Direct aortic route versus transaxillary route for transcatheter aortic valve replacement: a systematic review and meta-analysis

Hsiu-An Lee1, I-Li Su1, Shao-Wei Chen1, Victor Chien-Chia Wu2, Dong-Yi Chen2, Pao-Hsien Chu2, An-Hsun Chou3, Yu-Ting Cheng1, Pyng-Jing Lin1, Feng-Chun Tsai1

1Department of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan, Taiwan
2Department of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan, Taiwan
3Department of Anesthesiology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan, Taiwan

Corresponding Author: Feng-Chun Tsai
Email address: m8293@cgmh.org.tw

Background. The transfemoral route is contraindicated in nearly 10% of transcatheter aortic valve replacement (TAVR) candidates because of unsuitable iliofemoral vessels. Transaxillary (TAx) and direct aortic (DAo) routes are the principal nonfemoral TAVR routes; however, few studies have compared their outcomes.

Methods. We performed a systematic review and meta-analysis to compare the rates of mortality, stroke, and other adverse events of TAx and DAo TAVR. The study was prospectively registered with PROSPERO (registration number: CRD42017069788). We searched Medline, PubMed, Embase, and Cochrane databases for studies reporting the outcomes of DAo or TAx TAVR in at least 10 patients. Studies that did not use the Valve Academic Research Consortium definitions were excluded. We included studies that did not directly compare the 2 approaches and then pooled rates of events from the included studies for comparison.

Results. In total, 31 studies were included in the quantitative meta-analysis, with 2883 and 2172 patients in the DAo and TAx TAVR groups, respectively. Compared with TAx TAVR, DAo TAVR had a lower Society of Thoracic Surgery (STS) score, shorter fluoroscopic time, and less contrast volume use. The 30-day mortality rates were significantly higher in the DAo TAVR group [9.6%, 95% confidence interval (CI) = 8.4%-10.9%] than in the TAx TAVR group (5.7%, 95% CI = 4.8%-6.8%; P for heterogeneity <0.001). DAo TAVR was associated with a significantly lower risk of stroke in the overall study population (2.6% vs 5.8%, P for heterogeneity <0.001) and in the subgroup of studies with a mean STS score of ≥8 (1.6% vs 6.2%, P for heterogeneity = 0.005). DAo TAVR was also associated with lower risks of permanent pacemaker implantation (12.3% vs. 20.1%, P for heterogeneity = 0.009) and valve malposition (2.0% vs. 10.2%, P for heterogeneity = 0.023) than was TAx TAVR.

Conclusions. DAo TAVR increased 30-day mortality rate compared with TAx TAVR; by contrast, TAx TAVR increased postoperative stroke, permanent pacemaker implantation, and valve malposition risks compared with DAo TAVR.
Direct aortic route versus transaxillary route for transcatheter aortic valve replacement: a systematic review and meta-analysis

Hsiu-An Lee¹*, I-Li Su¹*, Shao-Wei Chen¹, Victor Chien-Chia Wu², Dong-Yi Chen², Pao-Hsien Chu², An-Hsun Chou³, Yu-Ting Cheng³, Pyng-Jing Lin¹, Feng-Chun Tsai¹

¹ Department of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan City, Taiwan
² Department of Cardiology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan City, Taiwan
³ Department of Anesthesiology, Chang Gung Memorial Hospital, Linkou Medical Center, Chang Gung University, Taoyuan City, Taiwan

* H.-A. Lee and I.-L. Su contributed equally to this work.

Corresponding Author:
Feng-Chun Tsai¹
No. 5 Fuxing Street, Gueishan District, Taoyuan City 33305, Taiwan
Tel: 886-3-3281200, Fax: 886-3-3285818
Email address: m8293@cgmh.org.tw
Abstract

Background. The transfemoral route is contraindicated in nearly 10% of transcatheter aortic valve replacement (TAVR) candidates because of unsuitable iliofemoral vessels. Transaxillary (TAX) and direct aortic (DAO) routes are the principal nonfemoral TAVR routes; however, few studies have compared their outcomes.

Methods. We performed a systematic review and meta-analysis to compare the rates of mortality, stroke, and other adverse events of TAX and DAO TAVR. The study was prospectively registered with PROSPERO (registration number: CRD42017069788). We searched Medline, PubMed, Embase, and Cochrane databases for studies reporting the outcomes of DAO or TAX TAVR in at least 10 patients. Studies that did not use the Valve Academic Research Consortium definitions were excluded. We included studies that did not directly compare the 2 approaches and then pooled rates of events from the included studies for comparison.

Results. In total, 31 studies were included in the quantitative meta-analysis, with 2883 and 2172 patients in the DAO and TAX TAVR groups, respectively. Compared with TAX TAVR, DAO TAVR had a lower Society of Thoracic Surgery (STS) score, shorter fluoroscopic time, and less contrast volume use. The 30-day mortality rates were significantly higher in the DAO TAVR group [9.6%, 95% confidence interval (CI) = 8.4%–10.9%] than in the TAX TAVR group (5.7%, 95% CI = 4.8%–6.8%; P for heterogeneity <0.001). DAO TAVR was associated with a significantly lower risk of stroke in the overall study population (2.6% vs 5.8%, P for heterogeneity <0.001) and in the subgroup of studies with a mean STS score of ≥8 (1.6% vs 6.2%, P for heterogeneity = 0.005). DAO TAVR was also associated with lower risks of permanent pacemaker implantation (12.3% vs. 20.1%, P for heterogeneity = 0.009) and valve malposition (2.0% vs. 10.2%, P for heterogeneity = 0.023) than was TAX TAVR.

Conclusions. DAO TAVR increased 30-day mortality rate compared with TAX TAVR; by contrast, TAX TAVR increased postoperative stroke, permanent pacemaker implantation, and valve malposition risks compared with DAO TAVR.
Introduction

Transcatheter aortic valve replacement (TAVR) enables the safe and effective treatment of inoperable or high-surgical-risk patients with severe aortic valve disease, without using a cardiopulmonary bypass (Kodali et al., 2012; Makkar et al., 2012). Randomized controlled trials have demonstrated that TAVR is an effective alternative to surgical aortic valve replacement in intermediate-risk patients (Leon et al., 2016; Reardon et al., 2017).

TAVR is more favorable than surgical aortic valve replacement when using transfemoral (TF) access (Gargiulo et al., 2016), which is thus used as the default approach for performing TAVR in numerous institutions. However, peripheral vascular occlusion, stenosis, calcification, or tortuosity precludes TF access in approximately 10% of patients (Grover et al., 2017), necessitating the use of an alternative route, such as transapical (TA), transaxillary (TAX), direct aortic (DAo), and transcarotid routes. To select the optimal treatment technique in patients unsuitable for TF TAVR, clinicians need to understand the outcomes of using different nonfemoral routes.

The TA route was the first alternative TAVR route developed for patients with unsuitable iliofemoral vessels (Grover et al., 2017; Walther et al., 2015). However, the procedure is associated with relatively high rates of bleeding, ventricular damage (Al-Attar et al., 2009), myocardial injury (Ribeiro et al., 2015a), and mortality (Fröhlich et al., 2015; Panchal et al., 2014). DAo and TAX routes are also principal alternatives to TF; both have results comparable to those of the TF route (Adamo et al., 2015; Arai et al., 2016; Chandrasekhar et al., 2015; Fröhlich et al., 2015). However, data comparing the outcomes of using the DAo and TAX TAVR routes are limited. Therefore, we conducted this systematic review and meta-analysis to compare the morbidity and mortality associated with these 2 approaches.

Materials & Methods

Literature Search

This systematic review of published studies was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with a PRISMA checklist provided as Supplementary Table 1. This study has been prospectively registered with PROSPERO (registration number: CRD42017069788). A computerized search of the Medline, PubMed, Embase, and Cochrane databases was performed to identify all relevant studies published before July 2017 by using the following keywords: “transcatheter,” “aortic valve,” “TAVR,” “TAVI,” “direct aortic,” “transaortic,” “transaxillary,” “axillary,” “trans-subclavian,” and “subclavian.” The exact string of keywords is reported in Supplementary Material 1. Review articles or meta-analyses were not included for analysis, but their citations and references were searched for additional relevant studies. Citations were screened at the title and abstract levels and retrieved as a full report if outcome data of TAVRs were provided. Two evaluators (H.A. Lee and S.W. Chen) independently searched for and reviewed the articles. Discrepancies were discussed and resolved through consensus.
**Study Selection**
Inclusion criteria were as follows: (1) original article in English with full-length content available, (2) at least 10 consecutive patients who underwent either DAo or TAx TAVR, (3) outcomes defined using the Valve Academic Research Consortium (VARC) definition (as VARC-1 or VARC-2) (Kappetein et al., 2012; Leon et al., 2011), and (4) separate results for patients undergoing DAo TAVR or TAx TAVR. Exclusion criteria were as follows: (1) overlapping patients or subgroup studies of the main study, (2) studies that focused on the valve-in-valve procedure, (3) studies that focused on TAVR combined with another procedure, and (4) the use of devices other than Medtronic CoreValve (MCV; Medtronic, Minneapolis, MN, USA) and Edwards Valve (EV; Edwards Lifesciences, Irvine, CA, USA). Studies that did not directly compare the 2 approaches were also included. The most recent publications were retained when 2 or more similar studies were reported by the same institution or author.

**Data Extraction**
Relevant information was collected by H.A. Lee and S.W. Chen. The study-level characteristics extracted were first author name, publication year, study type (e.g., single-centered or multicentered), number of studies, location, study period, route (DAo or TAx), patient number, and VARC version (Table 1). The arm-level characteristics items extracted included age, logistic EuroSCORE, Society of Thoracic Surgery (STS) score, comorbidities, previous cardiac surgery, left ventricular ejection fraction, and devices (Table 2). Data on the primary and secondary outcomes for either DAo or TAx were also collected.

**Outcome Measures**
The primary outcomes were 30-day stroke and mortality rates after TAx or DAo TAVR. These results were further stratified by mean STS scores of <8 and ≥8 after TAx or DAo TAVR. The 30-day stroke rates after MCV and EV use were also compared. If a study did not report the 30-day mortality or stroke rates, in-hospital mortality or stroke rates were used. The secondary outcomes were device success, conversion to traditional surgery, valve malposition, acute kidney injury, major bleeding, major vascular complication, new permanent pacemaker (PPM) implantation, paravalvular leakage (PVL) grade of ≥2, 30-day cardiovascular mortality, and 1-year mortality.

**Quality Assessment**
We assessed the quality of the included studies by using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). Quality scores ranged from 0 (lowest) to 8 (highest). The NOS was applied to each article separately by H.A. Lee and S.W. Chen and disagreements were resolved by consensus between the 2 reviewers.

**Statistical Analysis**
This meta-analysis included studies that did not directly compare the 2 approaches and pooled rates of events from the included studies for comparison. Random-effects models were used to pool the estimates of primary and secondary outcomes from individual studies for each arm (TAx or DAo). In contrast to a fixed-effects model, a random-effects model enables the true underlying effect to vary among individual studies. $I^2$ above 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity across the studies, respectively (Higgins et al., 2003). The pooled estimates between TAx and DAo TAVR were compared using mixed-effects models. Statistical significance was set at $P < 0.05$ with a two-tailed test. Data were analyzed using Comprehensive Meta-Analysis (version 2.2; Biostat, Englewood, NJ, USA).

Results

Literature Search

Our initial web-based literature search yielded 703 records. We screened the titles and abstracts of all 703 studies, of which 583 did not satisfy our inclusion and exclusion criteria. We downloaded and assessed the full-text of 120 articles for eligibility. After a review of the full-text articles, we excluded 19 articles that employed duplicated cohorts, 49 that did not report the outcomes of patients who received TAx or DAo TAVR, 13 that did not use VARC definitions for reporting the outcomes, 1 that included only TAVR with combined coronary artery bypass grafting procedure, 4 that used devices other than Edward or Medtronic, 1 that enrolled <10 cases, and 1 that employed a valve-in-valve procedure (Supplementary Material 2, Supplementary Table 2). Finally, we included 31 studies in the quantitative meta-analysis (Fig. 1), with 2883 and 2172 patients in the DAo TAVR and TAx TAVR groups, respectively (Adamo et al., 2015; Arai et al., 2016; Bonaros et al., 2017; Bruschi et al., 2017; Bruschi et al., 2015; Cocchieri et al., 2019; D’Ancona et al., 2019; Dahle & Rein, 2014; Dahle, Kaneko & McCabe, 2019; Damluji et al., 2018; Fiorina et al., 2016; Gilard et al., 2012; Gleason et al., 2018; Hysi et al., 2019; Jagielak et al., 2015; Khan et al., 2018; Laflamme et al., 2014; Muensterer et al., 2013; Okuyama et al., 2015; Petzina et al., 2017; Ramlawi et al., 2015; Ribeiro et al., 2015b; Romano et al., 2019; Ropponen et al., 2016; Schäfer et al., 2017; Spargias et al., 2014; Terzian et al., 2017; Testa et al., 2012; Thourani et al., 2015; Wendt et al., 2015; Zhan et al., 2020).

Quality Assessment

The quality of the 31 studies included in the meta-analysis was assessed using NOS, scored in the range of 0–8 points. The NOS scores for all 31 studies ranged between 5 and 7 points, with a median score of 6 points (Supplementary Table 3).

Baseline and Procedural Characteristics

Table 2 presents the available baseline and procedural characteristics. The mean age of the DAo TAVR and TAx TAVR groups was 82.7 ± 1.2 and 80.0 ± 1.7 years, respectively. No substantial differences in logistic EuroSCORE (22.0 ± 7.1 in DAo vs. 22.6 ± 5.3 in TAx) and STS score (7.5
± 1.8 in DAo vs. 8.9 ± 3.0 in TAx) were noted. The percentage of MCV use in the TAx TAVR
group seemed to be higher than that in the DAo TAVR group.

**TAx and DAo TAVR Outcomes**

We analyzed the 2 primary outcomes, the 30-day stroke and mortality rates (Fig. 2). The 30-day
mortality rates of the DAo TAVR and TAx TAVR groups were significantly different with
mortality rates of 9.6% [95% confidence interval (CI) = 8.4%–10.9%] and 5.7% (95% CI =
4.8%–6.8%), respectively (P for heterogeneity < 0.001). The pooled 30-day stroke rate in the
DAo TAVR group (2.6%, 95% CI = 1.9%–3.4%) was significantly lower than that in the TAx
TAx TAVR group (5.8%, 95% CI = 4.9%–7.0%; P for heterogeneity < 0.001).

We then analyzed secondary outcomes. Patients were more likely to require new PPM
implantation after TAx TAVR (20.1%, 95% CI = 15.5%–25.6%) than after DAo TAVR (12.3%,
95% CI = 9.4%–16.0%; P for heterogeneity = 0.009). Valve malposition occurred more
frequently in patients who underwent TAx TAVR (10.2%, 95% CI = 3.4%–27.1%) than in
patients who underwent DAo TAVR (2.0%, 95% CI = 0.9%–4.7%; P for heterogeneity = 0.023).
The conversion rate was higher in the DAo TAVR group (2.8%, 95% CI = 2.1%–3.6%) than in
the TAx TAVR group (0.9%, 95% CI = 0.6%–1.6%; P for heterogeneity < 0.001). No significant
differences in the other secondary outcomes were identified between the 2 groups (Fig. 2).

**Discussion**

**TAx Versus DAo TAVR**

TAx TAVR is the most commonly used percutaneous, nonfemoral approach that does not require
general anesthesia or endotracheal intubation. TAx TAVR is also less invasive than DAo and TA
TAVR because it does not require entering the chest cavity, thereby reducing lung complication
risks, thus shortening the ventilator time and intensive care unit stay.

In DAo TAVR, the delivery system enters directly through the ascending aorta, which
requires minimal manipulation of the peripheral vessels, thereby reducing the incidence of
peripheral vascular complications. Furthermore, cardiac surgeons are more familiar with DAo
TAVR than with TA TAVR; therefore, DAo TAVR use may improve bleeding control and
prevent myocardial injury, which can result in impaired ventricular function and ventricular
pseudoaneurysm.

Data from more than 5,000 patients were analyzed in our systematic review and meta-
analysis, which is the largest sample that has been used to compare TAx and DAo TAVR
outcomes. We found that TAx TAVR was associated with a lower 30-day mortality rate,
compatible with the findings of previous studies (Damluji et al., 2018; Fröhlich et al., 2015).
Moreover, TAx TAVR was associated with higher postoperative stroke and PPM implantation
rates than was DAo TAVR. Studies have reported similar trends; however, statistical
significance was not demonstrated in these studies, which may be due to insufficient sample
sizes (Adamo et al., 2015; Damluji et al., 2018; Fiorina et al., 2016; Fröhlich et al., 2015).
Post-TAVR stroke occurrence remains a major concern and cause of increased morbidity and mortality. In the present meta-analysis, the stroke rate was higher in the TAx group than in the DAo group. The mechanism for the lower stroke rate after DAo TAVR is unclear. Transcranial Doppler studies have reported that cerebral embolism predominantly occurred during manipulation of the calcified aortic valve while prostheses were being positioned and implanted (Kahlert et al., 2012). The shorter distance and straight course between the device entry site (on the ascending aorta) and the aortic annulus of the DAo route may enable surgeons to implant the stented valve more accurately and rapidly with less aortic valve manipulation, resulting in fewer distal embolisms.

In contrast to DAo TAVR, TAx TAVR involves the advancement of the delivery catheter from the right or left subclavian artery to the ascending aorta, thus traversing the origins of the vertebral artery, carotid artery, aortic arch, and ascending aorta, which may induce atherosclerotic plaques and cerebral embolism. The flow of the vertebral artery or right carotid artery may be compromised during the procedure, particularly when the diameter of the innominate artery or left subclavian artery is only marginally wider than the delivery catheter. Moreover, TAx TAVR can cause vessel wall disruption along the innominate and subclavian arteries and the origins of the carotid and vertebral arteries, resulting in enhanced thrombogenicity, which may be linked to stroke (Barthélémy, Collet & Montalescot, 2016).

**PPM Implantation**

A study comparing TAx and DAo TAVR in 4 high-volume Italian centers concluded that the TAx route is an independent predictor for increased PPM implantation (Fiorina et al., 2016)—compatible with our finding that PPM implantation rate was higher after TAx TAVR than after DAo TAVR. Implantation depth is known to be a predictor of PPM implantation after TAVR. DAo TAVR may provide better control over device placement than does TAVR with peripheral access, potentially resulting in better coaxial alignment and more accurate implant depth, thereby causing fewer conduction disturbances (Bruschi et al., 2017). Large-scale studies reported that TA TAVR was associated with a significantly lower rate of PVL than was TF TAVR (Kodali et al., 2014; Van Belle et al., 2014). This finding suggests that more direct routes, such as DAo or TA, provide increased device placement control and thus lower PVL and PPM implantation rates. Furthermore, our meta-analysis indicated that TAx TAVR was associated with significantly higher valve malposition and numerically higher PVL compared with DAo TAVR ($P = 0.113$).

**Study Limitations**

First, all studies included in our analysis were observational, and thus, heterogeneity between the 2 groups was inevitable. However, the 2 groups cannot be accurately balanced without undertaking a randomized controlled trial. Second, to ensure the standardization of the definitions of stroke and other complications, we enrolled only the studies that used the VARC
definitions; however, this limited the number of patients analyzed, thereby reducing the power of the meta-analysis. Third, the pace of reporting does not match the rapid advancement of TAVR technology; therefore, these results may not represent the real outcomes of the most recent devices.

Conclusions
The present meta-analysis compared the outcomes of DAo and TAx TAVR. We determined that the 30-day mortality rate was higher in patients who underwent DAo TAVR, but the postoperative stroke and PPM implantation rates were higher in patients who underwent TAx TAVR. Our findings could help TAVR candidates with unsuitable femoral access optimize their selection of alternative access.

Acknowledgments
The authors thank Alfred Hsing-Fen Lin for his assistance with the statistical analysis.

References
Adamo M, Fiorina C, Curello S, Maffeo D, Chizzola G, Di Matteo G, Mastropierro R, Nardi M,
Cervi E, De Cicco G, Chiari E, Curnis A, Bonardelli S, Coletti G, Manzato A, Metra M,
and Ettori F. 2015. Role of different vascular approaches on transcatheter aortic valve implantation outcome: A single-center study. *Journal of Cardiovascular Medicine* 16:279-285. 10.2459/JCM.0000000000000252

Al-Attar N, Ghodbane W, Himbert D, Rau C, Raffoul R, Messika-Zeitoun D, Brochet E,
Vahanian A, and Nataf P. 2009. Unexpected complications of transapical aortic valve implantation. *The Annals of Thoracic Surgery* 88:90-94. 10.1016/j.athoracsur.2009.03.070

Arai T, Romano M, Lefevre T, Hovasse T, Farge A, Le Houerou D, Hayashida K, Watanabe Y,
Garot P, Benamer H, Unterseeh T, Bouvier E, Morice MC, and Chevalier B. 2016. Direct Comparison of Feasibility and Safety of Transfemoral Versus Transaortic Versus Transapical Transcatheter Aortic Valve Replacement. JACC: Cardiovascular Interventions 9:2320-2325. 10.1016/j.jcin.2016.08.009

Barthélémy O, Collet JP, and Montalescot G. 2016. Cerebral Embolism. Journal of the American College of Cardiology 68:600-602. 10.1016/j.jacc.2016.05.054

Bonaros N, Petzina R, Cocchieri R, Jagielak D, Aiello M, Lapeze J, Laine M, Chocron S, Muir D, Eichinger W, Thielmann M, Labrousse L, Bapat V, Arne Rein K, Verhoey JP, Gerosa G, Baumbach H, Kofler M, Bramlage P, Deutsch C, Thoenes M, Frank D, and Romano M. 2017. Transaortic transcatheter aortic valve implantation as a first-line choice or as a last resort? An analysis based on the ROUTE registry. European Journal of Cardio-Thoracic Surgery 51:919-926.

Bruschi G, Branny M, Schiltgen M, Ettori F, Marcheix B, Amrane H, Bushnaq H, Tan MESH, Trivedi U, Branny P, Klugmann S, Coletti G, Dumonteil N, Porta F, Nordell A, and Moat N. 2017. One-Year Outcomes of Transcatheter Aortic Valve Implantation Using the Direct Aortic Approach. The Annals of Thoracic Surgery 103:1434-1440. 10.1016/j.athoracsur.2016.08.080

Bruschi G, De Marco F, Botta L, Barosi A, Colombo P, Mauri S, Cannata A, Morici N, Colombo
T, Fratto P, Nonini S, Soriano F, Mondino M, Giannattasio C, and Klugmann S. 2015. Right anterior mini-thoracotomy direct aortic self-expanding trans-catheter aortic valve implantation: A single center experience. *International Journal of Cardiology* 181:437-442. [https://dx.doi.org/10.1016/j.ijcard.2014.11.108](https://dx.doi.org/10.1016/j.ijcard.2014.11.108)

Chandrasekhar J, Hibbert B, Ruel M, Lam BK, Labinaz M, and Glover C. 2015. Transfemoral vs Non-transfemoral Access for Transcatheter Aortic Valve Implantation: A Systematic Review and Meta-analysis. *Canadian Journal of Cardiology* 31:1427-1438. 10.1016/j.cjca.2015.04.023

Cocchieri R, Petzina R, Romano M, Jagielak D, Bonaros N, Aiello M, Lapeze J, Laine M, Chocron S, Muir D, Eichinger W, Thielmann M, Labrousse L, Rein KA, Verhoye JP, Gerosa G, Bapat V, Baumbach H, Sims H, Deutsch C, Bramlage P, Kurucova J, Thoenes M, and Frank D. 2019. Outcomes after transaortic transcatheter aortic valve implantation: Long-term findings from the European ROUTE. *European Journal of Cardio-Thoracic Surgery* 55:737-743. 10.1093/ejcts/ezy333

D'Ancona G, Ince H, Raspé C, Öner A, Caglayan E, Safak E, and Bushnaq H. 2019. Transaortic transcatheter aortic valve implantation: Learning curve, perioperative, and midterm follow-up results of a single center. *Heart Surgery Forum* 22:E134-E139. 10.1532/hsf.2249
Dahle G, and Rein KA. 2014. Direct aorta ascending approach in transcatheter aortic valve implantation. Innovations (Phila) 9:1-9.

https://dx.doi.org/10.1097/IMI.0000000000000046

Dahle TG, Kaneko T, and McCabe JM. 2019. Outcomes Following Subclavian and Axillary Artery Access for Transcatheter Aortic Valve Replacement: Society of the Thoracic Surgeons/American College of Cardiology TVT Registry Report. JACC: Cardiovascular Interventions 12:662-669. 10.1016/j.jcin.2019.01.219

Damluji AA, Murman M, Byun S, Moscucci M, Resar JR, Hasan RK, Alfonso CE, Carrillo RG, Williams DB, Kwon CC, Cho PW, Dijos M, Peltan J, Heldman AW, Cohen MG, and Leroux L. 2018. Alternative access for transcatheter aortic valve replacement in older adults: A collaborative study from France and United States. Catheterization and Cardiovascular Interventions 92:1182-1193. 10.1002/ccd.27690

Fiorina C, Bruschi G, Testa L, De Carlo M, De Marco F, Coletti G, Bonardelli S, Adamo M, Curello S, Scioti G, Panisi P, Bedogni F, Petronio AS, and Ettori F. 2016. Trans-axillary versus trans-aortic approach for transcatheter aortic valve implantation with corevalve revalving system: insights from multicentre experience. The Journal of Cardiovascular Surgery.

Fröhlich GM, Baxter PD, Malkin CJ, Scott DJA, Moat NE, Hildick-Smith D, Cunningham D,
Maccarthy PA, Trivedi U, De Belder MA, Ludman PF, and Blackman DJ. 2015. Comparative Survival after Transapical, Direct Aortic, and Subclavian Transcatheter Aortic Valve Implantation (Data from the UK TAVI Registry). *American Journal of Cardiology* 116:1555-1559. 10.1016/j.amjcard.2015.08.035

Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C, Capranzano P, Indolfi C, Trimarco B, Tamburino C, and Esposito G. 2016. Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement: A Systematic Review and Meta-analysis. *Annals of Internal Medicine* 165:334-344. 10.7326/M16-0060

Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, and Laskar M. 2012. Registry of transcatheter aortic-valve implantation in high-risk patients. *New England Journal of Medicine* 366:1705-1715. 10.1056/NEJMoal114705

Gleason TG, Schindler JT, Hagberg RC, Deeb GM, Adams DH, Conte JV, Zorn GL, Hughes GC, Guo J, Popma JJ, and Reardon MJ. 2018. Subclavian/Axillary Access for Self-
Expanding Transcatheter Aortic Valve Replacement Renders Equivalent Outcomes as Transfemoral. *The Annals of Thoracic Surgery* 105:477-483.

10.1016/j.athoracsur.2017.07.017

Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, Brindis RG, Shahian DM, Ruiz CE, Jacobs JP, Hanzel G, Bavaria JE, Tuzcu EM, Peterson ED, Fitzgerald S, Kourtis M, Michaels J, Christensen B, Seward WF, Hewitt K, Holmes DR, Jr., and Registry SAT. 2017. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Journal of the American College of Cardiology* 69:1215-1230.

10.1016/j.jacc.2016.11.033

Higgins JP, Thompson SG, Deeks JJ, and Altman DG. 2003. Measuring inconsistency in meta-analyses. *British Medical Journal* 327:557-560. 10.1136/bmj.327.7414.557

Hysi I, Gommeaux A, Pécheux M, Hochart P, Hannebicque G, Pâris M, Manchuelle A, and Fabre O. 2019. Axillary Transcatheter Aortic Valve Replacement in Patients With Peripheral Vascular Disease. *Seminars in Thoracic and Cardiovascular Surgery* 31:175-180. 10.1053/j.semtcvs.2018.09.016

Jagielak D, Bramlage P, Pawłaczyk R, Brzezinski M, Fijalkowski M, Laskawski G, Ciecwierz D, Rogowski J, and Kozaryn R. 2015. Transaortic transcatheter aortic valve implantation:
Results of the Polish arm of the ROUTE registry. Cardiology Journal 22:651-656.

https://dx.doi.org/10.5603/CJ.a2015.0046

Kahlert P, Al-Rashid F, Dottger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, and Eggebrecht H. 2012. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. Circulation 126:1245-1255.

10.1161/CIRCULATIONAHA.112.092544

Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, and Leon MB. 2012. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. European Heart Journal 33:2403-2418. 10.1093/eurheartj/ehs255

Khan AA, Kovacic JC, Engstrom K, Stewart A, Ananywu A, Basnet S, Aquino M, Baber U, Garcia L, Gidwani U, Dangas G, Kini A, and Sharma S. 2018. Comparison of Transaortic and Subclavian Approaches for Transcatheter Aortic Valve Replacement in Patients with No Transfemoral Access Options. Structural Heart 2:463-468.

10.1080/24748706.2018.1497237
Kodali S, Pibarot P, Douglas PS, Williams M, Xu K, Thourani V, Rihal CS, Zajarias A, Doshi D, Davidson M, Tuzcu EM, Stewart W, Weissman NJ, Svensson L, Greason K, Maniar H, Mack M, Anwaruddin S, Leon MB, and Hahn RT. 2014. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. *European Heart Journal* 36:449-456. 10.1093/eurheartj/ehu384

Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, and Leon MB. 2012. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *New England Journal of Medicine* 366:1686-1695. 10.1056/NEJMoa1200384

Laflamme M, Mazine A, Demers P, Lamarche Y, Ibrahim R, Asgar A, and Cartier R. 2014. Transcatheter aortic valve implantation by the left axillary approach: A single-center experience. *The Annals of Thoracic Surgery* 97:1549-1554. 10.1016/j.athoracsur.2013.11.019

Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A,
van Es GA, Vranckx P, Webb JG, Windecker S, and Serruys PW. 2011. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *European Heart Journal* 32:205-217. 10.1093/eurheartj/ehq406

Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG, and Investigators P. 2016. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine* 374:1609-1620. 10.1056/NEJMoa1514616

Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, and Leon MB. 2012. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *New England Journal of Medicine* 366:1696-1704. 10.1056/NEJMoa1202277

Muensterer A, Mazzitelli D, Ruge H, Wagner A, Hettich I, Piazza N, Lange R, and Bleiziffer S.
2013. Safety and efficacy of the subclavian access route for TAVI in cases of missing transfemoral access. *Clinical Research in Cardiology* 102:627-636. 10.1007/s00392-013-0575-0

Okuyama K, Jilaihawi H, Mirocha J, Nakamura M, Ramzy D, Makkar R, and Cheng W. 2015. Alternative access for balloon-expandable transcatheter aortic valve replacement: comparison of the transaortic approach using right anterior thoracotomy to partial J- sternotomy. *The Journal of Thoracic and Cardiovascular Surgery* 149:789-797.

[https://dx.doi.org/10.1016/j.jtcvs.2014.10.062](https://dx.doi.org/10.1016/j.jtcvs.2014.10.062)

Panchal HB, Ladia V, Amin P, Patel P, Veeranki SP, Albalbissi K, and Paul T. 2014. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events in patients undergoing transfemoral versus transapical transcatheter aortic valve implantation using edwards valve for severe aortic stenosis. *Am J Cardiol* 114:1882-1890. 10.1016/j.amjcard.2014.09.029

Petzina R, Lutter G, Wolf C, Kuhl C, Freitag-Wolf S, Panholzer B, Bramlage P, Frey N, Cremer J, and Frank D. 2017. Transaortic transcatheter aortic valve implantation: experience from the Kiel study. *Interactive CardioVascular and Thoracic Surgery* 24:55-62.

10.1093/icvts/ivw277

Ramlawi B, Abu Saleh WK, Jabbari OA, Barker C, Lin C, Reyes M, Kleiman NS, and Reardon
Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, and Investigators S. 2017. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine* 376:1321-1331.

Ribeiro HB, Dahou A, Urena M, Carrasco JL, Mohammadi S, Doyle D, Le Ven F, Allende R, Amat-Santos I, Paradis JM, Delarochellière R, Puri R, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Pibarot P, Dumont É, and Rodés-Cabau J. 2015a. Myocardial injury after transaortic versus transapical transcatheter aortic valve replacement. *The Annals of Thoracic Surgery* 99:2001-2009.

Ribeiro HB, Dahou A, Urena M, Carrasco JL, Mohammadi S, Doyle D, Le Ven F, Allende R, Amat-Santos I, Paradis JM, DeLarochelliere R, Puri R, Abdul-Jawad Altisent O, del Trigo M, Campelo-Parada F, Pibarot P, Dumont E, and Rodes-Cabau J. 2015b.
Myocardial Injury After Transaortic Versus Transapical Transcatheter Aortic Valve Replacement. *The Annals of Thoracic Surgery* 99:2001-2009.

https://dx.doi.org/10.1016/j.athoracsur.2015.01.029

Romano M, Daprati A, Saitto G, Tizzano F, Le Houérou D, Donzeau-Gouge P, Farge A, Lefèvre T, Hovasse T, and Garatti A. 2019. Safety and effectiveness of a transaortic approach for TAVI: procedural and midterm outcomes of 265 consecutive patients in a single centre. *Interactive CardioVascular and Thoracic Surgery*. 10.1093/icvts/ivz269

Ropponen J, Vainikka T, Sinisalo J, Rapola J, Laine M, and Ihlberg L. 2016. Transaortic Transcatheter Aortic Valve Implantation as a Second Choice over the Transapical Access. *Scandinavian Journal of Surgery* 105:35-41.

Schäfer U, Deuschl F, Schofer N, Frerker C, Schmidt T, Kuck KH, Kreidel F, Schirmer J, Mizote I, Reichenspurner H, Blankenberg S, Treede H, and Conradi L. 2017. Safety and efficacy of the percutaneous transaxillary access for transcatheter aortic valve implantation using various transcatheter heart valves in 100 consecutive patients. *International Journal of Cardiology* 232:247-254. 10.1016/j.ijcard.2017.01.010

Spargias K, Bouboulis N, Halapas A, Chrissoheris M, Skardoutsos S, Nikolaou J, Tsolakis A, Mourmouris C, and Pattakos S. 2014. Transaortic aortic valve replacement using the Edwards Sapien-XT Valve and the Medtronic CoreValve: initial experience. *Hellenic
Terzian Z, Urena M, Himbert D, Gardy-Verdonk C, Iung B, Bouleti C, Brochet E, Ghodbane W, Depoix JP, Nataf P, and Vahanian A. 2017. Causes and temporal trends in procedural deaths after transcatheter aortic valve implantation. *Archives of Cardiovascular Diseases* 110:607-615. 10.1016/j.acvd.2016.12.008

Testa L, Brambilla N, Laudisa ML, De Carlo M, Lanotte S, Latini RA, Pizzocri S, Casavecchia M, Agnifili ML, Giannini C, Bortolotti U, Petronio AS, and Bedogni F. 2012. Right subclavian approach as a feasible alternative for transcatheter aortic valve implantation with the CoreValve ReValving System. *EuroIntervention* 8:685-690. 10.4244/EIJV8I6A107

Thourani VH, Jensen HA, Babaliaros V, Suri R, Vemulapalli S, Dai D, Brennan JM, Rumsfeld J, Edwards F, Tuzcu EM, Svensson L, Szeto WY, Herrmann H, Kirtane AJ, Kodali S, Cohen DJ, Lerakis S, Devireddy C, Sarin E, Carroll J, Holmes D, Grover FL, Williams M, Maniar H, Shahian D, and Mack M. 2015. Transapical and Transaortic Transcatheter Aortic Valve Replacement in the United States. *The Annals of Thoracic Surgery* 100:1718-1726; discussion 1726-1717. [https://dx.doi.org/10.1016/j.athoracsur.2015.05.010](https://dx.doi.org/10.1016/j.athoracsur.2015.05.010)

Van Belle E, Juthier F, Susen S, Vincentelli A, Iung B, Dallongeville J, Eltchaninoff H, Laskar
M, Leprince P, Lievre M, Banfi C, Auffray JL, Delhaye C, Donzeau-Gouge P, Chevreul K, Fajadet J, Leguerrier A, Prat A, Gilard M, and Teiger E. 2014. Postprocedural aortic regurgitation in balloon-expandable and self-expandable transcatheter aortic valve replacement procedures: Analysis of predictors and impact on long-term mortality: Insights from the France2 registry. *Circulation* 129:1415-1427. 10.1161/CIRCULATIONAHA.113.002677

Walther T, Hamm CW, Schuler G, Berkowitsch A, Kotting J, Mangner N, Mudra H, Beckmann A, Cremer J, Welz A, Lange R, Kuck KH, Mohr FW, Mollmann H, and Board GE. 2015. Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve Replacements: Prospective Data From the GARY Registry. *Journal of the American College of Cardiology* 65:2173-2180. 10.1016/j.jacc.2015.03.034

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, and Tugwell P. 2014. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at [http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Wendt D, Kleinbongard P, Knipp S, Al-Rashid F, Gedik N, El Chilali K, Schweter S, Schlamann M, Kahlert P, Neuhauser M, Forsting M, Erbel R, Heusch G, Jakob H, and Thielmann M. 2015. Intraaortic Protection From Embolization in Patients Undergoing Transaortic
Transcatheter Aortic Valve Implantation. *The Annals of Thoracic Surgery* 100:686-691.

https://dx.doi.org/10.1016/j.athoracsur.2015.03.119

Zhan Y, Kawabori M, Lofftus S, Cobey F, Rastegar H, Weintraub A, and Chen FY. 2020. Right Transaxillary Transcatheter Aortic Valve Replacement Using the “Flip-n-Flex” Technique. *The Annals of Thoracic Surgery* 109:57-62. 10.1016/j.athoracsur.2019.05.040

**Figure Legends**

**Figure 1. Flow of study selection process.**

CABG = coronary arterial bypass grafting; DAo = direct aortic approach; TAx = transaxillary; VARC = Valve Academic Research Consortium.

**Figure 2. Forrest plot of TAx and DAo TAVR outcomes.**

The pooled incidence of mortality, stroke, and other complications of TAx and DAo TAVR. DAo = direct aortic; TAVR = transcatheter aortic valve replacement; TAx = transaxillary.
Table 1 (on next page)

Study data

Basic information of studies included in the meta-analysis. DAo = direct aortic; NA = not available; VARC = Valve Academic Research Consortium, TAx = transaxillary, US = the United States
### Table 1. Study data

| First author | Year | Locations/country | Study type      | No. of centers | study period | Access  | Patient number | VARC |
|--------------|------|-------------------|-----------------|----------------|--------------|---------|----------------|------|
| Khan         | 2018 | US                | Single center   | 1              | 2013-2015    | TAx, DAo | 51             | 2    |
| Damluji      | 2018 | US, France        | Multi-center    | 3              | 2008-2017    | TAx, DAo | 84             | 2    |
| Fiorina      | 2016 | Italy             | Multi-center    | 4              | 2007-2014    | TAx, DAo | 147            | 2    |
| Adamo        | 2015 | Italy             | Single center   | 1              | 2007-2014    | TAx, DAo | 32             | 2    |
| Zhan         | 2020 | US                | Single center   | 1              | 2015-2018    | TAx      | 10             | 2    |
| Dahle        | 2019 | US                | Multi-center    | NA             | 2015-2018    | TAx      | 1249           | 2    |
| Hysi         | 2019 | France            | Single center   | 1              | 2015-2017    | TAx      | 43             | 2    |
| Gleason      | 2018 | US                | Multi-center    | 45             | NA           | TAx      | 202            | 1    |
| Terzian      | 2017 | France            | Single center   | 1              | 2006-2014    | TAx      | 36             | 1    |
| Schäfer      | 2017 | Germany           | Multi-center    | 2              | 2010-2016    | TAx      | 100            | 2    |
| Laflamme     | 2014 | Canada            | Single center   | 1              | 2010-2012    | TAx      | 18             | 2    |
| Muensterer   | 2013 | Germany           | Single center   | 1              | 2007-2011    | TAx      | 40             | 2    |
| Testa        | 2012 | Italy             | Single center   | 1              | NA           | TAx      | 70             | 1    |
| Gilard       | 2012 | France            | Multi-center    | 34             | 2010-2011    | TAx      | 184            | 1    |
| Romano       | 2019 | France            | Single center   | 1              | 2011-2014    | DAo      | 265            | 2    |
| Cocchieria   | 2019 | Europe            | Multi-center    | 18             | 2013-2015    | DAo      | 253            | 2    |
| D’Ancona     | 2019 | Germany           | Single center   | 1              | 2012-2014    | DAo      | 106            | 2    |
| Petzina      | 2017 | Germany           | Single center   | 1              | 2012-2014    | DAo      | 99             | 2    |
| Bruschi      | 2017 | Europe            | Multi-center    | 9              | 2012-2014    | DAo      | 92             | 2    |
| First author | Year | Locations/country | Study type     | No. of centers | study period | Access | Patient number | VARC |
|--------------|------|-------------------|----------------|----------------|--------------|--------|----------------|------|
| Bonaros      | 2017 | Europe            | Multi-center   | 18             | 2013-2015    | DAo    | 301            | 2    |
| Ropponen     | 2016 | Finland           | Single center  | 1              | 2008-2014    | DAo    | 36             | 1    |
| Arai         | 2016 | France            | Single center  | 1              | 2011-2014    | DAo    | 289            | 2    |
| Wendt        | 2015 | Germany           | Single center  | 1              | 2012-2014    | DAo    | 30             | 1    |
| Thourani     | 2015 | US                | Multi-center   | NA             | 2011-2014    | DAo    | 868            | 2    |
| Ribeiro      | 2015 | Canada            | Single center  | 1              | 2007-2015    | DAo    | 45             | 2    |
| Ramlawi      | 2015 | US                | Single center  | 1              | 2011-2015    | DAo    | 78             | 2    |
| Okuyama      | 2015 | US                | Single center  | 1              | 2007-2014    | DAo    | 51             | 2    |
| Jagielak     | 2015 | Poland            | Multi-center   | NA             | 2013-2014    | DAo    | 32             | 2    |
| Bruschi      | 2015 | Italy             | Single center  | 1              | 2008-2013    | DAo    | 50             | 2    |
| Spargias     | 2014 | Greece            | Single center  | 1              | NA           | DAo    | 25             | 1    |
| Dahle        | 2014 | Norway            | Single center  | 1              | 2009-2013    | DAo    | 30             | 1    |

Basic information of studies included in the meta-analysis.

DAo = direct aortic; NA = not available; VARC = Valve Academic Research Consortium, TAx = transaxillary, US = the United States.
Table 2 (on next page)

Baseline and procedural characteristics of patients.

DAo = direct aortic; TAx = transaxillary; SD = standard deviation
Table 2. Baseline and procedural characteristics of patients.

| Variable                      | DAo patients | TAx patients |
|-------------------------------|--------------|--------------|
|                               | Available data, n | Weight mean ± SD | Available data, n | Weight mean ± SD |
| Age, year                     | 2236         | 82.7 ± 1.2   | 2136         | 80.0 ± 1.7   |
| Logistic EuroSCORE            | 642          | 22.0 ± 7.1   | 681          | 22.6 ± 5.3   |
| STS score                     | 1161         | 7.5 ± 1.8    | 1737         | 8.9 ± 3.0    |
| Old Stroke, %                 | 1957         | 12.1         | 1957         | 12.1         |
| Atrial fibrillation, %        | 1152         | 28.6         | 590          | 39.0         |
| Peripheral arterial disease, %| 2035         | 41.6         | 1919         | 64.4         |
| Chronic kidney disease, %     | 1946         | 28.5         | 557          | 16.0         |
| Previous cardiac surgery, %   | 1961         | 23.6         | 870          | 23.5         |
| Left ventricular ejection fraction, % | 1965 | 62.3 ± 9.7   | 311          | 52.1 ± 1.6   |
| Device (CoreValve, %)         | 2847         | 23.2         | 1852         | 29.3         |

DAo = direct aortic; TAx = transaxillary; SD = standard deviation
Figure 1

Flow of study selection process.

CABG = coronary arterial bypass grafting; DAo = direct aortic approach; TAx = transaxillary; VARC = Valve Academic Research Consortium
Records identified through database searching: Cochrane group (n = 0), EMBASE (n = 558), Ovid (n = 388), PubMed (n = 426)

Records after duplicates removed (n = 703)

Records screened (n = 703)

Records excluded (n = 586)

Full-text articles assessed for eligibility (n = 117)

Full-text articles excluded, with reasons:
- Case number < 10 (n = 1)
- Combine CABG (n = 1)
- Devices other than Medtronic or Edward were used (n = 4)
- Duplicate cohort (n = 19)
- No outcome data of TAx or DAo (n = 47)
- Not using VARC definition (n = 13)
- Valve in valve procedure (n = 1)

Studies included in qualitative synthesis (n = 31)

Studies included in quantitative synthesis (meta-analysis) (n = 31)
Figure 2

Forrest plot of TAx and DAo TAVR outcomes.

The pooled incidence of mortality, stroke, and other complications of TAx and DAo TAVR. DAo = direct aortic; TAVR = transcatheter aortic valve replacement; TAx = transaxillary.

| Outcome / group       | No. of study | No. of event / Total number | Event rate, % (95% CI) | I² (%) | P for heterogeneity |
|-----------------------|--------------|----------------------------|------------------------|--------|---------------------|
| 30-Day mortality     |              |                            |                        |        |                     |
| DAo                   | 19           | 205 / 2355                 | 9.6 (8.4–10.9)         | 11.1   | <0.001              |
| TAx                   | 15           | 116 / 2172                 | 5.7 (4.8–6.8)          | 0.0    |                     |
| 30-Day CV death       |              |                            |                        |        |                     |
| DAo                   | 8            | 32 / 715                   | 5.5 (3.9–8.3)          | 51.7   | 0.933               |
| TAx                   | 8            | 37 / 668                   | 5.6 (3.9–8.3)          | 0.0    |                     |
| 1-year mortality      |              |                            |                        |        |                     |
| DAo                   | 8            | 351 / 1493                 | 22.8 (19.2–26.3)       | 70.7   | 0.600               |
| TAx                   | 7            | 197 / 517                  | 20.7 (15.4–27.3)       | 33.4   |                     |
| Stroke                |              |                            |                        |        |                     |
| DAo                   | 15           | 44 / 2035                  | 2.6 (1.9–3.4)          | 0.0    | <0.001              |
| TAx                   | 11           | 104 / 1879                 | 5.8 (4.4–7.0)          | 0.0    |                     |
| AKI                   |              |                            |                        |        |                     |
| DAo                   | 14           | 491 / 2177                 | 11.7 (8.8–15.3)        | 94.2   | 0.451               |
| TAx                   | 9            | 62 / 520                   | 8.2 (3.7–17.3)         | 61.8   |                     |
| Major bleeding        |              |                            |                        |        |                     |
| DAo                   | 10           | 83 / 980                   | 14.5 (7.5–26.3)        | 86.5   | 0.283               |
| TAx                   | 9            | 104 / 779                  | 8.5 (4.0–17.4)         | 85.6   |                     |
| Major vascular complication |     |                            |                        |        |                     |
| DAo                   | 12           | 45 / 1147                  | 4.4 (2.7–6.9)          | 0.0    | 0.670               |
| TAx                   | 13           | 79 / 2099                  | 3.8 (2.3–6.2)          | 70.9   |                     |
| PPI                   |              |                            |                        |        |                     |
| DAo                   | 15           | 161 / 1349                 | 12.3 (8.4–16.0)        | 57.5   | 0.009               |
| TAx                   | 13           | 338 / 2119                 | 20.1 (15.5–24.6)       | 79.5   | 0.113               |
| PVL grade 2/3         |              |                            |                        |        |                     |
| DAo                   | 13           | 75 / 1223                  | 7.3 (4.6–11.3)         | 77.9   | 0.943               |
| TAx                   | 11           | 86 / 834                   | 12.3 (7.7–19.2)        | 59.2   |                     |
| Device success        |              |                            |                        |        |                     |
| DAo                   | 15           | 73 / 1199                  | 6.6 (4.1–10.5)         | 40.1   | 0.031               |
| TAx                   | 11           | 91 / 1851                  | 6.8 (3.8–11.6)         | 85.0   |                     |
| Conversion            |              |                            |                        |        |                     |
| DAo                   | 10           | 59 / 1885                  | 2.8 (2.1–3.9)          | 0.0    | <0.001              |
| TAx                   | 7            | 12 / 1749                  | 0.8 (0.6–1.5)          | 6.9    |                     |
| Valve malposition     |              |                            |                        |        |                     |
| DAo                   | 7            | 5 / 488                    | 2.6 (0.9–4.7)          | 0.0    | 0.023               |
| TAx                   | 2            | 0 / 80                     | 10.2 (2.0–27.1)        | 70.3   |                     |