Meta-Analysis of Transcatheter Aortic Valve Implantation in Patients With Stenotic Bicuspid Versus Tricuspid Aortic Valve

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Most of the trials investigating the role of transcatheter aortic valve implantation (TAVI) across various strata of risk categories have excluded patients with bicuspid aortic stenosis (BAS) due to its anatomical complexities. The aim of this study was to perform a meta-analysis with meta-regression of studies comparing clinical, procedural, and after-procedural echocardiographic outcomes in BAS versus tricuspid aortic stenosis (TAS) patients who underwent TAVI. We searched the PubMed and Cochrane databases for relevant articles from the inception of the database to October 2019. Continuous and categorical variables were pooled using inverse variance and Mantel-Haenszel method, respectively, using the random-effect model. To rate the certainty of evidence for each outcome, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. Nineteen articles were included in the final analysis. There was no difference in the risk of 30-day mortality, 1-year mortality, 30-day cardiovascular mortality, major and/or life-threatening bleeding, major vascular complications, acute kidney injury, permanent pacemaker implantation, device success, annular rupture, after-procedural aortic valve area, and mean pressure gradient between the 2 groups. BAS patients who underwent TAVI had a higher risk of 30-day stroke, conversion to surgery, need for second valve implantation, and moderate to severe paravalvular leak. In conclusion, the present meta-analysis supports the feasibility of TAVI in surgically ineligible patients with BAS. However, the incidence of certain procedural complications such as stroke, conversion to surgery, second valve implantation, and paravalvular leak is higher among BAS patients compared with TAS patients, which must be discussed with the patient during the decision-making process. **(Am J Cardiol 2021;145:102−110)**

Transcatheter aortic valve implantation (TAVI) is currently approved for the treatment of tricuspid aortic stenosis (TAS) in patients with high, intermediate, and even low risk for surgery.[1] Most trials investigating the role of TAVI across various strata of risk categories have excluded patients with bicuspid aortic stenosis (BAS) due to its anatomical complexities. There is approximately 20% prevalence of BAS in patients > 80 years of age.[2] Elderly patients with BAS represent a unique therapeutic challenge in high risk and intermediate risk strata where surgery is not feasible. There has been significant growth in the utilization of TAVI for the treatment of aortic stenosis along with the increasing off-label use of TAVI in BAS.[3] Currently, no randomized clinical trials are available that

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investigate TAVI versus surgical aortic valve replacement (SAVR) in bicuspid anatomies (NOTION-2 Trial: SAVR vs TAVI is ongoing and has included patients with bicuspid aortic stenosis, NCT02825134). With regard to the unavailability of a randomized trial evaluating TAVI versus SAVR in BAS patients, and specific challenges imposed by the complex anatomy of the bicuspid aortic valve, it is imperative to compare the outcomes of TAVI in BAS versus TAS. Hence, we performed a meta-analysis of observational studies comparing TAVI in patients with BAS versus TAS. We compared procedural, clinical, and after-procedural echocardiography outcomes in TAS versus BAS patients who underwent TAVI.

Methods

We performed a systematic search of two databases, PubMed and/or MEDLINE, and the Cochrane database from the inception of the respective database to October 2019. The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and American Heart Association guidelines. Mendeley reference manager was used to handle searched citations. The authors have elaborated the search terms used and the search strategy applied in each database in the supplementary file (eMethod 1). The authors did not apply any restrictions based on the language in which the manuscript was published, the number of patients studied, a period of follow-up, type of device used for TAVI, or risk groups. The studies which examined TAVI in BAS only, and those without a comparator TAS group in the same study were excluded. Since individual studies included in the analysis had prior ethical clearance, no separate ethical clearance was required for this meta-analysis. The search strategy is detailed in eMethod 2.

The authors used the Mantel-Haenszel method with a random-effects model to calculate risk ratio (RR) with a 95% confidence interval (CI) for categorical variables, and inverse variance method with a DerSimonian and Laird estimator of tau to calculate the mean difference (MD) with a 95% CI for continuous variables. In the Mantel-Haenszel random-effects model, the amount of between-study variation is estimated by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result. With studies reporting median and range, the method described by Hozo et al. was used to calculate the mean and standard deviation.[4] Higgins I^2 statistics and chi-square tests were used to identify heterogeneity. $I^2 > 50\%$ or chi-square test p-value <0.05 was considered heterogeneous. Funnel plots were used to assess publication bias visually. All statistical analyses were performed using RevMan Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA 16 (StataCorp, LLC). We performed a sensitivity analysis of the primary outcomes using the Paule-Mandel estimator for tau^2 with Hartung-Knapp adjustment for the random-effects model to look for the robustness of our primary outcome. The sensitivity analysis was carried out using R version 3.6.2 statistical software.

Random effect meta-regression was used to explain heterogeneity observed with the pooled estimate of our primary end point.The selection of covariates and/or potential effect modifiers for meta-regression were based on a combination of observed differences in baseline characteristics and prior literature review. We used the Graphic Display of Heterogeneity (GOSH) plots to examine heterogeneity in our data. We then used supervised machine learning algorithms (k-means, DBSCAN, and GMM algorithm) to identify sub-clusters in our data and identify the source of heterogeneity.[5] The gosh.diagnostics function in R was used for the same. We used R version 3.6.2 statistical software for meta-regression analysis and supervised machine learning algorithms. To rate the certainty of evidence for each outcome, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach.

Results

The 2-database search after checking for duplicates identified a total of 62 studies. We included 19 studies in the final analysis, with 4,040 patients in the BAS and 8,084 patients in the TAS groups. [6–24] All included studies had patients with a mean age > 70 years, and the majority were males. Most of the included studies had mean Society of Thoracic Surgery (STS) or logistic EuroSCORE in the intermediate or high-risk range. Of the 19 included studies, 4 were propensity-matched studies and formed more than 50% of the patients in both cohorts. The baseline characteristics of the included studies are outlined in Table 1. The PRISMA flow chart for the inclusion of studies is outlined in Figure 1. Individual forest plots are provided in the supplementary file (Supplementary Figure S1-15).

Most of the included studies had a moderate risk of overall bias because of the bias due to confounding. Four propensity-score-matched studies had a low risk of overall bias. There was no statistically significant difference in the risk of 30-day or 1-year all-cause mortality among BAS versus TAS patients who underwent TAVI [RR: 1.52, CI: 0.80 to 2.89, p-value = 0.20, I^2=79%, chi-square p-value <0.05], [RR: 1.00, CI: 0.79 to 1.27, p-value = 0.99, I^2=24%, chi-square p-value = 0.24], respectively (Figure 2). 30-day mortality was associated with considerable heterogeneity. Thirty-day and 1-year mortality end points were not associated with any publication bias (Supplementary Figure S16, PANEL A and B). Sensitivity analysis of the primary outcomes using Paule-Mandel estimator for tau^2 with Hartung-Knapp adjustment for random-effects model reported similar pooled estimate [RR: 1.65, CI: 0.92 to 2.97, p-value = 0.08, I^2=77.5%, chi-square p-value <0.05].

There was no statistically significant difference in the risk of cardiovascular mortality at 30-day follow-up between the 2 groups who underwent TAVI [RR: 1.69, CI: 0.81 to 3.53, p-value = 0.16, I^2=0%, chi-square p-value = 0.75] (Figure 2). The funnel plot did not indicate any publication bias (Supplementary Figure S16, PANEL C).

Patients with BAS patient who underwent TAVI were associated with a higher incidence of 30-day stroke compared with patients with TAS [RR: 1.47, CI: 1.10 to 1.97, p-value < 0.05, I^2=0%, chi-square p-value = 1.00] (Figure 2). There was no heterogeneity or publication bias associated with the pooled estimate (Supplementary Figure S16, PANEL D).

Table 1
Baseline characteristics of included studies

Author, Years	Tchetche et al 2019		Aalaei-Andabili et al 2018		Arai et al 2017		Blackman et al 2019	
Group	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Number of patients	101	88	32	96	10	143	31	965
Age (years)	78.2±10.1	83.1±5.7	68.59 ± 11.07	73.96 ± 10.76	81.3 ± 5.1	82.6 ±6.2	76.4 ± 7.9	80.9 ± 6.4
Male	66(65%)	41(46%)	20 (62.50%)	54 (56.20%)	61 (43%)	7 (7%)	20 (64.5%)	470 (48.7%)
Body mass index (kg/m^2)	28.7±34.3	28.1±18.4	NA	NA	24.6 ± 5.2	26.5 ±5.4	28.1 ± 4.91	26.6 ± 4.82
STS score	11.3±8.5	7.6±4.4	6.01 ± 3.42	6.08 ± 3.76	NA	NA	6.0 ± 10.15	5.9 ± 6.74
Logistic EuroSCORE	NA	NA	NA	NA	19.0 ± 12.5	18.1 ± 11.0	6.1 ± 7.52	8.0 ± 8.38
DM	17(17%)	13(15%)	14(43.7%)	38(39.5%)	2 (20%)	37 (26%)	5 (16.1%)	217 (22.5%)
HTN	64(63%)	79(90%)	25(78.1%)	76(79.1%)	8 (80%)	100 (70%)	22 (71%)	760 (79.4%)
Dyslipidemia	37(37%)	50(57%)	NA	NA	3 (30%)	66 (46%)		
Chronic lung disease	26(26%)	23(26%)	13(40.6%)	37(38.5%)	0 (0%)	3 (3%)	3 (9.7%)	151 (15.7%)
CAD	NA	NA	NA	NA	NA	NA	8 (25.8%)	550 (57.1%)
MI	5(5%)	8(9%)	7(21.9%)	38(39.6%)	NA	NA		
Atrial fibrillation	24(24%)	27(31%)	NA	NA	NA	NA	8 (25.8%)	326 (34.2%)
Stroke/TIA	10(10%)	11(12%)	5(15.6%)	12(12.5%)	1 (10%)	1 (1%)	0(0%)	73(7.6%)
CKD ≥ 3	1(1%)	2(2%)	1(3.1%)	7(7.3%)	NA	NA		
Peripheral vascular disease	NA	NA	5(15.6%)	25(26%)	NA	NA		
NYHA Class III or IV	52(51%)	50(57%)	NA	NA	9 (90%)	142 (99%)	20 (66.7%)	623 (69.6%)
Previous PCI	32(32%)	8(9%)	NA	NA	1 (10%)	21 (15%)	4 (12.9%)	292 (30.4%)
Previous CABG	2(2%)	26(29%)	NA	NA	1 (10%)	9 (6%)	1 (3.2%)	122 (12.6%)

Author, Years	Zhou et al 2019		Mangieri et al 2018		Yoon et al 2017		Xiong et al 2018	
Group	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Number of patients	42	68	54	658	561	4546	67	49
Age (years)	76.41 ± 4.56	78.55 ± 4.76	80 ± 5.3	81.1 ± 3.3	77.2±8.2	77.2±8.8	74 (68-77)	75 (68-79)
Male	19 (45.2%)	41 (60.3%)	21 (38.9%)	31 (57.5%)	343(62.8%)	331(60.6%)	40 (59.7%)	28 (57.1%)
Body mass index (kg/m^2)			26.8±5.6	26.9±4.1			22.2 ± 3.9	21.6±3.3
STS score	7.42 ± 3.87	9.72 ± 6.28	4.7±2.7	4.69±2.75	4.6±4.6	4.3±3.0	6.5	8.3
Logistic EuroSCORE			17.7±10.7	17.2±7.42	16.1±12.0	16.9±13.9		
DM			13 (24.1%)	19 (35.1%)	128(23.4%)	127(23.3%)	14 (20.9%)	12 (24.5%)
HTN			48 (88.8%)	50 (90.5%)	382(70%)	385(70.5%)	30 (44.8%)	27 (55.1%)
Dyslipidemia			22 (40.7%)	20(37.1%)				
Chronic lung disease					98(17.9%)	81(15.0%)	36 (53.7%)	35 (71.4%)
CAD	21 (50%)	41 (60.3%)					20 (29.9%)	18 (36.7%)
MI			6 (11.1%)	7 (12.9%)			2 (3%)	1 (2%)
Atrial fibrillation			13 (24.1%)	13 (24.1%)			14 (20.9%)	6 (12.2%)
Stroke/TIA			5 (9.2%)	6(11.1%)	77(14.1%)	69(12.6%)		
CKD ≥ 3			14 (25.9%)	16 (29.6%)			8 (11.9%)	8 (16.3%)
Peripheral vascular disease			7 (12.9%)	6 (11.1%)	83(15.2%)	85(15.6%)	24 (35.8%)	13 (26.5%)
NYHA Class III or IV	31 (73.8%)	59 (86.8%)	46 (85.1%)	44(81.4%)	439(80.4%)	428(82.1%)	61 (91%)	41 (83.7%)
Previous PCI			11 (20.3%)	17 (31.4%)	121(22.2%)	128(23.4%)		
Previous CABG			6 (11.1%)	4 (7.41%)	62(11.4%)	67(12.3%)		

Author, Years	De Biase at el 2018		Kawamori et al 2018		Liao et al 2017		Song et al 2017	
Group	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Number of patients	83	166	41	239	87	70	44	53
Age (years)	81.4 ± 7.6	82.9 ± 5.7	80 (70.5 - 83)	83 (78 -87)	73.4 ± 6.4	74.3 ± 7	73.8 ± 5.2	76.5 ± 7.1
Male	69(57%)	66(108)	28 (68.3%)	142 (59.4%)	50 (57.5%)	45 (64.3%)	24 (54.5%)	30 (56.5%)
Body mass index (kg/m^2)	33.9 ± 54.3	33.8 ± 54.9			22.2 ± 3.7	22.1 ± 3.7	21.8 ± 3.6	23.6 ± 4.4
STS score	5.1 ± 3.3	5.1± 2.9			7.9 ± 4	8.6 ± 4.4	5 (3.8 - 8.2)	6.2 (3.9- 9.6)
Logistic EuroSCORE								
DM	19(16%)	15(26)	10 (24.3%)	78 (32.6%)	14 (16.1%)	13 (18.6%)	6 (13.6%)	9 (17%)
HTN	71(60%)	73(119)	35 (85.4%)	214 (89.5%)	43 (49.4%)	32 (45.7%)	17 (38.6%)	32 (60.4%)
Dyslipidemia	33(28%)	28(47)					13 (29.5%)	17 (32.1%)
Chronic lung disease			8 (19.5%)	57 (23.8%)	50 (57.5%)	45 (64.3%)	19 (43.2%)	20 (37.7%)
CAD	47(39%)	49(81)	19 (46.3%)	141 (59%)	32 (36.8%)	27 (38.6%)		
MI	2 (2%)	2 (2)					1 (2.3%)	4 (7.5%)
Atrial fibrillation	17(14%)	20(33)	9 (22%)	62 (25.9%)	19 (21.8%)	12 (17.1%)	4 (9.1%)	11 (20.8%)
Stroke/TIA	6(5%)	8(11)			13 (14.9%)	8 (11.4%)	6 (13.6%)	9 (17%)

(*continued*)

Table 1 (***Continued***)

Author, Years	De Biase at el 2018		Kawamori et al 2018		Liao et al 2017		Song et al 2017	
Group	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
CKD ≥ 3	1(1%)	2(3)			10 (16.1%)	13 (18.6%)	0	1 (1.9%)
Peripheral vascular disease			4 (9.8%)	50 (20.90%)	42 (48.3%)	29 (41.4%)	15 (34.1%)	17 (32.1%)
NYHA class III or IV	58 (69.88%)	53 (31.93%)	37 (90.2%)	220 (92.1%)	80 (92%)	61 (87.1%)	33 (75%)	43 (81.1%)
Previous PCI	36(30%)	38(66%)			7 (8%)	8 (11.4%)	1 (2.3%)	4 (7.5%)
Previous CABG	5(4%)	6(8%)					0	1 (1.9%)

Author, Years	Hayashida et al 2013		Kochman et al 2014		Costopoulos et al 2014		Bauer et al 2014	
Group	BAV	TAV	BAV	TAV	BAV	TAV	BAV	TAV
Number of patients	21	208	28	84	21	447	38	1357
Age (years)	82 ± 7	83.2 ± 6.5	77.6±5.5	79.1±6.8	76.7 ± 7.1	79.8 ± 7.4	80.7 ± 6.6	81.8 ± 6.2
Male	12 (57.1%)	111 (53.4%)	13 (46%)	40 (48%)	12 (57%)	212 (47%)	17 (45%)	570 (42%)
Body mass index (kg/m^2)	24.7 ± 4.1	26.1 ± 4.3			26.6 ± 4.4	26.1 ± 4.6	26 ± 5	27 ± 8
STS score					7.6 ± 4.2	7.8 ± 7.3		
Logistic EuroSCORE	19.9 ± 11.9	20.1 ± 11.4	19.2 ± 0.9	18.8 ± 8.7	23.9 ± 12	24.4 ± 17.3	18 ± 10	20 ±13
DM	1 (4.8%)	50 (24.0%)	11 (39%)	29 (35%)	6 (29%)	135 (30%)	14 (37%)	461 (34%)
HTN	12 (57.1 %)	142 (68.3%)	17 (60%)	55 (66%)	14 (67%)	345 (77%)		
Dyslipidemia	9 (42.9%)	98 (47.1%)						
Chronic lung disease	5 (23.8%)	50 (24%)	6 (21%)	17 (20%)	7 (33%)	137 (31%)	8 (21%)	326 (24%)
CAD			14 (50%)	54 (64%)				
MI	1 (4.8%)	18 (8.7%)	11 (39%)	26 (31%)	4 (19%)	88(20%)		
Atrial fibrillation								
Stroke/TIA	1 (4.8%)	13 (6.2%)	8 (29%)	14 (17%)	4 (19%)	72 (16%)	13 (5%)	108 (8%)
CKD ≥ 3	12 (57.1%)	124 (59.6%)			11 (52%)	257 (58%)	22 (58%)	828 (61%)
Peripheral vascular disease	5 (23.8%)	68 (32.7%)	6 (21%)	29 (35%)	7 (33%)	133 (30%)	4 (11%)	299 (22%)
NYHA class III or IV	19 (90.5%)	183 (88%)	20 (71%)	66 (79%)	15 (71%)	301 (67%)	32 (84%)	1208 (89%)
Previous PCI	4 (19%)	47 (22.6%)	6 (21%)	30 (36%)	6 (29%)	96 (22%)	13 (34%)	475 (35%)
Previous CABG	2 (9.5%)	28 (13.5%)	4(14%)	21(25%)			5 (13%)	244 (18%)

Author, Years	Liu et al 2015		Sannino et al 2017		Makkar 2019	
Group	BAV	TAV	BAV	TAV	BAV	TAV
Number of patients	15	25	88	735	2726	79096
Age (years)	75.4 ± 5.7	75.8 ± 5.5	80.2 ± 8.4	81.8 ± 7.9	74(66-81)	74(66-81)
Male	9 (60%)	17 (68%)	53 (60.2%)	389 (52.9%)	1621/2690 (60.3%)	1655/2691 (61.5%)
Body mass index (kg/m^2)	23.6 ± 4.8	21.7 ± 3.1	27 ± 6.8	27.6 ± 6.6	29.2±7.6	29.4±7.4
STS score	5.6 ± 4.1	7.5 ± 5.9	7.4 ± 3.9	7.6 ± 3.9	4.9±4	5.1±4.2
Logistic EuroSCORE	16.1 ± 11.1	21.8 ± 14.7			NA	NA
DM	0	3 (12%)	29 (37.7%)	283 (40.4%)	961/2685(35.8%)	989/2686(36.8%)
HTN	5 (33.3%)	14 (56%)	71 (81.6%)	612 (84.3%)	2269/2686(84.5%)	2263/2687(84.2%)
Dyslipidemia			62 (72.1%)	516 (71.7%)	NA	NA
Chronic lung disease	4 (26.7%)	4 (16%)	15 (19.5%)	149 (22.1%)	1113/2672 (41.7%)	1125/2678 (42.0%)
CAD	3 (20%)	9 (36%)	61 (70.9%)	487 (67.1%)	NA	NA
MI	0	0			NA	NA
Atrial fibrillation	1 (6.7%)	2 (8%)	15 (17.9%)	142 (19.6%)	779/2684 (29.0%)	790/2683 (29.4%)
Stroke/TIA	0	2(8%)	17 (22.4%)	132 (19.5%)	442/2685 (16.69%)	451/2685 (16.7%)
CKD ≥ 3	4 (26.7%)	12 (48%)	45 (52.3%)	330 (45.5%)	NA	NA
Peripheral vascular disease	2 (13.3%)	4 (16%)	35 (43.2%)	219 (31.5%)	653/2684 (24.3%)	657/2684 (24.5%)
NYHA class III or IV	13 (86.7%)	21 (84%)			1983/2667(74.4%)	1974/2664(74.1%)
Previous PCI	3 (20%)	3 (12%)	40(49.4%)	322(46.1%)	683/2683 (25.5%)	714/2685 (26.6%)
Previous CABG	0	0			426/2683 (15.9%)	463/2688 (17.2%)

Data are presented in number (percentage), or mean ± SD

Abbreviation: STS=Society of Thoracic Surgeons risk score, DM = diabetes mellitus, HTN = hypertension, CAD = coronary artery disease, MI = myocardial infarction, CKD = chronic kidney disease, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft, NYHA = New York Heart Association.

There was no statistically significant difference in the risk of after-procedural major/life-threatening bleeding (BARC 3 or 5), major vascular complications or acute kidney injury (AKI) between the 2 groups [RR: 0.94, CI: 0.71 to 1.25, p-value = 0.68, I^2=0%, chi-square p-value = 0.47], [RR: 1.06, CI: 0.77 to 1.46, p-value = 0.70, I^2=0%, chi-square p-value = 0.89], [RR: 1.04, CI: 0.61 to 1.78, p-value = 0.89, I^2=0%, chi-square p-value = 0.51] (Figure 2), respectively. There was no statistical heterogeneity or publication bias associated

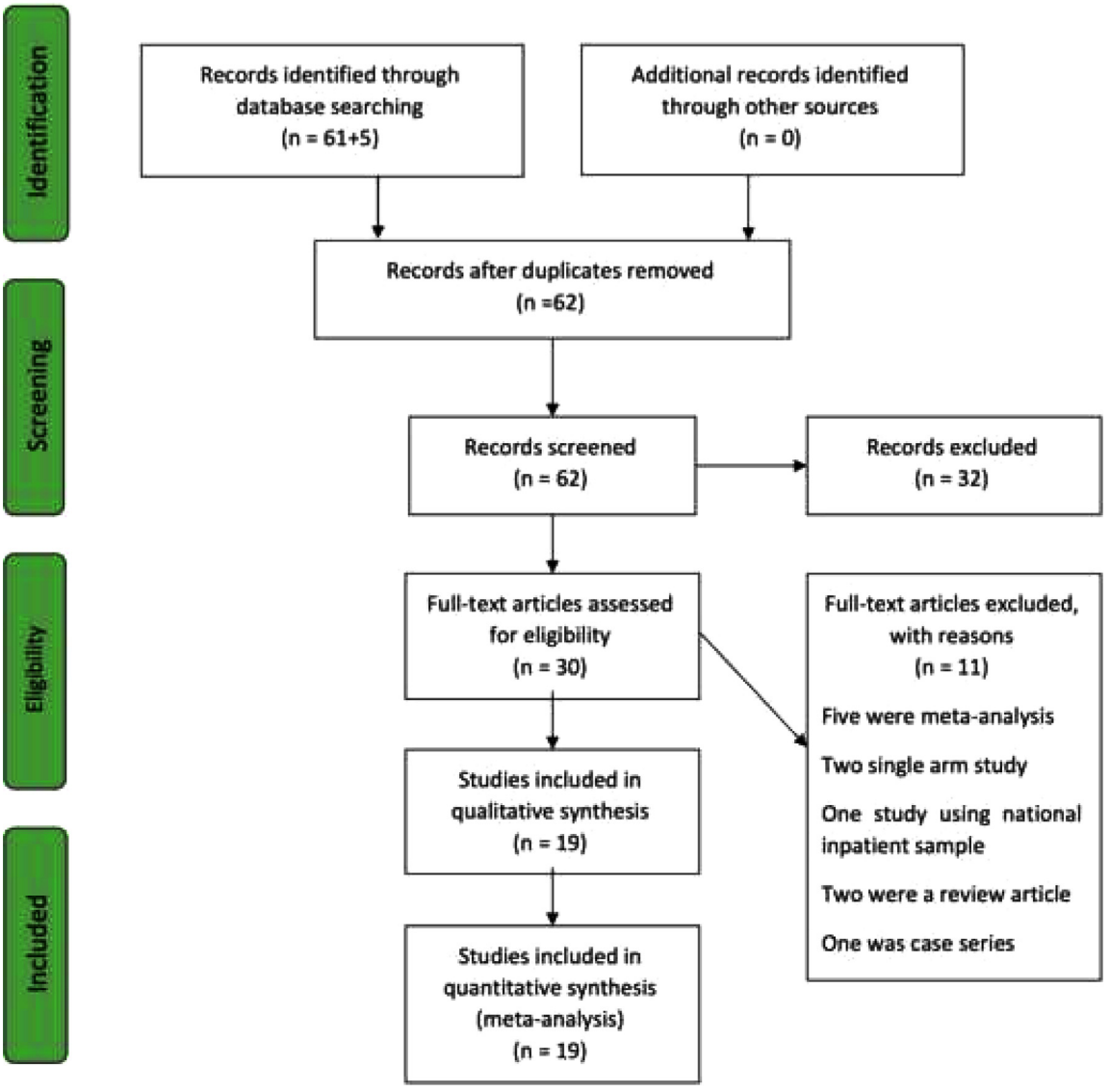

Figure 1. PRISMA flow chart for inclusion and exclusion of studies from the analysis.

with any of the pooled estimates (Supplementary Figure S16, PANEL E, F, and G1).

There was no statistically significant difference in the risk of permanent pacemaker implantation (PPI), device success and annulus rupture rates between the BAS and TAS group patient who underwent TAVI [RR: 1.06, CI: 0.94 to 1.21, p-value = 0.32, I^2=0%, chi-square p-value = 0.70], [RR: 0.98, CI: 0.95 to 1.02, p-value = 0.32, I^2=64%, chi-square p-value <0.05], [RR: 4.55, CI: 0.82 to 25.31, p-value = 0.08, I^2=0%, chi-square p-value=0.47], respectively (Figure 2). In subgroup analysis, neither mixed (old/new) generation nor new generation valve groups showed any difference in devices success between BAS versus TAS cohorts. Patients with BAS had a higher risk of conversion to open surgery and need for second valve implantation [RR: 2.65, CI: 1.47-4.76, p-value <0.05, I^2=0%, chi-square p-value = 0.63], [RR: 1.83, CI: 1.18 to 2.84, p-value <0.05, I^2=11%, chi-square p-value = 0.34], respectively (Figure 2). None of the procedural clinical outcomes were associated with publication bias (Supplementary Figure S17, PANEL A, B, C, D, E).

Patients with BAS treated with TAVI had a higher risk of paravalvular leak (PVL) (moderate/severe) than patients with TAS [RR: 1.47, CI: 1.05 to 2.04, p-value <0.05, I^2=0%, chi-square p-value = 1.00] (Figure 2). In subgroup analysis, BAS patients treated with mixed (old/new) generation valves had a higher risk of PVL, while there was no difference in the risk of PVL between the BAS and TAS patients treated with new-generation valves. There was no statistically significant difference in after-op mean aortic valve area or mean pressure gradient between the BAS and TAS patients who underwent TAVI; [MD: -0.05, CI: -0.18 to 0.07, p-value = 0.42, I^2=81%,chi-square p-value<0.05], [MD: 0.34, CI: -0.04 to 0.73, p-value <0.08, I^2=30%, chi-square p-value = 0.13], respectively (Figure 2). There was no publication bias associated with any of the after-procedural echocardiographic outcomes (Supplementary Figure S18, PANEL A, B, and C1).

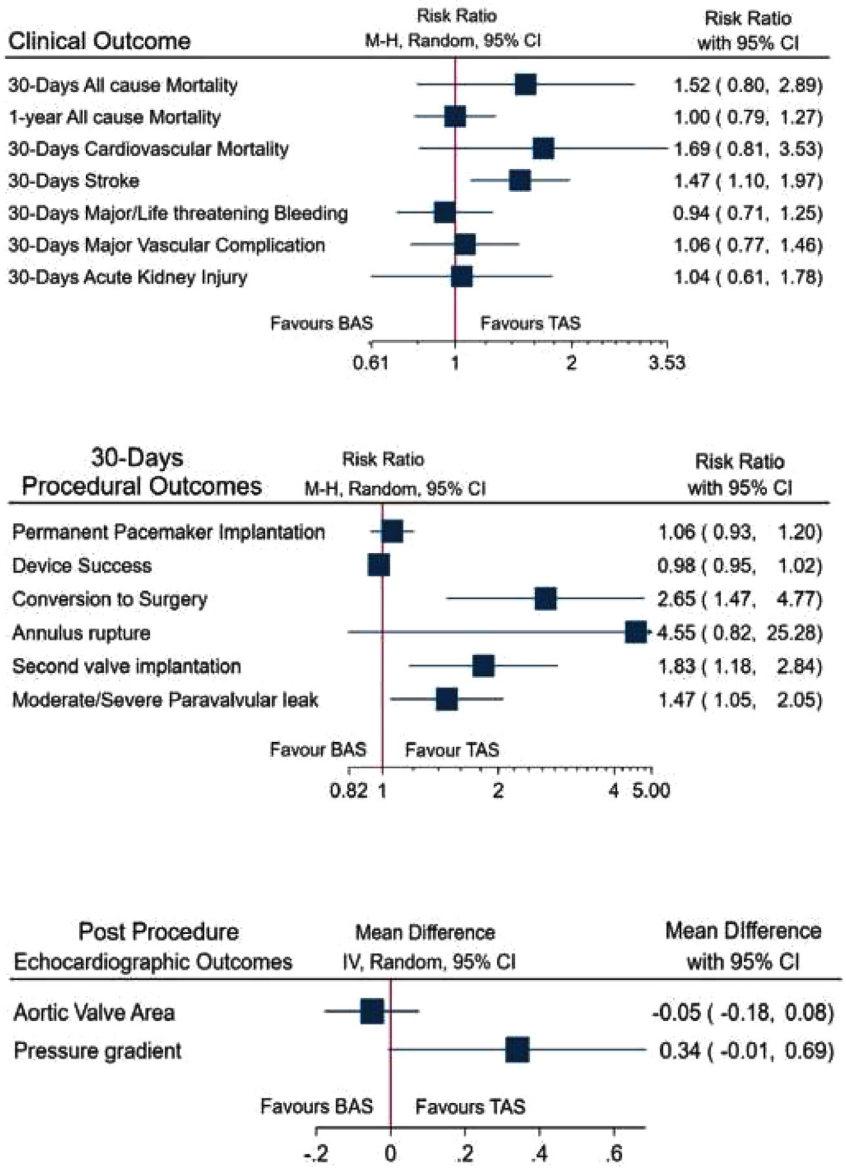

Figure 2. Forest plot for clinical, procedural, and after-procedural echocardiography outcomes; RR: Risk ratio. Mantel-Haenszel method with random effect model was used to pool categorical end points and Inverse Variance method with DerSimonian and Laird estimator of tau was used to pool continous end points.

Evidence of no statistically significant difference in the risk of 30-day, 1-year all-cause mortality, 30-day cardiovascular mortality, major and/or life-threatening bleeding (BARC 3 or 5), major vascular complications, AKI, PPI, device success, annulus rupture, after-op mean aortic valve area, mean pressure gradient, among BAS versus TAS patients who underwent TAVI, was of very low certainty. Evidence of statistically significant higher risk of 30-day stroke, conversion to open surgery, second valve implantation, and PVL among BAS as compared with TAS patients who underwent TAVI, was also of very low certainty.

We performed meta-regression analysis for 30-day mortality using a mean difference in STS score, a mean difference in left ventricular ejection fraction, a mean difference in age, a risk ratio of diabetes, a risk ratio of hypertension, a risk ratio of previous myocardial infarction, a risk ratio of chronic kidney disease, risk of NYHA class III and IV breathlessness and type (new generation) of valve used between the 2 groups. The coefficients for the mean difference in STS, mean difference in left ventricular ejection fraction, a mean difference in age, a risk ratio of diabetes, hypertension, previous myocardial infarctions, chronic kidney disease, NYHA class III and IV breathlessness, type (new generation) of valve used were statistically insignificant (Table 2). The meta-regression plots are provided in the supplementary file (Supplementary Figures S19 to S27).

From the GOSH plot, we observed two sub-clusters in our data, one with a lower effect size and lower heterogeneity, and another set with higher effect size and higher heterogeneity (Supplementary Figure S28). After the application of a supervised machine learning algorithm to detect clusters in the GOSH plots, we identified a study by Bauer et al. 2014 as

Table 2
Meta-regression analysis using potential confounders for 30-days all-cause mortality

Potential confounders	Coefficient	95% confidence interval	p-value
Mean Difference STS score	-0.123	-0.554, 0.308	0.577
Mean Difference LVEF	-0.158	-0.367, 0.052	0.140
Mean Difference age	0.059	-0.324, 0.442	0.763
RR of diabetes mellitus	1.172	-1.077, 3.421	0.307
RR of hypertension	0.477	-3.051, 2.786	0.767
RR of previous myocardial infarction	0.504	-0.734, 1.742	0.425
RR of chronic kidney disease	-0.142	-2.033, 1.750	0.883
RR of NYHA class III and IV	1.308	-8.700, 11.316	0.768
New generation valves	-2.419	-6.771, 1.934	0.276

LVEF = Left ventricular ejection fraction; RR = Risk Ratio; STS = Society of thoracic surgery risk score

a potential outlier (Supplementary Figure S29, S30). After excluding Bauer et al 2014 from the pooled estimate, the heterogeneity as described from I^2 value was reduced to 0% and relative risk was [RR: 1.16, CI: 0.91 to 1.48, p-value = 0.23, I2=0%, chi-square p-value = 0.71]. The study by Bauer et al. 2014 was the source of statistical heterogeneity in our 30-day mortality pooled estimate.[17]

Discussion

This is the largest meta-analysis to date comparing TAVI outcomes in patients with BAS versus TAS that included 19 studies with 12,124 patients (4040 BAS and 8084 TAS). The results of our meta-analysis concluded that there was no difference in all-cause mortality risk at 30-day and 1-year follow-up between the BAS and TAS patients who underwent TAVI. The findings of our study were consistent with a previous study by Makkar et al., and meta-analysis by Takagi et al. and Quintana et al., which also reported no difference in the risk of 30-day or 1-year all-cause mortality.[25–27] Since all included articles were observational studies and 30-day mortality showed 79% heterogeneity, we did meta-regression for 30-day mortality to look for any confounders. In meta-regression, none of the factors reported a significant association. Using the supervised machine learning algorithm, we could trace the source of the heterogeneity to 1 study by Bauer et al. (2014).[17] Finally, there was no difference in 30-day cardiovascular mortality, after-procedural major and/or life-threatening bleeding (BARC 3 or 5), major vascular complications, and AKI consistent with results of previous studies.[26,28]

There was a similar risk for post-procedure PPI between the 2 cohorts in our study. Several previous studies have demonstrated similar results.[26–29] This is likely due to improved device design as well as additional operator experience regarding appropriate valve sizing. The shape of the aortic root plays a vital role in deciding the size of the transcatheter valve.[30] According to Tchetche et al., the aortic root anatomy could have a tubular (straight), flared, or tapered (trapezoid) configuration based on the relationship between the annulus and intercommisural distance (ICD) 4 mm above the annulus in BAS.[13] It might be reasonable to size according to the annulus in a tubular or flared anatomy. However, sizing according to the ICD might avoid selecting a larger device in a patient with tapered aortic root anatomy.[13] This (sizing) question is being addressed in the ongoing BIVOLUTX study (ClinicalTrials.gov Identifier: NCT03495050).

Some concerns for TAVI in BAS patients stem from higher calcium deposits compared with patients with TAS.[31] The calcium deposits and the increased complexity of the procedure (e.g., enlarged aortic root, dilated ascending aorta, functional aortic incompetence, valve recapture, or need for the second valve) may increase the risk of periprocedural stroke. The risk of 30-day stroke was significantly higher in BAS patients who underwent TAVI as compared with TAS patients in our study. Makkar et al. reported a similar finding of higher 30-day stroke in BAS patients in a prior study.[25]

We also noted an increased risk of moderate and/or severe PVL in patients within the BAS cohort treated with TAVI, consistent with findings of prior studies.[26–29] The Sievers classification describes three categories of bicuspid aortic valve based on numbers of raphe and its spatial orientation to the coronary sinus. In the bicuspid valve, raphe and commissures are commonly associated with high calcium score and asymmetric leaflet calcification that sometimes make circular adaptation of the structures of aortic root difficult with valve deployment, enhancing the chances of PVL. Additionally, a wider ascending aorta, aortic annulus, and under-sizing of the valve to prevent PPI posit a higher potential for paravalvular leaks. Computed tomography for pre-procedural assessment of TAVI will help physicians to determine the correct size of the valve, and prevent PVL.[32] A subgroup analysis by valve generation showed higher events of PVL in the BAS cohort compared with the TAS cohort with mixed (old/new) generation valves. However, no difference in PVL between the two cohorts was noted with the use of newer generation valves. Technological advancements in device design with enhanced sealing skirts, repositionability, and re-capturability, as well as more accurate annular sizing have plausibly resulted in better outcomes with newer valves.[33]

Patients with BAS during TAVI were associated with an increased risk of conversion to open surgery and subsequently need for second valve implantation, probably due to the complex anatomy associated with the bicuspid aortic valve.[28] Although the proportion of patients in whom conversion to open surgery was required was less than 2%, it should caution operators as TAVI utilization expands to low-risk patients. Our meta-analysis reported similar device success between two cohorts, similar to the results of Quintana et al.[26] A subgroup analysis by valve generation did not show a difference in device success between 2 the cohorts. A recent study published by Halim et al. was not included in our meta-analysis due to the absence of primary end point (30-day all-cause mortality).[34] The inclusion of that study in the current meta-analysis did not alter other secondary outcomes, namely device success, conversion to open surgery, second valve implantation, PVL and mean aortic valve area between 2 cohorts of aortic stenosis. However, the mean pressure gradient was higher in the BAS cohort as compared with the TAS cohort (Supplementary Figure S31 to S36).

The present study has several limitations. Firstly, the use of aggregated summary values provided by study-level meta-analysis is limited in its ability to examine the source of heterogeneity, and a patient-level meta-analysis might provide additional evidence. Secondly, this is a meta-analysis of observational studies, and the prejudicial effect of selection bias cannot be excluded from the pooled estimates and evidence was of very low certainty. Thirdly, the analysis is not stratified based on various surgical risk groups, that is, high, intermediate, or low risk of surgery. This meta-analysis did not have any study with surgically low-risk patients. There may be differences in the definition of the outcomes, as each study had a slightly different definition for each outcome. Finally, a longer follow-up is needed to study the impact of TAVR in this patient population.

In conclusion, the present meta-analysis of observational studies supports the beneficial effect of TAVI in patients with BAS who are at increased risk of surgery. There was no difference in overall mortality at 30-day or 1-year between BAS and TAS patients who underwent TAVI. Improved TAVI technology has increased procedural success with no difference in PVL rates between BAS and TAS patients when using newer generation valves. However, we noted an increased incidence of stroke, conversion to surgery, and second valve implantation in patients with BAS, which must be discussed with the patient before the procedure.

Credit Author Statement

Monil Majmundar: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing; Ashish Kumar: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing; Rajkumar Doshi: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Supervision. Palak Shah: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Shilpkumar Arora: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Mariam Shariff: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Devina Adalja: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Ferdinand Visco: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Hosam Amin: Conceptualization, Writing - Original Draft, Writing - Review & Editing; Saraschandra Vallabhajosyula: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition; Nageshwara Gullapalli: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision; Samir Kapadia: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision; Ankur Kalra: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision; Sidakpal Panaich: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Supervision.

Disclosures

The authors declare no conflicts of interest.

Note: All authors had access to the data and a role in writing the manuscript. The present work was conducted at New York Medical College, Metropolitan Hospital Centre.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.085.

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