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CLINICAL INVESTIGATIONS

Comparing outcomes after transcatheter aortic valve replacement in patients with stenotic bicuspid and tricuspid aortic valve: A systematic review and meta-analysis

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Background: Transcatheter aortic valve replacement (TAVR) has become an alternative treatment to surgery in patients with severe aortic stenosis. However, patients with bicuspid aortic stenosis (BAV) are usually excluded from major TAVR studies. The aim of this study is to reexamine current evidence of TAVR in patients with severe aortic stenosis and BAV compared with tricuspid aortic valve (TAV).

Hypothesis: There might be differences in outcomes post TAVR between patients with BAV comparing to TAV.

Method: Databases were systematically searched for relevant articles featuring cohort studies that included patients with BAV and TAV who underwent TAVR studies, of which reported outcomes of interest included mortality and complications in both groups. Pooled effect size was calculated with a random-effect model and weighted for the inverse of variance, to compare outcomes post-TAVR between BAV and TAV.

Results: Nine studies were included in the meta-analysis. There was no difference in 30-day mortality rate in patients with BAV compared with TAV (OR: 1.27, 95% CI: 0.84–1.93, I^2 = 0). Patients with BAV were more likely to have a moderate to severe paravalvular leak (9 studies; OR: 1.42, 95% CI: 1.08–1.87, I^2 = 0) and conversion to surgery (5 studies; OR: 5.48, 95% CI: 1.74–17.27, I^2 = 0), and less likely to have device success compared with patients with TAV (5 studies; OR: 0.57, 95% CI: 0.40–0.81, I^2 = 0%).

Conclusions: There was no difference in mortality post-TAVR in patients with BAV compared with TAV. Further randomized studies should be done in newer-generation prostheses to assess this association.

KEYWORDS

Bicuspid Aortic Valve, Transcatheter Aortic Valve Replacement

1 | INTRODUCTION

Bicuspid aortic valve (BAV) is one of the most common valvular abnormalities in adults, with an estimated prevalence of 0.5% to 2%.[1,2] Individuals with BAV are at risk for rapidly progressing to aortic stenosis (AS) and ultimately requiring aortic valve surgery.[3] Transcatheter aortic valve replacement (TAVR) has become an alternative treatment to surgery in patients with severe AS who are at intermediate to high risk for surgical intervention.[4] However, BAV is a relative contraindication to TAVR, and patients with BAV are usually excluded from major TAVR studies. Patients with BAV undergoing TAVR are at risk of developing valve malposition, causing severe paravalvular leak, due to the asymmetrical structures of this valve.[5,6] Although studies[7,8] have shown that using newer-generation devices in TAVR[9] may be safe and feasible in some patients with BAV, there is a lack of strong evidence to suggest routine use in clinical practice.

A recent meta-analysis of 7 observational studies[10] has shown that there was no difference in midterm mortality in patients with tricuspid aortic valve (TAV) and BAV undergoing TAVR. However, more

studies[11–14] have emerged since this previous meta-analysis, which now suggest that these patients might have lower success rate and increased paravalvular leak after TAVR. The aim of this study is to reexamine the current evidence of TAVR in patients with severe AS and BAV compared with TAV.

2 | METHODS

Studies were systematically acquired from the MEDLINE and Embase electronic databases. The search terms were "Transcatheter aortic valve implantation" or "transcatheter aortic valve replacement" or "TAVR" or "TAVI" and "Bicuspid" or "Bicuspid aortic valve." The search was performed from the day of inception through December 20, 2017. The search was limited to studies that were in English. References sections of published studies were also manually scanned for potential relevant articles. Full-text articles of all relevant studies were reviewed. Any discrepancies were resolved through consensus. Studies that met these eligibility criteria were included in the meta-analysis: (1) cohort studies that included patients with BAV who underwent TAVR; (2) studies that reported outcomes of interest including mortality, paravalvular leak, pacemaker implantation, or other TAVR complications; and (3) studies in which outcomes were compared in patients with TAV.

Two independent investigators performed data extraction using a standardized data-collection form. Primary author's last name, year of publication, demographics, and crude outcome data were extracted from all studies.

Quality of the studies was evaluated by the Newcastle-Ottawa scale (NOS). The criteria are sample selection (S), comparability (C), and outcome assessment (O). Each domain could be scored from 0 to 9; higher scores represent higher study quality. A total score of ≥7 was considered good quality.

BAV was defined according to the classification by Sievers and Schmidtke[15] by the number of cusps, presence of raphe, and spatial position and symmetry of raphe and cusps. Outcomes including mortality, device success, complications including paravalvular leak (PVL), and major bleeding were defined according to the Valve Academic Research Consortium (VARC 2) or as defined in each study.[16] Due to differences in follow-up time among the studies, we defined mid-term mortality as mortality at 1 to 3 years postprocedure.

Random-effect meta-analyses were performed for each outcome of interest from all studies using the generic inverse variance method of DerSimonian and Laird.[17–19] Crude outcome events were used to estimate odds ratio (OR) and 95% confidence interval (CI) for each outcome. The heterogeneity of effect estimates across the studies was assessed using I^2. I^2 values were defined as I^2 < 25%, low heterogeneity; I^2 = 25% to 50%, moderate heterogeneity; and I^2 > 50%, substantial heterogeneity.[20] Publication bias was assessed with funnel plots.[21] Funnel-plot asymmetry was further confirmed with the Egger test if there were > 10 available studies.[22] Statistical analyses were

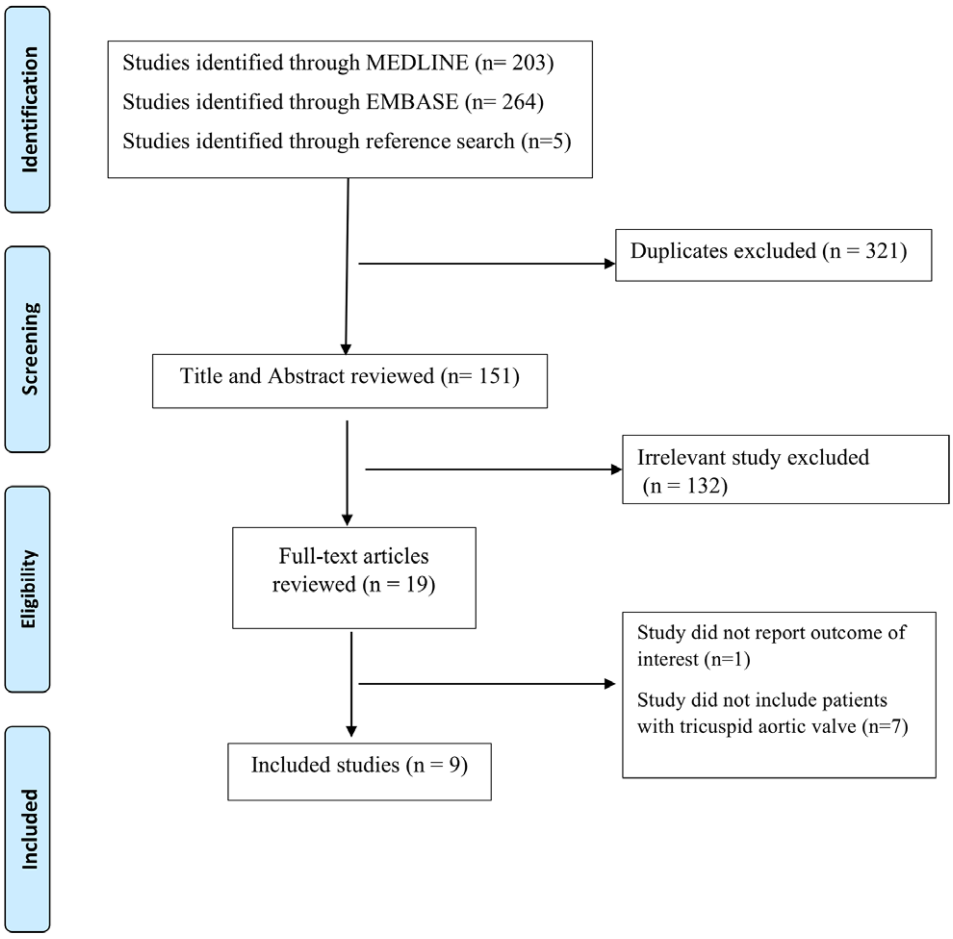

FIGURE 1 Outline of the search strategy

TABLE 1 Baseline characteristics of the included studies

	Yoon 2017		Sannino 2017		Liao 2017		Arai 2017		Liu 2015		Kochman 2014		Costopoulos 2014		Bauer 2014		Hayashida 2013	
	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
N	546	546	88	735	87	70	10	143	15	25	28	84	21	447	38	1357	21	208
Baseline characteristics																		
Male sex	63	61	60	53	58	64	43	7	60	68	46	48	57	47	45	42	57	53
Mean age, y	77 ± 8	77 ± 9	80 ± 8	82 ± 8	73 ± 6	74 ± 7	81 ± 5	83 ± 6	75 ± 6	76 ± 6	78 ± 6	79 ± 7	77 ± 7	80 ± 7	81 ± 7	82 ± 6	82 ± 7	83 ± 7
Logistic euroSCORE, %	16 ± 12	17 ± 14	N/A	N/A	N/A	N/A	N/A	N/A	16 ± 11	22 ± 15	19 ± 9	19 ± 9	24 ± 12	24 ± 17	18 ± 10	20 ± 13	20 ± 12	20 ± 11
STS score, %	4.6 ± 4.6	4.3 ± 3	7.4 ± 4	7.6 ± 4	8 ± 4	9 ± 4	N/A	N/A	6 ± 4	8 ± 6	N/A	N/A	8 ± 4	8 ± 7	N/A	N/A	N/A	N/A
DM	23	23	38	40	16	19	20	26	0	12	39	35	29	30	37	34	5	24
PAD	15	16	43	32	48	41	N/A	N/A	13	16	21	35	33	30	11	22	24	33
Prior CVA	14	13	22	20	15	11	10	1	0	8	29	17	19	16	13	8	5	6
AF	N/A	N/A	18	20	22	17	N/A	N/A	7	8	N/A	N/A	19	16	N/A	N/A	N/A	N/A
CKD	N/A	N/A	52	46	16	19	N/A	N/A	27	48	N/A	N/A	52	58	58	61	24	24
COPD	18	15	20	22	58	64	0	3	27	16	21	20	33	31	21	24	57	60
CAD	N/A	N/A	71	67	N/A	N/A	N/A	N/A	20	36	50	64	19	20	N/A	N/A	48	58
Prior PCI	22	23	49	46	8	11	10	15	20	12	N/A	N/A	29	22	34	35	19	23
Prior CABG	11	12	N/A	N/A	N/A	N/A	10	6	0	0	N/A	N/A	N/A	N/A	13	18	10	14
Echocardiographic findings																		
Mean gradient, mm Hg	47.7 ± 17.7	48.5 ± 17.1	47 ± 17	44 ± 14	65 ± 20	60 ± 17	46 ± 20	48 ± 14	64 ± 20	54 ± 14	56 ± 18	53 ± 19	54 ± 18	53 ± 16	N/A	N/A	48 ± 19	54 ± 14
Aortic valve area, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	N/A	N/A	0.67 ± 0.16	0.65 ± 0.14	0.47 ± 0.13	0.59 ± 0.14	0.6 ± 0.1	0.6 ± 0.2	0.7 ± 0.2	0.8 ± 0.5	0.7 ± 0.2	0.7 ± 0.4	0.67 ± 0.1	0.65 ± 0.1
LVEF, %	51.6 ± 15	51.6 ± 15.2	32% has EF<50%	27% has EF<50%	55 (42–68)	62 (47–68)	53 ± 19	56 ± 13	N/A	N/A	48 ± 13	50 ± 14	N/A	N/A	50 ± 16	53 ± 15	48 ± 15	54 ± 14
Bicuspid morphology, %	Type 0, 13; type 1, 86; type 2, 2.0		Type 0, 14; type 1, 85; type 2, 1.0		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Device types																		
Early generation (%)	Sapien XT, 28.4; CoreValve, 30	Sapien XT, 27.5; CoreValve, 31.3	75	75	100	100	0	0	CoreValve, 67; Venus A, 33	CoreValve, 68; Venus A, 32	Edwards, 18; CoreValve, 82	Edwards, 18; CoreValve, 82	Edwards, 38; CoreValve, 62	Edwards, 59; CoreValve, 41	Edwards, 32; Core Valve, 68	Edwards, 82; Core Valve, 18	Edwards, 52; Core Valve, 48	Edwards, 84; Core Valve, 16
New generation (%)	Sapien 3, 29.3; Lotus, 7.9; Evolut R, 4.2	Sapien 3 29.7; Lotus 8.6; Evolut R, 2.9	25	25	0	0	Edwards Sapien 3, 100	Edward Sapien 3, 100	0	0	0	0	0	0	0	0	0	0
NOS quality assessment	7 (S-3, C-1, O-3)		7 (S-4, C-0, O-3)		7 (S-4, C-0, O-3)		6 (S-4, C-0, O-2)		6 (S-4, C-0, O-2)		7 (S-4, C-0, O-3)		6 (S-3, C-0, O-3)		7 (S-4, C-0, O-3)		7 (S-4, C-0, O-3)	

Abbreviations: AF, atrial fibrillation; BAV, bicuspid aortic valve; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DM, diabetes mellitus; euroSCORE, Logistic European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; LVEF, left ventricular ejection fraction; N/A, not available/applicable; NOS, Newcastle-Ottawa Scale; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation; STS, Society of Thoracic Surgeons; TAV, tricuspid aortic valve. Data are presented as %, mean ± SD, or median (IQR).

performed using Review Manager, version 5.3 (Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark) and Stata software, version 13 (StataCorp LP, College Station, TX).

3 | RESULTS

Our search strategy yielded 472 potentially relevant studies (203 from MEDLINE, 264 from Embase, and 5 from reference search). Duplicates and irrelevant studies were excluded by abstract review. Nineteen studies underwent full-text review. Finally, a total of 9 studies with 854 BAV and 3615 TAV patients were included in this meta-analysis.[11–14,23–27] An outline of our search strategy is shown in Figure 1.

The NOS was used to evaluate the quality of the 9 included studies in selection (S), comparability (C), and outcomes (O). Six out of the 9 studies received a score of 7 to 9, which reflected high quality. Three studies received a score of 6, which indicated moderate quality.

Nine studies were included in the final analysis. Baseline characteristics of patients in each study are reported in the Table 1. All 9 studies reported 30-day mortality. There was no difference in 30-day mortality rate in patients with BAV compared with patients with TAV (OR: 1.27, 95% CI: 0.84–1.93). The analysis showed minimal heterogeneity (I^2 = 0%). Only 5 studies reported mid-term mortality. Four studies[13,24–26] reported a 1-year follow-up time, and 1 study[14] had a 3-year follow-up time. There was no difference in mid-term mortality between patients with BAV compared with patients with TAV (OR: 1.12, 95% CI: 0.76–1.64). There was moderate heterogeneity in this analysis (I^2 = 27%). Forest plots are shown in Figure 2. Funnel plots (Figure 3) and the Egger test did not suggest publication bias for 30 days (P = 0.84) and mid-term mortality (P = 0.97). Funnel plots are shown in the Supporting Information, Figures A and B, in the online version of this article.

Eight studies reported PVL; 6 of the studies[11,12,23–27] defined PVL as postoperative aortic regurgitation grade ≥ 2, and 2 studies[13,14] reported at least moderate PVL using the VARC 2 definition. PVL was more common in BAV than in TAV (OR: 1.42, 95% CI: 1.08–1.87, I^2 = 0). Subgroup analysis of 5 studies defining PVL using postoperative aortic regurgitation showed that there was no difference in PVL (OR: 1.44, 95% CI: 0.98–2.1, I^2 = 0%). Further subgroup analyses showed that the difference is mainly driven by a single large study by Yoon et al.[14]

Patients with BAV were more likely to have conversion to open aortic valve replacement (5 studies; OR: 5.48, 95% CI: 1.74–17.27, I^2 = 0) and less likely to have device success compared with patients with TAV (5 studies; OR: 0.57, 95% CI: 0.40–0.81, I^2 = 0%). There was a similar incidence of pacemaker placement, major bleeding, and major vascular complications in BAV and TAV. Forest plots are shown in Figure 3.

4 | DISCUSSION

This study reported no significant difference in 30-day mortality and mid-term mortality in patients with BAV who underwent TAVR, compared with patients with TAV. Our study found that there was no

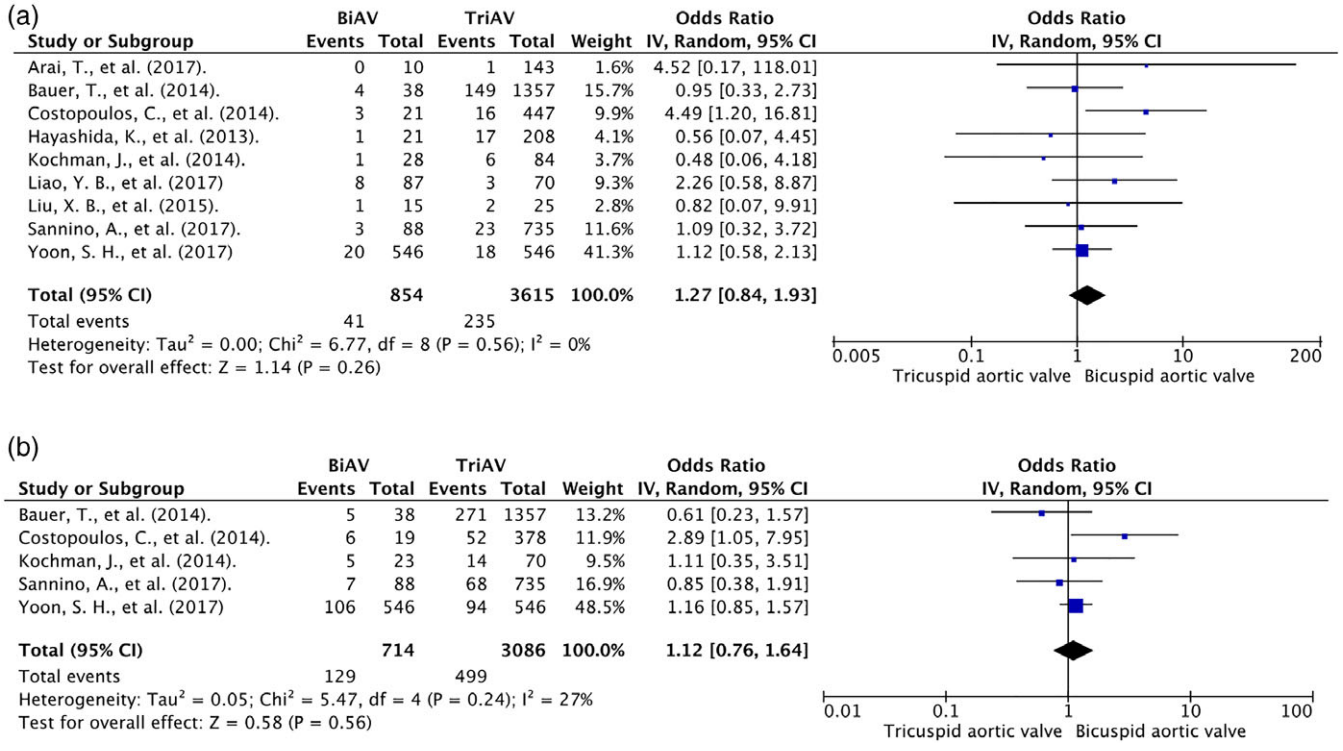

FIGURE 2 Forest plot of included studies comparing (a) 30-day mortality and (b) mid-term mortality in patients with BAV and TAV. Horizontal lines represent the 95% CIs, with marker size reflecting the statistical weight of the study using random-effects model. A diamond data marker represents the overall OR and 95% CI for the outcome of interest. Abbreviations: BiAV/BAV, bicuspid aortic valve; CI, confidence interval; df, degrees of freedom; OR, odds ratio; TriAV/TAV, tricuspid aortic valve

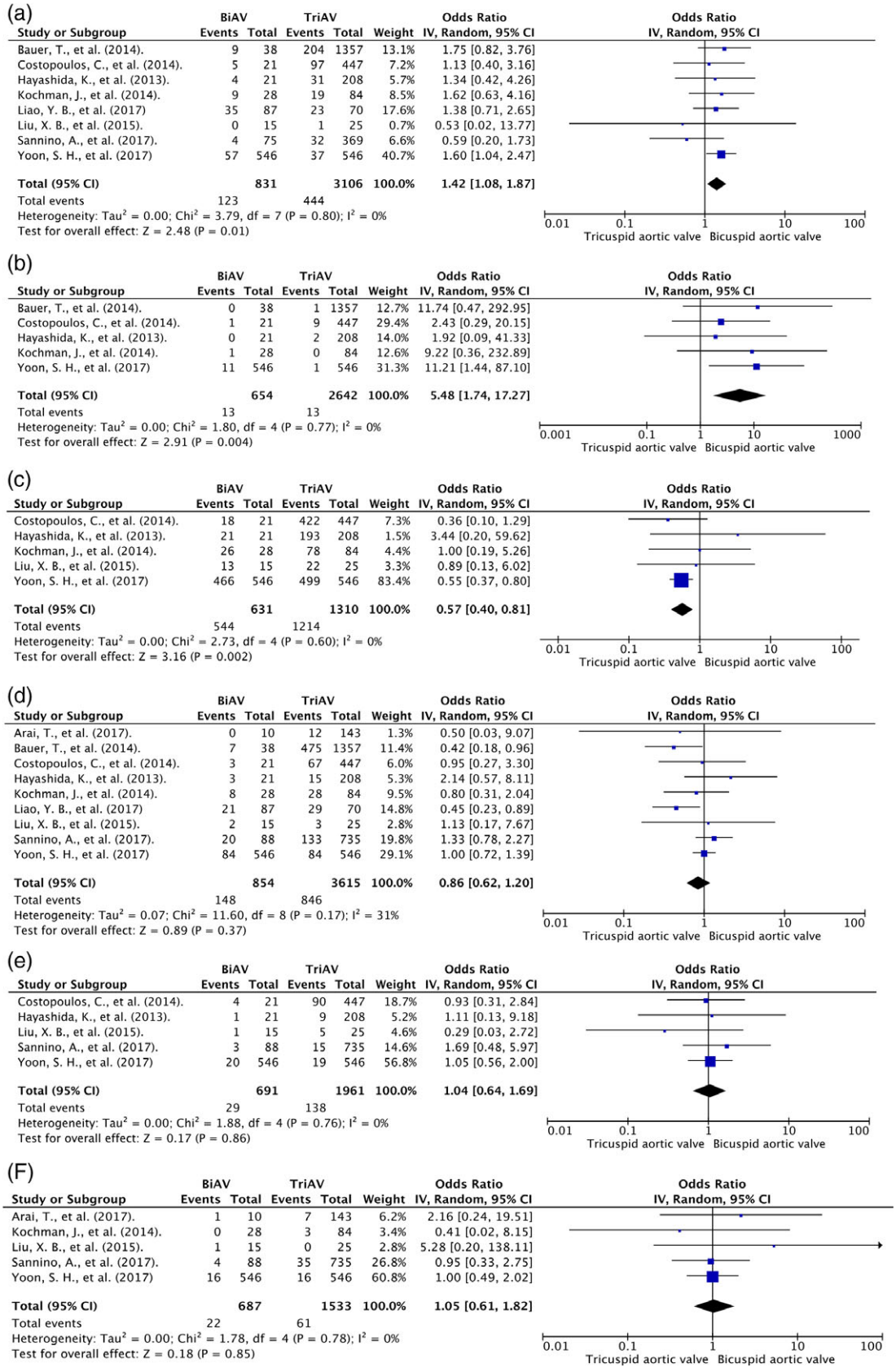

FIGURE 3 Forest plot of included studies comparing post-TAVR complications including (a) PVL, (b) conversion to surgery, (c) device success, (d) pacemaker implantation, (e) major bleeding, and (f) major vascular complication in patients with BAV and TAV. Horizontal lines represent the 95% CIs, with marker size reflecting the statistical weight of the study using random-effects model. A diamond data marker represents the overall OR and 95% CI for the outcome of interest. Abbreviations: BiAV/BAV, bicuspid aortic valve; CI, confidence interval; df, degrees of freedom; OR, odds ratio; PVL, paravalvular leak; TAVR, transcatheter aortic valve replacement; TriAV/TAV, tricuspid aortic valve

difference in pacemaker implantation, major bleeding, and major vascular complication. However, we did find that patients with BAV had lower success rates, more PVL, and conversion to open aortic valve replacement post-TAVR. To the best of our knowledge, this systematic review and meta-analysis incorporated the largest and most updated data on patients with BAV and TAV who underwent TAVR.

After the previous meta-analysis by Phan et al[10] was published, more recent studies have also shown no difference in mortality between BAV and TAV undergoing TAVR. Thus, our findings on 30-day mortality and mid-term mortality are similar to this prior study. We reported lower success rates, higher rates of PVL, and higher rates of conversion to open aortic valve replacement. This finding is mainly driven by a large observational study by Yoon et al[14] reporting higher incidence of these complications in BAV patients. The mechanism of PVL post-TAVR in BAV patients is unclear. BAV was believed to be more elliptical and would not fit well with prostheses, but a recent study has found that BAV is actually not more elliptical than TAV and should be able to fit commercially available prostheses.[7,28] Other possible hypotheses include asymmetrical leaflet calcification and resistance to valve expansion.[7,28,29] BAV is known to be associated with higher rates of pacemaker implantation in BAV cohorts compared with TAV cohorts.[7] However, we found no difference in pacemaker implantation in the BAV group when directly compared with the TAV group from the same cohort.

Newer-generation prostheses are associated with fewer postprocedural complications. Yoon et al[14] reported subgroup analyses of newer-generation devices (SAPIEN 3, Edwards Lifesciences, Irvine, CA; Lotus, Boston Scientific, Marlborough, MA; and CoreValve Evolut R, Medtronic, Minneapolis, MN) showing a similar rate of paravalvular leaks, device success rate, and conversion to open surgery between BAV and TAV patients. Higher rates of PVL and conversion to open heart surgery in our study could be driven by the fact that the majority of studies included in our meta-analysis were done using older-generation rather than newer-generation devices. Further studies are needed to assess the effect of prosthesis types on outcome post-TAVR in patients with BAV.

Currently, several randomized studies are being done to evaluate TAVR in patients with BAV. A randomized controlled trial (http://www.ClinicalTrials.gov NCT03163329) is taking place to compare TAVR and surgical aortic valve replacement in patients with BAV. Another randomized controlled trial is also being done to evaluate the appropriate valve sizing for BAV patients undergoing TAVR (http://www.ClinicalTrials.gov NCT02541877). Results from these trials will be important in the future management of patients with BAV.

4.1 | Study limitations

There are several limitations to our study. Baseline characteristics of patients with BAV and TAV are different within each of the cohorts included. Multivariate analyses adjusting for potential confounders were not reported. We could not perform a pool analysis of adjusted OR; thus, we could not conclude that the associations we found are independent of potential confounders. The studies included did not report specific outcomes in newer-generation devices; therefore, subgroup analysis comparing outcomes and complications between BAV and TAV patients undergoing TAVR with newer-generation prostheses could not be done. Studies also did not report outcomes within subtypes of BAV. As a result, pooled analysis could not be performed to compare outcomes within each subtype of BAV.

Although studies defined outcomes based on the VARC 2 definition, there are still differences in outcome definition. PVL was defined according to VARC 2 (mild, moderate, and severe) in only 2 studies, whereas other studies still used postoperative aortic regurgitation (trace, mild, moderate, and severe). This difference resulted in increased heterogeneity among the studies.

There is a lack of studies with a longer follow-up time to further evaluate the difference in long-term mortality between BAV and TAV patients undergoing TAVR. Quality of life is also an important outcome post-TAVR; however, the studies included in this meta-analysis did not include quality of life as one of the outcomes.

5 | CONCLUSION

Current evidence has shown that there was no difference in mortality post-TAVR in patients with BAV compared with TAV. However, there might be higher rate of PVL, lower success rate, and higher conversion to surgery in patients with BAV. Further randomized studies should be done in newer-generation prostheses to assess this association.

Conflicts of interest

The authors declare no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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