Temporal Trends in Gender-Related Differences and Outcomes in Patients Who Underwent Transcatheter Aortic Valve Implantation (from the Israeli Transcatheter Aortic Valve Implantation Multicenter Registry)

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We evaluated temporal trends in gender-related differences in patients who underwent transcatheter aortic valve implantation (TAVI) for severe symptomatic aortic stenosis from a multicenter TAVI registry during the years 2008 to 2016. Our final cohort included 1,159 males and 1,370 females, with a median follow-up of 2.3 (IQR 1.2, 4.4) years. For temporal trends analysis, the entire population was divided according to period of procedure: 2008 to 2012 and 2013 to 2016. During the 2008 to 2012 period, the rates of in-hospital aortic paravalvular leak, myocardial infarction, pacemaker implantation, and stroke were higher among men than women, but became comparable between the gender during the 2013 to 2016 period. Multivariate analysis demonstrated that female patients who underwent TAVI between the years 2008 and 2012 had a 26% lower risk of death compared with male patients ($p = 0.004$), but there were no gender-related differences in mortality risk between the years 2013 and 2016 (hazard ratio 1.07, $p = 0.6$; gender-by-year of procedure, $p = 0.027$ for interaction). In conclusion, the favorable long-term prognosis described in female patients during the earlier TAVI period seemed to diminish with contemporary TAVI. This might be attributed to current technological advances and improved valve sizing, with a more significant benefit in favor of male patients. **(Am J Cardiol 2019;123:108−115)**

Based on worldwide registries, approximately 50% of patients who underwent transcatheter aortic valve implantation (TAVI) are females.[1,2] Compared with male patients, women have distinct anatomic and physiologic characteristics,[2−8] and are thereby subject to different procedural and long-term outcomes.[1−3,6,7,9] Several studies have shown that female patients have increased long-term survival after TAVI compared with male patients,[1,2,10,11] yet more recent data show conflicting results, describing similar outcomes in women and men.[12] Defining and understanding these gender-related differences have important clinical implications for patients of both genders who underwent TAVI. This study was designed to investigate temporal trends in gender-related differences in patients who underwent TAVI who were included in an Israeli TAVI multicenter TAVI registry.

Methods

We collected data on 2,529 consecutive patients with severe symptomatic aortic stenosis (AS) who underwent TAVI at 4 tertiary medical centers in Israel between January 2008 and June 2017. Severe AS was defined by echocardiography as a transvalvular mean gradient ≥ 40 mm Hg and/or jet velocity > 4.0 m/s, although patients with symptomatic low flow/low gradient AS were included in the cohort as well. Patients who underwent a valve-in-valve procedure, or TAVI for the indication of aortic regurgitation, were excluded from the analysis.

Candidates for TAVI were evaluated by each institution's heart team and included a thorough clinical, anatomic, geriatric, and comprehensive image-based assessment. Surgical risk was calculated based on the EuroSCORE II and Society for Thoracic Surgeons predicted risk of mortality scores. The selection of the valve prosthesis was at the discretion of the heart team. Patients underwent implantation of the self-expandable Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) or the balloon-expandable Edwards SAPIEN valve (Edwards LifeSciences, Irvine, California). Transfemoral access was the

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See page 114 for disclosure information.

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default approach at all centers unless there were anatomic limitations that led to the selection of an alternative approach. All end points were defined using the Valve Academic Research Consortium-2 consensus definitions[13] and were pooled into a dedicated multicenter database.

For temporal trends analysis, we divided the entire cohort into 2 groups according to the period when the procedure was performed; 2008 to 2012 and 2013 to 2016. In the year 2008, only a few patients underwent TAVI; thus, each group included procedures performed over at least a 4-year period. The study complied with the declaration of Helsinki and the registry was approved by the local ethics committees at each participating center.

Statistical analysis

Characteristics of patients, categorized by gender and year of procedure, were compared by the Wilcoxon rank-sum test or chi-square test, as appropriate. Clinical end points were compared between males and females by the chi-square test.

The probability of death by gender and year of the TAVI procedure was graphically displayed according to the Kaplan−Meier method, with comparison of cumulative events by the log-rank test. Multivariate analysis was performed using Cox proportional hazards regression modeling. Prespecified covariates in the multivariate model included age, gender, Society of Thoracic Surgeons score, creatinine clearance, aortic valve peak pressure, and permanent pacemaker at baseline. The association between gender and mortality in patients who underwent TAVI during the periods 2008 to 2012 and 2013 to 2016 was assessed by including a gender-by-year of procedure interaction term to the multivariate models. We also conducted a sensitivity analysis, repeating the Cox proportional hazards regression modeling with a follow-up censored at 3 years.

Data were registered in an electronic file and analyzed using SAS software version 9.4 (SAS Institute, Inc., Cary, North Carolina). A 2-tailed p value < 0.05 was considered statistically significant.

Results

Our study cohort included 1,370 (54.2%) women and 1,159 (45.8%) men. Patients' baseline and procedural characteristics are presented in Supplementary Table 1. Female patients who underwent TAVI were more likely to be older and to present with smaller body-surface area and peripheral artery diameters, whereas male patients were more likely to present with a history of coronary heart disease, peripheral vascular disease, and smoking. Moreover, echocardiographic parameters demonstrated smaller aortic valve area and annulus with higher transvalvular gradients in female patients. However, estimated ejection fraction was lower in male patients. The preferred procedural access site in both genders was the transfemoral approach, with more male patients receiving larger-sized prostheses valves. These gender-related differences persisted during both follow-up periods.

In the period 2013 to 2016 (Table 1), female patients were more likely to be defined as frail and to present with a more advanced New York Heart Association functional class compared with male patients. However, female patients were less likely to have a history of stroke, and the poorer renal function observed in earlier years was no longer apparent. Also, although the ratio of self-expandable to balloon-expandable valves in female patients remained constant, there was an increased use of balloon-expandable valves in male patients in the years 2013 to 2016.

Procedural and in-hospital complications are presented in Table 2 and Figure 1. During the years 2008 to 2012, male patients more frequently required a second valve and an open surgery compared with female patients. Furthermore, the rates of in-hospital myocardial infarction, pacemaker implantation, stroke, and significant (moderate or greater) in-hospital paravalvular leak (PVL) were also significantly higher in men than in female patients.

During the years 2013 to 2016, procedural mortality and the rates of valve migration and malposition were lower in men than in women. The PVL rates were comparable between genders. During the years 2013 to 2016, newer generation prosthesis valves (Edwards SAPIEN 3 and Medtronic Evolut-R) became available. In a subanalysis of the 2013 to 2016 cohort, we found that the use of newer generation valves versus older generation valves was associated with a lower rate of greater than or equal to moderate PVL in male patients (7.6% vs 1%, $p = 0.001$), whereas the rate of greater than or equal to moderate PVL in female patients had not changed (5.6% vs 5.2%, $p = 0.837$; Figure 2).

Vascular complications and bleeding events were more common in female patients during both time periods analyzed ($p < 0.05$ for both comparisons).

The cumulative incidence of mortality through a median of 2.3 years intraquartile range (IQR 1.2, 4.4 years) of follow-up was significantly lower in female patients compared with male patients during the years 2008 to 2012 (median follow-up, 4.7 years [IQR 2.3, 5.7]), but not during the years 2013 to 2016 (median follow-up 1.7 years [IQR 0.9, 2.7; Figure 3]). Multivariate analysis (Table 3) showed that female patients who underwent TAVI between the years 2008 and 2012 had a 26% lower risk of death compared with male patients ($p = 0.004$), but there were no gender-related differences in mortality risk between the years 2013 and 2016 (hazard ratio 1.07, $p = 0.6$, gender-by-year of procedure, $p = 0.027$ for interaction). Consistent results were found in a sensitivity analysis, repeating the Cox proportional hazards regression modeling with follow-up censored at 3 years (gender-by-year of procedure, $p = 0.002$ for interaction).

Discussion

The main finding of the present study is that the survival advantage post-TAVI in female versus male patients during the early TAVI years has diminished in the contemporary TAVI era. Moreover, the majority of procedural and in-hospital complication rates decreased in male patients and became comparable between the genders.

Various studies worldwide have consistently shown favorable long-term survival following TAVI in female patients versus male patients.[1,2,7,11,14] This survival advantage in female patients has been hypothesized to be attributed

Table 1
Temporal trends in patient's baseline and procedural characteristics categorized by gender and period of the procedure

Variable	Procedure years 2008 to 2012		Procedure years 2013 to 2016	
	Men (n = 372)	Women (n = 523)	Men (n = 787)	Women (n = 847)
Age (years)	82.1± 6.7	83.1± 5.7	82± 6.9	82± 6.3
Body surface area (m^2)	1.87±0.16	1.68±0.7*	1.88 ± 0.17	1.69 ±0.17†
Hypertension	85%	89%	87%	85%
Dyslipidemia	79%	78%	76%	76%
Diabetes mellitus	36%	31%	42%	39%
Peripheral vascular disease	25%	15%*	16%	9%†
Current smoker	7%	4%*	7.5%	4%*
Ischemic heart disease	68%	42%†	66%	38%†
Prior thoracotomy	32%	10%†	21%	6%†
Prior stroke	16%	12%	18%	13%**
Porcelain aorta	4%	7%	3.9%	4.8%
Frailty	12%	17%	18%	37%†
EuroSCORE I (%)	15.8 (8.9, 24.7)	13.6 (9.0, 21.8)	12.7 (8, 22)	12.1(8.4, 18)*
EuroSCORE II (%)	4.7 (2.8, 9.1)	4.3 (2.6, 6.1)*	3.6 (2.1, 6.9)	3.4 (2.2, 5.6)
STS-PROM (%)	4.0 (2.8, 6.3)	4.7 (3.3, 6.8)*	3.4 (2.4, 5.3)	3.7 (2.7,5.5)*
New York Heart Association Functional Class 3 or 4	86.6%	86%	75.6%	82.5%†
Estimated glomerular filtration rate (ml/min/1.73 m^2)‡	47.7 (36.6, 61.6)	41.7 (31.9, 54.4)†	49.9 (38, 64)	48.7 (36, 62)
Echocardiographic parameters				
Aortic valve area (cm^2)	0.7 (0.6, 0.8)	0.6 (0.5, 0.76)†	0.7 (0.6, 0.87)	0.7(0.53,0.8)†
Aortic valve peak velocity (m/s)	4.0 (3.5, 4.6)	4.4 (3.8, 4.7)*	4.2 (3.8, 4.6)	4.2 (3.8,4.7)
Transvalvular gradient, mean (mmHg)	43 (34, 54)	48 (39,58)†	42 (34,52)	46 (37,57)†
Ejection fraction (%, Simpson)	55 (45, 60)	60 (60, 60)†	60 (45, 60)	60 (55, 60)†
Cardiac computed tomography parameters				
Preprocedural cardiac computed tomography evaluation	12	16	76	77
Aortic valve annulus area, (mm^2)	500(435, 532)	370 (343, 419)†	492 (445, 540)	385 (350, 418)†
Aortic valve annulus perimeter (mm)	80 (76, 84)	70 (68, 74)†	79 (75,83)	71 (68,74)†
Left common femoral (mm)	8 (7, 9.4)	7 (7, 8)†	7.0 (6.5,8.4)	7.0 (6,7.5)†
Right common femoral (mm)	8 (7, 9)	7 (6.5, 8.4)*	7.2 (6.4,8.2)	6.8 (6, 7.5)†
Procedural characteristics				
Access site				
Transfemoral	88%	89%	93%	94%
Transapical	6%	8%	5%	4%
Transaxillary	6%	3%	2%	2%
Self-expandable valves	76%	67%*	49%	69%†
Prosthesis size ≥29 mm	62.4%	16.1%†	59.5%	21.3%†

Data are presented as median (twenty-fifth, seventy-fifth quartiles) or as percentages.
* p value ≤0.05 for male patients versus female patients in the specified time period.
† p ≤0.001 for male patients versus female patients in the specified time period.
‡ Estimated glomerular filtration rate is calculated based on the Cockcroft−Gault formula.
EuroSCORE = European System for Cardiac Operative Evaluation; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2
Procedural complications categorized by gender and procedure period

	Procedure years 2008 to 2012			Procedure years 2013 to 2016		
	Men (n = 372)	Women (n = 523)	p value	Men (n = 787)	Women (n = 847)	p value
Procedure success	95.1%	97.4%	0.097	96.1%	94.9%	0.284
Need for a second valve	5.4%	2.1%	0.008	1.9%	3.4%	0.073
Valve migration/malposition	8.4%	4.4%	0.109	1.1%	3.2%	0.031
Balloon postdilation	14%	5%	<0.001	21.5%	19.3%	0.287
Conversion to open surgery	1.7%	0.2%	0.041	0.5%	0.6%	0.763
Annulus or aortic rupture	0.0%	0.0%	NA	0.4%	0.5%	0.703
Mitral valve apparatus damage/dysfunction	0.3%	0.2%	0.824	0.2%	0.2%	0.966
Cardiac tamponade	1.9%	4%	0.072	1.2%	2.0%	0.166
Ventricular septal perforation	0.0%	0.5%	0.226	0.3%	0.2%	0.529
Coronary obstruction	1%	0.5%	0.422	0.2%	0.8%	0.118
Procedural mortality	1.3%	1.1%	0.792	0.6%	1.9%	0.025

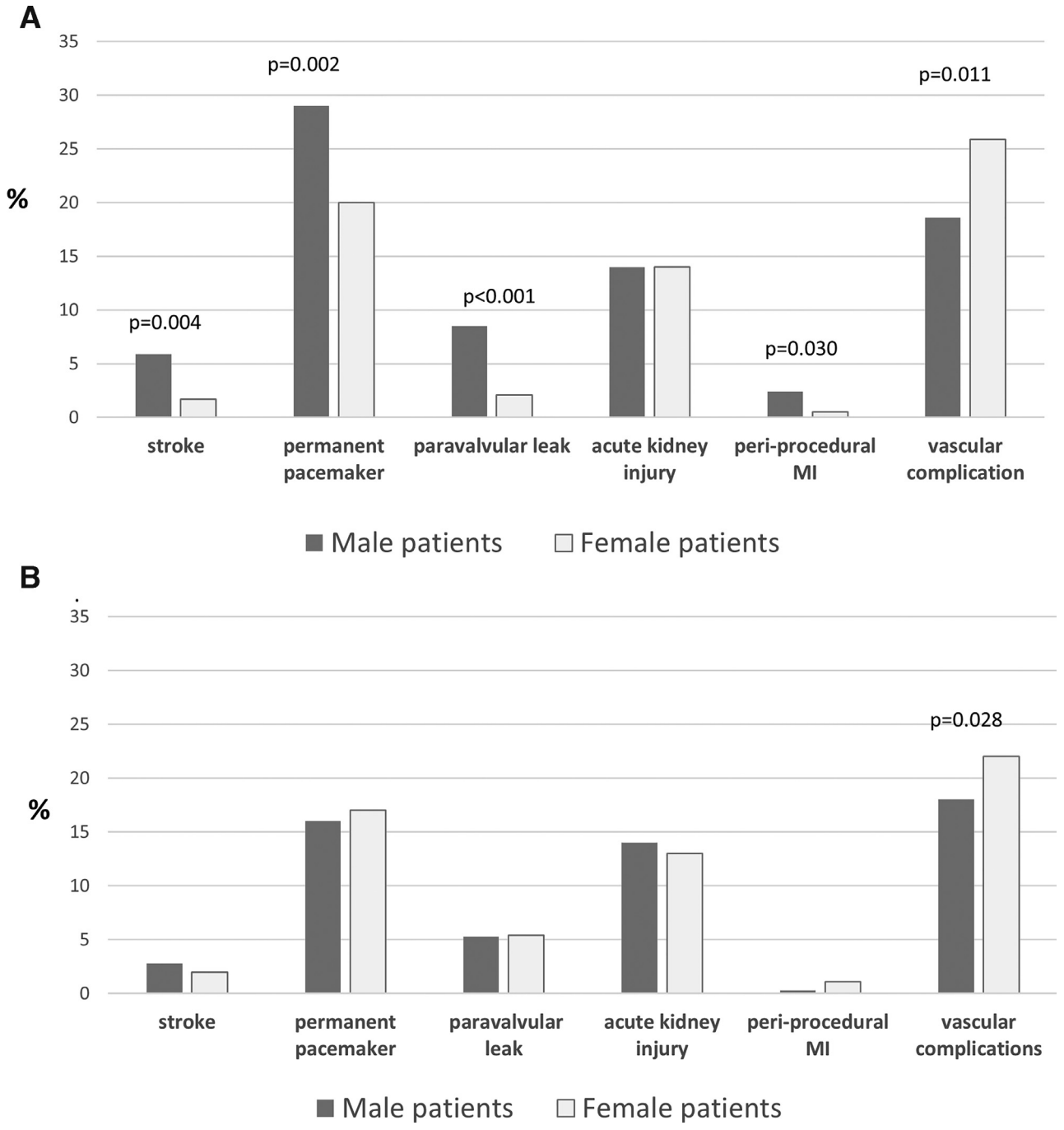

Figure 1. In-hospital complications post-TAVI categorized by gender and year of procedure. Data are presented as percentages. In-hospital complications post-TAVI in men versus women in the different range of years when the procedure was performed: (*A*) 2008 to 2012 and (*B*) 2013 to 2016. MI = myocardial infarction; TAVI = transcatheter aortic valve implantation.

to differences in left ventricular remodelling[15,16] and to a lower co-morbidity profile in women, which affects long-term survival.[2,17] Nevertheless, recently, a comparable long-term survival rate between genders was evident in a subanalysis of the PARTNER 2 S3 trial evaluating only patients with new-generation SAPIEN valves.[12] This trend is also demonstrated in our study, which consists of a large cohort with both self-expandable and balloon-expandable valves, and older and newer generations of valves. We clearly showed that although female patients had a long-term survival benefit in 2008 to 2012, no gender-related gaps in mortality risk were noted between the years 2013 and 2016, thus establishing an interaction between gender and period of procedure. Both prosthesis-related and patient-related characteristics may have contributed to these findings.

In this study, we describe temporal trends in gender-related disparities of valve implantation (such as a need for a second valve and valve malposition), all of which rely on proper prosthesis sizing. Importantly, significant (greater than or equal to moderate) PVL, a common complication of

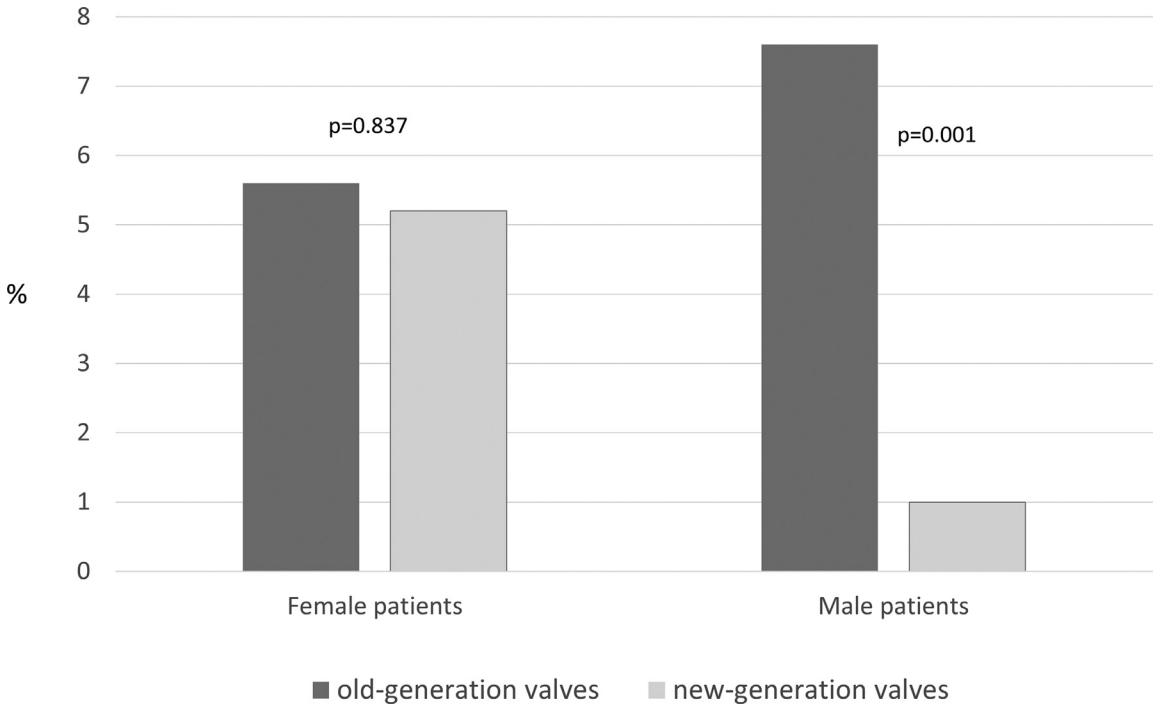

Figure 2. Rates of significant paravalvular leak in older versus newer generation prosthesis valves according to gender. Data are presented as percentages. Significant aortic paravalvular leak is defined as moderate or greater.

prosthesis undersizing[17,18] and an established risk factor for increased mortality,[18,19] was more prevalent in male patients during the early, but not the late, TAVI years.

Several advances in recent years have improved prosthesis valve sizing, and may therefore account for these temporal differences. First, use of multidetector computed tomography for annulus sizing has become a fundamental part of the pre-evaluation of patients, which allows better valve sizing, and consequently reduced PVL.[18,20] In our cohort, computed tomography annular sizing was performed in 14% versus 77% of patients in the years 2008 to 2012 and 2013 to 2016, respectively. Second, during the mid-late study period, newer generation prosthesis valves became available, with a broader size range and an emphasis on larger sizes. Moreover, the new-generation SAPIEN 3 valves have an additional subannular cuff, specifically designed to reduce the risk of PVL.[21−23]

Similar outcomes were recently reported from the PARTNER 2 S3 trial, which concluded that improved valve sizing predominantly benefitted male patients, with a decreased incidence of PVL.[12] Herein, we report a disproportionate benefit in males compared with females in a cohort receiving both SAPIEN and CoreValve prosthesis valves, possibly accounting for trends in survival. Female patients were more likely to receive an optimal valve size during the earlier TAVI era due to their smaller annular size, and thus experienced less adverse effects from prosthesis undersizing and PVL as opposed to male patients.[17,18] The relative female-to-male survival advantage in the earlier TAVI period was possibly due to the more frequent undersizing of valves in male patients and their higher rates of PVL, and not vice versa. Notably, several recent studies have linked improved prognosis in female patients with the use of first-generation valves.[24,25]

Differences in the baseline co-morbidities of female versus male patients might also have influenced the temporal trends in survival.[2,17] In the years 2008 to 2012, female patients who underwent TAVI presented with a more favorable cardiovascular co-morbidity profile compared with male patients, while in the years 2013 to 2016, female patients were more often defined as frail and presented with lower functional class. Furthermore, reduced rates of in-hospital complications in the late TAVI period in male patients, particularly the need for permanent pacemaker implantation and stroke, probably contributed to the comparable survival. Apart from improved device technology

Table 3
Multivariate analysis: analyzed by female gender and mortality by period of the procedure

Period of the procedure	HR (95% CI)	p value	p for interaction
2008-2016	0.86 (0.73-1.01)	0.064	0.027
2008-2012	0.74 (0.60-0.91)	0.004	
2013-2016	1.07 (0.83-1.38)	0.612	

Adjusted for age, STS score, creatinine clearance, aortic valve peak pressure, permanent pacemaker.
CI = confidence interval; HR = hazard ratio.

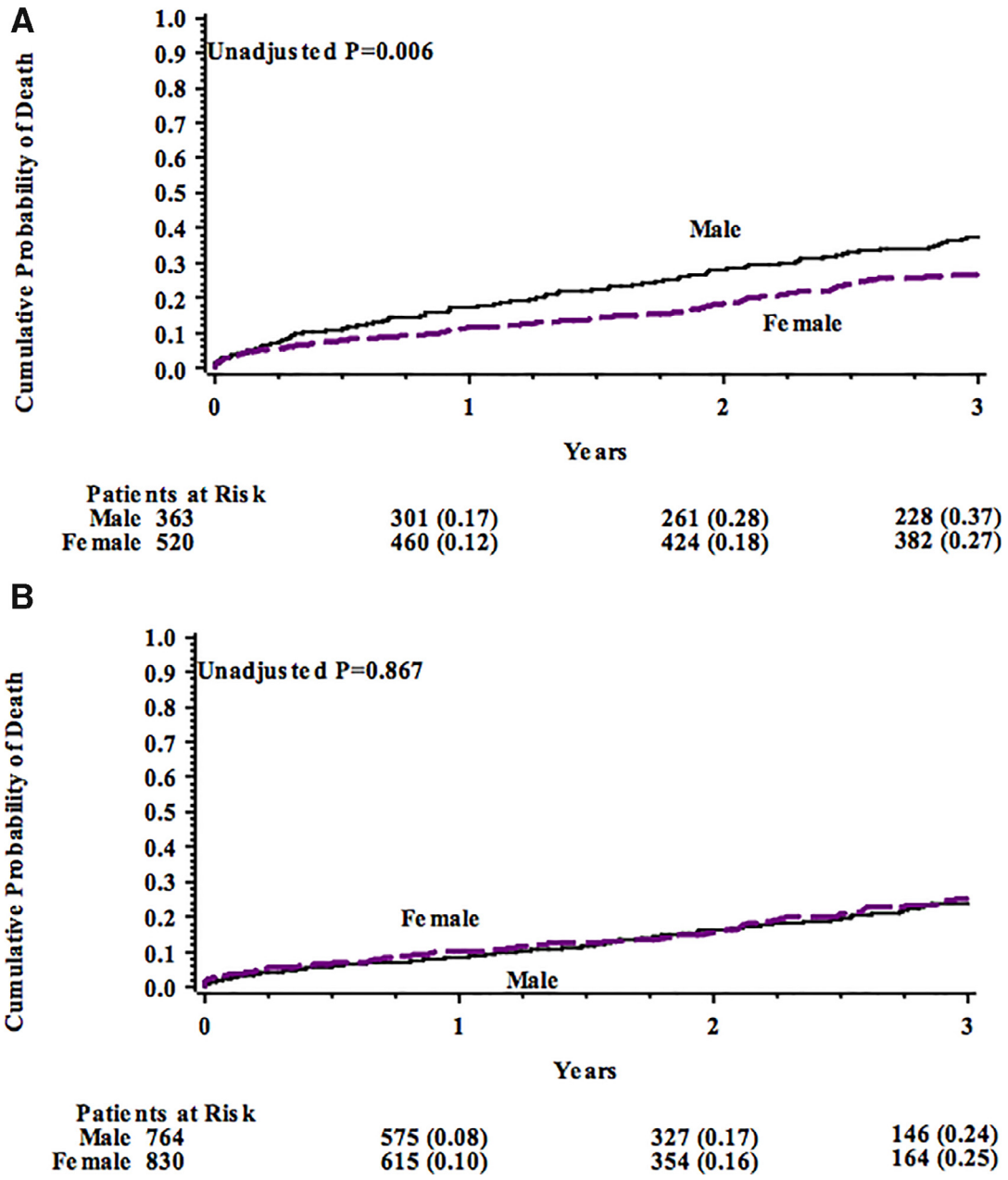

Figure 3. Cumulative long-term mortality post-TAVI during the years 2008 to 2012 and 2013 to 2016 categorized by gender. Kaplan–Meier estimates of probability of death in men versus women in the different range of years when the procedure was performed: (*A*) 2008 to 2012 and (*B*) 2013 to 2016.

and operators' experience, the more frequent usage of balloon versus self-expandable valves in male patients in contemporary TAVI years may explain the decline in pacemaker implantation rate in males,[26] whereas the increased need of balloon-post dilation in male versus female patients in early TAVI years may account for their higher stroke rate compared with females at that period.[27]

Surprisingly, despite the contemporary use of diminished sheath sizes, vascular and bleeding complications during the years 2013 to 2016 were still significantly higher in women versus men. Possible explanations for these findings could be females' older age and smaller diameter vessels.[2,28,29] Further study should focus on overcoming these inherent disadvantages.

Our study has several limitations. First, this was a retrospective study, with the inherit limitations associated with a retrospective cohort design. Second, the event rates of some outcome measures (e.g., annular rupture, tamponade) were small; therefore, our study was probably underpowered to detect any temporal changes associated with those outcomes. Third, the specific choice of prosthetic valve was partially influenced by institutional considerations. Importantly, our aim was to define temporal trends and associations; therefore, no cause-and-effect suppositions can be drawn.

Our study, which was diverse for valve type and generation, demonstrated temporal trends in gender-related disparities, both in clinical characteristics and in procedural complications and outcomes. We show that the more favorable long-term

prognosis that has been repeatedly described in female versus male patients in the early TAVI years has diminished over time with contemporary TAVI. This may be attributed to current technological advances and improved valve sizing, with a more significant benefit in favor of male patients.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.09.018.

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