Transcatheter aortic valve replacement versus surgery for symptomatic severe aortic stenosis: a reconstructed individual patient data meta-analysis

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Abstract

Objectives: We wished to undertake a reconstructed individual patient data meta-analysis of randomised clinical trials comparing transcatheter aortic valve replacement (TAVR) and surgery for patients with severe symptomatic aortic stenosis.

Background: TAVR and surgery are both well-established methods for treating patients with symptomatic severe aortic stenosis who are at low, intermediate and high risk for surgery.

Methods: Data were identified by searches of Medline, Embase, CENTRAL and ClinicalTrials.gov for all randomised clinical trials which compared TAVR and surgery, that had published at least 1 year of follow-up. Individual patient data were reconstructed from Kaplan-Meier curves.

Results: A total of 7770 patients from 7 randomised clinical trials were included in this meta-analysis. At 1 year, TAVR was associated with a lower risk of death from any cause (hazard ratio [HR], 0.85, 95% confidence interval [CI], 0.73-0.98; P=0.03), disabling stroke (HR, 0.71; 95% CI, 0.54-0.93; P=0.01) and the composite end point of death or disabling stroke (HR, 0.79; 95% CI, 0.67-0.92; P=0.002). Significant interactions were found for access suitability, with TAVR associated with a lower risk of these end points in patients suitable for transfemoral access. TAVR was associated with a lower risk of periprocedural events, whereas the risk of late events was similar between TAVR and surgery.

Conclusions: At 1 year, TAVR was associated with a lower risk of death, disabling stroke and the composite end point, when compared with surgery. These associations were strongest within the subgroup of patients in whom transfemoral access was feasible.

Introduction

Transcatheter aortic valve replacement (TAVR) and surgery are both well-established methods for treating patients with symptomatic severe aortic stenosis who are at low, intermediate and high risk for surgery.[1-7]

Previous meta-analyses have demonstrated that TAVR is associated with a either a similar or lower risk of death, when compared with surgery, but in patients who are suitable for transfemoral access, TAVR is associated with a lower risk of death.[8-19] However, previous meta-analyses have not undertaken landmark analysis to assess the risk of key clinical outcomes during both periprocedural and late time frames. This is of particular interest, as TAVR might be associated with a lower or similar risk of periprocedural events, but a higher risk of late events.[20] Secondly, previous meta-analyses have not assessed the important outcome of disabling stroke, nor the composite end point of death or disabling stroke. Thirdly, previous meta-analyses have not compared long-term transcatheter and surgical bioprosthetic valve durability. Finally, previous meta-analyses have not included the PARTNER 3 or Evolut Low Risk trials.

We therefore wished to undertake a reconstructed individual patient data meta-analysis of randomised clinical trials to compare the risk of key clinical outcomes between these two treatment modalities.

Methods

Search Strategy

Data were identified by searches of Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov for all randomised clinical trials which

compared TAVR and surgery, that had published at least 1 year of follow-up. Only articles published in English between 2012 and 2019 were included.

Data Collection

Two investigators independently reviewed the abstracts and collected data. Where possible, data were collected from the intention-to-treat population, followed by the modified intention-to-treat and finally the as-treated population. Conflicts were resolved by referral to a third investigator.

Risk of Bias

The Cochrane risk of bias assessment tool was used to assess sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting.[21] Risk of publication bias was assessed using a funnel plot.

End Points

The primary end point was the risk of death from any cause at 1 year. The secondary end points were the risk of disabling stroke, and the composite end point of death from any cause or disabling stroke, at 1 year. The tertiary end points were the risk of any stroke, transient ischemic attack, any neurological event, life-threatening or disabling bleeding, major bleeding, major vascular complication, cardiogenic shock, acute kidney injury, new-onset atrial fibrillation, myocardial infarction, new left bundle branch block, permanent pacemaker implantation, length of index hospitalisation, aortic valve reintervention, rehospitalization and endocarditis, at 1 year. Echocardiographic outcomes, symptom status and quality of life measures were assessed at serial time points. All end points were assessed using Valve Academic Research Consortium-2 criteria.[22]

Statistical Analysis

Fisher's exact test was used to compare categorical variables. Continuous variables, which are presented as means and standard deviations, were compared with a Student's t-test. For the primary and secondary end points, individual patient data was reconstructed from Kaplan-Meier curves using published methods.[23] After checking for the proportional-hazards assumption, we used a Cox proportional-hazards regression model to quantify the association between baseline covariates and various end points. Baseline covariates were assumed to be consistent within individual trials, unless otherwise specified in published reports. Associations for the primary and secondary end points were evaluated using hazard ratios and Kaplan-Meier estimates, and those for the tertiary end points were expressed as risk ratios. Meta-analysis was performed using the DerSimonian and Laird method.[24] Heterogeneity was quantified using the I^2 and τ^2 statistics.[25] For all outcomes a two-sided P value <0.05 was considered statistically significant. Numbers needed to treat were calculated for all outcomes with a significant hazard ratio.[26] Statistical analysis was performed using either SPSS version 25.0 (IBM Corporation), Comprehensive Meta-Analysis version 3.3.070 (Biostat), or RevMan version 5.3 (Cochrane Collaboration).

Results

Our search strategy returned 1573 titles (Supporting Information Figure 1 and Supporting Information Table I). Twenty-four manuscripts fulfilled the search criteria, encompassing up to 7770 patients from seven randomised clinical trials (PARTNER 1A,[1, 27-29] U.S. CoreValve High Risk,[2, 30-34] NOTION,[3, 35-38], PARTNER 2A,[4, 39-41] SURTAVI,[5, 42, 43] PARTNER 3[6] and Evolut Low Risk[7]). For each eligible clinical trial, the overall risk of bias was low, with no

observed publication bias (Supporting Information Figure 2 and Supporting Information Table II).

Baseline demographic and clinical characteristics of the patients are presented in Table I. Mean age was 79.1 ± 6.3 years and Society of Thoracic Surgeons Predicted Risk of Mortality 4.9 ± 2.0%. There were no clinically significant differences in baseline characteristics between the TAVR and surgery groups.

There was heterogeneity regarding the type of TAVR system studied (balloon-expandable vs. self-expanding) and use of transfemoral access (Supporting Information Table III). Revascularization was permitted in some trials, but was based on the Syntax score and the absence of unprotected left main coronary artery disease. Individuals with congenital bicuspid and unicuspid aortic valves were excluded from all trials, as were patients on haemodialysis. Further, most trials excluded patients with significantly impaired renal function (creatinine clearance <20 mL/min or serum creatinine >3 mg/dl).

Validation of Reconstructed Individual Patient Data

Kaplan-Meier event rates and hazard ratios calculated from reconstructed individual patient data closely mirrored reported values (Supporting Information Tables IV-V).

Death and Disabling Stroke

At 1 year, TAVR was associated with a lower risk of death from any cause, when compared with surgery, with low heterogeneity across published trials (hazard ratio, 0.85; 95% confidence interval [CI], 0.73-0.98; P=0.03, I^2=0%, τ^2<0.001) (Figure 1). There was a significant interaction for access approach ($P_{interaction}$=0.02), with TAVR favoured in patients who were suitable for transfemoral access (hazard ratio, 0.79; 95% CI, 0.67-0.93; P=0.005) (Figure 1, Figure 2).

TAVR was associated with a lower risk of disabling stroke, with low heterogeneity across published trials (hazard ratio, 0.71; 95% CI, 0.54-0.93; P=0.01, I^2=22%, τ^2=0.03) (Figure 1). There was a significant interaction for access approach ($P_{interaction}$=0.04), with TAVR favoured in patients who were suitable for transfemoral access (hazard ratio, 0.64; 95% CI, 0.48-0.85; P=0.002) (Figure 1, Supporting Information Figure 3).

TAVR was associated with a lower risk of the composite end point of death from any cause or disabling stroke, with low heterogeneity across published trials (hazard ratio, 0.79; 95% CI, 0.67-0.92; P=0.002, I^2=26%, τ^2=0.01) (Figure 1). There was a significant interaction for access approach ($P_{interaction}$=0.02), with TAVR favoured in patients who were suitable for transfemoral access (hazard ratio, 0.74; 95% CI, 0.62-0.87; P<0.001) (Figure 1, Supporting Information Figure 4).

Landmark analysis demonstrated that between 0 and 3 months, TAVR was associated with a lower risk of the primary and secondary end points. Between 3 months and 1 year, TAVR and surgery were associated with a similar risk of the primary and secondary end points (Supporting Information Figure 5).

Sensitivity analysis with exclusion of one trial at a time did not materially alter the findings of the primary end point (Supporting Information Figure 6).

At 1 year, the number needed to treat with TAVR to prevent one death or disabling stroke was 29 patients (95% CI, 45 to 117 patients). In patients suitable for transfemoral access, the number needed to treat with TAVR to prevent one death was 33 patients (95% CI, 53 to 159 patients), to prevent one disabling stroke was 51 patients (95% CI, 73 to 181 patients) and to prevent one death or disabling stroke was 27 patients (95% CI, 38 to 78 patients).

Only limited long-term data was available, but nonetheless, between 1 and 5 years, TAVR and surgery had a similar risk of death from any cause (hazard ratio, 1.05; 95% CI, 0.91-1.22; P=0.49) (Supporting Information Figure 7).

Other Outcomes

At 1 year, TAVR was associated with a lower risk of cardiogenic shock, life-threatening or disabling bleeding, acute kidney injury and new-onset atrial fibrillation (Supporting Information Figure 8). TAVR was associated with a higher risk of major vascular complication, new left bundle branch block, permanent pacemaker implantation, transient ischemic attack and aortic valve reintervention (Supporting Information Figure 9). The risk of major bleeding, any stroke, any neurological event, myocardial infarction, endocarditis and rehospitalisation was similar (Supporting Information Figure 10). There was significant heterogeneity between groups for some of these tertiary end points, including permanent pacemaker implantation and rehospitalisation.

TAVR was associated with a lower mean aortic valve gradient and a larger aortic valve area at all time points but had a higher incidence of aortic regurgitation (Figure 3).

TAVR was associated with a shorter length of index hospitalisation (5.9 ± 4.4 vs. 10.2 ± 6.8 days; P<0.001). TAVR and surgery were associated with similar improvements in symptom status and health-related quality of life measures, but improvements were faster with TAVR (Figure 4).

Discussion

The key finding of this meta-analysis is that at 1 year, TAVR was associated with a lower risk of death, when compared with surgery. Furthermore, these associations were strongest within the subgroup of patients in whom transfemoral access was feasible. These finding are consistent with the conclusions of several prior meta-analyses.[8, 9]

The clinical end point of disabling stroke is an important complication of aortic valve intervention. We demonstrated that TAVR was associated with a lower risk of disabling stroke and that this association was strongest within the subgroup of patients who were suitable for transfemoral access. This is, to our knowledge, the first time that a meta-analysis in this field has demonstrated the superiority of TAVR regarding this important clinical end point and this finding should assist in guiding the choice of treatment modality for patients being considered for intervention.

We established that TAVR was also associated with a lower risk of the composite end point of death or disabling stroke, again with a significant interaction for access suitability. In patients suitable for transfemoral access, we demonstrated a low number needed to treat to prevent one death or disabling stroke. This is an important observation, as with reduced sheath profiles in current-generation TAVR systems, transfemoral TAVR is now feasible in the vast majority of patients.[44, 45]

Cox proportional-hazards regression analysis of the primary and secondary end points did not show any significant interactions by baseline surgical risk or the type of TAVR system used, suggesting that the lower risk of death and disabling stroke associated with TAVR is not dependent on patient surgical risk, nor is it dependent on the type of TAVR system used. These observation suggests broad applicability of the findings of the primary and secondary end points.

We assessed the primary and secondary end points using reconstructed individual patient data. This methodology is more robust than aggregate data meta-analysis.[46] Furthermore, a strength of this methodology is that it allowed us to perform landmark analysis, which demonstrated that between 0 and 3 months, TAVR was associated with a lower risk of the primary and secondary end points, and that between 3 months and 12 months, TAVR and surgery were associated with a similar risk of these end points. This is an especially important

observation, which demonstrates that the benefit of TAVR is driven by a lower risk of periprocedural events and furthermore, TAVR is not associated with a higher risk of late events. In addition, while randomised data out to 5 years is limited, we demonstrated that the evidence to date does not suggest any presence of a very late "catch up" phenomenon, as there was no increased risk of very late events with TAVR.

At 1 year, TAVR was associated with a lower risk of life-threatening or disabling bleeding, cardiogenic shock, acute kidney injury and new-onset atrial fibrillation. These are most likely the drivers for the lower risk of the primary and secondary end points.

It is important to recognise that the benefits of transfemoral TAVR in regards to primary and secondary end points came at a higher risk for several important clinical outcomes. At 1 years, TAVR was associated with a higher risk of major vascular complication, new left bundle branch block, permanent pacemaker implantation, paravalvular regurgitation, transient ischemic attack and aortic valve reintervention. Many of these risks have been well-described, and it should be recognised that both permanent pacemaker implantation and paravalvular regurgitation have been associated with poorer outcomes after TAVR.[47-49] Furtheremore, the higher indence of moderate/severe paravalvular regurgitation is most likely the driver for the higher risk of aortic valve reintervention.

The finding that TAVR was associated with a higher risk of transient ischemic attack, with low heterogeneity across trials, has not been described. This is an interesting finding, especially given that TAVR was associated with a lower risk of atrial fibrillation. Whilst one might speculate as to the cause of this, it should be recognised that transient neurological deficits may be a challenging clinical end point to adjudicate.[50] Furthermore, given the large number of tertiary end points assessed in this meta-analysis, it is possible that this finding may represent a Type I statistical error.

Our meta-analysis showed that TAVR was associated with superior valve hemodynamics at all time points. Only limited mid-term follow-up was available for this meta-analysis and further work is needed to establish long-term TAVR prosthesis durability. Nonetheless, we found no evidence to suggest a higher incidence of structural valve deterioration with transcatheter heart valves.

TAVR was associated with a shorter duration of index hospitalisation. Furthermore, while TAVR and surgery were associated with similar long-term improvements in symptom status and health-related quality of life measures, these improvements were faster with TAVR, an important consideration for clinicians and patients.

Limitations

Our meta-analysis would be enhanced by a full individual patient data set, which would have allowed us to undertake a more detailed subgroup analysis of the primary and secondary end points. In particular, it would have also allowed us to better stratify patients baseline covariates such as access suitability and surgical risk, which were assumed to be consistent within individual trials, unless otherwise specified. This assumption meant that 3.6% of our transfemoral access cohort were actually treated via non-transfemoral access. However, as results strongly favoured TAVR in patients suitable for transfemoral access, this anomaly is unlikely to have materially altered our findings.

Our meta-analysis primarily focussed on 1-year outcomes, as this was the earliest time point that all major randomised trials had published outcomes. While 5-year data was encouraging, there remains potential concerns regarding longer-term TAVR prosthesis durability, leaflet thrombosis, permanent pacemaker implantation and paravalvular regurgitation, and therefore the potential for a very late “catch-up” phenomenon between treatment groups remains.

There were very few young patients in this meta-analysis and our findings should not be generalized to that patient cohort. Our findings should also not be generalized to patients who meet the exclusion criteria for these trials, such as 1) unprotected left main coronary artery disease requiring revascularization, 2) multivessel coronary artery disease with intermediate-to-high Syntax score requiring revascularization, 3) congenital bicuspid or unicuspid aortic valve, and 4) end-stage renal disease.

Nevertheless, our meta-analysis has significant strengths, in particular, the use of reconstructed individual patient data to explore both primary and secondary end points.

Conclusion

At 1 year, TAVR was associated with a lower risk of death, disabling stroke and the composite end point of death from any cause or disabling stroke, when compared with surgery. These associations were independent of both patient surgical risk and the type of TAVR system used and were strongest within the subgroup of patients in whom transfemoral access was feasible. Based on these findings, we propose that TAVR should become the recommended treatment modality for the majority of patients with symptomatic severe trileaflet aortic stenosis who have anatomy which is suitable for transfemoral access.

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Figure Titles and Descriptive Legends

Figure 1. Time-to-Event Curves for the Primary and Secondary End Points. (A) Death from any cause. (B) Death from any cause in patients suitable transfemoral access. (C) Disabling stroke. (D) Disabling stroke in patients suitable for transfemoral access. (E) Composite end point of death and disabling stroke. (F) Composite end point of death or disabling stroke in patients suitable for transfemoral access.

TAVR indicates Transcatheter Aortic Valve Replacement.

Figure 2. Subgroup Analyses for Death from Any Cause at 1 Year.

Figure 3. Echocardiographic Findings Over Time.* (A) Total aortic regurgitation. (B) Valve haemodynamics.

* Thirty-day findings were not reported in the SURTAVI trial, discharge findings have been used instead. Thirty-day findings were not reported in the NOTION trial, 3-month findings have been used instead.

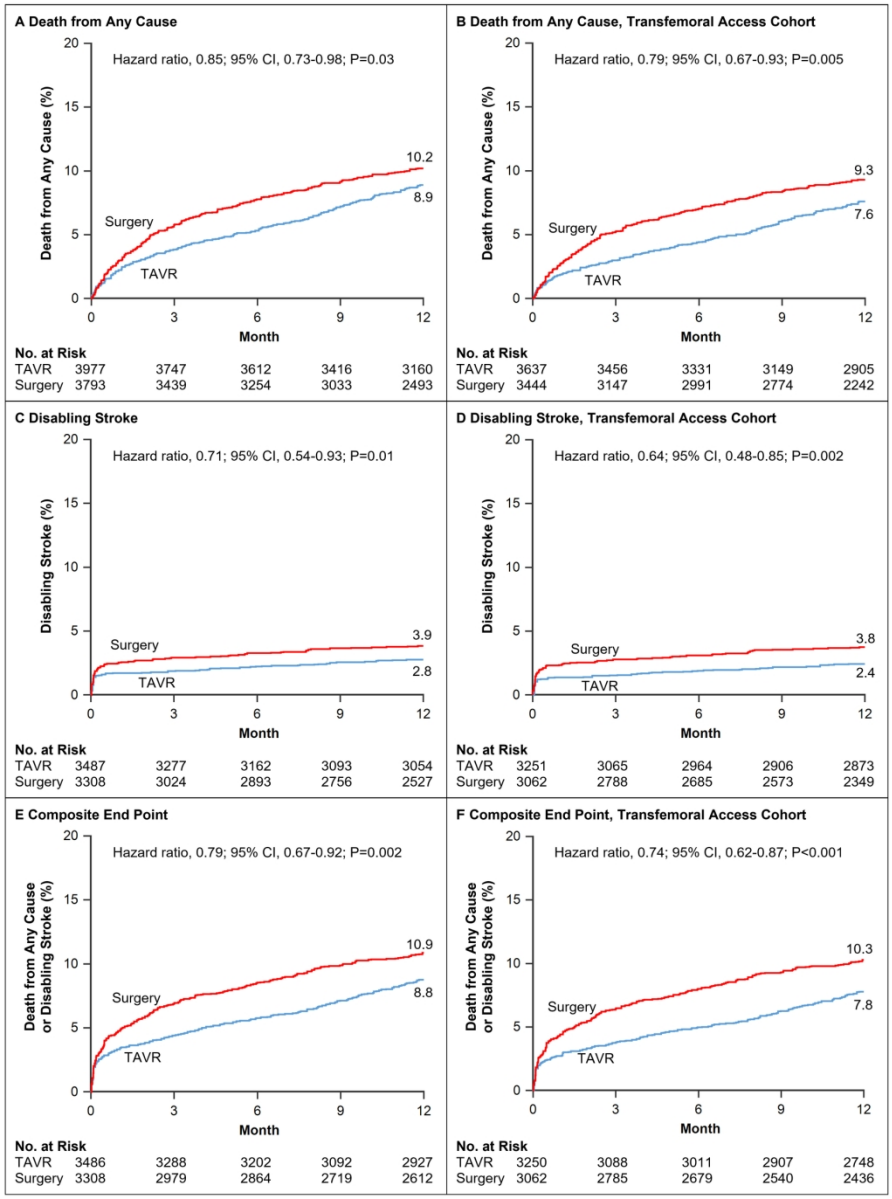
Error bars represent 1 SD.

Figure 4. Functional Status Over Time.* (A) New York Heart Association functional class. (B) Kansas City Cardiomyopathy Questionnaire score.

* Thirty-day symptom status was not reported in the NOTION trial, 3-month symptom status has been used instead.

KCCQ indicates Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association. KCCQ scores range from 0 to 100, with higher scores indicating better quality of life and fewer symptoms and a change of 5 points considered to be clinically meaningful.

Error bars represent 1 SD.



Time-to-Event Curves for the Primary and Secondary End Points. (A) Death from any cause. (B) Death from any cause in patients suitable transfemoral access. (C) Disabling stroke. (D) Disabling stroke in patients suitable for transfemoral access. (E) Composite end point of death and disabling stroke. (F) Composite end point of death or disabling stroke in patients suitable for transfemoral access. TAVR indicates Transcatheter Aortic Valve Replacement.

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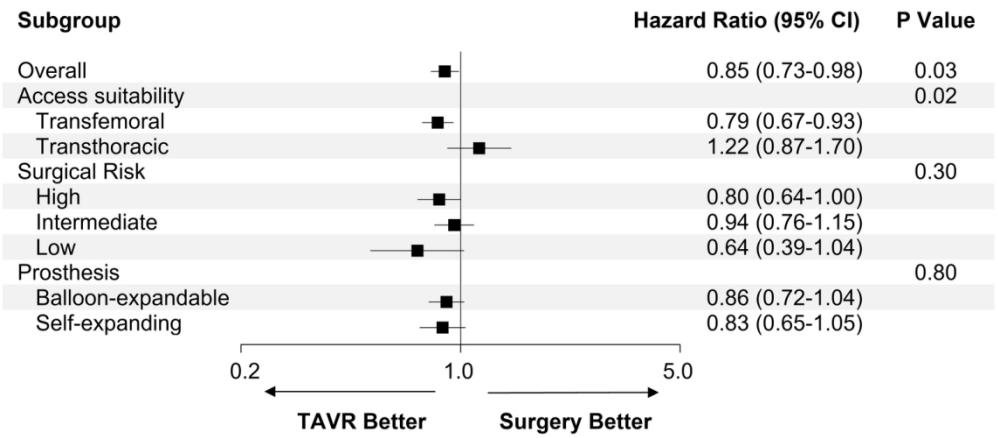

Subgroup Analyses for Death from Any Cause at 1 Year.

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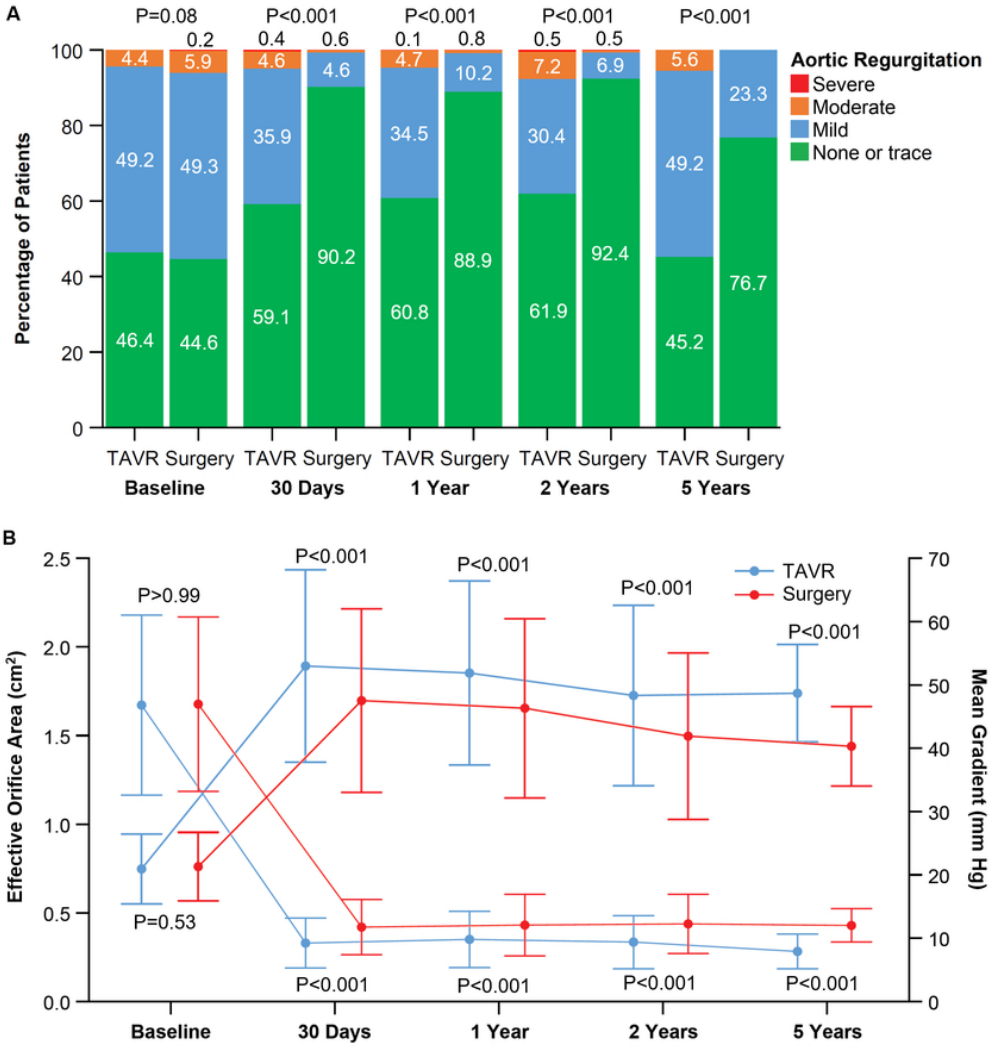

Echocardiographic Findings Over Time.* (A) Total aortic regurgitation. (B) Valve haemodynamics. * Thirty-day findings were not reported in the SURTAVI trial, discharge findings have been used instead. Thirty-day findings were not reported in the NOTION trial, 3-month findings have been used instead. Error bars represent 1 SD.

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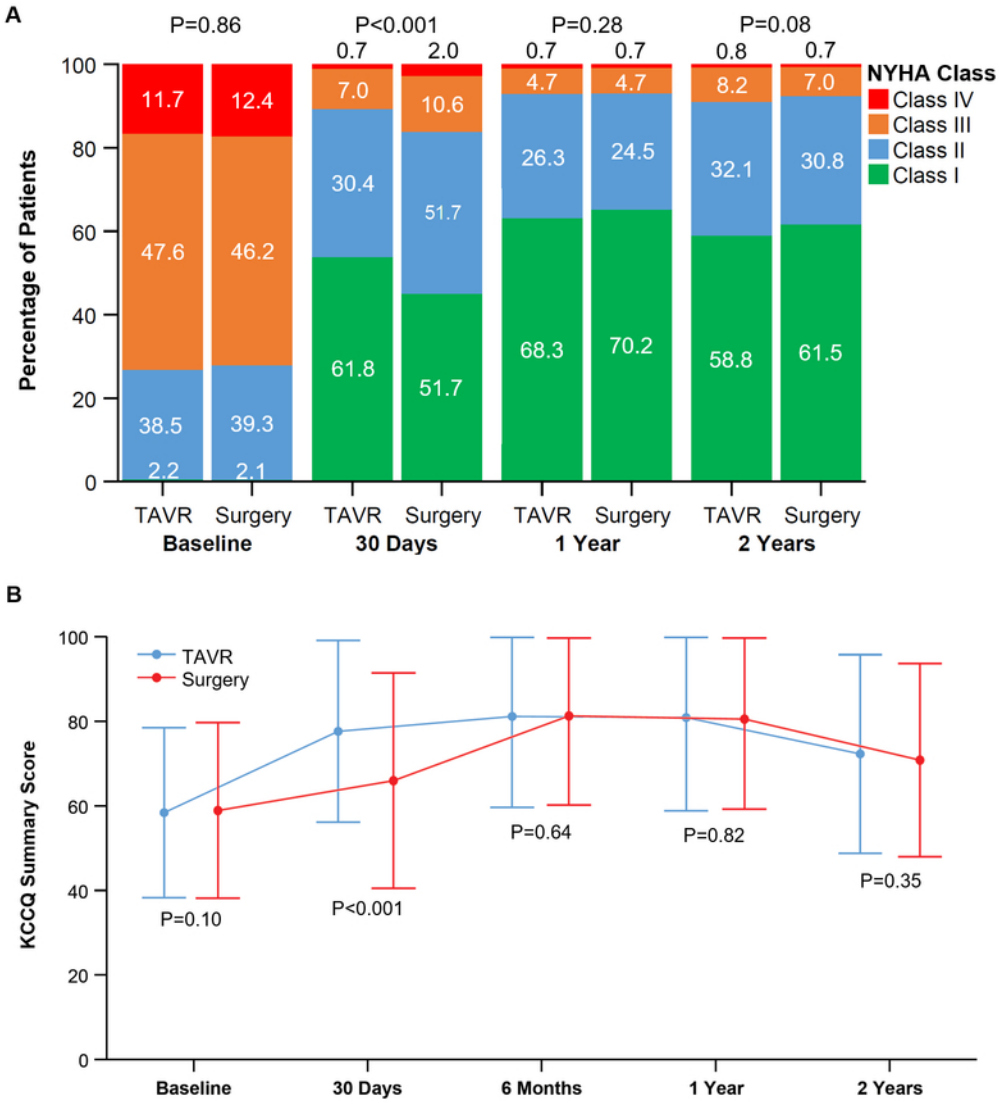

Functional Status Over Time.* (A) New York Heart Association functional class. (B) Kansas City Cardiomyopathy Questionnaire score. * Thirty-day symptom status was not reported in the NOTION trial, 3-month symptom status has been used instead. KCCQ indicates Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association. KCCQ scores range from 0 to 100, with higher scores indicating better quality of life and fewer symptoms and a change of 5 points considered to be clinically meaningful. Error bars represent 1 SD.

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Table I. Characteristics of the Patients at Baseline.

Characteristic	TAVR (N = 3979)*	Surgery (N = 3792)*	P Value
Age – yr	79.0±6.3	79.2±6.2	0.37
Male sex – no./total no. (%)	2331/3979 (58.6)	2226/3792 (58.7)	0.93
NYHA class III/IV – no./total no. (%)	2371/3978 (59.6)	2239/3788 (59.1)	0.66
STS-PROM score†	4.9±1.9	5.0±2.0	0.02
Medical condition – no./total no. (%)			
Diabetes mellitus	1221/3631 (33.6)	1160/3440 (33.7)	0.94
Serum creatinine >2 mg/dL	109/3584 (3.0)	98/3435 (2.9)	0.67
Hypertension	1889/2123 (89.0)	1724/1965 (87.7)	0.67
Previous stroke	641/3955 (16.2)	636/3756 (16.9)	0.41
Previous TIA	108/1254 (8.6)	94/1152 (8.2)	0.71
Peripheral vascular disease	949/3963 (23.9)	962/3779 (25.5)	0.13
Permanent pacemaker	402/3976 (10.1)	392/3788 (10.3)	0.74
Cardiac risk factors – no./total no. (%)			
Coronary artery disease	1932/3106 (62.2)	1854/2974 (62.3)	0.92
Previous CABG	657/3335 (19.7)	675/3196 (21.1)	0.16
Previous PCI	801/3476 (23.0)	794/3325 (23.9)	0.42
Previous myocardial infarction	585/3973 (14.7)	548/3782 (14.5)	0.77
Atrial fibrillation or flutter	1024/3822 (26.8)	1024/3609 (28.4)	0.13

COPD indicates chronic obstructive pulmonary disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TIA, transient ischemic attack.

* There are some slight differences in the number of patients in the baseline characteristics and the Kaplan-Meier analysis due to some early publication errors, which were corrected in later publications.

Supporting Information Figure Titles and Descriptive Legends

Supporting Information Figure 1. PRISMA Flow Diagram.

Supporting Information Figure 2. Funnel Plot for the Primary End Point.

Supporting Information Figure 3. Subgroup Analyses for Disabling Stroke at 1 Year.

Supporting Information Figure 4. Subgroup Analyses for the Composite End Point of Death from Any Cause or Disabling Stroke at 1 Year.

Supporting Information Figure 5. Landmark Analysis of the Primary and Secondary End Points.

(A) Death from any cause. (B) Death from any cause in patients suitable transfemoral access. (C) Disabling stroke. (D) Disabling stroke in patients suitable for transfemoral access. (E) Composite end point of death and disabling stroke. (F) Composite end point of death or disabling stroke in patients suitable for transfemoral access.

Supporting Information Figure 6. Sensitivity Analysis for Death from Any Cause, By Excluding Individual Clinical Trials from the Analysis.

Supporting Information Figure 7. Kaplan-Meier Time-to-Event Curves for the Primary End Point at Five Years.*

* There is significant censoring of low-risk patients at the 1-year time point and further censoring of intermediate-risk patients at the 2-year time point.

Supporting Information Figure 8. Outcomes Favouring TAVR.

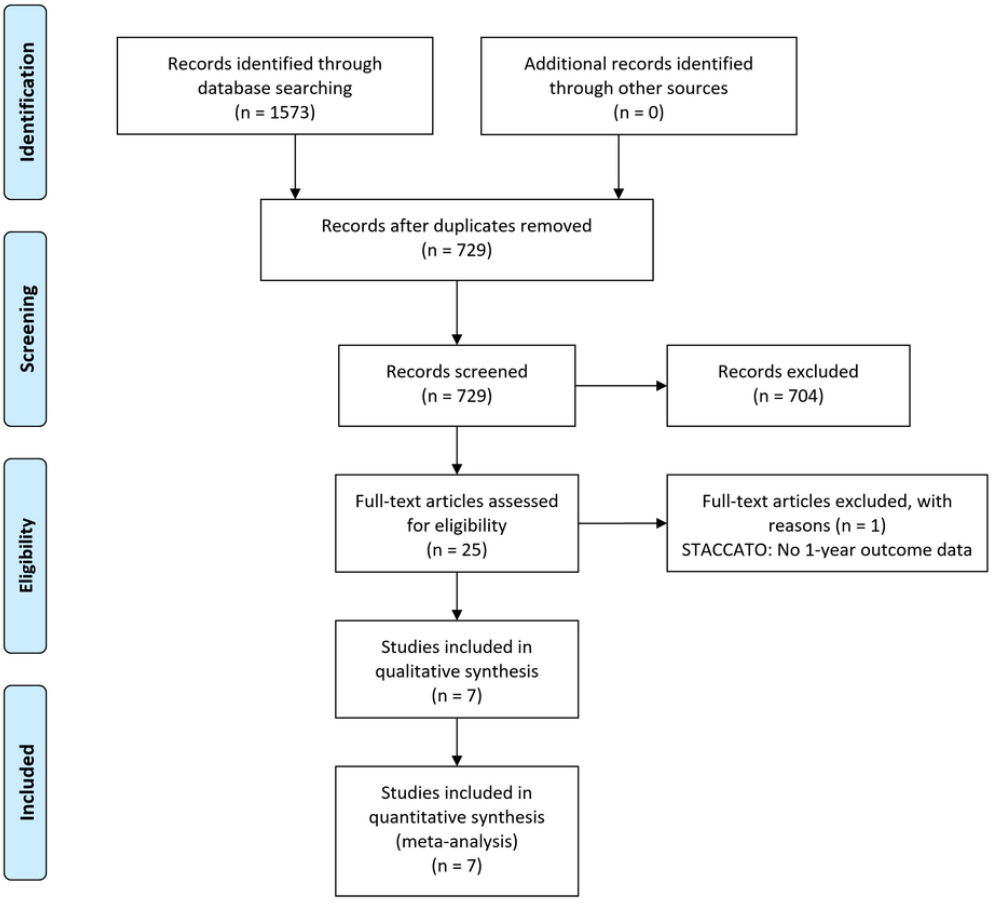
* At 30 days.

Supporting Information Figure 9. Outcomes Favouring Surgery.

* At 30 days.

Supporting Information Figure 10. Outcomes Not Favouring TAVR or Surgery.

* At 2 years.



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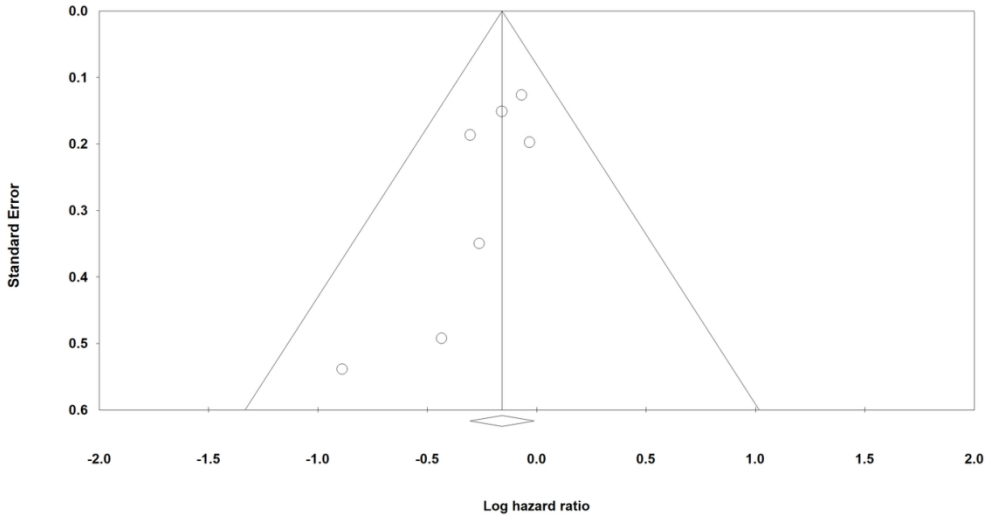

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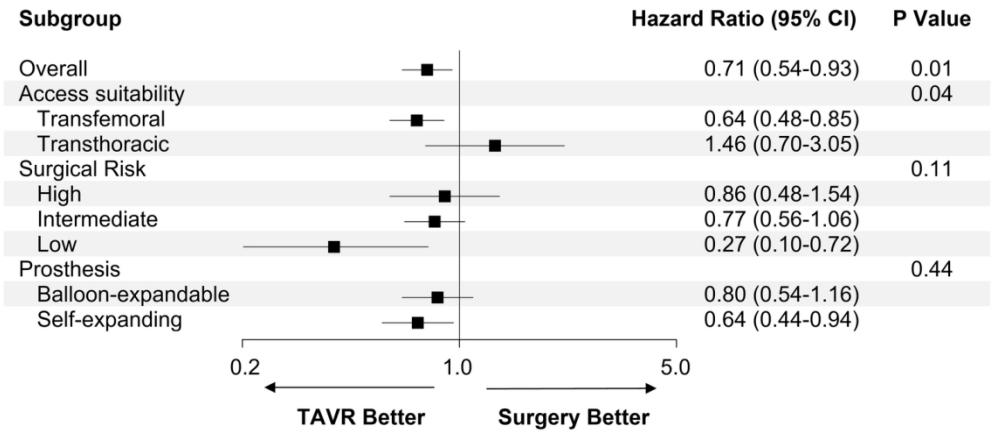

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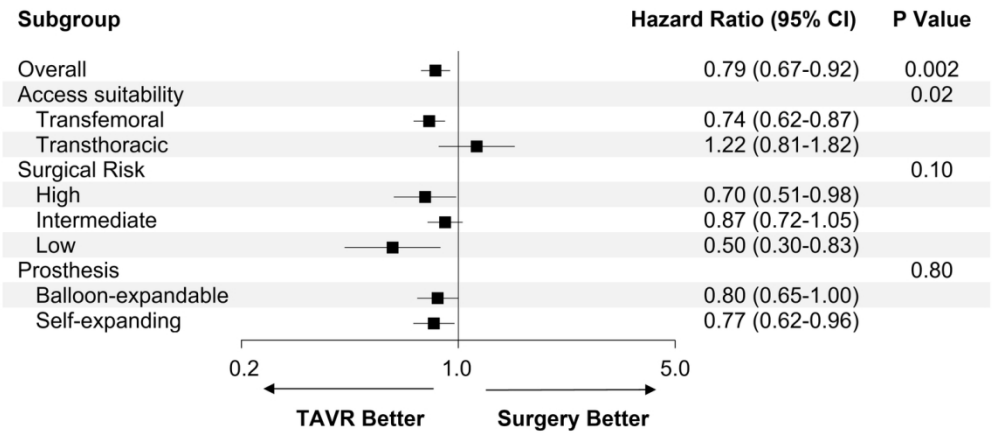

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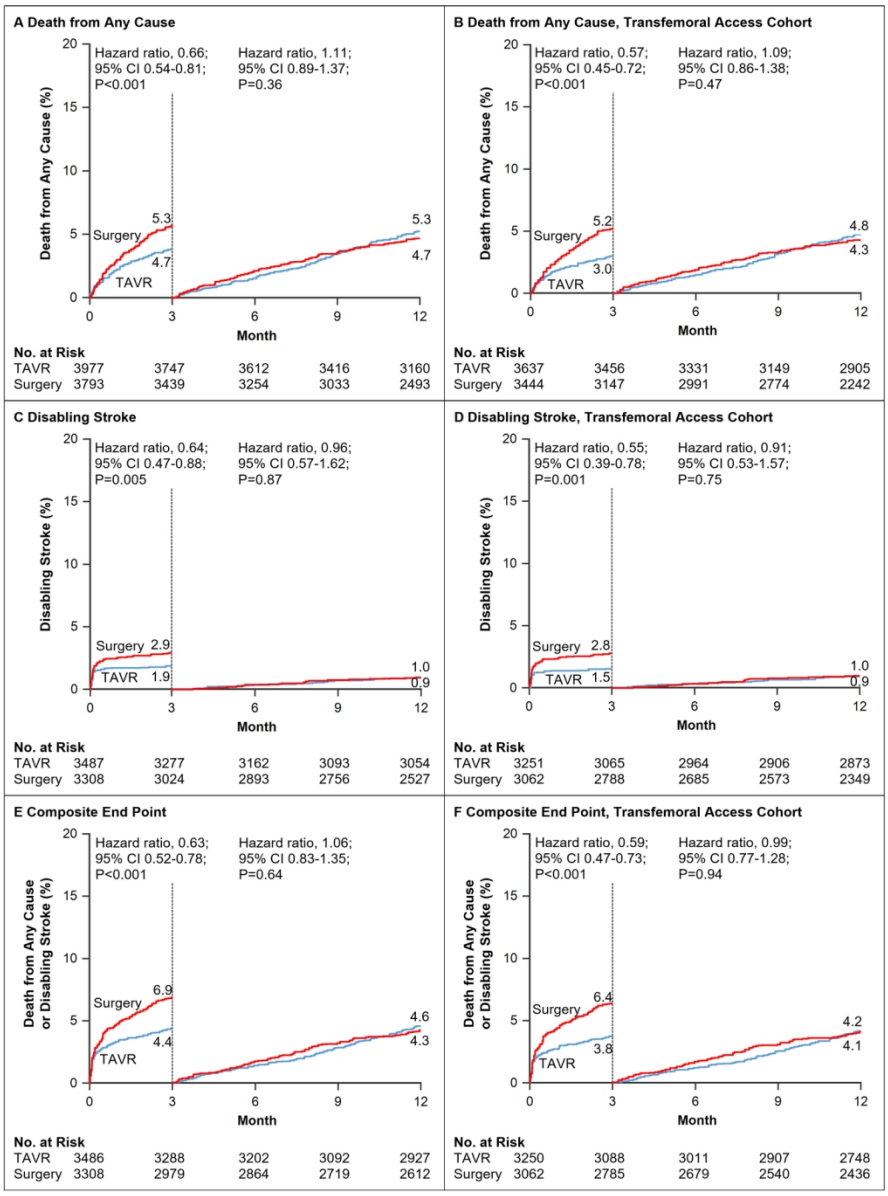

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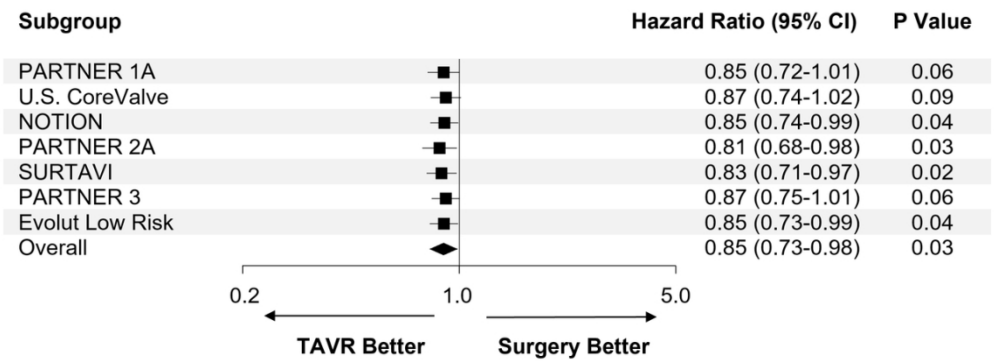

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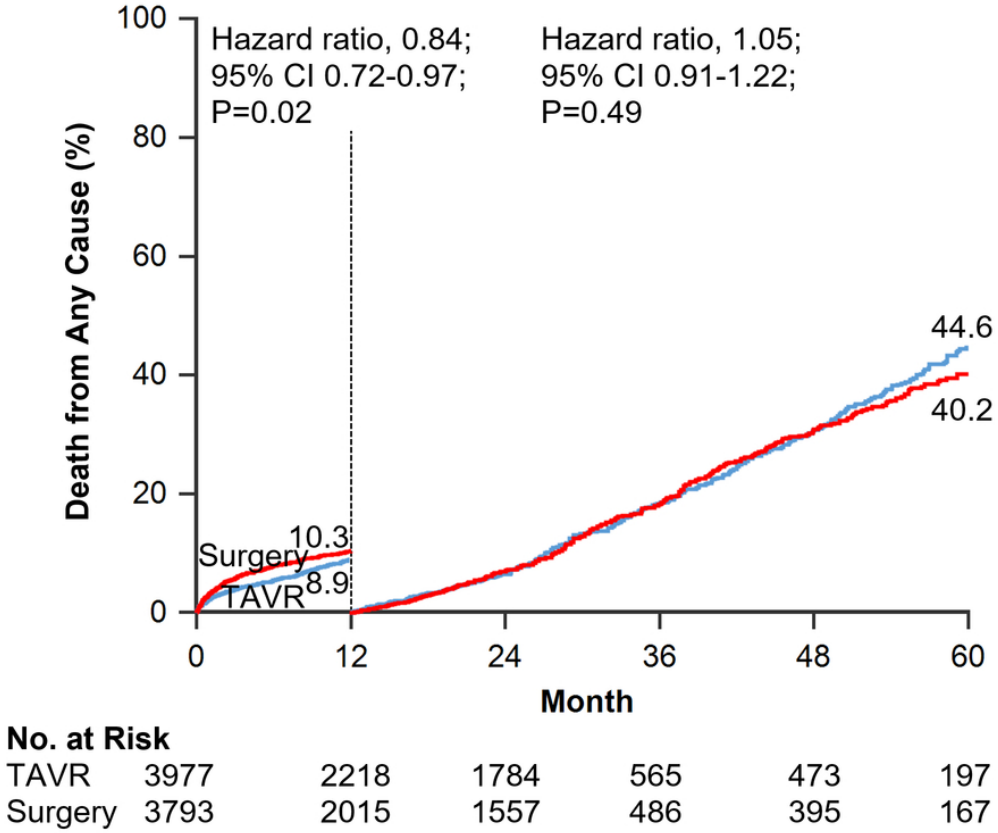

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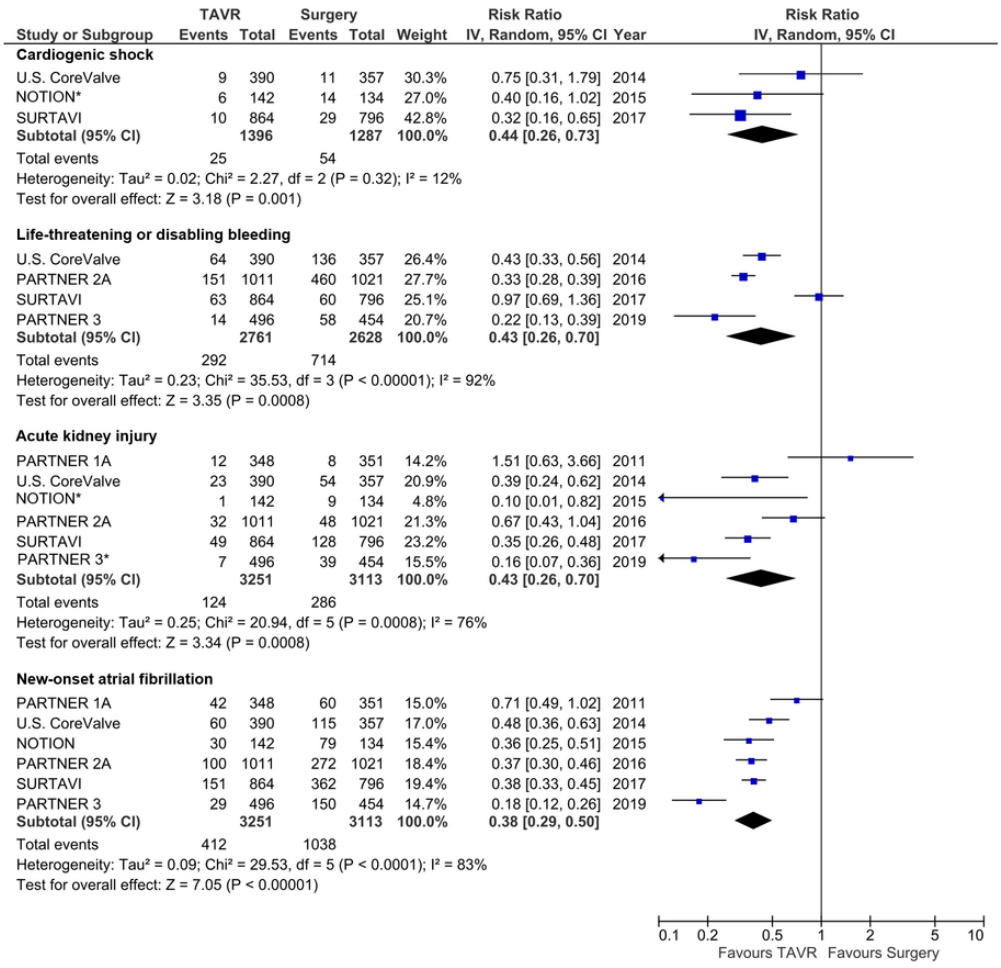

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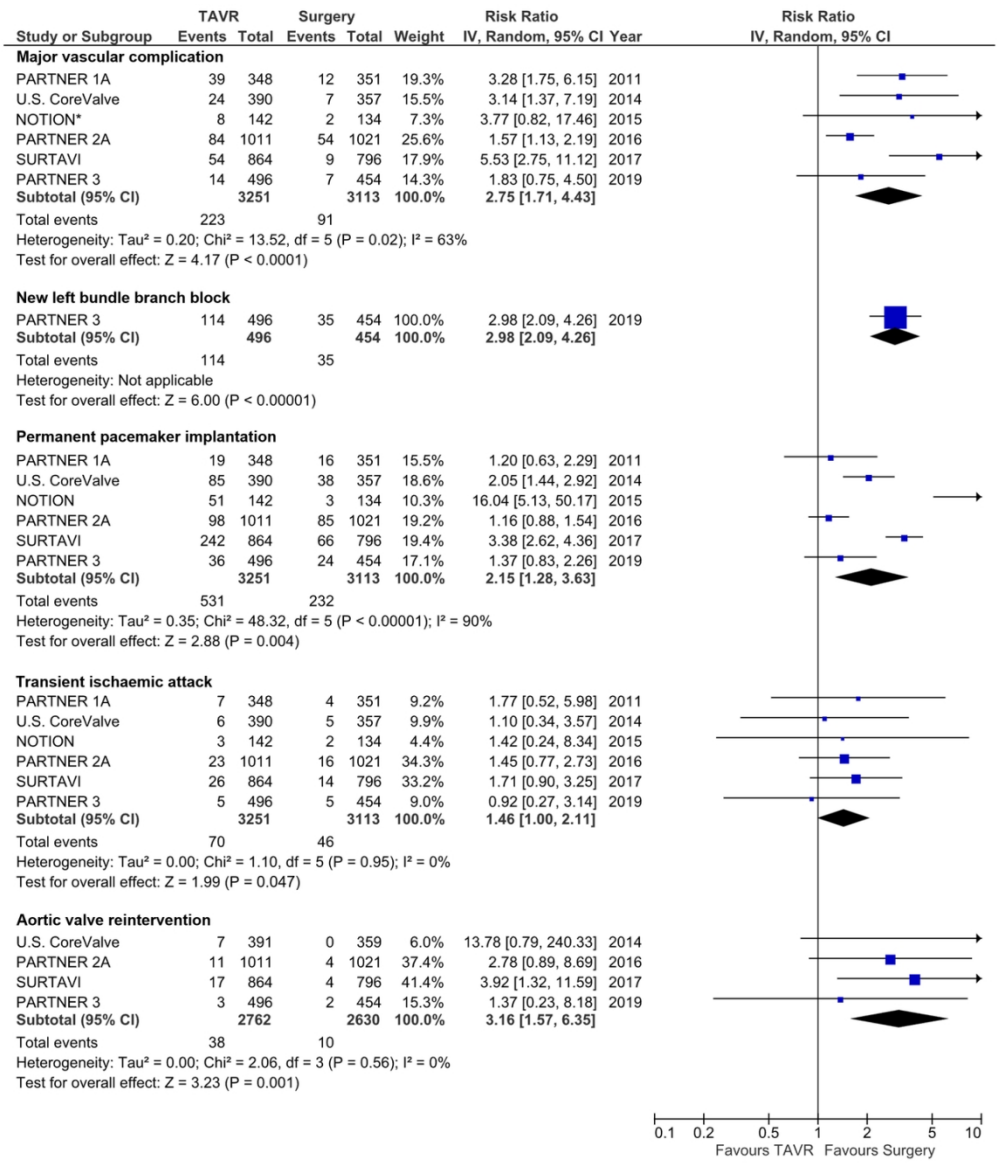

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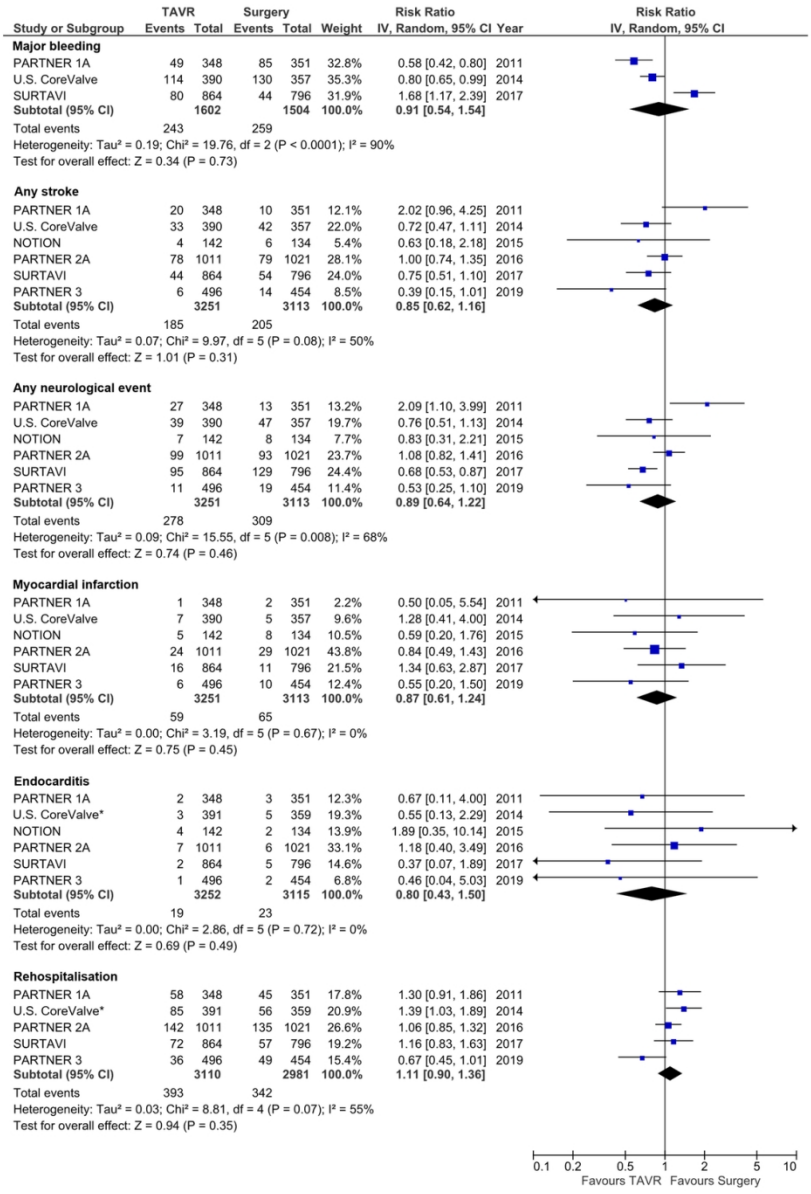

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Supporting Information Table I. Details of Literature Review.

Medline		
#1	(transcatheter aortic valve implantation OR TAVI OR transcatheter aortic valve replacement or TAVR)	
#2	(randomised or randomized)	
#3	(surgery or surgical aortic valve replacement or SAVR)	
#4	#1 and #2 and #3	
#5	Limit #4 Publication Date 2012/01/01 to 2019/03/27	**565 items**
Embase		
#1	aortic stenosis.mp. or exp aorta stenosis/	
#2	(aortic valve implantation or heart valve implantation or TAVR or TAVI or transcatheter or transfemoral or transapical or transaxillary or SAVR or heart valve replacement or surgical aortic valve replacement or surgical AVR or SAVR or aortic valve replacement or transvascular).af.	
#3	random:.tw. or placebo:.mp. or double-blind:.tw.	
#4	#1 and #2 and #3	
#5	limit 4 to yr="2012 -2019"	**729 items**
Cochrane CENTRAL		
#1	MeSH descriptor: [Aortic Valve Stenosis] explode all trees	
#2	aortic near stenosis*:ti,ab,kw	
#3	aortic near stenoses*:ti,ab,kw	
#4	#1 or #2 or #3	
#5	MeSH descriptor: [Transcatheter Aortic Valve Replacement] explode all trees	
#6	#4 and #5 Publication Year from 01/2012 to 03/2019	**107 items**
ClinicalTrials.gov		
#1	Intervention: transcatheter aortic valve	
#2	#1 and Recruitment: All recruitment status except “No yet recruiting, recruiting or enrolling by invitation”	**172 items**

Supporting Information Table II. Risk of Bias Assessment.

Trial	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting
PARTNER 1A	Low risk	Unclear risk	Low risk	Low risk	Low risk
U.S. CoreValve	Low risk	Unclear risk	Low risk	Low risk	Low risk
NOTION	Low risk	Low risk	Low risk	Low risk	Low risk
PARTNER 2A	Low risk	Unclear risk	Low risk	Low risk	Low risk
SURTAVI	Low risk	Unclear risk	Low risk	High risk*	Low risk
PARTNER 3	Low risk	Unclear risk	Low risk	Low risk	Low risk
Evolut Low Risk	Low risk	Unclear risk	Low risk	High risk*	Low risk

* The SURTAVI and Evolut Low Risk trials did not have complete follow-up at the time of publication.

Supporting Information Table III. Characteristics of TAVR Procedures.

Trial	TAVR system*	TF access	Alternative access	Revascularization
PARTNER 1A	SAPIEN	70.1%	Transapical 29.8%	Excluded
U.S. CoreValve	CoreValve	83.8%	Subclavian and Direct Aortic 16.2%	Excluded
NOTION	CoreValve	96.5%	Subclavian 3.5%	Excluded
PARNTER 2A	SAPIEN XT	76.3%	Transapical and Direct Aortic 23.7%	Allowed†
SURTAVI	CoreValve 84% Evolut R 16%	93.6%	Subclavian 2.3% Direct Aortic 4.1%	Allowed‡
PARNTER 3	SAPIEN 3	100.0%§		Allowed†
Evolut Low Risk	CoreValve 3.6% Evolut R 74.1% Evolut PRO 22.3%	99.0%	Subclavian 0.6% Direct Aortic 0.4%	Allowed‡

TF indicates transfemoral.

* The SAPIEN, SAPIEN XT and SAPIEN 3 heart valve systems are balloon-expandable, whereas the CoreValve, Evolut R and Evolut PRO are self-expanding.

† Unprotected left main and Syntax Score > 32 were excluded.

‡ Unprotected left main and Syntax Score > 22 were excluded.

§ Patients with iliofemoral anatomy not suitable for transfemoral access were excluded

Supporting Information Table IV. Validation of Reconstructed Individual Patient Data Event Rates.

Trial	Reported event rate			Reconstructed event rate		
	TAVR	Surgery	P Value	TAVR	Surgery	P Value
PARTNER 1A	114/348 (35.0)	116/351 (33.9)	0.78	116/348 (34.3)	115/351 (34.8)	0.60
U.S. CoreValve	85/391 (22.2)	99/359 (28.6)	0.04	81/391 (21.9)	96/359 (28.5)	0.04
NOTION	11/142 (8.0)	13/134 (9.8)	0.54	10/142 (7.6)	13/134 (10.0)	0.46
PARTNER 2A	166/1011 (16.7)	170/1021 (18.0)	0.45	165/1011 (16.6)	172/1021 (18.1)	0.36
SURTAVI*	(11.4)	(11.6)		77/864 (11.3)	70/796 (11.6)	0.99
PARTNER 3	5/496 (1.0)	11/454 (2.5)		5/496 (1.0)	11/454 (2.4)	0.09
Evolut Low Risk*	(2.4)	(2.9)		15/725 (2.3)	18/678 (2.9)	0.45

All percentages are Kaplan-Meier estimates and thus do not equal the number of patients divided by the total number in the study group.

* Event numbers and log-rank P values were not reported in the SURTAVI and Evolut Low Risk trials. Estimated incidences are presented.

Supporting Information Table V. Validation of Reconstructed Individual Patient Data Hazard Ratios.

Trial	Reported HR (95% CI)	P Value	Reconstructed HR (95% CI)	P Value
PARTNER 1A	0.90 (0.71-1.15)	0.41	0.90 (0.71-1.14)	0.37
PARTNER 2A	0.92 (0.74-1.13)	0.42	0.91 (0.73-1.12)	0.36
PARTNER 3	0.41 (0.14-1.17)		0.41 (0.14-1.18)	0.10

Hazard ratios were not reported in the U.S. CoreValve, NOTION and SURTAVI trials.
CI indicates confidence interval; HR, hazard ratio.