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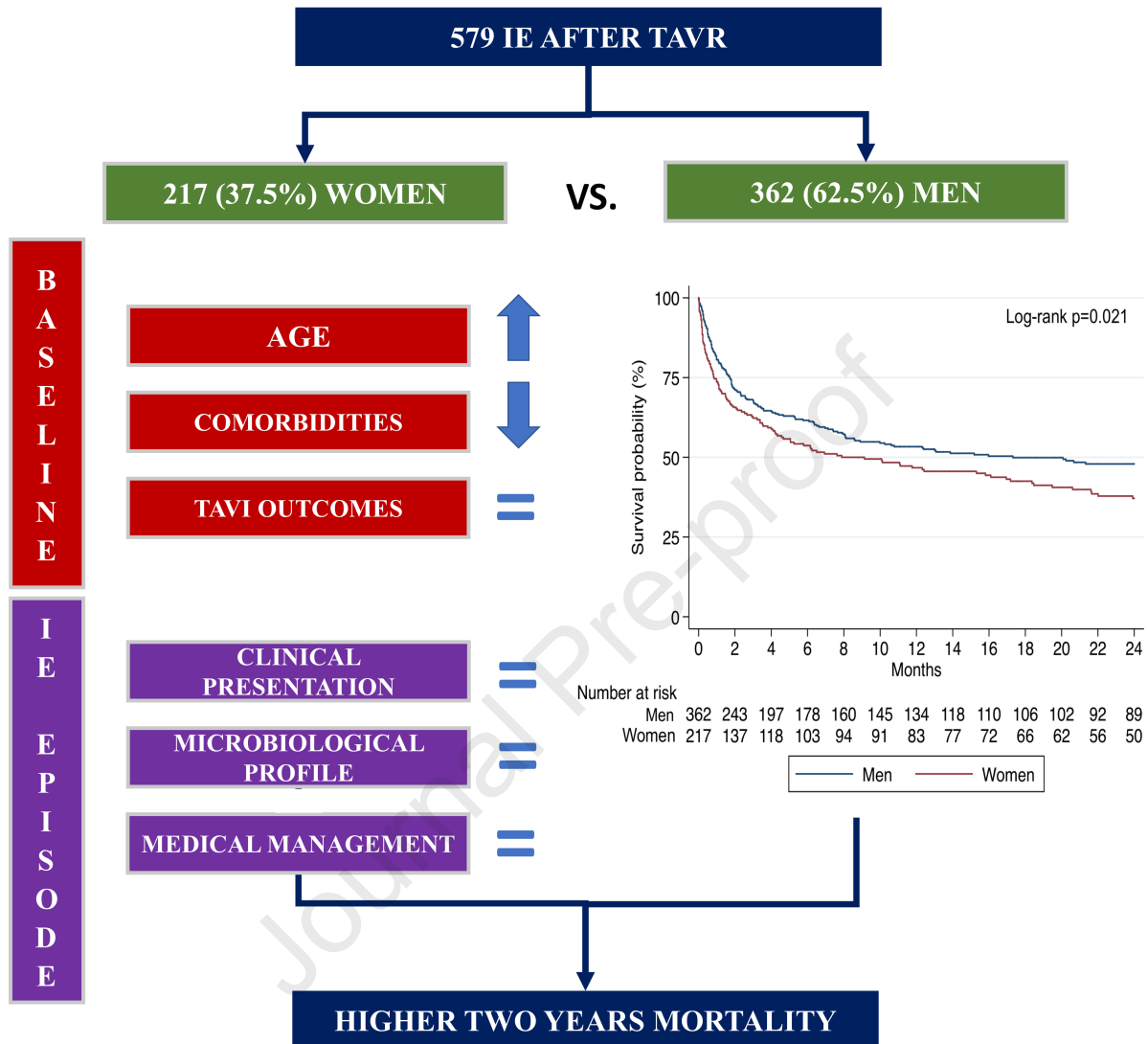
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Sex Differences in Infective Endocarditis After Transcatheter Aortic Valve Replacement

Vassili Panagides, MD^a; Mohamed Abdel-Wahab, MD^{b,c}, Norman Mangner, MD^{b,d}, Eric Durand, MD^e, Nikolaj Ihlemann, MD^f, Marina Urena, MD^g, Costanza Pellegrini, MD^h, Francesco Giannini, MD^{i,j}, Piotr Scislo, MD, PhD^k, Zenon Huczek, MD, PhD^k, Martin Landt, MD^l, Vincent Auffret, MD^l, Jan Malte Sinning, MD^m, Asim N. Cheema, MD^{n,o}, Luis Nombela-Franco, MD^p, Chekrallah Chamandi, MD^q, Francisco Campelo-Parada, MD^r, Erika Munoz-Garcia, MD^s, Howard C Herrmann, MD^t, Luca Testa, MD^u, Won-Keun Kim, MD^v, Helene Eltchaninoff, MD^e, Lars Sondergaard, MD^f, Dominique Himbert, MD^g, Oliver Husser, MD^{h,w}, Azeem Latib, MD^{i,x}, Hervé Le Breton, MD^l, Clement Servoz, MD^r, Philippe Gervais, MD^a; David del Val, MD^a, Axel Linke, MD^{b,d}, Lisa Crusius, MD^{b,d}, Holger Thiele^b, MD, David Holzhey, MD^b, Josep Rodés-Cabau, MD^a

^aQuebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada; ^bHeart Center, Leipzig University, Leipzig, Germany; ^cHeart Center, Segeberger Kliniken, Bad Segeberg, Germany; ^dHerzzentrum Dresden, Technische Universität Dresden, Germany; ^eNormandie Univ, UNIROUEN, U1096, CHU Rouen, Department of Cardiology, F-76000 Rouen, France; ^fRigshospitalet, Copenhagen University Hospital, Denmark; ^gBichat Hôpital, Paris, France; ^hDeutsches Herzzentrum München, Munich, Germany; ⁱMaria Cecilia Hospital, GVM Care and Research, Cotignola RA, Italy ^jOspedale San Raffaele, Milan, Italy; ^kDepartment of Cardiology, Medical University of Warsaw, Poland; ^lUniv Rennes, CHU Rennes, Inserm, LTSI - UMR1099, F 35000 Rennes, France; ^mHeart Center Bonn, Bonn, Germany; ⁿSt Michaels Hospital, Toronto, Canada; ^oSouthlake Hospital, Newmarket, Ontario, Canada; ^pCardiovascular Institute, Hospital Clínico San Carlos, IdISSC, Madrid, Spain; ^qHôpital Européen Georges-Pompidou, Paris, France; ^rHôpital Rangueil, Toulouse, France;

^sHospital Universitario Virgen de la Victoria, Malaga, Spain; ^tHospital of the University of Pennsylvania, Philadelphia, USA; ^uIRCCS Pol. San Donato, Milan, Italy; ^vKerckhoff Heart and Thorax Centre, Bad Nauheim, Germany; ^wAugustinum Klinik München, München, Germany; ^xMontefiore Medical Center, New York, NY, USA;

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Corresponding author:

Josep Rodés-Cabau, MD.

Quebec Heart & Lung Institute, Laval University

Quebec City, Quebec, Canada

Phone: 418-6568711; Fax: 418-6564544

E-mail: josep.rodés@criucpq.ulaval.ca

ABSTRACT

Background: Outcomes after transcatheter aortic valve replacement (TAVR) and infectious diseases may vary according to sex.

Methods: This multicenter study aimed to determine the sex differences in clinical characteristics, management, and outcomes of infective endocarditis (IE) after TAVR. A total of 579 patients (217 women, 37.5%) were included retrospectively from the Infectious Endocarditis after TAVR International Registry who had the diagnosis of definite IE following TAVR.

Results: Women were older (80 ± 8 vs. 78 ± 8 years, $p=0.001$) and exhibited a lower comorbidity burden. Clinical characteristics and microbiological profile were similar between men and women, but culture-negative IE was more frequent in women (9.9% vs. 4.3%, $p=0.009$). A high proportion of patients had a clinical indication for surgery (54.4% in both groups, $p=0.99$), but a surgical intervention was performed in a minority of patients (women: 15.2%, men: 20.3%, $p=0.13$). The mortality rate at index IE hospitalization was similar in both groups (women: 35.4%, men: 31.7%, $p=0.373$), but women exhibited a higher mortality rate at 2-year follow-up (63% vs. 52.1%, $p=0.021$). Female sex remained an independent risk factor for cumulative mortality in the multivariable analysis (HR_{adj} : 1.28, 95% CI: 1.02-1.62, $p=0.035$). After adjustment for in-hospital events, surgery was not associated with better outcomes in women.

Conclusions: There were no significant sex-related differences in the clinical characteristics and management of IE after TAVR. However, female sex was associated with increased two-years mortality risk.

KEYWORDS: Infective endocarditis, TAVR, heart surgery, sex

BRIEF SUMMARY

This study aimed to investigate differences between sexes in infective endocarditis (IE) after transcatheter valve replacement (TAVR). Clinical characteristics and microbiological profile of IE after TAVR were found to be similar between men and women. There were no major differences in the medical management. However, women have an impaired prognosis. Further research is required to better understand women's higher mortality.

ABBREVIATIONS LIST

IE: infective endocarditis

IQR: interquartile range

PVE: prosthetic valve endocarditis

TAVR: transcatheter aortic valve replacement

THV: trans-catheter heart valve

INTRODUCTION

The clinical characteristics, management, and outcomes of different diseases vary considerably between men and women, and the need for sex-specific research, reporting, and guideline considerations has been increasingly recognized (1). Major sex-related differences have been shown in multiple cardiovascular and infectious diseases (2,3). In the transcatheter aortic valve replacement (TAVR) field, several studies have shown improved long-term survival in women compared to men, despite a higher incidence of peri-procedural complications (4–6). On the other hand, female sex has been associated with poorer early and late outcomes in cases of non-TAVR infective endocarditis (IE) (7,8), and a potential sex-treatment bias including a lower likelihood of surgical intervention among women in this setting has been suggested as an important factor to explain such differences (9).

IE after TAVR is an infrequent but life-threatening event, with specific clinical, microbiological profile, and management characteristics along with very high early and late mortality rates (10). However, no data exist on potential sex-related differences in the context of IE after TAVR. A better knowledge of the clinical characteristics, treatment, and outcomes of IE following TAVR according to sex would therefore be of high clinical relevance. The objectives of this study were to evaluate sex-related differences in the clinical characteristics, management, and outcomes of IE after TAVR.

MATERIAL AND METHODS

Study population

Data were collected from The Infectious Endocarditis after TAVR International Registry. Details on the design of this observational, multicenter, international registry have been previously reported (11). At the time of this analysis, the registry included data from 579 patients with definite IE determined by the modified Duke criteria after TAVR from 59 centers

in 11 countries across Europe, North America, and South America between June 2005 and November 2020.

Patients were identified by each center according to the modified Duke criteria (12). To avoid duplicities, only the first episode of IE recorded for an individual patient was included in the analysis. A dedicated uniform case report form (database) was used at all sites for data collection including baseline and periprocedural TAVR features, as well as IE characteristics, microbiological profile, management, and in-hospital and follow-up outcomes (191 variables). Among 604 patients with definite IE, only 579 were included in the analysis (exclusion of 25 patients with missing data on the clinical status or without a date of follow-up). Informed consent was obtained from all patients before the procedure and the individual anonymized data sharing was performed according to the local ethics committee of each participating center. The research was performed without patient or public involvement.

Study definitions

The definition of definite IE was based on the modified Duke criteria (12). Transcatheter heart valve (THV) type was divided into two groups: balloon-expandable (Edwards Sapien™, Sapien XT™, and Sapien 3™ valves systems; Edwards Lifesciences, Irvine, CA, USA) and self- or mechanically- expandable valves (Medtronic CoreValve™ and Evolut R™ systems (Medtronic, Minneapolis, MN), Lotus™ Valve System (Boston Scientific, Marlborough, MA, USA), Portico™ valve (Abbott Vascular, Abbott Park, IL, USA), Acurate™ valve system (Symetis SA, a Boston Scientific company, Ecublens, Switzerland), Direct flow™ (Direct Flow Medical Inc. Santa Rosa, CA, USA), JenaValve™ (JenaValve Technology Inc. Irvine, CA, USA), Medtronic Engager™ (Medtronic, Minneapolis, MN, USA) and Centera™ (Edwards Lifesciences, Irvine, California, USA). Outcomes were defined according to the Valve Academic Research Consortium-2 criteria (13). Persistent bacteremia was defined as positive

blood cultures despite appropriate antibiotic therapy for > 7 days. IE complications with an indication for surgery were defined according to the European guidelines (12) as follows : (i) intra-hospital episode of heart failure attributed to a severe aortic or mitral valve dysfunction (ii) locally uncontrolled perivalvular extension, and (iii) aortic or mitral vegetation > 10 mm.

Statistical Analysis

Continuous variables were expressed as mean \pm standard deviation or median (interquartile range) depending on the variable distribution, which was assessed using the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers (%). Comparisons between groups were performed using the Student t-test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact test for categorical variables. Multivariable Cox proportional hazard models were performed to determine the factors independently associated with cumulative follow-up mortality. Likewise, the first model (whole population) included all significant ($p < 0.05$) baseline variables considered a priori to contribute to two-year mortality with the only exception of age that was forced in the model for its relevance. The second model (female population) included all significant variables from the IE-hospitalization with the only exception of the IE management (surgery vs. medical treatment) that was forced in the model due to its potential relevance. Surgery was included as a time-varying covariate in the Cox models to control for immortal time bias. The multivariable models were built by backward stepwise (likelihood ratio) selection. The Kaplan–Meier method was used to provide survival estimates, which were assessed with a log-rank test. Differences in the incidence of mortality were determined using the log-rank test. A 2-sided p-value of < 0.05 was considered statistically significant. Data analyses were performed using STATA 14.0 (StataCorp, College Station, TX, USA).

RESULTS

A total of 579 patients with definite IE were included, 217 (37.5%) of them were women. The main baseline and TAVR peri-procedural characteristics are shown in **Table 1**. Women were older (80 ± 8 vs. 78 ± 8 , $p=0.001$), and exhibited a lower rate of chronic obstructive pulmonary disease (21.7% vs. 30.7%, $p=0.019$), previous stroke (8.8 vs. 15.5%, $p=0.020$), and previous heart surgery (12.9% vs. 27.9%, $p<0.001$). There were no significant differences between women and men in TAVR procedural characteristics, periprocedural complications, and length of hospital stay.

Clinical presentation of IE episode and outcomes

The clinical characteristics and outcomes of the IE episode according to sex are presented in **Table 2**. Initial symptoms, perivalvular extension, and vegetation size were similar between the two sexes. IE involving the THV alone was more frequently observed in men (53.6% vs. 41.5%, $p=0.005$). There were no significant differences in the identified causative organism, but a higher proportion of culture-negative episodes were observed in women (9.9% vs. 4.3%, $p=0.009$). Complications related to the IE episode were also similar and 54.4% of both men and women had an indication for surgery. Up to 15.2% of women had a surgical intervention at index IE episode (vs. 20.3% of men, $p=0.125$) after a median of 27 days IQR [6-54] (vs. 14 days in men IQR [6-36] ($p=0.161$)). When there was an indication for surgery, 20.3% of women were operated on vs. 27.4% of men ($p=0.188$). Relapse of the IE episode during follow-up was similar between groups (6.0% in women vs. 9.4% in men, $p=0.147$).

Despite similar in-hospital mortality rates (31.7% in men vs. 35.4% in women, $p=0.373$), the 2-year mortality rate was higher in women compared to men (63% CI [56-69.8] vs. 52.1% [46.5-57.9], $p=0.021$) (**Figure 1**). Female sex was an independent risk factor of

death after adjustment to significant baseline characteristics including age (HR_{adj} : 1.28 [1.02-1.62], $p=0.035$) (**Table 3**).

Clinical profile of operated women

A total of 32 women underwent surgery (15.2% of the women cohort). The operated patients were younger 77 ± 9 years vs. 81 ± 7 years ($p=0.015$), had less chronic kidney disease (29.0% vs. 48.3%, $p=0.047$), a lower surgical risk (median Logistic EuroSCORE 9.8, IQR [6-18] vs. 15, IQR [10-23.6], $p=0.01$) and had TAVR less frequently through transfemoral approach (78.1% vs. 92.7%, $p=0.009$). Ten out of 32 patients (31.3%) died during index hospitalization after surgery (**supplementary table S1**). Two-year mortality rate similar in operated women compared to non-operated women (53.3% CI [35.9-72.9] vs. 63.2% [55.6-70.8], $p=0.203$) (**figure 2**).

Risk factors of mortality in the female population

After adjustment for in-hospital events during IE hospitalization, heart failure HR_{adj} : 1.66 CI [1.02-2.68], $p=0.04$, septic shock HR_{adj} : 3.88 CI [2.43-6.22], $p<0.001$ and persistent bacteremia HR_{adj} : 2.09 CI [1.32-3.32], $p=0.002$ were associated with mortality and surgery was not found to be protective when adjusted to in-hospital events (**Table 4**). Risk factors associated with mortality in the male population is available in supplemental table S2.

DISCUSSION

The main results of this study providing the first detailed description on sex differences in the clinical characteristics and outcomes of IE after TAVR can be summarized as follows:

- (i) IE symptoms, presentation, and causative microorganisms are similar between men and women after TAVR except for more culture-negative episodes among women; (ii) there were

no major differences in the medical management between sexes; (iii) early mortality was similar between women and men, but women had an impaired two-years survival compared to men.

Numerous studies investigating outcomes between men and women after TAVR have been published. In a meta-analysis including 17 studies, Saad et al. found that women were older, but with fewer comorbidities than men (6). Moreover, despite having more in-hospital complications (bleeding, major vascular events, and stroke), women had better long-term prognosis after TAVR than men. These results were consistent with another study from the TVT registry including 11 808 patients (5). In accordance with these previous studies, women were older and exhibited a lower comorbidity burden. Therefore, baseline characteristics between men and women in our study including only patients with definite IE parallel previous TAVR reports.

Both women and men had a similar microbiological profile. Sex distribution of non-TAVR IE causative organisms is not consistent in the existing literature. While Sambola et al. found no differences in the microbiological profile between men and women (9), Sevilla et al. reported more Gram-negative bacilli and fewer *Streptococcus viridians* in women compared to men (14), and Aksoy et al. described less coagulase-negative staphylococci in women (7). Interestingly, we found a higher rate of culture-negative episodes among women. This finding may be related to numerous factors: blood cultures sterilized by early antibacterial treatment, IE related to fastidious pathogens (e.g., HACEK group bacteria), organism requiring a serological diagnosis (e.g., Q fever, *Bartonella* infections), or non-infective endocarditis (auto-immune or marantic). The high relative proportion of culture-negative episodes found in women (10%) highlights the importance of serological analysis, antinuclear antibodies research, or valvular biopsies when available in this peculiar subpopulation (15).

It has been previously suggested that the impaired prognosis of women after IE in non-TAVR patients was related to the reduced likelihood to undergo surgery when indicated (9).

Moreover, it is known that women are less likely to receive cardiovascular therapies (16–18). This gap is likely related to numerous factors including differences in clinical presentation, socioeconomic disparities, or sex discrimination (1). Interestingly, the rate of surgery in our study was numerically lower in women compared to men (15.2% vs. 20.3%) without reaching a statistical difference. Therefore, the difference observed concerning outcomes is unlikely to be related to a major discrepancy in medical care.

Female sex was an independent predictor of mortality even after adjustment with age and baseline characteristics of the population. This finding is of clinical importance and difficult to explain. Sepsis prognosis may vary between males and females but largely depend on the infection site; moreover, sex is not an independent factor of outcome when examining all infections (19). In animal models, it has been found that hormones modulate the severity of sepsis, and castration of females worsens the septic lesions (3). The lack of hormonal protection of our elderly population could partly explain our findings. Nevertheless, the observed mortality is likely multifactorial and may not be solely related to the IE episode itself.

Surgery was not associated with better outcomes in women. Previous large studies of non-TAVR patients have shown higher in-hospital mortality in operated women after IE (despite a lower chance to be operated) (20,21). Further studies are required to precise the role of surgery in this context.

Perspectives

This study raises more questions than answers. The over mortality of women can be related to hormonal factors that can be further investigated using prespecified specific questionnaires and hormonal dosages. The high rate of culture negative episode is also of clinical interest and justify the realisation of a complete and exhaustive research of IE in women when the context is suggestive. Furthermore, this finding should justify research in the field to

better understand the exact causes of negative episodes in women. Unfortunately, the scarcity of these episodes is detrimental to the elaboration of prospective studies that are needed to answer these questions.

Limitations

Our study has some limitations. First, due to its retrospective observational design, some data were not available. Centers participated voluntarily and there was no external monitoring committee to verify the accuracy of data reported by each center. Lastly, due to its multicenter design, diagnosis and treatment modalities of patients may have been different between participating centers.

CONCLUSIONS

Women with IE after TAVR are older but present fewer comorbidities than men. The IE clinical presentation and microbiological profile are similar except for a higher rate of culture-negative episodes in women. This highlights the importance of starting antibiotic therapy and implementing multi-imaging modalities to rule out the diagnosis of IE in women with suggestive symptoms following TAVR. Also, women's two-years mortality was higher compared to men following the IE episode. Further studies are warranted.

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Table 1 - Baseline characteristics, comparison between men and women

	Women	Men	Unadjusted
	(n=217)	(n=362)	<i>p-value</i>
Baseline characteristics			
Age, years ± SD	80.0 ± 7.5	77.9 ± 7.5	0.001
Body mass index (kg/m2)	27.9 ± 6.1	28.0 ± 5.7	0.842
Diabetes mellitus, n (%)	71 (32.7)	145 (40.1)	0.077
COPD, n (%)	47 (21.7)	111 (30.7)	0.019
Atrial fibrillation, n (%)	99 (45.6)	148 (41.0)	0.276
Chronic kidney disease, n (%)	98 (45.6)	150 (42.1)	0.421
Previous Stroke, n (%)	19 (8.8)	56 (15.5)	0.020
Previous heart surgery, n (%)	28 (12.9)	101 (27.9)	<0.001
Previous infective endocarditis, n (%)	4 (1.9)	2 (0.6)	0.134
Logistic EuroSCORE, % (SD)	17.4 ± 12.2	17.0 ± 12.5	0.774
Left ventricular ejection fraction, % ± SD	57.7 ± 11.2	51.0 ± 13.9	<0.001
Mitral regurgitation ≥ 2, n (%)	58 (26.7)	84 (23.2)	0.340
Mean transaortic gradient, mean ± SD, mmHg	48.2 ± 16.1	43.4 ± 15.5	<0.001
Periprocedural characteristics			
Implantation site			
Catheterization laboratory, n (%)	87 (40.1)	147 (40.6)	0.670
Operating hybrid room, n (%)	16 (7.4)	20 (5.5)	
Hybrid room	114 (52.5)	195 (53.9)	
Approach, n (%)			

Transfemoral	197 (90.8)	311 (86.4)	0.115
Prosthesis type			
Balloon-expandable, n (%)	111 (51.9)	187 (52.5)	0.879
Self-expanding, n (%)	103 (48.1)	169 (47.5)	
Antibiotic prophylaxis			
B-Lactam alone, n (%)	182 (93.8)	296 (93.7)	0.930
Vancomycin alone or in combination, n (%)	8 (4.1)	12 (3.8)	
Other	4 (2.1)	8 (2.5)	
In-hospital Outcomes (TAVR)			
Acute renal failure, n (%)	27 (12.7)	47 (13.3)	0.827
Stroke, n (%)	9 (4.2)	18 (5.1)	0.637
Major vascular complication, n (%)	19 (8.9)	19 (5.4)	0.103
Major bleeding, n (%)	24 (11.3)	30 (8.5)	0.277
Sepsis, n (%)	23 (11.8)	33 (10.1)	0.543
New pacemaker implantation, n (%)	43 (19.8)	62 (17.2)	0.434
Residual aortic regurgitation ≥ 2 at discharge, n (%)	33 (15.6)	49 (13.9)	0.576
Mean residual transaortic gradient, mean ± SD, mm Hg	11.6 ± 7.1	10.9 ± 5.6	0.201
Length of hospital stay, median (IQR), days	9.0 [6.0-15.0]	9.0[6.0-14.0]	0.493

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321 **Table 2 - Main clinical characteristics, management, and outcomes of IE episode by sex**

	Women	Men	Unadjusted
	N=217	N=362	p-value
Time from TAVR, median (IQR), days	158 [45-428]	204 [70-493]	0.113
Initial symptoms			
Fever, n (%)	161 (76.3)	283 (79.9)	0.308
New-onset heart failure, n (%)	96 (45.5)	141 (40.1)	0.206
Neurological, n (%)	39 (18.7)	66 (18.7)	0.991
Systemic embolism, n (%)	28 (13.4)	45 (12.8)	0.825
Skin lesions	7 (3.4)	18 (5.1)	0.327
Healthcare-associated infection, n (%)	92 (42.4)	158 (43.7)	0.769
Echocardiographic findings, No./total (%)			
Perivalvular extension	35 (16.1)	70 (19.3)	0.332
Vegetation size [IQR], mm	11 [6-15]	10 [6-15]	0.384
Valve involved			
Mitral valve	38 (17.5)	48 (13.3)	0.164
Isolated THV	90 (41.5)	194 (53.6)	0.005
Right-sided	13 (5.9)	19 (5.2)	0.711
Multiple localizations	76 (35.0)	101 (27.0)	0.077
Causative microorganisms, No./total (%)			
<i>Staphylococcus aureus</i> , n (%)	56/203 (27.6)	81/350 (23.1)	0.243
<i>Methicillin-resistant</i>	11/56 (19.6)	14/81 (17.3)	
Coagulase-negative staphylococci, n (%)	32/203 (15.8)	65/350 (18.6)	0.403
<i>Methicillin-resistant</i>	9/32 (28.1)	19/65 (29.2)	

Enterococci, n (%)	52/203 (25.6)	91/350 (26.0)	0.921
Streptococci			
<i>S. viridans</i> , n (%)	21/203 (10.3)	50/350 (14.3)	0.182
<i>S. gallolyticus</i> (<i>S. bovis</i>), n (%)	7/203 (3.5)	19/350 (5.4)	0.289
Others, n (%)	7/203 (3.5)	15/350 (4.3)	0.627
Culture negative, n (%)	20/203 (9.9)	15/350 (4.3)	0.009
Presumed source of entry, n (%)			
Unknown, n (%)	80 (38.3)	126 (35.4)	N/A
Procedural TAVR related, n (%)	11 (5.3)	16 (4.5)	
Urological, n (%)	21 (10.1)	30 (8.4)	
Odontological, n (%)	3 (1.4)	16 (4.5)	
Pacemaker implantation, n (%)	5 (2.4)	7 (2.0)	
Skin/soft tissue infection, n (%)	5 (2.4)	14 (3.9)	
Digestive, n (%)	6 (2.9)	32 (9.0)	
Cancer, n (%)	2 (1.0)	3 (0.8)	
Complications during IE hospitalization No./total (%)			
Heart failure, n (%)	92/203 (45.3)	143/348 (41.1)	0.333
Acute renal failure, n (%)	72/189 (38.1)	142/324 (43.8)	0.204
Septic shock, n (%)	62/202 (30.7)	93/346 (26.9)	0.339
Stroke, n (%)	20/203 (9.9)	37/348 (10.6)	0.772
Systemic embolization, n (%)	22/202 (10.9)	36/347 (10.4)	0.849
Persistent bacteremia, n (%)	59/175 (33.7)	89/310 (28.7)	0.250
Indication for surgery	118 (54.4)	197 (54.4)	0.992
Management and Outcomes, No./Total (%)			
Antibiotic treatment alone, n (%)	179/211 (84.8)	282/354 (79.7)	0.125

Antibiotic + Surgery during IE hospitalization,	32/211 (15.2)	72/354 (20.3)	
n (%)			
Time to surgery, median (IQR), days	27 [6-54]	14 [6-36]	0.161
Transcatheter valve in valve, n (%)	2/85 (2.4)	1/157 (0.6)	0.249
Isolated pacemaker extraction, n (%)	4/86 (4.7)	4/157 (2.6)	0.380
In-hospital mortality, n (%)	75/212 (35.4)	113/356 (31.7)	0.373
Relapse during follow up	13 (6.0)	34 (9.39)	0.147
1-year mortality rate, (95% CI), %	53.3 [46.6-60.3]	46.7 [41.4-52.3]	0.065*
2-year mortality rate, (95% CI), %	63.0 [56.0-69.8]	52.1 [46.5-57.9]	0.021*
Follow-up, median (IQR), months	5.0 [0.8-23.1]	5.3 [1.3-23.8]	0.263

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Table 3 – Univariable and multivariable analysis of baseline characteristics associated with mortality

	Univariable Analysis		Multivariable	
	Hazard Ratio (95% CI)	Unadjusted	Analysis	Adjusted
		<i>p</i> -value	Hazard Ratio (95% CI)	<i>p</i> -value
Baseline characteristics				
Age	1.00 [1.00-1.02]	0.742		
Female sex	1.31 [1.04-1.65]	0.022	1.28 [1.02-1.62]	0.035
Body mass index	0.99 [0.97-1.02]	0.616		
Diabetes mellitus	1.04 [0.82-0.75]	0.747		
COPD	0.89 [0.69-1.16]	0.409		
Atrial fibrillation	1.05 [0.83-1.32]	0.675		
Chronic kidney disease	1.63 [1.29-2.05]	<0.001	1.61 [1.28-2.03]	<0.001
Previous stroke	0.79 [0.55-1.13]	0.187		
Previous heart surgery	1.03 [0.79-1.37]	0.799		
Previous infective endocarditis	0.76 [0.24-2.37]	0.620		
Logistic EuroSCORE*	1.01 [1.00-1.02]	0.002		
Left ventricular ejection fraction, % ± SD	0.99 [0.99-1.00]	0.217		
Mitral regurgitation ≥ 2, n (%)	1.15 [0.89-1.49]	0.302		
Mean transaortic gradient, mean ± SD, mmHg	0.99 [0.99-1.00]	0.178		

* Not included in the multivariable analysis because of collinearity

Table 4 – Univariable and multivariable analysis of IE hospitalization events associated with mortality in women

	Univariable Analysis	Unadjusted	Multivariable Analysis	Adjusted
	Hazard Ratio (95% CI)	<i>p</i> -value	Hazard Ratio (95% CI)	<i>p</i> -value
Complications during IE hospitalization				
Heart failure	2.55 [1.75-3.72]	<0.001	1.66 [1.02-2.68]	0.040
Acute renal failure	2.33 [1.60-3.41]	<0.001		
Septic shock	6.31 [4.29-9.29]	<0.001	3.88 [2.43-6.22]	0.002
Stroke	2.11 [1.24-3.59]	0.012		
Systemic embolization	1.92 [1.12-3.28]	0.027		
Persistent bacteriemia	3.19 [2.10-4.85]	<0.001	2.09 [1.32-3.32]	<0.001
Management				
Surgery	1.19 [0.65-2.18]	0.579		

FIGURE TITLE AND CAPTIONS

Graphical Abstract: Sex differences in infective endocarditis after transcatheter valve replacement

Figure 1: Kaplan-Meier curves comparing survival stratified by sex. Test comparing the two groups was based on the log-rank test

Figure 2: Kaplan-Meier curves comparing survival stratified by surgical status and sex. Test comparing women with and without surgery was based on the log-rank test

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