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Transcatheter aortic valve replacement outcomes in bicuspid compared to trileaflet aortic valves

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ABSTRACT

Aim: TAVR in patients with bicuspid aortic valves (BAV) is more challenging compared to individuals with trileaflet aortic valves (TAV). BAV have been excluded from the large randomized clinical trials assessing transcatheter aortic valve replacements (TAVR) and has been considered as a relative contraindication to TAVR. To report the outcomes of TAVR in BAV and compare them to TAV in the National Inpatient Sample (NIS).

Methods and results: TAVR procedures were identified between 2011 and 2014 in the NIS dataset. Endpoints assessed included in-hospital mortality, periprocedural complications, length of stay and cost. Of 40,604 identified TAVR procedures, 407 (1%) were BAV and the 40,197 (99%) were TAV. Patients with BAV were younger and had a lower comorbidity burden. In hospital mortality (4.89% vs 4.17%, OR: 1.71, 95%CI: 0.57–5.12, P = 0.21), AMI (3.49% vs 3.58%, OR: 1.12, 95%CI: 0.36–3.54, P = 0.85), stroke and TIA (2.49% vs 3.55%, OR: 0.75, 95%CI: 0.18–3.16, P = 0.70), vascular complications (2.39% vs 5.58%, OR:0.47, 95%CI: 0.11–1.93, P = 0.29), major bleeding (16.96% vs 23.50%, OR: 0.63, 95%CI: 0.34–1.17, P = 0.15) and rates of permanent pacemaker (PPM) (9.88% vs 10.88%, OR: 1.19, 95%CI: 0.57–2.51, P = 0.64) were similar in both cohorts.

Conclusions: With multimodality imaging and further improvement in technology, our study demonstrates off-label TAVR should not be considered prohibitive and can be successfully performed for BAV with similar periprocedural outcomes compared to those with TAV. However, there is a need for robust large prospective studies.

1. Introduction

Bicuspid aortic valves (BAV) are one of the most common forms of inherited heart disease affecting approximately 1% of adults, and are twice as common in males as in females [1,2]. With advancing age and abnormal turbulent flow, the process of calcification of the BAV is accelerated compared to trileaflet valves and fusion of the coronary cusps results in valvular stenosis and dysfunction [3–6]. BAV stenosis accounts for half of the patients undergoing aortic valve surgery for severe aortic stenosis [7,8]. The BAV stenosis cohort undergo surgery nearly 5–10 years earlier compared to their trileaflet counterparts, with less comorbidity burden. BAV have been excluded from the large randomized clinical trials assessing transcatheter aortic valve replacements (TAVR) and are considered to be a relative contraindication, due to the increased structural variation of the aortic valve [9–12]. BAV are less elliptical with commissural fusion, irregularities in shape and dense calcification, which may result in an increased probability of inadequate valve expansion and deployment, severe aortic regurgitation post valvuloplasty, and suboptimal valve function post TAVR [13,14]. In addition, BAV are often associated with an aortopathy that could increase the hazard of aortic dissection or rupture during TAVR. Accordingly, there are limited data regarding the short and long term outcomes for patients with BAV undergoing off-label TAVR for severe AS [15–23]. The National Inpatient Sample (NIS) offers an opportunity to study

Abbreviations: BAV, bicuspid aortic valves; TAV, trileaflet aortic valves; TAVR, transcatheter aortic valve replacements; NIS, National Inpatient Sample; PPM, permanent pacemaker.

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clinical characteristics and outcomes of patients undergoing TAVR in the setting of BAV in comparison to trileaflet aortic valves (TAV).

2. Materials and methods

2.1. Data source

The NIS is the biggest all-payer inpatient health care database, sponsored by the Agency for Healthcare Research and Quality (AHRQ) and established by Healthcare Cost and Utilization Project (HCUP) and was utilized for this analysis [24].

2.2. Study design

All patients treated with a TAVR between January 2011 and December 2014 documented with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes of 35.05 (Endovascular replacement of aortic valve) and 35.06 (Transapical replacement of aortic valve) were identified. Patient-specific and hospital-specific discharge weights were used for inference of national estimates. ICD-9-CM Diagnosis Code 746.4 was used to identified BAV.

Adults (over the age of 18) who underwent a TAVR procedure during their hospital stay were included in the study. Patient demographics for each hospital discharge, including: age, gender, race, admission type (elective or emergent), median household income according to ZIP code and patient comorbidity conditions using Elixhauser classification system were identified [25]. Comorbidities, defined by Elixhauser classification system [25] consisting of 30 comorbidity measures and a point based system (Elixhauser Comorbidity Score, ECS) reported by van Walraven et al. [26], were utilized for this analysis. Patients were classified into five ECS-based categories (ECS I < 0, ECS II = 0, ECS III = 1–5, ECS IV = 6–13, ECS V ≥ 14).

The ICD-9-CM codes used to identify each of the conditions. Procedural data from the TAVR procedure, including the access site and use of mechanical assist devices, were also recorded.

2.3. Clinical outcomes

In-hospital clinical outcomes including in-hospital mortality, length of stay on the discharge record, and the total charge of hospitalization for each individual discharge were assessed. Procedural complications within the hospitalization were identified using ICD-9-CM codes. This included need for bail-out, open surgical valve replacement, acute myocardial infarction (AMI) post TAVR, post-operative stroke or transient ischaemic attack (TIA), permanent pacemaker implantation (PPM), percutaneous coronary intervention (PCI) post TAVR, vascular injuries, acute kidney injury (AKI) and AKI resulting in dialysis. Major bleeding complications were identified and included: intra- or post-operative haemorrhage gastrointestinal, retroperitoneal, intracranial, intracerebral haemorrhage, unspecified haemorrhage, and requirement of a blood transfusion. Complications were identified by ICD-9-CM codes in any secondary diagnosis field.

2.4. Statistical analysis

Stata 15.1 MP was used to perform the statistical analysis. Continuous variables were reported as mean (standard deviation) and categorical variables were expressed as frequencies (percentages). An unbiased, complete-case-only analysis was performed, and survey estimation commands were using the "svy" prefix in Stata based on the recommendations from AHRQ for evaluation of the survey data to assess the multifaceted survey design of the NIS cohort. Records were appraised by hospital number and assembling of records within hospitals were taken into account in the survey estimation. The individual hospital was considered to be the primary sampling unit. For calculation of nationwide estimates and precise variances, sampling weights for each individual discharge, specified by the AHRQ, were utilized. The use of sampling weights is essential because the design of the study means that different observations may have different probabilities of selection.

A maximum likelihood, estimation multiple logistic regression analysis and multiple regression analysis was performed separately for categorical and continuous (length of stay in days, cost in USD) variables and model building processes were conducted. After univariate analyses, the variables with $P < 0.25$ were incorporated in the multivariable models, along with known predefined predictors, A backward stepwise method was employed to select the variables to build the final adjusted model, and variables with $P < 0.05$ were retained in the final model. Each variable that was not included in the original, baseline multivariable model was added one at a time to obtain a proficient model. Interaction terms were considered significant only if their P-values were <0.01. To assess the influence of BAV, the multivariable analysis was adjusted for all potential confounders that were measured. These covariates were: age, gender, ethnicity, median income, smoking status, elective admission, race, access site, comorbidity burden and mechanical support.

Given the differences between the BAV and TAV a propensity score matching exercise was undertaken. Using a logistic regression model, a propensity score was developed according to age, gender, elective, prior myocardial infarction, previous percutaneous and surgical coronary revascularization, mechanical support during TAVR, hypertension, Diabetes Miletus, renal failure, chronic pulmonary disease, peripheral vascular disease.(psmatch2 command in STATA) Following matching, continuous variables were assessed using linear regression and coefficient with 95% confidence interval (CI) as well as standard error were calculated. Subsequently, Odd ratio (OR) with 95% CI and P values were calculated. Dissimilarities for the matched categorical variables were analysed using logistic regression analysis. For mortality and peri-procedural complications, the OR with 95% CIs and P values of the logistic regression analysis for the propensity score–matched groups were calculated.

3. Results

A total of 40,604 TAVR procedures were identified between 2011 and 2014 for the indexed hospitalizations. Discharges with missing data for included outcomes as well as covariates of age, gender and elective surgery indication were excluded for this analysis, Fig. 1. A total of 40,601 TAVR procedures were identified of which 407 (1%) procedures were undertaken in BAV and 40,197 (99%) in TAV. Patients with BAV were more likely to be younger male smokers with higher prevalence of liver disease and a lower prevalence of congestive heart failure, diabetes mellitus, renal failure, previous percutaneous or surgical coronary revascularization (Table 1a). The distribution of comorbidity burden as assessed using the Elixhauser comorbidity score is presented in Table 1a. Individuals with BAV were less likely to be in the 2 most severe categories of Elixhauser comorbid burden (ECS IV & V) compared to those with TAV; 67.9% vs 82.3% respectively ($P = 0.02$).

During the study period of 2011–2014 the number of TAVR procedures in patients with BAV was noted to increase from 18 to 212 ($P = 0.53$) (Supplementary Fig. 1). The proportion of BAV undergoing TAVR remained similar throughout the period from 2011 to 14 (1.59%, 0.77%, 0.97%, 1.10%).

3.1. Clinical outcomes

Table 2a and 2b provide an overview of the clinical outcomes (unadjusted as well as post propensity matching) and Table 3 demonstrates the results of multivariate analysis. In-hospital mortality (OR 1.71, 95% CI 0.57–5.12, $P = 0.21$), AMI (OR 1.12, 95% CI 0.36–3.54, $P = 0.85$), stroke and TIA (OR 0.75, 95% CI 0.18–3.16, $P = 0.70$), need for PPM (OR 1.19, 95% CI 0.57–2.51, $P = 0.64$), vascular complications (OR 0.47, 95% CI 0.11–1.93, $P = 0.29$), major bleeding (OR 0.63, 95% CI

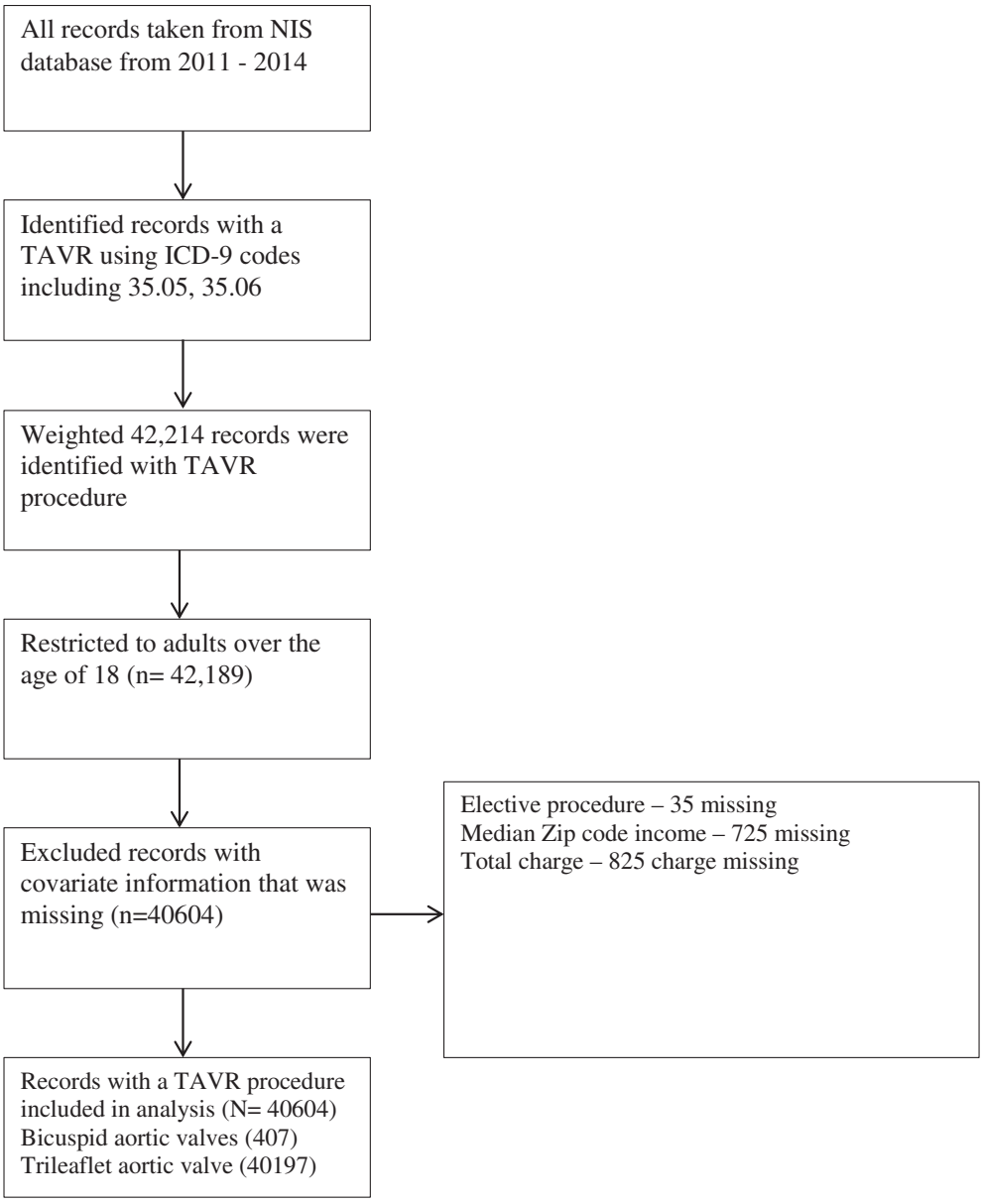

Fig. 1. Flow diagram of included/excluded records.

0.34–1.17, P = 0.15), and acute kidney injury(AKI) (OR 0.75, 95% CI 0.40–1.39, P = 0.36), were not significantly different between the BAV and TAVR groups following adjustment in baseline characteristics. Post propensity score matching the variables were balanced across the two cohorts resulting in 359 patients each (Table 1b). The rates for PPM (OR 2.90, 95% CI 0.72–11.58, P = 0.13), stroke and TIA (OR 0.49, 95% CI 0.08–2.82, P = 0.42), AMI (OR 0.94, 95%CI 0.13–7.05, P = 0.95), blood transfusion (OR 0.69, 95% CI 0.30–1.60, P = 0.39), acute kidney injury(AKI) (OR 1.10, 95% CI 0.45–2.72, P = 0.83), AKI needing haemodialysis (HD) (OR 0.17, 95% CI 0.02–1.49, P = 0.11), vascular complication (OR 0.17, 95% CI 0.02–1.56, P = 0.12), major bleeding (OR 0.70, 95% CI 0.31–1.60, P = 0.40) were similar across the two cohorts. In terms of in hospital mortality, the event rate was higher in the BAV group although it did not reach statistical significance (OR: 4.20, 95% CI 0.45–39.62, P = 0.21).

3.2. Length of stay and healthcare costs

A reduction in the mean length of stay from 2011 to 2014 for BAV from 12.2 days to 7.2 days (P value of 0.02, Supplementary Fig. 2). Both length of stay (TAV: mean 8.1 days SD 0.1, BAV: mean 8.7 days SD 1.0, P value = 0.45) and total hospitalization charge (TAV: mean $235,803.60 SD 19, 207.4, BAV: mean $226,640 SD 1684.7, P value = 0.97) were similar across the two cohorts (Table 4). Similarly, post propensity score matching the length of stay (TAV: mean 8.2 days SD 7.6, BAV: mean 8.9 days SD 9.5, P = 0.64) and total charge (TAV: mean $214, 635, SD $136,950, BAV: mean $239,254, SD $181,538, P = 0.36) were similar across the two cohorts.

4. Discussion

Our analysis of over 40,000 TAVR procedures reports that TAVR is seldom undertaken in patients with BAV and severe AS, representing only 1% of all TAVR procedures undertaken in the United States as captured by the National Inpatient Sample from 2011 to 14. Patients with BAV undergoing TAVR, tend to be younger with less comorbidities and fewer adverse clinical characteristics compared with TAV-TAVR patients, and so represent a lower risk in traditional risk-profiling of clinical cohorts. Furthermore, this analysis suggests that in the modern era of TAVR, the in-hospital peri-procedural and health economic

Table 1a
Patient demographics stratified by aortic valve morphology.

	Tricupsid aortic valve	Bicuspid aortic valve	
Continuous variables	Mean (SD)	Mean (SD)	P value
Mean age, years	81.3 (8.3)	67.1 (13.4)	<0.0001
	Tricupsid aortic valve	Bicuspid aortic valve	
Categorical variables	Number (percentage)	Number (percentage)	P value
Number of discharges with TAVR procedure	40,197 (99.00%)	407 (1.00%)	
Men	20,932 (52.07%)	268 (65.85%)	0.01
Elective admission	30,531 (75.95%)	325 (79.81%)	0.48
Congestive heart failure	29,662 (73.79%)	236 (57.86%)	0.0009
Cardiac arrhythmias	19,799 (49.25%)	179 (43.90%)	0.32
Peripheral vascular disorders	11,658 (29.00%)	89 (21.95%)	0.17
Hypertension, combined	32,764 (81.51%)	300 (73.83%)	0.06
Chronic pulmonary disease	13,343 (33.19%)	106 (25.94%)	0.14
Diabetes	13,509 (33.61%)	103 (25.31%)	0.04
Renal failure	14,504 (36.08%)	89 (21.95%)	0.01
Liver disease	954 (2.37%)	25 (6.19%)	0.03
Obesity	5384 (13.39%)	35 (8.58%)	0.20
Myocardial infarction	5226 (13.00%)	25 (6.19%)	0.07
Smoking	1210 (3.01%)	30 (7.28%)	0.03
Prior PCI	7638 (19.00%)	35 (8.58%)	0.02
Prior CABG	9022 (22.45%)	49 (11.97%)	0.02
Transfemoral	32,139 (79.95%)	280 (68.84%)	0.01
Transapical	8060 (20.05%)	130 (31.93%)	
Mechanical support	950 (2.36%)	5 (1.20%)	0.50
Elixhauser comorbidity score			
ECS < 0 (I)	2185 (5.4%)	46 (11.3%)	0.02
ECS = 0 (II)	325 (0.8%)	0 (0.0%)	
ECS = 1 to 5 (III)	4617 (11.5%)	81 (20.0%)	
ECS = 6 to 13 (IV)	16,327 (40.6%)	122 (29.9%)	
ECS ≥ 14 (V)	16,743 (41.7%)	158 (38.9%)	

Table 1b
Patient demographics stratified by aortic valve morphology post matching.

	Tricupsid aortic valve	Bicuspid aortic valve	
Number of discharges with TAVR procedure	359	359	
Continuous variables	Mean (SD)	Mean (SD)	P value
Mean age, years	68.15 (12.71)	68.01 (13.42)	0.95
	Tricupsid aortic valve	Bicuspid aortic valve	
Categorical variables	Number (percentage)	Number (percentage)	P value
Number of discharges with TAVR procedure	359	359	
Men	135 (37.61%)	125 (34.83%)	0.75
Elective admission	265 (73.82%)	293 (81.73%)	0.23
Congestive heart failure	265 (73.82%)	215 (59.88%)	0.09
Cardiac arrhythmias	130 (36.21%)	163 (45.48%)	0.25
Peripheral vascular disorders	65 (18.11%)	70 (19.49%)	0.82
Hypertension, combined	285 (79.39%)	269 (74.93%)	0.57
Chronic pulmonary disease	95 (26.47%)	89 (24.77%)	0.83
Diabetes, uncomplicated	85 (23.67%)	65 (18.11%)	0.43
Diabetes, complicated	25 (6.96%)	25 (6.96%)	0.99
Renal failure	105 (29.25%)	75 (20.77%)	0.25
Liver disease	50 (13.94%)	25 (6.96%)	0.18
Obesity	60 (16.71%)	30 (8.36%)	0.14
Myocardial infarction	25 (6.96%)	15 (4.18%)	0.48
Smoking	40 (11.14%)	25 (6.84%)	0.37
Prior PCI	25 (6.96%)	25 (6.96%)	0.99
Prior CABG	50 (13.94%)	49 (13.64%)	0.97
Transfemoral	285 (79.39%)	244 (67.90%)	0.14
Transapical	75 (20.61%)	114 (32.03%)	
Mechanical support	5 (1.40%)	5 (1.40%)	1.00

outcomes in patients with severe AS and BAV were similar to those with TAV after adjustment for differences in baseline characteristics.

The permanent pacemaker insertion rates post TAVR reported in the literature range from 6.0% to 25% that correspond to Edwards SAPIEN (Edwards Lifesciences; Irvine, CA) balloon-expandable valve (BEV) and the Medtronic CoreValve (Medtronic, Inc.; Minneapolis, MN) self-expanding valve (SEV) [27–32]. The Edwards SAPIEN 3 (Edwards Lifesciences; Irvine, CA) BEV and the Medtronic Evolut R (Medtronic, Inc.; Minneapolis, MN) SEV have reduced this PPM implantation to half [29,31]. SAPIEN XT (Edwards Lifesciences; Irvine, CA) BEV has an implantation rate of 8.5% [33]. Our study reports a PPM rate of around 10% could potentially reflect the adoption of new generation valves (SAPIEN XT), large number of transapical cases, and a greater understanding of procedural factors that may predispose to PPM requirement such as balloon valvuloplasty and depth of implantation [34,35].

The rate of vascular complications of 2.4% that we observe in the bicuspid cohort was low and probably represents a younger cohort with less comorbidities, that is commonly encountered in older patients with TAV that undergo TAVR. Our reported mortality rates were similar to previously reported cohorts of BAV [18–20,22]. Post matching BAV cohort had numerically higher mortality rate compared to the TAV cohort although this was not statistically significant. This study also adds health services resource utilization and health economic information to the literature of TAVR. Our study results show that the average length of stay of around 8 days that was similar in the BAV and TAV cohorts. We observed a reduction in the mean length of stay from 2011 to 2014 for BAV from approximately 12 days to 7 days and for TAV from 10 days to 7 days, which may reflect more optimal case selection, improvements in valve technology and procedural techniques, a move from general anaesthetic to sedation and a move towards a lower risk cohort over time. Similarly, the expenses of the off label TAVR procedure were not statistically higher compared to conventional indications.

Patients with BAV undergoing TAVR are far more challenging when compared to individuals with TAV, with a potential for greater risk of complications including aortic dissection/rupture [36] due to concomitant ascending aortic pathology and a higher risk of severe aortic regurgitation due to fused commissures [12]. BAV patients are commonly younger with larger aortic annulus areas, sinus of Valsalva diameters and ascending aorta diameters as well as eccentric annular calcification [14]. Other procedural challenges include suboptimal positioning of the valve due to a less elliptical annulus and asymmetric that hinders adequate valve expansion and anchoring [12,13]. Hence, BAV were largely excluded from many contemporary TAVR trials due to these morphologic characteristics [37].

Table 2a
In hospital mortality and post procedural complications by aortic valve morphology.

Outcomes	Trileaflet aortic valve (40197)	Bicuspid aortic valve (407)
	Number (percentage)	Number (percentage)
Death	1677 (4.17%)	20 (4.89%)
SAVR	150 (0.37%)	0 (0.00%)
PCI post TAVR	1385 (3.44%)	5 (1.20%)
PPM	4142 (10.30%)	40 (9.88%)
Stroke and TIA	1425 (3.55%)	10 (2.49%)
AMI	1437 (3.58%)	14 (3.49%)
Blood transfusion	9140 (22.74%)	65 (15.96%)
AKI needing dialysis	1807 (4.50%)	4 (1.10%)
AKI	7561 (18.81%)	65 (15.96%)
Vascular complications	2241 (5.58%)	10 (2.39%)
Major bleeding	9445 (23.50%)	69 (16.96%)

Table 2b
In hospital mortality and post procedural complications by aortic valve morphology post propensity score matching.

Outcomes	Trileaflet aortic valve (359)	Bicuspid aortic valve (359)
	Number (percentage)	Number (percentage)
SAVR	0 (0.00%)	0 (0.00%)
PCI post TAVR	5 (1.39%)	0 (0.00%)
PPM	15 (4.18%)	40 (11.14%)
Stroke and TIA	20 (5.57%)	10 (2.79%)
AMI	10 (2.79%)	9 (2.51%)
Blood transfusion	80 (22.28%)	59 (16.43%)
AKI	55 (15.32%)	59 (16.43%)
AKI needing HD	5 (1.39%)	4 (1.11%)
Vascular complication	25 (6.96%)	5 (1.39%)
Major bleeding	85 (23.68%)	64 (17.83%)
Death	5 (1.39%)	20 (5.57%)

A number of meta-analyses and systematic reviews [20,38–40] have been published to assess the outcomes in this group of patients. A meta-analysis of seven studies [40] that included 149 BAV and 2096 non-BAV individuals demonstrated an equipoise in 30-day mortality, moderate or severe paravalvular leak, permanent pacemaker implantations, vascular complications and major bleeding. Another meta-analysis [20] of 13 observational studies (minimum one month follow-up) with 758 patients demonstrated a device success rate of 95%, and an all-cause mortality rate of 3.7%. The one-month incidence of moderate to severe paravalvular leak was 12.2% and pacemaker implantation was 17.9%.

In a large propensity score matching analysis of 546 pairs of patients [16] with bicuspid and tricuspid aortic valve stenosis, similar mortality rates at 24 months (17.2% vs. 19.4%) were noted with a lower device success rate (85.3 vs 91.4%; P = 0.002) BAV vs. TAV patients undergoing TAVR with early-generation devices had a higher risk of aortic root injury, (4.5% vs. 0.0%; P = 0.015) with balloon expandable device and moderate-to-severe paravalvular leak (19.4% vs. 10.5%; P = 0.02) and lower device success (72.1% vs. 86.0%; P = 0.002) when receiving a self-expanding device. With early-generation devices, conversion to surgery was higher in BAV patients (2.5% vs. 0.3%; P = 0.02) and a second valve implantation was more likely (7.2% vs. 2.2%; P = 0.003). In contrast, new generation devices, both balloon expandable and self-expanding, such as Sapien 3 and Lotus have demonstrated similar outcomes in BAV cohort when compared with the TAV patients. Data regarding longer-term outcomes are limited in this arena. A caveat to the earliest registry studies is that first generation TAVR devices were restricted to prohibitive and high-risk patients, and not approved for intermediate-risk patients. The Bicuspid TAVR registry [18] assessed the outcomes of TAVR in 301 patients with BAV with early and new-generation devices. The new-generation devices had a higher success rate, with a far lower incidence of moderate-to-severe paravalvular leak compared to early generation valves. Post-procedural outcomes including major vascular complications, life-threatening bleeding, stroke, acute kidney injury, and 30-day all-cause mortality were similar with early and new-generation devices in the BAV patients. Notably, the experience of TAVR operators along with improved devices have played a major role in improving outcomes.

Table 3
Odds ratio and confidence intervals for in hospital mortality and post procedural complications by aortic valve morphology.

Outcomes	Logistic regression		Propensity matching analysis	
	Odd ratio (95%CI)	P value	Odd ratio (95%CI)	P value
SAVR	NA	NA	NA	NA
PPM	1.19 (0.57–2.51)	0.64	2.90 (0.72–11.58)	0.13
Stroke and TIA	0.75 (0.18–3.16)	0.70	0.49 (0.08–2.82)	0.42
AMI	1.12 (0.36–3.54)	0.85	0.94 (0.13–7.05)	0.95
AKI	0.75 (0.40–1.39)	0.36	1.10 (0.45–2.72)	0.83
Vascular complication	0.47 (0.11–1.93)	0.29	0.17 (0.02–1.56)	0.12
Major bleeding	0.63 (0.34–1.17)	0.15	0.70 (0.31–1.60)	0.40
Death	1.71 (0.57–5.12)	0.33	4.20 (0.45–39.62)	0.21

Cardiac computed tomography has optimised the approach to aortic valve disease in contemporary practice [41]. A multicentre study of 130 patients with BAV undergoing TAVR demonstrated that the independent predictors of paravalvular aortic regurgitation were intercommissural dimensions for bicommissural bicuspids (OR: 1.37, 95%CI: 1.02–1.84) and absence of a reference computed tomography for annular dimension (OR: 3.03, 95% CI: 1.20 to 7.69).

Despite the fact that up to half of all SAVR procedures are undertaken in patients with BAV [7], in our current analysis BAV contributed to only 1% of TAVR activity in the United States. Patients with BAV generally present with severe AS a decade earlier than TAV and might be considered an acceptable risk for SAVR. It is therefore possible that only a small minority of BAV patients would be considered high risk and therefore eligible for TAVR. None-the-less, in one of the largest analysis to date to assess the clinical characteristics and outcomes of patients with BAV undergoing TAVR compared to those patients with TAV, our analysis demonstrates that in-hospital clinical outcomes are similar to those with TAV.

4.1. Limitations

As inherent to all observational studies, our study is subject to several limitations that include coding errors or suboptimal coding that could be a potential source of bias. An important limitation is that it is likely that the patients were likely referred for TAVR as they were deemed to be high risk for surgery, particularly in the time point studied. Whilst the NIS captures a broad range of comorbid conditions, it does not capture severity of comorbidity or other factors such as frailty that we cannot adjust for. Therefore our findings may not be applicable to lower risk patients that are surgical candidates. A major limitation of this study is the lack of imaging information regarding the diagnosis of BAV based on either transoesophageal echocardiography or cardiac CT. More specifically to TAVR, the NIS dataset does not capture important information like the Sievers classification [42], valve calcification and distribution, type of TAVR device (balloon-expandable or self-expanding), sedation technique (local or general anaesthesia), the presence and quantification of post procedural paravalvular leak, operator or centre volume and lacks longer-term follow-up data. However, it would be reasonable to assume that the valves used in this time period were mostly likely to be SAPIEN 3 and EVOLUT-R valves after FDA approval [43,44]. In addition, the study reflects practice till 2014 and current therapy in 2018 is fairly robust with balloon expandable SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) [45]. The valvular academic research consortium 2 (VARC) endpoints [46] could not be utilized for the purpose of this study and hence the vascular complication rate even though quite low cannot be directly compared with the outcomes described in TAVR literature so far. It was interesting to see higher utilization transapical access for the BAV group indicating complex vascular anatomy unsuitable for transfemoral TAVR suggesting that it is difficult to correct for every subgroup (peripheral vascular disease) in a registry analysis.

Whilst this analysis is subject to selection biases, our findings provide one of the largest analysis, to date, assessing the clinical characteristics and peri-procedural outcomes of patients with BAV undergoing TAVR compared to those patients with TAV. Hence, we provide real-world data that may significantly contribute to the current practice of TAVR operators as well as influence future perspectives. Further randomized-controlled trials might be needed to ascertain the peri-procedural and long-term impact of TAVR in patients with BAV.

Table 4
Length of stay and total charge by aortic valve morphology.

	Continuous variables	Tricuspid aortic valve (40197)		Bicupsid aortic valve (407)		Coefficient (95%CI)	Standard error	Odd ratio (95%CI)	P value
		Mean	SD	Mean	SD				
Multiple regression	Length of stay, days	8.1	0.1	8.7	1.0	−0.17	0.48	0.31 (0.02–6.3)	0.45
	Total charge, USD	235,803.6	19,207.39	226,640	1684.7	0.01	0.18	1.01 (0.70–1.45)	0.97
Propensity matching	Length of stay, days	8.2	7.6	8.9	9.49	0.67 (−2.15 to 3.50)	1.43	1.96 (0.12–33.08)	0.64
	Total charge, USD	214,635.4	136,950.9	239,254.8	181,538.5	0.25 (−0.28 to 0.77)	0.27	1.28 (0.75–2.17)	0.36

5. Conclusion

Not infrequently, clinicians encounter patients with BAV who are deemed high risk for conventional open-heart surgery, resulting in a management dilemma. Despite the concerns regarding the morphological characteristics of the BAV, our study demonstrates off-label TAVR should not be considered prohibitive in BAV and has a similar safety profile compared to those with TAV. Meanwhile, in the absence of definitive randomized evidence, careful evaluation of patients on an individual basis by a dedicated heart team is of paramount importance to identify patients, for whom, the benefits of elective TAVR as well as the type of device, versus surgical replacement, are balanced against the potential risks.

Funding statement

None.

Conflict of interest

None.

Impact on daily practice

Despite the concerns regarding the morphological characteristics of the BAV, our study demonstrates off-label TAVR should not be considered prohibitive and can be successfully preformed for BAV with similar peri-procedural outcomes compared to those with TAV. Meanwhile, in the absence of definitive randomized evidence, careful evaluation of patients on an individual basis by a dedicated heart team is of paramount importance to identify patients, for whom, the benefits of elective TAVR as well as the type of device, versus surgical replacement, are balanced against the potential risks.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2018.09.013.

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