International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Clinical outcomes in women and men with small aortic annuli undergoing transcatheter aortic valve implantation: A multicenter, retrospective, propensity score-matched comparison

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ARTICLE INFO

Keywords:
TAVI
Prosthesis-patient mismatch
Small annuli
Women
Sex

ABSTRACT

Background: Sex-specific characteristics in patients with aortic stenosis and small annuli undergoing transcatheter aortic valve implantation (TAVI) might affect clinical outcomes and hemodynamics.

Methods: TAVI-SMALL 2 international retrospective registry included 1378 patients with severe aortic stenosis and small annuli (annular perimeter <72 mm or area < 400 mm2) treated with transfemoral TAVI at 16 high-volume centers between 2011 and 2020. Women ($n = 1233$) were compared with men ($n = 145$). One-to-one propensity score (PS) matching resulted in 99 pairs. Primary endpoint was incidence of all-cause mortality. Incidence of pre-discharge severe prosthesis-patient mismatch (PPM) and its association with all-cause mortality

Abbreviations: BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; EOA, effective orifice area; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; PPM, prosthesis-patient mismatch; PS, propensity score; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

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https://doi.org/10.1016/j.ijcard.2023.02.044
Received 17 December 2022; Received in revised form 5 February 2023; Accepted 26 February 2023
Available online 28 February 2023

were investigated. Binary logistic and Cox regression were performed to adjust the treatment effect for PS quintiles.
Results: Incidence of all-cause mortality at a median follow-up of 377 days did not differ between sex in the overall (10.3 vs. 9.8%, $p = 0.842$) and PS-matched (8.5 vs. 10.9%, $p = 0.586$) populations. After PS matching, pre-discharge severe PPM was numerically higher in women vs. men (10.2 vs. 4.3%), even though no evidence of a difference was found ($p = 0.275$). Within the overall population, women with severe PPM suffered a higher incidence of all-cause mortality when compared to those with less than moderate PPM (log-rank $p = 0.024$) and less than severe PPM ($p = 0.027$).
Conclusions: No difference in all-cause mortality at medium-term follow-up was observed between women and men with aortic stenosis and small annuli undergoing TAVI. Incidence of pre-discharge severe PPM was numerically higher in women than men, and it was associated with increased all-cause mortality in women.

1. Introduction

Non-rheumatic, calcific aortic stenosis is the most prevalent valvular heart disease in high-income countries [1]. Although men are at increased risk overall, most of patients over 80 years old or with small aortic annuli are women [2,3].

Women are less likely than men to undergo aortic valve replacement and are often older and with more advanced disease at time of surgery [4]. Also, they have increased operative mortality and morbidity after surgical aortic valve replacement (SAVR) as well as a higher 1-year mortality when compared with men [5]. Among unmeasured confounders, prosthesis-patient mismatch (PPM) due to small annular dimensions may contribute to worse short-term and long-term outcomes [6].

Women with aortic stenosis who are treated, are more likely to undergo transcatheter aortic valve implantation (TAVI) compared with men [4]. Although no inter-sex differences in device success are present among patients undergoing TAVI, women do suffer from higher incidence of major vascular complications and major bleeding events [7]. Although the consensus is that sex disparities in terms of mid- and long-term outcomes after TAVI are in favor of women [8], more recent evidence found no sex-specific differences in survival [9], while older women were shown to have an increased risk of mortality than men [10].

Considering that TAVI is currently performed more commonly than SAVR [11], it is important to recognize whether particular scenarios might yield different clinical outcomes across sexes.

Hemodynamics might differ in women and men with aortic stenosis and small annuli undergoing TAVI, and sex-specific outcomes have not been addressed so far in such a population. The aim of this study was to assess clinical outcomes and trans-valvular hemodynamics in women and men with small aortic annuli undergoing TAVI.

2. Methods

2.1. Study design and definitions

The observational, retrospective TAVI-SMALL 2 registry was conducted between June 2011 and April 2020 at 16 high-volume centers, and included 1378 patients with severe native aortic valve stenosis and small aortic annuli treated with transfemoral implantation of current-generation self-expanding (Evolut R and Evolut Pro, Medtronic, Minneapolis, Minnesota; Acurate neo, Boston Scientific, Marlborough, Massachusetts; Portico, Abbott Vascular, Santa Clara, California) and balloon-expandable valves (Sapien 3, Edwards Lifesciences, Irvine, California). This study complied with the Declaration of Helsinki and was approved by local ethics committees. All patients provided written informed consent for the procedure and subsequent data collection based on local practice and/or local institutional review board approval. Inclusion criteria were implantation via transfemoral route of current-generation transcatheter heart valves in native aortic stenosis in patients with small aortic annuli (defined as an annular area < 400 mm2 and/or annular perimeter <72 mm on computed tomography). Exclusion criteria were valve-in-valve procedures, TAVI for pure aortic regurgitation and lack of pre-procedural computed tomography data. Local multidisciplinary heart teams evaluated all patients and confirmed the indications for TAVI. All patients underwent pre-procedural screening by means of clinical assessment, echocardiography, and computed tomography. Aortic annular, leaflet, and left ventricular outflow tract (LVOT) calcifications were classified and graded using a semiquantitative scoring system, as previously described [12]. Valve type and size selection, as well as implantation technique and subsequent antithrombotic therapy, were left to the discretion of the treating physician at each center.

The rationale of the study was to evaluate the impact of sex on clinical outcomes and transvalvular hemodynamics, so that primary analyses were performed according to sex. Additional analyses were conducted per degree of PPM, which was defined following Valve Academic Research Consortium-3 updated endpoint definition [13]. Effective orifice area (EOA) was calculated at pre-discharge echocardiography with the continuity equation method; stroke volume was estimated via LVOT diameter (outer-to-outer border of the valve stent) and velocity-time integral measured just underneath the ventricular margin of the valve stent [13]. Primary endpoint of the study was all-cause mortality. Incidence of pre-discharge severe PPM and its association with all-cause mortality were also investigated.

2.2. Statistical analysis

Continuous variables are reported as mean ± standard deviation or median ± interquartile range, and were compared using Student's *t*-test or the Mann-Whitney U or Wilcoxon test in case of 2-group comparisons on the basis of normality of data distribution, verified using the Shapiro-Wilk test. In case of continuous variable comparisons between >2 groups, analysis of variance was performed; Bartlett's test for equal variances was performed to assess if the variances were comparable between groups, and Bonferroni correction was applied to adjust for multiple comparisons. Categorical variables are reported as percentage (number) and were compared using the chi-square test without Yates' correction for continuity or the Fisher exact test, as appropriate. Survival curves for all-cause mortality were constructed with the use of Kaplan–Meier estimates and compared with the log-rank test. Propensity score (PS) matching was performed to adjust for differences in potential confounders that may lead to bias in estimation of treatment outcomes [14,15]. A PS was calculated for each patient to estimate the propensity towards belonging to a specific group (women vs. men). This was done by means of a non-parsimonious multivariate logistic regression including the following covariates: age, body mass index, body surface area, hypertension, chronic obstructive pulmonary disease, coronary artery disease, prior myocardial infarction, peripheral vascular disease or previous percutaneous transluminal angioplasty, prior coronary artery bypass grafting (CABG), previous pacemaker (PM) or implantable cardioverter-defibrillator (ICD) implantation, New York Heart Association (NYHA) functional class III or IV, Society of Thoracic Surgeons Predicted Risk of Mortality score and aortic annular perimeter. The C statistic for the PS model was 0.853, indicating good discrimination. A 1-to-1 nearest neighbor matching algorithm without replacement (caliper 0.20) was performed to identify PS-matched pairs. Rubin's B (22.6) and R (0.81) values, and 4.2% mean bias among covariates demonstrated high standard matching [16]. The pseudo-R^2 value was 0.283 ($p < 0.001$) before matching and very low (0.009, $p =$ 0.999) after matching, thus confirming good quality of the match and adequate balancing of covariate distribution between matched groups [17]. Primary and secondary endpoints were compared between the women and men groups in both the overall and PS-matched cohorts. In the overall cohort, binary logistic and Cox regression were also performed to adjust the treatment effect for the PS quintiles; results are presented as adjusted odds ratio (ORadj) or adjusted hazard ratio (HRadj) with 95% confidence interval (CI).

Clinical follow-up was censored at the date of death or latest available follow-up. Data for patients lost to follow-up were censored at the time of the last contact. A two-sided p value <0.05 was considered statistically significant. Statistical analyses were performed using Stata version 13.0 (StataCorp, College Station, Texas).

3. Results

3.1. Study population and clinical features

Among 1378 patients with aortic stenosis and small aortic annuli treated with transfemoral TAVI, 1233 (89.5%) were women and 145 (10.5%) were men. Baseline characteristics of patients stratified according to sex are reported in **Supplemental Table 1**. Compared with men, women were older (83.1 ± 6.0 vs. 80.9 ± 7.4 years, $p < 0.001$) and had lower weight, height and body surface area (all $p < 0.001$). Comorbidities, including dyslipidemia, chronic obstructive pulmonary disease, peripheral artery disease, coronary artery disease, previous myocardial infarction, percutaneous coronary intervention, CABG and PM or ICD, were more common among men (all $p < 0.025$), except for hypertension that was more common in women ($p = 0.006$). Women were more often in NYHA III or IV functional class at baseline (68.5% vs. 57.9%, $p = 0.016$), while no significant differences between groups were observed in terms of diabetes mellitus, atrial fibrillation and Society of Thoracic Surgeons Predicted Risk of Mortality ($p = 0.285$, 5.7 ± 4.0% overall). The 1-to-1 PS matching analysis resulted in 99 matched pairs of women and men, and no significant difference in any baseline characteristic was evident (**Supplemental Table 1**).

3.2. Echocardiographic and computed tomography features

Baseline echocardiographic and computed tomography features are shown in **Supplemental Table 2**. Left ventricular ejection fraction in the whole cohort was 59.2 ± 10.7% and did not differ between groups ($p = 0.266$), while tricuspid annular plane systolic excursion was higher in women (21.0 ± 3.6 vs. 20.0 ± 3.4, $p = 0.047$). Bicuspid aortic valves were more frequent in men, with borderline significance (4.0 vs. 7.6%, $p = 0.064$). Lower baseline EOA at echocardiography was present in women ($p = 0.046$), with no differences in mean and maximum aortic valve gradients. At computed tomography, women had smaller mean annular diameter (21.2 ± 1.28 vs. 21.8 ± 1.26, $p < 0.001$), perimeter (66.7 ± 4.32 vs. 68.4 ± 3.84, $p < 0.001$) and area (348.4 ± 34.2 vs. 364.6 ± 32.5, $p < 0.001$). In addition, women had shorter distance to ostia of both right coronary artery ($p < 0.001$) and left main ($p = 0.003$) and had smaller diameter of sinotubular junction (25.8 ± 2.63 vs. 27.0 ± 2.82, $p < 0.001$) and sinus of Valsalva (28.5 ± 2.33 vs. 30.7 ± 3.03, $p < 0.001$). No inter-sex difference in ascending aorta diameter was present ($p = 0.258$). There was no difference between sexes in terms of proportion of patients with porcelain aorta ($p = 0.393$), severe LVOT ($p = 0.217$) or annular calcification ($p = 0.610$), while men had a higher proportion of severe leaflet calcification (17.8 vs. 31.2%, $p = 0.001$). Among PS-matched pairs (**Supplemental Table 2**), women had shorter right coronary artery and left main ostia heights (both $p = 0.037$) and smaller sinotubular junction ($p = 0.053$) and sinuses of Valsalva diameters ($p < 0.001$).

3.3. Procedural features

Procedural data are shown in Table 1. The type of valve implanted in women and men was not different when assessed according to mechanism of valve expansion ($p = 0.697$), position of leaflets with respect to native annulus ($p = 0.809$) or single valve type ($p = 0.587$ for Evolut R/Pro, $p = 0.633$ for Acurate *neo*, $p = 0.410$ for Portico and $p = 0.697$ for Sapien 3). Of note, a higher proportion of valves 25 mm or less in diameter were implanted in women (54.1 vs. 35.9%, $p < 0.001$), even though no differences in oversizing according to both perimeter (15.3 ± 8.5 vs. 16.1 ± 10.1, $p = 0.319$) and area (36.8 ± 20.9 vs. 38.3 ± 24.0, $p = 0.424$) were observed. While predilation was performed in 41.9% of cases in the overall sample, with no inter-sex differences ($p = 0.566$), postdilation was more common in men (26.8 vs. 36.5%, $p = 0.013$). No significant difference in annular rupture was observed according to sex. In PS-matched cohorts, differences in the proportion of patients implanted with valves of 25 mm or less in diameter ($p = 0.010$) and postdilation ($p = 0.099$) persisted, and oversizing ≥15% was more common in men vs. women according to both perimeter (63.6 vs. 45.4%, $p = 0.010$) and area (84.4 vs. 71.7%, $p = 0.025$).

3.4. Procedural and clinical outcome

Clinical and procedural outcomes are reported in Table 1. In the whole cohort, pre-discharge mean and maximum aortic valve gradients were 9.3 ± 4.8 and 16.5 ± 8.2, respectively, and were similar in women and men ($p = 0.880$ and $p = 0.978$, respectively). Similarly, indexed EOA (1.00 ± 0.30 vs. 1.00 ± 0.27, $p = 0.857$) and incidence of both moderate PPM (21.5 vs. 26.1%, $p = 0.825$) and severe PPM (6.3 vs. 4.3%, $p = 0.788$) did not differ significantly between groups (Fig. 1). Compared with men, women had similar incidence of more than mild (9.2 vs. 11.0%, $p = 0.518$) and more than moderate (1.2 vs. 0%, $p = 0.381$) paravalvular leak. Also, proportion of patients requiring permanent PM (12.2 vs. 13.9%, $p = 0.561$) or second valve implantation (1.7 vs. 1.4%, $p = 1.000$) was similar between groups. The proportion of patients with any or major vascular complication was higher among women than men (14.9 vs. 6.9%, $p = 0.020$ and 5.2 vs. 0.7%, $p = 0.011$, respectively). Similarly, Bleeding Academic Research Consortium (BARC) major bleeding was more common in women vs. men (6.3 vs. 2.1%, $p = 0.039$), as shown in Fig. 1.

Incidence of all-cause mortality at median follow-up of 377 (interquartile range 168–700) days was similar in women and men (10.3 vs. 9.8%, $p = 0.842$), and time-to-event analysis (Fig. 2) showed no difference in all-cause mortality between groups (5.7 vs. 4.0% at 1-year, log-rank $p = 0.942$). No difference between sexes was observed in terms of cardiovascular mortality ($p = 0.307$), myocardial infarction ($p = 0.375$), transient ischemic attack or stroke ($p = 0.789$), acute kidney injury ($p = 1.000$) and hospitalization for heart failure ($p = 0.734$).

After adjustment for PS quintiles, all-cause mortality was similar in women and men (adjusted hazards ratio 1.22, 95% CI 0.60–2.50). The risk of moderate or more PPM was increased among women to different degrees according to BMI adjustment ($p = 0.036$ and $p = 0.109$ without and with BMI adjustment, respectively), while risk of severe PPM did not vary according to sex ($p = 0.173$ and $p = 0.310$ without and with BMI adjustment). The increased risk of any and major vascular complications ($p = 0.096$ and $p = 0.101$) and of BARC major bleeding ($p = 0.072$) had borderline significance. Sex did not have a significant impact on other outcomes at follow-up (**Supplemental Table 3**).

Women remained at increased risk of any and major vascular complications ($p = 0.102$ and $p = 0.091$, respectively) and BARC major bleeding ($p = 0.065$) with borderline significance after PS matching (Fig. 1). Of note, significant differences in mean aortic valve gradient (11.3 ± 5.7 vs. 9.2 ± 4.9 mmHg, $p = 0.011$), indexed EOA (0.86 ± 0.25

Table 1
Post-procedural characteristics and follow-up according to sex before and after propensity score matching.

Characteristic	Overall (*n* = 1378)	Women (*n* = 1233)	Men (*n* = 145)	P value	Overall (*n* = 198)	Women (*n* = 99)	Men (n = 99)	P value
Procedural								
Valve size 25 mm or less	52.2 (719)	54.1 (667)	35.9 (52)	**<0.001**	45.4 (90)	54.5 (54)	36.4 (36)	**0.010**
Oversizing by perimeter	15.0 ± 8.7	15.3 ± 8.5	16.1 ± 10.1	0.319	15.7 ± 9.4	14.6 ± 8.9	16.9 ± 9.7	**0.087**
Oversizing by perimeter ≥15%	54.1 (745)	53.4 (659)	59.3 (86)	0.237	54.5 (108)	45.4 (45)	63.6 (63)	**0.010**
Oversizing by area	36.9 ± 21.2	36.8 ± 20.9	38.3 ± 24.0	0.424	36.4 ± 23.2	33.5 ± 23.2	39.5 ± 22.7	**0.085**
Oversizing by area ≥ 15%	82.6 (1138)	82.6 (1019)	82.1 (119)	0.863	78.3 (155)	71.7 (71)	84.8 (84)	**0.025**
Oversizing ≥15%	54.3 (748)	53.7 (662)	59.3 (86)	0.260	50.5 (100)	39.4 (39)	61.6 (61)	**0.002**
Valve type								
Evolut R/Pro	54.4 (750)	54.2 (668)	56.5 (82)	0.587	53.0 (105)	48.5 (48)	57.6 (57)	0.200
Acurate Neo	12.3 (170)	12.4 (153)	11.7 (17)	0.633	9.6 (19)	9.1 (9)	10.1 (10)	0.809
Portico	12.5 (172)	12.7 (157)	10.3 (15)	0.410	14.6 (29)	15.1 (15)	14.1 (14)	0.841
Sapien 3	20.7 (286)	20.7 (255)	21.4 (31)	0.697	22.7 (45)	27.3 (27)	18.2 (18)	0.127
Supra-annular valve	66.8 (920)	66.6 (821)	68.3 (99)	0.809	62.6 (124)	57.6 (57)	67.7 (67)	0.142
Self-expanding valve	79.2 (1092)	79.3 (978)	78.6 (114)	0.697	77.3 (123)	72.7 (72)	81.8 (81)	0.127
Pre-dilation	41.9 (573)	41.6 (509)	44.1 (64)	0.566	36.9 (73)	33.3 (33)	40.4 (40)	0.302
Post-dilation	27.8 (380)	26.8 (327)	36.5 (53)	**0.013**	31.0 (61)	25.5 (25)	36.4 (36)	**0.099**
Annular rupture	0.3 (4)	0.3 (4)	0	1.000	0.5 (1)	1.0 (1)	0	1.000
Pre-discharge								
Any vascular complication	14.0 (192)	14.9 (182)	6.9 (10)	**0.020**	12.2 (24)	16.2 (16)	8.2 (8)	0.102
Major vascular complication	4.7 (65)	5.2 (64)	0.7 (1)	**0.011**	3.1 (6)	5.0 (5)	1.0 (1)	**0.091**
Need for second valve implantation	1.7 (23)	1.7 (21)	1.4 (2)	1.000	3.0 (6)	4.0 (4)	1.0 (1)	0.445
Mean AV gradient, mmHg	9.3 ± 4.8	9.2 ± 4.8	9.3 ± 4.9	0.880	10.3 ± 5.3	11.3 ± 5.7	9.2 ± 4.9	**0.011**
Maximum AV gradient, mmHg	16.5 ± 8.2	16.5 ± 8.2	16.5 ± 7.7	0.978	16.9 ± 7.8	18.1 ± 8.2	16.0 ± 7.3	0.124
Indexed EOA, cm^2/m^2	1.00 ± 0.30	1.00 ± 0.30	1.00 ± 0.27	0.857	0.93 ± 0.27	0.86 ± 0.25	1.01 ± 0.26	**0.006**
Moderate or more PPM (non BMI-adjusted)	33.6 (211)	33.6 (188)	33.3 (23)	0.961	41.0 (39)	55.1 (27)	26.1 (12)	**0.004**
Moderate or more PPM	28.0 (176)	27.7 (155)	30.4 (21)	0.637	34.7 (33)	46.9 (23)	21.7 (10)	**0.010**
Moderate PPM (non BMI-adjusted)	25.0 (157)	24.9 (139)	26.1 (18)	0.825	28.4 (27)	36.7 (18)	19.6 (9)	**0.064**
Moderate PPM	22.0 (138)	21.5 (120)	26.1 (18)	0.382	27.4 (26)	36.7 (18)	17.4 (8)	**0.035**
Severe PPM (non BMI-adjusted)	8.6 (54)	8.8 (49)	7.2 (5)	0.822	12.6 (12)	18.4 (9)	6.5 (3)	0.122
Severe PPM	6.0 (38)	6.3 (35)	4.3 (3)	0.788	7.4 (7)	10.2 (5)	4.3 (2)	0.275
More than mild PVL	9.4 (107)	9.2 (93)	11.0 (14)	0.518	12.4 (22)	10.1 (9)	14.8 (13)	0.347
More than moderate PVL	1.1 (12)	1.2 (12)	0	0.381	0.6 (1)	1.1 (1)	0	0.319
New permanent PM	12.4 (169)	12.2 (149)	13.9 (20)	0.561	12.7 (25)	12.1 (12)	13.3 (13)	0.809
BARC major bleeding	5.9 (81)	6.3 (78)	2.1 (3)	**0.039**	4.0 (8)	7.1 (7)	1.0 (1)	**0.065**
Follow-up								
All-cause mortality	10.3 (129)	10.3 (116)	9.8 (13)	0.842	9.7 (18)	8.5 (8)	10.9 (10)	0.586
Cardiovascular mortality	3.4 (42)	3.6 (40)	1.5 (2)	0.307	4.3 (7)	5.9 (5)	2.6 (2)	0.446
Myocardial infarction	1.1 (12)	1.0 (10)	1.7 (2)	0.375	2.6 (4)	2.6 (2)	2.6 (2)	1.000
TIA/stroke	3.3 (36)	3.4 (33)	2.5 (3)	0.789	4.4 (7)	6.3 (5)	2.5 (2)	0.442
Acute kidney injury	2.9 (27)	3.0 (24)	2.8 (3)	1.000	3.4 (5)	5.3 (4)	1.4 (1)	0.367
Hospitalization for HF	6.2 (65)	6.1 (57)	6.9 (8)	0.734	6.4 (10)	5.1 (4)	7.7 (6)	0.746

Values are mean ± standard deviation or %(n). The values in **bold** represent differences between groups with $p < 0.100$.
AV = aortic valve; BARC = Bleeding Academic Research Consortium; BMI = body mass index; EOA = effective orifice area; HF = heart failure; PM = pacemaker; PPM = prosthesis patient mismatch; PVL = paravalvular leak; TIA = transient ischemic attack.

vs. 1.01 ± 0.26, $p = 0.006$), moderate PPM (36.7 vs. 17.4%, $p = 0.035$) and moderate or more PPM (46.9 vs. 21.7%, $p = 0.010$) arose when comparing PS-matched women vs. men, while incidence of severe PPM (10.2 vs. 4.3%, $p = 0.275$) was numerically more common among women (Fig. 1). Incidence of all-cause mortality remained similar in women vs. men (8.5 vs. 10.9%, $p = 0.586$). No difference in cardiovascular mortality, myocardial infarction, transient ischemic attack or stroke, acute kidney injury or hospitalization for heart failure was observed between groups.

3.5. Sex and PPM

Characteristics of patients with and without information on pre-discharge EOA according to sex are collected in **Supplemental Tables 4–7**. **Supplemental Tables 8–11** include baseline demographic, echocardiographic, computed tomography, procedural, post-procedural and follow-up characteristics of patients with information on pre-discharge EOA, stratified according to sex and degree of PPM. A total of 559 (45.3%) women and 69 (47.6%) men were included in this analysis. Women with moderate PPM and men with severe PPM were younger than those with lesser degree of PPM ($p = 0.017$ for women, both $p < 0.001$ for men) and a higher proportion of patients with moderate and severe PPM among both sexes was in NYHA functional class III or IV than those with less than moderate PPM (overall $p \leq 0.001$ for both sexes). Women with moderate and severe PPM had higher weight, height and BSA than those with less than moderate PPM (all overall $p < 0.001$). Differences were present in terms of proportion of patients with previous PM or ICD among women ($p = 0.042$) and with previous CABG among men ($p = 0.036$). No relevant differences were present in echocardiographic data, while women with moderate PPM had a smaller perimeter ($p < 0.001$) and proportion of patients with severe annular ($p = 0.010$) and LVOT ($p = 0.034$) calcifications than those with less than moderate PPM. Men with moderate PPM had smaller sinus of Valsalva diameter than those with less than moderate PPM ($p = 0.092$).

Among both women and men, patients with moderate and severe PPM had more valves 25 mm or less in diameter implanted (overall $p < 0.001$ and $p = 0.015$) and a lower degree of oversizing by area than in less than moderate PPM (overall $p < 0.001$ and $p = 0.049$). Women with moderate PPM and severe PPM had more balloon-expandable (overall $p < 0.001$) and less supra-annular valves (overall $p < 0.001$) implanted, and a similar trend was observed among men. Predilation and post-dilation were more common in women with less than moderate PPM than in those with moderate PPM ($p < 0.001$ and $p = 0.001$). Among

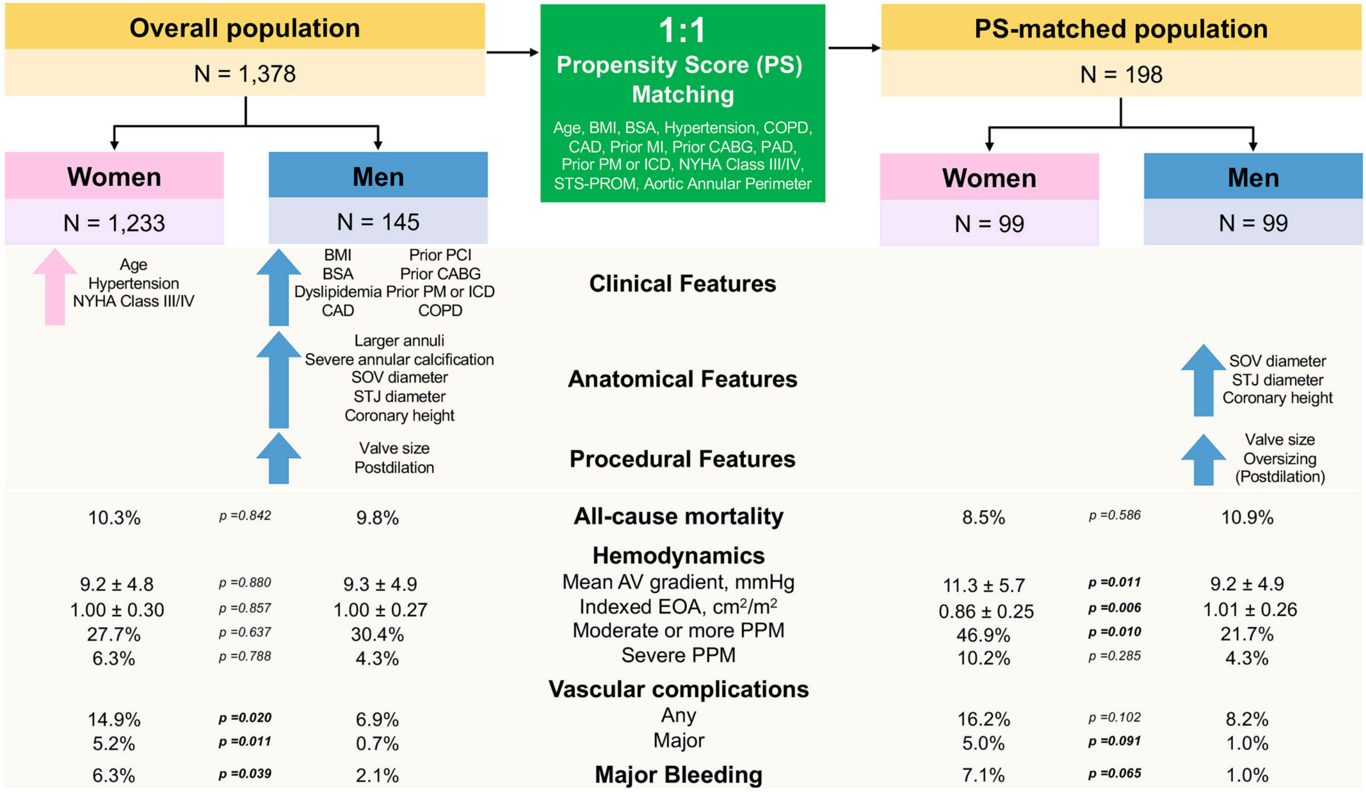

Fig. 1. Differences in baseline characteristics and outcomes according to sex in the overall and propensity score (PS)-matched populations. Characteristics reported next to upward pointing arrows are more represented in that group than in the other (that is women or men). AV = aortic valve, BMI = body mass index, BSA = body surface area, CABG = coronary artery bypass grafting, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, EOA = effective orifice area, ICD = implantable cardioverter defibrillator, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, PM = pacemaker, PPM = prosthesis-patient mismatch, SOV = sinus of Valsalva, STJ = sino-tubular junction.

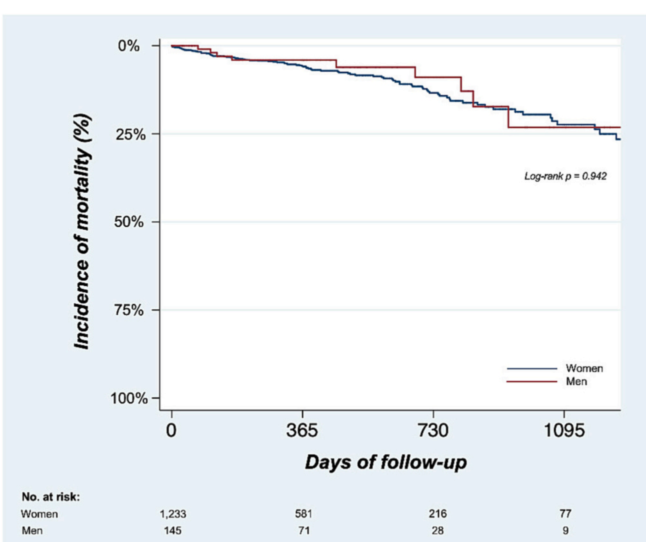

Fig. 2. Time-to-event analysis of all-cause mortality according to sex. No difference (log-rank $p = 0.942$) was observed between women and men at median follow-up of 377 days.

women, mean and maximum gradients were higher with moderate and severe PPM than less than moderate PPM (both overall $p < 0.001$), and the same was true when comparing moderate and less than moderate PPM in men (overall $p = 0.036$ and $p = 0.015$, respectively). All-cause mortality in women differed between groups at 1-year (overall $p = 0.028$), and was higher with severe PPM than in less than moderate PPM ($p = 0.008$). At time-to-event analysis (Fig. 3), women with severe PPM had increased risk of all-cause mortality when compared to those with less than moderate (log-rank $p = 0.024$) and less than severe PPM (log-rank $p = 0.027$). On the other hand, no difference between groups was evident among men (**Supplemental Table 11** and **Supplemental Fig. 1**), although underpowering for such outcome needs to be recognized.

4. Discussion

The main findings of the present study evaluating clinical outcomes and trans-valvular hemodynamics in women vs. men with small aortic annuli undergoing TAVI are as follows:

- Incidence of all-cause mortality at medium-term follow-up was similar in women and men;
- The proportion of women with severe PPM at discharge was numerically higher than that of men, even though evidence of a difference was not found in the entire population, after adjustment for PS quintiles and in the PS-matched cohort;
- Women with severe PPM had a higher incidence of all-cause mortality when compared to those with less than moderate PPM and less than severe PPM.

4.1. Clinical outcomes

Women were younger, smaller in size and often more symptomatic at baseline. As already described [3], hypertension was more common among women, while men suffered more often from chronic obstructive pulmonary, cerebrovascular, peripheral artery and coronary artery

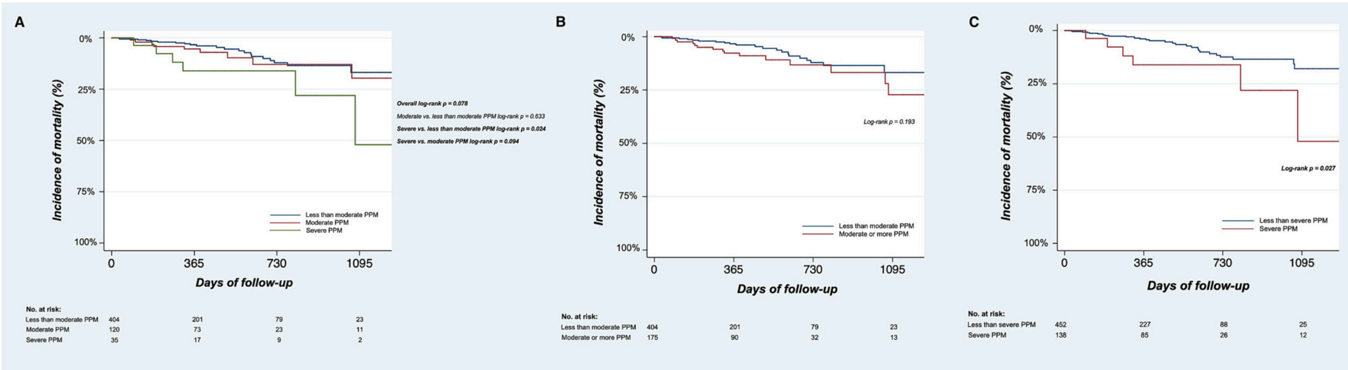

Fig. 3. Time-to-event analysis of all-cause mortality according to degree of PPM in women. Comparison of less than moderate vs. moderate vs. severe PPM (A), less than moderate vs. moderate or more PPM (B) and less than severe vs. severe PPM (C). PPM = prosthesis-patient mismatch.

disease, and had a higher proportion of PM or ICD implanted at baseline. The worse survival observed in women after SAVR has not been confirmed among patients undergoing TAVI. In this context, most of the evidence so far signals towards better outcomes in women as compared with men [8]. Given that women, when undergoing intervention, are more likely to be treated with TAVI [4], it is of utmost importance to investigate whether particular subsets might increase the risk of poor outcomes. Most patients with small aortic annuli treated with TAVI are women [18], and no difference in incidence of all-cause mortality at medium-term follow-up was observed in this study between sexes. An increased incidence of any and major vascular complications as well as major bleeding was observed in women both in the overall and PS-matched cohorts, even though with borderline significance in the latter setting. These results confirm evidence from previous studies pointing towards an increased risk of access-related complications with larger sheath-to-femoral artery ratio, which is possibly related to worse short-term mortality or major morbidity in older women when compared with men [7,10,19]. At the same time, the trend towards more complications in women vs. men of the same body size might suggest that additional factors such as the higher degree of vascular tortuosity described in women [7] might contribute to such outcomes, especially considering the lower size of valves implanted in women in the PS-matched population. Conversely, the improved long-term survival in women vs. men in the general population has been attributed, among others, to the lower rate of PVL deriving from the fact that men, often with larger annuli, tend to receive more undersized valves [8]. On the other hand, in our study, oversizing was similar among sexes in the overall population and lower in women within the PS-matched cohort, and no differences were noted between groups in terms of either more than mild or more than moderate PVL. Of note, the type of valve implanted did not differ between women and men both in the overall and PS-matched cohorts. In addition, the known higher proportion of atherosclerotic burden and comorbidities in men [20] was adequately buffered with PS matching. Overall, these factors might all have mitigated the survival advantage of women in this study including solely patients with small aortic annuli.

4.2. Incidence of severe PPM

Increased incidence of PPM after SAVR in women has been argued to be among possible confounders of worse outcomes with respect to men [6]. Although difference in incidence of severe PPM between sexes was not significant when assessing both overall and PS-matched populations, important considerations do arise from our results. In particular, it is important to acknowledge that women in the overall population had smaller annuli, less severely calcified leaflets, smaller valves implanted, same degree of oversizing and of moderate or more PPM as compared with men. On the other hand, women not only had smaller valves implanted, but also less oversizing and almost double the incidence of moderate or more PPM when considering patients with similar annular size from the PS-matched cohort. Even though statistical significance was not reached for the difference in incidence of severe PPM alone in the latter cohort, the large numerical difference, together with the strikingly smaller EOA and the higher mean aortic gradient observed in women need to be highlighted. Indeed, this signals that, considering patients with similar body size and annular dimensions, women are offered smaller valves than men. Overall, incidence of moderate or more PPM was similar to that previously described in women [21]. Of note, while performance of predilation did not vary across groups, post-dilation was more common in men both in the overall and in the PS-matched cohorts, and this needs to be taken into account since it is a known factor mitigating incidence of PPM [22]. Finally, height of coronary arteries ostia and diameter of sinotubular junction and sinuses of Valsalva remained smaller among women in the PS-matched cohort, in line with previous evidence, and likely contributed to our findings [14].

4.3. PPM and all-cause mortality

Notwithstanding the inconsistent evidence of clinical impact of PPM after TAVI in previous reports [23], recent evidence points to higher risk of events in patients with severe PPM when compared with those with less than severe PPM [22,24]. Particular subsets of patients, such as those with reduced left ventricular ejection fraction, have been shown to be more vulnerable to negative impact of PPM [25]. In addition, sex might modify the effect of PPM on outcomes. Indeed, when considering patients from PARTNER 3 study, severe PPM increased the risk of all-cause mortality when compared with less than moderate PPM among women, while this was not the case among men [26]. Similarly, women represented most of patients with severe PPM in our study, and had increased risk of all-cause mortality when compared with women with less than moderate PPM. No significant difference in outcomes was seen in men according to the degree of pre-discharge PPM, even though the low number of patients with severe PPM ($n = 3$), the few events and the medium-term follow-up might have influenced such results. Finally, it is important to recognize that although moderate PPM seems harmless among TAVI cohorts as of today, longer-term follow-up will be key to reveal any possible negative impact on outcomes [27]. Overall, it is likely that implementation of strategies to prevent PPM might reveal beneficial in terms both of clinical outcomes and bioprosthetic valve durability.

4.4. Study limitations

The observational nature of this study cannot exclude presence of selection or confounding bias. The study was retrospective, so that underreporting or missing echocardiographic and follow-up data might have occurred and might have influenced study findings. No independent clinical event adjudication committee was available for the study. No core-laboratory assessment of echocardiographic or computed tomography variables was available. The relatively low number of men included is another relevant limitation of the present analysis, since many comparisons could be underpowered.

5. Conclusions

Women and men had a similar incidence of all-cause mortality at medium-term follow-up among 1378 patients with aortic stenosis and small annulus from TAVI-SMALL 2 multicenter retrospective registry. Incidence of severe PPM was numerically higher in women among 198 PS-matched patients. Incidence of all-cause mortality was higher in women with severe PPM than in those with less than moderate or less than severe PPM. Clinical outcomes and impact of severe PPM after TAVI in women will need to be assessed at long-term follow-up in future large-scale, prospective studies.

Disclosures

Dr. Barbanti is consultant for Medtronic Inc., Boston Scientific and Edwards Lifesciences. Dr. Teles has received a received a research grant (to the institution) from Abbott. Dr. Adamo discloses speaker fees from Abbott and Medtronic. Dr. Taramasso discloses consultant or consultancy fees from Abbott Vascular, Edwards Lifescience, Boston Scientific, Medtronic, Shenqi Medical, VentriMend, Simulands, Occlufit, MTEx, MEDIRA, HI-D Imaging and CoreMedic. Dr. Stefanini has received a research grant (to the institution) from Boston Scientific; and has received speaking and consulting fees from B. Braun, Biosensors, and Boston Scientific. Dr. Kim is a proctor for Boston Scientific, Meril Lifesciences and Abbott; and has received speaking fees from Boston Scientific, Abbott, Medtronic, and Edwards. Dr. Maisano discloses Grant and/or Research Institutional Support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo; Consulting fees, Honoraria personal and Institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve, Occlufit, Simulands, Mtex.; Royalty Income/IP Rights Edwards Lifesciences; Shareholder position (including share options) of Cardiogard, Cardiovalve, Magenta, SwissVortex, Transseptalsolutions, 4Tech, Perifect. Dr. Tamburino has received speaking fees from Boston Scientific and Abbott. Dr. Van Mieghem has received institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, Abiomed, PulseCath BV, Daiichi Sankyo. Dr. Reimers has received speaking honoraria from Boston Scientific. Dr. Latib serves on the advisory boards of Medtronic, Boston Scientific and Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Sources of funding

none.

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Funding acquisition: NA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.02.044.

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