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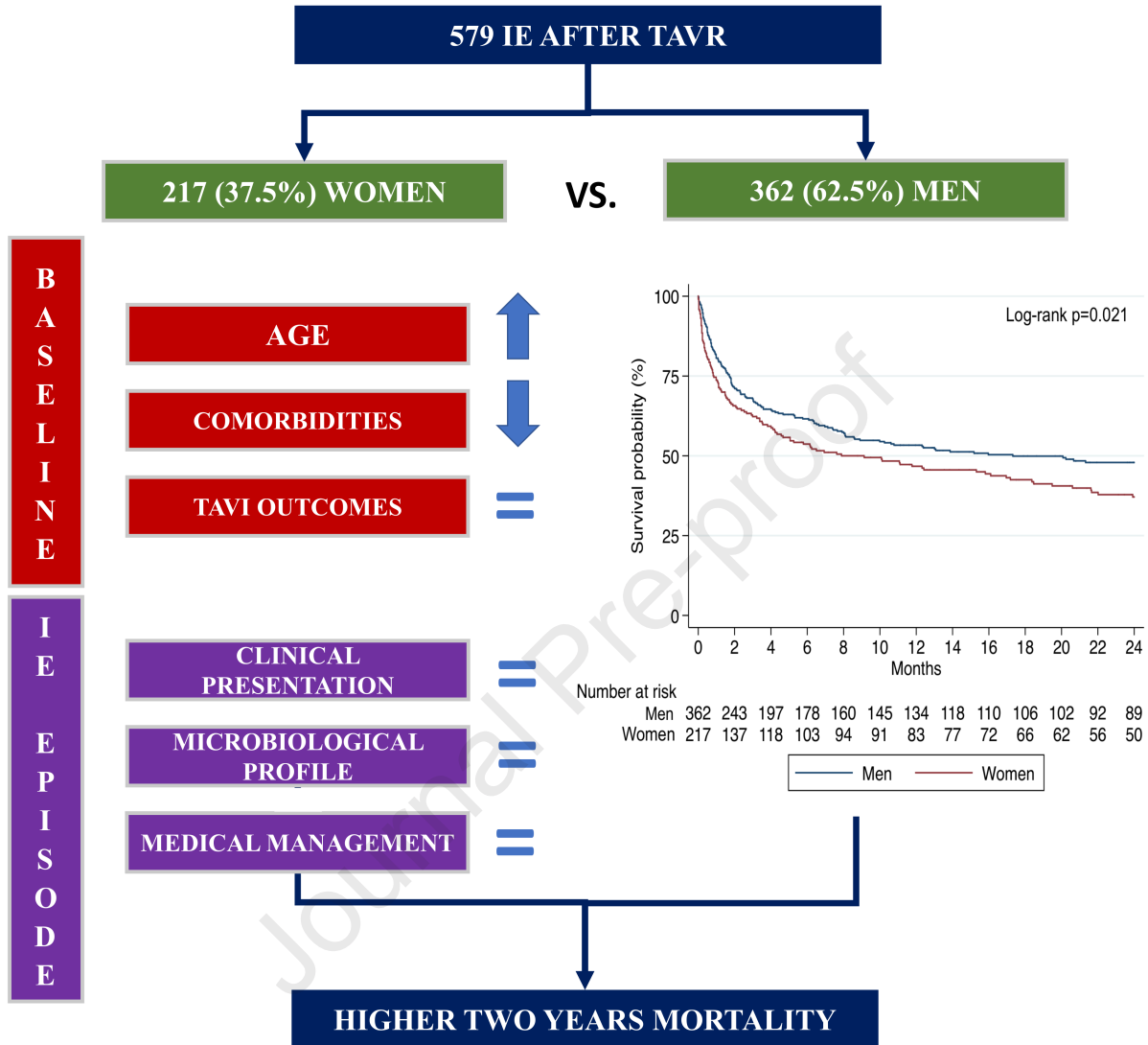
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Sex Differences in Infective Endocarditis After Transcatheter Aortic Valve Replacement

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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

1 INTRODUCTION

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

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

19

20 MATERIAL AND METHODS

21 Study population

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

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

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

39 **Study definitions**

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

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

55

56 **Statistical Analysis**

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

75

76 RESULTS

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

84

85 *Clinical presentation of IE episode and outcomes*

86 The clinical characteristics and outcomes of the IE episode according to sex are
87 presented in **Table 2**. Initial symptoms, perivalvular extension, and vegetation size were similar
88 between the two sexes. IE involving the THV alone was more frequently observed in men
89 (53.6% vs. 41.5%, $p=0.005$). There were no significant differences in the identified causative
90 organism, but a higher proportion of culture-negative episodes were observed in women (9.9%
91 vs. 4.3%, $p=0.009$). Complications related to the IE episode were also similar and 54.4% of
92 both men and women had an indication for surgery. Up to 15.2% of women had a surgical
93 intervention at index IE episode (vs. 20.3% of men, $p=0.125$) after a median of 27 days IQR
94 [6-54] (vs. 14 days in men IQR [6-36] ($p=0.161$)). When there was an indication for surgery,
95 20.3% of women were operated on vs. 27.4% of men ($p=0.188$). Relapse of the IE episode
96 during follow-up was similar between groups (6.0% in women vs. 9.4% in men, $p=0.147$).

97 Despite similar in-hospital mortality rates (31.7% in men vs. 35.4% in women,
98 $p=0.373$), the 2-year mortality rate was higher in women compared to men (63% CI [56-69.8]
99 vs. 52.1% [46.5-57.9], $p=0.021$) (**Figure 1**). Female sex was an independent risk factor of

100 death after adjustment to significant baseline characteristics including age (HR_{adj} : 1.28 [1.02-
101 1.62], $p=0.035$) (**Table 3**).

102

103 *Clinical profile of operated women*

104 A total of 32 women underwent surgery (15.2% of the women cohort). The operated
105 patients were younger 77 ± 9 years vs. 81 ± 7 years ($p=0.015$), had less chronic kidney disease
106 (29.0% vs. 48.3%, $p=0.047$), a lower surgical risk (median Logistic EuroSCORE 9.8, IQR [6-
107 18] vs. 15, IQR [10-23.6], $p=0.01$) and had TAVR less frequently through transfemoral
108 approach (78.1% vs. 92.7%, $p=0.009$). Ten out of 32 patients (31.3%) died during index
109 hospitalization after surgery (**supplementary table S1**). Two-year mortality rate similar in
110 operated women compared to non-operated women (53.3% CI [35.9-72.9] vs. 63.2% [55.6-
111 70.8], $p=0.203$) (**figure 2**).

112

113 *Risk factors of mortality in the female population*

114 After adjustment for in-hospital events during IE hospitalization, heart failure
115 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
116 persistent bacteriemia HR_{adj} : 2.09 CI [1.32-3.32], $p=0.002$ were associated with mortality and
117 surgery was not found to be protective when adjusted to in-hospital events (**Table 4**). Risk
118 factors associated with mortality in the male population is available in supplemental table S2.

119

120 **DISCUSSION**

121 The main results of this study providing the first detailed description on sex differences
122 in the clinical characteristics and outcomes of IE after TAVR can be summarized as follows:
123 (i) IE symptoms, presentation, and causative microorganisms are similar between men and
124 women after TAVR except for more culture-negative episodes among women; (ii) there were

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

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

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

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

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

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

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

168

169 *Perspectives*

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

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

178

179 *Limitations*

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

185

186 **CONCLUSIONS**

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

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206

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309 Heart Association*. 2021 Oct 19;10(20):e020095.

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313 **Table 1 - Baseline characteristics, comparison between men and women**

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	Women (n=217)	Men (n=362)	Unadjusted <i>p-value</i>
Baseline characteristics			
Age, years \pm SD	80.0 \pm 7.5	77.9 \pm 7.5	0.001
Body mass index (kg/m ²)	27.9 \pm 6.1	28.0 \pm 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 \pm 12.2	17.0 \pm 12.5	0.774
Left ventricular ejection fraction, % \pm SD	57.7 \pm 11.2	51.0 \pm 13.9	<0.001
Mitral regurgitation \geq 2, n (%)	58 (26.7)	84 (23.2)	0.340
Mean transaortic gradient, mean \pm SD, mmHg	48.2 \pm 16.1	43.4 \pm 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 \pm SD, mm Hg	11.6 \pm 7.1	10.9 \pm 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)	
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)	N/A
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, n (%)	32/211 (15.2)	72/354 (20.3)	
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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323 *By log-rank test

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337 **Table 3 – Univariable and multivariable analysis of baseline characteristics associated**
 338 **with mortality**
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	Univariable Analysis		Multivariable	
	Hazard Ratio (95% CI)	Unadjusted <i>p</i> -value	Analysis Hazard Ratio (95% CI)	Adjusted <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		

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341 * Not included in the multivariable analysis because of collinearity

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

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	Univariable Analysis	Unadjusted	Multivariable Analysis	Adjusted
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-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		

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357 **FIGURE TITLE AND CAPTIONS**

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

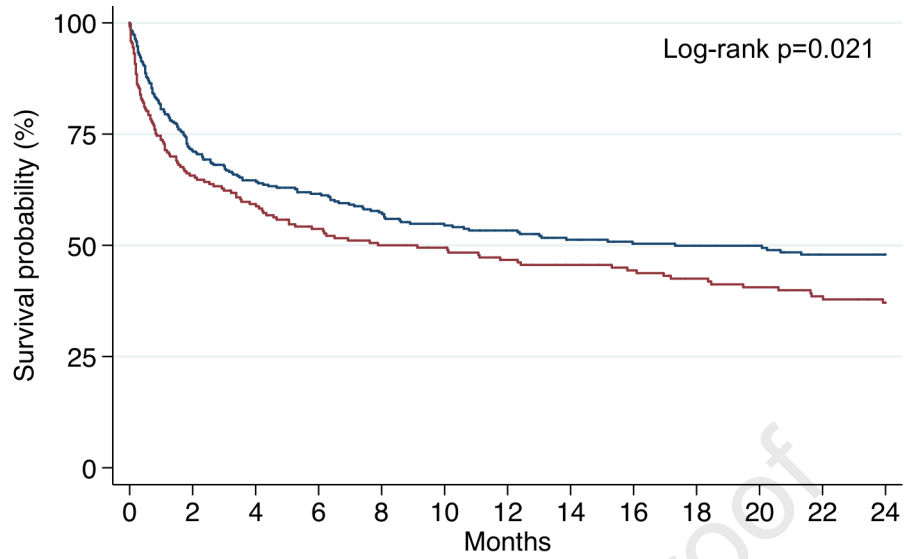
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362 **Figure 1:** Kaplan-Meier curves comparing survival stratified by sex. Test comparing the two
363 groups was based on the log-rank test

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

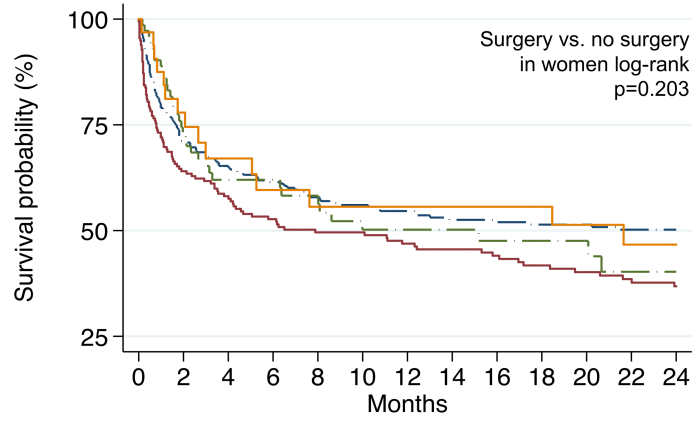
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Number at risk

Men	362	243	197	178	160	145	134	118	110	106	102	92	89
Women	217	137	118	103	94	91	83	77	72	66	62	56	50





Men no surgery	282	189	156	140	128	118	109	97	92	90	88	81	78
Women no surgery	179	111	97	85	78	76	69	63	58	53	50	46	42
Men surgery	72	49	36	33	29	25	23	20	17	15	13	10	10
Women surgery	32	23	18	15	14	14	14	14	14	13	12	10	8

