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# 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 > 1.83$m^2$ (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).

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## 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

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## 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.

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## 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

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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 ≥ 30 $kg/m^2$).

**Data collection and clinical follow-up**

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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

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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,

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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

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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

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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**).

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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 (≥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 (≤1.83$m^2$). 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**

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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

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PPM.

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## 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.

Accepted author's manuscript. JACC. Cardiovascular interventions.
Publisher DOI: https://doi.org/10.1016/j.jcin.2019.07.027

## References

1. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation 1978;58:20-4.

2. Pibarot P, Weissman NJ, Stewart WJ et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort--a analysis. J Am Coll Cardiol 2014;64:1323-34.

3. Little SH, Oh JK, Gillam L et al. Self-Expanding Transcatheter Aortic Valve Replacement Versus Surgical Valve Replacement in Patients at High Risk for Surgery: A Study of Echocardiographic Change and Risk Prediction. Circ Cardiovasc Interv 2016;9:e003426.

4. Herrmann HC, Daneshvar SA, Fonarow GC et al. Prosthesis-Patient Mismatch in 62,125 Patients Following Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. J Am Coll Cardiol 2018;72:2701-2711.5.

Badano LP, Pavoni D, Musumeci S et al. Stented bioprosthetic valve hemodynamics: is the supra-annular implant better than the intra-annular? J

Heart Valve Dis 2006;15:238-46.

6. Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur J Cardiothorac Surg 2012;42:S45-60.

7. Thyregod HGH, Steinbrüchel DA, Ihlemann N et al. No clinical effect of prosthesis–patient mismatch after transcatheter versus surgical aortic valve replacement in intermediate- and low-risk patients with severe aortic valve stenosis at mid-term follow-up: an analysis from the NOTION trial †. Eur J Cardiothorac Surg 2016;50:721-728.

8. Zorn GL, 3rd, Little SH, Tadros P et al. Prosthesis-patient mismatch in high-risk patients with severe aortic stenosis: A randomized trial of a self-expanding prosthesis. J Thorac Cardiovasc Surg 2016;151:1014-22, 1023.e1-3.

9. Tzikas A, Piazza N, Geleijnse ML et al. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the medtronic CoreValve system in patients with aortic stenosis. Am J Cardiol 2010;106:255-60.

10. Ewe SH, Muratori M, Delgado V et al. Hemodynamic and clinical impact of prosthesis-patient mismatch after transcatheter aortic valve implantation. J Am Coll Cardiol 2011;58:1910-8.

11. Mauri V, Kim WK, Abumayyaleh M et al. Short-Term Outcome and Hemodynamic Performance of Next-Generation Self-Expanding Versus Balloon-Expandable Transcatheter Aortic Valves in Patients With Small Aortic Annulus: A Multicenter Propensity-Matched Comparison. Circ Cardiovasc Interv 2017;10:e005013.

12. Miyasaka M, Tada N, Taguri M et al. Incidence, Predictors, and Clinical Impact of Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement in Asian Patients: The OCEAN-TAVI Registry. J Am Coll Cardiol Intv 2018;11:771-780.

13. Theron A, Pinto J, Grisoli D et al. Patient-prosthesis mismatch in new generation trans-catheter heart valves: a propensity score analysis. European heart journal cardiovascular Imaging 2018;19:225-233.

14. Nombela-Franco L, Ruel M, Radhakrishnan S et al. Comparison of

hemodynamic performance of self-expandable CoreValve versus balloon-expandable Edwards SAPIEN aortic valves inserted by catheter for aortic stenosis. Am J Cardiol 2013;111:1026-33.

15. Yashima F, Yamamoto M, Tanaka M et al. Transcatheter aortic valve implantation in patients with an extremely small native aortic annulus: The OCEAN-TAVI registry. Int J Cardiol 2017;240:126-131.

16. Daneshvar SA, Rahimtoola SH. Valve prosthesis-patient mismatch (VP-PM): a long-term perspective. J Am Coll Cardiol 2012;60:1123-35.

17. Head SJ, Mokhles MM, Osnabrugge RLJ et al. The impact of prosthesis–patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J 2012;33:1518-1529.

18. Fallon JM, DeSimone JP, Brennan JM et al. The Incidence and Consequence of Prosthesis-Patient Mismatch After Surgical Aortic Valve Replacement. Ann Thorac Surg 2018;106:14-22.

19. Bakhtiary F, Schiemann M, Dzemali O et al. Impact of patient-prosthesis

mismatch and aortic valve design on coronary flow reserve after aortic valve replacement. J Am Coll Cardiol 2007;49:790-6.

20. Tasca G, Brunelli F, Cirillo M et al. Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement. Ann Thorac Surg 2005;79:505-10.

21. Sannino A, Grayburn PA. Mitral regurgitation in patients with severe aortic stenosis: diagnosis and management. Heart 2018;104:16-22.

22. Vincentelli A, Susen S, Le Tourneau T et al. Acquired von Willebrand Syndrome in Aortic Stenosis. N Engl J Med 2003;349:343-349.

23. Mannacio VA, De Amicis V, Di Tommaso L, Iorio F, Vosa C. Influence of prosthesis-patient mismatch on exercise-induced arrhythmias: a further aspect after aortic valve replacement. J Thorac Cardiovasc Surg 2009;138:632-8.

24. Ruel M, Rubens FD, Masters RG et al. Late incidence and predictors of persistent or recurrent heart failure in patients with aortic prosthetic valves. J Thorac Cardiovasc Surg 2004;127:149-59.

25. Moon MR, Pasque MK, Munfakh NA et al. Prosthesis-patient mismatch after

aortic valve replacement: impact of age and body size on late survival. Ann Thorac Surg 2006;81:481-8; discussion 489.

26. Mohty D, Dumesnil JG, Echahidi N et al. Impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: influence of age, obesity, and left ventricular dysfunction. J Am Coll Cardiol 2009;53:39-47.

27. Flameng W, Herregods MC, Vercalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. Circulation 2010;121:2123-9.

28. Hahn RT, Leipsic J, Douglas PS et al. Comprehensive Echocardiographic Assessment of Normal Transcatheter Valve Function. J Am Coll Cardiol Img 2019;12:25-34.

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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 (≥430mm$^2$), 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 (≤1.83m$^2$). 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).

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**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).

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## 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 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 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 |

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| | | | | | | |
|---|---|---|---|---|---|---|
| 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 ($mm^2$) | 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 ($mm^3$) | 348.4 ± 322.1 | 319.3 ± 332.6 | 0.223 | 338.1 ± 317.7 | 334.8 ± 356.8 | 0.918 |
| LVOT calcium ($mm^3$) | 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.

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| **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 |

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| | | | |
|---|---|---|---|
| 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 |

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**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.

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**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 ($cm^2/m^2$) | Moderate PPM (%) | Severe PPM (%) | Valve size (n) | EOAi ($cm^2/m^2$) | 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.

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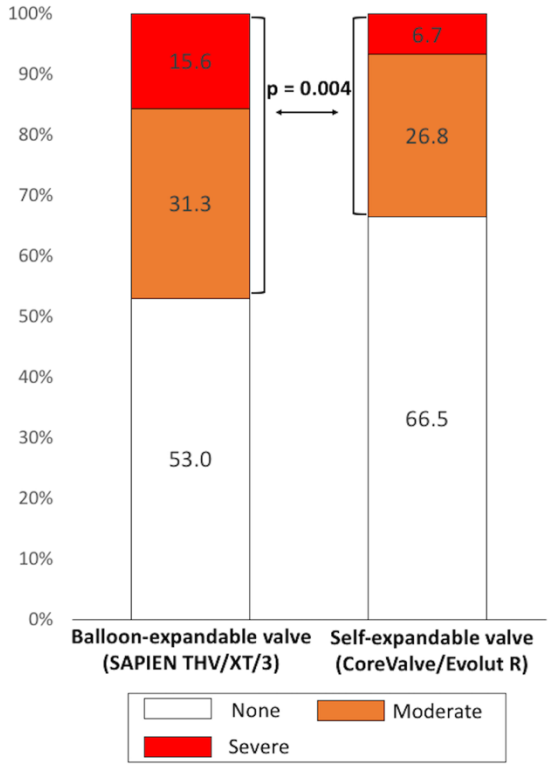
## Central Figure




**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) | 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 |

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**Figure 1.**

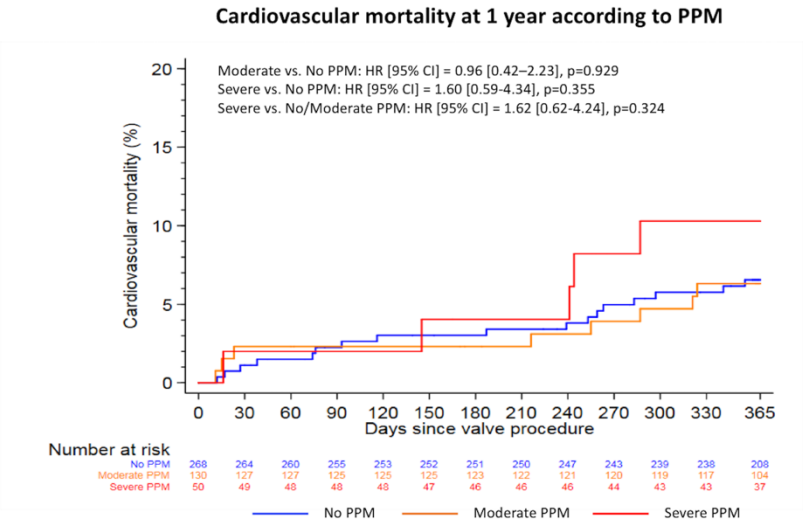


**Figure 2.**