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

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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 patients [1-7]), 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 patients [7]); 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 patients [1-9]); 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 patients [1-9]), 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 patients [7]) (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

patients [3 7]) (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 patients [2-4]) (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 patients [7]); 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 patients [2]); 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 patients [5-8]) (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 patients [8]). 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 1A[2]	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 CoreValve[7]	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 ≤0.5cm^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 ≥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 mm3), thrombocytopenia (platelet count <50,000 cells/mm3), 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; congential 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 2A[3]	Intermediate	Symptomatic senile degenerative aortic valve stenosis (mean gradient >40 mmHg or jet velocity >4.0 m/s and initial aortic valve area of ≤0.8cm^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 or 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 obsctruction; 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
SURTAVI[6]	Intermediate	Co-morbidities resulting in predicted risk of operative mortality of ≥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 ≤1.0 cm^2 or aortic valve area index <0.6 cm^2/m^2 AND (b) mean gradient > 40 mmHg or Vmax > 4 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 (WBC <1000 mm^3), thrombocytopenia (platelet count <50,000 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 LVEF <20%; uncontrolled atrial fibrillation; end-stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min; pulmonary hypertension (systolic pressure >80mmHg); severe COPD (FEV1<750cc); Marfan syndrome or other connective tissue disease; native aortic annulus <18mm or >29mm; 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; congential bicuspid or unicuspid valve; sinus of valsalva anatomy that would prevent adequate coronary perfusion; transarterial access not able to accommodaye an 18-Fr sheath.

Study ID	Risk Level	Inclusion criteria	Exclusion criteria
Low Risk			
EVOLUT[1]	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 cm2 (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 <1000mm3), thrombocytopenia (platelet count <50,000 cells/mm3), 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 3[4]	Low	Severe, calcific aortic stenosis (defined as AVA ≤1.0cm^2 or AVA index ≤0.6 cm^2/m^2 and jet velocity ≥4.0m/s or mean gradient ≥40mmHg 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 prevention 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			
NOTION[8]	All	Patients ≥70 years of age with severe degenerative aortic valve stenosis (defined as an effective orifice area <1 cm^2 or indexed for body surface area <0.6 cm^2/m^2 and a mean aortic valve gradient >40 mm Hg or peak systolic velocity >4 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 ≥17 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
STACCATO[5]	"Operable"	Significant valvular aortic stenosis (valve area <1 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 contract 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.

[a]Defined 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.
[b]Defined 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 1A[2]	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 CoreValve[7]	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 2A[3]	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)
SURTAVI[6]	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 ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) OR mean gradient ≥40 mmHg OR maximal aortic valve velocity ≥4.0 m/s by transthoracic echocardiography at rest. <u>For asymptomatic patients:</u> i. Very severe aortic stenosis with an aortic valve area ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) AND maximal aortic velocity ≥5.0 m/sec or mean gradient ≥60 mmHg by transthoracic echocardiography at rest ii. Aortic valve area of ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) AND a mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 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 ≤1.0 cm^2 (or AVA index of ≤0.6 cm^2/m^2) AND mean gradient ≥40 mmHg or maximal aortic valve velocity ≥4.0 m/s by transthoracic	Low	Risk of death ≤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 3[4]	Severe calcific aortic stenosis	Aortic valve area ≤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 ≥ 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 (≥70y) or Any (≥80y) Risk				
UK TAVI[9]	Severe symptomatic aortic stenosis	NR	Intermediate-High (≥70 years) or Any (≥80 years)	NR
All Risk				
NOTION[8]	Severe degenerative aortic stenosis	Effective orifice area <1 cm^2 or indexed for body surface area <0.6 cm^2/m^2 and a mean aortic valve gradient >40 mm Hg or peak systolic velocity >4 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 ≥17 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
STACCATO[5]	Significant aortic stenosis	Valve area <1cm^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 [2679]	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

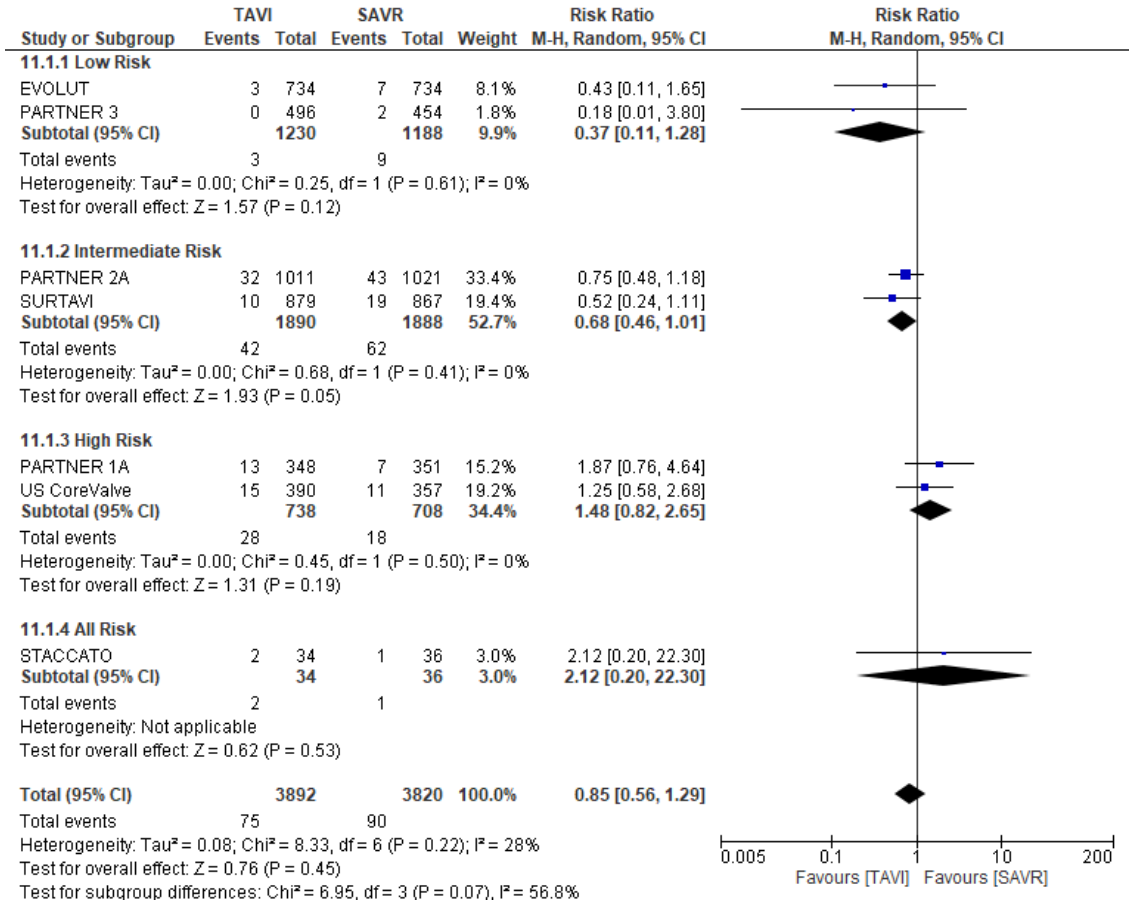
Study ID	Follow-Up Period	Treatment Arm	Definition of SVD	No. of Patients Experiencing Event	Total No. of Patients	%	P-Value	Effect Estimate
High Risk								
PARTNER 1A[2]	5 Years	TAVI	Structural valve deterioration	0	348	0	NR	NE
		SAVR		0	351	0		
All Risk								
NOTION[8]	6 Years	TAVI	Moderate/severe 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		

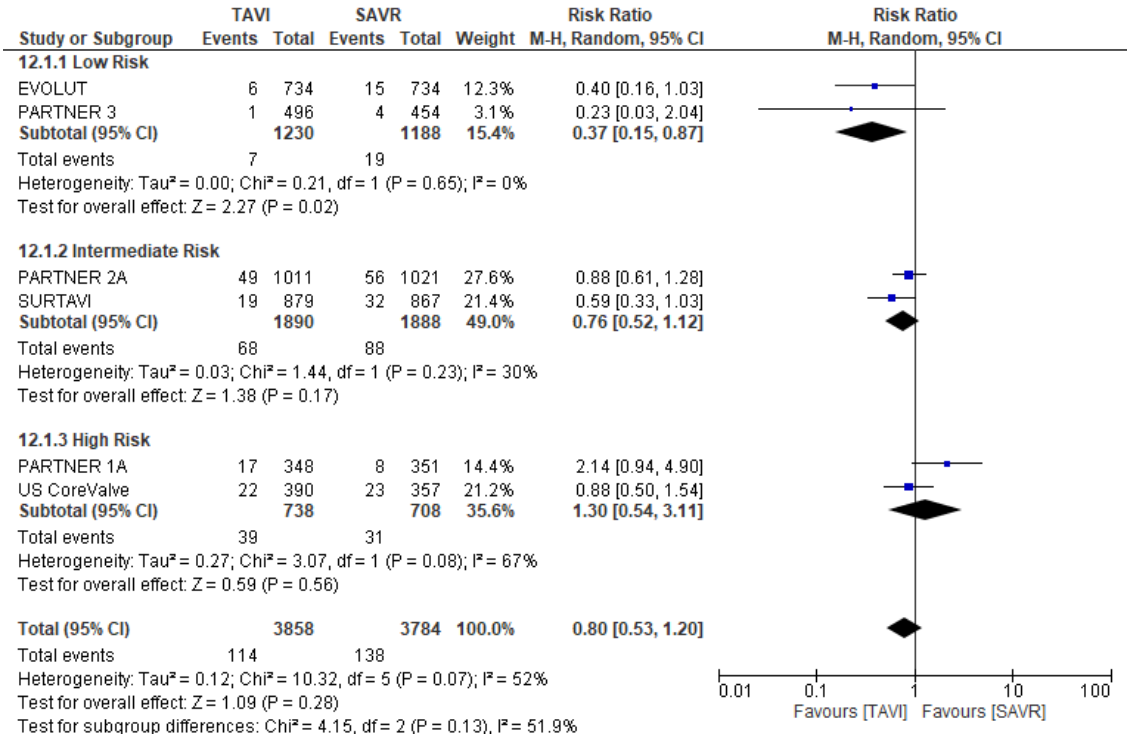
Abbreviations: AR = aortic regurgitation; BVD = bioprosthetic valve dysfunction; NE = not estimable; NR = not reported; PPM = patient-prosthesis mismatch; PVL = paravalvular leakage; RR = risk ratio; SAVR = surgical aortic valve replacement; SVD = structural valve deterioration; TAVI = transcatheter aortic valve implantation.

SUPPLEMENTARY FIGURE S1: FOREST PLOTS FOR MAJOR OR DISABLING STROKE

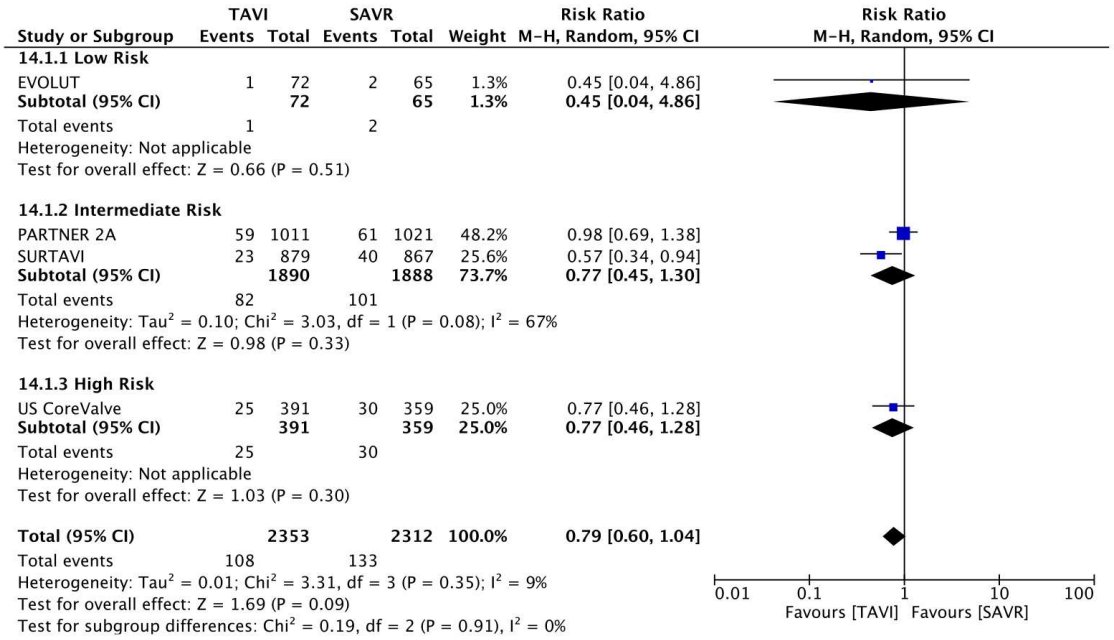
a. 30 Days



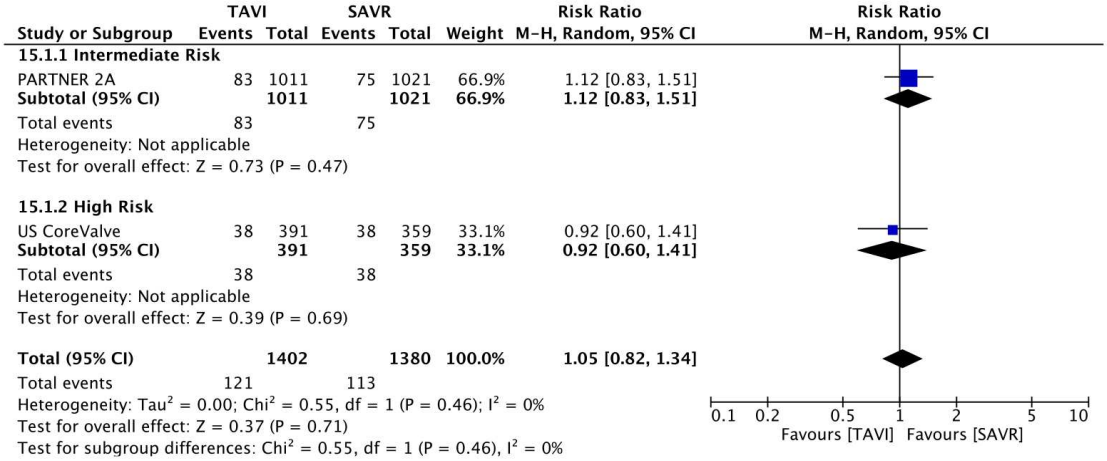
b. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
12.1.1 Low Risk
EVOLUT 6 734 15 734 12.3% 0.40 [0.16, 1.03]
PARTNER 3 1 496 4 454 3.1% 0.23 [0.03, 2.04]
Subtotal (95% CI) 1230 1188 15.4% 0.37 [0.15, 0.87]
Total events 7 19
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)
12.1.2 Intermediate Risk
PARTNER 2A 49 1011 56 1021 27.6% 0.88 [0.61, 1.28]
SURTAVI 19 879 32 867 21.4% 0.59 [0.33, 1.03]
Subtotal (95% CI) 1890 1888 49.0% 0.76 [0.52, 1.12]
Total events 68 88
Heterogeneity: Tau² = 0.03; Chi² = 1.44, df = 1 (P = 0.23); I² = 30%
Test for overall effect: Z = 1.38 (P = 0.17)
12.1.3 High Risk
PARTNER 1A 17 348 8 351 14.4% 2.14 [0.94, 4.90]
US CoreValve 22 390 23 357 21.2% 0.88 [0.50, 1.54]
Subtotal (95% CI) 738 708 35.6% 1.30 [0.54, 3.11]
Total events 39 31
Heterogeneity: Tau² = 0.27; Chi² = 3.07, df = 1 (P = 0.08); I² = 67%
Test for overall effect: Z = 0.59 (P = 0.56)
Total (95% CI) 3858 3784 100.0% 0.80 [0.53, 1.20]
Total events 114 138
Heterogeneity: Tau² = 0.12; Chi² = 10.32, df = 5 (P = 0.07); I² = 52%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Chi² = 4.15, df = 2 (P = 0.13), I² = 51.9%
0.01
0.1
1
10
100
Favours [TAVI]
Favours [SAVR]

c. 2 Years

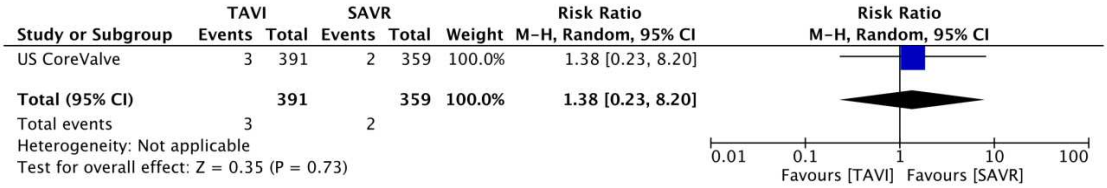


d. 5 Years

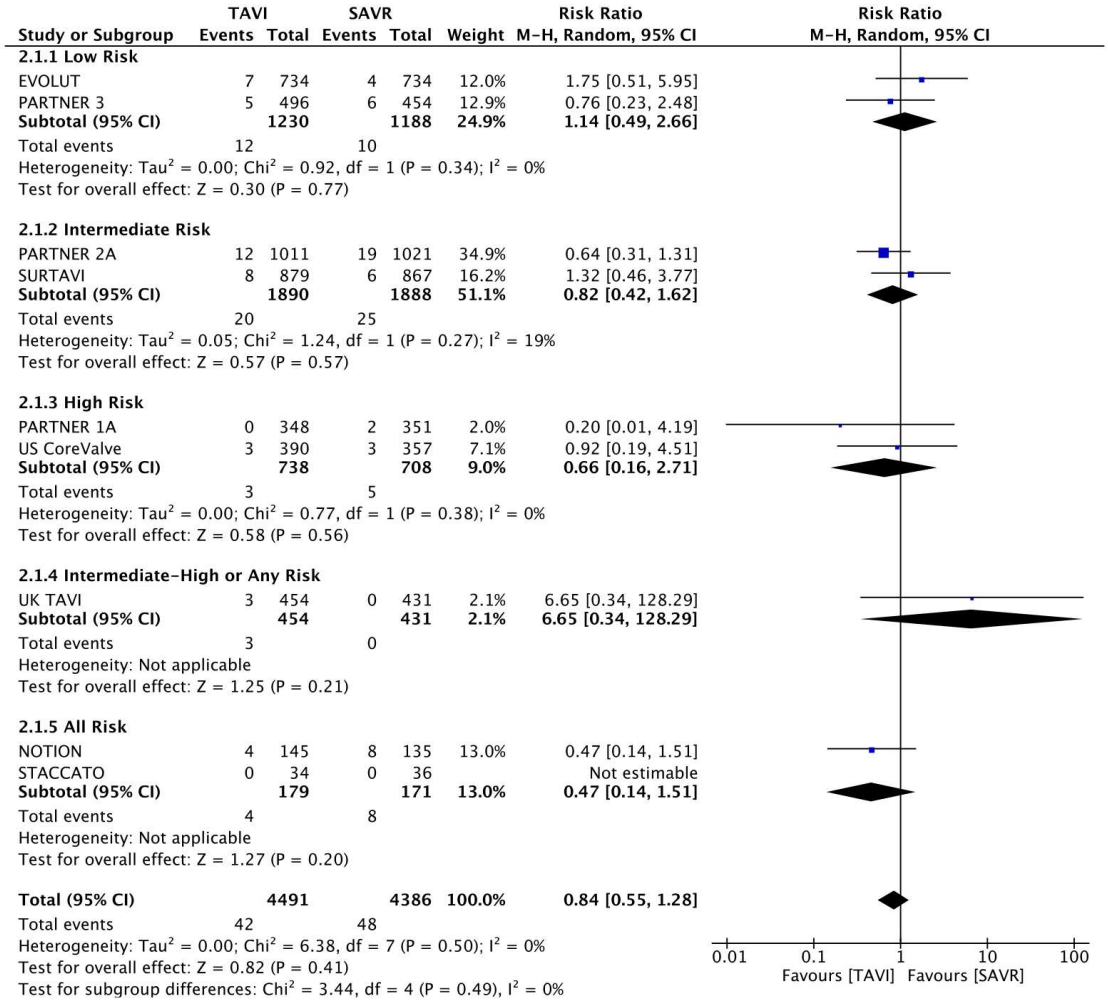


SUPPLEMENTARY FIGURE S2: FOREST PLOTS FOR MYOCARDIAL INFARCTION

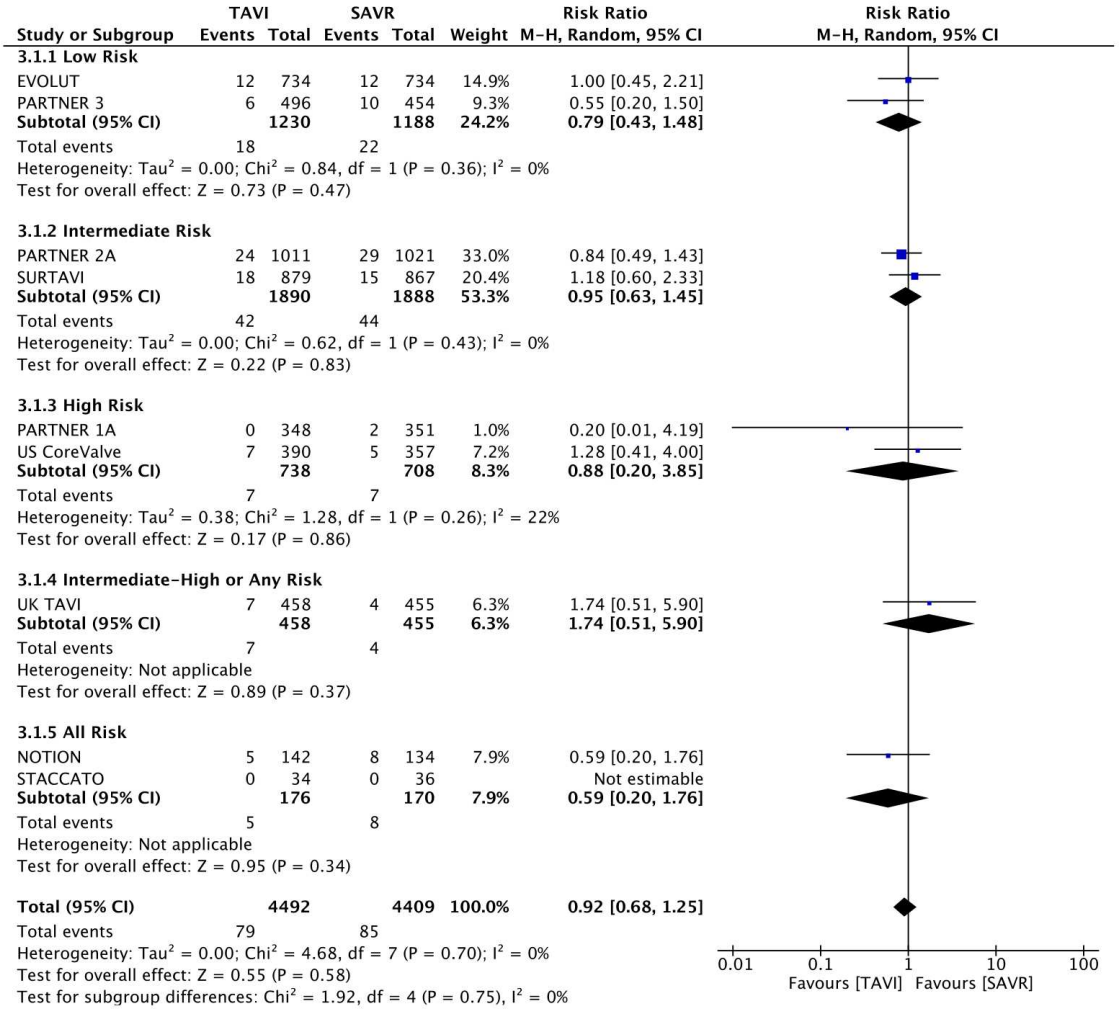
a. Periprocedural



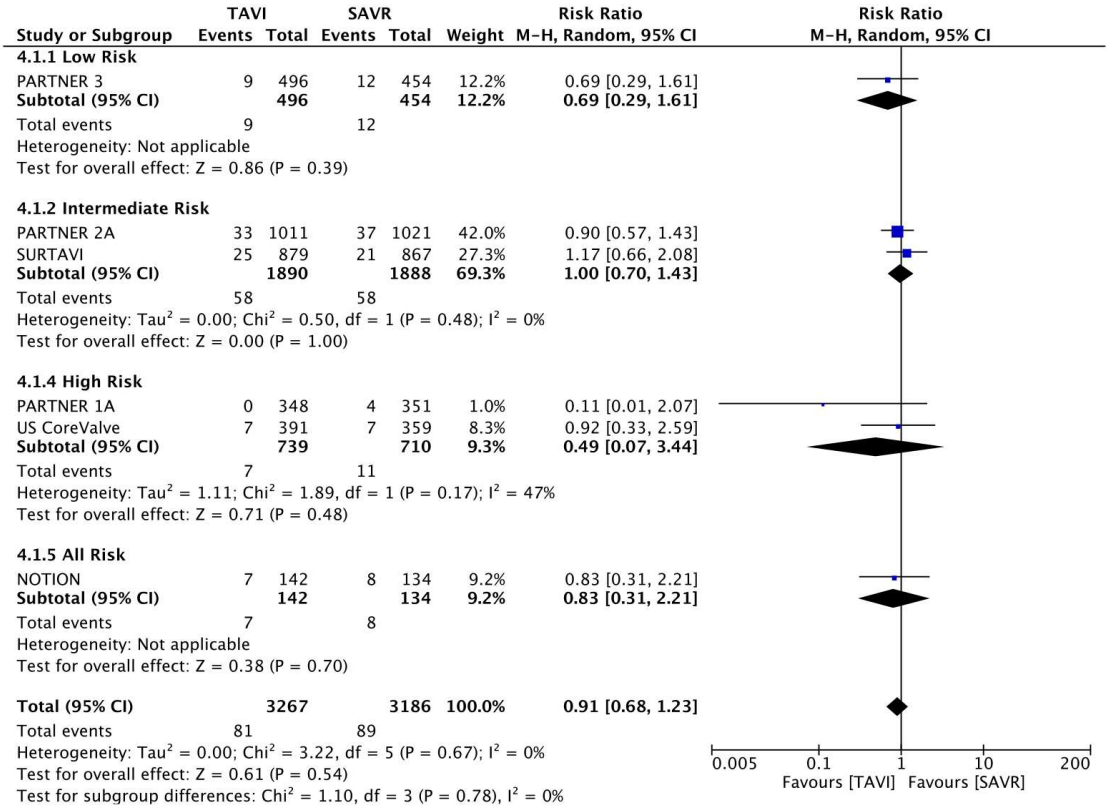
b. 30 Days



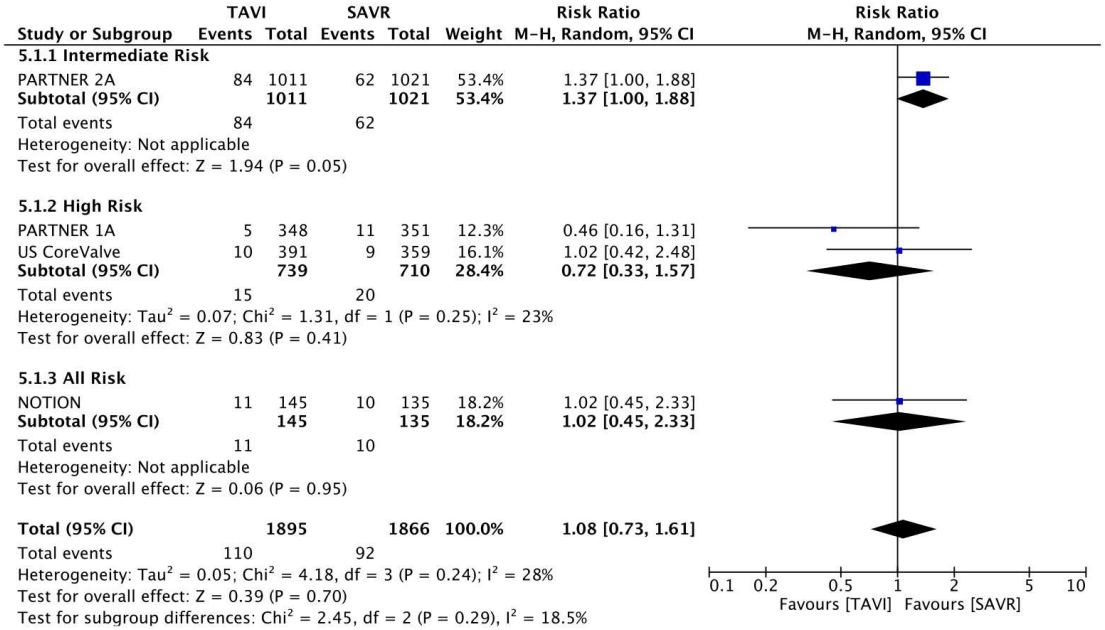
c. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.1.1 Low Risk
EVOLUT 12 734 12 734 14.9% 1.00 [0.45, 2.21]
PARTNER 3 6 496 10 454 9.3% 0.55 [0.20, 1.50]
Subtotal (95% CI) 1230 1188 24.2% 0.79 [0.43, 1.48]
Total events 18 22
Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)
3.1.2 Intermediate Risk
PARTNER 2A 24 1011 29 1021 33.0% 0.84 [0.49, 1.43]
SURTAVI 18 879 15 867 20.4% 1.18 [0.60, 2.33]
Subtotal (95% CI) 1890 1888 53.3% 0.95 [0.63, 1.45]
Total events 42 44
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
3.1.3 High Risk
PARTNER 1A 0 348 2 351 1.0% 0.20 [0.01, 4.19]
US CoreValve 7 390 5 357 7.2% 1.28 [0.41, 4.00]
Subtotal (95% CI) 738 708 8.3% 0.88 [0.20, 3.85]
Total events 7 7
Heterogeneity: Tau² = 0.38; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 0.17 (P = 0.86)
3.1.4 Intermediate-High or Any Risk
UK TAVI 7 458 4 455 6.3% 1.74 [0.51, 5.90]
Subtotal (95% CI) 458 455 6.3% 1.74 [0.51, 5.90]
Total events 7 4
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)
3.1.5 All Risk
NOTION 5 142 8 134 7.9% 0.59 [0.20, 1.76]
STACCATO 0 34 0 36 Not estimable
Subtotal (95% CI) 176 170 7.9% 0.59 [0.20, 1.76]
Total events 5 8
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Total (95% CI) 4492 4409 100.0% 0.92 [0.68, 1.25]
Total events 79 85
Heterogeneity: Tau² = 0.00; Chi² = 4.68, df = 7 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Chi² = 1.92, df = 4 (P = 0.75), I² = 0%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

d. 2 Years

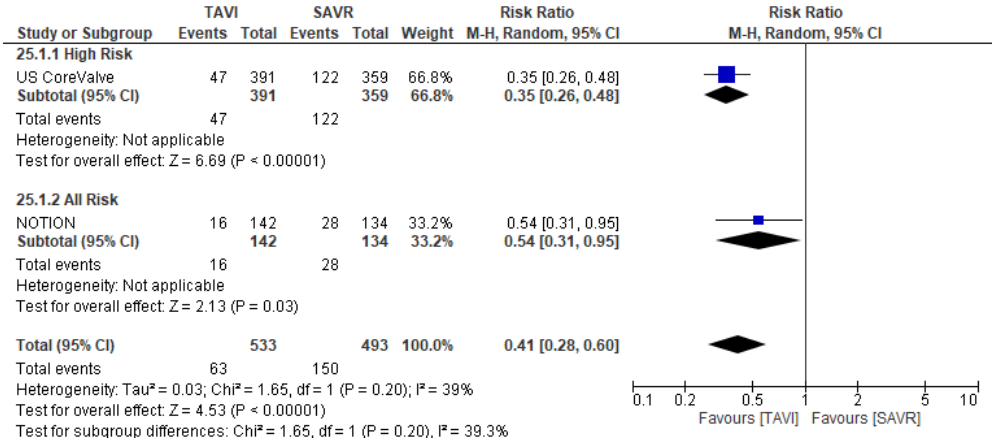

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
4.1.1 Low Risk
PARTNER 3 9 496 12 454 12.2% 0.69 [0.29, 1.61]
Subtotal (95% CI) 496 454 12.2% 0.69 [0.29, 1.61]
Total events 9 12
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
4.1.2 Intermediate Risk
PARTNER 2A 33 1011 37 1021 42.0% 0.90 [0.57, 1.43]
SURTAVI 25 879 21 867 27.3% 1.17 [0.66, 2.08]
Subtotal (95% CI) 1890 1888 69.3% 1.00 [0.70, 1.43]
Total events 58 58
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
4.1.4 High Risk
PARTNER 1A 0 348 4 351 1.0% 0.11 [0.01, 2.07]
US CoreValve 7 391 7 359 8.3% 0.92 [0.33, 2.59]
Subtotal (95% CI) 739 710 9.3% 0.49 [0.07, 3.44]
Total events 7 11
Heterogeneity: Tau² = 1.11; Chi² = 1.89, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 0.71 (P = 0.48)
4.1.5 All Risk
NOTION 7 142 8 134 9.2% 0.83 [0.31, 2.21]
Subtotal (95% CI) 142 134 9.2% 0.83 [0.31, 2.21]
Total events 7 8
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)
Total (95% CI) 3267 3186 100.0% 0.91 [0.68, 1.23]
Total events 81 89
Heterogeneity: Tau² = 0.00; Chi² = 3.22, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Chi² = 1.10, df = 3 (P = 0.78), I² = 0%
0.005 0.1 1 10 200
Favours [TAVI] Favours [SAVR]

e. 5 Years

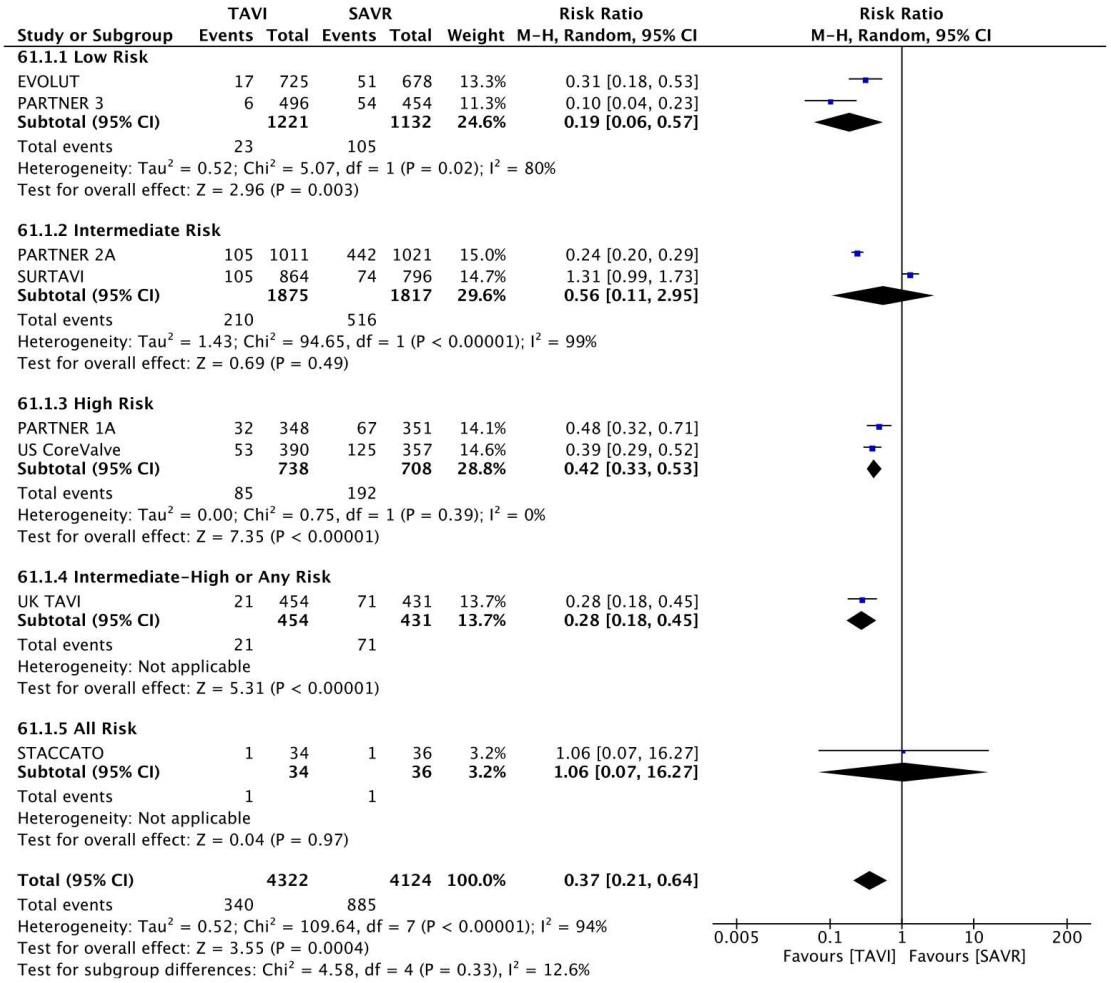

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
5.1.1 Intermediate Risk
PARTNER 2A 84 1011 62 1021 53.4% 1.37 [1.00, 1.88]
Subtotal (95% CI) 1011 1021 53.4% 1.37 [1.00, 1.88]
Total events 84 62
Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
5.1.2 High Risk
PARTNER 1A 5 348 11 351 12.3% 0.46 [0.16, 1.31]
US CoreValve 10 391 9 359 16.1% 1.02 [0.42, 2.48]
Subtotal (95% CI) 739 710 28.4% 0.72 [0.33, 1.57]
Total events 15 20
Heterogeneity: Tau² = 0.07; Chi² = 1.31, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 0.83 (P = 0.41)
5.1.3 All Risk
NOTION 11 145 10 135 18.2% 1.02 [0.45, 2.33]
Subtotal (95% CI) 145 135 18.2% 1.02 [0.45, 2.33]
Total events 11 10
Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)
Total (95% CI) 1895 1866 100.0% 1.08 [0.73, 1.61]
Total events 110 92
Heterogeneity: Tau² = 0.05; Chi² = 4.18, df = 3 (P = 0.24); I² = 28%
Test for overall effect: Z = 0.39 (P = 0.70)
Test for subgroup differences: Chi² = 2.45, df = 2 (P = 0.29), I² = 18.5%
0.1 0.2 0.5 1 2 5 10
Favours [TAVI] Favours [SAVR]

SUPPLEMENTARY FIGURE S3: FOREST PLOTS FOR MAJOR BLEEDING

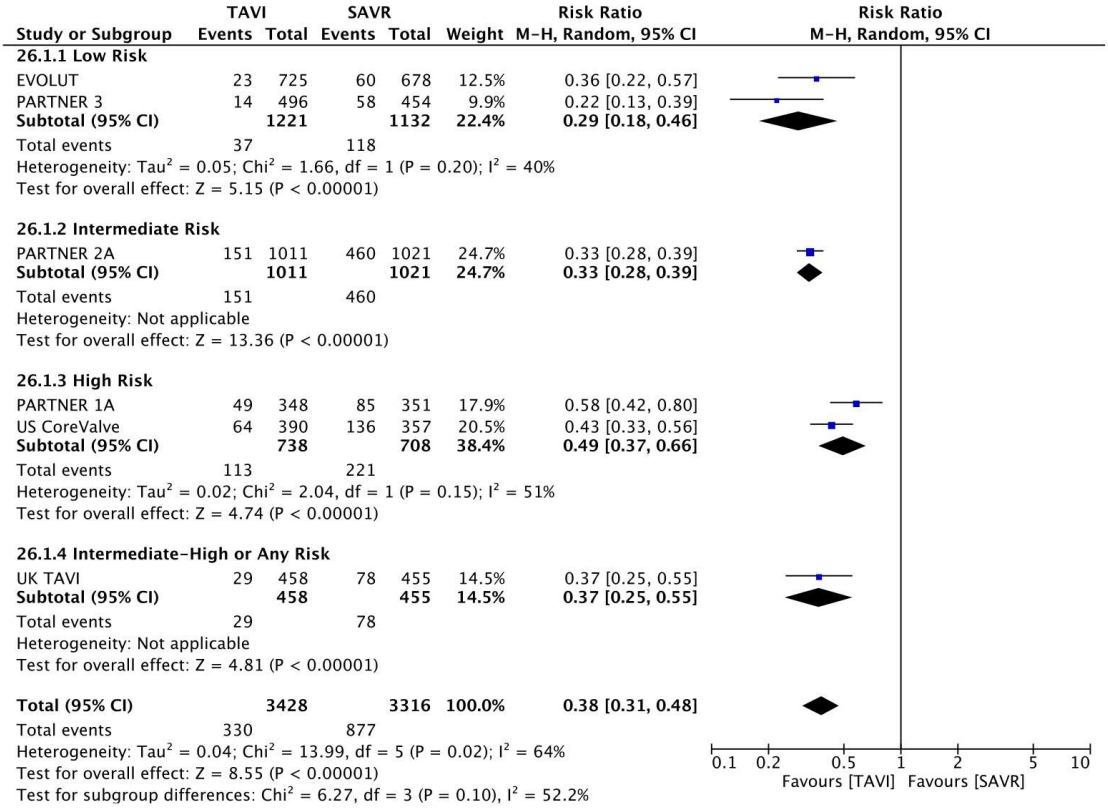
a. Periprocedural or In-Hospital



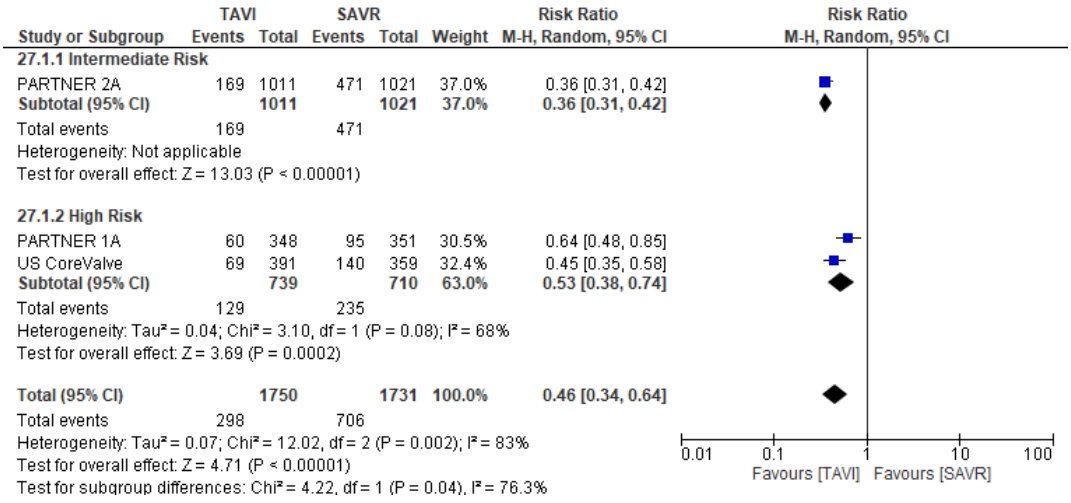
b. 30 Days


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
61.1.1 Low Risk
EVOLUT 17 725 51 678 13.3% 0.31 [0.18, 0.53]
PARTNER 3 6 496 54 454 11.3% 0.10 [0.04, 0.23]
Subtotal (95% CI) 1221 1132 24.6% 0.19 [0.06, 0.57]
Total events 23 105
Heterogeneity: Tau² = 0.52; Chi² = 5.07, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 2.96 (P = 0.003)
61.1.2 Intermediate Risk
PARTNER 2A 105 1011 442 1021 15.0% 0.24 [0.20, 0.29]
SURTAVI 105 864 74 796 14.7% 1.31 [0.99, 1.73]
Subtotal (95% CI) 1875 1817 29.6% 0.56 [0.11, 2.95]
Total events 210 516
Heterogeneity: Tau² = 1.43; Chi² = 94.65, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.69 (P = 0.49)
61.1.3 High Risk
PARTNER 1A 32 348 67 351 14.1% 0.48 [0.32, 0.71]
US CoreValve 53 390 125 357 14.6% 0.39 [0.29, 0.52]
Subtotal (95% CI) 738 708 28.8% 0.42 [0.33, 0.53]
Total events 85 192
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 7.35 (P < 0.00001)
61.1.4 Intermediate-High or Any Risk
UK TAVI 21 454 71 431 13.7% 0.28 [0.18, 0.45]
Subtotal (95% CI) 454 431 13.7% 0.28 [0.18, 0.45]
Total events 21 71
Heterogeneity: Not applicable
Test for overall effect: Z = 5.31 (P < 0.00001)
61.1.5 All Risk
STACCATO 1 34 1 36 3.2% 1.06 [0.07, 16.27]
Subtotal (95% CI) 34 36 3.2% 1.06 [0.07, 16.27]
Total events 1 1
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Total (95% CI) 4322 4124 100.0% 0.37 [0.21, 0.64]
Total events 340 885
Heterogeneity: Tau² = 0.52; Chi² = 109.64, df = 7 (P < 0.00001); I² = 94%
Test for overall effect: Z = 3.55 (P = 0.0004)
Test for subgroup differences: Chi² = 4.58, df = 4 (P = 0.33), I² = 12.6%
0.005
0.1
1
10
200
Favours [TAVI]
Favours [SAVR]

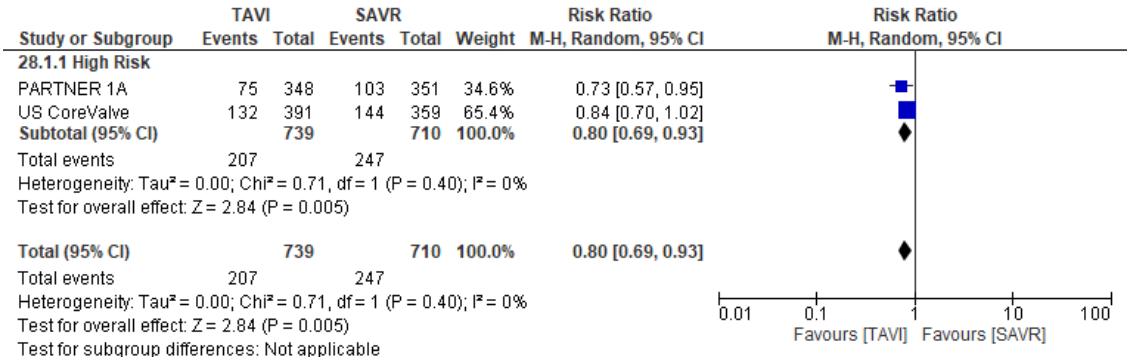
c. 1 Year



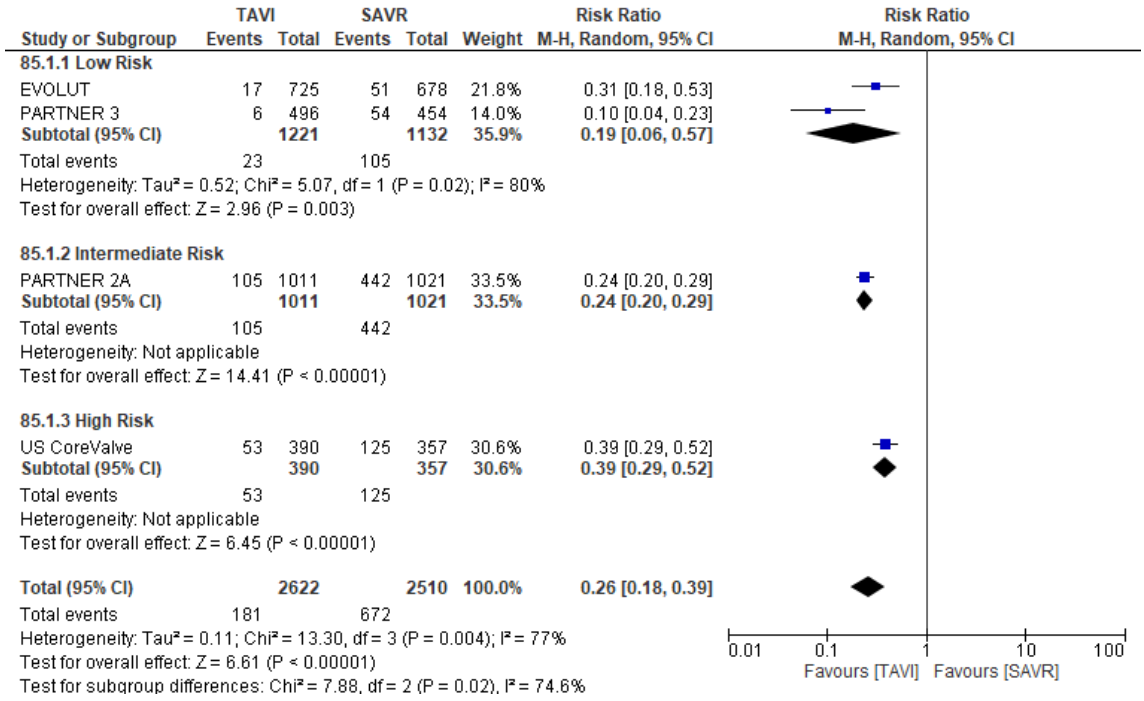
d. 2 Years



e. 5 Years

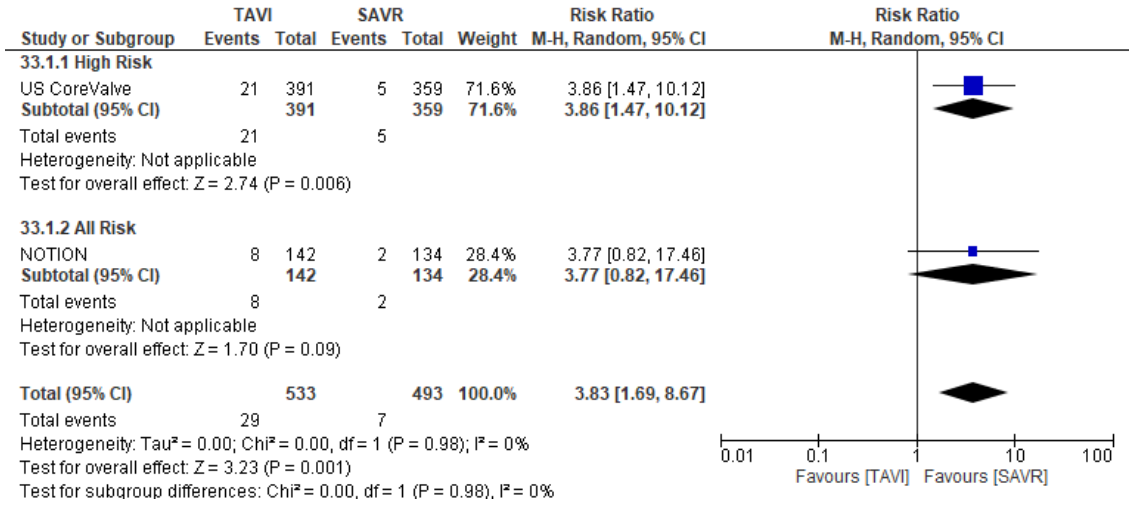

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
28.1.1 High Risk
PARTNER 1A 75 348 103 351 34.6% 0.73 [0.57, 0.95]
US CoreValve 132 391 144 359 65.4% 0.84 [0.70, 1.02]
Subtotal (95% CI) 739 710 100.0% 0.80 [0.69, 0.93]
Total events 207 247
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)
Total (95% CI) 739 710 100.0% 0.80 [0.69, 0.93]
Total events 207 247
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable
0.01
0.1
1
10
100
Favours [TAVI]
Favours [SAVR]

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

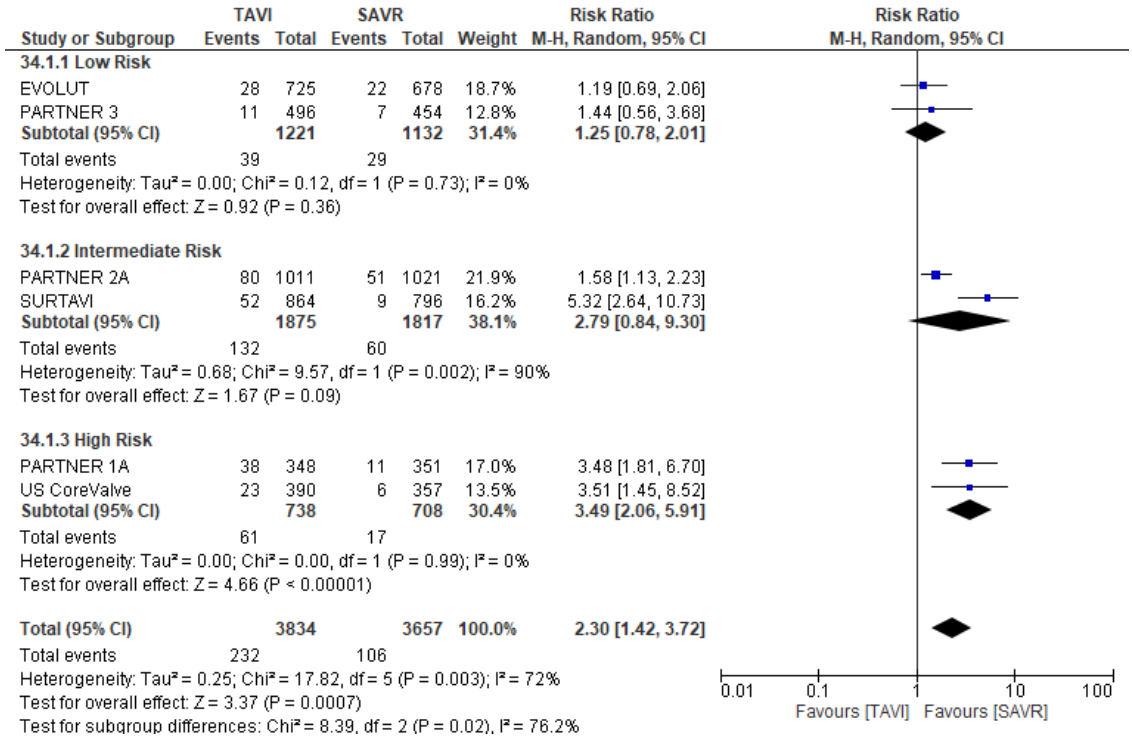


SUPPLEMENTARY FIGURE S5: FOREST PLOTS FOR MAJOR VASCULAR COMPLICATIONS

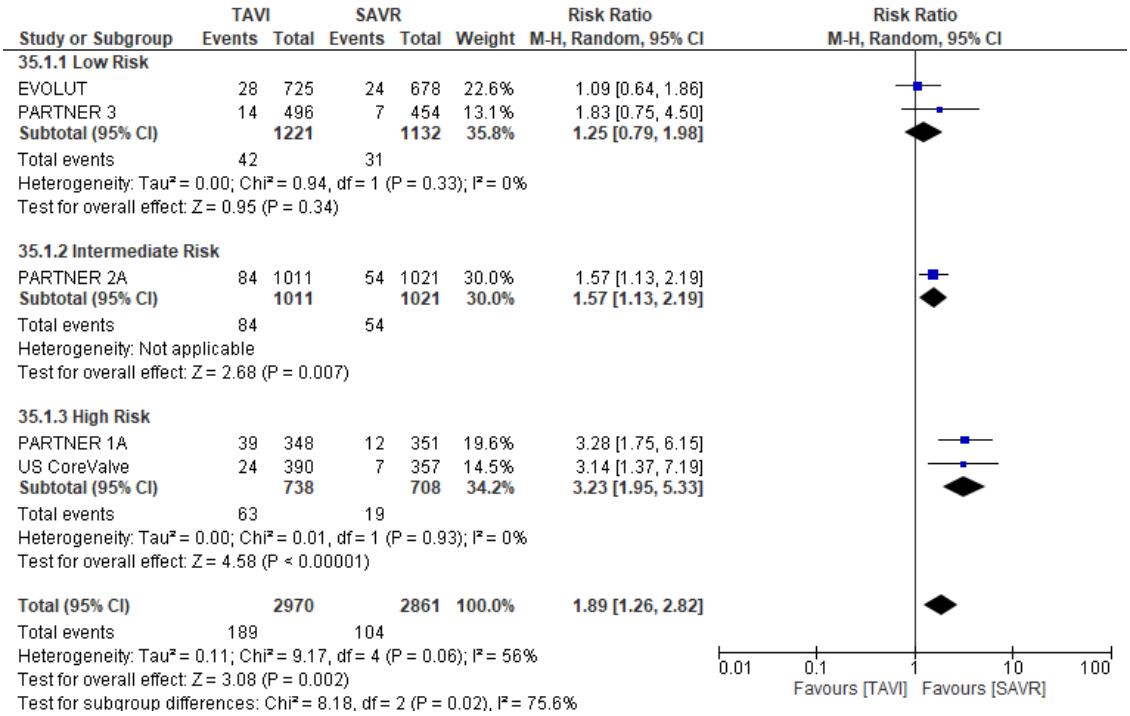
a. Periprocedural or In-Hospital



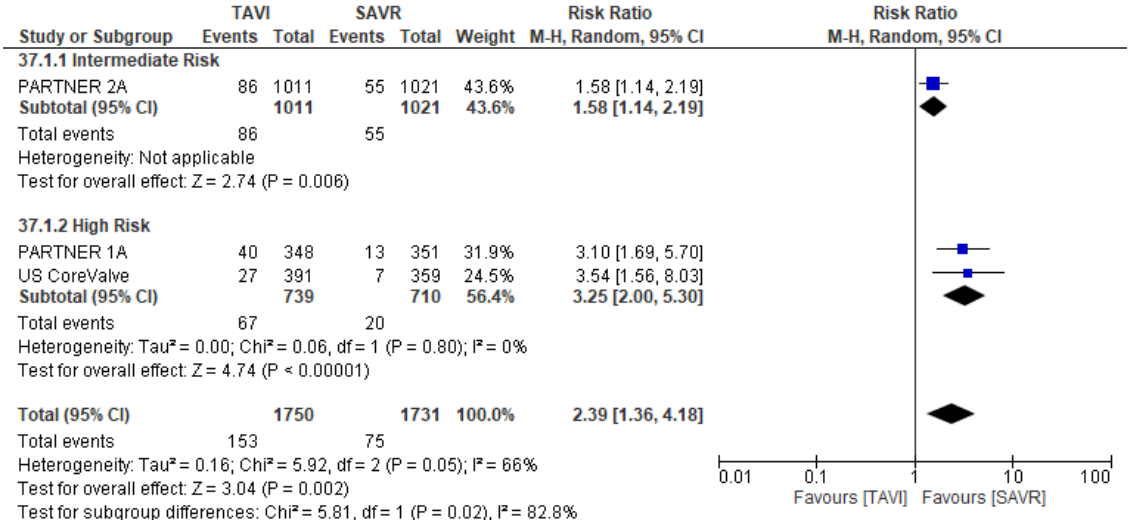
b. 30 Days



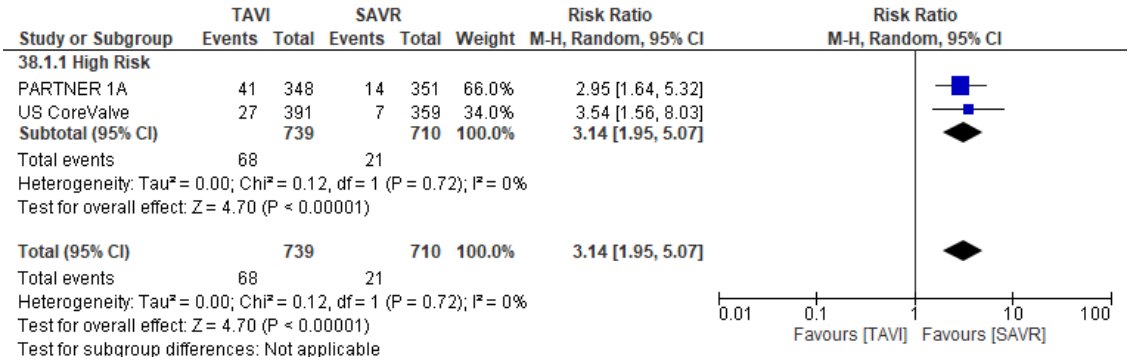
c. 1 Year



d. 2 Years

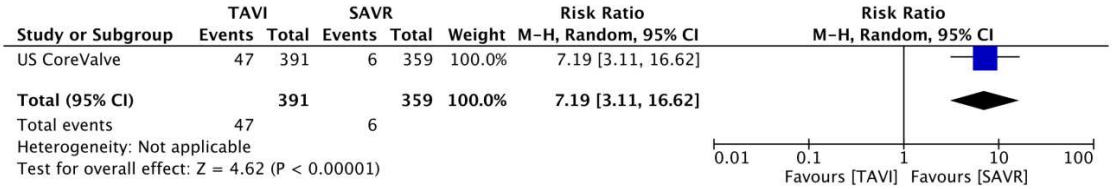


e. 5 Years

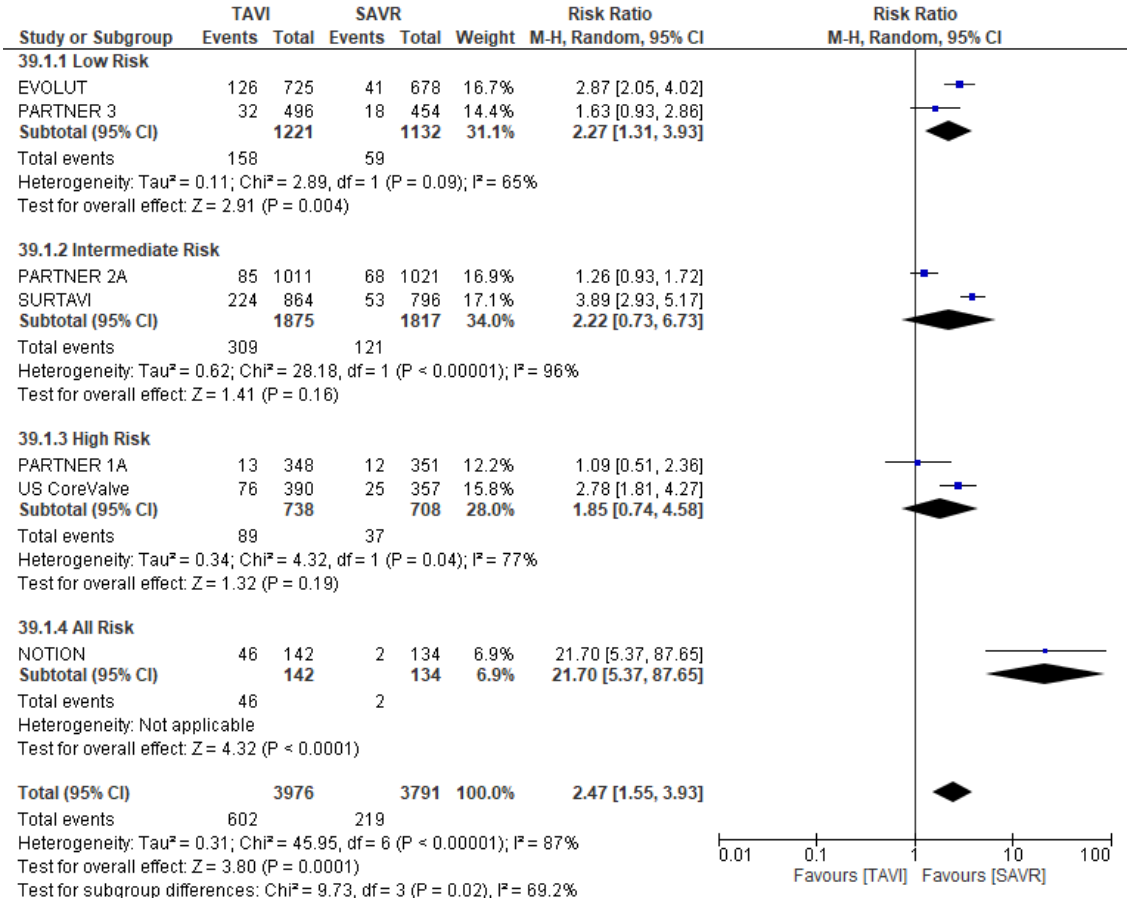

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
38.1.1 High Risk
PARTNER 1A 41 348 14 351 66.0% 2.95 [1.64, 5.32]
US CoreValve 27 391 7 359 34.0% 3.54 [1.56, 8.03]
Subtotal (95% CI) 739 710 100.0% 3.14 [1.95, 5.07]
Total events 68 21
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.70 (P < 0.00001)
Total (95% CI) 739 710 100.0% 3.14 [1.95, 5.07]
Total events 68 21
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 4.70 (P < 0.00001)
Test for subgroup differences: Not applicable
0.01
0.1
1
10
100
Favours [TAVI]
Favours [SAVR]

SUPPLEMENTARY FIGURE S6: FOREST PLOTS FOR NEW PERMANENT PACEMAKER IMPLANTATION

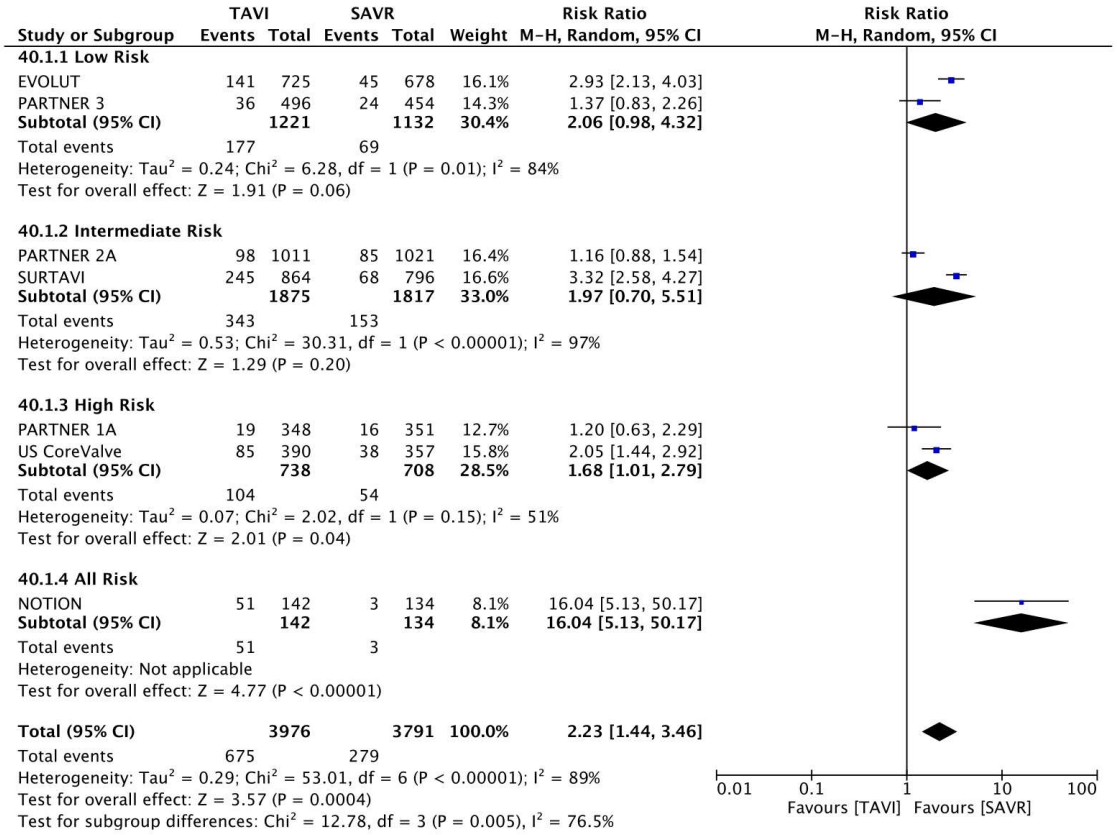
a. Periprocedural



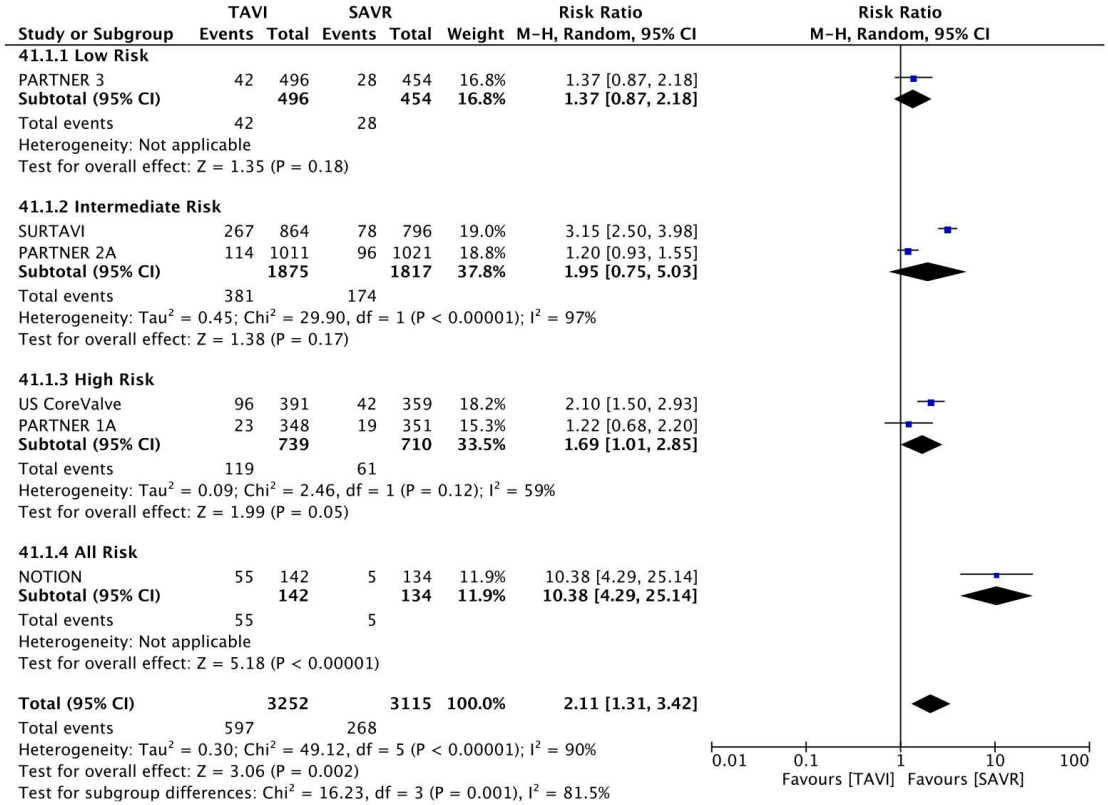
b. 30 Days



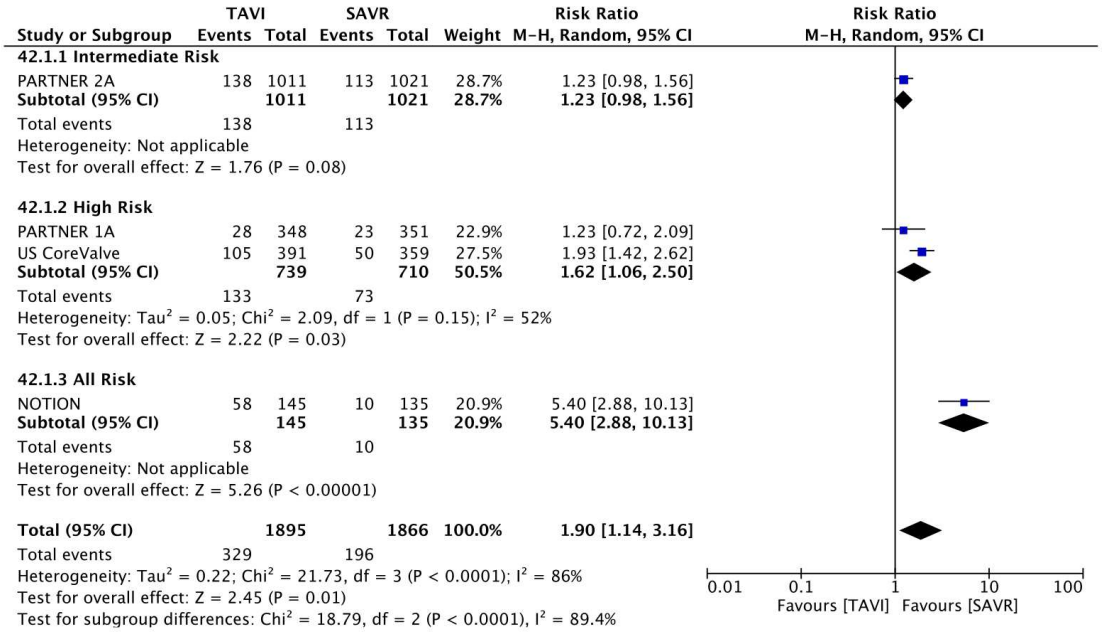
c. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
40.1.1 Low Risk
EVOLUT 141 725 45 678 16.1% 2.93 [2.13, 4.03]
PARTNER 3 36 496 24 454 14.3% 1.37 [0.83, 2.26]
Subtotal (95% CI) 1221 1132 30.4% 2.06 [0.98, 4.32]
Total events 177 69
Heterogeneity: Tau² = 0.24; Chi² = 6.28, df = 1 (P = 0.01); I² = 84%
Test for overall effect: Z = 1.91 (P = 0.06)
40.1.2 Intermediate Risk
PARTNER 2A 98 1011 85 1021 16.4% 1.16 [0.88, 1.54]
SURTAVI 245 864 68 796 16.6% 3.32 [2.58, 4.27]
Subtotal (95% CI) 1875 1817 33.0% 1.97 [0.70, 5.51]
Total events 343 153
Heterogeneity: Tau² = 0.53; Chi² = 30.31, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.29 (P = 0.20)
40.1.3 High Risk
PARTNER 1A 19 348 16 351 12.7% 1.20 [0.63, 2.29]
US CoreValve 85 390 38 357 15.8% 2.05 [1.44, 2.92]
Subtotal (95% CI) 738 708 28.5% 1.68 [1.01, 2.79]
Total events 104 54
Heterogeneity: Tau² = 0.07; Chi² = 2.02, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 2.01 (P = 0.04)
40.1.4 All Risk
NOTION 51 142 3 134 8.1% 16.04 [5.13, 50.17]
Subtotal (95% CI) 142 134 8.1% 16.04 [5.13, 50.17]
Total events 51 3
Heterogeneity: Not applicable
Test for overall effect: Z = 4.77 (P < 0.00001)
Total (95% CI) 3976 3791 100.0% 2.23 [1.44, 3.46]
Total events 675 279
Heterogeneity: Tau² = 0.29; Chi² = 53.01, df = 6 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.57 (P = 0.0004)
Test for subgroup differences: Chi² = 12.78, df = 3 (P = 0.005), I² = 76.5%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

d. 2 Years

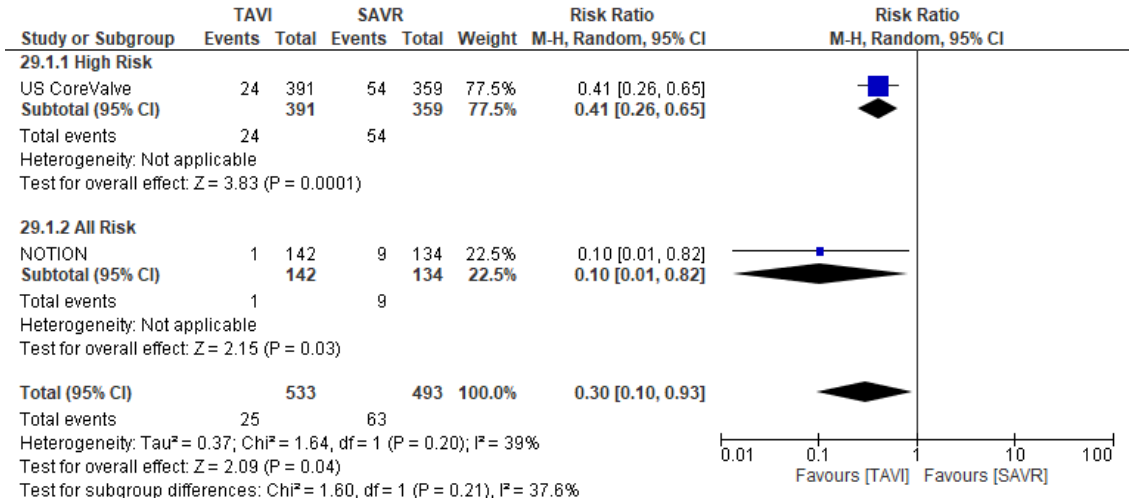

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
41.1.1 Low Risk
PARTNER 3 42 496 28 454 16.8% 1.37 [0.87, 2.18]
Subtotal (95% CI) 496 454 16.8% 1.37 [0.87, 2.18]
Total events 42 28
Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)
41.1.2 Intermediate Risk
SURTAVI 267 864 78 796 19.0% 3.15 [2.50, 3.98]
PARTNER 2A 114 1011 96 1021 18.8% 1.20 [0.93, 1.55]
Subtotal (95% CI) 1875 1817 37.8% 1.95 [0.75, 5.03]
Total events 381 174
Heterogeneity: Tau² = 0.45; Chi² = 29.90, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.38 (P = 0.17)
41.1.3 High Risk
US CoreValve 96 391 42 359 18.2% 2.10 [1.50, 2.93]
PARTNER 1A 23 348 19 351 15.3% 1.22 [0.68, 2.20]
Subtotal (95% CI) 739 710 33.5% 1.69 [1.01, 2.85]
Total events 119 61
Heterogeneity: Tau² = 0.09; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 1.99 (P = 0.05)
41.1.4 All Risk
NOTION 55 142 5 134 11.9% 10.38 [4.29, 25.14]
Subtotal (95% CI) 142 134 11.9% 10.38 [4.29, 25.14]
Total events 55 5
Heterogeneity: Not applicable
Test for overall effect: Z = 5.18 (P < 0.00001)
Total (95% CI) 3252 3115 100.0% 2.11 [1.31, 3.42]
Total events 597 268
Heterogeneity: Tau² = 0.30; Chi² = 49.12, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.06 (P = 0.002)
Test for subgroup differences: Chi² = 16.23, df = 3 (P = 0.001), I² = 81.5%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

e. 5 Years

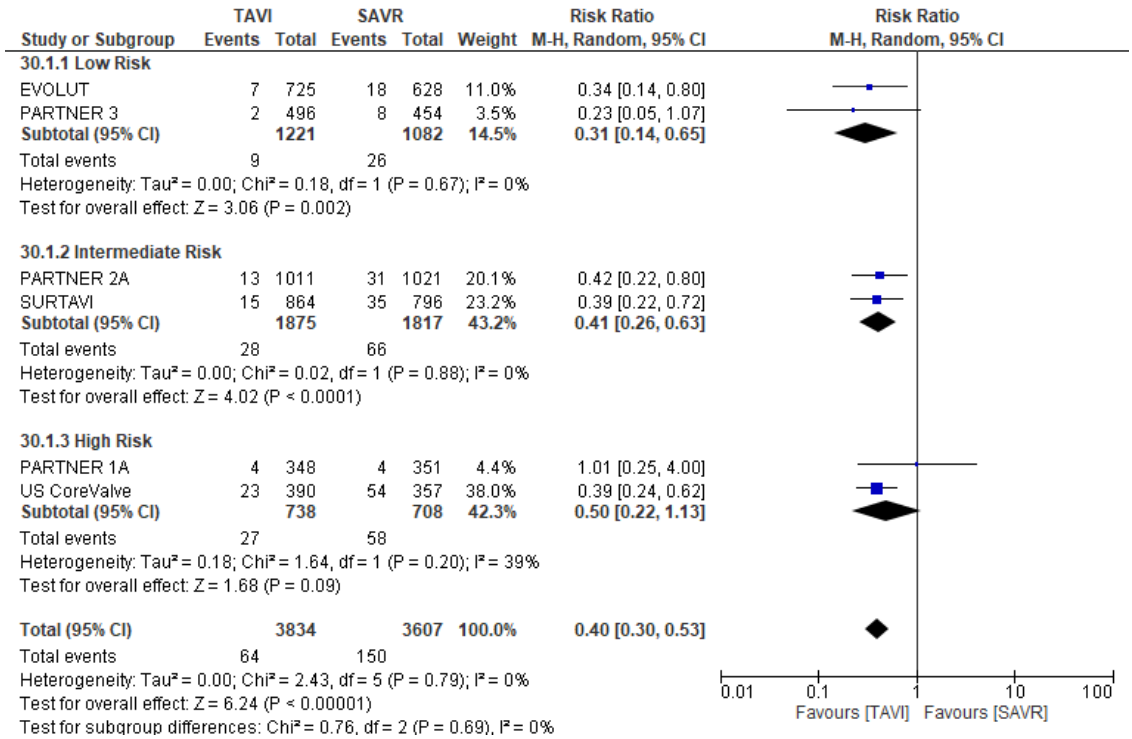

TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
42.1.1 Intermediate Risk
PARTNER 2A 138 1011 113 1021 28.7% 1.23 [0.98, 1.56]
Subtotal (95% CI) 1011 1021 28.7% 1.23 [0.98, 1.56]
Total events 138 113
Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)
42.1.2 High Risk
PARTNER 1A 28 348 23 351 22.9% 1.23 [0.72, 2.09]
US CoreValve 105 391 50 359 27.5% 1.93 [1.42, 2.62]
Subtotal (95% CI) 739 710 50.5% 1.62 [1.06, 2.50]
Total events 133 73
Heterogeneity: Tau² = 0.05; Chi² = 2.09, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 2.22 (P = 0.03)
42.1.3 All Risk
NOTION 58 145 10 135 20.9% 5.40 [2.88, 10.13]
Subtotal (95% CI) 145 135 20.9% 5.40 [2.88, 10.13]
Total events 58 10
Heterogeneity: Not applicable
Test for overall effect: Z = 5.26 (P < 0.00001)
Total (95% CI) 1895 1866 100.0% 1.90 [1.14, 3.16]
Total events 329 196
Heterogeneity: Tau² = 0.22; Chi² = 21.73, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Chi² = 18.79, df = 2 (P < 0.0001), I² = 89.4%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

SUPPLEMENTARY FIGURE S7: FOREST PLOTS FOR ACUTE KIDNEY INJURY

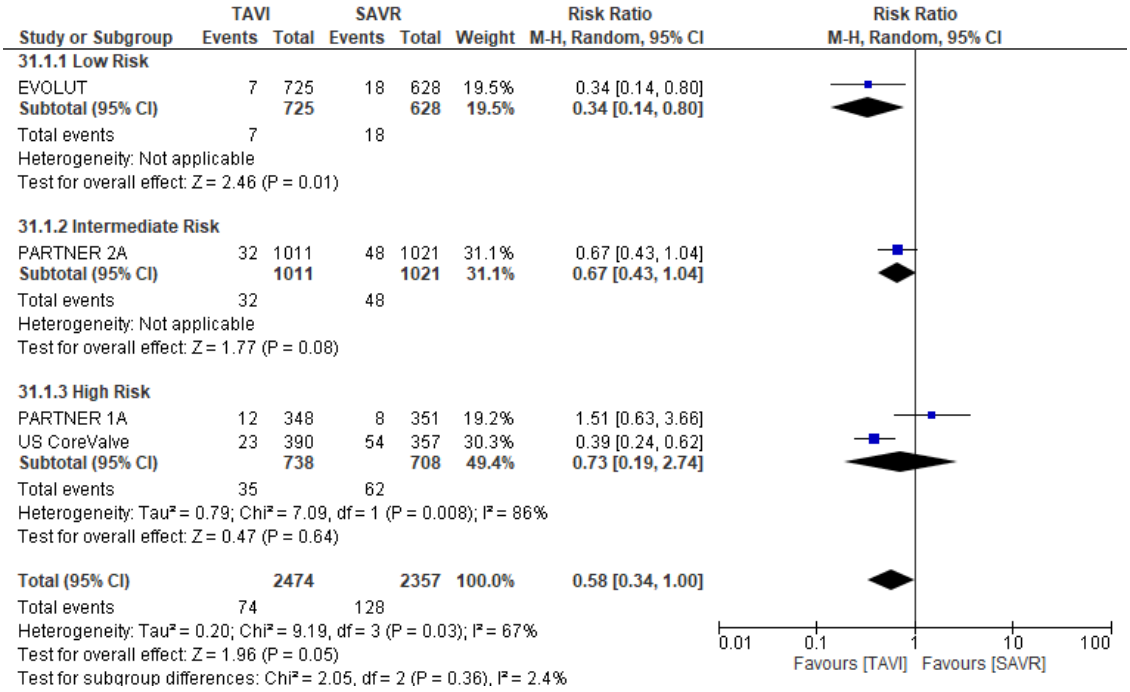
a. Periprocedural or In-Hospital



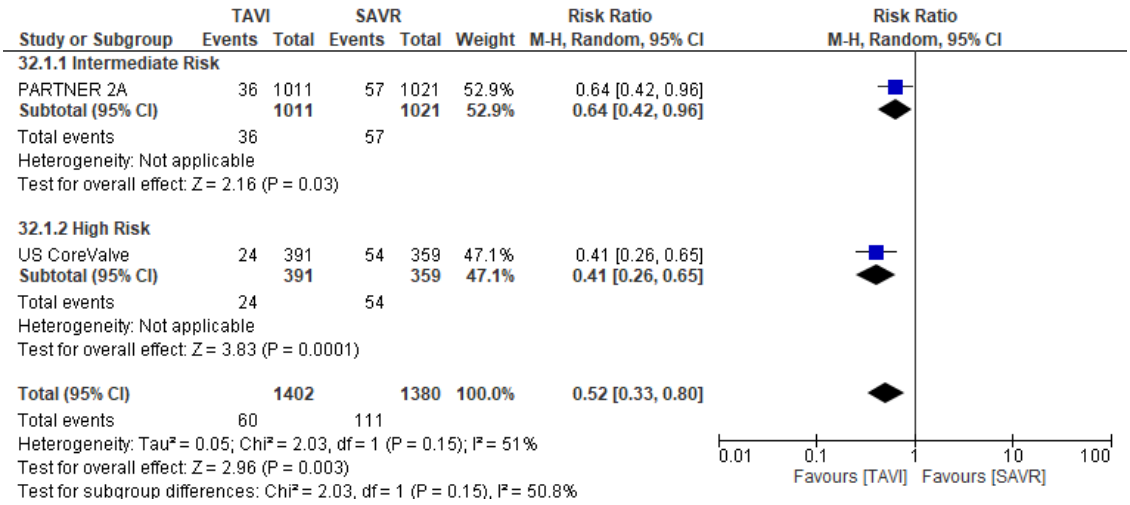
b. 30 Days



c. 1 Year

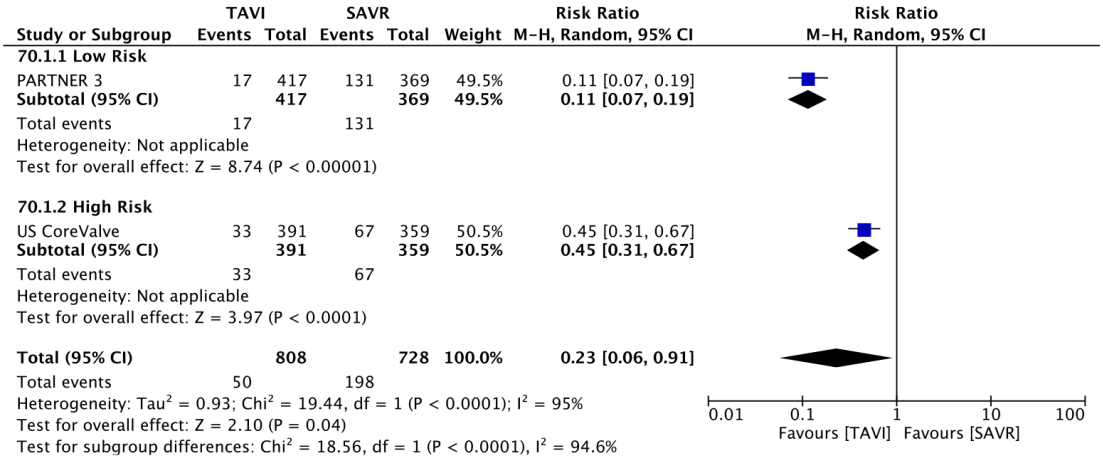


d. 2 Years

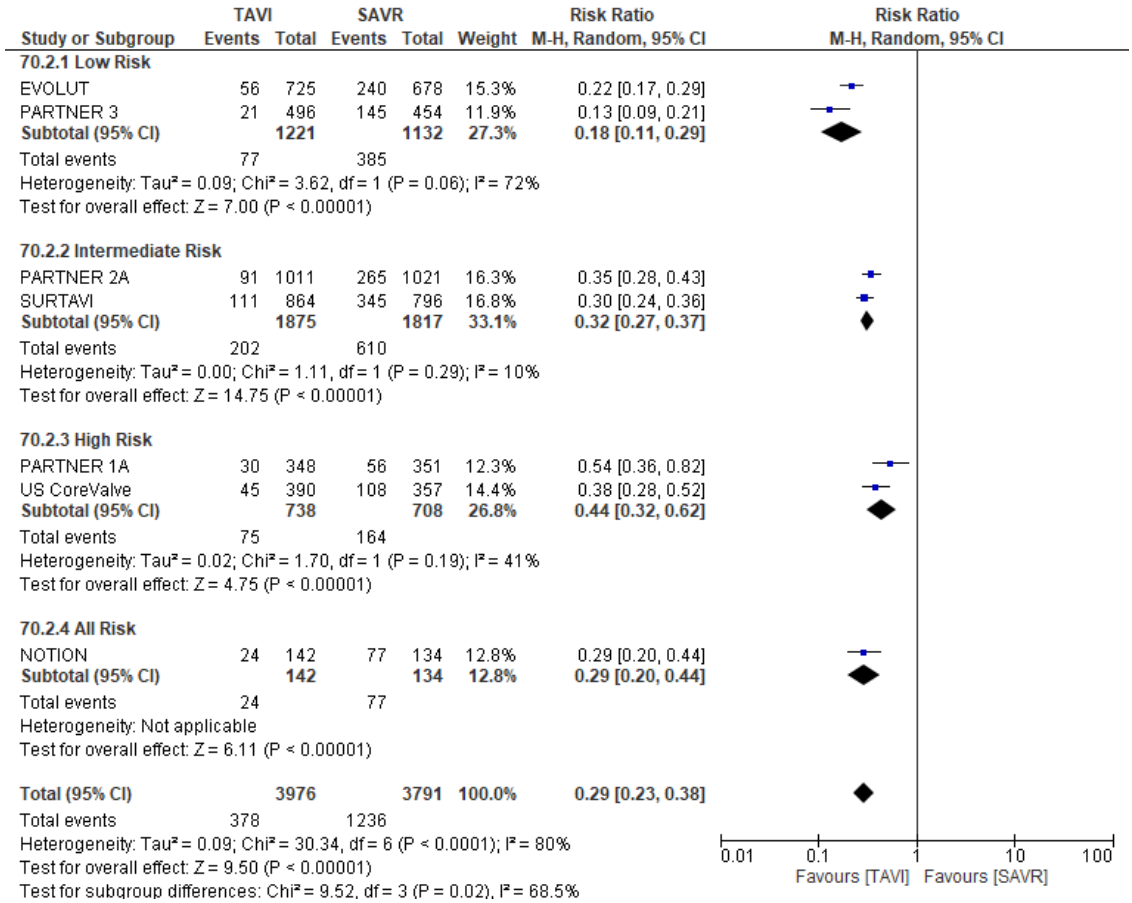


SUPPLEMENTARY FIGURE S8: FOREST PLOTS FOR NEW-ONSET OR WORSENING ATRIAL FIBRILLATION

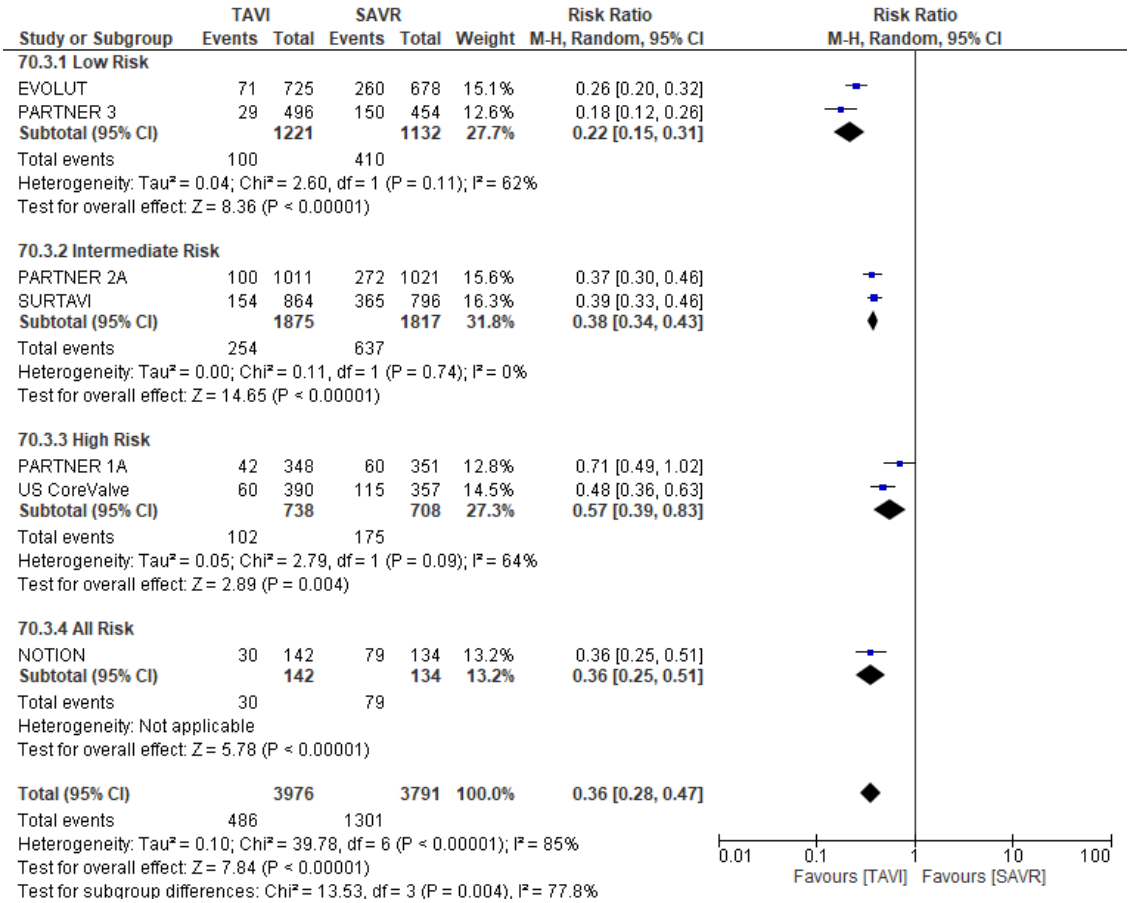
a. Periprocedural or In-Hospital



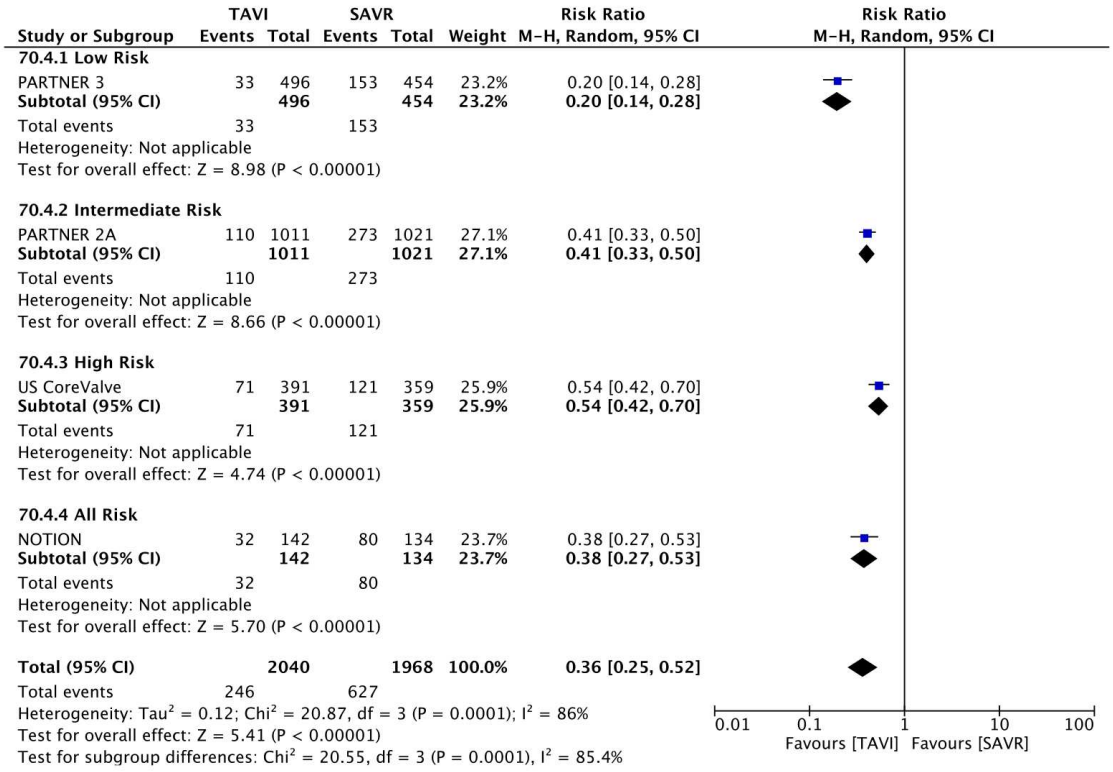
b. 30 Days


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
70.2.1 Low Risk
EVOLUT 56 725 240 678 15.3% 0.22 [0.17, 0.29]
PARTNER 3 21 496 145 454 11.9% 0.13 [0.09, 0.21]
Subtotal (95% CI) 1221 1132 27.3% 0.18 [0.11, 0.29]
Total events 77 385
Heterogeneity: Tau² = 0.09; Chi² = 3.62, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 7.00 (P < 0.00001)
70.2.2 Intermediate Risk
PARTNER 2A 91 1011 265 1021 16.3% 0.35 [0.28, 0.43]
SURTAVI 111 864 345 796 16.8% 0.30 [0.24, 0.36]
Subtotal (95% CI) 1875 1817 33.1% 0.32 [0.27, 0.37]
Total events 202 610
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%
Test for overall effect: Z = 14.75 (P < 0.00001)
70.2.3 High Risk
PARTNER 1A 30 348 56 351 12.3% 0.54 [0.36, 0.82]
US CoreValve 45 390 108 357 14.4% 0.38 [0.28, 0.52]
Subtotal (95% CI) 738 708 26.8% 0.44 [0.32, 0.62]
Total events 75 164
Heterogeneity: Tau² = 0.02; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 4.75 (P < 0.00001)
70.2.4 All Risk
NOTION 24 142 77 134 12.8% 0.29 [0.20, 0.44]
Subtotal (95% CI) 142 134 12.8% 0.29 [0.20, 0.44]
Total events 24 77
Heterogeneity: Not applicable
Test for overall effect: Z = 6.11 (P < 0.00001)
Total (95% CI) 3976 3791 100.0% 0.29 [0.23, 0.38]
Total events 378 1236
Heterogeneity: Tau² = 0.09; Chi² = 30.34, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 9.50 (P < 0.00001)
Test for subgroup differences: Chi² = 9.52, df = 3 (P = 0.02), I² = 68.5%
0.01
0.1
1
10
100
Favours [TAVI]
Favours [SAVR]

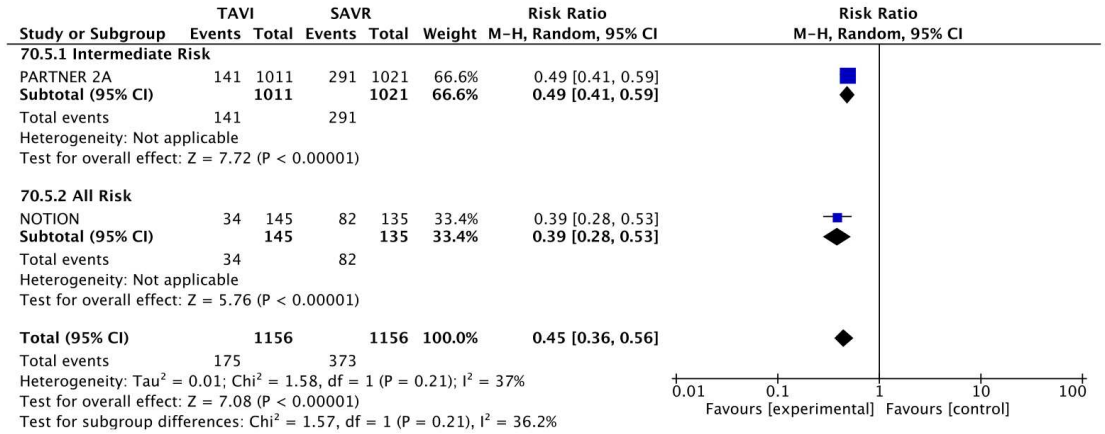
c. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
70.3.1 Low Risk
EVOLUT 71 725 260 678 15.1% 0.26 [0.20, 0.32]
PARTNER 3 29 496 150 454 12.6% 0.18 [0.12, 0.26]
Subtotal (95% CI) 1221 1132 27.7% 0.22 [0.15, 0.31]
Total events 100 410
Heterogeneity: Tau² = 0.04; Chi² = 2.60, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 8.36 (P < 0.00001)
70.3.2 Intermediate Risk
PARTNER 2A 100 1011 272 1021 15.6% 0.37 [0.30, 0.46]
SURTAVI 154 864 365 796 16.3% 0.39 [0.33, 0.46]
Subtotal (95% CI) 1875 1817 31.8% 0.38 [0.34, 0.43]
Total events 254 637
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 14.65 (P < 0.00001)
70.3.3 High Risk
PARTNER 1A 42 348 60 351 12.8% 0.71 [0.49, 1.02]
US CoreValve 60 390 115 357 14.5% 0.48 [0.36, 0.63]
Subtotal (95% CI) 738 708 27.3% 0.57 [0.39, 0.83]
Total events 102 175
Heterogeneity: Tau² = 0.05; Chi² = 2.79, df = 1 (P = 0.09); I² = 64%
Test for overall effect: Z = 2.89 (P = 0.004)
70.3.4 All Risk
NOTION 30 142 79 134 13.2% 0.36 [0.25, 0.51]
Subtotal (95% CI) 142 134 13.2% 0.36 [0.25, 0.51]
Total events 30 79
Heterogeneity: Not applicable
Test for overall effect: Z = 5.78 (P < 0.00001)
Total (95% CI) 3976 3791 100.0% 0.36 [0.28, 0.47]
Total events 486 1301
Heterogeneity: Tau² = 0.10; Chi² = 39.78, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: Chi² = 13.53, df = 3 (P = 0.004), I² = 77.8%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

d. 2 Years

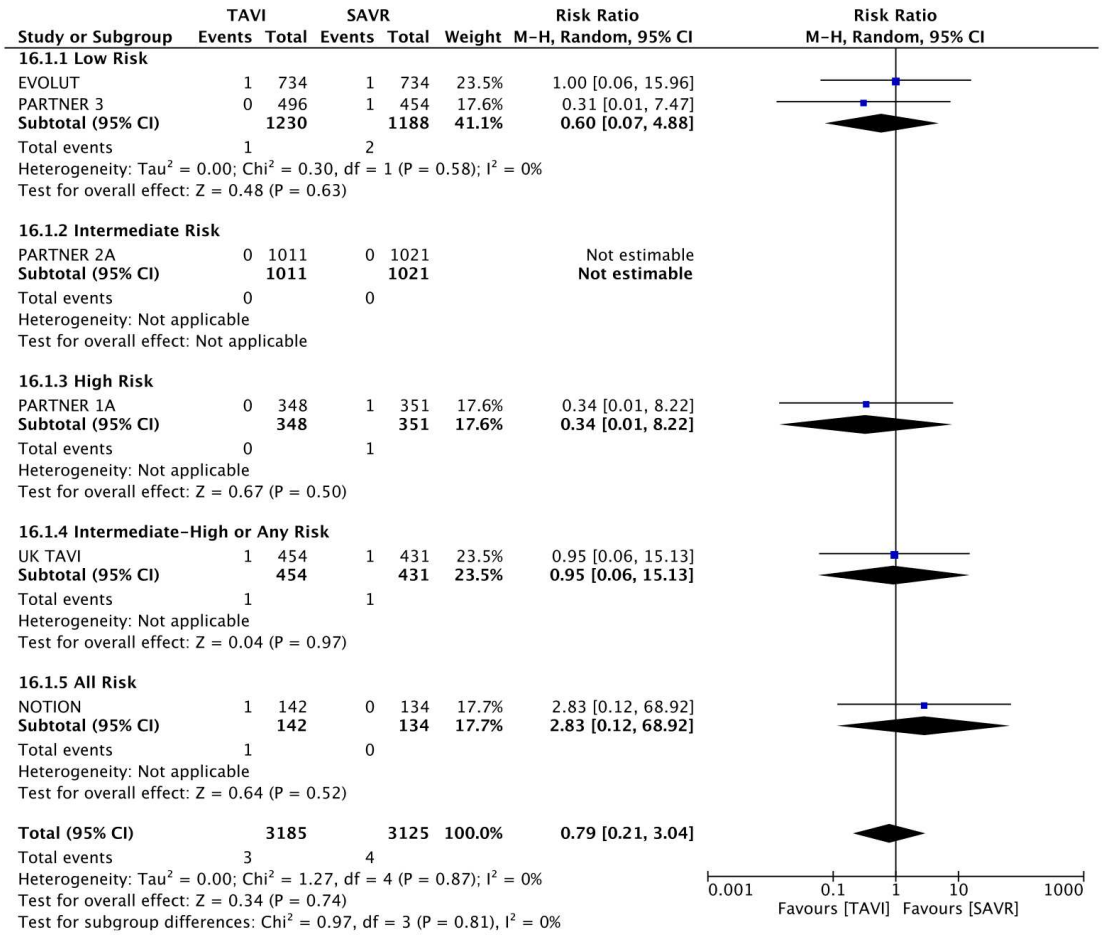


e. 5 Years

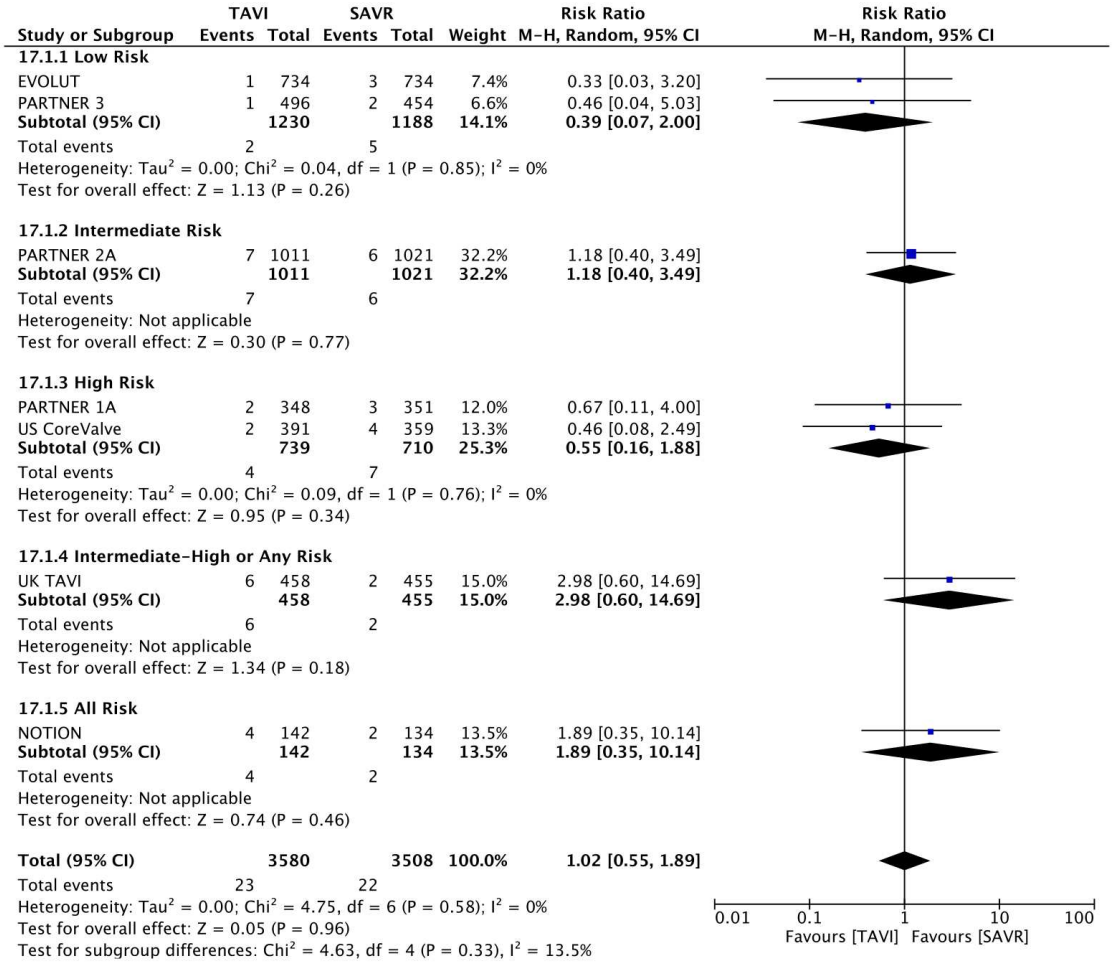


SUPPLEMENTARY FIGURE S9: FOREST PLOTS FOR ENDOCARDITIS

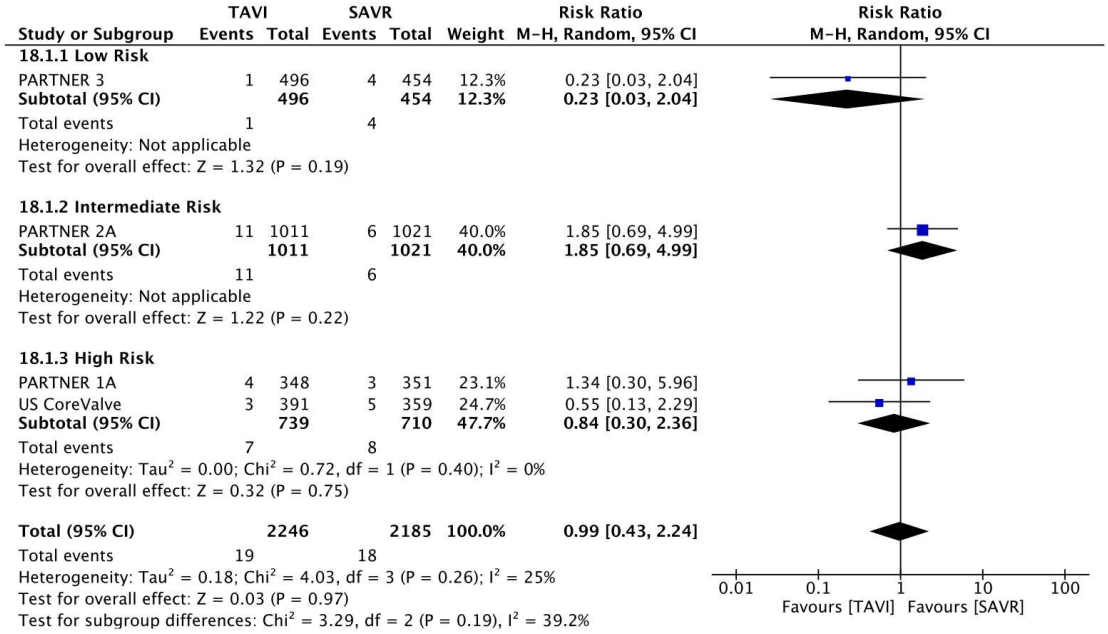
a. 30 Days



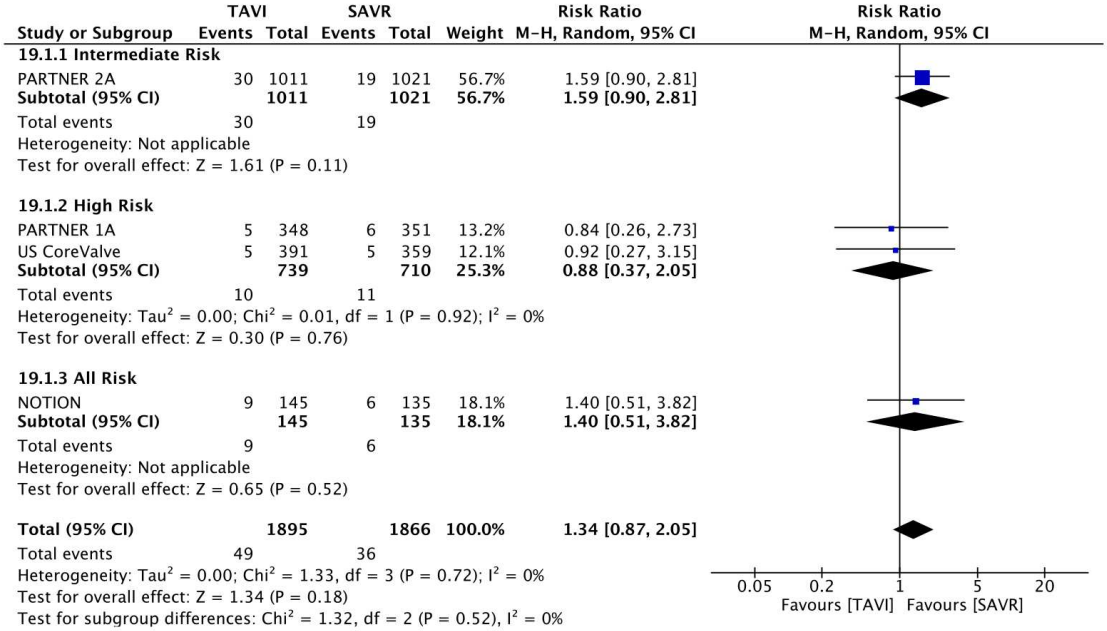
b. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
17.1.1 Low Risk
EVOLUT 1 734 3 734 7.4% 0.33 [0.03, 3.20]
PARTNER 3 1 496 2 454 6.6% 0.46 [0.04, 5.03]
Subtotal (95% CI) 1230 1188 14.1% 0.39 [0.07, 2.00]
Total events 2 5
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)
17.1.2 Intermediate Risk
PARTNER 2A 7 1011 6 1021 32.2% 1.18 [0.40, 3.49]
Subtotal (95% CI) 1011 1021 32.2% 1.18 [0.40, 3.49]
Total events 7 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
17.1.3 High Risk
PARTNER 1A 2 348 3 351 12.0% 0.67 [0.11, 4.00]
US CoreValve 2 391 4 359 13.3% 0.46 [0.08, 2.49]
Subtotal (95% CI) 739 710 25.3% 0.55 [0.16, 1.88]
Total events 4 7
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
17.1.4 Intermediate-High or Any Risk
UK TAVI 6 458 2 455 15.0% 2.98 [0.60, 14.69]
Subtotal (95% CI) 458 455 15.0% 2.98 [0.60, 14.69]
Total events 6 2
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
17.1.5 All Risk
NOTION 4 142 2 134 13.5% 1.89 [0.35, 10.14]
Subtotal (95% CI) 142 134 13.5% 1.89 [0.35, 10.14]
Total events 4 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)
Total (95% CI) 3580 3508 100.0% 1.02 [0.55, 1.89]
Total events 23 22
Heterogeneity: Tau² = 0.00; Chi² = 4.75, df = 6 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Chi² = 4.63, df = 4 (P = 0.33), I² = 13.5%
0.01 0.1 1 10 100
Favours [TAVI] Favours [SAVR]

c. 2 Years

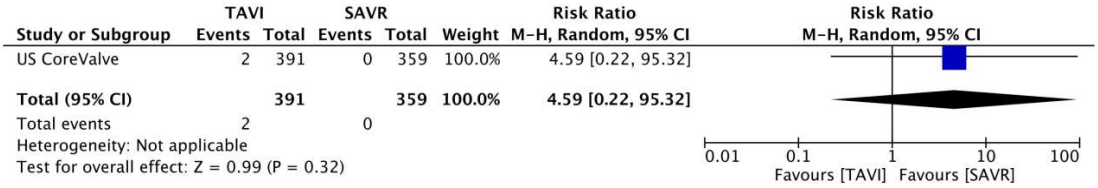


d. 5 Years

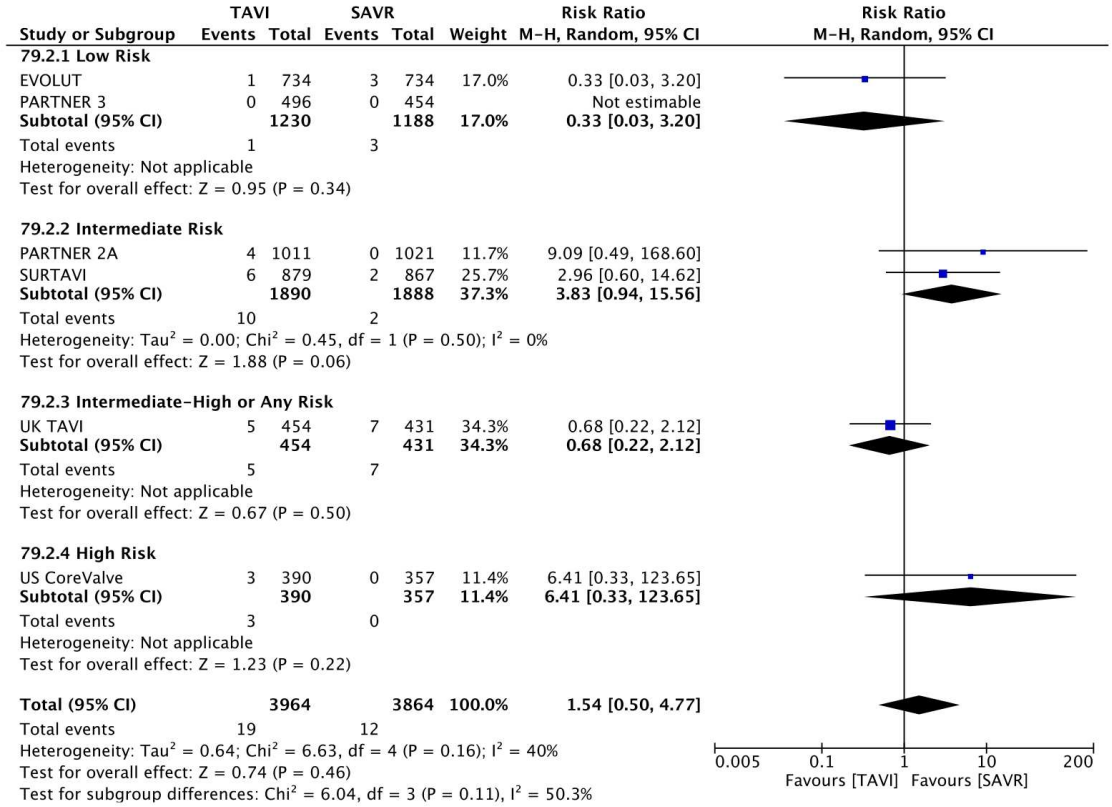


SUPPLEMENTARY FIGURE S10: FOREST PLOTS FOR REINTERVENTION OR REOPERATION

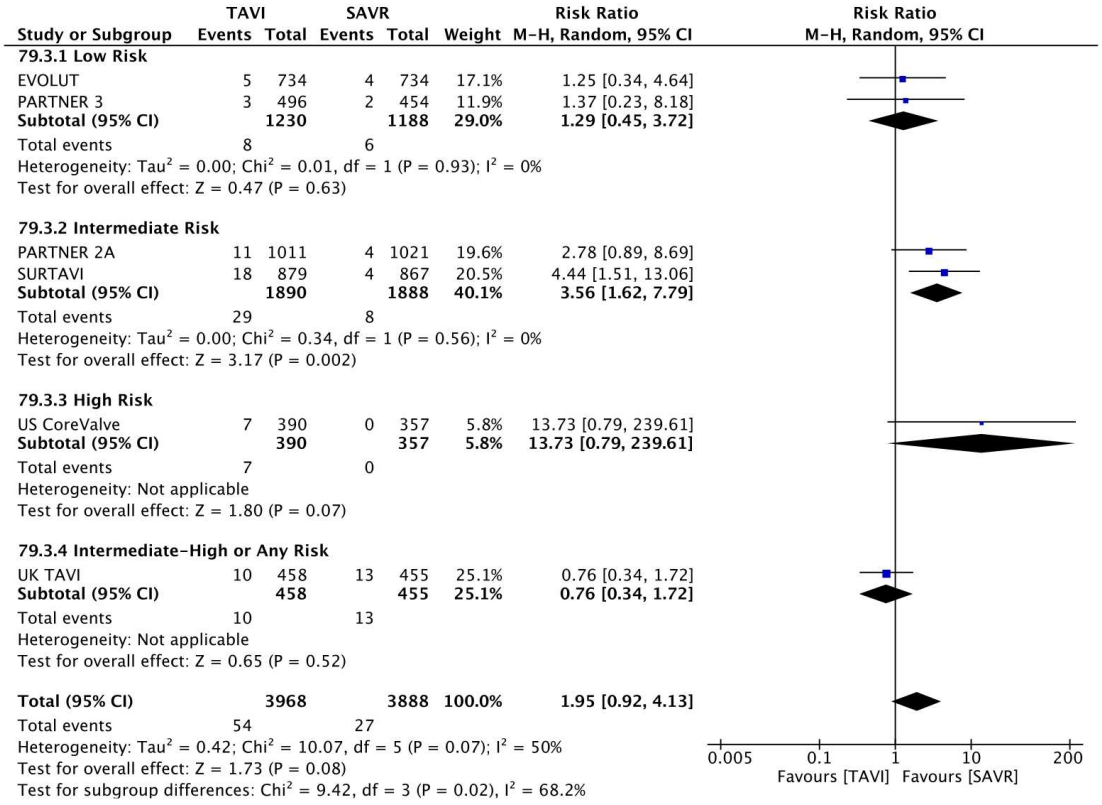
a. Periprocedural



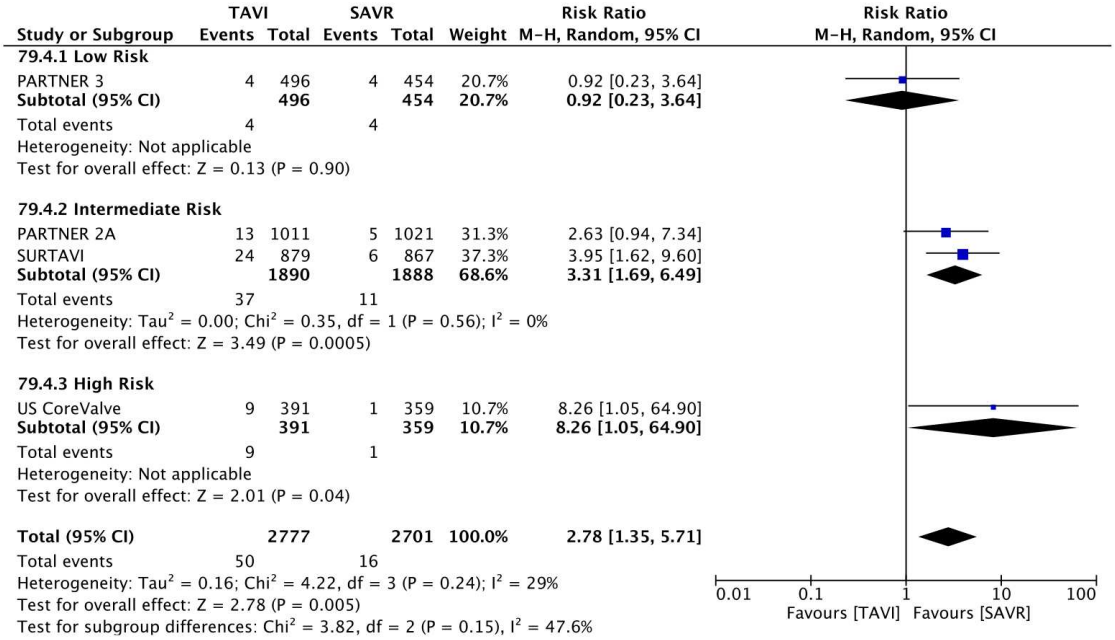
b. 30 Days



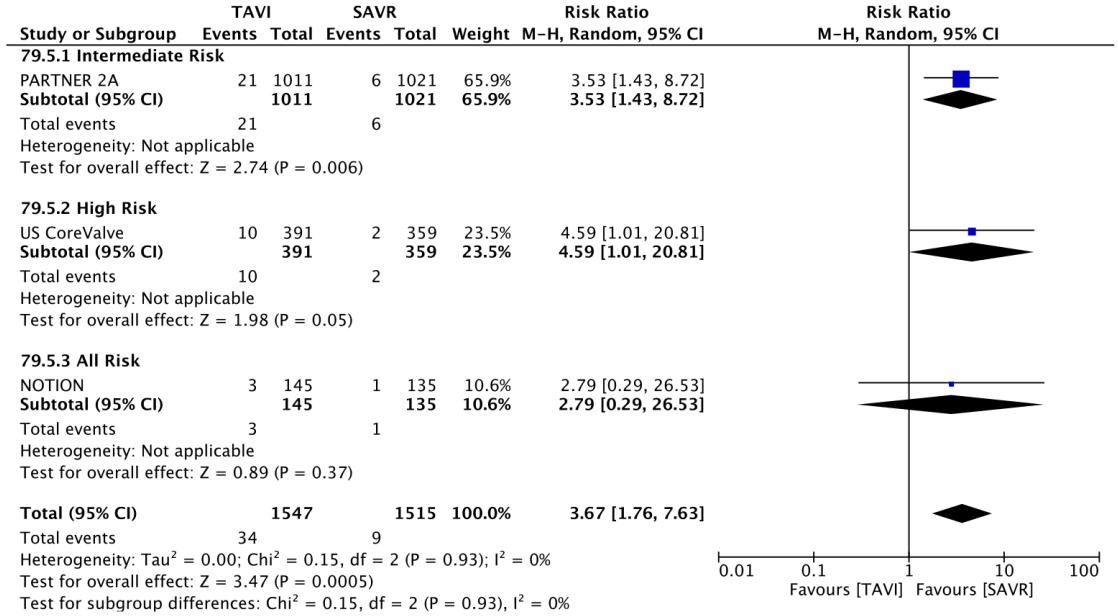
c. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
79.3.1 Low Risk
EVOLUT 5 734 4 734 17.1% 1.25 [0.34, 4.64]
PARTNER 3 3 496 2 454 11.9% 1.37 [0.23, 8.18]
Subtotal (95% CI) 1230 1188 29.0% 1.29 [0.45, 3.72]
Total events 8 6
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.63)
79.3.2 Intermediate Risk
PARTNER 2A 11 1011 4 1021 19.6% 2.78 [0.89, 8.69]
SURTAVI 18 879 4 867 20.5% 4.44 [1.51, 13.06]
Subtotal (95% CI) 1890 1888 40.1% 3.56 [1.62, 7.79]
Total events 29 8
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 3.17 (P = 0.002)
79.3.3 High Risk
US CoreValve 7 390 0 357 5.8% 13.73 [0.79, 239.61]
Subtotal (95% CI) 390 357 5.8% 13.73 [0.79, 239.61]
Total events 7 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.80 (P = 0.07)
79.3.4 Intermediate-High or Any Risk
UK TAVI 10 458 13 455 25.1% 0.76 [0.34, 1.72]
Subtotal (95% CI) 458 455 25.1% 0.76 [0.34, 1.72]
Total events 10 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)
Total (95% CI) 3968 3888 100.0% 1.95 [0.92, 4.13]
Total events 54 27
Heterogeneity: Tau² = 0.42; Chi² = 10.07, df = 5 (P = 0.07); I² = 50%
Test for overall effect: Z = 1.73 (P = 0.08)
Test for subgroup differences: Chi² = 9.42, df = 3 (P = 0.02), I² = 68.2%
0.005 0.1 1 10 200
Favours [TAVI] Favours [SAVR]

d. 2 Years

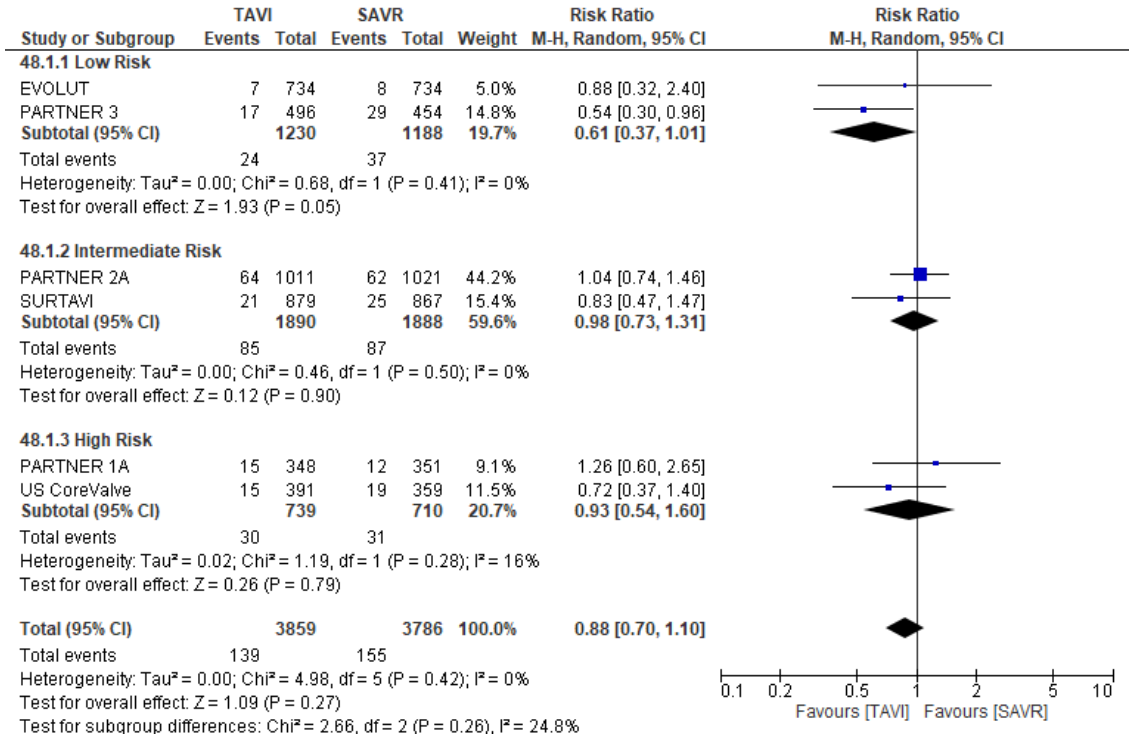


e. 5 Years

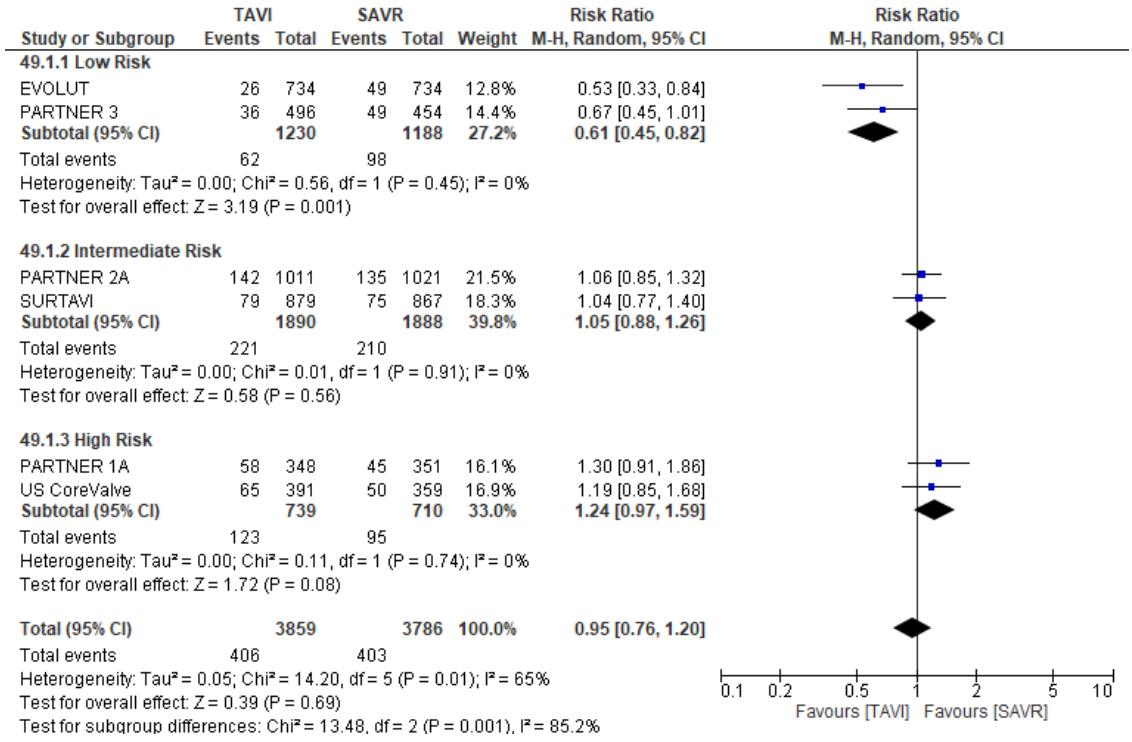


SUPPLEMENTARY FIGURE S11: FOREST PLOTS FOR REHOSPITALISATION

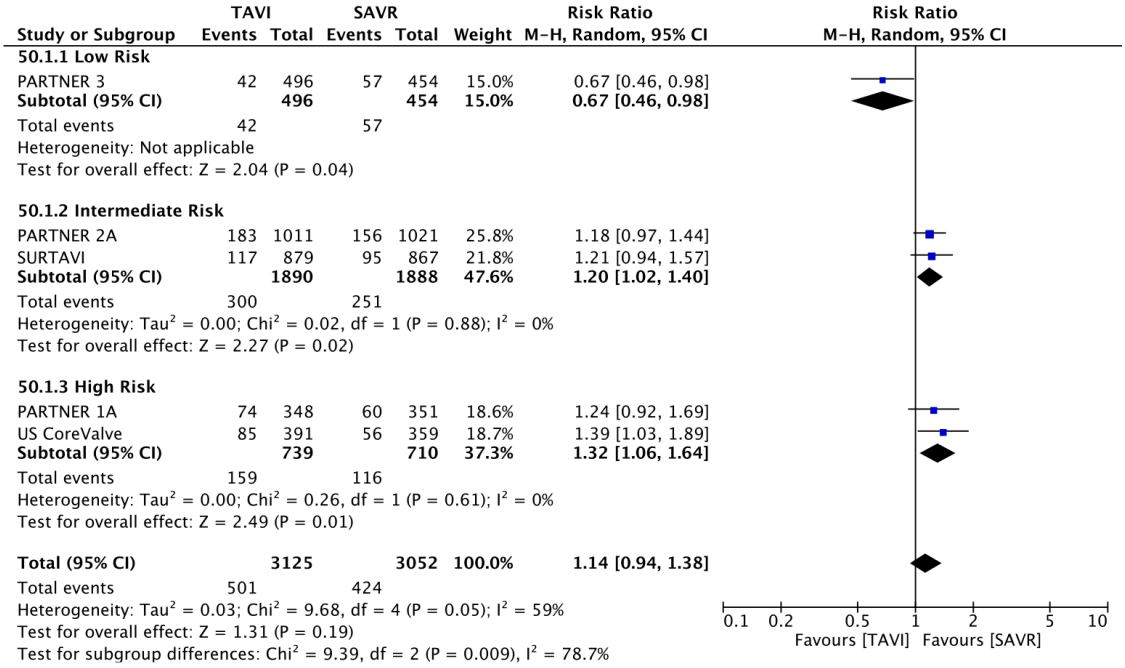
a. 30 Days



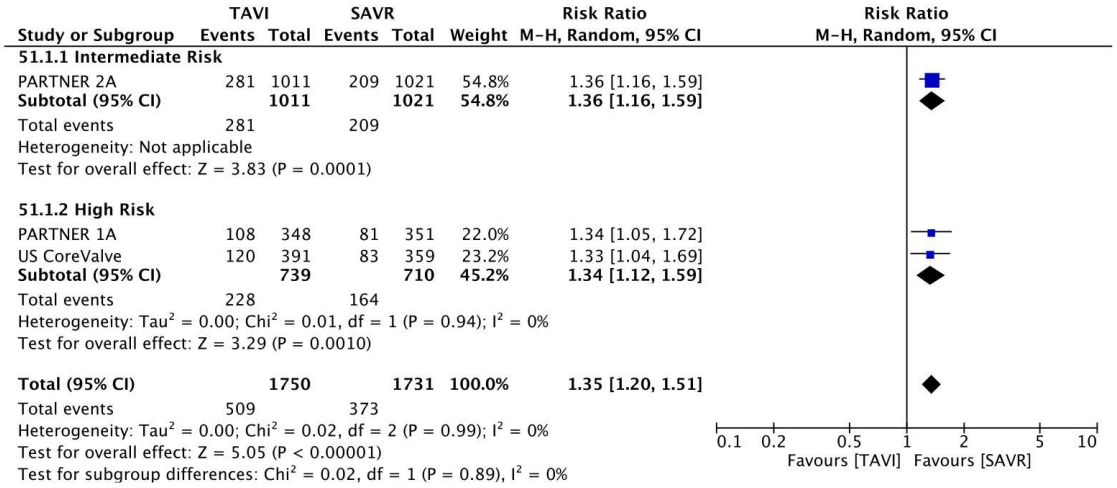
b. 1 Year


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
49.1.1 Low Risk
EVOLUT 26 734 49 734 12.8% 0.53 [0.33, 0.84]
PARTNER 3 36 496 49 454 14.4% 0.67 [0.45, 1.01]
Subtotal (95% CI) 1230 1188 27.2% 0.61 [0.45, 0.82]
Total events 62 98
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.19 (P = 0.001)
49.1.2 Intermediate Risk
PARTNER 2A 142 1011 135 1021 21.5% 1.06 [0.85, 1.32]
SURTAVI 79 879 75 867 18.3% 1.04 [0.77, 1.40]
Subtotal (95% CI) 1890 1888 39.8% 1.05 [0.88, 1.26]
Total events 221 210
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
49.1.3 High Risk
PARTNER 1A 58 348 45 351 16.1% 1.30 [0.91, 1.86]
US CoreValve 65 391 50 359 16.9% 1.19 [0.85, 1.68]
Subtotal (95% CI) 739 710 33.0% 1.24 [0.97, 1.59]
Total events 123 95
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.08)
Total (95% CI) 3859 3786 100.0% 0.95 [0.76, 1.20]
Total events 406 403
Heterogeneity: Tau² = 0.05; Chi² = 14.20, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 0.39 (P = 0.69)
Test for subgroup differences: Chi² = 13.48, df = 2 (P = 0.001), I² = 85.2%
0.1 0.2 0.5 1 2 5 10
Favours [TAVI] Favours [SAVR]

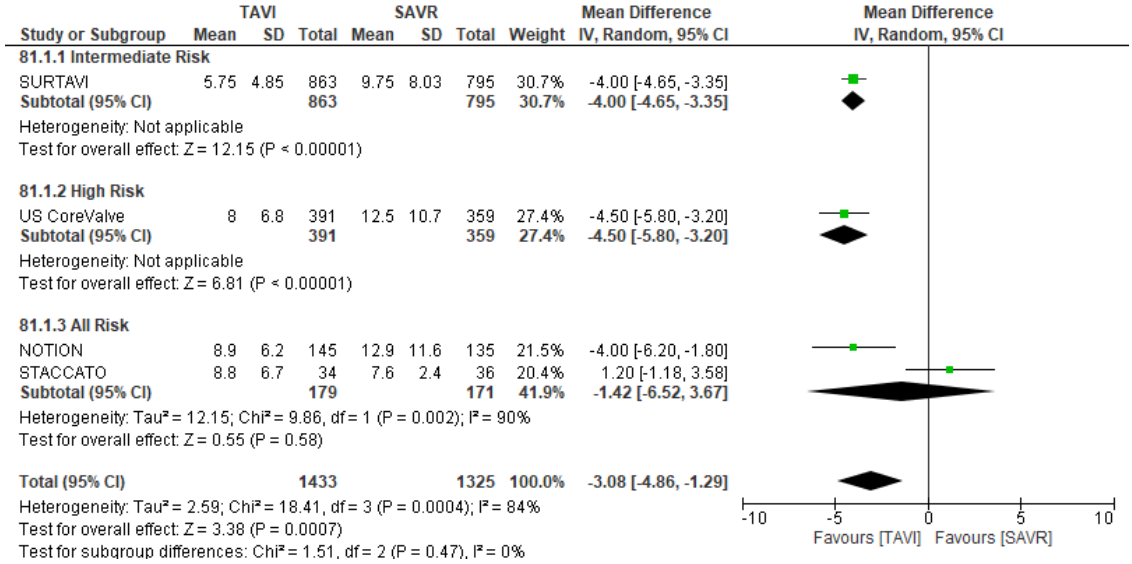
c. 2 Years


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
50.1.1 Low Risk
PARTNER 3 42 496 57 454 15.0% 0.67 [0.46, 0.98]
Subtotal (95% CI) 496 454 15.0% 0.67 [0.46, 0.98]
Total events 42 57
Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)
50.1.2 Intermediate Risk
PARTNER 2A 183 1011 156 1021 25.8% 1.18 [0.97, 1.44]
SURTAVI 117 879 95 867 21.8% 1.21 [0.94, 1.57]
Subtotal (95% CI) 1890 1888 47.6% 1.20 [1.02, 1.40]
Total events 300 251
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%
Test for overall effect: Z = 2.27 (P = 0.02)
50.1.3 High Risk
PARTNER 1A 74 348 60 351 18.6% 1.24 [0.92, 1.69]
US CoreValve 85 391 56 359 18.7% 1.39 [1.03, 1.89]
Subtotal (95% CI) 739 710 37.3% 1.32 [1.06, 1.64]
Total events 159 116
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)
Total (95% CI) 3125 3052 100.0% 1.14 [0.94, 1.38]
Total events 501 424
Heterogeneity: Tau² = 0.03; Chi² = 9.68, df = 4 (P = 0.05); I² = 59%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Chi² = 9.39, df = 2 (P = 0.009), I² = 78.7%
0.1 0.2 0.5 1 2 5 10
Favours [TAVI] Favours [SAVR]

d. 5 Years


TAVI
SAVR
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
51.1.1 Intermediate Risk
PARTNER 2A 281 1011 209 1021 54.8% 1.36 [1.16, 1.59]
Subtotal (95% CI) 1011 1021 54.8% 1.36 [1.16, 1.59]
Total events 281 209
Heterogeneity: Not applicable
Test for overall effect: Z = 3.83 (P = 0.0001)
51.1.2 High Risk
PARTNER 1A 108 348 81 351 22.0% 1.34 [1.05, 1.72]
US CoreValve 120 391 83 359 23.2% 1.33 [1.04, 1.69]
Subtotal (95% CI) 739 710 45.2% 1.34 [1.12, 1.59]
Total events 228 164
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.29 (P = 0.0010)
Total (95% CI) 1750 1731 100.0% 1.35 [1.20, 1.51]
Total events 509 373
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 5.05 (P < 0.00001)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours [TAVI] Favours [SAVR]

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.org[10]

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.org[10]

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.org[10]

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

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[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

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[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.