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Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Low-risk Patients: A Meta-Analysis Based on a 2-Year Follow-Up

META-ANALYSIS

ABSTRACT

Background: Previous studies have shown that transcatheter aortic valve implantation is the best alternative therapy to surgical aortic valve replacement in high-risk surgical patients with aortic stenosis. However, it is not clear whether transcatheter aortic valve implantation can be utilized in low-risk surgical patients with aortic stenosis. This study aimed to evaluate the safety and efficacy of transcatheter aortic valve implantation in low-risk patients.

Methods: From the outset of our initiative until April 2022, PubMed, EMBASE, and the Cochrane database were thoroughly searched, yielding the selection of 3 randomized controlled trials including 2644 patients with aortic stenosis, to assess outcome measures at distinct follow-up time.

Results: The mean Society of Thoracic Surgeons Predicted Risk of Mortality score of patients was 2.2. At the 30-day and 1-year follow-up, transcatheter aortic valve implantation was associated with a lower incidence of all-cause mortality, cardiovascular mortality, acute kidney injury (stage 2 or 3), life-threatening or significant bleeding, and new atrial fibrillation but an increased risk of permanent pacemaker implantation. At the 2-year follow-up, transcatheter aortic valve implantation only had an advantage in new atrial fibrillation (relative risk, 0.27; 95% CI, 0.14-0.51; $P < .0001$), with no significant difference in all-cause mortality or cardiovascular mortality.

Conclusions: For low-risk surgical patients with aortic stenosis, compared to surgical aortic valve replacement, transcatheter aortic valve implantation was associated with lower all-cause mortality at 30-day follow-up and lower cardiovascular mortality at 1-year follow-up. Except for the advantages in new atrial fibrillation, transcatheter aortic valve implantation had no significant impact on mortality at 2-year follow-up.

Keywords: TAVI, SAVR, aortic stenosis, meta-analysis, low risk

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INTRODUCTION

Aortic stenosis (AS) is a common heart valve disorder in the elderly with increasing incidence in the aging population.[1] Currently, there is no effective therapy for this condition as valve replacement is the standard of care. Historically, surgical aortic valve replacement (SAVR) is regarded as the gold standard for patients with severe AS.[2] As a novel modality, transcatheter aortic valve implantation (TAVI) has garnered significant support for its use over the years since its first application in 2002,[3] and it is currently the best alternative to SAVR in high-risk surgical patients with AS.[4]

The PARTNER II trial shows that the efficacy of TAVI is non-inferior to that of SAVR in intermediate-risk patients with AS,[5] prompting the American College of Cardiology to recommend TAVI for intermediate-risk patients (class IIa).[6] However, complications due to TAVI, such as paravalvular leakage and inadequate durability, are still a cause for concern.[7] Industry experts are debating whether TAVI can be widely used in low-risk surgical patients with AS. Several randomized controlled trials (RCTs) have been conducted on this matter,[8,9] but the results from

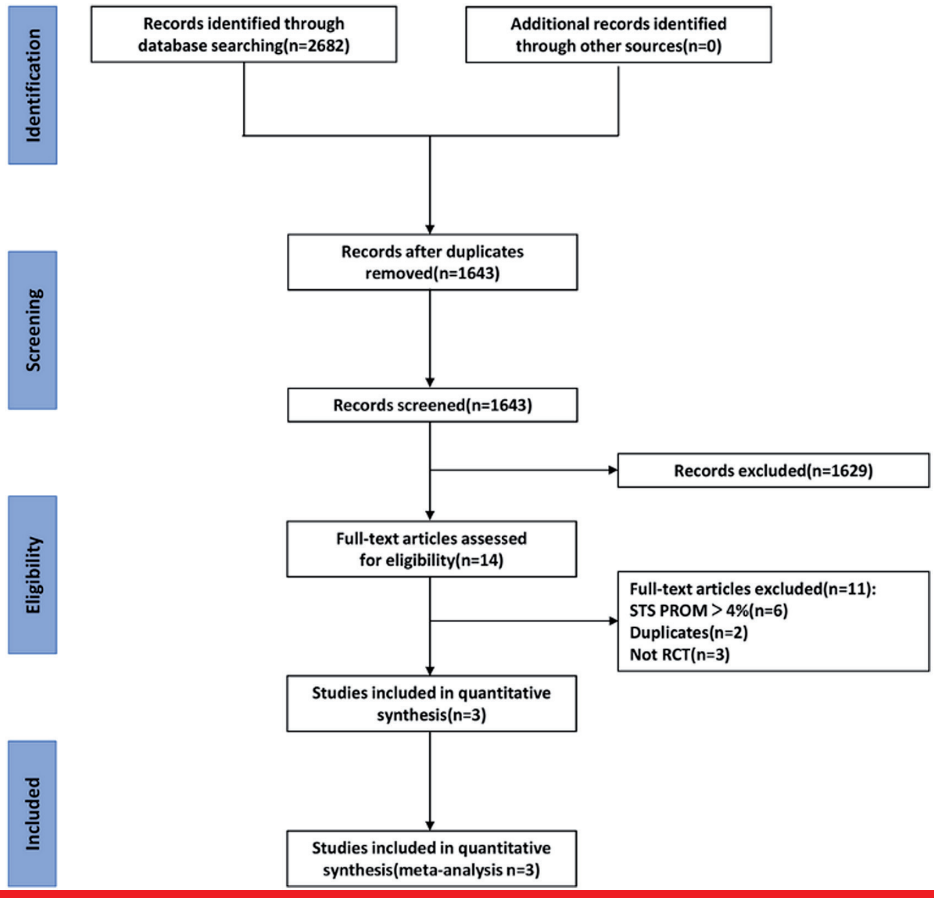

Figure 1. Flowchart for screening and study selection process.

these experiments and meta-analyses are not consistent. The latest 2020 guideline still lists only SAVR as a class I treatment for low-risk surgical patients without recommending TAVI for this patient subset.[10] The 2-year follow-up results published in the PARTNER III and EVOLUT study did provide some evidence to suggest that further investigation of the efficacy of TAVI in low-risk surgical patients with AS—versus that of SAVR—would be prudent.[11,12] As a result, we conducted a new meta-analysis to compare TAVI with SAVR to clearly delineate their performance based on different time frames and patient risk stratification.

HIGHLIGHTS

- In low-risk surgical patients with aortic stenosis, compared to surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI) is associated with lower all-cause mortality at 30-day follow-up and lower cardiovascular mortality at 1-year follow-up.
- Except for advantages in new atrial fibrillation, TAVI had no significant differences in mortality at 2-year follow-up, compared to SAVR.
- In lieu of 2-year follow-up results and potential valve degradation risks, the decision to use TAVI in patients with a longer life expectancy is yet to be recommended.

METHODS

Eligibility Criteria

The research follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines-P guidelines and is based on those guidelines.[13,14] The inclusion criteria were as follows: (1) populations of low-risk surgical patients (Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) <4%); (2) comparison of TAVI; (3) SAVR as a control; (4) primary outcome—measured over a 2-year period—as all-cause mortality and secondary outcomes as cardiovascular mortality, stroke, transient ischemic attack (TIA), myocardial infarction (MI), acute kidney injury (stage 2 or 3), life-threatening or significant bleeding, permanent pacemaker implantation (PPI), and new atrial fibrillation (NAF)[15]; and (5) study designs as RCTs.

Literature Search

From the outset to April 21, 2022, we conducted a comprehensive, systematic search of PubMed, EMBASE, and the Cochrane database. ClinicalTrials.gov trial registries were also reviewed to determine if the available results were reported from ongoing or completed studies. Our supplement details the study strategy.

Data Analyses

Two authors separately collected the required, relevant data—any discrepancies between them were

resolved by group consultation. The 2 authors used the Cochrane collaborative risk of bias tool to assess the risk of bias independently in 5 aspects and used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) to estimate the quality of evidence for each outcome.[16] The results of each RCT were converted to dichotomous data, analyzed using the Mantel-Haenszel method, and presented as relative risk (RR). The summary RR and 95% CI of the survey results were calculated using a random-effect model.[17] $P \leq .5$ was considered statistically significant, and heterogeneity was assessed through I-squared (I^2) and Q statistics; $I^2 > 50\%$ was considered substantial.[18,19] Because fewer than 10 studies were included, we performed neither Egger's nor Begg's tests to evaluate the publication bias of studies.[20]

RESULTS

Figure 1 details the study selection process, illustrating a total of 2682 retrieved articles with 1039 duplicates, which were deleted by the Endnote X9 software. After reviewing the titles and abstracts, 1629 repetitive literature reviews, case reports, meta-analyses, and unrelated articles were excluded. Eleven items were further excluded based on the inclusion criteria, resulting in the final 3 articles. Table 1 comprises the details of the included studies; 2633 patients with AS across the 3 cohorts were enrolled (EVOLUT,[12] NOTION,[15] and PARTNER III[11]). In the assessment of deviation risk, due to specific study designs, it is impossible to blind operators or patients (Supplement Figure 1A and B.). The summary of findings and strength of evidence (GRADE) are shown in the supplement (Supplement Tables 1A-D.); the quality of evidence for the most results was evaluated to be high.

The results of the 30-day, 1-year, and 2-year follow-ups are shown in Figures 2, 3, and 4, respectively. There were several patients enrolled at sites in Japan later in the EVOLUT trial who are included in this analysis at the 2-year baseline; thus, the population in the second year of the EVOLUT trial is different from that before. At the 30-day follow-up of the low-risk surgical patients with AS, TAVI was associated with a lower incidence of all-cause mortality (RR: 0.44; 95% CI: 0.20-0.98; $P = .04$), acute kidney injury (stage 2 or 3) (RR: 0.27; 95% CI: 0.14-0.56; $P = .0003$), life-threatening or significant bleeding (RR: 0.29; 95% CI: 0.14-0.61; $P = .001$), and NAF (RR: 0.21; 95% CI: 0.14-0.31; $P < .00001$) but showed an increased risk of PPI (RR: 3.59; 95% CI, 1.43-9.03; $P = .006$).

At the 1-year follow-up of the low-risk surgical patients with AS, the cardiovascular mortality (RR: 0.56; 95% CI: 0.33-0.94; $P = .03$), presence of life-threatening or significant bleeding (RR: 0.32; 95% CI: 0.24-0.42; $P < .00001$), and the NAF (RR: 0.25; 95% CI, 0.18-0.36; $P < .00001$) results in the TAVI group were significantly decreased compared to those in the SAVR group. However, the incidence of PPI in the TAVI group

Table 1. Characteristics of Studies and Patients

Study		NOTION	PARTNER III	EVOLUT
Number of centers		3	71	86
Recruitment period		2011-2013	2012-2016	2016-2018
Valve type		CoreValve, Evolut R, or Evolut PRO	Sapien 3	CoreValve
Sample size	TAVI	145	496	725
	SAVR	135	454	678
Male, no. (%)	TAVI	78 (53.8)	335 (67.5)	464 (64.0)
	SAVR	71 (52.6)	323 (71.1)	449 (66.2)
Mean year	TAVI	79.2 ± 4.9	73.3 ± 5.8	74.1 ± 5.8
	SAVR	79 ± 4.7	73.6 ± 6.1	73.6 ± 5.9
Mean STS-PROM score	TAVI	2.9 ± 1.6	1.9 ± 0.7	1.9 ± 0.7
	SAVR	3.1 ± 1.7	1.9 ± 0.6	1.9 ± 0.7
Prior cerebrovascular accident, n (%)	TAVI	24 (16.6)	17 (3.4)	74 (10.2)
	SAVR	22 (16.3)	23 (5.1)	80 (11.8)
Prior myocardial infarction, n (%)	TAVI	8 (5.5)	28 (5.7)	48 (6.6)
	SAVR	6 (4.4)	26 (5.8)	33 (4.9)
Peripheral vascular disease, n (%)	TAVI	6 (4.1)	34 (6.9)	54 (7.5)
	SAVR	9 (6.7)	33 (7.3)	56 (8.3)
Chronic lung disease, n. (%)	TAVI	17 (11.7)	25 (5.1)	104 (15.0)
	SAVR	16 (11.9)	28 (6.2)	117 (18.0)
Diabetes mellitus, n. (%)	TAVI	26 (17.9)	155 (31.2)	228 (31.4)
	SAVR	28 (20.7)	137 (30.2)	207 (30.5)
Creatinine level >2 mg/dL, no. (%)	TAVI	2 (1.4)	1 (0.2)	3 (0.4)
	SAVR	1 (0.7)	1 (0.2)	1 (0.1)

TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.

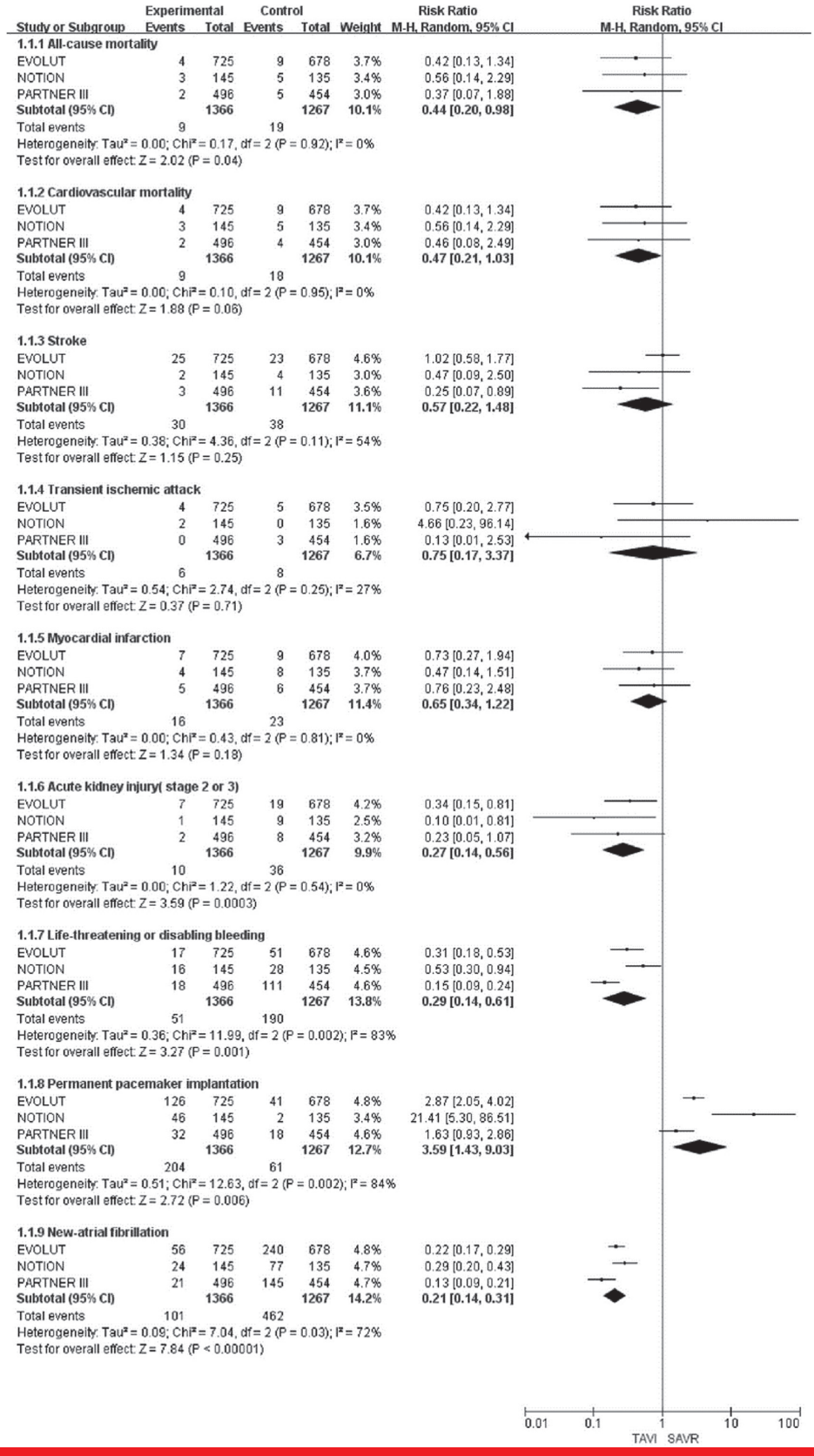

Figure 2. Forest plot for incidence of all-cause mortality, cardiovascular mortality, stroke, transient ischemic attack, myocardial infarction, acute kidney injury, life-threatening or disabling bleeding, permanent pacemaker implantation, and new-atrial fibrillation at the 30-day follow-up.

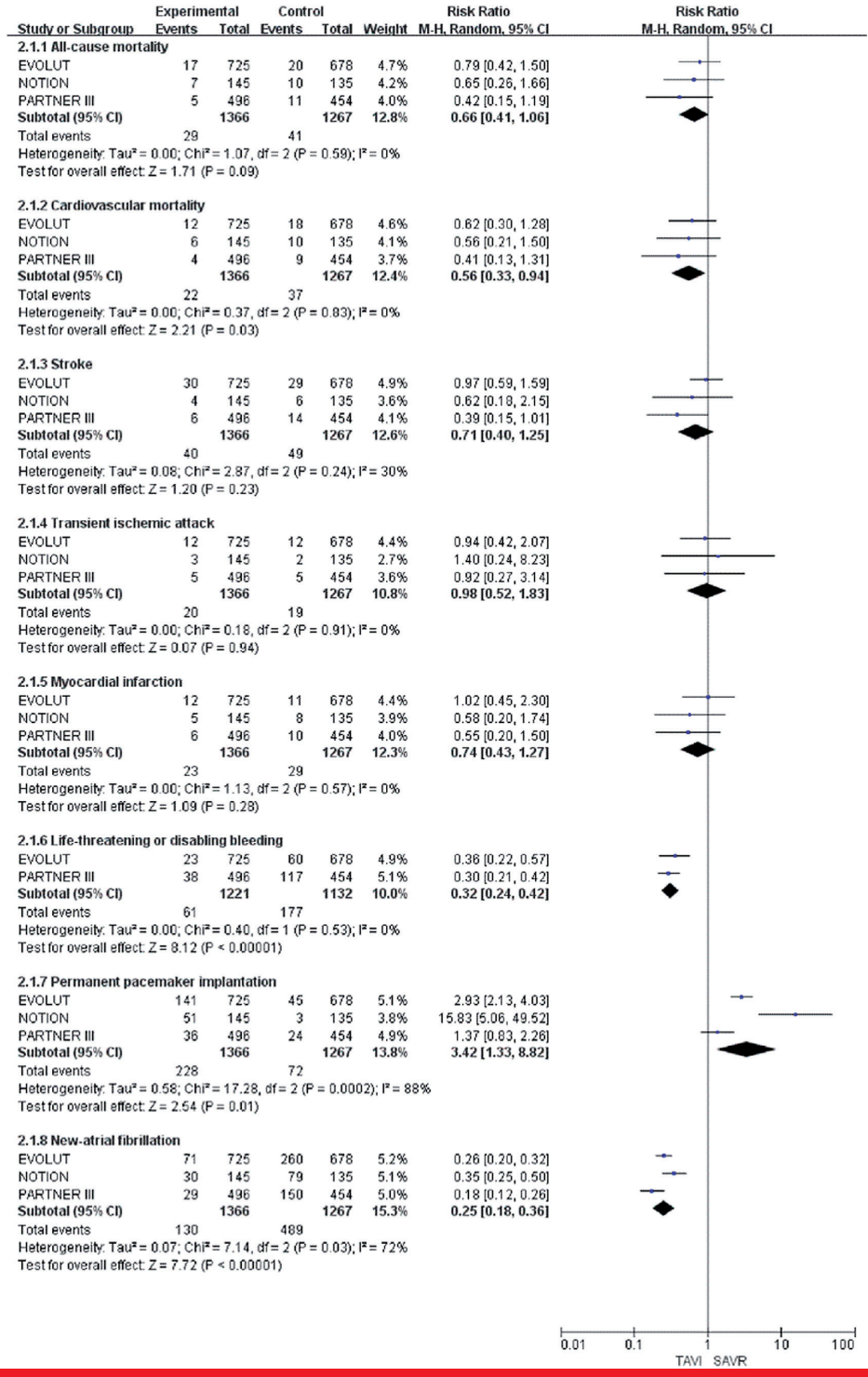

Figure 3. Forest plot for incidence of all-cause mortality, cardiovascular mortality, stroke, transient ischemic attack, myocardial infarction, life-threatening or disabling bleeding, permanent pacemaker implantation, and new-atrial fibrillation at the 1-year follow-up.

was significantly increased when compared to that of the SAVR group (RR: 3.42; 95% CI: 1.33-8.82; *P* = .01).

At the 2-year follow-up of low-risk surgical patients with AS, only the NAF results in the TAVI group were significantly decreased (RR: 0.27; 95% CI: 0.14 to 0.51; *P* < .0001), compared to those in the SAVR group. Transcatheter aortic valve implantation was also associated with a higher incidence of PPI (RR: 3.02; 95% CI: 1.31-6.97; *P* = .01). The differences in all-cause mortality, cardiovascular mortality, stroke, TIA, and MI between the TAVI and SAVR groups were not statistically significant.

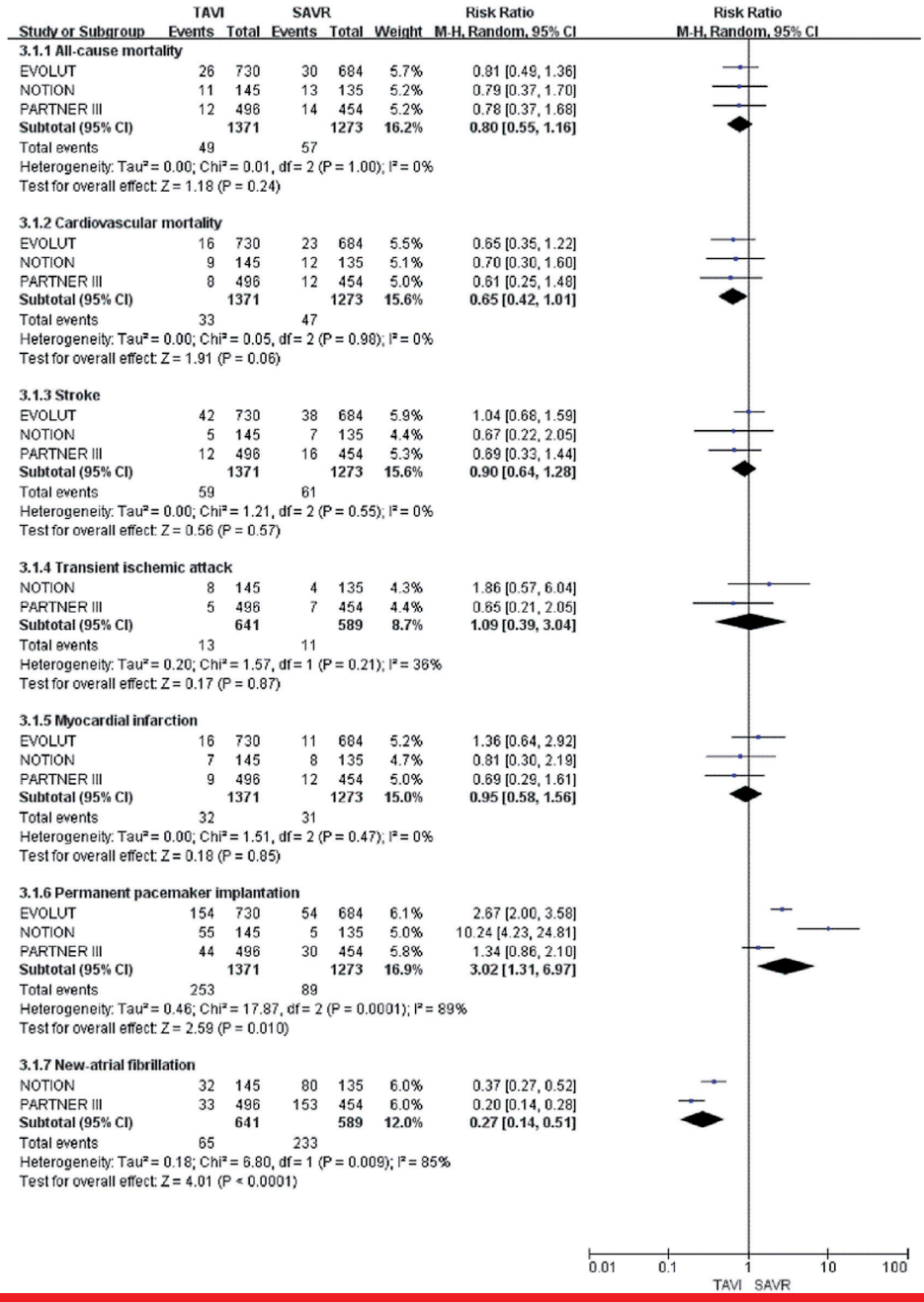

Figure 4. Forest plot for incidence of all-cause mortality, cardiovascular mortality, stroke, transient ischemic attack, myocardial infarction, permanent pacemaker implantation, and new-atrial fibrillation at the 2-year follow-up.

DISCUSSION

Since currently established guidelines do not recommend the use of TAVI in low-risk surgical patients with AS, our study aimed to evaluate the efficacy and effectiveness of TAVI in this patient subset by comparing the clinical outcomes of TAVI and SAVR at 30-day, 1-year, and 2-year follow-up time frames. This study included 3 RCTs, comprising 2644 patients, and used a meta-analysis to compare the aforementioned outcomes. Kolte et al[21] reported that TAVI was associated with a lower risk of cardiovascular and all-cause mortality at 1 year. Our 1-year follow-up had similar results; however, their study did not report outcomes at other follow-up time intervals. In reviewing the 2-year results of the newly released PARTNER III and EVOLUT trial, we found that the low-risk patients who underwent TAVI at the 30-day and 1-year follow-up outperformed those who underwent SAVR in cardiovascular mortality, acute kidney injury (stage 2 or 3), NAF, and life-threatening or significant bleeding. However, TAVI resulted in a higher risk of PPI during the same time period. Compared with SAVR at the 2-year follow-up, there was no significant difference in cardiovascular and all-cause mortality for patients who underwent TAVI. Therefore, TAVI can reduce mortality and complications at the 30-day and

1-year follow-up; however, at the 2-year follow-up, most of the results demonstrated no significant difference. Most notably, the 5-year follow-up of the PARTNER II trial noted that patients who underwent TAVI had a higher risk of death or disabling strokes.[22,23] Furthermore, Barili et al[24] performed time-interval modeling, incorporating 3 RCTs (including the PARTNER II trial), and found that TAVI was associated with better survival in the first few months after implantation but was a risk factor for all-cause mortality after 40 months. Although these trials were conducted with patients at intermediate and high risk, the results still have important significance to our research conclusions. It reminds us that, over time, the risk of mortality and complications after TAVI may increase rapidly, which corresponds to our discovery in the 2-year clinical results.

The PARTNER III trial using the SAPIEN 3 valve has achieved superior results. According to the analysis of Deharo, the design of SAPIEN 3 is easier to fit the landing zone, which reduces the risk of cardiovascular complications after TAVI.[25,26] This may also be the reason for the large heterogeneity of TIA and PPI in our findings. Different valves used in various experiments affect the heterogeneity of the analysis. Although the new generation of the valve reduces the incidence of PPI, compared to SAVR, the incidence of PPI after TAVI is still higher. Recent studies have shown that PPI is associated with late all-cause mortality and increased risk of hospitalization due to cardiac failure.[27] Therefore, reducing the incidence of PPI after TAVI is an important issue to be considered and an interesting area for valve improvement.

Valve degeneration is another TAVI-associated complication that should be considered. Once it occurs, valve-in-valve implantation is indicated,[28,29] and it is a complex operative procedure. Postoperatively, device malposition and ostial coronary obstruction are also common TAVI-associated complications. Only the NOTION trial reports data on valve conditions in low-risk surgical patients with AS undergoing TAVI for more than 5 years[30]; therefore, there are insufficient data to analyze this problem. Moreover, most of the patients undergoing TAVI in the current RCTs are over 75 years old; therefore, their life expectancy is much less than the expected valve use time, hindering the valve durability study. Randomized controlled trials need to be conducted among relatively younger patients to assess long-term follow-up, providing more effective data for future meta-analyses.

Finally, based on the optimal performance of TAVI at the 30-day and the 1-year clinical follow-up and the continuous replacement of the operative valve, TAVI appears to be a very promising procedure in low-risk surgical patients with AS. The eventual use of TAVI in older patients with a shortened life expectancy is reasonable. However, we should also note the changes at the 2-year TAVI follow-up and the potential clinical complications of PPI and valve degeneration. In lieu of these results, the decision to use TAVI in patients with a longer life expectancy is yet to be recommended.

Study Limitations

First, study omissions occurred due to their non-inclusion in the search database, resulting in eventual publication bias. Second, some inevitable differences in baseline characteristics between studies affect the accuracy of the results. Third, there is significant variability in the literature of the definitions for valve type, surgical risk, and outcomes, leading to possible discrepancies in the results.

CONCLUSIONS

In low-risk surgical patients with AS, compared to SAVR, TAVI was associated with lower all-cause mortality at 30-day follow-up and lower cardiovascular mortality at 1-year follow-up. At the 2-year follow-up, with the exception of decreased NAF risk, there was no significant difference in all-cause mortality, cardiovascular mortality, and mi between TAVI and SAVR. However, potential late TAVI-associated complications, such as valvular degeneration and PPI, are important clinical concerns that must be considered when weighing treatment options for AS.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Union Hospital, Fujian Medical University, (Approval No: 2020KJT091).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.G.C., B.B.X.; Design – C.G.C., Q.F.D.; Supervision – L.W.C., Z.H.Q.; Fundings – L.W.C., Z.H.Q.; Materials – C.G.C., B.B.X.; Data collection &/or processing –X.Y.Z., W.C.L.; Analysis &/or interpretation – C.G.C., B.B.X.; Literature search – Z.H.Q.; Writing –C.G.C., B.B.X.; Critical review – L.W.C., Z.H.Q.

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Declaration of Interests: The authors have nothing to disclose.

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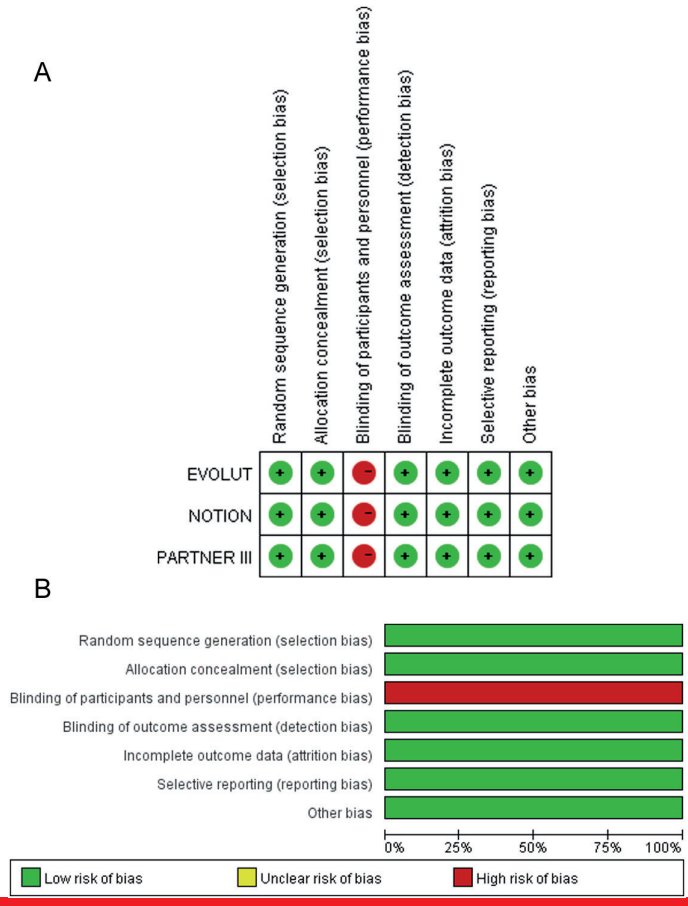

Supplement Figure 1. A. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. B. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Supplement Table 1A. Search Strategy		
PubMed		
1	"Aortic Valve Stenosis"[Mesh]	48093
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3	1 OR 2	53638
4	"Transcatheter Aortic Valve Replacement"[Mesh]	9162
5	((((((((((((((((((((((((percutaneous aortic valve implantation[Title/Abstract]) OR (percutaneous aortic valve replacement[Title/Abstract])) OR (TAVI[Title/Abstract])) OR (trans-apical aortic valve implantation[Title/Abstract])) OR (trans-apical aortic valve replacement[Title/Abstract])) OR (trans-arterial aortic valve implantation[Title/Abstract])) OR (trans-arterial aortic valve replacement[Title/Abstract])) OR (trans-catheter aortic valve implantation[Title/Abstract])) OR (trans-catheter aortic valve replacement[Title/Abstract])) OR (trans-cutaneous aortic valve implantation[Title/Abstract])) OR (trans-cutaneous aortic valve replacement[Title/Abstract])) OR (trans-femoral aortic valve implantation[Title/Abstract])) OR (trans-femoral aortic valve replacement[Title/Abstract])) OR (transapical aortic valve implantation[Title/Abstract])) OR (transapical aortic valve replacement[Title/Abstract])) OR (transarterial aortic valve implantation[Title/Abstract])) OR (transarterial aortic valve replacement[Title/Abstract])) OR (transcatheter aortic valve replacement[Title/Abstract])) OR (transcutaneous aortic valve implantation[Title/Abstract])) OR (transcutaneous aortic valve replacement[Title/Abstract])) OR (transfemoral aortic valve implantation[Title/Abstract])) OR (transfemoral aortic valve replacement[Title/Abstract])) OR (TAVR[Title/Abstract]).	12828
6	(((((((((aorta valve replacement[Title/Abstract]) OR (aorta valve transplantation[Title/Abstract])) OR (aortic valve transplantation[Title/Abstract])) OR (aortic valve xenotransplantation[Title/Abstract])) OR (heart valve transplantation, aortic valve[Title/Abstract])) OR (transplantation, aortic valve[Title/Abstract])) OR (surgical aortic valve replacement)) OR (surgical aortic valve implantation)) OR (SAVR)) OR (surgical AVR)	36581

(*Continued*)

Supplement Table 1A. Search Strategy Supplement Table 1A. Search Strategy		
7	4 OR 5 OR 6	38222
8	randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]	945899
9	3 AND 7 AND 8	943
Embase		
1	"aortic valve stenosis"/exp	20578
2	"aortic valve stenoses":ab,ti OR "stenoses, aortic valve":ab,ti OR "stenosis, aortic valve":ab,ti OR "valve stenoses, aortic":ab,ti OR "valve stenosis, aortic":ab,ti OR "aortic stenosis":ab,ti OR "stenoses, aortic":ab,ti OR "stenosis, aortic":ab,ti	31812
3	1 OR 2	44747
4	"transcatheter aortic valve implantation"/exp	27560
5	"percutaneous aortic valve implantation":ab,ti OR "percutaneous aortic valve replacement":ab,ti OR tavi:ab,ti OR "trans-apical aortic valve implantation":ab,ti OR "trans-apical aortic valve replacement":ab,ti OR "trans-arterial aortic valve implantation":ab,ti OR "trans-arterial aortic valve replacement":ab,ti OR "trans-catheter aortic valve implantation":ab,ti OR "trans-catheter aortic valve replacement":ab,ti OR "trans-cutaneous aortic valve implantation":ab,ti OR "trans-cutaneous aortic valve replacement":ab,ti OR "trans-femoral aortic valve implantation":ab,ti OR "trans-femoral aortic valve replacement":ab,ti OR "transapical aortic valve implantation":ab,ti OR "transapical aortic valve replacement":ab,ti OR "transarterial aortic valve implantation":ab,ti OR "transarterial aortic valve replacement":ab,ti OR "transcatheter aortic valve replacement":ab,ti OR "transcutaneous aortic valve implantation":ab,ti OR "transcutaneous aortic valve replacement":ab,ti OR "transfemoral aortic valve implantation":ab,ti OR "transfemoral aortic valve replacement":ab,ti	22178
6	"aorta valve replacement":ab,ti OR "aorta valve transplantation":ab,ti OR "aortic valve transplantation":ab,ti OR "aortic valve xenotransplantation":ab,ti OR "heart valve transplantation, aortic valve":ab,ti OR "transplantation, aortic valve":ab,ti OR "surgical aortic valve replacement":ab,ti OR "surgical aortic valve implantation":ab,ti OR savr:ab,ti OR "surgical avr":ab,ti	5186
7	4 OR 5 OR 6	31214
8	"randomized controlled trial":ab,ti OR "randomized":ab,ti OR "placebo":ab,ti	1038314
9	3 AND 7 AND 8	822
Cochrane CENTRAL		
1	MeSH descriptor: [Aortic Valve Stenosis] explode all trees	975
2	(Aortic Valve Stenoses):ti,ab,kw OR (Stenoses, Aortic Valve):ti,ab,kw OR (Stenosis, Aortic Valve):ti,ab,kw OR (Valve Stenoses, Aortic):ti,ab,kw OR (Valve Stenosis, Aortic):ti,ab,kw OR (Aortic Stenosis):ti,ab,kw OR (Stenoses, Aortic):ti,ab,kw OR (Stenosis, Aortic):ti,ab,kw	1898
3	1 OR 2	2111
4	MeSH descriptor: [Transcatheter Aortic Valve Replacement] explode all trees	203
5	(percutaneous aortic valve implantation):ti,ab,kw OR (percutaneous aortic valve replacement):ti,ab,kw OR (TAVI):ti,ab,kw OR (trans-apical aortic valve implantation):ti,ab,kw OR (trans-apical aortic valve replacement):ti ,ab,kw OR (trans-arterial aortic valve implantation):ti,ab,kw OR (trans-arterial aortic valve replacement):ti,ab,k w OR (trans-catheter aortic valve implantation):ti,ab,kw OR (trans-catheter aortic valve replacement):ti,ab,kw OR (trans-cutaneous aortic valve implantation):ti,ab,kw OR (trans-cutaneous aortic valve replacement):ti,ab,kw OR (trans-femoral aortic valve implantation):ti,ab,kw OR (trans-femoral aortic valve replacement):ti,ab,kw OR (transapical aortic valve implantation):ti,ab,kw OR (transapical aortic valve replacement):ti,ab,kw OR (transarterial aortic valve implantation):ti,ab,kw OR (transarterial aortic valve replacement):ti,ab,kw OR (transcutaneous aortic valve implantation):ti,ab,kw OR (transcatheter aortic valve replacement):ti,ab,kw OR (transcutaneous aortic valve replacement):ti,ab,kw OR (transfemoral aortic valve implantation):ti,ab,kw OR (transfemoral aortic valve replacement):ti,ab,kw	1094
6	(aorta valve replacement):ti,ab,kw OR (aorta valve transplantation):ti,ab,kw OR (aortic valve transplantation):ti, ab,kw OR (aortic valve xenotransplantation):ti,ab,kw OR (heart valve transplantation, aortic valve):ti,ab,kw OR (transplantation, aortic valve):ti,ab,kw OR (surgical aortic valve replacement):ti,ab,kw OR (surgical aortic valve implantation):ti,ab,kw OR (SAVR):ti,ab,kw OR (surgical AVR):ti,ab,kw	1152
7	4 OR 5 OR 6	1706
8	3 AND 7	917

Supplement Table 1B. Summary of Findings and Strength of Evidence (GRADE) for 30-Day Results

TAVI Compared to SAVR for Low-Risk Surgical Patients with Aortic Stenosis

Patient or population: Low-risk surgical patients with aortic stenosis
Settings:
Intervention: TAVI[1]
Comparison: SAVR[2]

Outcomes	Illustrative Comparative Risks* (95% CI) Assumed Risk	Corresponding Risk	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	SAVR	**TAVI**				
All-cause mortality Follow-up: 30 days	**Study population**		**RR 0.44** (0.2-0.98)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	15 per 1000	**7 per 1000** (3-15)				
	Moderate					
	13 per 1000	**6 per 1000** (3-13)				
Cardiovascular mortality Follow-up: 30 days	**Study population**		**RR 0.47** (0.21-1.03)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	14 per 1000	**7 per 1000** (3-15)				
	Moderate					
	13 per 1000	**6 per 1000** (3-13)				
Stroke Follow-up: 30 days	**Study population**		**RR 0.57** (0.22-1.48)	2633 (3 studies)	⊕⊕⊕⊖ **Moderate**[3]	
	30 per 1000	**17 per 1000** (7-44)				
	Moderate					
	30 per 1000	**17 per 1000** (7-44)				
Transient ischemic attack Follow-up: 30 days	**Study population**		**RR 0.75** (0.17-3.37)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	6 per 1000	**5 per 1000** (1-21)				
	Moderate					
	7 per 1000	**5 per 1000** (1-24)				
Myocardial infarction Follow-up: 30 days	**Study population**		**RR 0.65** (0.34-1.22)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	18 per 1000	**12 per 1000** (6-22)				
	Moderate					
	13 per 1000	**8 per 1000** (4-16)				
Acute kidney injury (stage 2 or 3) Follow-up: 30 days	**Study population**		**RR 0.27** (0.14-0.56)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	28 per 1000	**8 per 1000** (4-16)				
	Moderate					
	28 per 1000	**8 per 1000** (4-16)				
Life-threatening or disabling bleeding Follow-up: 30 days	**Study population**		**RR 0.29** (0.14-0.61)	2633 (3 studies)	⊕⊕⊕⊖ **Moderate**[3]	
	150 per 1000	**43 per 1000** (21-91)				
	Moderate					
	207 per 1000	**60 per 1000** (29-126)				
Permanent pacemaker implantation Follow-up: 30 days	**Study population**		**RR 3.59** (1.43-9.03)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	48 per 1000	**173 per 1000** (69-435)				
	Moderate					
	40 per 1000	**144 per 1000** (57-361)				
New-atrial fibrillation Follow-up: 30 days	**Study population**		**RR 0.21** (0.14-0.31)	2633 (3 studies)	⊕⊕⊕⊕ **High**[3,4]	
	365 per 1000	**77 per 1000** (51-113)				
	Moderate					
	354 per 1000	**74 per 1000** (50-110)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
RR, risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Transcatheter aortic valve implantation; [2]surgical aortic valve replacement; [3]inconsistency;[4]large effect.

Supplement Table 1C. Summary of Findings and Strength of Evidence (GRADE) for 1-Year Results

TAVI Compared to SAVR for Low-Risk Surgical Patients with Aortic Stenosis

Patient or population: low-risk surgical patients with aortic stenosis
Settings:
Intervention: TAVI[1]
Comparison: SAVR[2]

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	SAVR	**TAVI**				
All-cause mortality Follow-up: 1 year	**Study population**		**RR 0.66** (0.41-1.06)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	32 per 1000	**21 per 1000** (13-34)				
	Moderate					
	30 per 1000	**21 per 1000** (12-32)				
Cardiovascular mortality Follow-up: 1 year	**Study population**		**RR 0.56** (0.33-0.94)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	29 per 1000	**16 per 1000** (10-27)				
	Moderate					
	27 per 1000	**15 per 1000** (9-25)				
Stroke Follow-up: 1 year	**Study population**		**RR 0.71** (0.4-1.25)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	39 per 1000	**27 per 1000** (15-48)				
	Moderate					
	43 per 1000	**31 per 1000** (17-54)				
Transient ischemic attack Follow-up: 1 year	**Study population**		**RR 0.98** (0.52-1.83)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	15 per 1000	**15 per 1000** (8-27)				
	Moderate					
	15 per 1000	**15 per 1000** (8-27)				
Myocardial infarction Follow-up: 1 year	**Study population**		**RR 0.74** (0.43-1.27)	2633 (3 studies)	⊕⊕⊕⊕ **High**	
	23 per 1000	**17 per 1000** (10-29)				
	Moderate					
	22 per 1000	**16 per 1000** (9-28)				
Life-threatening or disabling bleeding Follow-up: 1 year	**Study population**		**RR 0.32** (0.24-0.42)	2353 (2 studies)	⊕⊕⊕⊕ **High**	
	156 per 1000	**50 per 1000** (38-66)				
	Moderate					
	173 per 1000	**55 per 1000** (42-73)				
Permanent pacemaker implantation Follow-up: 1 year	**Study population**		**RR 3.42** (1.33-8.82)	2633 (3 studies)	⊕⊕⊕⊖ **Moderate**[3,4]	
	57 per 1000	**194 per 1000** (76-501)				
	Moderate					
	53 per 1000	**181 per 1000** (70-467)				
New-atrial fibrillation Follow-up: 1 year	**Study population**		**RR 0.25** (0.18-0.36)	2633 (3 studies)	⊕⊕⊕⊕ **High**[3,4]	
	386 per 1000	**96 per 1000** (69-139)				
	Moderate					
	384 per 1000	**96 per 1000** (69-138)				

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
RR, risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Transcatheter aortic valve implantation; [2]surgical aortic valve replacement; [3]inconsistency; [4]large effect.

Supplement Table 1D. Summary of Findings and Strength of Evidence (GRADE) for 2-Year Results

TAVI Compared to SAVR for Low-Risk Surgical Patients with Aortic Stenosis

Patient or population: Low-risk surgical patients with aortic stenosis
Settings:
Intervention: TAVI[1]
Comparison: SAVR[2]

Outcomes	Illustrative Comparative Risks* (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	SAVR	**TAVI**				
All-cause mortality Follow-up: 2 years	**Study population**		**RR 0.8** (0.55-1.16)	2644 (3 studies)	⊕⊕⊕⊕ **High**	
	45 per 1000	**36 per 1000** (25-52)				
	Moderate					
	44 per 1000	**35 per 1000** (24-51)				
Cardiovascular mortality Follow-up: 2 years	**Study population**		**RR 0.65** (0.42-1.01)	2644 (3 studies)	⊕⊕⊕⊕ **High**	
	37 per 1000	**24 per 1000** (16-37)				
	Moderate					
	34 per 1000	**22 per 1000** (14-34)				
Stroke Follow-up: 2 years	**Study population**		**RR 0.9** (0.64-1.28)	2644 (3 studies)	⊕⊕⊕⊕ **High**	
	48 per 1000	**43 per 1000** (31-61)				
	Moderate					
	52 per 1000	**47 per 1000** (33-67)				
Transient ischemic attack Follow-up: 2 years	**Study population**		**RR 1.09** (0.39-3.04)	1230 (2 studies)	⊕⊕⊕⊕ **High**	
	19 per 1000	**20 per 1000** (7-57)				
	Moderate					
	23 per 1000	**25 per 1000** (9-70)				
Myocardial infarction Follow-up: 2 years	**Study population**		**RR 0.95** (0.58-1.56)	2644 (3 studies)	⊕⊕⊕⊕ **High**	
	24 per 1000	**23 per 1000** (14-38)				
	Moderate					
	26 per 1000	**25 per 1000** (15-41)				
Permanent pacemaker implantation Follow-up: 2 years	**Study population**		**RR 3.02** (1.31-6.97)	2644 (3 studies)	⊕⊕⊕⊖ **Moderate**[3]	
	70 per 1000	**211 per 1000** (92-487)				
	Moderate					
	66 per 1000	**199 per 1000** (86-460)				
New atrial fibrillation Follow-up: 2 years	**Study population**		**RR 0.27** (0.14-0.51)	1230 (2 studies)	⊕⊕⊕⊕ **High**[3,4]	
	396 per 1000	**107 per 1000** (55-202)				
	Moderate					
	465 per 1000	**126 per 1000** (65-237)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
RR, risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Transcatheter aortic valve implantation; [2]surgical aortic valve replacement; [3]inconsistency; [4]large effect.