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Safety of Transcatheter Aortic Valve Replacement for High-Risk Patients with Severe Aortic Stenosis

Background	Severe aortic stenosis (AS) is a life-threatening condition that necessitates prompt intervention, even in high-risk patients with contraindications to surgical aortic valve replacement (SAVR). Transcatheter aortic valve replacement (TAVR) has become a transformative treatment, utilizing various access routes, including transfemoral (TF), transapical, and other, alternative pathways. The selection of the access route significantly impacts procedural safety and outcomes. The purpose of this study is to compare the safety profiles of different TAVR access routes in high-risk patients with severe AS.
Material and methods	Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a comprehensive literature search was performed in PubMed and Cochrane Library databases to identify studies that evaluated the safety outcomes of TAVR via various access routes in high-risk patients. Key endpoints analyzed were procedural complications, 30-day mortality, cardiac electrophysiological abnormalities, stroke incidence, and vascular complications. Meta-analysis utilizing RevMan 5.3 was performed, employing fixed or random effects models based on heterogeneity.
Results	Seven studies encompassing 2,351 patients were included in the analysis. The pooled analysis revealed that the non-TF access routes were associated with a significantly higher risk ratio (RR) for procedural complications [RR=1.76; 95% confidence interval (CI): 1.63–1.89, p<0.00001] compared to the TF approach. No statistically significant difference in 30-day mortality was observed among the access routes [OR=0.79; 95% CI: 0.60–1.05, p=0.11]. However, alternative routes had increased odds of cardiac electrophysiological abnormalities [OR=1.44; 95% CI: 1.12–1.84, p=0.004]. There was no significant difference in stroke incidence between access routes [OR=1.16; 95% CI: 0.75–1.79, p=0.51], but vascular complications were significantly more frequent with non-femoral routes [OR=1.70; 95% CI: 1.29–2.24, p=0.0001].
Conclusion	This meta-analysis underscores the critical role of access route selection in the safety of TAVR. While the TF approach remains the gold standard due to its lower complication rates, alternative routes are indispensable for anatomically or clinically challenging cases. Refinements in procedural techniques, patient selection, and advanced imaging are essential to optimizing outcomes across all access routes. Further large-scale studies are warranted to validate these findings and enhance clinical decision-making.

Keywords	Transcatheter aortic valve replacement; aortic stenosis; transfemoral access; transapical access; procedural safety; meta-analysis
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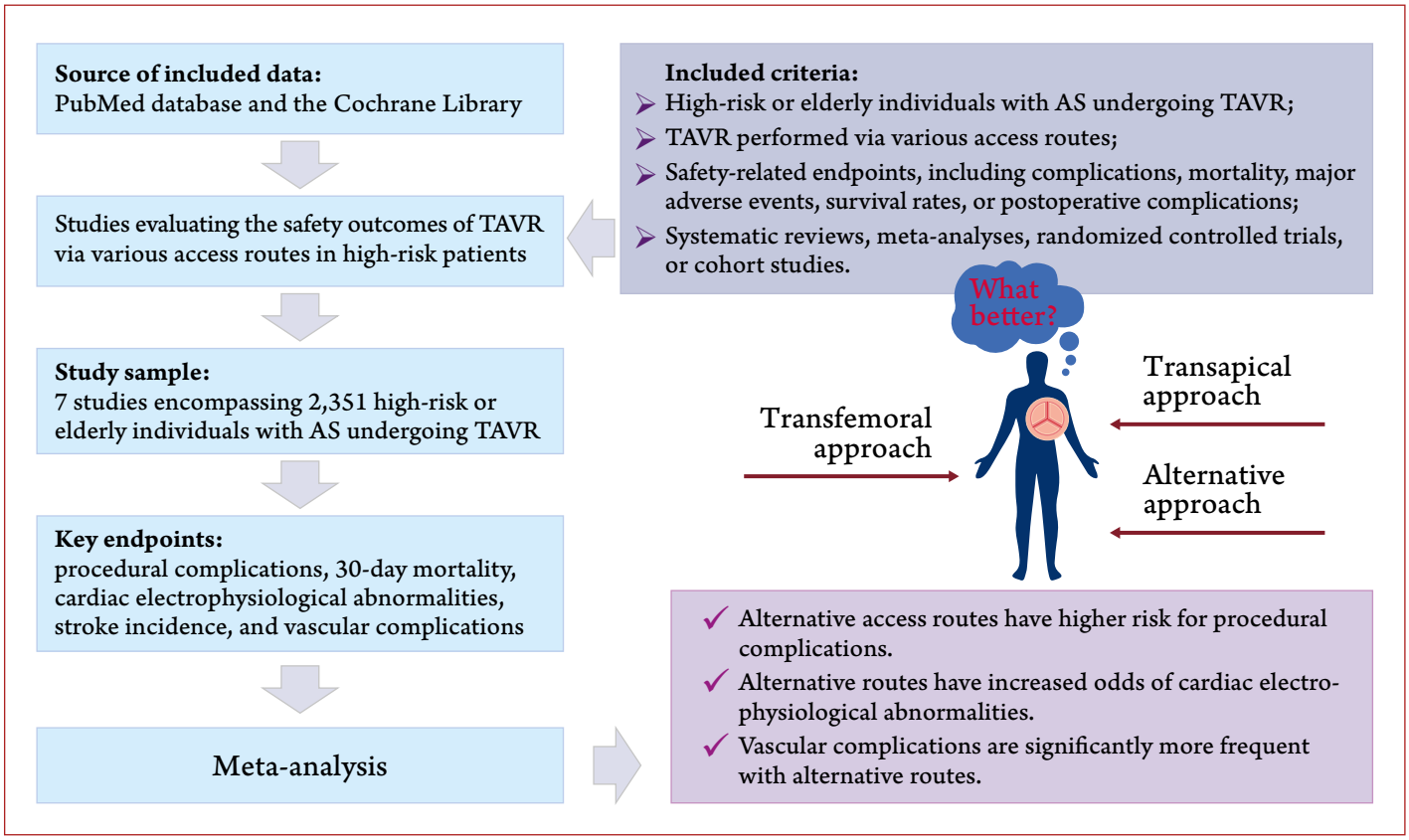
Introduction

Severe aortic stenosis (AS) is a critical valvular heart disease that disproportionately affects elderly and high-risk patients [1]. Without timely intervention, the prognosis for severe AS is poor, with a high likelihood of rapid progression to heart failure and death. For many years, the usual therapy for severe AS has been surgical aortic valve replacement (SAVR) [2]. However, many patients with advanced age, multiple comorbidities, or frailty are deemed ineligible or at high risk for conventional surgery. This has contributed to the development and adoption of transcatheter aortic valve replacement (TAVR), a minimally invasive alternative to SAVR, which has transformed the therapeutic landscape for patients with severe AS [3].

Since its initial approval, TAVR has been widely implemented for treating AS patients. It has demonstrated comparable or superior outcomes to SAVR in terms of mortality and functional recovery [4]. A pivotal aspect of TAVR's success is its ability to utilize multiple vascular access routes, including transfemoral (TF), transapical, transaortic, and other pathways, such as transsubclavian or transcaval approaches [5, 6]. While the TF route is generally favored due to its less invasive nature and lower complication rates, anatomical or vascular limitations may necessitate alternative access strategies in a significant subset of patients. However, each access route poses unique procedural challenges and is associated with distinct profiles of safety and efficacy outcomes. Consequently, identifying the optimal

Central illustration. Safety of Transcatheter Aortic Valve Replacement for High-Risk Patients with Severe Aortic Stenosis



access route for individual patients remains a critical aspect of preprocedural planning.

The safety of TAVR is impacted by numerous factors, including patient comorbidities, anatomical complexity, operator experience, and device advancements [7]. Complications associated with TAVR, such as vascular injury, conduction disturbances, and stroke, are significant concerns that necessitate meticulous evaluation of alternative procedures [8, 9]. Since TF access is often associated with an increased incidence of vascular complications [10], this raises further questions about comparative safety and utility of TF TAVR in high-risk populations.

In recent years, systematic reviews and meta-analyses have emerged as valuable tools the synthesized evidence from multiple studies to provide comprehensive insights into the safety and efficacy of TAVR via various access routes [11, 12]. By aggregating data across diverse clinical contexts, meta-analyses can address critical knowledge gaps and provide information for making clinical decisions. By conducting a meta-analysis and presenting systematic review the aim of this report was to assess the safety outcomes of TF TAVR in high-risk patients with severe AS. By examining key safety endpoints, including procedural complications, 30-day mortality, and adverse events, this analysis aimed to provide evidence-based recommendations for optimizing access route selection in this vulnerable patient population. Specifically, results of TF TAVR (identified below as "experimental") were compared with results of transapical access and SAVR (identified below as "control").

Material and methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [13] were followed in performing this systematic review and meta-analysis. To find studies assessing the safety of TF TAVR in high-risk patients with AS, a thorough literature search was conducted using PubMed and the Cochrane Library. Both free-text keywords and Medical Subject Headings (MeSH) phrases were used in the search. The details of searching keywords and steps are shown in Supplementary Material. No language restrictions were applied. Additional studies were identified by screening references of the included articles. After removing duplicates, two independent reviewers assessed all abstracts and titles. Studies considered potentially eligible were retrieved for full-text assessment. Disagreements were resolved by consensus.

Inclusion and exclusion criteria

The included studies met the following criteria:

1) Population, groups of high-risk or elderly individuals with AS
2) Intervention, TF TAVR or transapical TAVR/SAVR;

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3) Outcomes, safety-related endpoints, including complications, mortality, major adverse events, survival rates, or postoperative complications;
4) Study Design, systematic reviews, meta-analyses, randomized controlled trials (RCTs), or cohort studies (including multicenter studies).

Articles that did not provide extractable outcomes, case reports, conference abstracts, reviews without systematic methodology, and reports that did not address safety endpoints were also excluded.

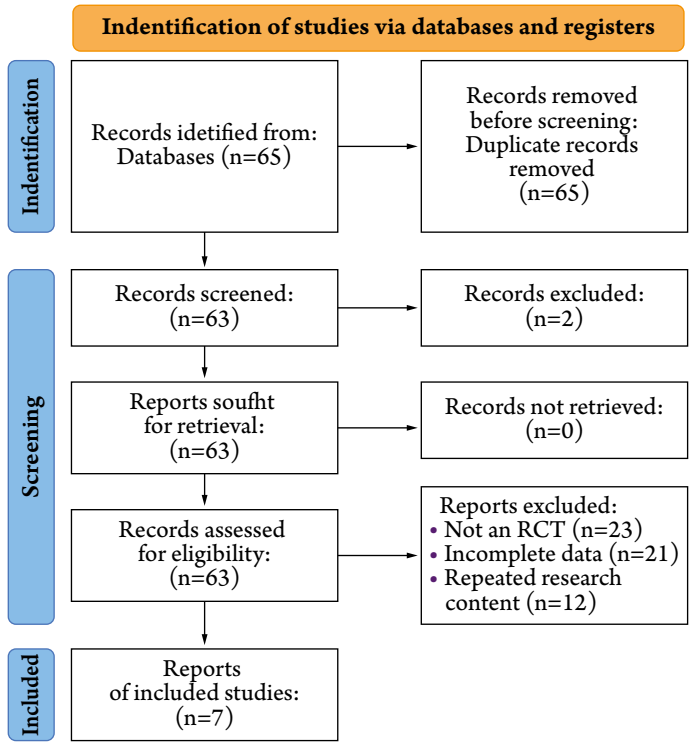
Risk of bias assessment

The application of the ROBINS-I tool [14] indicated that the included cohort studies generally achieved low to moderate risk of bias across most domains. While some concerns were noted regarding patient selection (e.g., non-randomized allocation, potential confounding from baseline comorbidities) and the classification of interventions (e.g., differing procedural techniques across centers), no study was thought to have a high risk of bias that would preclude its inclusion in the meta-analysis. Missing data and measurement of outcomes were managed sufficiently in most instances, with robust reporting measures and follow-up procedures. Selective reporting was not prevalent, as all included studies provided their primary safety outcomes in a transparent manner.

Meta analysis

RevMan 5.3 software (https://www.risetku.com/blog/revman) was used for the meta-analysis. For count data, the 95% confidence interval (CI) was computed for the relative risk, i.e., odds ratio (OR), as the impact indicator. When p>0.05 and the heterogeneity statistic (I^2) <50%, the heterogeneity between studies was deemed to be small, and the fixed effects model was chosen for analysis; if p≤0.05 and I^2≥50%, it was deemed that there was significant heterogeneity, and a random effects model was employed for analysis. The heterogeneity test uses both the chi squared test and the I^2 statistic to assess the homogeneity between studies. A p value < 0.05 was considered statistically significant. A funnel plot was inverted and its symmetry tested using Egger's test to assess the publication bias of the contained literature. The existence of publication bias was revealed if the Egger's test p value was less than 0.1. Potential publication bias's influence on the cumulative effect was corrected and adjusted using the TrimandFill approach [15].

Figure 1. PRISMA flow diagram of the literature search and study selection process



Results

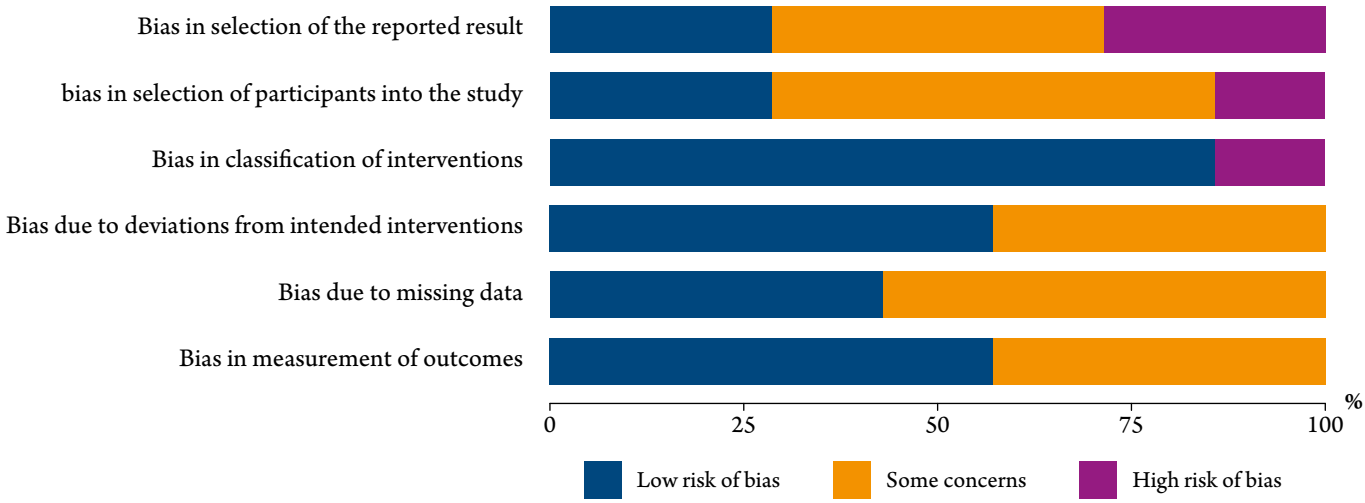
Results of literature search

The initial search yielded 65 references (PubMed, n=11; Cochrane, n=54). Two papers that did not fit the inclusion criteria were eliminated through title and abstract screening. The remaining 63 full-text papers were then further evaluated for eligibility. Of these, 56 were excluded due to irrelevance to the predefined outcomes, lack of full-text availability, inappropriate study populations, or insufficient data quality. Finally, the qualitative synthesis and meta-analysis comprised seven studies. Figure 1 shows a PRISMA flow di-

Table 1. A summary of the main information of the included studies

Authors	Year	Study design	Total sample, n	Groups	
				Experimental, n	Control, n
Smith et al. [16]	2011	Multicenter RCT	351	TF TAVR 248	Transapical TAVR 103
Sawa et al. [17]	2015	Multicenter n-RCT	64	TF TAVR 37	Transapical TAVR 27
Gleason et al. [18]	2016	Multicenter RCT	750	TF TAVR 391	SAVR 359
Ito et al. [19]	2020	Multicenter RCT	742	TF TAVR 389	SAVR 353
Blieziffer et al. [20]	2009	SCCS	152	TF TAVR 121	Transapical TAVR 26
Casado et al. [21]	2021	SCCS	282	TF TAVR 235	Transapical TAVR 47
Yuan et al. [22]	2013	SCCS	10	TF TAVR 6	Transapical TAVR 4

Figure 2. Risk bias diagram



agram that illustrates the research selection process. The seven included studies encompassed a range of study designs, including multicenter cohort studies and randomized controlled trials, with sample size varying from 10 to 750 (Table 1). Follow-up durations and reporting methods for safety outcomes varied, but all studies provided data on at least one of the following: mortality, major adverse events, procedural complications, or short-term survival rates.

n-RCT, non-randomized clinical trial; RCT, randomized clinical trial; SAVR, surgical aortic valve replacement; SCCS, single-center cohort studies; TF, transfemoral; TAVR, transcatheter aortic valve replacement.

Risk of bias in included studies

As described above, the included cohort studies generally achieved low to moderate risk of bias across most domains. Overall, the risk-of-bias assessment suggested that the body of eve was sufficiently reliable to support meaningful conclusions (Figures 2 and 3).

Safety and efficacy outcomes

Adverse events. A total of seven studies were included in the analysis to evaluate the relative safety outcomes of TAVR via different access routes for high-risk patients with AS. The pooled analysis indicated a notable increase in the event rate in the TF (experimental) group compared with the non-TF (control) group. Specifically, the overall risk ratio (RR) was 1.76 (95% confidence interval [CI]: 1.63–1.89), and the test for the overall effect was highly significant (Z=14.84, p<0.00001, Figure 4). This indicated that the non-TF approach was associated with a 76% higher relative risk of events compared to the TF approach.

Figure 3. Summary of risk bias

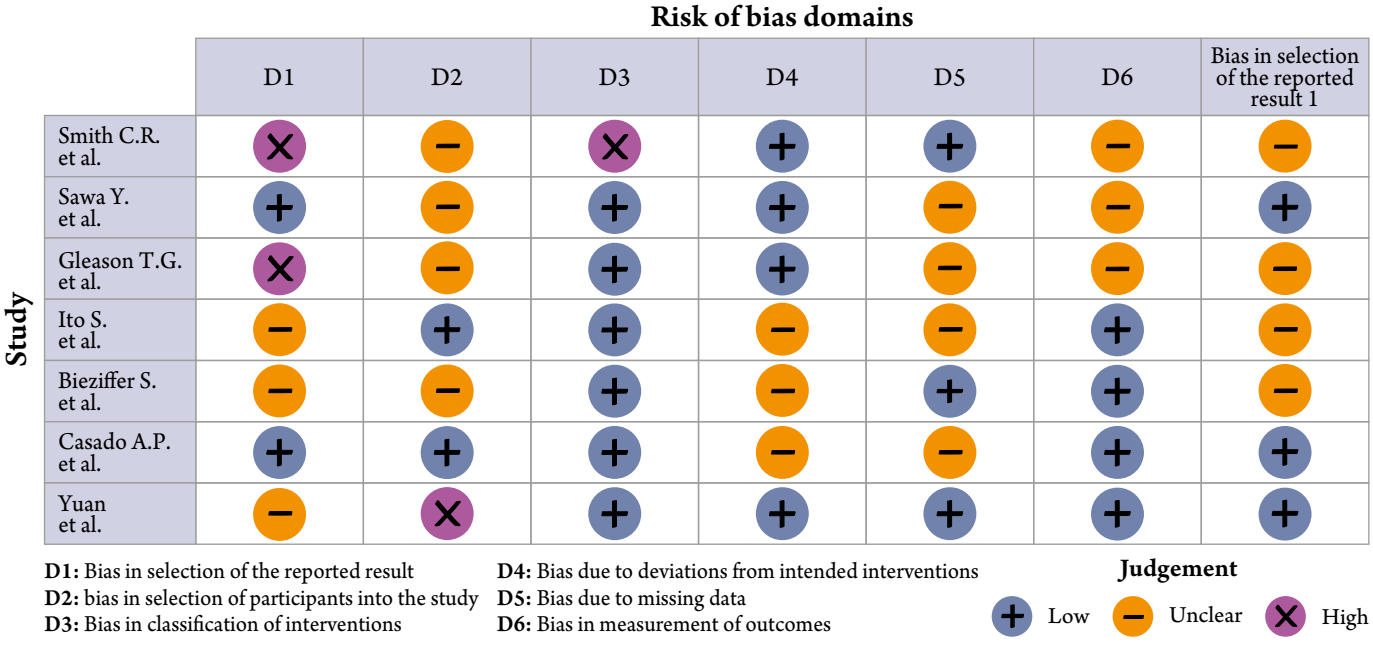


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Figure 4. Forest plot of adverse events in the non-TF (experimental) and TF (control) groups

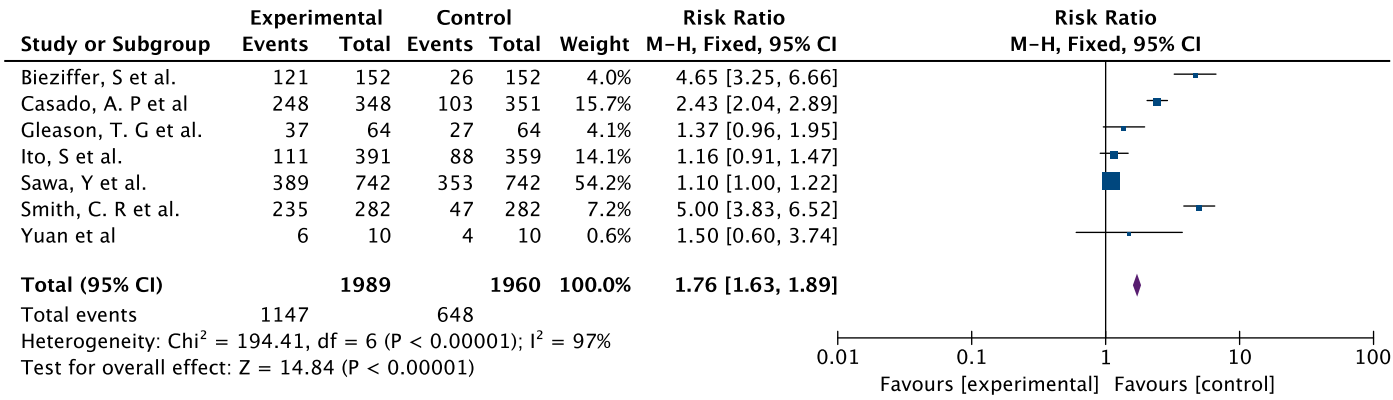


Figure 5. Forest plot of 30-day mortality in the non-TF (experimental) and TF (control) groups

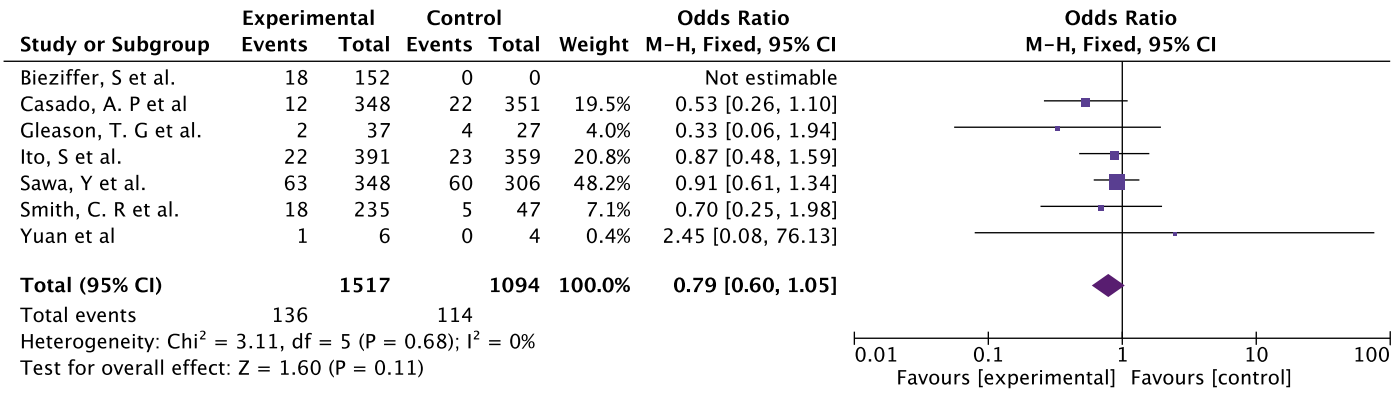
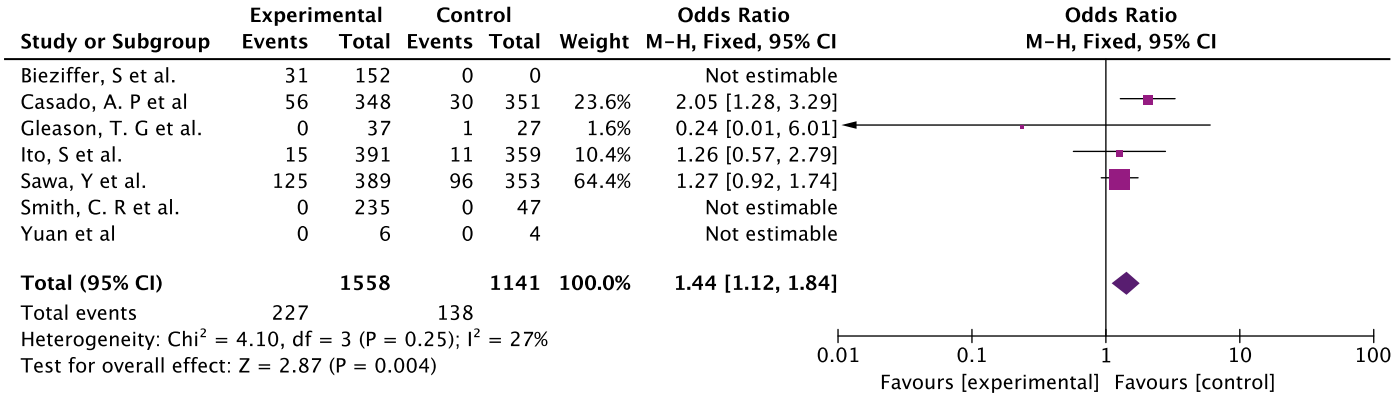


Figure 6. Forest plot of the ORs for cardiac electrophysiological abnormalities in the non-TF (experimental) and TF (control) groups



30-day mortality

The pooled analysis of 30-day mortality in seven studies yielded an odds ratio (OR) of 0.79 (95% CI: 0.60–1.05) when comparing the non-TF group with the TF group (Figure 5). The test for the overall effect (Z=1.60, p=0.11) did not reach statistical significance, indicating that the observed difference was not robust enough to exclude the influence of random variation.

Heterogeneity across these studies was minimal, as evidenced by a chi-squared value of 3.11 with five degrees of freedom (p=0.68) and an I^2 of 0%. Given the negligible between-study variation, a fixed-effects model was deemed appropriate. Although the direction of the point estimate suggests a potential reduction in 30-day mortality favoring the non-TF group (OR <1), the lack of statistical significance implies that any true effect, if present, was modest and warrants further investigation.

Incidence of cardiac electrophysiological abnormalities

Seven studies provided data on the incidence of cardiac electrophysiological abnormalities (Figure 6). The pooled

analysis revealed a statistically significant increase in risk associated with the non-TF group compared to the TF group. Specifically, the OR was 1.44 (95% CI: 1.12–1.84), and this effect was significance (Z=2.87, p=0.004). This suggests that patients treated via the non-TF route had approximately 44% higher odds of developing cardiac electrophysiological abnormalities.

Assessment of heterogeneity indicated only moderate variability among the included studies. The chi squared test for heterogeneity was 4.10 (df=3, p=0.25), and the I^2 was 27%, denoting relatively low between-study inconsistency. This supports the use of a fixed-effects model and enhances the reliability of the pooled estimate. While the study of Casado et al. [21] demonstrated a pronounced effect of the non-transmural approach, others Sawa et al. [17] and Ito et al. [19] did not observe significant differences. Such discrepancies may stem from differences in patient populations, procedural techniques, or study design limitations, such as sample size.

Incidence of stroke

Seven studies reported data on the incidence of stroke following TAVR (Figure 7). The pooled OR was 1.16 (95% CI: 0.75–1.79) for the non-TF experimental group relative to the TF group. The test for the overall effect (Z=0.65, p=0.51) did not reach statistical significance, indicating that the observed differences were not convincingly different from chance. Thus, no clear association emerged between the experimental TAVR approach and an increased or decreased risk of stroke.

Heterogeneity assessments showed a Tau^2 of 0.08, Chi^2 of 5.95 with 4 degrees of freedom (p = 0.20), and an I^2 of 33%. This suggests low-to-moderate heterogeneity among the included studies. Considering this, a random-effects model was deemed appropriate, providing a conservative estimate of the pooled effect. Although one study (Casado et al. [21]) suggested a potentially increased risk of stroke in the experimental group, the remaining studies did not demonstrate consistent differences. Overall, the findings indicate that there was no notable variation in the incidence of stroke between the experimental and control groups among the included studies.

Incidence of vascular abnormalities

Seven studies evaluated the incidence of vascular abnormalities (Figure 8). The pooled analysis indicated that the non- TF group had a considerably higher rate of vascular abnormalities in contrast to the TF group [OR=1.70

Figure 7. Forest plot of pooled ORs for stroke incidence in the non-TF (experimental) and TF (control) groups

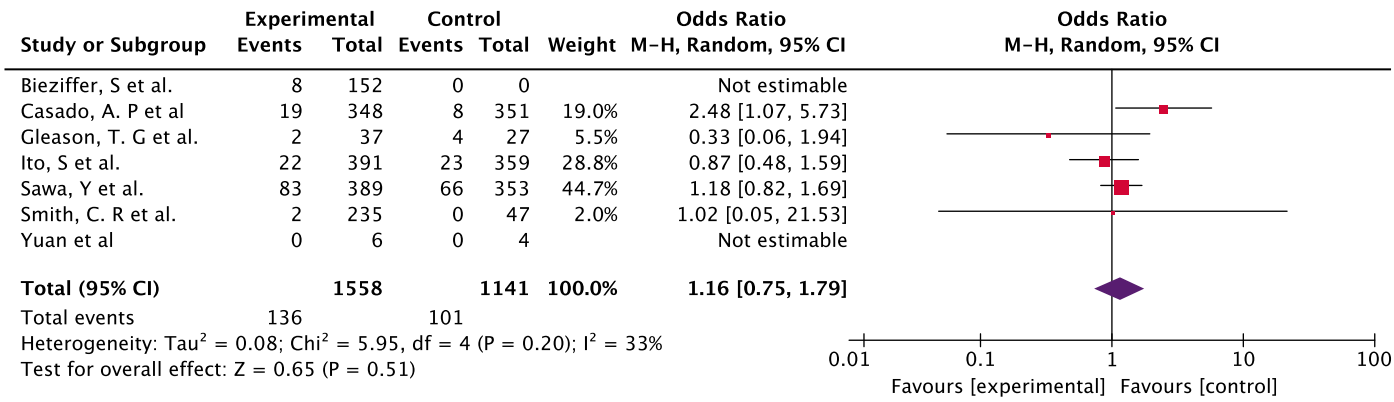
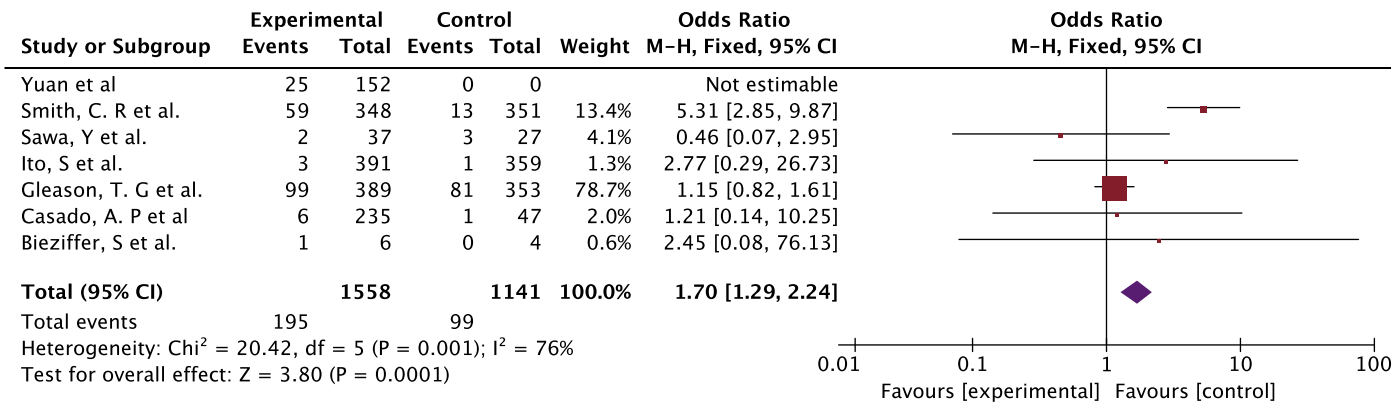


Figure 8. Forest plot of ORs for vascular abnormalities in the non-TF (experimental) and TF (control) groups



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(95% CI: 1.29–2.24)]. This finding was significant (Z=3.80, p=0.0001).

However, considerable heterogeneity was detected among the included studies (chi-squared = 20.42, df=5, p=0.001; I^2 = 76%), suggesting substantial variability among the patient populations, procedural factors, and study methodologies. While Smith et al. [16] demonstrated a pronounced increase in vascular abnormalities within the non-TF group, others (e.g., Sawa et al. [17] and Gleason et al. [18]) did not observe such a marked difference. These discrepancies may stem from differences in patient selection criteria, device technology, operator experience, or outcome definitions.

Discussion

This systematic review and meta-analysis investigated the safety of TAVR via different access routes in high-risk individuals with AS. Our findings contribute valuable insights into the procedural outcomes and associated risks, while also highlighting areas requiring further investigation.

The significantly higher overall event rate observed in the non-femoral access group undergoing TAVR has critical implications for clinical practice and patient management. Understanding these findings requires a comprehensive examination of the procedural risks associated with various access routes and has broad implications for patient selection in high-risk populations. The greater number of adverse events with non-femoral access can be attributed to several intrinsic factors associated with TAVR procedures. This is especially true when performed via alternative access routes, such as transapical or transsubclavian, as these routes are often reserved for patients with specific anatomical challenges or high-risk profiles.

Prior studies have consistently reported a spectrum of TAVR complications, which can include but are not limited to stroke, acute kidney injury, major vascular complications, and conduction abnormalities such as the need for permanent pacemaker implantation [23]. For instance, the complication rates are significantly elevated when accessing the aorta through the transapical route, as patients generally present with advanced cardiovascular disease and complex anatomical considerations. It is well-established that anatomical considerations play a crucial part in the outcomes of TAVR. Complexities such as severe calcification of the aortic valve, the presence of bicuspid aortic valves, or significant vascular disease can exacerbate procedural risks and increase the likelihood of complication [24, 25]. Complications are more likely to occur in those with significant left ventricular outflow tract calcification, including paravalvular leaks and device malfunction.

The findings from the present meta-analysis align with literature suggesting that careful patient selection based on anatomical profiles and risk stratification is crucial in mitigating the risks associated with TAVR [26]. The higher overall event rates indicate a pressing need for refinements in procedural protocols and patient selection criteria. Enhanced imaging techniques, such as advanced 3D echocardiography and preprocedural computed tomography (CT) assessments, can provide valuable insights into vascular anatomy and patient-specific risks, thereby facilitating more informed decisions regarding the choice of access route [27]. Moreover, the implementation of multidisciplinary heart valve teams can ensure thorough evaluation and adaptation of treatment strategies tailored to the individual patient's profile, significantly improving clinical outcomes [28].

Additionally, our findings highlight a pivotal concern in the management of patients undergoing TAVR procedures. There was a notable rise in the incidence of cardiac electrophysiological abnormalities in the non-femoral access group. This observation underscores the intricate relationship between procedural complexity and the amplification of existing conduction system vulnerabilities, particularly among patients with pre-existing cardiac conditions. Cardiac electrophysiological abnormalities are notably prevalent in individuals with AS, primarily due to the underlying degenerative processes affecting the cardiac conduction system. Prior studies have revealed that these patients often present with baseline conduction disturbances, including left bundle branch block and atrioventricular block, which significantly contribute to the procedural risks associated with TAVR [29]. The incidence of new-onset conduction abnormalities post-TAVR has been reported to range from 10% to 60%, based on the device and procedural techniques employed [29]. This variability is critical, as certain valve types, especially self-expanding devices, have been associated with higher rates of conduction disturbances due to their anatomical and mechanical characteristics [29]. The procedural techniques involved in TAVR, including valve deployment, balloon pre-dilation, and guidewire manipulation, all pose a direct risk to the atrioventricular conduction system, primarily due to the proximity of these structures to the aortic valve. The injury mechanisms, ranging from direct trauma to ischemic changes induced by valve expansion, further exacerbate the risks of transient or permanent high-degree AV block. These findings align with meta-analyses revealing that procedural factors, such as the depth of valve implantation and patient anatomical profiles, play a significant role in predicting the likelihood of postoperative conduction abnormalities [29]. Furthermore, the association between pre-existing conduction abnormalities and increased rates of new-onset conduction disturbances post-TAVR is well documented. For instance, patients presenting with baseline right bundle branch block or left anterior hemiblock were reported to have significantly higher rates of postoperative mechani-

cal pacing requirements and adverse outcomes [30]. This necessitates an urgent call for enhanced risk stratification and monitoring strategies, especially in high-risk patients with established conduction disorders. Clinical guidelines advocate pre-procedural assessments that incorporate detailed cardiac imaging and electrophysiological evaluations to optimize outcomes.

In response to these concerns, state-of-the-art monitoring technologies, such as remote telemetry and mobile health applications, are poised to transform the landscape of post-TAVR care, enabling continuous assessment of cardiac rhythms and timely intervention [31]. Implementing preemptive monitoring protocols could provide early warnings of conduction disturbances, allowing clinicians to tailor pacing strategies more effectively and potentially avert the need for permanent pacing installations in a significant cohort of patients [29].

Moreover, the current meta-analysis highlights a significant correlation between alternative access routes in TAVR procedures and an increased incidence of vascular complications. The observed odds ratio illustrates a substantial risk for patients undergoing TAVR via non-TF access routes compared to those using the TF approach. Such findings align with existing literature that consistently reports heightened vascular complications associated with alternative access sites, reinforcing the importance of an evidence-based approach to access selection in high-risk populations [32]. The considerable heterogeneity indicated by an I^2 statistic of 76% is noteworthy, as it reflects variability in study outcomes due to factors such as patient-specific anatomical considerations, the types of devices employed, and operator experience. These variables are crucial since they directly affect the rate of vascular complications, emphasizing the need for tailored strategies in preoperative assessment and procedural planning. Vascular anatomy plays a pivotal role in determining access route safety. TF access is generally preferred because it allows for direct access to the aorta with minimal displacement of vascular structures [33]. In contrast, alternative routes, such as transapical, transcarotid, or subclavian, bypass more favorable vascular anatomy, increasing the likelihood of complications like dissection or rupture due to the inherent difficulties in navigating tortuous or calcified vessels. Studies have shown that patients with severe peripheral vascular disease (PAD) or anatomical deformities are particularly vulnerable [34, 35], leading to higher complication rates when alternative access routes are employed.

The type of TAVR device utilized can also influence vascular outcomes. Current-generation TAVR systems have demonstrated improved deliverability, but the size and profile of delivery systems remain critical factors [36]. Larger delivery sheaths used in conjunction with alternative access routes are associated with a notable increase in vascular trauma. A meta-analysis comparing vascular complications across different delivery systems emphasizes that smaller sheaths (low-profile sheaths) significantly decrease the incidence of vascular complications, underscoring the importance of advancements in device technology in enhancing patient safety [37]. The significant increase in vascular complications among patients undergoing TAVR via alternative access routes reinforces the need for a multidisciplinary approach in patient selection and procedural planning. Future directions should include further exploration into how advanced imaging techniques and device innovations can mitigate these risks. Continued collaboration among interventional cardiologists, cardiovascular surgeons, and imaging specialists will be essential in refining access strategies for TAVR. This will ultimately improve patient outcomes and expand the clinical applicability of this life-saving procedure to high-risk patients with compromised vascular anatomy.

The pooled analysis indicates no discernible change in 30-day mortality between experimental and control groups underscores an essential shift in the landscape of TAVR. This finding aligns with the growing body of literature suggesting that TAVR has become increasingly safe and effective, reflecting notable advancements in both device technology and clinical practice. The historical context for these findings reveals that early iterations of TAVR were often associated with significant procedural risks, including higher short-term mortality rates that could reach as high as 12–20% in vulnerable patient populations [38]. However, the evolution of transcatheter valve design, such as the introduction of the Sapien 3 and Evolut R/Pro devices, has improved procedural outcomes and minimized complications significantly [39]. These devices have demonstrated enhanced performance characteristics, allowing for better hemodynamic profiles and reduced rates of major adverse cardiovascular events post-implantation. Furthermore, multivariate analyses consistently show that patient outcomes following TAVR have improved over time. Evidence suggests that continuous refinement of procedural techniques, including advancements in operator training and multidisciplinary team approaches, contributes to enhanced short-term survival rates [40]. The declining mortality rates observed in more recent randomizes clinical trials highlight a paradigm shift, where the procedural risk associated with both transapical and TF access routes has been significantly mitigated. Moreover, it is vital to consider that the lack of significant mortality differences may also reflect improved patient selection criteria. As guidelines for TAVR have evolved, practitioners have increasingly employed a heart team approach to identify patients who could derive the greatest benefit from the procedure while minimizing risks. This strategic screening has led to narrower mar-

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gins of disparate outcomes between different access routes and a more comprehensive evaluation of intricate comorbid conditions, disease severity, and functional capacity, ensuring that only those patients most likely to benefit undergo TAVR. Therefore, the findings presented in the pooled analysis are pivotal, supporting the assertion that TAVR now offers similar short-term mortality outcomes compared to traditional surgical approaches. This trajectory towards parity is a testament to the continuous improvements in TAVR technology and procedural methodologies, reaffirming TAVR's position as a viable, low-risk alternative for high-risk patients with AS. The ongoing commitment to research and innovation in this field is expected to further enhance the safety profile of TAVR, ultimately leading to even better patient outcomes in the future.

TAVR has become an established treatment option for high-risk patients suffering from AS. The recent meta-analysis, which found no significant difference in stroke incidence between non-femoral and femoral access groups, underscores the complexity of stroke outcomes in this patient population. Although there appeared be a trend towards higher stroke rates in the non-femoral group, the results were not statistically significant. This finding still raises important considerations regarding the interplay of procedural techniques, patient characteristics, and underlying health conditions. Variability in procedural techniques across studies could influence stroke outcomes significantly. The method of valve deployment, whether it is balloon-expandable or self-expanding, can affect embolic debris generation, which is a known risk factor for cerebrovascular events. Research indicates that balloon-expandable valves may produce embolic debris during deployment, while self-expanding valves might generate emboli during positioning [41]. Furthermore, the timing of valve deployment and manipulation of catheters within the aorta are critical moments where embolic events peak. Standardizing procedural techniques across different studies could minimize the confounding effect of such variables and provide a clearer picture of stroke risk associated with TAVR [41]. Patient comorbidities have been shown to significantly impact stroke risk post-TAVR. Factors such as age, history of atrial fibrillation, prior stroke, reduced renal function, and diabetes mellitus have been recognized as predictors of post-procedural stroke [41, 42]. The PARTNER trial highlighted that patients with pre-existing atrial fibrillation or those who experienced new-onset atrial fibrillation following TAVR face an increased risk of stroke [27]. The existing literature emphasizes that higher CHA2DS2-VASc scores, which account for these risk factors, correlate with increased cerebrovascular events [42]. Meta-analyses may benefit from stratification based on these comorbidities to identify specific subgroups at greater risk.

There are some limitations in the analysis reported here. First, there was little information on long-term durability and quality of life, with the majority of included research concentrating on short- to intermediate-term results. In addition, some studies included in the analysis had small sample sizes, which may have limited statistical power and contributed to variability in the results. Hence, additional research is needed to evaluate the long-term safety and efficacy of TAVR via different access routes, including impacts on survival, quality of life, and device durability. Moreover, future studies should focus on identifying patient subgroups who may benefit most from alternative access routes, based on individual anatomical and clinical characteristics. Larger randomized controlled trials and real-world registry data are needed to validate the findings of this meta-analysis and provide robust evidence to guide clinical decision-making.

Conclusion

This meta-analysis highlights significant differences in safety outcomes between TAVR access routes, particularly regarding vascular abnormalities and cardiac electrophysiological issues. While TF TAVR remains the gold standard, alternative approaches play a critical role in specific high-risk populations. Future research should aim to refine patient selection criteria and procedural techniques to optimize outcomes across all access routes.

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Ethics approval and consent to participate
All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

Author Contributions
We declare that all the listed authors have participated actively in the study, and all meet the requirements of the authorship. Dr. QHM designed the study and wrote the paper, Dr. MTY managed the literature searches and analyses, Dr. HYZ contributed to the correspondence and paper revision. All authors reviewed the manuscript.

Data Availability Statement
The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

No conflicts of interest are reported.

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