Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Femoral Versus Nonfemoral Subclavian/Carotid Arterial Access Route for Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis

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BACKGROUND: Some concerns remain regarding the safety of transcarotid and transsubclavian approaches for transcatheter aortic valve replacement. We aimed to compare the risk of 30-day complications and death in transcarotid/transsubclavian versus transfemoral transcatheter aortic valve replacement recipients.

METHODS AND RESULTS: Data from 20 studies, including 79 426 patients (16 studies) and 3992 patients (4 studies) for the evaluation of the unadjusted and adjusted impact of the arterial approach were sourced, respectively. The use of a transcarotid/transsubclavian approach was associated with an increased risk of stroke when using unadjusted data (risk ratio [RR], 2.28; 95% CI, 1.90–2.72) as well as adjusted data (odds ratio [OR], 1.53; 95% CI, 1.05–2.22). The pooled results deriving from unadjusted data showed an increased risk of 30-day death (RR, 1.46; 95% CI, 1.22–1.74) and bleeding (RR, 1.53; 95% CI, 1.18–1.97) in patients receiving transcatheter aortic valve replacement through a transcarotid/transsubclavian access (compared with the transfemoral group), but the associations between the arterial access and death (OR, 1.22; 95% CI, 0.89–1.69), bleeding (OR, 1.05; 95% CI, 0.68–1.61) were no longer significant when using adjusted data. No significant effect of the arterial access on vascular complication was observed in unadjusted (RR, 0.84; 95% CI, 0.66–1.06) and adjusted (OR, 0.79; 95% CI, 0.53–1.17) analyses.

CONCLUSIONS: Transcarotid and transsubclavian approaches for transcatheter aortic valve replacement were associated with an increased risk of stroke compared with the transfemoral approach. However, these nonfemoral arterial alternative accesses were not associated with an increased risk of 30-day death, bleeding, or vascular complication when taking into account the confounding factors.

Key Words: stroke ■ transcarotid ■ transcatheter aortic valve replacement ■ transsubclavian

Since the first description of transcatheter aortic valve replacement (TAVR) in 2002, its use expanded at a rapid pace to finally become an alternative to surgery for patients considered at low surgical risk.[1] The transfemoral approach is the most widely used access for TAVR procedures, allowing an exclusive percutaneous intervention and exhibiting a relatively low complication rate.[2] However, an alternative access is required in patients with severe peripheral artery disease or small iliofemoral arteries.[3,4]

Initially, the transapical and transaortic approaches were used whenever a transfemoral approach was not anatomically feasible. However, the use of these nonarterial accesses was associated with worse

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.017460

For Sources of Funding and Disclosures, see page 12.

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CLINICAL PERSPECTIVE

What Is New?

- The transcarotid/transsubclavian approach for transcatheter aortic valve replacement was associated with a higher risk of periprocedural stroke as compared with the transfemoral approach.
- The type of arterial approach was not associated with an increased risk of 30-day death, bleeding, or vascular complications when taking into account the confounding factors.

What Are the Clinical Implications?

- Future investigations are needed to better define the selection criteria for transcarotid and transsubclavian transcatheter aortic valve replacement.
- The potential benefit of embolic protection devices in this population should be further evaluated.

Nonstandard Abbreviation and Acronym

TAVR	transcatheter aortic valve replacement

outcomes, partially because of the need for thoracotomy.[5,6] Thus, novel arterial accesses such as the transsubclavian and transcarotid approaches were developed, and their use expanded rapidly,[3,7] mainly related to the easy accessibility of the carotid/subclavian arteries and the avoidance of thoracotomy. In addition, the use of the transcarotid/transsubclavian approach as an alternative approach has been associated with improved outcomes compared with transapical/transaortic TAVR.[8,9] However, some concerns remain regarding the safety of the transcarotid/transsubclavian approach, especially concerning the risk of periprocedural stroke.[10,11] The current systematic review and meta-analysis aimed to compare the risk of 30-day complications and death in transcarotid/transsubclavian versus transfemoral TAVR.

METHODS

Search Strategy and Study Selection

The data, analytic methods, and study materials will be available to other researchers for purposes of reproducing the results (the author for correspondence should be contacted for the data). A systematic review of the published data on outcomes of TAVR through a transcarotid or transsubclavian approach was conducted in accordance with the guidance and the reporting items specified the Preferred Reported Items for Systematic Reviews and Meta-Analysis statement.[12] A computerized search was performed to identify all relevant studies from PubMed and EMBASE databases. MeSH terms used were *TAVR, transcarotid, transsubclavian, transaxillary, carotid, subclavian, axillary*. Keywords used were *transcatheter aortic valve implantation, transcarotid, transsubclavian, transaxillary, carotid, subclavian, axillary*. The search strategy is outlined in Data S1. Databases were last accessed on June 30, 2020. Citations were screened at the title and abstract level and retrieved as full text if they reported on outcome after TAVR through a transcarotid or transsubclavian access.

Studies were included if the following criteria applied: (1) original design and (2) reported data on mortality, stroke, bleeding or vascular complication following TAVR through a transcarotid or transsubclavian approach. When 2 similar studies were reported from the same institution or author, the most recent publication or the publication with most information was included in the analysis. Case reports or studies published in a non-English language were excluded. For the purpose of the present meta-analysis, TAVR performed through the subclavian and axillary arteries were both classified as transsubclavian TAVR.

Data Extraction

Data of the patients and studies was extracted using a standardized data abstraction sheet. Two investigators (L.F., L.J.) conducted the literature search, selection, and data extraction in duplicate. Any discrepancies were resolved by consensus, when needed, with a third investigator (J.R.C.).

Outcomes

The end points that were pooled were (1) 30-day all-cause mortality, (2) periprocedural stroke, (3) bleeding, and (4) vascular complication. For each outcome, 2 separate analyses were performed including (1) unadjusted data and (2) adjusted data.

Statistical Analysis

Crude risk ratio (RR) (unadjusted data) and odds ratio (OR) (adjusted data) were calculated with the corresponding 95% CI for each end point and entered into the primary analysis. Heterogeneity across studies was assessed using the I^2 index (25%, 50%, and 70% being the cutoff of low, medium, and high heterogeneity, respectively). The choice between a random- or fixed-effect model was not determined by the results of the degree of heterogeneity but, according to the recent recommendations from a scientific statement of the American Heart Association,

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by evaluating the functional similarity between the included studies and the goal of estimating a common effect size that would be applicable to similar populations to those included in the meta-analysis.[13] Thus, the Mantel-Haenszel fixed-effect model was the primary meta-analysis method, and sensitivity analyses were performed by comparing results of fixed-effect and random-effect (DerSimonian and Laird) models. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry, and the Begg rank correlation was performed. Results of the transcarotid and transsubclavian subgroups for the unadjusted data analysis were also compared (sensitivity analysis). No multiplicity adjustment was applied. Descriptive characteristics were presented as mean (SD) or median (interquartile range) when appropriate for continuous variables and frequencies and percentages for categorical variables. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and RevMan (version 5.3.5; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

A PubMed search identified 971 records, whereas an EMBASE search uncovered 1135, yielding 1759 records that were reviewed at the title and abstract level after exclusion of duplicates. Of those, 114 articles were selected and assessed for eligibility at full-text level. Finally, 20 studies were included for assessing primary end points (Tables 1 and 2), and of these, 16 studies provided results without propensity-score matching[8,10,11,14–26] (30-day all-cause mortality, 15 studies; periprocedural stroke, 14 studies; bleeding, 12 studies; vascular complication, 12 studies), whereas 4 studies performed a propensity-score matching.[27–30] Three studies provided adjusted OR for the 4 outcomes of interest,[10,26,29] and 1 study reported adjusted hazard ratio only for mortality.[14] Given the differences in comorbidity burden between transfemoral and transcarotid/transsubclavian patients, the outcomes for studies without propensity-score matching (unadjusted data),[8,10,11,14–26] and with propensity-score matching (adjusted data)[27–30] were analyzed separately. Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram. A total of 14 studies included transsubclavian TAVR (n=2233),[8,11,14–23,27,28] 4 studies included transcarotid TAVR (n=677),[10,24–26] and 2 studies included both transsubclavian and transcarotid TAVR (n=710 and n=943, respectively).[29,30] Quantitative synthesis was performed on 79 426 patients to assess the unadjusted impact of the arterial approach, and on 3992 patients to assess the adjusted impact of the arterial approach. All studies were observational registries, and all devices implanted were either the balloon-expandable Edwards Sapien XT/3 valve (Edwards Lifesciences, Irvine, CA) or the self-expanding Medtronic CoreValve/Evolut revalving system (Medtronic, Minneapolis, MN), except for the van Wely et al[11] study that included patients receiving the Portico valve (St. Jude Medical, St. Paul, MN). The rate of nontransfemoral arterial access in studies without propensity matching was about 10%,[8,10,14–26] with the exception of van Wely et al[11] study that reported results from a center where the preferred access was the left subclavian artery (used in 76% of patients).

Impact of the Arterial Approach on 30-Day Mortality

The unadjusted risk of 30-day all-cause death was assessed using 15 studies.[8,10,11,14–18,20–26] Overall, the 30-day mortality was of 2.9%. The pooled results demonstrated a higher risk of all-cause death at 30 days in patients receiving transcarotid/transsubclavian TAVR (RR, 1.46; 95% CI, 1.22–1.74; Figure 2A). Heterogeneity across studies was observed (I^2=40%), and no potential publication bias was identified. Sensitivity analysis found a significantly higher risk of death in the transsubclavian subgroup (RR, 1.54; 95% CI, 1.26–1.89) but not in the transcarotid subgroup (RR, 1.25; 95% CI, 0.87–1.80) (Table S1 and Figure S1). Four studies were used to assess an adjusted risk of 30-day death.[27–30] No significant impact of the arterial access on the risk of death was found (OR, 1.22; 95% CI, 0.89–1.69; Figure 2B). No heterogeneity was observed (I^2=0%), and the pooled risk did not vary significantly when a random effects model was used in a sensitivity analysis (Table S2).

Impact of the Arterial Approach on Periprocedural Stroke

Most studies reported periprocedural stroke, with the exception of Taramasso et al,[17] van Wely et al,[11] and Junquera et al[26] studies that reported neurological event and transient ischemic attack/stroke. After pooling the results from 14 studies,* the transcarotid/transsubclavian approach was associated with a higher unadjusted risk of periprocedural stroke (RR, 2.28; 95% CI, 1.90–2.72; Figure 3A). Heterogeneity across studies was observed (I^2=42%), and no publication bias was observed. The sensitivity analysis found similar results in both transsubclavian and transcarotid subgroups (Table S1 and Figure S2). The adjusted risk of stroke was evaluated from 4

*References 8,10,11,14–18,20,21,23–26.

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Table 1. Summary of Selected Studies Comparing Transsubclavian and Transcarotid to Transfemoral Access for TAVR

Study	Year	Region	Centers	Sample Size	Inclusion Period	Arterial Accesses (%)	Transsubclavian/ Transcarotid Approach Side (%)	Exclusion Criteria for Transsubclavian/ Transcarotid
Studies without propensity-score matching								
Petronio et al[15]	2010	Italy	13	514	June 2007 to July 2009	Transfemoral (89) Transsubclavian (11)	Left (100) Right (0)	Subclavian artery diameter <6 mm (<7 mm if patent left internal mammary artery graft), heavy calcifications, excessive tortuosity, tight subclavian stenosis not amenable to percutaneous balloon angioplasty
Eltchaninoff et al[16]	2010	France	16	173	February 2009 to July 2009	Transfemoral (93) Transsubclavian (7)	N/A	N/A
Taramasso et al[17]	2011	Italy	1	159	November 2007 to June 2010	Transfemoral (94) Transsubclavian (6)	N/A	N/A
Gilard et al[18]	2012	France	34	2545	January 2010 to October 2011	Transfemoral (93) Transsubclavian (7)	N/A	N/A
Pilgrim et al[19]	2012	Swiss	1	313	August 2007 to October 2011	Transfemoral (98) Transsubclavian (2)	N/A	N/A
Muensterer et al[20]	2013	Germany	1	341	June 2007 to February 2011	Transfemoral (88) Transsubclavian (12)	N/A	N/A
Saia et al[21]	2013	Italy	1	78	February 2008 to November 2010	Transfemoral (85) Transsubclavian (15)	N/A	N/A
Ussia et al[22]	2014	Italy	1	61	January 2012 to July 2013	Transfemoral (93) Transsubclavian (7)	Left (100) Right (0)	N/A
Fröhlich et al[14]	2015	United Kingdom	33	3016	January 2007 to December 2012	Transfemoral (94) Transsubclavian (6)	N/A	N/A
Adamo et al[23]	2015	Italy	1	278	September 2007 to March 2014	Transfemoral (88) Transsubclavian (12)	N/A	N/A
Watanabe et al[24]	2018	France	1	726	September 2012 to October 2017	Transfemoral (89) Transcarotid (11)	N/A	Diameter <5.5 mm or massive calcification of the selected common carotid artery, stenosis >50% of the contralateral common carotid artery, or malformation in the circle of Willis
Paone et al[25]	2018	United States	1	405	January 2015 to March 2017	Transfemoral (92) Transcarotid (8)	Left (22) Right (78)	Diameter <5 mm or excessive tortuosity/calcification of the selected carotid artery, stenosis >50% of the contralateral carotid
van Wely et al[11]	2018	Netherlands	1	120	September 2015 to July 2017	Transfemoral (24) Transsubclavian (76)	Left (100) Right (0)	Diameter, tortuosity or extensive calcification (left internal mammary artery as a coronary bypass conduit was considered a relative contraindication)
Folliguet et al[10]	2019	France	48	11 033	January 2013 to December 2015	Transfemoral (96) Transcarotid (4)	N/A	Diameter <7 mm or excessive tortuosity/calcification of the selected common carotid artery, carotid stenosis >30% (selected or contralateral carotid), prior stroke related to carotid plaques
Dahle et al[8]	2019	United States	277	59 138	June 2015 to February 2018	Transfemoral (98) Transsubclavian (2)	N/A	N/A

(*Continued*)

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Table 1. Continued

Study	Year	Region	Centers	Sample Size	Inclusion Period	Arterial Accesses (%)	Transsubclavian/ Transcarotid Approach Side (%)	Exclusion Criteria for Transsubclavian/ Transcarotid
Junquera et al[26]	2020	Canada	1	526	May 2015 to February 2019	Transfemoral (76) Transcarotid (24)	Left (92) Right (8)	Diameter <7 mm of the selected common carotid artery, contralateral ≥50% internal or common carotid artery stenosis or carotid artery occlusion
Studies with propensity-score matching								
Petronio et al[27]	2012	Italy	13	282	June 2007 to March 2011	Transfemoral (50) Transsubclavian (50)	Left (96) Right (4)	Subclavian artery diameter <6 mm (<7 mm if patent left internal mammary artery graft), heavy calcifications, excessive tortuosity, tight subclavian stenosis not amenable to percutaneous balloon angioplasty
Gleason et al[28]	2017	United States	45	404	February 2011 to September 2012	Transfemoral (50) Transsubclavian (50)	Left (91) Right (9)	N/A
Beurtheret et al[29]	2019	France	50	3226	January 2013 to December 2017	Transfemoral (50) Transsubclavian (22) Transcarotid (28)	N/A	N/A
Villecourt et al[30]	2020	France	1	80	January 2015 to August 2018	Transfemoral (50) Transsubclavian (10) Transcarotid (40)	N/A	N/A

ESV indicates Edwards Sapien valve; MCRS, Medtronic CoreValve revalving system; N/A, not applicable; and TAVR, transcatheter aortic valve replacement.

studies.[27–30] The pooled overall OR was 1.53 (95% CI, 1.05–2.22; Figure 3B). Inconsistency across studies was low (I^2=0%), and a random effects model found similar results (Table S2).

Impact of the Arterial Approach on Bleeding Events

The unadjusted risk of bleeding was evaluated from 12 studies.[8,10,11,15,18–24,26] Most studies reported life-threatening bleeding.[8,11,18–23,27,28,30] However, some studies used another bleeding definition: Folliguet et al[10] reported bleeding, Petronio et al[15] reported major bleeding, Watanabe et al[24] reported bleeding with shock, Junquera et al[26] reported major and life-threatening bleeding, and Beurtheret et al[29] reported hemorrhagic shock. The overall pooled RR was 1.53 (95% CI, 1.18–1.97; Figure 4A). Heterogeneity across studies was low (I^2=24%), and no publication bias was observed. Sensitivity analysis found a significantly higher risk of bleeding in the transcarotid subgroup (RR, 1.65; 95% CI, 1.24–2.20) but not in the transsubclavian subgroup (RR, 1.16; 95% CI, 0.64–2.08) (Table S1 and Figure S3). The adjusted risk of bleeding was pooled from 4 studies.[27–30] No significant effect of the arterial access on bleeding was observed (OR, 1.05; 95% CI, 0.68–1.61; Figure 4B). No inconsistency was observed (I^2=0%), and a random effects model found similar results (Table S2).

Impact of the Arterial Approach on Vascular Complications

All studies reported major vascular complications, except for the 2 studies[15,16] published before the first Valve Academic Research Consortium publication[31] and for Muensterer et al[20] and Folliguet et al[10] studies, which reported access vessel injury and vascular complication, respectively. After pooling results from 12 studies,[†] no significant effect of the arterial access on vascular complication was observed (RR, 0.84; 95% CI, 0.66–1.06; Figure 5A). Heterogeneity across studies was high (I^2=72%), and no publication bias was observed. Sensitivity analysis found a lower risk of vascular complication in the transcarotidsubgroup (RR, 0,42; 95% CI, 0.27–0.67) and a trend toward a higher risk of vascular complication in the transsubclavian subgroup (RR, 1.30; 95% CI, 0.98–1.73) (Table S1 and Figure S4). Four studies were pooled to assess the adjusted risk of vascular complication,[27–30] and no significant effect of the arterial access on vascular complication was observed (OR, 0.79; 95% CI, 0.53–1.17; Figure 5B). Heterogeneity across studies was observed (I^2=13%), and a random effect model found similar results (Table S2).

[†]References 8,10,11,14–16,18,20,23–26.

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Table 2. Clinical and Procedural Characteristic of the Population From Selected Studies Comparing Transsubclavian and Transcarotid to Transfemoral Access for TAVR

Study	Year	Valve Type (%)	Logistic EuroSCORE	30-d Mortality (%)	Periprocedural Stroke (%)	Bleeding (%)	Bleeding Definition	Vascular Complication (%)	Vascular Complication Definition
Studies without propensity-score matching									
Petronio et al[15]	2010	MCRS (100)	20.1 (12.8–30.5)	5.4	1.8	2.7	Major bleeding	1.8	Vascular rupture with fatal bleeding or need for urgent vascular surgery or dissection of the aorta
Eltchaninoff et al[16]	2010	ESV (55) MCRS (45)	25.6±11.4	12.7	3.6	Not reported	Not reported	7.0	Aortic rupture, iliofemoral dissection, thrombosis/ distal embolization, retroperitoneal hematoma, left ventricle apex bleeding
Taramasso et al[17]	2011	ESV (48) MCRS (52)	26.7±15.8	2.0	2.7*	Not reported	Not reported	Not reported	Not reported
Gilard et al[18]	2012	ESV (67) MCRS (33)	21.9±14.3	8.2	2.2	1.2	Life-threatening bleeding (VARC)	5.4	Major vascular complication (VARC)
Pilgrim et al[19]	2012	ESV (28) MCRS (72)	24.3±14.2	Not reported	Not reported	16.5	Life-threatening bleeding (VARC)	Not reported	Not reported
Muensterer et al[20]	2013	MCRS (100)	19.2±12.8	8.2	4.1	4.7	Life-threatening bleeding (VARC)	10.3	Access vessel injury
Saia et al[21]	2013	ESV (15) MCRS (85)	22.6±12.4	4.9	2.0	4.9	Life-threatening bleeding (VARC)	Not reported	Not reported
Ussia et al[22]	2014	MCRS (100)	36±24	3.3	0	3.3	Life-threatening bleeding (VARC)	0	Major vascular complication (VARC)
Fröhlich et al[14]	2015	ESV (40) MCRS (60)	22 (14–34)	4.2	2.1	Not reported	Not reported	3.4	Major vascular complication
Adamo et al[23]	2015	MCRS (100)	20 (13–29)	5.4	2.5	1.1	Life threatening bleeding (VARC-2)	2.5	Major vascular complication (VARC-2)
Watanabe et al[24]	2018	ESV (49) MCRS (51)	24.1±13.3	5.4	2.5	1.1	Bleeding with shock	4.5	Major vascular complication
Paone et al[25]	2018	ESV (81) MCRS (19)	N/A†	2.0	2.2	Not reported	Not reported	0.5	Major vascular complication
van Wely et al[11]	2018	N/A	15.0±9.8	3.3	5.8‡	2.5	Life-threatening bleeding	1.7	Major vascular complication
Folliguet et al[10]	2019	N/A	18.2±13.0	3.8	2.0	4.8	Bleeding	7.5	Vascular complication
Dahle et al[8]	2019	ESV (100)	N/A†	2.3	1.9	0.1	Life-threatening bleeding	1.1	Major vascular complication
Junquera et al[26]	2020	ESV (62) MCRS (38)	N/A†	3.2	3.0‡	5.7	Major or life-threatening bleeding (VARC-2)	4.0	Major vascular complication (VARC-2)

(*Continued*)

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Table 2. Continued

Study	Year	Valve Type (%)	Logistic EuroSCORE	30-d Mortality (%)	Periprocedural Stroke (%)	Bleeding (%)	Bleeding Definition	Vascular Complication (%)	Vascular Complication Definition
Studies with propensity-score matching									
Petronio et al[27]	2012	MCRS (100)	23.7 (15.8–33.6)	6.0	2.1	6.7	Life-threatening bleeding (VARC)	6.4	Major vascular complication (VARC)
Gleason et al[28]	2017	MCRS (100)	20.7±14.3	5.7	5.0	10.9	Life-threatening bleeding (VARC)	11.1	Major vascular complication (VARC)
Beurtheret et al[29]	2019	Balloon-expandable (49) Self-expanding (51)	19.4±13.8	3.4§	2.8	0.7	Hemorrhagic shock	10.2	Major vascular complication (VARC-2)
Villecourt et al[30]	2020	ESV (91) MCRS (9)	10.9 (7.0–15.9)	5.0	3.8	6.3	Life-threatening bleeding (VARC-2)	15.0	Major vascular complication (VARC-2)

ESV indicates Edwards Sapien valve; MCRS, Medtronic CoreValve revalving system; N/A, not applicable; TAVR, transcatheter aortic valve replacement; and VARC, Valve academic research consortium.
*Neurological event.
†Logistic Euroscore not available; mean STS at 6.1±4.3 (Paone et al[25]), mean STS at 6.6±4.6 (Dahle et al[8]), median STS at 4.3 (2.9–6.8) (Junquera et al[26]).
‡Transient ischemic attack and stroke.
§Procedural mortality.

DISCUSSION

The present meta-analysis, which included about 80 000 and 4000 patients in the unadjusted and adjusted analyses, respectively, compared the outcomes of transcarotid/transsubclavian and transfemoral TAVR. The main findings can be summarized as follows: (1) The transcarotid/transsubclavian approach was associated with a higher risk of periprocedural stroke (unadjusted and adjusted analyses); (2) patients receiving TAVR through a transcarotid/transsubclavian approach exhibited higher 30-day mortality and bleeding rates, but no differences between transcarotid/transsubclavian and transfemoral groups were observed after adjustment; and (3) the type of arterial approach had no significant effect on the rate of vascular complications.

When using the unadjusted data, the present meta-analysis demonstrated an increased risk of 30-day all-cause death among patients receiving TAVR through a transcarotid and transsubclavian approach compared with the transfemoral approach. This finding was likely related to a selection bias resulting from differences in the baseline characteristics of patients,[8,10] the transfemoral approach being the preferred approach whenever feasible in all studies but one.[11] This hypothesis is supported by the fact that the association between arterial access and 30-day mortality was no longer significant when considering adjusted data. Interestingly, sensitivity analyses assessing separately outcomes of transsubclavian and transcarotid TAVR reported a significantly higher risk of death only in the transsubclavian subgroup. This discrepancy is probably explained by a time effect, with studies including transsubclavian TAVR being generally more dated and therefore including patients at higher risk than transcarotid TAVR studies, as evidenced by the very high Logistic EuroScore found in the oldest transsubclavian TAVR studies.[15–17,19,22]

The present meta-analysis demonstrated a significantly higher rate of periprocedural stroke among patients receiving TAVR through a transsubclavian or transcarotid approach in comparison with the (gold standard) transfemoral approach. In addition, this increased risk remained significant when using adjusted data (about 2000 transcarotid/transsubclavian TAVRs matched with 2000 transfemoral TAVRs on the basis of a propensity score). While the presence of the TAVR sheath may be protective regarding the embolization of debris during valvuloplasty and valve implantation, several potential stroke mechanisms directly related to transcarotid TAVR have been described: (1) embolization of carotid artery plaque attributable to arterial puncture and instrumentation, (2) access site trauma providing nidus for thrombosis with subsequent embolization, (3) and inadequate

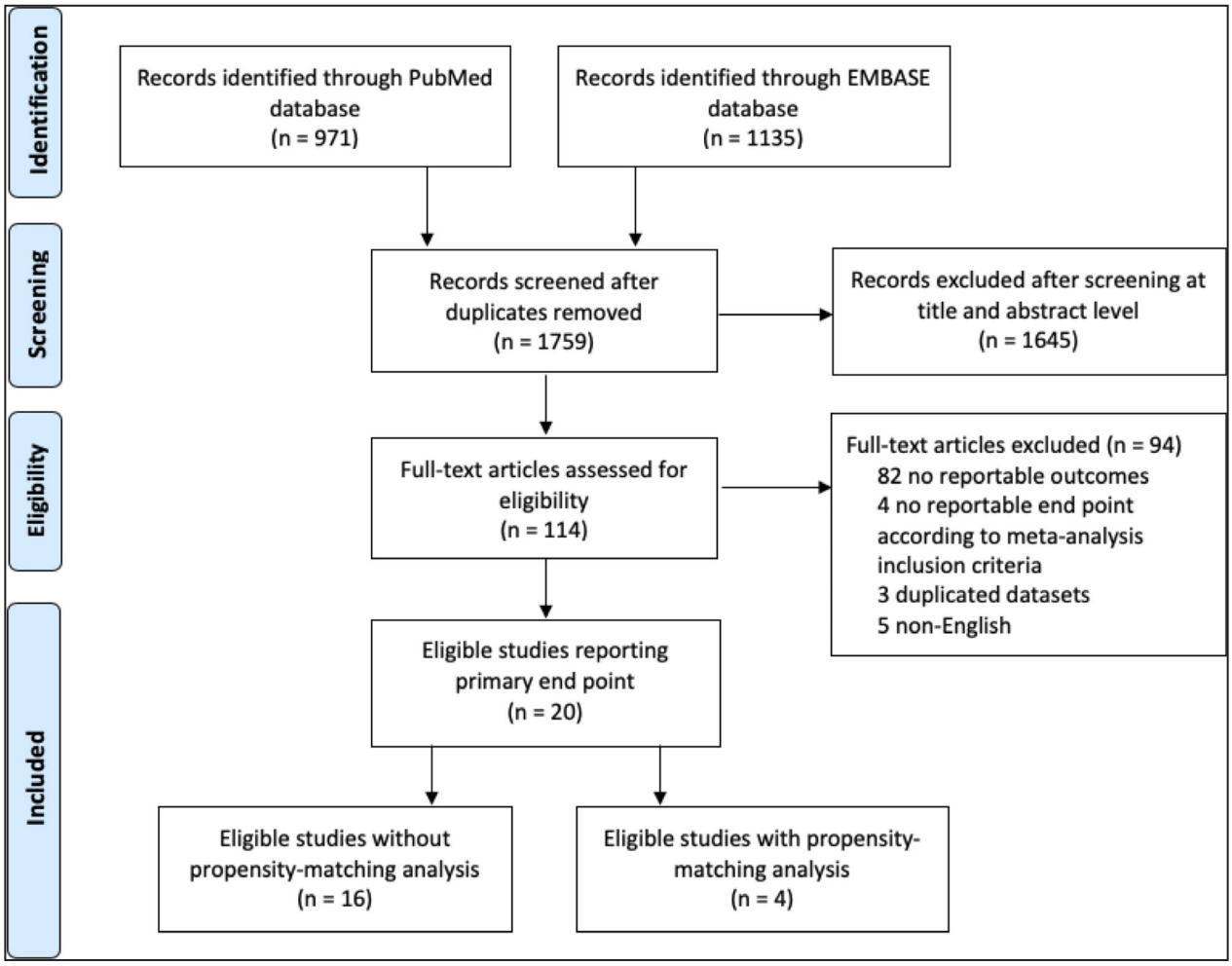

Figure 1. Flowchart of selected studies.
Flowchart, based on the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, of studies selected comparing outcomes of transsubclavian or transcarotid to transfemoral approach for transcatheter aortic valve replacement recipients.

collateral perfusion through the circle of Willis.[32] In addition, Chamandi et al[33] reported a higher burden of subclinical cerebral ischemic lesions as determined by cerebral magnetic resonance imaging in the cerebral hemisphere irrigated by the carotid artery used during transcarotid TAVR. Watanabe et al[24] selected transcarotid TAVR candidates on the basis of the circle of Willis examination, but exclusion criteria for transcarotid approach varied widely from one study to another.[10,24–26] This large intercenter variability emphasizes the need to better identify the anatomic characteristics associated with an increased risk of periprocedural stroke during transcarotid TAVR. Tsai et al[34] reported the feasibility of a double sheath connection to increase carotid flow during TAVR through transcarotid approach, and the potential clinical benefit of this technique deserves further evaluation. Sensitivity analysis showed an increased risk of periprocedural stroke during both transcarotid and transsubclavian TAVR. Thus, embolization of an atheromatous plaque located on the aortic arch or the proximal part of the carotid or subclavian artery is an additional mechanism, making potentially relevant the use of embolic protection during transcarotid and transsubclavian TAVR. A meta-analysis reported that the use of embolic protection during TAVR was associated with a significant reduction in death or stroke,[35] but no specific data are available during transcarotid or transsubclavian TAVR. Future efforts are therefore needed to develop embolic protection dedicated to transcarotid and transsubclavian approaches. Finally, despite adjustment, it cannot be completely excluded that some particular characteristics of patients not candidates for a transfemoral TAVR may increase the risk of periprocedural stroke (besides the arterial access).

Pooled results deriving from unadjusted data found an increased risk of bleeding during transcarotid/

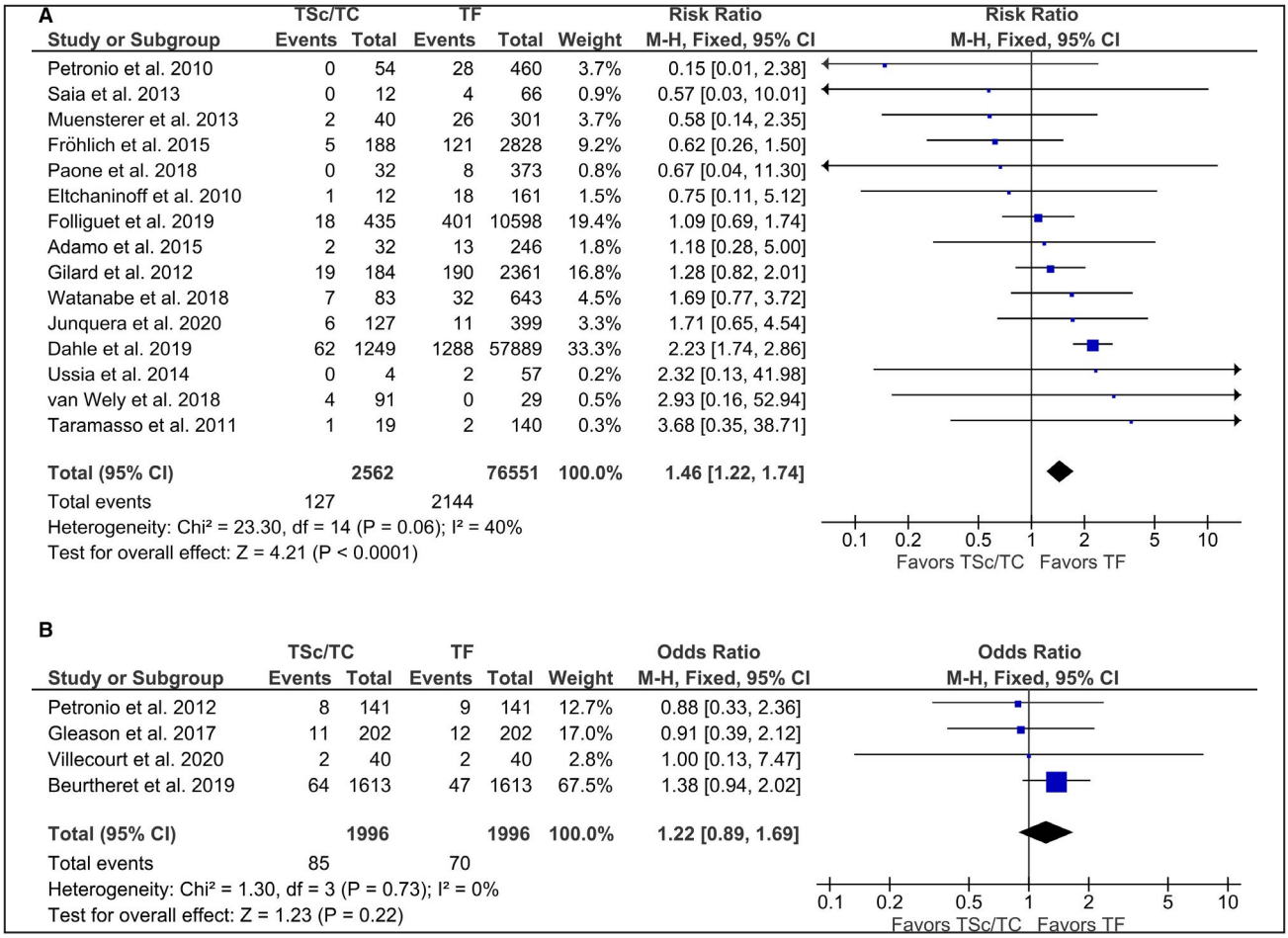

Figure 2. Risk of 30-day all-cause death after transcatheter aortic valve replacement according to the arterial approach.
A, Studies without propensity-score matching[8,10,11,14–18,20–26]; **B**, Studies with propensity-score matching.[27–30]

transsubclavian TAVR in comparison with transfemoral TAVR. However, when using adjusted data, the arterial approach was no longer associated with an increased bleeding risk. Thus, the increased risk of bleeding observed was likely related to a selection bias resulting from differences in comorbidity burden according to arterial access. Chollet et al[36] showed in a propensity-matched analysis an increased risk of life-threatening bleeding during transaortic TAVR in comparison with transfemoral TAVR. Our findings are therefore in line with previous studies reporting better outcomes during transcarotid/transsubclavian TAVR than transapical/transaortic TAVR.[8,9] Subgroup analysis demonstrated an increased risk of bleeding in the transcarotid population but not in patients undergoing transsubclavian TAVR. This finding is consistent with the study of Debry et al,[37] who reported a higher rate of minor bleeding and main access hematoma within transcarotid TAVR recipients versus transaxillary TAVR. Finally, transcaval access for TAVR is an emerging alternative approach that holds its own vascular complications such as aortocaval fistula.[25,38] One may consider that transcaval TAVR becomes identical to a transfemoral procedure once the aorta has been accessed and therefore expect to have a similar risk of stroke during transcaval than transfemoral TAVR. However, further investigations are required regarding feasibility and safety of this alternative approach.

Both pooled analyses derived from unadjusted and adjusted data did not demonstrate any significant difference in regard to the risk of vascular complication according to the arterial access. In fact, there was a trend toward a decreased risk of vascular complication in the transcarotid/transsubclavian TAVR population, without reaching statistical significance. This tendency may be related to the fact that unlike the transfemoral approach, which is fully percutaneous in most cases, transcarotid and transsubclavian approaches are performed with a surgical cutdown in most cases, which may confer an additional safety. However, Kawashima et al[39] reported fewer major vascular complication events during percutaneous transfemoral TAVR compared

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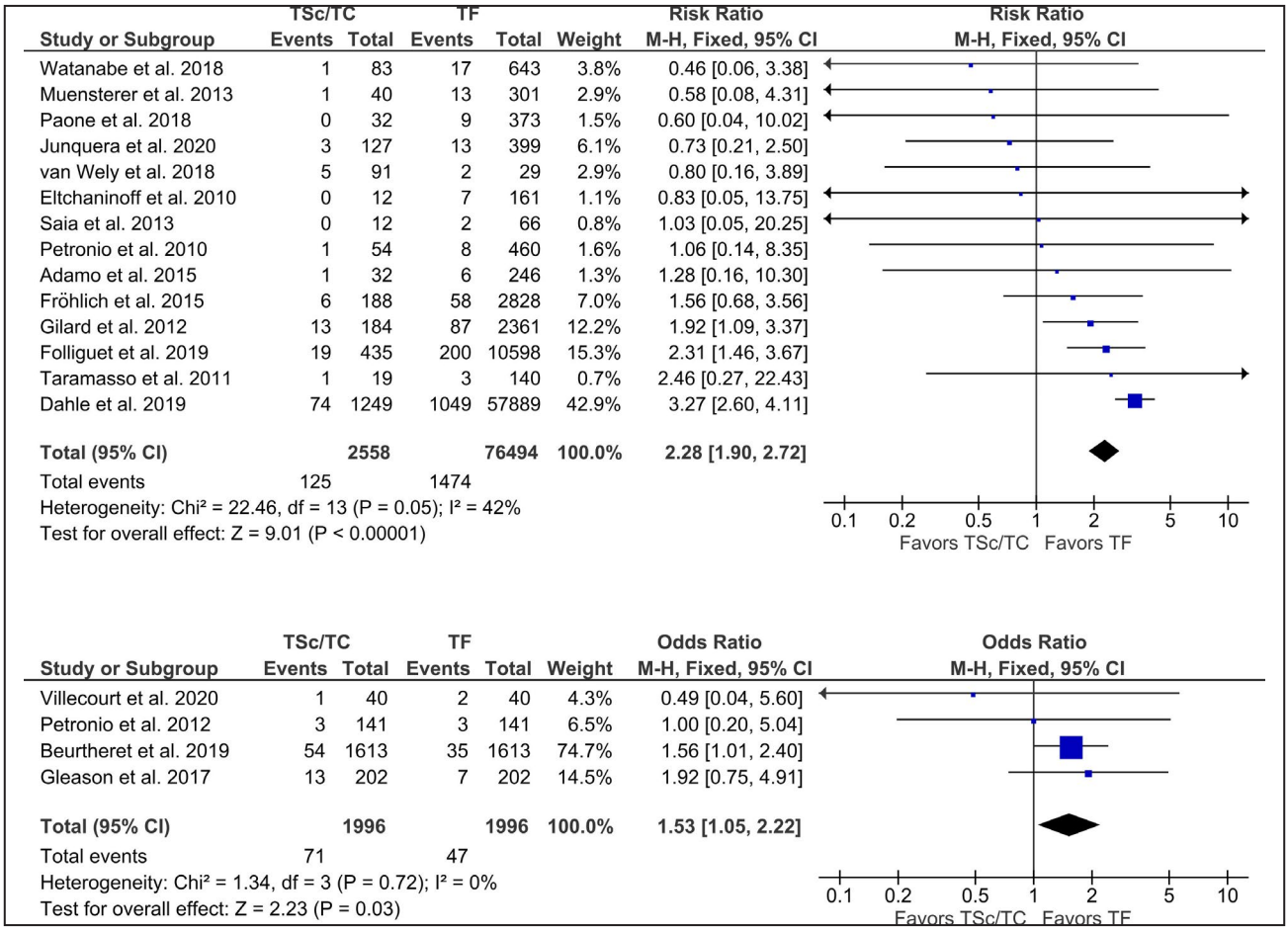

Figure 3. Risk of periprocedural stroke after transcatheter aortic valve replacement according to the arterial approach. **A**, Studies without propensity-score matching[‡]; **B**, Studies with propensity-score matching.[27–30]

with the surgical cutdown approach. Sensitivity analysis reported a significantly lower risk of vascular complication in the transcarotid subgroup, while a trend toward a higher risk of vascular complication was observed in the transsubclavian subgroup. This discrepancy may be related to several points. First, carotid arteries are more superficial than subclavian arteries, and access to the aortic valve is often less tortuous from carotid arteries than from subclavian arteries. Second, most studies including transsubclavian TAVR[8,11,14–23,27,28] preceded studies including transcarotid TAVR.[10,24–26] Thus, transsubclavian TAVR recipients were likely to be at higher risk of complication than transcarotid TAVR recipients. Third, sheaths used during the first studies were larger than during recent studies, and most studies including transsubclavian TAVR preceded those including transcarotid TAVR. The association between the sheath to femoral artery ratio and the risk of vascular complication is well known,[40] and it is likely that the sheath to carotid/subclavian artery ratio is also in relation with the risk of vascular complication during transcarotid/transsubclavian TAVR. Finally, a more aggressive strategy including peripheral interventions or pushing the limits of transfemoral approach in patients with small iliofemoral arteries to use the transfemoral access for close to 100% of TAVR cases may increase the risk of significant vascular complications, and the potential risks/benefits of such a strategy (versus a more conservative one including alternative accesses) should be determined in future studies.

Study Limitations

Most selected studies were retrospective in nature. Definitions of bleeding and vascular complications did not comply with Valve Academic Research Consortium[31] or Valve Academic Research Consortium–2[41] definitions in some studies.[§] A percutaneous transaxillary ap-

[‡]References 8,10,11,14–18,20,21,23–26.

[§]References 8,10,11,14–16,20,24,25,29.

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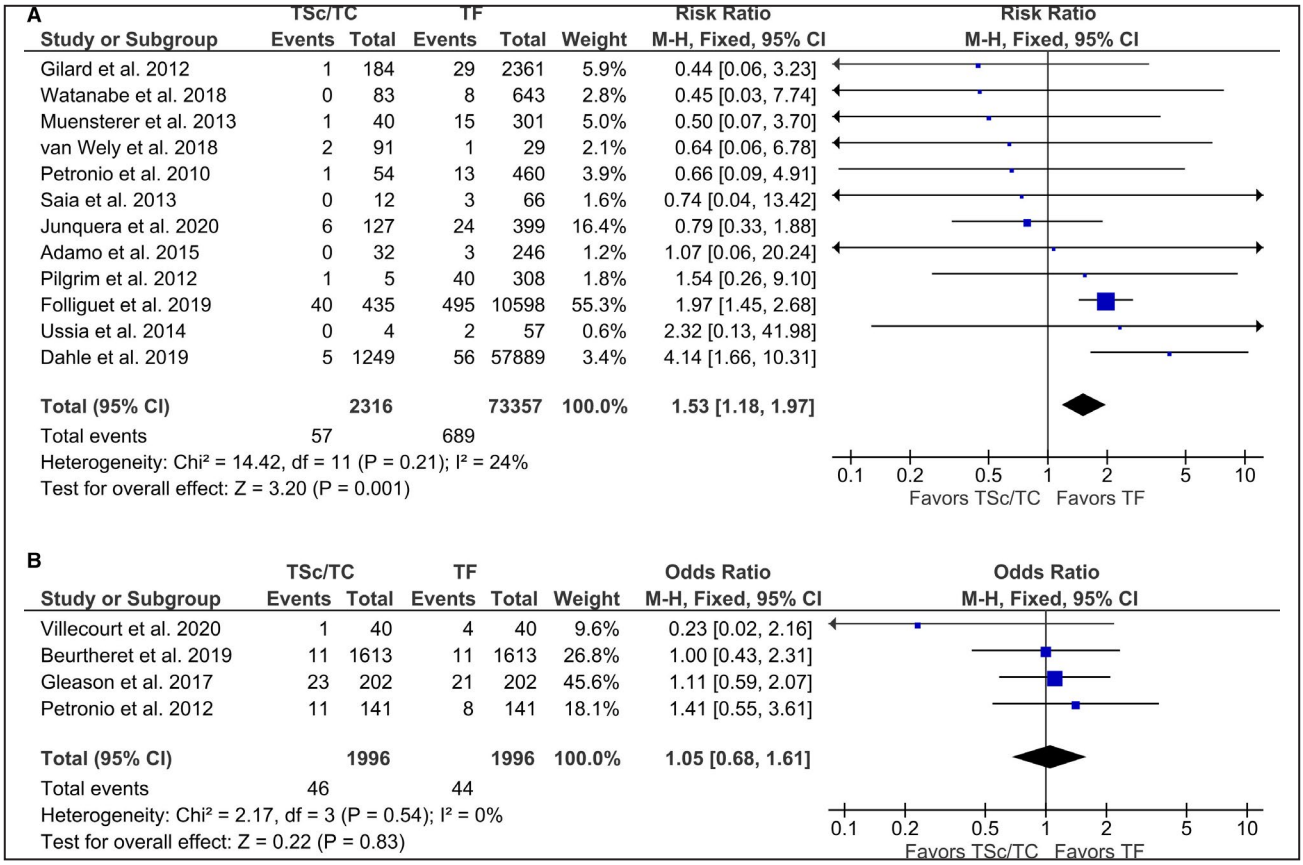

Figure 4. Risk of bleeding after transcatheter aortic valve replacement according to the arterial approach.
A, Studies without propensity-score matching[8,10,11,15,18–24,26]; **B**, Studies with propensity-score matching.[27–30]

proach for TAVR has been described,[42] but all transsubclavian accesses included in the present meta-analysis were performed through a surgical cutdown. This may preclude the application of our findings to percutaneous transsubclavian approach, especially regarding the risk of bleeding and vascular complications. Atrial fibrillation increases the risk of stroke, but analyses were not adjusted on this specific parameter. However, the rate of atrial fibrillation in studies with propensity matching did not differ according to the arterial approach.[28–30] An increased risk of bleeding alongside with a lower risk of vascular complications were associated with transcarotid (versus transfemoral TAVR) in the subgroup analysis. This discrepancy may be related to the variation in event definition across studies and to the lack of accurate bleeding description in some studies. Most of the studies included patients at increased surgical risk, and our findings may not apply to low surgical risk patients. The present meta-analysis used models that directly involved a number of events in each group, to calculate RR and OR. The power of the study could have been increased by using adjusted OR/hazard ratio. However, the approach was selected because only 3 studies provided adjusted OR for the 4 outcomes of interest[10,26,29] and 1 study reported adjusted hazard ratio only for mortality.[14]

In conclusion, the present meta-analysis provides evidence that alternative arterial (transcarotid/transsubclavian) approaches for TAVR were not associated with an increased risk of 30-day death, bleeding, or vascular complications when taking into account the confounding factors. However, both transcarotid and transsubclavian accesses were associated with an increased risk of stroke in comparison with the transfemoral approach. These findings should stimulate future efforts to better define the selection criteria for transcarotid and transsubclavian TAVR. In addition, the potential benefit of embolic protection devices in this population should be further evaluated. This has become an urgent need considering the rate of TAVR recipients with suboptimal transfemoral access (≈10%–15%) and the likely expansion of TAVR toward the treatment of the majority of patients with aortic stenosis in the near future.

ARTICLE INFORMATION

Received May 7, 2020; accepted August 21, 2020.

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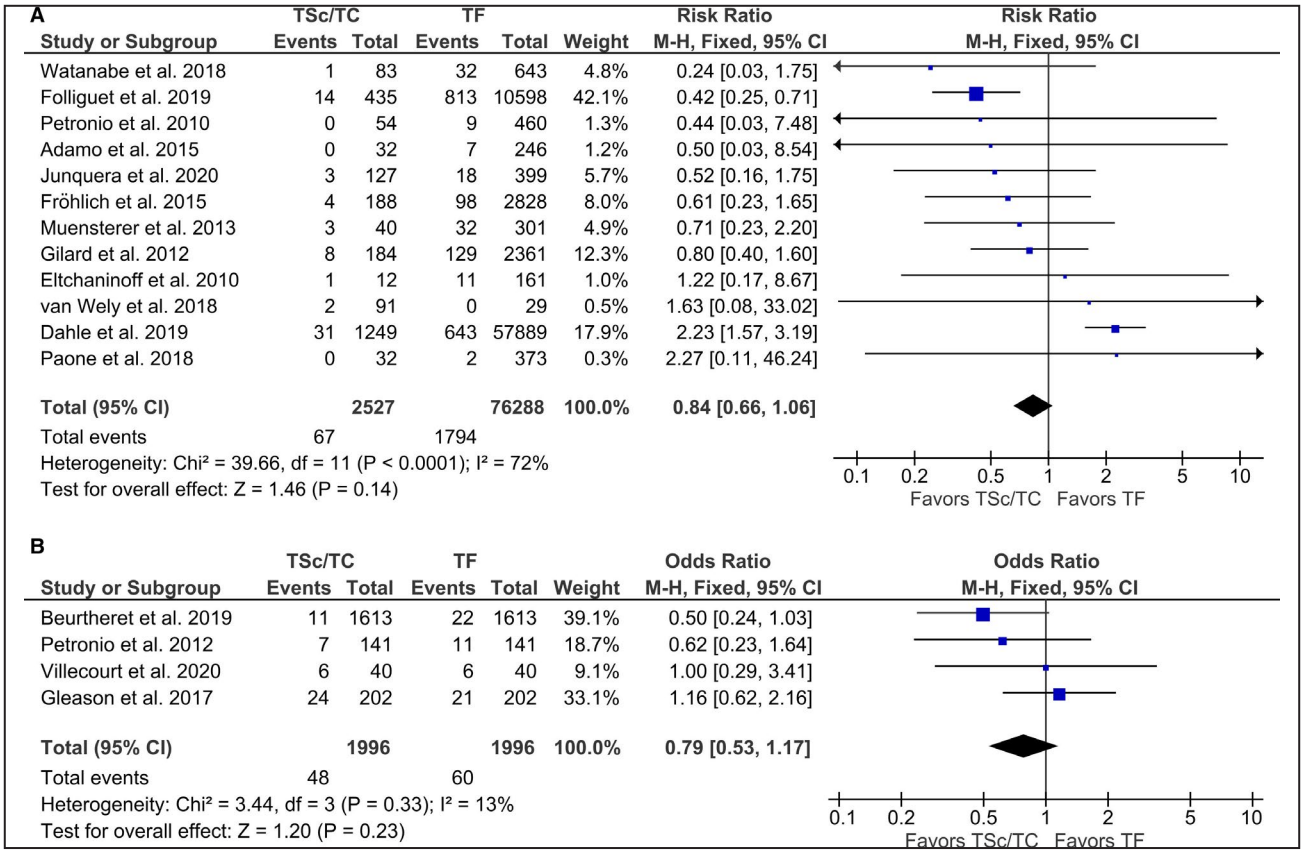

Figure 5. Risk of vascular complication after transcatheter aortic valve replacement according to the arterial approach. **A**, Studies without propensity-score matching[‖]; **B**, Studies with propensity-score matching.[27–30]

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Sources of Funding

None.

Disclosures

Dr Faroux received fellowship support from Institut Servier and the Association Régionale de Cardiologie de Champagne-Ardenne (ARCCA), and research grant from Biotronik, Edwards Lifesciences, and Medtronic. Dr Rodés-Cabau has received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific. The remaining authors have no disclosures to report. Dr Rodés-Cabau holds the Research Chair "Fondation Famille Jacques Larivière" for the Development of Structural Heart Disease Interventions. Drs. Junquera, Del Val, Muntané-Carol and Alperi were supported by a grant from the Fundacion Alfonso Martin Escudero (Madrid, Spain).

Supplementary Materials

Data S1
Tables S1–S2
Figures S1–S4

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Search Strategy

Database: Medline <1946 to 2020 June 30>

((Transcatheter Aortic Valve Replacement[MESH Terms]) OR (Percutaneous aortic) OR (Transcatheter aortic) OR TAVI OR TAVR) AND (transcarotid OR transsubclavian OR transaxillary OR trans-carotid OR trans-subclavian OR trans-axillary OR carotid OR subclavian OR axillary)

Database: Embase <1946 to 2020 June 30>

('transcatheter aortic valve implantation'/exp OR 'transcatheter aortic valve implantation') AND ('transcarotid' OR 'transsubclavian' OR 'transaxillary' OR 'trans-carotid' OR 'trans-subclavian' OR 'trans-axillary' OR 'carotid'/exp OR 'carotid' OR 'subclavian' OR 'axillary')

Table S1. Results of sensitivity analysis and research of publication bias for studies without propensity matching analysis.

Endpoint	Model	Risk Ratio [95% CI]	Begg rank correlation	p-value
All-cause death	Fixed	1.46 [1.22-1.74]	1.1442	0.2525
	Random	1.31 [0.95-1.80]		
	TSc subgroup	1.54 [1.26-1.89]		
	TC subgroup	1.25 [0.87-1.80]		
Stroke	Fixed	2.28 [1.90-2.72]	0.5913	0.5543
	Random	1.72 [1.19-2.49]		
	TSc subgroup	2.52 [2.07-3.08]		
	TC subgroup	1.59 [1.05-2.41]		
Bleeding	Fixed	1.53 [1.18-1.97]	1.7158	0.0862
	Random	1.40 [0.89-2.21]		
	TSc subgroup	1.16 [0.64-2.08]		
	TC subgroup	1.65 [1.24-2.20]		
Vascular complication	Fixed	0.84 [0.66-1.06]	1.5764	0.1149
	Random	0.76 [0.41-1.40]		
	TSc subgroup	1.30 [0.98-1.73]		
	TC subgroup	0.42 [0.27-0.67]		

CI: Confidence interval; TC: Transcarotid; TSc: Transsubclavian

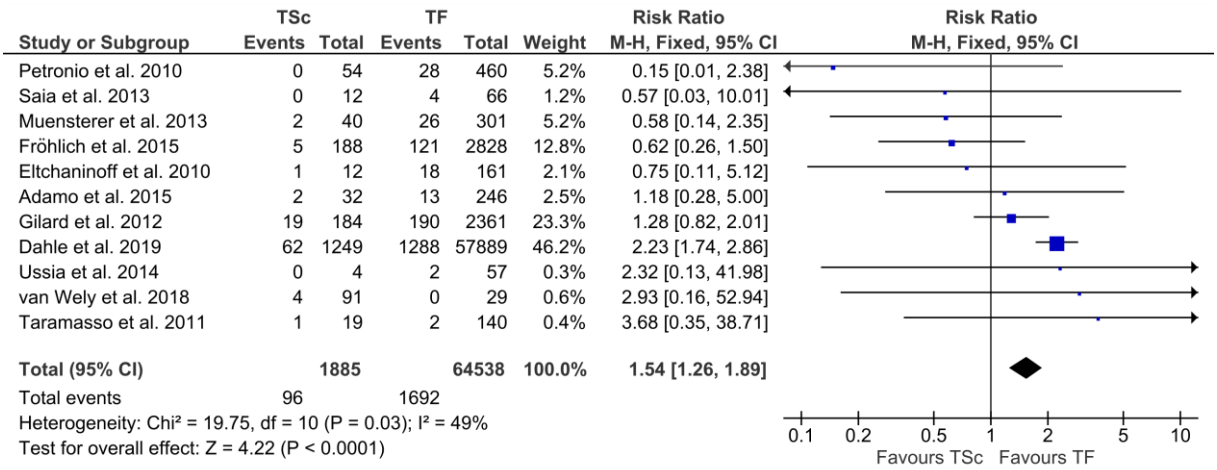
Table S2. Results of sensitivity analysis for studies with propensity-matching analysis.

Endpoint	Model	Odds Ratio [95% CI]
All-cause death	Fixed	1.22 [0.89-1.69]
	Random	1.22 [0.88-1.69]
Stroke	Fixed	1.53 [1.05-2.22]
	Random	1.53 [1.05-2.23]
Bleeding	Fixed	1.05 [0.68-1.61]
	Random	1.07 [0.69-1.65]
Vascular complication	Fixed	0.79 [0.53-1.17]
	Random	0.79 [0.51-1.22]

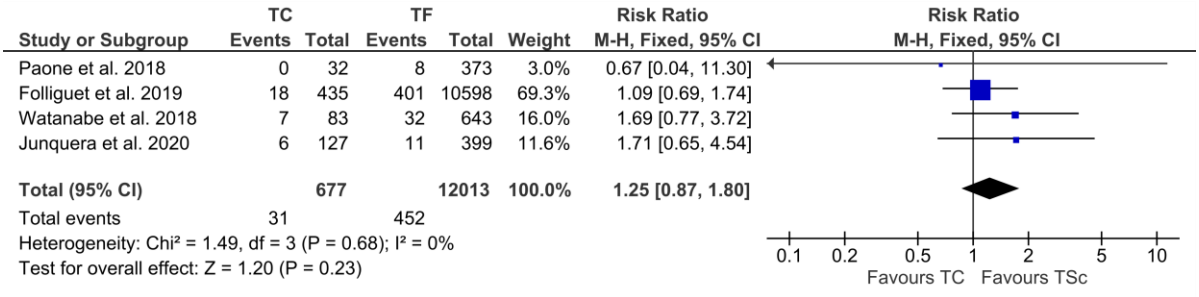
CI: Confidence interval

Figure S1. Risk of 30-day all-cause death according to the arterial approach.

A



B

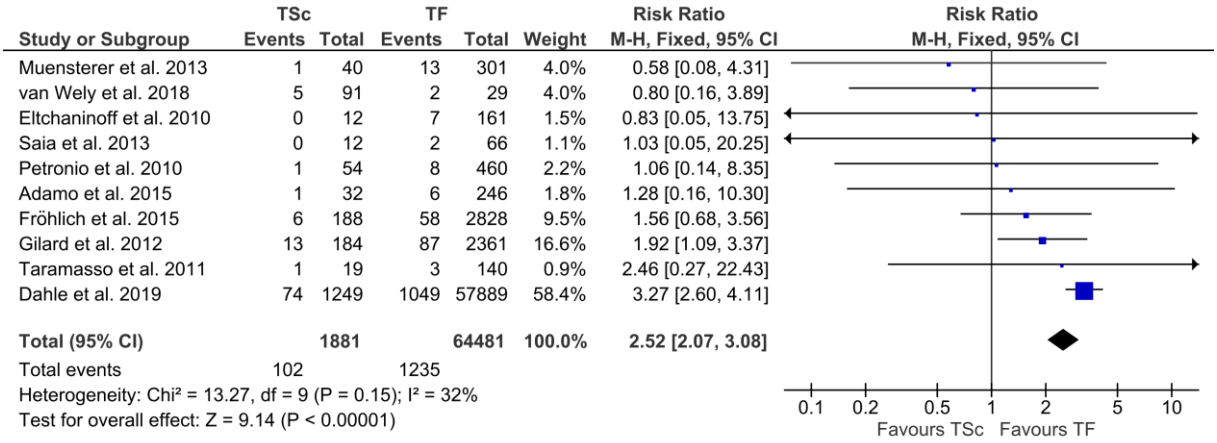


A: Transsubclavian versus transfemoral (8, 11, 14-18, 20-23)

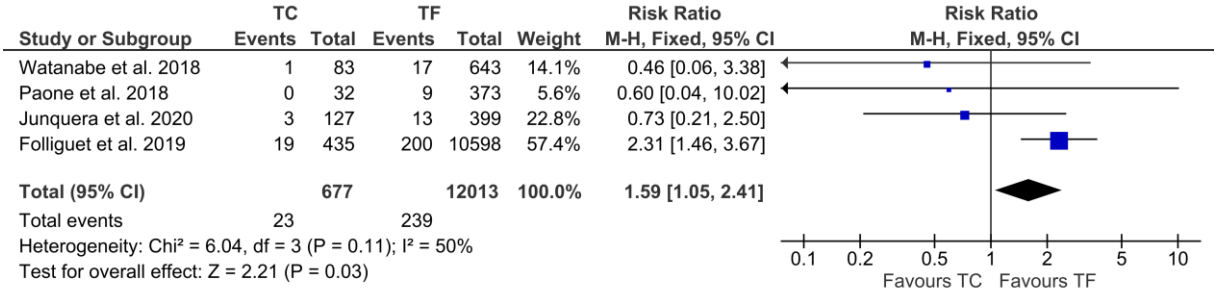
B: Transcarotid versus transfemoral (10, 24-26)

Figure S2. Risk of periprocedural stroke according to the arterial approach.

A



B

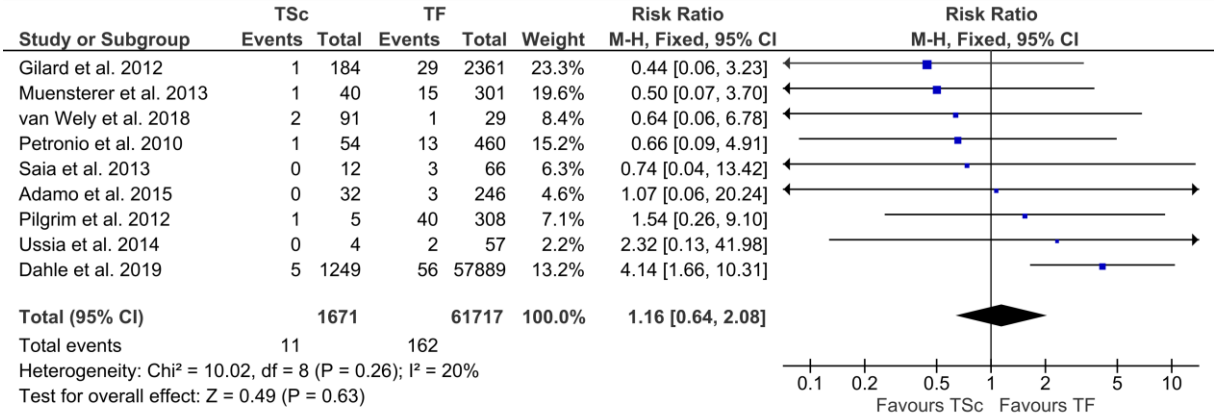


A: Transsubclavian versus transfemoral (8, 11, 14-18, 20, 21, 23)

B: Transcarotid versus transfemoral (10, 24-26)

Figure S3. Risk of bleeding according to the arterial approach.

A



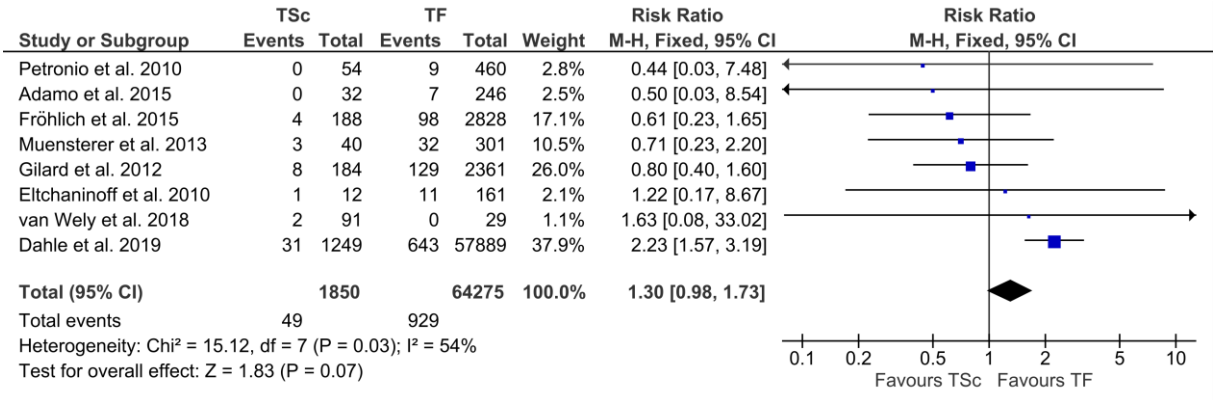
B

A: Transsubclavian versus transfemoral (8, 11, 15, 18-23)

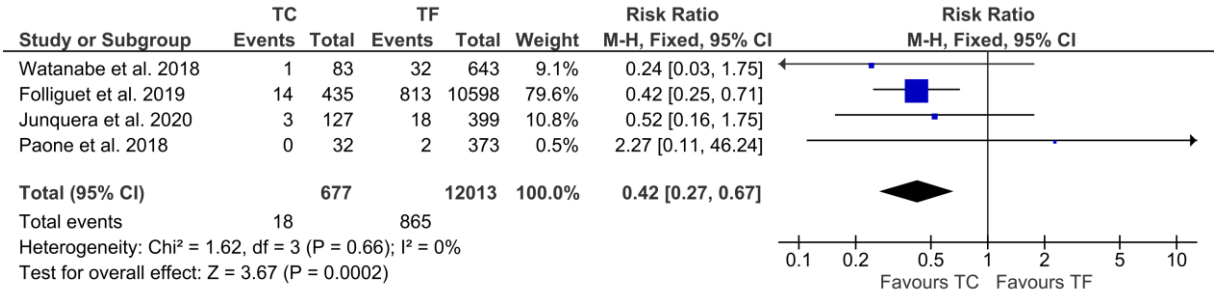
B: Transcarotid versus transfemoral (10, 24, 26)

Figure S4. Risk of vascular complication according to the arterial approach.

A



B



A: Transsubclavian versus transfemoral (8, 11, 14-16, 18, 20, 23)

B: Transcarotid versus transfemoral (10, 24-26)