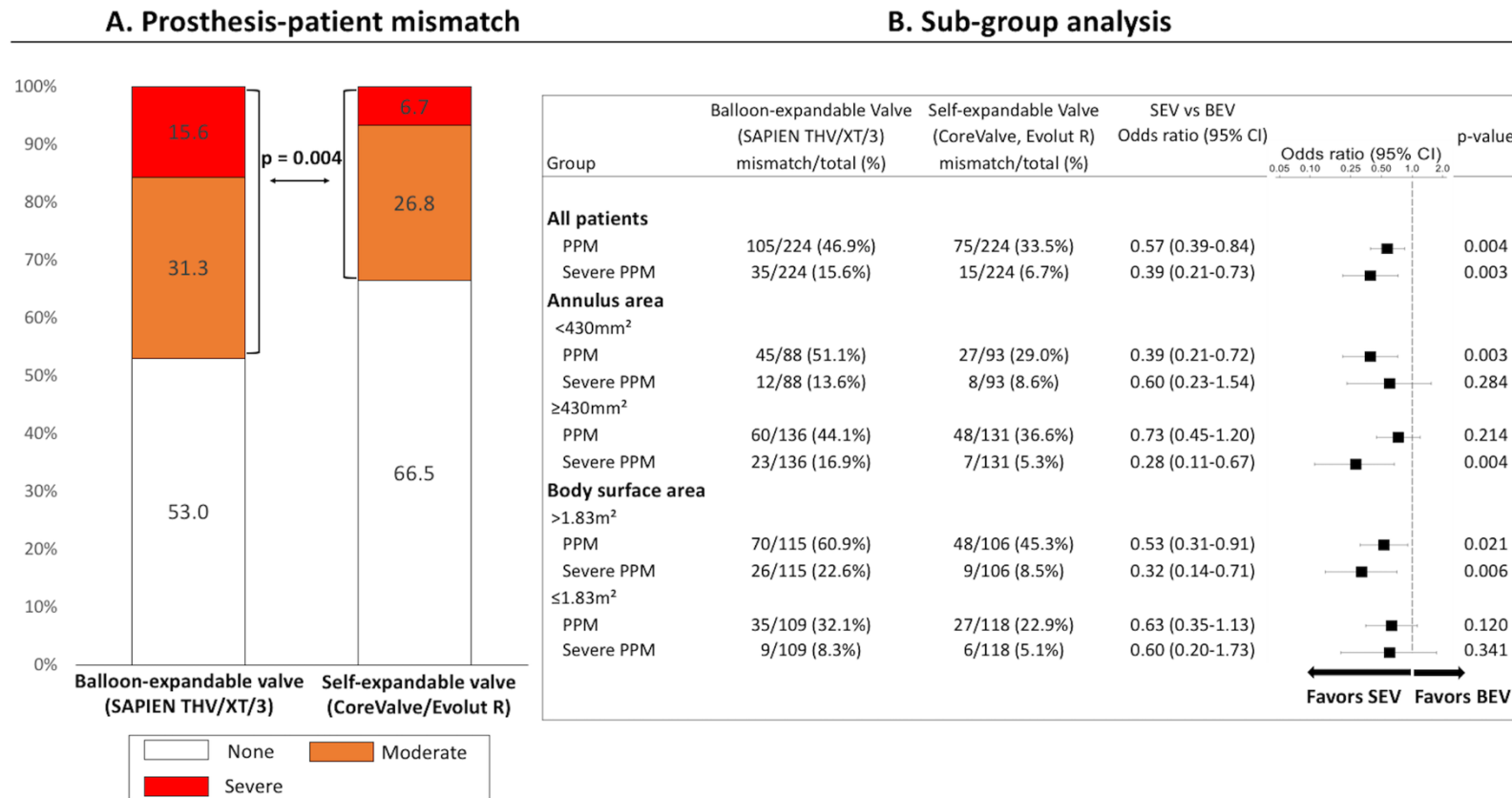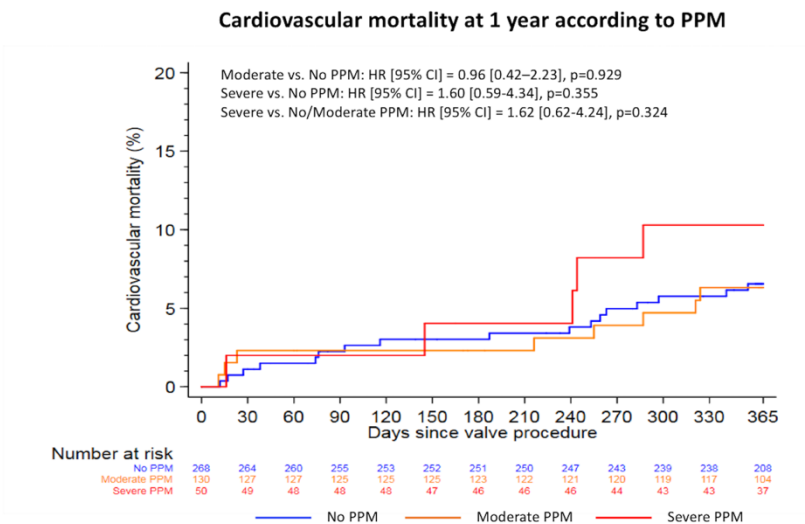| Table 4. Post-procedural EOAi and PPM rate according to valve type and sizes in the matched population							
Intra-annular valves (SAPIEN THV/XT/3) (n=224)				**Supra-annular valves (CoreValve, Evolut R) (n=224)**			
Valve size (n)	EOAi (cm²/m²)	Moderate PPM (%)	Severe PPM (%)	Valve size (n)	EOAi (cm²/m²)	Moderate PPM (%)	Severe PPM (%)
23-mm (n=68)	0.88 ± 0.29	25 (36.8%)	12 (17.6%)	23-mm (n=1)	0.86	0 (0.0%)	0 (0.0%)
26-mm (n=106)	0.98 ± 0.32	32 (30.2%)	11 (10.4%)	26-mm (n=67)	1.03 ± 0.30	14 (20.9%)	6 (9.0%)
29-mm (n=50)	0.88 ± 0.30	13 (26.0%)	12 (24.0%)	29-mm (n=109)	1.00 ± 0.26	31 (28.4%)	4 (3.7%)
				31-mm (n=40)	0.91 ± 0.24	13 (32.5%)	4 (10.0%)
				34-mm (n=7)	0.93 ± 0.33	2 (28.6%)	1 (14.3%)
BSA = body surface area; EOAi = Effective orifice area index; PPM = Prosthesis-patient mismatch.							

Central Figure

A. Prosthesis-patient mismatch

B. Sub-group analysis

Group	Balloon-expandable Valve (SAPIEN THV/XT/3) mismatch/total (%)	Self-expandable Valve (CoreValve, Evolut R) mismatch/total (%)	SEV vs BEV Odds ratio (95% CI)	Odds ratio (95% CI)	p-value
All patients					
PPM	105/224 (46.9%)	75/224 (33.5%)	0.57 (0.39-0.84)		0.004
Severe PPM	35/224 (15.6%)	15/224 (6.7%)	0.39 (0.21-0.73)		0.003
Annulus area					
<430mm²					
PPM	45/88 (51.1%)	27/93 (29.0%)	0.39 (0.21-0.72)		0.003
Severe PPM	12/88 (13.6%)	8/93 (8.6%)	0.60 (0.23-1.54)		0.284
≥430mm²					
PPM	60/136 (44.1%)	48/131 (36.6%)	0.73 (0.45-1.20)		0.214
Severe PPM	23/136 (16.9%)	7/131 (5.3%)	0.28 (0.11-0.67)		0.004
Body surface area					
>1.83m²					
PPM	70/115 (60.9%)	48/106 (45.3%)	0.53 (0.31-0.91)		0.021
Severe PPM	26/115 (22.6%)	9/106 (8.5%)	0.32 (0.14-0.71)		0.006
≤1.83m²					
PPM	35/109 (32.1%)	27/118 (22.9%)	0.63 (0.35-1.13)		0.120
Severe PPM	9/109 (8.3%)	6/118 (5.1%)	0.60 (0.20-1.73)		0.341

Favors SEV   Favors BEV

38

Figure 1.

Cardiovascular mortality at 1 year according to PPM

Figure 2.

NYHA functional class at 1 year according to PPM