

Transcatheter aortic valve replacement in patients with bicuspid aortic valve stenosis: national trends and in-hospital outcomes

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ABSTRACT

Background: Bicuspid aortic valve (BAV) disease is considered the most common congenital heart disease and the main etiology of aortic valve stenosis (AS) in young adults. Although transcatheter aortic valve replacement (TAVR) is routinely used in high- and intermediate-risk patients with AS, BAV patients with AS were excluded from all pivotal trials that led to TAVR approval. We sought, therefore, to examine in-hospital outcomes of patients with BAV who underwent TAVR in comparison with surgical aortic valve replacement (SAVR). **Methods:** Using the National Inpatient Sample from 2011 to 2014, we identified patients with BAV with International Classification of Diseases-Ninth Revision-CM code 746.4. Patients who underwent TAVR were identified using ICD-9 codes 35.05 and 35.06 and those who underwent SAVR were identified using codes 35.21 and 35.22 during the same period. **Results:** A total of 37,052 patients were found to have BAV stenosis. Among them, 36,629 patients (98.8%) underwent SAVR, whereas 423 patients (1.14%) underwent TAVR. One-third of enrolled patients were female, and the majority of the patients were White with a mean age of 65.9 ± 15.1 years. TAVR use for BAV stenosis significantly increased from 0.39% in 2011 to 4.16% in 2014 ($P < 0.001$), which represents a 3.77% overall growth in procedure rate. The median length of stay decreased significantly throughout the study period (mean 12.2 ± 8.2 days to 7.1 ± 5.9 days, $P < 0.001$). There was no statistically significant difference between SAVR and TAVR groups in the in-hospital mortality (0% vs. 5.9%; adjusted $P = 0.119$). **Conclusion:** There is a steady increase in TAVR use for BAV stenosis patients along with a significant decrease in length of stay.

Key words: Bicuspid aortic valve stenosis, surgical aortic valve replacement, transcatheter aortic valve replacement

INTRODUCTION

Bicuspid aortic valve (BAV) disease is considered the most common congenital heart disease and the most common cause of aortic valve stenosis (AS) in young adults. Up to 50% of patients with BAV require aortic valve replacement in their lifetime.^[1] This is because of the flow hemodynamics of the aortic valve which expedites the degeneration of the valve leaflets prematurely. The current guidelines recommend

routine echocardiogram follow-up of patients with BAV to evaluate the valve hemodynamics, severity of the valve stenosis, and the left ventricular function.

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Although transcatheter aortic valve replacement (TAVR) has been used routinely in high- and extreme-risk AS patients, BAV patients with AS were excluded from many pivotal trials that led to approval of TAVR in the United States.^[2-5] This is mainly due to the concomitant aortopathy, which requires aortic root repair with a potential increased risk of aortic dissection and numerous technical challenges related to bicuspid anatomy.^[6-8] Therefore, the treatment of choice for symptomatic bicuspid stenosis has been surgical aortic valve replacement (SAVR).^[9]

With the advances in device technology, and with the accumulated experience, there has been an increased off-label use of TAVR for bicuspid stenosis in the absence of aortopathy.^[10] Majority of the evidence for safety and feasibility of TAVR in patients with BAV is based on registry data and single-center experiences. There are limited data regarding the use and outcome of TAVR in BAV stenosis in the United States. We sought, therefore, to assess the trend of TAVR use in patients with BAV stenosis over the past few years and examine the subsequent in-hospital and procedural outcomes.

MATERIALS AND METHODS

Data were obtained from the Agency for Healthcare and Research, and Quality Healthcare Cost and Utilization Project National Inpatient Sample (NIS) files from January 1, 2011 through December 31, 2014. The NIS is the largest, publicly available, all-payer administrative claims database in the United States. It contains de-identified patient and clinical data from approximately 1,000 nonfederal hospitals in 45 states, including approximately 5–8 million discharges annually.^[11]

We identified patients with BAV with International Classification of Diseases-Ninth Revision-CM (ICD-9) code 746.4. Patients undergoing TAVR were identified using ICD-9 codes 35.05 and 35.06. We also obtained the data of those who underwent SAVR were identified using ICD-9 codes 35.21 and 35.22 during the same period. To maintain a homogenous study population and to limit confounding, those with concomitant aortic valve disease were excluded from the analysis in addition to patients undergoing concomitant procedures. Procedure-related complications were identified using appropriate ICD-9-CM codes in any secondary diagnosis field. All measures for comorbidities, except coronary artery disease and anticoagulation history, were created from definitions in the Elixhauser Co-morbidity Index, which assigns variables that identify comorbidities in hospital discharge records using the diagnosis coding of ICD-9-CM.^[12]

Major complications were recorded using established Valve Academic Research Consortium (VARC II) definitions for death, major bleeding, myocardial infarction, stroke, vascular complications, valve-related dysfunction, and acute kidney injury.^[13] Hospital length of stay (LOS) was defined as the number of days from the date of the procedure to the date of being discharged home or to a rehabilitation facility.

A value of $P < 0.05$ was considered statistically significant. We used the Statistical Package for the Social Sciences software version 25.0 software (IBM, Armonk, NY) for all statistical analyses.

To account for potential confounding factors and reduce the effect of selection bias, a propensity-score-matching model was developed to derive two matched groups for comparative outcomes analysis. Propensity score was calculated using multivariable logistic regression models derived from hospital level, clinical, and demographic covariates, including the Elixhauser comorbidities. For calculation of the propensity score, the dependent variable was the TAVR vs. SAVR procedure use. We performed matching on the propensity score implementing a greedy algorithm to construct a balanced match of TAVR cases to SAVR cases in a 1:1 ratio using a caliper of 0.1. As we used publicly accessible, de-identified administrative level aggregate data, rather than patient-specific data, approval from the institutional review board was not required to conduct the study.

RESULTS

A total of 37,052 patients were found to have BAV stenosis. Among them, 36,629 patients (98.8%) underwent SAVR, whereas 423 patients (1.14%) underwent TAVR between January 1, 2011, and December 31, 2014. Compared with SAVR counterparts, patients with BAV who underwent TAVR were older (65.9 years \pm 15.1 vs. 56.7 years \pm 14.7), had more Caucasian women (34.3% vs. 26.3%), but had more co-morbidities, particularly CAD, hyperlipidemia, prior stroke, and complicated diabetes [Table 1]. The vast majority of TAVR procedures were performed in large teaching hospitals. Baseline differences existed between the groups after the propensity-adjusted analysis [Table 2].

The number of patients with a BAV stenosis who underwent TAVR significantly increased from 0.39% in 2011 to 4.16% in 2014 ($P < 0.001$), which represents a 3.77% overall growth in procedure rate [Figure 1]. The median LOS was 10.2 days and decreased significantly throughout the above period (mean [SD] 12.2 [8.2] days to 7.1 [5.9] days, $P < 0.001$) [Figure 2].

Table 1: Baseline characteristics and comorbidities in bicuspid aortic valve stenosis patients who underwent either surgical or transcatheter aortic valve replacement

Variable	SAVR (N = 36,629)	TAVR (N = 423)	P value
Age	56.7 ± 14.7	65.9 ± 15.1	<0.001
Sex			
Female	26.3	34.3	<0.001
Race			0.027
White	85.3	89.2	
Black	2.1	2.4	
Hispanic	5.9	4.8	
Asian or Pacific Islander	1.4	2.4	
Native American	0.4	0.0	
Other	3.6	1.2	
Elective hospitalization	78.8	79.6	0.112
Primary expected payer			<0.001
Medicare	31.1	31.4	
Medicaid	6.8	6.8	
Private insurance	55.6	55.4	
Self-pay	2.9	2.9	
No charge	0.4	0.4	
Other	3.2	3.1	
Median household income (percentile)			<0.001
0–25	19.0	19.1	
26–50	24.6	24.5	
51–75	27.3	27.3	
76–100	29.1	29.1	
Bed size			<0.001
Small	7.4	2.4	
Medium	19.0	14.2	
Large	73.6	83.5	
Location/teaching status			0.001
Rural	1.7	0.0	
Urban nonteaching	18.7	10.4	
Urban teaching	79.6	89.6	
Hospital region			0.114
Northeast	21.8	22.2	
Midwest	26.2	23.1	
South	31.5	33.1	
West	20.5	23.4	
Carotid artery disease	2.4	3.5	0.153
Coronary artery disease	32.6	42.3	<0.001
Smoking	12.9	7.1	<0.001
Hyperlipidemia	48.9	55.5	0.008
Prior stroke	4.9	8.1	0.003
Atrial fibrillation	33.5	35.3	0.469
Alcohol abuse	3.6	3.5	1.000
Deficiency anemia	13	15.4	0.165
RA/collagen vascular disease	1.9	5.9	<0.001
Chronic blood loss anemia	0.9	2.4	0.008
Congestive heart failure	0.9	15.4	<0.001
Chronic lung disease	16.7	16.7	<0.001
Coagulopathy	28.1	23.6	0.045
Depression	7.9	10.6	0.043
Obesity	17.5	9.5	<0.001
Weight loss	2.8	8.3	<0.001
Uncomplicated DM	14.9	17.7	0.112
Complicated DM	2.4	7.1	<0.001
Drug abuse	0.0	2.1	<0.001
Hypertension	61.3	70.7	<0.001
Hypothyroidism	8.5	8.5	0.111
Liver disease	1.8	1.8	<0.001
Lymphoma	0.4	0.0	0.417
Fluid and Electrolyte disorders	33.9	33.8	0.003
Other neurological disorders	3.9	3.9	0.377
Paralysis	0.9	1.0	0.008

Table 1: Continued

Variable	SAVR (N = 36,629)	TAVR (N = 423)	P value
PVD	30.4	30.3	<0.001
Renal failure	6.6	6.8	<0.001
Pulmonary circulation disorders	0.4	0.4	<0.001
Psychosis	2.1	2.1	0.056

PCI = percutaneous coronary intervention;

CABG = coronary artery bypass graft; RA = Rheumatoid arthritis; DM = diabetes; PVD = peripheral vascular disease.

No statistically significant difference in the need for permanent pacemaker placement or the incidence postoperative aortic rupture was observed. On the contrary, the overall vascular complications, the need for blood transfusion, and the requirement for emergent open cardiac surgery have declined over the same period [Figure 3].

After propensity matching of 68 patients [Table 3 and Figure 4], there was no statistically significant difference between SAVR and TAVR groups in the in-hospital mortality (0% vs. 5.9%; adjusted $P = 0.119$), vascular and cardiac complications, perioperative stroke, acute kidney injury, and permanent pacemaker placement between the two groups. On the contrary, respiratory complications were significantly lower in patients who underwent TAVR (11.8% vs. 29.4%, adjusted $P = 0.011$).

DISCUSSION

The findings of our study suggest an increase in the adoption of TAVR for BAV stenosis patients in the United States with overall comparable in-hospital outcomes in those who underwent TAVR and their counterpart in the SAVR cohort.

Patients with BAV were excluded from major early TAVR trials^[2-5] because of several concerns that BAV anatomy might lead to a less than optimal prosthetic valve positioning and expansion leading to significant paravalvular regurgitation or annulus rupture. In addition, the presence of concomitant aortopathy with a potential increased risk of aortic dissection or rupture as well as a questionable long-term durability of transcatheter valves in younger patients with longer life expectancy. Nevertheless, the accumulated experience and advances in device technology have led to the increased off-label use of TAVR for bicuspid AS.^[10] Early report by Wijesinghe *et al.*^[14] showed the feasibility of TAVR in 11 patients with severe BAV stenosis. Edwards SAPIEN valves (Edwards Lifesciences, Irvine, CA) were implanted successfully in all patients with significant hemodynamic improvement, but two patients (18.2%) had a moderate paravalvular leak. Although Mylotte *et al.*^[15] showed that TAVR using the first-generation balloon-expandable valves

Table 2: Baseline characteristics and comorbidities in a matched cohort of bicuspid aortic valve stenosis patients who underwent either surgical or transcatheter aortic valve replacement

Variable	SAVR (N = 68)	TAVR (N = 68)	P value
Age	64.6 ± 12.4	65.0 ± 14.8	0.871
Sex			
Female	27.9	32.4	0.709
Race			0.126
White	85.3	88.2	
Black	10.3	1.2	
Hispanic	2.9	5.9	
Asian or Pacific Islander	0.0	2.9	
Other	1.5	1.5	
Elective hospitalization	80.9	77.9	0.832
Primary expected payer			0.676
Medicare	45.6	52.9	
Medicaid	5.9	5.9	
Private insurance	48.5	41.2	
Median household income (percentile)			0.618
0–25	23.5	29.4	
26–50	25.0	16.2	
51–75	25.0	26.5	
76–100	26.5	27.9	
Bed size			0.603
Small	5.9	2.9	
Medium	16.2	13.2	
Large	77.9	83.8	
Location/teaching status			0.325
Urban nonteaching	4.4	7.4	
Urban teaching	95.6	92.6	
Hospital region			0.158
Northeast	235	22.1	
Midwest	27.9	19.1	
South	36.8	32.4	
West	11.8	26.5	
Carotid artery disease	44.1	44.1	1.000
Coronary artery disease	4.4	4.4	1.000
Smoking	11.8	5.9	0.365
Hyperlipidemia	42.6	57.4	0.122
Prior stroke	10.3	10.3	1.000
Atrial fibrillation	33.8	36.8	0.858
Alcohol abuse	1.5	4.4	0.619
Deficiency anemia	13.2	14.7	1.000
RA/collagen vascular disease	2.9	4.4	1.000
Chronic blood loss anemia	1.5	1.5	1.000
Congestive heart failure	4.4	0.0	0.244
Chronic lung disease	23.5	25.0	1.000
Coagulopathy	29.4	23.5	0.560
Depression	13.2	11.8	1.000
Obesity	10.3	13.2	0.449
Weight loss	5.9	5.9	1.000
Uncomplicated DM	19.1	17.6	1.000
Complicated DM	4.4	5.9	1.000
Drug abuse	2.9	0.0	0.496
Hypertension	36.8	72.1	0.849
Hypothyroidism	11.8	11.8	1.000
Liver disease	5.9	2.9	0.680
Fluid and electrolyte disorders	30.9	25.0	0.567
Other neurological disorders	4.4	5.9	1.000
Paralysis	1.5	2.9	1.000

Table 2: Continued

Variable	SAVR (N = 68)	TAVR (N = 68)	P value
PVD	19.1	23.5	0.676
Renal failure	20.6	19.1	1.000
Pulmonary circulation disorders	1.5	0.0	1.000
Psychosis	1.5	4.4	0.619

PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, RA = rheumatoid arthritis, DM = diabetes, PVD = peripheral vascular disease

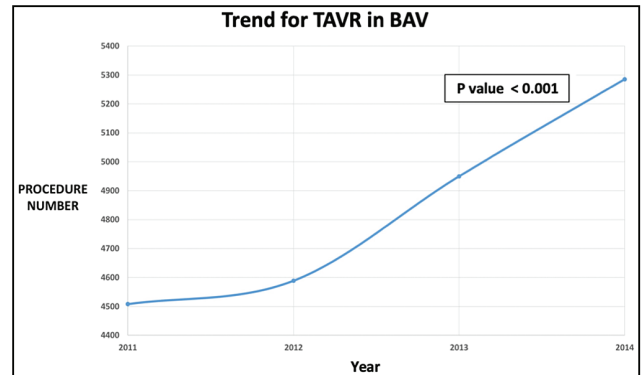


Figure 1: Trend of transcatheter aortic valve replacement (TAVR) in patients with bicuspid aortic valve (BAV) stenosis

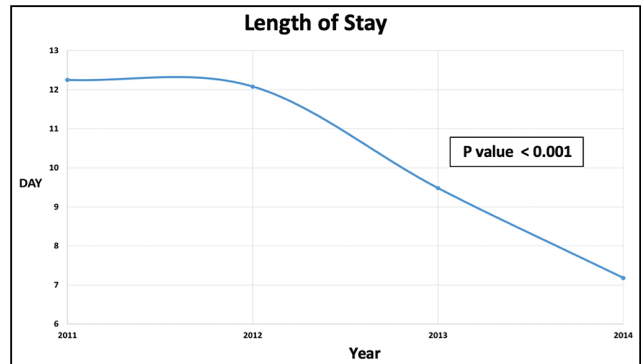


Figure 2: Trends in length of hospital stay

(SAPIEN) or self-expanding valves (Medtronic CoreValve, Medtronic, Dublin, Ireland) were feasible with encouraging short- and intermediate-term clinical outcomes reporting a device success rate of 89.9% and a one-year mortality rate of 17.5% however, a high incidence of post-implantation aortic regurgitation was observed in about 28% of the cases.

More recently, Perlman *et al.*^[16] showed that TAVR in BAV stenosis using a new-generation device was feasible and effective with favorable valve performance and no cases of moderate or severe aortic regurgitation. Yoon *et al.*^[17] provided a head-to-head comparison between the early- and new-generation devices in BAV stenosis patients

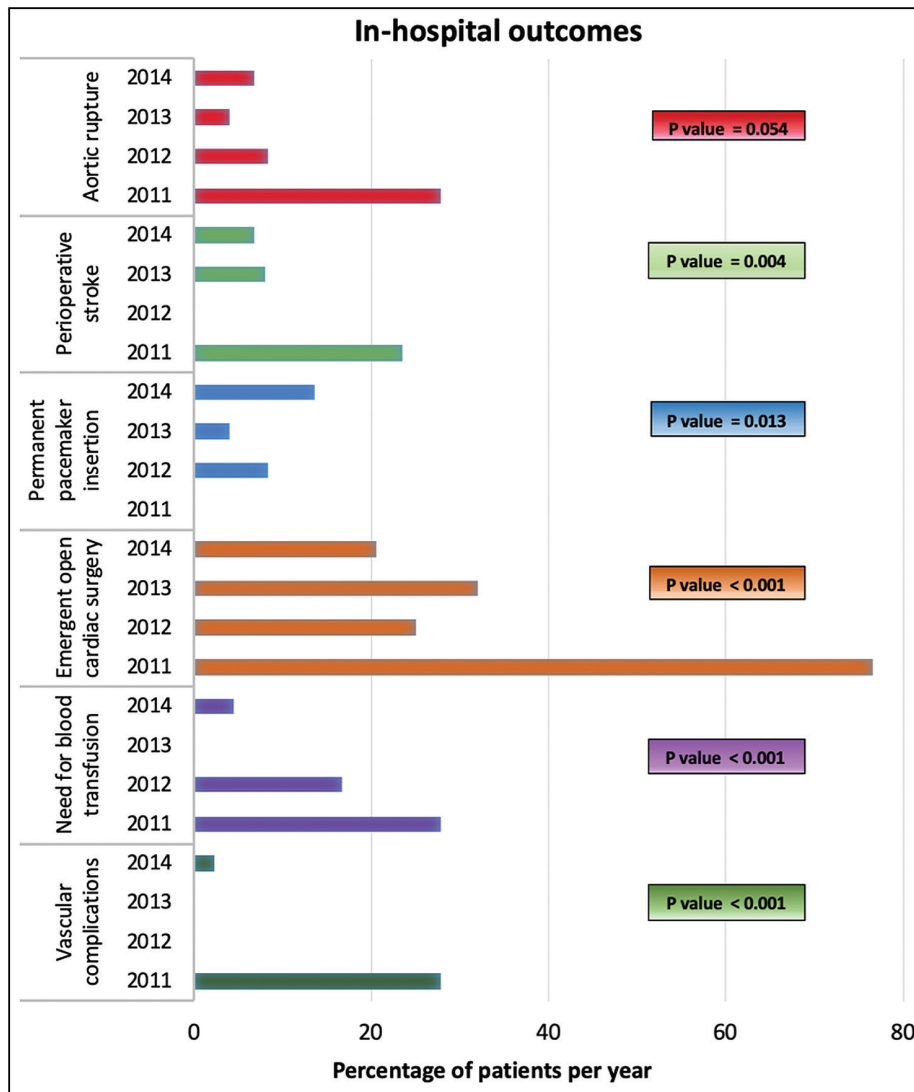


Figure 3: In-hospital outcomes following TAVR in patient with BAV stenosis

undergoing TAVR and showed an all-cause mortality rate of 4.3% at 30 days and 14.4% at 1 year. The outcome was comparable to TAVR outcomes in patients with tricuspid AS. Interestingly, there were no cases of moderate or severe paravalvular regurgitation with new-generation devices, as compared with 8.5% incidence of paravalvular regurgitation with the early-generation devices, resulting in higher device success. Recent data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies (STS/ACC TVT) registry from June 2015 to November 2018 compared outcomes of 2,691 matched BAV patients with an equal number who had a tricuspid valve who were considered intermediate or high risk for open-heart surgery and underwent TAVR. There were similar rates for all-cause mortality rates at 30 days (2.6% vs. 2.4%) and one-year (10.8% vs. 12.1%) post-procedure. However, patients with a BAV had a 50% higher risk of stroke at 30 days (2.4%, vs. 1.6% for tricuspid patients).

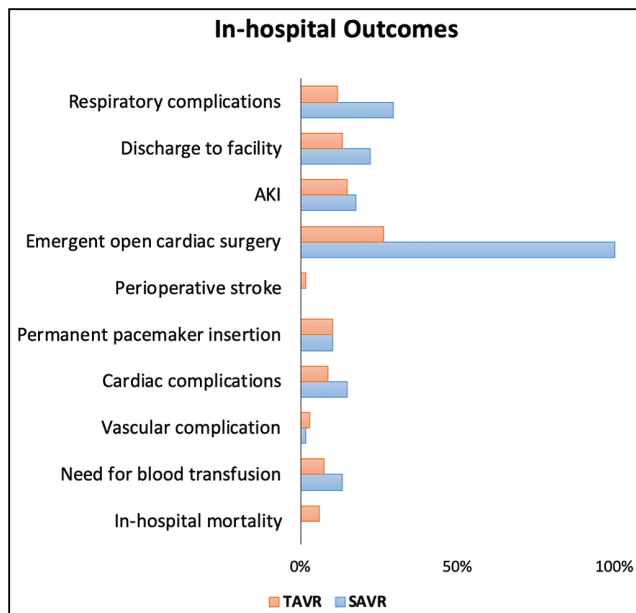
Among patients with a BAV, 0.9% encountered problems during the TAVR procedure that required converting to open-heart surgery, compared with 0.4% of patients in the tricuspid group.^[18]

In terms of respiratory complications, our analysis showed a significantly fewer respiratory-related complications (including post-operative pneumothorax, pulmonary edema, pulmonary collapse, prolonged mechanical ventilation, and tracheostomy) in the TAVR group. This favorable respiratory-related outcomes in TAVR is in line with previous reports and could be explained by the shorter intubation period during TAVR procedures compared to SAVR as well as the fact that open cardiac surgery would likely cause more pain and hence increased use of analgesics that can suppress the respiratory drive thus might result in respiratory failure, atelectasis, or aspiration pneumonia.^[19]

Table 3: In-hospital outcomes of a matched cohort of bicuspid aortic valve stenosis patients who underwent either surgical or transcatheter aortic valve replacement

Outcome	SAVR (N = 68)	TAVR (N = 68)	P value
In-hospital mortality	0%	5.9%	0.11
Need for blood transfusion	13.2%	7.4%	0.39
Vascular complication	1.5%	2.9%	1.00
Injury to blood vessels, accidental puncture, injury to retro-peritoneum, other vascular complications, vascular complications requiring surgery			
Cardiac complications	14.7%	8.8%	0.42
Permanent pacemaker insertion	10.3%	10.3%	1.00
Perioperative stroke	0%	1.5%	1.00
Emergent open cardiac surgery	100%	26.5%	<0.001
AKI	17.6%	14.7%	0.81
Discharge to facility	22.1%	13.2%	0.26
Including short term in other hospitals, skilled nursing facility, intermediate care facility, and another type of facility			
Respiratory complications	29.4%	11.8%	0.01
Post-operative acute pneumothorax, postoperative pulmonary edema, pulmonary collapse, prolonged mechanical ventilation >96 h, tracheostomy			

SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement, AKI = acute kidney injury

**Figure 4:** In-hospital outcomes of a matched cohort of bicuspid aortic valve stenosis patients who underwent either surgical or transcatheter aortic valve replacement

Limitation

Our study has the following limitations. The analysis of the large administrative data is inherently prone to error because of potential inaccurate coding. However, the NIS database is a reliable source with broad applicability, given its large sample size. Outcome analysis was limited to in-hospital outcomes with no outcomes or complications after discharge were not recorded. Given the patients with BAV are often, younger compared with tricuspid AS, the durability of TAVR prosthesis is of interest, and this is what not captured in this database. In addition, TAVR procedures in this cohort of patients were done using old generation valves, and we were unable to delineate a change of outcome based on the prosthesis or delivery system that was used. However,

we can assume that the Edwards SAPIEN Valve (Edwards Lifesciences, Irvine, CA) was dominantly used between the years 2011 and 2014 as the Medtronic CoreValve (Medtronic, Minneapolis, MN) received Food and Drug Administration approval in early 2014. Lastly, because of the small sample of matched patients' population, this study might not be powered enough to detect a statistically significant difference in the in-hospital mortality between SAVR and TAVR groups (0% vs. 5.9%; adjusted $P = 0.119$).

CONCLUSIONS

This study shows a steadily increase in the adoption of TAVR for BAV stenosis patients in the United States along with a significant decrease in LOS. TAVR seems a safe and effective therapy in patients with BAV stenosis without aortopathy as compared with SAVR. Further research with multi-institutional studies is warranted to assess the long-term durability and complications associated with TAVR in this patient population.

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Conflicts of interest

There are no conflicts of interest.

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