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Original Article

Sex-Specific Outcomes After Transcatheter Aortic Valve Replacement: FDA Patient-Level Meta-Analysis of Premarket Clinical Trials

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Abstract

Background: Transcatheter aortic valve replacement (TAVR) is a less invasive alternative approach to surgery. Individual randomized clinical trials evaluating the safety and efficacy of TAVR were mostly underpowered for conducting separate analyses for women and men. We pooled data from premarket TAVR clinical trials comparing short (30 days)- and long-term (~2 years) outcomes by sex.

Methods: Patient-level data from the TAVR arms of six clinical trials were pooled (2515 patients). Random-effects models for time-to-event outcomes (odds ratios [ORs] for 30-day outcomes and hazard ratios [HRs] for complete follow-up for mortality, ischemic stroke, kidney injury, major bleeding, myocardial infarction, and device migration) and dichotomous outcomes (ORs for reintervention, rehospitalization, and pacemaker implantation) were then fit to directly compare outcomes between women and men.

Results: Overall, the pattern of individual comorbidities was more severe in men. There was no difference in mortality risk at 30 days (female-to-male OR = 1.00 [0.69–1.46]); however, at follow-up completion (~2 years post-TAVR), women had a 24% lower mortality risk than men (HR = 0.76 [95% CI: 0.65–0.89]). Women also had a 30% lower risk of kidney injury at 30 days (OR = 0.70 [0.49–0.98]), which increased to 33% over the complete follow-up period (HR = 0.67 [0.51–0.87]). Major bleeding was more common in women compared to men at both 30 days (OR = 1.44 [1.19–1.76]) and long-term follow-up (HR = 1.22 [1.04–1.43]). For dichotomous outcomes, women had a 68% lower risk for reinterventions (OR = 0.32 [0.18–0.58]). We did not observe any difference in the risk of ischemic stroke, myocardial infarction, device migration, rehospitalizations, or pacemaker implantations between sexes.

Conclusions: This patient-level data meta-analysis of six premarket clinical trials found that women who received TAVR had fewer comorbidities at baseline. Acute outcomes (30 day) with respect to mortality were similar. Women were observed to have a lower risk of kidney injury, but higher risk of major bleeding compared to men receiving TAVR at 30 days. At complete follow-up, statistically significant advantages for women emerged in improved survival and lower reintervention risk. No differences in ischemic stroke, pacemaker implantation, or rehospitalization were observed. That women are healthier at baseline and develop fewer postprocedural complications than men may explain their higher survival.

Keywords: transcatheter aortic valve replacement, women, survival, outcomes

Introduction

As envisioned by the U.S. Food and Drug Administration's (FDA) 2012[1] and 2013[2] White Papers and further promoted by the multi-stakeholder National Medical Device Evaluation System Planning Board and the National Medical Device Registry Task Force, a national evaluation system would be created to generate evidence across the total product life cycle of medical devices.[3–5] The national infrastructure will be shared by the entire medical device ecosystem,

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including patients, clinicians, researchers, providers, health plans, industry, and government agencies, and will become sustainable by adding value to all the stakeholders. The system would harness data collected during patient care, facilitate the linkage between various data sources, and enable effective synthesis of all available and relevant evidence across different resources, including clinical trials, clinical registries, electronic health records, and administrative claims. The aim will be to improve the quality of evidence that can be used to make better informed treatment decisions by healthcare providers as well as patients. In addition, there is the possibility of strengthening safety and effectiveness measures for medical devices in patient subgroups underrepresented in clinical trials.[6]

Transcatheter aortic valve replacement (TAVR) is a medical device therapy for patients with severe aortic valve stenosis, approved for patients at high or greater risk for standard surgical aortic valve replacement (SAVR) due to advanced age or preexisting comorbidities. TAVR is a less invasive alternative approach to SAVR and has been shown to have outcomes that are noninferior or superior to surgery in patients who are inoperable or are at high risk for surgery.[7–10] Some studies demonstrated that women have better survival after TAVR compared with men, while others have shown no difference, and these were summarized in a recent review[11]; however, most of the studies included were small single-center studies and more robust evidence is lacking.

Even though the enrollment of women in TAVR clinical trials has been ~50%, which is more than many other cardiovascular device areas,[12–14] the individual trials are mostly underpowered to assess outcomes after TAVR in women and men separately. Therefore, for this particular study, we pooled patient-level data from six large premarket TAVR clinical trials with the objective of comparing short- and long-term outcomes of women and men receiving TAVR.

Methods

This study was approved by the FDA Research in Human Subjects Committee. Informed consent was obtained from patients in the original trials. We included de-identified patient-level data from the following six premarket clinical trials that enrolled either TAVR and SAVR patients or TAVR patients alone: Edwards PARTNER I SAPIEN High Risk (HiR)[8] and Inoperable[7] (Cohorts A and B respectively), PARTNER II SAPIEN XT Inoperable (Cohort B),[15] SAPIEN 3 High Risk,[16] Medtronic CoreValve Extreme Risk (ExR),[10] and CoreValve High-Risk trials.[9] These were all the clinical trials that were submitted to FDA as part of premarket approval applications, were approved between November 2, 2011, and June 17, 2015, and included patients that were at high risk or extreme risk for surgery or were inoperable. Newer clinical trials that also included intermediate- or low-risk patients were not included in this analysis as they have just finished or are still being conducted; therefore, complete information for these patient populations is currently not available. In PARTNER I, the safety and effectiveness of the Edwards SAPIEN valve was compared to SAVR for high-risk patients (cohort A) or to optimal medical management for inoperable patients (cohort B), randomized in a 1:1 ratio. In PARTNER II, nonsurgical patients were randomized 1:1 to either the SAPIEN XT valve or the first-generation SAPIEN valve (cohort B), while everyone received the SAPIEN 3 valve in the SAPIEN 3 High-Risk clinical study. For the Medtronic CoreValve trials, in the extreme risk cohort, all patients received the TAVR valve and were compared to an objective performance goal, while in the high-risk trial, the CoreValve was compared to SAVR in a 1:1 randomized ratio. The data from some of these clinical trials were discussed at FDA advisory committee meetings[17] and their inclusion and exclusion criteria have been published previously.[7–10,15,16] This report only included data that were submitted to the FDA and differences between sponsors' devices were not considered.

This report only included the patients who received TAVR in PARTNER I HiR ($n=349$), PARTNER I Inoperable ($n=179$), PARTNER II XT ($n=543$), SAPIEN 3 HiR ($n=583$), CoreValve ExR ($n=471$), and CoreValve HiR ($n=390$) and not those who were part of the intention-to-treat analysis. Patient baseline characteristics that were commonly measured across the different trials are presented with all six trials combined (Table 1). The presence of congestive heart failure at baseline was not reported in all the available individual trial data. The main outcomes of interest were mortality, ischemic stroke, kidney injury, major bleeding, myocardial infarction, device migration (time-to-event outcomes), reintervention, rehospitalization, pacemaker implantation during follow-up (dichotomous outcomes), and length of stay after the procedure. Major bleeding was defined according to the original trials, while kidney injury was defined as a creatinine level >2 mg/dL; other endpoints were similar across trials. The full follow-up from each trial was used for analysis.

Continuous variables for baseline comparisons are summarized using mean ± standard deviation and frequencies and percentages are presented for categorical variables. To address potential heterogeneity between the different trials, we performed mixed-effects Cox proportional hazards analysis for time-to-event outcomes (~2 years, including the 30-day window) and mixed-effects logistic regression over the complete follow-up period for dichotomous outcomes at full follow-up, as well as binary outcomes at 30 days. The model assumes a random intercept to accommodate for trial-by-trial difference, with sex (women vs. men) as the only fixed effect in the model. Cumulative time-to-event curves were created by the Kaplan–Meier method. The percentage of missing data was low (maximum of 1% for time-to-event endpoints and 3% for baseline variables) and complete case analysis was performed. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and the ''coxme package'' (version 2.2.5)[18] for R version 3.3.1 (Vienna, Austria). Ninety-five percent confidence intervals (CIs) were reported for all hazard ratios (HRs) and odds ratios (ORs) and a two-sided $p<0.05$ (without multiplicity adjustment) was considered statistically significant.

Results

A total of 2515 TAVR patients were included in the analysis, 1180 women (47%) and 1335 men (53%); ~90% had an iliofemoral approach (Table 1). Women had substantially fewer preexisting comorbidities and prior cardiac procedures compared to men, even though their Society of Thoracic Surgeons (STS) risk scores were slightly higher (10.4% in women vs. 9.3% in men). The STS risk score includes patient characteristics such as age, sex, renal function, cardiac history

Table 1. Baseline Characteristics of Transcatheter Aortic Valve Replacement Patients in the Total Population and According to Sex

	Total Population	*Men*	*Women*
	TAVR (N = 2515)	*TAVR (N = 1335)*	*TAVR (N = 1180)*
	n/N *(%)* or *Mean ± SD*	n/N *(%)* or *Mean ± SD*	n/N *(%)* or *Mean ± SD*
Demographics			
Age (years)	83 ± 8	83 ± 8	84 ± 8
Medical history			
Arrhythmia	959/2514 (38.2)	518/1334 (38.8)	441/1180 (37.4)
Diabetes mellitus	940/2510 (37.5)	522/1335 (39.1)	418/1175 (35.6)
Coronary artery disease	1507/2515 (59.9)	906/1335 (67.9)	601/1180 (50.9)
Carotid disease	506/2471 (20.5)	314/1315 (23.9)	192/1156 (16.6)
Congestive heart failure	1346/1932 (69.7)	703/997 (70.5)	643/935 (68.8)
Creatinine >2 mg/dL	258/2496 (10.3)	186/1325 (14.0)	72/1171 (6.2)
Chronic obstructive pulmonary disease	929/2508 (37.0)	515/1331 (38.7)	414/1177 (35.2)
Hypertension	1813/2514 (72.1)	968/1334 (72.6)	845/1180 (71.6)
Myocardial infarction	488/2507 (19.5)	332/1329 (24.9)	156/1178 (13.2)
Peripheral vascular disease	733/2505 (29.3)	457/1329 (34.4)	276/1176 (23.5)
Stroke/transient ischemic attack	401/2512 (15.9)	222/1334 (16.6)	179/1178 (15.2)
Coronary bypass surgery	706/2515 (28.1)	549/1335 (41.1)	157/1180 (13.3)
Percutaneous coronary intervention	671/2513 (26.7)	427/1333 (32.0)	244/1180 (20.7)
Prior pacemaker	492/2500 (19.7)	314/1329 (23.6)	178/1171 (15.2)
Biomarkers			
Aortic valve area (cm^2)	*N* = 2445 0.67 ± 0.24	*N* = 1304 0.71 ± 0.25	*N* = 1141 0.63 ± 0.22
Mean aortic valve gradient (mmHg)	*N* = 2452 44 ± 16	*N* = 1301 42 ± 14	*N* = 1151 46 ± 16
Ejection fraction (%)	*N* = 2437 54 ± 14	*N* = 1290 51 ± 14	*N* = 1147 58 ± 13
NYHA heart failure class			
II	205/2515 (8.2)	119/1335 (8.9)	86/1180 (7.3)
III	1400/2515 (55.7)	714/1335 (53.5)	686/1180 (58.1)
IV	910/2515 (36.2)	502/1335 (37.6)	408/1180 (34.6)
Procedure type			
Iliofemoral	2175/2429 (89.5)	1141/1282 (89.0)	1034/1147 (90.2)
Risk scores			
STS score	*N* = 2514 9.8 ± 4.8	*N* = 1334 9.3 ± 4.6	*N* = 1180 10.4 ± 5.0
EuroSCORE	*N* = 2498 15.0 ± 16.0	*N* = 1323 16.0 ± 16.6	*N* = 1175 14.0 ± 15.3

(*continued*)

TABLE 1. (CONTINUED)

	Total Population	*Men*	*Women*
	TAVR (N = 2515)	*TAVR (N = 1335)*	*TAVR (N = 1180)*
	n/N *(%)* or *Mean ± SD*	n/N *(%)* or *Mean ± SD*	n/N *(%)* or *Mean ± SD*
Clinical trial			
CoreValve extreme risk[10]	471 (19)	231 (17)	240 (20)
CoreValve increased risk[9]	390 (16)	207 (16)	183 (16)
SAPIEN high risk[8]	349 (14)	202 (15)	147 (12)
SAPIEN inoperable[7]	179 (7)	82 (6)	97 (8)
SAPIEN XT[15]	543 (22)	275 (21)	268 (23)
SAPIEN 3 high risk[16]	583 (23)	338 (25)	245 (21)

EuroSCORE, European system for cardiac operative risk evaluation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; SD, standard deviation; TAVR, Transcatheter aortic valve replacement.

and current symptoms, diabetes, hypertension, echocardiography measures, and other factors that predict the risk of operative mortality and morbidity, and are used by physicians and patients as a tool for understanding the possible risks of surgery. The degree of aortic valve stenosis as indicated by aortic valve area (0.63 in women vs. 0.71 cm^2 in men) and mean aortic valve gradient (46 in women vs. 42 mmHg in men) (Table 1) was more severe in women. Of all the included patients, close to 92% had New York Heart Association class III or IV heart failure symptoms at baseline. The median

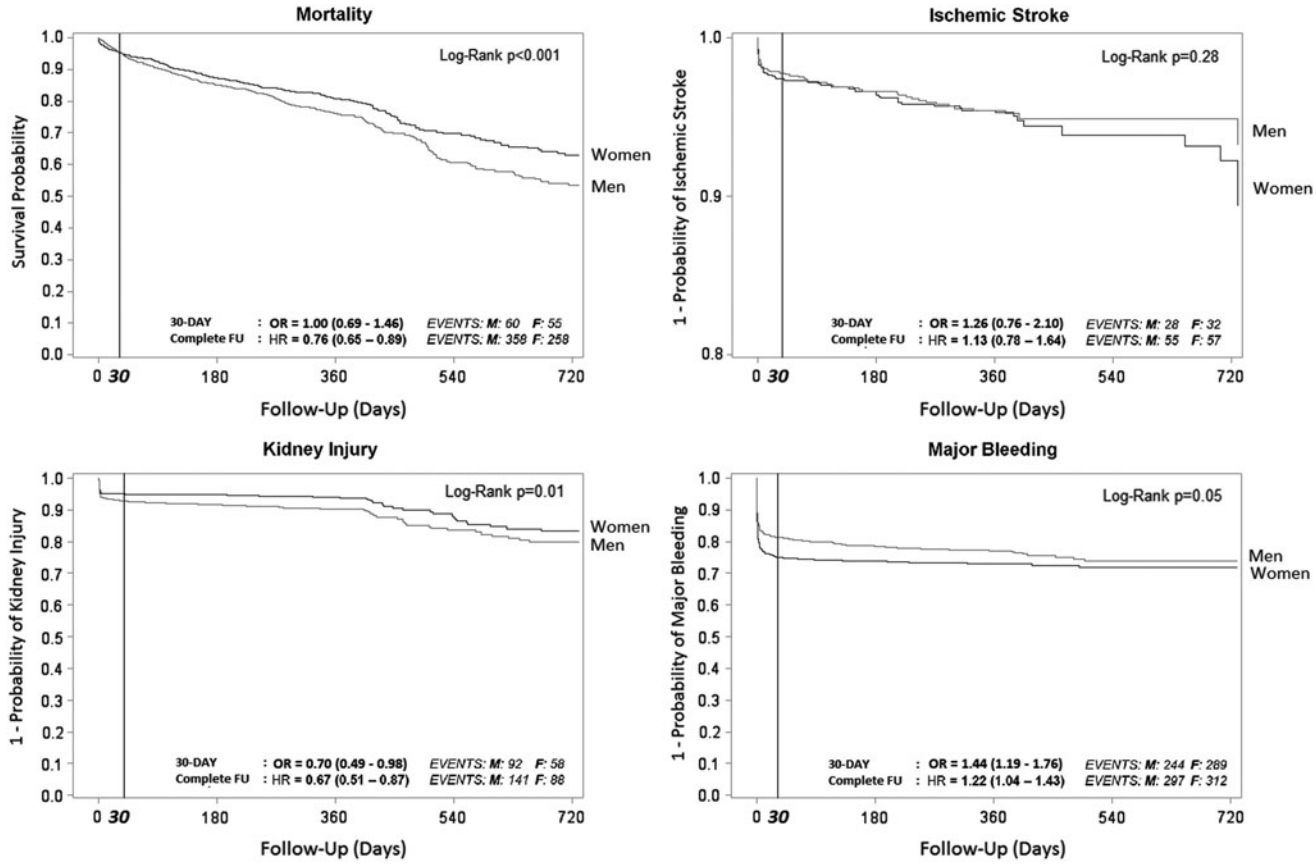

FIG. 1. Kaplan–Meier curves for mortality, ischemic stroke, kidney injury, and major bleeding by sex. Curves reflect the probability of the outcome for mortality (*top left*), ischemic stroke (*top right*), kidney injury (*bottom left*), and major bleeding (*bottom right*) for women (*blue*) and men (*red*). The vertical line represents the 30-day cutoff after the procedure. Event rates in women and men and female-to-male odds ratios (30-day) and hazard ratios (over complete follow-up [FU]) for each outcome at the different time periods are reported in each graph. Log-rank *p* values for comparison of survival curves are included on each graph.

follow-up of all trials combined was 366 days (interquartile range [IQR] 191–405 days).

During the combined follow-up of all the trials, 616 patients (24%) died: 258 women (21.9% of all women) and 358 men (26.8% of all men). In the overall cohort, women had a 24% lower mortality risk (hazard rate) than men at complete follow-up (female-to-male HR = 0.76 [95% CI: 0.65–0.89]), while there was no difference at 30 days (OR = 1.00 [0.69–1.46]) (Fig. 1, top left). The risk of ischemic stroke was not different between sexes at short- and long-term follow-up (Fig. 1, top right). For the outcome of kidney injury after TAVR, at 30 days, women had a 30% lower risk than men, while this difference slightly increased to 33% over the complete follow-up period (Fig. 1, bottom left). Major bleedings was more common in women with an increased risk of 44% compared to men at 30 days and 22% at long-term follow-up (Fig. 1, bottom right). For the remaining time-to-event outcomes, myocardial infarction and device migration, there were no differences between the sexes at 30 days or long-term follow-up, but event rates were low (Table 2). While there were no differences between women and men with regard to rehospitalizations or pacemaker implantations, women did have a 68% lower risk for reinterventions compared to men after the index TAVR procedure (OR = 0.32 [0.18–0.58]) (Table 2). The median length of hospital stay after the first TAVR procedure was 5 (IQR: 3–8) days for both women and men, while 24 patients (12 women and 12 men) died during this period.

Discussion

In this patient-level meta-analysis of six premarket clinical trials, we found that there was an approximately equal enrollment of women and men across trials. Women who received TAVR tended to have fewer preexisting comorbidities and prior cardiac procedures than men, with similar early and improved late survival. The early and late observed risks of kidney injury and the late risk of reinterventions also favored women, while the risk of major bleeding was lower in men. There was no difference in the risk for ischemic stroke, device migration, myocardial infarction, pacemaker implantation, rehospitalization, or length of stay between sexes.

Table 2. Female-to-Male Odds Ratios and Hazard Ratios, Including Absolute Event Rates for Myocardial Infarction and Device Migration at 30 Days and Long-Term Follow-Up, and Reintervention, Rehospitalization, and Pacemaker Implantation at Complete Follow-Up

	F:M OR	*95% CI*	*M*	*F*
30 days				
Myocardial infarction	0.68	0.29–1.59	14	8
Device migration	1.03	0.35–3.03	8	6
Complete follow-up				
Myocardial infarction	0.81	0.42–1.54	22	16
Device migration	0.81	0.34–1.97	13	8
Reintervention	0.32	0.18–0.58	50	15
Rehospitalization	1.09	0.92–1.30	607	593
Pacemaker	0.86	0.68–1.08	199	160

CI, confidence interval; OR, odds ratio.

No difference in the observed mortality rate was seen at 30 days. The preprocedural risk scores (EuroSCORE and STS Score) for SAVR trended in opposite directions for surgical mortality risk prediction in each group. Even though women had less preprocedural comorbidity, their STS risk score was generally higher, but their EuroSCORE was lower than that in men (Table 1). These divergences, in combination with the incongruences between STS predicted and observed mortalities for both women and men, indicate that the current risk stratification used for determining the risk of postprocedural complications in SAVR may not be well suited for predicting procedural (30 day) risks for patients undergoing TAVR, and reinforce the need for development of TAVR-specific risk scores that accurately predict procedural morbidity and mortality risks at 30 days.[19]

The late survival advantage seen in women may partly be explained by women having fewer comorbidities and better preserved left ventricular function (higher ejection fraction) at baseline. These observations are in line with those of a prior review summarizing sex-specific results after TAVR.[11] The lower risks for kidney injury and late reinterventions in women compared with men are also likely to contribute to this late survival difference. Other possible factors include sex-related differences in remodeling, which may occur following relief of stenosis. Although not the subject of this study, other investigators have shown myocardium in women remodels differently compared to men with less residual scar tissue, and a more rapid decrease of ventricular hypertrophy allowing better long-term cardiac function after TAVR.[20,21] In addition, lower post-TAVR kidney injury may be related to less decreased blood flow during the procedure in women or due to women having better kidney function at baseline (Table 1).

Women had an increased risk of major bleeding after TAVR. This is not surprising given anatomic differences disfavoring women, including smaller body stature and smaller vasculature compared to men. Newer generation TAVR devices with lower profile delivery systems (and higher rates of transfemoral access) are likely to, at least partially, mitigate these risks going forward.

With regard to ischemic strokes, prior reports have shown conflicting results, with some demonstrating a higher risk in women[22] compared to men and others showing no difference.[23,24] This study also found no difference in the risk of ischemic stroke between sexes after TAVR. In addition, we did not observe any sex differences in device migration, myocardial infarctions, or rehospitalizations, but the number of events for device migration and myocardial infarction was low in both women and men.

Despite a higher overall incidence of baseline comorbidities and more early evidence of kidney injury, men did not have a longer hospital stay compared to women. Whether these disadvantages were offset by a higher bleeding risk in women is not known. Our analysis was not able to identify risk factors for procedural morbidity or mortality, or for prolonged hospitalization.

The differences in outcomes after TAVR between women and men have been described earlier in smaller single-center studies and *post hoc* analyses of clinical trials,[25,26] which were also summarized in systematic reviews[11] and meta-analyses.[22–24] However, compared to the *post hoc* clinical trial analyses and meta-analyses, which often also included

nonrandomized data from the continued access registries in addition to the original trial data, this study only included premarket randomized or single-arm clinical trial data. In addition, our analysis was based on patient-level data from multiple sponsors with similar endpoint definitions, in which we were better able to account for potential heterogeneity between trials.

TAVR has proven to be a suitable alternative to optimal medical management for patients who are at extreme risk for SAVR or are inoperable, and to SAVR for patients at high surgical risk. This study further supports that women undergoing TAVR had fewer overall comorbidities at baseline, better late survival, and in general, fewer complications and late reinterventions compared with men. These differences could potentially be attributed to factors described above, but it is difficult to pinpoint what the exact causes were without further research. In support of the National Medical Device Evaluation System, a first step could be to try to confirm the results in a large real-world population such as the patients included in the STS/American College of Cardiology (ACC) Transcatheter Valve Therapies (TVT) Registry. Ideally, such a study would account for differences in valve size, structure, implantation route, and other important patient-specific factors such as frailty and quality of life. This could provide stronger safety and effectiveness analysis across the total medical device product life cycle.

The role of patient-specific factors should not be underestimated in a time where we are moving toward precision/personalized medicine. The FDA has recently initiated a Patient Engagement Advisory Committee (PEAC)[27,28] that will give advice on patient-related topics with the goal of increasing integration of patient perspectives into the regulatory process for the approval of new products. In addition, the FDA has released a final guidance document for the inclusion of patient preference information in the assessment of the risk-benefit profile of medical products evaluated in nonclinical as well as clinical studies.[28]

Limitations

A limitation of this study is that it is a *post hoc* analysis of clinical trial data that were available to the FDA. It does not include real-world published data. Patient-level data from six premarket clinical trials were pooled and these trials included patients with a somewhat different risk for surgery according to STS risk scores (four trials enrolled patients with high risk for surgery and two trials enrolled patients with extreme risk for surgery, or were inoperable) as well as different valve sizes, implantation routes, and follow-up periods. The median follow-up for all six trials combined was 366 days; however, the individual trials had median follow-up times between 189 and 673 days. We tried to account for these factors by performing random-effects analysis with random trial intercepts. In addition, some important echocardiographic endpoints, such as paravalvular regurgitation and postprocedural ejection fraction, and complications of the conduction system were not available in most trials and could potentially influence postprocedural survival in women and men; ideally, these would be included in further research. The endpoints of kidney injury and major bleeding were defined as in the original trials and their definitions were not necessarily similar across all studies. In addition, the available data did not include the type of bleeding experienced (*e.g.*, access site or nonaccess site). Frailty and disability measures, which have been shown to be important predictors of outcome for TAVR, were not adequately captured in the individual trials and are therefore not included in this pooled analysis. The results of this analysis may not be applicable to less severe surgical risk categories. Finally, it would be helpful if future studies include a large real-world population (*e.g.*, TVT registry) of patients undergoing TAVR and perform a direct comparison of premarket and postmarket data sources. Such an analysis should also assess additional endpoints and can hopefully lead to the development of accurate predictors of procedural morbidity and mortality risks for patients undergoing TAVR.

Conclusions

This patient-level meta-analysis of six premarket clinical trials submitted to the FDA found that women who received TAVR had fewer comorbidities at baseline and had better survival, lower risk of kidney injury, and fewer reinterventions compared to men receiving TAVR. However, women had a higher risk of bleeding after the procedure. There was no difference in the risk of ischemic stroke, pacemaker implantation, rehospitalization, or length of index hospital stay between sexes. The fact that women were healthier at baseline and developed fewer postprocedural complications than men could explain their higher survival.

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Author Disclosure Statement

No competing financial interests exist.

References

1. US Food and Drug Administration. Strengthening our national system for medical device postmarket surveillance, 2012 Available at: www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM301924.pdf Accessed July 13, 2017.
2. US Food and Drug Administration. Strengthening our national system for medical device postmarket surveillance—Update and next steps, 2013. Available at: www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf Accessed July 13, 2017.
3. Duke-Margolis Center for Health Policy. Better evidence on medical devices: A coordinating center for a 21st Cen-

tury National Medical Device Evaluation System, 2016. Available at: https://healthpolicy.duke.edu/sites/default/files/atoms/files/med-device-report-web.pdf Accessed July 13, 2017.
4. US Food and Drug Administration. Recommendations for a national medical device evaluation system: Strategically coordinated registry networks to bridge clinical care and research, 2015. Available at: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM459368.pdf Accessed July 13, 2017.
5. US Food and Drug Administration. Strengthening patient care: Building an effective national medical device surveillance system, 2015. Available at: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM435112.pdf Accessed July 13, 2017.
6. Shuren J, Califf RM. Need for a National Evaluation System for Health Technology. JAMA 2016;316:1153–1154.
7. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–1607.
8. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–2198.
9. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–1798.
10. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972–1981.
11. Azarbaijani Y, O'Callaghan K, Sanders W, et al. Sex-specific outcomes after transcatheter aortic valve replacement: A review of the literature. Cardiol Rev 2018;26:73–81.
12. Herz ND, Engeda J, Zusterzeel R, et al. Sex differences in device therapy for heart failure: Utilization, outcomes, and adverse events. J Womens Health (Larchmt) 2015;24:261–271.
13. Zusterzeel R, Selzman KA, Sanders WE, et al. Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data. JAMA Intern Med 2014;174:1340–1348.
14. Zusterzeel R, O'Callaghan KM, Canos DA, Sanders WE, Marinac-Dabic D, Strauss DG. Improving the safety and effectiveness of medical device therapy in women. J Womens Health (Larchmt) 2016;25:428–430.
15. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. JACC Cardiovasc Interv 2015;8:1797–1806.
16. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37:2252–2262.
17. US Food and Drug Administration. Circulatory systems devices panel transcript for Edwards SAPIEN valve, 2011. Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM262931.pdf Accessed July 13, 2017.
18. Package ''coxme'' for R. 2015. Available at: hhtp://cran.r-project.org/web/packages/coxme/coxme.pdf Accessed February 1, 2017.
19. O'Brien SM, Cohen DJ, Rumsfeld JS, et al. Variation in hospital risk-adjusted mortality rates following transcatheter aortic valve replacement in the United States: A report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circ Cardiovasc Qual Outcomes 2016;9:560–565.
20. Dobson LE, Fairbairn TA, Plein S, Greenwood JP. Sex differences in aortic stenosis and outcome following surgical and transcatheter aortic valve replacement. J Womens Health (Larchmt) 2015;24:986–995.
21. Dobson LE, Fairbairn TA, Musa TA, et al. Sex-related differences in left ventricular remodeling in severe aortic stenosis and reverse remodeling after aortic valve replacement: A cardiovascular magnetic resonance study. Am Heart J 2016;175:101–111.
22. O'Connor SA, Morice MC, Gilard M, et al. Revisiting sex equality with transcatheter aortic valve replacement outcomes: A collaborative, patient-level meta-analysis of 11,310 patients. J Am Coll Cardiol 2015;66:221–228.
23. Conrotto F, D'Ascenzo F, Presbitero P, et al. Effect of gender after transcatheter aortic valve implantation: A meta-analysis. Ann Thorac Surg 2015;99:809–816.
24. Stangl V, Baldenhofer G, Laule M, Baumann G, Stangl K. Influence of sex on outcome following transcatheter aortic valve implantation (TAVI): Systematic review and meta-analysis. J Interv Cardiol 2014;27:531–539.
25. Forrest JK, Adams DH, Popma JJ, et al. Transcatheter aortic valve replacement in women versus men (from the US CoreValve Trials). Am J Cardiol 2016;118:396–402
26. Kodali S, Williams MR, Doshi D, et al. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: A cohort study. Ann Intern Med 2016;164:377–384.
27. US Food and Drug Administration. FDA Announces First-ever Patient Engagement Advisory Committee. 2015. Available at: http://blogs.fda.gov/fdavoice/index.php/2015/09/fda-announces-first-ever-patient-engagement-advisory-committee Accessed July 13, 2017.
28. US Food and Drug Administration. Why Partnerships are Key to the Science of Patient Input. 2015. Available at: http://blogs.fda.gov/fdavoice/index.php/tag/patient-reported-outcome-consortium Accessed July 13, 2017.

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