



Patients With Bicuspid Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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Objective: We sought to conduct a systematic review and meta-analysis of clinical adverse events in patients undergoing transcatheter aortic valve replacement (TAVR) with bicuspid aortic valve (BAV) vs. tricuspid aortic valve (TAV) anatomy and the efficacy of balloon-expandable (BE) vs. self-expanding (SE) valves in the BAV population. Comparisons aforementioned will be made stratified into early- and new-generation devices. Differences of prosthetic geometry on CT between patients with BAV and TAV were presented. In addition, BAV morphological presentations in included studies were summarized.

Method: Observational studies and a randomized controlled trial of patients with BAV undergoing TAVR were included according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Results: A total of 43 studies were included in the final analysis. In patients undergoing TAVR, type 1 BAV was the most common phenotype and type 2 BAV accounted for the least. Significant higher risks of conversion to surgical aortic valve replacement (SAVR), the need of a second valve, a moderate or severe paravalvular leakage (PVL), device failure, acute kidney injury (AKI), and stroke were observed in patients with BAV than in patients with TAV during hospitalization. BAV had a higher risk of new permanent pacemaker implantation (PPI) both at hospitalization and a 30-day follow-up. Risk of 1-year mortality was significantly lower in patients with BAV than that with TAV [odds ratio (OR) = 0.85, 95% CI 0.75–0.97, p = 0.01]. BE transcatheter heart valves (THVs) had higher risks of annular rupture but a lower risk of the need of a second valve and a new PPI than SE THVs. Moreover, BE THV was less expanded and more elliptical in BAV than in TAV. In general, the rates of clinical adverse events were lower in new-generation THVs than in early-generation THVs in both BAV and TAV.

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Conclusions: Despite higher risks of conversion to SAVR, the need of a second valve, moderate or severe PVL, device failure, AKI, stroke, and new PPI, TAVR seems to be a viable option for selected patients with severe bicuspid aortic stenosis (AS), which demonstrated a potential benefit of 1-year survival, especially among lower surgical risk population using new-generation devices. Larger randomized studies are needed to guide patient selection and verified the durable performance of THVs in the BAV population.

Keywords: transcatheter aortic valve replacement (TAVR), meta-analysis, bicuspid aortic valve (BAV), aortic stenosis (AS), systematic review

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is now a wellestablished treatment option for patients with symptomatic severe aortic stenosis (AS) in all spectrums of surgical risk (1). According to surgical experience, bicuspid aortic valve (BAV) anatomy may comprise up to 50% of low-risk patients (2). Therefore, when expanded to patients of lower risks and younger age, TAVR procedures are anticipated to treat more patients with BAV. However, all pivotal randomized controlled trials comparing TAVR with surgical aortic valve replacement (SAVR) excluded patients with BAV due to a higher risk of procedural complications, such as paravalvular leakage (PVL), stroke, new permanent pacemaker implantation (PPI), and annular rupture (3). Anatomical features such as the nontubular shape from the annulus to the leaflet tips and heavier calcification in patients with BAV often result in more common malposition of transcatheter heart valves (THVs) than patients with tricuspid aortic valve (TAV), as well as in conduction disturbances or PVL (4, 5). Previous meta-analyses of cohort studies have reported that, compared to patients with TAV, patients with BAV were at a higher risk of procedural complications, such as the conversion to SAVR, the implantation of a second valve, a moderate or severe PVL, and the device failure (6). In addition, new-generation devices were reported to have a lower risk of adverse events compared to early-generation devices in BAV, while balloonexpandable (BE) valves were associated with the lower need of a second valve and a new PPI than self-expanding (SE) valves (6).

With the accumulation of experience and an iteration of prosthesis, TAVR is now used more frequently for patients with BAV (7–10), enabling detailed comparisons to be updated. Because of the lack of the corresponding guideline and normative practical guidance for TAVR in the BAV population, pressing the need for a reliable assessment on the efficacy and safety of TAVR procedures in patients with BAV existed. Therefore, we systematically reviewed related researches and hereby summarized the BAV morphological presentations, clinical adverse events of TAVR in patients with BAV vs. TAV, as well as the efficacy of BE vs. SE valves in patients with BAV. Comparisons of early- vs. new-generation devices were performed where available. Moreover, the geometry of THV on CT after TAVR was compared between patients with BAV and TAV.

METHOD

Search Strategy, Selection Criteria, and Data Extraction

The composition of this current review was in line with an evidence-based set of items in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11). Associated checklist is presented in Supplementary Table S9. The search of original articles was conducted by two independent investigators, YZ and TYX, on Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), conference proceedings for the Scientific Sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, EuroPCR, and Transcatheter Valve Therapeutics. Search code included TAVI OR TAVR OR "percutaneous aortic valve" OR "transcatheter aortic valve") AND (bicuspid OR BAV) on Medline, Embase and conference proceedings; #1 TAVI, #2 TAVR, #3 percutaneous aortic valve, #4 transcatheter aortic valve, #5 bicuspid, #6 BAV, #7 (#1 OR #2 OR #3 OR #4) AND (#5 OR #6) on CENTRAL. The search was last updated on September 22, 2021. Exclusion criteria were: (1) duplicate publication; (2) articles without primary data; and (3) non-English research. Inclusion criteria were one of the followings: (1) a comparison of clinical adverse events of TAVR between BAV and TAV, or a comparison of BE and SE valve outcomes in patients with BAV; (2) a comparison of THV geometry on CT after TAVR between BAV and TAV; both with the availability of binary primary outcome data. The assessment of article quality and extraction of relevant data were done by YZ and YML independently. Data extracted from the included studies and used for all analyses in the review are presented in Supplementary Material.

The aim of this study was set to answer: (1) the proportion of different phenotypes of BAV in the included studies; (2) a comparison of clinical outcomes and procedural complications after TAVR in patients with BAV vs. TAV, including a subgroup analysis stratified by early- and new-generation devices; (3) a comparison of clinical outcomes and procedural complications in patients with BAV after TAVR between BE and SE valves, including a subgroup analysis stratified into early- and newgeneration devices; and (4) differences of BE and SE THV geometry on CT after TAVR in patients with BAV.

Early-generation TAVR devices included Sapien (Edwards Lifesciences), Sapien XT (Edwards Lifesciences), CoreValve (Medtronic), and Venus A-Valve (Venus MedTech Inc.). Newgeneration devices included Sapien 3 (Edwards Lifesciences), Lotus (Boston Scientifics), Evolut R and Pro (Medtronic), Acurate Neo (Boston Scientific), and Portico (Abbott). BE devices included Sapien, Sapien XT, and Sapien 3 valves (Edwards Lifesciences); SE devices included CoreValve, Evolut R and Pro (Medtronic), Accurate Neo (Boston Scientifics), Portico (Abbott), Venus A-Valve (Venus MedTech), and Lotus (Boston Scientifics). The year of publication, study design, the number of enrolled centers, countries, the mean or median age of population, the mean or median score of surgical risks, and the number of enrolled patients were collected from each study. Overlapping population of the included articles was screened. The publication of a smaller sample size in studies with overlapping population was then excluded from the subsequent meta-analysis. Discrepancies in the selection of relevant studies and data extraction were solved by a discussion with a third evaluator (YML).

Outcomes of Interest

Bicuspid aortic valve was subclassified as type 0, type 1 (grouped by left–right coronary cusp fusion, left noncoronary cusp fusion, and right noncoronary cusp fusion), and type 2 according to Sievers' classification (12). The proportions of each subtype were compared among regions grouped into the USA, Europe, China, and multiregional areas (data from multicenter studies including Europe, North America, and other Asia-Pacific regions).

Transcatheter aortic valve replacement-specific outcomes were defined according to the Valve Academic Research Consortium 3 (VARC-3), while study-specific definitions remained as they were based on the corresponding articles (13). Adverse events of interest at hospitalization included the conversion to SAVR, coronary obstruction, the need of a second valve, device failure (procedural mortality, the incorrect positioning of a single prosthetic heart valve into the proper anatomical location, prosthesis-patient mismatch, mean aortic valve gradient > 20 mmHg, peak velocity > 3 m/s, or moderate/severe prosthetic valve regurgitation), annular rupture, new-onset atrial fibrillation (NO-AF), life-threatening or major bleeding, major vascular complications, acute kidney injury (AKI), myocardial infarction (MI), a moderate or severe PVL, stroke, a new PPI, MI, and mortality; adverse events of interest at a 30-day follow-up included life-threatening or major bleeding, major vascular complications, AKI, and MI; and adverse events of interest at a 1-year follow-up included a moderate or severe PVL, stroke, a new PPI, MI, and mortality.

Transcatheter heart valve geometry and position were demonstrated by: (1) THV expansion, i.e., (the observed THV external area/device labeled size) \times 100% at inflow, annulus, and the outflow of the valve frame; (2) THV eccentricity index = [1-(minimum external THV diameter/maximum external THV diameter)] \times 100%; and (3) THV implantation depth, i.e., the distance from the inflow of the prosthesis to the floor of right, left, and non-coronary cusps.

Statistical Analysis

The results of meta-analysis were summarized as odds ratios (ORs) or mean difference (MD) and 95% CIs. Heterogeneity across studies was tested by the Cochran's Q statistic and Higgins' and Thompson's I^2 statistics (14). The Freeman-Tukey Double Arcsine method were used for each pooled event rate (%) according to valve generations and aortic valve morphologies. $I^2 > 50\%$ and $p \le 0.1$ was considered to be a significant heterogeneity, where random-effect models were used. Otherwise, fixed-effect model was used for an analysis. p < 0.05 was considered as statistically significant for other results. All analyses were conducted using Review Manager version 5.3 (available from http://tech.cochrane.org/revman).

Quality Assessment

All included studies [except one (15)] were non-randomized studies, so study qualities were evaluated by the ROBINS-I tool (16). Publication bias was presented in funnel plots. The conduction and composition of this review were conformed to the PRISMA 2020 guideline (17).

RESULTS

The study flow is presented as the PRISMA 2020 flow diagram (**Figure 1**). A total of 22 studies (2,546 patients with BAV) were included for the analysis of BAV phenotypes (8, 10, 18–37). A total of 35 studies (including 139,058 patients: 15,700 BAV and 123,358 TAV) were analyzed for comparisons between BAV and TAV (7–10, 15, 18–30, 38–54), while 10 studies (including 1,294 patients: 805 BE and 489 SE) were analyzed for the difference of BE vs. SE in patients with BAV after TAVR (32–38, 40, 55). In addition, four studies (including 551 patients: 149 patients with BAV and 402 patients with TAV) were analyzed for the difference of THV geometry between BAV and TAV after TAVR (21, 31, 41, 53).

Proportion of the Different Types of BAV in the Included Studies

Type 1 BAV accounted for 74.5% (1,897/2,546) of patients, being the most frequently encountered BAV subtype (Figure 2A). The predominance of type 1 BAV was presented in Europe, the USA, and multiregional studies, accounting for 78.7% (829/1,053), 72.4% (197/272), and 74.1% (829/1,119) of patients, respectively. However, Chinese patient population demonstrated a different distribution, with 58.8% (60/102) of type 0 and 41.2% (42/102) of type 1 BAV. In addition, type 2 BAV was least commonly seen in all studies with a proportion of 2.5% (64/2,546) in total, 4.4% (49/1,119), 0.9% (9/1,053), 1.8% (5/272), and 0, respectively, in multiregional studies, Europe, the USA, and China. A total of 398 patients with type 1 BAV were included for further analysis of fusion patterns (Figure 2B). The L-R coronary cusp fusion was the most common pattern with a proportion of 76.6% (305/398), and the L-N coronary cusp fusion was the least common pattern with a proportion of 5.8% (23/398). Similar distributions of the L-R and L-N fusion was presented in type 1 BAV from Europe, the USA, and multiregional studies.



Comparisons Between BAV and TAV

Baseline of patients and the characteristics of the included studies are summarized in **Supplementary Table S1**. In-hospital, 30-day and 1-year procedural complications and outcomes are presented in **Figures 3A–C**, respectively. All original records of metaanalysis are presented in **Supplementary Figure S1**. In terms of in-hospital analysis, patients with BAV treated by TAVR were at a higher risk of the need of a second valve (OR = 2.31, 95% CI 1.67–3.19, p < 0.00001) and a moderate or severe PVL (OR = 1.50, 95% CI 1.17–1.93, p = 0.002) than patients with TAV, with consistent results stratified by early- and new-generation devices. Moreover, patients with BAV were at an increased risk of the



		в	AV	п	AV	Odds Ratio	Odda antia	05% 01		11-4
A	Conversion to SAVR	event	total	event	total	I.	Odds ratio	95% CI	Р	Heterogeneity I* (%)
	All THVs Early generation THVs	85 13	9116 574	158 30	13510 2586	→		[1.33, 2.46] [1.15, 6.12]	0.0001	38 0
	New generation THVs Coronary obstruction	45	7607	37	8087	† •-	1.37	[0.89, 2.11]	0.16	21
1	All 1HVs Early generation THVs	5	254	11	2265		2.52	[0.83, 7.65]	0.1	0 26
Ne	ed of a second valve	215	8566	78	10697		2.31	[1.67, 3.19]	<0.00001	0
	Early generation THVs New generation THVs	41 159	508 7843	20 38	558 9194		2.19 2.38	[1.25, 3.83] [1.49, 3.79]	0.006	22 0
Мо	derate or Severe PVL All THVs	137	7298	159	10209		1.50	[1.17, 1.93]	0.002	0
	Early generation THVs New generation THVs	57 69	466 6548	39 63	490 8257	-	1.64 1.49	[1.07, 2.53] [1.04, 2.13]	0.02 0.03	0
Major v	ascular complication All THVs	95 14	7659	209	9772	+.	0.96	[0.74, 1.25]	0.77	0
	New generation THVs	80	7349	139	8303		0.90	[0.68, 1.21]	0.49	ő
0	All THVs Farly generation THVs	516	8350	857	10621	• -	1.42 1.87	[1.03, 1.96]	0.03	58 0
2	New generation THVs	390	7730	658	8461	+	1.02	[0.88, 1.19]	0.79	0
	All THVs Early generation THVs	313 5	1695 57	713 165	4492 680	+	1.23 0.48	[1.04, 1.45] [0.18, 1.26]	0.01 0.14	0
	New generation THVs Annulus rupture	0	71 7278	2 160	343 8582		2.70	[0.12, 59.85]	0.53	NA
	Early generation THVs	4	183	147	890 7131		0.58	[0.22, 1.57]	0.29	ő
Life-threateni	ing or major bleeding All THVs	210	4254	5714	108058	1	0.92	[0.80, 1.06]	0.25	8
	Early generation THVs New generation THVs	9 194	57 4049	189 5499	680 105983		0.61 0.91	[0.29, 1.29] [0.79, 1.06]	0.2 0.23	0
~	All THVs	48	7623	168	11015	-	0.85	[0.61, 1.19]	0.35	0
	New generation THVs	15	7056	23	7195	- +	1.50	[0.40, 5.80]	0.45	ŇĂ
	NU-AF All THVs Farly generation THV/a	47 0	2817 15	89 0	3433 25	-+	0.89 NA	[0.68, 1.16] NA	0.38 NA	0 NA
	New generation THVs	46	2752	54	2891	-+	0.92	[0.70, 1.21]	0.56	0
1	All THVs Early generation THVs	790 89	9307 536	1030 188	13316 1229	↓•	1.30 0.98	[1.17, 1.44] [0.72, 1.34]	<0.00001 0.9	17 0
	New generation THVs Stroke	510	7022	458	8289	•	1.29	[1.13, 1.47]	0.0001	48
1	All THVs Early generation THVs	150	8849 161	171	12308 1899	+	1.28	[1.01, 1.61] [0.49, 10.74]	0.04	0
In-hospit	New generation THVs tal all-cause mortality	109 166	7056	304	7195	•	1.28	[0.97, 1.70]	0.08	37
	All THVs Early generation THVs	6	82 7483	112	1431	_ t -	1.28	[0.51, 3.22]	0.59	0
	ivew generation THVs	00	1403	92	Favors BAV	10 0.25 0.50 1.0 2.0 4	Favors TAV	[0.02, 1.40]	0.52	v
в			BAV		TAV	Odds Ratio	Odd+	05% 01		Hotorogo-it. 12 (01)
M	oderate or Severe P	ev /L	ent tot	al eve	nt total	I	Ouus ratio	95 % CI	P	meterogeneity i* (%)
	All TH	Vs	87 50	14 78	5134	- +•	1.27	[0.56, 2.92]	0.57	32
	Early generation TH	Vs	/ / 83 49	/ 31 73	4968		1.19	[0.27, 5.16]	0.82	47
	Strol	ke	0		1000					
	All TH	Vs 1	50 78	23 171	9618	 ⊷	1.18	[0.93, 1.49]	0.17	6
	Early generation TH	Vs 1	10 36	64 7	395	-	1.60	[0.60, 4.30]	0.35	0
	New generation THV	vs 1 Pl	40 73	/0 103	902/	T	1.10	[0.91, 1.48]	0.22	30
	All TH	Vs 6	31 75	74 981	9687	•	1.17	[1.04, 1.31]	0.01	20
	Early generation TH	Vs	8 4	4 18	74	-•[-	0.69	[0.27, 1.76]	0.44	NA 28
Life-threater	ning or major bleedir	vs 6 ng	10 74	+/ 943	9447	Г		[0.005	20
	All TH	Vs 4	19 76	52 10	2 1492	-	0.89	[0.60, 1.32]	0.58	40
	Early generation TH	Vs	1	/ /	1		1 20	/	/	/
Major	vascular complication	vs ' on	18 21	16 6	946	- •	1.30	[0.67, 2.54]	0.44	41
	All TH	Vs 3	33 80	06 79	1566	+	1.40	[0.87, 2.27]	0.16	0
	Early generation TH	Vs 1	17 36	54 14	395	+	1.36	[0.66, 2.78]	0.41	33
	New generation TH	Vs 1 KI	16 44	12 6	5 1171	†•	1.45	[0.77, 2.75]	0.25	0
	AII TH'	Vs	0 7	1 2	343		- 2.70	[0.12, 59.85]	0.53	NA
		1-	1	1 1	1		1	1	1	1
	Early generation TH	vs	/ ·		,					
	New generation TH	Vs	0 7	1 2	343		2.70	[0.12, 59.85]	0.53	NA
	New generation TH	VS VS MI VS	0 7 4 11	1 2 35 ค	343		- 2.70	[0.12, 59.85]	0.53	NA 0
	Early generation TH New generation TH I All TH Early generation TH	VS MI VS VS	, , 0 7 4 11: 1 4	1 2 35 6 4 2	343 1291 74		- 2.70 0.94 - 0.84	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51]	0.53 0.92 0.98	NA O NA
	Early generation TH' New generation TH' All TH Early generation TH New generation TH	VS MI VS VS VS	0 7 4 11: 1 4 3 10	1 2 35 6 4 2 91 4	, 343 1291 74 1217		- 2.70 0.94 - 0.84 0.98	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81]	0.53 0.92 0.98 0.98	NA O NA O
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	Early generation TH' New generation TH' All TH' Early generation TH' New generation TH' 30-day mortali All THH Early generation TH'	vs Vs Vs Vs Vs ity Vs 1 Vs 3	9 7 4 11: 1 4 3 10 92 89 34 57	1 2 35 6 4 2 91 4 34 57 74 21	, 343 1291 74 1217 9 14542 4 2586		- 2.70 0.94 - 0.84 0.98 1.16 1.03	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.66, 1.61]	0.53 0.92 0.98 0.98 0.14 0.88	NA 0 NA 0 0 5
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с	Early generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH	vs Wi Vs Vs Vs Vs 1 Vs 1 Vs 1 Ws 1 BAV vent to	7 7 4 11: 1 4 3 10 92 89 34 57 46 80	1 2 335 6 4 2 91 4 34 57 74 21 63 32 TAV eent tot	, 343 1291 74 1217 9 14542 4 2586 4 10398 Favors I	1 025 05 1 2 4 AAV Odds Ratio	- 2.70 0.94 - 0.84 0.98 1.16 1.03 1.16 1.03 1.16 Vorse TAV Odds ratio	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.66, 1.61] [0.92, 1.47] 95% Cl	0.53 0.92 0.98 0.98 0.14 0.88 0.21	NA 0 NA 0 5 0 Heterogeneity I ² (%)
C Moderate or	Early generation TH New generation TH All TH Early generation TH 30-day mortail All TH Early generation TH New generation TH New generation TH Severe PVL	VS MI VS VS VS VS 1 VS 1 VS 1 VS 1 BAV vent to	0 7 4 11: 1 4 3 10 92 89 34 57 46 80 5746 80	1 2 35 6 4 2 91 4 34 57 74 21 63 32 TAV rent tot	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I		- 2.70 0.94 - 0.84 0.98 1.16 1.03 1.16 1.03 1.16 Voros TAV Odds ratio	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.92, 1.47] 955% CI	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P	NA 0 NA 0 5 0 Heterogeneity 1 ² (%)
C Moderate or	Early generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH New generation TH New generation TH Severe PVL All TH/s 4	vs Ws Vs Vs Vs 1 Vs 1 Vs 1 Vs 1 Vs 1 0	7 7 4 11: 1 4: 1 4: 3 10 92 89 34 57 46 80 57 46 80 57 46 80 57 46 80	1 2 35 6 4 2 91 4 34 57 74 21 63 32 TAV ent tot	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al		- 2.70 0.94 - 0.84 0.98 1.16 1.03 1.16 1.03 1.16 Odds ratio 1.53 NA	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.92, 1.47] 95% CI [0.99, 2.35] NA	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05	NA 0 NA 0 5 5 0 Heterogeneity I ² (%) 7 NA
C Moderate or Early gen	Early generation TH New generation TH Early generation TH 30-day mortail all Th Early generation TH New generation TH New generation TH New generation TH All THVs 4 eration THVs 4 eration THVs 4	VS MI VS VS VS VS 1 VS 1 VS 1 VS 1 VS 1 0 4 9 2 0 2 0 2 1 9 2 1 9 2 1 9 2 1 9 2 1 9 2 1 1 9 2 1 1 1 1	7 7 4 11: 1 4 3 10 92 89 934 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 57 57 57 57 57 57 57 57 57	1 2 35 6 4 2 91 4 34 57 74 21 63 32 TAV ent tot 40 330 0 68 36 227	, 343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 7		- 2.70 0.94 - 0.84 0.98 1.16 1.03 1.10 1.03 1.16 1.03 1.16 Odds ratio Odds ratio NA 1.51	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.66, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 NA 26
C Moderate or Early gen New gen	Early generation TH New generation TH All TH Early generation TH 30-day mortail All TH Early generation TH New generation TH New generation TH ev Severe PVL All THVs 4 eration THVs 4 Stroke	VS MI VS VS VS VS 1 VS 1 VS 1 VS 1 US 2 0 19 2 0	7 7 4 11: 1 4 3 10 92 89 84 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 46 80 57 57 57 57 57 57 57 57 57 57 57 57 57	1 2 335 6 4 2 91 4 34 57 74 21 63 32 TAV TAV 40 330 0 68 36 227	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 7	1 025 05 1 2 4 AW Odds Ratio	- 2.70 0.94 - 0.84 0.98 1.16 1.03 1.16 1.03 1.16 0 0 0 0 0 0 0 0 0 0 0 0 0	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.66, 1.61] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 NA 26
C Moderate or Early gen New gen	Early generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH New generation TH New generation TH New generation TH Severe PVL All THVs 4 Stroke All THVs 11	vs Vs Mil Vs Vs Vs Vs Vs Vs 1 Vs 1 BAV vent to 19 2 0 49 20 66 7	7 0 7 4 11: 1 4: 3 10 92 89 84 57 46 80 049 3 049 3 374 22	1 2 335 6 4 2 91 4 34 57 74 21 63 32 TAV tot 40 330 0 68 36 227 27 967	343 1291 74 9 14542 4 2586 4 10398 Favors I al 7 4	1 02 05 1 2 4 WW Fr Odds Ratio	- 2.70 0.94 0.84 0.98 1.16 1.03 1.16 1.05 0 Odds ratio 1.53 NA 1.51 0.95	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.95, 1.41] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18]	0.53 0.92 0.98 0.98 0.98 0.98 0.98 0.98 0.98 0.21 P 0.05 NA 0.06 0.64	NA 0 NA 0 5 0 Heterogeneity 1 ² (%) 7 NA 26 0
C Moderate or Early gen New gen Early gen	Early generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH New generation TH All THVs 4 eration THVs 4 Stroke All THVs 11 eration THVs 5	vs Vs Vs Vs Vs Vs Vs Us BAV BAV BAV 19 2 19 2 19 2 19 5 1 19 5 1 1 19 5 1 10 10 10 10 10 10 10 10 10 10 10 10 1	7 0 7 4 11: 1 4: 3 10 92 89 84 57 46 80 049 3 049 3 374 22 24 1	1 2 335 6 4 2 91 4 34 57 74 21 63 32 TAV ent tot 40 330 0 68 36 227 27 967 0 149	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 7 4	Odds Ratio	 2.70 0.94 0.84 0.96 1.16 1.03 1.16 1.03 1.05 0.95 1.24 	[0.12, 59.85] [0.29, 3.06] [0.07, 9.51] [0.25, 3.81] [0.66, 1.61] [0.62, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.74, 4.09]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.61	NA 0 NA 0 5 5 0 Heterogeneity I ² (%) 7 NA 26 0 0
C Moderate or Early gen New gen Early gen New gen	Early generation TH New generation TH Early generation TH 30-day mortain All TH Early generation TH All TH Early generation TH New generation TH New generation TH New generation TH Storke All THVs 4 Storke All THVs 11 eration THVs 11	vs Vs Mi Vs vs Vs Vs Ny EAV Vs 19 2 19 2 19 2 19 2 19 2 19 2 19 2 19 2 19 2 10 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	7 0 7 4 11: 1 4 3 10 92 89 94 57 46 80 044 57 46 80 049 3 374 22 24 10 183 21	1 2 335 6 4 2 91 4 34 57 74 21 63 32 TAV ent tot 40 330 0 68 36 227 27 967 0 149 16 812	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 1 7 4 0 9		 2.70 0.94 0.98 1.16 1.03 1.16 1.16 1.04 1.51 0.95 1.53 NA 1.51 0.95 1.34 0.94 	[0.12, 59.85] [0.29, 3.08] [0.25, 3.81] [0.95, 1.41] [0.92, 1.41] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17]	0.53 0.92 0.98 0.98 0.98 0.94 0.21 P 0.05 NA 0.06 0.64 0.58	NA 0 NA 0 5 5 0 Heterogeneity I ² (%) 7 NA 26 0 0 0
C Moderate or Early gen New gen New gen	Early generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH New generation TH New generation TH New generation TH Severe PVL All THVs 4 eration THVs 4 All THVs 11 eration THVs 11 New PPI	vs vs MII √s vs ty vs 1 vs 1 vs 1 vs 1 vs 1 19 2 0 4 19 2 19 2 19 2 19 2 10 4 19 2 10 4 10 4 10 4 10 4 10 4 10 4 10 4 10 4	, 7 , 1 , 1 , 4 , 1 , 1 , 4 , 1 , 1 , 4 , 1 , 4 , 1 , 1 , 9 , 9 , 9 , 9 , 9 , 9 , 9 , 9	1 2 335 6 4 2 91 4 34 57 63 32 TAV ent 40 330 0 68 36 227 27 967 0 149 16 812	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 1 4 0 9 2	Odds Ratio	 2.70 0.94 0.84 0.98 1.16 1.03 1.16 1.16 1.16 1.16 1.51 0.95 1.24 0.94 	[0.12, 59.85] [0.29, 3.06] [0.27, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17]	0.53 0.92 0.98 0.98 0.44 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.51	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 NA 26 0 0 0
C Moderate or Early gen New gen New gen	Lany generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH Save generation TH New generation TH New generation TH Savere PVL All THVs 4 Stroke All THVs 11 eration THVs 11 eration THVs 12 eration THVs 11 New PPI All THVs 14 New PPI All THVs 14	vs vs MII √s vs vs 1 vs 1 vs 1 vs 1 vs 1 vs 1 vs 1	7 7 4 11: 1 4 4 3 10 92 89 92 89 93 80 92 89 93 80 93 80 94 80 95 80	1 2 335 6 4 2 4 2 91 4 334 57 74 21 63 32 TAV 10 330 0 68 68 227 27 967 0 149 16 812 32 8555; 2;	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 7 4 0 9 2 2	Odds Ratio	- 2.70 0.94 0.84 0.98 1.16 1.03 1.05 1.03 1.05 1.03 1.51 1.53 1.34 0.95 1.34 0.94 0.94 0.95 1.34 0.94	[0.12, 59.85] [0.29, 3.08] [0.7, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.52	NA 0 NA 0 5 0 Heterogeneity 1 ² (%) 7 NA 26 0 0 0 0 0
C Moderate or Early gen New gen New gen	Early generation TH New generation TH Early generation TH 30-day mortail All TH Early generation TH New generation TH New generation TH New generation TH New generation TH 4 Storke All THVs 10 eration THVs 11 New PPI All THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 New PPI All THVs 60 eration THVs 10	vs vs MII √s vs vs 1 vs 1 vs 1 vs 1 vs 1 vs 1 vs 1	9 7 0 7 4 11:1 1 4 3 10 92 89 92 89 92 89 92 89 92 89 92 89 92 89 92 89 00 7 01 122 442 11 122 4 122 4 122 4 122 4 124 12 124 12 124 12 124 12 124 12 123 12 124 12 123 12 124 12 123 12 124 12 125 12 125 12 125 12 125	1 2 335 6 4 2 991 4 334 57 74 21 663 32 TAV TAV 10 3300 68 36 27 967 0 1499 16 8125 33 1422 28 852 33 1422	343 1291 74 1217 9 14542 4 2586 4 10398 Favors 1 al 7 4 0 9 2 2	ddds Ratio	- 2.70 0.94 0.84 0.98 1.16 1.03 1.51 0.95 1.34 0.94 0.94 0.94 0.94 0.94 0.95 1.12 0.94 0.94 0.94 0.94 0.95 1.12 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.95 1.12 0.94	[0.12, 59.85] [0.29, 3.08] [0.07, 9.51] [0.25, 3.81] [0.66, 1.61] [0.92, 1.47] 955% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 27]	0.53 0.92 0.98 0.98 0.14 0.89 0.21 P 0.05 NA 0.06 0.64 0.58 0.12 0.05	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 7 NA 26 0 0 0 0 65 0 19
C Moderate or Early gen New gen Early gen New gen	Early generation TH New generation TH Early generation TH 30-day mortail All TH Early generation TH New generation TH New generation TH New generation TH New generation TH All THVs 4 eration THVs 4 Stroke All THVs 4 eration THVs 4 eration THVs 10 New PPI All THVs 11 New PPI All THVs 11 neation THVs 11 eration THVs 11 neation THVs 11 New PPI	vvs vs MI vs vs vs vs vs vs 1 vs 1 <	9 7 0 7 4 11: 13 10 32 89 34 57 34 57 34 57 524 91 374 22 24 11 1183 21 524 95 36 4 328 91	1 2 335 6 4 2 991 4 334 57 74 21 663 32 TAV ent tot 10 3300 0 68 36 2277 27 967 0 1494 16 812 32 425/3 13 142 18 826 ²	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 4 0 9 2 2	0dds Ratio	 2.70 0.94 0.84 1.16 1.03 1.16 1.16 1.51 0.95 1.54 0.94 0.72 0.61 1.12 	[0.12, 59.85] [0.29, 3.08] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.58 0.12 0.12 0.05	NA 0 NA 0 5 5 0 Heterogeneity I² (%) 7 NA 26 0 0 0 0 65 0 19
C Moderate or Early gen New gen New gen	Lany generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH New generation TH New generation TH All THVs 4 Stroke All THVs 11 eration THVs 11 eration THVs 12 eration THVs 12 eration THVs 13 New PPI All THVs 14 eration THVs 15 eration THVs 15 eration THVs 16 Mit All THVs 16 All THVs 16	vvs MI Vs MI Vs vs vs vs vs sty Vs Vs Vs Vs Vs 10 Vs 10 11 12 13 13 13 13 13 13 14 15	9 7 0 7 4 11: 13 10 32 89 34 57 34 57 524 89 524 95 524 91 524 92 328 91 773 7	1 2 335 6 4 2 991 4 334 57 74 212 63 32 TAV tot 10 330 0 680 36 227 27 967 0 149 916 812 92 8555/3 142 88 938 8267 7 10000	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I al 7 4 0 9 2 2 3	Odds Ratio	- 2.70 0.94 0.84 0.84 1.16 1.03 1.16 1.03 1.51 0.95 1.24 0.94 0.72 0.61 1.12 0.81	[0.12, 59.85] [0.29, 3.06] [0.79, 9.51] [0.25, 3.81] [0.96, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27] [0.25, 2.57]	0.53 0.92 0.98 0.98 0.98 0.98 0.93 0.93 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.12 0.12 0.05 0.72	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 NA 26 0 0 0 0 0 0 19
C Moderate or Early gen New gen Early gen New gen Early gen	Lany generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH New generation TH New generation TH New generation TH Savere PVL All THVs 4 Stroke All THVs 11 eration THVs 11 eration THVs 11 New PPI All THVs 64 eration THVs 65 MI MI All THVs 64 eration THVs 15	vs vs MI vs vs vs vs vs vs vs vs vs vs	9 0 7 4 11: 1 4 3 10 92 89 92 89 94 55 14 55 14 55 14 57 14 2 14 57 14 57 14 57 14 57 14 57 14 57 14 12 14 12	TAV TAV TAV TAV TAV TAV TAV TAV TAV 10 336 36 227 967 16 812 22 28 23 142 18 8265: 7 1000:02 2 74 100:02 2 74	, 343 1291 74 1217 9 14542 4 2586 4 10398 4 2586 4 10398 7 Favors k 9 9 9 2 2 2 2	Odds Ratio	- 2.70 0.94 0.84 0.84 0.94 0.84 1.61 1.03 1.51 0.95 1.34 0.94 0.72 0.61 1.12 0.81 0.84	[0.12, 59.85] [0.29, 3.06] [0.79, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27] [0.25, 2.57] [0.07, 9.51]	0.53 0.92 0.98 0.98 0.98 0.94 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.62 0.58 0.12 0.05 0.12 0.05	NA 0 NA 0 5 0 7 Heterogeneity 1 ² (%) 7 NA 26 0 0 0 65 0 19 19 0 NA
C Moderate or Early gen New gen Early gen New gen New gen	Lany generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH New generation TH New generation TH New generation TH All THVs 4 eration THVs 4 Stroke All THVs 10 All THVs 10 All THVs 10 New PPI All THVs 10 Heration THVs 10 eration THVs 10 eration THVs 10 All THVs 10 All THVs 10 All THVs 10 All THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 eration THVs 10 All	vs vs MI Vs Vs Vs Vs Vs Vs Vs Vs 1 PAV Vs Vs Vs Vs Vs Vs Vs Vs Vs V	9 7 4 11131 1 4 11131 1 4 143 3 100 92 89 92 89 92 89 94 57 144 6 80 122 4 144 8 122 4 142 1 122 4 142 2 124 1 143 2 144 2 1	TAV TAV TAV TAV TAV TAV Constraint <	343 1291 74 1217 9 1442 2586 4 10398 8 7 7 4 4 0 9 2 2 2 3	Odds Ratio	- 2.70 0.94 0.84 0.98 1.16 1.03 1.10 0.05 1.34 0.95 0.95	[0.12, 59.85] [0.29, 3.08] [0.7, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27] [0.07, 9.51] [0.07, 9.51] [0.21, 2.99]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.12 0.12 0.12 0.12 0.05 0.72 0.89 0.74	NA 0 NA 0 5 0 5 0 5 0 7 7 NA 26 0 0 0 65 0 19 10 NA NA
C Moderate or Early gen New gen Early gen New gen Early gen New gen	Early generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH New generation TH New generation TH All THVs 4 eration THVs 4 Stroke All THVs 4 eration THVs 4 eration THVs 4 eration THVs 4 MI THVs 10 eration THVs 10 eration THVs 10 MI All THVs 11 All THVs 10 eration THVs 10 eration THVs 10 aration THVs 4 All THVs 10 eration THVs 10 aration THVs 10 eration	vs vs MI vs vs vs vs vs vs vs vs	9 7 4 1113 1 4 1113 1 4 113 1 4 3 10 92 89 92 89 94 146 80 122 4 146 80 122 4 142 1 124 1 124 1 124 1 123 2 143 2 144 2 129 5 144 2 129 5 144 1 129 5 144 1 144 1	1 2 335 6 4 2 91 4 91 4 91 4 91 4 91 4 91 4 91 4 91 4 91 4 40 330 96 227 967 0 149 16 812 3 92 8555 33 1422 92 74 92 74 92 74 92 74 93 142 94 7 92 74 92 74 93 124 93 124	343 1291 74 1217 9 14542 4 2586 4 10398 Favors I 7 4 0 9 2 2 2 3	0dds Ratio	 2.70 0.94 0.94 0.84 1.16 1.03 1.16 1.04 1.51 0.95 1.53 NA 1.51 0.95 1.34 0.94 0.72 0.61 1.12 0.81 0.85 0.85 	[0.12, 59.85] [0.29, 3.08] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27] [0.27, 2.99] [0.27, 0.97]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.12 0.05 0.72 0.89 0.74 0.01	NA 0 NA 0 5 5 0 Heterogeneity I ² (%) 7 NA 26 0 0 0 0 0 65 0 19 0 19 0 NA NA
C Moderate or Early gen New gen Early gen New gen New gen New gen New gen New gen New gen New gen	Lany generation TH New generation TH Early generation TH New generation TH 30-day mortali All TH Early generation TH New generation TH New generation TH New generation TH All THVs 4 Garation THVs 4 Stroke All THVs 4 Garation THVs 10 New PPI All THVs 10 New PPI All THVs 10 Garation THVs 10 New PPI All THVs 10 Garation THVs 10 Ga	vs Ws Mi vs Vs Vs Vs Vs Vs Vs Vs Ns Ns Ns Ns Ns Ns Ns N	y y y y y y 0 7 q 1 1 4 1 1 4 3 10 g 92 89 g 94 57 g 954 6 80 otal ev 1 122 4 4 122 4 1 1249 5 3 374 22 1 183 2 1 524 96 4 328 91 1 773 73 2 229 5 1 3316 111 1	1 2 355 6 4 2 91 4 291 4 4 2 91 4 4 2 91 4 4 2 91 4 4 2 63 32 TAV ent 10 330 0 68 68 227 967 149 16 812 32 48 8266 7 7 1002 2 74 5 929 13 1219 52 284	343 1291 74 1217 9 14542 4 2586 4 10388 4 2586 4 10388 7 8 7 7	0dds Ratio	 2.70 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.94 0.95 1.54 0.92 0.61 1.12 0.81 0.85 1.03 	[0.12, 59.85] [0.29, 3.06] [0.7, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 955% Cl [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.32, 1.15] [1.00, 1.27] [0.25, 2.57] [0.77, 9.51] [0.21, 2.99] [0.76, 0.97] [0.76, 0.97] [0.76, 0.97] [0.76, 0.97]	0.53 0.92 0.98 0.98 0.44 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.12 0.12 0.25 0.72 0.89 0.74 0.84	NA 0 NA 0 5 0 Heterogeneity I ² (%) 7 NA 26 0 0 0 0 0 0 0 0 19 0 NA NA NA 0 13
C Moderate or Early gen New gen New gen New gen Early gen New gen Starly gen New gen Starly gen New gen New gen	Lany generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH New generation TH New generation TH New generation TH New generation TH New generation THVs 4 Stroke All THVs 14 eration THVs 19 eration THVs 19 eration THVs 19 eration THVs 19 eration THVs 19 eration THVs 19 eration THVs 10 All THVs 10 eration THVs 10	vss vss MI vss Vss	9 7 4 11:1 1 4 3 10 92 89 94 57 94 80 00 7 144 80 0049 3 374 22 11 11 11 44 11 11 11 122 122 4 11 11 11 123 11 133 11 133 11 1332 11 1332 11 1332 11 1332 11 1332 11 1332 11 1332 11 1333 11 134 1222 1 1316 11 1316 11 1316 151 1316 151	1 2 335 6 4 2 91 4 21 4 21 4 234 57 663 322 TAV TAV TAV TAV 100 686 227 27 967 06 642 31 142 32 8655 33 142 34 8 35 142 36 7 100 2 74 5 35 2284 31 12/19 32 2844 32 2844	343 1291 74 1217 4 2586 4 2586 4 2586 4 2586 4 2586 4 2586 7 7 7 7 7	Odds Ratio	- 2.70 0.94 0.84 0.84 0.84 0.84 1.16 1.03 1.51 0.95 1.34 0.95 1.34 0.94 0.72 0.61 1.12 0.81 0.85 1.08 0.85 1.08 0.83	[0.12, 59.85] [0.29, 3.06] [0.79, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.32, 1.15] [1.00, 1.27] [0.25, 2.57] [0.77, 9.51] [0.21, 2.99] [0.76, 0.87] [0.76, 0.85]	0.53 0.92 0.98 0.98 0.94 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.12 0.05 0.72 0.89 0.74 0.01 0.84 0.008	NA 0 NA 0 5 0 5 0 7 NA 26 0 0 0 0 65 0 0 19 0 0 85 0 19 0 0 85 0 19 0 0 85 0 19 0 0 85 0 19 0 0 19 0 0 0 0 19 0 0 0 19 0 10 10 10 10 10 10 10 10 10 10 10 10 1
C Moderate or Early gen New gen Early gen New gen New gen New gen 1-ye	Early generation TH New generation TH Early generation TH 30-day mortain All TH Save generation TH Save generation TH New generation TH New generation TH eration THVs 4 eration THVs 4 All THVs 4 eration THVs 4 All THVs 4 eration THVs 6 and THVs 6 aration THVs 6 aration THVs 6 aration THVs 6 aration THVs 6 aration THVs 6 All THVs 6 aration THVs 7 aration THVs 4 aration THVs 4 aration THVs 4 aration THVs 4 aration THVs 4 aration THVs 7 aration THVs 7 aration THVs 3 aration THVs 7 aration THVs 3	vs vs MI vs MI vs vs	9 7 1 4 1 4 1 4 3 10 92 89 92 89 14 57 44 57 122 4 122 4 122 4 122 4 122 4 133 21 173 7 174 2 122 4 14 2 173 7 1744 2 122 4 144 2 122 4 144 5 151 45 616 56	1 2 335 6 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 5 2 7 4 5 9 13 142 5 9 13 12 14 5 9 12 2 4 5 9 13 12 12 2 13 12 14 2 15 2 16 3 17 12 18	343 1291 74 1217 14542 4 2596 4 10398 7 4 5 5 7 7 7 7	Odds Ratio	- 2.70 . 0.94 0.84 0.84 0.84 1.16 1.03 1.16 1.03 1.51 0.95 1.34 0.94 0.72 0.61 1.12 0.81 0.84 0.80 0.85 1.03 0.83 0.83	[0.12, 59.85] [0.29, 3.06] [0.79, 9.51] [0.25, 3.81] [0.95, 1.41] [0.96, 1.61] [0.92, 1.47] 95% CI [0.99, 2.35] NA [0.98, 2.33] [0.77, 1.18] [0.44, 4.09] [0.76, 1.17] [0.47, 1.10] [0.32, 1.15] [1.00, 1.27] [0.25, 2.57] [0.25, 2.57] [0.76, 1.41] [0.75, 0.97] [0.76, 1.41] [0.72, 0.95]	0.53 0.92 0.98 0.98 0.14 0.88 0.21 P 0.05 NA 0.06 0.64 0.61 0.58 0.72 0.89 0.74 0.01 0.84 0.008	NA 0 NA 0 5 0 Heterogeneity 1 ² (%) 7 NA 26 0 0 0 65 0 0 0 65 0 19 0 NA NA NA 0 13 0



conversion to SAVR (OR = 1.81, 95% CI 1.33-2.46, p = 0.0001) and device failure (OR = 1.42, 95% CI 1.03-1.96, p = 0.03), with a consistent result in patients receiving early-generation devices. A new PPI (OR = 1.30, 95% CI 1.17–1.44, p < 0.00001) was more common in patients with BAV than patients with TAV, as well as in new-generation devices receivers. Patients with BAV were at a higher risk of AKI (OR = 1.23, 95% CI 1.04-1.45, p =0.01) and stroke (OR = 1.28, 95% CI 1.01–1.61, p = 0.04) than patients with TAV, but no significant differences were observed when stratified into early and new-generation devices. At 30-day post TAVR, the new PPI (OR = 1.17, 95% CI 1.04–1.31, p =0.01) tended to be more common in BAV than in TAV, with the results in accordance with new-generation devices (OR = 1.17, 95% CI 1.04–1.32, p = 0.009). In addition, no differences were observed in 30-day mortality (OR = 1.16, 95% CI 0.95–1.41, *p* = 0.14). At a 1-year follow-up, patients with BAV demonstrated a lower mortality rate than patients with TAV (OR = 0.85, 95% CI 0.75–0.97, p = 0.01), with consistent results presented in patients using early-generation devices (OR = 0.83, 95% CI 0.72-0.95, p = 0.008).

Rates of complications and adverse outcomes were generally higher in population using early-generation devices than using new-generation devices, including the conversion to SAVR, the need for a second valve, a moderate or severe PVL, major vascular complications, the device failure, AKI, life-threatening or major bleeding, MI, a new PPI, stroke, and mortality in hospital; stroke, major vascular complications, mortality at a 30day follow-up; stroke, new PPI, mortality at a 1-year followup in BAV and TAV subjects, in addition with an in-hospital coronary obstruction, a new 30-day PPI, a 30-day MI in the BAV population (Figures 4A,B, Supplementary Tables S7, S8). A significant heterogeneity existed in the analysis of in-hospital device failure in all THVs ($I^2 = 58\%$, p = 0.003) and a 1-year new PPI in all THVs ($I^2 = 65\%$, p = 0.006) between patients with BAV and TAV. The risk of bias of the included studies is summarized in Supplementary Table S2, and publication bias is presented as a funnel plot in Supplementary Figure S3.

Comparisons Between BE and SE Valves in Patients With BAV

The characteristics of the included studies and baseline of patients in the subanalysis of the efficacy of BE vs. SE in patients with BAV are presented in Supplementary Table S3. The inhospital and follow-up results are presented in Figures 5A,B, respectively. Patients with BAV using BE THVs were at a lower risk of the need of a second valve (OR = 0.35, 95% CI 0.17-0.70, p = 0.003) than SE THVs, and the consistent trend was also observed in early-generation devices (OR = 0.18, 95% CI 0.05–0.70, p = 0.01). A new PPI tended to be less common only in the early generation of BE THVs than SE THVs (OR =0.53, 95% CI 0.29–0.98, p = 0.04), while a moderate or severe PVL was less common in only new-generation BE THVs than SE THVs (OR = 0.07, 95% CI 0.02–0.31, *p* = 0.0005). However, patients with BAV were at a higher risk of annular rupture in BE THVs than in SE THVs (OR = 4.84, 95% CI 1.39-16.85, p = 0.01), similarly in early-generation devices (OR = 8.11, 95% CI 1.34–49.18, p = 0.02). In addition, the 30-day (OR = 0.96, 95% CI 0.53–1.76, p = 0.9) and 1-year mortality (OR = 1.11, 95% CI 0.73–1.71, p = 0.62) between BE and SE THVs were not different. All original records of the meta-analysis are presented in **Supplementary Figure S2**. The pooled results of meta-analyses of in-hospital moderate or severe PVL in all THVs ($I^2 = 78\%$, p = 0.001), vascular complications in all THVs and first-generation THVs ($I^2 = 54\%$, p = 0.11; $I^2 = 85\%$, p = 0.009), device failure in all THVs and new-generation THVs ($I^2 = 51\%$, p = 0.13; $I^2 = 74\%$, p = 0.05), and a life-threatening or major bleeding one in new-generation THVs ($I^2 = 55\%$, p = 0.13) between BE and SE THVs in patients with BAV had a significant heterogeneity. The risk of bias of the included studies is summarized in **Supplementary Table S4**, and publication bias is presented as a funnel plot in **Supplementary Figure S4**.

THV Geometry After TAVR in Patients With BAV vs. TAV

The characteristics of studies and baseline of patients for the subanalysis of THV geometry are summarized in Supplementary Table S5, and the results of meta-analysis are presented in Figure 6. The mean BE THV expansion after TAVR at the annulus (MD -2.15, 95% CI -4.03 to -0.28, p =0.02) and outflow level (MD $-2.14,\ 95\%$ CI -4.21 to -0.08,p = 0.04) was significantly smaller in patients with BAV than in patients with TAV. According to one original article (41), the mean SE THV expansion of the BAV population on CT at the inflow (MD -13.00, 95% CI -25.84 to -0.16, p = 0.05), annulus (MD -15.60, 95% CI -29.37 to -1.83, p = 0.03), and outflow level (MD -16.60, 95% CI -27.89 to -5.31, p = 0.004) was smaller than that of the TAV population. Moreover, BE THV eccentricity index was larger in patients with BAV than in patients with TAV at the inflow (MD 1.93, 95% CI 1.06-2.79, p < 0.0001), annulus (MD 2.35, 95% CI 1.14-3.55, p = 0.0001), and outflow level (MD 2.08, 95% CI 0.81–3.36, p = 0.01). No significant differences were witnessed in SE THV. In addition, BE THV implantation depth was not different between the two groups. No significant heterogeneity was observed in the pooled analysis. The risk of bias of the included studies is summarized in Supplementary Table S6, and the publication bias is presented as a funnel plot in Supplementary Figure S5.

DISCUSSION

This meta-analysis represents the up-to-date pooling of most extensive evidence of TAVR in patients with BAV. The major findings are: (1) type 1 BAV accounted for the largest proportion of BAV subtypes in multiregional studies and studies in Europe and the USA, while type 0 was more prevalent than type 1 in China. type 2 BAV was the least common finding in all regions. In terms of type 1 morphology, L-R coronary cusp fusion was the most common pattern while L-N coronary cusp fusion was the least common pattern. (2) Patients with BAV were at a higher risk of the conversion to SAVR, the need of a second valve, a moderate or severe PVL, the device failure, AKI, a new PPI, and stroke during hospitalization than TAV. A new PPI remained more



Δ	BE	ſHVs	SE T	HVs	Odds Rati	0 0.11		_	
	event	total	event	total	1	Odds	ratio 95% Cl	Р	Heterogeneity I ² (%)
Conversion to SAVR All THVs	9	304	7	287	_	1.1	[0.46, 3.14	4] 0.49	0
Early generation THVs	6	135	4	203	+-	• 2.2	20 [0.61, 7.93	3] 0.23	0
New generation THVs Need of a second value	0	91	1	11		0.0	04 [0.00, 1.00	0.05	NA
All THVs	14	546	28	398	- -	0.3	32 [0.16, 0.6	3] 0.001	2
Early generation THVs	2	143	18	216		0.1	18 [0.05, 0.7 32 [0.24, 1.6	0] 0.01 0] 0.32	0
Moderate or Severe PVL	11	333	'	122		0.0	[0.24, 1.0	0.02	U
All THVs	26	572	33	322		0.4	6 [0.10, 2.1	0.32	78
Early generation THVs New generation THVs	2	396	14	143		0.0	07 [0.02, 0.3	31] 0.0005	NA
Vascular complication									
All THVs	39 13	468	38 26	325 203		0.8	8 [0.38, 2.0	0.77 0.77 0.85	54 85
New generation THVs	26	333	12	122		0.9	1 [0.44, 1.8	[37] 0.8	22
Device failure	54	469	50	205		0.6	5 [0 35 1 2	0.19	51
All THVs Early generation THVs	54 18	135	53 34	203	_	0.7	71 [0.38, 1.3	33] 0.29	0
New generation THVs	36	333	19	122		- 0.4	[0.08, 2.2	0.32	74
Annulus rupture	14	550	0	404	_	5.9	0 [1.48, 23.	.59] 0.01	0
Early generation THVs	6	148	0	222	-	— 8.1	1 [1.34, 49.	.18] 0.02	0
New generation THVs	5	333	0	122		2.0	5 [0.26, 16.	.38] 0.5	20
All THVs	33	468	32	325	_ • -	0.8	31 [0.48, 1.3	38] 0.44	0
Early generation THVs	14	135	23	203	-+-	0.9	95 [0.47, 1.9	0.88	0
New generation THVs New PPI	19	333	9	122		- 0.8	5 [0.13, 2.4	14] 0.43	55
All THVs	67	470	61	330	-+	3.0	31 [0.55, 1.	21] 0.31	0
Early generation THVs	16	137	44	208		0.5	53 [0.29, 0.	.98] 0.04	0
Coronary obstruction	51	555	17	122		1.0	[0.59, 1.	.99] 0.78	0
All THVs	6	355	5	334		— 1. 1	32 [0.39, 4	.46] 0.65	5 2
New generation THVs	0	91	0	203		I. N	57 [0.47, 5 A NA	.22] 0.46 NA	NA NA
In-hospital all-cause mortality	4	206	7	274		0	62 [0 17 2	221 0.44	
All THVs Early generation THVs	3	135	5	203		. 0.	98 [0.22, 4.1	29] 0.98	3 7
New generation THVs	1	1	1	1		/	1	1	1
В			Favors	BE THVs	0.1 0.25 0.5 1 2	4 10 Favors	SE THVs		
BE	THVs	SE T	HVs	C	Odds Ratio	Odds ratio	95% CI	Р	Heterogeneity I ² (%)
30-day mortality	t total	event	total						
All THVs 27	601	22	437		_	0.94	[0.52, 1.70]	0.85	0
Early generation THVs 11	198	15	255			0.91	[0.41, 1.99]	0.81	0
	222	4	100			1.20	[0.42, 2.00]	0.65	20
New generation THVs 14	333	4	122			1.29	[0.42, 3.99]	0.65	29
Stroke									
All THVs 12	599	10	432		-	0.92	[0.39, 2.15]	0.84	0
Early generation THVs 5	196	6	250		_	1.03	[0.31, 3.42]	0.96	0
New generation THVs 4	333	3	122			0.36	[0 08 1 64]	0 19	0
New PPI	000	0				0.00	[0100, 1101]	0110	Ū.
New PPI									
All THVs 22	131	27	107			0.60	[0.32, 1.13]	0.11	19
Early generation THVs 8	61	13	47		•	0.39	[0.15, 1.05]	0.06	NA
New generation THVs /	1	1	1			1	/	/	1
- 1-vear mortality									
	440	40	271			1 23	[0 81 1 86]	0.34	0
All Trivs 61	449	49	5/1			1.20		0.04	0
Early generation THVs 38	207	39	260		+•-	1.30	[0.80, 2.13]	0.29	U
New generation THVs 23	242	10	111		+	1.06	[0.49, 2.31]	0.88	0
				0.1 0.2	1 1 1 1 5 0.5 1 2 4 1	I 0			
		Favo	rs BE TI	lVs		Favors SE THVs	5		

FIGURE 5 | A comparison between balloon-expandable (BE) and self-expanding (SE) valves in patients with BAV at in-hospital time (A), and in a 30-day and a 1-year (B) follow-up. SAVR, surgical aortic valve replacement; PVL, paravalvular leakage; PPI, permanent pacemaker implantation.



FIGURE 6 | Transcatheter heart valve (THV) expansion (A), implantation depth (B), and eccentricity index (C) on CT at different levels after TAVI in patients with BAV vs. TAV. CT image analysis of THVs, dividing into balloon-expandable and SE valves, in terms of the expansion at the inflow, annulus, and outflow level (A); implantation depth below left, right and none coronary sinus (B), and the eccentricity index at the inflow, annulus, and outflow level (C). BE, balloon-expandable; SE, self-expanding; BE-L, balloon-expandable valve—left coronary sinus; BE-R, balloon-expandable valve—right coronary sinus; BE-N, balloon-expandable valve—non-coronary sinus.

common among patients with BAV than among patients with TAV at a 30-day follow-up. Both in-hospital and 30-day mortality between the two groups were not different, but 1-year mortality was lower in patients with BAV than in patients with TAV. (3) BE THVs were at a higher risk of annular rupture but the lower need for a second valve than SE THVs for patients with BAV. In addition, the incidence of a new PPI was higher in BE THVs than in SE THVs only in case of early-generation valves. (4) In terms of BE THV, it was less expanded at the annular and outflow level in BAV than in TAV, while more elliptical in BAV than in TAV at the inflow, annular, and outflow level. The implantation depth of BE THV was similar in the two morphologies. (5) Adverse events were less in new-generation devices than in early-generation devices in general, for patients with both BAV and TAV.

Bicuspid aortic valve is the most common isolated cause of AS among patients aged 50-70 years (56). Now that a series of randomized controlled trials demonstrate noninferior or superior outcomes of TAVR vs. SAVR irrespective of risk profiles, TAVR is expected to expand its utilization and more and more younger patients with bicuspid AS would become the candidates for TAVR. In addition, the latest guideline for valvular heart disease has recommended TAVR as an alternative to SAVR in patients with symptomatic BAV having severe AS despite no solid evidence (1). However, patients with BAV remain challenging for TAVR given its complex anatomical features such as heavy calcification with or without raphe and a concomitant dilatation of the ascending aorta, thus are still at a high risk of device malposition, underexpansion, and other procedural complications even using new-generation devices (19, 34). Thus, in this meta-analysis, we updated current evidence in TAVR for BAV while exploring regional differences in BAV subtypes, device performance, and THV geometry.

According to the number of cusps and presence of raphes, Sievers et al. have classified BAV into different phenotypes (12). The proportion of type 0 BAV seems to be higher in China than in western countries, which was confirmed by our pooled analysis. Although a previous study on Asian patients has shown a prevalence of type 1 BAV, the differences in imaging modality (i.e., MSCT vs. echocardiography), targeting patient population (i.e., AS being evaluated for TAVR vs. BAV being diagnosed with echocardiography), and the enrollment without Chinese centers might explain the divergence from our result (57-59). Type 0 morphology can pose additional challenges to TAVR. Difficulties exist in determining the virtual annulus with only two hinge points (60). A lower rate of VARC-2 defined device success (72% vs. 86.7%; p = 0.07) and a higher rate of mean trans-prosthetic gradient \geq 20 mmHg (24% vs. 6%, p = 0.007) was reported in type 0 BAV than in type 1 (57). Such regional disparities might be a hint for underlying ethnic issues in the development of BAV, while also suggesting the need to consider BAV subtypes when interpreting TAVR results from different countries.

The in-hospital and 30-day mortality between patients with BAV and TAV receiving TAVR were not different, but patients with TAV (n = 12,197) seemed to have 1-year mortality higher than patients with BAV (n = 8,316), as well as in patients with TAV (n = 8,694) and BAV (n = 7,616) who received new-generation devices. The significance of survival risk differences

in all THV receivers was presented when verified by fixed- (as presented in our results) and random-effect models (OR = 0.86, 95% CI = 0.76–0.98, p = 0.02; $I^2 = 0\%$, p = 0.80), which indicated the validity of the result. Most patients included in this analysis were from a latest propensity score matched research (including 6,995 BAV and 6,995 TAV; weighted 74.5% in overall meta-analysis), which analyzed consecutive patients undergoing TAVR with third-generation SAPIEN 3 and fourth-generation SAPIEN 3 Ultra valve in the STS/TVT Registry from June 2015 to October 2020, with a relatively low STS-PROM (4.0 \pm 3.7 in BAV and 4.0 \pm 3.5 in TAV) (54). Although the result in the original research did not show significant differences in 1-year survival (HR = 0.90, 95% CI = 0.78-1.04), the 1-year mortality of BAV (8.6%, 357/6,995) was numerically lower than that of TAV (9.8%, 417/6,995). Consequently, patients with BAV showed better 1-year survival than patients with TAV in the pooled results, indicating the potential survival benefit of the latest BE THVs applied in relatively low-risk patients with TAVR.

Although the rates of procedural complications decreased significantly with the improvement of devices, patients with BAV were still at a higher risk of the conversion to SAVR, the need of a second valve, a moderate or severe PVL, the device failure, AKI, stroke, and a new PPI. Anatomical features (i.e., longer leaflets, more severe valve calcification, and unequalsized leaflets) and practical challenges (i.e., difficulty in valve sizing and determining the virtual annulus with only two hinge points) in BAV As subjects might bring the THV eccentricity and an incomplete prosthesis expansion during the procedure, as shown in our results, resulting in THV malposition or even aortic root injury (61). Therefore, there were higher risks of the implantation of two valves, PVL and urgent conversion to SAVR, consequently leading to a higher device failure. More AKIs in patients with BAV might be related to the volume of contrast used and the longer procedural time (7). A higher risk of stroke in patients with BAV was demonstrated during hospitalization but not at a 30-day and 1-year follow-up. This might be related to a heavier calcium burden in BAV and more usage of balloon predilation during the procedure. Therefore, the cautious usage of balloon pre-dilation and limitation of the dilation times might be considered during the TAVR procedure in BAV subjects to achieve lower risk of stroke. In addition, a new PPI in hospital and in a 30-day follow-up were more common in patients with BAV than in patients with TAV, particularly in subjects receiving new-generation THVs, which might be caused by the compression on the conduction system beneath the membranes part of interventricular septum by the inflow stent of THVs, leading to conduction disturbances. Newly developed retrievable new-generation devices seemed to be invalid in lowering the risk of a new PPI in patients with BAV even with a potential advantage of implanting in the target landing zone. However, clinical adverse events were comprehensively reduced when devices were iterated into new generations, in both BAV and TAV population, indicating the importance of an improvement in the device design.

The need of a second valve were higher in self-expanding valves than in BE valves. The anchoring of BE THVs is achieved by actively pushing away native structures through balloon

dilatation, which is easier to be implanted in the target landing zone. However, the SE THVs are more likely to be malpositioned because of the passive adaptation of native valve structures. New generations of SE valves have largely overcome malposition by the ability of recapturing and repositioning. Additionally, BE THVs demonstrated a higher risk of annular rupture than SE THVs, which indicated the preference of SE THVs in patients with BAV with risk factors for annular rupture such as asymmetric calcification. Moreover, less aggressive inflating of balloons should be taken into consideration in these patients if BE THV is used. A new PPI was more common in the early generation of SE THVs than BE THVs in BAV but not in new generations of devices, which was related to an inherent difference of the designation of SE and BE THVs. However, the risk of a moderate and severe PVL still seemed to be higher in SE than in BE THVs in BAV even with new-generation devices in one study (36). Valve sizing (i.e., discretion of supra-annular sizing vs. annular sizing) for patients with BAV undergoing TAVR is important, which is frequently encountered in clinical practice. Further analysis in this aspect was not conducted because of limited original articles. There was one published meta-analysis elucidating the outcomes of supra-annular sizing for TAVR in the BAV population (62).

Our result updated new findings of higher risks of AKI and a 30-day new PPI in patients with BAV than in patients with TAV undergoing TAVR when compared with previous metaanalyses. Moreover, 1-year mortality was firstly demonstrated to be significantly higher in TAV than in BAV TAVR receivers. We also identified a higher risk of in-hospital new PPI in patients with early-generation SE THVs than BE THVs in patients with BAV. In addition, the pooled results for the proportion of BAV subtypes being treated by TAVR in different regions and the THV geometry on CT in patients with BAV vs. TAV were displayed, which were not covered previously. Although the use of TAVR in BAV is promising, to further expand indications for TAVR in bicuspid AS, large randomized trials comparing TAVR and SAVR in this population are needed, especially for low-risk patients. So far, the only RCT enrolling low-risk patients with BAV treated by TAVR is "Notion-2 trial" (NCT02825134). A good practice of patient selection, preprocedural planning, intraprocedural techniques, and the prevention of complications are still prerequisites to achieve good outcomes. Advances in device design and treatment strategies should further improve the results of TAVR in patients with BAV.

LIMITATIONS

There were some limitations in this article. Firstly, the majority of the included studies were not randomized trials in design, neither had core laboratory adjudications. The choice of prosthesis was not randomized but up to the operator's discretion. A significant heterogeneity existed in some analyses. Secondly, although consecutive patients were enrolled, a plenty of articles did not use propensity score matching to eliminate an inherent baseline difference. Patients with BAV with different anatomical phenotypes and a varying degree of calcification might lead

to disparate outcomes but was not further delineated in many studies. Thirdly, the absence of long-term survival and hemodynamic results of patients with BAV makes it difficult to explore some questions of interest, e.g., THV durability. Fourthly, patients with BAV in our included population were not representable enough for all symptomatic patients with BAV because those who were not suitable for TAVR had already been excluded. Moreover, some studies only enrolled patients with BAV using BE or SE THVs alone were not included. Both resulted in a selection bias in our report. Fifthly, although we have been cautious in overlapping population, it may still present in our result when single-center data were reported both alone and among multicenter studies. Sixthly, we divided the Lotus valve into self-expandable THVs when analyzing although they are mechanically expandable valves academically. However, the sample size is small (about 11 patients). Seventhly, in 37 of 49 funnel plots of our meta-analyses, the number of original studies was < 10, leading to insufficient power of test of the funnel plots. Finally, we only screened the articles in English.

CONCLUSION

Despite higher risks of conversion to SAVR, the need of a second valve, moderate or severe PVL, device failure, AKI, stroke and new PPI, TAVR seems to be a viable option for selected patients with bicuspid severe AS, which had a potential benefit of 1-year survival, especially among lower surgical risk population using new-generation devices. Larger randomized studies were needed to guide candidate selection and verified the durable performance of THVs in the BAV population.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ, T-YX, Y-ML, and MC participated in the design of the study. YZ, T-YX, and Y-ML were responsible for the coordination and acquisition of the data. YZ and T-YX performed the statistical analysis. All authors contributed to the preparation, critical review, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm. 2022.794850/full#supplementary-material

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Conflict of Interest: MC and YF are consultants/proctors of Venus MedTech, MicroPort, and Peijia Medical.

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