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Transcatheter versus Surgical Aortic Valve Replacement for Stenotic Bicuspid Aortic Valve: Systematic Review and Meta-Analysis

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Disclosure: Dr. Latib is a consultant for and on the advisory board of Medtronic, Abbott, Boston Scientific, Edwards Lifesciences, and Philips. Dr. Thourani is a research/advisor for Abbott Vascular, Artivion, Atricure, Boston Scientific, Edwards Lifesciences, Jenavalve, Medtronic, Shockwave. Dr. Kaneko has received consulting fees from Edwards Lifesciences, Medtronic, 4C Medical, CardioMech, Cook Medical; and has been a speaker for Abbott and Baylis. The remaining authors have nothing to disclose.

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ABSTRACT (249/250 words)

Objectives: Bicuspid aortic valves (BAV) has been excluded from randomized trials comparing transcatheter aortic valve replacement (TAVR) with surgical aortic valve replacement (SAVR). We aimed to evaluate the outcomes of TAVR versus SAVR in patients with severe BAV stenosis using a meta-analysis.

Methods: MEDLINE and EMBASE were searched through March 2022 to identify observational studies comparing TAVR and SAVR for severe BAV stenosis. Outcomes of interest were in-hospital outcomes, including all-cause mortality, stroke, vascular complication, permanent pacemaker implantation, acute kidney injury, blood transfusion, paravalvular leak, and all-cause mortality during follow-up.

Results: Four propensity score-matched studies and 58,108 patients (TAVR, n = 3,841; SAVR, n = 50,206) yielding 3,142 pairs using propensity score were included. Median follow-up periods were 21 to 24 months. There were no significant differences in in-hospital mortality or stroke (Risk Ratio [RR]: 0.69; 95% confidence interval [CI]: 0.40-1.20; p = 0.19, RR: 0.86; 95% CI: 0.64-1.14; p = 0.29, respectively). While TAVR was associated with higher risks of permanent pacemaker implantation rate (RR: 1.87; 95% CI: 1.23-2.84; p = 0.0003), TAVR was associated with lower risks of acute kidney injury (RR: 0.58; 95% CI: 0.38-0.88; p = 0.01), and transfusion (RR: 0.25; 95% CI: 0.21-0.29; p = 0.0001). There were no significant differences in in-hospital vascular complication, paravalvular leak, and all-cause mortality during follow-up.

Conclusions: In selected patients with severe BAV stenosis, no significant differences in in-hospital mortality or stroke were observed between TAVR and SAVR. Further investigations with long-term follow-up and morphological features are warranted.
KEY WORDS: transcatheter aortic valve replacement, surgical aortic valve replacement, bicuspid aortic valve

Glossary of Abbreviations:

BAV = bicuspid aortic valve
CI = confidence interval
HR = hazard ratio
PVL = paravalvular leak
RCT = randomized controlled trial
RR = risk ratio
SAVR = surgical aortic valve replacement
TAVR = transcatheter aortic valve replacement

Central Message (194/200 characters)
In-hospital mortality or stroke did not differ between TAVR and SAVR in patients with severe bicuspid aortic stenosis. Long-term comparative studies with morphological features are still needed.

Perspective Statement (401/405 characters)
In this meta-analysis of comparative studies for TAVR versus SAVR among 6,284 patients with bicuspid aortic valve, there were no significant differences in in-hospital mortality or stroke between TAVR and SAVR, whereas long-term outcomes are limited. Long-term comparative
studies with detailed morphological features are needed to identify the patient population who would benefit the most from TAVR.

Central Picture Legends (80/90 characters)

In-hospital outcomes for TAVR versus SAVR in patients with bicuspid aortic valve
INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac disease, which frequently results in aortic stenosis requiring aortic valve intervention at a younger age in comparison with tricuspid aortic valve (TAV) stenosis. Transcatheter aortic valve replacement (TAVR) is a valid alternative to surgical aortic valve replacement (SAVR) since indications have been expanded to low-risk patients with symptomatic severe aortic stenosis with TAV. Consequently, TAVR has been increasingly utilized in patients with BAV during the past decade. However, most of the landmark randomized controlled trials (RCTs) for TAVR versus SAVR excluded patients with BAV, posing unique challenges for performing TAVR due to anatomical features for these patients. Numerous studies compared outcomes of TAVR for BAV with TAV, which showed conflicting results with potential higher risks of stroke and paravalvular leak (PVL) in patients with BAV. Moreover, even though recent registry data showed comparable risks of 1-year mortality, stroke, or PVL undergoing TAVR using new-generation devices between BAV and TAV, those results could not be extrapolated to outcomes of SAVR for patients with BAV.

In addition to the paucity of comparative data between TAVR and SAVR among patients with BAV, those conflicting data highlight the importance of head-to-head comparison of TAVR versus SAVR to provide better guidance for clinical decision-making. Herein, we conducted a meta-analysis comparing the outcomes of TAVR versus SAVR for patients with severe BAV stenosis.

METHODS
The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards and was prospectively registered with the PROSPERO (CRD42022329713).

**Search Strategy and Eligibility**

All RCTs and observational studies with comparative outcomes of TAVR and SAVR for BAV were considered using MEDLINE and EMBASE. Databases were searched through March 22nd, 2022, using web-based search engines (PubMed and OVID). Search terms included “transcatheter aortic valve replacement”, “transcatheter aortic valve implantation”, “bicuspid aortic valve”, and “surgical aortic valve replacement”. No language or sample size restrictions were applied. This systematic review was based on PICOS Frameworks as follows: P (Population), patients with stenotic BAV who underwent either transcatheter or surgical aortic valve replacement; I (Intervention), TAVR; C (Comparison), SAVR; O (Outcome), in-hospital outcomes including all-cause mortality, stroke, PVL, acute kidney injury, bleeding requiring blood transfusion, vascular complication, and permanent pacemaker implantation, as well as all-cause mortality at the longest follow-up; and S (Study type), RCTs and observational studies.

Included studies met the following criteria: the study design was a RCT or an observational study, the study population was patients with BAV who underwent TAVR or SAVR, and comparative outcomes included in-hospital mortality, stroke, any PVL, acute kidney injury, bleeding requiring blood transfusion, permanent pacemaker implantation, vascular complication, and all-cause mortality during follow-up. We excluded case reports, case series, and studies not reporting any adjusted outcomes.

**Study Selection and Data Collection**
Relevant studies were identified through a manual search of secondary sources including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Two independent authors (Y.S. and Y.Y.) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria. Disagreements were resolved by consensus. The quality of the studies was assessed using the Cochrane Collaboration tool for RCTs and The Risk of Bias in Non-Randomized Studies of Interventions tool (ROBINS-I). 13,14

Summary Measures

The primary endpoints were in-hospital mortality and stroke. The secondary endpoints were in-hospital periprocedural outcomes, including PVL, acute kidney injury, bleeding requiring blood transfusion, permanent pacemaker implantation, vascular complication, and all-cause mortality at the longest follow-up on each study. For each in-hospital outcome, risk ratios (RRs) were calculated from the event number and the patient number. Odds ratios without reporting events number were transformed to RRs using a validated formula. 15 For all-cause mortality at follow-up, hazard ratios (HRs) were extracted from each study. For studies without describing HR, HR was calculated from a Kaplan-Meier curve of the matched population using a spreadsheet programmed to estimate the overall HR with a 95% confidence interval (CI) with an inverse variance-weighted average which is provided by Tierney et al. 16 based on standard statistical methods reported by Parmar et al. 17 and Williamson et al. 18

Meta-Analysis
The Review Manager (RevMan) Version 5.4 (Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) was used to combine RRs or HRs in the random-effects model with inverse variance method. The random-effects model was used in each outcome regardless of the heterogeneity among studies, as it allowed for a more conservative assessment of the pooled effect size.

Funnel-plot asymmetry was examined, and sensitivity analyses were conducted using ProMeta 3 Software (https://idostatistics.com/prometa3/) Funnel plot asymmetry suggesting publication bias was assessed mathematically using Egger’s linear-regression test. Substantial heterogeneity was considered to be present when the $I^2$ index was over 50% or $P$ for heterogeneity was <.05. Leave-one-out sensitivity analyses for in-hospital mortality and stroke were conducted to assess the influence of a single study on outcomes by sequentially removing one study. A meta-regression analysis was conducted to evaluate the relationship between mean age or median year of enrollment of each study and in-hospital mortality or stroke.

RESULTS

Study Selection

The database search identified 797 articles that were reviewed based on the title and abstract. Of those, 19 articles were considered relevant for the meta-analysis. After evaluating the full-text articles, 15 articles were excluded for reasons as follows: 3; no outcomes of interest, 5; no comparison with SAVR, 1; overlapping dataset, 1; review, 1; commentary, 4; meta-analysis. Four articles published from 2019 to 2022 met the inclusion criteria and were assessed for the systematic review and the meta-analysis (Figure 1). All of four studies were propensity-
score matched studies\(^5\),\(^6\),\(^20\)-\(^22\) which enrolled a total of 58,108 patients (TAVR, \(n = 3,841\); SAVR, \(n = 50,206\)) yielding 3,142 pairs using propensity score.

**Study Characteristics**

Study profile and patient characteristics are summarized in Table 1. Outcomes were defined according to Valve Academic Research Consortium 2 (VARC-2)\(^5\) in one study,\(^21\) whereas other studies used the International Classification of Desease-9th or 10th Revision codes\(^5\),\(^22\) (Table E1) without reporting of the grade of PVL or vascular complication. Study periods ranged from 2008 to 2018. Two studies reported outcomes from the National Inpatient Sample (NIS) or Nationwide Readmission Database (NRD),\(^5\),\(^22\); however, the study periods did not overlap. The exclusion criteria of each study were described in Table E2. Most studies excluded patients undergoing concomitant ascending aortic replacement, coronary artery bypass grafting (CABG), or other valvular intervention. Before propensity score matching, the TAVR population was older than the SAVR group (mean age, 66.2 to 77.1 years versus 56.9 to 70.9 years)\(^5\),\(^21\) with a higher prevalence of comorbidities, including diabetes, chronic lung disease, chronic kidney disease, prior CABG, and prior percutaneous coronary intervention (Table E3). After propensity matching, there were no significant differences in the baseline characteristics (Table 1).

Variables to generate the propensity score in each study were summarized in Table E4. Mean age of patients was 65.2 to 75.8 years old.\(^5\),\(^21\) Median follow-up ranged from 21 to 24 months.\(^20\),\(^21\) The mean Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) was reported in one study, which were 2.9 ± 1.7 for the TAVR group and 3.1 ± 3.2 for SAVR.\(^21\) The other three studies mainly included patients at intermediate-risk since TAVR was not approved in the United States for low-risk patients during the study period.\(^5\),\(^20\),\(^22\) Transapical access rate ranged
The type or generation of transcatheter valves were described in one study reporting that 81.6% were new-generation devices and 77.7% were balloon-expandable valve. The morphology of BAV was also reported in one study with 81.6% being Sievers type I. Other anatomical features, including raphe calcification, excess leaflet calcification, or ascending aorta diameter, were not described. The risk of bias was summarized in Table E5, showing that all studies were considered as a moderate risk of bias. Publication bias in each outcome was assessed using funnel plots (Figure E1), which showed no evidence of publication bias except for in-hospital stroke and blood transfusion.

**In-hospital Outcomes**

There was no significant difference in in-hospital mortality or stroke (RR: 0.69; 95% CI: 0.40-1.20; p = 0.19; I^2 = 49%, RR: 0.86; 95% CI: 0.64-1.14; p = 0.29; I^2 = 0%, respectively) (Figure 2A, 2B). TAVR was associated with higher risks of permanent pacemaker implantation (RR: 1.87; 95% CI: 1.23-2.84; p = 0.0003; I^2 = 80%) (Figure 3A). In contrast, TAVR was associated with a lower rate of acute kidney injury (RR: 0.58; 95% CI: 0.38-0.88; p = 0.01; I^2 = 89%), and transfusion (RR: 0.25; 95% CI: 0.21-0.29; p = 0.0001; I^2 = 0%) (Figure 3B, 3C). Vascular complications and PVL were similar in both groups. (RR: 0.58; 95% CI: 0.18-1.91; p = 0.37; I^2 = 74%, RR: 1.56; 95% CI: 0.85-2.85; p = 0.15; I^2 = 0%, respectively) (Figure 3D, 3E).

**All-cause Mortality During Follow-up**

There was no significant difference in all-cause mortality during follow-up with median follow-up period of 21 to 36 months. (HR: 0.83; 95% CI: 0.40-1.70; p = 0.60; I^2 = 67%) (Figure 4).
Leave-One-Out Analysis and Meta-Regression

Leave-one-out analyses did not indicate any significant effect on in-hospital mortality or stroke with any one study being removed (Figure E2A, 2B). A meta-regression model investigating the effects of changes in practice over time did not reveal a significant relationship between the median year of enrollment and in-hospital mortality or stroke. (Figure E3A, 3B). In addition, there was no significant association between mean age at baseline and in-hospital mortality or stroke. (Figure E4A, 4B)

DISCUSSION

The main findings of our meta-analysis of comparative studies for TAVR and SAVR in patients with stenotic BAV are as follows (Figure 5): 1) there was no significant difference in in-hospital mortality, stroke, PVL, or vascular complications between TAVR and SAVR; 2) TAVR was associated with lower risks of acute kidney injury or any transfusion; 3) TAVR was associated with higher risks of permanent pacemaker implantation than SAVR; and 4) there was no significant difference in all-cause mortality during follow-up with a median follow-up of 21 to 24 months. Our main findings were in line with previous RCTs for TAVR versus SAVR in patients with TAV,2,3 uniquely supporting the short-term feasibility of the transcatheter approach for selected patients with BAV stenosis.

The risks of stroke or PVL following TAVR for patients with BAV have been conflicting and remained controversial,8 potentially resulting in increased mortality during follow-up.24,25 In this regard, the short-term feasibility of TAVR was supported by comparable risks of stroke between TAVR and SAVR in this study. However, the risks of stroke were still relatively high
ranging from 2.1 to 4.0% among the studies, which we included with a mean age of 68 to 75 years. Similar numerically higher risks of stroke were observed in a prospective registry of BAV TAVR, even among low-risk populations. Previous studies showed longer procedure duration and post-dilation during TAVR, which are associated with unique morphological features of BAV, were independent predictors of new ischemic lesions. These observations underscore the need for further studies to elucidate the potential efficacy of the cerebral embolic protection devices for patients undergoing TAVR for BAV stenosis.

Additionally, our analysis demonstrated lower risks of periprocedural complication with TAVR, including acute kidney injury and blood transfusion, along with comparable risks of vascular complication, supporting the feasibility of TAVR despite the complexity of the TAVR procedure for BAV. Relevantly, cardiac tamponade, pericardiocentesis, or an open conversion following TAVR were extremely rare among the studies which we included. Since VARC-3 technical success is reported to affect cardiovascular mortality and stroke at the follow-up, those findings would add another piece of reassuring information that TAVR can be safely performed for BAV in comparison with SAVR. Similarly, we did not find significant differences in PVL rates between TAVR and SAVR, whereas previous studies showed higher risks of PVL following TAVR for BAV compared to TAV. However, only two of four studies reported the incidence of PVL and we could not account for the grades of PVL. Since the incidence of mild PVL following TAVR is consistently higher than SAVR even with the new-generation devices, our findings need to be interpreted cautiously.

Our systematic review revealed limited data on long-term comparative outcomes with morphological features of BAV between TAVR and SAVR, whereas the long-term outcome of SAVR for BAV has been well established and promising. Additionally, the present analysis
data cannot necessarily be extrapolated to outcomes of patients who need concomitant surgical procedures since many studies excluded those patients. Interestingly, ascending aortic dilation (>40mm) is reported as an independent factor of long-term mortality following TAVR as opposed to SAVR. The prospective registry of TAVR for BAV excluded patients with ascending aortic diameter > 40mm. In contrast, real-world data on bicuspid TAVR showed that 42.2% of patients had aortic diameter > 40mm, potentially playing a role in conflicting reported outcomes of TAVR with these discrepancies. Even though our analysis did not include granular data on ascending aorta diameter, since SAVR with concomitant ascending aorta replacement can be performed without adding morbidity, patients with aortopathy who are surgical candidates should undergo surgical repair. Moreover, imaging-based anatomical risk assessment of TAVR is an essential part of the heart team discussion since BAV anatomy is highly heterogeneous and calcified raphe or excess leaflet calcification are unfavorable for TAVR. It should be noted that the majority of patients undergoing SAVR with BAV are still in the low-risk category with substantial estimated survival. In this context, long-term follow-up data with detailed anatomical features is of key importance in the selection of appropriate treatment strategies between TAVR and SAVR. Furthermore, the impacts of long-term pacing need to be carefully investigated given the higher risks of permanent pacemaker implantation following TAVR in our analysis since patients undergoing TAVR for BAV tend to have a long life expectancy, and a previous meta-analysis showed that pacemaker implantation was independently associated with increased all-cause mortality following TAVR for TAVR. Ultimately, well-designed randomized trials are warranted to validate the present findings. Nevertheless, since there are no upcoming randomized trials and it might be difficult to conduct
an RCT given the complexity of the BAV, the current comparable outcomes with real-world patients would support the feasibility of TAVR among the selected patients with BAV.

This study has several limitations. No randomized studies were included in this analysis, and observational studies are subject to confounding, and studies using administrative data are subject to coding errors although the NIS database is internally and externally validated.

Furthermore, two studies included patients undergoing SAVR with concomitant CABG or ascending aorta replacement, which may compromise the comparability between TAVR and SAVR. However, both studies conducted the sensitivity analysis excluding patients undergoing the concomitant procedures, confirming the robustness of the primary analysis. Nevertheless, the HRs of those sensitivity analyses were not reported, precluding us from conducting another analysis for patients undergoing isolated SAVR. On the other hand, a small portion of the TAVR was performed via transapical access, which could lead to worse outcomes in the TAVR group.

Nevertheless, despite the heterogeneities in the study population and potential publication bias, we only included propensity score-matched studies with well-balanced baseline characteristics and almost identical variables to generate the propensity scores. Second, analyzing and comparing granular datasets were not possible, particularly related to individual anatomical features or details of the procedure including aortic diameter, excess leaflet calcifications, raphe calcification, the frequency of pre or post-dilation during TAVR, type of TAVR valve, and use of the cerebral embolic protection devices. Notably, TAVR tended to be performed on selected patients with favorable anatomy, limiting the generalizability of this study. Finally, the effect of potential overlapping cohorts in the Medicare, NIS, or NRD based studies could not be excluded. However, two studies from the NIS and the NRD database were not overlapped based on the enrollment year. In addition, the NIS database includes Medicare Advantage patients which
are often missing from the Medicare claims data. Moreover, the leave-one-out analyses showed that removal of any of those studies did not change the robustness of the results. We, therefore, presume that the effect of overlapping patients might be minimal.

CONCLUSIONS

In selected patients with BAV stenosis, TAVR was associated with similar in-hospital mortality or stroke compared with SAVR. Long-term comparative data needs to be investigated with detailed morphological features.

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Data availability statement: The data supporting this study's findings are available from the corresponding author upon reasonable request.

Conflict of interest: Dr. Latib is a consultant for and on the advisory board of Medtronic, Abbott, Boston Scientific, Edwards LiveScience, and Philips. Dr. Thourani is a research/advisor for Abbott Vascular, Artivion, Atricure, Boston Scientific, Edwards Lifesciences, Jenavalve, Medtronic, Shockwave. Dr. Kaneko has received consulting fees from Edwards Lifesciences, Medtronic, 4C Medical, CardioMech, Cook Medical; and has been a speaker for Abbott and Baylis. The remaining authors have nothing to disclose.
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doi:10.1002/sim.1303


21


Figure legends

FIGURE 1.
Workflow for selecting eligible papers according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria in search of original studies for our original meta-analysis.

FIGURE 2.
Comparisons of the in-hospital (A) all-cause mortality and (B) stroke for transcatheter aortic valve replacement versus surgical aortic valve replacement using a random effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). (Right) Forest plot of the data. The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an HR of 1. IV: Inverse variance
Abbreviations: TAVR; transcatheter aortic valve replacement, SAVR; surgical aortic valve replacement, CI: confidence interval

FIGURE 3.
Comparisons of the periprocedural outcomes for transcatheter aortic valve replacement versus surgical aortic valve replacement using a random effects model; A, permanent pacemaker implantation. B, acute kidney injury. C, blood transfusion. D, major vascular complication. E, any paravalvular leak. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). (Right) Forest plot of the data. The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an HR of 1. IV:
Inverse variance. Abbreviations: TAVR; transcatheter aortic valve replacement, SAVR; surgical aortic valve replacement, CI: confidence interval

FIGURE 4.
Comparisons of all-cause mortality during follow-up for transcatheter aortic valve replacement versus surgical aortic valve replacement using a random effects model. (Left) Studies analyzed with their corresponding hazard ratios (HRs) and 95% confidence intervals (CIs). (Right) Forest plot of the data. The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an HR of 1. IV: Inverse variance

Abbreviations: TAVR; transcatheter aortic valve replacement, SAVR; surgical aortic valve replacement, CI: confidence interval.

FIGURE 5.
In-hospital outcomes for TAVR versus SAVR in patients with bicuspid aortic valve. TAVR; transcatheter aortic valve replacement, SAVR; surgical aortic valve replacement.

FIGURE E1:
Funnel plots for assessment for publication bias for in-hospital outcomes. A) all-cause mortality, B) stroke, C) acute kidney injury, D) permanent pacemaker implantation, E) blood transfusion, F) vascular complication

FIGURE E2:
Forest plot of the leave-one-out analysis for A) in-hospital mortality, B) in-hospital stroke. Pooled estimates are calculated by omitting one study at a time. A study name indicates the omitted study.

ES, effect size (Hazard ratio); CI, confidence interval; Sig, p value; N, patients number

FIGURE E3:
Meta-regression of A) in-hospital mortality, B) in-hospital stroke across different study periods (median year of enrollment).

FIGURE E4:
Meta-regression of A) in-hospital mortality, B) in-hospital stroke for mean age at baseline.
| Author         | Publication Year | Study Period       | Dataset                        | Adjustment | Total | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR | TAVR | SAVR |
|----------------|------------------|--------------------|-------------------------------|------------|-------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Elbadawi      | 2019             | 2012-2016          | National Inpatient Sample     | PSM        | 1950  | 975  | 975  | 65.7 | 65.2 | 40   | 36.4 | 64.6 | 64.6 | 29.7 | 30.8 | 20.5 | 20.5 | 32.3 | 25.6 | 19.5 | 24.1 | NA   | NA   |
| Mentias       | 2020             | 2015-2017          | Medicare                      | PSM        | 1398  | 699  | 699  | 72.2 | 72.8 | 40   | 40   | 88   | 88   | 36   | 37   | 17   | 16   | 38   | 38   | 27   | 28   | NA   | NA   |
| Husso         | 2021             | 2008-2017          | Finn Valve Registry           | PSM        | 150   | 75   | 75   | 75.8 | 75.7 | 44   | 45.3 | NA   | NA   | 21.3 | 14.7 | NA   | NA   | NA   | NA   | NA   | NA   | 4.1  | 4    |
| Majmunder     | 2022             | 2016-2018          | Nationwide Readmission Database | PSM       | 2786  | 1393 | 1393 | 68.3 | 68.1 | 37.8 | 38.4 | 78.8 | 75.6 | 28   | 29.4 | 36.8 | 34.3 | 31.3 | 28.7 | 23.8 | 23.8 | NA   | NA   |

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PSM = propensity score match, TAVR = transcatheter aortic valve replacement, SAVR = surgical aortic valve replacement, NA = not available, COPD = chronic obstructive pulmonary disease, TIA = transient ischemic attack, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, STS PROM = Society of Thoracic Surgeons predicted risk of mortality.
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<tr>
<th>Author</th>
<th>Year</th>
<th>Stroke</th>
<th>Paravalvular Leak</th>
<th>Blood Transfusion</th>
<th>Vascular Complications</th>
<th>Acute Kidney Injury</th>
<th>Permanent Pacemaker Placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbadawi</td>
<td>2019</td>
<td>ICD-9 or ICD-10 codes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>as follows</td>
<td>CCS-109</td>
<td>ICD-9 or ICD-10 codes as follows</td>
<td>99.01-99.09 30243N0 30243N1 30243P0 30243P1 30243H0 30243H1 30240N0 30240N1 30240P0 30240P1 30230N0 30230N1 30230P0 30230P1 30233N0 30233N1 30233P0 30233P1</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mentias</td>
<td>2020</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hasso</td>
<td>2021</td>
<td>VARC 2</td>
<td>Transthoracic echocardiogram before discharge</td>
<td>bleeding requiring any blood transfusion</td>
<td>VARC 2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Majmunder</td>
<td>2022</td>
<td>ICD-9 or ICD-10 codes</td>
<td>T8203, T82223</td>
<td>ICD-9 or ICD-10 codes as follows</td>
<td>T8203, T82223</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

KDIGO criteria: postoperative increase of creatinine ≥ 1.5 times, increase of creatinine ≥ 26.5 mmol/L, or need for renal replacement therapy

VARC-2, Valve Academic Research Consortium-2; NA, not available; KDIGO, Kidney Disease: Improving Global Outcomes; ICD, International Classification of Diseases
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Period</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbadawi</td>
<td>2019</td>
<td>2012-2016</td>
<td>age &lt; 18 years, concomitant aortic root repair, CABG, other valvular heart surgeries, or atrial or ventricular septal defect repair, isolated aortic regurgitation</td>
</tr>
<tr>
<td>Mentias</td>
<td>2020</td>
<td>2015-2017</td>
<td>concomitant mitral valve surgery</td>
</tr>
<tr>
<td>Hussu</td>
<td>2021</td>
<td>2008-2017</td>
<td>age &lt; 18 years, previous surgical or transcatheter intervention on the aortic valve, acute endocarditis, isolated aortic valve regurgitation, or major concomitant other valve or thoracic aortic procedures</td>
</tr>
<tr>
<td>Majumdar</td>
<td>2022</td>
<td>2016-2018</td>
<td>age &lt; 18 years, concomitant CABG, mitral, pulmonary, and tricuspid valve surgeries, atrial or ventricular septal defect repair, and aortic root surgery</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting
| Author       | Publication Year | Study Period | Dataset                              | Adjustment | Patient Number (n) | Total TAVR | SAVR TAVR | SAVR SAVR | TAVR SAVR | SAVR TAVR | SAVR SAVR | TAVR SAVR | TAVR SAVR | SAVR TAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR | TAVR SAVR | SAVR SAVR |
|-------------|------------------|--------------|-------------------------------------|------------|--------------------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Elbadawi    | 2019             | 2012-2016    | National Inpatient Sample           | PSM        | 35956              | 1055      | 30840     | 66.2   | 56.9   | 38.9   | 30       | 65.4   | 61.9   | 31.3   | 16.5   | 21.8   | 17       | 32.2   | 16       | 20.9   | 6.1     | NA       | NA       |
| Mentias     | 2020             | 2015-2017    | Medicare                            | PSM        | 4061               | 1054      | 3007      | 74.7   | 69.9   | 42.1   | 35       | 90.4   | 80.3   | 41.2   | 26.2   | 20.5   | 9        | 44.3   | 23.9   | 37      | 13.6    | NA       | NA       |
| Husso       | 2021             | 2008-2017    | Finn Valve Registry                 | PSM        | 1023               | 103       | 920       | 77.1   | 70.9   | 41.7   | 42       | NA     | NA     | 27.2   | 19.2   | NA     | NA       | 25.2   | 13.7   | NA     | NA      | 4.9      | 3.7      |
| Majmunder   | 2022             | 2016-2018    | Nationwide Readmission Database     | PSM        | 17068              | 1629      | 15439     | 69.6   | 58.5   | 36.3   | 31.2     | 80.2   | 68.1   | 30.4   | 25.2   | 37.3   | 30.8     | 32.5   | 17.3   | 27.9   | 8.1      | NA       | NA       |

<table>
<thead>
<tr>
<th>Stroke/TIA (%)</th>
<th>Peripheral artery disease (%)</th>
<th>Prior CABG (%)</th>
<th>Prior PCI (%)</th>
<th>EuroSCORE II</th>
<th>STS PROM</th>
<th>Bicuspid aortic valve type</th>
<th>TAVR access</th>
<th>TAVR Valve used</th>
<th>Concomitant procedure with SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>4.1</td>
<td>27.5</td>
<td>30.5</td>
<td>13.7</td>
<td>1.2</td>
<td>TAVR</td>
<td>SAVR</td>
<td>TAVR SAVR</td>
<td>TAVR</td>
</tr>
<tr>
<td>14.4</td>
<td>8.2</td>
<td>37.7</td>
<td>38</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
<td>3.3</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9.7</td>
<td>4.7</td>
<td>9.7</td>
<td>7.4</td>
<td>13.6</td>
<td>1.3</td>
<td>18.4</td>
<td>6.6</td>
<td>4.8</td>
<td>3</td>
</tr>
<tr>
<td>7.9</td>
<td>4.2</td>
<td>27.2</td>
<td>25.2</td>
<td>9.6</td>
<td>1.4</td>
<td>12.6</td>
<td>3.8</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

PSM = propensity score match, TAVR = transcatheter aortic valve replacement, SAVR = surgical aortic valve replacement, NA = not available, COPD = chronic obstructive pulmonary disease, TIA = transient ischemic attack, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, STS PROM = Society of Thoracic Surgeons predicted risk of mortality.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Period</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbadawi</td>
<td>2019</td>
<td>2012-2016</td>
<td>age, sex, race, diabetes mellitus, hypertension, obesity (defined as body mass index &gt;30 kg/m²), history of heart failure, chronic lung disease, peripheral artery disease, pulmonary circulation disorders, chronic liver disease, chronic kidney disease, chronic anemia, fluid or electrolyte disturbance, coagulopathy, hypothyroidism, smoking, implantable cardioverter-defibrillator, history of cardiac pacemaker, carotid artery disease, prior stroke, prior percutaneous coronary intervention, prior CABG, hospital bed size, hospital region, and hospital teaching status.</td>
</tr>
<tr>
<td>Mentias</td>
<td>2020</td>
<td>2015-2017</td>
<td>age, sex, race, hypertension, diabetes, heart failure, coronary artery, lung, kidney, liver, and peripheral arterial disease, atrial fibrillation, stroke, pulmonary hypertension, coronary revascularization, coagulopathy, anemia, weight loss, obesity, electrolyte abnormalities, psychosis, depression, drug and alcohol abuse, connective tissue disease, hypothyroidism, lymphoma, prior bleeding, gastrointestinal bleed, prior implantable cardioverter-defibrillator or pacemaker, sleep apnea, smoking, ascending aortic aneurysm, and frailty.</td>
</tr>
<tr>
<td>Husso</td>
<td>2021</td>
<td>2008-2017</td>
<td>age, sex, body mass index, hemoglobin, estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration equation, diabetes, stroke, pulmonary disease, atrial fibrillation, extracardiac arteriopathy, New York Heart Association class IV, Geriatric Frailty Status Scale 2–3, urgent/emergency procedure, prior pacemaker, acute heart failure within 60 days from the index procedure, prior cardiac surgery, prior percutaneous coronary intervention, left ventricular ejection fraction &lt; 50%, number of diseased vessels and STS score.</td>
</tr>
<tr>
<td>Majumdar</td>
<td>2022</td>
<td>2016-2018</td>
<td>age, sex, hypertension, diabetes, hyperlipidemia, peripheral vascular disease, stroke/TIA, chronic heart failure, atrial fibrillation, prior PCI, prior CABG, obesity, chronic pulmonary disease, chronic renal failure, chronic liver disease, smoking, carotid artery disease, pulmonary circulation disorder, history of pacemaker/defibrillator, hospital bed size, teaching status, hospital region, hospital procedure volume, type of admission.</td>
</tr>
</tbody>
</table>

CABG; coronary artery bypass grafting, TIA; transient ischemic attack, STS; Society thoracic surgeons, PCI; percutaneous coronary intervention
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Confounding</th>
<th>Selection of participants</th>
<th>Classification of interventions</th>
<th>Deviations from intended intervention</th>
<th>Missing data</th>
<th>Measurement of outcomes</th>
<th>Selection of the reported results</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbadawi</td>
<td>2019</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mentias</td>
<td>2020</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Husso</td>
<td>2021</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
<tr>
<td>Majmunder</td>
<td>2022</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
In-hospital Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratios</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.69</td>
<td>(0.40-1.20)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86</td>
<td>(0.64-1.14)</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>0.58</td>
<td>(0.38-0.88)</td>
</tr>
<tr>
<td>Blood Transfusion</td>
<td>0.25</td>
<td>(0.21-0.29)</td>
</tr>
<tr>
<td>Vascular Complication</td>
<td>0.58</td>
<td>(0.18-1.91)</td>
</tr>
<tr>
<td>Paravalvular Leak</td>
<td>1.56</td>
<td>(0.85-2.85)</td>
</tr>
<tr>
<td>Permanent Pacemaker Implantation</td>
<td>1.87</td>
<td>(1.23-2.84)</td>
</tr>
</tbody>
</table>

Favors TAVR n = 3142
Favors SAVR n = 3142
Records identified through PubMed/MEDLINE and EMBASE (n = 797)

- Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 435)

Records screened by title (n = 435)

- Records excluded after abstract analysis (n = 414)

Full-text articles assessed for eligibility (n = 19)

- Full-text articles excluded, with reason (n = 15)
  - Overlapping dataset (n = 1)
  - No outcomes of interest (n = 3)
  - No comparison (n = 5)
  - Review (n = 1)
  - Commentary (n = 1)
  - Meta-analysis (n = 4)

Studies included in qualitative synthesis (n = 4)

Studies included in quantitative synthesis (meta-analysis) (n = 4)
**A**  

In-hospital Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Elbadawi 2019</td>
<td>0</td>
<td>0.2542</td>
<td>37.5%</td>
<td>1.00 [0.61, 1.65]</td>
<td></td>
</tr>
<tr>
<td>Husso 2021</td>
<td>-1.3863</td>
<td>1.106</td>
<td>5.7%</td>
<td>0.25 [0.03, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Majmunder 2022</td>
<td>-0.9555</td>
<td>0.3702</td>
<td>27.8%</td>
<td>0.38 [0.19, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Mentias 2020</td>
<td>-0.0645</td>
<td>0.3554</td>
<td>28.9%</td>
<td>0.94 [0.47, 1.88]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**  

100.0%  

0.69 [0.40, 1.20]

Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 5.91$, df = 3 ($p = 0.12$); $I^2 = 49$

Test for overall effect: $Z = 1.30$ ($p = 0.19$)

---

**B**  

In-hospital Stroke

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Risk Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV, Random, 95% CI</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Elbadawi 2019</td>
<td>-0.2231</td>
<td>0.2966</td>
<td>25.1%</td>
<td>0.80 [0.45, 1.43]</td>
<td>2019</td>
</tr>
<tr>
<td>Mentias 2020</td>
<td>-0.1054</td>
<td>0.3205</td>
<td>21.5%</td>
<td>0.90 [0.48, 1.69]</td>
<td>2020</td>
</tr>
<tr>
<td>Husso 2021</td>
<td>-0.6931</td>
<td>0.688</td>
<td>4.7%</td>
<td>0.50 [0.13, 1.93]</td>
<td>2021</td>
</tr>
<tr>
<td>Majmunder 2022</td>
<td>-0.0931</td>
<td>0.2125</td>
<td>48.8%</td>
<td>0.91 [0.60, 1.38]</td>
<td>2022</td>
</tr>
</tbody>
</table>

**Total (95% CI)**  

100.0%  

0.86 [0.64, 1.14]

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.77$, df = 3 ($p = 0.86$); $I^2 = 0$

Test for overall effect: $Z = 1.05$ ($p = 0.29$)
All-cause Mortality during Follow-up

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mentias 2020</td>
<td>0.077</td>
<td>0.0763</td>
<td>65.4%</td>
<td>1.08 [0.93, 1.25]</td>
<td>2020</td>
</tr>
<tr>
<td>Husso 2021</td>
<td>-0.6931</td>
<td>0.4338</td>
<td>34.6%</td>
<td>0.50 [0.21, 1.17]</td>
<td>2021</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.83 [0.40, 1.70]

Heterogeneity: Tau² = 0.20; Chi² = 3.06, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.52 (P = 0.60)
### In-hospital Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>ES</th>
<th>95% CI</th>
<th>Sig.</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasawi 2019</td>
<td>0.55</td>
<td>0.26 / 1.16</td>
<td>0.117</td>
<td>4334</td>
</tr>
<tr>
<td>Husso 2021</td>
<td>0.73</td>
<td>0.41 / 1.31</td>
<td>0.297</td>
<td>6134</td>
</tr>
<tr>
<td>Majmunder 2022</td>
<td>0.93</td>
<td>0.63 / 1.39</td>
<td>0.737</td>
<td>3498</td>
</tr>
<tr>
<td>Mentias 2020</td>
<td>0.57</td>
<td>0.26 / 1.32</td>
<td>0.192</td>
<td>4886</td>
</tr>
</tbody>
</table>

### In-hospital Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>ES</th>
<th>95% CI</th>
<th>Sig.</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbasawi 2019</td>
<td>0.88</td>
<td>0.64 / 1.20</td>
<td>0.417</td>
<td>4334</td>
</tr>
<tr>
<td>Husso 2021</td>
<td>0.88</td>
<td>0.66 / 1.17</td>
<td>0.375</td>
<td>6134</td>
</tr>
<tr>
<td>Majmunder 2022</td>
<td>0.82</td>
<td>0.56 / 1.19</td>
<td>0.295</td>
<td>3498</td>
</tr>
<tr>
<td>Mentias 2020</td>
<td>0.84</td>
<td>0.61 / 1.17</td>
<td>0.306</td>
<td>4886</td>
</tr>
</tbody>
</table>
A Enrollment year and in-hospital mortality

Intercept: 170
Slope: -0.09
p = 0.727

B Enrollment year and in-hospital stroke

Intercept: -150
Slope: 0.07
p = 0.154
A Mean age and in-hospital mortality

Intercept: 2.85
Slope: -0.06
p = 0.700

B Mean age and in-hospital stroke

Intercept: 0.57
Slope: -0.01
p = 0.771