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Long-term Follow up after Transfemoral Transcatheter Aortic Valve Implantation in Lower Risk Patients Using the Balloon-Expandable Bioprosthesis: Gender-Dependent Outcomes

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ABSTRACT

Introduction: Long-term data on gender-related outcomes after transfemoral transcatheter aortic valve implantation (TF-TAVI) using newer generations heart valves in lower-risk patients are sparse. We aimed to evaluate gender-dependent long-term outcomes after TF-TAVI in lower-risk patients using the third-generation balloon expandable bioprosthesis.

Methods: Data of 103 patients undergoing TF-TAVI using the third-generation balloon expandable bioprosthesis were analyzed. We conducted up to six years follow up and performed comparison on gender basis: men (45 patients; 82 ± 4.7 years; STS Score 3.7 ± 1.6%) vs. women (58 patients; 83.2 ± 4.5 years; STS Score 3.6 ± 1.8%). The mean follow-up time was 30 months.

Results: Cardiovascular risk factors at baseline were similar, without significant differences between men and women. The 30-day mortality was 4.4% in men vs. 3.4% in women (P = 0.745). The 30-day stroke was 4.4% in men vs. 1.7% in women (P = 0.582). The major vascular injury rate and the pacemaker rate was 2.3% vs. 10.7% (P = 0.134) and 19.5% vs. 18.9% (P = 1) in men vs. women, respectively. There was a significant difference of mean long-term survival: men, 42.1 months [95%CI: 33.154–51.101] vs. women, 57.3 months [95%CI: 50.618–64.159], P = 0.015.

Conclusion: Although considerably more prone to procedural complications, women had a significantly long-term survival benefit after TF-TAVI in lower-risk patients despite similar baseline characteristics.

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INTRODUCTION

The expansion of transcatheter aortic valve implantation (TAVI) from the higher-risk to the lower-risk patient profile has been supported by the use of a newer transcatheter valve generation [Mack 2019]. Gender-related outcomes after TAVI have been a research focus since earlier TAVI experiences [Chandrasekhar 2016; Al-Lamee 2014; Buja 2013; Forrest 2016]. Common characteristics of all these studies with initial gender-related comparisons were high risk patient profile, significant higher cardiac-comorbidities in men, and use of early generation valve systems. Even in the recently published studies concerning gender-related outcomes using newer transcatheter valve generation, the trend of higher risk profile patients with distinct differences in cardiac-comorbidities between both genders at baseline is evident [Tarantini 2021; Wang 2019]. The relevant baseline differences between men and women might have affected the gender-related outcomes of earlier studies. In addition, data on long-term outcomes after TAVI in lower-risk patients are sparse. We aimed to evaluate the impact of gender on long-term outcomes after transfemoral (TF)-TAVI with the balloon expandable bioprosthesis focusing on patients with lower surgical risk.

METHODS

Data of 103 consecutive patients with symptomatic severe aortic stenosis undergoing TF-TAVI using the Edwards SAPIEN 3 (ES3) (Edwards Lifesciences Inc., Irvine, CA, USA) were analyzed. The appropriate size of the ES3 was determined with computed tomographic findings. We divided the cohort into two gender groups: men and women. We employed the VARC-2 criteria to define all clinical end points [Kappetein 2012]. We collected the data from hospital records and through telephone interviews with patients and referring physicians. The cause of death was obtained from the last physician involved in the patient's treatment. All patients provided informed consent for data collection, and approval for the study was obtained from the Ethics Committee of the Medical Faculty of the RUHR University, Bochum, Germany (Reg. No. 18-6339).

Table 1. Baseline characteristics. (STS, Society of Thoracic Surgery-Predicted Risk of Mortality score; PTCA/PCI, percutaneous transluminal coronary angioplasty/intervention)

	Men (*N* = 45) *N* = %	Women (*N* = 58) *N* = %	*P*-value
Age (years)	82 ± 4.7	83.2 ± 4.5	0.109
Body mass index (kg/m²)	28.6 ± 5.9	26.8 ± 4.5	0.213
STS-Score (%)	3.7 ± 1.6	3.6 ± 1.8	0.723
EuroScore II (%)	6.2 ± 2.8	5.5 ± 2.8	0.161
Hypertension	36 (80)	50 (86.2)	0.433
Pulmonary hypertension	6 (13.3)	13 (22.4)	0.309
Diabetes mellitus	11 (24.4)	18 (31)	0.513
Coronary artery disease	27 (60)	24 (41.4)	0.093
Myocardial infarction	9 (20)	8 (13.8)	0.433
Previous coronary bypass	9 (20)	5 (8.8)	0.147
PTCA/PCI	21 (46.7)	19 (32.8)	0.161
Left ventricular ejection fraction (%)	54.5± 9.5	57.3 ± 8	0.089
Peripheral artery disease	4 (8.9)	2 (3.4)	0.400
Central artery disease	4 (8.9)	2 (3.4)	0.400
Previous stroke	7 (15.6)	7 (12.1)	0.773
Chronic kidney failure	25 (55.6)	18 (31)	<0.05
Chronic obstructive pulmonary disease	8 (17.8)	3 (5.2)	0.055
Atrial fibrillation	20 (44.4)	26 (44.8)	1
Previous cardiac operation	8 (17.8)	6 (10.5)	0.387
Mitral regurgitation ≥ 2	12 (27.3)	10 (17.5)	0.331
Tricuspid regurgitation ≥ 2	6 (14)	5 (8.9)	0.525
Permanent pacemaker	6 (13.3)	8 (14)	1

Definition of early and long-term follow-up timing: The early follow-up timing was defined as the first 30 postoperative days. The long-term follow-up timing was defined as a time interval from the second postoperative month up to six years. The mean follow up was 30 months.

Primary and secondary endpoints: The primary endpoints of the study were the 30-day mortality and long-term survival. The secondary endpoints were the 30-day stroke and long-term freedom from stroke, the 30-day new permanent pacemaker implantation (PPI) and long-term freedom from PPI, procedural major vascular injury rates, paravalvular leakage (PVL) rates at discharge, and the new onset left bundle branch block (LBBB).

Statistics: Distributions of quantitative variables are described as means (± standard deviation) and compared with the use of the Mann–Whitney U test. Qualitative variables are summarized by count and percentage and compared with the use of the chi-square test or Fisher's exact test. The Kaplan-Meier method was used to calculate the mean survival time and group comparisons were made with the log-rank test. Data were managed with the SPSS statistical package, (IBM SPSS Statistics for Windows, Version 23.0.0.2 Armonk, NY: IBM Corp.). A two-sided P-value of less than 0.05 was considered to indicate statistical significance. No adjustment for multiple testing was performed. All analyses were considered to be exploratory.

RESULTS

Patient characteristics: Table 1 shows the baseline data of our patient population. (Table 1) The mean age in men was 82 ± 4.7 years, whereas in women, it was 83.2 ± 4.5 years; $P = 0.109$. The mean Society of Thoracic Surgery-Predicted Risk of Mortality (STS) score was 3.7 ± 1.6% in men and 3.6 ± 1.8% in women; $P = 0.723$. Interestingly, the baseline cardiovascular risk factors, such as hypertension, diabetes and pulmonary hypertension, were numerically higher in women. On the other hand, men exhibited higher incidence of cardiac-comorbidities. However, the differences were not significant. Chronic kidney failure rate was significantly higher in men ($P < 0.05$).

Procedural characteristics: All patients underwent TF-TAVI under conscious sedation. The implanted prosthesis

Table 2. Procedural characteristics and procedural complications. (AOA, aortic orifice area; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation)

	Men (*N* = 45) *N* = %	Women (*N* = 58) *N* = %	*P*-value
Baseline ΔPmax (mm Hg)	65 ± 23.6	80.3 ± 28.3	0.103
Baseline ΔPmean (mm Hg)	42.6 ± 16.4	49.7 ± 17.1	0.156
Baseline AOA (cm^2)	0.74 ± 0.2	0.67 ± 0.2	0.251
Procedure time (min)	72 ± 24.1	70.3 ± 28	0.660
Fluoroscopy time (min)	14.9 ± 5.6	12.4 ± 4.8	0.073
Radiation ($cGycm^2$)	4866 ± 3523	2648 ± 1564	<0.05
Contrast agent (ml)	162.9 ± 51.7	171.3 ± 56.9	0.703
Prosthesis diameter (mm)	26.9 ± 1.8	24.5 ± 1.7	<0.05
Predilatation	36 (90)	36 (80)	0.240
Postdilation	4 (10)	6 (13.3)	0.743
Intra-operative mortality	0 (0)	1 (1.7)	1
Life-threatening bleeding	1 (2.2)	2 (3.4)	0.768
Conversion to SAVR	1 (2.2)	1 (1.7)	1
Annulus rupture	0 (0)	1 (1.7)	1
Valve embolization	0 (0)	1 (1.7)	1
Re-TAVI	0 (0)	1 (1.7)	1
Left ventricle perforation	1 (2.2)	0 (0)	0.869
Major vascular complications	1 (2.3)	6 (10.7)	0.134
Paravalvular leakage ≥ 2	1 (2.2)	0 (0)	0.869

size was significantly smaller in women ($P < 0.05$). Radiation and fluoroscopy time was significantly higher among men ($P < 0.05$). The other procedural variables were almost identical in both groups. (Table 2)

Procedural complications: Women were clearly more prone to procedural complications. Table 2 highlights detailed procedural adverse events that occurred more often in women. Necessity of surgical vascular treatment after major vascular injury was more frequent among women (10.7% vs. 2.3%; $P = 0.134$).

Thirty-day clinical outcomes: There were no significant differences regarding 30-day outcomes between the two groups. The 30-day all-cause mortality in men was 4.4%, whereas in women, it was 3.4% ($P = 0.745$). The all-stroke rate was 4.4% in men and 1.7% in women ($P = 0.582$). Post-procedural delirium occurred in 8.9% of men and 10.5% of women ($P = 1$). We registered 19.5% PPI in men and 18.9% in women ($P = 1$). The LBBB rate was 23.7% in men and 35.4% in women ($P = 0.345$). (Table 3)

Long-term clinical outcomes: The mean long-term survival probability was 42.1 months [95%CI: 33.154–51.101] in men vs. 57.3 months [95%CI: 50.618–64.159] in women, $P = 0.015$. (Figure 1A) The mean freedom from stroke was 59.8 months [95%CI: 52.604–66.924] in men vs. 66.2 months [95%CI: 61.740–70.647] in women, $P = 0.109$. (Figure 1B) The mean freedom from PPI was 51 months [95%CI: 42.204–59.712] in men vs. 56.5 months [95%CI: 49.256–63.766] in women, $P = 0.402$. (Figure 1C)

At long term, we registered one degenerated valve (woman), exhibiting high grade aortic stenosis and mild regurgitation requiring Re-TF-TAVI (six years after initial implantation). Two men suffered from prosthesis endocarditis on the 6th and 10th postoperative month. Both patients died with endocarditis.

Causes of death: Overall, cardiac death was the most common cause. Cardiac cause of death was 13.3% in men and 8.6% in women ($P = 0.369$). (Figure 2)

Hemodynamics: At discharge, the peak gradients were similar in both groups: 18.4 ± 7.8 mmHg in men and 20.6 ± 7.1 mmHg in women; $P = 0.303$. At discharge, the maximal flow velocity was similar in both groups: 2.3 ± 0.4 m/s in men and 2.2 ± 0.5 m/s in women; $P = 0.293$.

Paravalvular leak: We found at discharge significantly lower PVL rate in men. In men, we observed none in 48.9% of the patients, trace–mild in 22.3% of the patients, and moderate in 2.2% of the patients. In women, we observed none in 48.3% of the patients, trace–mild in 43.1% of the patients, and moderate in 0% of the patients; $P < 0.05$. No severe PVL was registered in both groups.

DISCUSSION

The present study provides long-term gender-dependent

Table 3. Thirty-day outcomes. (AKIN, acute kidney injury network; LBBB, left bundle branch block)

	Men (*N* = 45) *N* = %	Women (*N* = 58) *N* = %	*P*-value
All-cause mortality	2 (4.4)	2 (3.4)	0.745
Cardiovascular mortality	1 (2.2)	1 (1.7)	1
All-stroke	2 (4.4)	1 (1.7)	0.582
Myocardial infarction	0 (0)	1 (1.7)	1
AKIN stage 1	6 (18.8)	3 (6.4)	0.147
AKIN stage 2	0 (0)	1 (2.1)	1
AKIN stage 3	1 (3.1)	0 (0)	0.405
Delirium	4 (8.9)	6 (10.5)	1
New permanent pacemaker	8 (19.5)	10 (18.9)	1
LBBB	9 (23.7)	17 (35.4)	0.345
Endocarditis	0 (0)	0 (0)	

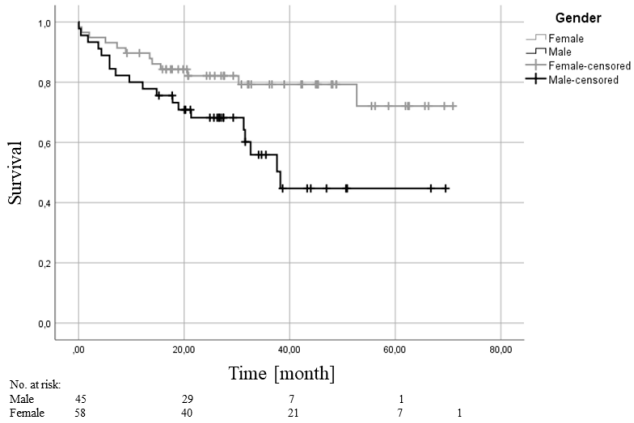

Figure 1A. Kaplan-Meier survival curves

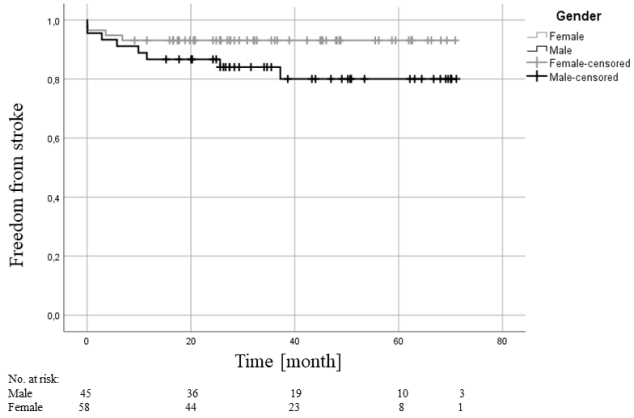

Figure 1B. Kaplan-Meier curves: Freedom from stroke

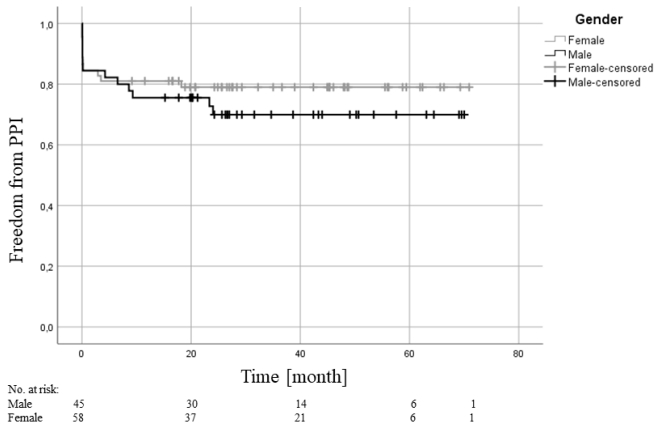

Figure 1C. Kaplan-Meier curves: Freedom from new pacemaker implantation

outcomes after TF-TAVI in lower-risk patients. In patients at lower surgical risk, both genders had similar baseline cardiovascular risk factors and cardiac-comorbidities. Interestingly, intra-procedural vascular complications in women are considerably high, despite the use of newer generation valve systems. Long-term survival after TF-TAVI was significantly higher in women than men. Women showed significantly higher rates of trace to mild PVL and considerably higher rate of LBBB. These complications appear not to negatively affect the long-term survival in women. Long-term freedom from PPI is very satisfactory, without gender-dependent difference.

Long-term gender-dependent data after TF-TAVI in lower-risk patients by the use of newer generation valves are sparse. One novelty of our study is the long-term follow up in patients at lower risk. In addition, previous studies comparing the two genders reported significant differences, regarding the baseline characteristics [Chandrasekhar 2016; Tarantini 2021; Bière 2015]. Unequal baseline characteristics, such as a significant cardiovascular history burden among men, might have appear to be milder. Therefore, we observed similar data regarding left ventricular ejection fraction, previous myocardial infarction, atrial fibrillation, and previous pacemaker implantation. Cardiovascular risk factors, such as

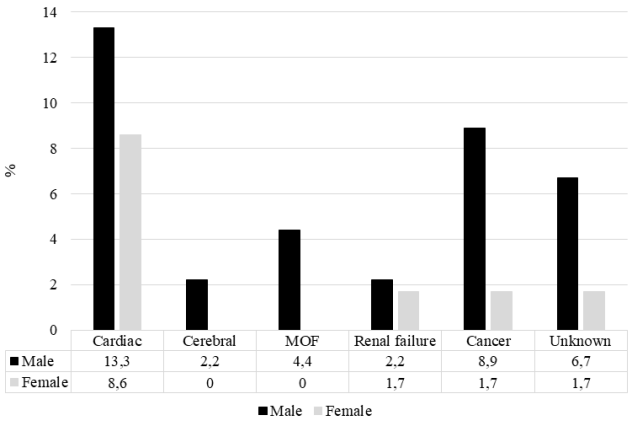

Figure 2. Causes of mortality. MOF, multiple organ failure

hypertension, diabetes and pulmonary hypertension, were slightly higher in women. Nevertheless, women showed significantly longer long-term survival than men. These findings are in line with previous studies [Stangl 2014; Azarbaijani 2018]. In addition, the current analysis showed that higher incidence of major vascular injury and LBBB among women did not affect gender-related outcomes after TAVI. In the PARTNER (Placement of Aortic Transcatheter Valve) trial moderate-to-severe PVL was considerably higher (3-fold) in men compared with women [Williams 2014]. This fact was considered to be one of the explanations for the lower mortality rates among women. Our data show that by use of new valve generations, the incidence of at least moderate PVL outcomes is minimized. Hence, incidence of relevant PVL cannot explain better long-term survival in women. Moreover, women exhibited significantly higher rate of trace–mild PVL. Furthermore, LBBB after TAVI has been associated with worse mid-term clinical outcome [Nazif 2019]. In our study, we registered considerably higher rate of LBBB in women without affecting outcome.

Studies have shown that incidence of vascular injuries is higher among women compared with men [Hayashida 2012; Buchanan 2011; Stangl 2014]. Other analyses have confirmed that women are more prone to major/ life-threatening bleeding [Zhao 2013; O'Connor 2015]. All these finding have been ascribed to the smaller iliofemoral vessels in women, implicating an unfavorable introducer sheath-to-femoral artery ratio. Despite a very low rate of peripheral artery disease in our study and the use of lower profile contemporary delivery system, the problem of vascular injuries is still present, especially in the female collective.

After the release of the ES3, initial data reported an incidence of PPI between 13% and 25.5% [Webb 2014; Murray 2015]. Experience over time and research on the underlying mechanisms leading to PPI have contributed to a further decrease in the PPI rate. Recent studies reported PPI rates between 6.6% [Mack 2019] and 16% [Husser 2016]. Our PPI rate was similar in both genders and consistent with the initial data. A possible explanation could be the fact that we did not exclude patients at high risk for PPI, such as patients with complete right bundle branch block or high calcification burden at the height of the non-coronary cusp, which have been shown to be predictors for PPI [Mack 2019; Husser 2016]. Moreover, data on long-term rhythm disturbances after TAVI requiring PPI are limited. Our analysis showed no necessity for PPI on the long term without differences between men and women, which represents a novelty.

Limitations: This is a retrospective and non-randomized single-center study using a limited number of patients.

Conflict of interest: Polykarpos C Patsalis is proctor for Edwards Lifesciences. All other authors declare no potential conflict of interest.

CONCLUSION

Despite higher rate of vascular injuries, mild PVL and LBBB women had a significantly long-term survival benefit after TF-TAVI in lower-risk patients.

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