Sex Differences in In-Hospital Outcomes of Transcatheter Aortic Valve Replacement

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Abstract: Since the introduction of transcatheter aortic valve replacement (TAVR), there has been a paradigm shift in the management of severe aortic stenosis. While women represent almost half of the patients undergoing TAVR, there are limited data on sex-based comparisons in hospital outcomes and predictors of mortality in women and men. The National Inpatient Sample database from 2012 to 2015 was used to identify TAVR using international classification of diseases-9 clinical modification procedure codes 35.05 and 35.06. We identified 61,239 patients who underwent TAVR between 2012 and 2015. After adjusting for potential confounders, women had higher odds of all-cause mortality as compared to men [odds ratio (OR) 1.25, 95% confidence interval (CI): 1.01-1.54; $P = 0.036$]. Moreover, women had significantly increased odds of cardiac complications [OR 2.41, 95% CI: 1.67-3.49; $P \leq 0.01$], respiratory complications [OR 1.20 95% CI: 1.07-1.34; $P = 0.001$], major hemorrhage

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requiring transfusion [OR 1.51, 95% CI: 1.37-1.67; $P \leq 0.001$], neurological complications [OR 1.38, 95% CI: 0.95-1.99; $P = 0.08$], need for vasopressor treatment [OR 1.33, 95% CI: 1.01-1.75; $P = 0.04$], and vascular complications [OR 1.73, 95% CI: 1.19-2.52; $P = 0.004$]. On the contrary, the odds of pacemaker requirement [OR 0.85, 95% CI: 0.75-0.97; $P = 0.02$], and acute kidney injury [OR 0.80, 95% CI: 0.71-0.91; $P = 0.001$] were significantly lower in women. Among patients undergoing TAVR, women were more likely to have in-hospital complications and mortality as compared with men. Further studies are needed to identify the discrepancy in in-hospital outcomes with sex-specific factors being considered. (Curr Probl Cardiol 2021;46:100694.)

Introduction

Since the introduction of transcatheter aortic valve replacement (TAVR), it has become the mainstay of treatment for patients with severe symptomatic aortic stenosis (AS) who are intermediate- or high-risk for surgical aortic valve replacement.[1–3] With the development of newer valve iterations, better delivery techniques, conscious sedation, and better screening of patients by the Heart Team, the indication of TAVR has now expanded to include low surgical risk patients.[4,5] As the use of TAVR in low-risk population increases[5] the number of TAVR procedures is expected to rise. Women constitute approximately half of the study population in major TAVR studies.[6] Outcome characteristics in female population are of utmost importance as women tolerate severe AS differently from male with differential ventricular remodeling.[7] Data regarding sex-specific outcomes differences after TAVR are sparse in the literature. Prior studies have reported conflicting data regarding mortality and procedural complications in women as compared to men.[8-11] Therefore, we conducted a retrospective cohort study to identify the difference of in-hospital outcomes in women compared to men and predictors of mortality in both genders.

Methods

Data Source

We performed retrospective data analysis using the National Inpatient Sample (NIS) database from 2012 to 2015 (up to the third quarter of

2015). NIS database is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project and is the largest all-payer inpatient database in the United States, containing information of more than 7 million hospital admissions (unweighted), which corresponds to more than 35 million hospitalizations (weighted) nationally. From NIS 2012 to 2014, diseases were identified with international classification of diseases-9 clinical modification (ICD-9-CM) codes for diagnosis. NIS 2015 identifies disease with both ICD-9-CM codes (January to September) and international classification of diseases-10 clinical modification (ICD-10-CM) codes (October to December). We only used data from the first three quarters of NIS 2015 for our study.

Study Population

Patients undergoing transcatheter aortic valve replacement procedure were captured using ICD-9-CM procedure codes 35.05 and 35.06. Only patients above 18 years of age were included in the study.

Patient and Hospital Characteristics

Baseline patient characteristics, including demographics and clinically relevant comorbidities, are shown in Table 1. A list of ICD-9-CM codes used to identify comorbidities is included in Supplementary Table 1. Hospital-level characteristics were the region (Northeast, Midwest, South, and West), bed size (small, medium, and large), location (urban and rural), and teaching status. Congestive heart failure, peripheral arterial disease, chronic kidney disease (CKD), dyslipidemia, obesity, history of previous percutaneous coronary intervention (PCI), history of previous coronary artery bypass grafting (CABG), history of previous stroke, history of previous myocardial infarction (MI), hypertension (HTN), diabetes mellitus (DM), anemia, pulmonary hypertension (PH), and chronic lung disease were considered as relevant comorbidities.

Outcomes Measured

The primary outcome of our study was all-cause in-hospital mortality. Secondary outcomes of interest were in-hospital complications, length of stay, and total cost. In-hospital complications were identified using appropriate ICD-9-CM codes (Supplementary Table 1).

Table 1. Difference in baseline characteristics in men vs women

Variable	Male	Female	*P* value
Hospitalization (*n*)	32,119	29,115	
Race		<0.001	
Caucasian (%)	28,412 (88.46)	25,152 (86.39)	
African American (%)	905 (3.03)	1375 (5.05)	
Hispanic (%)	1175 (3.94)	1100 (4.04)	
Asian (%)	395 (1.32)	245 (0.9)	
Native American (%)	60 (0.2)	45 (0.17)	
Others (%)	910 (3.05)	940 (3.45)	
Mean Age (%)	80 ± 9.19	81 ± 8.15	<0.001
Charlson comorbidity Index (%)		<0.001	
0	1745 (5.43)	2050 (7.04)	
1	4625 (14.4)	6130 (21.05)	
2	6175 (19.22)	6460 (22.19)	
3	19,573 (60.94)	14,475 (49.72)	
Insurance type (%)		<0.001	
Medicare (%)	28, 865 (89.87)	26,975 (92.65)	
Medicaid (%)	395 (1.26)	300 (1.04)	
Private (%)	2605 (8.28)	1705 (5.9)	
Uninsured (%)	185 (0.59)	120 (0.42)	
Chronic comorbidity			
Anemia (%)	905 (2.82)	1255 (4.31)	<0.001
Prior stroke (%)	3530 (10.99)	3220 (11.06)	0.90
Prior PCI (%)	7165 (22.31)	4815 (16.54)	<0.001
Prior CABG (%)	9825 (30.59)	3455 (11.87)	<0.001
Prior AMI (%)	5175 (16.11)	2815 (9.67)	<0.001
Pulmonary (%) HTN	6595 (20.53)	7240 (24.87)	<0.001
CAD and CAD equivalent (%)	18,693 (58.2)	15,573 (53.49)	<0.001
HTN (%)	13,563 (42.23)	15,244 (52.36)	<0.001
Obesity (%)	4035 (12.56)	5185 (17.81)	<0.001
Dyslipidemia (%)	21,612 (67.29)	18,511 (63.58)	<0.001
Peripheral vascular disease (%)	7120 (22.17)	5185 (17.81)	<0.001
Chronic lung disease (%)	14,743 (45.91)	13,806 (47.42)	0.09
Diabetes (%)	11,837 (36.86)	9669 (33.21)	<0.001
Congestive heart failure (%)	23,912 (74.46)	21,745 (74.69)	0.77
Chronic Kidney disease (%)	13,732 (42.76)	9334 (32.06)	<0.001

PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; AMI, acute myocardial infarction; HTN, hypertension; CAD, coronary artery disease.

Statistical Analysis

All statistical analyses were conducted as per the best practice recommendations accounting for the complex survey design of the NIS database.[12] Demographic and baseline characteristics of patients undergoing TAVR were summarized using descriptive statistics and compared between women versus men. Continuous variables are expressed as mean ± standard deviation and analyzed using Student's *t* test. Categorical variables are presented as frequency (percentage) and analyzed using

Pearson's chi-square test. To examine temporal trends, national estimates for the annual rates of TAVR-related hospitalization were determined using the discharge weights provided in the NIS database.

For sex differences in outcomes, the adjusted odds ratios [ORs] were calculated using multivariate logistic regression. Adjusted variables were age, hospital characteristics, prior history of stroke, prior history of MI, prior history of PCI, prior history of CABG, PH, coronary artery disease (CAD), HTN, obesity, dyslipidemia, chronic lung disease, atrial fibrillation, DM, congestive heart failure, CKD, calendar years, access site, and type of procedure. Results were considered statistically significant for a two-sided P value <0.05. STATA/MP 15.10 (Stata Corp LLC) was used for statistical analysis.

Results

Baseline Demographics

Among 61,234 TAVR hospitalizations included in the study, 47.5% were women. The number of TAVR procedures progressively increased over time both in women [3750 (48.9%) admissions in 2012 to 9544 (47.3%) in 2015] and in men [3910 (51.04%) admissions in 2012 to 10,664 (52.7%) in 2015] but the proportion did not change in both genders over the years (Fig). The majority of patients undergoing TAVR were octogenarians in both sexes. The proportion of women with Charlson comorbidity index >3 was lower as compared to men undergoing TAVR (49.7% vs 60.9%, P < 0.001). Medicare was the primary payer (>90%) in both genders (Table 1).

Comorbidities

Women had a higher prevalence of anemia, PH, HTN, obesity in comparison to males (Table 1). Women were less likely to have CAD, CKD, prior acute myocardial infarction (AMI), prior PCI, prior CABG, and peripheral vascular disease.

Primary and Secondary In-Hospital Outcomes

Women had a higher risk of all-cause in-hospital mortality [adjusted OR: 1.25, confidence interval (CI): 1.01-1.54; $P = 0.036$] in comparison to men. The incidence of cardiac complications [OR 2.41, CI: 1.67-3.49; $P \leq 0.001$], respiratory complications [OR 1.20, CI: 1.07-1.34; $P = 0.001$], major hemorrhage requiring transfusion [OR 1.51, CI: 1.37-

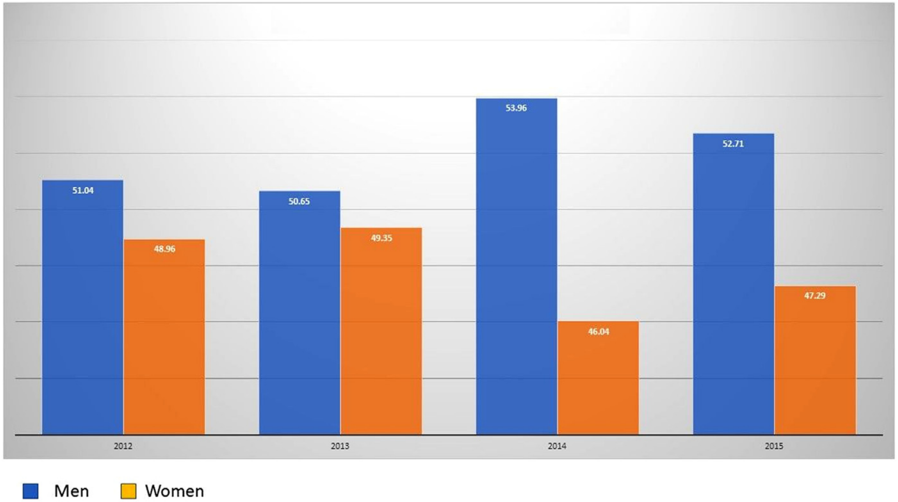

Fig. Trends of hospitalization for men/women over the years.

1.67; $P \leq 0.001$], need for vasopressor requirement [OR 1.33, CI: 1.01-1.75; $P = 0.04$], and vascular complications [OR 1.73, CI: 1.19-2.52; $P = 0.004$] were all significantly higher in women. On the contrary, the odds of permanent pacemaker requirement [OR 0.85, CI: 0.75-0.97; $P = 0.02$] and acute kidney injury (AKI) [OR 0.80, CI: 0.71-0.91; $P = 0.001$] were lower in women compared with men undergoing TAVR (Table 2).

In our study predictors for in hospital mortality in women were vascular complications [OR 7.85, CI: 3.93-15.69; $P < 0.001$], the need for mechanical ventilation [OR 2.53, CI: 1.48-4.31; $P < 0.001$], vasopressor requirement [OR 2.15, CI: 1.12-4.15; $P = 0.02$], respiratory complications [OR 3.10, CI: 2.23-4.37; $P < 0.001$], cardiac complications [OR 5.77, CI: 3.07-10.87; $P < 0.001$], shock [OR 5.57, CI: 3.57-8.68; $P < 0.001$], major bleeding requiring transfusion [OR 1.76, CI: 1.29-2.41; $P < 0.001$], AMI [OR 3.86, CI: 2.00-7.46; $P < 0.001$], and PH [OR 1.54, CI: 1.12-2.13; $P < 0.001$]. Predictors of mortality in men were nonwhite race [OR 1.16, CI: 1.01-1.33; $P = 0.02$], vascular complications [OR 6.30, CI: 2.14-18.54; $P < 0.001$], respiratory complications [OR 7.80, CI: 5.29-11.48; $P < 0.001$], cardiac complications [OR 2.97, CI: 1.02-8.60; $P = 0.04$], shock [OR 6.83, CI: 4.30-10.84; $P < 0.001$], neurological

Table 2. Primary and secondary in-hospital outcomes of transcatheter aortic valve replacement (TAVR) in women compared to men

Variable	Male (%)	Female (%)	Odds ratio	95% CI	*P* value
In-patient Mortality	1020 (3.1)	1220 (4.19)	1.25	1.01-1.54	0.036
AMI	730 (2.27)	605 (2.08)	0.95	0.73-1.24	0.73
AKI	4960 (15.44)	3535 (12.16)	0.80	0.71-0.91	0.001
Pacemaker insertion	3690 (11.49)	2885 (9.91)	0.85	0.75-0.97	0.015
Major bleeding requiring blood transfusion	6330 (19.71)	7900 (27.15)	1.51	1.37-1.67	<0.001
Neurological complication	295 (1.46)	400 (2.1)	1.38	0.95-1.99	0.08
Post-op shock	1180 (3.67)	1205 (4.14)	1.03	0.84-1.27	0.71
Post-op Infection	64 (0.2)	125 (0.43)	1.71	0.84-3.63	0.18
Complete heart block	3445 (10.77)	2935 (10.08)	0.94	0.84-1.07	0.39
Cardiac complication	225 (0.7)	605 (2.08)	2.41	1.67-3.49	<0.001
Respiratory complication	4155 (12.95)	4600 (15.83)	1.20	1.07-1.34	0.001
DVT/PE	675 (2.10)	825 (2.83)	1.14	0.88-1.48	0.30
Pressor support requirement	670 (2.09)	835 (2.87)	1.33	1.01-1.75	0.041
Mechanical ventilation	735 (2.29)	845 (2.9)	1.10	0.87-1.39	0.38
Vascular complication	210 (0.65)	320 (1.1)	1.73	1.19-2.52	0.004
Length of stay	7.31 ± 7.32	7.83 ± 7.01			0.007
Total cost	61,012	62,004			0.48

AMI, acute myocardial infarction; AKI, acute kidney injury; DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 3. Predictors of mortality in women undergoing transcatheter aortic valve replacement (TAVR)

Variable	Odds ratio	95% confidence interval	*P* value
Vascular complication	7.85	3.93-15.69	<0.001
Mechanical ventilation	2.53	1.48-4.31	<0.001
Pressor requirement	2.15	1.12-4.15	0.02
Respiratory complication	3.10	2.23-4.37	<0.001
Cardiac complication	5.77	3.07-10.87	<0.001
Complete heart block	1.65	0.91-3.01	0.09
Shock	5.57	3.57-8.68	<0.001
Neurological complication including iatrogenic stroke	0.96	0.37-2.44	0.93
Major bleeding requiring transfusion	1.76	1.29-2.41	<0.001
Pacemaker requirement	0.40	0.19-0.87	0.02
Acute kidney injury	1.15	0.78-1.70	0.46
AMI	3.86	2.00-7.46	<0.001
Atrial fibrillation	1.35	0.65-2.70	0.41
Charlson category	0.98	0.79-1.22	0.87
CKD	0.86	0.52-1.40	0.55
DM	0.81	0.56-1.16	0.26
Dyslipidemia	0.85	0.62-1.18	0.36
Obesity	0.62	0.38-1.01	0.05
Hypertension	0.54	0.35-0.83	<0.001
Pulmonary hypertension	1.54	1.12-2.13	<0.001
Prior CABG	0.92	0.53-1.58	0.76
Prior PCI	0.71	0.44-1.15	0.17
Prior Stroke	0.87	0.49-1.55	0.65

AMI, acute myocardial infarction; CKD, chronic kidney disease; DM, diabetes mellitus; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

complications including iatrogenic stroke [OR 6.08, CI: 2.74-13.49; $P < 0.001$], AKI [OR 1.77, CI: 1.19-2.63; $P < 0.001$; Tables 3 and 4].

Discussion

The most important findings of the current study were (1) increased all-cause in-hospital mortality in female compared to male; (2) increased in in-hospital complications in women than men except AKI and need for pacemaker implantation; (3) predictors of increased mortality in women were vascular complications, major bleeding requiring transfusion, AMI, PH, the need for mechanical ventilation, respiratory complications, cardiac complications, shock, and vasopressor requirement.

While most registries focus on the overall trends of outcomes from TAVR implantation, few studies have been done to compare the outcomes after TAVR based on gender. Females representing half the patient population undergoing TAVR, it is noteworthy that the physiology of AS

Table 4. Predictors of mortality in men undergoing transcatheter aortic valve replacement (TAVR)

Variables	Odds ratio	95% confidence interval	*P* value
Nonwhite race	1.16	1.01-1.33	0.02
Vascular complication	6.30	2.14-18.54	<0.001
DVT	2.53	1.48-4.31	<0.001
Pressor requirement	1.02	0.30-3.44	0.97
Respiratory complication	7.80	5.29-11.48	<0.001
Cardiac complication	2.97	1.02-8.60	0.04
Complete heart block	1.13	0.69-1.85	0.61
Shock	6.83	4.30-10.84	<0.001
Neurological complication including iatrogenic stroke	6.08	2.74-13.49	<0.001
Major bleeding requiring transfusion	1.33	0.90-1.94	0.14
Pacemaker requirement	0.40	0.19-0.87	0.02
Acute kidney injury	1.77	1.19-2.63	<0.001
AMI	1.37	0.59-3.19	0.45
Atrial fibrillation	1.46	0.70-3.05	0.30
Charlson category	0.79	0.61-1.03	0.08
CKD	1.50	0.84-2.67	0.16
DM	1.01	0.69-1.47	0.94
Dyslipidemia	0.77	0.54-1.09	0.15
Obesity	0.70	0.38-1.30	0.26
Hypertension	0.83	0.48-1.44	0.52
Prior CABG	0.97	0.65-1.44	0.88
Prior PCI	0.85	0.54-1.33	0.49
Prior Stroke	0.46	0.21-0.98	0.04

DVT, deep vein thrombosis; AMI, acute myocardial infarction; CKD, chronic kidney disease; DM, diabetes mellitus; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

is significantly different in women and warrants a closer look. The female heart undergoes predominantly left ventricular (LV) hypertrophy (smaller LV cavity size with preserved systolic function) in response to the increased afterload in AS as opposed to LV dilatation seen in males.[13,14] Concentric remodeling and LV hypertrophy as mentioned before is associated with worse prognosis in AS patients.[15] Women are also found to have narrower LV outflow tract, smaller aortic annulus, and smaller calculated aortic area.[8] Additionally, females have a lower prevalence of concurrent CAD, which delays symptom onset causing first presentation at an old age with often a lower body mass index.[9,16] Therefore, extreme caution is warranted in preoperative planning of female patients with AS toward calculation of aortic valve area and selection of appropriate prosthesis.

One of the international databases focused on TAVR in female population, the Women's INternational Transcatheter Aortic Valve Implantation registry includes majority high-risk patient (above 80 years of age) and reports an all-cause mortality of 3.4%, like our report.[17,18] Although most studies on TAVR outcomes do not show a difference in mortality compared to males,[19,20] some studies showed a survival advantage attributable to preservation of ejection fraction, lower risk of AKI and improved remodeling postintervention in women,[21,22] further confirmed in a subsequent meta-analysis of 6 premarket clinical trials.[23] Contrary to this, we found a higher odds of in-hospital all-cause mortality in females in our study. One possible explanation could be difference in comorbidity distribution in female. Although females had lower rates of dyslipidemia, CAD, prior PCI, prior CABG, peripheral vascular disease, and CKD in our study, they had higher prevalence of hypertension, pulmonary hypertension, obesity and anemia. Women can have prosthesis mismatch owing to smaller aortic annulus and difficult access because of obesity.[24] Society of Thoracic surgeons (STS) and American College of Cardiology Transcatheter Valve Registry also reported more use of nontransfemoral access from 2011 to 2014.[10] The risk of major bleeding and vascular complications are higher in females as described below and more prevalence of coexisting anemia can worsen outcome related to major bleeding events.[25] Presence of preexisting PH is an independent predictor of worse outcome in patients undergoing TAVR.[26] The higher incidence of respiratory complication observed in female is more likely due to obesity and pulmonary hypertension. The observed increase in all-cause in-hospital mortality could also be related to higher STS score and increased frailty in female, variables that are not captured in the NIS database. Women have higher STS score as reported in Placement of AoRTic TraNscathetER

Valve Trial cohort previously.[27] Mortality difference between men and women seems to even out during long term follow-up after TAVR as reported consistently by different studies[10,27] likely secondary to less vascular risk factors in women and favorable LV remodeling after correction of AS.[21] We don't have long-term follow-up data to comment on this finding.

The risks of major bleeding and vascular complications are increased in females undergoing TAVR which is likely due to smaller vessel diameter in female and a higher rate of nontransfemoral access[8,20,27,28] and this can contribute to the increased mortality as seen in our study. As in our analysis, a recent meta-analysis demonstrated that female gender appears to be protective for AKI,[23] possibly due to a better baseline renal function and lesser disruption of blood flow during the procedure. While the existing data is conflicting for complications like pacemaker requirement and stroke incidence in females, we found no statistically increased risk of neurological complication including stroke as well as lower risk of permanent pacemaker implantation in women.[27,29-31]

Limitation

The major limitation of our study is the use of an administrative database where coding practices are not uniform. Being a retrospective observational study, there is potential for selection bias. Moreover, not all potential confounders may be available in the database, and despite the use of multivariate logistic regression residual confounding is likely to be present. Data regarding follow-up beyond the hospital admission is not available in the database. Data on STS score, frailty, type of valve, anesthesia used, medications including anticoagulation, and echocardiographic parameters to identify the valve hemodynamics are also not available in the database.

Conclusion

Among patients undergoing TAVR, women had an increased risk of in-hospital complications and mortality as compared with men. More studies are needed to understand this finding despite less vascular risk factors in women.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cpcardiol.2020.100694.

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