ORIGINAL RESEARCH

Sex Differences in the Utilization and Outcomes of Surgical Aortic Valve Replacement for Severe Aortic Stenosis

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Background**—**Studies assessing the differential impact of sex on outcomes of aortic valve replacement (AVR) yielded conflicting results. We sought to investigate sex-related differences in AVR utilization, patient risk profile, and in-hospital outcomes using the Nationwide Inpatient Sample.

Methods and Results**—**In total, 166 809 patients (63% male and 37% female) who underwent AVR between 2003 and 2014 were identified, and 48.5% had a concomitant cardiac surgery procedure. Compared with men, women were older and had more nonatherosclerotic comorbid conditions including hypertension, diabetes mellitus, obstructive pulmonary disease, atrial fibrillation/flutter, and anemia but fewer incidences of coronary and peripheral arterial disease and prior sternotomies. In-hospital mortality was significantly higher in women (5.6% versus 4%, $P<0.001$). Propensity matching was performed to assess the impact of sex on the outcomes of isolated AVR and yielded 28 237 matched pairs of male and female participants. In the propensity-matched groups, in-hospital mortality was higher in women (3.3% versus 2.9%, $P<0.001$). Along with vascular complications and blood transfusion (6% versus 5.6%, $P=0.027$ and 40.4% versus 33.9%, $P<0.001$, respectively). Rates of stroke, permanent pacemaker implantation, and acute kidney injury requiring dialysis were similar (2.4% versus 2.4%, $P=0.99$; 6% versus 6.3%, $P=0.15$; and 1.4% versus 1.3%, $P=0.14$, respectively). Length of stay median and interquartile range were both similar between groups (7±6 days). Rates of nonhome discharge were higher among women (27.9% versus 19.6%, $P<0.001$).

Conclusions**—**Women have worse in-hospital mortality following AVR compared with men. Coupled with the accumulating evidence suggesting higher magnitude of benefit of transcatheter AVR over AVR in women, women should perhaps be offered transcatheter AVR over AVR at a lower threshold than men. **(*J Am Heart Assoc*. 2017;6:e006370. DOI: 10.1161/JAHA.117.006370.)**

Key Words: aortic valve replacement • aortic valve stenosis • disparities • outcome

Sex-related differences in the incidence, pathophysiology, presentation, treatment, and outcomes of cardiovascular diseases including aortic stenosis (AS) have been studied extensively.[1] Aortic valve replacement (AVR) has historically been the gold standard treatment of calcific AS.[2] The outcomes of AVR have improved significantly nationwide in the past decade.[3] Several studies have assessed the differential impact of sex on outcomes of AVR but yielded conflicting results.[4–13] The interest in examining the sex gap in AS patients has been renewed with the introduction and widespread adoption of transcatheter AVR (TAVR). Recently, a report from the American College of Cardiology (ACC) and TVT registry and a large meta-analysis showed superior outcomes with TAVR in women compared with men.[1,14] We hypothesized that female patients have worse outcomes following AVR compared with propensity-matched male patients. We propose that if our hypothesis is true, perhaps women should be offered TAVR over surgical AVR at a lower threshold compared with men, given the mounting evidence of better outcomes of TAVR in women versus men.

We aimed to utilize a large national database to investigate (1) trends of AVR utilization in women versus men over a 12-year period, (2) sex differences in risk profile of patients undergoing AVR, (3) in-hospital morbidity and mortality of AVR in men versus women and (4) the trends of these outcomes over time.

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Accompanying Tables S1 through S4 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/6/9/e006370/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In a large contemporary US database, women underwent aortic valve replacement for aortic stenosis less than men.
- Aortic valve replacement in women was associated with worse in-hospital mortality and higher cost compared with men.

What Are the Clinical Implications?

- Women had worse outcomes with aortic valve replacement compared with men, and this was consistent over 12 years.
- These data should be considered when assessing suitability of women for transcatheter or surgical aortic valve replacement.

Methods

Study Data

The Nationwide Inpatient Sample (NIS) was used to derive patient-relevant information between January 2003 and December 2014. The NIS is the largest publicly available all-payer administrative claims–based database and contains information about patient discharges from ≈1000 nonfederal hospitals in 45 states. It contains clinical and resource utilization information on 5 million to 8 million discharges annually, with safeguards to protect the privacy of individual patients, physicians, and hospitals. These data are stratified to represent ≈20% of US inpatient hospitalizations across different hospital and geographic regions (random sample). National estimates of the entire US hospitalized population were calculated using the Agency for Healthcare Research and Quality sampling and weighting method.

Study Population

Patients with a discharge diagnosis of aortic valve stenosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 424.1, 395.0, 395.2, 396.2, 746.3) who underwent AVR (ICD-9-CM procedure code 35.20 and 35.21) during the study period were identified from the NIS database.

Trends of Utilization and Outcomes of AVR

The trend of surgical AVR during the 12-year study period were assessed using weighted values (national estimates). The Mann–Kendall test was used to evaluate trends of AVR in male and female patients. Baseline comorbidities were described, and in-hospital morbidity and mortality were assessed and compared between sexes.

Comparative Outcomes Analysis

To account for potential confounding factors and to reduce the effect of selection bias, a propensity score–matching model was developed using logistic regression to derive 2 matched groups for comparative outcomes analysis. After excluding patients who underwent concomitant cardiac surgery, patients who underwent "isolated" AVR were entered into a nearest neighbor 1:1 variable ratio, parallel, balanced propensity score–matching model using a caliper of 0.01 to ensure perfect matching. Table S1 lists all covariates that we included in the propensity score models. We performed multiple imputations to impute missing values for race (missing in 16% of observations) using the fully conditional specification method (an iterative Markov chain Monte Carlo algorithm) using age, sex, insurance status, comorbid conditions, hospital region, and clinical characteristics. This method adheres to the recommendations provided by the Healthcare Cost and Utilization Project (HCUP)[15] for handling missing racial data. To estimate the cost of hospitalization, the NIS data were merged with cost-to-charge ratios available from the HCUP. We estimated the cost of each inpatient stay by multiplying the total hospital charge with cost-to-charge ratios.

The primary end point was in-hospital death. Secondary outcomes included procedural mortality (defined as death occurring on the same hospital day as AVR), vascular complications, pacemaker implantation, transient ischemic attack, stroke, blood transfusion, acute kidney injury requiring dialysis, cardiac tamponade, hospital length of stay, cost of hospitalization, and discharge disposition. Subgroup analyses were performed for the outcomes of in-hospital mortality in the propensity score–matched groups to assess the impact of age, age, race, teaching status, and primary and selected relevant major comorbidities on the differences in mortality between male and female participants.

Statistical Analyses

Descriptive statistics are presented as frequencies with percentages for categorical variables. Mean, standard deviation, median, and interquartile range were reported for continuous measures. Baseline characteristics were compared using a Pearson χ^2 test and Fisher exact test for categorical variables and an independent-samples *t* test for continuous variables. Trend weights accounting for changes in the NIS sampling design are available only for data between 1998 and 2011. For 2012 and 2013, trend weights were not available, and the standard survey weights were used. Matched categorical variables were presented as frequencies with percentages and compared using the McNemar test. Matched continuous variables were presented as means with standard deviations and compared using a paired-samples *t* test. A type I error rate of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 24 (IBM Corp) and R, version 3.3.1 (R Foundation for Statistical Computing).

Results

In total, 166 809 patients underwent AVR between 2003 and 2014 (weighted national estimates: 825 721 patients), of whom 105 106 (63%) were male and 61 703 (37%) were female. The utilization disparity in AVR was constant throughout the study period (Figure 1). Baseline characteristic profiles were distinctly different between men and women, as detailed in Table 1. Compared with men, women were older (70±13 versus 67±14 years, $P<0.001$) and had higher rates of hypertension, diabetes mellitus, chronic obstructive lung disease, and anemia. In contrast, coronary and peripheral arterial disease and history of prior sternotomy were more prevalent in men. The majority of AVRs (67.4%) were performed at teaching hospitals, and 32.8% were performed during an unplanned admission. More women had Medicare/Medicaid insurance compared with men (75.4% versus 63.6%, $P<0.001$). Bioprosthetic valve utilization increased from 46% in 2003 to 65% in 2014, and this upward trend was similar for men and women (Figure 1). Concomitant cardiac surgery was common (48.5%); men were more likely to undergo simultaneous coronary artery bypass grafting (42.8% versus 33.6%, $P<0.001$), whereas women were more likely to undergo simultaneous mitral valve replacement (8.7% versus 4.8%, $P<0.001$). In-hospital mortality was significantly higher in women than in men (5.6% versus 4%, $P<0.001$; Table 2). Women had higher rates of vascular complications (5.8% versus 5.5%, $P<0.001$), permanent pacemaker implantation (7.2% versus 6.6%, $P<0.001$), and blood transfusion (40.9% versus 35.4%, $P<0.001$). Rates of stroke were similar in men and women (2.7% versus 2.9%, $P=0.096$).

Outcomes of Isolated AVR

Among the 166 809 patients who underwent AVR during the study period, 85 975 (51.5%) had isolated AVR. The majority of these patients (60.8%) were men. Baseline characteristics and in-hospital outcomes of the unmatched groups of men and women who underwent isolated AVR are shown in Tables S2 and S3. Propensity score matching yielded 28 237 matched pairs of male and female patients who underwent isolated AVR (Figure 2). Variables used in propensity matching are listed in Table S1. Baseline characteristics were well matched between groups (Table 3, Figure S1). After propensity matching, in-hospital mortality remained significantly higher in women than in men (3.3% versus 2.9%, $P=0.001$; Table 4). Although in-hospital mortality decreased among both men and women over time, the significant gap between men and women remained constant throughout the study period (Figure 3). Vascular complications and blood transfusions were more frequent in female than male patients (6% versus 5.6%, $P=0.027$; and 40.4% versus 33.9%, $P<0.001$, respectively; Table 4). Rates of stroke, permanent pacemaker implantation, and acute kidney injury requiring dialysis were similar in male and female patients (2.4% versus 2.4%, $P=0.99$; 6.1% versus 6.3%, $P=0.36$; and 1.4% versus 1.3%, $P=0.14$, respectively). Length of stay was longer for women (10.1±9.6 versus 9.6±9 days, $P<0.001$), and rates of non-home discharge (skilled nursing facility, nursing home, or intermediate care) were higher for women (27.9% versus 19.6%, $P<0.001$). Cost of hospitalization was similar for the 2 groups ($50 111±24 372 for women versus $49 774±34 701 for men, $P=0.248$).

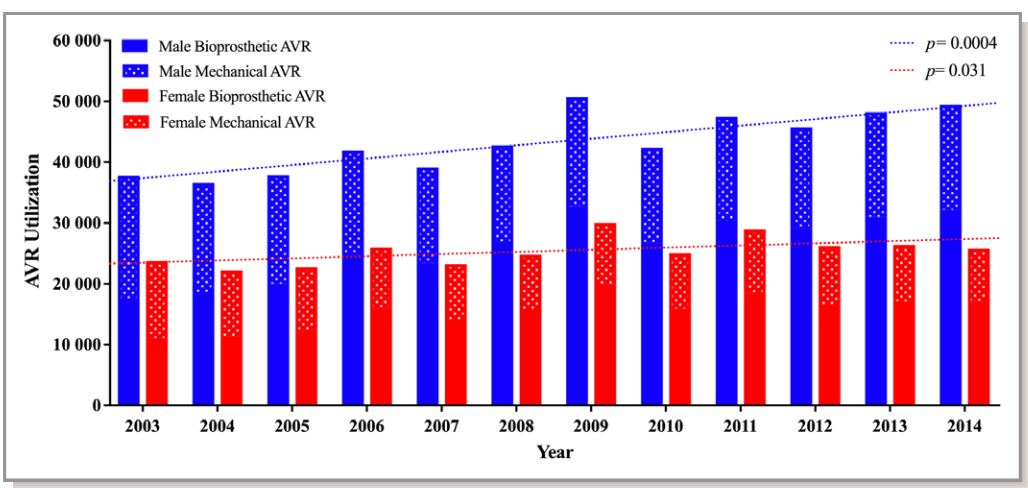

Figure 1. Utilization trends of surgical aortic valve replacement in men and women between 2003 and 2014. AVR indicates aortic valve replacement.

Table 1. Characteristics of Patients Undergoing Surgical AVR Between 2003 and 2014 (Including Combined Procedures)

Characteristic	All Patients (n=166 809)	Male (n=105 106)	Female (n=61 703)	*P* Value
Age, y, mean (SD)	68 (14)	67 (14)	70 (13)	<0.0001
Race, n (%)				<0.0001
White	139 714 (83.8)	87 946 (83.7)	51 768 (83.9)	
Black	8516 (5.1)	5186 (4.9)	3330 (5.4)	
Hispanic	10 084 (6)	6745 (6.4)	3339 (5.4)	
Medical comorbidity, n (%)				
Hypertension	106 535 (63.9)	66 374 (63.1)	40 161 (65.1)	<0.0001
Diabetes mellitus	42 900 (25.7)	26 503 (25.2)	16 397 (26.6)	<0.0001
Prior sternotomy	7195 (4.3)	5592 (5.3)	1603 (2.6)	<0.0001
Chronic pulmonary disease	33 513 (20.1)	20 342 (19.4)	13 171 (21.3)	<0.0001
Atrial fibrillation/flutter	72 999 (43.8)	45 971 (43.7)	27 028 (43.8)	0.794
Cardiogenic shock	6565 (3.9)	4051 (3.9)	2514 (4.1)	0.026
Anemia	30 713 (18.4)	18 366 (17.5)	12 347 (20)	<0.0001
Coagulopathy	39 755 (23.8)	25 040 (23.8)	14 715 (23.8)	0.91
Conduction abnormalities	5438 (3.3)	3578 (3.4)	1860 (3)	<0.0001
Peripheral vascular disease	29 535 (17.7)	20 115 (19.1)	9420 (15.3)	<0.0001
Chronic renal disease	21 029 (12.6)	14 239 (13.5)	6790 (11)	<0.0001
Coronary artery disease	82 622 (49.5)	55 339 (52.7)	27 283 (44.2)	<0.0001
Metastatic cancer	293 (0.2)	207 (0.2)	86 (0.1)	0.007
Liver disease	2542 (1.5)	1740 (1.7)	802 (1.3)	<0.0001
Aortic prosthesis				
Bioprosthetic	100 999 (60.50)	63 399 (60.3)	37 600 (60.9)	0.013
Mechanical	66 005 (39.6)	41 816 (39.8)	24 189 (39.2)	0.019
Concomitant procedures, n (%)				
Coronary artery bypass	65 781 (39.4)	44 960 (42.8)	20 821 (33.7)	<0.0001
Percutaneous coronary intervention	699 (0.4)	461 (0.4)	238 (0.4)	0.106
Mitral valve valvuloplasty	5278 (3.2)	3406 (3.2)	1872 (3)	0.02
Mitral valve replacement	10 441 (6.3)	5050 (4.8)	5391 (8.7)	<0.0001
Annuloplasty	5278 (3.2)	3406 (3.2)	1872 (3)	0.02
Open ASD\VSD repair	3403 (2)	2108 (2)	1295 (2.1)	0.194
IABP/LV assist device use	7462 (4.5)	4905 (4.7)	2557 (4.1)	<0.0001
Hospital characteristics, n (%)				
Teaching hospital	112 372 (67.4)	71 079 (67.6)	41 293 (66.9)	0.003
Hospital bed size				0.074
Small	11 249 (6.7)	6993 (6.7)	4256 (6.9)	
Medium	30 336 (18.2)	19 226 (18.3)	11 110 (18)	
Large	125 224 (75.1)	78 887 (75.1)	46 337 (75.1)	
Rural location	5924 (3.6)	3782 (3.6)	2142 (3.5)	0.177
Nonelective admission status, n (%)	54 717 (32.8)	34 718 (33)	19 999 (32.4)	0.009

Continued

Table 1. Continued

Characteristic	All Patients (n=166 809)	Male (n=105 106)	Female (n=61 703)	*P* Value
Primary payer, n (%)				<0.0001
Medicare/Medicaid	113 333 (67.9)	66 835 (63.6)	46 498 (75.4)	
Private including HMO	46 358 (27.8)	33 143 (31.5)	13 215 (21.4)	
Self-pay/no charge/other	7118 (4.3)	5128 (4.9)	1990 (3.2)	
Median household income, n (%)				<0.0001
0 to 25th percentiles	35 947 (21.5)	21 889 (20.8)	14 058 (22.8)	
26th to 50th percentiles	43 307 (26)	26 958 (25.6)	16 349 (26.5)	
51st to 75th percentiles	43 431 (26)	27 572 (26.2)	15 859 (25.7)	
76th to 100th percentiles	44 124 (26.5)	28 687 (27.3)	15 437 (25)	

ASD indicates atrial septal defect; AVR, aortic valve replacement; HMO, health maintenance organization; IABP, intra-aortic balloon pump; LV, left ventricular; VSD, ventricular septal defect.

A subgroup analysis of the propensity score–matched cohorts showed that the differential impact of sex on in-hospital mortality was consistent among subcohorts of patients stratified based on age (<65 versus >65 years); hospital teaching status; race; insurance status; and the presence of diabetes mellitus, peripheral vascular disease, or atrial fibrillation (Figure S2).

Sensitivity Analysis

To further assess for residual confounding, a rule-out approach to sensitivity analysis was used to illustrate how strongly a single unmeasured confounder would need to be associated with female sex and a significant outcome end point to fully explain our findings (Figure S3).[16] To fully explain the observed difference in blood transfusion rates between male and female patients undergoing AVR, a confounder would have to be 2 times more likely to be associated with female than male sex and, concurrently, increase the risk of blood transfusion by 6 times.

Discussion

The major findings of the current investigations are as follows. First, men undergo surgical AVR for AS more than women,

Table 2. In-Hospital Outcomes of Patients Undergoing Surgical AVR Between 2003 and 2014 (Including Combined Procedures)

	All Patients (n=166 809)	Male (n=105 106)	Female (n=61 703)	*P* Value
Clinical outcome, n (%)				
In-hospital death	7591 (4.6)	4165 (4)	3426 (5.6)	<0.0001
Procedural death	947 (0.6)	493 (0.5)	454 (0.7)	<0.0001
Vascular complications	9392 (5.6)	5815 (5.5)	3577 (5.8)	0.024
Vascular complications requiring surgery	6810 (4.1)	4344 (4.1)	2466 (4)	0.174
Permanent pacemaker implantation	11 453 (6.9)	6980 (6.6)	4473 (7.2)	<0.0001
Transient ischemic attack	570 (0.3)	345 (0.3)	225 (0.4)	0.219
Clinical stroke	4634 (2.8)	2866 (2.7)	1768 (2.9)	0.096
Acute kidney injury	26 264 (15.7)	17 432 (16.6)	8832 (14.3)	<0.0001
Acute kidney injury requiring dialysis	2934 (1.8)	1811 (1.7)	1123 (1.8)	0.146
Blood transfusion	62 473 (37.5)	37 254 (35.4)	25 219 (40.9)	<0.0001
Cardiac tamponade	1512 (0.9)	985 (0.9)	527 (0.9)	0.084
Discharge status, n (%)				<0.0001
Discharged home	114 714 (68.8)	77 727 (74)	36 987 (59.9)	
Discharged SNF/NH/IC	44 134 (26.5)	22 996 (21.9)	21 138 (34.3)	
Length of stay, d, median (IQR)	8 (7)	8 (7)	8 (8)	<0.0001
Cost of hospitalization, $, mean (SD)	56 260 (41 280)	55 834 (40 937)	56 985 (41 849)	<0.0001

AVR indicates aortic valve replacement; IC, intermediate care; IQR, interquartile range; NH, nursing home; SNF, skilled nursing facility.

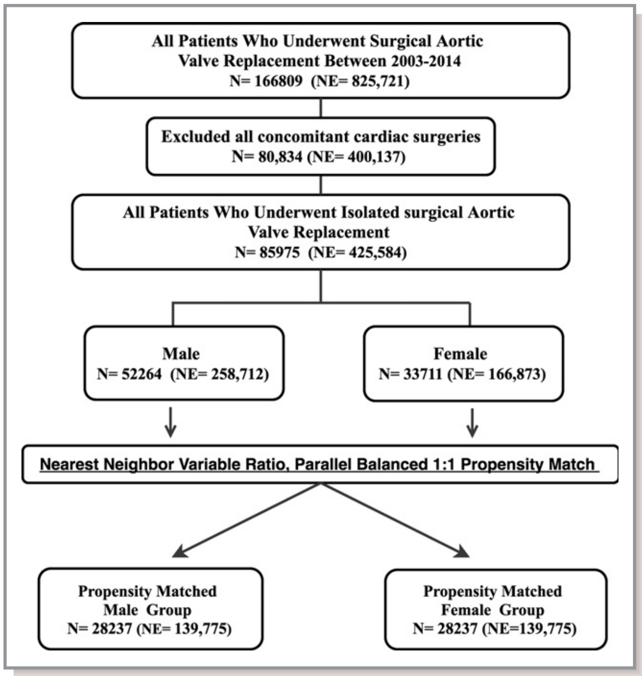

Figure 2. Study flow chart. NE indicates national estimate.

Second, women who underwent AVR in the United States between 2003 and 2014 were older and had distinctive risk profiles and demographics compared with men. Third, women had higher unadjusted and adjusted in-hospital mortality following AVR than men, and this was consistent over time. Fourth, after risk adjustment, women had more vascular complications and blood transfusions than men and were more likely to be discharged to a skilled nursing facility, nursing home, or intermediate care center.

The higher utilization of AVR in men compared with women in this study (63% versus 37%, $P<0.001$) is consistent with previous studies.[17–19] Several plausible explanations can be postulated from the existing literature. Regarding disparity in the incidence of AS, historical echocardiographic data showed that the risk of developing AS was 2-fold higher in men than in women[20]; however, nationwide claim-based studies in hospitalized patients showed a less pronounced disparity in AS diagnosis between men and women. Among 113 847 patients admitted with an aortic valve disorder diagnosis in the United States, 55.1% were men.[21] A similar study in Sweden showed that men constituted 52% of all patients newly diagnosed with AS.[22] Even a lower incidence of new AS diagnosis in men was observed in a large Scottish registry of 19 733 patients, of whom 46.8% were men.[23] Regarding disparity in referral for testing, women with AS were less likely to be seen by a specialist and less likely to be referred for testing.[19] Regarding disparity in referral to surgery, women diagnosed with AS had unfavorable preoperative baseline characteristics compared with men at the time of presentation and thus were less likely to be referred to surgical treatment.[4,9,24] Interestingly, this disparity in referral to valve replacement is not seen with the current TAVR practice; in the United States and Germany, women composed 52% and 55%, respectively, of all patients undergoing TAVR, respectively.[25,26] Furthermore, compared with women, men had much higher prevalence of coronary artery disease (52.7% versus 44.2%, $P<0.001$) and were more likely to undergo coronary artery bypass grafting (42.8% versus 33.7%, $P<0.001$). Although speculative, perhaps many men underwent AVR for lesser degrees of aortic valve disease at the time of coronary bypass, contributing to the larger number of men undergoing AVR overall. The disparity of AVR utilization in women seems to be more pronounced in the most recent year (Figure 1). This could be related to the introduction of TAVR. Since TAVR became commercially available in the United States in 2011, women have been referred more often to TAVR versus AVR compared with men (Figure S4). This may explain the later divergence of utilization trends of AVR between men and women (Figure 1).

In line with the majority of previous studies, we found distinctive risk profiles for men and women undergoing AVR.[4,6,11,12,17,27] Women undergoing AVR (isolated or combined) were older and had more nonatherosclerotic comorbid conditions at presentation including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation/flutter, and anemia compared with men. In contrast, men presented with higher incidences of coronary and peripheral arterial disease and prior sternotomies. The impact of sex on the pathophysiology of valvular heart disease has not been studied extensively. In addition, the focus of research on this topic has been to investigate sex differences in ventricular responses to pressure and volume overload posed by valvular disease rather than evaluating differences in the mechanism of AS itself.[28] Nevertheless, 3 recent studies found important differences between men and women with regard to the development, extent, and progression of aortic valve calcifications supporting sex-related differences in the mechanism of AS.[29–31] Our findings of distinct risk profiles between men and women with AS at a community level support this notion and call for further research in sex-specific disease mechanisms.

To date, there is no contemporary large-scale study assessing sex-related differences in clinical outcomes following AVR. Evidence from the available series conflicts with older studies showing no difference in post-AVR mortality between men and women and more contemporary studies showing worse short- and long-term outcomes in women compared with men (Table S4). In this real-world study of 166 809 patients, in-hospital mortality was significantly

Table 3. Characteristics of Propensity Score–Matched Patients Undergoing Isolated Surgical AVR Between 2003 and 2014

Characteristic	Male (n=28 237)	Female (n=28 237)	*P* Value
Age, y, mean (SD)	68 (13.3)	68 (14.1)	0.561
Race, n (%)			0.988
White	23 721 (84)	23 732 (84)	
Black	1475 (5.2)	1469 (5.2)	
Hispanic	1591 (5.6)	1560 (5.5)	
Medical comorbidity, n (%)			
Hypertension	18 255 (64.6)	18 278 (64.7)	0.846
Diabetes mellitus	6757 (23.9)	6774 (24)	0.874
Prior sternotomy	1017 (3.6)	960 (3.4)	0.262
Chronic pulmonary disease	5713 (20.2)	5708 (20.2)	0.966
Atrial fibrillation/flutter	11 429 (40.5)	11 537 (40.9)	0.354
Cardiogenic shock	716 (2.5)	687 (2.4)	0.45
Anemia	5259 (18.6)	5293 (18.7)	0.72
Coagulopathy	6166 (21.8)	6136 (21.7)	0.767
Conduction abnormalities	936 (3.3)	924 (3.3)	0.796
Peripheral vascular disease	4586 (16.2)	4634 (16.4)	0.586
Chronic renal disease	2781 (9.8)	2782 (9.9)	0.99
Coronary artery disease	6905 (24.5)	6943 (24.6)	0.714
Metastatic cancer	41 (0.1)	39 (0.1)	0.911
Liver disease	368 (1.3)	375 (1.3)	0.825
Aortic prosthesis			
Bioprosthetic	16 954 (60)	16 961 (60.1)	0.958
Mechanical	11 324 (40.1)	11 313 (40.1)	0.931
Concomitant procedures, n (%)			
Percutaneous coronary intervention	109 (0.4)	103 (0.4)	0.73
IABP/LV assist device use	549 (1.9)	529 (1.9)	0.557
Hospital characteristics, n (%)			
Teaching hospital	19 207 (68)	19 207 (68)	0.99
Hospital bed size			0.617
Small	1874 (6.6)	1868 (6.6)	
Medium	5075 (18)	5068 (17.9)	
Large	21 288 (75.4)	21 301 (75.4)	
Rural location	1012 (3.6)	1029 (3.6)	0.719
Nonelective admission status, n (%)	7957 (28.2)	7968 (28.2)	0.962
Primary payer, n (%)			0.165
Medicare/Medicaid	19 489 (69)	19 301 (68.4)	
Private including HMO	7648 (27.1)	7818 (27.7)	
Self-pay/no charge/other	1100 (3.9)	1118 (4)	
Median household income, n (%)			0.866
0 to 25th percentiles	6257 (22.2)	6232 (22.1)	
26th to 50th percentiles	7303 (25.9)	7342 (26)	
51st to 75th percentiles	7357 (26.1)	7352 (26)	
76th to 100th percentiles	7320 (25.9)	7311 (25.9)	

AVR indicates aortic valve replacement; HMO, health maintenance organization; IABP, intra-aortic balloon pump; LV, left ventricular.

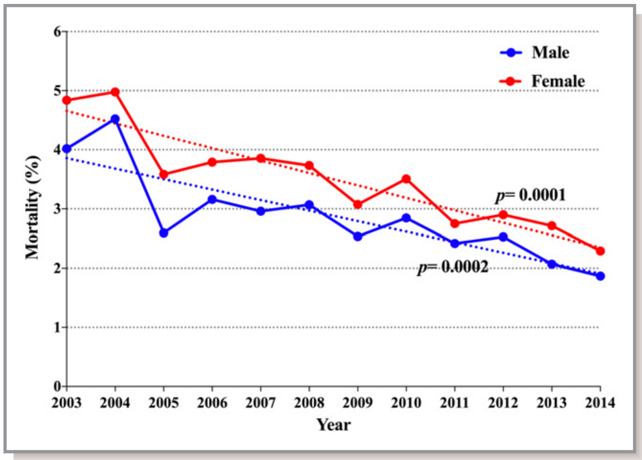

Figure 3. Trends of in-hospital mortality following isolated surgical aortic valve replacement in men and women between 2003 and 2014.

higher in women compared with men following both combined AVR (odds ratio: 1.4; 95% confidence interval [CI], 1.36–1.49; $P<0.0001$) and isolated AVR (unadjusted odds ratio: 1.3; 95% CI, 1.45–1.39; $P<0.0001$; adjusted odds ratio: 1.2; 95% CI, 1.07–1.29; $P=0.001$). The higher mortality rate in women was consistent throughout the 12-year study period and was seen among most subgroups of patients (Figure S2). Compared with men, women had more vascular complications and blood transfusions but similar rates of stroke, permanent pacemaker implantation, and acute kidney injury requiring dialysis. Although cost of hospitalization was similar, resource utilization was higher for women because of the significantly higher need for intermediate care or skilled nursing after discharge (27.9% versus 19.6%, $P<0.001$). This could be related to the higher incidence of vascular complications and blood transfusions in women but also could be related to the higher incidence of frailty among older women with AS.[32]

The discussion of our findings would be incomplete without alluding to the emerging data demonstrating superior outcomes of TAVR in women compared with men and a higher magnitude of benefit of TAVR versus surgical AVR in women than in men.[1,14,24,33] A large report from the ACC/TVT registry examined sex differences among 11 808 patients who underwent TAVR and found no difference in in-hospital mortality in women versus men after TAVR but significantly better 1-year mortality in women versus men (adjusted hazard ratio: 0.73; 95% CI, 0.63–0.85; $P<0.001$).[14] Similarly, in a patient-level meta-analysis including 11 310 patients, women had similar mortality to men at 30 days but had significantly better long-term survival (adjusted hazard ratio: 0.79; 95% CI, 0.73–0.86; $P=0.001$), despite higher rates of in-hospital complications.[1] A subgroup analysis of the PARTNER trial showed that women who underwent TAVR had better short-term (6.8% versus 13.1%; $P=0.07$) and long-term (hazard ratio: 0.67; 95% CI, 0.44–1.0; $P=0.049$) mortality compared with women who underwent AVR.[24] Likewise, a subgroup analysis

Table 4. In-Hospital Outcomes of Propensity Score–Matched Patients Undergoing Isolated Surgical AVR Between 2003 and 2014

	Male (n=28 237)	Female (n=28 237)	*P* Value
Clinical outcome, n (%)			
In-hospital death	806 (2.9)	943 (3.3)	0.001
Procedural death	87 (0.3)	117 (0.4)	0.042
Vascular complications	1581 (5.6)	1705 (6)	0.027
Vascular complications requiring surgery	1178 (4.2)	1237 (4.4)	0.228
Permanent pacemaker implantation	1686 (6)	1769 (6.3)	0.15
Transient ischemic attack	108 (0.4)	81 (0.3)	0.059
Clinical stroke	682 (2.4)	682 (2.4)	0.99
Acute kidney injury	3881 (13.7)	2968 (10.5)	<0.0001
Acute kidney injury requiring dialysis	404 (1.4)	363 (1.3)	0.144
Blood transfusion	9563 (33.9)	11 386 (40.4)	<0.0001
Cardiac tamponade	267 (0.9)	209 (0.7)	0.009
Discharge status, n (%)			<0.0001
Discharged home	21 831 (77.3)	19 342 (68.5)	
Discharged SNF/NH/IC	5545 (19.6)	7882 (27.9)	
Length of stay, d, median (IQR)	7 (6)	7 (6)	<0.0001
Cost of hospitalization, $, mean (SD)	49 774 (34 701)	50 111 (24 372)	0.248

AVR indicates aortic valve replacement; IC, intermediate care; IQR, interquartile range; NH, nursing home; SNF, skilled nursing facility.

of the pivotal CoreValve trial showed superior 1-year survival in women who underwent TAVR versus those who underwent AVR (12.7% versus 21.8%; P=0.03).[33] It is worth noting that in this study, we found that ≈28% of isolated AVRs were performed during nonelective admissions (Table 3). Isolated AVR during a nonelective admission is associated with a 43% increase in cost (\$217 660±187 318 versus \$151 817±124 094, P<0.001). Further studies are needed to assess the impact of procedural status (elective versus nonelective) on cost of AVR in the TAVR era.

Limitations

This study has a number of limitations. First, the NIS is an administrative database that aims to gather data for billing purposes and can be limited by erroneous coding; however, the HCUP quality control measures should minimize these possibilities. Furthermore, the hard clinical end points used in our analysis are difficult to miscode. Second, the NIS allows detailed assessment of in-hospital outcomes; however, certain laboratory and echocardiographic data as well as some procedural details such as aortic valve gradient, valve size, and ejection fractions are not captured. In addition, long-term mortality data are unavailable in this database. Third, the potential for unmeasured confounders may bias the outcome results in the propensity score–matched cohorts; however, we believe that our rigorous propensity matching and the sensitivity analysis adequately addressed this selection bias.

Conclusion

In a contemporary nationwide analysis, AVR is performed less often in women then in men. Women also have worse in-hospital mortality and are more likely to be discharged to a nursing home or intermediate care facility compared with men. These data, coupled with the accumulating evidence suggesting superiority of TAVR over AVR in women, underscore the need for a rigorous controlled trial specifically in female patients to properly study mortality differences between treatment modalities.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Variable Used for Propensity Score Matching

Age	Blood loss anemia
Race	Iron deficiency anemia
Hypertension	Paralysis
Hyperlipidemia	Neurological disorders
Diabetes mellitus without complications	Chronic lung disease
Diabetes mellitus with complications	Hypothyroidism
Congestive heart failure	Liver disease
Chronic kidney disease	AIDS*
Peripheral vascular disease	Lymphoma
Pulmonary hypertension	Metastatic disease
Hypercoagulable state	Solid tumors without metastasis
Obesity	Collagen vascular disease
Coronary artery disease	Weight loss
Valvulopathy	Alcoholism
Electrolyte abnormalities	Depression
Conduction abnormality	Drug abuse
Coronary artery disease	Psychosis
Percutaneous intervention	Hospital teaching status
Intraaortic balloon pump	Admission Status
Atrial fibrillation\flutter	Prior sternotomy

* Acquired immunodeficiency syndrome

Table S2. Characteristics of Patients Undergoing Isolated Surgical Aortic Valve Replacement Between 2003-2014

Characteristic	All Patients (n=85975)	Male (n=52264)	Female (n=33711)	P value
Age- mean (SD), y	66 (15)	64 (15)	69 (14)	<0.0001
Race- no. (%)				<0.0001
Caucasian	71994 (83.7)	43686 (83.6)	28308 (84)	
African American	4440 (5.2)	2613 (5)	1827 (5.4)	
Hispanic	5086 (5.9)	3300 (6.3)	1786 (5.3)	
Medical Comorbidity- no (%)				
Hypertension	54850 (63.8)	32508 (62.2)	22342 (66.3)	<0.0001
Diabetes	19907 (23.2)	11566 (22.1)	8341 (24.7)	<0.0001
Prior Sternotomy	4701 (5.5)	3716 (7.1)	985 (2.9)	<0.0001
Chronic Pulmonary Disease	16595 (19.3)	9473 (18.1)	7122 (21.1)	<0.0001
Atrial Fibrillation/Flutter	34508 (40.1)	20819 (39.8)	13689 (40.6)	0.024
Cardiogenic Shock	2232 (2.6)	1405 (2.7)	827 (2.5)	0.034
Anemia	15502 (18)	8750 (16.7)	6752 (20)	<0.0001
Coagulopathy	18909 (22)	11633 (22.3)	7276 (21.6)	0.02
Conduction Abnormalities	2900 (3.4)	1840 (3.5)	1060 (3.1)	0.003
Peripheral Vascular Disease	15633 (18.2)	10458 (20)	5175 (15.4)	<0.0001
Chronic Renal Disease	9106 (10.6)	5982 (11.4)	3124 (9.3)	<0.0001
Coronary Artery Disease	22035 (25.6)	14043 (26.9)	7992 (23.7)	<0.0001
Metastatic Cancer	147 (0.2)	107 (0.2)	40 (0.1)	0.003
Liver Disease	1383 (1.6)	947 (1.8)	436 (1.3)	<0.0001
Aortic Prosthesis				
Bioprosthetic	50371 (58.6)	29923 (57.3)	20448 (60.7)	<0.0001
Mechanical	35713 (41.5)	22407 (42.9)	13306 (39.5)	<0.0001
Concomitant Procedures- no (%)				
Percutaneous Coronary Intervention	298 (0.3)	184 (0.4)	114 (0.3)	0.735
IABP*/LV† Assist Device Use	1851 (2.2)	1260 (2.4)	591 (1.8)	<0.0001
Hospital characteristics- no (%)				
Teaching Hospital	59215 (68.9)	36449 (69.7)	22766 (67.5)	<0.0001
Hospital bed size				0.485
Small	5597 (6.5)	3360 (6.4)	2237 (6.6)	
Medium	15477 (18)	9421 (18)	6056 (18)	
Large	64901 (75.5)	39483 (75.5)	25418 (75.4)	
Rural location	3065 (3.6)	1862 (3.6)	1203 (3.6)	0.964
Non-elective Admission Status- no (%)	24447 (28.4)	15079 (28.9)	9368 (27.8)	0.001
Primary Payer- no (%)				<0.0001
Medicare / Medicaid	53337 (62)	29136 (55.7)	24201 (71.8)	
Private including HMO	28513 (33.2)	20184 (38.6)	8329 (24.7)	
Self-pay/No charge/Other	4125 (4.8)	2944 (5.6)	1181 (3.5)	
Median Household Income- no (%)				<0.0001
1. 0-25th percentile	18411 (21.4)	10794 (20.7)	7617 (22.6)	
2. 26-50th percentile	21939 (25.5)	13073 (25)	8866 (26.3)	
3. 51-75th percentile	22387 (26)	13700 (26.2)	8687 (25.8)	

4. 76-100th percentile	23238 (27)	14697 (28.1)	8541 (25.3)	

* Intra-aortic balloon pump
† Left ventricular

Table S3. In-Hospital Outcomes of Patients Undergoing Isolated Surgical Aortic Valve Replacement Between 2003-2014

	All Patients (n=85975)	Male (n=52264)	Female (n=33711)	P value
Clinical Outcome- no (%)				
In-Hospital Death	2512 (2.9)	1404 (2.7)	1108 (3.3)	<0.0001
Procedural Death	284 (0.3)	158 (0.3)	126 (0.4)	0.075
Vascular Complications	5143 (6)	3176 (6.1)	1967 (5.8)	0.144
Vascular Complications Requiring Surgery	3912 (4.6)	2502 (4.8)	1410 (4.2)	<0.0001
Permanent Pacemaker Implantation	5169 (6)	3072 (5.9)	2097 (6.2)	0.039
Transient Ischemic Attack	273 (0.3)	170 (0.3)	103 (0.3)	0.616
Clinical Stroke	2056 (2.4)	1257 (2.4)	799 (2.4)	0.743
Acute Kidney Injury	10456 (12.2)	6854 (13.1)	3602 (10.7)	<0.0001
Acute Kidney Injury Requiring Dialysis	1175 (1.4)	750 (1.4)	425 (1.3)	0.032
Blood Transfusion	31196 (36.3)	17470 (33.4)	13726 (40.7)	<0.0001
Cardiac Tamponade	758 (0.9)	502 (1)	256 (0.8)	0.002
Discharge Status- no (%)				<0.0001
Discharged Home	64659 (75.2)	42117 (80.6)	22542 (66.9)	
Discharged SNF*/NH†/IC‡	18631 (21.7)	8651 (16.6)	9980 (29.6)	
Length of Stay- mean (SD), d	10 (9)	9 (900)	10 (900)	<0.0001
Cost of hospitalization- mean (SD), $	50074 (34799)	50137 (35334)	49975 (33953)	0.504

* Skilled nursing facility
† Nursing home
‡ Intermediate care

Table S4. Summary of the Literature on Gender Disparity Following Surgical and Transcatheter Aortic Valve Replacement

Combined Surgical AVR[*] and CABG[†]				
Author, Year	**# Patients (F)**	**Settings**	**Results**	**Conclusions**
Arank[1]i et al. 1993	717 (326)	Single Center, Retrospective	30-day mortality: M[‡]: 5.6% AVR vs 7.4% AVR+CABG (p=0.31) F[§]: 2.9% AVR vs 10.3% AVR+CABG (p=0.006)	Short term Mortality better in females after isolated AVR but worse after AVR/CABG
Morris[2] et al. 1994	1012 (329)	Single Center, Retrospective	Combined AVR+ CABG: 30-day mortality: 6% F, 2% M (p<0.02). 5-year mortality: 23% F, 17% M (p<0.02).	Short and long term mortality worse in females.
Ibrahim[3] et al. 2003	1570 (497)	Single Center, Retrospective	In-hospital mortality: Isolated AVR: 2.3% F vs. 1.7% M (p=NS) Combined AVR/CABG 7% F vs. 4% M (p=0.02).	Short-term mortality similar for isolated AVR but worse in females after combined AVR+CABG.
Doenst[4] et al. 2006	1567 (496)	Single Center, Retrospective	Combined AVR+ CABG: 30-day mortality: 7% in F vs. 4% in M (p=0.026). 5-yr survival rate: 77% F vs 78% M (p= 0.062). 10-yr survival rate: 50% F vs 56% M (p= 0.062).	Short-term mortality worse in females in combined AVR+CABG but long term mortality similar
Isolated Surgical AVR				
Author, Year	**# Patients (F)**	**Settings**	**Results**	**Conclusions**
Hanssen[5] et al. 1999	195 (99)	Single Center, Prospective	30-day mortality: 5.6% F vs. 3.1% M (p=0.229).	Similar short term mortality (underpowered)
Duncan[6] et al. 2006	2212 (782)	Single Center, Retrospective	In-hospital mortality: Unadjusted 3.5% F vs. 1.6% M (p=0.005) Adjusted 3.9% F vs. 3.9% M (p=0.99)	Similar short term mortality
Caballero-Borrego[7] et al. 2009	577 (254)	Single Center, Retrospective	In-hospital mortality: Unadjusted 13% F vs. 7.4% M (p=0.019) Adjusted HR in F 2.5 (CI 0.79-7.26, P=0.12)	Similar short term mortality
Hamed[8] et al. 2009	406 (183)	Single Center, Retrospective	30-day mortality: 3.4% overall with no difference between F and M	Similar short term mortality
Kulik[9] et al. 2009	3118 (1261)	Single Center, Retrospective	10-yr actuarial survival rate: Bioprosthetic AVR: 70% F vs. 55.9% M (p<0.001). Mechanical AVR: 79.1% F vs. 73.3% (p=0.74).	Long term mortality better in females only in bioprosthetic AVRs
Fuchs[10] et al. 2010	408 (215)	Single Center, Retrospective	1,2,5 years actuarial survival rates: 92.8%, 89.8%, 81.4% F vs. 89.1%, 86.6%, 76.3% M (p=0.31)	Similar short term mortality
Elhmidi[11] et al. 2014	2197 (907)	Single Center, Retrospective	30-day mortality: 4.4% F vs. 1.6% M (p<0.001) 1-yr mortality: 13% F vs. 9.6% M (p=0.04)	Short and long term mortality worse in females
Transcatheter AVR				
Author, Year	**# Patients (F)**	**Settings**	**Results**	**Conclusions**
Buchanan[12] et al. 2011	305 (146)	Single Center, Retrospective	30-day mortality following TAVR: 4.7% F vs. 4.7% M (p=0.99)	Similar short term mortality
Humphries[13] et al. 2012	641 (329)	Multicenter, Retrospective	30-day mortality: 6.5% F, 11.2% M (p=0.05).	Better short term mortality in females
Hayashida[14] et al. 2012	260 (131)	Single Center, Prospective	30-day mortality: 12.2% F, 17.8% M (p=0.207) 1-yr mortality: (HR 1.62, CI 1.03-2.53, p=0.037)	Similar short term but better 1-yr mortality in females
Zhao[15] et al. 2013	9118 (4942)	Meta analysis (through April 2013)	30-day mortality: Higher in males (HR 1.37, 95% CI 1.07-1.76). 1-yr mortality: Higher in males (HR 1.30, 95% CI 1.14-1.49).	Short and long term mortality better in females
Conrotto[16] et al. 2014	836 (464)	Multicenter, Retrospective	30-day mortality: 6.5% F, 5.6% M (p=0.62) 1-yr mortality: 18.1% F, 22.6% M (p=0.11)	Similar short and long term mortality
Stangl[17] et al. 2014	7973 (4242)	Meta analysis (through June 2014)	30-day mortality: Lower in F (HR 0.78, CI 0.64-0.96) Long-term mortality: Lower in F (HR 0.70, CI 0.59, 0.82)	Short and long term mortality better in females
Erez[18] et al. 2014	224 (127)	Single Center, Retrospective	30-day mortality: 4% F, 5% M (p=0.45).	Similar short term mortality
Williams[19] et al. 2014	699 (300)	Multicenter, Prospective	2-yr mortality: In F, 28.2% TAVR vs. 38.2% SAVR (p=0.049) In M, 37.7% TAVR vs. 32.3% SAVR (p=0.42)	Long term survival benefit for female but not for males with TAVR

Biere[20] et al 2015	3972 (1967)	National Registry	30-day mortality: 9.5% in F vs. 9.2% in M (p=0.27) 1-yr mortality: 19.3% in F vs. 23.7% in M (p=0.021)	Long term survival better in females than males after TAVR
Chandrasekhar[21] et al 2016	23652 (11808)	National Registry	1-yr mortality: 21.3% in F vs. 24.5% in M (Adjusted HR: 0.73; 95% CI: 0.63 to 0.85; p < 0.001)	Long term survival better in females than males after TAVR
Kodali[22] et al 2016	2559 (1220)	Multicenter, Prospective	30-day mortality: 6.5% in F vs. 5.9% in M (p=0.52) 1-yr mortality: 19% in F vs. 25.9% in M (p<0.001)	Similar short term mortality but better long term survival in females
Czarnecki[23] et al 2017	999 (453)	Multicenter, Retrospective	30-day mortality: 7.2% in F vs. 5.4% in M (p=0.34) 1-yr mortality: 18.2% in F vs. 19.2% in M (p=0.85)	Similar short term and long term mortality

* Aortic Valve Replacement.
† Coronary Artery Bypass Grafting.
‡ Female
§ Male

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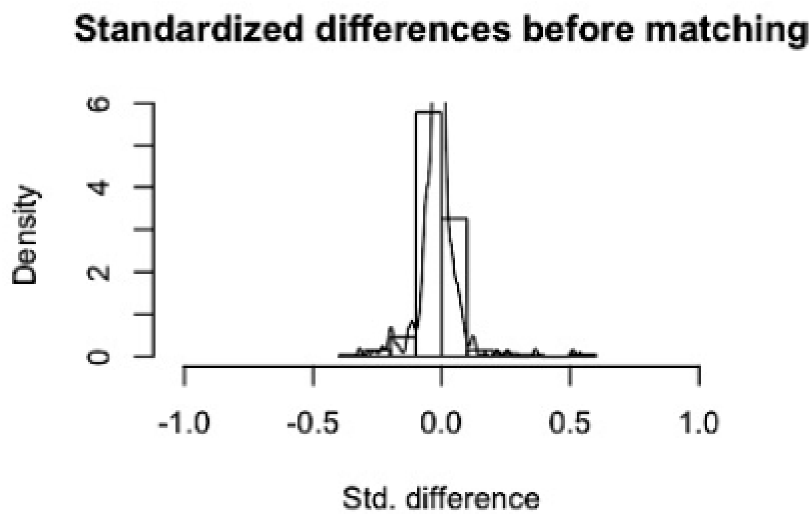
Figure S1. Standardized mean differences before and after propensity Score Matching.



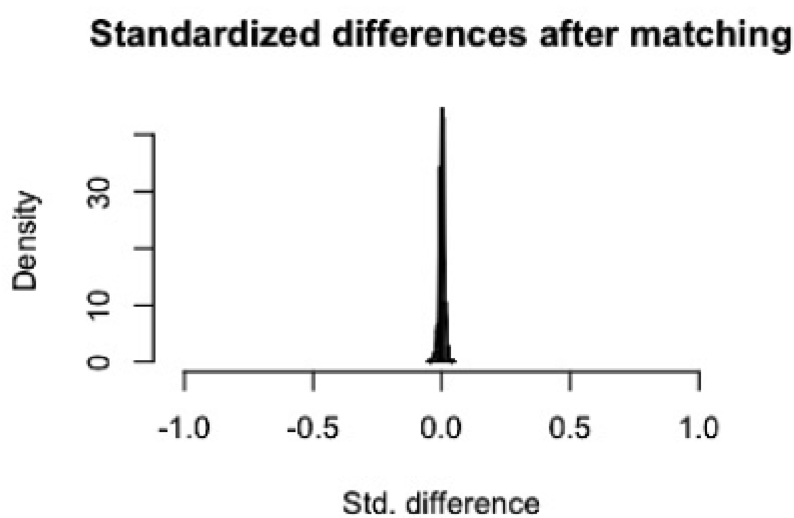


Figure S2. Subgroup Analysis of Sex Disparity in In-Hospital Mortality Following Isolated Surgical Aortic Valve Replacement (male used as a reference group).

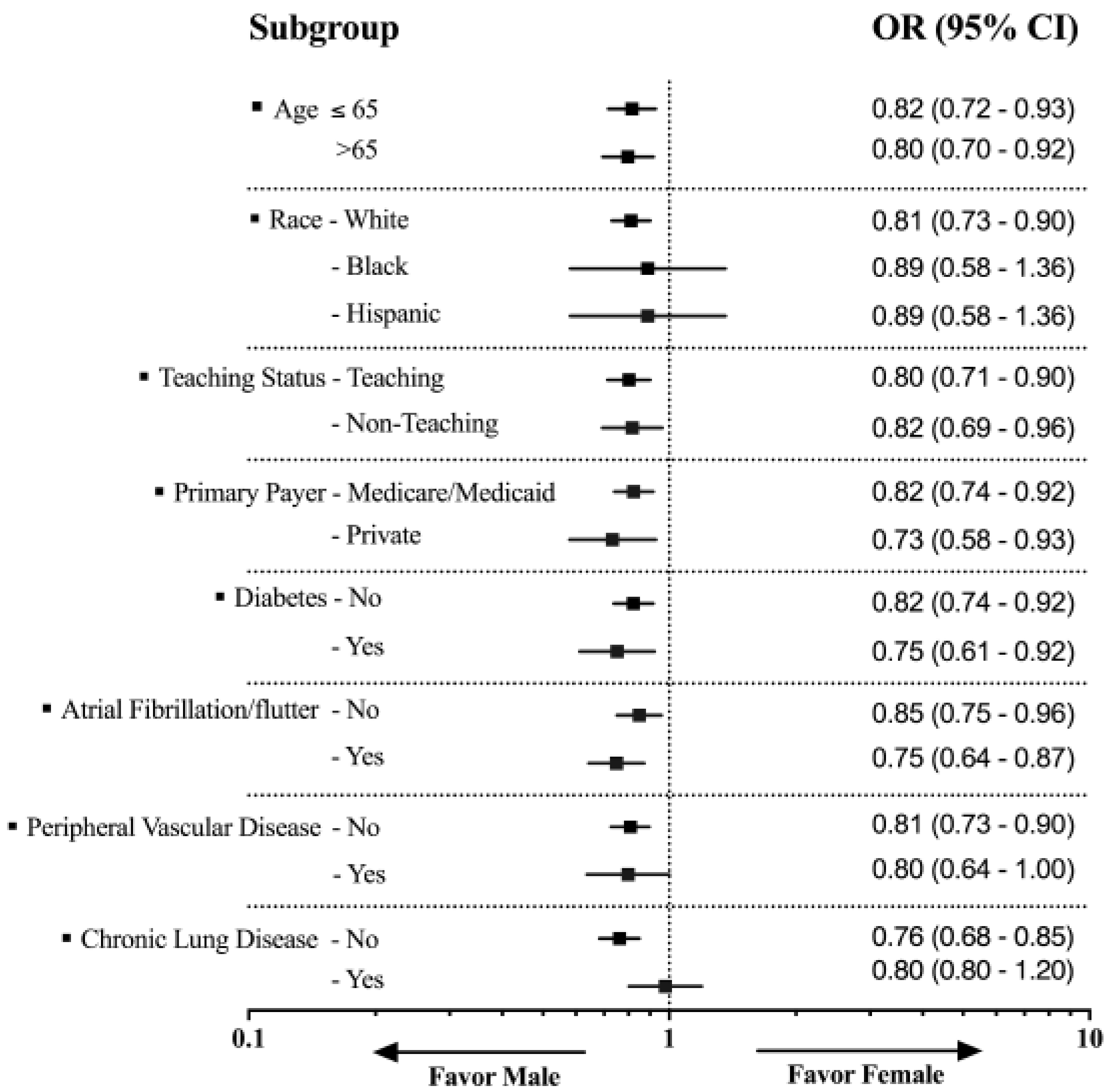


Figure S3. Sensitivity Analysis for Required Strength of an Unmeasured Confounder. Each line splits the area into two: The upper right corner of the graph above the confines of a line represents all parameter combinations of an association between an unmeasured confounder to the treatment (AVR in female patients; y axis) and the outcome (blood transfusion; x axis) required to move the measured OR to null. Conversely, the lower left corner represents all parameter combinations of an association between an unmeasured confounder to the treatment and outcome that would not move the measure OR to null.

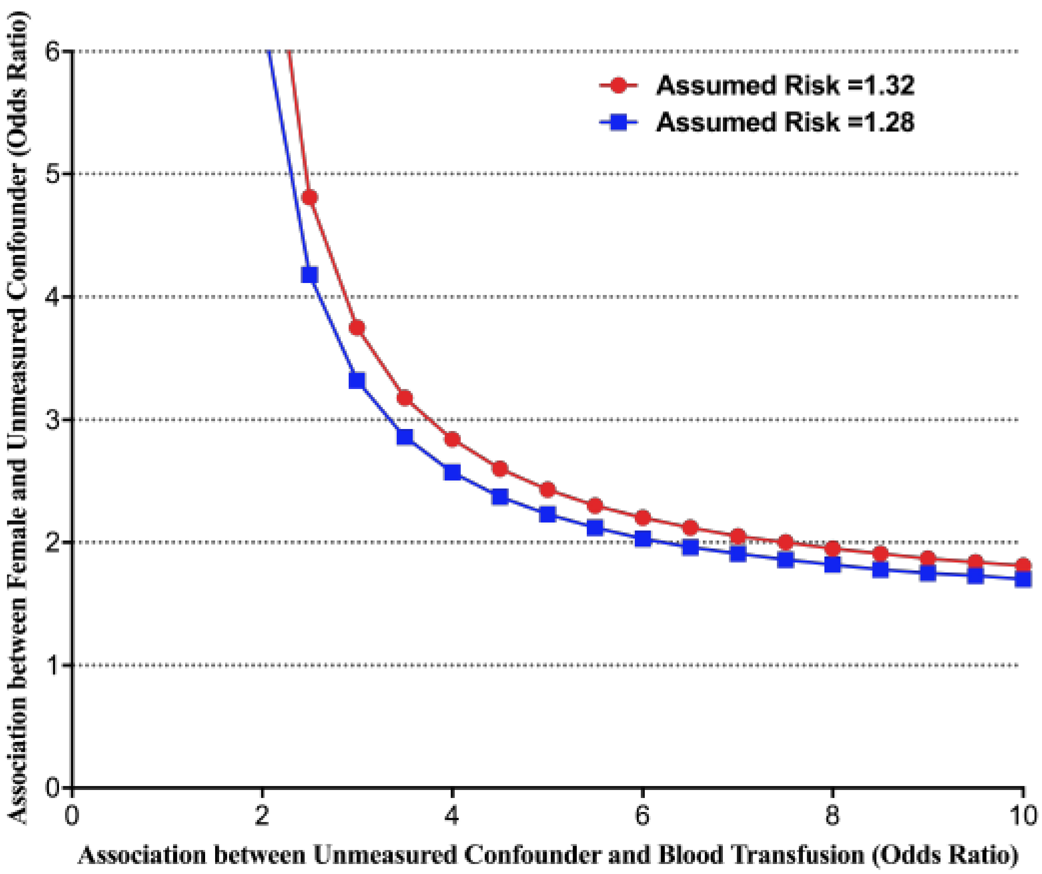


Figure S4. Proportion of TAVR and SAVR among Males and Females who underwent aortic valve replacement since commercial approval of TAVR. (TAVR; transcatheter aortic valve replacement, SAVR; surgical aortic valve replacement.)