Received: 13 July 2019 | Revised: 5 August 2020 | Accepted: 8 August 2020

DOI: 10.1002/ccd.29227

ORIGINAL STUDIES

WILEY

Prevalence, predictors, and outcomes of patient prosthesis mismatch in women undergoing TAVI for severe aortic stenosis: Insights from the WIN-TAVI registry

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Abbreviations: BMI, body mass index; iEOA, indexed effective orifice area; PPM, patient prosthesis mismatch; TAVI, transcatheter aortic valve intervention.

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Abstract

Objective: To evaluate the incidence, predictors and outcomes of female patients with patient-prosthesis mismatch (PPM) following transcatheter aortic valve intervention (TAVI) for severe aortic stenosis (AS).

Background: Female AS TAVI recipients have a significantly lower mortality than surgical aortic valve replacement (SAVR) recipients, which could be attributed to the potentially lower PPM rates. TAVI has been associated with lower rates of PPM compared to SAVR. PPM in females post TAVI has not been investigated to date.

Methods: The WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry is a multicenter registry of women undergoing TAVR for severe symptomatic AS. Two hundred and fifty patients with detailed periprocedural and follow-up echocardiographic investigations were included in the WIN-TAVI echocardiographic sub-study. PPM was defined as per European guidelines stratified by the presence of obesity.

Results: The incidence of PPM in our population was 32.8%. Patients with PPM had significantly higher BMI (27.4 ± 6.1 vs. 25.2 ± 5.0, p = .002), smaller sized valves implanted (percentage of TAVI ≤23 mm 61% vs. 29.2%, PPM vs. no PPM, p < .001) and were more often treated with balloon expandable valves (48.3 vs. 32.5%, p < .001) rather than self expanding ones (26.3 vs. 52.8%, <.001). BMI (OR = 1.08; 95%CI 1.02–1.14, p = .011) and valve size ≤23 mm (OR = 3.00 95%CI 1.14–7.94, p = .027) were the only independent predictors of PPM. There was no significant interaction between valve size and valve type (p = .203). No significant differences were observed in 1-year mortality or major adverse cardiovascular events.

Conclusions: PPM in females undergoing TAVI occurs in one third of patients. BMI and valve size ≤23 mm are independent predictors. Larger registries are required to determine the impact of PPM on future clinical outcomes.

KEYWORDS
females, outcomes, patient-prosthesis mismatch, TAVI

1 | INTRODUCTION

The concept of patient prosthesis mismatch (PPM) was first described by Rahimtoola in 1978: "Mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve."[1] This concept was revisited by Pibarot et al[2] who suggested the process of selecting the appropriate sized prosthesis using the indexed effective orifice area (iEOA), derived from the EOA of the prosthesis and the body surface area of the patient. Pibarot et al proposed avoiding an iEOA less than 0.85 cm^2/m^2 to prevent PPM. This is based on the steep increase in the mean pressure gradient whenever iEOA falls below this cut off. PPM is considered to be haemodynamically insignificant if the iEOA is >0.85 cm^2/m^2, moderate if between 0.65 and 0.85 cm^2/m^2, and severe if <0.65 cm^2/m^2. However, for obese patients (body mass index [BMI] ≥30 kg/m^2) lower criteria may be more appropriate, given the hyperdynamic cardiac output state.[3] Indeed new definitions of PPM were introduced in the 2016 European Guidelines for obese patients with BMI over 30.[4,5]

In a recent meta-analysis[6] PPM was seen in 35% of patients undergoing transcatheter aortic valve implantation (TAVI), a figure

TABLE 1 Baseline demographics, comorbidities, echocardiographic, and CT parameters in the two groups

Variable	PPM = 1, N = 82 (32.8%)	PPM = 0, N = 168 (67.2%)	p-value
General demographics			
Age, years	82.3 ± 7.3	83.1 ± 6.2	.374
BMI, kg/m^2	27.4 ± 6.1	25.2 ± 5.0	.002
Height, cm	161 ± 5.4	157 ± 9.7	<.001
Weight, kg	71.4 ± 17.0	63.6 ± 15.2	<.001
Caucasian	76 (95.0%)	155 (97.5%)	.447
Past medical history			
Hypertension	62 (76.5%)	126 (75.4%)	.850
Diabetes	24 (29.3%)	38 (22.6%)	.253
Current smoker	2 (2.4%)	9 (5.4%)	.512
Previous MI	5 (6.1%)	19 (11.3%)	.189
Previous PCI	15 (18.3%)	46 (27.4%)	.116
Previous CABG	10 (12.3%)	15 (8.9%)	.401
Previous cardiac surgery	14 (17.1%)	26 (15.6%)	.761
Previous stroke	9 (11.1%)	19 (11.3%)	.963
Peripheral arterial disease	11 (13.4%)	14 (8.4%)	.220
COPD	17 (20.7%)	47 (28.0%)	.218
Home O_2	2 (2.5%)	5 (3.0%)	1.000
CKD	24 (29.3%)	60 (36.1%)	.282
Euroscore I	18.9 ± 12.8	19.2 ± 12.2	.854
STS score	8.7 ± 8.2	9.6 ± 9.4	.477
Porcelain aorta	4 (4.9%)	18 (10.7%)	.132
High surgical risk	71 (86.6%)	143 (85.1%)	.757
Pulmonary hypertension	21 (25.6%)	47 (28.1%)	.673
Prior pacemaker	6 (7.3%)	13 (7.7%)	.906
Anemia	26 (31.7%)	47 (28.3%)	.581
Baseline echocardiography			
LVEF<30%	3 (3.8%)	4 (2.4%)	.685
LVEF	54.6 ± 11.3	56.4 ± 10.5	.220
Echo annulus size	21.9 ± 2.2	21.7 ± 2.0	.557
Peak gradient	78.5 ± 18.3	77.1 ± 24.3	.682
Mean gradient	47.9 ± 11.5	48.6 ± 15.6	.730
AVA	0.7 ± 0.4	0.6 ± 0.2	.448
Baseline AR			.152
None	24 (31.2%)	50 (32.3%)	
Mild	35 (45.5%)	80 (51.6%)	
Moderate	14 (18.2%)	24 (15.5%)	
Severe	4 (5.2%)	1 (0.6%)	
Baseline MR			.266
None	12 (15.8%)	29 (18.1%)	
Mild	44 (57.9%)	72 (45.0%)	
Moderate	17 (22.4%)	53 (33.1%)	
Severe	3 (3.9%)	6 (3.8%)	
MSCT parameters (data available on 148 patients)			
Aortic annulus perimeter (mm)	64.9 ± 21.5	71.6 ± 23.5	.159
Aortic annular calcification			.801

(Continues)

TABLE 1 (Continued)

Variable	PPM = 1, N = 82 (32.8%)	PPM = 0, N = 168 (67.2%)	p-value
None	5 (8.1%)	8 (6.2%)	
Mild	4 (6.5%)	12 (9.2%)	
Moderate	29 (46.8%)	66 (50.8%)	
Severe	24 (38.7%)	44 (33.8%)	
Aortic root calcium score	711 ± 540	720 ± 532	.933
Minimal iliofemoral dimesion (mm)	7.3 ± 2.3	8.5 ± 2.9	.012
Coronary angiography			
Number of coronary vessels diseased			.354
0	35 (64.8%)	78 (62.4%)	
1	14 (25.9%)	23 (18.4%)	
2	2 (3.7%)	12 (9.6%)	
3	3 (5.6%)	12 (9.6%)	
LMS disease	5 (10.6%)	9 (8.7%)	.765

Abbreviations: AR, aortic regurgitation; AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass surgery; CKD, chronic kindey disease; COPD, chronic obstructive pulmonary artery disease; iEOA, indexed estimated orifice area; LMS, left main stem; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; MSCT, mutlislice computed tomography; PCI, percutaneous coronary intervention; PPM, patient-prosthesis mismatch.

TABLE 2 Female specific characteristics

Variable	PPM = 1, N = 82 (32.8%)	PPM = 0, N = 168 (67.2%)	p-value
Hx of pregnancy	63 (76.8%)	111 (66.1%)	.083
Gestational diabetes	1 (1.7%)	0 (0.0%)	.365
Gestational hypertension	2 (3.4%)	2 (2.0%)	.623
Age at menopause	49.2 ± 5.6	50.0 ± 4.4	.289
History of HRT use	5 (7.1%)	4 (2.7%)	.150
Hx of gynecolofical Ca	1 (1.3%)	6 (3.7%)	.432
Hx of gynecologic surgery	9 (11.3%)	28 (17.0%)	.241
Hx of breast Ca	6 (8.1%)	14 (8.9%)	.838
Hx of osteoporosis	17 (23.3%)	23 (15.2%)	.140

Abbreviations: Ca, cancer; HRT, hormonal replacement therapy; Hx, history; iEOA, indexed estimated orifice area; PPM, patient prosthesis mismatch.

significantly lower to the one seen in patients undergoing surgical aortic valve replacement (SAVR) (OR 0.23;95%CI 0.07–0.79). This finding may be related to differences in TAVI valve design, such as the absence of a sewing ring and the supra-annular location of the neo valve in some of the TAVI valves. Although the annulus is not prepared by excising calcium, as is done in surgery, transcatheter valves are associated with a larger EOA and iEOA, and lower peak as well as mean transprosthetic gradients.[7-17]

Large surgical registries and a recent meta-analysis have demonstrated an association between PPM and decreased long-term survival.[18-20] Female gender was found to be a predictor of PPM in a recent literature review.[21] A predisposition of female patients to PPM was demonstrated. This effect of PPM on survival, however, was not shown in a recent meta-analysis of TAVI trials.[6] This finding, however, needs to be interpreted cautiously given the much shorter follow up times. Of interest, recent reports[22] point toward an association between severe PPM with subclinical valve thrombosis.

In a meta-analysis of patients with aortic stenosis (AS),[23] among females, TAVI recipients had a significantly lower mortality than SAVR recipients, at 1 year (OR 0.68; 95%CI 0.50–0.94) and at 2 years (OR 0.74; 95%CI 0.58–0.95). One of the suggested mechanisms for the increased survival amongst females treated with TAVI was the lower PPM rates which could facilitate greater recovery in left ventricular systolic function.[9,16,24]

In the current study we aim to investigate the prevalence of PPM, its predictors and associated outcomes in females undergoing TAVI included in the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry.

2 | METHODS

The WIN-TAVI registry (NCT01819181) is an international, multicenter, prospective, observational registry of women undergoing TAVR at

19 European and North American centers treated with commercially available and approved TAVR devices and delivery systems for the treatment of severe symptomatic AS. Details of the registry and eligibility criteria have been described in previous publications.[25] Out of the total of 1,019 patients, 250 patients who had detailed periprocedural and follow-up echocardiographic investigations were included in the WIN TAVI echocardiographic sub-study. PPM was defined[4,5] as

- moderate if iEOA 0.85–0.66 and severe if iEOA ≤0.65 in patients with BMI <30 kg/m^2
- moderate if iEOA 0.70–0.56 and severe if iEOA ≤0.55 in patients with BMI ≥30 kg/m^2

All patients underwent multislice computed tomography (MSCT) in their participating centre. Reporting of echocardiographic and MSCT parameters was performed at each participating centre.

2.1 | Endpoints

The primary endpoint was Valve Academic Research Consortium (VARC)-2 early safety (at 30 days); this is a composite of all-cause mortality, stroke, life-threatening bleeding, acute kidney injury (Stages 2 and 3), coronary artery obstruction, major vascular complication, and valve-related dysfunction requiring repeat procedure

TABLE 3 Procedural parameters in patients with and without patient prosthesis mismatch

Variable	PPM = 1, *N* = 82 (32.8%)	PPM = 0, *N* = 168 (67.2%)	*p*-value
Type of valve inserted			<.001
Edwards S3	22 (27.5%)	26 (16.0%)	
Edwards XT	17 (21.3%)	28 (17.2%)	
Evolut R	6 (7.5%)	16 (9.8%)	
Corevalve	15 (18.8%)	70 (42.9%)	
Direct flow	10 (12.5%)	5 (3.1%)	
Portico	0 (0.0%)	2 (1.2%)	
Lotus	9 (11.3%)	16 (9.8%)	
ACURATE neo	1 (1.3%)	0 (0.0%)	
Valve type			<.001
Balloon expandable	39 (48.8%)	54 (33.1%)	
Self-expanding	21 (26.3%)	86 (52.8%)	
Others	20 (25.0%)	23 (14.1%)	
Valve size			<.001
20 mm	1 (1.2%)	0 (0.0%)	
23 mm	49 (59.8%)	49 (29.2%)	
25 mm	7 (8.5%)	13 (7.7%)	
26 mm	19 (23.2%)	67 (39.9%)	
27 mm	2 (2.4%)	2 (1.2%)	
29 mm	4 (4.9%)	36 (21.4%)	
31 mm	0 (0.0%)	1 (0.6%)	
Valve ≤23 mm	50 (61.0%)	49 (29.2%)	<.001
Paravalvular AR post TAVI			.898
None	29 (55.8%)	37 (51.4%)	
Mild	21 (40.4%)	32 (44.4%)	
Moderate	2 (3.8%)	3 (4.2%)	
Paravalvular AR at 6/12			1.000
None	13 (46.4%)	24 (49.0%)	
Mild	14 (50.0%)	23 (46.9%)	
Moderate	1 (3.6%)	2 (4.1%)	
New pacemaker	11 (13.4%)	18 (10.7%)	.531
Major vascular complications	9 (11.0%)	15 (8.9%)	.606
Life threatening bleeding	2 (2.4%)	12 (7.1%)	.154

Abbreviations: AR, aortic regurgitation; iEOA, indexed estimated orifice area; PPM, patient prosthesis mismatch.

(BAV, TAVI, or SAVR).[26] Secondary endpoints included 1-year all cause mortality, cardiovascular mortality, stroke and the composites death or stroke, and major adverse cardiovascular events (death, MI, or stroke).

2.1.1 | Statistical analysis

All continuous variables were tested for normality using the Kolmogorov–Smirnov test. Categorical data are presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. Continuous variables are presented as mean ± *SD* or medians and interquartile range and were compared using Student's *t* test or Wilcoxon signed rank test. Time-to-event curves were represented using Kaplan–Meier methods. Using logistic regression methods, we generated a multivariable model for predictors of PPM. Variables that were significantly different in the two PPM groups in the univariable analysis (Tables 1-3) were included in the regression model ($p < .05$). Computed tomography (CT) parameters were not included in the model due to large numbers of missing data that would weaken the model.

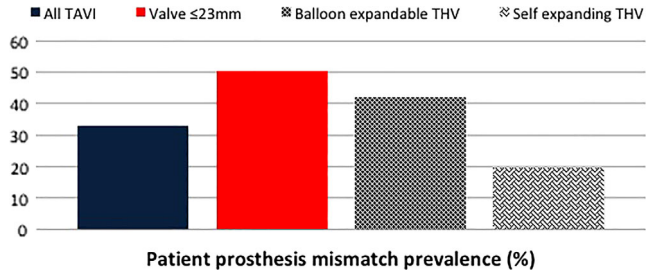

FIGURE 1 Incidence of patient prosthesis mismatch in various groups. Balloon expandable transcatheter heart valves (THV) include all the Edwards valves (S3, XT) and self-expanding THV all the Medtronic iterations (CoreValve and Evolut R) [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

Incidence of PPM in our population was 32.8% (82/250 patients). Severe PPM was seen in 18 (7.2%) patients. Baseline demographic, echocardiographic, CT, and procedural characteristics in patients with and without PPM are shown in Table 1.

3.1 | Baseline characteristics

3.1.1 | Demographics, risk factors, and past medical history

Female patients with PPM had a significantly higher BMI (27.4 ± 6.1 vs. 25.2 ± 5, $p = .002$). Hypertension, diabetes, smoking status, previous stroke, peripheral arterial disease, chronic kindey disease, previous cardiac surgery, or CABG did not differ between the two groups (Table 1). Both groups had similar Euroscore I and STS scores.

TABLE 4 Multivariable regression model identifying independent predictors for patient-prosthesis mismatch

Model excluding interaction between valve type and valve size≤23 mm				
	OR	**95% confidence interval**		***p*-value**
BMI	1.077	1.02	1.14	.009
Valve type				
Balloon expandable	Ref			
Self-expanding	0.669	0.32	1.39	.281
Others	1.552	0.70	3.42	.276
Valve ≤23 mm	3.385	1.77	6.46	<.001
Model including interaction between valve type and valve size ≤23 mm				
	OR	**95% confidence interval**		***p*-value**
BMI	1.075	1.02	1.14	.011
Valve type				
Balloon expandable	Ref			
Self-expanding	0.498	0.18	1.40	.185
Others	1.994	0.62	6.40	.246
Valve ≤23 mm	3.003	1.14	7.94	.027
Valve type * valve ≤23 mm				.203 (interaction test)

Abbreviations: BMI, body mass index; OR, odds ratio.

3.1.2 | Echocardiographic data

Baseline echocardiographic data pre-TAVI were similar in the two groups (Table 1). Baseline left ventricular ejection fraction was 54.6 ± 11.3 and 56.4 ± 10.5 in the PPM and no PPM groups, respectively (p = .220). Peak and mean gradients alongside aortic valve area were all similar in the two groups.

3.1.3 | CT parameters

CT measured aortic annulus perimeter (64.9 ± 21.5 PPM vs. 71.6 ± 23.5 mm no PPM, p = .159) and aortic annular calcification were similar in the two groups. There was a smaller minimal iliofemoral dimension in patients with PPM (7.3 ± 2.3 vs. 8.5 ± 2.9 mm, p = .012) (Table 1).

No significant differences were seen in terms of coronary artery disease severity.

3.2 | Female specific characteristics

With regards to female specific characteristics, there was a small trend for increase in history of pregnancy amongst patients with PPM post TAVI (Table 2). Gestational diabetes and hypertension, age at menopause, history of HRT use, history of gynecological or breast Ca and osteoporosis did not differ between the two groups.

TABLE 5 One year follow-up echocardiographic parameters

	PPM = 1, N = 82 (32.8%)	PPM = 0, N = 168 (67.2%)	p-value
LVEF	57.8 ± 9.1	58.5 ± 8.6	.650
Peak AV gradient (mmHg)	24.5 ± 13.0	19.8 ± 10.5	.040
Mean AV gradient (mmHg)	14.0 ± 5.9	10.7 ± 5.4	.001
Aortic paravalvular regurgitation			.898
None	29 (55.8%)	37 (51.4%)	
Mild	21 (40.4%)	32 (44.4%)	
Moderate	2 (3.8%)	3 (4.2%)	

Abbreviations: AV, aortic valve; LVEF, left ventricular ejection fraction; PPM, patient prosthesis mismatch.

TABLE 6 Clinical outcomes in the two groups at 30-days and 1-year

	PPM = 1, N = 82 (32.8%)	PPM = 0, N = 168 (67.2%)	p-value
30-day outcomes	*No. of events (%)*		
All-cause death	0 (0.0%)	3 (1.8%)	.225
All stroke	0 (0.0%)	2 (1.2%)	.322
Life-threatening bleeding	9 (11.0%)	19 (11.3%)	.948
Acute kidney injury	2 (2.4%)	3 (1.8%)	.728
Coronary artery obstruction	1 (1.2%)	2 (1.2%)	.984
Major vascular complication	9 (11.0%)	14 (8.3%)	.494
Valve-related dysfunction	0 (0.0%)	0 (0.0%)	n.a
VARC2 early safety	21 (25.6%)	43 (25.6%)	.888
1-year outcomes			
Death	4 (4.9%)	14 (8.5%)	.296
Cardiovascular death	2 (2.5%)	12 (7.4%)	.122
Stroke	4 (4.9%)	5 (3.0%)	.480
MACE (death, MI, stroke)	6 (7.3%)	19 (11.5%)	.289
Death or stroke	6 (7.3%)	19 (11.5%)	.289
Arrhythmia or conduction disturbance	16 (19.5%)	36 (21.4%)	.717

Abbreviations: MACE, major adverse cardiovascular endpoints; MI, myocardial infarction.

3.3 | Procedural parameters

PPM was associated with significantly higher rates of balloon expandable valve implantation (48.8 vs. 33.1%) and significantly lower rates of self-expanding valve implantation (26.3 vs. 52.8%, $p < .001$) (Table 3). Patients in the PPM group were more frequently implanted smaller sized valves (61 vs. 29.2% had valve size ≤23 mm, $p < .001$) (Table 3, Figure 1 and Supplementary Table). There were no significant differences in rates of new pacemaker, moderate paravalvular leak, major vascular or bleeding complications.

3.4 | Predictors of PPM

In the multivariable regression model independent predictors of PPM included raised BMI (per unit increase OR 1.08, (95%CI: 1.02–1.14) and valve size equal to or under 23 mm (≤23 vs. >23, OR 3, 95%CI 1.14–7.94, $p = .027$). There was no significant interaction between valve type and valve size $p = .203$. (Table 4).

3.5 | Follow-up

At 1-year echocardiographic follow-up there were significantly increased peak and mean gradients across the aortic valve in the PPM group (Table 5).

No significant differences were seen in VARC-2 early safety endpoint at 30-days (25.6% PPM group vs. 25.6% no PPM group, $p = .888$) or in any of the clinical outcomes at 1 year (Table 6).

4 | DISCUSSION

In the current study, prevalence of PPM in this all-female TAVI cohort was 32.8%. Independent predictors of PPM included larger BMI and valve size ≤23 mm, whereas there was no interaction between valve size and valve type. There does not appear to be any significant difference in 1-year clinical outcomes in the two groups; however, these results should be interpreted cautiously given the small sample size of our study and relatively short-term follow-up.

Despite several studies demonstrating that PPM incidence is reduced when patients are treated with TAVI compared to SAVR,[6,9] in the current cohort nearly one third of females treated with TAVI appear to have at least moderate PPM. This finding is important as PPM has the potential implication of reduced LV hypertrophy regression and persistence of residual LV afterload[11,27,28] which impacts on coronary flow reserve.[9] PPM post-TAVI has been associated with less regression of LV hypertrophy, LV diastolic dysfunction, LV filling pressure (measured by E/e'), less improvement in LV systolic function (LVEF and myocardial strain), and less reduction of left atrial volume.[11,28,29]

Interestingly, however, there may be a differential impact of PPM on mortality in patients treated with TAVI and those with SAVR.[6,9,13,27,29] In the study by Pibarot et al[9] an increased mortality was seen in surgical patients with PPM but not in TAVI patients. In that particular study, as in the current study, TAVI PPM patients had significantly higher BMI, a previous shown independent predictor of PPM.[6] Body surface area greater than 1.88 m^2 independently predicted severe PPM with satisfactory sensitivity (0.71) and specificity (0.70).[30] A higher BMI has been shown to be a powerful independent predictor of improved 2-year survival post TAVI in the PARTNER-A TRIAL.[31] Such a higher BMI was not seen in PPM patients post surgery.[9] Furthermore, indexing the EOA to the patient's BSA may overestimate PPM severity in obese individuals.[32] The higher than expected valve gradient can be due, at least in part, to patient's supranormal cardiac output and high flow state due to morbid obesity.[33] In the current study we did not identify any survival benefit in females with no PPM, concurring with the study from Pibarot et al[9]; however, the small patient numbers and reduced power limit our ability to answer this question with certainty.

Smaller valve size (≤23 mm) was associated with PPM in our cohort. Given that the CT annulus perimeter was not significantly different in the two groups, and assuming optimal sizing, this can be explained by valve choice (balloon expandable vs. self expanding). This highlights the importance of optimal valve sizing based on CT parameters[34] and raises the question of a potential benefit in implantation of supra-annular self-expanding valves in female patients with small aortic annuli. In the randomized CHOICE study,[35] implantation of balloon-expandable valves was associated with significantly reduced oversizing percent and significantly higher mean transvalvular gradients (8.9 mmHg; 95% CI, 8.3–9.7 vs. 6.6 mmHg; 95%CI, 6.0–7.3; $p < .001$). In the same study, despite having a significantly larger MSCT calculated aortic annulus perimeter, the balloon-expandable group ended up with a significantly higher % of 23 mm valves (9.9 vs 1.7%, $p < .001$). Our results agreed with the large retrospective TVT registry from Herrman et al on 62,125 TAVI patients which confirmed small valve size (≤23 mm) to be a significant predictor of severe PPM.[36]

Previous studies have shown a hemodynamic benefit of TAVR over SAVR in the subset of patients with small aortic annulus.[9] In high-risk patients with severe AS and a small aortic annulus (diameter < 20 mm), TAVI compares favorably with currently available surgical options, and may provide a reasonable alternative to conventional AVR in elderly patients with a small aortic annulus.[37] In a recent meta-analysis,[23] female AS patients treated with TAVI had improved survival to those treated with SAVR and one of the potential explanations was the presence of a larger iEOA post procedure. Therefore, TAVI valve size and type selection becomes more important in females who are known to have smaller size aortic annuli than their male counterparts.[38,39]

In the current study no differences were observed in new pacemaker rates, paravalvular leak, or major adverse cardiovascular events in the PPM versus no PPM groups, probably secondary to improvements in valve design and increasing operator experience. This is in line with other studies which have shown no significant differences in terms of major adverse cardiovascular, cerebrovascular and valve-

related events, cardiac-related hospitalizations, improvement in functional status, NYHA class, and self-assessed health state between patients with PPM and those without PPM after TAVI.[11,13,27,28,40,41]

4.1 | Study limitations

One of the main limitations of the current study is the small sample size. However, this represents the largest echocardiographic study on PPM in female patients undergoing TAVI implantation. Another limitation is the solely echocardiographic definition of PPM and absence of a central echocardiographic core-lab. A recent study by Mooney et al,[42] however, showed that even though the incidence of PPM was reduced when EOA was estimated using left ventricular outflow tract measured from CT ($iEOA_{CT}$), this did not associate with outcomes. Furthermore, in that study it was the echo—$iEOA_{TTE}$ and not the CT—$iEOA_{CT}$ that correlated with LV mass regression, posing questions on the clinical value of the need for $iEOA_{CT}$. The small proportion of patients with severe PPM (7.2%) may be the reason for the lack of differences in clinical outcomes at 1-year. In the large TVT registry it was only the severe PPM mismatch group that exhibited increased mortality at 1 year.[36] However, even in patients with moderate PPM, differences in clinical outcomes may only become evident at a later time (>5 years), due to faster valve degeneration, as shown in surgical bioprosthetic valve PPM registries.[9] Detailed longitudinal data on LV mass, diastolic dysfunction, LV filling pressures, and LA size were lacking in the current study. PPM may have a particular impact on these variables and should be the focus of future longitudinal echocardiographic studies.

4.2 | Conclusions

PPM in female patients with AS undergoing TAVI is seen in almost one third of cases. Main predictors include raised BMI and small valve size. Appropriate sizing, and potentially use of self-expanding valves, which allows for the use of larger valves in smaller anatomies, may contribute to reduce the incidence of PPM. Even though in our study at least moderate PPM was not associated with clinical endpoints, results should be validated in larger, adequately powered cohorts.

ACKNOWLEDGEMENTS

The authors would like to thank the Society for Cardiovascular Angiography and Interventions for supporting the launch of this study.

CONFLICT OF INTEREST

Dr. P. P. has served as a consultant for Boston Scientific, Medtronic, and Abbott Vascular. Dr. J. M. has received lecture fees from Edwards Lifesciences, Abbott, Vascular, Biotronik, Lilly/Daiichi-Sankyo, Terumo, and Bristol-Myers Squibb; and institutional research grant support from Abbott Vascular and Edwards Lifesciences. Dr. T. L. has served as a proctor for Edwards Lifesciences. Dr. V. F. P. has served as a proctor for Medtronic. Dr. G. S. has received proctor fees for Edwards Lifesciences; and speaker fees from Direct Flow. Dr. N. M. M. has received research grant support from Boston Scientific, Edwards Lifesciences, Medtronic, St. Jude Medical, Abbott Vascular, and Claret Medical. Dr. N. D. has received proctor fees from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott Vascular. Dr. Mikhail is the director of the Imperial Valve and Cardiovascular Course. Dr. S. S. has served on the Speakers Bureau for Boston Scientific, Abbott Vascular, Cardiovascular Systems Inc., and TriReme. Dr. C. F. N. has received speaker fees from Edwards Lifesciences, Direct Flow Medical, Medtronic, and Claret; is a minor shareholder with Claret; and has served as an advisor for Direct Flow Medical. Dr. R. M. has received institutional research grant support from Eli Lilly/Daiichi-Sankyo Inc., AstraZeneca, The Medicines Company, Bristol-Myers Squibb, OrbusNeich, Beth Israel Deaconess, and Bayer; has served as a consultant for Boston Scientific, Cardiovascular Systems Inc., Medscape, and Shanghai BraccoSine Pharmaceutical; has received institutional advisory board funding from Bristol-Myers Squibb; has received institutional funding from Claret Medical; owns equity in Claret Medical and Elixir Medical; has served on the executive committee for Janssen Pharmaceuticals and Osprey Medical; has served on the data safety monitoring board for Watermark Research Partners; and has a spouse who has served as a consultant for Abiomed and the Medicines Company. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. Circulation. 1978;58(1):20-24.
2. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis-patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol. 2000;36(4):1131-1141.
3. Kappetein AP, Head SJ, Généreux 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(5):S45-S60.
4. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the inter-American Society of

Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17(6):589-590.
5. Pibarot P, Magne J, Leipsic J, et al. Imaging for predicting and assessing prosthesis-patient mismatch after aortic valve replacement. JACC Cardiovasc Imaging. 2019;12(1):149-162.
6. Takagi H, Umemoto T, Group A. Prosthesis-patient mismatch after transcatheter aortic valve implantation. Ann Thorac Surg. 2016;101(3):872-880.
7. Ghanta RK, Kron IL. Patient-prosthesis mismatch: surgical aortic valve replacement versus transcatheter aortic valve replacement in high risk patients with aortic stenosis. J Thorac Dis. 2016;8(10):E1441-E1443.
8. Dayan V, Vignolo G, Soca G, Paganini JJ, Brusich D, Pibarot P. Predictors and outcomes of prosthesis-patient mismatch after aortic valve replacement. JACC Cardiovasc Imaging. 2016;9(8):924-933.
9. 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(13):1323-1334.
10. Rodés-Cabau J, Pibarot P, Suri RM, et al. Impact of aortic annulus size on valve hemodynamics and clinical outcomes after transcatheter and surgical aortic valve replacement: insights from the PARTNER trial. Circ Cardiovasc Interv. 2014;7(5):701-711.
11. Bleiziffer S, Hettich I, Hutter A, et al. Incidence and impact of prosthesis-patient mismatch after transcatheter aortic valve implantation. J Heart Valve Dis. 2013;22(3):309-316.
12. Kukucka M, Pasic M, Dreysse S, et al. Patient-prosthesis mismatch after transapical aortic valve implantation. Ann Cardiothorac Surg. 2012;1(2):172-175.
13. Van Linden A, Kempfert J, Blumenstein J, et al. Prosthesis-patient mismatch after transcatheter aortic valve implantation using the Edwards SAPIEN™ prosthesis. Thorac Cardiovasc Surg. 2013;61(5):414-420.
14. Kamperidis V, van Rosendael PJ, de Weger A, et al. Surgical sutureless and transcatheter aortic valves: hemodynamic performance and clinical outcomes in propensity score-matched high-risk populations with severe aortic stenosis. JACC Cardiovasc Interv. 2015;8(5):670-677.
15. Reardon MJ, Adams DH, Kleiman NS, et al. 2-year outcomes in patients undergoing surgical or self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol. 2015;66(2):113-121.
16. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 2009;53(20):1883-1891.
17. Morita S. Aortic valve replacement and prosthesis-patient mismatch in the era of trans-catheter aortic valve implantation. Gen Thorac Cardiovasc Surg. 2016;64(8):435-440.
18. Rao V, Jamieson WR, Ivanov J, Armstrong S, David TE. Prosthesis-patient mismatch affects survival after aortic valve replacement. Circulation. 2000;102(19 suppl 3):5-9.
19. Walther T, Rastan A, Falk V, et al. Patient prosthesis mismatch affects short- and long-term outcomes after aortic valve replacement. Eur J Cardiothorac Surg. 2006;30(1):15-19.
20. Takagi H, Yamamoto H, Iwata K, Goto SN, Umemoto T. A meta-analysis of effects of prosthesis-patient mismatch after aortic valve replacement on late mortality. Int J Cardiol. 2012;159(2):150-154.
21. Bilkhu R, Jahangiri M, Otto CM. Patient-prosthesis mismatch following aortic valve replacement. Heart. 2019;105(Suppl 2):s28-s33.
22. Yanagisawa R, Tanaka M, Yashima F, et al. Early and late leaflet thrombosis after Transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2019;12(2):e007349.
23. Panoulas VF, Francis DP, Ruparelia N, et al. Female-specific survival advantage from transcatheter aortic valve implantation over surgical aortic valve replacement: meta-analysis of the gender subgroups of randomised controlled trials including 3758 patients. Int J Cardiol. 2018;250:66-72.
24. Clavel MA, Webb JG, Rodes-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation. 2010;122(19):1928-1936.
25. Chieffo A, Petronio AS, Mehilli J, et al. Acute and 30-day outcomes in women after TAVR: results from the WIN-TAVI (Women's INternational Transcatheter aortic valve implantation) real-world registry. JACC Cardiovasc Interv. 2016;9(15):1589-1600.
26. 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. Eur Heart J. 2012;33(19):2403-2418.
27. 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(18):1910-1918.
28. Thyregod HG, 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(4):721-728.
29. Poulin F, Yingchoncharoen T, Wilson WM, et al. Impact of prosthesis-patient mismatch on left ventricular myocardial mechanics after transcatheter aortic valve replacement. J Am Heart Assoc. 2016;5(2):e002866. https://doi.org/10.1161/JAHA.115.002866.
30. Kukucka M, Pasic M, Dreysse S, et al. Patient-prosthesis mismatch after transapical aortic valve implantation: incidence and impact on survival. J Thorac Cardiovasc Surg. 2013;145(2):391-397.
31. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012;366(18):1686-1695.
32. 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(1):39-47.
33. Airhart S, Medvedev I, Dean LS. Relative prosthesis-patient mismatch after transcatheter aortic valve replacement: the impact of morbid obesity. Catheter Cardiovasc Interv. 2017;90(2):341-345.
34. Tzikas A, Schultz CJ, Piazza N, et al. Assessment of the aortic annulus by multislice computed tomography, contrast aortography, and transthoracic echocardiography in patients referred for transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2011;77(6):868-875.
35. Abdel-Wahab M, Mehilli J, Frerker C, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA. 2014;311(15):1503-1514.
36. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. J Am Coll Cardiol. 2018;72(22):2701-2711.
37. Kalavrouziotis D, Rodés-Cabau J, Bagur R, et al. Transcatheter aortic valve implantation in patients with severe aortic stenosis and small aortic annulus. J Am Coll Cardiol. 2011;58(10):1016-1024.
38. Buellesfeld L, Stortecky S, Kalesan B, et al. Aortic root dimensions among patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2013;6(1):72-83.
39. Chieffo A, Petronio AS, Mehilli J, et al. 1-year clinical outcomes in women after transcatheter aortic valve replacement: Results from the First WIN-TAVI Registry. JACC Cardiovasc Interv. 2018;11(1):1-12.
40. 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(2):255-260.
41. Zorn GL, 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(4):1014-1022.
42. Mooney J, Sellers SL, Blanke P, et al. CT-defined prosthesis-patient mismatch downgrades frequency and severity, and demonstrates no association with adverse outcomes after transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2017;10(15):1578-1587.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Panoulas VF, Chandrasekhar J, Busi G, et al. Prevalence, predictors, and outcomes of patient prosthesis mismatch in women undergoing TAVI for severe aortic stenosis: Insights from the WIN-TAVI registry. *Catheter Cardiovasc Interv*. 2020;1–11. https://doi.org/10.1002/ccd.29227