

SYSTEMATIC REVIEW AND META-ANALYSIS

Meta-Analysis of Stroke and Mortality Rates in Patients Undergoing Valve-in-Valve Transcatheter Aortic Valve Replacement

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BACKGROUND: During the past decade, the use of transcatheter aortic valve replacement (TAVR) was extended beyond treatment-naïve patients and implemented for treatment of degenerated surgical bioprosthetic valves. Selection criteria for either valve-in-valve (viv) TAVR or redo surgical aortic valve replacement are not well established, and decision making on the operative approach still remains challenging for the interdisciplinary heart team.

METHODS AND RESULTS: This review was intended to analyze all studies on viv-TAVR focusing on short- and mid-term stroke and mortality rates compared with redo surgical aortic valve replacement or native TAVR procedures. A structured literature search and review process led to 1667 potentially relevant studies on July 1, 2020. Finally, 23 studies fulfilled the inclusion criteria for qualitative analysis. All references were case series either with or without propensity score matching and registry analyses. Quantitative synthesis of data from 8509 patients revealed that viv-TAVR is associated with mean 30-day stroke and mortality rates of 2.2% and 4.2%, respectively. Pooled data analysis showed no significant differences in 30-day stroke rate, 30-day mortality, and 1-year mortality between viv-TAVR and comparator treatment (native TAVR [n=11 804 patients] or redo surgical aortic valve replacement [n=498 patients]).

CONCLUSIONS: This review is the first one comparing the risk for stroke and mortality rates in viv-TAVR procedures with native TAVR approach and contributes substantial data for the clinical routine. Moreover, this systematic review is the most comprehensive analysis on ischemic cerebrovascular events and early mortality in patients undergoing viv-TAVR. In this era with increasing numbers of bioprosthetic valves used in younger patients, viv-TAVR is a suitable option for the treatment of degenerated bioprostheses.

Key Words: aortic valve surgery ■ mortality ■ redo aortic valve replacement ■ stroke ■ valve-in-valve transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) procedures as well as implantation experiences increased rapidly since first TAVR in 2002.¹ Meanwhile, TAVR is a recommended treatment approach in high- and intermediate-risk patients with severe aortic stenosis.^{2,3} The latest randomized trials proved a noninferiority of TAVR even in low-risk patients in comparison to surgical aortic valve replacement (SAVR).⁴⁻⁶ During the past decade, the use of TAVR was extended beyond treatment-naïve patients

and implemented for treatment of failed surgical bioprosthetic valves.⁷ From the surgeon's perspective, the transcatheter approach remains controversial in these patients in an era with considerable experience in redo SAVR.⁸ This knowledge must be weighed against the high procedural risk of redo SAVR in even young and old patients.^{9,10} Selection criteria for either valve-in-valve (viv) TAVR or redo SAVR are not well established, and decision making still remains challenging for the

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CLINICAL PERSPECTIVE

What Is New?

- Valve-in-valve transcatheter aortic valve replacement demonstrates comparable or even lower 30-day stroke and mortality rate than redo surgical aortic valve replacement.
- The rate for early stroke and mortality in patients undergoing valve-in-valve transcatheter aortic valve replacement was not even elevated in comparison with a transcatheter aortic valve replacement cohort for native aortic stenosis.

What Are the Clinical Implications?

- In selected patients, valve-in-valve transcatheter aortic valve replacement is an appropriate treatment option.

Nonstandard Abbreviations and Acronyms

AVR	aortic valve replacement
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
viv	valve in valve

interdisciplinary heart team; this process is based on individual patient characteristics.^{2,3,11}

As peri-interventional mortality and stroke rates are 2 of the most impactful and likely assessable outcomes to judge the safety of the aortic valve replacement (AVR) procedure (either interventional or surgical), this review was intended to analyze all studies on viv-TAVR with respect to these end points. This review was intended to be the first one comparing the risk for stroke and mortality rates in viv-TAVR procedures with native TAVR approach.

The aim of this meta-analysis was to assess the impact of viv-TAVR on the stroke and mortality rates compared with (a) redo SAVR or (b) native TAVR procedures.

METHODS

This meta-analysis was conducted using a prespecified protocol and explicit reproducible plan for literature search and synthesis, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹² The data that support the findings of this study are available from the corresponding author on reasonable request. The study selection was independently performed by 2 reviewers (S.M. and M.M.). In case of any disagreement, this was resolved

by consensus with the senior author (T.S.). We included all trials fitting the following inclusion criteria: case series including at least 10 patients and case-control studies and randomized controlled trials reporting on ischemic cerebrovascular events and mortality after viv-TAVR. Articles published in either German or English were eligible for analysis. Case reports, case series with <10 patients, and publications written in other languages were excluded. Trials with no sufficient report on stroke or mortality data were excluded, too. We performed an electronic search of the bibliographic databases (Medline and Cochrane Database of Systematic Reviews) and hand searching of reference lists. We used the following search terms, “valve-in-valve TAVR,” “valve in valve TAVR,” “valve-in-valve TAVI (transcatheter aortic valve implantation),” “valve in valve TAVI,” “stroke,” “cerebral infarction,” and “embolism,” and connected these terms with Boolean operators.

Stroke incidence after AVR in general was preliminary defined as primary outcome of this review. We extracted data on the 30-day and 1-year stroke incidence. Secondary end point was death from any cause at 30 days and at 1 year. All data were collected from text, tables, and figures.

We collected the following data from the original trials: first author, year of publication, country, operation period, number of patients enrolled, patients' age, sex distribution, prosthesis type, prosthesis failure mechanism, study design, Society of Thoracic Surgeons score, stroke rates, and mortality rates.

Statistical Analysis

Random-effects meta-analyses were performed using the Mantel-Haenszel method for dichotomous data to estimate pooled risk ratios (RRs) and CIs. Weights were calculated by using Mantel-Haenszel methods. In a further step, the I^2 statistic to quantify possible heterogeneity was calculated (30%< I^2 <75%: moderate heterogeneity; I^2 >75%: considerable heterogeneity; Review Manager 5.3, Nordic Cochrane Centre, Cochrane Collaboration). We defined P <0.05 as a statistically significant difference. The level of evidence of the original trials was evaluated according to the criteria of the Oxford University.¹³ To assess the studies' quality, we judged the individual and overall risk of bias. Initially, we intended to use the risk of bias tool provided by the Cochrane Collaboration, but as we were only able to include nonrandomized and a relevant number of noncontrolled trials, we changed to the ROBINS-IAQ8 (Risk Of Bias In Non-randomized Studies - of Interventions) tool. The application of the ROBINS-IAQ8 tool has been described previously.¹⁴ Two reviewers independently judged the risk of bias according to the given criteria (S.M. and M.M.).

We did not obtain ethical approval for this meta-analysis because we did not collect data from individual human subjects.

RESULTS

The above search strategy led to 1667 studies in Medline (via PubMed) and 1 reference in the Cochrane Database of Systematic Reviews on July 1, 2020. After meticulous revision of the studies included, we defined 3 subgroups for qualitative and quantitative analyses:

1. Noncomparative case series and registries reporting on the outcome of patients undergoing viv-TAVR.
2. Case series and case-control studies comparing viv-TAVR with redo SAVR.
3. Case series comparing viv-TAVR with native TAVR.

Finally, 23 studies fulfilled the inclusion criteria for qualitative analysis (Figure 1). None of these was a randomized controlled trial. All references were case series either with or without propensity score matching and registry analyses (Tables 1–3). According to the criteria of the Oxford University, these references represent a level of evidence of 4.¹³ Twelve studies were included in quantitative synthesis.

Noncomparative Case Series and Registries Reporting on the Outcome of Patients Undergoing viv-TAVR

Eleven studies reporting on 8509 patients undergoing viv-TAVR could be included in the statistical analysis of noncomparative case series and registry data (Table 1).^{15–25} All studies have been published from 2010 to 2019. Surgically implanted bioprostheses had failed in the patients, and mechanisms of failure were regurgitation, stenosis, or both. The patients' age varied from 74 to 83.9 years, and they had a Society of Thoracic Surgeons score of 6.6% to 21.9%. Data on prior stroke events and history of atrial fibrillation were infrequently reported and heterogeneous. All but 2 studies defined stroke according to the VALVE Academic Research Consortium or the VALVE Academic Research Consortium-2 criteria.^{26,27}

Qualitative analysis revealed in-hospital stroke rates of 0% and mortality rates of 2.2% to 7.4%.^{15–18,20,24,25} Event rates after a 12-month period were only published by few author groups and were 4.4% to 5.9% for stroke. Corresponding rates for 1-year mortality ranged from 8.4% to 13.6%.^{17,18,22}

Quantitative synthesis with pooled data analysis resulted in a calculated 30-day stroke rate of 2.2% and a 30-day mortality rate of 4.2% after viv-TAVR (Table 1).

Case Series and Case-Control Studies Comparing viv-TAVR With Redo SAVR

Six studies reporting on 498 patients undergoing viv-TAVR (N=254) or redo SAVR (N=244) were eligible for statistical analysis (Table 2).^{28–33} There was a trend toward older patients in the viv-TAVR group (Table 2). Data on prior stroke or prior episodes of atrial fibrillation were infrequently reported. An amount of 8% to 14.1% of patients undergoing viv-TAVR and 0% to 12% of patients undergoing redo SAVR had a documented stroke in the individual patient history.^{28,31–33} Corresponding rates for prior atrial fibrillation or atrial flutter were 32% to 39% and 14% to 39%, respectively.^{28,32,33} None of the trials reported on anticoagulants used in patients with atrial arrhythmia. Four of these studies defined stroke according to the VALVE Academic Research Consortium-2 criteria.^{28,31–33} Patients with endocarditis of the aortic valve prosthesis were excluded from the trials. In 3 trials, patients in the open surgery group solely underwent AVR.^{28,29,31} In the remaining studies, concomitant coronary artery bypass grafting procedure or reconstruction of other valves than the aortic valve was permitted, but not frequently performed. Most patients in the redo SAVR group underwent isolated AVR.^{32,33}

A total of 3 of 226 participants treated with viv-TAVR and 4 of 214 patients undergoing redo SAVR experienced a stroke during the first 30 postoperative days (N=4 trials; RR, 0.86; 95% CI, 0.20–3.59; $P=0.83$; $I^2=0\%$; Figure 2A). None of the studies included reported sufficient data on the 1-year stroke incidence.

The 30-day mortality was 4.3% for patients undergoing viv-TAVR and 4.5% for patients undergoing redo SAVR. This difference was not significantly different between both groups (N=6 trials; RR, 0.90; 95% CI, 0.40–2.05; $P=0.80$; $I^2=0\%$; Figure 2B). The 1-year mortality rates were 13.3% and 13.6%, respectively (N=2 trials; RR, 0.98; 95% CI, 0.49–1.94; $P=0.94$; $I^2=0\%$; Figure 2C).

Case Series Comparing viv-TAVR With Native TAVR

Six studies reporting on 11 804 participants undergoing viv-TAVR (N=4052) and native TAVR (N=7752) were included in statistical analysis (Table 3).^{34–39} Akodad et al, Huczek et al, and Deharo et al reported prior stroke in 4.1% to 12% of patients undergoing viv-TAVR and 4.7% to 16% of patients undergoing native TAVR.^{36,38,39} Corresponding rates for prior atrial fibrillation or atrial flutter were 22.9% to 57.9% for viv-TAVR and 21.7% to 57.7% for native TAVR group.^{36–39} None of the trials reported on anticoagulants used in patients with atrial arrhythmia. Three studies provided data on

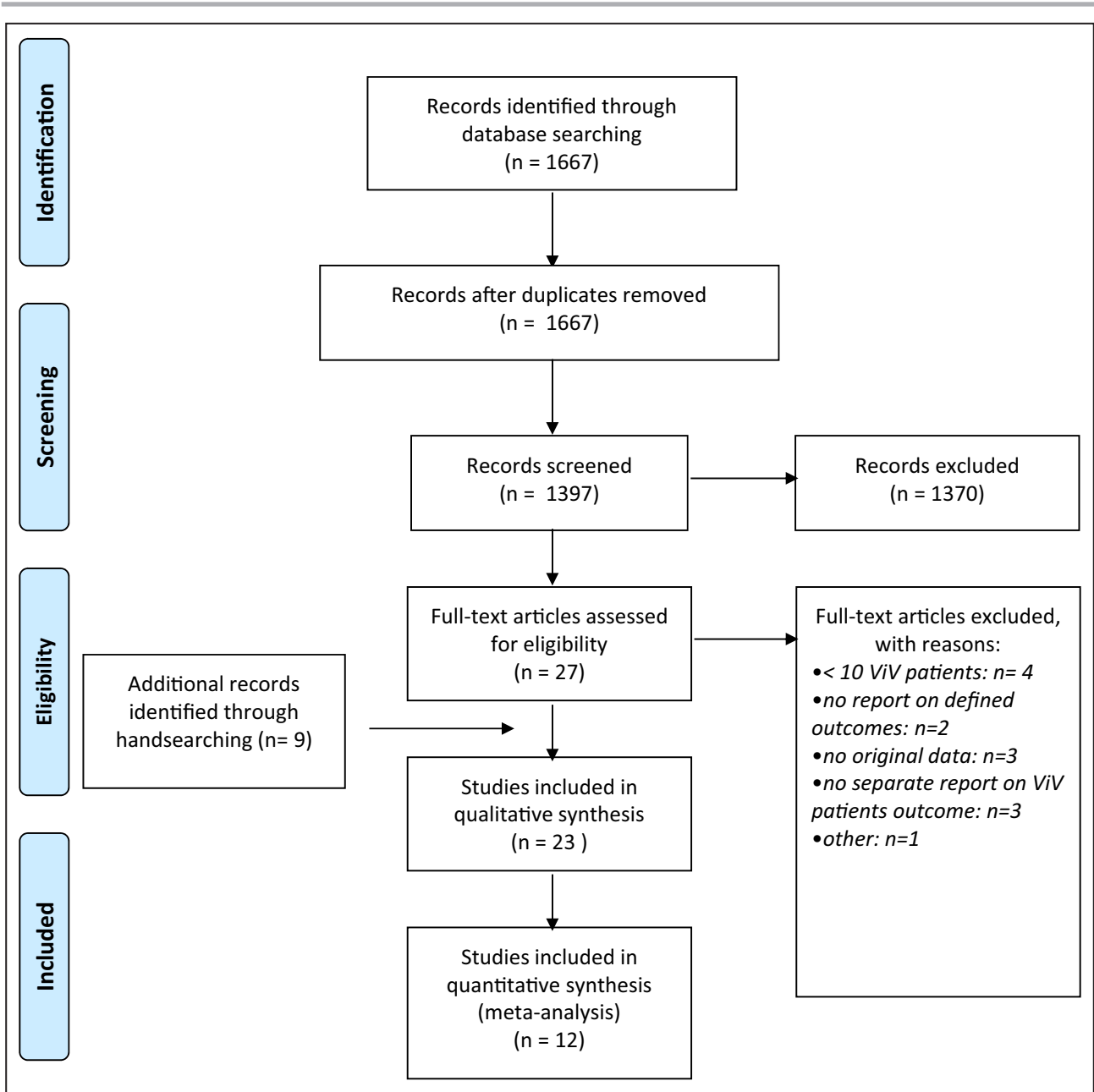


Figure 1. Flowchart diagram.
viv indicates valve in valve.

the outcome definition (VALVE Academic Research Consortium-2).^{36,38,39}

The 30-day stroke rate was 1.1% for patients undergoing viv-TAVR and 2.2% for patients undergoing native TAVR (N=5 trials; RR, 0.95; 95% CI, 0.58–1.58; $P=0.24$; $I^2=27\%$; Figure 3A). The stroke events after 1 year were only reported by Akodad et al, and in this cohort, 1 of 49 patients undergoing viv-TAVR and 1 of 83 patients undergoing native TAVR experienced stroke.³⁸ This difference was not statistically significant.³⁸

A total of 3.2% of patients treated with viv-TAVR and 4.9% of participants undergoing native TAVR died during

the first 30 days after operation (N=6 trials; RR, 0.87; 95% CI, 0.58–1.31; $P=0.10$; $I^2=46\%$; moderate heterogeneity; Figure 3B). The corresponding 1-year mortality rates were 7.7% and 13.5%, respectively (N=2 trials; RR, 1.20; 95% CI, 0.51–2.86; $P=0.68$; $I^2=0\%$; Figure 3C).

DISCUSSION

Main Findings

This systematic review is the most comprehensive analysis on stroke and mortality in patients undergoing

Table 1. Case Series and Registries With viv-TAVR Procedures

Authors, Studies, Year of Publication	Countries	Operation Period	Patients	viv Prosthesis	Failure Mechanism of Bioprosthesis	Study Design	Median Age, y	Sex: Male Patients, %	STS Score, %	Outcome Definition	30-d Stroke (Events)	1-y Stroke (Events)	30-d Mortality (Events)	1-y Mortality (Events)
Kempfert et al, 2010	Germany	3/2007–12/2009	11	Edwards Sapien	...	Single-center, retrospective case series	78	63.6	7.2	0	...
Pasic et al, 2011	Germany	Since 10/2008	14	Edwards Sapien	Regurgitation and/or stenosis	Single-center, retrospective case series	73.3	64.3	21.9	0	...
Linke et al, 2012	Germany	...	27	Medtronic: Core Valve	Regurgitation and/or stenosis	Multicentric case series	74.8	70	...	VARC	2	...	2	...
Ihberg et al, 2013, Nordic viv registry	Finland, Denmark, Sweden, Norway	5/2008–1/2012	45	Medtronic: Core Valve, Edwards: Sapien	Regurgitation and/or stenosis	Multicentric, retrospective registry analysis	80.6*	58*	15	VARC	1	...	2	...
Duncan et al, 2015	United Kingdom	10/2009–6/2014	22	Medtronic: Core Valve	Regurgitation	Single-center, case series	74	63.6	14	VARC-2	0	...	0	3
Webb et al, 2017, PARTNER 2	United States	1/2012–12/2014	365	Edwards Sapien XT	Regurgitation and/or stenosis	Multicentric, prospective case series	78.9*	64.1	9.1*	VARC-2	10	16	10	43
Ribeiro et al, 2018, VIVID	Worldwide	4/2007–5/2016	1612	Mix	Regurgitation and/or stenosis	Multicentric, retrospective, and prospective registry analysis	77.8	57.9	9.5	VARC-2	22/1566	...	74/1545	...
Scholtz et al, 2018	Germany	2/2009–12/2016	37	Medtronic: CoreValve, Evolut R	Regurgitation and/or stenosis	Single-center, retrospective case series	83.9*	18.9	7.2	VARC-2	1	...
Huded et al, 2019, STS/ACC registry	United States	11/2011–5/2017	6147	Mix	Regurgitation and/or stenosis	Multicentric, retrospective registry analysis	VARC-2	143
Tchéché et al, 2019, VIVA registry	Europe	...	202	Medtronic: CoreValve, Evolut R	Regurgitation and/or stenosis	Multicentric, prospective case series/registry	79.9*	47.5	6.6*	VARC-2	6	12	5	17
Stankowski et al, 2019	Germany	1/2010–7/2018	27	Medtronic: CoreValve, Evolut R	...	Single-center, retrospective case series	81	14.8	16.6	VARC-2	0	...	3	0
Pooled data analysis														

... Indicates data not reported; ACC, American College of Cardiology; PARTNER, Placement of Aortic Transcatheter Valves; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TVT, transcatheter valve therapy; VARC, VALVE Academic Research Consortium; viv, valve in valve; and VIVA, valve in valve; VIVID, valve in valve international data.
*Mean instead of median.

Table 2. Studies Comparing viv-TAVR and rSAVR Procedures

Authors, Studies, Year of Publication	Countries	Operation Period	Patients	viv Prosthesis	Failure Mechanism of Bioprosthesis	Study Design	Median Age, y	Sex: Male Patients, %	STS Score, %	Outcome Definition	30-d Stroke (Events)	1-y Stroke (Events)	30-d Mortality (Events)	1-y Mortality (Events)
Erlbach et al, 2015	Germany	1/2001–10/2014	102 viv: 50 rSAVR: 52	Mix	Regurgitation and/or stenosis	Single-center, retrospective case series	viv: 78.1 rSAVR: 66.2	viv: 54 rSAVR: 73	...	VARC-2	viv: 2 rSAVR: 1	...	viv: 2 rSAVR: 0	...
Ejiofor et al, 2016	United States	1/2002–5/2015	44 viv: 22 rSAVR: 22	Mix	...	Retrospective case series, bicentric study, propensity-matched analysis	viv: 75 rSAVR: 74.5	viv: 63.6 rSAVR: 59.1	viv: 7.4 rSAVR: 7.7%	...	viv: 0* rSAVR: 2*	...	viv: 0 rSAVR: 1	...
Santarpino et al, 2016	Germany	Since 2010	14 viv: 6 rSAVR: 8	Edwards Sapien, Sapien XT	...	Single-center, retrospective case series	viv: 80.2 rSAVR: 78.8	viv: 66.7 rSAVR: 25	viv: 0† rSAVR: 0†	...	viv: 0 rSAVR: 0	...
Silvaschi et al, 2017	Europe	2002–2015	130 viv: 71 rSAVR: 59	...	Regurgitation and/or stenosis	Bicentric study, retrospective case-control study	viv: 78.6 rSAVR: 72.9	viv: 57.7 rSAVR: 61	...	VARC-2	viv: 0 rSAVR: 2	...	viv: 3 rSAVR: 3	...
Spaziano et al, 2017	Europe, Canada	2007–2015	156 viv: 78 rSAVR: 78	Mix	Regurgitation and/or stenosis	Retrospective case series, bicentric study, propensity-matched analysis	viv: 78 rSAVR: 77.4	viv: 50 rSAVR: 56	viv: 7.2 rSAVR: 5.8	VARC-2	viv: 1 rSAVR: 0	...	viv: 3 rSAVR: 5	viv: 9 rSAVR: 10
Grubitzsch et al, 2017	Germany	2010–2015	52 viv: 27 rSAVR: 27	Mix	Regurgitation and/or stenosis	Retrospective case series	viv and rSAVR: 72.3	viv and rSAVR: 77	...	VARC-2	viv: 0 rSAVR: 1	...	viv: 3 rSAVR: 2	viv: 5 rSAVR: 4

Within the table, viv indicates patients treated by viv-TAVR; and rSAVR, patients treated by rSAVR. ... Indicates data not reported; rSAVR, redo surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; VARC, VALVE Academic Research Consortium; and viv, valve in valve.

*Overall stroke events during follow-up period.

†Stroke rates during in-hospital stay.

Table 3. Studies Comparing viv-TAVR and nTAVR

Authors, Studies, Year of Publication	Countries	Operation Period	Patients	viv Prosthesis	Failure Mechanism of Bioprosthesis	Study Design	Median Age, y	Sex: Male Patients, %	STS Score, %	Outcome Definition	30-d Stroke (Events)	1-y Stroke (Events)	30-d Mortality (Events)	1-y Mortality (Events)
Makkar et al, PARTNER, 2013	United States	...	2554 viv: 63 nTAVR: 2491	Edwards Sapien	Regurgitation and/or stenosis	Multicenter study, observational case series	viv: 83.2 nTAVR: 84.5	viv: 81 nTAVR: 51.6	viv: 11.4 nTAVR: 11.5	...	viv: 3 nTAVR: 81	...	viv: 6 nTAVR: 148	...
Stundl et al, 2016	Germany	2011–2013	141 viv: 16 nTAVR: 125	Medtronic Core Valve	...	Single-center study, retrospective case series	viv: 80.1 nTAVR: 80.6	viv: 68.8 nTAVR: 53.6	viv: 6.2 nTAVR: 6.3	...	viv: 0* nTAVR: 3*	...	viv: 2 nTAVR: 6	viv: 4 nTAVR: 27
Huczek et al, 2018, POL-TAVI	Poland	4/2010–5/2016	45 viv: 25 nTAVR: 45	Mix	Regurgitation and/or stenosis	Multicentric, retrospective case series	viv: 65.6/75.6† nTAVR: 80.1	viv: 55/60† nTAVR: 58	...	VARC-2	viv: 2 nTAVR: 2	...	viv: 0 nTAVR: 2	0
Tuzou et al, TVT registry, 2018	United States	11/2011–6/2016	3409 viv: 1150 nTAVR: 2259	Mix	Regurgitation and/or stenosis	Multicenter study, retrospective case series	viv: 79 nTAVR: 84	viv: 60.8 nTAVR: 61	viv: 6.9 nTAVR: 6.8	...	viv: 20 nTAVR: 68	...	viv: 33 nTAVR: 108	...
Akoadad et al, 2019	France	2013–2017	132 viv: 49 nTAVR: 83	Mix	Regurgitation and/or stenosis	Bicentric study, retrospective case series	viv and nTAVR: 82.8	viv and nTAVR: 44.7	viv and nTAVR: 5.2	VARC-2	viv: 1 nTAVR: 1	viv: 1 nTAVR: 1	viv: 1 nTAVR: 0	viv: 1 nTAVR: 2
Deharo et al, 2020	France	2010–2019	5498 viv: 2749 nTAVR: 2749	Mix	Regurgitation and/or stenosis	Multicenter study, retrospective cohort study	viv: 80.75 nTAVR: 80.59	viv: 49.3 nTAVR: 51.3	...	VARC-2	viv: 18 nTAVR: 14	...	viv: 87 nTAVR: 116	...

Within the table, viv indicates patients treated by viv TAVR; and nTAVR, patients treated by nTAVR. ... Indicates data not reported; ACC, American College of Cardiology; nTAVR, first (native) TAVR; PARTNER, Placement of Aortic Transcatheter Valves; POL-TAVI: Polish National TAVI Registry; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TVT, transcatheter valve therapy; VARC, VALVE Academic Research Consortium; and viv, valve in valve; VIVA, valve in valve; VIVID, valve in valve international data.

*Stroke rates during in-hospital stay.

†Patients were divided into stentless and stented prosthesis groups.

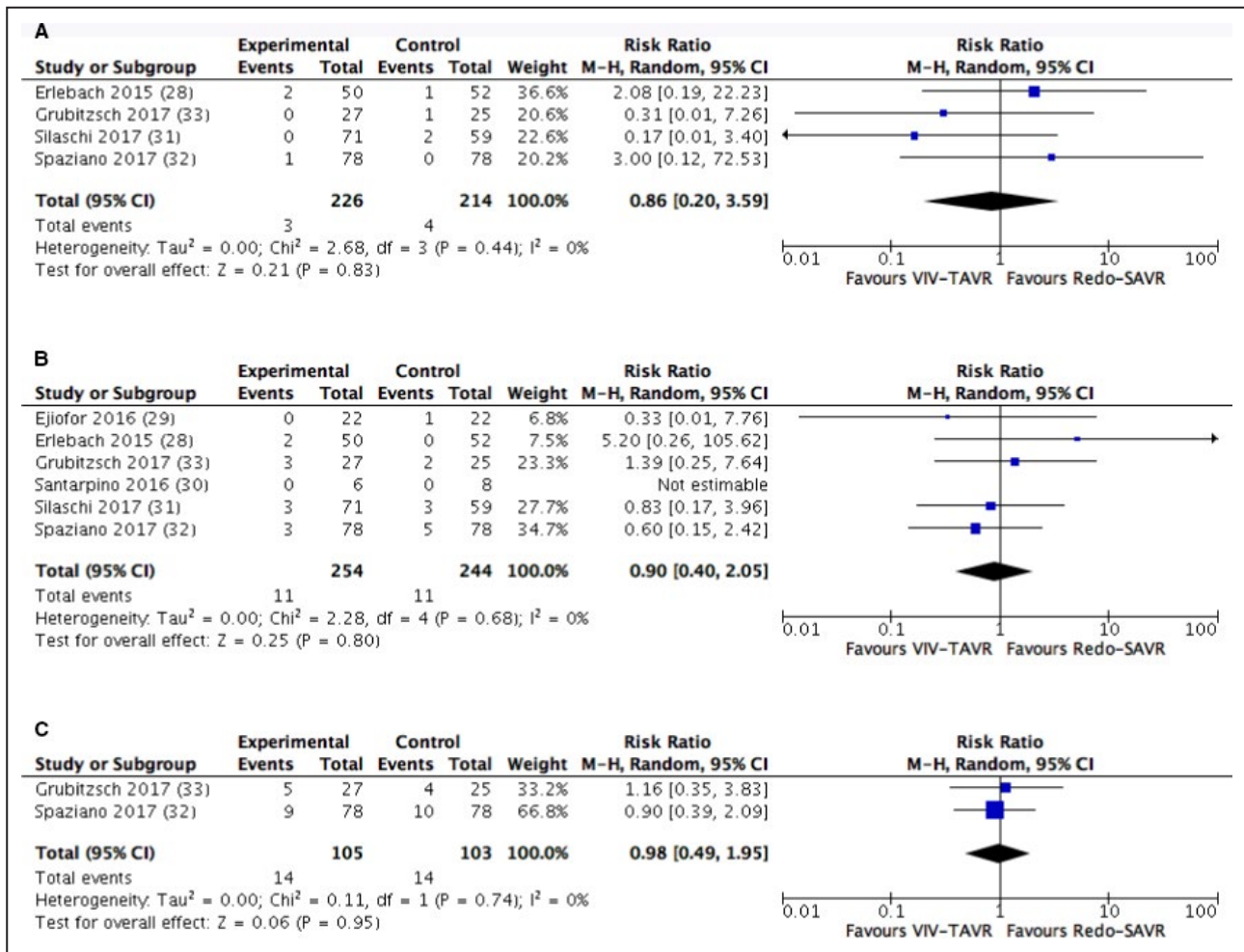


Figure 2. Comparison of valve-in-valve (viv) transcatheter aortic valve replacement (TAVR) vs redo surgical aortic valve replacement (SAVR). **A**, viv-TAVR vs redo SAVR, 30-day stroke incidence. **B**, viv-TAVR vs redo SAVR, 30-day mortality. **C**, viv-TAVR vs redo SAVR, 1-year mortality. M-H indicates Mantel-Haenszel.

viv-TAVR. Within this article, case series, registries, and trials comparing viv-TAVR with either redo SAVR or native TAVR are included.

Main findings in this review are as follows:

- viv-TAVR is associated with mean 30-day stroke and mortality rates of 2.2% and 4.2%, respectively, based on registry data.
- Quantitative analysis showed no significant differences in 30-day stroke rate, 30-day mortality, and 1-year mortality between viv-TAVR and redo SAVR (Figure 4).
- This review is the first one comparing the risk for stroke and mortality rates in viv-TAVR procedures with native TAVR approach.
- Quantitative analysis showed no significant differences in 30-day stroke rate, 30-day mortality, and 1-year mortality between viv-TAVR and native TAVR.

Agreement and Disagreement With Other Reviews

Four systematic reviews analyzing studies dealing with the outcome of patients undergoing either viv-TAVR or redo SAVR were identified (Table 4).⁴⁰⁻⁴³ In conclusion and consistent with the current meta-analysis, there were no significant differences observed in stroke or 30-day mortality rates in these reviews. In comparison with Neupane et al and Gozdek et al, we were able to include additional studies during the review process and statistical analysis.^{40,42} In distinction to Tam et al and Nalluri et al, we defined the stroke outcome more sensitive by differentiation between 30-day and 1-year event data.^{41,43} The inclusion of additional studies and the precise methodological approach resulted in a more solid and detailed review.

No other meta-analysis comparing viv-TAVR with native TAVR was identified. This review is the first one comparing

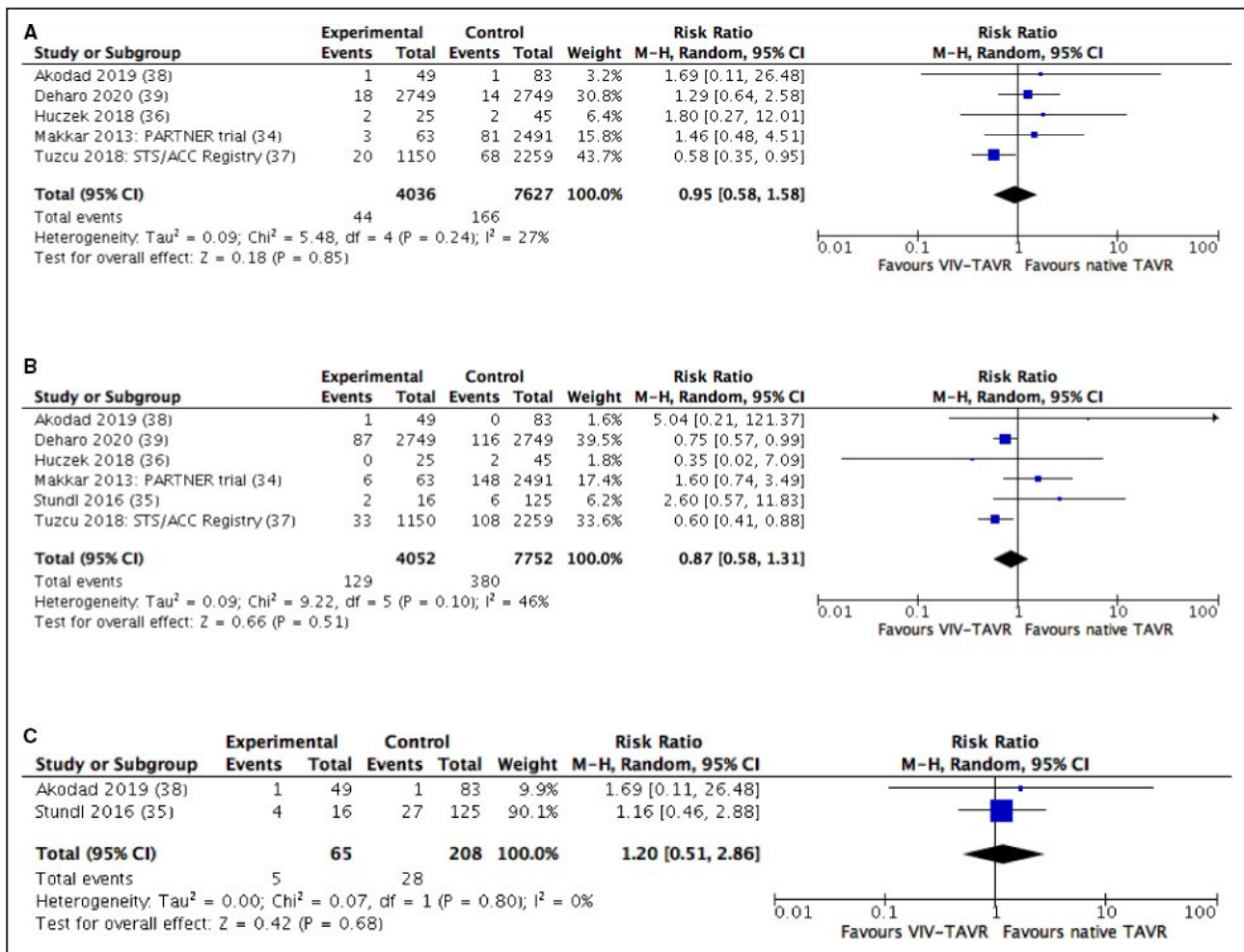


Figure 3. Comparison of valve-in-valve (viv) transcatheter aortic valve replacement (TAVR) vs native TAVR. **A**, viv-TAVR vs native TAVR, 30-day stroke incidence. **B**, viv-TAVR vs native TAVR, 30-day mortality. **C**, viv-TAVR vs native TAVR, 1-year mortality. ACC indicates American College of Cardiology; M-H, Mantel-Haenszel; PARTNER, Placement of Aortic Transcatheter Valves; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

the risk for stroke and mortality rates in these cohorts and contributes substantial data for the clinical routine.

Clinical Implications

Stroke Prevention

Cerebral embolic events following TAVR might stay silent, but each clinically relevant stroke is meaningful for the individual patient. Stroke was previously described as an independent risk factor for increased mortality following TAVR.⁴⁴ Discussions about higher stroke rates for viv procedures are often raised, but larger or randomized studies on stroke rates for viv-TAVR or a comparison to native TAVR procedures is missing. The argument on the stroke incidence often leads to a debate about the need for embolic protection devices.

Studies on cerebral protection were mainly performed for native aortic stenosis and demonstrated that cerebral protection seems to be beneficial in these patients.⁴⁵⁻⁴⁸ Predominantly, the filtered debris contained

thrombus, valve tissue, aortic wall, or calcification, resulting from structures that were touched during the TAVR procedure.^{45,49-51} Debris material captured by an embolic protection device during viv-TAVR is similar to the findings after native TAVR procedures.⁵² Higher stroke rates following viv-TAVR attributable to friable material from degenerated bioprostheses cannot be concluded from these data. Therefore, on the basis of the stroke rates presented above, the discussion on embolic protection seems not to be different for viv-TAVR than in native TAVR procedures (Figure 3A). The individual patient stroke risk following viv-TAVR might depend on the history of stroke, supraventricular arrhythmia, and cerebrovascular risk factors.

Surgical Mortality

The viv-TAVR approach is associated with a low 30-day mortality rate in the current analysis, but as presented above, the use of this technique is restricted to

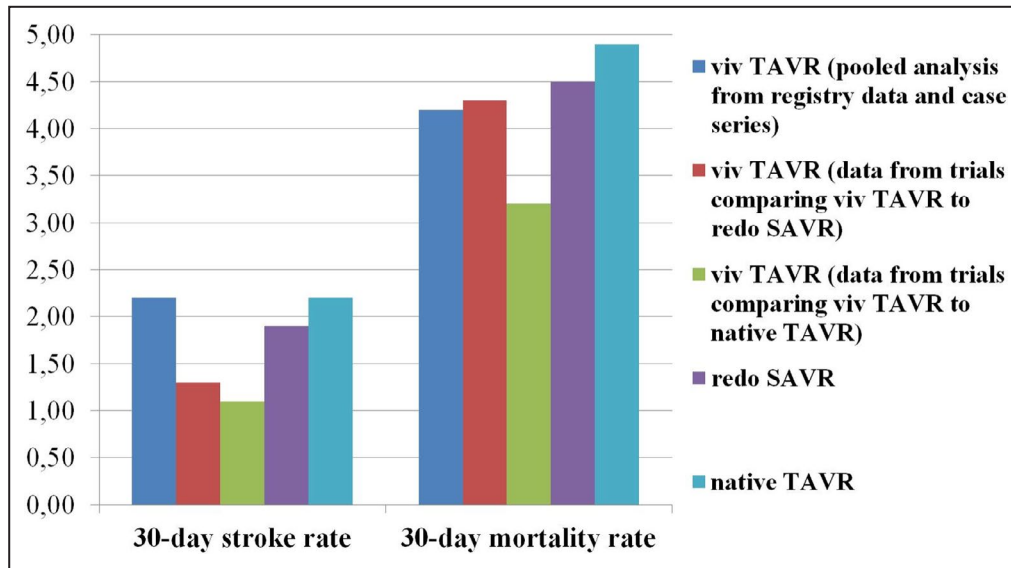


Figure 4. The 30-day stroke and mortality rates following valve-in-valve (viv) transcatheter aortic valve replacement (TAVR).

SAVR indicates surgical aortic valve replacement.

several indications. In the original trials analyzed in this systematic review, viv-TAVR was used for treatment of degenerated valves with stenosis, regurgitation, or both. Endocarditis was a contraindication for TAVR approach in the registries and the trials included in this meta-analysis.^{15-25,28-39}

The evidence on operative or early mortality in patients undergoing redo SAVR is mainly based on retrospective series.^{9,53-55} Overall, the early or operative mortality rates in patients undergoing surgical redo AVR ranged between 5.2% and 6.8%.^{9,53-55} Mortality rates of <6% were described in studies including younger patients.^{9,55} In detail, Leontyev et al analyzed a patient cohort with a median age of 58.1 years and Vogt et al reported surgical mortality for a subgroup of patients with a median age of 56 years.^{9,55}

Besides a younger age, elective surgery and other indications than endocarditis were identified as beneficial prognostic factors.^{9,53} In contrast, the need for

aortic root surgery increases the patients’ surgical mortality.⁹

An immediate transfer of these data from surgical series to the current results is not appropriately feasible as young patients or individuals with aortic disease do not represent the usual viv-TAVR cohort. On the other hand, one might carefully draw the following conclusions from these data:

- Even in an era with increasing number of viv-TAVR procedures, redo SAVR is an irreplaceable approach for selected patients, especially for those experiencing endocarditis or concomitant thoracic aortic disease.
- In patients with the need for reoperation for solely aortic valve prosthesis dysfunction, viv-TAVR offers low early mortality rates in comparison with redo SAVR (Figure 2B).

Current guidelines discuss the implantation of bio-prostheses even in younger patients as a therapeutic

Table 4. Results From Other Reviews Comparing TAVR With Redo SAVR

Studies	Included Trials	Included Patients	Main Results
Neupane et al	4 trials	viv-TAVR: N=227 Redo SAVR: N=262	Overall stroke rate: OR, 1.00; 95% CI, 0.28–3.59; no significant difference 30-d Mortality: OR, 1.08; 95% CI, 0.44–2.62; no significant difference
Tam et al	6 trials	viv-TAVR: N=204 Redo SAVR: N=192	Overall stroke rate: RR, 0.73; 95% CI, 0.18–3.02; no significant difference 30-d Mortality: RR, 0.78; 95% CI, 0.33–1.84; no significant difference
Gozdek et al	5 trials	viv-TAVR: N=176 Redo SAVR: N=166	30-d Stroke rate: RR, 0.62; 95% CI, 0.16–2.42; no significant difference 30-d Mortality: RR, 1.29; 95% CI, 0.44–3.78; no significant difference
Nalluri et al	6 trials	viv-TAVR: N=255 Redo SAVR: N=339	Overall stroke rate: OR, 0.64; 95% CI, 0.17–2.41; no significant difference 30-d Mortality: OR, 0.97; 95% CI, 0.39–2.39; no significant difference

OR indicates odds ratio; RR, risk ratio; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and viv, valve in valve.

Table 5. RoB Assessment (ROBINS-I)

Studies	Confounding	Selection of Participants	Classification of Interventions	Deviations From Intended Interventions	Missing Data	Outcome Measurement	Selection of Reported Results
Case Series and Case-Control Studies Comparing viv-TAVR With Redo SAVR							
Erlebach et al, 2015	Serious RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Ejfor et al, 2016	Moderate RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Santarpino et al, 2016	Serious RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Silaschi et al, 2017	Serious RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Spaziano et al, 2017	Low RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Low RoB	Moderate RoB
Grubitzsch et al, 2017	Serious RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Case Series Comparing viv-TAVR With Native TAVR							
Makkar et al, 2013	Serious to moderate RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	Low RoB
Stundl et al, 2016	Critical RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Huczek et al, 2018	Moderate RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Tuzcu et al, 2018	Low to moderate RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	Low to moderate RoB
Akodad et al, 2019	Low to moderate RoB	Moderate RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	No sufficient information
Deharo et al, 2020	Low to moderate RoB	Moderate to serious RoB	Moderate RoB	Low RoB	No sufficient information	Moderate RoB	Moderate RoB

RoB indicates risk of bias; ROBINS-I, Risk Of Bias In Non-randomized Studies - of Interventions; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and viv, valve in valve.

concept.² Consequently, there will be a need of a redo intervention strategy in these patients in the future.² viv-TAVR might be a feasible treatment approach in this cohort.

Limitations/Risk of Bias

This systematic review and meta-analysis underlies methodological and content-related limitations. First, only a low level of evidence could be identified. Because randomized controlled trials are still missing, case series or registry data represent the current evidence of cerebrovascular events and mortality in patients undergoing viv-TAVR.

Different strategies were used to minimize the risk of bias during the review process. All published abstracts and full-text articles were considered, but unpublished data (eg, from ongoing trials) were not included. We planned to calculate not only forest, but also funnel plots to assess publication bias. As we did not include the minimum of 10 studies in statistical analysis of any outcome, funnel plot calculation was not appropriately feasible. Nevertheless, we assess the risk of publication bias as moderate to low, overall. We were able to extract valid data from registries and even data with equal stroke and mortality rates for viv-TAVR and comparator treatment. This does not rule out publication bias, but bearing these data in mind, we suspect only a slight effect.

Moreover, our analysis is affected by a language bias, because we only considered articles published in English and German. Furthermore, this analysis might be affected by a substantial performance bias, because the anticoagulatory treatment during the perioperative and postoperative period was not reported in all studies included. In addition to the nature of a review, the original studies were designed heterogeneously, with potential differences in baseline data, different valve prostheses, different risk profiles (Society of Thoracic Surgeons score), and possible difficult measurable differences in patients' clinical conditions (Tables 2 and 3). To evaluate the individual risk of bias of each study, we used the ROBINS-I tool, as described in the Methods section. Results are summarized in Table 5. In summary, most studies included comparing viv-TAVR with redo SAVR were uncontrolled case series and resulted in serious to moderate risk of bias in most categories (Table 5). Thoroughly, we rate the overall risk of bias for these studies as "moderate."

In the evaluation of viv-TAVR versus native TAVR, data from controlled trials (eg, case-control studies with matched pairs) were included. Nevertheless, we judge the overall risk of bias as moderate, because we observed moderate risk of bias for most categories and no sufficient information for management of missing data or selection of reported outcomes in some trials (Table 5).

Finally, we decided to not perform any form of additional testing to address heterogeneity (eg, subgroup or sensitivity analysis) because of low event rates in total.

In addition, a source of detection bias was identified, because 7 trials did not describe the precise definition of stroke (Tables 1–3).

To produce reliable data on our research question randomized or at least larger, controlled prospective trials are needed to preserve more valid results.

CONCLUSIONS

Viv-TAVR is an appropriate alternative to redo SAVR, referring to the comparable or even lower 30-day stroke and mortality rate. The rate for early stroke and mortality in patients undergoing viv-TAVR was not even elevated in comparison with a TAVR cohort for native aortic stenosis.

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