Efficacy and safety of Transcatheter Aortic Valve Replacement in patients with stenotic bicuspid aortic valve: a meta-analysis

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Abstract

Objective: To assess clinical outcomes of Transcatheter Aortic Valve Replacement in stenotic bicuspid aortic valve patients. **Methods:** The search of clinical articles was conducted by using Pubmed, Embase, The Cochrane Library databases. We compared clinical outcomes of efficacy and safety endpoints between stenotic bicuspid aortic valve(BAV) and tricuspid aortic valve(TAV) patients according to Valve Academic Research Consortium-2 criteria. **Results:** 20 studies were included in the current meta analysis. BAV groups showed higher post-procedural paravalvular leakage and stroke rate compared with TAV groups. No discrepancy were detected in the mean aortic gradient and aortic valve area between two groups. The 30-day and 1-year mortality were similar in both groups. BAV group was more likely to be associated with lower device success and higher incidence of conversion to surgical aortic valve replacement, second valve implantation and annular rupture. No difference was found in the incidence of permanent pacemaker implantation, acute kidney disease, life-threatening bleeding and myocardial infarction between bicuspid and tricuspid patients. **Conclusion:** The efficacy and safety of TAVR in BAV patients were not as ideal as those in TAV patients. Cautious and adequate discussion must be made before we decide to perform TAVR procedure for BAV patients.

1 INTRODUCTION

Since transcatheter aortic valve replacement(TAVR) was initially performed in 2002, several clinical trials conducted by worldwide cardiovascular centers have confirmed its obvious efficacy and safety. The indication for TAVR was symptomatic severe Aortic Stenosis(AS) patients with high risks for surgical aortic valve replacement. However, bicuspid aortic valve stenosis, the most common congenital anomaly of heart valve[1], has been deemed as a relative contraindication for TAVR and excluded from many randomized clinical trials[2,3]. Perhaps due to the special anatomy such as asymmetrical calcification, oval annulus, and concomitant aortopathy[4], the BAV group represented higher incidences of annular rupture, paravalvular leakage and permanent pacemaker implantation[5]. Moreover, BAV patients were always younger and at lower risk compared with TAV patients, which made it difficult to perform a comparison. With the expanding indication of TAVR into low risk patients[6], large scale of clinical trials comparing TAVR in BAV versus TAV AS patients were feasible. Therefore, we conducted the current meta-analysis to evaluate the efficacy and safety of TAVR in BAV AS patients.

2 MATERIAL AND METHODS

The current meta-analysis was performed following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA)[7](see **Supplementary PRISMA 2009 Checklist**). All the studies included were approved by each single-center Ethical Committees, in retrospective studies the informed consent was waived and in prospective studies patients were excluded if they did not provide their informed consent.

2.1 Literature Search strategy

Literature search was performed systematically by using Pubmed, Embase, The Cochrane Library databases up to May 12, 2021. The key words were "Transcatheter aortic valve replacement" or "Transcatheter aortic valve implantation" and "bicuspid". The language of studies was limited to English. Conference abstracts and case reports were excluded. The detailed search strategy and results were shown in **Figure 1** .

2.2 Data selection criteria and Quality assessment

Literatures should fullfil the following inclusion criteria: 1) enrollment of consecutive patients; 2) comparison of clinical outcomes of TAVR between BAV and TAV patients; 3)reported at least 30 days clinical outcomes. The exclusion criteria: 1) duplicate studies; 2) the full text cannot be retrieved; 3) the outcomes we focused on were not mentioned; 4) baseline characteristics of patients in each group showed significant difference(P $<$0.05) and propensity score match was not performed. Two authors(HX and QS) evaluated the eligibility of literatures independently. Any discrepancies were settled by consensus. Clinical outcomes of each literature we focused on were extracted for the current meta-analysis. The quality of each study selected was assessed by Newcastle-Ottawa Scale(NOS). Case selection, comparability and outcome were criterion of assessment, and a score of [?] 7 was considered to be high quality.

2.3 Outcomes for comparison

According to Valve Academic Research Consortium 2 (VARC-2)[8], we selected the adverse events which might impact patients' prognosis. Efficacy was evaluated by post-procedural mean aortic valve gradient(MAG), aortic valve area(AVA) and paravalvular leakage(PVL). Safety endpoints included device success, all cause mortality, peri- and post-procedural complications such as conversion to surgical aortic valve replacement(SAVR), permanent pacemaker implantation(PPM), life-threatening bleeding, stroke, annular rupture, second valve implantation, acute kidney disease(AKD) and myocardial infarction(MI). Due to the different follow-up time of studies, 30-day and 1-year mortality were chosen for comparison.

2.4 Statistical analysis strategy

The continuous data of each group were studied by mean difference(MD) with 95% confidence interval(CI). For dichotomous variables, odds ratio(OR) with 95% confidence interval(CI) were used. Heterogeneity across studies were assessed by Cochran's Q-test and I^2 statistics. When heterogeneity was less than moderate degree(I^2 0-50% or P$>$ 0.10), fixed effects models combined with inverse variance method were chosen for data analysis firstly. In case of significant heterogeneity($I^2 > 50\%$ or P $<$0.10), we selected DerSimonian and Laird random effects models[9] combined with inverse variance method for data analysis. In order to confirm the stability of studies in the second situation, a sensitivity analysis was performed by removing one of all the studies at a time. Publication bias was checked by funnel plot and egger's test[10]. Data analyses were conducted by using Review Manager (Version 5.4) and STATA (Version 13). A p-value of $<$0.05 was considered to be significant discrepancy.

3 RESULTS

A total of 14924 patients(BAV: 4986 patients; TAV: 9938 patients) in 20 studies[11-30] were eligibility for the current meta analysis. According to the Newcastle-Ottawa Scale(0-9), 18 studies represented high quality(a score of[?] 7), and the other 2 studies represented moderate quality(a score of 6). All the 20 articles were retrospective cohort studies. Patient's baseline characteristics were listed in **Table 1a-b** and**SupplementaryMaterial Table S1a-d** . The detailed clinical outcomes of efficacy and safety endpoints extracted from each study were listed in **Supplementary Material Table S2a-d** . The forest plots were performed for comparison of efficacy(**Figure 2**) and safety(**Figure 3, Supplementary Material Figure S1**) endpoints.

3.1 Comparison of efficacy endpoints

19 studies[11-25,27-30] reported post-procedural MAG, and 7 studies[11,14-17,25,27] reported post-procedural AVA. The data of MAG in the 15 studies[11,13-17,20,22-25,27-30] and AVA in all the 7 studies were expressed as the mean±SD(n), and were taken into comparison independently. 4 studies[12,18,19,21] were excluded because the data were expressed as median and interquatile range. Post-procedural MAG tended to be similar between BAV and TAV group(MD 0.15, 95%CI -0.06-0.36, I^2=46%). Moreover, post-procedural AVA of BAV patients was also the same as that of TAV patients(MD -0.03, 95%CI -0.11-0.05, I^2=77%). Due to the significant heterogeneity in the comparison of AVA, DerSimonian and Laird random effects models were used, and we also performed a sensitivity analysis to check the stability of the result. After 1 of the 7 studies in AVA subgroup was removed at a time, we investigated a range of MD from -0.06(95%CI -0.13-0.01) to 0.00(95%CI -0.08-0.07), and no difference was found.

Paravalvular leakage(PVL) was defined as a post-procedure aortic regurgitation more than moderate. 13 studies[11-14,16,17,19-25] were selected for comparison of PVL. The other 7 studies were excluded of which 1 study[15] stratified PVL into mild-moderate and severe group, 3 studies[18,26,27] defined PVL as more than mild aortic regurgitation and 3 studies[28-30] evaluated PVL as [?] 2 grade. BAV group was associated with higher PVL than TAV group(OR 1.89, 95%CI 1.47-2.42, I^2=0%). No publication bias was detected by using funnel plot and egger's test(P=0.838) (**SupplementaryMaterial Table S3 and Figure S2**).

3.2 Comparison of safety endpoints

Among the safety endpoints, all cause mortality was considered to be the most important one. All the 20 studies[11-30] showed 30-day mortality. It had no difference in 30-day mortality between BAV and TAV group(OR 1.20, 95%CI 0.96-1.50, I^2=0%). Only Pineda's[12] and Costopoulos's[28] study reported higher 30-day mortality in BAV group compared with TAV group. 14 studies[11-14,16-19,23-25,27-29] reported 1-year mortality, and the result of BAV group was almost the same as that of TAV group(OR 0.91, 95%CI 0.78-1.05, I^2=0%). Funnel plots(**Figure 4**) and egger's test of 30-day(P=0.565) and 1-year mortality(P=0.063) group showed no significant publication bias(**Supplementary Material Table S3**).

When we compared device success that reported in 15studies[11-14,16,19,20,22-30], the result of BAV group was lower than that of TAV group(OR 0.77, 95%CI 0.65-0.92, I^2=49%). Finally, the comparison of post-procedural complications between the two groups was performed. BAV group was more likely to be associated with an increasing incidence of stroke(20 studies[11-30], OR 1.51, 95%CI 1.15-1.99, I^2=0%), conversion to SAVR(12 studies[12-14,16,21-24,27-30], OR 2.50, 95%CI 1.52-4.11, I^2=0%), second valve implantation(13 studies[11,13,15,16,18-22,24-26,28], OR 2.37, 95%CI 1.68-3.33, I^2=0%) and annular rupture(11 studies[11,12,16,19,21-24,26,27,30], OR 7.11, 95%CI 2.58-19.60, I^2=0%). There was no discrepancy in PPM(20 studies[11-30], OR 1.08, 95%CI 0.95-1.22, I^2=0%), AKD(11 studies[11-13,16,19,24-28,30], OR 1.01, 95%CI 0.69-1.49, I^2=0%), life-threatening bleeding(13 studies[11,12,14-16,19,20,24-28,30], OR 0.80, 95%CI 0.50-1.28, I^2=0%) and MI(10 studies[12-16,19,27-30], OR 1.21, 95%CI 0.62-2.39, I^2=0%) between the two groups. The detailed results of egger's test and funnel plots of each subgroup were listed in**SupplementaryMaterial Table S3 and Figure S2** , and no significant publication bias were found.

4 DISCUSSION

Many previous meta-analysis[31,32] always compared safety endpoints of TAVR procedure in BAV versus TAV AS patients. However, seldom of them studied the efficacy aspect of TAVR systematically. Therefore, we conducted the current meta-analysis to confirm it. The efficacy endpoints of TAVR were defined as hemodynamics changes measured by echocardiogram after procedure. It revealed that the post-procedural MAG of BAV group was similar compared with the TAV group. However, in Forrest's study[14], patients in BAV group who represented post-procedural MAG[?] 20mmHg were more than those in TAV group. This might be attributed to the possible incomplete expansion of valve prostheses associated with bicuspid anatomy such as two commissures and oval annulus. But Forrest's 1-year following data of MAG showed no difference in both groups. As an important efficacy endpoint, the post-procedural aortic valve area(AVA) in BAV group was the same as that in TAV group. Just in Tchetche's[15]and Blackman's[17] study, BAV patients tended to be associated with lower AVA compared with TAV patients. The result might be effected by the selection of valve prosthesis size. Therefore, adequate and accurate evaluation of aortic root anatomy preoperation should be the important guidance of prosthesis selection, to guarantee enough post-procedural AVA. For example, ECG-gated MDCT had advantage in evaluating aortic annular size, which could also measure the annulus during systolic period of cardiac cycle, and avoid undersizing of valve prosthesis[33].

In previous study[30], it was widely acknowledged that incidence of post-procedural PVL in BAV patients was higher than that in TAV patients, which was also confirmed by the current mata-analysis. The special morphology features of BAV patients including dilation of aortic root and ascending aorta, asymmetrical and severe leaflet calcification, elliptical annulus, and higher calcium scores[34,35], made it challenging to perform TAVR procedure, and enhanced the incidence of valve prosthesis malposition, incomplete expansion, and concomitant PVL.

The BAV group showed not only higher incidence of PVL, but also annular rupture, second valve implantation and conversion to SAVR, as well as lower device success. In Yoon's study[24], BAV patients represented higher frequency of aortic annular rupture, which was mainly related to application of Sapien XT valve. Moreover, the higher incidence of second valve implantation was considered to be induced by implantation of CoreValve system. Nevertheless, as time gone on, new-generation valve prostheses(Sapien 3, Lotus, and Evolut R) were widely used. In some degree, the advanced modifications of new-generation valve prostheses such as supra-annular technique, external sealing cuff and recapture valve platform decreased the technical difficulty, reduced procedure-related adverse events, and enhanced device success rate[36]. In order to assess long-term results of new-generation valve prostheses, subsequent large scale of multi-center studies are needed to perform.

Although some of adverse events were higher in BAV group, 30-day and 1-year mortality in BAV group, the most important safety endpoints, were the same as that in TAV group. In Pineda's study[12], after adjusting for STS score, bicuspid patients represented higher 30-day all-cause mortality(8.0% vs. 1.9%, $p<0.001$), while 30-day cardiovascular mortality was similar compared with tricuspid patients(2.5% vs. 1.7%, $p=0.450$). Such a statistical discrepancy was explained by one non-cardiac death in the bicuspid group. Moreover, the 1- and 2-year mortality(15% vs. 11%, $p=0.557$, 15.6% vs. 17.3%, $p=0.110$) was similar between the two groups in Pineda's study. Therefore, TAVR for BAV and TAV patients could have similar mortality endpoints.

Compared with TAV patients, BAV patients were always considered to be related to higher incidence of post-procedural PPM[37]. However, there was no difference in our meta-analysis. It was suggested to position the valve more into the aorta to avoid the injury of atrioventricular conduct system, and might decreased the incidence of PPM in some degree[38]. Nevertheless, no difference was found between early- and new-generation group[36,39]. All the 20 studies reported post-procedural stroke. The heavy and asymmetrical calcification of bicuspid patients might result in higher stroke rate theoretically, which was also demonstrated by our meta-analysis. This result was largely determined by Makkar's study[16], but the long term follow-up between BAV and TAV patients showed no difference. Moreover, Yoon's study[36] demonstrated that valve generation didn't act as a key role in the incidence of post-procedural stroke as well. The incidence of other adverse events such as post-procedural AKD, life-threatening bleeding and MI were also similar in our meta-analysis, which also supported the safety of performing TAVR procedure for BAV AS patients in some degree.

5 LIMITATION

The following limitation existed in the current meta-analysis: The classification standard of post-procedure PVL showed discrepancy. Five[11,14,19,21,23] of the thirteen studies stratified PVL into five grade(none, trace/trivial, mild, moderate, severe), two studies[12,20] stratified it into four grade(none, mild, moderate, severe), while the other two studies[16,17]mentioned three grade(none/mild, moderate, severe). There were four studies[13,22,24,25] didn't mention detailed standard of classification. This discrepancy might increase heterogeneity among studies.

6 CONCLUSION

The efficacy and safety of TAVR in BAV patients were not as ideal as those in TAV patients. Cautious and adequate discussion must be made before we decide to perform TAVR procedure for BAV patients. Moreover, in order to assess long-term results of new-generation valve prostheses, subsequent large scale of multi-center studies are needed to perform.

Authors' Contributions The followings authors have contributed to the study design(BW), literature search and evaluation(HX, QS), data analyses(BW, GZ, YC), preparation of tables and figures(GZ, JW, XW), leading article writing(BW), contributors of article writing(HX, QS) and critical article revision(TG, GZ).

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Figure Legends

Figure 1 The detailed strategy and results of literature search.

Figure 2 Forest plots of efficacy endpoints comparison: (a)mean aortic gradient. (b)aortic valve area. (c)paravalvular leakage.

Figure 3 Forest plots of safety endpoints comparison: (a)30-day mortality. (b)1-year mortality. (c)device success.

Figure 4 Funnel plots of: (a) 30-day mortality; (b) 1-year mortality.

Table 1a: Baseline characteristics of patients in each study.

Study	Chodór2021	Chodór2021	Pineda 2020	Pineda 2020	Fu 202
	BAV(n=21)	TAV(n=62)	BAV(n=50)	TAV(n=517)	BAV(n
Age, years	75.76 ±7.96	78.03 ±8.44	69.3±7.6	80.6±8.2	73.6±6
Male	14(66.67%)	37(59.67%)	32(64.0%)	289(55.9%)	23(52.3
NYHA III/IV	11(52.38%)	37(59.68%)	33(66.0%)	374(72.3%)	33(75%
STS score, %	-	-	5.1±3.6	7.0±4.1	6.70±2
EuroSCORE, %	21.63 ±11.49	22.59 ±17.22	-	-	-
Hypertension	16(76.19%)	52(83.87%)	42(84.0%)	427(82.6%)	14(31.8
Diabetes mellitus	10(47.62%)	26(41.93%)	23(46.0%)	195(37.7%)	7(15.9%
CKD	11(52.38%)	37(59.68%)	14(28.0%)	148(28.6%)	1(2.3%
Prior TIA	5(23.81%)	5(8.06%)	5(10.0%)	102(19.7%)	8(18.2%
COPD	4(19.05%)	16(25.8%)	26(52.0%)	159(30.8%)	13(29.5
Prior PCI	3(14.29%)	13(20.97%)	-	-	2(4.5%
Prior CABG	9(42.86%)	19(30.64%)	-	-	0(0%)
Prior MI	9(42.86%)	22(35.48%)	5(10.0%)	102(19.7%)	1(2.3%
PVD	10(47.62%)	22(35.48%)	13(26.0%)	183(35.4%)	-
CAD	-	-	32(64.0%)	397(76.8%)	-
Atrial fibrillation	-	-	6(12.0%)	78(15.1%)	3(6.8%
Device Early generation New generation	18(85.7%) 2(9.5%)	52(83.9%) 9(14.5%)	- -	- -	44(100
Quality assessment	S3, C1, O3	S3, C1, O3	S3, C1, O3	S3, C1, O3	S3, C1

*Datas were presented in mean±SD or n(n/N (%)). For more detailed patient characteristics please see Supplementary Table S1.

Abbreviation: BAV=bicuspid aortic valve; TAV=tricuspid aortic valve; NYHA=New York Heart Association; STS=Society of Thoracic Surgeons; EuroSCORE=European System for Cardiac Operative Risk Evaluation; CKD=Chronic kidney disease; TIA=Transient ischemic attack; COPD=Chronic obstructive pulmonary disease; PCI=Percutaneous coronary intervention; CABG=Coronary artery bypass graft; MI=Myocardial infarction; PVD=Peripheral vascular disease; CAD=Coronary artery disease.

Table 1b: Baseline characteristics of patients in each study.

Study	Liao2018	Liao2018	De Biase2018	De Biase2018	Aala
	BAV(n=87)	TAV(n=70)	BAV(n=83)	TAV(n=166)	BAV
Age, years	73.4±6.4	74.3±7.0	81.4±7.6	82.9±5.7	68.5
Male	50(57.5%)	45(64.3%)	57(69%)	108(66%)	20(6
NYHA III/IV	80(92.0%)	61(87.1%)	48(58%)	90(53%)	-
STS score, %	7.9±4.0	8.6±4.4	5.1±3.3	5.1±2.9	6.01
EuroSCORE, %	-	-	-	-	-
Hypertension	43(49.4%)	32(45.7%)	60(71%)	119(73%)	25(7
Diabetes mellitus	14(16.1%)	13(18.6%)	16(19%)	26(15%)	14(4
CKD	10(16.1%)	13(18.6%)	1(1%)	3(2%)	1(3.1
Prior TIA	13(14.9%)	8(11.4%)	5(6%)	11(8%)	5(15
COPD	50(57.5%)	45(64.3%)	24(28%)	39(21%)	13(4
Prior PCI	7(8.0%)	8(11.4%)	30(36%)	66(38%)	-

Study	Liao2018	Liao2018	De Biase2018	De Biase2018	Aala
Prior CABG	-	-	4(5%)	8(6%)	-
Prior MI	-	-	2(2%)	2(2%)	7(21
PVD	42(48.3%)	29(41.4%)	-	-	5(15
CAD	32(36.8%)	27(38.6%)	39(47%)	81(49%)	-
Atrial fibrillation	19(21.8%)	12(17.1%)	14(17%)	33(20%)	-
Device Early generation New generation	47(100%) 0(0%)	70(100%) 0(0%)	18(22%) 65(78%)	8(5%) 158(95%)	22(6
Quality assessment	S3, C1, O3	S3, C1, O3	S3, C1, O3	S3, C1, O3	S3, C

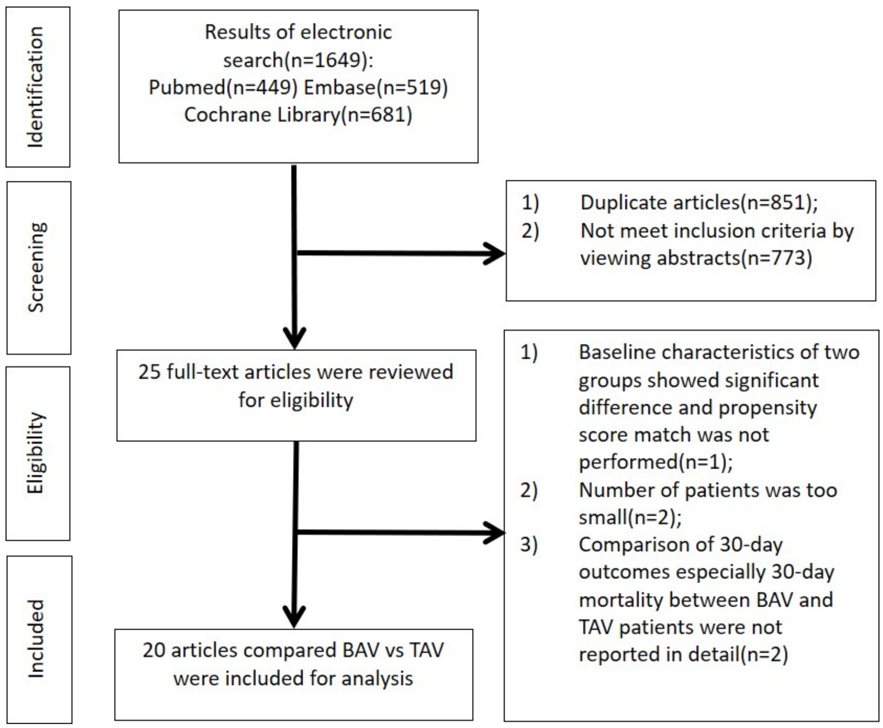

Figure 1 The detailed strategy and results of literature search.

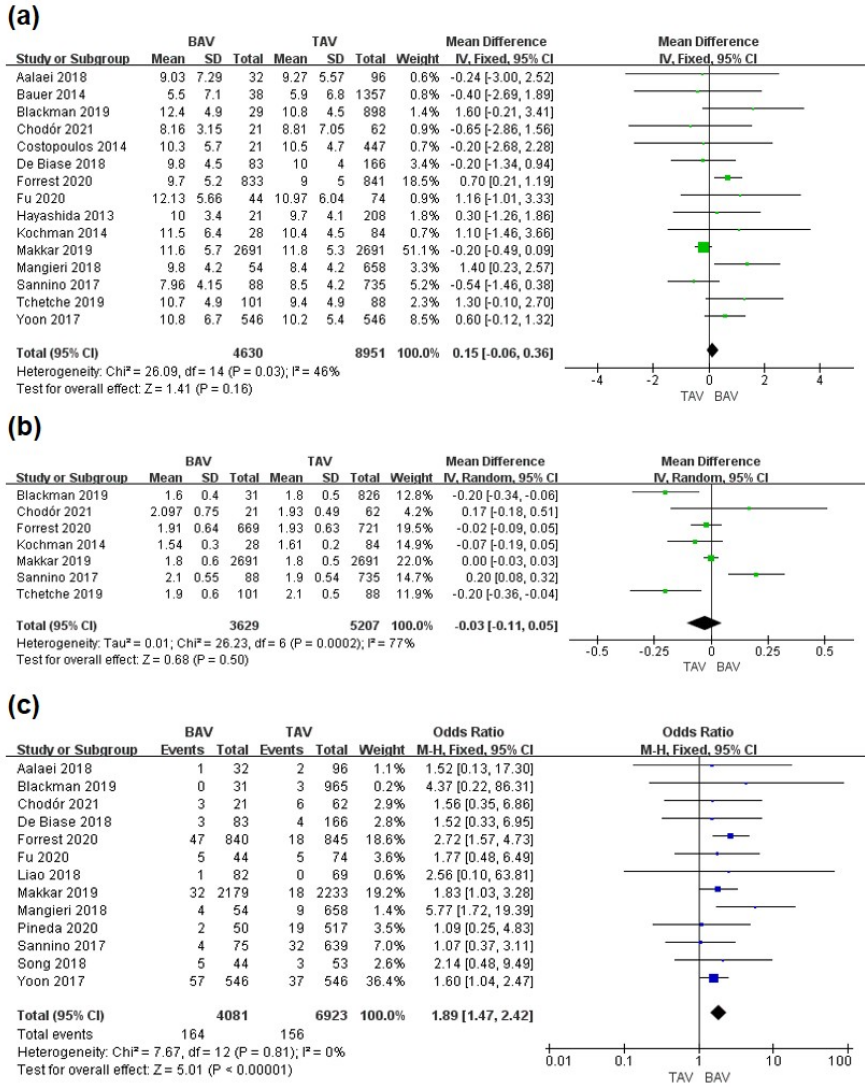

Figure 2 Forest plots of efficacy endpoints comparison: (a)mean aortic gradient. (b)aortic valve area. (c)paravalvular leakage.

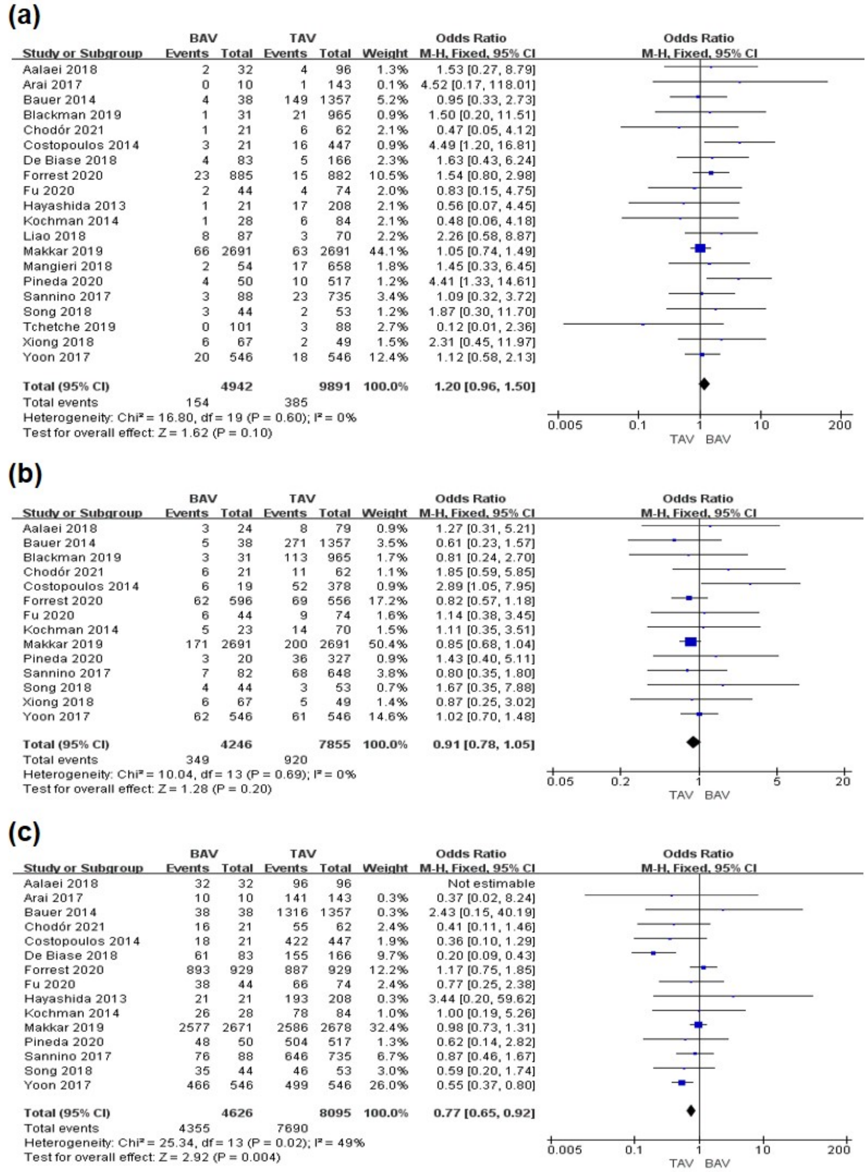

Figure 3 Forest plots of safety endpoints comparison: (a)30-day mortality. (b)1-year mortality. (c)device success.

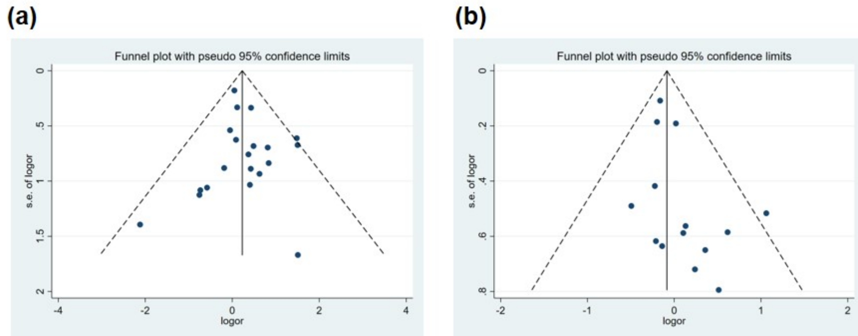

Figure 4 Funnel plots of: (a) 30-day mortality; (b) 1-year mortality.