

BMJ Open Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review and meta-analysis

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ABSTRACT

Objectives Patients undergoing surgery for severe aortic stenosis (SAS) can be treated with either transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR). The choice of procedure depends on several factors, including the clinical judgement of the heart team and patient preferences, which are captured by actively informing and involving patients in a process of shared decision making (SDM). We synthesised the most up-to-date and accessible evidence on the benefits and risks that may be associated with TAVI versus SAVR to support SDM in this highly personalised decision-making process.

Design Systematic review and meta-analysis.

Data sources MEDLINE (Ovid), Embase (Ovid) and the Cochrane Central Register of Controlled Trials (CENTRAL; Wiley) were searched from January 2000 to August 2020 with no language restrictions. Reference lists of included studies were searched to identify additional studies.

Eligibility criteria Randomised controlled trials (RCTs) that compared TAVI versus SAVR in patients with SAS and reported on all-cause or cardiovascular mortality, length of stay in intensive care unit or hospital, valve durability, rehospitalisation/reintervention, stroke (any stroke or major/disabling stroke), myocardial infarction, major vascular complications, major bleeding, permanent pacemaker (PPM) implantation, new-onset or worsening atrial fibrillation (NOW-AF), endocarditis, acute kidney injury (AKI), recovery time or pain were included.

Data extraction and synthesis Two independent reviewers were involved in data extraction and risk of bias (ROB) assessment using the Cochrane tool (one reviewer extracted/assessed the data, and the second reviewer checked it). Dichotomous data were pooled using the Mantel-Haenszel method with random-effects to generate a risk ratio (RR) with 95% CI. Continuous data were pooled using the inverse-variance method with random-effects and expressed as a mean difference (MD) with 95% CI. Heterogeneity was assessed using the I^2 statistic.

Results 8969 records were retrieved and nine RCTs (61 records) were ultimately included (n=8818 participants). Two RCTs recruited high-risk patients, two RCTs recruited intermediate-risk patients, two RCTs recruited low-risk

Strengths and limitations of this study

- This systematic review (SR) assesses two treatments (transcatheter aortic valve implantation (TAVI) vs surgical aortic valve replacement, SAVR) for patients with severe aortic stenosis.
- Aims to support shared decision making by presenting evidence across a broad range of treatment outcomes, a wide range of surgical risk levels and a uniquely large number of subgroups which can inform decision-making of individual patients.
- Patients were involved in an initial needs assessment based on their priorities and experience, which ultimately evolved into the prespecified outcomes of interest.
- Methods follow guidance by Cochrane, the Centre for Reviews and Dissemination as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guideline and the SR was registered on PROSPERO.
- Includes several new randomised controlled trials or long-term study outcomes that have not yet been incorporated into pooled analysis for TAVI versus SAVR across different risk levels, especially in low-risk patients and in key subgroups of interest.

patients, one RCT recruited high-risk (≥ 70 years) or any-risk (≥ 80 years) patients; and two RCTs recruited all-risk or 'operable' patients. While there was no overall change in the risk of dying from any cause (30 day: RR 0.89, 95% CI 0.65 to 1.22; ≤ 1 year: RR 0.90, 95% CI 0.79 to 1.03; 5 years: RR 1.09, 95% CI 0.98 to 1.22), cardiovascular mortality (30 day: RR 1.03, 95% CI 0.77 to 1.39; ≤ 1 year: RR 0.90, 95% CI 0.76 to 1.06; 2 years: RR 0.96, 95% CI 0.83 to 1.12), or any type of stroke (30 day: RR 0.83, 95% CI 0.61 to 1.14; ≤ 1 year: RR 0.94, 95% CI 0.72 to 1.23; 5 years: RR 1.07, 95% CI 0.88 to 1.30), the risk of several clinical outcomes was significantly decreased (major bleeding, AKI, NOW-AF) or significantly increased (major vascular complications, PPM implantation) for TAVI vs SAVR. TAVI was associated with a significantly shorter hospital stay vs SAVR (MD -3.08 days, 95% CI -4.86

to -1.29; 4 RCTs, n=2758 participants). Subgroup analysis generally favoured TAVI patients receiving implantation via the transfemoral (TF) route (vs non-TF); receiving a balloon-expandable (vs self-expanding) valve; and those at low-intermediate risk (vs high risk). All RCTs were rated at high ROB, predominantly due to lack of blinding and selective reporting.

Conclusions No overall change in the risk of death from any cause or cardiovascular mortality was identified but 95% CIs were often wide, indicating uncertainty. TAVI may reduce the risk of certain side effects while SAVR may reduce the risk of others. Most long-term (5-year) results are limited to older patients at high surgical risk (ie, early trials), therefore more data are required for low risk populations. Ultimately, neither surgical technique was considered dominant, and these results suggest that every patient with SAS should be individually engaged in SDM to make evidence-based, personalised decisions around their care based on the various benefits and risks associated with each treatment.

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INTRODUCTION

In the pretranscatheter aortic valve implantation (TAVI) era, patients with severe degenerative symptomatic aortic stenosis (SAS) at high surgical risk had limited access to treatment options, as surgical aortic valve replacement (SAVR) was considered to have an unacceptably elevated risk of complications or death.¹ TAVI was developed as a lower impact, minimally invasive surgical alternative to provide such patients with a much-needed therapeutic option to ameliorate disease symptoms and improve quality of life. TAVI is now being more widely discussed as a useful option for patients at intermediate or even lower levels of surgical risk.

While guidelines do not yet formally recommend TAVI as a first-choice therapy in low-risk patients,²⁻⁴ several new trials have recently reported promising early-term and mid-term data for patients at lower levels of risk. However, current evidence suggests that clinical practice has not yet effectively incorporated TAVI into shared decision making (SDM) processes in patients with SAS who are at lower levels of risk.⁵ The use of decision aids in SDM for patients with SAS has been shown to increase patient knowledge and satisfaction.⁶ Yet the provision of too little information within decision aids is frequently described by patients as a critical barrier to the SDM process.⁵ Therefore, the aim of our systematic review (SR) was to generate a highly accessible and comprehensive dataset that clearly described the current evidence around the risks that may be associated with TAVI versus SAVR.

Several recent SRs and meta-analyses (MAs) have been published that compare patient outcomes following TAVI versus SAVR.⁷⁻⁹ For example, Barili *et al* and Wang *et al* reported exclusively on all-cause mortality, and indicated similar risks of death for TAVI vs SAVR at early time points^{7 8}; Barili *et al* further reported that at late time points (40 months), all-cause mortality was higher for TAVI vs SAVR.⁷ In initial consultations carried out in our clinic (which informed the final outcomes investigated by our study), patients indicated that they wanted to consider outcomes beyond the risk of death from any cause. This highlighted a clear need for a SR and MA that included a

broad range of outcomes beyond mortality, and reported results in an accessible way to enable the evidence and conclusions to be used directly in a SDM context. We also identified that extensive subgroup analysis by route of TAVI, level of surgical risk and valve type across all patient outcomes was largely absent in recent SRs and MAs, and yet was considered by our team to be critical, since these three factors can, in large part, be dictated by issues such as patient frailty; anatomical restrictions that limit transfemoral (TF) access, precluding a TF-first approach; and policies and practices that are implemented at either the national or institutional level that govern which valves are available. Finally, we aimed to incorporate new trial data from the UK TAVI study,^{10 11} which has not, to our knowledge, been incorporated into any existing MAs.

The ultimate goal of this study was to generate accessible data that could be used by patients, together with their doctors, to make tailored treatment decisions based on the types of benefits and risks they were willing to accept. This SR was performed as part of a wider project to implement a formal decision aid-based SDM process for patients at the University Hospital of Kiel using the most up-to-date, comprehensive and methodologically rigorous evidence available.¹²

METHODS

This SR was carried out in accordance with the methodologies recommended by Cochrane¹³ and the Centre for Reviews and Dissemination¹⁴ following Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.^{15 16}

Search strategy and selection criteria

In order to identify relevant studies, several databases were searched from January 2000 to August 2020, including MEDLINE, In-Process & Other Non-Indexed Citations, Daily Update, Epub Ahead of Print (Ovid), Embase (Ovid) and Cochrane Central Register of Controlled Trials (CENTRAL; Wiley). The lower search date limit (2000) was set 2 years earlier than the first-in-man report of the TAVI procedure.¹⁷ Searches used a combination of text and database thesaurus terms. The search strategies were adapted to each resource and no limits or restrictions on language or publication status were applied. Reference lists of included articles were searched to identify additional studies. All search strategies are provided in online supplemental appendix S1.

Key inclusion criteria were defined using a Population, Intervention, Comparator, Outcome, Study Design approach. The population of interest was patients with severe aortic valve stenosis. The intervention of interest was TAVI compared with SAVR. Only randomised controlled trials (RCTs) were included to ensure that the conclusions and findings of the review were based on the best available evidence.

Titles and abstracts identified through electronic database and web searching, and subsequently full paper

copies of all potentially eligible references were screened independently by two reviewers; any disagreements were resolved by discussion. No restrictions were placed on language or publication status.

Data extraction

Microsoft Excel was used to compile data extraction sheets. Data extraction was performed by two reviewers. One reviewer extracted the data while the second reviewer checked the extractions. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

Outcomes of interest

Primary outcomes included: all-cause or cardiovascular mortality. Secondary outcomes included: length of stay in intensive care unit (ICU) or hospital; valve durability; rehospitalisation/reintervention; stroke (any stroke or major/disabling stroke); myocardial infarction (MI); major vascular complications; major bleeding; permanent pacemaker (PPM) implantation; new-onset or worsening atrial fibrillation (NOW-AF); endocarditis; acute kidney injury (AKI); recovery time and pain. These were included for all time points up to the longest available. Additional methodological details are reported in the online supplemental appendix.

We originally aimed to identify evidence on additional secondary outcomes (including: minor or non-disabling stroke; symptoms such as dyspnoea; 6 min walk test; exercise intensity; exercise duration; impact on activities of daily living; impact on family and carers; health-related quality of life (EQ-5D; KCCQ; SF-12; SF-36); and inconvenience/costs from treatment (eg, need for rehabilitation)), but ultimately had to streamline the final outcomes of interest (after the full-text screening stage) due to budget restraints.

Risk of bias

The risk of bias (methodological quality) of each included study was assessed using the Cochrane Risk of Bias Tool for RCTs.¹⁸ Risk of bias assessment was performed by one reviewer and checked by a second reviewer. Any discrepancies were resolved by discussion or the intervention of a third reviewer.

Data synthesis and statistical analysis

All MAs were conducted using random-effects models. Dichotomous outcomes (eg, proportion of patients experiencing each type of outcome) were assessed using the Mantel-Haenszel method applying random-effects models to generate a risk ratio (RR) with 95% CI. Continuous outcomes were assessed using inverse variance applying random-effects models to generate a mean difference with 95% CI. If studies reported time-to-event outcomes, these were planned to be reported as hazard ratios (HRs) with 95% CI; however, this type of data was not identified. The selection of random-effects and fixed-effect models was made based on a judgement of both clinical and statistical heterogeneity.

We further presented our narrative results in an accessible way by calculating the rates from MAs (intervention vs

comparator) and transforming these into absolute numbers (and percentages of these; $X/100$ (%)) so that patients might be better able to understand them (following the International Patient Decision Aid Standards criteria for patient decision aids).¹⁹ The desire to report our results in a patient-accessible way also informed our choice of effect estimates, since presenting the data in this way would not have been possible with HRs or ORs. For dichotomous outcomes, no evidence of a difference in the effect estimate was set at ≥ 0.9 to ≤ 1.1 . Statistical significance was considered at $p \leq 0.05$. Pooled effect sizes and 95% CIs were only presented where there were two or more trials that were considered to be clinically and statistically homogeneous. The judgement of clinical heterogeneity was based on baseline characteristics of the trial populations (eg, age, gender). Statistical heterogeneity was assessed using the I^2 statistic. For the purposes of this review, a simplified categorisation of heterogeneity was used: low (0% to 25%), moderate (26% to 75%) and high ($>75\%$). Sensitivity analyses were considered in cases where high statistical or clinical heterogeneity was present.

We preferentially used the intention-to-treat (ITT) population, where reported. For major bleeding, we preferentially used the definition of 'life-threatening or disabling bleeding', where available. For AKI, we preferentially used the definition, 'stage 2–3 AKI', where available. All MAs were double-checked by a second reviewer. Forest plots for the main analyses were grouped by the stated study risk level, as defined by the study inclusion criteria; subgroup analyses by level of surgical risk were based exclusively on Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores within each study.

Subgroup analysis was prespecified based on TAVI route (TF vs non-TF), level of surgical risk (based on absolute STS-PROM scores) and valve type (balloon vs self-expanding).

All MAs were performed using Review Manager V.5.3. Publication bias was planned to be assessed where there were sufficient numbers of trials (ie, a minimum of ten trials), in line with published recommendations.²⁰

Patient and public involvement

Patients were involved in an initial needs assessment based on their priorities and experience, which ultimately evolved into our prespecified outcomes of interest. Patients were not involved in the formal design, conduct, analysis or reporting of this study.

RESULTS

Search results

We searched three main databases, and retrieved a total of 8969 records. Eight additional records were identified from reference checking included studies, and two records were identified by clinical experts. After deduplication, 6082 records remained. The flow of studies through the search and screening processes is summarised in figure 1.

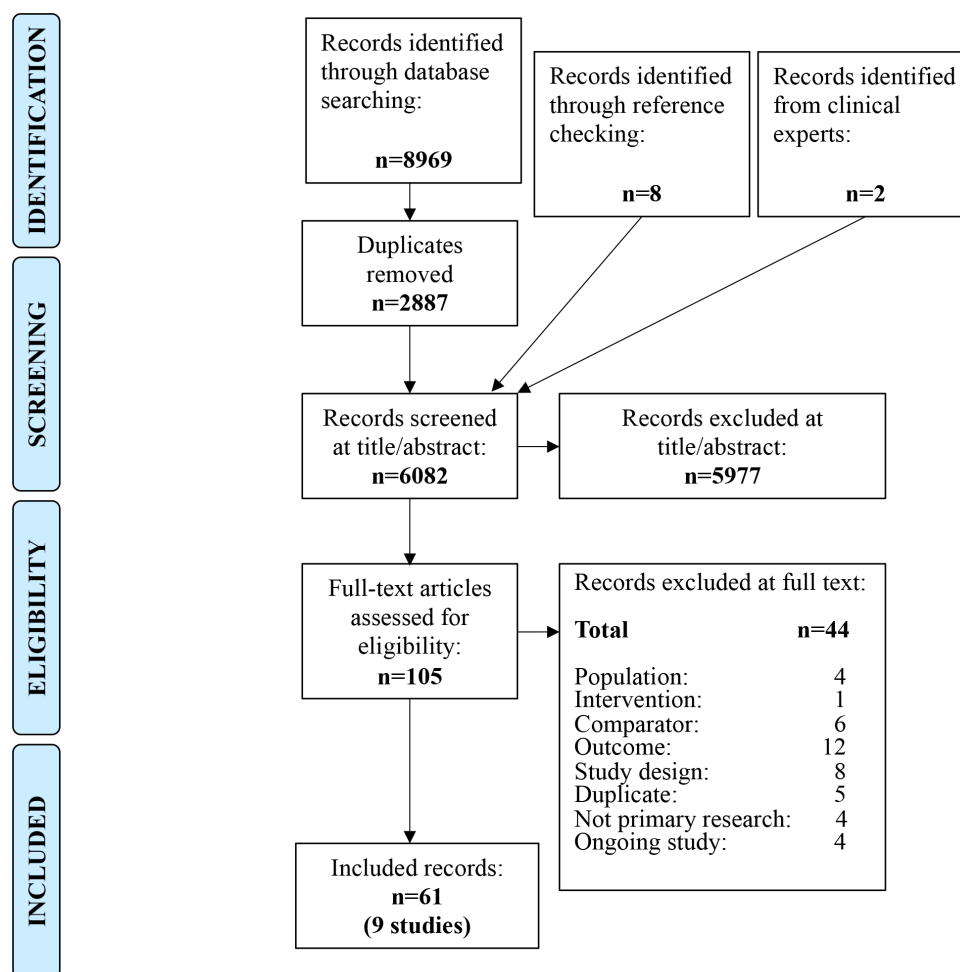


Figure 1 PRISMA study flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

In total, 6082 records were screened based on the title and abstracts; 105 were ordered for full text screening and 5977 were excluded. After the full-text screening stage, 61 records (9 studies) were identified for inclusion in the review.

Baseline characteristics of included studies

Nine RCTs (61 records; most studies had more than one associated publication) with a total of 8818 patients were identified that fit the inclusion criteria (table 1). Inclusion and exclusion criteria are provided in online supplemental table S1. Primary and secondary outcomes are provided in online supplemental table S2.

In terms of the disease of interest, all nine studies reported recruiting patients with SAS (table 1, online supplemental table S3). In terms of the level of surgical risk at the study level (which was based on the multifaceted, study-specific definitions provided in online supplemental table S3), two studies reported recruiting low-risk patients (EVOLUT, PARTNER 3), two studies reported recruiting intermediate-risk patients (PARTNER 2A, SURTAVI), two studies reported recruiting high-risk patients (PARTNER 1A, US CoreValve), one study reported recruiting intermediate-to-high-risk (≥ 70 years) or any risk (≥ 80 years) patients (UK-TAVI), one

study reported recruiting patients across all levels of risk (NOTION) and one study simply reported that patients should be 'operable' (STACCATO) (table 1, online supplemental table S3). The definitions of surgical risk varied substantially between studies (online supplemental table S3). In terms of the valve type, four of nine studies (50%) reported using a self-expanding valve, four of nine studies (50%) reported using a balloon-expandable valve, and one of nine studies reported using any type of CE-marked valve (table 1).

Publication bias

It was not possible to assess publication bias due to the relatively small number of included studies (<10).²⁰

Risk of bias assessment

All nine studies were assessed for risk of bias using the Cochrane risk of bias tool for RCTs, which contains eight assessment domains.¹³ Two studies had five domains at high risk of bias (SURTAVI, UK TAVI); five studies had four domains at high risk of bias (NOTION, PARTNER 1A, PARTNER 2A, PARTNER 3, STACCATO); and two studies had three domains at high risk of bias (EVOLUT, US CoreValve) (table 2). All studies were rated at high risk of bias for blinding

Table 1 Study characteristics

Study ID*, linked publications	Recruit-ment dates	Total sample size	Disease	Patient age (years)†	Level of surgical risk‡	TAVI route	Valve type(s)	Valve name	Funding source
High risk									
PARTNER 1A ^{26 35 59-67}	May 2007 to Aug 2009	699	SAS and cardiac symptoms	Not prespecified TAVI: 83.6 (6.8) SAVR: 84.5 (6.4)	TAVI: 11.8 (3.3); SAVR: 11.7 (3.5)	TF-first; TA if vascular access was limited	Balloon-expandable	Edwards Sapien	Pharma (EW)
US CoreValve ⁶⁸⁻⁸¹²³	Feb 2011 to Sep 2012	797	SAS and heart failure symptoms	No limits TAVI: 83.1 (7.1) SAVR: 83.2 (6.4)	TAVI: 7.3 (3.0); SAVR: 7.5 (3.4)	TF or non-TF (SC or direct aortic)	Self-expanding	MDT CoreValve	Pharma (MDT)
High-intermediate risk									
UK TAVI ¹¹ ¶	Apr 2014 to Apr 2018	913	Symptomatic SAS	≥80 or ≥70† TAVI: 81.1 (4.4) SAVR: 81.0 (4.5)	TAVI: 2.6 (2.0 to 3.5); SAVR: 2.7 (2.0 to 3.4)§	TF, TA, SC, direct aortic	Any CE-marked valve	SAPIEN, SAPIEN XT; SAPIEN 3 (all EW); CoreValve, Evolut/ Evolut R, Evolut Pro (all MDT); Lotus, Symetis Acurate/Neo (all BSX); Other (Portico, Direct Flow Medical)	Public/government (NIHR)
Intermediate risk									
PARTNER 2 A2 ^{134 21 34 82 83}	Dec 2011 to Nov 2013	2032	SAS	No limits TAVI: 81.5 (6.7) SAVR: 81.7 (6.7)	TAVI: 5.8 (2.1); SAVR: 5.8 (1.9)	TF or transthoracic (TA or TAO)	Balloon-expandable	SAPIEN XT (EW)	Pharma (EW)
SURTAV ^{28 84-92}	Jun 2012 to Jun 2016	1660	Symptomatic SAS	No limits TAVI: 79.9 (6.2) SAVR: 79.7 (6.1)	TAVI: 4.4 (1.5); SAVR: 4.5 (1.6)	TF-first; SC or TAO in the case of unsuitable iliofemoral anatomy	Self-expanding	CoreValve, Evolut R (all MDT)	Pharma (MDT)
Low risk									
EVOLUT ^{24 93}	Mar 2016 to Nov 2018	1468	SAS	No limits TAVI: 74.0 (5.9) SAVR: 73.8 (6.0)	TAVI: 1.9 (0.7); SAVR: 1.9 (0.7)	TF, subclavian or TAO	Self-expanding	CoreValve, Evolut R, Evolut PRO (all MDT)	Pharma (MDT)
PARTNER 3 ^{22 94-97}	Mar 2016 to Oct 2017	950	SAS	No limits TAVI: 73.3 (5.8) SAVR: 73.6 (6.1)	TAVI: 1.9 (0.7); SAVR: 1.9 (0.6)	TF	Balloon-expandable	SAPIEN 3 (EW)	Pharma (EW)
All risk									
NOTION ^{25 98-105}	Dec 2009 to Apr 2014	280	Degenerative SAS	≥70 TAVI: 79.2 (4.9) SAVR: 79.0 (4.7)	TAVI: 2.9 (1.6); SAVR: 3.1 (1.7)	TF-first; left SC access considered when the TF route not accessible	Self-expanding	CoreValve (MDT)	Charity (The Danish Heart Foundation)
STACCATO ^{27 106 107}	Nov 2008 to May 2011	70	SAS	Initially ≥70; later modified to ≥75 TAVI: 80 (3.6) SAVR: 82 (4.4)	'Operable' TAVI: 3.1 (1.5); SAVR: 3.4 (1.2)	TA	Balloon-expandable	Edwards Sapien	Public/government (University, DHF)

All studies are randomised controlled trials, as per our inclusion criteria.

*Main publication provided.

†Mean (SD) are provided.

‡STS-PROM scores are provided (mean (SD)).

§Median and IQR.

¶If patients are considered at intermediate or high operative risk from conventional AVR by a multidisciplinary heart team.

EW, Edward Lifesciences; MDT, Medtronic; NA, not applicable; NIHR, National Institute for Health Research; NYHA, New York Heart Association; SAS, severe aortic stenosis; SAVR, surgical aortic valve replacement; SC, subclavian; STS, society for thoracic surgeons; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TA, transapical; TAO, transaortic; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

Table 2 Risk of bias assessment

Study ID	Level of surgical risk	Randomisation	Allocation concealment	Are participants blinded?	Are personnel blinded?	Blinding of assessors	Incomplete outcome data	Selective reporting	Other biases	N High	N Low	N Unclear
PARTNER 1 A ²⁶	High	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
US CoreValve ²³	High	Low	Unclear	High	High	Unclear	Low	Low	High	3	3	2
PARTNER 2 A ²¹	Intermediate	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
SURTAVI ²⁸	Intermediate	Low	Unclear	High	High	High	Low	High	High	5	2	1
EVOLUT ²⁴	Low	Low	Unclear	High	High	Low	Low	Low	High	3	4	1
PARTNER 3 ²²	Low	Low	Unclear	High	High	Unclear	Low	High	High	4	2	2
UK TAVI ¹⁰	Intermediate-high (≥70 y) or any (≥80 years)	Low	Unclear	High	High	High	Low	High	High	5	2	1
NOTION ²⁵	All	Low	Low	High	High	Low	Low	High	High	4	4	0
STACCATO ²⁷	'Operable'	Low	Unclear	High	High	Unclear	High	Low	High	4	2	2

TAVI, transcatheter aortic valve implantation.

of participants, blinding of personnel and other biases. Other biases were typically based on a disparity between the number of patients randomised versus the number of patients implanted per treatment arm (where a greater proportion of TAVI patients tended to receive their assigned implant compared with SAVR patients) or a disparity between the numbers of patients who crossed over per treatment arm.

Clinical outcomes

A visual overview of all main results is presented in figure 2, and a tabular overview of all main results is presented in table 3.

Mortality

All-cause mortality

The risk of dying from any cause either within the periprocedural period (which was typically defined as before, during or soon after surgery) or during the in-hospital stay was numerically increased by 16% for TAVI compared with SAVR (RR 1.16, 95% CI 0.52 to 2.27. $p=0.67$, I^2 0%; 3 studies, $n=3732$ patients^{21–23}); however, this was not a statistically significant difference (figure 3). No heterogeneity was evident in this analysis.

The risk of dying from any cause by 30 days following surgery was numerically decreased by 15% for TAVI compared with SAVR (RR 0.89, 95% CI 0.65 to 1.22. $p=0.48$, I^2 14%; 9 studies, $n=8873$ patients^{10 21–28}); however, this was not a statistically significant difference. Heterogeneity was moderate for intermediate-risk and all-risk studies at 30 days.

There was no evidence of a difference in the overall risk of dying from any cause by 1 year following surgery (RR 0.90, 95% CI 0.79 to 1.03. $p=0.13$, I^2 0%; 9 studies, $n=8936$ patients^{10 21–28}) by 2 years (RR 0.95, 95% CI 0.85 to 1.06. $p=0.38$, I^2 0%; 8 studies, $n=6648$ patients^{21–28}) or by 5 years (RR 1.09, 95% CI 0.98 to 1.22. $p=0.10$, I^2 48%; 5 studies, $n=3866$ patients^{21 23 25–27}). Heterogeneity was moderate at 2 years and 5 years in high-risk studies.

At 6 years following surgery, a single small study reported that the risk of dying from any cause was numerically increased by 12% for all-risk TAVI patients compared with all-risk SAVR patients (RR 1.12, 95% CI 0.84 to 1.50. $p=0.43$, I^2 N/A; 1 study, $n=274$ ²⁵); however, this was not a statistically significant difference. Across study risk groups (defined by the criteria reported in online supplemental table S3, which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference between study risk groups (figure 3).

Cardiovascular mortality

There was no evidence of a difference in the risk of dying from cardiovascular or cardiac causes for TAVI compared with SAVR by 30 days following surgery (RR 1.03, 95% CI 0.77 to 1.39. $p=0.83$, I^2 0%; 8 studies, $n=8803$ patients^{10 21–26 28}), by 1 year (RR 0.90, 95% CI 0.76 to 1.06. $p=0.20$, I^2 0%; 8 studies, $n=8831$ patients^{10 21–26 28}) or by

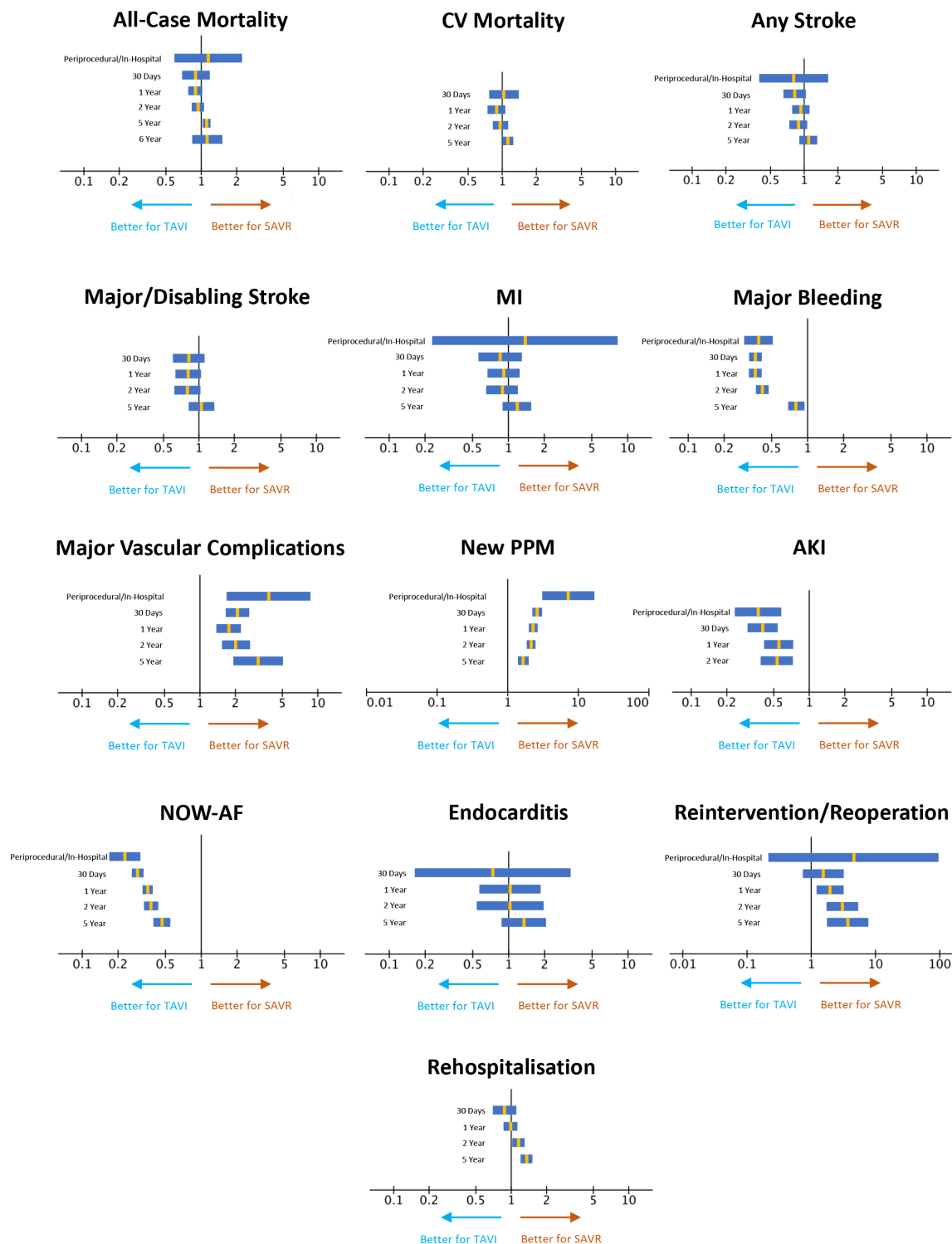


Figure 2 Visual summary of key findings over time. The blue bars represent the uncertainty in the result (wide bars mean more uncertainty) while the yellow bars represent the relative risk. A yellow bar to the right of 1 means that the risk of the outcome is lower for SAVR, while a yellow bar to the left of 1 means that the risk of the outcome is lower for TAVI. If the yellow and blue bars are all to the left of 1, this means that the result is statistically significant in favour of TAVI. If the yellow and blue bars are all to the right of 1, this means that the result is statistically significant in favour of SAVR. AKI, acute kidney injury; CV, cardiovascular; MI, myocardial infarction; NOW-AF, new-onset or worsening atrial fibrillation; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

2 years (RR 0.96, 95% CI 0.83 to 1.12, $p=0.61$, I^2 0%; 5 studies, $n=5503$ patients^{21 23 25 26 28}) (figure 4). Heterogeneity was low at 30 days and moderate for high-risk studies at 1 and 2 years.

By 5 years following surgery, the overall risk of dying from cardiovascular or cardiac causes was significantly increased by 11% for TAVI compared with SAVR (RR 1.11, 95% CI 1.01 to 1.23, $p=0.04$, I^2 0%; 4 studies, $n=3761$

Table 3 Summary of key findings

Outcome	In-hospital/periprocedural (RR (95% CI))	30 days (RR (95% CI))	1 year (RR (95% CI))	2 years (RR (95% CI))	5 years (RR (95% CI))
All-cause mortality	Favours SAVR 1.16 (0.59 to 2.27; 3 studies, n=3732)	Favours TAVI 0.89 (0.65 to 1.22; 9 studies, n=8873)	No difference 0.90 (0.79 to 1.03; 9 studies, n=8936)	No difference 0.95 (0.85 to 1.06; 8 studies, n=6648)	No difference 1.09 (0.98 to 1.22; 5 studies, n=3866)
Cardiovascular mortality	NR	No difference 1.03 (0.77 to 1.39; 8 studies, n=8803)	No difference 0.90 (0.76 to 1.06; 8 studies, n=8831)	No difference 0.96 (0.83 to 1.12; 5 studies, n=5503)	Favours SAVR 1.11 (1.01 to 1.23; 4 studies, n=3761)
All stroke	Favours TAVI 0.80 (0.40 to 1.62; 1 study; n=750)	Favours TAVI 0.83 (0.61 to 1.14; 9 studies, n=8873)	No difference 0.94 (0.72 to 1.23; 8 studies, n=8831)	Favours TAVI 0.88 (0.67 to 1.16; 6 studies, n=6453)	No difference 1.07 (0.88 to 1.30; 4 studies, n=3761)
Major or disabling stroke	NR	Favours TAVI 0.85 (0.56 to 1.29; 7 studies, n=7712)	Favours TAVI 0.80 (0.53 to 1.20; 6 studies, n=7642)	Favours TAVI 0.79 (0.60 to 1.04; 4 studies, n=4665)	No difference 1.05 (0.82 to 1.34; 2 studies, n=2782)
Myocardial infarction	Favours SAVR 1.38 (0.23 to 8.20; 1 study; n=750)	Favours TAVI 0.84 (0.55 to 1.28; 9 studies, n=8877)	No difference 0.92 (0.68 to 1.25; 9 studies, n=8901)	No difference 0.91 (0.68 to 1.23; 6 studies, n=6453)	No difference 1.08 (0.73 to 1.61; 4 studies, n=3761)
Major bleeding	Favours TAVI 0.41 (0.28 to 0.60; 2 studies, n=1026)	Favours TAVI 0.37 (0.21 to 0.64; 8 studies, n=8446)	Favours TAVI 0.38 (0.31 to 0.48; 6 studies, n=6744)	Favours TAVI 0.46 (0.34 to 0.64; 3 studies, n=3481)	Favours TAVI 0.80 (0.69 to 0.93; 2 studies, n=1449)
Major vascular complications	Favours SAVR 3.83 (1.69 to 8.67; 2 studies, n=1026)	Favours SAVR 2.42 (1.55 to 3.80; 7 studies, n=8376)	Favours SAVR 2.05 (1.38 to 3.04; 6 studies, n=6744)	Favours SAVR 2.39 (1.36 to 4.18; 3 studies, n=3480)	Favours SAVR 3.14 (1.95 to 5.07; 2 studies, n=1449)
Permanent pacemaker implantation	Favours SAVR 7.19 (3.11 to 16.62; 1 study, n=750)	Favours SAVR 2.47 (1.55 to 3.93; 7 studies, n=7767)	Favours SAVR 2.23 (1.44 to 3.46; 7 studies, n=7767)	Favours SAVR 2.11 (1.31 to 3.42; 6 studies, n=6367)	Favours SAVR 1.90 (1.14 to 3.16; 4 studies, n=3761)
Acute kidney injury	Favours TAVI 0.30 (0.10 to 0.93; 2 studies, n=1026)	Favours TAVI 0.40 (0.30 to 0.53; 6 studies, n=7441)	Favours TAVI 0.58 (0.34 to 1.00; 4 studies, n=4831)	Favours TAVI 0.52 (0.33 to 0.80; 2 studies, n=2782)	NR
New-onset or worsening atrial fibrillation	Favours TAVI 0.23 (0.06 to 0.91; 2 studies, n=1536)	Favours TAVI 0.29 (0.23 to 0.38; 7 studies, n=7767)	Favours TAVI 0.36 (0.28 to 0.47; 7 studies, n=7767)	Favours TAVI 0.36 (0.25 to 0.52; 4 studies, n=4008)	Favours TAVI 0.45 (0.36 to 0.56; 2 studies, n=2312)
Endocarditis	NR	Favours TAVI 0.79 (0.21 to 3.04; 6 studies, n=6310)	No difference 1.02 (0.55 to 1.89; 7 studies, n=7088)	No difference 0.99 (0.43 to 2.24; 4 studies, n=4431)	Favours SAVR 1.34 (0.87 to 2.05; 4 studies, n=3761)
Reintervention/reoperation	Favours SAVR 4.59 (0.22 to 95.32; 1 study; n=750)	Favours SAVR 1.54 (0.50 to 4.77; 6 studies, n=7828)	Favours SAVR 1.95 (0.92 to 4.13; 6 studies, n=7856)	Favours SAVR 2.78 (1.35 to 5.71; 4 studies, n=5478)	Favours SAVR 3.67 (1.76 to 7.63; 3 studies, n=3062)

Continued

Table 3 Continued

Outcome	In-hospital/periprocedural (RR (95% CI))	30 days (RR (95% CI))	1 year (RR (95% CI))	2 years (RR (95% CI))	5 years (RR (95% CI))
Rehospitalisation	NR	Favours TAVI 0.88 (0.70 to 1.10; 6 studies, n=7645)	No difference 0.95 (0.76 to 1.20; 6 studies, n=7645)	Favours SAVR 1.14 (0.94 to 1.38; 5 studies, n=6177)	Favours SAVR 1.35 (1.20 to 1.51; 3 studies, n=3481)
Length of hospital stay	Favours TAVI* -3.08 days (-4.86 to -1.29; 4 studies, n=2758)	NA	NA	NA	NA
Valve durability	NR	NR	NR	NR	NE†
Recovery time	NR	NR	NR	NR	NR
Pain	NR	NR	NR	NR	NR

Values in bold that are coloured blue (favours TAVI) or yellow (favours SAVR) represent statistically significant ($p \leq 0.05$) results.

*Mean difference.

†Three studies reported on this outcome, but one reported zero events in both arms (ie, could not be incorporated into a RR).

NA, not applicable; NR, not reported; RR, risk ratio; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

patients).^{21 23 25 26} Heterogeneity was low at 5 years. By study risk group (defined by the criteria reported in online supplemental table S3), which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference between study risk groups (figure 4).

All stroke

A single study reported that the risk of having any type of stroke at periprocedural time points was numerically decreased by 20% for TAVI compared with SAVR (RR 0.80, 95% CI 0.4 to 1.62, $p=0.54$, I^2 N/A; 1 study, $n=750$ patients²³); however, this was not a statistically significant difference (figure 5).

The risk of having any type of stroke was numerically decreased by 18% for TAVI compared with SAVR by 30 days following surgery (RR 0.83, 95% CI 0.61 to 1.14, $p=0.26$, I^2 36%; 9 studies, $n=8873$ patients^{10 21-28}) and by 12% by 2 years (RR 0.88, 95% CI 0.67 to 1.16, $p=0.37$, I^2 48%; 6 studies, $n=6,453$ patients^{21-23 25 26 28}); however, these differences were not statistically significant.

There was no evidence of a difference in the risk of having any type of stroke by 1 year following surgery (RR 0.94, 95% CI 0.72 to 1.23, $p=0.65$, I^2 48%; 8 studies, $n=8831$ patients^{10 21-26 28}) or by 5 years (RR 1.07, 95% CI 0.88 to 1.30, $p=0.51$, I^2 11%; 4 studies, $n=3761$ patients).^{21 23 25 26} Heterogeneity was moderate at 30 days, at 1 year; high for high-risk studies and moderate for intermediate-risk studies at 2 years; and low at 5 years. By study risk group (defined by the criteria reported in online supplemental table S3, which were not exclusively based on STS-PROM scores), the CIs overlapped between each group at all time points, suggesting no significant difference in the risk of all stroke between study risk groups (figure 5).

Other outcomes

The risk of major or disabling stroke was numerically decreased by 15%–21% for TAVI compared with SAVR between 30 days to 2 years following surgery (although this was not a statistically significant difference); there was no evidence of a difference in risk at 5 years (online supplemental figure 1). The risk of MI was numerically increased by 38% at periprocedural time points, but numerically decreased by 16% at 30 days following surgery; there was no evidence of a difference in risk of MI between 1 and 5 years following surgery (online supplemental figure 2). The risk of major bleeding was significantly decreased by between 20% and 63% for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 3; sensitivity analysis based on definition of major bleeding presented in online supplemental figure 4). The risk of major vascular complications was significantly increased by between 205% and 383% for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 5). The risk of PPM implantation was significantly increased by between 190% and 719%

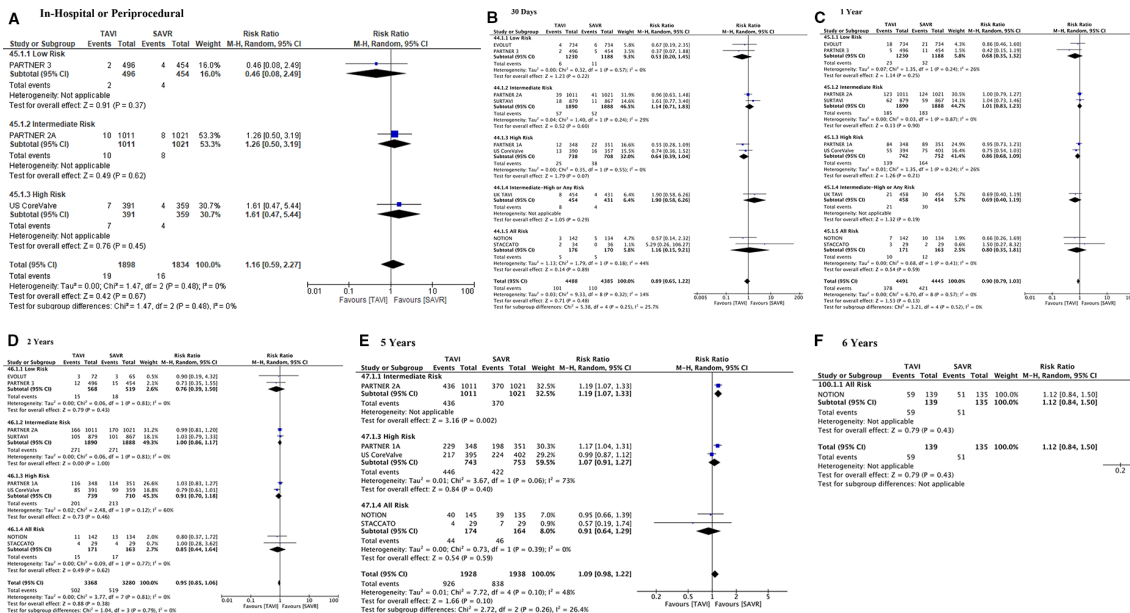


Figure 3 Forest plots for death from any cause. (A) In-hospital or periprocedural, (B) 30 days, (C) 1 year, (D) 2 years, (E) 5 years, and (F) 6 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

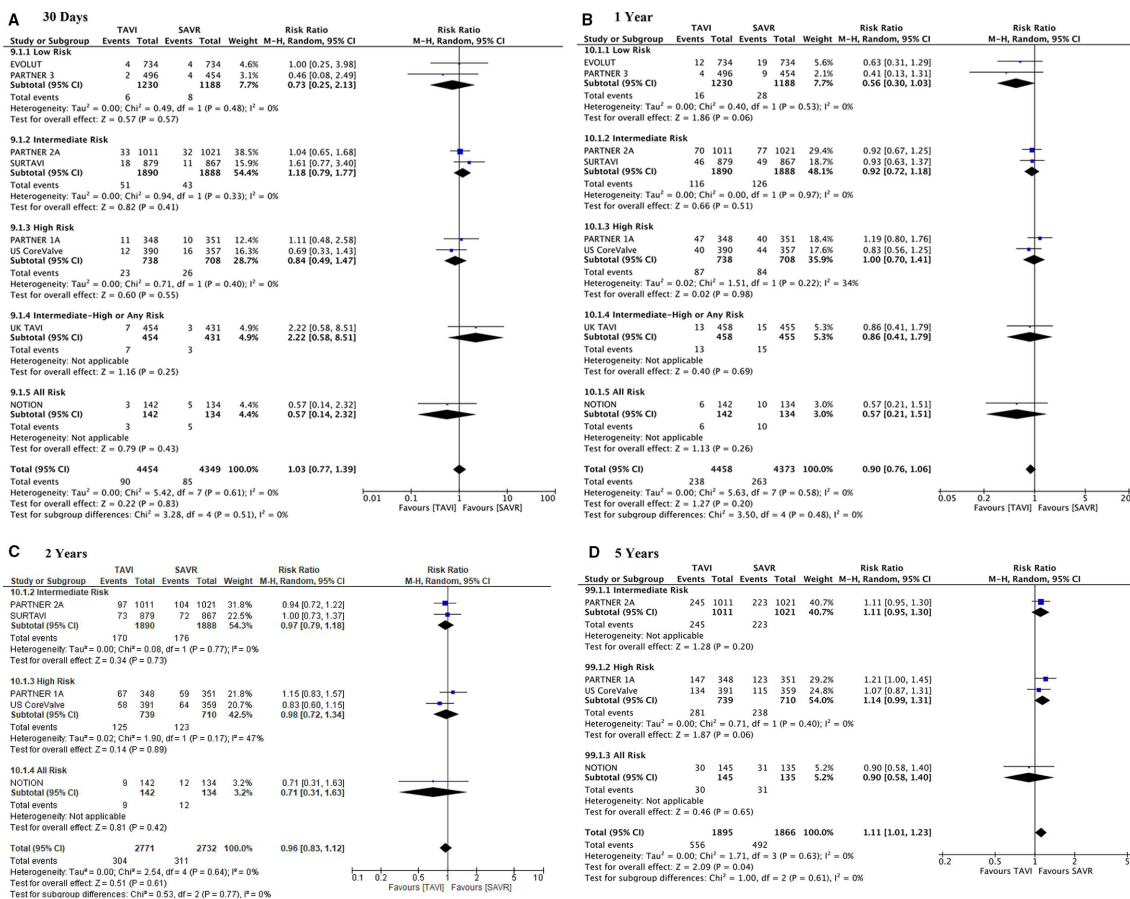


Figure 4 Forest plots for death from cardiovascular causes. (A) 30 days, (B) 1 year, (C) 2 years and (D) 5 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

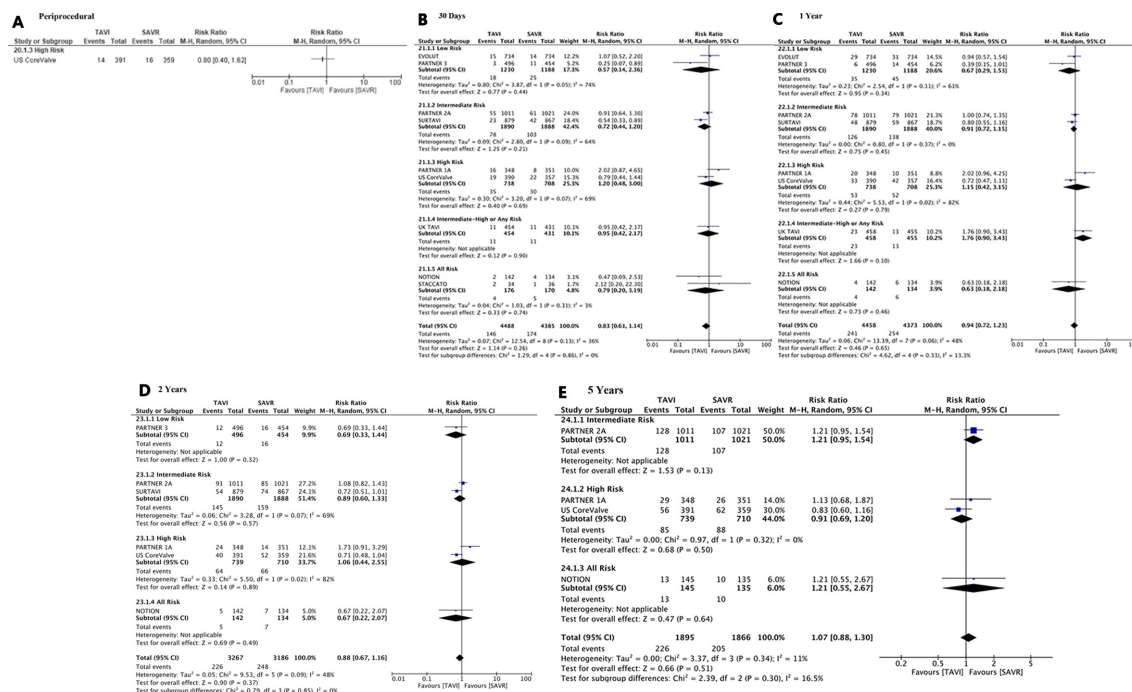


Figure 5 Forest plots for any stroke. (A) Periprocedural, (B) 30 days, (C) 1 year, (D) 2 years and (E) 5 years time points are presented. Risk subgroups represent the study risk level and not necessarily the patient risk level. M-H, Mantel-Haenszel; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

for TAVI compared with SAVR at all time points between periprocedural and 5 years following surgery (online supplemental figure 6). The risk of AKI was significantly decreased by between 42% and 70% for TAVI compared with SAVR at all time points between periprocedural time points and 2 years following surgery (online supplemental figure 7). The risk of NOW-AF was significantly decreased by between 55% and 77% for TAVI compared with SAVR for all time points between periprocedural and 5 years following surgery (online supplemental figure 8). The risk of endocarditis varied between being numerically reduced (30 days), no different (1 year, 2 years, 6 years) or numerically increased (5 years) for TAVI compared with SAVR (online supplemental figure 9). The risk of reintervention or reoperation was numerically increased by 154%–459% for TAVI versus SAVR from periprocedural time points up to 1 year following surgery; and was significantly increased by 278% for TAVI vs SAVR by 2 years following surgery (online supplemental figure 10). The risk of rehospitalisation varied between being numerically reduced (30 days), no different (1 year), numerically increased (2 years) or significantly increased (5 years) for TAVI compared with SAVR (online supplemental figure 11). The length of stay in the ICU and the overall length of hospital stay were generally shorter for TAVI compared with SAVR (online supplemental figure 12, tables S4 and S5).

Subgroup analysis

For the primary outcome of all-cause mortality, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone)

had a significantly lower risk of dying from any cause after TAVI compared with patients at high risk from 1 to 5 years following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a significantly lower risk of dying from any cause compared with patients who had TAVI through a non-TF route from 30 days to 5 years following surgery (online supplemental table S7).

For the primary outcome of cardiovascular mortality, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of dying from cardiovascular causes after TAVI compared with patients at high risk by 1 year following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a significantly lower risk of dying from cardiovascular causes than patients who had TAVI through a non-TF route from 30 days to 5 years following surgery (online supplemental table S7). Results for the subgroup analysis by valve type for the outcome ‘new PPM implantation’ are presented in online supplemental table S8, showing higher rates for self-expanding TAVI compared with balloon expandable TAVI.

For any-stroke outcomes, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of any type of stroke after TAVI compared with patients at high risk by 1 year following surgery (online supplemental table S6); and that patients who had TAVI through the TF route had a lower risk of any type of stroke than patients who had TAVI through

a non-TF route from 30 days to 5 years following surgery (online supplemental table S7).

Valve durability of the two treatments was comparable. However, NOTION reported a statistically significantly lower rate of moderate/severe haemodynamic structural valve deterioration after 6 years follow-up, see online supplemental table S9.

Sensitivity analysis

As we noted an inconsistency in how studies reported subgroup data by level of surgical risk, we performed sensitivity analyses to address this. Most studies reported two subgroups based on low-intermediate vs high risk (NOTION (STS <4 vs STS ≥4); PARTNER 1A (STS ≤11 vs STS >11); US CoreValve (STS-PROM ≤7 vs STS-PROM >7); however, one study reported three subgroups based on low-risk, intermediate-risk and high-risk (SURTA VI (STS <3% vs STS ≥3% to <5% vs STS ≥5%). Therefore, we combined low-risk and intermediate-risk groups to make the data more comparable across studies.

To test whether this affected the outcome, we performed sensitivity analyses where we assigned subgroups to low vs high instead of low-intermediate versus high for the SURTA VI study. For most outcomes, this did not change the direction of the effect or push the result into or out of significance. However, for reintervention/reoperation, the comparison of low versus high was significant (RR 5.79, 95% CI 1.19 to 28.31, $p=0.03$; 1 study, $n=384$ patients²⁸) whereas the comparison of low-intermediate versus high was not (RR 3.11, 95% CI 0.72 to 13.48, $p=0.13$; 1 study, $n=864$ patients).²⁸ Conversely, for all stroke, the comparison of low-intermediate versus high was significant (RR 0.54, 95% CI 0.31 to 0.97, $p=0.04$; 1 study, $n=864$ patients²⁸) whereas the comparison of low vs high was not (RR 0.51, 95% CI 0.19 to 1.33, $p=0.17$; 1 study, $n=384$ patients).²⁸ Similarly, for PPM implantation, the comparison of low-intermediate versus high was significant (RR 1.41, 95% CI 1.08 to 1.83, $p=0.01$; 1 study, $n=864$ patients²⁸) whereas the comparison of low versus high was not (RR 1.12, 95% CI 0.77 to 1.65, $p=0.55$; 1 study, $n=384$ patients).²⁸

DISCUSSION

Strengths and limitations

SDM is a critical form of professional–patient interaction that enables patients to make informed and uniquely personal decisions on their own care using evidence-based medical information. SRs and MAs provide important evidence to inform and generate a comprehensive overview pertaining to a particular research question, and therefore may naturally feed into decision aids and SDM-based patient–physician communication. This SR includes data from a new study (UK TAVI), plus long-term data from several other studies (EVOLUT, PARTNER 2, PARTNER 3). Our MAs have revealed several critical differences in clinical outcomes for TAVI compared with SAVR that should be highlighted and carefully considered

when patients, together with their physicians, are making decisions regarding treatment options for SAS.

While the STACCATO trial was terminated early due to safety concerns, we nevertheless included these data in our analysis as the study met our inclusion/exclusion criteria. This is in line with the approaches of several other SRs.^{29–33} We performed sensitivity analyses to test whether the inclusion of the STACCATO study impacted any main analyses; this did not change the direction or statistical significance of any results (data not shown).

Regarding study-level surgical risk, the two high-risk studies included in our analyses (PARTNER 1A, US CoreValve) recruited elderly (mean age >83 years) patients at increased risk of intraoperative death or death within 30 days of the procedure. These risk levels were further elevated by including high proportions of patients who had undergone previous coronary artery bypass graft (CABG) surgeries in the SAVR arms of both studies (44.2% (PARTNER 1A) or 30.2% (US CoreValve)). The two intermediate-risk studies included in our analyses (PARTNER 2A, SURTA VI) might be expected to produce more representative results based on recruiting larger numbers of slightly younger patients (mean age >79 years), fewer of whom in the SAVR arm had previously undergone CABG (25.6% (PARTNER 2A) or 16.7% (SURTA VI)). The results from the two low-risk studies included in our analyses (EVOLUT, PARTNER 3), which recruited relatively young patients (mean age >73 years), are of key interest to the field. While these studies actively excluded patients with prior cardiac surgery, they nevertheless included patients who underwent concomitant surgical procedures (26.4% (PARTNER 3) or 13.6% (EVOLUT)). Therefore, in all studies, the inclusion of patients who had undergone prior cardiac procedures may have introduced bias (or at least clinical heterogeneity) that may have been disadvantageous to the SAVR arm, as surgical redo aortic valve procedures typically confer a higher risk of mortality compared with primary surgeries, a difference that does not manifest *per se* in patients receiving the TAVI procedure.

No overall change in the risk of death from any cause was identified for TAVI compared with SAVR; however, CIs around the point estimates for low risk and all-risk studies were often wide, which introduced substantial uncertainty. Follow-up duration is currently relatively short for low-risk studies, and longer-term data will be of great relevance to future updates of this review. For example, 5-year all-cause mortality data have recently been published for the intermediate-risk PARTNER 2A study,³⁴ however, 5-year data for the intermediate-risk SURTA VI study are still outstanding. A significant increase was observed in the risk of dying from cardiovascular or cardiac causes for TAVI vs SAVR at 5 years.

Of note, TAVI was associated with a significantly lower risk of major bleeding, NOW-AF and AKI compared with SAVR. Patients also spent fewer days in the ICU and in hospital overall after TAVI compared with SAVR. In contrast, TAVI appeared to be associated with a

significantly increased risk of major vascular complications and new PPM implantations at all time points following surgery; and a significantly increased risk of rehospitalisation or reintervention/reoperation at late time points compared with SAVR.

Based on subgroup analyses, patients undergoing TAVI via the TF route generally had improved outcomes compared with patients undergoing TAVI via the non-TF route (with the exception of major vascular complications); and patients at low or intermediate risk (based exclusively on STS-PROM scores) generally had improved outcomes compared with patients at high risk (with the exception of new PPM implantation or reintervention/reoperation).

In terms of valve durability, we identified three studies (NOTION, PARTNER 1A, US CoreValve) that either reported no cases of structural valve deterioration in TAVI or SAVR patients at 5 years (PARTNER 1A); mixed outcomes depending on the definition of valve deterioration used (ranging from significantly lower rate of haemodynamic structural valve deterioration for TAVI patients compared with SAVR patients at 6 years (based on one definition) to no difference between TAVI vs SAVR (based on three separate definitions) at 6 years (NOTION); or no cases of valve frame fracture in 21 TAVI patients who had undergone implant explantation or autopsy after death a median of 17 days (range: 0–503 days) after implantation (US CoreValve). Thus, there was only limited and heterogeneous evidence to inform this outcome, and further research into the long-term durability of the TAVI valves is clearly required.

No evidence comparing TAVI vs SAVR was identified for recovery time or pain, therefore further research is needed to address these areas of interest.

We noted several study limitations. A major limitation was a discrepancy in the number of events reported for the same time point in different publications within the same study series. For example, in the PARTNER study, Smith 2011 reported 1-year MI as one event in the TAVI arm (out of $n=348$) and two events in the SAVR arm (out of $n=351$),²⁶ while Kodali *et al* reported 1-year MI as zero events in the TAVI arm (out of $n=348$) and two events in the SAVR arm (out of $n=351$).³⁵ In these cases, we chose to use the first published set of numbers reported for consistency. Several studies (EVOLUT, SURTAVI) only reported percentages of patients experiencing an event based on an estimated incidence derived from a Bayesian analysis rather than absolute numbers. This was an issue for pooled data analysis, as absolute values had to be estimated from already-estimated values, compounding any potential numerical variation.

Multiple studies that prespecified reporting the ITT population in a sensitivity analysis failed to do this across all published time points. While we used ITT as our preferred analysis population, this meant that in some cases, only the as-treated population was available for pooled analysis, which may have contributed to heterogeneity.

Most studies were only powered for the primary outcome, which was generally read out at 12 or 24 months. This meant that long-term results and durability analyses in particular may have been underpowered. For all outcomes except all-cause mortality, subgroup analysis by level of surgical risk was also only reported at 1 year, preventing any longitudinal analyses.

The clinical relevance of some of the acute procedural outcomes, such as NOW-AF, was in some cases uncertain. It was often not clearly reported whether such clinical symptoms had recovered, such as converting to a sinus rhythm, or whether long-term sequelae were present.

There was substantial variation in the definitions used by each study for certain outcomes, which impacted study comparability and increased clinical heterogeneity. For example, 'major bleeding' was reported under several definitions, including life-threatening or disabling bleeding (EVOLUT, PARTNER 2A, PARTNER 3, US CoreValve), major bleeding (PARTNER 1A, US CoreValve), life-threatening, disabling or major bleeding (PARTNER 3), life-threatening or major bleeding (SURTAVI) or simply 'bleeding' (STACCATO). Only two studies reported two different definitions of bleeding (PARTNER 3 (life-threatening or disabling bleeding and life-threatening, disabling or major bleeding; and US CoreValve (life-threatening or disabling bleeding and major bleeding)).

Finally, we have only focused on RCTs in our SR, as we considered this to be the highest level of available evidence. We acknowledge that other levels of evidence (such as large registries and propensity-score matched datasets^{36–39}) are available, with more patients reported, especially for longer follow-up periods. However, only one of these sources reported information for low-risk patients. The number of patients at risk is rather small at 5 years and this evidence is based on studies with considerable differences in baseline characteristics (e.g. post malignant disease) that might account for the long-term differences in outcomes.³⁹ The other two sources provide data for high-risk patients only and do not include many more patients than the RCTs identified in our SR.^{36–37} Several potential sources of bias (miscoding, no data/deaths out of hospital, different time intervals for outcome assessments) could lower the level of evidence even further, especially when compared with results obtained in RCTs.

Ongoing studies

Three ongoing studies with no published data at the time of our literature searches were identified during screening: DEDICATE,^{40–41} RHEIA⁴² and VIVA.⁴³ The DEDICATE study is currently recruiting patients with SAS at low-to-intermediate levels of surgical risk to analyse whether TAVI is non-inferior to SAVR. The RHEIA study will recruit female patients with SAS who are at any level of surgical risk to determine whether TAVI may be more effective than SAVR. The VIVA study will recruit patients with SAS and a small aortic annulus to compare TAVI vs SAVR in this specific subpopulation.

Comparison with other SRs

We identified at least 18 previous SRs that compared TAVI vs SAVR in patients with SAS.^{9 29–33 44–55} One SR/MA was identified that reported a difference in findings in terms of mortality based on a pooled analysis of RCT and observational studies. However, this discrepancy disappeared when only RCT study data were considered (ie, results were similar when based on the most robust evidence base).⁵⁵ None of these studies incorporated new UK TAVI study data; none analysed the same broad range of outcomes we have presented; and most tended to focus on a specific risk level (low or intermediate low) rather than comparing across and within all levels of risk. Only one SR reported results for more than one outcome stratified by route subgroup.⁵⁶ The results of these SRs were broadly in line with those we have reported.

Overall, this SR highlights that the choice between TAVI versus SAVR will undoubtedly be a highly personalised one, which in most cases will include a trade-off between an increase in the risk of certain outcomes and a decrease in the risk of others. The findings of this SR support the growing approach to enable patients to make physician-guided choices on their own care based on their personal preferences and values in the context of the Heart Team's assessment of their inherent anatomical features, comorbidities and frailties, life expectancy and valve durability rather than the classical approach of assigning treatments simply based on estimated surgical risk.^{57 58}

Conclusions

Current evidence suggests that while all-cause or cardiovascular mortality may not be different for TAVI compared with SAVR, TAVI may reduce the risk of certain side effects (such as major bleeding, AKI, NOW-AF) and reduce the length of hospital stay, while SAVR may reduce the risk for other side effects (such as major vascular complications, new PPM implantation or reinterventions/rehospitalisations). Consequently, each individual patient should be engaged in a SDM framework to enable highly personalised trade-off decisions to be made based on a carefully balanced review of this evidence.

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Transcatheter aortic valve implantation versus surgical aortic valve replacement in patients with severe aortic stenosis: a systematic review and meta-analysis

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SUPPLEMENTARY MATERIAL

- Supplementary Results
- Supplementary Tables
- Supplementary Figures
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- Supplementary Reference List

Supplementary Results

Main Analyses (Primary Outcomes)

Major or Disabling stroke

Pooled analysis suggested that the overall risk of having a major or disabling stroke was numerically decreased by 15% for TAVI compared to SAVR by 30 days following surgery (RR 0.85, 95% CI 0.56 to 1.29, $P=0.45$, I^2 28%; 7 studies, $n=7,712$ patients¹⁻⁷), by 20% at one year (RR 0.80, 95% CI 0.53 to 1.20, $P=0.28$, I^2 52%; 6 studies, $n=7,642$ patients^{1-4 6 7}) and by 21% at two years (RR 0.79, 95% CI 0.60 to 1.04, $P=0.09$, I^2 9%; 4 studies, $n=4,665$ patients^{1 3 6 7}); however, these differences were not statistically significant (Supplementary Figure S1).

Pooled analysis reported no evidence of a difference in the risk of major or disabling stroke at five years for TAVI compared to SAVR (RR 1.05, 95% CI 0.82 to 1.34, $P=0.71$, I^2 0%; 2 studies, $n=2,782$ patients^{3 7}) (Supplementary Figure S1). Heterogeneity was moderate at 30 days, moderate for high-risk studies at one year and moderate for intermediate-risk studies at two years.

By study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in the risk of major or disabling stroke between study risk groups. Generally, the trend appeared to be towards a lower risk of major or disabling stroke in the low-risk studies, which increased for intermediate-risk, high-risk and all-risk studies (Supplementary Figure S1).

Main Analyses (Secondary Outcomes)

Myocardial Infarction

A single study reported that the risk of MI at periprocedural time points was numerically increased by 38% for TAVI compared to SAVR (RR 1.38, 95% CI 0.23 to 8.20, $P=0.73$, I^2 N/A; 1 study, $n=750$ patients⁷); however, this was not statistically significant (Supplementary Figure S2). The risk of MI was numerically decreased by 16% for TAVI compared to SAVR at 30 days (RR 0.84, 95% CI 0.55 to 1.28, $P=0.41$, I^2 0%; 9 studies, $n=8,877$ patients¹⁻⁹); however, this was not statistically significant (Supplementary Figure S2).

There was no evidence of a difference in the risk of MI for TAVI vs. SAVR at one year (RR 0.92, 95% CI 0.68 to 1.25, $P=0.58$, I^2 0%; 9 studies, $n=8,901$ patients¹⁻⁹), at two years (RR 0.91, 95% CI 0.68 to 1.23, $P=0.54$, I^2 0%; 6 studies, $n=6,453$ patients^{2-4 6-8}) or at five years following surgery (RR 1.08, 95% CI 0.73 to 1.61, $P=0.70$, I^2 28%; 4 studies, $n=3,761$ patients^{2 3 7 8}); however, these were not statistically significant changes (Supplementary Figure S2).

Heterogeneity was moderate at 30 days and one year for intermediate-risk studies; moderate for high-risk studies at two years; and low at five years.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in the risk of MI between study risk groups (Supplementary Figure S1).

Major Bleeding

The risk of major bleeding was significantly decreased by 59% for TAVI compared to SAVR at periprocedural or in-hospital timepoints (RR 0.41, 95% CI 0.28 to 0.60, $P<0.00001$, I^2 39%; 2 studies, $n=1,026$ patients^{7 8}), by 63% at 30 days (RR 0.37, 95% CI 0.21 to 0.64, $P=0.0004$, I^2 94%; 8 studies, $n=8,446$ patients^{1-7 9}), by 62% at one year (RR 0.38, 95% CI 0.31 to 0.48, $P<0.00001$, I^2 64%; 6 studies, $n=6,744$ patients^{1-4 7 9}), by 54% at two years (RR 0.46, 95% CI 0.34 to 0.64, $P<0.00001$, I^2 83%; 3 studies, $n=3,481$ patients^{2 3 7}) and by 20% at five years (RR 0.80, 95% CI 0.69 to 0.93, $P=0.005$, I^2 0%; 2 studies, $n=1,449$ patients^{2 7}) (Supplementary Figure S3). Heterogeneity was moderate at periprocedural or in-hospital and one year timepoints, and high at 30 days and two years, possibly due to the different definitions of major bleeding in the two intermediate-risk studies (PARTNER 2A: life-threatening or disabling bleeding; SURTAVI: life-threatening or major bleeding). Although there was no evidence of heterogeneity at five years, it should be noted that these studies only used the definition 'major bleeding' in comparison with studies that reported data at the earlier time points, which predominantly used the definition 'life-threatening or disabling bleeding'. This was assessed further in sensitivity analysis (see 'Sensitivity Analyses' section; Supplementary Figure S4).

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in major bleeding between study risk groups (Supplementary Figure S3).

Major Vascular Complications

The risk of major vascular complications was significantly increased by 383% for TAVI compared to SAVR at periprocedural or in-hospital time points (RR 3.83, 95% CI 1.69 to 8.67, $P=0.001$, I^2 0%; 2 studies, $n=1,026$ patients^{7 8}), by 242% at 30 days (RR 2.42, 95% CI 1.55 to 3.80, $P=0.0007$, I^2 72%; 7 studies, $n=8,376$ patients^{1-4 6 7 9}), by 205% at one year (RR 2.05, 95% CI 1.38 to 3.04, $P=0.002$, I^2 56%; 6 studies, $n=6,744$ patients^{1-4 7 9}), by 239% at two years (RR 2.39, 95% CI 1.36 to 4.18, $P=0.002$, I^2 66%; 3 studies,

n=3,480 patients^{2 3 7}) and by 314% at five years (RR 3.14, 95% CI: 1.95 to 5.07, $P<0.00001$, I^2 0%; 2 studies, n=1,449 patients^{2 7}) (Supplementary Figure S5).

Based on study risk group (defined by the criteria reported in Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in major vascular complications between study risk groups (Supplementary Figure S5).

Permanent Pacemaker Implantation (PPM)

A single study reported that the risk of permanent pacemaker (PPM) implantation was significantly increased by 719% for TAVI compared to SAVR at periprocedural timepoints (RR 7.19, 95% CI 3.11 to 16.62, $P<0.00001$, I^2 N/A; 1 study, n=750 patients⁷) (Supplementary Figure S6). Similarly, the risk of PPM implantation was significantly increased by 247% for TAVI compared to SAVR at 30 days (RR 2.47, 95% CI 1.55 to 3.93, $P=0.0001$, I^2 87%; 7 studies, n=7,767 patients^{1-4 6-8}), by 223% at one year (RR 2.23, 95% CI 1.44 to 3.46, $P=0.0004$, I^2 89%; 7 studies, n=7,767 patients^{1-4 6-8}), by 211% at two years (RR 2.11, 95% CI 1.31 to 3.42, $P=0.002$, I^2 90%; 6 studies, n=6,367 patients^{2-4 6-8}) and by 190% at five years (RR 1.90, 95% CI 1.14 to 3.16, $P=0.01$, I^2 86%; 4 studies, n=3,761 patients^{2 3 7 8}) (Supplementary Figure S6). However, all analyses had high levels of heterogeneity. While this heterogeneity could not be explained by the different study risk levels, it may be explained through differences in the definition of permanent pacemaker implantation, which in some cases did not specify whether pre-existing pacemakers at baseline were included or excluded in the analysis. Since these definitions were not consistently reported, sensitivity analyses were not possible.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped for low-risk, intermediate-risk and high-risk study risk groups at all timepoints; however, the confidence intervals for all-risk patients did not overlap with these other study risk groups at several timepoints, suggesting a significantly greater decrease in the risk of new PPM for SAVR compared to TAVI in all-risk patients (Supplementary Figure S6).

Acute Kidney Injury

The risk of acute kidney injury (AKI) was significantly decreased by 70% for TAVI compared to SAVR at periprocedural or in-hospital timepoints (RR 0.30, 95% CI 0.10 to 0.93, $P=0.04$, I^2 39%; 2 studies, n=1,026 patients^{7 8}), by 60% at 30 days (RR 0.40, 95% CI 0.30 to 0.53, $P<0.00001$, I^2 0%; 6 studies, n=7,441 patients^{1-4 6 7}), by 42% at one year (RR 0.58, 95% CI 0.34 to 1.00, $P=0.05$, I^2 67%; 4 studies, n=4,831 patients^{1-3 7}) and by 48% at two years (RR 0.52, 95% CI 0.33 to 0.80, $P=0.003$, I^2 51%; 2 studies, n=2,782

patients³⁷) (Supplementary Figure S7). Moderate heterogeneity was observed for the periprocedural, one-year and two-year analyses; no heterogeneity was observed at 30 days. One possible contributing factor to the observed heterogeneity was the different definitions of AKI used within the studies. Some studies included Stage 3 disease alone (PARTNER 1A), whilst other studies included Stage 2 to 3 (EVOLUT) or Stage 1 to 3 (PARTNER 2A) disease.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in the risk of AKI between study risk groups (Supplementary Figure S7).

New-Onset or Worsening Atrial Fibrillation

The risk of new-onset or worsening atrial fibrillation (NOW-AF) was significantly reduced by 77% for TAVI compared to SAVR at periprocedural or in-hospital timepoints (RR 0.23, 95% CI 0.06 to 0.91, $P=0.04$, I^2 95%; 2 studies, $n=1,536$ patients^{4 7}), by 71% at 30 days (RR 0.29, 95% CI 0.23 to 0.38, $P<0.00001$, I^2 80%; 7 studies, $n=7,767$ patients^{1-4 6-8}), by 64% at one year (RR 0.36, 95% CI 0.28 to 0.47, $P<0.00001$, I^2 85%; 7 studies, $n=7,767$ patients^{1-4 6-8}), by 64% at two years (RR 0.36, 95% CI 0.25 to 0.52, $P<0.00001$, I^2 86%; 4 studies, $n=4,008$ patients^{3 4 7 8}) and by 55% at five years (RR 0.45, 95% CI 0.36 to 0.56, $P<0.00001$, I^2 37%; 2 studies, $n=2,312$ patients^{3 8}) (Supplementary Figure S8). Heterogeneity was high at periprocedural/in-hospital, 30 day, one year and two year timepoints, and moderate at five years.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped for intermediate-risk and high-risk groups at all timepoints; however, the confidence intervals for low-risk patients did not overlap with those in these two study risk groups at several timepoints, suggesting a significantly greater decrease in the risk of new-onset or worsening atrial fibrillation for TAVI compared to SAVR in low-risk patients (Supplementary Figure S8).

Endocarditis

The risk of endocarditis was numerically reduced by 21% for TAVI compared to SAVR at 30 days (RR 0.79, 95% CI 0.21 to 3.04, $P=0.74$, I^2 0%; 6 studies, $n=6,310$ patients^{1-4 8 9}); however, this was not a statistically significant difference (Supplementary Figure S9).

There was no evidence of a difference in the risk of endocarditis for TAVI compared to SAVR at one year (RR 1.02, 95% CI 0.55 to 1.89, $P=0.96$, I^2 0%; 7 studies, $n=7,088$ patients^{1-4 8 9}) or at two years (RR 0.99, 95% CI 0.43 to 2.24, $P=0.97$, I^2 25%; 4 studies; $n=4,431$ patients²⁻⁴) (Supplementary Figure S9).

At five years, the risk of endocarditis was numerically increased by 134% for TAVI compared to SAVR (RR 1.34, 95% CI 0.87 to 2.05, $P=0.18$, I^2 0%; 4 studies, $n=3,761$ patients^{2 3 7 8}); however, this was not a statistically significant difference. Low or no heterogeneity was evident in any of these analyses (Supplementary Figure S9).

At six years, a single study reported no evidence of a difference in the risk of endocarditis in all-risk patients (RR 0.97, 95% CI 0.38 to 2.51, $P=0.95$, I^2 N/A; 1 study, $n=274$ ⁸).

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in the risk of endocarditis between study risk groups (Supplementary Figure S9).

Reintervention or Reoperation

A single study reported that the risk of reintervention or reoperation was numerically increased by 459% for TAVI compared to SAVR at periprocedural timepoints (RR 4.59, 95% CI 0.22 to 95.32, $P=0.32$, I^2 N/A; 1 study, $n=750$ patients⁷); however, this was not a statistically significant difference and there was a large amount of uncertainty in the result (Supplementary Figure S10). The risk of reintervention or reoperation was numerically increased by 154% for TAVI compared to SAVR at 30 days (RR 1.54, 95% CI 0.50 to 4.77, $P=0.46$, I^2 40%; 6 studies, $n=7,828$ patients^{1 3 4 6 7 9}) and by 195% at one year (RR 1.95, 95% CI 0.92 to 4.13, $P=0.08$, I^2 50%; 6 studies, $n=7,856$ patients^{1 3 4 6 7 9}); however, very few events were identified by any study (especially at 30 days), this result was not statistically significant, and there was a large amount of uncertainty in the result (Supplementary Figure S10). There was moderate heterogeneity at 30 days. The risk of reintervention or reoperation was significantly increased by 278% for TAVI compared to SAVR at two years (RR 2.78, 95% CI 1.35 to 5.71, $P=0.005$, I^2 29%; 4 studies, $n=5,478$ patients^{3 4 6 7}) and by 367% at five years (RR 3.67, 95% CI 1.76 to 7.63, $P=0.0005$, I^2 0%; 3 studies, $n=3,062$ patients^{3 7 8}) (Supplementary Figure S10). There was low heterogeneity across these analyses.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped between each group at all timepoints, suggesting no significant difference in the risk of reintervention or reoperation between study risk groups (Supplementary Figure S10). Generally, there was a trend towards a lower risk of reintervention or reoperation for TAVI compared to SAVR in low-risk studies (EVOLUT, PARTNER 3), but a trend towards a higher risk of reintervention or reoperation for TAVI compared to SAVR in intermediate-, high- and all-risk studies.

Rehospitalisation

The risk of rehospitalisation across all levels of surgical risk was numerically reduced by 12% for TAVI compared to SAVR at 30 days (RR 0.88, 95% CI 0.70 to 1.10, $P=0.27$, I^2 0%; 6 studies, $n=7,645$ patients^{1-4 6 7}); however, this did not reach statistical significance (Supplementary Figure S11). There was no evidence of a difference in the risk of rehospitalisation for TAVI compared to SAVR at one year following surgery (RR 0.95, 95% CI 0.76 to 1.20, $P=0.69$, I^2 65%; 6 studies, $n=7,645$ patients^{1-4 6 7}) (Supplementary Figure S11). The risk of rehospitalisation was numerically increased by 14% for TAVI compared to SAVR at two years (RR 1.14, 95% CI 0.94 to 1.38, $P=0.19$, I^2 59%; 5 studies, $n=6,177$ patients^{2-4 6 7}); however, this was not a statistically significant difference (Supplementary Figure S11). The risk of rehospitalisation was significantly increased by 35% for TAVI compared to SAVR at five years (RR 1.35, 95% CI 1.20 to 1.51, $P<0.00001$, I^2 0%; 3 studies, $n=3,481$ patients^{2 3 7}) (Supplementary Figure S11). Heterogeneity was low at 30 days, two years and five years, and moderate at one year.

One study also reported continuous data for the number of hospital days from the index surgical procedure or randomisation into the control arm up to one-year post procedure or randomisation. This study reported that the total number of days spent in hospital after the index procedure was numerically reduced for TAVI compared to SAVR (17.42 days (19.05 SD) vs. 20.14 days (20.14 SD); 1 study, $n=699$ patients²); however, no statistical comparisons were provided.

Based on study risk group (defined by the criteria reported in Supplementary Table S3, which were not exclusively based on STS-PROM scores), the confidence intervals overlapped for intermediate-risk and high-risk patients at 1 year; however, the confidence intervals for low-risk patients at this timepoint did not overlap with those in other study risk groups at several timepoints, suggesting a significantly greater decrease in the risk of rehospitalisation for TAVI compared to SAVR in low-risk patients (Supplementary Figure S11).

Length of Hospital Stay

Length of Stay in ICU

Four studies reported on the length of stay in the intensive care unit (ICU)^{2-4 9}. All studies reported that patients spent fewer days in the ICU after TAVI treatment (2-3 days) than after SAVR treatment (3-5 days); the mean difference ranged from -1 to -2 days (based on $n=4,549$ patients) (Supplementary Table S4).

Length of Stay in Hospital

Four studies reported sufficient information (mean and SD values) to enable meta-analysis to be performed to analyse length of hospital stay.⁵⁻⁸ Pooled analysis suggested that the total length of hospital stay after the index procedure was significantly shorter following TAVI compared to SAVR (mean difference [MD]

3.08 days, 95% CI -4.86 to -1.29 days, $P=0.0007$, I^2 84%; 4 studies, $n=2,758$ patients⁵⁻⁸) (Supplementary Figure S12). Overall, seven out of the eight studies that presented data for length of hospital stay reported a reduction in the length of hospital stay for TAVI compared to SAVR (Supplementary Table S5)^{1-4 6-9}. The difference in stay generally ranged from -3.0 to -4.0 days for TAVI compared to SAVR (Supplementary Table S5). One of eight studies reported a non-significant increase of 1.2 days in the length of hospital stay for TAVI compared to SAVR (Supplementary Table S5).⁵

Valve Durability

Two studies reported on rates of structural valve deterioration for TAVI compared to SAVR.^{2 8} At five years, the rate of structural valve deterioration (not further defined) was reported to be zero in both TAVI and SAVR patients in the PARTNER 1A trial (Supplementary Table S9).² At six years, the rate of structural valve deterioration was reported to be significantly lower in the TAVI arm (4.8%) compared to the SAVR arm (24%) in the NOTION study (Supplementary Table S9) (79% reduced risk; RR 0.21, 95% CI 0.10 to 0.46, $P<0.0001$; 1 study, $n=274$ patients⁸). This was based on a definition of structural valve deterioration as moderate/severe hemodynamic structural valve deterioration (mean gradient ≥ 20 mm Hg, increase in mean gradient ≥ 10 mm Hg from three months post-procedure, or $>$ mild intraprosthetic aortic regurgitation either new or worsening from three months post-procedure. However, three other definitions of valve dysfunction were reported by the NOTION study, with no statistically significant differences between TAVI vs. SAVR arms (Supplementary Table S9).

A single study (US CoreValve) reported on rates of valve frame fracture for the TAVI arm alone.⁷ No cases of valve frame fracture were reported in 21 TAVI patients who had undergone surgical valve explantation or autopsy after death. Transcatheter valves had been implanted for a median duration of 17 days (range: 0 to 503 days).

Recovery Time

No studies were identified that reported on recovery time.

Pain

No studies were identified that reported on pain.

Subgroup Analyses

For the major or disabling stroke outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a higher risk of a major or disabling stroke after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a significantly or numerically

lower risk of a major or disabling stroke than patients who had TAVI through a non-TF route from periprocedural timepoints through to 5 years following surgery (Supplementary Table S7).

For the myocardial infarction outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a higher risk of MI after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a significantly or numerically lower risk of MI than patients who had TAVI through a non-TF route from 30 days to 2 years following surgery (Supplementary Table S7).

For the major bleeding outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a higher risk of major bleeding after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a significantly or numerically lower risk of major bleeding than patients who had TAVI through a non-TF route from periprocedural timepoints through to 2 years following surgery (Supplementary Table S7).

For the major vascular complications outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of major vascular complications after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a numerically higher risk of major vascular complications than patients who had TAVI through a non-TF route from periprocedural timepoints through to 2 years following surgery (Supplementary Table S7).

For the PPM implantation outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a significantly higher risk of PPM implantation after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); that patients who had TAVI through the transfemoral route had no difference in the risk of PPM implantation compared to patients who had TAVI through a non-TF route from 1 to 2 years following surgery (Supplementary Table S7); and that patients receiving a self-expanding valve were at higher risk of PPM implantation compared to patients receiving a balloon expandable valve from 30 days to 5 years following surgery (Supplementary Table S8).

For the acute kidney injury outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a numerically lower risk of AKI after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a numerically or significantly lower risk of AKI

than patients who had TAVI through a non-TF route at periprocedural timepoints and at 30 days or 2 years following surgery (Supplementary Table S7).

For the new-onset or worsening atrial fibrillation outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a numerically lower risk of NOW-AF after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a numerically or significantly lower risk of NOW-AF than patients who had TAVI through a non-TF route from 30 days to 2 years following surgery (Supplementary Table S7).

For the endocarditis outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a numerically lower risk of endocarditis after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had no difference in the risk of endocarditis than patients who had TAVI through a non-TF route up to 1 year following surgery (Supplementary Table S7).

For the reintervention or reoperation outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a numerically higher risk of reintervention or reoperation after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a numerically lower risk of reintervention or reoperation from periprocedural timepoints through to 2 years, and a numerically higher risk at 5 years compared to patients who had TAVI through a non-TF route up to 1 year following surgery (Supplementary Table S7).

For the rehospitalisation outcome, subgroup results generally suggested that patients at low or intermediate risk (based exclusively on STS-PROM scores alone) had a numerically lower risk of rehospitalisation after TAVI compared to patients at high risk by one year following surgery (Supplementary Table S6); and that patients who had TAVI through the transfemoral route had a numerically lower risk of rehospitalisation compared to patients who had TAVI through a non-TF route from 30 days to 5 years (Supplementary Table S7).

Sensitivity Analyses

For the major bleeding outcome, a sensitivity analysis focussing on the four studies that reported exclusively on major bleeding defined as “life-threatening or disabling bleeding” at one year reduced the overall level of heterogeneity but it still remained high (Supplementary Figure S6).

SUPPLEMENTARY TABLE S1: INCLUSION AND EXCLUSION CRITERIA

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
High Risk			
PARTNER 1A²	High	Patients with severe aortic stenosis (aortic-valve area of less than 0.8cm ² plus either a mean valve gradient of at least 40 mm Hg or a peak velocity of at least 4.0m per second), and cardiac symptoms (New York Heart Association class II function or worse). Included patients were considered candidates for conventional surgical aortic-valve repair with a high risk for operative complications or death on the basis of coexisting conditions that were associated with a risk of death of at least 15% by 30 days after the procedure, as defined by surgeons at each study centre (based on a guideline score of at least 10% on the risk model developed by the Society of Thoracic Surgeons).	Bicuspid or non-calcified valve, coronary artery disease requiring revascularisation, a left ventricular ejection fraction of less than 20%, an aortic annulus diameter of less than 18mm or more than 25mm, severe (4+) mitral or aortic regurgitation, a recent neurological event, and severe renal insufficiency.
US CoreValve⁷	High	Patients with senile degenerative severe aortic stenosis (defined as an initial aortic valve area of ≤ 0.8 cm ² or an aortic valve area index ≤ 0.5 cm ² /m ² AND either mean aortic-valve gradient > 40mm Hg or a peak aortic-jet velocity >4.0m/s); symptomatic as defined by NYHA class II or higher; considered to be at increased risk for undergoing surgical aortic-valve replacement (defined as whether two cardiac surgeons and one interventional cardiologist estimated that the risk of death within 30 days after surgery was $\geq 15\%$ and predicted operative mortality or serious irreversible morbidity risk <50% within 30 days after surgery)	Evidence of acute MI ≤ 30 days before treatment; any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure with bare metal stents and 6 months with drug eluting stents; blood dyscrasias as defined by leukopenia (WBC <1000 mm ³), thrombocytopenia (platelet count <50,000 cells/mm ³), history of bleeding diathesis or coagulopathy or hypercoagulable states; untreated clinically significant coronary artery disease requiring revascularization; cardiogenic shock manifested by low cardiac output, vasopressor dependence or mechanical haemodynamic support; need for emergency surgery for any reason; severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram; recent (within 6 months) cerebrovascular accident or transient ischaemic attack; end stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min; GI bleeding within the past 3 months; known hypersensitivity to medications including aspirin, heparin, nitinol, ticlopidine/clopidogrel or contrast media; ongoing sepsis, including active endocarditis; refusal of blood transfusion; life expectancy <12 months due to associated non-cardiac comorbidities; severe dementia; symptomatic carotid or vertebral

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
			artery disease; declined surgical aortic valve replacement; native aortic annulus <18mm or >29mm; pre-existing prosthetic heart valve in any position; mixed aortic valve disease; moderate to severe (3-4+) mitral regurgitation or (4+) tricuspid regurgitation; moderate to severe mitral stenosis; hypertrophic obstructive cardiomyopathy; intracardiac mass, thrombus or vegetation; severe basal septal hypertrophy with an outflow gradient; aortic root angulation; ascending aorta that exceeds the maximum diameter for any given native aortic annulus; congenital bicuspid or unicuspid valve; sinus of valsalva anatomy that prevents adequate coronary perfusion; transarterial access not able to accommodate an 18F sheath
Intermediate Risk			
PARTNER 2A³	Intermediate	Symptomatic senile degenerative aortic valve stenosis (mean gradient >40 mmHg or jet velocity >4.0 m/s and initial aortic valve area of $\leq 0.8\text{cm}^2$ or indexed EOA <0.5 cm ² /m ²); symptomatic from aortic valve stenosis as demonstrated by NYHA Functional Class II or greater; consensus from heart team that valve implantation would likely benefit the patient; agreement to comply with all post-procedure follow-up visits through 5 years; STS ≥ 4 or <4 if the heart team determines intermediate-risk patient profile	Heart team assessment of inoperability; evidence of an acute MI ≤ 1 month before intended treatment; congenital unicuspid or congenital bicuspid valve or non-calcified valve; mixed aortic valve disease; preexisting mechanical or bioprosthetic valve in any position; complex coronary artery disease (unprotected left main coronary artery or syntax score >32); any therapeutic invasive cardiac procedure resulting in a permanent implant performed within 30 days of procedure; balloon valvuloplasty within 30 days of procedure (unless a bridge to procedure with a qualifying ECHO); planned concomitant surgical or transcatheter ablation for atrial fibrillation; leukopenia (WBC <3000 cell/ml), acute anaemia (Hgb <9 g/dl), thrombocytopenia (Plt <50,000 cell/ml); hypertrophic cardiomyopathy with or without obstruction; severe ventricular dysfunction with LVEF <20%; echocardiographic evidence of intracardiac mass, thrombus or vegetation; active upper GI bleeding within 3 months prior to procedure; contraindication or hypersensitivity to all anticoagulation regimens; native aortic annulus size < 18mm or > 27 mm as measured by echocardiogram; clinical or neuroimaging confirmed stroke or transient ischemic attack within 6 months of procedure, renal insufficiency (creatinine >3.0 mg/dl) and/or renal replacement therapy at the time of screening; estimated life expectancy of <24 months due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease; expectation that patient

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
			will not improve despite treatment; active bacterial endocarditis within 6 months of procedure
SURTAVI⁶	Intermediate	Co-morbidities resulting in predicted risk of operative mortality of $\geq 3\%$ and $< 15\%$ at 30 days; heart team unanimously agree on treatment proposal and eligibility for randomisation based on clinical judgement; severe aortic stenosis presenting with a) initial aortic valve area $\leq 1.0 \text{ cm}^2$ or aortic valve area index $< 0.6 \text{ cm}^2/\text{m}^2$ AND (b) mean gradient $> 40 \text{ mmHg}$ or $V_{\text{max}} > 4 \text{ m/sec}$ by resting echocardiogram or simultaneous pressure recordings at cardiac catheterisation or velocity ratio < 0.25 ; symptomatic from aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater; subject meets minimum age required to provide informed consent	Refused SAVR as a treatment option; any condition considered a contraindication for placement of bioprosthetic valve; known hypersensitivity or contraindication to all anticoagulation/antiplatelet regimens, nitinol or sensitivity to contrast media which cannot be adequately pre-medicated; blood dyscrasias defined as: leukopenia ($\text{WBC} < 1000 \text{ mm}^3$), thrombocytopenia (platelet count $< 50,000 \text{ cells/mm}^3$), history of bleeding diathesis or coagulopathy; ongoing sepsis, including active endocarditis; any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to randomisation; symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within six weeks of randomisation; cardiogenic shock manifested by low cardiac output, vasopressor dependence or mechanical hemodynamic support; recent (within 6 months of randomisation) cerebrovascular accident or transient ischemic attack; active gastrointestinal bleeding; refusal of blood transfusion; severe dementia; multivessel coronary artery disease with a Syntax score > 22 and/or unprotected left main coronary artery; estimated life expectancy of < 24 months due to associated non-cardiac comorbidities; evidence of an acute myocardial infarction ≤ 30 days before index procedure; true porcelain aorta; extensive mediastinal radiation; liver failure (Child-C); reduced ventricular function with $\text{LVEF} < 20\%$; uncontrolled atrial fibrillation; end-stage renal disease requiring chronic dialysis or creatinine clearance $< 20 \text{ cc/min}$; pulmonary hypertension (systolic pressure $> 80 \text{ mmHg}$); severe COPD ($\text{FEV}_1 < 750 \text{ cc}$); Marfan syndrome or other connective tissue disease; native aortic annulus $< 18 \text{ mm}$ or $> 29 \text{ mm}$; pre-existing prosthetic heart valve in any position; mixed aortic valve disease; severe mitral or tricuspid regurgitation; severe mitral stenosis; hypertrophic obstructive cardiomyopathy; evidence of new or untreated intracardiac mass, thrombus or vegetation; aortic root angulation; congenital bicuspid or unicuspid valve; sinus of valsalva anatomy that would prevent adequate coronary perfusion; transarterial access not able to accommodate an 18-Fr sheath.

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
Low Risk			
EVOLUT¹	Low	Severe aortic-valve stenosis with suitable anatomy for TAVI or surgery and no more than a predicted 3% risk of death by 30 days with surgery, as assessed by members of the local heart team. For symptomatic patients, aortic stenosis was defined as an aortic-valve area ≤ 1.0 cm ² (or area index of ≤ 0.6 cm ² /m ²) or a mean gradient of 40 mm Hg or more or maximal aortic-valve velocity of 4.0 m or more per second as assessed by transthoracic echocardiography performed with the patient at rest. For asymptomatic patients, aortic stenosis was defined as: i. valve area of ≤ 1.0 cm ² (or aortic valve area index of ≤ 0.6 cm ² /m ²) AND maximal aortic velocity ≥ 5.0 m/sec or mean gradient ≥ 60 mmHg by transthoracic echocardiography at rest; OR ii. Aortic valve area of ≤ 1.0 cm ² (or aortic valve area index of ≤ 0.6 cm ² /m ²) AND a mean gradient ≥ 40 mmHg or maximal aortic valve velocity ≥ 4.0 m/sec by transthoracic echocardiography at rest AND an exercise tolerance test that demonstrates a limited exercise capacity, abnormal blood pressure response or arrhythmia; OR iii. Aortic valve area of ≤ 1.0 cm ² (or aortic valve area index of ≤ 0.6 cm ² /m ²) AND mean gradient ≥ 40 mmHg or maximal aortic valve velocity ≥ 4.0 m/sec by transthoracic echocardiography at rest AND a left ventricular ejection fraction $< 50\%$.	Patients with bicuspid aortic valves; candidates for mechanical valves; severe mitral/tricuspid regurgitation or moderate/severe mitral stenosis amenable to surgical replacement or repair; pre-existing prosthetic heart valve in any position; hypertrophic obstructive cardiomyopathy with left ventricular outflow gradient; prohibitive left ventricular outflow tract calcification; sinus of Valsalva diameter unsuitable for placement of the self-expanding bioprosthesis; aortic annulus diameter < 18 or > 30 mm; significant aortopathy requiring ascending aortic replacement; blood dyscrasias (defined as leukopenia (WBC < 1000 /mm ³), thrombocytopenia (platelet count $< 50,000$ cells/mm ³), history of bleeding diathesis or coagulopathy of hypercoagulable states); ongoing sepsis (including active endocarditis); percutaneous coronary or peripheral interventional procedure with a bare metal stent within 30 days prior to randomisation; drug eluting stent implanted within 180 days prior to randomisation; multivessel coronary artery disease with a synergy between percutaneous coronary intervention with SYNTAX score > 22 and/or unprotected left main coronary artery; symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of heart team assessment; cardiogenic shock manifested by low cardiac output, vasopressor dependence or mechanical haemodynamic support; recent cerebrovascular accident or transient ischaemic attack; gastrointestinal bleeding that would preclude anti-coagulation; severe dementia; estimated life expectancy < 24 months; evidence of an acute myocardial infarction ≤ 30 days before the trial procedure due to unstable coronary artery disease
PARTNER 3⁴	Low	Severe, calcific aortic stenosis (defined as AVA ≤ 1.0 cm ² or AVA index ≤ 0.6 cm ² /m ² and jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg AND NYHA functional class ≥ 2 or exercise tolerance test that demonstrates a limited exercise capacity, abnormal blood pressure response or arrhythmia OR asymptomatic with LVEF $< 50\%$); heart team agrees the patient has a risk of operative mortality and has an STS < 4 .	Native aortic annulus size unsuitable for sizes 20, 23, 26 or 29mm THV based on 3-D imaging analysis; ilio-femoral vessel characteristics that would preclude safe placement of the introducer sheath; evidence of an acute myocardial infarction ≤ 1 month (30 days) before randomisation; congenital unicuspid, bicuspid or non-calcified aortic valve; severe aortic regurgitation ($> 3+$); severe mitral regurgitation ($> 3+$) or moderate (or more than moderate) stenosis; pre-existing mechanical or bioprosthetic valve in any position; complex coronary artery disease (unprotected left main coronary artery, syntax score > 32 in

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
			absence of prior revascularisation or heart team assessment that optimal revascularisation cannot be performed); symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 30 days of randomisation; leukopenia (WBC <3000 cells/ml), anaemia (Hgb <9g/dl), thrombocytopenia (Plt <50,000 cells/ml), history of bleeding diathesis or coagulopathy or hypercoagulable states; haemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of randomisation; hypertrophic cardiomyopathy with obstruction; ventricular dysfunction with LVEF <30%; cardiac imaging evidence of intracardiac mass, thrombus or vegetation; inability to tolerate or a condition precluding treatment with anti-thrombotic/anti-coagulation therapy during or after valve implant procedure; stroke or transient ischaemic attack within 90 days of randomisation; renal insufficiency (eGFR <30 ml/min per the Cockcroft-Gault formula) or renal replacement therapy at the time of screening; active bacterial endocarditis within 180 days of randomisation; severe lung disease (FEV1 <50% predicted) or currently on home oxygen; severe pulmonary hypertension; history of cirrhosis or active liver disease; significant frailty as determined by the heart team; significant abdominal or thoracic aortic disease (such as porcelain aorta, aneurysm, severe calcification, aortic coarctation etc) that would preclude safe passage of the delivery system or cannulation and aortotomy for surgical AVR; hostile chest or conditions or complications from prior surgery that would preclude safe reoperation; patient refuses blood products; BMI >50 kg/m ² ; estimated life expectancy <24 months; absolute contraindications or allergy to iodinated contrast that cannot be adequately treated with pre-medication; immobility that would prevent completion of study procedures (e.g. six-minute walk tests)
Intermediate-High (≥70y) or Any (≥80y) Risk			
UK TAVI ⁹	Intermediate-High (≥70 years) or	Severe symptomatic aortic stenosis referred for intervention; aged ≥ 80 or ≥70 with intermediate or high operative risk from conventional AVR, as determined by the MDT; both conventional AVR and	Intervention deemed inappropriate due to co-morbidity or frailty; life expectancy less than one year due to co-morbidity; previous AVR or TAVI; technically unsuitable for either AVR or TAVI; concomitant coronary artery disease (CAD) requiring

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
	Any (≥ 80 years)	TAVI deemed to be acceptable treatment options; participant able and willing to give written consent; participant able and willing to comply with all trial requirements.	revascularisation for which only surgery is considered appropriate; predominant aortic regurgitation; severe mitral regurgitation or need for concomitant surgery other than planned coronary revascularisation.
All Risk			
NOTION⁸	All	Patients ≥ 70 years of age with severe degenerative aortic valve stenosis (defined as an effective orifice area $< 1 \text{ cm}^2$ or indexed for body surface area $< 0.6 \text{ cm}^2/\text{m}^2$ and a mean aortic valve gradient $> 40 \text{ mm Hg}$ or peak systolic velocity $> 4 \text{ m/s}$) who were referred for SAVR and also candidates for TAVI; symptomatic patients had to have dyspnea, NYHA functional class II or higher, angina pectoris or cardiac syncope; asymptomatic patients could be included if they had left ventricular posterior wall thickness $\geq 17 \text{ mm}$, decreasing left ventricular ejection fraction or new-onset atrial fibrillation; expected to survive for more than 1 year	Severe heart valve disease or CAD requiring intervention; previous cardiac surgery; MI or stroke within 30 days; severe renal failure requiring dialysis; pulmonary failure with a FEV1 or diffusion capacity $< 40\%$ of expected
STACCATO⁵	“Operable”	Significant valvular aortic stenosis (valve area $< 1 \text{ cm}^2$); age initially ≥ 70 later ≥ 75 years (at the Aarhus University site) or > 80 years (at other participating sites); condition accessible both by SAVR and transapical TAVI; expected survival > 1 year following successful treatment; patient acceptance of participation in study and follow-up investigations	Coronary artery disease to be treated by PCI or CABG; previous MI or previous PCI within the previous 12 months; previous heart surgery (added as exclusion criteria during study); the need for other heart surgery (such as mitral or tricuspid valve surgery) or emergency surgery (within 24 hours of indication for surgery); unstable cardiac condition (requiring an assist device, inotropes or i.v. nitrates in operating room); ongoing infection requiring antibiotics; stroke within one month; reduced pulmonary function (FEV1 < 11 or $< 40\%$ of expected); renal failure to be treated by haemodialysis; allergy to acetylsalicylic acid, clopidogrel, prasugrel or x-ray contrast material; kidney failure requiring any dialysis
Abbreviations: 6MWT = 6 minute walk test; AR = aortic regurgitation; AVA = aortic valve area; AVR = aortic valve replacement; cm = centimetres; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DAOH = days alive and out of hospital; DVI = Doppler velocity index; EOA = effective orifice area; FEV1 = forced expiratory volume in one second; HgB = haemoglobin; ICU = intensive care unit; i/v. = intravenous; KCCQ = Kansas City cardiomyopathy questionnaire; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiac and cerebrovascular events; MAE = major adverse events; MDT = multi-disciplinary heart team; MI = myocardial infarction; ml = millilitre; mm = millimetre; NYHA = New York heart association; PCI = percutaneous coronary intervention; Plt = platelets; SAVR = surgical aortic valve replacement; STS = society for thoracic surgeons; TAVI = transcatheter aortic valve implantation; THV = transcatheter heart valve; TIA = transient ischaemic attack; VARC = Valve Academic Research Consortium; WBC = white blood cell; y = years			

SUPPLEMENTARY TABLE S2: PRIMARY AND SECONDARY OUTCOMES

Study ID	Risk Level	Primary Outcomes	Secondary Outcomes
High Risk			
PARTNER 1A ²	High	All-cause mortality at 12 months	Death from cardiovascular causes; functional change in NYHA; repeat hospitalisation due to valve- or procedure-related clinical deterioration; myocardial infarction; stroke; acute kidney injury; vascular complications; bleeding; 6MWT; valve performance (as assessed on echocardiography)
US CoreValve ⁷		All-cause mortality at 12 months	Composite outcome (death from any cause, myocardial infarction, any stroke, or reintervention); composite outcome (all-cause mortality or major stroke); all-cause mortality; myocardial infarction; any stroke; reintervention; improvement in symptoms based on NYHA classification; QoL (KCCQ, SF-12); aortic valve gradient; effective orifice area; acute kidney injury; cardiac tamponade; prosthetic valve dysfunction; cardiogenic shock; valve endocarditis; life-threatening, disabling or major bleeding; major vascular complications; cardiac perforation; device migration/valve embolism; permanent pacemaker implantation; 6MWT; aortic regurgitation; aortic valve hospitalisation; cardiovascular death and valve-related death; composite outcome (stroke and TIA); index procedure-related MAEs; length of index hospitalisation; device success (defined as: successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system, correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function), intended performance of the prosthetic valve (aortic valve area > 1.2 cm ² for 26, 29 and 31mm valves, ≥ 0.9 cm ² for 23mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve aortic regurgitation) and only one valve implanted in the proper anatomical location); procedural success (defined as device success and absence of in-hospital MACCE);
Intermediate Risk			
PARTNER 2A ³	Intermediate	Composite of all-cause mortality or disabling stroke ^a at 24 months	Adjusted Days Alive and Out of Hospital (DAOH); Total AR; 6MWT change from baseline; NYHA Classification; EOA
SURTAVI ⁶		Composite of all-cause mortality or disabling stroke ^b at 24 months	Major adverse cardiovascular and cerebrovascular events (death from any cause, MI, all types of strokes, any reintervention); gradient;

Study ID	Risk Level	Primary Outcomes	Secondary Outcomes
			effective orifice area; NYHA; KCCQ; length of index hospitalisation; days alive and out of hospital
Low Risk			
EVOLUT ¹	Low	Composite of all-cause mortality or disabling stroke ^b at 24 months	Transvalvular mean gradient; EOA, NYHA classification; KCCQ score; composite of death, disabling stroke, life-threatening bleed, major vascular complications or stage II/III acute kidney injury; new permanent pacemaker implantation; new endocarditis; valve thrombosis; all stroke (disabling and non-disabling); life-threatening bleeding; valve-related dysfunction requiring repeat procedure
PARTNER 3 ⁴		Composite of all-cause mortality, all stroke or rehospitalisation (valve- or procedure-related, including HF) at 12 months	Stroke; a composite of death or stroke; a composite of death or disabling stroke; all-cause death; all stroke; rehospitalisation (valve- or procedure-related); new-onset atrial fibrillation at 30 days; length of index hospitalisation; ICU days; a poor treatment outcome (composite outcome of death or a low KCCQ overall summary score (KCCQ <45 or KCCQ decrease from baseline of ≥10 points at 30 days); major vascular complications; life threatening/disabling or major bleeding complications; myocardial infarction; acute kidney injury; requirement for renal replacement therapy; new permanent pacemaker implantation; coronary obstruction requiring intervention; NYHA functional class; 6MWT; KCCQ summary score; haemodynamic evaluations; discharge location; days alive and out of hospital; EQ-5DL; SF-36; structural valve deterioration (valve-related dysfunction (mean aortic valve gradient ≥= 20 mm Hg, EOA≤= 0.9-1.1 cm ² and/or DVI<0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation) AND requiring repeat procedure (TAVI or Surgery))
Intermediate-High (≥70y) or Any (≥80y) Risk			
UK TAVI ⁹	Intermediate-High (≥70 years) or Any (≥80 years)	All-cause mortality at 12 months	All-cause mortality (at 2, 3, 4 & 5 years); stroke; composite of death from any cause or stroke; conduction disturbance requiring pacing; infective endocarditis; myocardial infarction; re-intervention; vascular complications; major bleeding; renal replacement therapy; quality of life (MLWHF & EQ-5D-5L); functional capacity (NYHA, 6-MWT); echocardiographic measures; costs and cost-utility; all at 30 days and 1-year, with definitions based on VARC2
All Risk			
NOTION ⁸	All	Composite of all-cause mortality, stroke or MI at 12 months	The rate of individual components of the composite outcome; the rate of cardiovascular death; prosthesis reintervention; cardiogenic shock; valve endocarditis; conduction abnormalities requiring permanent

Study ID	Risk Level	Primary Outcomes	Secondary Outcomes
			pacemaker; atrial fibrillation or flutter; and vascular, renal, and bleeding complications after 1 and 12 months. Clinical improvement was assessed according to NYHA functional classification. Echocardiographic outcomes included aortic valve effective orifice area, mean pressure gradient, and degree of total aortic valve regurgitation (graded as none/trace, mild, moderate, and severe) at 3 and 12 months. All outcomes were defined according to VARC-2 definitions.
STACCATO ⁵	“Operable”	Composite of all-cause mortality, major stroke or renal failure requiring dialysis at 30 days	All-cause death, cardiac death, stroke, myocardial infarction, NYHA functional class, SF-36 composite physical and mental functional scores, echocardiographic parameters (aortic valve area, peak aortic valve gradient, aortic valve leakage, LVEF), duration of hospital stay, operation for bleeding; permanent pacemaker treatment; valve performance.
Abbreviations: 6MWT = 6 minute walk test; AR = aortic regurgitation; cm = centimetres; DAOH = days alive and out of hospital; DVI = Doppler velocity index; EOA = effective orifice area; HF = heart failure; ICU = intensive care unit; KCCQ = Kansas City cardiomyopathy questionnaire; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiac and cerebrovascular events; MAE = major adverse events; MI = myocardial infarction; mm = millimetre; NYHA = New York heart association; SAVR = surgical aortic valve replacement; SF-36 = short-form survey 36; TAVI = transcatheter aortic valve implantation; TIA = transient ischaemic attack; VARC = Valve Academic Research Consortium; y = years. ^aDefined as a score of ≥ 2 on the modified Rankin scale (which ranges from 0 (no symptoms) to 6 (death)) at 90 days after the index clinical event. ^bDefined as a score of ≥ 2 on the modified Rankin scale at 90 days AND an increase in at least one modified Rankin scale category from the individual’s pre-stroke baseline.			

SUPPLEMENTARY TABLE S3: STUDY DEFINITIONS OF DISEASE AND LEVEL OF SURGICAL RISK

Study ID	Disease	Definition of Disease	Level of Surgical Risk	Definition of Surgical Risk
High Risk				
PARTNER 1A²	Symptomatic senile degenerative severe aortic stenosis and cardiac symptoms	Aortic valve area <0.8 cm ² (or AVA index <0.5cm ² /m ²) plus either a mean valve gradient of ≥40 mmHg or a peak velocity of ≥4.0 m/s AND NYHA class II or greater	High	Risk of death ≥15% by 30 days following surgery and/or STS ≥ 10%
US CoreValve⁷	Senile degenerative symptomatic severe aortic stenosis and heart failure symptoms	Initial aortic valve area ≤0.8cm ² (or AVA index ≤ 0.5 cm ² /m ²) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterisation AND mean gradient >40 mmHg or jet velocity >4.0 m/s by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterisation (either resting or dobutamine stress) AND NYHA class II or greater	High	Risk of operative mortality ≥15% by 30 days following surgery; risk of serious irreversible morbidity <50% by 30 days following surgery
Intermediate Risk				
PARTNER 2A³	Senile degenerative severe aortic stenosis	Initial aortic valve area <0.8 cm ² or indexed effective orifice area <0.5cm ² /m ² plus a mean gradient >40 mmHg or jet velocity >4.0 m/s AND NYHA class II or greater	Intermediate	STS ≥4.0% (or <4% if determined as intermediate risk by the heart team)
SURTAVI⁶	Severe symptomatic severe aortic stenosis	Initial aortic valve area of ≤1.0 cm ² (or AVA index <0.6cm ² /m ²) AND mean gradient > 40mmHg or peak velocity >4m/s by resting echocardiogram or simultaneous pressure recordings at cardiac catheterisation [or with dobutamine stress, if subject has a LVEF <55%] or velocity	Intermediate	Risk of operative mortality ≥3 to <15% by 30 days following surgery; plus consideration of overall clinical status and co-morbidities not measured by the STS score

Study ID	Disease	Definition of Disease	Level of Surgical Risk	Definition of Surgical Risk
		ratio < 0.25 AND NYHA class II or greater		
Low Risk				
EVOLUT ¹	Severe aortic stenosis	<u>For symptomatic patients:</u> Aortic valve area $\leq 1.0 \text{ cm}^2$ (or AVA index $\leq 0.6 \text{ cm}^2/\text{m}^2$) OR mean gradient $\geq 40 \text{ mmHg}$ OR maximal aortic valve velocity $\geq 4.0 \text{ m/s}$ by transthoracic echocardiography at rest. <u>For asymptomatic patients:</u> i. Very severe aortic stenosis with an aortic valve area $\leq 1.0 \text{ cm}^2$ (or AVA index $\leq 0.6 \text{ cm}^2/\text{m}^2$) AND maximal aortic velocity $\geq 5.0 \text{ m/sec}$ or mean gradient $\geq 60 \text{ mmHg}$ by transthoracic echocardiography at rest ii. Aortic valve area of $\leq 1.0 \text{ cm}^2$ (or AVA index of $\leq 0.6 \text{ cm}^2/\text{m}^2$) AND a mean gradient $\geq 40 \text{ mmHg}$ or maximal aortic valve velocity $\geq 4.0 \text{ m/s}$ by transthoracic echocardiography at rest AND an exercise tolerance test that demonstrates a limited exercise capacity, abnormal blood pressure response or arrhythmia iii. Aortic valve area of $\leq 1.0 \text{ cm}^2$ (or AVA index of $\leq 0.6 \text{ cm}^2/\text{m}^2$) AND mean gradient $\geq 40 \text{ mmHg}$ or maximal aortic valve velocity $\geq 4.0 \text{ m/s}$ by transthoracic	Low	Risk of death $\leq 3\%$ by 30 days following the procedure per multidisciplinary local heart team assessment

Study ID	Disease	Definition of Disease	Level of Surgical Risk	Definition of Surgical Risk
		echocardiography at rest AND a LVEF <50%.		
PARTNER 3⁴	Severe calcific aortic stenosis	Aortic valve area $\leq 1.0 \text{ cm}^2$ or AVA index $\leq 0.6 \text{ cm}^2/\text{m}^2$ AND jet velocity $\geq 4.0 \text{ m/s}$ or mean gradient $\geq 40 \text{ mmHg}$ AND NYHA Functional Class $\geq \text{II}$ or exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response or arrhythmia or asymptomatic with LVEF <50%	Low	STS <4 and low operative mortality risk
Intermediate-High ($\geq 70\text{y}$) or Any ($\geq 80\text{y}$) Risk				
UK TAVI⁹	Severe symptomatic aortic stenosis	NR	Intermediate-High (≥ 70 years) or Any (≥ 80 years)	NR
All Risk				
NOTION⁸	Severe degenerative aortic stenosis	Effective orifice area $< 1 \text{ cm}^2$ or indexed for body surface area $< 0.6 \text{ cm}^2/\text{m}^2$ and a mean aortic valve gradient $> 40 \text{ mm Hg}$ or peak systolic velocity $> 4 \text{ m/s}$. Symptomatic patients had to have dyspnea, NYHA functional class II or higher, angina pectoris or cardiac syncope. Asymptomatic patients could be included if they had left ventricular posterior wall thickness $\geq 17 \text{ mm}$, decreasing LVEF or new-onset AF	All (High, Intermediate and Low)	Regardless of predicted risk of death following surgery; but must be expected to survive > 1 year
STACCATO⁵	Significant aortic stenosis	Valve area $< 1 \text{ cm}^2$	“Operable”	Expected survival > 1 year
Abbreviations: AF = atrial fibrillation; AVA = aortic valve area; BP = blood pressure; cm = centimetre; LVEF = left ventricular ejection fraction; m = metres; NA = not applicable; NR = not reported; NYHA = New York heart association; s = second; STS = society for thoracic surgeons; y = years.				

SUPPLEMENTARY TABLE S4: LENGTH OF STAY IN ICU

Study ID	Treatment Arm	No. of Patients in Treatment Arm	Median Time in ICU (Days)	Median Difference	P-Value
Low Risk					
PARTNER 3 ⁴	TAVI	496	2*	-1.0	NR
	SAVR	454	3*		
Intermediate Risk					
PARTNER 2A ³	TAVI	1011	2	-2.0	<0.001
	SAVR	1021	4		
High Risk					
PARTNER 1A ²	TAVI	348	3*	-2.0	<0.001
	SAVR	351	5*		
Intermediate-High (≥70y) or Any (≥80y) Risk					
UK TAVI ⁹	TAVI	449	0	-1.0	NR
	SAVR	419	1		
Abbreviations: ICU = intensive care unit; NR = not reported; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation; y = years.					
*Average measure unclear					

SUPPLEMENTARY TABLE S5: LENGTH OF STAY IN HOSPITAL FOLLOWING INDEX PROCEDURE

Study ID	Treatment Arm	No. of Patients in Treatment Arm	Measure	Time in Hospital (Days)	Error	Error Type	Difference (Days)	P-Value
Low Risk								
PARTNER 3 ⁴	TAVI	496	NR	3	2 to 3	95% CI	-4.0	<0.001
	SAVR	454		7	6 to 8	95% CI		
Intermediate Risk								
PARTNER 2A ³	TAVI	1011	Median	6	NR	NR	-3.0	<0.001
	SAVR	1021		9	NR	NR		
SURTAVI ⁵	TAVI	863	Mean	5.75	4.85	SD	-4.0	NR
	SAVR	795		9.75	8.03	SD		
High Risk								
PARTNER 1A ²	TAVI	348	NR	8	NR	NR	-4.0	<0.001
	SAVR	351		12	NR	NR		
US CoreValve ⁷	TAVI	391	Mean	8.0	6.8	SD	-4.5	NR
	SAVR	359		12.5	10.7	SD		
Intermediate-High (≥70y) or Any (≥80y) Risk								
UK TAVI ⁹	TAVI	449	Median	3	2 to 5	IQR	-5.0	NR
	SAVR	419		8	6 to 13	IQR		
All Risk								
NOTION ⁸	TAVI	145	Mean	8.9	6.2	SD	-4.0	NR
	SAVR	135		12.9	11.6	SD		
STACCATO ⁵	TAVI	34	Mean	8.8	6.7	SD	+1.2	NS
	SAVR	36		7.6	2.4	SD		
Abbreviations: CI = confidence interval; ICU = intensive care unit; IQR = interquartile range; NR = not reported; NS = not significant (as reported by the authors); SAVR = surgical aortic valve replacement; SD = standard deviation; TAVI = transcatheter aortic valve implantation.								

SUPPLEMENTARY TABLE S6: SUBGROUP ANALYSIS BY LEVEL OF SURGICAL RISK BASED ON STS-PROM SCORES (TAVI ONLY)

Outcome	Timepoint	# Studies	Total # Patients in Low-Intermediate Risk Arm	Total # Patients in High Risk Arm	Risk Ratio	95% CI (Lower)	95% CI (Upper)	I ² (%)	Favours?
All-Cause Mortality	1 Year	4 ^{2 6 7 9}	1368	691	0.59	0.46	0.75	0	Low-Int risk*
	2 Year	1 ⁷	202	189	0.51	0.34	0.76	NA	Low-Int risk*
	5 Year	1 ⁸	121	24	0.41	0.25	0.68	NA	Low-Int risk*
Cardiovascular Mortality	1 Year	1 ⁶	611	253	0.41	0.23	0.76	NA	Low-Int risk*
All Stroke	1 Year	1 ⁶	611	253	0.54	0.31	0.97	NA	Low-Int risk*
Major or Disabling Stroke	1 Year	1 ⁶	611	253	0.65	0.26	1.66	NA	Low-Int risk
Myocardial Infarction	1 Year	1 ⁶	611	253	0.53	0.20	1.41	NA	Low-Int risk
Major Bleeding	1 Year	1 ⁶	611	253	0.67	0.41	1.09	NA	Low-Int risk
Major Vascular Complications	1 Year	1 ⁶	611	253	0.52	0.31	0.87	NA	Low-Int risk*
New Permanent Pacemaker Implantation	1 Year	1 ⁶	611	253	1.41	1.08	1.83	NA	High risk*
Acute Kidney Injury	1 Year	1 ⁶	611	253	0.55	0.19	1.58	NA	Low-int risk
New-Onset or Worsening Atrial Fibrillation	1 Year	1 ⁶	611	253	0.79	0.58	1.07	NA	Low-int risk
Endocarditis	1 Year	1 ⁶	611	253	0.41	0.03	6.59	NA	Low-int risk
Reintervention or Reoperation	1 Year	1 ⁶	611	253	3.11	0.72	13.48	NA	High risk
Rehospitalisation	1 Year	1 ⁶	611	253	0.88	0.55	1.42	NA	Low-int risk

Outcome	Timepoint	# Studies	Total # Patients in Low-Intermediate Risk Arm	Total # Patients in High Risk Arm	Risk Ratio	95% CI (Lower)	95% CI (Upper)	I ² (%)	Favours?
Abbreviations: # = number; CI = confidence interval; NA = not applicable.									
*Significant result (i.e. 95% CI crosses 1.00)									

SUPPLEMENTARY TABLE S7: SUBGROUP ANALYSIS BY ROUTE (TAVI ONLY)

Outcome	Timepoint	# Studies	Total # Patients in TF Arm	Total # Patients in non-TF Arm	Risk Ratio	95% CI (Lower)	95% CI (Upper)	I ² (%)	Favours?
All-Cause Mortality	Periprocedural	1 ⁷	324	67	1.24	0.15	10.14	NA	Non-TF
	30 Day	2 ^{2,3}	1019	340	0.51	0.29	0.88	0	TF*
	1 Year	2 ^{2,3}	1019	340	0.62	0.41	0.92	60	TF*
	2 Year	2 ^{2,3}	1019	340	0.65	0.49	0.86	44	TF*
	5 Year	2 ^{3,7}	1099	303	0.82	0.66	1.03	63	TF
Cardiovascular Mortality	30 Day	2 ^{2,3}	1019	340	0.63	0.34	1.17	1	TF
	1 Year	2 ^{2,3}	1019	340	0.63	0.44	0.89	0	TF*
	2 Year	2 ^{2,3}	1019	340	0.72	0.53	0.97	0	TF*
	5 Year	2 ^{2,3}	1019	340	0.77	0.69	0.85	0	TF*
All Stroke	Periprocedural	1 ⁷	324	67	0.76	0.22	2.64	NA	TF
	30 Day	3 ^{2,3,7}	1339	407	0.51	0.32	0.81	7	TF*
	1 Year	3 ^{2,3,7}	1334	405	0.66	0.46	0.94	0	TF*
	2 Year	3 ^{2,3,7}	1323	405	0.73	0.44	1.23	45	TF
	5 Year	2 ^{3,7}	1099	303	0.80	0.60	1.09	0	TF
Major or Disabling Stroke	Periprocedural	1 ⁷	324	67	0.76	0.22	2.64	NA	TF
	30 Day	3 ^{2,3,7}	1343	407	0.47	0.28	0.80	0	TF*
	1 Year	3 ^{2,3,7}	1335	406	0.60	0.39	0.93	0	TF*
	2 Year	2 ^{3,7}	1079	302	0.70	0.40	1.23	18	TF
	5 Year	1 ³	775	236	0.67	0.43	1.04	NA	TF
Myocardial Infarction	Periprocedural	1 ⁷	324	67	1.46	0.08	28.03	NA	Non-TF
	30 Day	2 ^{2,3a}	1019	340	0.22	0.07	0.68	NA	TF*
	1 Year	2 ^{2,3}	1019	340	0.45	0.21	0.99	0	TF*
	2 Year	2 ^{2,3a}	1019	340	0.53	0.27	1.07	NA	TF
Major Bleeding	Periprocedural	1 ⁷	324	67	0.36	0.21	0.62	NA	TF*
	30 Day	2 ^{2,3}	1019	340	0.55	0.15	1.96	90	TF
	1 Year	2 ^{2,3}	1019	340	0.73	0.19	2.78	93	TF
	2 Year	2 ^{2,3}	1019	340	0.86	0.23	3.21	94	TF
Major Vascular Complications	Periprocedural	1 ⁷	324	67	4.14	0.56	30.29	NA	Non-TF
	30 Day	2 ^{2,3}	1019	340	2.07	0.84	5.07	60	Non-TF
	1 Year	2 ^{2,3}	1019	340	2.01	0.71	5.68	71	Non-TF

Outcome	Timepoint	# Studies	Total # Patients in TF Arm	Total # Patients in non-TF Arm	Risk Ratio	95% CI (Lower)	95% CI (Upper)	I ² (%)	Favours?
	2 Year	2 ^{2,3}	1019	340	2.00	0.66	6.12	75	Non-TF
New Permanent Pacemaker Implantation	Periprocedural	1 ⁷	324	67	1.41	0.63	3.19	NA	Non-TF
	30 Day	2 ^{2,3}	1019	340	0.84	0.55	1.28	0	TF
	1 Year	2 ^{2,3}	1019	340	0.90	0.61	1.32	0	NA
	2 Year	2 ^{2,3}	1019	340	0.91	0.63	1.30	0	NA
Acute Kidney Injury	Periprocedural	1 ⁷	324	67	0.50	0.22	1.16	NA	TF
	30 Day	2 ^{2,3}	1019	340	0.56	0.02	17.15	79	TF
	1 Year	2 ^{2,3}	1019	340	1.47	0.03	81.53	87	Non-TF
	2 Year	1 ³	775	236	0.30	0.16	0.58	NA	TF*
New-Onset or Worsening Atrial Fibrillation	30 Day	2 ^{2,3}	1019	340	0.36	0.13	1.03	86	TF
	1 Year	2 ^{2,3}	1019	340	0.43	0.14	1.29	90	TF
	2 Year	1 ³	775	236	0.30	0.22	0.43	NA	TF*
Endocarditis	30 Day	2 ^{2,3}	1019	340	NC ^b	NC ^b	NC ^b	NA	NA
	1 Year	2 ^{2,3}	1019	340	1.07	0.20	5.72	0	NA
	2 Year	2 ^{2,3}	1019	340	2.05	0.45	9.36	0	Non-TF
Reintervention or Reoperation	Periprocedural	1 ⁷	324	67	0.21	0.01	3.26	NA	TF
	30 Day	1 ³	775	236	0.91	0.10	8.74	NA	NA
	1 Year	1 ³	775	236	0.81	0.22	3.04	NA	TF
	2 Year	1 ³	775	236	0.69	0.21	2.20	NA	TF
	5 Year	1 ³	775	236	2.89	0.68	12.33	NA	Non-TF
Rehospitalisation	30 Day	2 ^{2,3}	1019	340	0.68	0.38	1.23	21	TF
	1 Year	2 ^{2,3}	1019	340	0.82	0.49	1.38	65	TF
	2 Year	2 ^{2,3}	1019	340	0.80	0.63	1.02	0	TF
	5 Year	1 ²	244	104	0.82	0.64	1.05	NA	TF
Abbreviations: CI = confidence interval; NA = not applicable; NC = not calculable; TF = transfemoral. *Significant result (i.e. 95% CI crosses 1.00) ^a 1 study reported no events in either arm and therefore did not contribute to the estimate (not estimable). ^b Both studies reported zero events in both arms and therefore no effect estimate could be calculated (not estimable).									

SUPPLEMENTARY TABLE S8: SUBGROUP ANALYSIS BY VALVE TYPE

Outcome	Timepoint	Valve Type	# Studies	Total # Patients in TAVI Arm	Total # Patients in SAVR Arm	Risk Ratio	95% CI (Lower)	95% CI (Upper)	I ² (%)
New Permanent Pacemaker Implantation	30 Days	Balloon Expandable	3 ²⁻⁴	1855	1826	1.31	1.01	1.69	0
		Self -Expanding	4 ^{1 6-8}	2121	1965	3.62	2.43	5.39	69
	1 Year	Balloon Expandable	3 ²⁻⁴	1855	1826	1.21	0.96	1.52	0
		Self -Expanding	3 ^{1 7 8}	1257	1169	3.58	1.79	7.15	84
	2 Year	Balloon Expandable	2 ^{2 3}	1359	1372	1.20	0.95	1.52	0
		Self -Expanding	2 ^{7 8}	533	493	4.44	0.87	22.52	92
	5 Year	Balloon Expandable	1 ²	348	351	1.23	0.72	2.09	NA
		Self-Expanding	2 ^{7 8}	536	494	3.11	1.12	8.62	88
Abbreviations: # = number; CI = confidence interval; NA = not applicable; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.									

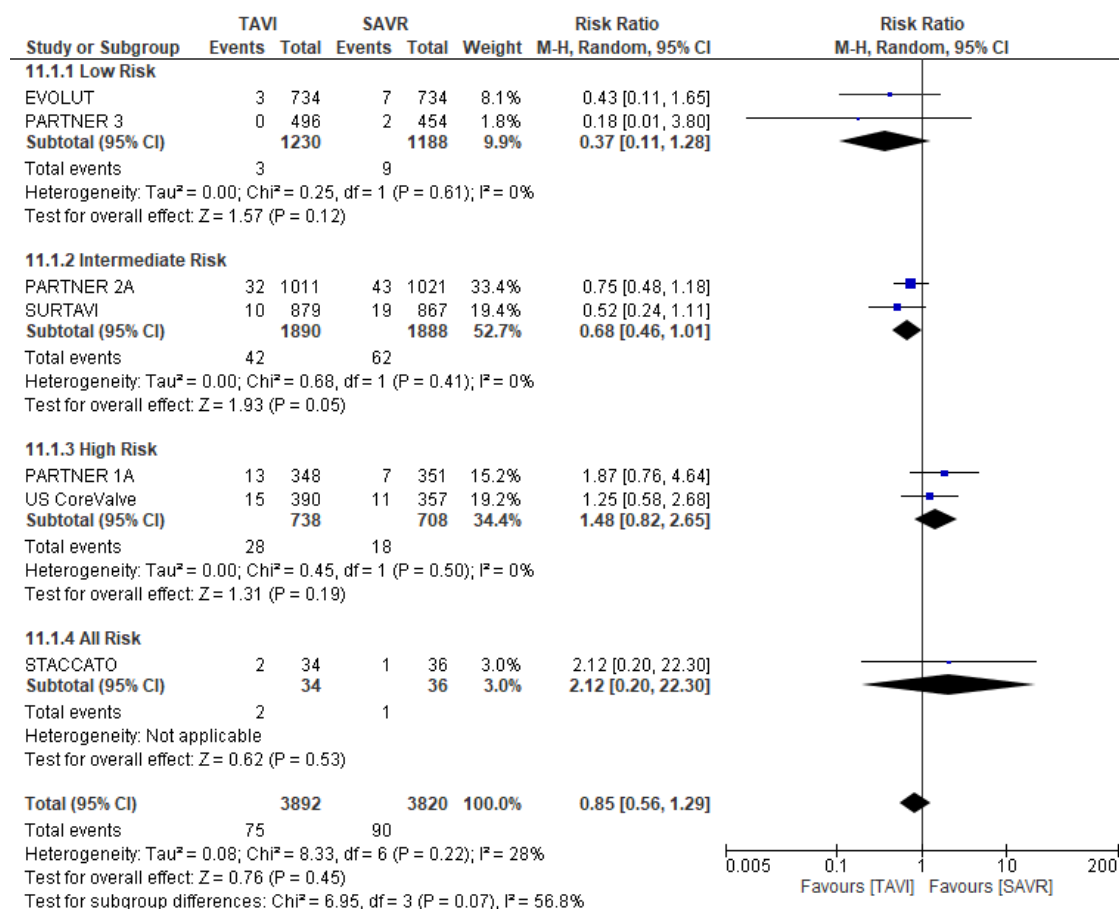
SUPPLEMENTARY TABLE S9: VALVE DURABILITY

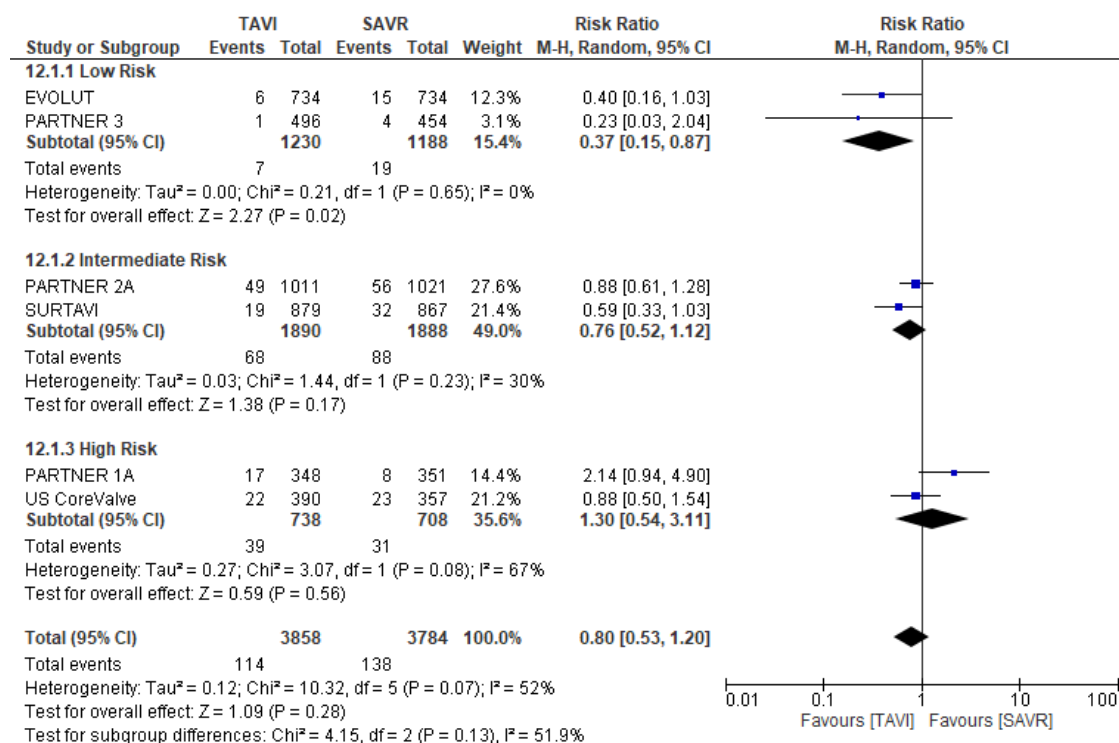
Study ID	Follow-Up Period	Treatment Arm	Definition of SVD	No. of Patients Experiencing Event	Total No. of Patients	%	P-Value	Effect Estimate
High Risk								
PARTNER 1A ²	5 Years	TAVI	Structural valve deterioration	0	348	0	NR	NE
		SAVR		0	351	0		
All Risk								
NOTION ⁸	6 Years	TAVI	Moderate/severe haemodynamic structural valve deterioration (mean gradient ≥20 mm Hg, increase in mean gradient ≥10 mm Hg from 3 months post-procedure or > mild intraprosthetic aortic regurgitation either new or worsening from 3 months post-procedure	7	139	4.8	<0.0001	RR 0.21, 95% CI 0.10 to 0.46
		SAVR		32	135	24.0		
		TAVI	Bioprosthetic valve dysfunction defined as as one or more of the following: structural valve deterioration, non-structural valve deterioration, bioprosthetic valve thrombosis or endocarditis.	78	139	56.1	0.073	RR 0.84, 95% CI 0.70 to 1.02
		SAVR		90	135	66.7		
		TAVI	Non-structural valve deterioration defined as defined as moderate/severe	75	139	54.0	0.52	RR 0.93, 95% CI 0.76 to 1.15
		SAVR		78	135	57.8		

Study ID	Follow-Up Period	Treatment Arm	Definition of SVD	No. of Patients Experiencing Event	Total No. of Patients	%	P-Value	Effect Estimate
			PPM at 3 months or moderate/severe PVL					
		TAVI	Bioprosthetic valve failure defined as at least 1 of the following: valve-related death (death caused by BVD or sudden unexplained death following diagnosis of BVD), aortic valve reintervention (TAVR or SAVR following diagnosis of BVD), or severe hemodynamic SVD (mean gradient ≥40 mm Hg, increase in mean gradient ≥20 mm Hg from 3 months post-procedure, or severe intraprosthetic AR either new or worsening from 3 months post-procedure)	10	139	7.5	0.89	RR 1.08, 95% CI 0.45 to 2.57
		SAVR		9	135	6.7		
Abbreviations: AR = aortic regurgitation; BVD = bioprosthetic valve dysfunction; NE = not estimable; NR = not reported; PPM = patient-prosthesis mismatch; PVL = paravalvular leakage; RR = risk ratio; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVI = transcatheter aortic valve implantation.								

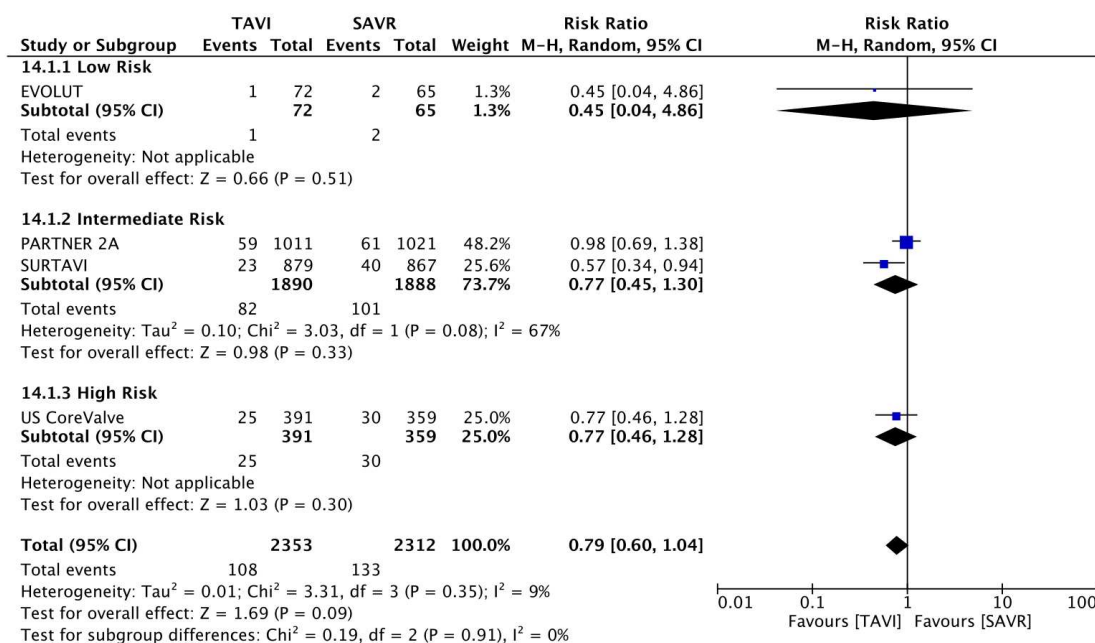
SUPPLEMENTARY FIGURE S1: FOREST PLOTS FOR MAJOR OR DISABLING STROKE

a. 30 Days

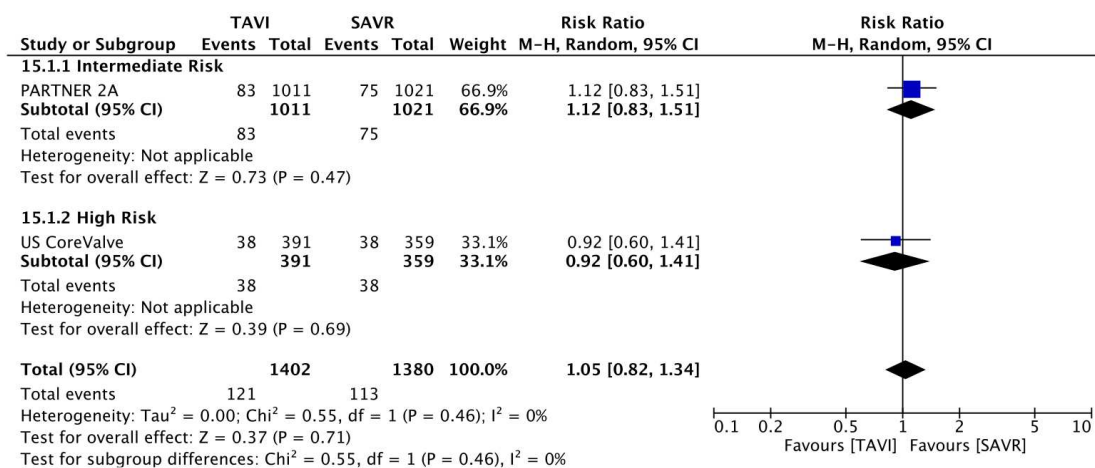


b. 1 Year

c. 2 Years

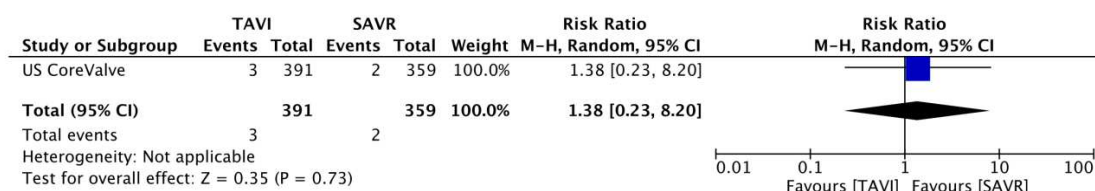


d. 5 Years

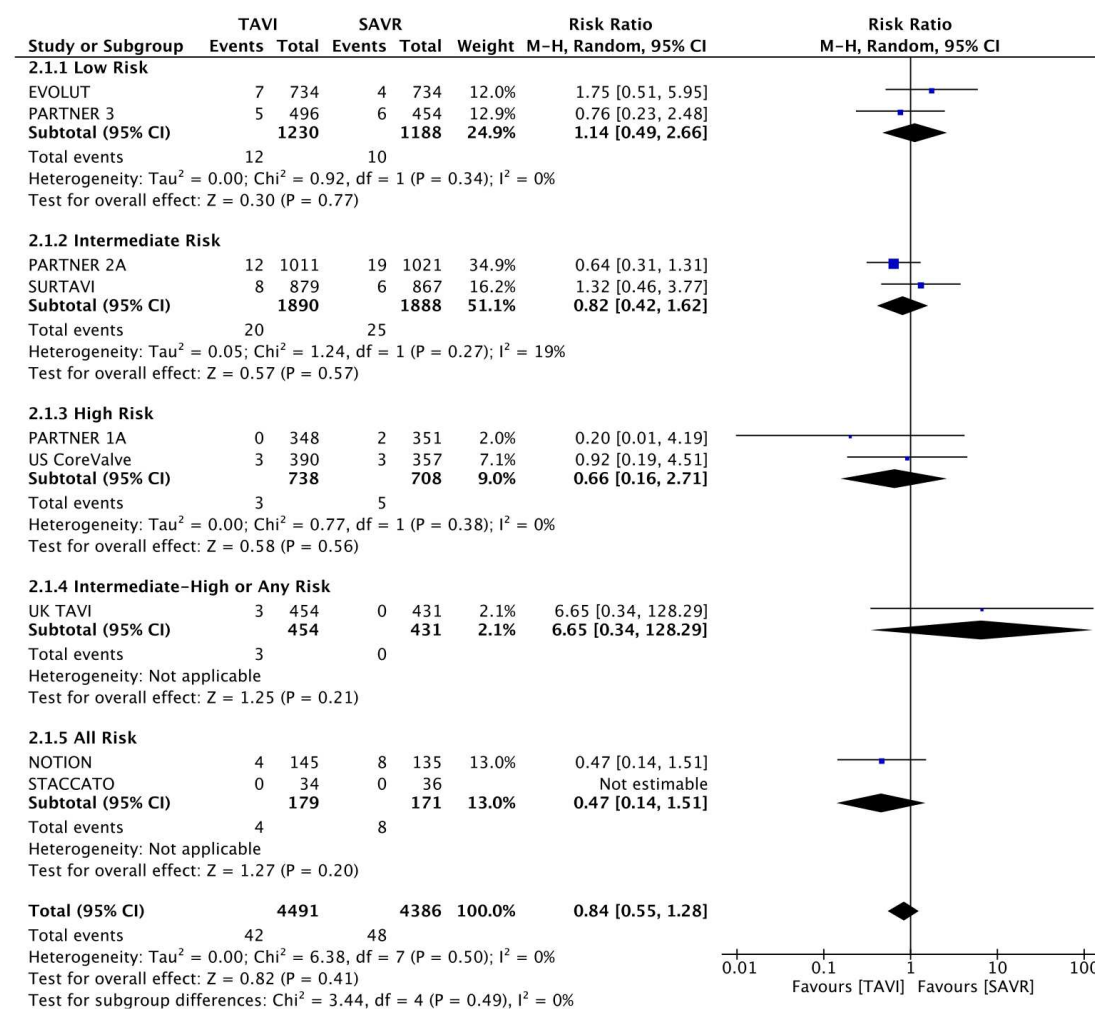


SUPPLEMENTARY FIGURE S2: FOREST PLOTS FOR MYOCARDIAL INFARCTION

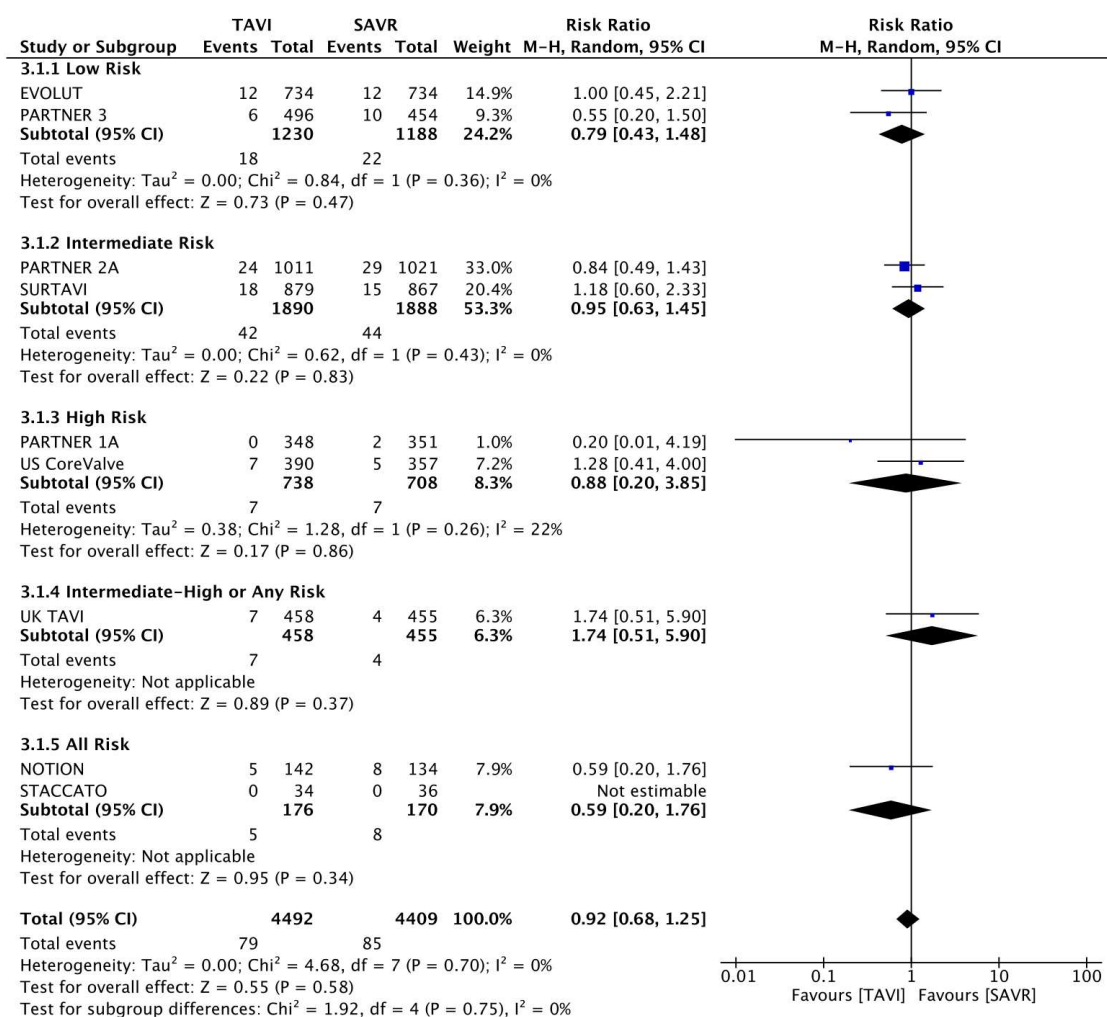
a. Periprocedural



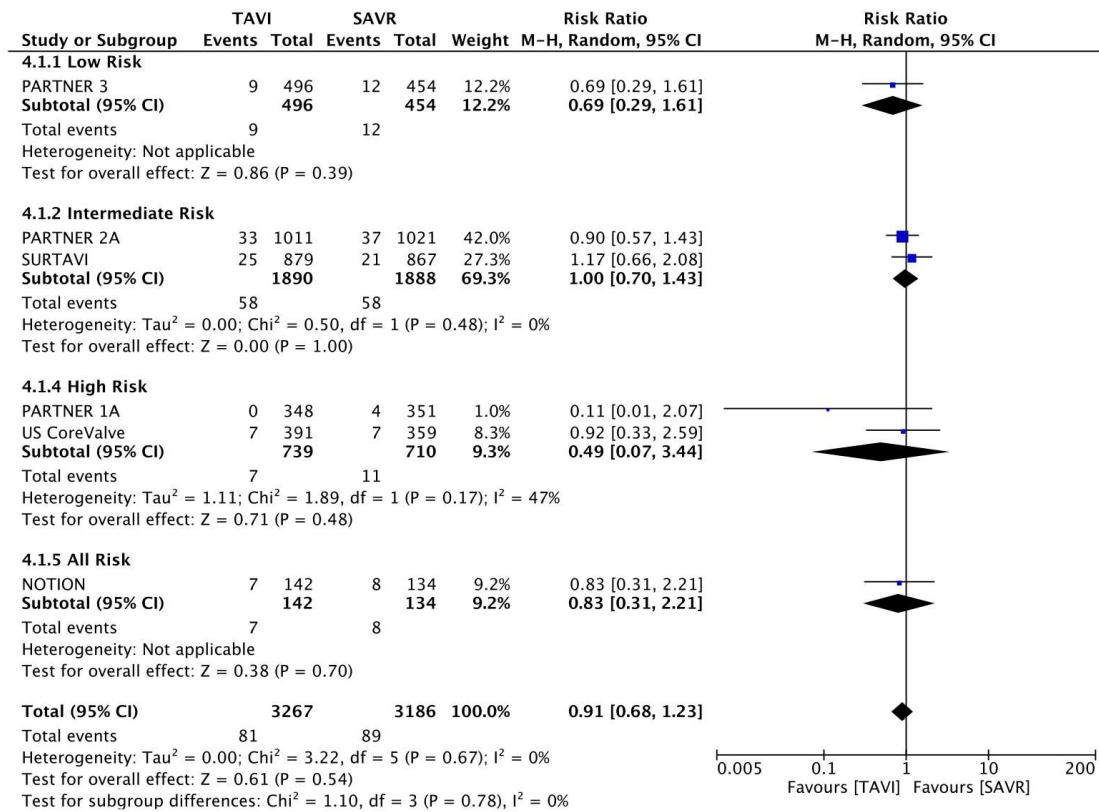
b. 30 Days



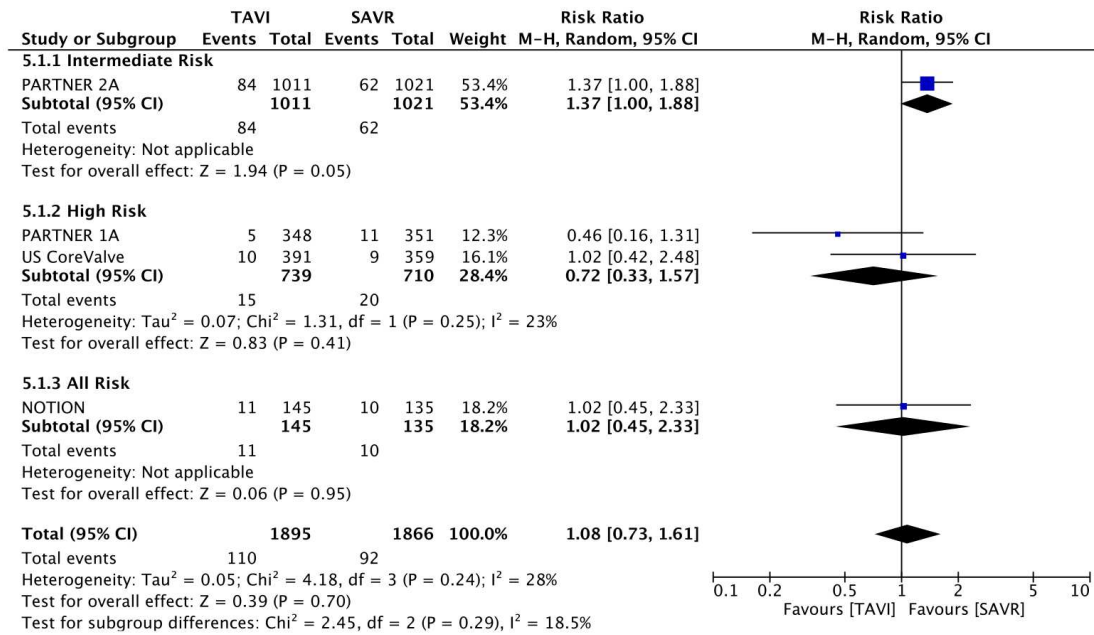
c. 1 Year



d. 2 Years

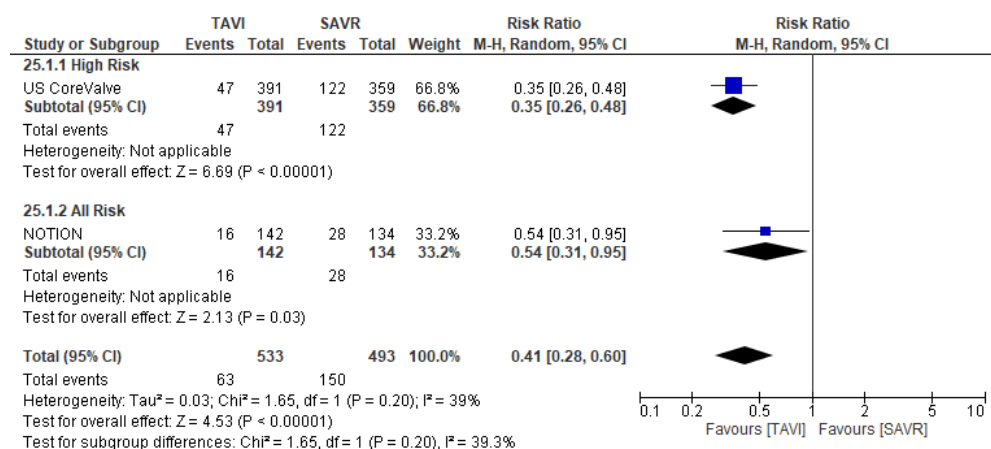


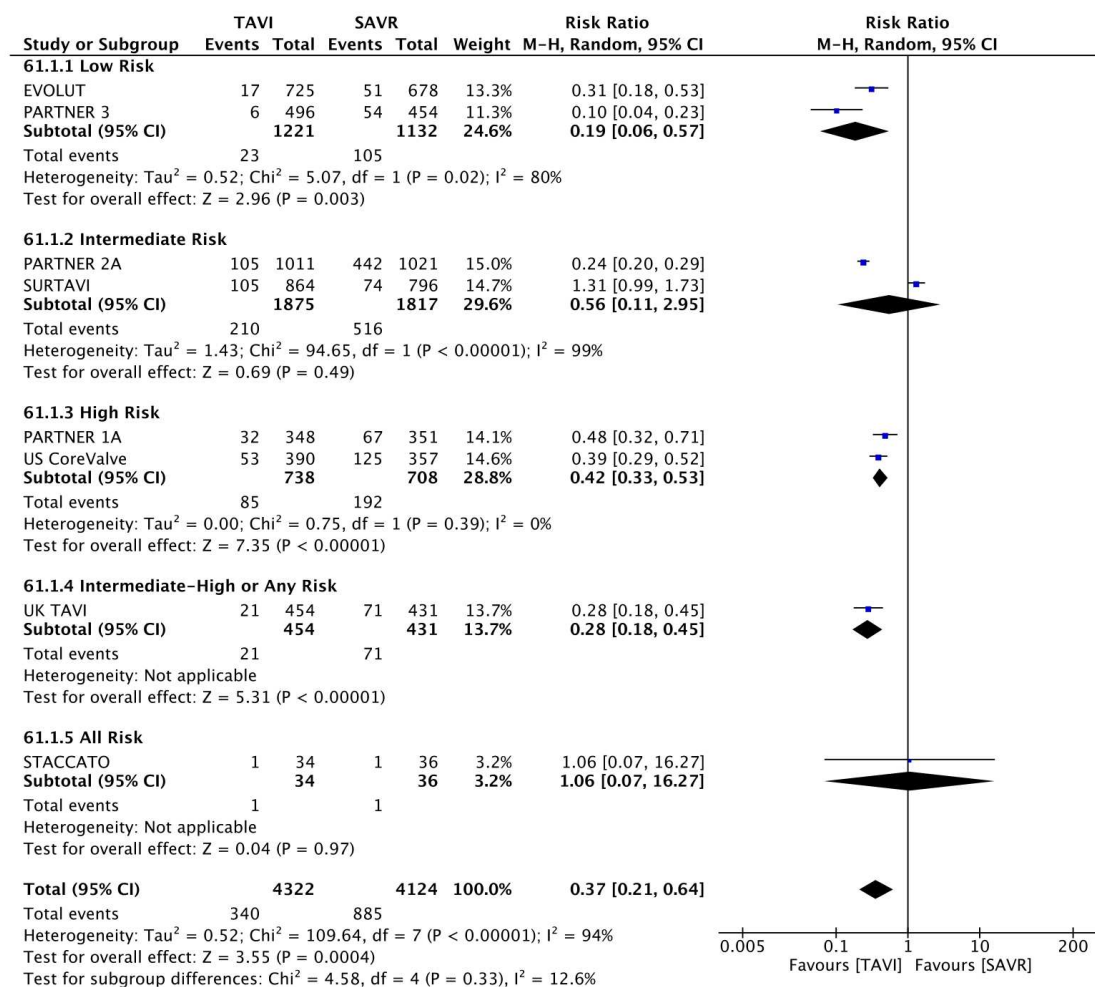
e. 5 Years

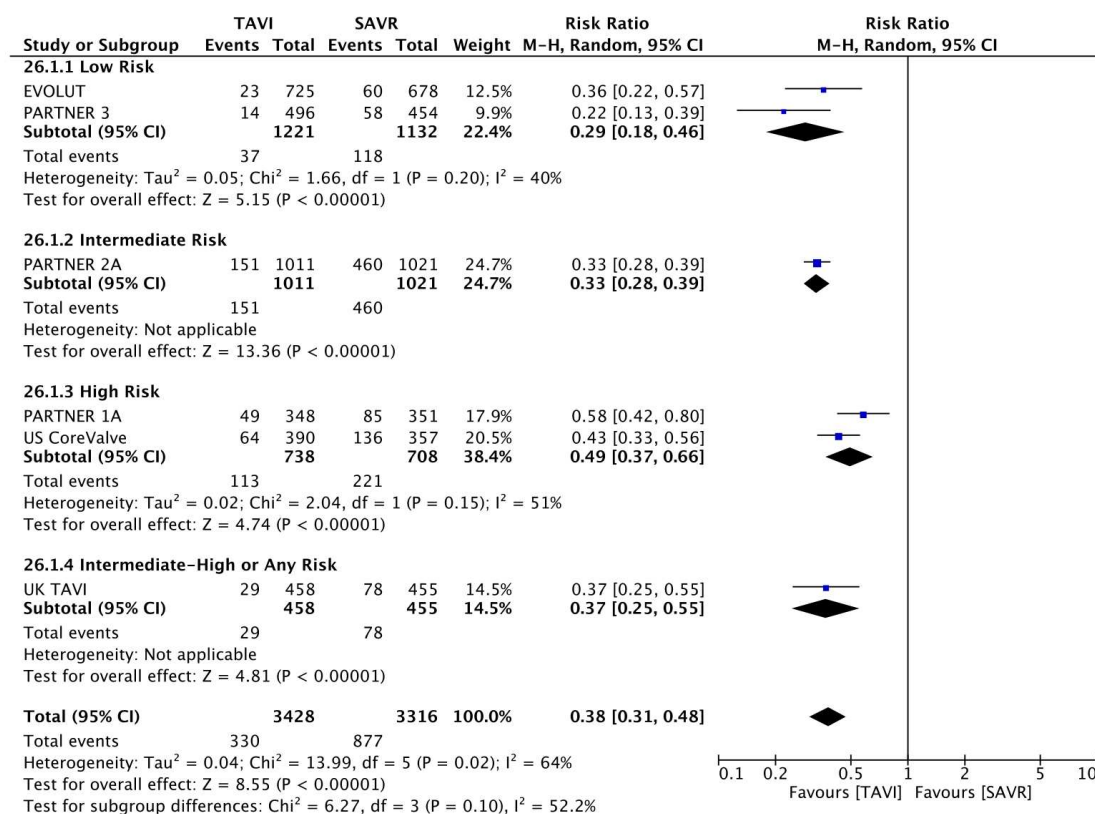
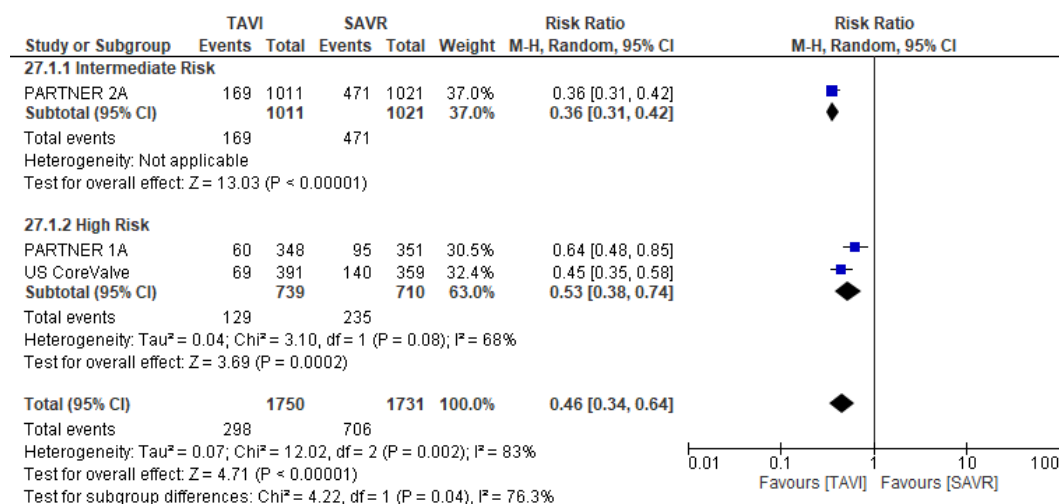


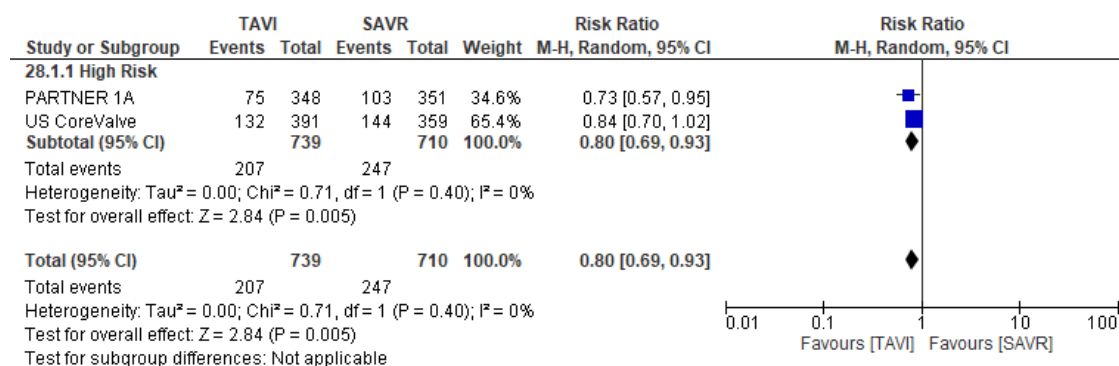
SUPPLEMENTARY FIGURE S3: FOREST PLOTS FOR MAJOR BLEEDING

a. Periprocedural or In-Hospital

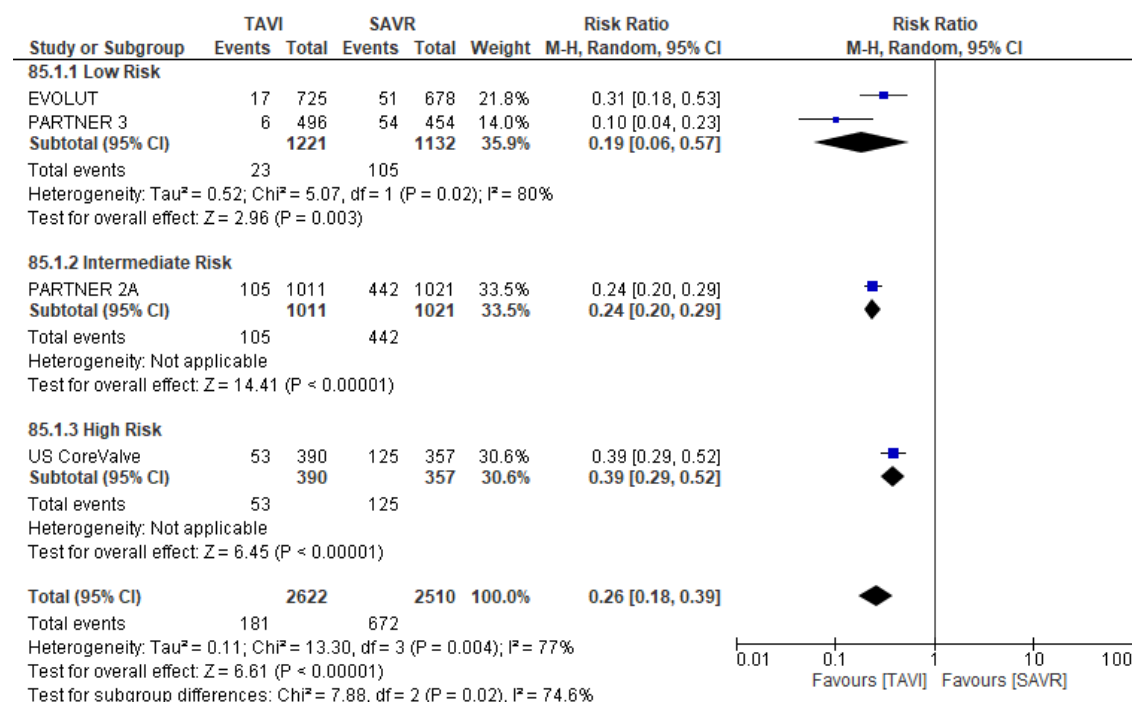


b. 30 Days

c. 1 Year**d. 2 Years**

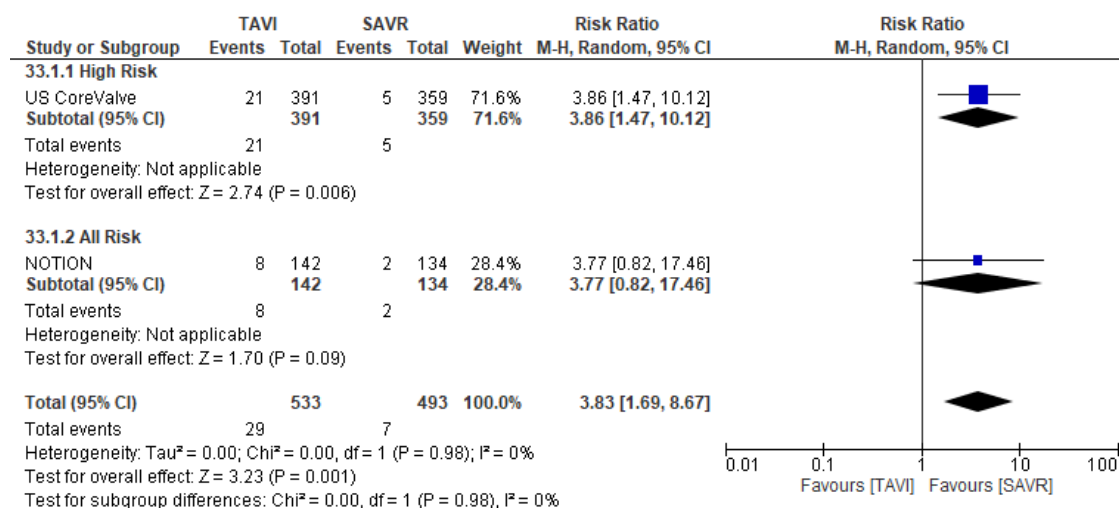
e. 5 Years

SUPPLEMENTARY FIGURE S4: SENSITIVITY ANALYSIS FOR MAJOR BLEEDING AT 1 YEAR

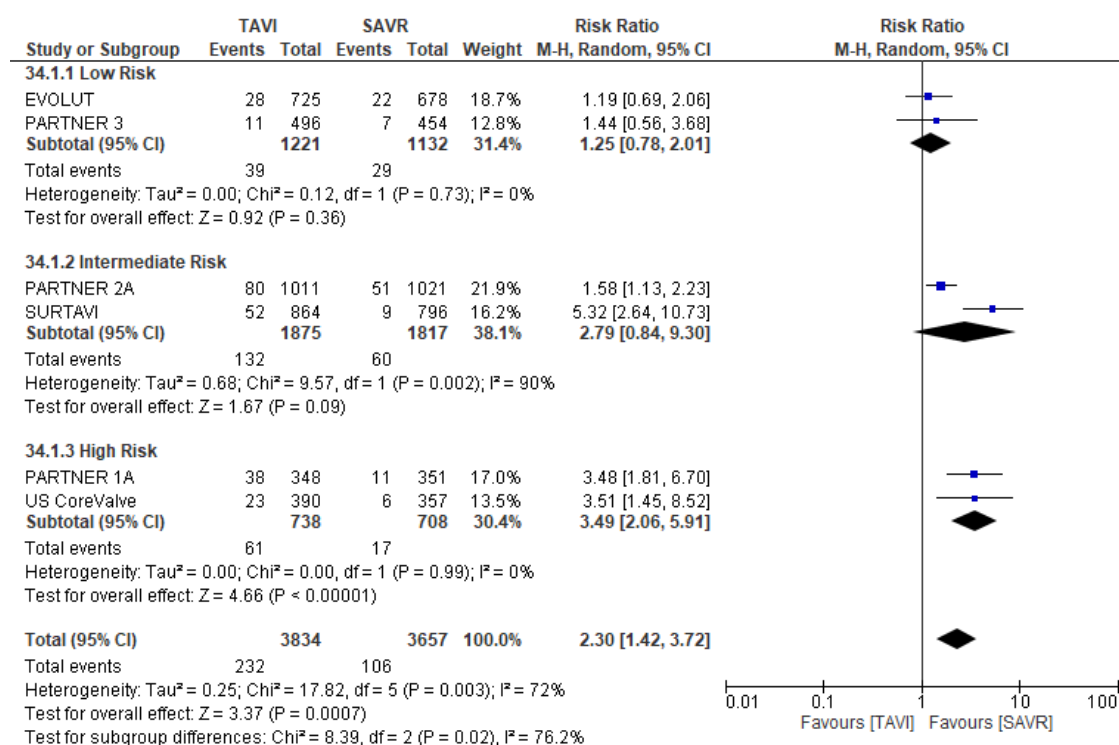


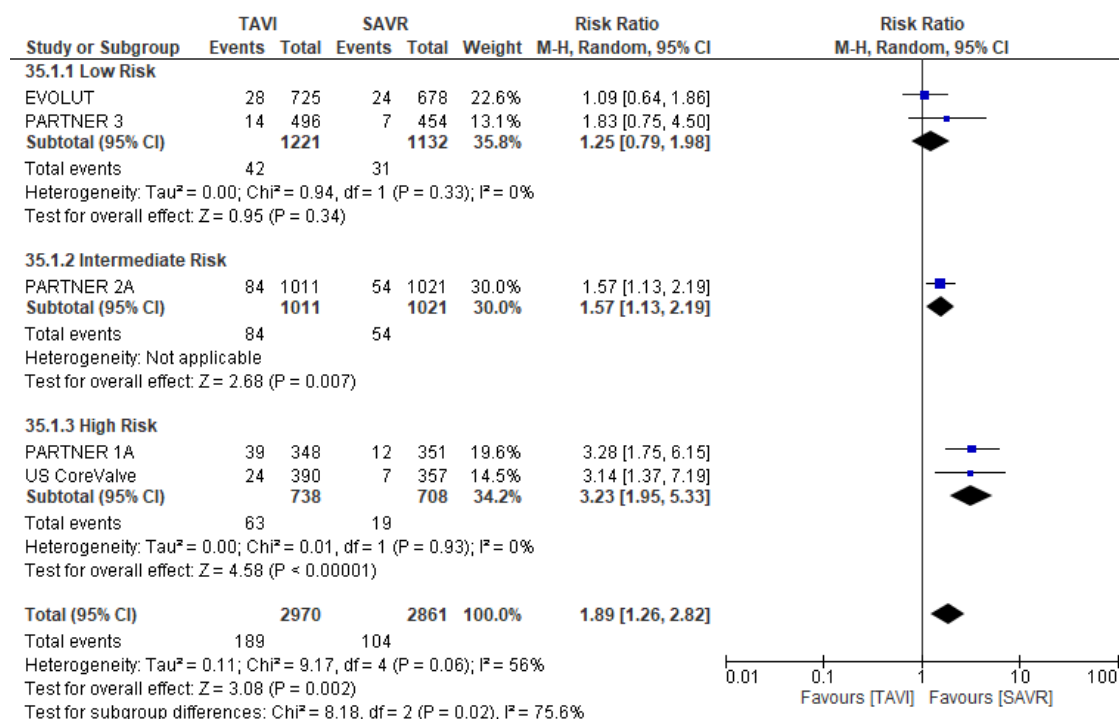
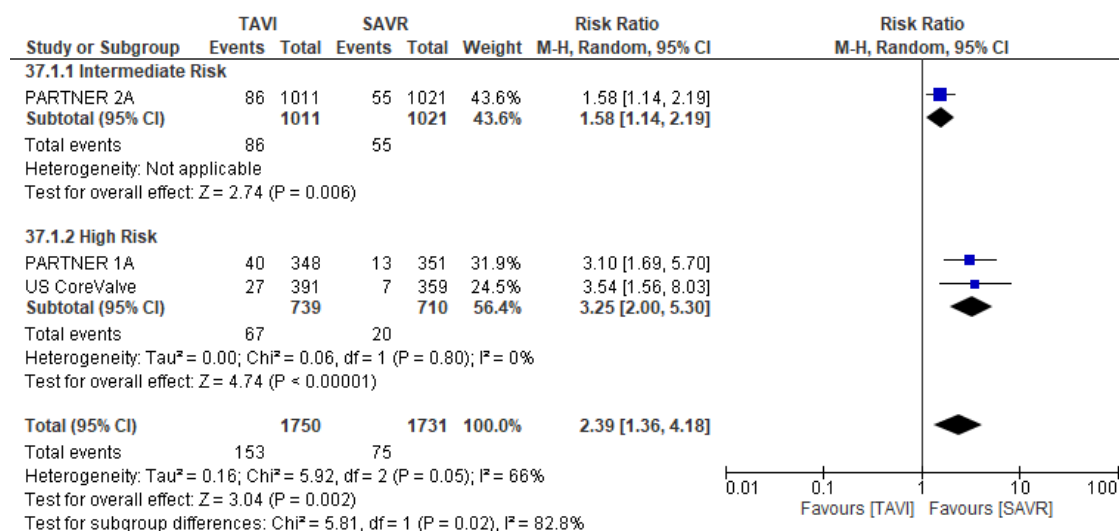
SUPPLEMENTARY FIGURE S5: FOREST PLOTS FOR MAJOR VASCULAR COMPLICATIONS

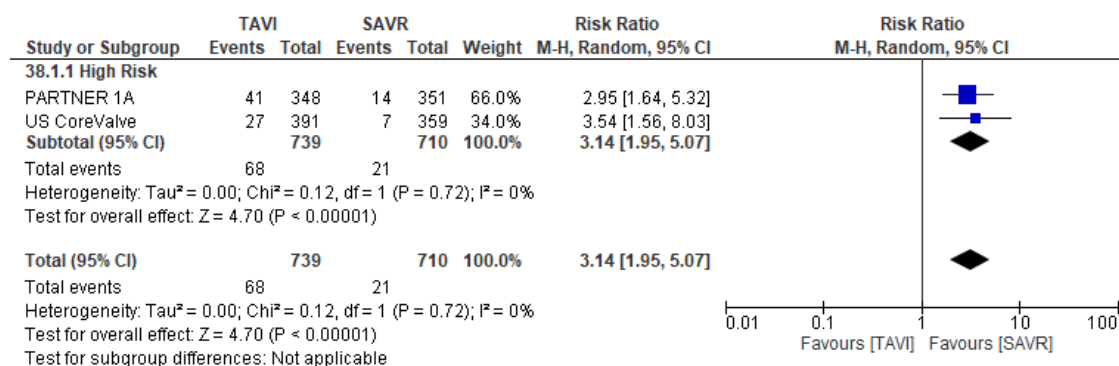
a. Periprocedural or In-Hospital



b. 30 Days

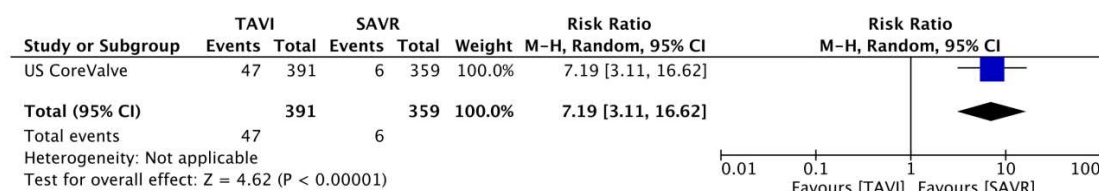


c. 1 Year**d. 2 Years**

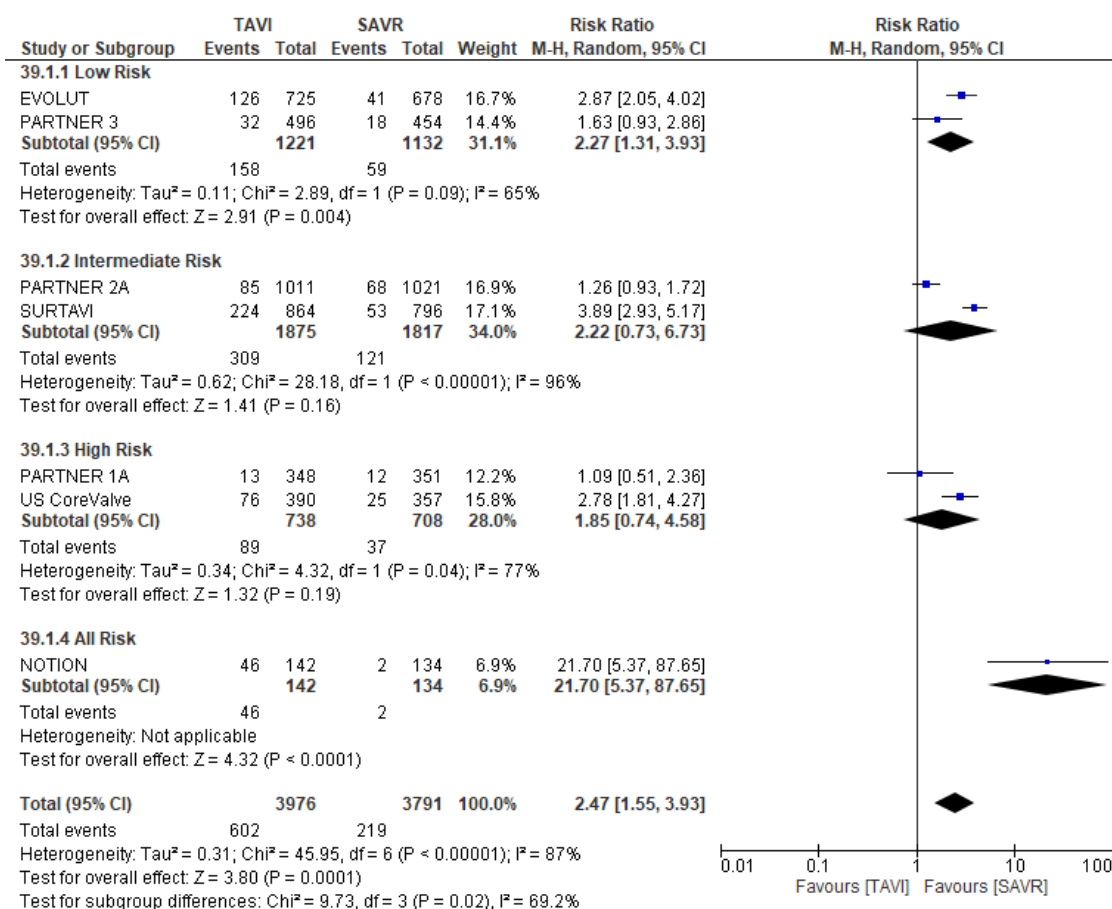
e. 5 Years

SUPPLEMENTARY FIGURE S6: FOREST PLOTS FOR NEW PERMANENT PACEMAKER IMPLANTATION

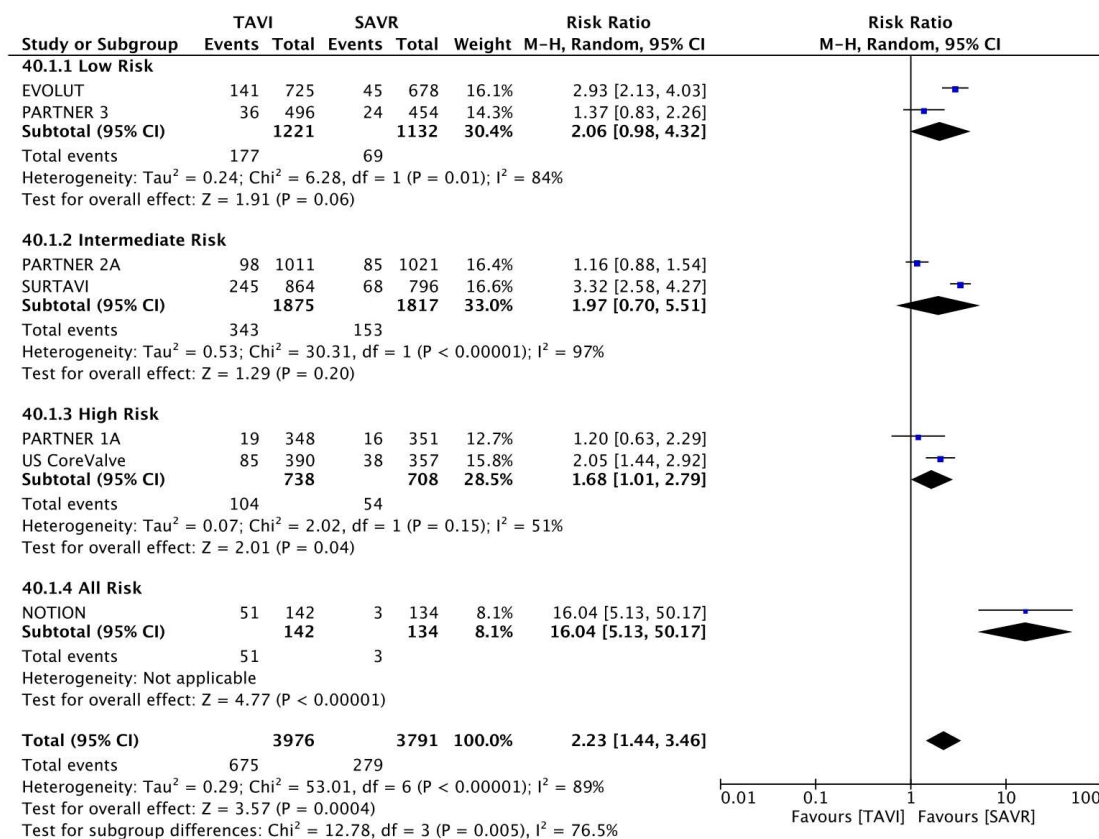
a. Periprocedural

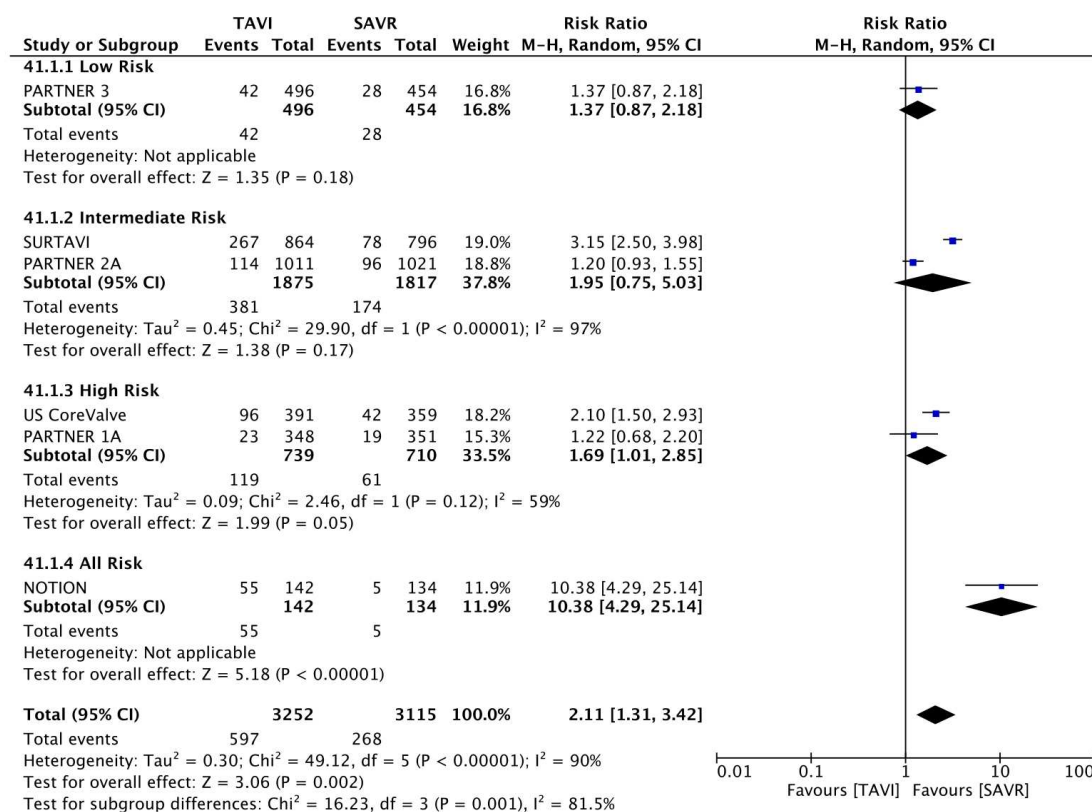


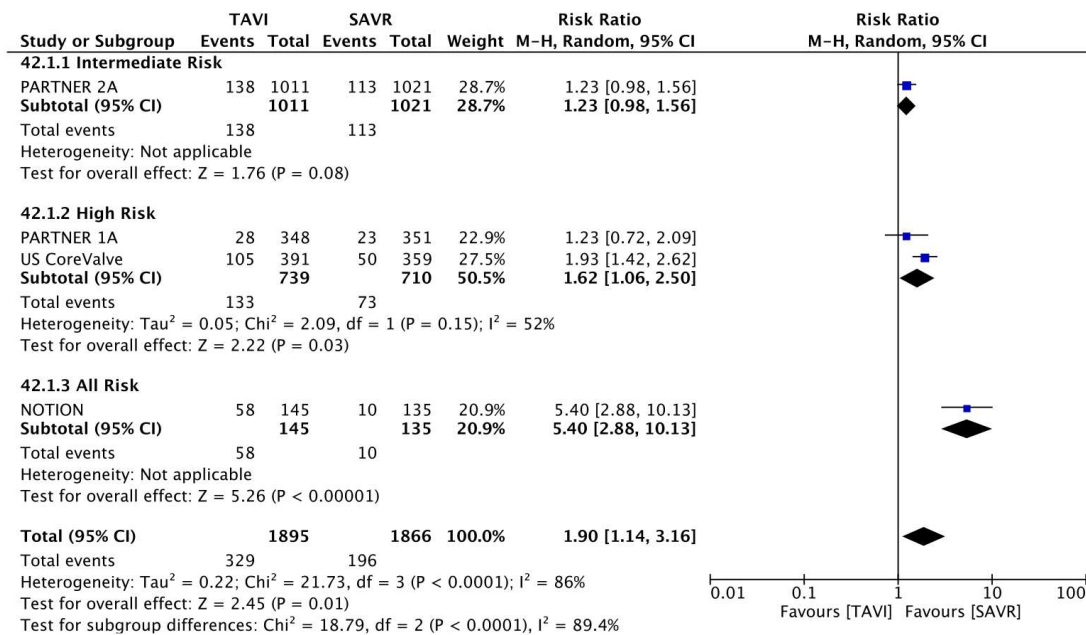
b. 30 Days



c. 1 Year

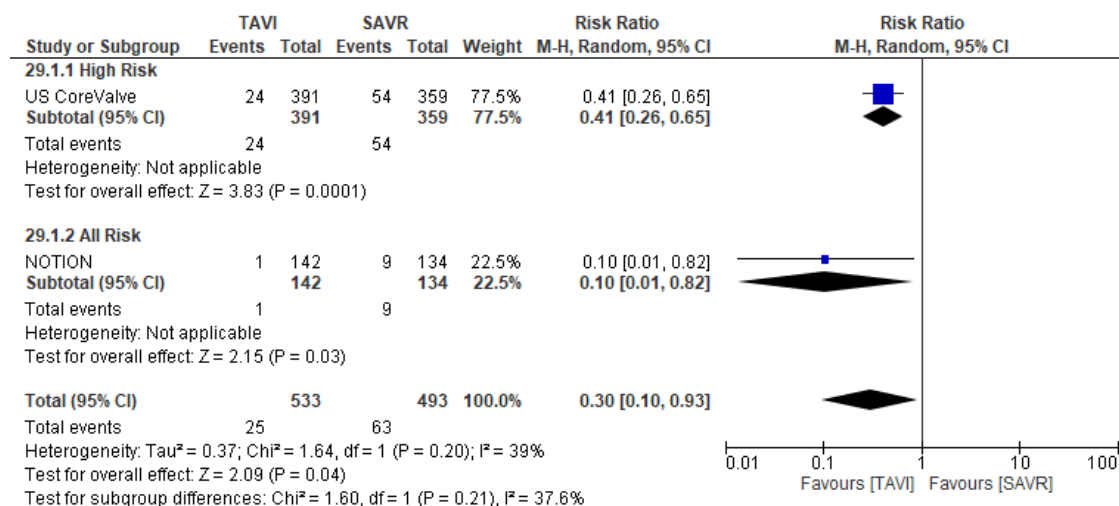


d. 2 Years

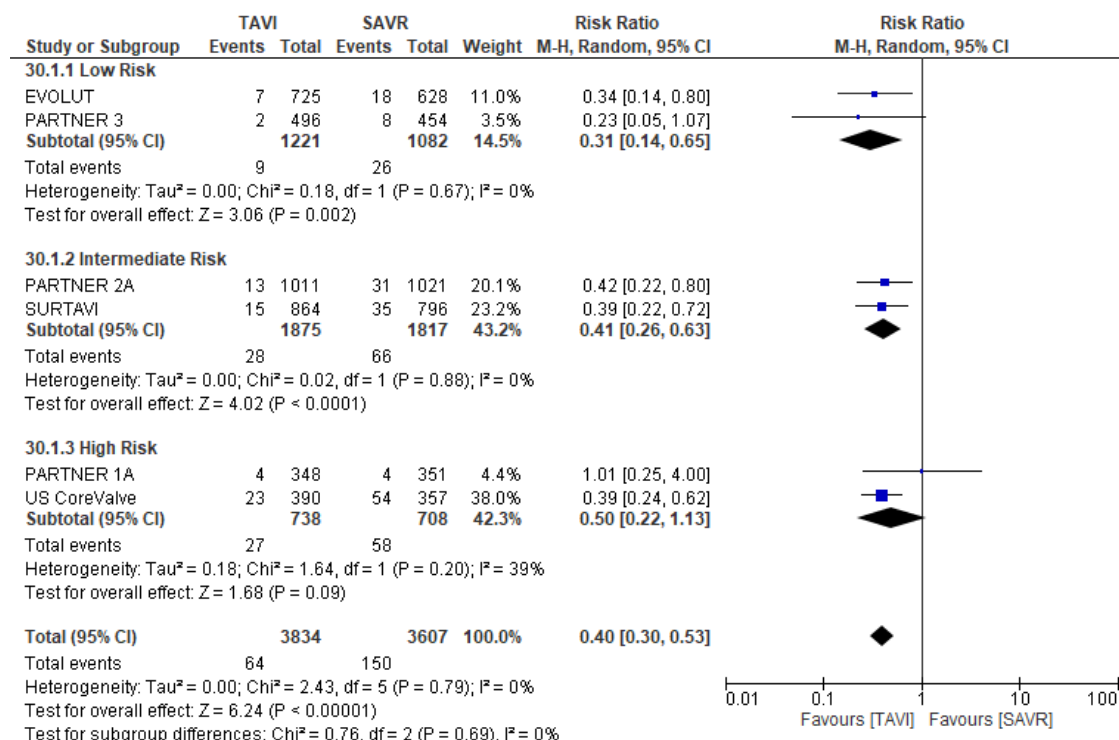
e. 5 Years

SUPPLEMENTARY FIGURE S7: FOREST PLOTS FOR ACUTE KIDNEY INJURY

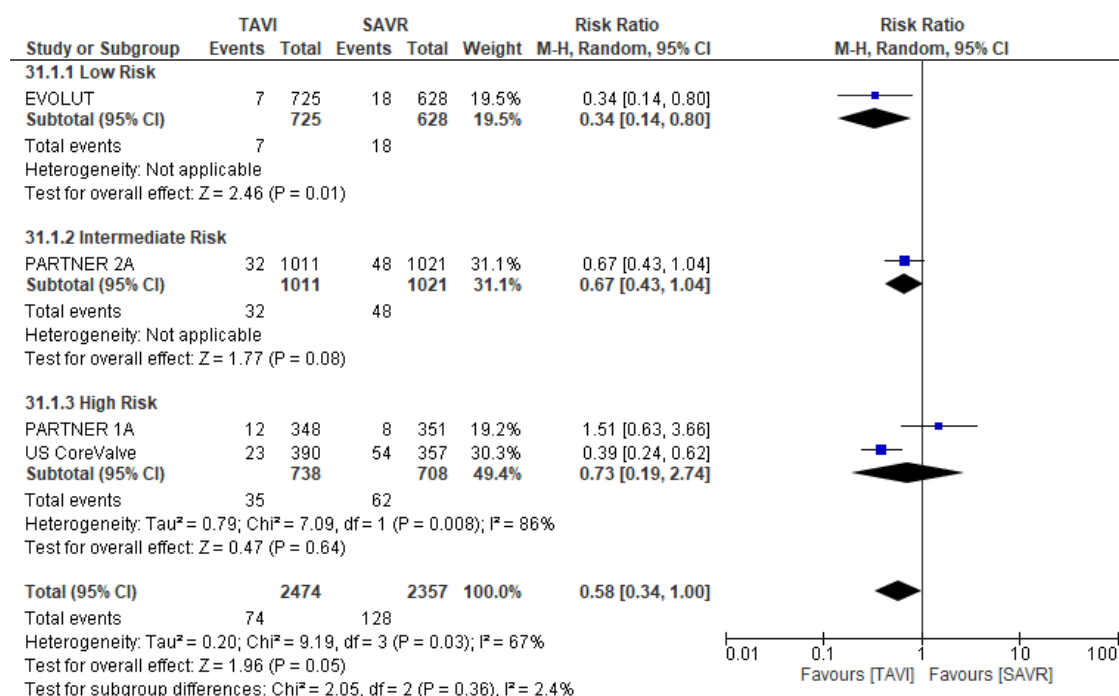
a. Periprocedural or In-Hospital



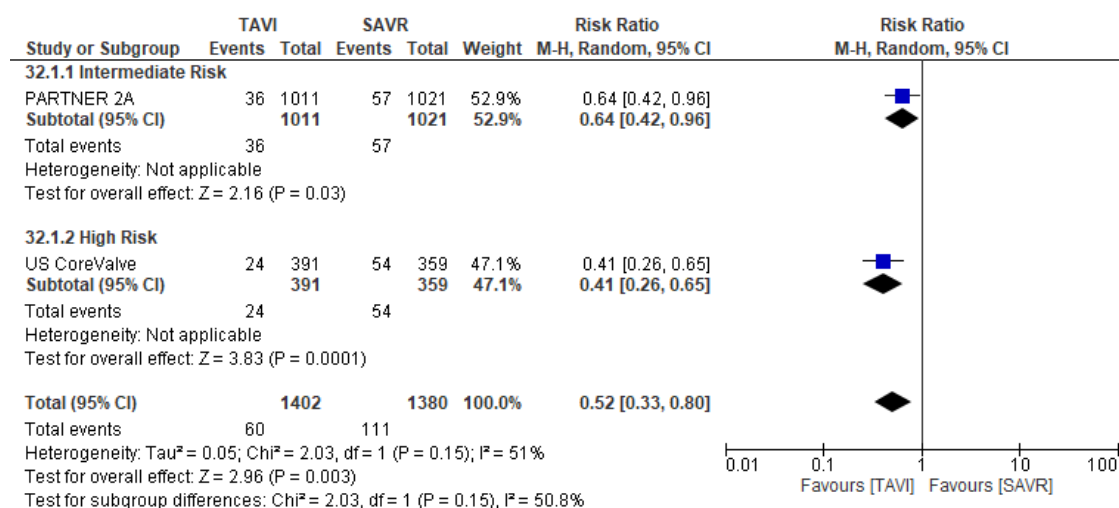
b. 30 Days



c. 1 Year

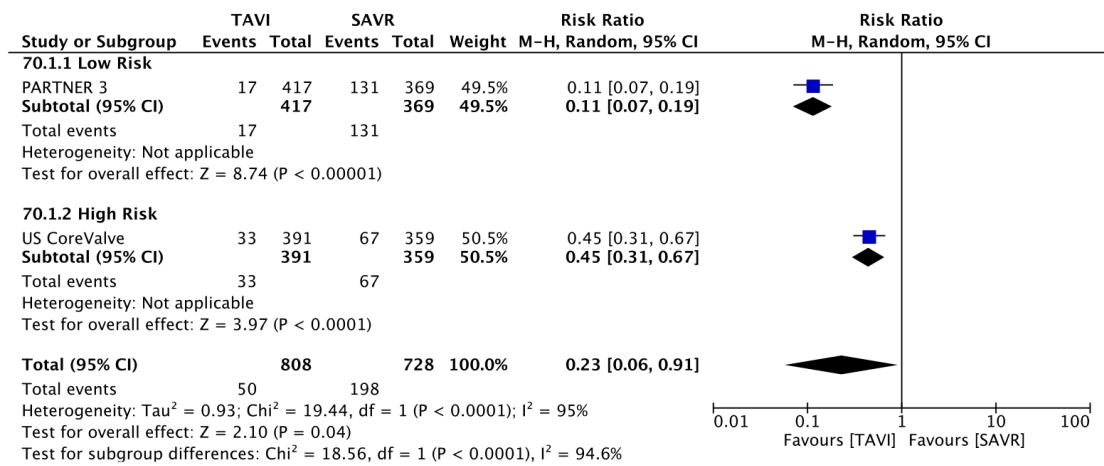


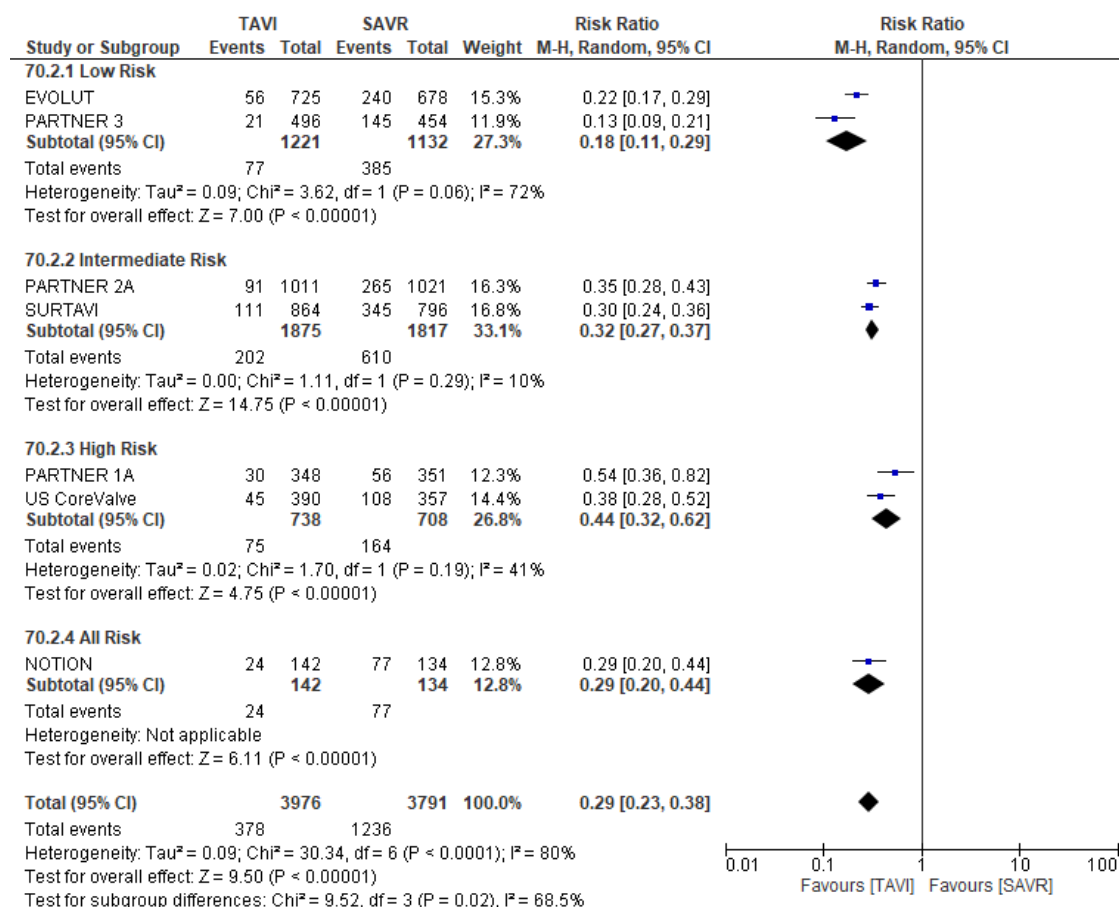
d. 2 Years

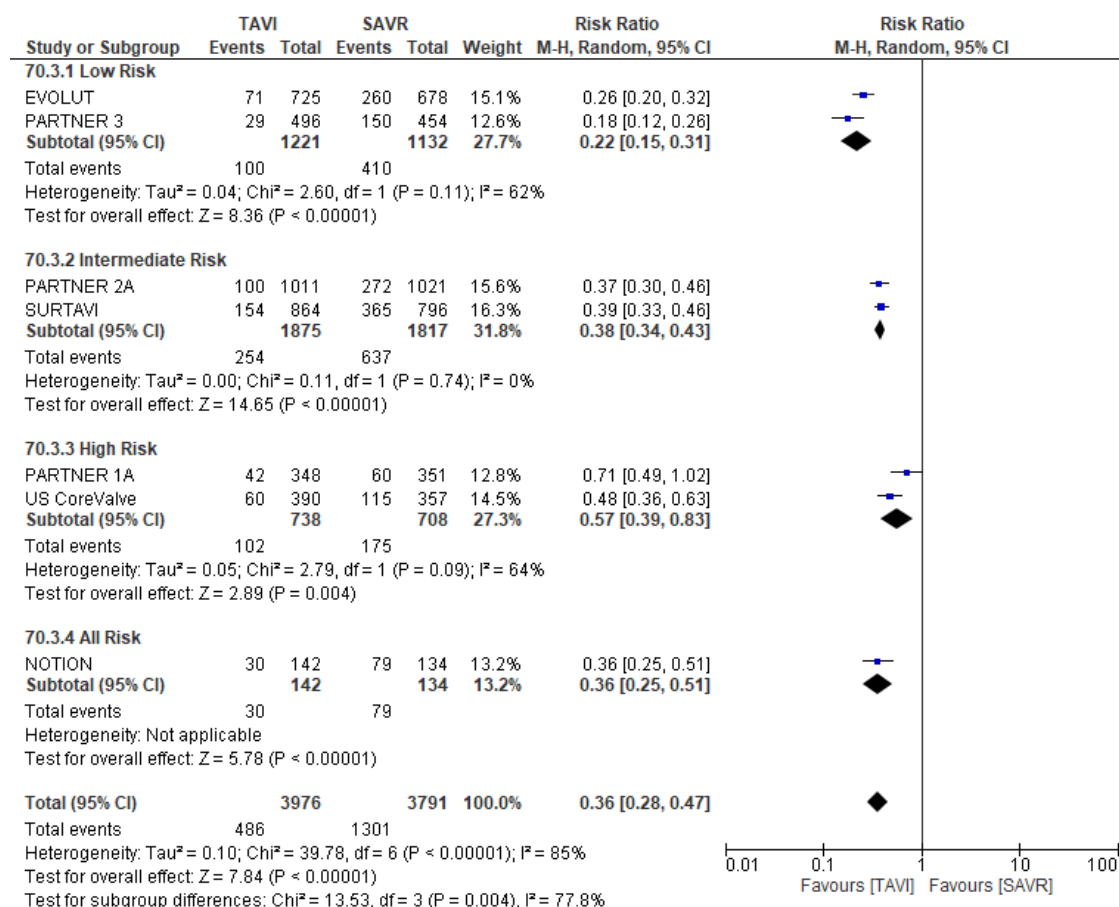


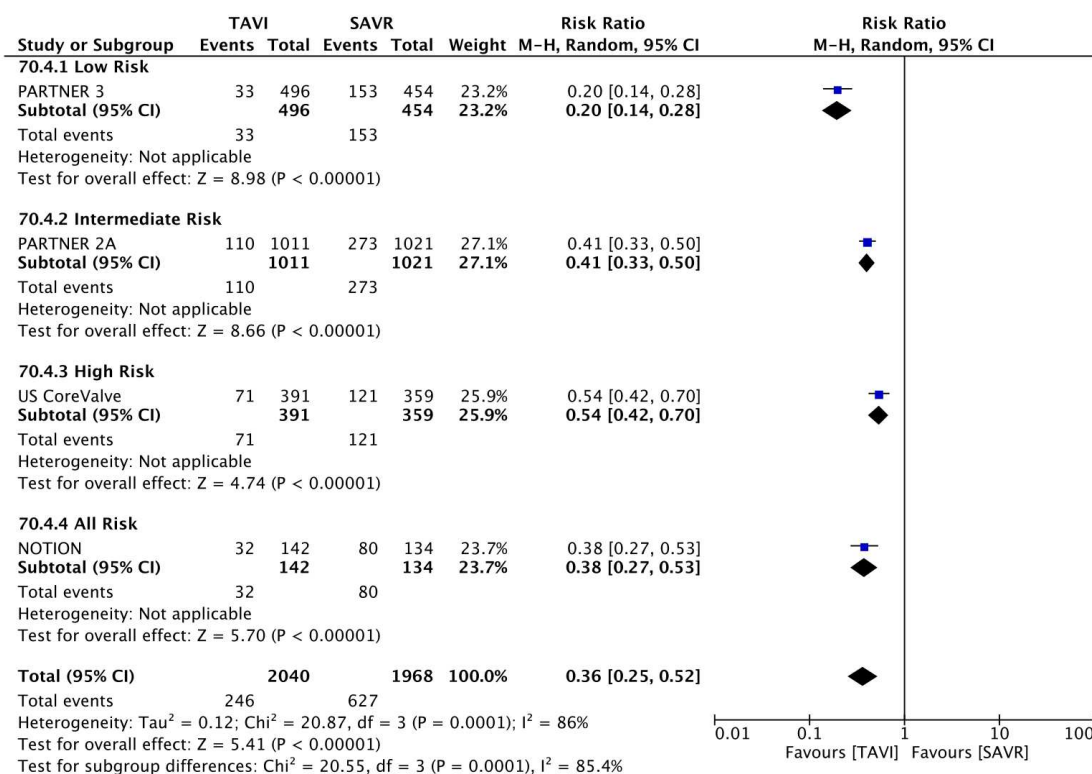
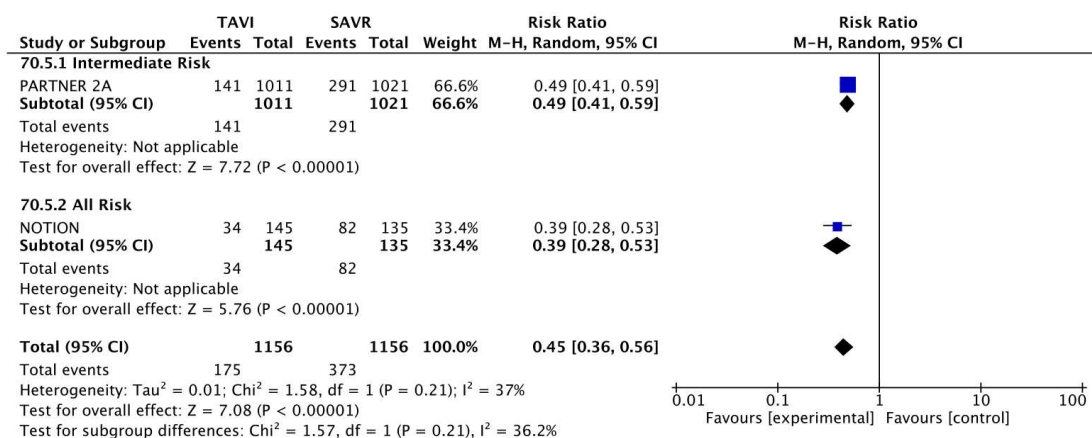
SUPPLEMENTARY FIGURE S8: FOREST PLOTS FOR NEW-ONSET OR WORSENING ATRIAL FIBRILLATION

a. Periprocedural or In-Hospital



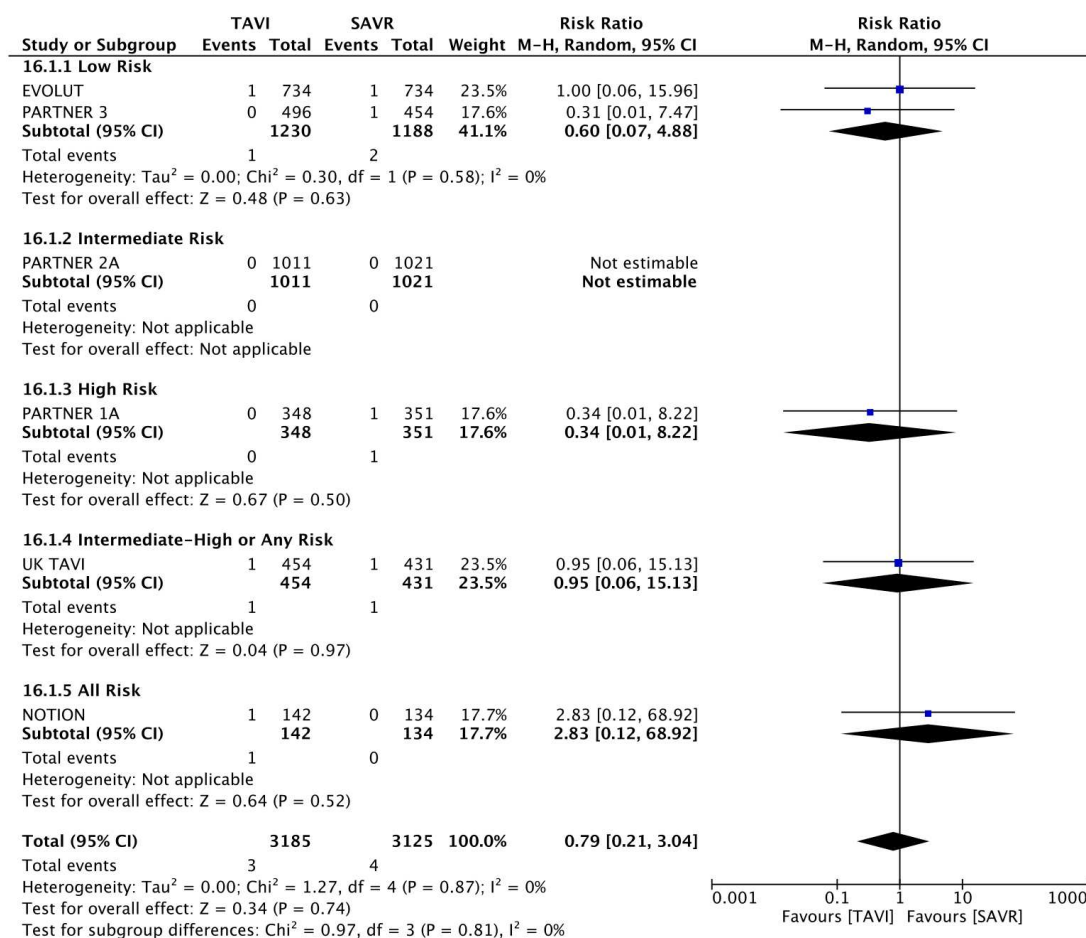
b. 30 Days

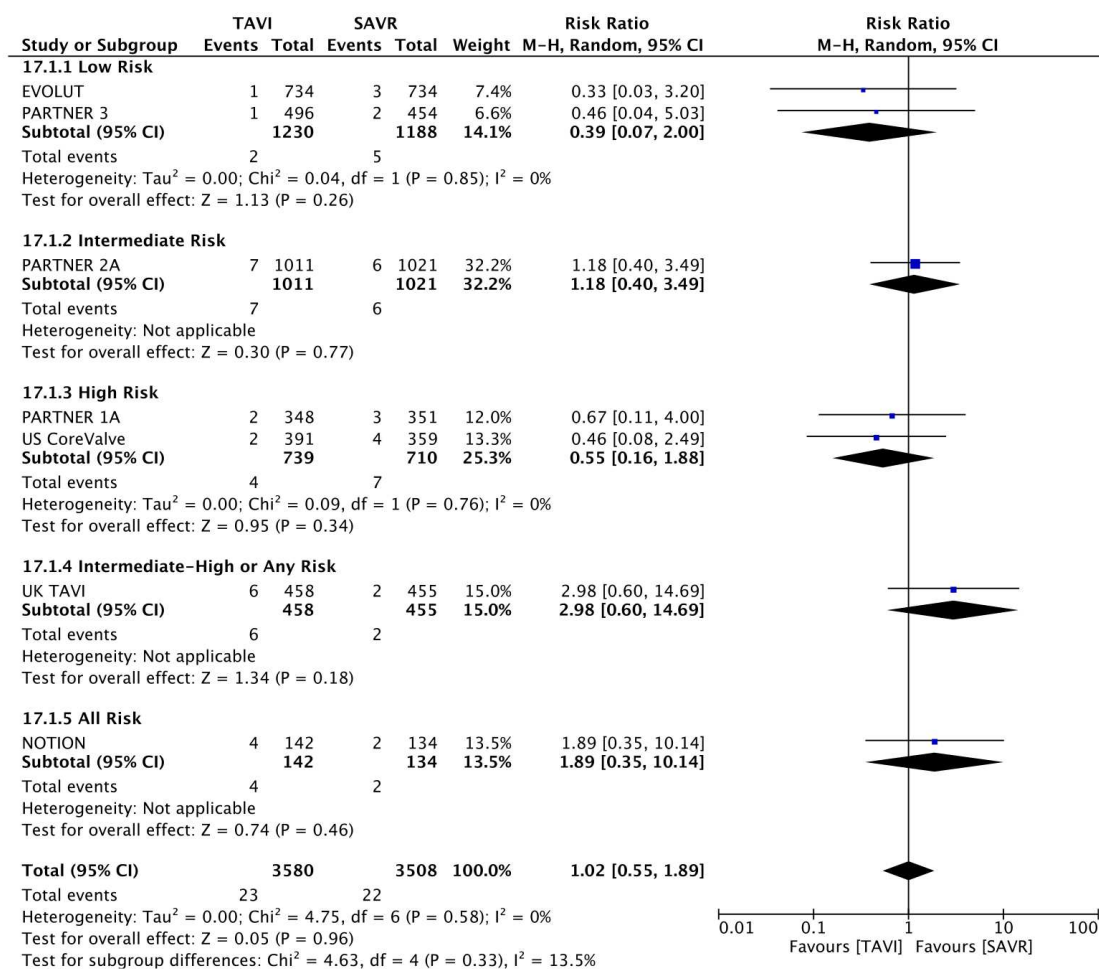
c. 1 Year

d. 2 Years**e. 5 Years**

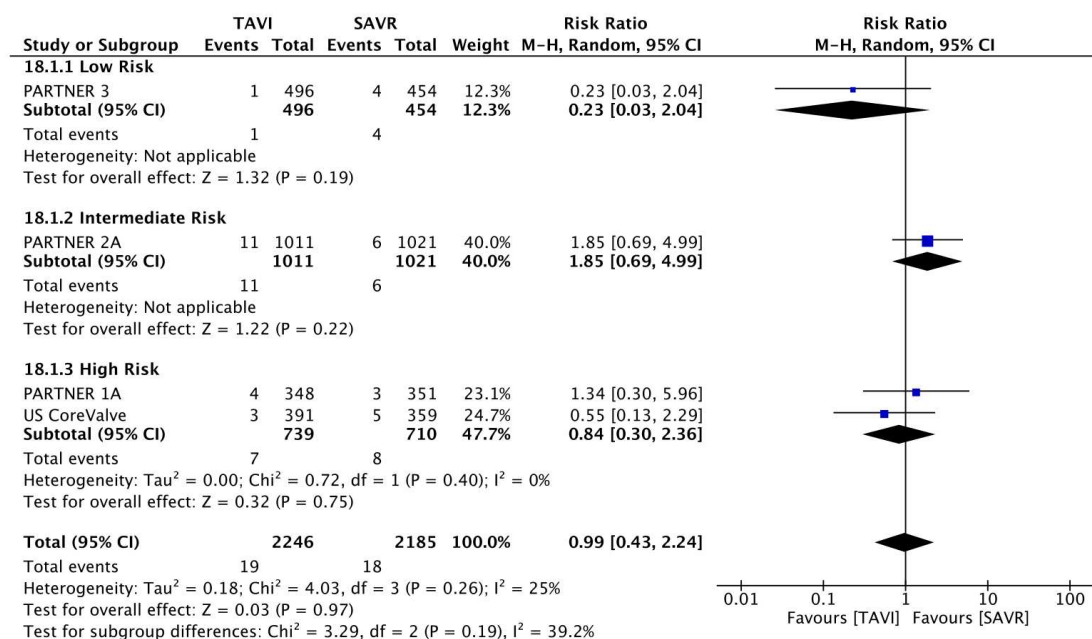
SUPPLEMENTARY FIGURE S9: FOREST PLOTS FOR ENDOCARDITIS

a. 30 Days

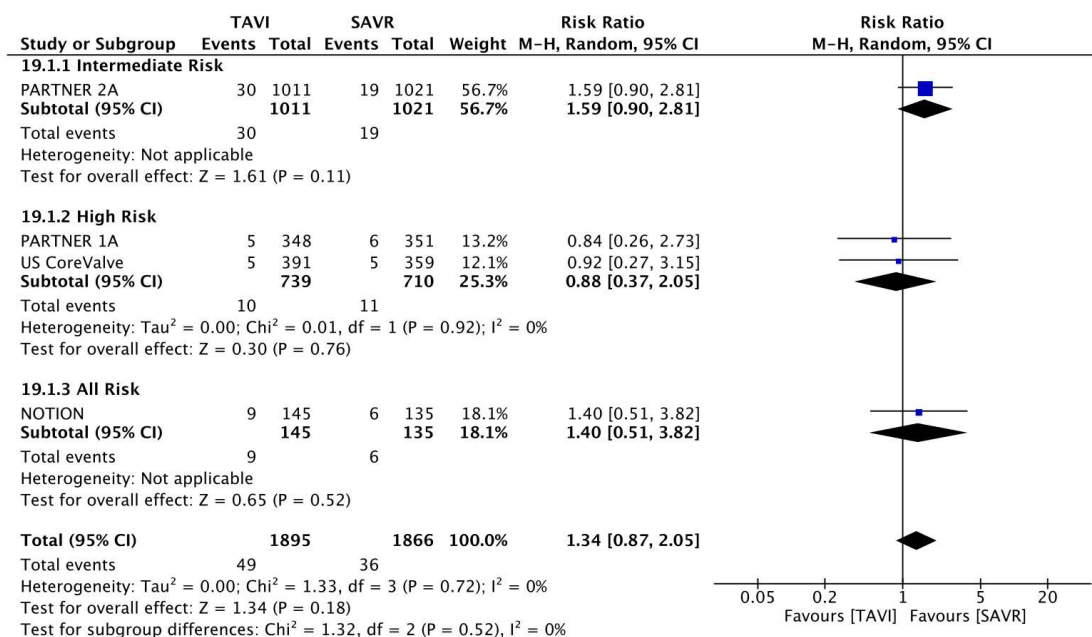


b. 1 Year

c. 2 Years

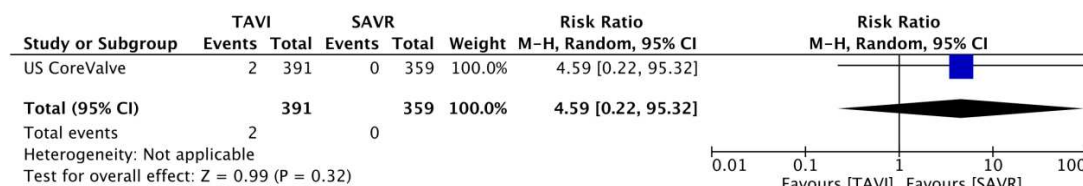


d. 5 Years

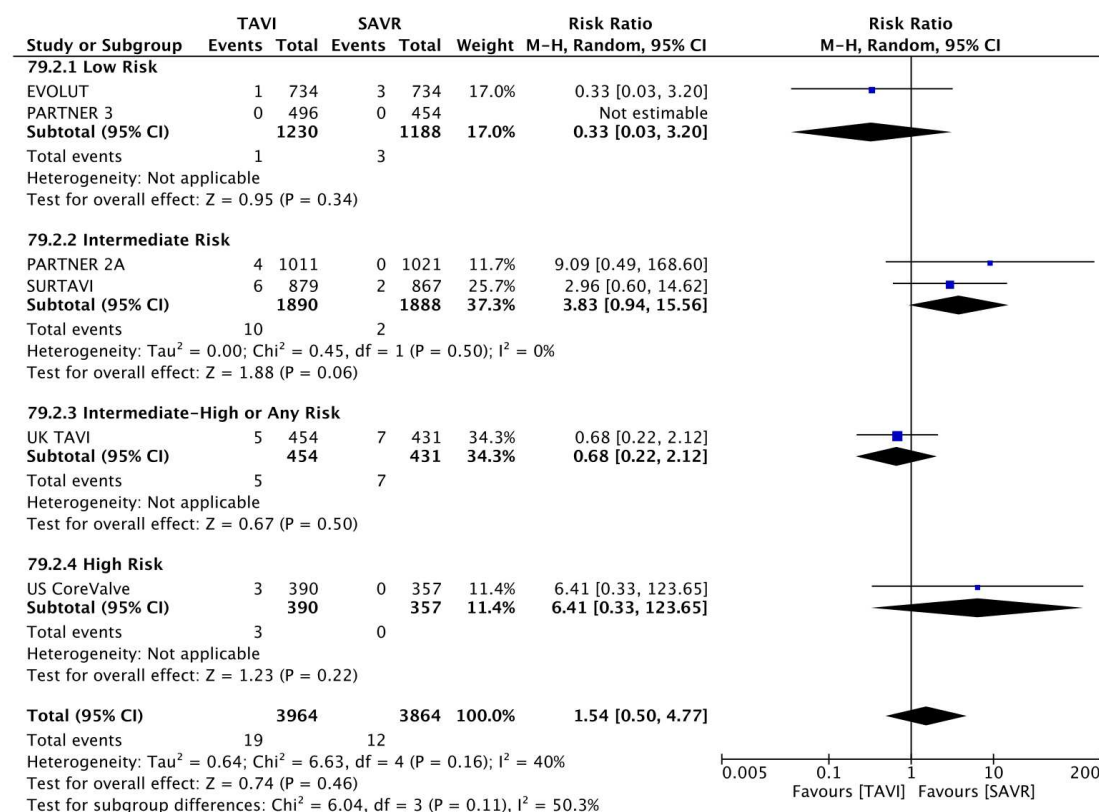


SUPPLEMENTARY FIGURE S10: FOREST PLOTS FOR REINTERVENTION OR REOPERATION

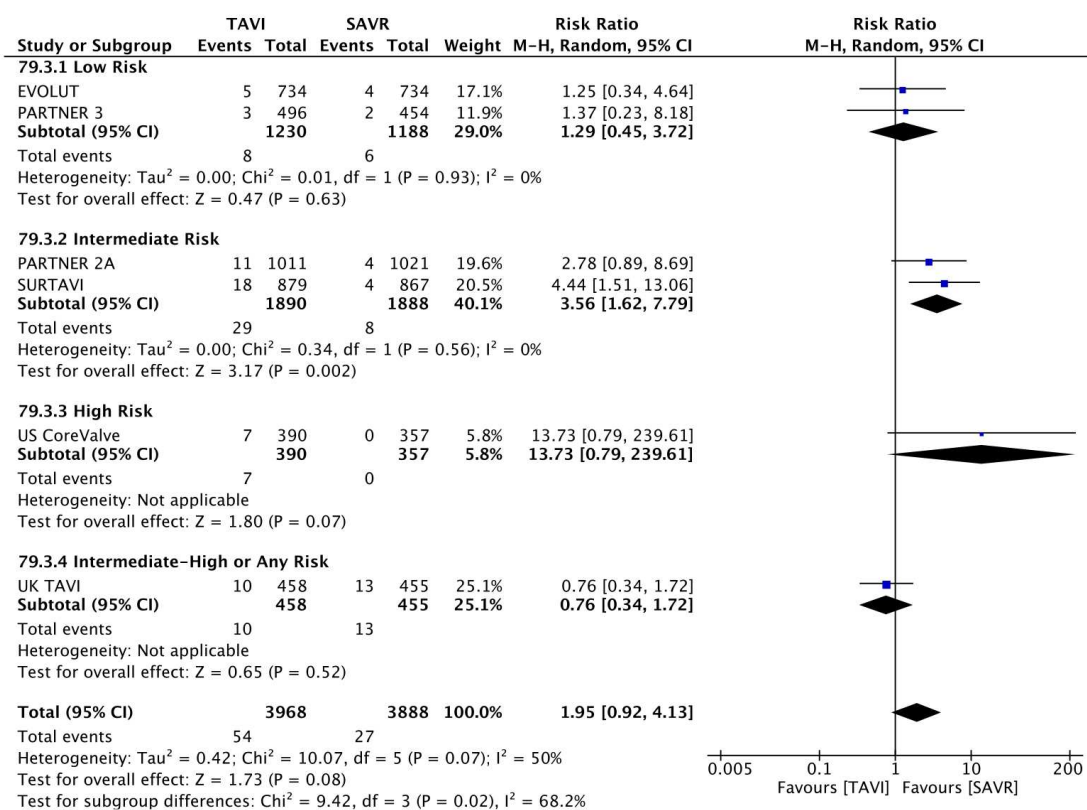
a. Periprocedural

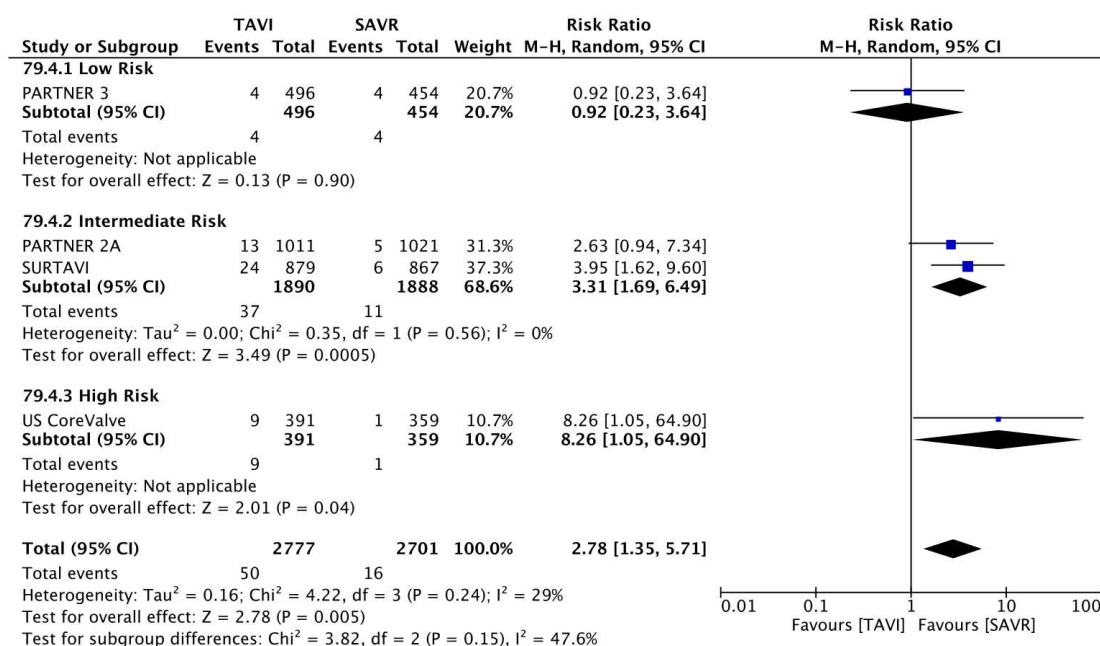
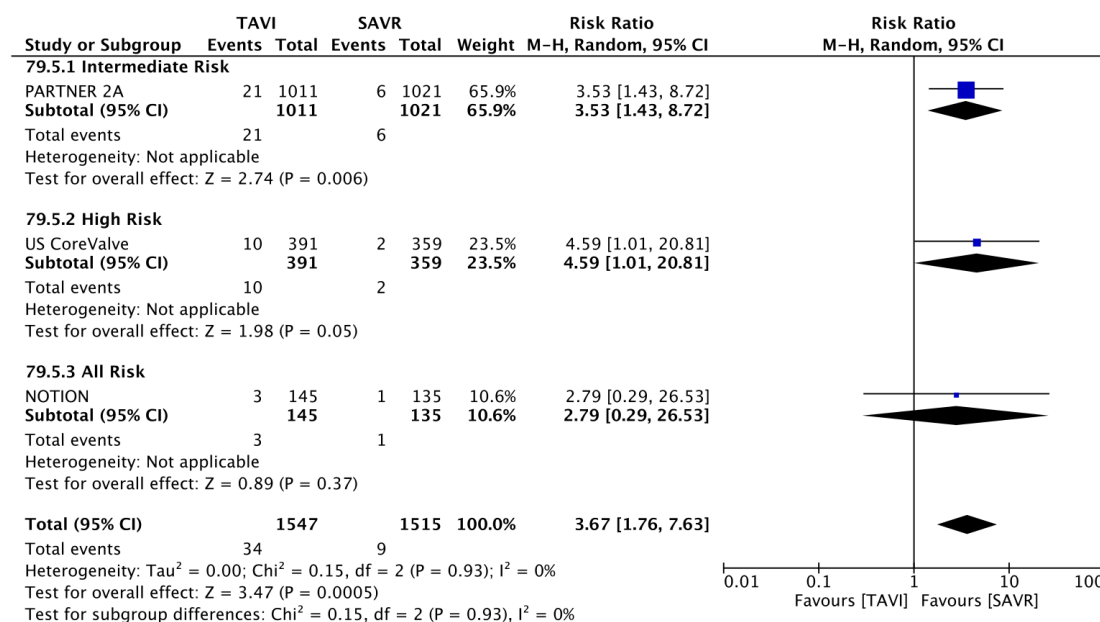


b. 30 Days



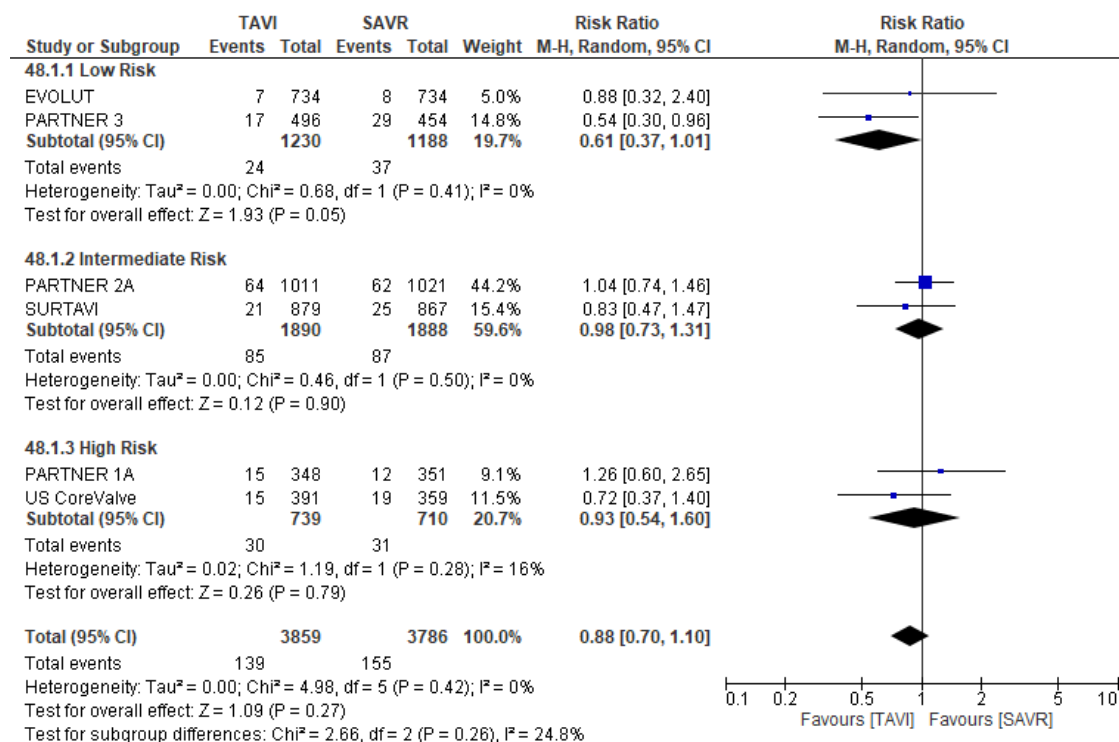
c. 1 Year

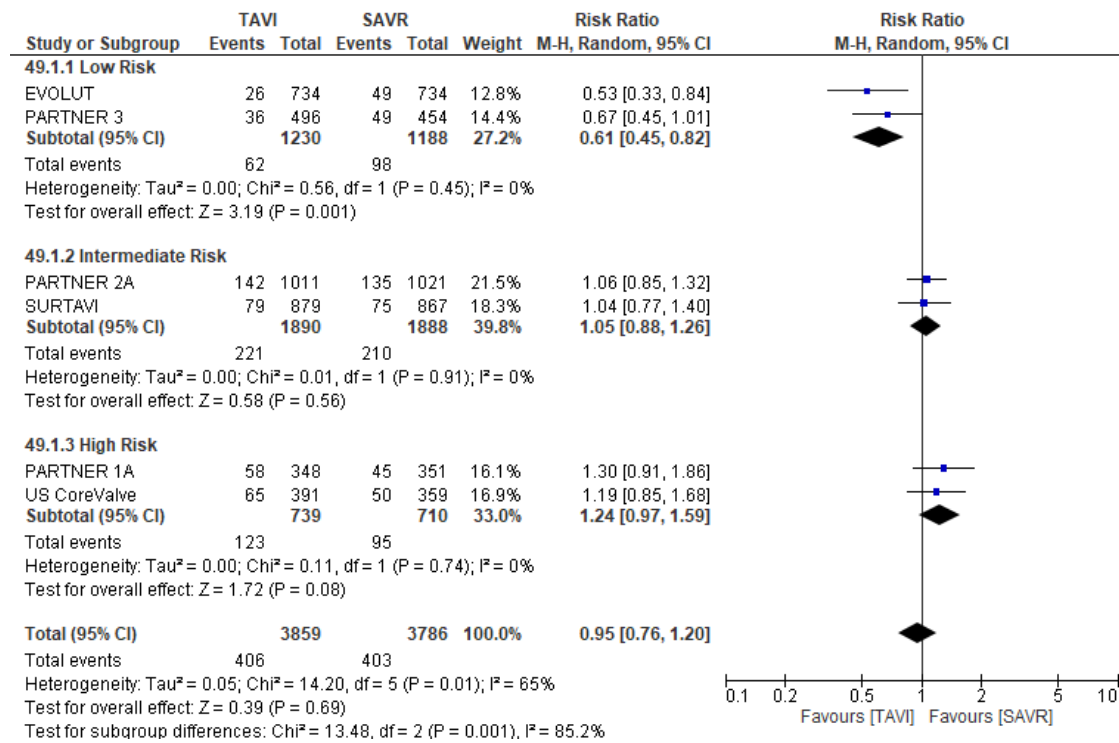


d. 2 Years**e. 5 Years**

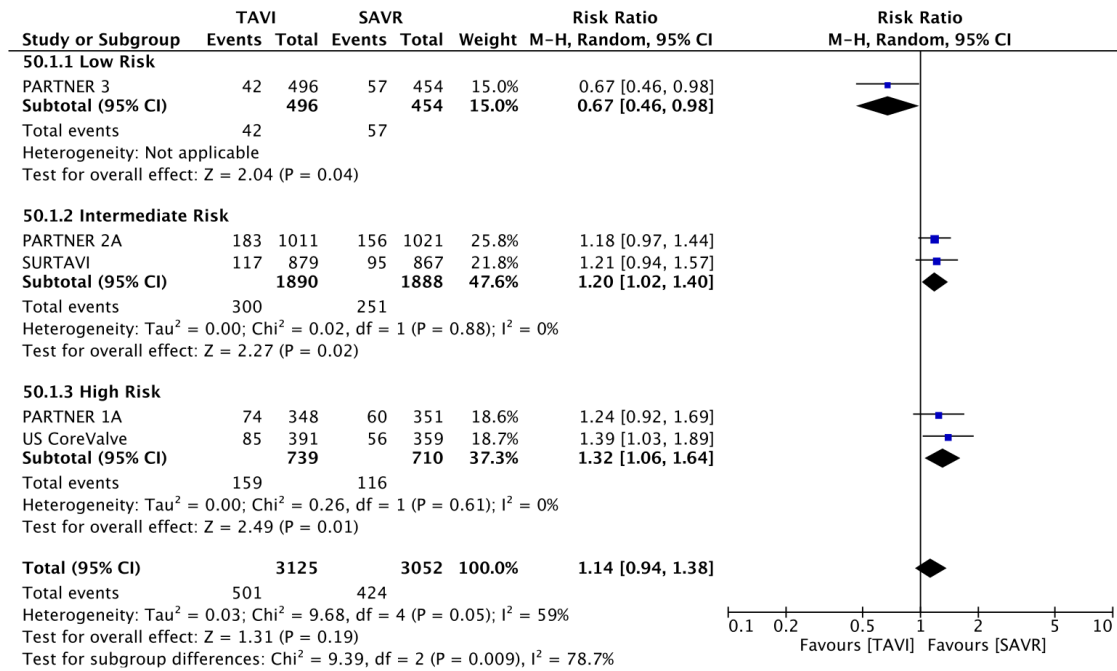
SUPPLEMENTARY FIGURE S11: FOREST PLOTS FOR REHOSPITALISATION

a. 30 Days

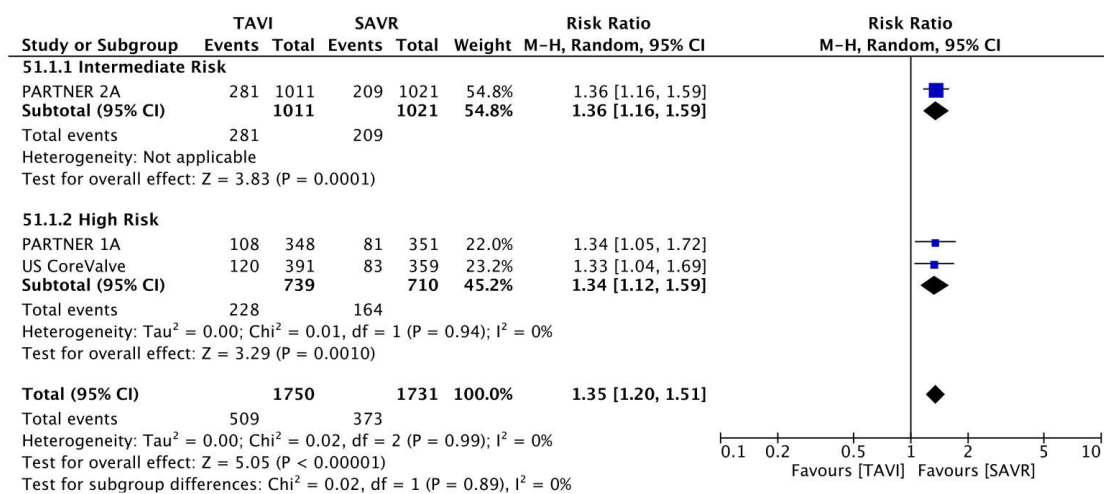


b. 1 Year

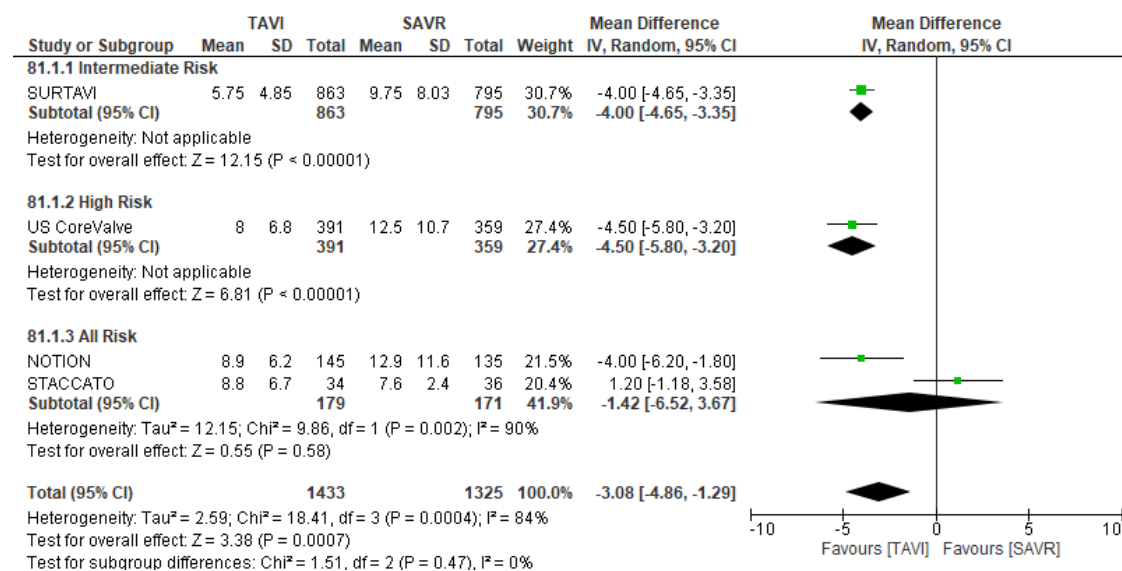
c. 2 Years



d. 5 Years



SUPPLEMENTARY FIGURE S12: FOREST PLOTS FOR MEAN LENGTH OF HOSPITAL STAY



SUPPLEMENTARY APPENDIX S1: SEARCH STRATEGY

Embase (Ovid): 1974-2020/08/05

Searched 6.8.20

- 1 transcatheter aortic valve implantation/ (21568)
- 2 (TAVI or TAVR or PAVR or ViV-TAVI or VIVTAVI or "ViV TAVI").ti,ab,ot. (16298)
- 3 ((implant\$ or replac\$) adj3 (aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular)).ti,ab,ot. (38029)
- 4 ((aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular) adj3 (implant\$ or replac\$)).ti,ab,ot. (38790)
- 5 (("valve in valve" or "valve-in-valve") adj3 (aortic or aorta or aortae)).ti,ab,ot. (467)
- 6 or/1-5 (44351)
- 7 crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ (686556)
- 8 (random\$ or factorial\$ or crossover\$ or cross over\$ or cross-over\$ or placebo\$ or (doubl\$ adj blind\$) or (singl\$ adj blind\$) or assign\$ or allocat\$ or volunteer\$).ti,ab,ot. (2260655)
- 9 or/7-8 (2360211)
- 10 animal/ or animal experiment/ (4013567)
- 11 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6782516)
- 12 or/10-11 (6782516)
- 13 exp human/ or human experiment/ (21200909)
- 14 12 not (12 and 13) (5203614)
- 15 9 not 14 (2115522)
- 16 6 and 15 (2829)
- 17 limit 16 to yr="2000 -Current" (2700)

Trials filter based on terms suggested by the Cochrane Handbook:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. 6.3.2.2. What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from EMBASE? In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org¹⁰

Medline & In-Process Citations (Ovid): 1946-2020/08/04

Searched 6.8.20

- 1 Transcatheter Aortic Valve Replacement/ (5612)
- 2 (TAVI or TAVR or PAVR or ViV-TAVI or VIVTAVI or "ViV TAVI").ti,ab,ot. (6737)
- 3 ((implant\$ or replac\$) adj3 (aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular)).ti,ab,ot. (23151)
- 4 ((aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular) adj3 (implant\$ or replac\$)).ti,ab,ot. (23701)
- 5 (("valve in valve" or "valve-in-valve") adj3 (aortic or aorta or aortae)).ti,ab,ot. (287)
- 6 or/1-5 (25309)
- 7 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (639320)
- 8 controlled clinical trial.pt. (93772)
- 9 random\$.ti,ot. (223430)
- 10 placebo.ab. (206592)
- 11 random\$.ab. (1092052)

12 trial.ab. (502818)
 13 groups.ab. (2036666)
 14 or/7-13 (3219382)
 15 exp animals/ not (exp animals/ and humans/) (4720549)
 16 14 not 15 (2751689)
 17 6 and 16 (4584)
 18 **limit 17 to yr="2000 -Current" (4016)**

Based on Trials filter:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org¹⁰

Medline Epub Ahead of Print & Daily Update (Ovid): up to 2020/08/04

Searched 6.8.20

1 Transcatheter Aortic Valve Replacement/ (45)
 2 (TAVI or TAVR or PAVR or ViV-TAVI or VIVTAVI or "ViV TAVI").ti,ab,ot. (399)
 3 ((implant\$ or replac\$) adj3 (aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular)).ti,ab,ot. (724)
 4 ((aortic or aorta or aortae) adj3 (valve\$ or valva or cusp or valvular) adj3 (implant\$ or replac\$)).ti,ab,ot. (732)
 5 (("valve in valve" or "valve-in-valve") adj3 (aortic or aorta or aortae)).ti,ab,ot. (17)
 6 or/1-5 (795)
 7 randomized controlled trial.pt. or "randomized controlled trials as topic"/ (965)
 8 controlled clinical trial.pt. (13)
 9 random\$.ti,ot. (6823)
 10 placebo.ab. (3385)
 11 random\$.ab. (24421)
 12 trial.ab. (12305)
 13 groups.ab. (40640)
 14 or/7-13 (63981)
 15 exp animals/ not (exp animals/ and humans/) (2684)
 16 14 not 15 (63582)
 17 6 and 16 (190)
 18 **limit 17 to yr="2000 -Current" (186)**

Based on Trials filter:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org¹⁰

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 8/12, August 2020

Date limit: 2019/05-2020/08

Searched 6.8.20

#1	MeSH descriptor: [Transcatheter Aortic Valve Replacement] this term only	146
#2	(TAVI or TAVR or PAVR or ViV-TAVI or VIVTAVI or "ViV TAVI"):ti,ab	742

#3 ((implant* or replac*) NEAR/3 (aortic or aorta or aortae) NEAR/3 (valve* or valva or cusp or valvular)):ti,ab 1490
#4 ((aortic or aorta or aortae) NEAR/3 (valve* or valva or cusp or valvular) NEAR/3 (implant* or replac*)):ti,ab 1510
#5 ("valve in valve" or "valve-in-valve") NEAR/3 (aortic or aorta or aortae)):ti,ab 6
#6 **#1 or #2 or #3 or #4 or #5 with Cochrane Library publication date Between Jan 2000 and Aug 2020, in Trials 1517**

SUPPLEMENTARY REFERENCE LIST

- [1] Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019;380(18):1706-15. doi: <https://dx.doi.org/10.1056/NEJMoa1816885>
- [2] Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364(23):2187-98. doi: <https://dx.doi.org/10.1056/NEJMoa1103510>
- [3] Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374(17):1609-20. doi: <https://dx.doi.org/10.1056/NEJMoa1514616>
- [4] Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380(18):1695-705. doi: <https://dx.doi.org/10.1056/NEJMoa1814052>
- [5] Nielsen HH, Klaaborg KE, Nissen H, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. *EuroIntervention* 2012;8(3):383-9. doi: <https://dx.doi.org/10.4244/EIJV8I3A58>
- [6] Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376(14):1321-31. doi: <https://dx.doi.org/10.1056/NEJMoa1700456>
- [7] Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370(19):1790-8. doi: <https://dx.doi.org/10.1056/NEJMoa1400590>
- [8] Thyregod HG, Steinbruchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the All-Comers NOTION randomized clinical trial. *J Am Coll Cardiol* 2015;65(20):2184-94. doi: <https://dx.doi.org/10.1016/j.jacc.2015.03.014>
- [9] Toff WD. United Kingdom Transcatheter Aortic Valve Implantation - UK TAVI. Presented at ACC 2020 (World Congress of Cardiology); 28-30 March 2020; Chicago, IL [Internet] Washington, DC: American College of Cardiology; 2020 [accessed 14.8.20] [Available from: <https://www.acc.org/latest-in-cardiology/clinical-trials/2020/03/26/21/14/uk-tavi>].
- [10] Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. 6.3.2.2. What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from EMBASE? . In: Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011]; Cochrane Collaboration 2011.