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Revisiting Sex Equality With Transcatheter Aortic Valve Replacement Outcomes

A Collaborative, Patient-Level Meta-Analysis of 11,310 Patients

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ABSTRACT

BACKGROUND There has been conflicting clinical evidence as to the influence of female sex on outcomes after transcatheter aortic valve replacement.

OBJECTIVES The aim of this study was to evaluate the impact of sex on early and late mortality and safety end points after transcatheter aortic valve replacement using a collaborative meta-analysis of patient-level data.

METHODS From the MEDLINE, Embase, and the Cochrane Library databases, data were obtained from 5 studies, and a database containing individual patient-level time-to-event data was generated from the registry of each selected study. The primary outcome of interest was all-cause mortality. The safety end point was the combined 30-day safety end points of major vascular complications, bleeding events, and stroke, as defined by the Valve Academic Research Consortium when available.

RESULTS Five studies and their ongoing registry data, comprising 11,310 patients, were included. Women constituted 48.6% of the cohort and had fewer comorbidities than men. Women had a higher rate of major vascular complications (6.3% vs. 3.4%; $p < 0.001$), major bleeding events (10.5% vs. 8.5%; $p = 0.003$), and stroke (4.4% vs. 3.6%; $p = 0.029$) but a lower rate of significant aortic incompetence (grade ≥2; 19.4% vs. 24.5%; $p < 0.001$). There were no differences in procedural and 30-day mortality between women and men (2.6 % vs. 2.2% [$p = 0.24$] and 6.5% vs. 6.5% [$p = 0.93$], respectively), but female sex was independently associated with improved survival at median follow-up of 387 days (interquartile range: 192 to 730 days) from the index procedure (adjusted hazard ratio: 0.79; 95% confidence interval: 0.73 to 0.86; $p = 0.001$).

CONCLUSIONS Although women experience more bleeding events, as well as vascular and stroke complications, female sex is an independent predictor of late survival after transcatheter aortic valve replacement. This should be taken into account during patient selection for this procedure. (J Am Coll Cardiol 2015;66:221–8) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

OR = odds ratio

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is the new standard of care for patients with symptomatic aortic stenosis who are deemed to have high or prohibitive surgical risk, with >80,000 procedures performed to date in >40 countries worldwide (1,2). The current evidence with regard to the impact of sex on outcomes in TAVR is insufficient and conflicting, with some studies reporting improved mid- to long-term survival in women (3–5) and other studies demonstrating similar or worse survival compared with men (6,7). This remains an overall unresolved and poorly described issue that has significant implications with regard to patient selection for this procedure. Therefore, to evaluate the influence of sex on clinical outcomes in high-risk patients undergoing TAVR, we performed a collaborative meta-analysis of individual patient-level data.

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METHODS

STUDY COHORT. We conducted searchers of the Cochrane Controlled Trials Registry and MEDLINE and Embase databases for reports published from January 2002 through June 2014 using the following pre-defined search terms: transcatheter aortic valve implantation/replacement and outcome or gender or sex. We restricted our analysis to published data. References from reviews and selected reports were also examined for potential relevant citations. No language restrictions were applied. Studies were selected by 2 independent reviewers (S.A.O., M.-C.M.).

We restricted our analysis to trials that met all of the following inclusion criteria: 1) inclusion of patients with severe aortic valve stenosis undergoing TAVR via the transfemoral, transapical, transaortic, transcarotid, or transsubclavian approach; 2) either a single-group cohort or a controlled comparison between TAVR and surgical aortic valve replacement through random or nonrandom allocation; and 3) available data on at least short-term (30-day or in-hospital) and 1-year all-cause mortality. Randomized controlled trials, registries, and pre-specified subgroups of studies reporting TAVR data were considered for analysis. Full-text articles were included.

Exclusion criteria were duplicate reports, unpublished meeting abstracts and studies with <200 patients, and studies that did not perform multivariable adjustment. The quality of randomized controlled trials included in the meta-analysis was assessed for descriptive purpose using the Jadad score for randomized controlled trials and the quality of non-randomized studies (8) using the Newcastle-Ottawa Scale for cohort studies (Online Table 1). A database containing individual patient-level time-to-event data was generated from the registry of each of the studies selected.

DEFINITIONS AND ENDPOINTS. The primary efficacy end point was mortality from any cause at longest follow-up. The safety end point was the combined 30-day safety end points, as defined by the individual studies and by the Valve Academic Research Consortium when used, of major vascular complications, bleeding, stroke, and myocardial infarction (9). The secondary end points were the individual safety end points of the combined Valve Academic Research Consortium safety end point and device success, which was defined as successful vascular access, delivery, and deployment of 1 prosthesis and correct position and performance of the prosthetic valve. Other secondary end points included all-cause mortality at 1- and 2-year follow-up.

STATISTICAL ANALYSIS. A database containing individual patient-level, time-to-event data was generated from the registry of each of the studies selected. The primary analysis was performed on all patients. Pre-specified analyses were performed on the subgroups according to valve type (the balloon-expandable SAPIEN [Edwards Lifesciences, Irvine, California] or the self-expandable CoreValve [Medtronic, Dublin, Ireland]) and access (femoral or apical). Categorical variables were compared using chi-square or Fisher exact tests. Continuous variables are reported as mean ± SD and were compared using Student *t* tests. For variables that were not normally distributed, Wilcoxon tests were used to compare groups. Time-to-event data are reported and displayed using the Kaplan-Meier method, with comparisons between groups performed using log-rank tests. Cumulative survival curves by sex were constructed using the Kaplan-Meier method. A stepwise

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Cox multivariate analysis including all variables with p values <0.05 in each univariate analysis were used. Results are presented as hazard ratios with 95% confidence intervals (CIs). The p value threshold for statistical significance was set at 0.05. Analyses were conducted using SPSS version 21 (SPSS, Inc., Chicago, Illinois).

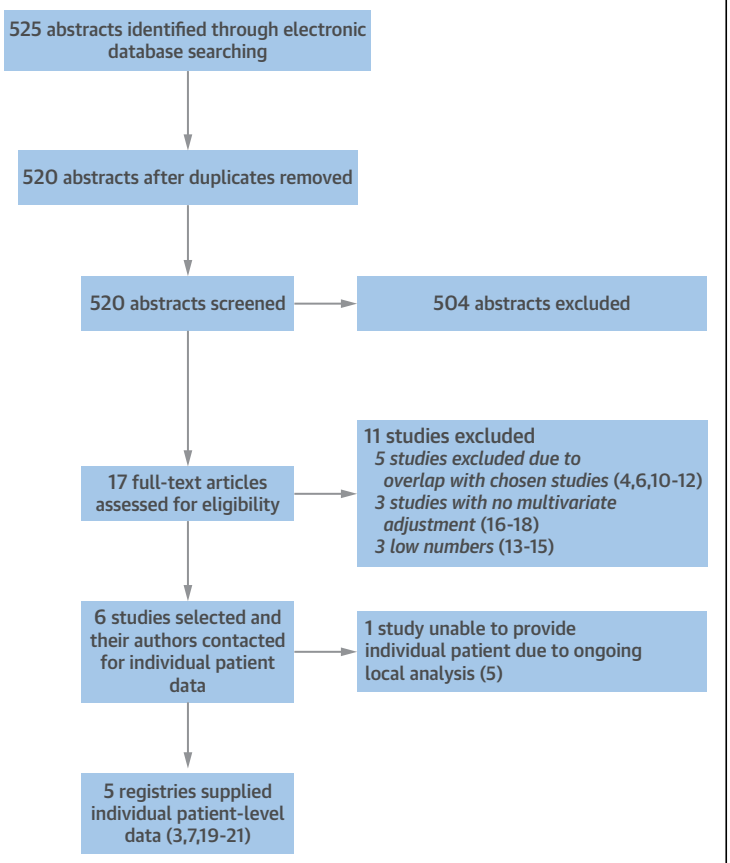
RESULTS

Our search identified 520 reports (**Figure 1**), of which 508 were excluded after abstract screening. Of the 17 full-text reports assessed, 5 studies were excluded because they contained patient data that overlapped with our selected studies (4,6,10-12), 3 were excluded because of small sample sizes (n < 200) (13-15), and 3 were excluded because the investigators did not perform multivariate adjustment and/or reported 30-day follow-up only (16-18). Finally, 6 studies were selected and the principal investigators contacted (3,5,7,19-21). Five investigators answered positively, leaving a total of 5 studies and their registry data, comprising a total of 11,310 patients, for inclusion in the analysis (3,7,19-21).

PATIENT POPULATION. The characteristics of the studies and patient population are described in Online Table 2. Overall, patients were prospectively enrolled from January 2005 to December 2012 in 1 of the 5 international multicenter trials or registries. The criteria for inclusion are detailed in each individual study, but all patients had severe symptomatic aortic stenosis and were at high risk or were ineligible for conventional surgery. TAVR was performed using conventional techniques, as have been previously described, via the transfemoral, transapical, transsubclavian, transaxillary, and transaortic approaches. Valves implanted included the SAPIEN and SAPIEN XT devices in 23-, 26-, and 29-mm sizes (Edwards Lifesciences); the CoreValve device in 23-, 26-, 29-, and 31-mm sizes (Medtronic); and the repositionable Portico valve (St. Jude Medical, St. Paul, Minnesota).

BASELINE CHARACTERISTICS. The baseline clinical demographics of the patients are presented in **Table 1**. Of the 11,310 patients included in the final cohort, 48.6% (n = 5,502) were women. Men had a higher rate of risk factors than women, with a higher prevalence of diabetes, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft surgery, peripheral vascular disease, poor left ventricular systolic function (left ventricular ejection fraction <30%), 3-vessel coronary artery disease, a higher logistic European System for Cardiac Operative Risk Evaluation score, and pulmonary disease. Women were older, had higher transvalvular gradients and higher pulmonary artery pressures, and had smaller annular sizes.

FIGURE 1 Study Selection



A flow diagram of study selection and exclusion is shown (3-7,10-21).

PROCEDURAL CHARACTERISTICS AND OUTCOMES. The procedural characteristics are presented in **Table 1**. The majority of the overall cohort underwent TAVR via the transfemoral approach, followed by the transapical and transsubclavian approaches. The transfemoral approach was more common in women than in men. Balloon-expandable devices were used more frequently than self-expandable valves in the overall cohort, and a higher proportion of women than men received balloon-expandable valves.

Clinical outcomes are listed in **Table 2**. In the whole group, procedural success was achieved in 97% of patients, irrespective of sex. There was no difference in the incidence of valve migration or embolization, conversion to conventional surgery, or procedure-related death. There was, however, a higher rate of

major vascular complications and major bleeding including cardiac tamponade in women. Men had a significantly higher rate of aortic incompetence (grade >2) and were more likely to need pacemaker implantation post-procedurally than women.

TABLE 1 Baseline Characteristics

	Women (n = 5,502)	Men (n = 5,808)	All Patients (n = 11,310)	p Value
Age, yrs	83.3 ± 7.5	81.6 ± 8.2	82.4 ± 7.9	<0.001
BMI, kg/m^2	26.5 ± 6.1	26.6 ± 4.8	26.5 ± 5.5	0.46
BSA	1.7 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	<0.001
Myocardial infarction	805 (14.6)	1,657 (28.6)	2,462 (21.8)	<0.001
Any smoking history	1,204 (21.9)	2,279 (39.3)	3,483 (30.8)	<0.001
Peripheral vascular disease	1,345 (24.5)	2,053 (35.4)	3,398 (30.1)	<0.001
Diabetes (any)	1,367 (24.9)	1,713 (29.5)	3,080 (27.2)	<0.001
Previous stroke (CVA)	836 (15.2)	992 (17.2)	1,828 (16.2)	0.005
Previous PCI	929 (17.6)	1,300 (23.4)	2,229 (20.6)	<0.001
CABG	771 (14.1)	2,381 (41.1)	3,152 (28)	<0.001
Pulmonary disease	1,553 (28.2)	1,824 (31.4)	3,377 (29.9)	<0.001
CrCl, ml/min/1.73 m^2	54.1 ± 26	55.6 ± 25.7	54.9 ± 25.9	<0.001
Renal insufficiency (CrCl <60 ml/min/1.73 m^2)	3,553 (66.1)	3,652 (64.3)	7,205 (65.2)	0.041
Coronary artery disease	2,120 (38.6)	3,319 (57.3)	5,439 (48.2)	<0.001
1-vessel disease	901 (18.8)	986 (19)	1,887 (18.9)	0.80
2-vessel disease	529 (11)	818 (15.8)	1,347 (13.5)	<0.001
3-vessel disease	519 (10.8)	1,363 (26.3)	1,882 (18.9)	<0.001
LVEF <50%	1,342 (24.4)	2,404 (41.5)	3,746 (33)	<0.001
30% < LVEF < 50%	813 (14.8)	1,408 (24.3)	2,221 (19.7)	<0.001
LVEF <30%	251 (4.6)	581 (10)	832 (7.3)	<0.001
Logistic EuroSCORE	22.2 ± 13.9	23.9 ± 15.4	23.1 ± 14.7	<0.001
Aortic valve gradient, mm Hg	61.2 ± 26.7	55.8 ± 23.9	58.4 ± 25.4	<0.001
Aortic valve area, cm^2	0.7 ± 1.9	0.8 ± 2.1	0.7 ± 2	<0.001
Annular size, mm	20.7 ± 3.6	22.8 ± 5.1	21.8 ± 4.5	<0.001
PAP, mm Hg	51 ± 18.8	47.4 ± 15	49.2 ± 17.1	<0.001
PAP ≥60 mm Hg	1,089 (22.1)	869 (16.7)	1,958 (19.3)	<0.001
Procedural characteristics				
Implantation approach				
Transapical	1,236 (22.5)	1,353 (23.3)	2,589 (22.9)	0.29
Transfemoral	3,874 (70.4)	3,945 (67.9)	7,819 (69.1)	0.004
Transsubclavian	219 (4)	356 (6.1)	575 (5.1)	<0.001
Transaxillary	10 (0.2)	6 (0.1)	16 (0.1)	0.27
Transaortic and other	103 (1.9)	93 (1.6)	196 (1.7)	0.27
Valve type				
CoreValve	2,038 (35.2)	1,724 (31.4)	3,762 (33.3)	<0.001
SAPIEN	3,762 (64.8)	3,736 (67.9)	7,498 (66.3)	<0.001
Portico	0 (0)	38 (0.7)	38 (0.3)	<0.001
Valve size (mm)				
23	2,879 (52.9)	620 (10.8)	3,499 (31.2)	<0.001
26	2,097 (38.5)	3,236 (56.2)	5,333 (47.6)	<0.001
29	449 (8.2)	1,714 (29.8)	2,163 (19.3)	<0.001
31	19 (0.3)	185 (3.2)	204 (1.8)	<0.001
Femoral diameter (left), mm	7.2 ± 1.2	7.9 ± 1.4	7.5 ± 1.3	<0.001
Femoral diameter (right), mm	7.5 ± 1.1	7.7 ± 1.7	7.6 ± 1.4	<0.001

Values are mean ± SD or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; CrCl = creatinine clearance; CVA = cerebrovascular accident; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; PAP = pulmonary artery pressure.

PROCEDURAL CHARACTERISTICS AND OUTCOMES BY VALVE TYPE. In a subanalysis of procedural and 30-day outcomes according to valve type, pacemaker implantation was significantly more common in men among the patients who received self-expandable valves (26.4% vs. 19.4%; p < 0.001), but there was no statistically significant difference between the sexes in the balloon-expandable valve group (9.3% vs. 8.4%; p = 0.15) (Online Table 3). Valve migration also was more common in men treated with balloon-expandable valves (2.5% vs. 0.8%; p = 0.008), but no statistical difference existed between the sexes in patients treated with self-expandable valves (1.5% vs. 0.8%; p = 0.067). Likewise, significant aortic incompetence (grade > 2) occurred more frequently in men than in women treated with balloon-expandable valves (5.2% vs. 2.8%; p < 0.001), but there was no difference between women and men treated with self-expandable valves (3.4% vs. 2.5%; p = 0.16). The rate of stroke at 30-day follow-up was higher in women who received self-expandable valves, but no difference existed in patients who received self-expandable valves. However, major vascular complications and major bleeding were consistently higher in women regardless of the type of valve implanted.

ALL-CAUSE MORTALITY. All-cause mortality rates at 30 days were the same in men and women, despite the differences in baseline risk profiles. The median duration of follow-up was 387 days (interquartile range: 192 to 730 days) from the index procedure. The Kaplan-Meier survival curve demonstrates a significant survival advantage for women (log-rank p < 0.001) (**Figure 2**). The 1- and 2-year survival estimates were 82.7% (95% CI: 81.6% to 84.0%) and 74.0% (95% CI: 72.5% to 75.4%), respectively, for women and 78.2% (95% CI: 77.0% to 79.3%) and 67.8% (95% CI: 66.3 to 69.3%), respectively, for men.

In the Cox model for all-cause mortality, the adjusted hazard ratio for female sex was 0.79 (95% CI: 0.73 to 0.86; p < 0.001). The independent predictors of late mortality are listed in **Table 3**.

Female sex was consistently associated with improved survival regardless of valve type and route of access when subanalyses were performed in these subgroups (Online Figure 1).

In a subanalysis comparing the predictors of mortality between women and men, both sexes shared the predictors body mass index, pulmonary disease, creatinine clearance, aortic incompetence post-implantation (grade >2), and a nonfemoral approach (Online Table 4). However, age was a predictor of mortality in men but not in women.

DISCUSSION

We performed a patient-level pooled meta-analysis of 5 prospective studies and their registries including a total of 11,310 patients. The most important finding of our study is that female sex was associated with a survival advantage compared with male patients, even after adjustment for baseline demographic and clinical factors and valve type. There was, however, no difference between male and female patients with respect to 30-day mortality (**Central Illustration**). This was despite women having higher rates of major vascular, bleeding, and stroke events.

We observed an almost 2-fold increase in the rate of vascular complications in women regardless of the type of valve used. This observation is consistent with previously published studies (3,6,7), and a number of factors have been reported to be predictors of vascular complications after transfemoral TAVR, including introducer sheath-to-femoral artery ratio and femoral artery calcium score (22,23). Women were of smaller stature and had smaller femoral arteries than men in this combined cohort, and this may explain the higher rate of complications.

Major bleeding at 30 days was significantly more frequent in female patients, an observation that has also been reported in some other studies (3,6); however, this finding has not been consistent across all studies (7,12). Again, the likely mechanisms for this are the lower body surface area and older age of female patients. These data are comparable to peri-percutaneous coronary intervention bleeding data, in which female sex is a significant risk factor (24).

To our knowledge, this is the first analysis to demonstrate a significantly higher rate of stroke in women undergoing TAVR (**Central Illustration**). This is a somewhat surprising finding, and it is difficult to explain given the lower baseline vascular risk in women. We also demonstrated that this increased stroke risk seems to occur in patients who receive self-expandable valves but not in those who receive balloon-expandable valves, without a clear explanation.

Although female patients had significantly higher rates of adverse events periprocedurally, there was no impact on short-term mortality, and female patients continued to show better late survival. There are some potential mechanisms for the observed advantage. First, the impact of these periprocedural events may be less in women compared with men. To evaluate this, we performed an analysis of the associations of these periprocedural events with 30-day mortality. There were no significant differences between women and men with respect to the impact of major vascular complications (odds ratio [OR]: 2.57; 95% CI: 1.87 to 3.57; $p < 0.001$ vs. OR: 2.78; 95% CI: 1.85 to 4.12; $p < 0.001$) and major bleeding (OR: 9.64; 95% CI: 7.27 to 12.79; $p < 0.001$ vs. OR: 10.20; 95% CI: 7.64 to 13.65; $p < 0.001$).

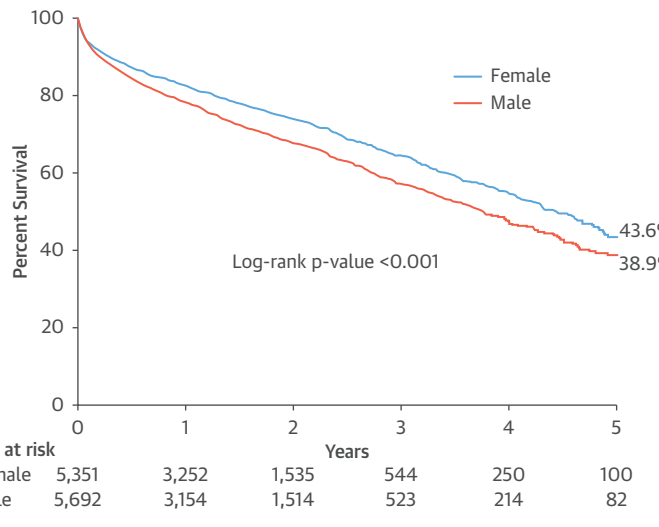
However, stroke appeared to have a more significant impact on short-term mortality in men than in women (OR: 15.4; 95% CI: 11.59 to 20.48; $p < 0.001$ vs. OR: 20.65; 95% CI: 15.30 to 27.87; $p < 0.001$). This may in some part explain the lack of sex difference at 30 days despite more procedural events.

TABLE 2 Procedural and 30-Day Outcomes

	Women (n = 5,502)	Men (n = 5,808)	All Patients (n = 11,310)	p Value
Device success	5,341 (97.3)	5,620 (96.9)	10,961 (97.1)	0.22
Conversion to conventional surgery	53 (1)	50 (0.9)	103 (0.9)	0.57
Valve embolization	45 (1)	74 (1.5)	119 (1.2)	0.018
New permanent pacemaker	650 (11.9)	881 (15.3)	1,531 (13.7)	<0.001
Cardiac tamponade	71 (1.3)	41 (0.7)	112 (1)	0.002
Major vascular complication	349 (6.3)	195 (3.4)	544 (4.8)	<0.001
Aortic incompetence (grade ≥2)	914 (19.4)	1,243 (24.5)	2,157 (22)	<0.001
Aortic incompetence (grade >2)	128 (2.7)	235 (4.6)	363 (3.7)	<0.001
Procedure-related death (<72 h)	140 (2.6)	129 (2.2)	269 (2.4)	0.24
All-cause death (30-day)	351 (6.5)	371 (6.5)	722 (6.5)	0.93
Myocardial infarction (30-day)	124 (2.3)	128 (2.2)	252 (2.2)	0.86
Stroke (30-day)	243 (4.4)	210 (3.6)	453 (4)	0.029
Major bleeding (30-day)	379 (10.5)	313 (8.5)	692 (9.5)	0.003

Values are n (%).

FIGURE 2 Kaplan-Meier Plot of All-Cause Mortality



Women's survival advantage throughout the follow-up period is depicted.

TABLE 3 Predictors of Long-Term All-Cause Mortality

	Death (n = 3,072)	No Death (n = 8,417)	p Value	HR (95% CI) Univariate Model	HR (95% CI) Multivariate Model (Cox)	p Value
Age, yrs	82.2 ± 8.2	83.1 ± 7.2	<0.001		1.00 (1.00–1.02)	0.002
Women	1,359 (44.2)	4,037 (50.1)	<0.001	0.79 (0.72–0.86)	0.79 (0.72–0.87)	<0.001
BMI, kg/m^2	26.7 ± 5.4	25.9 ± 5.5	<0.001		0.98 (0.98–0.99)	<0.001
Previous myocardial infarction	751 (24.5)	1,666 (20.7)	<0.001	1.24 (1.13–1.37)		
Active smoker	1,102 (35.9)	2,320 (28.8)	<0.001			
Peripheral vascular disease	1,069 (34.9)	2,287 (28.5)	<0.001	1.38 (1.27–1.51)	1.11 (1.01–1.21)	0.026
Diabetes (any)	864 (28.1)	2,174 (27.0)	0.23	1.06 (0.97–1.16)		
Previous stroke (CVA)	536 (17.6)	1,260 (15.7)	0.018	1.14 (1.02–1.28)		
Previous PCI	658 (23.4)	1,526 (19.4)	<0.001	1.27 (1.15–1.41)	0.93 (0.84–1.03)	0.17
CABG	868 (28.3)	2,253 (28.1)	0.82	1.01 (0.92–1.10)		
PAP ≥60 mm Hg	497 (19.3)	1,449 (19.6)	0.70	0.98 (0.87–1.09)		
Pulmonary disease	1,070 (34.8)	2,258 (28.0)	<0.001	1.37 (1.26–1.50)	1.32 (1.22–1.44)	<0.001
CrCl, ml/min/1.73 m^2	56.4 ± 26.2	50.8 ± 24.9	<0.001			
Renal insufficiency (CrCl <60 ml/min/1.73 m^2)	2,138 (70.8)	4,952 (63)	<0.001	1.43 (1.30–1.56)	1.22 (1.11–1.35)	<0.001
Coronary artery disease	1,587 (51.8)	3,789 (47.1)	<0.001	1.21 (1.11–1.31)		
LVEF <30%	244 (8.8)	580 (7.5)	0.025	1.19 (1.02–1.40)		
EuroSCORE	22.1 ± 14	25.9 ± 15.9	<0.001			
Aortic valve gradient, mm Hg	58.4 ± 24.7	57.2 ± 27.0	0.058			
Aortic valve area, cm	0.7 ± 1.0	0.8 ± 3.5	0.12			
Annular size, mm	21.6 ± 3.0	21.8 ± 5.0	0.82			
Femoral diameter (left), mm	7.5 ± 1.3	7.4 ± 1.4	0.59			
Femoral diameter (right), mm	7.6 ± 1.4	7.5 ± 1.3	0.063			
Transfemoral access	1,911 (62.2)	5,745 (71.3)	<0.001	0.66 (0.61–0.72)	0.77 (0.71–0.85)	<0.001
Balloon-expandable valve	1,385 (45.1)	3,521 (43.7)	0.18	1.06 (0.97–1.15)		
Aortic incompetence (grade ≥2)	658 (26.1)	1,486 (20.9)	<0.001	1.33 (1.20–1.48)	1.74 (1.46–2.07)	<0.001

Values are mean ± SD or n (%).

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

Second, although women were older than men, they had a lower baseline cardiovascular risk profile and fewer comorbidities. Although the sex difference in mortality outcomes remained significant after adjustment for these demographic, procedural, and clinical differences, the potential impact of these factors and other unidentified confounders cannot be underestimated. Furthermore, the recognized longer life expectancy described in women contributes to this explanation.

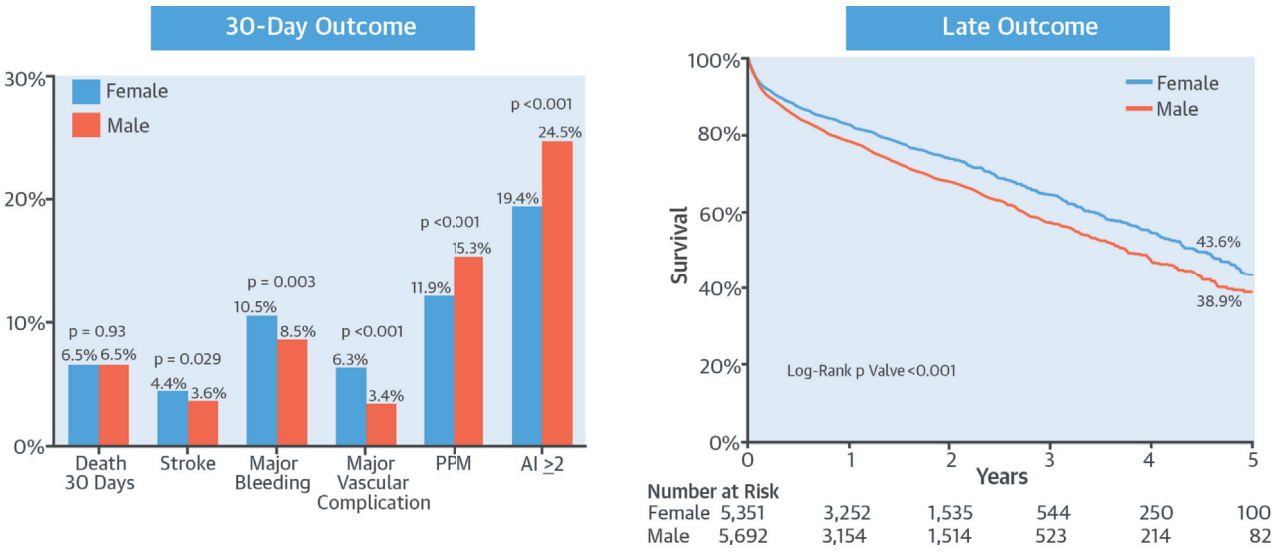
Third, women had a significantly lower incidence of moderate to severe paravalvular aortic incompetence post-procedurally than men, probably because of more frequent undersizing in men due to larger annular sizes. This appeared to occur more exclusively with balloon-expandable valves. Post-TAVR aortic regurgitation has been shown to be associated with increased mortality (20,21,25).

Finally, it has been demonstrated that women adapt differently than men with aortic stenosis, with higher levels of interstitial fibrosis in men (26) and a more rapid reversal of myocardial hypertrophy in women post-surgical aortic valve replacement (27). This may also be 1 reason for the favorable evolution in female patients post-TAVR.

The evidence for the effect of sex on clinical outcomes after conventional surgical aortic valve appears to be conflicting. There are some purely surgical series suggesting better late survival (28), or no difference (29,30), in women undergoing surgical aortic valve replacement, but there are more contemporary studies focusing on older women and high-risk TAVR-eligible patients that demonstrate worse early (31) and late (32) outcomes. Indeed, in a retrospective analysis of the PARTNER (Placement of Aortic Transcatheter Valves) trial, women appeared to have better late mortality with TAVR than with surgical aortic valve replacement (12). Although we cannot draw definite conclusions from these data, if further studies suggest worse outcomes, it may have important implications for the choice of procedure for female patients, suggesting earlier access to TAVR for women than for men.

STUDY STRENGTHS AND LIMITATIONS. The strength of this analysis is that it included individual patient-level data from a large patient population from

CENTRAL ILLUSTRATION **Impact of Female Sex on Short- and Long-Term Outcomes in Patients Undergoing TAVR**



O'Connor, S.A. et al. J Am Coll Cardiol. 2015; 66(3):221–8.

The Kaplan-Meier curves demonstrate 30-day through 5-year outcomes for men and women who underwent transcatheter aortic valve replacement (TAVR), on the basis of a collaborative meta-analysis of patient-level data. AI = aortic incompetence/paravalvular leak; PPM = permanent pacemaker implantation.

multinational, multicenter, randomized and non-randomized real-world studies. Also, it was adequately powered to assess mortality outcomes. Our study, however, was subject to selection bias, as we were able to include data from only 5 of the 6 studies identified by our systematic search strategy. Because this study was an analysis of a global population, we could not perform a sensitivity analysis. With regard to the studies included, individual study effect was adjusted for by introducing the study as a covariate. Results with and without studies' factors were similar, and therefore we may conclude that the characteristics of the studies do not modify the results.

CONCLUSIONS

This is the largest study to date of sex differences in outcomes after TAVR. Women had significantly better late survival despite higher rates of major bleeding, vascular, and stroke complications. Given the natural longer life expectancy of women, TAVR should be even more cost effective in women than in men. If it is confirmed that conventional surgery has worse outcomes in women than in men, these findings may have significant implications for future patient selection for TAVR. However, the definitive answer will be provided by ongoing trials comparing conventional surgery with TAVR in medium-risk patients, which may demonstrate that women can benefit earlier from TAVR than men.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although women undergoing TAVR are subject to higher rates of periprocedural complications, they enjoy favorable mortality outcomes compared with men.

TRANSLATIONAL OUTLOOK: Future studies should be directed toward developing advances in device technology and patient selection to reduce the risk for procedural morbidity associated with TAVR, particularly for women.

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KEY WORDS aortic stenosis, gender, transcatheter aortic valve implantation, transcatheter aortic valve replacement

APPENDIX For supplemental tables and a figure, please see the online version of this article.