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Transaxillary Versus Transaortic Transcatheter Aortic Valve Implantation in the Treatment of Aortic Stenosis: An Updated Systematic Review and Meta-Analysis

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Abstract

Transcatheter aortic valve replacement (TAVR) is a technique that can be performed through multiple approaches, and the benefits of one approach over another are still being evaluated to make sure patients receive the best possible care. Our meta-analysis aims to compare clinical and procedural outcomes of the transaxillary (TAx) and transaortic (TAo) approaches to validate the more optimal procedure.

The systematic literature search was done via PubMed/MEDLINE, Embase, and the Cochrane Central databases from inception to December 2021, to identify articles reporting data on both TAx TAVR and TAO TAVR. In addition, we checked ClinicalTrials.gov for more published or unpublished trials. Baseline patient characteristics, procedure results, and clinical results were extracted from the article and pooled for analysis. A quantitative meta-analysis was conducted using Review Manager (RevMan) version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The outcomes extracted included blood transfusion, conversion to sternotomy, tamponade, contrast amount, procedure time, bleeding incidents (minor, major, or life-threatening), length of stay (LOS), vascular complications (minor or major), acute kidney injury (AKI), paravalvular leak (PVL), permanent pacemaker (PPM) implantation, 30-day mortality, one-year mortality, 30-day stroke, and device success.

The final analysis included 11 articles, consisting of 10 observational studies and a pivotal trial. Cumulative results revealed that the TAo approach had a significantly lower incidence of vascular complications (RR = 2.30; 95% CI = 1.22 to 4.35), and the need for implantation of a permanent pacemaker (RR = 1.82; 95% CI = 1.30 to 2.54) along with a lower amount of contrast (mean difference (MD) = 27.40; 95% CI = 3.73 to 51.08) needed to be used. The TAx group was associated with a significantly lower 30-day mortality (RR = 0.46; 95% CI = 0.31 to 0.69), AKI (RR = 0.47; 95% CI = 0.33 to 0.67), and length of hospital stay (MD = -1.95; 95% CI = -2.51 to -1.38). No significant difference was observed between the outcomes of 30-day stroke (RR = 1.38; 95% CI = 0.81 to 2.33), PVL (RR = 1.05; 95% CI = 0.50 to 2.18), tamponade (RR = 0.71; 95% CI = 0.12 to 4.03), conversion to sternotomy (RR = 0.51; 95% CI = 0.51 to 1.10), and procedure time (MD = 4.44; 95% CI = -96.30 to 105.17).

Both the procedures were associated with their benefits and risks. Although most of the outcomes favored TAx transcatheter aortic valve implantation (TAVI), it is too early to say if it would be better than TAo TAVI. To authenticate the findings concluded in this meta-analysis and further improve our understanding of the efficacy, safety, and risk profile between TAx and TAo approaches for TAVI, large sample randomized clinical trials are required on a wide scale.

Categories: Cardiac/Thoracic/Vascular Surgery, Cardiology, Internal Medicine **Keywords:** transcatheter aortic valve implantation (tavi), transaxillary, transaortic, meta-analysis, a systematic review

Introduction And Background

Calcific aortic stenosis (AS) constitutes a significant health problem in the elderly, the prevalence of which is about 8.1% at 85 years of age [1]. After symptoms have developed, the only effective treatment is aortic valve replacement (AVR)/aortic valve implantation (AVI). The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend AVR as a Class I indication for severe, symptomatic AS (i.e., the proposed treatment, procedure, or intervention is effective and should be performed for the majority of patients under most circumstances). However, nearly one-third of patients are deemed unsuitable for surgery due to concerns about age, comorbidities, patient frailty, and severe left ventricular dysfunction [2]. Transcatheter aortic valve implantation (TAVI) is a technique that has revolutionized the management of AS and has risen exponentially as the standard of care for patients at prohibitive surgical

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risk, emerging as a promising treatment for patients of moderate to high-risk levels [3].

As TAVI comes of age, significant variability exists in the alternative access techniques available for its utility. Transfemoral access (TF) dominates as the most preferred route, owing to its less invasive approach, higher rates of survival, and considerably lower complications [4]. However, a considerable proportion of individuals are not eligible for the TF route due to luminal narrowing, atherosclerosis, obstruction, calcification, or tortuosity of the iliofemoral vessels [5]. Despite the progress in the miniaturization of delivery systems, unfavorable anatomy and peripheral vascular disease preclude TF access in approximately 17.2% of patients [6]. Thus, various alternate accesses have been proposed over the years and are in use, of which this article examines in depth two: the transaortic (TAo) and transaxillary (TAx) approaches.

The TAx method uses local anesthetic and mild sedation, followed by a convenient surgical cutdown from the deltopectoral groove to the pectoralis major: dissection or retraction of the pectoralis then yields exposition of the subclavian artery [7,8]. This avoids the invasiveness of other techniques and overcomes peripheral vascular disease [8]. Further, progressive advancement has led to fully percutaneous procedures without surgical cutdown [7], making TAx comparable to the TF approach and potentially, the safer non-TF route. The TAo access is achievable through a mini-sternotomy or a right thoracotomy, allowing exposure of the proximal ascending aorta [8]. This route is advantaged by eluding smaller arteries (iliofemoral or the subclavian) en route by direct insertion of the sheath in the aorta, thus decreasing the risk of complications. Additionally, it employs a highly accurate transfer of the operator's maneuvers to the delivery system while using safe and easy valve placement [8]. The detailed evaluation of these vascular surgical approaches, in terms of anatomy and technique, has been included by Pascual et al. in their article on the same [8].

Both TAo and TAx approaches offer specific procedural advantages that cannot be ignored. However, the limited documentation in the literature comparing the two accesses does not allow operators to favor one approach over the other. The relative benefits and risks of each are still subject to much debate, indicating the need for them to be better defined so that the choice of one over the other can be fully delineated. Therefore, our study aimed to compare clinical and procedural outcomes of the TAx and TAo approaches such as mortality, 30-day stroke, and acute kidney injury (AKI).

Review

Methods

Data Sources and Search Strategy

Two independent researchers (I.H. and M.O.K.) searched PubMed, Embase, and Cochrane Central from inception until December 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this meta-analysis [9]. We used the following keywords and terms to search each database: "Transaxillary," "Trans-axillary," "Transsubclavian," "Trans-subclavian," "Trans-aortic," "Direct aortic," "Trans-cervical," "Transthoracic," "Transcatheter aortic valve implantation," "Transcatheter aortic valve replacement," "TAVI," and "TAVR." The comprehensive search algorithm for the database is in Appendix A. The reference lists of the retrieved publications and previous meta-analyses were manually screened for potentially relevant studies. In addition, we checked ClinicalTrials.gov for more published or unpublished trials. The term "transaxillary access" was employed instead of "transubclavian access" because transsubclavian access is regarded as a misnomer unless a supraclavicular cut-down is performed. Furthermore, transsubclavian and transaxillary techniques are interchangeable terms in the literature [10].

Study Selection and Eligibility Criteria

The studies were considered eligible if they were randomized controlled trials (RCTs) or observational studies, irrespective of publication status. In addition, to be included, articles had to report outcomes for mortality, length of stay (LOS), stroke, bleeding, or vascular complications between TAx and TAo transcatheter aortic valve replacement (TAVR). We omitted the studies if the data were insufficient or inadequate for analysis, if the study was a case report or review, or if the study was in a non-English language.

Data Extraction and Assessment of Study Quality

The articles found through the systematic search were imported into the EndNote Reference Library software (Clarivate, London, UK), identifying and eliminating duplicates. Two separate reviewers (I.H. and M.O.K.) thoroughly reviewed the remaining publications, and only articles that satisfied the previously specified criteria were accepted. Dialogue resolved disagreements, failing which a third reviewer (S.A.S.) was consulted. We extracted the patients' baseline characteristics and diverse set outcomes from the finalized articles, including device success, blood transfusion, conversion to sternotomy, tamponade, contrast amount, procedure time, bleeding incidents (minor, major, or life-threatening), LOS, vascular complications (minor or major), AKI, PVL, permanent pacemaker (PPM) implantation, 30-day mortality, 30-day stroke, and one-year mortality. Furthermore, the Newcastle-Ottawa Scale was utilized to evaluate the quality of

observational studies (Appendix B).

Statistical Analysis

Review Manager (RevMan) version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform all the statistical analyses. We calculated the dichotomous data using RRs with 95% CIs as meaningful effect measures for 30-day mortality, one-year mortality, 30-day stroke, PPM implantation, AKI, PVL, and vascular complications. Some papers reported medians and interquartile ranges transformed to mean and standard deviation using the methods presented by Wan et al. [11]. The random-effects model and the Higgins I² statistic were used for the analysis and heterogeneity calculation. We defined an I² of <50%, 50-75%, and >75% representing low, moderate, and high heterogeneity, respectively. The statistical significance level for hypothesis testing was set at 0.05. We used subgroup analysis for the comparisons between observational studies and RCTs. Furthermore, we performed sensitivity analysis when heterogeneity was >50% or when the same institution or author reported two similar studies; in such cases, we included the more recent publication or the one with the greatest information (Appendix C). A funnel plot for the primary outcome of 30-day mortality was generated to evaluate the possibility of publication bias.

Results

Literature Search and Baseline Characteristics

The initial database search yielded a total of 156 potentially relevant articles. After removing the duplicates, 146 articles were screened for suitability and relevance based on their titles and abstracts. Out of these, 49 full-text articles on the objective of the manuscript were reviewed. After the full-text screening, 36 articles were excluded. Two articles were also excluded during data extraction. The final analysis included 11 articles, consisting of 10 observational studies and a pivotal trial. Figure *1* represents the PRISMA flowchart, outlining our systematic review's search and screening process. The baseline characteristics are included in Table *1*.



FIGURE 1: PRISMA flow diagram

The PRISMA diagram details the search and selection processes applied during the overview.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Study Year Region		Denier	Approach	Age,	Gender	BMI,	UTN	DM	LVEF,	Prior	0000	Prior	Prior	NYHA	Peripheral	Logisti EuroS0	CORE	STS P	ROM	Newcastle-
Study	Year	Region	(n)	(SD)	(M:F)	mean (SD)	HIN	DM	(SD)	мі	COPD	AF	cardiac surgery	III/IV	disease	Mean (SD)	P- value	Mean (SD)	P- value	Scale
Myat et	2020		TAx (82)	78.3 (6.8)	54:28	27.6 (5.4)	N/R	24	N/R	11	27	N/R	23	N/R	47	N/R	NO	N/R	ND	
al. [12]	2020	UK	TAo (142)	80 (8.9)	69:73	27.2 (6.4)	N/R	37	N/R	34	43	N/R	26	N/R	77	N/R	N/IX	N/R	N/N	0/3
Lin et al.	2021	N/R	TAx (56)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	7/9
[13]			TAo (11)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R		N/R		
Pineda et	2019	USA	TAx (30)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	7/9
al. [14]	2013	UUN	TAo (24)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	NUT	N/R	MAX	113
Beve et	2019	France	TAx (73)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	7/9
al. [15]	2013	Tance	TAo (41)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	NUT	N/R	N/IX	113
Codner et	2010	1104	TAx (11)	84 (5.1)	2:9	27.2 (9.1)	11	3	59.5 (12.8)	1	N/R	N/R	2	10	5	N/R	NO	7.6 (2.1)	0.400	7/0
al. [16]	2016	USA	TAo (11)	83 (4.3)	7:4	25.4 (5.5)	11	1	54 (14.9)	3	N/R	N/R	3	11	4	N/R	N/R	8.5 (3.8)	0.499	113
Damluji et	Damluii et France	France	TAx (17)	80.3 (9.7)	10:7	27.3 (5.6)	13	4	59.3 (9.7)	1	N/R	5	N/R	7	N/R	N/R		N/R		8/9
al. [17]	2018	and USA	TAo (67)	84.3 (5.3)	30:37	25.6 (5.3)	55	19	58.3 (11.3)	17	N/R	21	N/R	38	N/R	N/R	N/R	N/R	N/R	
Khan et	2019	1124	TAx (24)	84.7 (7.9)	13:11	27 (5.2)	22	9	52.2 (17.3)	N/R	6	11	7	22	6	25 (15)	1	8.66 (6)	0.06	9/0
al. [5]	2018	USA	TAo (27)	82.6 (7)	10:17	26 (6.4)	27	10	55.8 (15.9)	N/R	8	10	8	24	9	25 (16)		11.3 (4)	0.00	0.9
Fiorina et	0017		TAx (147)	83 (5)	72:75	N/R	N/R	N/R	51 (12)	N/R	N/R	N/R	22	119	N/R	15.3 (15.7)	0.0004	7.3 (6)	0.000	70
al. [18]	2017	nany	TAo (95)	82 (6)	44:51	N/R	N/R	N/R	52 (14)	N/R	N/R	N/R	25	78	N/R	27.3 (17.3)	0.0001	9.6 (6.8)	0.006	//9
Fröhlich	2015	1 IK	TAx (188)	82.3 (5.9)	123:65	26 (4.4)	N/R	45	N/R	52	52	32	63	N/R	N/R	23.3 (14.9)	0.891	N/R	N/P	8/9
et al. [19]	2013	UK	TAo (185)	83 (8.2)	90:95	25.6 (4.4)	N/R	39	N/R	43	71	30	44	N/R	N/R	23.1 (14.9)	0.031	N/R	N/R	0.5
Adamo et	2015	Italy	TAx (32)	82 (6)	14:18	25 (4)	23	8	49 (13)	5	5	15	4	24	21	26.3 (10.1)	0 006	9.3 (6.5)	0.412	8/9
al. [20]	2010	reaty	TAo (44)	83 (6)	27:17	25 (6)	29	15	48 (15)	7	3	6	10	35	31	26 (11.5)	0.000	8.23 (4.83)	0.412	013
Reardon	2044	N/R	TAx (146)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/P	N/R	N/D	7/0
et al. [21]	2014	IN/PC	TAo (340)	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	IN/IK	N/R	IN/K	119

TABLE 1: Baseline characteristics of the included studies

TAo = transaortic; TAx = transaxillary; N/R = not reported; BMI = body mass index; HTN = hypertension; DM = diabetes mellitus; LVEF = left ventricular ejection fraction; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; AF = atrial fibrillation; NYHA = New York Heart Association; EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Quality Assessment and Publication Bias

The methodological quality assessment of included studies showed that all 11 studies were of good quality (Appendix C). The funnel plot for the publication bias is given below (Figure 2).



FIGURE 2: Funnel plot for 30-day mortality

Result of Meta-Analysis

Mortality: All studies in our meta-analysis compared the 30-day mortality in both TAx and TAo approaches for TAVI. Pooling the estimates revealed that TAx group has significantly lower 30-day mortality compared to the TAo group (4.2% vs. 9.6%; RR: 0.46; 95% CI: 0.31, 0.69; P = 0.0001; Figure 3*A*) with no heterogeneity ($I^2 = 0\%$). Out of 11 studies, only six studies reported data on one-year mortality. Although one-year mortality incidence was lower in the TAx group compared to the TAo group (15.3% vs. 20.4%), our cumulative findings revealed that this difference was not significant (RR: 0.73; 95% CI: 0.53, 1.00; P = 0.05; Figure 3*B*). These findings from observational studies and RCTs were consistent (P-value for subgroup differences = 0.62). In addition, the heterogeneity level was low ($I^2 = 3\%$).



FIGURE 3: Forest plot for (A) 30-day mortality and (B) one-year mortality

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Codner et al. (2018) [16], Damluji et al. (2018) [17], Khan et al. (2018) [5], Beve et al. (2019) [15], Pineda et al. (2019) [14], Lin et al. (2021) [13], and Myat et al. (2020) [12].

Thirty-day stroke: Ten studies reported the incidence of 30-day stroke after TAVI. The incidences were reasonably similar (3.2% for TAo and 3.6% for TAx). The differences between the groups are not statistically significant (RR: 1.38; 95% CI: 0.81, 2.33; P = 0.23; Figure 4). The heterogeneity was low ($I^2 = 0$ %). This finding was seen in both observational studies and RCTs (P-value for subgroup differences = 0.78).

	Trans-Ax	illary	Trans-A	ortic		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl	
1.6.1 Observational	studies								
Adamo 2015	1	32	1	44	3.7%	1.38 [0.09, 21.17]	2015	·	
Frohlich 2015	6	188	1	185	6.2%	5.90 [0.72, 48.57]	2015	+	
Fiorina 2017	2	147	1	95	4.8%	1.29 [0.12, 14.06]	2017		
Codner 2018	0	11	1	11	2.9%	0.33 [0.02, 7.39]	2018		
Damluji 2018	0	17	3	67	3.2%	0.54 [0.03, 9.98]	2018		
Khan 2018	1	24	0	27	2.8%	3.36 [0.14, 78.79]	2018		
Beve 2019	0	73	1	41	2.7%	0.19 [0.01, 4.54]	2019		
Lin 2020	3	56	1	11	5.9%	0.59 [0.07, 5.16]	2020		
Myat 2020	3	82	3	142	11.1%	1.73 [0.36, 8.38]	2020		
Subtotal (95% CI)		630		623	43.2%	1.26 [0.57, 2.80]		+	
Total events	16		12						
Heterogeneity: Tau ² =	= 0.00; Chi ² :	= 5.50,	df = 8 (P =	0.70);	l² = 0%				
Test for overall effect	Z = 0.57 (P	= 0.57)							
1.6.2 RCTs									
Reardon 2014	12	146	19	340	56.8%	1.47 [0.73, 2.95]	2014		
Subtotal (95% CI)		146		340	56.8%	1.47 [0.73, 2.95]		•	
Total events	12		19						
Heterogeneity: Not a	oplicable								
Test for overall effect	Z = 1.09 (P	= 0.28)							
Total (95% CI)		776		963	100.0%	1.38 [0.81, 2.33]		*	
Total events	28		31						
Heterogeneity: Tau ² =	= 0.00; Chi ² :	= 5.56,	df = 9 (P =	0.78);	² = 0%				
Test for overall effect	Z=1.19 (P	= 0.23)						Eavoure Trans-Avillany Eavoure Trans-Aortic	
Test for subgroup dif	ferences: C	$hi^2 = 0.0$	08, df = 1 (P = 0.7	8), I ² = 0%	, ,		ravours mans-Annary ravours mans-Aonuc	

FIGURE 4: Forest plot for 30-day stroke

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Codner et al. (2018) [16], Damluji et al. (2018) [17], Khan et al. (2018) [5], Beve et al. (2019) [15], Lin et al. (2021) [13], and Myat et al. (2020) [12].

AKI: Seven studies included in our analysis reported the data on AKI after TAVI. Stratifying the data for AKI revealed that the TAx approach was associated with a lower incidence compared to the TAo approach (9.9% vs. 18.6%; RR: 0.47; 95% CI: 0.33, 0.67; P < 0.0001; Figure 5) with a low heterogeneity ($I^2 = 8\%$). These findings were consistent in observational studies and RCTs (P-value for subgroup = 0.31).

	Trans-Ax	illary	Trans-A	ortic		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.7.1 Observational	studies							
Adamo 2015	4	32	13	44	10.6%	0.42 [0.15, 1.18]	2015	
Fiorina 2017	33	147	35	95	50.0%	0.61 [0.41, 0.91]	2017	-
Damluji 2018	0	17	3	67	1.4%	0.54 [0.03, 9.98]	2018	
Khan 2018	1	24	0	27	1.2%	3.36 [0.14, 78.79]	2018	
Beve 2019	0	73	4	41	1.4%	0.06 [0.00, 1.14]	2019	
Myat 2020	5	82	26	142	13.0%	0.33 [0.13, 0.83]	2020	
Subtotal (95% CI)		375		416	77.5%	0.52 [0.36, 0.76]		◆
Total events	43		81					
Heterogeneity: Tau ² =	0.01; Chi2	= 5.22,	df = 5 (P =	0.39); I	² = 4%			
Test for overall effect	Z = 3.40 (F	= 0.00	07)					
1.7.2 RCTs								
Reardon 2014	9	146	60	340	22.5%	0.35 [0.18, 0.68]	2014	
Subtotal (95% CI)		146		340	22.5%	0.35 [0.18, 0.68]		◆
Total events	9		60					
Heterogeneity: Not ap	plicable							
Test for overall effect	Z = 3.06 (P	= 0.00	2)					
Total (95% CI)		521		756	100.0%	0.47 [0.33, 0.67]		◆
Total events	52		141					
Heterogeneity: Tau ² =	0.02; Chi2	= 6.54,	df = 6 (P =	0.37);1	l² = 8%			
Test for overall effect	Z = 4.25 (P	< 0.00	01)					Eavours Trans-Avillary Eavours Trans-Aortic
Test for subgroup diff	ferences: C	hi ² = 1.0	02, df = 1 (P = 0.3	1), I ² = 1.9	9%		ravous mana-yonary ravous mana-yonuc

FIGURE 5: Forest plot for acute kidney injury

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Fiorina et al. (2017) [18], Damluji et al. (2018) [17], Khan et al. (2018) [5], Beve et al. (2019) [15], and Myat et al. (2020) [12].

Pacemaker implantation: Nine studies reported the incidence of pacemaker implantation after TAVR. The TAx approach was associated with a significantly higher incidence of implanting a supportive PPM than the TAo group (22.6% vs. 12.9%; RR: 1.82; 95% CI: 1.30, 2.54; P = 0.0004; Figure *6*). The heterogeneity was low ($I^2 = 32\%$). This finding was only consistent with the subgroup of observational studies (P-value for subgroup difference = 0.05).

Trans-Axillary Tr			Trans-A	ortic		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.4.1 Observational s	studies							
Adamo 2015	5	32	5	44	6.9%	1.38 [0.43, 4.36]	2015	
Frohlich 2015	43	188	13	185	17.6%	3.25 [1.81, 5.85]	2015	
Fiorina 2017	41	147	11	95	16.8%	2.41 [1.30, 4.45]	2017	
Khan 2018	3	24	2	27	3.5%	1.69 [0.31, 9.26]	2018	
Codner 2018	2	11	1	11	2.1%	2.00 [0.21, 18.98]	2018	
Beve 2019	10	66	2	35	4.6%	2.65 [0.61, 11.44]	2019	
Lin 2020	20	56	2	11	5.6%	1.96 [0.53, 7.22]	2020	
Myat 2020	20	82	21	142	18.9%	1.65 [0.95, 2.85]	2020	
Subtotal (95% CI)		606		550	76.0%	2.20 [1.63, 2.96]		•
Total events	144		57					
Heterogeneity: Tau ² =	0.00; Chi2	= 3.74,	df = 7 (P =	0.81);	² = 0%			
Test for overall effect:	Z = 5.17 (P	< 0.00	001)					
1.4.2 RCTs								
Reardon 2014	26	146	58	340	24.0%	1.04 [0.69, 1.59]	2014	+
Subtotal (95% CI)		146		340	24.0%	1.04 [0.69, 1.59]		•
Total events	26		58					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 0.20 (P	= 0.84)						
		-						
l otal (95% CI)		752		890	100.0%	1.82 [1.30, 2.54]		•
Total events	170		115					
Heterogeneity: Tau ² =	0.07; Chi ²	= 11.84	, df = 8 (P	= 0.16)	; I [≠] = 32%			0.005 0.1 1 10 200
Test for overall effect:	Z = 3.51 (P	= 0.00	D4)					Favours Trans-Axillary Favours Trans-Aortic
Test for subgroup diff	ferences: C	hi² = 8.0	01. df = 1 (P = 0.0	05), I ^z = 8	7.5%		

FIGURE 6: Forest plot for permanent pacemaker implantation

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Khan et al. (2018) [5], Codner et al. (2018) [16], Beve et al. (2019) [15], Lin et al. (2021) [13], and Myat et al. (2020) [12].

Length of hospital stay: Eight studies included in our analysis reported the data on the length of hospital stay. The aggregated results showed significantly shorter LOS in TAx approach compared to the TAo approach (mean difference: -1.95; 95% CI: -2.51, -1.38; P < 0.00001; Figure 7) with no heterogeneity amongst studies (I² = 0%).

	Trans	-Axillary		Tran	s-Aortic			Mean Difference		Mean Difference
Study or Subgroup	Mean [Days]	SD [Days]	Total	Mean [Days]	SD [Days]	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Adamo 2015	8.6	4.6	32	10	3	44	9.6%	-1.40 [-3.22, 0.42]	2015	
Frohlich 2015	7.3	3.7	188	9.6	8.2	185	19.0%	-2.30 [-3.59, -1.01]	2015	_ _
Fiorina 2017	9	3.7	147	10.6	4.5	95	27.1%	-1.60 [-2.68, -0.52]	2017	
Damluji 2018	8.6	4.8	17	11	7.5	67	3.8%	-2.40 [-5.30, 0.50]	2018	
Khan 2018	6.21	3.79	24	8.19	4.96	27	5.5%	-1.98 [-4.39, 0.43]	2018	
Codner 2018	7.9	3.8	11	9.1	6.1	11	1.8%	-1.20 [-5.45, 3.05]	2018	
Beve 2019	5.6	2.2	73	7.6	3	41	29.0%	-2.00 [-3.05, -0.95]	2019	
Myat 2020	8.6	9.5	82	11.9	10.8	142	4.3%	-3.30 [-6.02, -0.58]	2020	
Total (95% CI)			574			612	100.0%	-1.95 [-2.51, -1.38]		◆
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2.1	20, df = 7 (P	= 0.95)	; I ² = 0%						
Test for overall effect:	Z = 6.76 (P < 0	.00001)								Favours Trans-Axillary Favours Trans-Aortic

FIGURE 7: Forest plot for the length of hospital stay

References: Adamo et al. (2015) [20], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Damluji et al. (2018) [17], Khan et al. (2018) [5], Codner et al. (2018) [16], Beve et al. (2019) [15], and Myat et al. (2020) [12].

Vascular complications: Seven out of 11 selected articles reported the incidence of vascular complications after TAVI. The pooled results were in favor of the TAo approach as the rate of vascular complications was higher in the TAx approach (9.0% vs. 3.8%; RR: 2.30; 95% CI: 1.22, 4.35; P = 0.01; Figure 8) with low heterogeneity between studies ($I^2 = 40\%$). These findings were consistent with the RCTs subgroup. However, there was no statistically significant difference between the two subgroups (P-value for subgroup difference = 0.32).

	Trans-Ax	illary	Trans-A	ortic		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.8.1 Observational s	studies							
Frohlich 2015	4	188	6	185	15.7%	0.66 [0.19, 2.29]	2015	
Fiorina 2017	20	147	5	95	21.1%	2.59 [1.00, 6.65]	2017	
Damluji 2018	1	17	6	67	7.8%	0.66 [0.08, 5.10]	2018	
Khan 2018	1	24	1	27	4.8%	1.13 [0.07, 17.02]	2018	
Beve 2019	2	73	0	41	4.0%	2.84 [0.14, 57.73]	2019	
Myat 2020	17	82	5	142	20.8%	5.89 [2.26, 15.37]	2020	
Subtotal (95% CI)		531		557	74.3%	1.92 [0.83, 4.46]		◆
Total events	45		23					
Heterogeneity: Tau ² =	0.46; Chi2:	= 9.35,	df = 5 (P =	0.10);1	I ² = 46%			
Test for overall effect:	Z = 1.53 (P	= 0.13						
1.8.2 RCTs								
Reardon 2014	16	146	11	340	25.7%	3.39 [1.61, 7.12]	2014	
Subtotal (95% CI)		146		340	25.7%	3.39 [1.61, 7.12]		•
Total events	16		11					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 3.22 (P	= 0.00	1)					
Total (95% CI)		677		897	100.0%	2.30 [1.22, 4.35]		◆
Total events	61		34					
Heterogeneity: Tau ² =	0.27; Chi2:	= 10.05	df = 6 (P	= 0.12)	² = 40%			
Test for overall effect:	Z = 2.56 (P	= 0.01)						U.UU1 U.1 1 1U 1000
Test for subgroup diff	ferences: C	hi ² = 0.9	98, df = 1 (P = 0.3	2), I ² = 0%	5		Favours frans-Avinary Favours frans-Avint
Test for overall effect: Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	Z = 3.22 (P 61 : 0.27; Chi ² : Z = 2.56 (P ferences: Cl	= 0.00 677 = 10.05 = 0.01) hi ² = 0.9	34 , df = 6 (P 38, df = 1 (897 = 0.12) P = 0.3	100.0% ; I ² = 40% 2), I ² = 0%	2.30 [1.22, 4.35]		0.001 0.1 1 10 1000 Favours Trans-Avillary Favours Trans-Aortic

FIGURE 8: Forest plot for vascular complications

References: Reardon et al. (2014) [21], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Damluji et al. (2018) [17], Khan et al. (2018) [5], Beve et al. (2019) [15], and Myat et al. (2020) [12].

Other outcomes: The pooled results did not show any significant difference in the incidence of PVL (RR: 1.05; 95% CI: 0.50, 2.18; P = 0.91; Figure 9A) (I² = 22%), blood transfusion (RR: 0.47; 95% CI: 0.13, 1.62; P = 0.23; Figure 9B) (I² = 0%), tamponade (RR: 0.71; 95% CI: 0.12, 4.03; P = 0.70, Figure 9C) (I² = 45%), and conversion to sternotomy (RR: 0.51; 95% CI: 0.06, 4.30; P = 0.54; Figure 9D) (I² = 0%) between both groups (Figure 9).

A- Paravalvular Leak

Study or Subgroup Beve 2019		xillary	Irans-A	ortic		Risk Ratio	Risk Ratio
Codeex 2010	Events 22	I otal 60	Events	i otal	Weight	M-H, Kandom, 95% Cl	M-H, Kandom, 95% Cl ——————
Counter 2018	1	11	14	40	7.1%	1.00 [0.07, 14 05]	
Damluji 2018	ó	17	3	67	5.9%	0.54 [0.03, 9.98]	
Khan 2018	7	24	1	27	11.4%	7.88 [1.04, 59.47]	
Lin 2020	6	56	2	11	19.3%	0.59 [0.14, 2.55]	
T-t-LOEN OF					400 00	4.05 10 50 0	1
Total (95% CI)		177		156	100.0%	1.05 [0.50, 2.18]	-
Heterogeneity: Tau ² =	36 0.17; Chi	= 5.10,	21 df = 4 (P =	= 0.28);	I ² = 22%		
Test for overall effect	Z=0.12 (P = 0.91)					Favours Trans-Axillary Favours Trans-Aortic
3- Blood Transfu	ISION Trans-A	xillary	Trans-A	ortic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Tota	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Codner 2018	2	11	4	11	71.0%	0.50 [0.11, 2.19]	
Lin 2020	2	56	1	11	29.0%	0.39 [0.04, 3.96]	
Total (95% CI)		67		22	100.0%	0.47 [0.13, 1.62]	-
Total events	4	0.	5		1001070	0.41 [0.15, 1.02]	
Heterogeneity: Tau ² =	: 0.00: Chi	= 0.03.	df = 1 (P =	= 0.86);	$ ^{2} = 0\%$		k
Test for overall effect	Z=1.20 (P = 0.23)					0.001 0.1 1 10 10 Favours Trans-Axillary Favours Trans-Aortic
C- Cardiac Tamp	onade						
Study or Subgroup	Trans-Axi Events	Ilary 1 Total F	rans-Aor	tic Total V	Neight M	Risk Ratio H. Random, 95% Cl. Ye	Risk Ratio ar M.H. Random, 95% Cl
Eroblich 2015	4	188	1	185	34.0%	3 94 10 44 34 891 20	
Beve 2019	2	73	3	41	42.0%	0.37 [0.07, 2.15] 20	19
Myat 2020	0	82	4	142	24.0%	0.19 [0.01, 3.51] 20	20
T-1-1 (051) 00		3/2		200	100.0**	0 74 10 40 1 000	
rotal (95% CI)		343	~	368	100.0%	0.71 [0.12, 4.03]	
Heterogeneity Tour? -	5 1.09: CMP-	267 ~	- 2 (0 - 0	161-12	- 45%		
Test for overall effect:	1.08, UNI*: 7 = 0.39 /P	= 0.70)	- 2 (P = 0	. 10), P	- 40%		0.001 0.1 1 10 10
. Sation overall ellect 2	L = 0.38 (P	- 0.70)					Favours Trans-Axillary Favours Trans-Aortic
- Conversion to	Sterno	tomy					
	Trans-A	xillary	Trans-A	ortic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Tota	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Damluji 2018	0	17	2	67	50.5%	0.76 [0.04, 15.05]	
Myat 2020	0	82	2	142	49.5%	0.34 [0.02, 7.09]	
T-1-1 (051) OD		0-			100 5	0.5410.00	
rotal (95% CI)		99		209	100.0%	0.51 [0.06, 4.30]	
Lotar events	0	- 0 - 2	4	. 0.70	12 - 0%		
Test for everall effect	7 = 0.62 /	= 0.13,1	31 = 1 (P =	= 0.72),	1-= 0%		0.001 0.1 1 10 10
restion overall ellect.	2 = 0.02 (r = 0.54)					Favours Trans-Axillary Favours Trans-Aortic
E- Device Succes	SS						
	Trans-Axi	ilary 1	rans-Aor	tic		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total E	vents	Total I	Neight M	H, Random, 95% CI Ye	ar M-H, Random, 95% Cl
Adamo 2015 Fiorina 2017	124	32	39	44	10.5%	0.78[0.60, 1.00] 20	17
Codner 2018	11	11	11	11	17 0%	1 00 (0.85 1 18) 20	18
Damluji 2018	17	17	61	67	25.4%	1.07 [0.96, 1.20] 20	18
Khan 2018	22	24	25	27	18.6%	0.99 [0.84, 1.16] 20	18
Total (95% CI)		231		244	100.0%	0.97 [0.88, 1.07]	•
Total events	196	0.00	222		6704		
Helefodenelly Laure:	0.04.01.7	= 9 3U AT	= 4 (P = 0	(.05); 1-	= 57%		0.2 0.5 1 2
Test for overall effect: 2	0.01; Chi ² : Z = 0.59 (P	= 0.55)					Favours frams-Autic Favours frams-Admary
Test for overall effect 2	0.01; Chi ² : Z = 0.59 (P leeding	= 0.55)					
Test for overall effect: 3	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axil	= 0.55)	ans.Aorti	c		Risk Ratio	Risk Ratio
Test for overall effect: ; F- Incidents of B Study or Subgroup	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events	= 0.55) lary Tr Total Ev	ans-Aorti ents To	c otal W	eight M.H	Risk Ratio I, Random, 95% Cl Year	Risk Ratio M-H, Random, 95% Cl
Test for overall effect: ; F- Incidents of B Study or Subgroup 1.15.1 Observational s	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events tudies	ary Tr	ans-Aorti ents To	c btal W	eight M-H	Risk Ratio , Random, 95% Cl Year	Risk Ratio M-H, Random, 95% Cl
Test for overall effect: ; F- Incidents of B Study or Subgroup 1.15.1 Observational s Adamo 2015 Study 2	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events tudies 3	ary Tr Total Ev	ans-Aorti ents To	c otal W	eight M-H 4.3%	Risk Ratio , Random, 95% Cl Year 2.06 [0.37, 11.64] 2015	Risk Ratio M-H, Random, 95% Cl
Test for overall effect: ; F- Incidents of Bi Study or Subgroup 1.15.1 Observational s Adamo 2015 Fiorina 2017 Dambuii 2018	0.01; Chi ^a : Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3	= 0.55) lary Tr Total Ev 32 147 17	ans-Aorti <u>ents To</u> 2 36 5	c tal W 44 95 2 67	eight M-H 4.3% 8.3% 6.8%	Risk Ratio , Random, 95% Cl Year 2.06 (0.37, 11.64) 2015 0.93 (0.67, 1.31) 2017 2.36 (0.63 2.93) 2040	Rink Ratio M H, Random, 95% Cl
Test for overall effect: J F- Incidents of B Study or Subgroup 1.15.1 Observational s Adamo 2015 Fiorina 2017 Damluji 2018 Beve 2019	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3 6	= 0.55) ary Tr Total Ev 32 147 17 73	ans-Aorti ents To 2 36 5 10	c tal W 44 95 2 67 41 1	eight M-H 4.3% 8.3% 6.8% 1.5%	Risk Ratio , Random, 95% CI Year 2.06 [0.37, 11.64] 2015 0.93 [0.67, 1.31] 2017 2.36 [0.63, 8.93] 2018 0.34 [0.13, 0.86] 2014	Risk Ratio M.H. Random, 95% Cl
Testfor overall effect: : F- Incidents of B. Study or Subgroup 1.15.1 Observational st Adamo 2015 Fiorina 2017 Damluji 2018 Beve 2019 Myał 2020	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3 6 10	ary Tr Total Ev 32 147 17 73 82	ans-Aorti ents To 2 36 5 10 25 1	c 44 95 2 67 41 1 142 1	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9%	Risk Ratio , Random, 95% CI Year 2.06 [0.37, 11.64] 2015 0.39 [0.67, 1.31] 2017 2.36 [0.63, 8.93] 2018 0.34 [0.13, 0.86] 2019 0.69 [0.35, 1.37] 2020	Risk Ratio MH, Random, 95% CI
Test for overall effect: J F- Incidents of B Study or Subgroup 115.1 Observational s Adamo 2015 Fiorina 2017 Damiluji 2018 Beve 2019 Myał 2020 Subtotal (95% CI)	0.01; Chi ² : Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3 6 10	ary Tr Total Ev 32 147 17 73 82 351	ans-Aortii ents To 2 36 5 10 25 1 3	c 44 95 2 67 41 1 142 1 389 6	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9% 7.8%	Risk Ratio Random, 95% Cl Year 2.06 [0 37, 11.64] 2015 0.93 [0.67, 1.31] 2017 2.36 [0.63, 9.83] 2018 0.34 [0.13, 0.66] 2019 0.69 [0.35, 1.37] 2020 0.68 [0.51, 1.41]	Risk Ratio MH, Random, 95% CI
Test for overall effect: J F- Incidents of B Study or Subgroup 1.15.1 Observational s Adamo 2015 Fiorina 2017 Damluji 2018 Beve 2019 Myał 2020 Subtotai (95% CI) Total events	0.01; Chi#: Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3 6 10 74	any Tr Total Ev 32 147 17 73 82 351	ans-Aorti ents To 2 36 5 10 25 1 3 78	c 44 95 2 67 41 1 142 1 389 6	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9% 7.8%	Risk Ratio , Random, 95% Cl Year 2.06 [0.37, 11.64] 2015 0.93 (0.67, 1.31] 2017 2.36 [0.63, 9.53] 2018 0.34 [0.13, 0.66] 2019 0.69 [0.35, 1.37] 2020 0.85 [0.51, 1.41]	Risk Ratio M.H., Random, 95% CI
Test for overall effect : F- Incidents of B Study or Subgroup 1.15.1 Observational s Adamo 2015 Fiorina 2017 Damluj 2018 Beve 2019 Myal 2020 Subtotal (95% CI) Total events Heterogeneity. Tau [*] = 0 Fest for overall effect Z	0.01; Chi [#] : Z = 0.59 (P leeding Trans-Axill Events itudies 3 52 3 6 10 74 0.15; Chi [#] = = 0.64 (P =	ary Tr Total Ev 32 147 17 73 82 351 7.70, df = :0.52)	ans-Aorti ents To 36 5 10 25 1 3 78 4 (P = 0.1	c 44 95 2 67 41 1 142 1 389 6 0); P=	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9% 7.8% 48%	Risk Ratio Random, 95% Cl Year 2.06 [0.37, 11.64] 2015 0.93 [0.67, 1.31] 2017 2.36 [0.63, 9.83] 2018 0.34 [0.13, 0.66] 2019 0.69 [0.35, 1.37] 2020 0.85 [0.51, 1.41]	Risk Ratio MH, Random, 95% CT
Test for overall effect : F- Incidents of B Study or Subgroup 1 1.15.1 Observational s Adamo 2015 Fiorina 2017 Damluij 2018 Beve 2019 Myal 2020 Subtotal (95% Cl) Total events Hederogeneiky: Tau*= 0 Test for overall effect Z 1452 DC7.	0.01; Chi [#] : Z = 0.59 (P leeding Trans-Axill Events 3 52 3 6 10 74 0.15; Chi [#] = = 0.64 (P =	ary Tr Total Ev 32 147 17 73 82 351 7.70, df= : 0.52)	ans-Aorti ents To 2 36 5 10 25 1 3 78 4 (P = 0.1	c 44 95 2 67 41 1 42 1 389 6 10); I ² =	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9% 7.8% 48%	Risk Ratio Random, 95% CI Year 2.06 [0.37, 11.64] 2015 0.93 [0.67, 1.31] 2017 2.36 [0.38, 933] 2018 0.34 [0.13, 0.68] 2019 0.38 [0.51, 1.41]	Risk Ratio MH, Bandom, 95% CI
Test for overall effect : F- Incidents of B Study or Subgroup 1.15.1 Observational st Adamo 2015 Fiorina 2017 Damilui 2018 Beve 2019 Myat 2020 Subtotal (95% CI) Total events Heterogeneity Tau ² = 0 Test for overall effect Z 1.152.PCTs Pacetro 2014	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axiil Events tudies 3 5 2 3 6 10 74 74 74 2 5 6 10 74 5 6 10 5 6 10 5 6 10 5 6 10 5 10 10 10 10 10 10 10 10 10 10	ary Tr Total Ev 32 147 17 73 82 351 7.70, df = 0.52)	ans-Aorti ents To 2 36 5 10 25 1 3 78 4 (P = 0.1	c 44 95 2 67 41 1 42 1 389 6 10); I ^a =	eight M.H 4.3% 6.8% 6.8% 6.9% 7.8% 48%	Risk Ratio ,Random, 95% CI Year 2.06 [0 37, 11.64] 2015 2.36 [0.53, 0.83] 2018 0.34 [0.13, 0.66] 2019 0.38 [0.51, 1,44] 0.68 [0.51, 1,44]	Risk Ratio MH, Random, 95% CI
Test for overall effect : F- Incidents of B Study or Subgroup 1.15.1 Observational s Adamo 2015 Fionna 2017 Damulij 2018 Beve 2019 Myat 2020 Subtotal (95% CI) Test for overall effect 2 1.52.RCTS Readon 2014 Subtotal (95% CI)	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axiil Events studies 3 52 3 6 10 74 2.15; Chi [#] = = 0.64 (P = 54	ary Tr Total Ev 32 147 17 73 82 351 7.70, df= 0.52) 146 146	ans-Aorti ents To 2 36 5 10 25 1 3 78 4 (P = 0.1	c 44 95 2 67 41 1 142 1 389 6 10); P= 340 3 340 3	eight M.H 4.3% 6.8% 6.8% 6.9% 7.8% 48% 2.2%	Risk Ratio Random, 95% CI Year 2.06 [037, 11.64] 2015 0.93 [0.67, 1.31] 2017 2.36 [0.53, 8.33] 2018 0.68 [0.53, 8.33] 2018 0.68 [0.55, 1.44] 0.58 [0.46, 0.73] 2014 0.58 [0.46, 0.73] 2014	Risk Ratio
Test for overall effect : F- Incidents of B Study or Subgroup 1.15.0 Diservational s' Adamo 2015 Piroina 2017 Damibil 2018 Beve 2019 Myal 2020 Damibil 2018 Beve 2019 Myal 2020 Total events Hotorpanetic for overall effect Z 1.15.2 RCTs Rearding 2014 Subtotal (95% CI) Total events	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axill Events tudies 3 52 3 6 10 74 0.15; Chi [#] = 54 54	ary Tr Total Ev 32 147 17 73 82 351 7.70, df= 0.52) 146 146	ans-Aorti rents To 2 36 5 10 25 1 3 78 4 (P = 0.1 217 3 217	c 44 95 2 67 41 1 142 1 389 6 10); P= 340 3 340 3	eight M.H 4.3% 6.8% 6.9% 7.8% 48% 2.2%	Risk Ratio <u>Random, 95% CI Year</u> 2.06 (0.37, 11.64) (0.15 0.39) (0.67, 13.11 (2017) 2.36 (0.63, 0.83) 2016 0.43 (0.13, 0.68) (0.68) 0.69 (0.51, 1.37) 2020 0.85 (0.46, 0.73) 2014 0.58 (0.46, 0.73)	Risk Ratio MH, Random, 95% CI
Testfor overall effect 2 F-Incidents of B Study or subgroup 1151 Observation Adamo 2015 Fiorina 2017 Damibij 2018 Beve 2019 Myat 2020 Subdral (95% CI) Total events Hetrogenetic, Tau* e O Test for overall effect 2 1.152.PCTS Reardon 2014 Subdral (95% CI) Total events Hetrogenetic, Not appl	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axill Events itudies 3 52 3 6 10 74 2.15; Chi [#] = = 0.64 (P = 54 54 54	= 0.55) lary Tr Total Ev 32 147 73 82 351 7.70, df= = 0.52) 146 146	ans-Aorti eents To 2 36 5 10 25 1 3 78 4 (P = 0.1 217 3 217	c 44 95 2 67 41 1 142 1 389 6 10); I [#] = 340 3 340 3	eight M-H 4.3% 8.3% 6.8% 6.9% 6.9% 48% 48% 2.2%	Risk Ratio Random, 95% CI Year 2.06 [0.37, 11.64] 2015 2.36 [0.33, 0.87], 311 2017 2.36 [0.35, 0.83] 2019 0.45 [0.35, 1.37] 2020 0.45 [0.35, 1.37] 2020 0.45 [0.46, 0.73] 2014 0.58 [0.46, 0.73] 2014	Risk Ratio
Test for overall effect : F- Incidents of B Study or subgroup 1.15.1 Observational Addition 2015 Daming 2015 Daming 2018 Beve 2019 Myat 2020 Subdral (95% CI) Total events Heterogeneity, Tau" = 0 Total events Heterogeneity, Class Subdral (95% CI) Total events Heterogeneity, Not app Test for overall effect 2	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axill Events itudies 3 52 3 6 10 74 0.15; Chi [#] = = 0.64 (P = 54 54 54 54 54	= 0.55) lary Tr Total Ev 32 147 73 82 351 7.70, df = 0.52) 146 146 146	rans-Aorti rents To 2 36 5 10 25 1 3 78 4 (P = 0.1 217 3 217	c tal W 95 2 67 41 1 442 1 442 1 889 6 0); P= 340 3 340 3	eight M-H 4.3% 8.3% 6.8% 6.9% 6.9% 7.8% 48% 48% 2.2%	Risk Ratio Randem, 95%, CI Year 2.06 (0.2.7, 1.54), 2015 0.39 (0.67, 1.51), 2017 0.34 (0.13, 0.86), 2019 0.36 (0.51, 1.41) 0.56 (0.46, 0.73), 2014 0.58 (0.46, 0.73)	Risk Ratio MH, Randem, 95% CI
Test for overall effect 2 F-Incidents of B Study or Subgroup 1151 Observation Adamo 2015 Fiorina 2015 Fiorina 2017 Damilyi 2018 Beve 2019 Med 2020 Beve 2019 Med 2020 Med 2020 Test for overall effect 2 Test for overall effect 2 Test overall effect 2	0.01; Chi [#] = Z = 0.59 (P leeding Trans-Axill Events 3 52 3 6 10 74 0.15; Chi [#] = 54 54 54 54 54 54	= 0.55) lary Tr Total Ev 147 17 73 82 351 7.70, df= 0.52) 146 146 146 0.00001, 497	ans-Aorti- eents To 2 36 5 10 25 1 25 1 25 1 2 7 8 4 (P = 0.1 2 217 2 217 2 7	c <u>stal W</u> 44 95 2 67 41 1 142 1 142 1 142 1 14389 6 0); P= 340 3 340 3 340 3	eight M-H 4.3% 8.3% 6.8% 1.5% 6.9% 48% 48% 2.2% 2.2% 2.2%	Risk Ratio <u>Random, 95% CI Year</u> 2.06 [0.37, 11.64] 2015 2.36 [0.33, 0.67, 13] 2017 2.36 [0.33, 0.83] 2016 0.48 [0.46, 0.73] 2014 0.56 [0.46, 0.73] 2014 0.56 [0.46, 0.73] 2014	Risk Ratio
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FIGURE 9: Forest plots for the following outcomes: (A) paravalvular leak, (B) blood transfusion, (C) cardiac tamponade, (D) conversion to sternotomy, (E) device success, (F) incidents of bleeding, (G) contrast amount, and (H) procedure time

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Fröhlich et al. (2015) [19], Fiorina et al. (2017) [18], Codner et al. (2018) [16], Damluji et al. (2018) [17], Khan et al. (2018) [5], Beve et al. (2019) [15], Lin et al. (2021) [13], and Myat et al. (2020) [12].

Regarding device success, there was no significant difference observed between both approaches (RR: 0.97; 95% CI: 0.88, 1.07; P = 0.55; Figure *9E*), with heterogeneity being of moderate nature ($I^2 = 57\%$). We performed a sensitivity analysis to lower the heterogeneity to an acceptable level ($I^2 = 31\%$), which still depicted no significant difference in device success between the approaches (RR: 0.99; 95% CI: 0.92, 1.07; P = 0.90; Figure *10*).

	Trans-Ax	illary	Trans-A	ortic		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% CI
Fiorina 2017	124	147	86	95	35.6%	0.93 [0.85, 1.02]	2017	
Codner 2018	11	11	11	11	16.7%	1.00 [0.85, 1.18]	2018	
Damluji 2018	17	17	61	67	30.1%	1.07 [0.96, 1.20]	2018	+
Khan 2018	22	24	25	27	17.6%	0.99 [0.84, 1.16]	2018	_
Total (95% CI)		199		200	100.0%	0.99 [0.92, 1.07]		+
Total events	174		183					
Heterogeneity: Tau ² =	0.00; Chi ²	= 4.38,	df = 3 (P =	0.22);	² = 31%			
Test for overall effect:	Z = 0.13 (F	= 0.90)	i.					Favours Trans-Aortic Favours Trans-Axillary

FIGURE 10: Forest plot for device success (sensitivity analysis)

References: Fiorina et al. (2017) [18], Codner et al. (2018) [16], Damluji et al. (2018) [17], and Khan et al. (2018) [5].

Similarly, no significant difference was found in the incidence of bleeding between both groups (RR: 0.75; 95% CI: 0.51, 1.10; P = 0.14; Figure 9*F*), with heterogeneity being of moderate nature (I² = 60%). Heterogeneity was decreased using sensitivity analysis (I² = 49%), and the pooled estimates remained insignificant (RR: 0.70; 95% CI: 0.43, 1.13; P = 0.14; Figure 11).

	Trans-Ax	illary	Trans-A	ortic		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl
1.15.1 Observational	studies							
Adamo 2015	3	32	2	44	6.7%	2.06 [0.37, 11.64]	2015	
Damluji 2018	3	17	5	67	10.3%	2.36 [0.63, 8.93]	2018	
Beve 2019	6	73	10	41	16.9%	0.34 [0.13, 0.86]	2019	
Myat 2020	10	82	25	142	24.1%	0.69 [0.35, 1.37]	2020	
Subtotal (95% CI)		204		294	58.1%	0.86 [0.38, 1.97]		
Total events	22		42					
Heterogeneity: Tau ² =	0.39; Chi²	= 7.03,	df = 3 (P =	0.07);	² = 57%			
Test for overall effect:	Z = 0.36 (P	= 0.72)						
1.15.2 RCTs								
Reardon 2014	54	146	217	340	41.9%	0.58 [0.46, 0.73]	2014	
Subtotal (95% CI)		146		340	41.9%	0.58 [0.46, 0.73]		◆
Total events	54		217					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 4.72 (P	< 0.00	001)					
Total (95% CI)		350		634	100.0%	0.70 [0.43, 1.13]		•
Total events	76		259					
Heterogeneity: Tau ² =	0.13; Chi2	= 7.77,	df = 4 (P =	0.10);	² = 49%			
Test for overall effect:	Z=1.47 (P	= 0.14)						Eavours Trans-Avillany Eavours Trans-Aortic
Test for subgroup diff	erences: C	$hi^2 = 0.8$	31, df = 1 (P = 0.3	7), $I^2 = 0\%$	6		ravours mans-romary ravours mans-Autuc

FIGURE 11: Forest plot for incidents of bleeding (sensitivity analysis)

References: Reardon et al. (2014) [21], Adamo et al. (2015) [20], Damluji et al. (2018) [17], Beve et al. (2019) [15], and Myat et al. (2020) [12].

Three studies in our analysis reported data concerning the contrast amount used in the TAVI procedure. The TAo route used significantly less contrast amount as compared to the TAx approach (mean difference: 27.40; 95% CI: 3.73, 51.08; P = 0.02; Figure 9G) with moderate heterogeneity in the studies ($I^2 = 50\%$).

Additionally, two studies reported procedure time. The cumulative results revealed no significant mean difference between the groups (mean difference: 4.44; 95% CI: –96.30, 105.17; P = 0.93; Figure 9H), with high heterogeneity amongst studies (I² = 97%).

Discussion

Femoral access, the conventional approach to TAVI, is associated with significantly fewer adverse outcomes than other approaches [4]. Even so, in less than half of the cases, it is denied due to complicated anatomies, such as small body habitus and severe peripheral vascular disease. In these cases, non-femoral techniques such as transapical (TA), TAo, and TAx approaches are considered. This updated meta-analysis compares two such techniques, i.e., the TAx versus TAo approach.

Our meta-analysis showed that the TAx had statistically significant lower 30-day mortality than the TAo approach, a finding also concluded by a previous meta-analysis [22]. This is in contrast to Myat et al., Pineda et al., and Beve et al., where there was no significant difference in in-hospital, 30-day, and one-year all-cause mortality [12,14,15]. It is speculated that this is related to the invasiveness between the two approaches, with TAx being less invasive than TAo and thus favoring a better outcome. Differences in the patients' baseline characteristic profile may also have been contributory, with TAo having individuals with higher comorbid factors including hypertension, diabetes mellitus, prior myocardial infarction, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, higher Society of Thoracic Surgeons (STS) score, and higher logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (shown in Table 1). The higher mortality score predicted by STS and EuroSCORE for the TAo group was, however, not significant. With respect to patient comorbidities, similar reasoning has been cited in the previous literature,

notably one of the most extensive studies assessing the outcome so far [19].

Furthermore, the TAVI approach has been linked with an overall higher 30-day stroke incidence than traditional surgical replacement. This has been made evident by the appearance of new, clinically silent cerebral lesions on post-procedure MRI [23]. The likely reason for this is the dislodged atherosclerotic or calcific debris from the aorta or the calcified aortic valve [23]. Our meta-analysis evaluated the 30-day stroke incidence between the TAx and TAo approaches. The results concluded that no technique was superior when considering this particular complication. Considering the pooled estimates of studies included in this meta-analysis, the frequency was reasonably similar between the two approaches (28/776 events in TAx and 31/963 events in TAo). Prior atrial fibrillation has been cited as a risk factor for the development of stroke post-TAVR [24]. Since both approaches recorded a fairly similar incidence of prior atrial fibrillation (2.4% for TAx vs. 2.0% for TAo), this may also have been a contributing factor to the similar stroke rates between the two approaches [24]. However, another plausible explanation for these results may be the inadequate sample size of the included studies.

One other complication of TAVI is AKI. It is possibly caused by prerenal azotemia and nephrotoxic injuries, leading to renal ischemia and acute tubular necrosis (ATN) [25]. Renal ischemia is also attributed to hypovolemia, hemorrhage, low cardiac output, or renal vasoconstriction caused by vasoconstrictive medication [25]. When focusing on the non-femoral approaches and the AKI events associated with each approach, our results highlighted that the TAx approach was significantly safer than the TAo approach (9.9% vs. 18.6%). Despite lower contrast media being used in the TAo group, the incidence of AKI was much higher in the TAo group. This finding was also corroborated by Fiorina et al., where baseline creatinine levels were similar amongst the patient populations of the two approaches [18]. In a study conducted by Aregger et al., it was noted that amongst patients undergoing TAVI, higher rates of AKI were linked to lower hemoglobin concentration, higher blood transfusions rates, higher post-procedure thrombocytopenia, higher leukocyte count due to ongoing severe inflammatory response syndrome (SIRS), and an increased length of hospital stay [26]. Moreover, hypertension, diabetes, peripheral arterial disease, higher STS, and higher EuroSCORE have all been identified as factors associated with increased risk of AKI in patients undergoing TAVR [27]. With respect to our study, while many factors could not be ascertained due to paucity of the available data, the incidence of diabetes mellitus, hypertension, peripheral arterial disease, and mortality predictive scores was lower in the TAx group and these may have been crucial contributing reasons why lower AKI rates were observed in that group.

PPM implantation remains one of the frequent complications of TAVI. Conduction abnormalities originating from anatomic interaction between the valve prosthesis and the atrioventricular node and bundle of His are the implicated causes requiring pacemakers' implantation [28]. According to a meta-analysis conducted by Zhan et al., male sex, baseline atrioventricular conduction delays, intra-procedural atrioventricular block, and use of mechanically expandable or self-expanding prosthesis serve as positive predictors of PPM implantation in patients undergoing TAVI [29]. Furthermore, with respect to comorbidities, literature has reported diabetes as a significant predictor while hypertension, COPD, prior percutaneous coronary intervention (PCI), or prior aortic valve procedures were not [30]. Our meta-analysis concluded that the TAx approach had a higher pacemaker implantation rate. One possible confounder for this could be that most patients undergoing the TAx have self-expandable valves implanted, which are linked to higher rates of PPM placement [22]. This higher rate is attributed to the difference in design and frame of the valve that exerts a radial force on the conduction tissue [30]. However, the proximity of aortic access to the aortic valve annulus in the TAo approach possibly mediates a lesser risk of conduction interruption and ensures more precise valve placement.

When stratified for the length of hospital stay, our analysis concluded that the TAx group was associated with a shorter stay than the TAo group. This finding coincides with the previous meta-analysis [22]. The favorable outcomes in the TAx approach could be due to a less invasive surgical cut-down than the TAo approach, leaving the chest cavity untouched. Similarly, the requirement for ventilation and intensive care unit stay and duration of general anesthesia might also be less in TAx than TAo approach [19]. Literature on healthcare optimization has shown that patients may be optimized with reduced procedural times, and the risk of in-hospital infections is reduced with a shorter hospital stay [16]. Furthermore, same-day discharge and next-day discharge in patients undergoing uncomplicated TAVI have been associated with lower mortality, stroke, and 30-day rehospitalization [31].

Moreover, vascular complications are one of the significant concerns of TAVI due to the predominant use of large-bore sheaths for vascular access [32]. Major complications include aortic dissection, aortic rupture, annulus rupture, access site vascular injury, distal embolization, and ipsilateral lower extremity ischemia [32]. The rate of vascular complications was higher in the TAx approach in our analysis, which is consistent with the literature [33]. One reason could be that in a TAx TAVI, the proximal third of the axillary artery can be feasibly punctured in a fully percutaneous approach [32]. In this case, the minimum vessel diameter should be 6 mm, but it can exceed 7 mm in cases of prior coronary artery bypass grafting (CABG) surgery using the ipsilateral internal mammary artery [32]. The pattern of vascular complications in TAx TAVI is similar to that seen in the transfemoral approach. However, it is relatively difficult to achieve hemostasis with manual compression. This is due to the lack of supporting structures to reinforce during compression at the TAx site [32]. On the contrary, the TAo approach can lead to tearing suture lines and an

incommodious arterial closure due to the fragility of ascending aorta.

Among the other outcomes evaluated in this meta-analysis, the pooled estimates showed no statistically significant difference between TAx and TAo approaches to TAVI in the incidence of PVL, blood transfusion, tamponade, conversion to sternotomy, bleeding, device success, contrast amount, and procedure time. Inadequate sample size and heterogeneity might have affected these results. In addition, the sensitivity analysis did not reveal a significant difference amongst the outcomes showing moderate/high heterogeneity. Although most of the outcomes were in favor of TAx TAVI, it is too early to say if it would be better than TAo TAVI. More studies, especially RCTs, are recommended to monitor the sequelae of both approaches.

The major limitation of our study stems from the small number of studies that qualified for the metaanalysis and only one available RCT. These studies involve self-expandable and balloon-expandable valves of different generations, and with the mixed-use of devices, the small number of studies did not allow a device stratification. Therefore, our study could be confounded by a device-related bias. In addition, most of the studies included were unmatched retrospective cohort studies. Although these studies reported outcomes using the Valve Academic Research Consortium (VARC) criteria, data reporting still has significant heterogeneity, including baseline characteristics and outcome measures. There could be inherent publication bias with the present meta-analysis due to the nature of retrospective studies that tend to report favorable outcomes. These necessitate improved data collection and standardization of the health centers to remove the surgical bias [19], and studies should also focus on other aspects of these procedures (e.g. procedural success and rate of re-operations). To authenticate the findings concluded in this metaanalysis and further improve our understanding of the efficacy, safety, and risk profile between TAx and TAo approaches for TAVI, large sample randomized clinical trials are required on a wide scale.

Conclusions

To our knowledge, this meta-analysis is the largest to date consisting of 1793 patients, directly comparing the TAx and TAo techniques for AVR. We observed that the TAx approach had a more favorable profile regarding outcomes such as lower 30-day mortality, lower incidence of AKI, and shorter hospital stay. In others, TAo reported a better result, for instance, lower incidence of PPM implantation and lesser vascular complications. Other outcomes such as conversion to sternotomy, paravalvular leak, blood transfusion, procedure time, and contrast amount had no significant differences, regardless of the technique used. Truly reaching a definite verdict regarding the better technique overall will require further studies with rigorous data collection and standardization. However, at present, this meta-analysis provides physicians with an indepth evaluation of the advantages and disadvantages of each method, guiding their decisions according to the outcomes desired in each patient.

Appendices

Appendix A

Search strategy

("transcatheter aortic valve replacement" [MeSH Terms] OR ("transcatheter" [All Fields] AND "aortic" [All Fields] AND "valve" [All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields] OR (("percutaneous"[All Fields] OR "percutaneously"[All Fields] OR "percutaneous"[All Fields]) AND ("aorta"[MeSH Terms] OR "aorta"[All Fields] OR "aortic"[All Fields] OR "aortics"[All Fields])) OR ("transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "implantation"[All Fields]) OR "transcatheter aortic valve implantation"[All Fields]) OR "TAVI"[All Fields] OR "TAVR"[All Fields]) AND ("axilla"[MeSH Terms] OR "axilla"[All Fields] OR "axillary"[All Fields] OR "axillaries"[All Fields] OR "axillaris"[All Fields] OR "Transaxillary"[All Fields] OR "Trans-axillary"[All Fields] OR ("subclavian"[All Fields] OR "subclavians"[All Fields]) OR "Trans-subclavian"[All Fields] OR ("transcervical"[All Fields] OR "transcervically"[All Fields])) AND ("transthoracal"[All Fields] OR "transthoracic"[All Fields] OR "transthoracical"[All Fields] OR "transthoracically"[All Fields] OR (("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directional"[All Fields] OR "directions"[All Fields] OR "directivities" [All Fields] OR "directivity" [All Fields] OR "directs" [All Fields]) AND ("aorta" [MeSH Terms] OR "aorta" [All Fields] OR "aortic"[All Fields] OR "aortics"[All Fields])) OR "trans-aortic"[All Fields] OR ("transaortal"[All Fields] OR "transaortic"[All Fields]) OR (("direct"[All Fields] OR "directed"[All Fields] OR "directing"[All Fields] OR "direction"[All Fields] OR "directions" [All Fields] OR "directivities"[All Fields] OR "directivity"[All Fields] OR "directs"[All Fields]) AND ("aorta"[MeSH Terms] OR "aorta"[All Fields] OR "aortic"[All Fields] OR "aortics"[All Fields])))

TABLE 2: Search strategy

Appendix B

Cureus

Newcastle	e-Ottawa	Scale								
		Selection				Comparability	Outcome			
Author	Year	Representativeness of the exposed cohort	Selection of the non- exposed cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score
Damluji et al. [17]	2018		-	•						8
Fiorina et al. [18]	2017						•		•	7
Fröhlich et al. [19]	2015		-	•			*		*	8
Khan et al. [5]	2018	*	-	*		**	*	*	·	8
Adamo et al. [20]	2015		-				•		•	8
Beve et al. [15]	2019	*	-	*			•	•		7
Codner et al. [16]	2018	•	-	·			*	-	*	7
Lin et al. [13]	2021	*	-	*		*	*	*	*	7
Myat et al. [12]	2020	•	-	*			•	•		8
Pineda et al. [14]	2019		-	·			*	•	*	7
Reardon et al. [21]	2014			*			*		*	7

TABLE 3: Newcastle-Ottawa Scale for quality assessment

Appendix C

Outcomes	No. of studies	Risk ratio (RR)/weighted mean difference (WMD), 95% Cl	Heterogeneity (%)	P-value
30-day mortality	10	0.45 (0.30, 0.68)	0	0.0001
30-day stroke	9	1.38 (0.81, 2.35)	0	0.24
Permanent pacemaker implantation	8	1.87 (1.30, 2.71)	40	0.0008
Acute kidney injury	6	0.46 (0.29, 0.72)	23	0.0007
Length of hospital stay	7	-2.01 (-2.60, -1.41)	0	<0.00001
Device success	4	0.99 (0.92, 1.07)	31	0.22
Contrast amount	2	33.02 (1.86, 64.18)	50	0.04
Incidents of bleeding	5	0.71 (0.48, 1.05)	63	0.08

TABLE 4: Outcomes after sensitivity analysis for the possible overlapping studies

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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