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Transcarotid Access Versus Transfemoral Access for Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

Henri Lu[1], Pierre Monney[1], Roger Hullin[1], Stephane Fournier[1], Christian Roguelov[1], Eric Eeckhout[1], Vladimir Rubimbura[1], Laurent Faroux[2], Adelin Barrier[3], Olivier Muller[1] and Matthias Kirsch[4]*

[1] Service of Cardiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [2] Cardiology Department, Reims University Hospital, Reims, France, [3] Service of Internal Medicine, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, [4] Service of Cardiovascular Surgery, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Background: The transfemoral (TF) route is the gold-standard access for transcatheter aortic valve replacement (TAVR). In 10–15% of patients, alternative accesses are needed, such as the transcarotid (TC) access. We performed a meta-analysis to compare 30-day mortality and complications between TC-TAVR and TF-TAVR.

Methods: We searched PubMed/MEDLINE and EMBASE from inception to January 2021 to identify articles comparing TC-TAVR and TF-TAVR. Patients' baseline characteristics, procedural outcomes, and clinical 30-day outcomes were extracted.

Results: We identified 9 studies, among which 2 used propensity-score matching, including 1,374 TC patients and 3,706 TF patients. TC-TAVR was associated with significantly higher EuroSCORE II and Logistic EuroSCORE values (respectively 8.0 ± 6.7 vs. 6.3 ± 5.4, $p = 0.002$ and 20.8 ± 14.2% vs. 20.0 ± 13.4%, $p = 0.04$), a higher prevalence of peripheral artery disease (52.6 vs. 32.8%, $p = 0.001$), previous cardiac surgery (26.3 vs. 22.4%, $p = 0.008$) and coronary artery disease (64.6 vs. 60.5%, $p = 0.020$). The pooled results found TC-TAVR to be associated with a significantly higher 30-day mortality risk (RR, 1.41, 95% CI, 1.02–1.96, $p = 0.040$), and a lower rate of 30-day major vascular complications (RR, 0.48, 95% CI, 0.25–0.92, $p = 0.030$). No significant difference was found regarding permanent pacemaker implantation, major bleeding and acute kidney injury. A subgroup analysis of the two propensity-score matched studies found a statistically increased risk of 30-day neurovascular complications (RR, 1.61, 95% CI, 1.02–2.55, $p = 0.040$).

Conclusion: Compared with TF-TAVR, TC-TAVR was associated with an increased risk of 30-day mortality, likely related to a higher surgical risk and comorbidity burden, and with an increased risk of 30-day neurovascular complications. Careful preprocedural patient selection and close periprocedural neurological monitoring are paramount.

Keywords: transcatheter aortic valve replacement, aortic valve stenosis, transcarotid, transfemoral, meta-analysis

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****Correspondence:***
Henri Lu
henri.lu@chuv.ch

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INTRODUCTION

The transfemoral (TF) access is considered as the standard route for transcatheter aortic valve replacement (TAVR), due to its minimally invasive nature and to relatively low complication rates. However, it is not suitable in 10–15% of patients, mainly because of anatomical considerations: iliofemoral atherosclerosis, small or heavily calcified vessels, extreme vessel tortuosity or abdominal aortic aneurysms (1). Alternative accesses such as the transapical (TAp) (2), transaortic (TAo) (3), transcarotid (TC), and transsubclavian (TSc) ones (4, 5), have been developed for these settings. The TC access is interesting as it avoids thoracotomy and allows a direct and shorter pathway to the aortic valve from the puncture site, with the benefit of stable catheter delivery and improved movement precision (6). Several studies have suggested that the TC access might yield better periprocedural and 30-day outcomes than the "transthoracic" ones (TAp or TAo) (7–9), and even outcomes comparable to the TF access (10, 11). Some concerns remain regarding the risk of neurovascular complications associated with TC-TAVR, which could theoretically be higher due to direct injury to the carotid artery, embolic events during vessel manipulation, or transient reduction in blood flow during the procedure (11). So far, no guideline regarding the choice of the first-line alternative pathway exists, as the options depend on the patient's anatomy and local experience. Previous meta-analyses compared TC-TAVR to other alternative accesses (12, 13), while others analyzed the pooled results of TC and TSc accesses vs. the TF access (14). To our knowledge, no meta-analysis was conducted on the comparison of TC-TAVR alone vs. TF-TAVR.

The objective of this meta-analysis was to access the risk of 30-day all-cause mortality and other 30-day complications of TC-TAVR, compared with TF-TAVR.

METHODS

This study followed the guidelines of the Cochrane handbook for systematic reviews of interventions (15). The results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (16).

Literature Search and Selection Criteria

A systematic literature search of all relevant data from inception to January 31st, 2021, was conducted via the online databases PubMed/MEDLINE (Medical Literature Analysis and Retrieval System Online) and EMBASE (Excerpta Medica Database), using the following keywords and Medical Subject Headings (MeSH): "transcatheter aortic valve implantation," "transcatheter aortic valve replacement," "TAVI," "TAVR," "transcarotid," "carotid," "transcervical." The search strategy is presented in **Supplementary Table 1**. Studies were included if they met the following criteria: (1) original articles, (2) comparison of TC and TF-TAVR, (3) reported data on population characteristics, periprocedural and 30-day clinical outcomes. Abstracts, case series, review articles, meta-analyses, non-human studies, and non-English language publications were excluded. When 2 similar studies were found from the same author, the most recent one was included in the final analysis. In the case of overlapping populations (based on a common data registry), only the most recent study, with the biggest and most thorough population sample was included. The eligibility of studies was independently assessed by two authors (HL and SF), with any disagreement resolved by consensus, or with the help of a third senior author (MK). The Newcastle-Ottawa scale was used to assess the quality of each study (17).

Outcomes

Pooled-data outcomes included 30-day all-cause mortality and 30-day complications: neurovascular complications [stroke or transient ischemic attack (TIA)], major vascular complications, major bleeding, permanent pacemaker implantation (PPM), and acute kidney injury (AKI). For each outcome, a subgroup analysis was performed with propensity-score matched studies only. Outcomes were defined as reported in the studies; whenever possible, the Valve Academic Research Consortium-2 (VARC-2) definitions were used (18).

Statistical Analyses

Data were summarized using descriptive statistics, with medians and interquartile ranges (IQR) or means with standard deviation (SD) for continuous variables, and frequencies with percentages for dichotomous variables. When data were reported as medians with IQR, they were not incorporated in the comparison analyses as they supposedly did not follow a normal distribution. Meta-analyses were performed by combining the results of the published incidence of the predetermined outcomes. The relative risks (RR) and their 95% confidence intervals (CI) were used as summary statistics. The I^2 statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance: intervals of $<25\%$, 25–50%, and $>50\%$ were used to classify heterogeneity as low, moderate, and high. The random-effects model was used to account for population diversity and methodological variation among studies. All *p*-values were two-sided. Publication bias was assessed by examination of the funnel plots for each outcome (**Supplementary Figure 1**).

Statistical analyses were carried out using the SPSS 24.0 (SPSS Inc., Chicago, Illinois, USA) and Review Manager 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark) softwares.

RESULTS

Search Results

A total of 1,027 references were identified through the PubMed/MEDLINE and EMBASE databases. After removing duplicates, 725 publications remained; 664 were excluded after screening at titles and abstracts. Sixty-one full-text articles were assessed for eligibility, with a further 52 being excluded. A large registry-based study using propensity-score matching was excluded because of overlapping population with another study (19, 20): the same registry was used in both cases, and the study period of the first was included in the study period of the

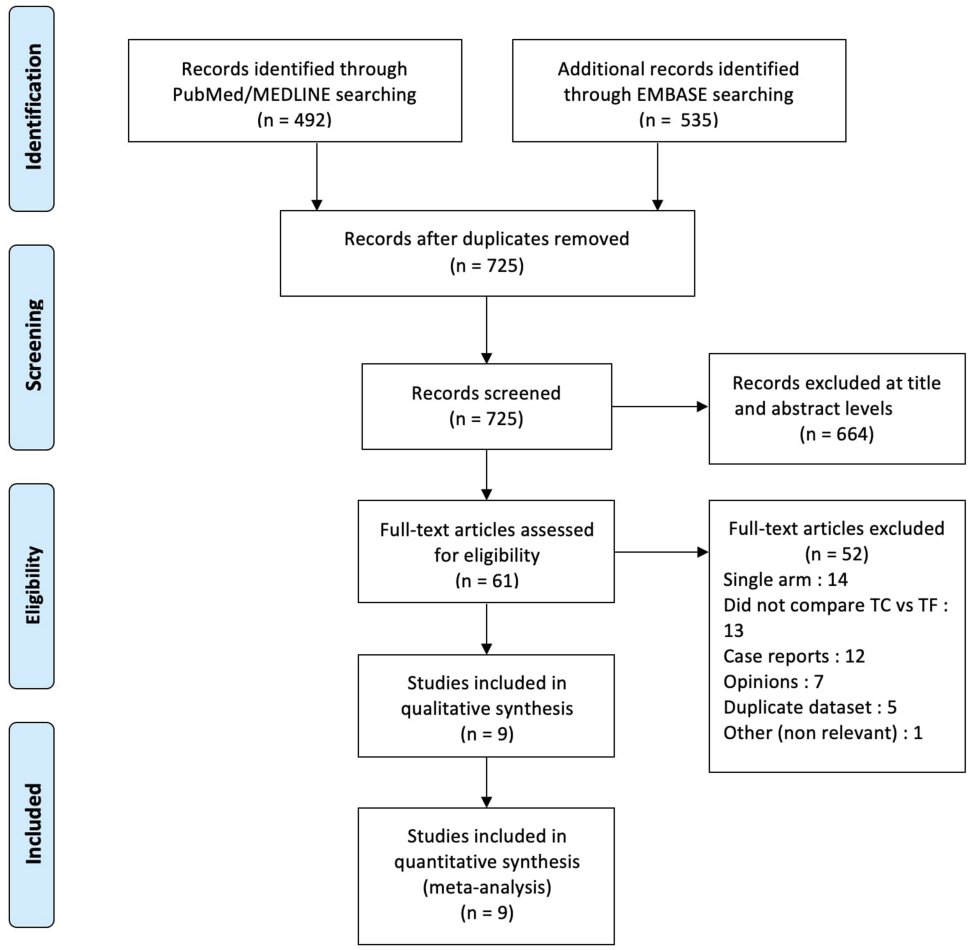

FIGURE 1 | PRISMA flow diagram.

second. Nine articles were finally identified and selected. The PRISMA diagram presents the search strategy (**Figure 1**). All nine studies were observational and retrospective in nature. One study used data from a multicenter prospective data registry (20), and two studies performed propensity-score matching (20, 21). In two studies, TC and TSc patients were pooled in one same extra-thoracic pathway group and compared with TF patients (20, 21): in the first case, **Supplementary Materials** were available online and were used to analyze TC patients; in the second case, two co-authors provided the data regarding TC patients. Following a quality assessment of each study, seven publications were considered high-quality and two publications medium quality, all being suitable for inclusion in the meta-analysis (**Supplementary Table 2**).

Study and Patient Characteristics

The nine studies included a total of 5,080 patients (TC-TAVR: 1374, TF-TAVR: 3706). Baseline patient characteristics, main comorbidities and surgical risk are presented in **Table 1**, while comparisons between the TC group and the TF group are presented in **Table 2** (dichotomous variables) and **Table 3** (continuous variables). There were differences regarding the way surgical risk was assessed: the EuroSCORE II was reported in 5 studies (11, 21–24), the Society of Thoracic Surgeons (STS) score in 6 (11, 22–27), and the Logistic EuroSCORE in 2 (20, 22). Overall, TC patients had a significantly higher prevalence of peripheral artery disease (PAD) (52.6 vs. 32.8%, $p = 0.001$), previous cardiac surgery (26.3 vs. 22.4%, $p = 0.008$), and coronary artery disease (64.6 vs. 60.5%, $p = 0.020$). TC patients presented a significantly higher surgical risk, as assessed by the EuroSCORE II and the Logistic EuroSCORE (respectively 8.0 ± 6.7 vs. 6.3 ± 5.4, $p = 0.002$ and 20.8 ± 14.2% vs. 20.0 ± 13.4%, $p = 0.04$); there was no significant difference regarding the STS score (6.9 ± 4.4 vs. 6.4 ± 4.3, $p = 0.29$).

Finally, TC patients were significantly younger than TF patients (81.4 ± 7.8 vs. 81.7 ± 8.0 years, $p = 0.04$). There was no significant difference regarding gender, hypertension, chronic obstructive pulmonary disease, diabetes, or history of neurovascular disease.

TABLE 1 | Characteristics of patients undergoing transcarotid transcatheter aortic valve replacement.

References	Study arm	Sample size	Age (years)	Male gender (%)	Surgical risk					Comorbidities (%)				
					EuroSCORE II	STS score	Logistic EuroSCORE	HTA	CAD	Previous cardiac surgery	Diabetes	PAD	COPD	Stroke/TIA
Kirker et al. (25)	TC	25	77.0 (72.0–83)	52.0	Unknown	6.1 (4.1–9.6)	Unknown	88.0	Unknown	44.0	48.0	80.0	28.0	16.0
	TF	100	83.0 (79.0–88.0)	51.0	Unknown	6.0 (4.4–8.1)	Unknown	85.0	Unknown	37.0	34.0	39.0	19.0	13.0
Paone et al. (27)	TC	32	79.0 ± 9.6	50.0	Unknown	6.9 ± 4.4	Unknown	93.8	Unknown	Unknown	34.4	78.1	62.5	40.6
	TF	373	80.4 ± 9.2	55.0	Unknown	6.1 ± 4.3	Unknown	91.4	Unknown	Unknown	41.0	23.3	27.4	21.2
Watanabe et al. (22)	TC	83	80.0 ± 7.5	65.1	8.2 ± 6.7	6.4 ± 3.3	24.2 ± 13.3	80.7	Unknown	24.0	31.3	61.4	34.9	9.6
	TF	643	81.4 ± 8.4	53.7	6.4 ± 5.5	6.7 ± 4.3	21.3 ± 12.4	75.1	Unknown	23.4	26.9	20.5	36.2	11.8
Beurtheret et al. (20)	TC	911	81.6 ± 7.8	60.0	Unknown	Unknown	20.54 ± 14.26	Unknown	63.9	26.3	30.3	52.6	23.1	12.6
	TF	1613	82.1 ± 7.6	63.3	Unknown	Unknown	19.43 ± 13.81	Unknown	62.4	22.1	29.1	49.9	25.1	13.6
Villecourt et al. (21)	TC	32	86.0 (79.2–88.0)	50.0	2.9 (2.0–4.4)	Unknown	Unknown	75.0	43.7	Unknown	31.2	46.9	15.6	12.5
	TF	40	84.0 (81.0–87.0)	42.5	3.2 (2.1–4.5)	Unknown	Unknown	80.0	47.5	Unknown	42.5	37.5	17.5	12.5
Junquera et al. (26)	TC	127	78.0 (72.0–82.0)	57.5	Unknown	4.7 (3.2–6.8)	Unknown	89.8	74.0	Unknown	44.1	47.2	33.9	11.8
	TF	399	82.0 (72.0-86.0)	56.9	Unknown	4.2 (2.8–6.7)	Unknown	84.2	59.9	Unknown	32.1	10.5	22.3	10.0
Lu et al. (11)	TC	51	83.0 (80.0–85.0)	60.8	3.9 (2.7–5.9)	4.06 (3.1–6.6)	Unknown	70.6	62.7	23.5	27.5	41.2	17.6	21.6
	TF	255	83.0 (79.0–87.0)	49.8	3.3 (2.0–5.7)	3.0 (2.1–4.9)	Unknown	75.7	52.1	11.0	24.3	14.1	12.9	11.4
Leclercq et al. (23)	TC	80	81.6 ± 7.5	68.8	7.8 ± 8.6	7.3 ± 5.4	Unknown	Unknown	Unknown	22.5	36.3	Unknown	Unknown	12.5
	TF	51	81.8 ± 6.3	33.3	5.5 ± 3.4	4.5 ± 2.5	Unknown	Unknown	Unknown	19.6	42.0	Unknown	Unknown	11.8
Hudziak et al. (24)	TC	33	77.0 (72.0–85.0)	51.5	6.0 (4.8–10.7)	Unknown	Unknown	100.0	Unknown	30.3	57.6	36.4	24.2	3.0
	TF	232	79 (74–83)	43.5	4.8 (2.8–7.9)	Unknown	Unknown	90.1	Unknown	28.9	43.1	18.1	12.5	11.2

Age, EuroSCORE II, and STS score are expressed as mean ± SD or median (IQR). STS, Society of Surgeons; HTA, hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

TABLE 2 | Comparison of dichotomous patient characteristics between TF-TAVR and TC-TAVR cohorts.

Characteristics	Number of studies (references)	TC-TAVR		TF-TAVR		*P*-value
		n	%	*n*	%	
Male gender	All (11, 20–27)	822	59.8	2,115	57.1	0.077
Comorbidities						
• HTA	7 (11, 21, 22, 24–27)	326	85.1	1,676	82.1	0.150
• CAD	4 (11, 20, 21, 26)	724	64.6	2,307	60.5	0.020
• Previous cardiac surgery	6 (11, 20, 22–25)	311	26.3	649	22.4	0.008
• Diabetes	All (11, 20–27)	453	33.0	1,153	31.1	0.206
• PAD	8 (11, 20–22, 24–27)	680	52.6	1,199	32.8	<0.001
• COPD	8 (11, 20–22, 24–27)	331	25.7	916	25.1	0.712
• TIA/stroke	All (11, 20–27)	193	14.0	493	13.3	0.491

STS, score: Society of Surgeons score; HTA, hypertension; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; TC, transcarotid; TF, transfemoral; TAVR, transcatheter aortic valve replacement; M-H, Mantel-Haenszel.

TABLE 3 | Comparison of continuous patient characteristics between TF-TAVR and TC-TAVR cohorts.

Characteristics	Number of studies (references)	TC-TAVR	TF-TAVR	Mean difference (95% CI)	*P*-value
Age (years)	4 (20, 22, 23, 27)	81.4 ± 7.8	81.7 ± 8.0	−0.59 (−1.15, −0.02)	0.04
Surgical risk					
• EuroSCORE II	2 (22, 23)	8.0 ± 6.7	6.3 ± 5.4	1.97 (0.75, 3.19)	0.002
• STS score	3 (22, 23, 27)	6.9 ± 4.4	6.4 ± 4.3	1.05 (−0.89, 2.98)	0.29
• Logistic EuroSCORE (%)	2 (20, 22)	20.8 ± 14.2	20.0 ± 13.4	1.44 (0.08, 2.80)	0.04

TC, transcarotid; TF, transfemoral; TAVR, transcatheter aortic valve replacement. Studies where data were reported as medians (IQR) were not incorporated in the comparison analyses as they supposedly did not follow a normal distribution.

Technical Aspects of TC-TAVR

Although TC-TAVR interventions were performed in heterogeneous ways in the 9 studies, some convergent points could be found: all cases used a surgical approach, with a 4–7 cm incision made along the anterior border of the sterno-cleido-mastoid muscle, which was then retracted to expose the common carotid artery. Subsequent technique for artery puncture and transcatheter heart valve (THV) placement then depended on the THV type that was used and local experience. Some technical aspects of TC-TAVR are presented in **Supplementary Table 3**. Self-expendable (SE) THVs were used in 52.7% of cases. All SE THVs belonged to the Medtronic CoreValve family (Medtronic, Minneapolis, MN, USA). Almost all remaining cases benefited from the Edwards SAPIEN family THVs (Edwards Lifesciences, Irvine, CA, USA), except one, reported by Hudziak et al., in which an Abbott Portico THV (Abbott Vascular, Santa Clara, CA, USA) was implanted (24). 70.8% of interventions were performed via the left common carotid artery (CCA). General anesthesia was used in 99.1% of cases. Finally, continuous cerebral monitoring via cerebral oximetry was reported in all but three studies: two did not describe cerebral monitoring (20, 23), while one reported not using cerebral monitoring (27). **Supplementary Table 4** shows the proportion of SE and balloon-expandable (BE) THVs used in TC and TF-TAVR interventions: SE THVs were more frequently used in the TC group compared with the TF group (46.3 vs. 36.0, $p < 0.001$).

Meta-Analysis of Outcomes

Thirty-day complications of TC-TAVR and their respective incidence are presented in **Supplementary Table 5**.

Thirty-Day All-Cause Mortality

Data regarding 30-day mortality were provided by all 9 studies. The pooled results found TC-TAVR to be associated with a significantly higher mortality risk (RR, 1.41, 95% CI, 1.02–1.96, $p = 0.04$), with no heterogeneity ($I^2 = 0\%$; **Figure 2A**). However, in a subgroup pooled analysis of the 2 propensity-score matched studies (20, 21), this association was no longer found (RR, 1.27, 95% CI, 0.83–1.93, $p = 0.28$, $I^2 = 0\%$; **Figure 2B**).

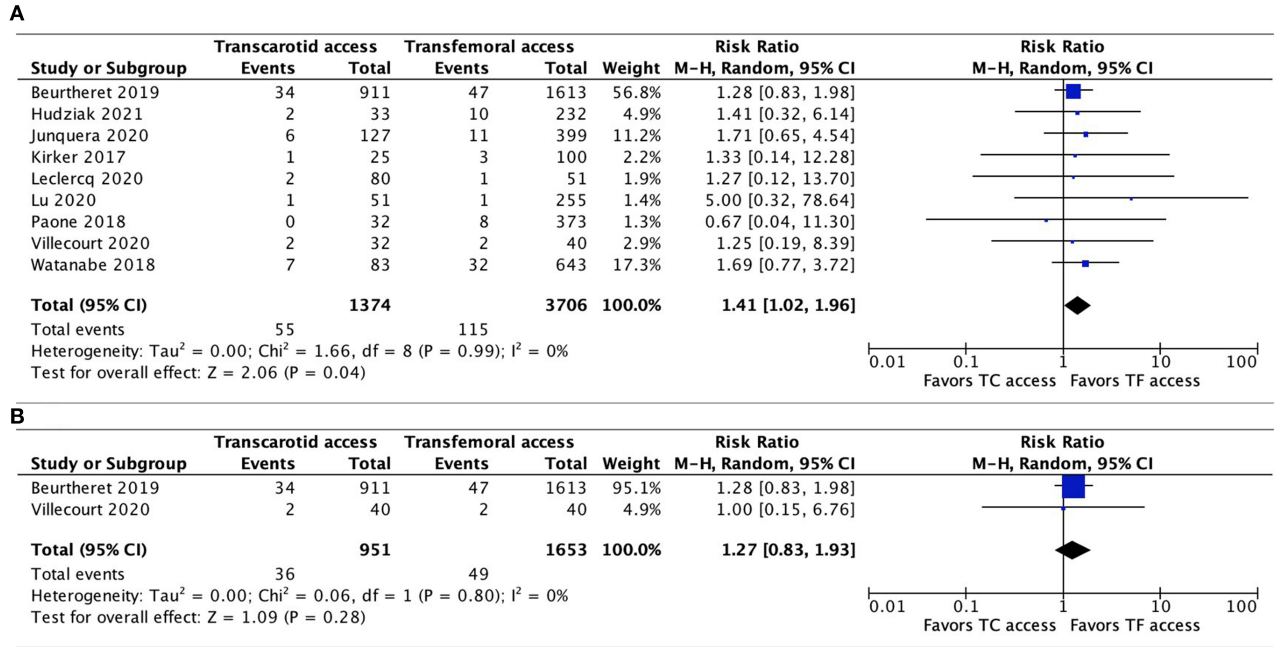

FIGURE 2 | Forest plots comparing 30-day all-cause mortality rates between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from all studies. **(B)** Pooled data from propensity-score matched studies. TC, transcarotid; TF, transfemoral.

Neurovascular Complications

Data regarding 30-day neurovascular complications were available in all 9 studies. The pooled results showed a trend toward a higher risk of neurovascular complications associated with TC-TAVR, without reaching statistical significance (RR, 1.36, 95% CI, 0.94–1.99, $p = 0.11$), and with no heterogeneity ($I^2 = 0\%$; **Figure 3A**). Interestingly, in the subgroup pooled analysis of the two propensity-score matched studies (20, 21), the association between TC-TAVR and neurovascular complications was statistically significant (RR, 1.61, 95% CI, 1.02–2.55, $I^2 = 0\%$, $p = 0.04$; **Figure 3B**).

Major Vascular Complications

Data on the incidence of major vascular complications were available in all 9 studies. In the pooled analysis, TC-TAVR was associated with a lower risk of major vascular complications (RR, 0.48, 95% CI, 0.25–0.92, $p = 0.03$; **Figure 4A**). Heterogeneity was low ($I^2 = 18\%$). In the subgroup pooled analysis of the 2 propensity-score matched studies (20, 21), this association was no longer found (RR, 0.43, 95% CI, 0.06–3.02, $p = 0.40$), but heterogeneity was high ($I^2 = 78\%$; **Figure 4B**).

Permanent Pacemaker Implantation

Seven studies reported the incidence of PPM implantation (11, 20, 22–24, 26, 27). There was no significant difference between TC-TAVR and TF-TAVR, either when all 7 studies were included (RR, 1.01, 95% CI, 0.87–1.17, $I^2 = 0\%$, $p = 0.94$), or in the subgroup of propensity-score matched studies (only data from one study were available, RR, 1.06, 95% CI, 0.88–1.27, $p = 0.54$; **Figures 5A,B**).

Major Bleeding

The incidence of major bleeding was reported in all 9 studies, with no significant difference between TC-TAVR and TF-TAVR observed after pooling all the results (RR, 1.04, 95% CI, 0.73–1.48, $I^2 = 10\%$, $p = 0.83$), and pooling only of propensity-score matched studies (RR, 0.97, 95% CI, 0.3–3.15, $I^2 = 43\%$, $p = 0.96$; **Figures 6A,B**).

Acute Kidney Injury

AKI was reported in 4 studies (20, 21, 26, 27), without any significant difference evidenced between TC-TAVR and TF-TAVR in the pooled results (RR, 0.89, 95% CI, 0.35–2.26, $I^2 = 51\%$, $p = 0.81$) and in propensity-score matched studies (RR, 1.17, 95% CI, 0.28–4.93, $I^2 = 34\%$, $p = 0.83$; **Figures 7A,B**).

DISCUSSION

This meta-analysis of 1,374 TC patients and 3,706 TF patients is the first to exclusively compare TC-TAVR to TF-TAVR. A previous meta-analysis has pooled data from TC and TSc patients (14), however, some studies have suggested these two pathways yield slightly different outcomes (28, 29).

The main findings of our meta-analysis can be summarized as follows: (1) TC-TAVR was associated with a significantly higher risk of 30-day mortality, (2) TC patients presented a significantly higher risk of neurovascular complications in the propensity-score matched studies, (3) TC-TAVR was associated with a significantly lower risk of major vascular complications, (4) there was no significant difference between the TC and TF accesses regarding the other 30-day outcomes (PPM implantation, major

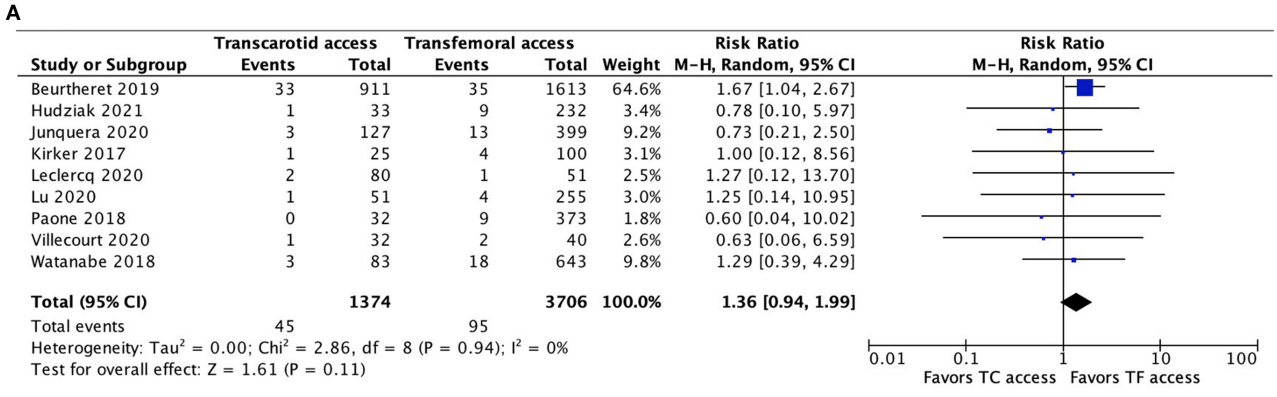

FIGURE 3 | Forest plots comparing neurovascular complications at 30 days between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from all studies. **(B)** Pooled data from propensity-score matched studies. TC, transcarotid; TF, transfemoral.

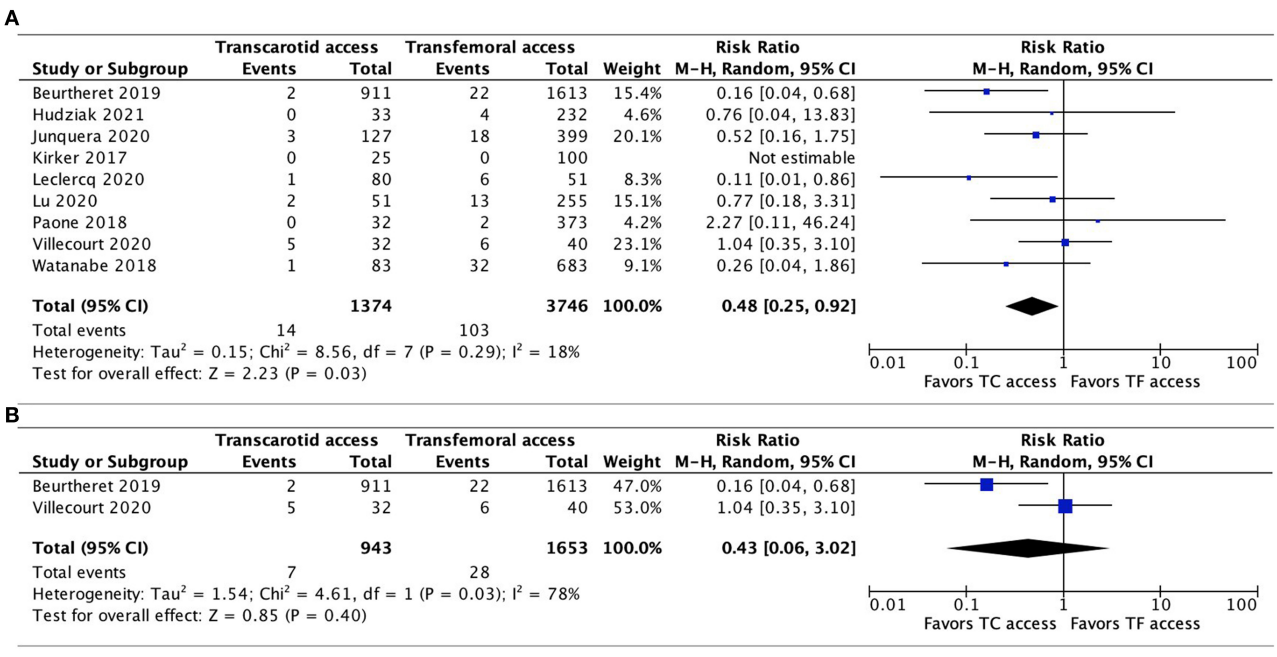

FIGURE 4 | Forest plots comparing major vascular complications between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from all studies. **(B)** Pooled data from propensity-score matched studies. TC, transcarotid; TF, transfemoral.

bleeding, or AKI). However, in the propensity-score matched studies, TC-TAVR was no longer associated with a significantly higher risk of 30-day mortality and a lower risk of major vascular complications.

The increased risk of 30-day mortality associated with TC-TAVR is likely related to the higher surgical risk and comorbidity burden TC patients exhibited. Supporting this hypothesis, the association was not found in the subgroup of propensity-score

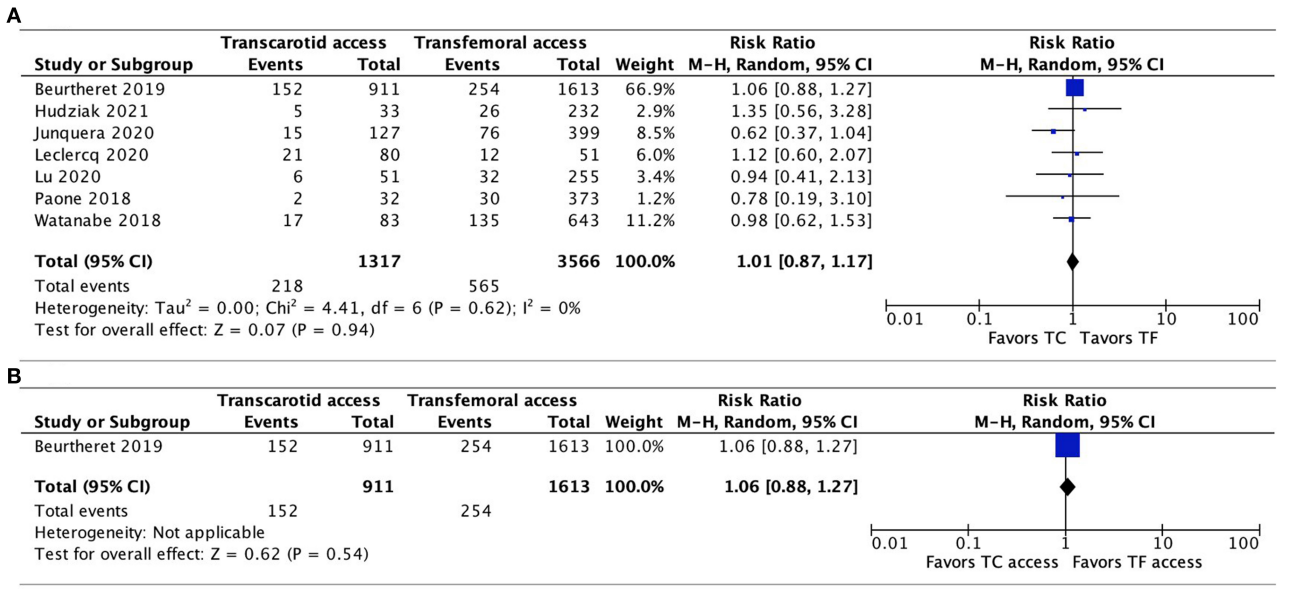

FIGURE 5 | Forest plots comparing permanent pacemaker implantation between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from all available studies. **(B)** Data from propensity-score matched study. TC, transcarotid; TF, transfemoral.

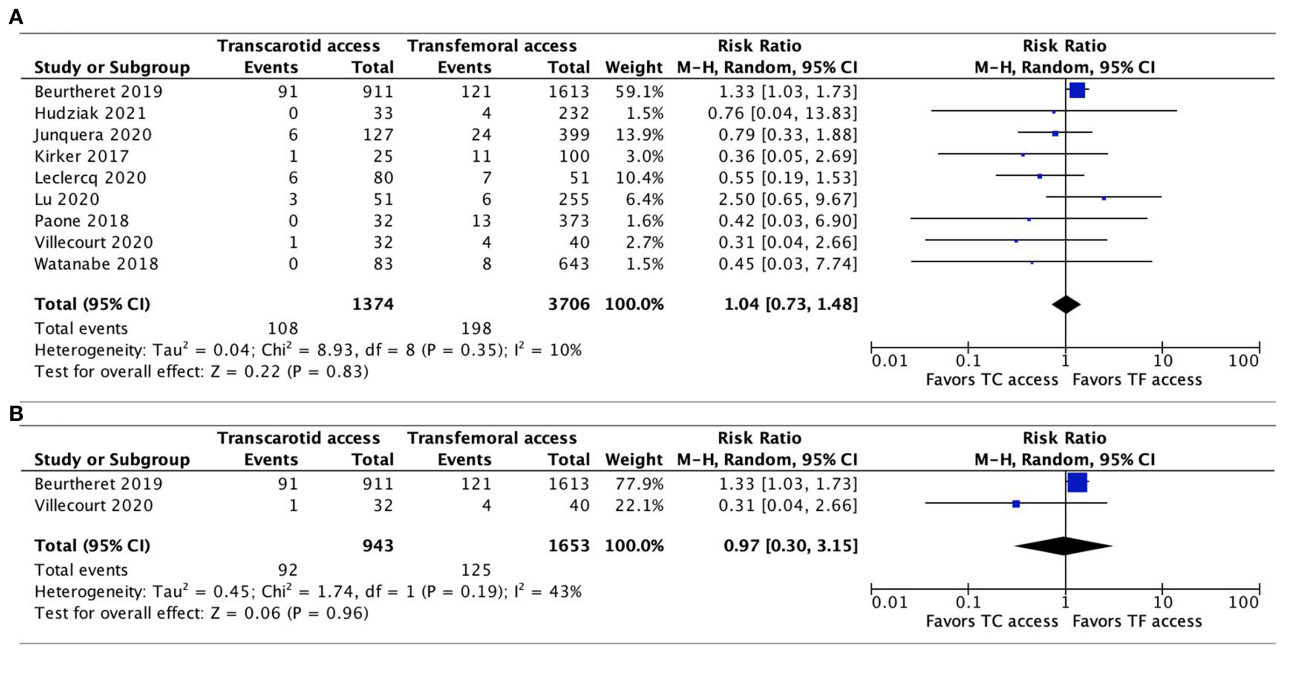

FIGURE 6 | Forest plots comparing major bleeding between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from all studies. **(B)** Data from propensity-score matched study. TC, transcarotid; TF, transfemoral.

matched studies, where patients' baseline characteristics and surgical risk were similar. Furthermore, the higher surgical risk and cardiovascular disease burden found in TC patients were expected, as these patients, by definition, have more chance to present contraindications to TF-TAVR. These observations regarding the association between increased mortality and higher surgical risk and comorbidity burden in TC-TAVR must be taken with caution: by comparison the same argument was used in some early studies to explain why TAp-TAVR presented with higher mortality, compared with TF-TAVR (30). However, in subanalyses of the randomized PARTNER trial, TAp-TAVR was found to be associated with a significant risk of cardiac

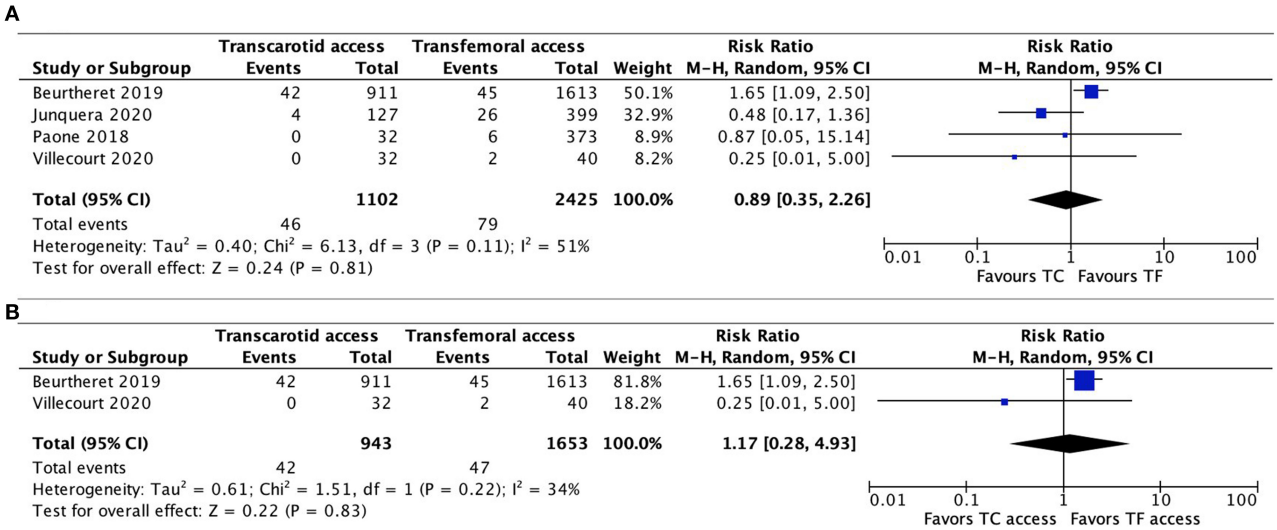

FIGURE 7 | Forest plots comparing acute kidney injury between TC and TF transcatheter aortic valve replacement procedures. **(A)** Pooled data from available studies. **(B)** Data from propensity-score matched studies. TC, transcarotid; TF, transfemoral.

mortality, despite the lack of differences regarding baseline population characteristics (31). Another possible limitation to these observations resides in the way surgical risk was assessed in the studies: the Logistic EuroSCORE, EuroSCORE II, and STS score were originally developed for a cardiac surgical setting and, although they are commonly used in TAVR studies, they may have less predictive value in comparing two TAVR interventions.

The reason why the prevalence of PAD in TC-TAVR patients was only 52% and not higher is not clear. Precise definition of PAD was not given in most articles, and it is possible that there was some heterogeneity in the way it was defined and assessed. We have to keep in mind that contraindications to the TF approach, beside PAD, also include, among others: extreme vessel tortuosity or abdominal aortic aneurysms, which would not necessarily be defined as PAD. It is possible that the latter contraindications may account for a significant part of TC-TAVR interventions. Leclercq et al. did report the characteristics of the ilio-femoral vascular access in patients undergoing TC-TAVR: out of 80 patients, 48 (60%) had severe femoral tortuosity or complex aortic access (23). Another possible explanation to the relatively low prevalence of PAD in the TC group is the fact that one single propensity-matched study accounted for nearly two-thirds of patients (911 out of 1,374) undergoing TC-TAVR (20). These 911 patients were matched with corresponding TF-TAVR patients and this may have somewhat biased the patients' baseline characteristics, as prevalence of PAD was relatively low among them (50%). Still, overall, the prevalence of PAD was increased in TC-TAVR patients, when compared with TF-TAVR patients, and this reflected the contraindications to the transfemoral access. Some data suggest the atherosclerotic process may preferentially affect the femoral arteries, more than the carotid arteries (32).

The incidence of 30-day neurovascular complications was significantly higher in TC patients, when considering the propensity-score matched studies, but not when all studies were pooled together (although there was a trend toward significance). This difference may be due to a selection bias resulting from patients' characteristics according to arterial access, when unadjusted studies are included. We also have to consider the heterogeneity concerning the way TC-TAVR interventions were performed, e.g., the side of the CCA that was used, the type of THVs (SE or BE), the surgeon's operative technique, and the modality of anesthesia (general or local): it is unknown if all this may have influenced the risk of stroke. Furthermore, the way neurovascular complications were assessed may be subject to caution: by comparison recent prospective trials regarding TAVR interventions used a very robust evaluation of neurological events [e.g., systematic neurological functional assessment before and after procedure; (33)]. In this regard, the result from the subgroup of propensity-score matched studies is possibly more reliable, as some potential confounding factors due to population differences were controlled. The higher incidence of neurovascular complications observed in this subgroup may be explained by several factors: embolization of CCA plaque due to arterial puncture, access site trauma providing a nidus for thrombosis with subsequent embolization, inadequate collateral perfusion through the circle of Willis and embolization of debris during balloon valvuloplasty or THV implantation (34). These findings are in line with a pilot study, which found TC-TACR to be associated with more abundant and larger subclinical ischemic lesions (assessed by brain magnetic resonance imaging) in the hemisphere of the brain perfused by the CCA that was punctured (35). A thorough evaluation of atherosclerotic plaques before intervention via appropriate imaging exams (e.g., Doppler ultrasound, with exclusion of patients presenting >50% CCA stenosis) and of the functional integrity of the circle of Willis intraoperatively using the CCA clamping test, may contribute

to lower the risk of cerebral complications (9, 13). Continuous monitoring of cerebral oximetry throughout the procedure is paramount. By analogy with carotid endarterectomy, some authors propose to abort the intervention if a significant drop of oximetry parameters (>20%) is detected, the limit of 20% being associated with an increased risk of cerebral ischemia (11, 36). Others suggest that local anesthesia with sedation may be preferable over general anesthesia by allowing "real-time" neurological evaluation (37). Although embolic protection systems have been studied in TF-TAVR, to our knowledge, no literature in the setting of TC-TAVR exists (11). Their role in TC patients requires further investigations to determine usefulness in the reduction of the risk of stroke (38).

The risk of major vascular complications was significantly lower in TC patients, in the overall pooled analysis, but not in the propensity-score matched studies analysis. The reason of the difference between the two analyses is not clear, as the risk of vascular complications should in theory only depend on local anatomy and surgical technique. Previous meta-analyses have also found a decreased risk of vascular complications associated with TC-TAVR (39). An explanation may be that, in TC-TAVR, the CCA is approached, cannulated, and reconstructed surgically, while most TF cases are performed percutaneously, which does not allow direct vascular control (1, 40).

Our data showed no significant difference regarding the risk of PPM implantation, major bleeding or AKI. Overall, our results regarding the incidence of 30-day mortality (4.0%), neurovascular complications (3.1%), PPM implantation (16.6%), AKI (4.8%) in the TC group lie in the same range as those of recently published meta-analyses: Bob-Manuel et al. reported respective incidence of 4.2, 5.0, and 15.3% (no data concerning AKI) (12), while Usman et al. described respective incidence of 5.3, 3.4, 15.3, and 3.4% (39). However, our data on major bleeding and vascular complications were different: respectively 7.9 and 1.0% vs. 3.7 and 4.2% for Bob-Manuel et al., and 4.3 and 2.4% for Usman et al. This is mainly explained by the inclusion in our analysis of the study by Beurtheret et al., which had the biggest population sample and reported high rates of major bleeding (10.0%) and low rates of vascular complications (0.2%) (20). The reason for these differences is not clear, but it is worth noting that the bleeding rate was higher in the 2013–2015 period, compared with the 2015–2017 period, suggesting a temporal trend associated with the incidence of that complication. In fact, this "time factor" may have to be taken into account when considering the incidence of all complications associated with TC-TAVR: using a cumulative meta-analysis model, Usman et al. showed that there was a temporal trend of decreasing incidence of stroke/TIA, major vascular complications and AKI for TC-TAVR (39). Possible explanations include the continuing advances in TAVR technology with the development of newer-generation valves with better deliverability, lower profile, an increase in operator expertise, and also to evolving modalities of screening of patients suitable to this approach. Furthermore, whether the difference regarding the types of THV used between TC- and TF-TAVR may have impacted the outcomes is unclear. In a propensity-matched comparison of the two types of THVs in TF-TAVR interventions, no difference was found regarding the risk of stroke, major bleeding, vascular complications, while significant differences existed regarding intra-hospital mortality and PPM (higher incidence with SE-THV) (41).

LIMITATIONS

Our study had some limitations. The most important one is the lack of randomized controlled trials comparing TC and TF-TAVR, hence this meta-analysis included only observational studies; and it is limited by their potential flaws and unidentified sources of bias. Patients' baseline characteristics and surgical risk were not comparable. However, a prospective randomized trial cannot in theory be performed to compare TC- and TF-TAVR as TC patients, by definition, present contraindications to TF-TAVR, and the latter remains the standard approach. Two studies used propensity-score matching, with similar patient demographics in the TC and TF groups, but the other studies had major differences in patient characteristics between the two groups. Furthermore, in two studies, the outcomes were not defined according to the VARC-2 criteria (22, 27). Finally, we included the data of both SE and BE THVs in our analysis. A comparative analysis between these two types of device might reveal one to be superior to the other in TC-TAVR, but this was out of the scope of this study.

CONCLUSIONS

Our study showed that TC-TAVR was associated with an increased risk of 30-day mortality, likely related to a higher surgical risk and higher comorbidity burden, and in the subgroup of propensity-score matched studies, with an increased risk of neurovascular complications. A lower risk of major vascular complications was found in the TC group, and TC-TAVR and TF-TAVR yielded similar results regarding PPM implantation, major bleeding, and AKI. Overall, our results highlight the importance of careful preprocedural patient selection, with a thorough neurovascular evaluation, as well as the need for close periprocedural neurological monitoring. Studies to better define the selection criteria of TC-TAVR are warranted.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

HL: conceptualization, data curation, formal analysis, methodology, and writing—original draft. PM: methodology and supervision. RH and EE: supervision and validation. SF: data curation, methodology, and supervision. CR, VR, LF, AB, and OM: validation. MK: methodology, supervision, validation, and writing—review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.687168/full#supplementary-material

Supplementary Figure 1 | Funnel plots for assessment of publication bias in each outcome.

Supplementary Table 1 | Search term strategy.

Supplementary Table 2 | Quality of assessment using the Newcastle-Ottawa Scale.

Supplementary Table 3 | Technical aspects of transcarotid transcatheter aortic valve implantation procedures.

Supplementary Table 4 | Type of prosthesis used according to TAVR access.

Supplementary Table 5 | Thirty-day complications of patients who underwent TC transcatheter aortic valve replacement.

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