Dose approach matter? A Meta-analysis of outcomes following transfemoral versus transapical transcatheter aortic valve replacement

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Research article

Keywords: Transfemoral, Transapical, Transcatheter Aortic Valve Replacement, Meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-96658/v1

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Abstract

Background: Transcatheter aortic valve replacement (TAVR) has gained increasing acceptance for patients with aortic disease. Both transfemoral (TF-TAVR) and transapical (TA-TAVR) approach were widely adopted while their performances are limited to a few studies with controversial results. This meta-analysis aimed to compare the mortality and morbidity of complications between TF- versus TA-TAVR based on the latest data.

Methods: Electronic databases were searched from January 2005 to December 2019. RCTs and observational studies comparing the outcomes between TF-TAVR versus TA-TAVR patients were included. Heterogeneity assumption was assessed by an I² test. The pooled odds ratios (OR) or mean differences with corresponding 95% confidence intervals (CI) were used to evaluate the difference for each end point using a fixed-effect model or random-effect model based on I² test.

Results: The meta-analysis included 1 RCT and 18 observational studies, enrolling 12,953 patients (TF-TAVR, n=8,649 and TA-TAVR, n=4,304). Compared with TA-TAVR, TF-TAVR patients showed significantly lower rate of postoperative in-hospital death (OR=0.63, 95%CI 0.54-0.74, P<0.001) and 1-year death (OR=0.53, 95%CI 0.41-0.69, P<0.001). Incidence of major bleeding and acute kidney injury were lower, whereas those of permanent pacemaker and major vascular complication were higher in TF-TAVR patients. There were no significant differences between TF-TAVR versus TA-TAVR for stroke and mid-term mortality.

Conclusions: There were fewer early deaths in patients with transfemoral approach, whereas the number of mid-term deaths and stroke was not significantly different between two approaches. TF-TAVR was associated with lower risk of bleeding, acute kidney injury as well as shorter in-hospital stay, but higher incidence of vascular complication and permanent pacemaker implantation.

Background

Transcatheter aortic valve replacement (TAVR) already becomes a recognized alternative to surgical aortic valve replacement (SAVR) with superior in mini-invasiveness and noninferior outcomes of postoperative myocardial infarctions, cerebrovascular events, mid-term mortality and stroke [1]. Trials like PARTNER and CoreValve Pivotal Trial have resulted in a Class I, Level of Evidence: A recommendation for patients with symptomatic severe aortic stenosis (AS) and high surgical mortality risk to undergo TAVR [2, 3]. The Indications of TAVR would be further expanded since some ongoing RCT trials provide promising interim results. As the exclusive percutaneous approach, transfemoral (TF) access is the most preferred and widely adopted choice for TAVR for its safety and less-invasiveness [4]. However, approximately 10–15% of the patients with unsuitable iliofemoral anatomy (iliofemoral arteriopathy, tortuosity, severe calcifications, aortic aneurysm, mural thrombus, previous vascular surgery, or small size) require alternative approaches for valve deployment [5]. Differed from the retrograde TF approach, another main access - transapical (TA) TAVR - use anterograde access with apical mini-thoracotomy. TA approach expands the feasibility and broadens indication of TAVR, therefore, it is performed in a reasonable proportion of patients [3]. Nevertheless, TA-TAVR is a more invasive procedure associated with high risk of mortality and morbidity, especially for elder patient with severe comorbidities. Some researchers have suggested that TA-TAVR showed poor outcomes compared with SAVR [6, 7]. However, most of the previous studies have assessed the performance TF and TA approaches separately, while comparative studies examining the safety, efficacy, and efficiency of TA-TAVR versus TF-TAVR were rarely performed. We systematically reviewed the latest literature regarding this topic and employed a meta-analytic strategy to determine the short and mid-term mortality and incidence of major adverse events between TF- versus TA-TAVR.

Methods

This meta-analysis was performed in accordance with the PRISMA guidelines statement [8], the MOOSE statement [9] and the Cochrane Handbook Cochrane Handbook recommendations [10]. A systematic literature search was conducted through PubMed, ClinicalKey, the Web of Science and Google Scholar from January 2005 to December 2019 for English language, peer-reviewed publications. The following key words and Medical Subject Headings (MeSH) terms were used: “transcatheter aortic valve replacement (MeSH),” “transcatheter aortic valve implantation,” “TAVR,” “TAVI,” “transfemoral,” “transapical,” “transapical aortic valve implantation,” “transfemoral aortic valve implantation,” “transapical aortic valve replacement” and “transfemoral aortic valve replacement”.

References of original articles were reviewed manually and cross-checked. Two investigators (R.G. and M.X.) conducted the search. Two or more studies published from the same database were included if the studies reported outcomes from different follow-up periods or compared different groups.

Studies were included if they fulfilled the following criteria: (1) randomized controlled trials (RCTs) or observational studies published as original articles; (2) compared TF-TAVR versus TA-TAVR; (3) reported at least one of the following events: death (in-hospital, 1-year, and mid-term), stroke, major vascular events, major bleeding, pacemaker implantation, acute kidney injury, reintervention, endocarditis and length of hospital stay; (4) sample size per group of at least 10 patients. Two investigators (R.G. and M.X.) selected the studies for the inclusion, and studies did not meet any of these criteria were excluded.

The eligibility and quality of included studies was evaluated independently two reviewers (Y.W. and X.H.), and a standardized data collection sheet was used for data extraction. Data on investigators, year, journal, design, study period, follow-up duration, procedural approach, sample size, patient characteristics and outcomes were extracted. Disagreements were resolved by consensus. The quality of RCTs was appraised by utilizing the components recommended by the Cochrane Collaboration [11], and observational studies was appraised by utilizing ROBINS-I (Risk of Bias in Nonrandomized Studies-of Interventions)[12].

The primary outcome of interest was death postoperative in hospital, at 1-year and mid-term. Secondary outcomes included stroke, major vascular events, major bleeding, pacemaker implantation, acute kidney injury.

The pooled odds ratio (OR) or mean difference and corresponding 95% confidence interval (CI) was calculated for dichotomous and continuous outcomes, respectively. Heterogeneity of the studies was assessed using the Higgins I² statistic for each outcome. An I² of 0–25% renders insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and > 75% high heterogeneity [13]. Fixed-effect models of Mantel-Haenszel were used for studies
that were homogenous, while Random-effect models of Inverse Variance were used for studies that were heterogenous. Publication bias was assessed visually using a funnel-plot method. All tests were 2-tailed with a p value of < 0.05 considered significant. Analyses were performed using Review Manager Software from the Cochrane Collaboration (Version 5.3, Copenhagen, Denmark).

Results

Nineteen studies enrolling 12,953 patients (8,649 undergoing TF-TAVR and 4,304 undergoing TA-TAVR) met the inclusion criteria and were included for the final meta-analysis [5, 14–31]. The search and selection process are shown in Fig. 1. The main characteristics of the included studies are shown in Table 1. Of the 19 studies, 1 was RCT, 9 were prospective observational studies and 9 were retrospective observational studies. The Study quality assessment is summarized in Table 2. Publication bias and heterogeneity for each outcome are listed in Table 3.

Table 1. Study characteristics

| Lead Author | Mohammed Al-Hijji[25] | Takahide Arai[26] | Edward Koifman[27] | Takashi Murashita[20] | Martine Gilard[29] | Vinod H Thourani[23] |
|-------------|----------------------|------------------|-------------------|----------------------|------------------|---------------------|
| Publication | 2019 | 2016 | 2016 | 2016 | 2016 | 2016 |
| Year        | Catheter Cardio Inte | JACC-Cardiovasc Inte | Cardiovasc Revasc Med | Ann Thorac Surg | JACC | Lancet |
| Study design | retrospective | prospective | retrospective | retrospective | prospective | prospective |
| Study period | 2012-2016 | 2011-2014 | 2007-2014 | 2008-2015 | 2010-2012 | 2014.2-2014.9 |
| Procedure   | TP-TAVR | TA-TAVR | TP-TAVR | TA-TAVR | TP-TAVR | TA-TAVR |
| Cohort number | 115 | 115 | 467 | 42 | 516 | 132 |
| Age, years  | 82.5±7.7 | 82.8±7.8 | 83.8±7.1 | 81.3±7.7 | 83±8 | 84±7 |
| Male sex    | 60(52.2%) | 63(55.3%) | 234(50%) | 30(71%) | 264(51%) | 58(44%) |
| Cohort number | 216 | 351 | 216 | 3064 | 735 | 948 |

Table 1. Study characteristics (Continued)

Data are n (%), or mean±SD; TF-TAVR= transfemoral transcatheter aortic valve replacement; TA-TAVR= transapical transcatheter aortic valve replacement; COPD =chronic obstructive pulmonary disease; STS=Society of Thoracic Surgeons
Table 2. Publication bias analysis

Data are n (%), or mean±SD; TF-TAVR= transfemoral transcatheter aortic valve replacement; TA-TAVR= transapical transcatheter aortic valve replacement; COPD=chronic obstructive pulmonary disease; STS=Society of Thoracic Surgeons

Table 1. Study characteristics (Continued)

| Publication Year | Study Journal | Lead Author | Study design | Procedure | Study period | Design | Study | Data | Number | Data | Number | Data | Number | Data | Number |
|------------------|--------------|-------------|-------------|-----------|-------------|--------|-------|------|--------|------|--------|------|--------|------|--------|
| 2011             | Circulation  | Eugene H. Blackstone[24] | Circulation prospective | TP-TAVR | 2017-2012 | retrospective | 501 | 18(44%) | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Circ-Cardiovasc Int | Gerhard Schymik[28] | Circ-Cardiovasc Int prospective | TP-TAVR | 2008-2012 | retrospective | 354 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Circulation  | Martyn Thomas[5] | Circulation prospective | TA-TAVR | 2007-2009 | retrospective | 575 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | NEJM         | Craig R. Smith[22] | NEJM | TP-TAVR | 2007-2009 | retrospective | 492 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Inter Cardiov Th | Johan M. Bosmans[15] | Inter Cardiov Th | TA-TAVR | 2007-2009 | retrospective | 207 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |

Data are n (%), or mean±SD; TF-TAVR= transfemoral transcatheter aortic valve replacement; TA-TAVR= transapical transcatheter aortic valve replacement; COPD=chronic obstructive pulmonary disease; STS=Society of Thoracic Surgeons

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| Publication Year | Study Journal | Lead Author | Study design | Procedure | Study period | Design | Study | Data | Number | Data | Number | Data | Number | Data | Number |
|------------------|--------------|-------------|-------------|-----------|-------------|--------|-------|------|--------|------|--------|------|--------|------|--------|
| 2011             | Circulation  | Eugene H. Blackstone[24] | Circulation prospective | TP-TAVR | 2017-2012 | retrospective | 501 | 18(44%) | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Circ-Cardiovasc Int | Gerhard Schymik[28] | Circ-Cardiovasc Int prospective | TP-TAVR | 2008-2012 | retrospective | 354 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Circulation  | Martyn Thomas[5] | Circulation prospective | TA-TAVR | 2007-2009 | retrospective | 575 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | NEJM         | Craig R. Smith[22] | NEJM | TP-TAVR | 2007-2009 | retrospective | 492 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |
| 2011             | Inter Cardiov Th | Johan M. Bosmans[15] | Inter Cardiov Th | TA-TAVR | 2007-2009 | retrospective | 207 | 218 | 85±6.3 | 81.7±5.0 | 81.7±6.7 | 84.4±6.7 | 84±5 | 82±6 | 82 |

Data are n (%), or mean±SD; TF-TAVR= transfemoral transcatheter aortic valve replacement; TA-TAVR= transapical transcatheter aortic valve replacement; COPD=chronic obstructive pulmonary disease; STS=Society of Thoracic Surgeons
### Table 3. Test of heterogeneity and publication bias for each outcome

| Outcomes                     | Chi-Square | df | P value | I² | Heterogeneity | Publication bias |
|------------------------------|------------|----|---------|----|---------------|-----------------|
| In-hospital mortality        | 32.05      | 17 | 0.01    | 47% | low           | none            |
| 1-year mortality             | 1.84       | 4  | 0.77    | 0%  | insignificant | none            |
| Mid-term mortality           | 17.08      | 3  | 0.0007  | 82% | high          | none            |
| Major vascular complication  | 36.06      | 10 | 0.00001 | 72% | moderate      | none            |
| Pacemaker implantation       | 22.66      | 15 | 0.09    | 34% | low           | none            |
| Major bleeding               | 31.07      | 8  | 0.0001  | 74% | moderate      | none            |
| Acute kidney injury          | 69.19      | 11 | 0.00001 | 84% | high          | none            |
| Length of hospital stay      | 10.86      | 5  | 0.05    | 54% | moderate      | none            |
| Stroke                       | 13.36      | 9  | 0.15    | 33% | low           | none            |

### Mortality

Postoperative in-hospital mortality was reported in 18 studies. One RCT and 17 observational studies with 11,915 patients were included. In the pooled analysis, in-hospital mortality was significantly lower with TF-TAVR compared with TA-TAVR (OR = 0.63, 95% CI 0.54–0.74, P < 0.001, Fig. 2A). Postoperative 1-year mortality was reported in 5 studies. One RCT and 4 observational studies with 2,313 patients were included. In the pooled analysis, 1-year mortality was still significantly lower with TF-TAVR compared with TA-TAVR (OR = 0.53, 95% CI 0.41–0.69, P < 0.001, Fig. 2B). Postoperative mid-term mortality was reported in 4 observational studies with 5,907 patients. The pooled analysis did not demonstrate a statistically significant difference in the risk of mid-term mortality when comparing TF-TAVR versus TA-TAVR (OR = 0.68, 95% CI 0.46–1.01, P = 0.06, Fig. 2C).

### Morbidity and Other Complications
Results for the other outcomes are summarized in Fig. 3. The pooled analysis of 11 studies (5,456 patients) demonstrated a higher risk of major vascular complication with TF-TAVR compared with TA-TAVR (OR = 3.21, 95% CI 1.90–5.42, P < 0.001, Fig. 3A). Meanwhile, in the pooled analysis of 16 studies (n = 7,837), there was a significantly higher incidence of pacemaker implantation in TF-TAVR when compared with TA-TAVR (OR = 1.47, 95% CI 1.22–1.76, P < 0.001, Fig. 3B).

On the other hand, pooled analyses revealed that TF-TAVR was associated with lower risk for major bleeding (9 studies, 5,174 patients, OR = 0.52, 95% CI 0.32–0.85, P = 0.009, Fig. 3C) and acute kidney injury (12 studies, 5,622 patients, OR = 0.40, 95% CI 0.21–0.76, P = 0.005, Fig. 3D), while TF-TAVR has a shorter length of hospital stay (6 studies, 6,890 patients, mean difference=-2.92 days, 95% CI -3.71 to -2.14, P < 0.001, Fig. 3E). Pooled analysis of 10 studies (5,716 patients) demonstrated no statistically significant difference in the risk of stroke among patients assigned to TF-TAVR versus TA-TAVR (OR = 0.80 95% CI 0.59–1.09, P = 0.160, Fig. 3F). Funnel plots for each outcome are shown in Supplementary Figures. No significant publication biases were detected.

**Discussion**

Since its first clinical application in 2002, TAVR has gone through several generations of evolution and expanded rapidly to be a nonnegligible alternative to SAVR in patients with high and intermediate procedural risk. There is little doubt that the numbers of TAVR procedures will continue to increase as the appearance of novel generations of prosthetic valves and delivery devices, as well as expanded indications from high-risk and inoperable elderly patients to younger and low-risk patients [32]. Even the patients with native aortic valve regurgitation can be treated successfully with TAVR and there are randomized trials under designing aimed to prove its mid and long-term performance [33, 34]. Minimal invasive is the most attractive merit of TAVR, which makes TF approach the preferred one, given its less inherent risk for postoperation complications by avoiding more invasive steps such as mini-thoracotomy and left ventricular puncture in TAVR. However, despite the improvement in device profiles and procedure techniques, TF access still faces technical limitations such as the sheath size and the prosthetic orifice area, and cannot be performed in a considerable proportion of patients. For that, TA access still has application scenario in clinic practice. The attendant problem is whether these two different approaches have similar performances. Several previous studies have compared the outcomes of TF-TAVR versus those of TA-TAVR based on observational studies with relatively early data (before 2014) and small sample size and drew contradictory results. Panchal et al. reported that 1-year mortality was similar in both approaches while TF approach resulted in lower 30-day mortality [35]. Liu et al. concluded a comparable result for both 30-day and 1-year mortality [36]. Conversely, Ghatak et al. reported superior 30-day and mid-term mortality with TF-TAVR [37]. The discrepancy will cause dilemma and confusion for treatment decisions.

By pooling data from 1 RCT and 18 observational trials, this large sample volume meta-analysis has included the latest and most comprehensive studies in this area. The results demonstrated that the mid-term deaths and stroke incidences were comparable between TF versus TA-TAVR, while the number of early deaths (30-d and 1-y) was smaller with TF approach than with TA approach. Since there was no obvious difference in patient risk factors (using STS or EuroSCORE in different studies) between two approaches, it may be speculated that the higher early mortality with TA approach could be related to i) the physical damage to the myocardium through direct puncture of the apex, ii) surgical chest trauma, and iii) effects of general anesthesia. TA-TAVR has been also associated with cardiac biomarkers level elevation and poorer cardiac function improvement [38]. These perioperative complications appeared to have early rather than mid to long-term consequences. Therefore, if the patients have passed through the early postoperative convalescence, the performance of patients in TA group would gradually catch up with those in TF group.

The postoperative complications that call for special attention during the early convalescence in patients with TA-TAVR are acute kidney injury and major bleeding events since they present significantly higher occurrences than those in TF group. Both two complications had previously been identified as predictors of adverse outcome including mortality and longer hospital stay following TAVR [39, 40]. Postoperative renal dysfunction is not uncommon in TAVR patients since the side-effect of contrast media and inadequate renal perfusion during the hemodynamic alterations in the procedure. Moreover, the high incidence of AKI in TA-TAVR patients can also be ascribed to the transfusion for there were more major bleeding events in TA group. Transfusion has been proved to be an independent predictor of AKI as it is associated with the coadministration of some other causative molecular and cellular substances causing kidney injury, such as interleukin-8 which typically accumulates in stored packed red cells [41]. So it is reasonable to emphasize the importance of close monitoring of perioperative renal function, as well as a strict surgical discipline in the execution of TA-TAVR by - among others - strict control of hemostasis, especially the puncture site on heart.

Despite accumulated experiences and meticulous efforts to redesign the transcatheter prosthesis and sheath (smallest sheath size has been reduced to 14 Fr or equivalent nowadays), more vascular complications and conduction abnormalities were still observed with TF-TAVR. Consistently higher incidence of vascular complications may reflect the inherent defect of TF approach. Some new echo-guided puncture and closure devices were emerged to ensure proper entry and hemostasis of the femoral artery. However, vascular complications may be inevitable in patients with bad artery condition and the key to prevention is a comprehensive preoperative assessment and proper patient selection. On the other hand, the higher incidence of pacemaker implantation in TF-TAVR patients may lead to adverse clinical sequelae on their long-term outcomes through the loss of atrioventricular synchrony, lack of physiological rate control, and unphysiological right ventricular stimulation. The conduction tissue injury is speculated due to the mechanical pressure from metal struts. Some researchers suggested that the likelihood of pacemaker implantation differs according to valve design (significantly higher with self-expandable valves, marginally elevated with balloon-expandable valves) [42, 43]. And the higher rate of pacemaker implantation in TF-TAVR patients may be associated with the position difficulty and repeated attempts during the angiographic deployment. So, further technical refinements in valve and sheath design as well as precise image-guided puncture and positioning are warranted to improve the performance of TF-TAVR given the significant impact of conduction abnormalities and major vascular complications.

Several limitations to the current meta-analysis need to be acknowledged. The baseline characteristics between the two approaches could not be compared entirely, because of the inherent nature of the meta-analysis. The use of various type and generation prostheses in these studies may limit the validity of the findings in the current meta-analysis, since there are certain, albeit minor, differences in different TAVR prostheses. Part of these trials were small volumes with limited data to assess outcomes, some of these studies may have been underpowered. The overall follow-up period was short to intermediate, which is why
some other crucial outcomes such as durability of the prostheses is not investigated. Because of the unavailability of combined MACCE outcomes data in the original studies, we were unable to include them in our analysis. Finally, the data analyzed in this study are mainly observational and only one randomized concerning transfemoral and transapical access, leading to an indication bias. However, in the shortage of randomized data, the findings of our analysis can further advise the practice of TAVR clinicians and influence future studies. In the future, more randomized controlled trials and comprehensive registries with longer follow-up (> 5-y) will help us to better define the safety and durability, and subsequently, indications of the technique, and the respective places of transfemoral and transapical approaches.

**Conclusions**

Nowadays, not only elder patients at very high surgical risk or with contraindications to SAVR, but also younger and low-risk patients with aortic valve disease will benefit from TAVR, and the availability of both transfemoral and transapical approaches increases the number of patients who can be treated. In our analysis, the mid-term mortality and risk of stroke are similar with TA- and TF-TAVR. TF-TAVR has significantly less early mortality, but a higher incidence of major vascular complications and pacemaker implantation. On the other hand, TA-TAVR is associated with a significant increase in the risk of major bleeding, AKI and has a longer length of hospitalization. Hereby, both TA and TF are effective approaches with satisfactory short to mid-term outcomes for patients need TAVR treatment. However, it is reasonable to make the approach choice based on detailed individualized evaluation and the experience of local heart teams.

**Abbreviations**

AKI, Acute Kidney Injury; CI, Confidence Interval; MACCE, Main Adverse Cardiovascular and Cerebrovascular Events; OR, Odds ratio; RCT, Randomized Controlled Trial; SAVR, Surgical Aortic Valve Replacement; STS, The Society of Thoracic Surgeons; TA, Transapical; TAVR, Transcatheter Aortic Valve Replacement; TAVI, Transcatheter Aortic Valve Implantation; TF, Transfemoral.

**Declarations**

**Ethics approval and consent to participate**

Not applicable as this is a meta-analysis.

**Consent for publication**

All authors participated in this work have reviewed the content of the article and agreed with publication.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This study was financially supported by the National Natural Science Foundation of China (NO.81700317) to Y.W. and (NO. 81400290) to X.H.

**Authors’ contributions**

Conceptualization, Y.W. and X.H.; Methodology, Y.W. and X.H.; Software, W.W.; Formal Analysis, W.W. and W.J.; Data Curation, M.X. and R.G. and W.Y.; Writing – Original Draft Preparation, M.X. and R.G. and W.Y.; Writing – Review & Editing, Y.W. and X.H.; Visualization, W.J.; Supervision, X.H. and Y.W.; Project Administration, M.X. and R.G. and W.Y.; Funding Acquisition, Y.W. and X.H.

**Acknowledgements**

Not applicable.

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