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SYSTEMATIC REVIEW AND META-ANALYSIS

Ross Procedure Versus Mechanical Versus Bioprosthetic Aortic Valve Replacement: A Network Meta-Analysis

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BACKGROUND: The Ross operation appears to restore normal survival in young and middle-aged adults with aortic valve disease. However, there are limited data comparing it with conventional aortic valve replacement. Herein, we compared outcomes of the Ross procedure with mechanical and bioprosthetic aortic valve replacement (M-AVR and B-AVR, respectively).

METHODS AND RESULTS: MEDLINE and EMBASE were searched through March 2022 to identify randomized controlled trials and propensity score–matched studies that investigated outcomes of patients aged ≥16 years undergoing the Ross procedure, M-AVR, or B-AVR. The systematic literature search identified 2 randomized controlled trials and 8 propensity score–matched studies involving a total of 4812 patients (Ross: n=1991; M-AVR: n=2019; and B-AVR: n=802). All-cause mortality was significantly lower in the Ross procedure group compared with M-AVR (hazard ratio [HR] [95% CI], 0.58 [0.35–0.97]; *P*=0.035) and B-AVR (HR [95% CI], 0.32 [0.18–0.59]; *P*<0.001) groups. The reintervention rate was lower after the Ross procedure and M-AVR compared with B-AVR, whereas it was higher after the Ross procedure compared with M-AVR. Major bleeding rate was lower after the Ross procedure compared with M-AVR. Long-term stroke rate was lower following the Ross procedure compared with M-AVR and B-AVR. The rate of endocarditis was also lower after the Ross procedure compared with B-AVR.

CONCLUSIONS: Improved long-term outcomes of the Ross procedure are demonstrated compared with conventional M-AVR and B-AVR options. These results highlight a need to enhance the recognition of the Ross procedure and revisit current guidelines on the optimal valve substitute for young and middle-aged patients.

Key Words: aortic valve substitute ■ bioprosthetic aortic valve replacement ■ mechanical aortic valve replacement ■ Ross procedure ■ surgical aortic valve replacement

The landscape of aortic valve therapy has evolved substantially over the past few decades. Transcatheter aortic valve replacement (TAVR) has become an established alternative to bioprosthetic surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and appropriate anatomical features, irrespective of patient risk profile.[1–4] In addition, further expansion of TAVR indications now includes bicuspid pathology.[5] However, the ideal aortic valve substitute for young and middle-aged adults remains debated.

Among the available aortic valve substitute options, the conventional option has been to use either a mechanical or a bioprosthetic valve, although the use of bioprostheses has increased substantially in the past 2 decades.[6,7] Bioprosthetic SAVR or TAVR for young/middle-aged individuals may be regarded as a

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CLINICAL PERSPECTIVE

What Is New?

- Our meta-analysis of 2 randomized control trials and 8 propensity score–matched studies showed that the Ross procedure was associated with improved late clinical end points, including all-cause mortality and stroke, compared with conventional mechanical and bioprosthetic aortic valve replacement.
- The Ross procedure was associated with lower rates of endocarditis compared with bioprosthetic aortic valve replacement and lower rates of permanent pacemaker implantation and bleeding compared with mechanical aortic valve replacement.

What Are the Clinical Implications?

- Our results highlight a need to enhance the recognition of the Ross procedure and revisit the optimal valve substitute selection in the guidelines for young and middle-aged patients needing an aortic valve replacement.

Nonstandard Abbreviations and Acronyms

B-AVR	bioprosthetic aortic valve replacement
M-AVR	mechanical aortic valve replacement
PSM	propensity score matched
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement

noncurative measure, as it inevitably requires at least ≥1 reoperations in the future. Mechanical prostheses have been implanted for the benefit of durability at the expense of more major bleeding or thromboembolic events. However, the use of mechanical prostheses does not eliminate the risk of reoperation. It is associated with reoperation rates ranging between 7% and 10% by 15 years after implantation.[6,8,9] The Ross procedure, also known as the pulmonary autograft procedure, is a surgical technique in which the diseased aortic valve is removed and replaced with the patient's own pulmonary valve, and a human homograft valve is attached where the pulmonary valve was removed. Several long-term observational studies of the Ross procedure, some of which contain series of contemporary modifications of surgical techniques, have shown favorable results.[10–18] Despite the large body of cumulative evidence demonstrating restored survival after the Ross procedure, the recognition of the Ross procedure in our community remains sparse. In the 2020 American College of Cardiology/American Heart Association valve guidelines, there is a class IIb recommendation for use of the Ross procedure in patients aged <50 years,[19] whereas there is no description of the Ross procedure in the 2021 European guidelines.[20] One of the reasons for the poor recognition of the Ross procedure despite the uniformly excellent long-term outcomes includes an inadequate number of prospective randomized controlled trials (RCTs), scattered reports with inconsistent study designs with or without control groups, and perhaps limited availability of the Ross procedure.

In this context, we compared the Ross procedure with mechanical and bioprosthetic aortic valve replacement (M-AVR and B-AVR, respectively) by applying the latest methods of network meta-analysis to provide insights for the choice of valve options in young and middle-aged adults.

METHODS

Given the nature of the study, this study was deemed exempt from institutional review board review or written informed consent for publication by all participating institutions. The data that support the findings of this study are available from the corresponding author on reasonable request. Network meta-analysis performed in this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[21]

Protocol and Registration

The study protocol was registered on PROSPERO (identifier=319471).

Eligibility Criteria

Included studies met the following criteria: the research was peer reviewed with comparative study designs and included either RCTs or propensity score–matched (PSM) studies that reported clinical outcomes in patients aged ≥16 years who underwent SAVR or aortic root replacement using the Ross procedure, M-AVR, or B-AVR. Patients who received an aortic homograft (n=108)[10] were assigned to the B-AVR group.

Information Source and Search

All RCTs and PSM studies that investigated clinical outcomes in patients aged ≥16 years who underwent the Ross procedure, M-AVR, or B-AVR were identified using a 2-level strategy. First, a database, including MEDLINE and EMBASE, was searched through March 19, 2022, using Web-based search engines (PubMed and OVID). Search terms included the following: "Ross procedure" or "autograft" and "mechanical valve" or "bioprosthetic valve" or "homograft" and "aortic valve

replacement" or "aortic root replacement" and "randomized" or "randomize" or "propensity" or "propensity-score". Language restriction was not applied.

Study Selection and Data Collection Process

Relevant studies were identified through a manual search of secondary sources, including references of initially identified articles, reviews, and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analyses. Two independent and blinded authors (Y.Y. and S.F.) reviewed the search results separately to select the studies based on present inclusion and exclusion criteria. Disagreements were resolved by consensus.

Data Items

We sought the data according to the following PICOS: P (population), patients aged ≥16 years with aortic valve diseases; I (intervention), the Ross procedure; C (comparison), M-AVR and B-AVR; O (outcome), short- and long-term outcomes; and S (study type), RCTs and PSM studies.

Risk of Bias in Individual Studies

Study quality was assessed by 2 independent and blinded authors (Y.Y. and S.F.) using the Cochrane Collaboration risk of bias 2.0 tool for an RCT[22] and the Newcastle-Ottawa Scale for observational studies.[23] Disagreements were resolved by consensus.

Summary Measures

The outcomes of interest were short-term outcomes, including 30-day mortality and rates of stroke, myocardial infarction, permanent pacemaker implantation, new-onset atrial fibrillation, and reoperation for bleeding; and long-term outcomes, including all-cause mortality and rates of reintervention, major bleeding, long-term stroke, and infectious endocarditis. Reinterventions include both aortic and pulmonary valve reinterventions for the Ross procedure group. The definition of each outcome was applied according to each study protocol. We extracted the risk ratios (RRs) for short-term outcomes and hazard ratios (HRs) for long-term outcomes from each study. If HR was not described in a study, HR was calculated from a Kaplan-Meier curve[24] using the spreadsheet programmed to estimate the overall HR with 95% CI with an inverse variance-weighted average, which was provided by Tierney et al[25] based on standard statistical methods reported by Parmar et al[26] and Williamson et al.[27] If a Kaplan-Meier curve was not provided in a study, RRs were calculated from the event number and the patient number.

Synthesis of Results and Risk of Bias Across Studies

We performed a network meta-analysis using "netmeta" 3.6.2 package (R Foundation for Statistical Computing, Vienna, Austria). Within the framework, I^2 and the Q statistics, which represent the proportion of total variation in study estimates attributable to heterogeneity, were used to quantify heterogeneity. The I^2 statistic represents the proportion of variability that is not attributable to chance. We used the random-effects model for the analysis. The procedures were ranked using *P* scores of 0% to 100%, where higher scores indicate more effective or safer procedures compared with those with lower scores. Funnel plot asymmetry, suggesting publication bias, was assessed using Egger linear regression test.[28]

RESULTS

Study Selection

The database search identified 102 articles that were reviewed on the basis of the title and abstract. Of those, 71 articles were excluded on the basis of the titles and abstracts. In addition, 21 articles were excluded with the following reasons: n=10: no comparison or control groups; n=4: neither randomized nor PSM; n=3: pediatric patients aged <16 years; n=2: review article; n=1: no outcomes of interest reported; and n=1: trial protocol. Ten articles met the inclusion criteria and were assessed for the systematic review and the meta-analysis[10–18,29] (Figure S1). Of those, 2 were RCTs[10,29] and 8 were PSM studies,[11–18] which enrolled a total of 4812 patients who received the Ross procedure (n=1991), M-AVR (n=2019), or B-AVR (n=802).

Study Characteristics

Study profiles and patient characteristics are summarized in the Table. Three articles were from Canada,[12,14,18] 2 each were from Germany[11,29] and the United Kingdom,[10,13] and 1 each was from Australia,[15] Czech Republic,[16] and the United States.[18] Six articles were single-center studies,[10,12,14,15,18,29] and 4 were registry-based studies.[11,13,16,17] Although 30-day mortality was reported in 7 articles,[10,12,14–16,18,29] no events were observed in 4 studies. Therefore, we could not analyze the 30-day mortality. The number of articles that provided each outcome are follows: stroke, 6[10,12,14,16–18]; myocardial infarction, 5[12,14,16–18]; permanent pacemaker implantation, 4[10,14–16]; new-onset atrial fibrillation, 5[10,12,14,17,18]; reoperation for bleeding, 5[10,14,16,18,29]; all-cause mortality, 9[10–13,15–18,29]; reintervention, 7[10–12,16–18,29]; major bleeding, 5[10–12,17,29]; long-term stroke, 5[10–12,17,18]; and endocarditis, 5.[10–12,17,18] The definition of each outcome was shown in Table S1. Inclusion age criteria and exclusion

Table. Patient Characteristics and Study Profiles

Author	Doss[29]	El-Hamamsy[10]	Mokhles[11]	Mazine[12]	Sharabiani[13]	Bouhout[14]	Buratto[15]	Gofus[16]	El-Hamamsy[17]	Mazine[18]
Year	2005	2010	2011	2016	2016	2017	2018	2022	2022	2022
Periods	1999–2001	1994–2001	1994–2008	1990–2014	2000–2012	2007–2015	1992–2016	2009–2020	1997–2014	1990–2014
Follow-up	1 y	10.2±3.2 y	5.1 vs 6.3 y	14.2±6.5 y	5.3 (2.1–8.6) y	30 d	10±7 y	4.1 vs 6.1 y	12.5 (9.3–15.7) y	14.5±7.2 y
Design	RCT	RCT	PSM study	PSM study	PSM study	PSM study	PSM study	PSM study	PSM study	PSM study
Patients, n	40	216	506	416	844	140	550	582	1302	216
Ross, n	20	108	253	208	224	70	275	291	434	108
Mechanical, n	20	N/A	253	208	468	70	275	291	434	N/A
Bioprosthetic, n	N/A	108	N/A	N/A	152	N/A	N/A	N/A	434	108
Median age, y	49	N/A	47.6±9.8	37±10	N/A	52±10	44±11	42	36±9	41 (34–47)
Men, %	57	88	75	63	N/A	71	72	76	75	69
Hypertension, %	33	23	33	20	N/A	22	21	38	18	18
Dyslipidemia, %	N/A	3.2	N/A	11	N/A	7.8	N/A	20	N/A	13
Diabetes, %	N/A	1.4	4	1.9	N/A	19	1	1.7	0.2	2.5
COPD, %	N/A	N/A	2.8	1.2	N/A	6.4	5	6	4	0.9
CAD, %	N/A	N/A	N/A	N/A	N/A	2.1	N/A	7	N/A	N/A
CKD, %	N/A	6	N/A	N/A	N/A	4.3	N/A	N/A	N/A	N/A
CVD, %	N/A	N/A	N/A	4.1	N/A	N/A	5	2.6	0.3	1.9
Afib, %	2.5	2.8	N/A	2.2	N/A	2.1	N/A	N/A	4	0.9
Pacemaker, %	N/A	2.3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AS, %	100	30	32	45	N/A	69	46	28	N/A	52
AR, %	0	44	18	37	N/A	14	34	34	N/A	26
Mixed AS/AR, %	N/A	26	47	18	N/A	17	20	38	N/A	22
Aneurysm, %	N/A	1.4	N/A	N/A	N/A	36	N/A	N/A	N/A	N/A
Degenerative, %	N/A	44	80	65	N/A	N/A	N/A	3.5	N/A	N/A
Congenital, %	N/A	50	N/A	9.3	N/A	N/A	N/A	89	N/A	N/A
Rheumatic, %	N/A	6	7	7.2	N/A	N/A	N/A	0	N/A	N/A
Endocarditis, %	0	N/A	N/A	2.2	N/A	N/A	0	6	N/A	N/A
Previous intervention, %	N/A	43	3.2	20	N/A	0	9	9	N/A	N/A
Elective, %	100	88	N/A	N/A	N/A	100	100	N/A	N/A	N/A
Urgent/emergent, %	0	12	N/A	N/A	N/A	0	0	1.9	N/A	N/A
Concomitant CABG, %	2.5	N/A	13	2.9	N/A	N/A	N/A	N/A	N/A	N/A

Follow-up periods are expressed as numbers, means ± standard deviations, or medians (interquartile range).

Afib indicates atrial fibrillation; AR, aortic regurgitation; AS, aortic stenosis; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; N/A, not applicable; PSM, propensity score matched; and RCT, randomized control trial.

criteria were summarized in Table S2. Variables used in PSM studies were summarized in Table S3.

Risk of Bias Within Studies

The quality of observational studies was shown in Figure S2 and Table S4. All the PSM studies were considered as having low risk of bias.

Short-Term Outcomes

In the network meta-analysis of 2 studies comparing the Ross and B-AVR, 3 studies for the Ross and M-AVR, and 1 study for B-AVR and M-AVR, the rate of permanent pacemaker implantation was significantly lower in the Ross procedure compared with M-AVR (RR [95% CI], 0.53 [0.31–0.91]; P=0.021; I^2=66.6%) (Figure 1). There was no inconsistency (P=0.93). No significant difference was observed between the Ross and B-AVR or between M-AVR and B-AVR. Other short-term outcomes, including rates of stroke, myocardial infarction, new-onset atrial fibrillation, and reoperation for bleeding, were similar among the groups (Figure S3). There was no inconsistency for each outcome (P=0.36, P=0.55, and P=0.18 for stroke, myocardial infarction, and new-onset atrial fibrillation, respectively).

Long-Term Outcomes

Mean follow-up periods were 7.4 years (range, 1–14.5 years).

All-cause mortality (4 studies for the Ross versus B-AVR and 6 studies for the Ross versus M-AVR) was significantly lower in patients with the Ross procedure compared with M-AVR (HR [95% CI], 0.58 [0.35–0.97]; P=0.035) and B-AVR (HR [95% CI], 0.32 [0.18–0.59]; P<0.001; I^2=44.7%) (Figure 2).

The reintervention rate (3 studies for the Ross versus B-AVR and 5 studies for the Ross versus M-AVR) was lower in the Ross procedure and M-AVR groups compared with the B-AVR group (HR [95% CI], 0.31 [0.15–0.65]; P=0.002; I^2=66.6%; and HR [95% CI], 0.15 [0.05–0.41]; P<0.001; I^2=66.6%, respectively), whereas it was higher in the Ross procedure group compared with the M-AVR group (HR [95% CI], 2.12 [1.04–4.33]; P=0.039; I^2=66.6%) (Figure 3A).

The rate of major bleeding event (2 studies for the Ross versus B-AVR and 4 studies for the Ross versus M-AVR) was lower in the Ross procedure compared with M-AVR (HR [95% CI], 0.25 [0.11–0.60]; P=0.0014; I^2=11.6%) (Figure 3B). No significant differences were observed in the other comparison pairs.

The rate of long-term stroke (3 studies for the Ross versus B-AVR and 3 studies for the Ross versus M-AVR) was lower in the Ross procedure compared with M-AVR (HR [95% CI], 0.34 [0.12–0.98]; P=0.044; I^2=37.6%) and B-AVR (HR [95% CI], 0.33 [0.12–0.87]; P=0.028; I^2=37.6%) (Figure 4A).

The rate of infectious endocarditis (3 studies for the Ross versus B-AVR and 3 studies for the Ross versus M-AVR) was lower in the Ross procedure compared with B-AVR (HR [95% CI], 0.38 [0.21–0.70]; P=0.002; I^2=0%) (Figure 4B). No significant difference was observed between the Ross and M-AVR or M-AVR and B-AVR.

Direct and indirect comparisons for each outcome were presented in Figure S4.

Ranking of the Treatment Strategies

For short-term outcomes, the Ross procedure was the most effective for reducing risks of stroke and permanent pacemaker implantation (P scores: 64.3% for stroke and 96.8% for permanent pacemaker implantation). M-AVR was best for reducing myocardial infarction and atrial fibrillation events (P scores: 88.4% for myocardial infarction and 70.5% for atrial

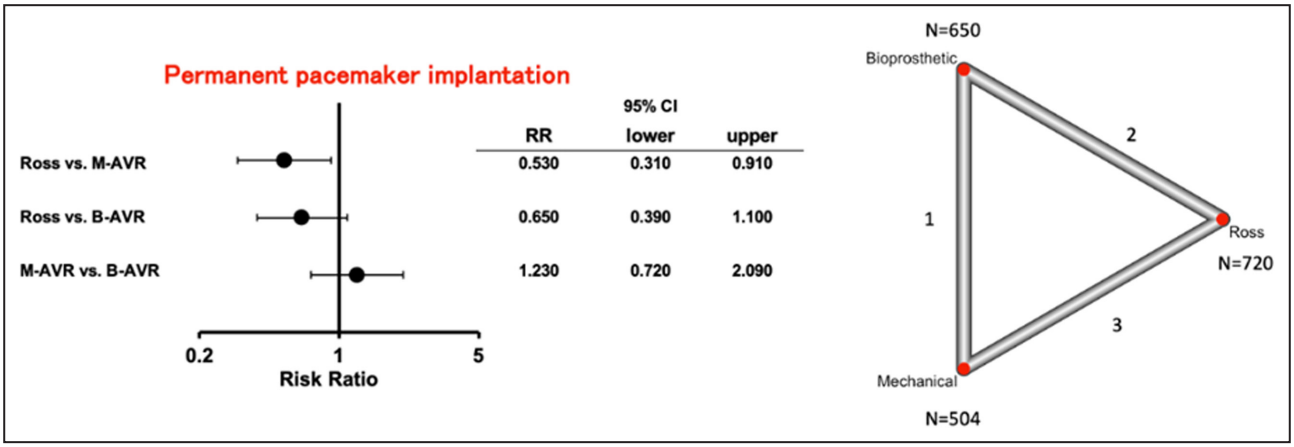

Figure 1. Forest plots of rates of permanent pacemaker implantation among treatment strategies (random-effects model).
The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an incident risk ratio (RR) of 1. B-AVR indicates bioprosthetic aortic valve replacement; and M-AVR, mechanical aortic valve replacement.

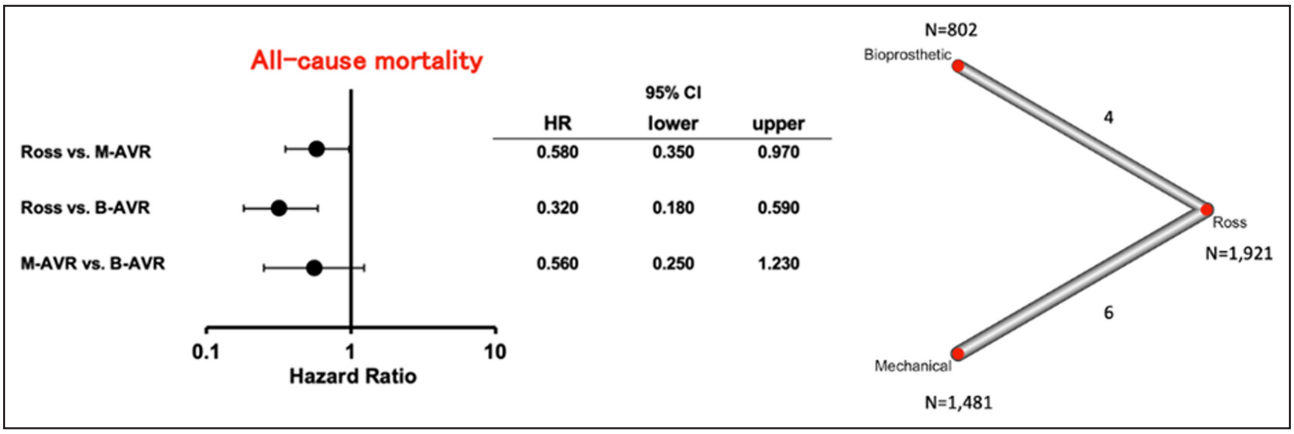

Figure 2. Forest plots of long-term all-cause mortality among treatment strategies (random-effects model).
The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an incident hazard ratio (HR) of 1. B-AVR indicates bioprosthetic aortic valve replacement; and M-AVR, mechanical aortic valve replacement.

fibrillation), whereas B-AVR was the best procedure for reducing reoperation for bleeding (*P* score: 92.9%) (Figure S5).

For long-term outcomes, the Ross procedure was ranked as the best procedure for 4 of 5 outcomes (*P* scores: 99.0% for all-cause mortality, 83.9% for major bleeding, 98.2% for long-term stroke, and 90.7% for infectious endocarditis), except for reintervention rates, for which M-AVR was ranked as the best (*P* score: 99.0%) (Figure S6).

Risk of Bias Across Studies

Publication bias was assessed using funnel plots (Figure S7).

DISCUSSION

To the best of our knowledge, this is the first network meta-analysis, involving exclusively RCTs and PSM studies, to compare the outcomes of the Ross procedure with M-AVR and B-AVR in adults. We observed that the Ross procedure was associated with improved late clinical end points, including mortality, stroke, and endocarditis. Although reintervention was higher after the Ross procedure compared with M-AVR, this did not impact long-term patient survival.

Since the original description of the Ross procedure >5 decades ago,[30] its role in our clinical practice in adults remains controversial, despite the cumulative evidence of proven benefits.[10–18,29] The fundamental driving force for the clinical advantage of the Ross operation is not only the long-term advantages of survival, avoidance of anticoagulant therapy, rare endocarditis, and infrequent reintervention, but also the fact that the autograft is alive: the leaflets retain the native valve physiology and contractile and neurohumoral responsiveness, with resultant superior hemodynamics and quality of life.[31]

Selecting the optimal substitute for young and middle-aged patients has been an ongoing debate. The advent and expansion of TAVR has heavily shifted the choice of substitute toward bioprostheses with expected future valve-in-valve TAVR.[7] However, despite the worldwide trend of favoring B-AVRs, valve-in-valve TAVR options remain limited to high-risk cohorts with limited long-term data. It is of critical importance to note that patients in the B-AVR group demonstrated worse long-term clinical outcomes across the board, including all-cause mortality, reintervention, long-term stroke, and endocarditis, compared with patients undergoing the Ross procedure in the present study. Irrespective of receiving a mechanical or a biological prosthesis, a reduction in life expectancy compared with an age- and sex-matched population was previously observed in large series, and this trend appeared more evident for younger populations.[6,32] In contrast, considerable data with the Ross procedure have accumulated worldwide in recent years. These long-term studies demonstrated restored late survival in the Ross procedure recipients up to 25 years compared with a matched general population.[18,33]

A few factors need to be considered when interpreting the reintervention rate data among the described SAVR options. Reinterventions in the Ross group are a result of 2 valves rather than 1, representing the Achilles heel of the Ross procedure. However, the mortality of post-Ross reoperations in experienced hands, regardless of autograft or right ventricular outflow tract, is low,[34,35] and autograft valve-sparing operations are frequently achievable.[34] Furthermore, the Ross operation has been modified to include specific technical elements: trimming of any excess muscle off the autograft; trimming of any

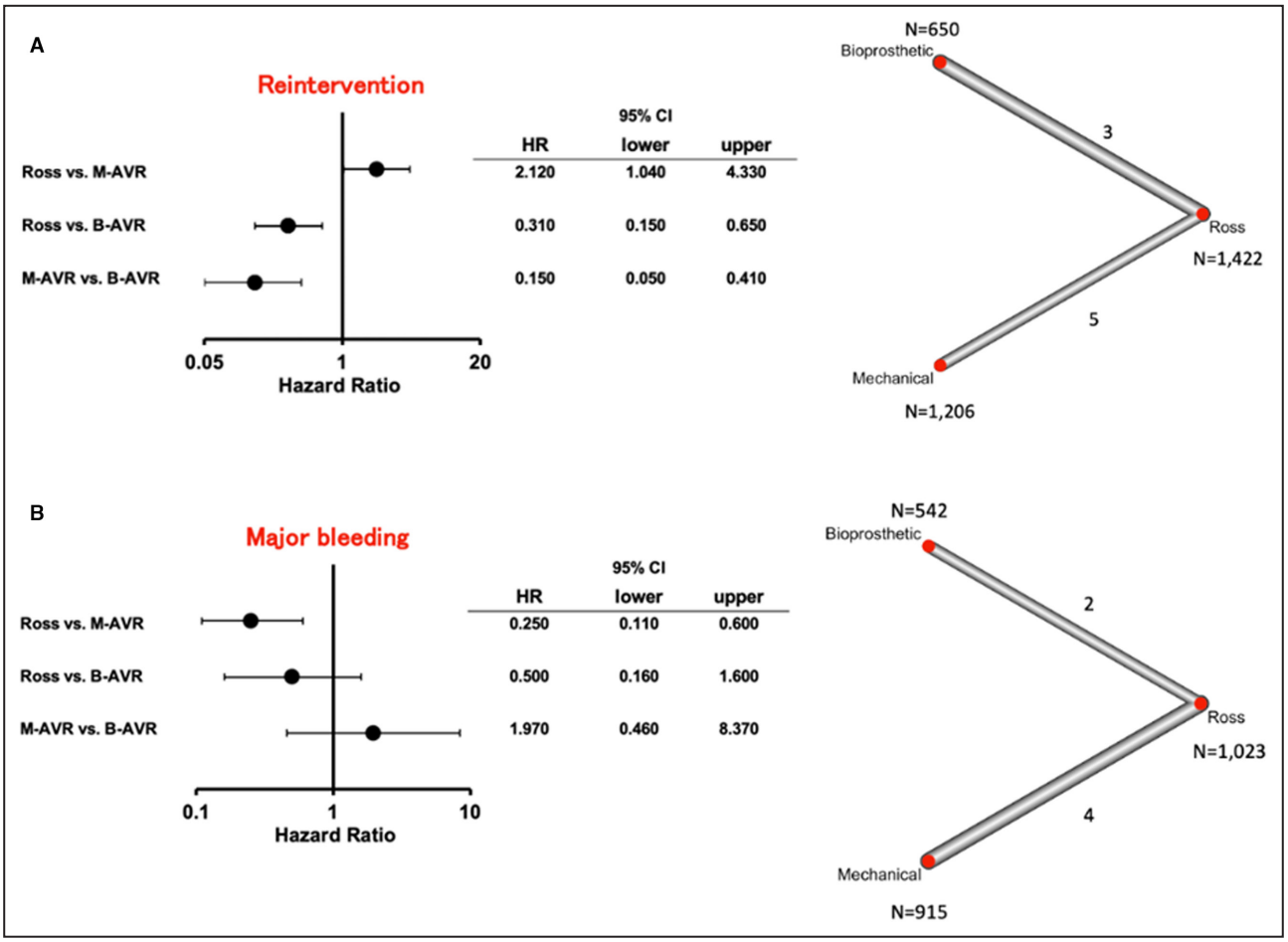

Figure 3. Forest plots of rates of long-term reintervention (A) and long-term major bleeding (B) among treatment strategies (random-effects model).
The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an incident hazard ratio (HR) of 1. B-AVR indicates bioprosthetic aortic valve replacement; and M-AVR, mechanical aortic valve replacement.

excess autograft above the neosinotubular junction; placement of the autograft deep into the left ventricular outflow tract by meticulous attention to each suture (intra-annular implantation for external annulus support); and providing external supports of the autograft annulus and the neosinotubular junction using various materials, particularly in patients with aortic insufficiency or large aortic annulus.[36] In addition to these technical aspects, the role of tight postoperative blood pressure regulation should not be understated. These modifications with various meticulous refinements have become standard of care in current practice and are associated with reduction of late autograft dilatation and improved durability.[34] Although reintervention rates were higher with the Ross procedure compared with M-AVR, the upper limit of CI was approaching 1; therefore, further follow-up is necessary considering recent surgical and medical modifications. As for right-side reinterventions after the Ross procedure, percutaneous therapies have emerged as the first-line therapy for failed homografts or prostheses in the pulmonary position,[37] although the feasibility of these transcatheter approaches is not guaranteed, and the risk of procedure-related complications, such as coronary compression,[38] and late complications, such as transcatheter pulmonary valve endocarditis,[39] exists. M-AVR appears favorable for the reintervention rate alone, but the reintervention risk is not trivial, with an estimated cumulative risk of 0.5% per year, mostly attributable to nonstructural valve dysfunction and endocarditis.[40] Furthermore, reinterventions following M-AVR mandate a redo open heart surgery. As for reinterventions following B-AVR, most patients in the present study were before or at the beginning of the TAVR era. Therefore, the long-term outcomes following B-AVR may be different in the contemporary series in the presence of valve-in-valve TAVR options in selected patients.

Meta-analyses comparing the Ross procedure with prosthetic SAVR have been conducted in the

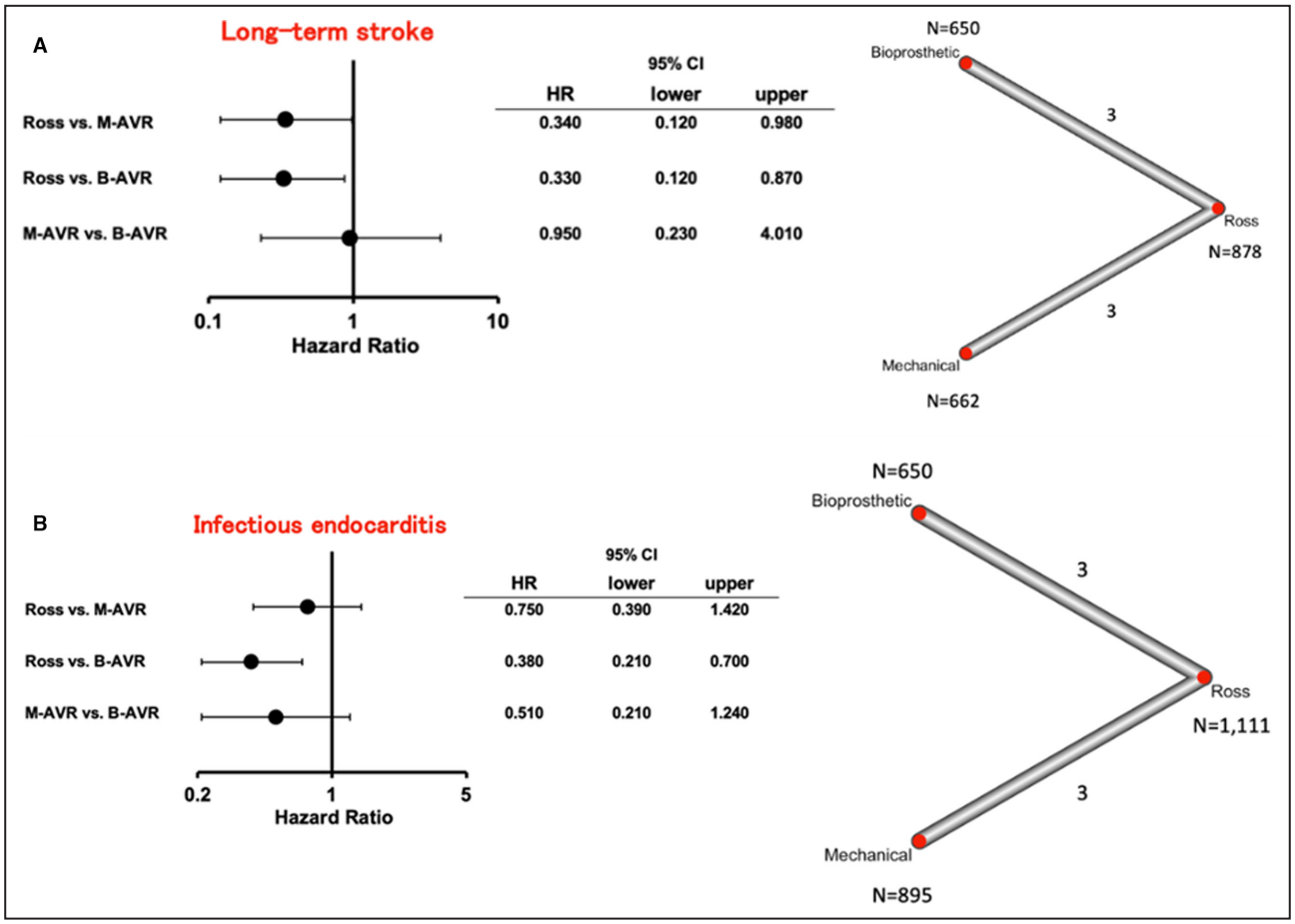

Figure 4. Forest plots of rates of long-term stroke (A) and infectious endocarditis (B) among treatment strategies (random-effects model).
The horizontal lines represent the values within the 95% CI of the underlying effects. The vertical line indicates an incident hazard ratio (HR) of 1. B-AVR indicates bioprosthetic aortic valve replacement; and M-AVR, mechanical aortic valve replacement.

past. Mazine et al compared the Ross procedure with M-AVR using 1 RCT and 17 observational studies,[41] which showed similar results to our analysis (ie, lower mortality and higher rates of reintervention in Ross procedure). However, the included 7 studies were unmatched/unadjusted observational studies; therefore, there remains a concern for significant selection bias. McClure et al performed a meta-analysis comparing the Ross procedure with conventional aortic valve replacement with 2 RCTs, 6 matched observational studies, and 7 unmatched/unadjusted observational studies, which showed decreased mortality in the Ross procedure.[42] However, the control group of the study was conventional aortic valve replacement by combining both M-AVR and B-AVR, and the follow-up was only 2.6 years. Our meta-analysis is the first network meta-analysis that compared the Ross procedure with M-AVR and B-AVR separately, exclusively using RCTs or PSM studies. Furthermore, we reported the important outcome measures, such as rates of pacemaker implantation and infectious endocarditis, which were not reported in the previous meta-analyses.

Study Limitations

Our study contains several limitations. First, one of the included studies compared the Ross procedure with homograft in the aortic position (n=108), which was included within the B-AVR group, representing 13.5% of the B-AVR group. However, homografts and conventional bioprostheses are known to offer similar survival and freedom from reoperation.[43] Second, the details of reintervention procedures were not available in most studies, and the breakdowns of percutaneous versus conventional open approach among reinterventions, which may provide additional insights, were unable to be described. Furthermore, we were unable to separately compare the reintervention rate on autograft alone because of lack of available data. Third, this study analyzed data sets from multiple studies. Although fundamental study conclusions should not be affected, small discrepancies in the definitions of relevant clinical variables exist.

Fourth, mean follow-up periods were 7.4 years in this analysis; therefore, longer follow-up is necessary to conclude the optimal valve substitute in this population. Fifth, we exclusively included RCTs or PSM studies; however, this does not completely alleviate selection bias. Sixth, our analysis included a few comparisons between M-AVR and B-AVR; thus, the outcomes comparing those 2 methods were derived mainly from indirect comparisons. Last, the Ross procedure is generally performed only at selected centers with experience. Although most conventional SAVRs in this analysis were also performed in high-volume SAVR centers, surgeons' experience could have influenced the outcomes. In addition, differences in surgical techniques could not be accounted for in the present analysis. The lack of RCTs remains one of the major criticisms of the Ross procedure that has not highly impacted the guideline recommendations. Major barriers to conducting RCTs include lack of equipoise on surgeon experience, clinical features obviously favoring one particular therapy to the others (such as younger age and extremely small annulus), and necessity of long-term follow-up. As a result, clinical trial feasibility and patient enrollment are subject to be challenged in such circumstances.

In summary, excellent long-term clinical outcomes of the Ross procedure are demonstrated in the present network meta-analysis compared with conventional M-AVR and B-AVR options. Future studies should include even longer follow-up and breakdowns of re-intervention approaches (open versus transcatheter) with corresponding outcomes. Our results highlight a need to enhance the recognition of the Ross procedure and revisit the optimal valve substitute selection in the guidelines for young and middle-aged patients needing an aortic valve replacement.

ARTICLE INFORMATION

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Disclosures

Dr Fukuhara serves as a consultant for Terumo Aortic, Artivion, and Medtronic Inc. Dr Ouzounian serves as a consultant for Terumo Aortic and Medtronic Inc. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figures S1–S3

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Supplemental Material

Table S1. Definition of each outcome.

Author	Year	Major bleeding	Stroke	Reintervention
Doss	2005	Bleeding requiring hospitalization	Stroke	Any operation involving the aortic and/or pulmonary valves
El-Hamamsy	2010	N/A	Stroke	Any operation involving the aortic and/or pulmonary valves
Mokhles	2011	Bleeding requiring transfusion, surgical or endoscopic intervention, or inpatient care or causing long-term impairment	N/A	N/A
Mazine	2016	Bleeding leading to death or stroke or requiring hospitalization and/or transfusion	Stroke and transient ischemic attack	Any surgical or percutaneous reintervention on any operated valve
Sharabiani	2016	N/A	N/A	N/A
Bouhout	2017	N/A	N/A	N/A
Buratto	2018	N/A	N/A	N/A
Gofus	2022	N/A	N/A	Any operation involving the aortic and/or pulmonary valves
El-Hamamsy	2022	Bleeding which required inpatient	Hemorrhagic or ischemic stroke.	Any operation involving the aortic and/or pulmonary valves
Mazine	2022	N/A	Stroke, transient ischemic attack, and noncerebral systemic embolism	Any surgical or percutaneous reintervention on any operated valve

N/A=not applicable.

Table S2. Inclusion age criteria and exclusion criteria.

Author	Year	Age (yrs)	Exclusion criteria
Doss	2005	18-55	Patients with isolated or predominant aortic regurgitation, previous valve surgeries, concomitant valve procedures, active endocarditis, emergency procedures, and a history of myocardial infarction, and severe calcification of the aortic root.
El-Hamamsy	2010	18-69	Patients with Marfan’s syndrome, rheumatoid arthritis, Reiter’s syndrome.

Mokhles	2011	18-60	Patients with an urgent operation, aortic dissection or aortic aneurysm, concomitant mitral valve replacement.
Mazine	2016	16-63	Patients with acute aortic dissection, active endocarditis, or requiring emergency surgery
Sharabiani	2016	16-40	Patients with complex heart abnormalities, rheumatic fever, unclassified aortic valve procedures.
Bouhout	2017	18-65	Patients with concomitant procedures other than ascending aortic replacement, redo operations, or urgent surgery
Buratto	2018	18-65	Patients with urgent surgery, concomitant cardiovascular procedures, aortic dissection, or endocarditis.
Gofus	2022	18-60	Patients with concomitant procedure, acute aortic syndrome and in a critical preoperative state (those in need of artificial ventilation, catecholamines, cardiopulmonary resuscitation or in cardiogenic shock).
El-Hamamsy	2022	18-50	Patients with concomitant valve surgery or coronary artery bypass grafting, end-stage renal disease, intravenous drug use, acute aortic dissection, infective endocarditis, history of carcinoid disease or Marfan syndrome.
Mazine	2022	16-60	Patients with active endocarditis, acute aortic dissection, end-stage renal disease, or emergency surgery.

Table S3. Variables used in propensity-score matching studies.

Author	Year	Variables
Mokhles	2011	Age, sex, pathology, endocarditis, hemodynamic manifestation, preoperative NYHA grade, creatinine, preoperative rhythm, diabetes, hypertension, lung disease, LVEF, LVEDO, LVESD, previous cardiac operation, concomitant surgery.
Mazine	2016	Age, sex, residential location, year of surgery, body weight and body surface area, preoperative creatinine level, diabetes control (if applicable), history of cardiac intervention (i.e. previous aortic/mitral valve surgery, any other cardiac surgery, non-surgical intervention), clinical presentation (i.e. congestive heart failure, severe angina pectoris, left ventricular ejection fraction, results of stress testing and NYHA functional classification) 10. presence of cardiovascular risk factors (i.e. diabetes mellitus, hypertension, hyperlipidemia and smoking history) 11. presence of other associated diseases (i.e. chronic obstructive pulmonary disease, previous stroke or transient ischemic attack, peripheral vascular disease, atrial

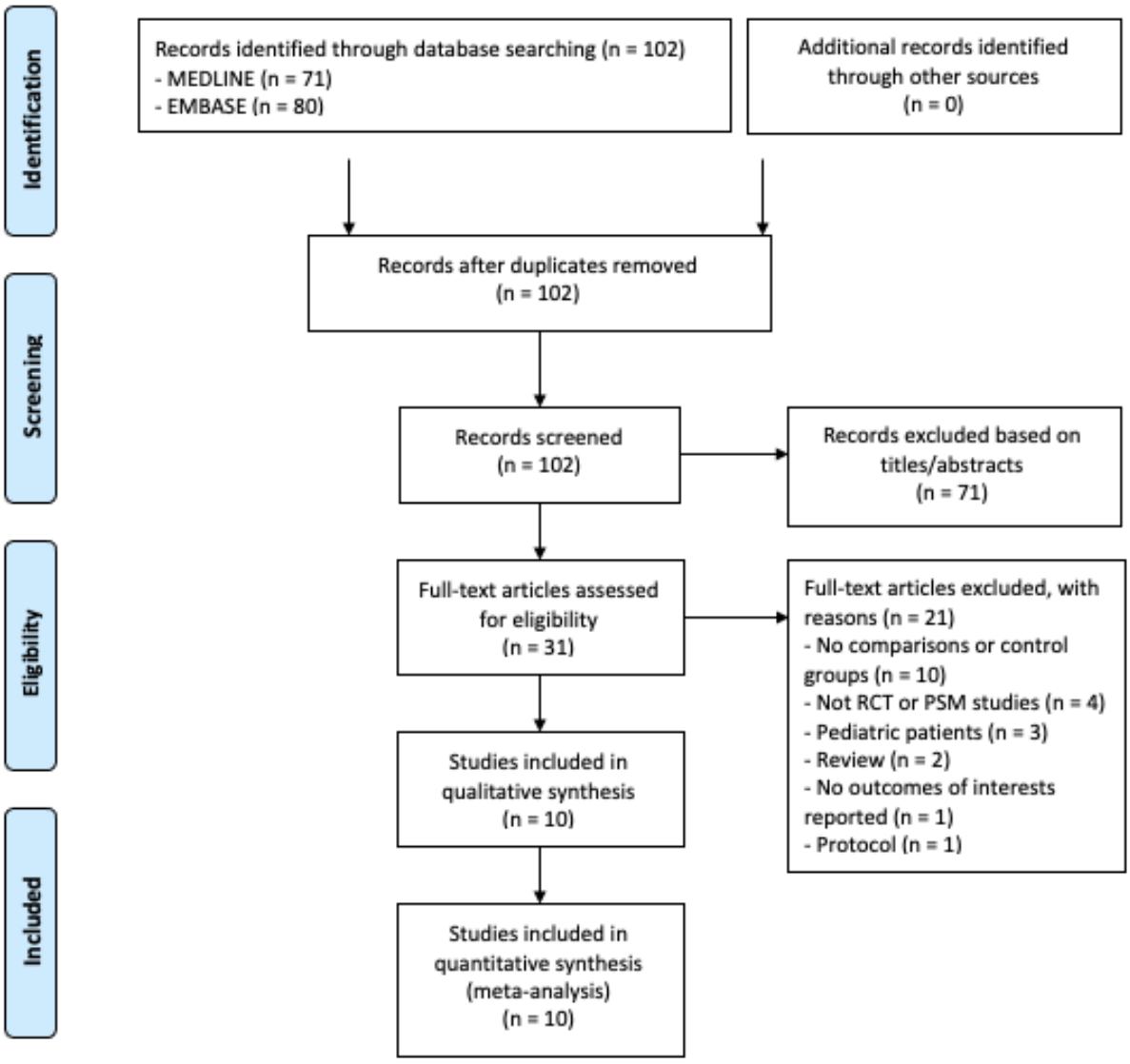
		fibrillation, complete heart block) 12. pre-operative use of medications (i.e. statin or aspirin within 7 days before the surgery) 13. disease characteristics (i.e. aortic valve pathology, presence of ascending aortic disease, mitral valve disease and coronary artery disease 14. concomitant procedures
Sharabiani	2016	Age, sex, aortic disease type, mitral disease, coarctation, subaortic stenosis, genetic syndrome, mitral valve procedure, coarctation repair, and subaortic stenosis repair at index
Bouhout	2017	Age, ascending aorta aneurysm, aortic root aneurysm, NYHA functional class, hypertension, pulmonary hypertension, surgical indication for AVR, left ventricle ejection fraction <50% and dyslipidemia.
Buratto	2018	Age, sex, era of surgery, hypertension, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, myocardial infarction, dialysis, New York Heart Association functional class, ejection fraction <45%, aortic stenosis, aortic regurgitation, mixed aortic valve disease, reoperation, congestive heart failure.
Gofus	2022	Age, sex, body mass index, creatinine, LVEF, angina pectoris, NYHA class, heart failure, previous heart surgery, smoking status, diabetes, hypertension, dyslipidemia, chronic pulmonary disease, rhythm, cerebral vascular disease, coronary artery disease, endocarditis, urgent surgery, valve pathology, concomitant procedures
El-Hamamsy	2022	Age, sex, race, history of hypertension, diabetes, congestive heart failure, chronic kidney disease, coronary artery disease, atrial fibrillation, peripheral vascular disease, chronic obstructive pulmonary disease, liver disease, cancer, cerebrovascular disease, coagulation disorders, previous endocarditis), and admission year.
Mazine	2022	Age, sex, year of surgery, weight, body surface area, preoperative diabetes, congestive heart failure, angina, severe chronic obstructive pulmonary disease, hypertension, medically treated hyperlipidemia, previous stroke or transient ischemic attack, atrial fibrillation or complete heart block preoperatively, ascending aortic disease, use of aspirin or statins within 7 days before surgery, concurrent coronary artery bypass grafting, concurrent mitral and/or tricuspid valve procedure, and history of cardiac intervention (ie, previous aortic or mitral valve surgery, any other cardiac surgery, or nonsurgical cardiac intervention).

Table S4. Quality assessment based on NOS (range, 1-9). NOS score≥8 is low risk, 6-7 is moderate risk and ≤5 is high risk.

Studies	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts	Outcome assessment	Length of follow-up	Adequacy of follow-up	NOS score
Mokhles	1	0	1	1	2	1	1	1	8
Mazine	1	1	1	1	2	1	1	1	9
Sharabiani	1	1	1	1	2	1	1	1	9
Bouhout	1	1	1	1	2	1	0	1	8
Buratto	1	0	1	1	2	1	1	1	8
Gofus	1	1	1	1	2	1	1	1	9
El-Hamamsy	1	1	1	1	2	1	1	1	9
Mazine	1	1	1	1	2	1	1	1	9

NOS=Newcastle-Ottawa Scale

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



RCT, randomized controlled trial; PSM, propensity-score-matched

Figure S2. Risk of bias summary according to the Cochrane Collaboration Manual.

Yellow: unclear risk; Green: low risk, Red: high risk.

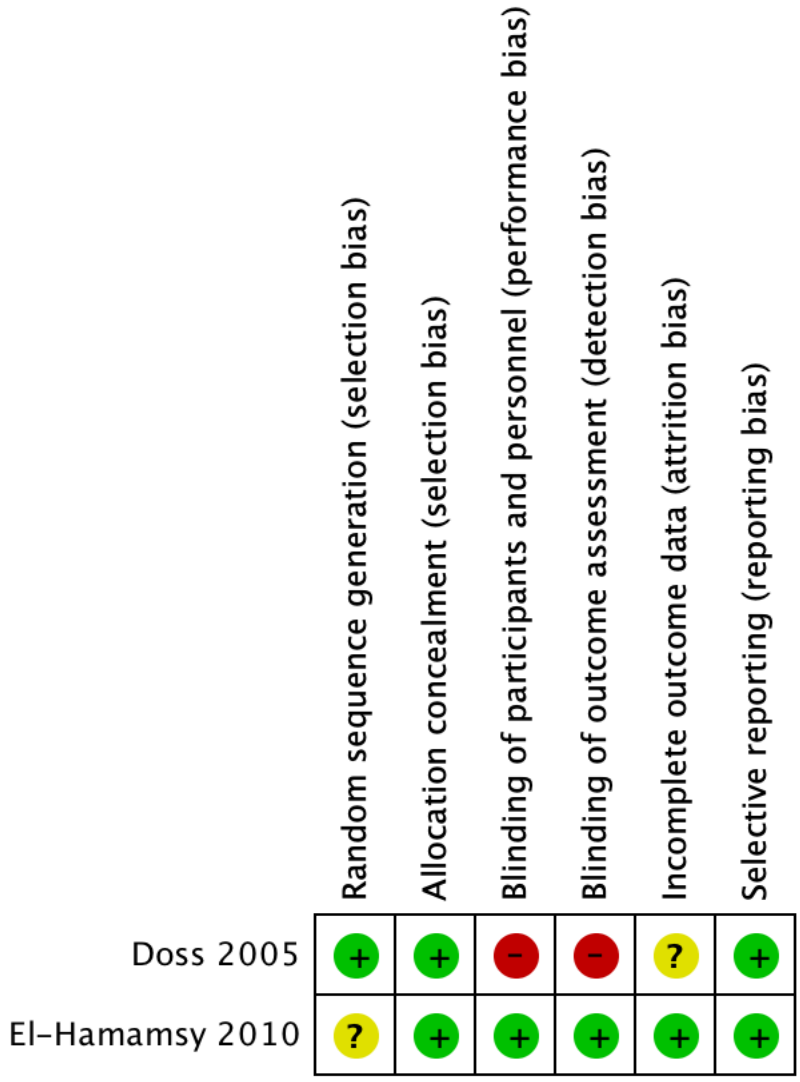
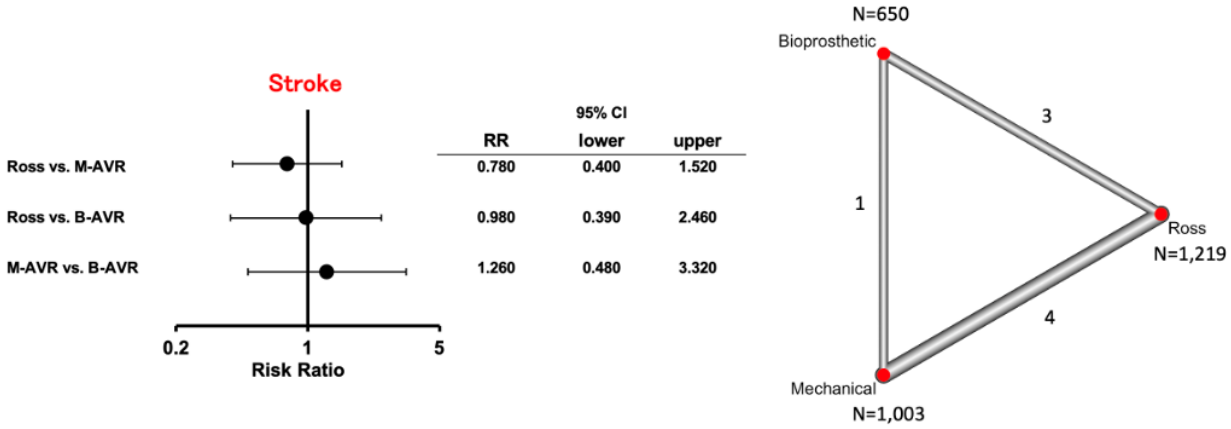
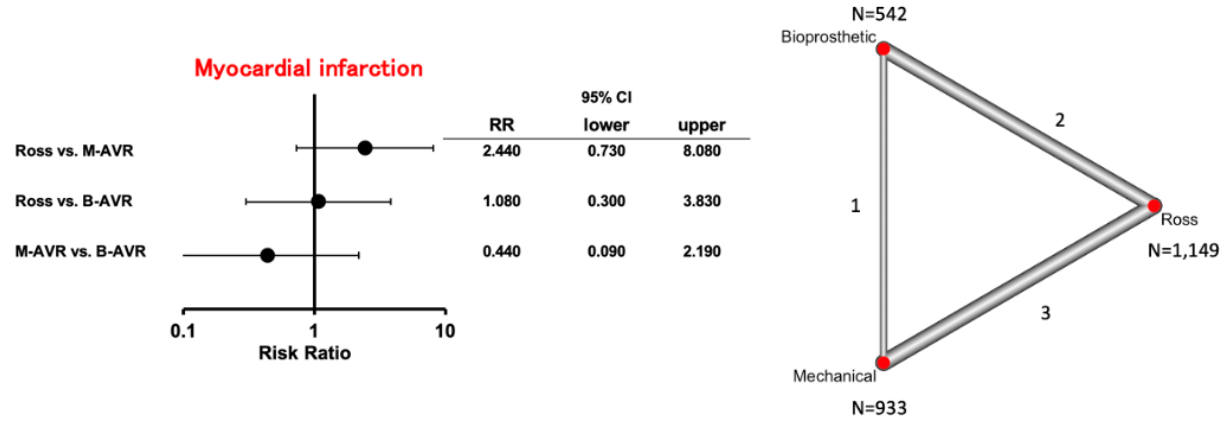


Figure S3. Forest plots of A) stroke, B) myocardial infarction, C) new onset atrial fibrillation, and D) reoperation for bleeding all-cause mortality among treatment strategies (random-effects model). The horizontal lines represent the values within the 95% confidence interval of the underlying effects. The vertical line indicates an incident hazard ratio of 1. B-AVR=bioprosthetic aortic valve replacement, CI=confidence interval, HR=hazard ratio, M-AVR=mechanical aortic valve replacement.

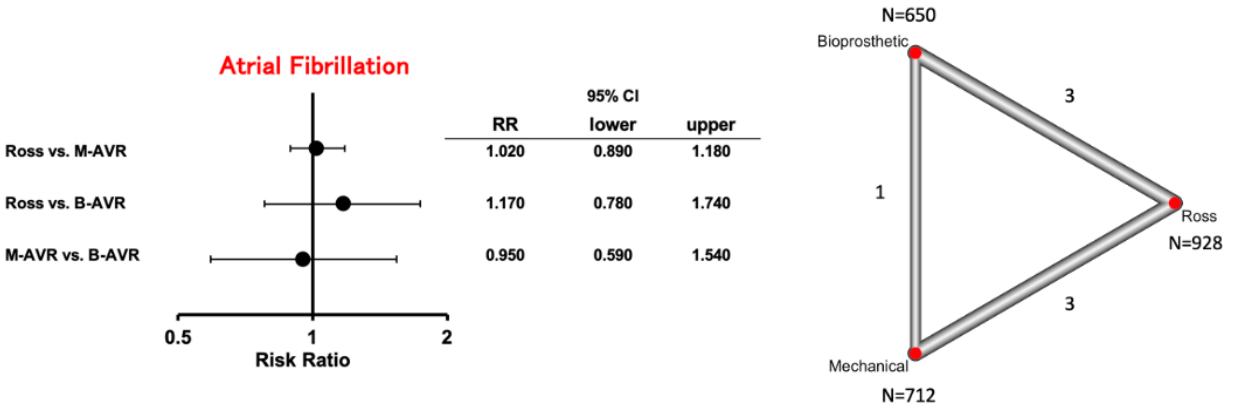
A)



B)



C)


Atrial Fibrillation
95% CI
RR lower upper
Ross vs. M-AVR 1.020 0.890 1.180
Ross vs. B-AVR 1.170 0.780 1.740
M-AVR vs. B-AVR 0.950 0.590 1.540
0.5
1
2
Risk Ratio
N=650
Bioprosthetic
3
1
Ross
N=928
3
Mechanical
N=712

D)

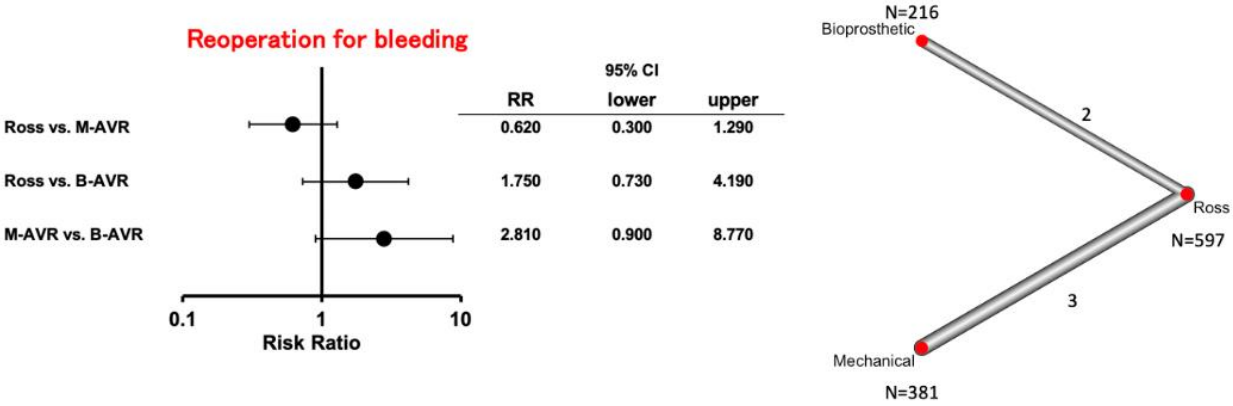
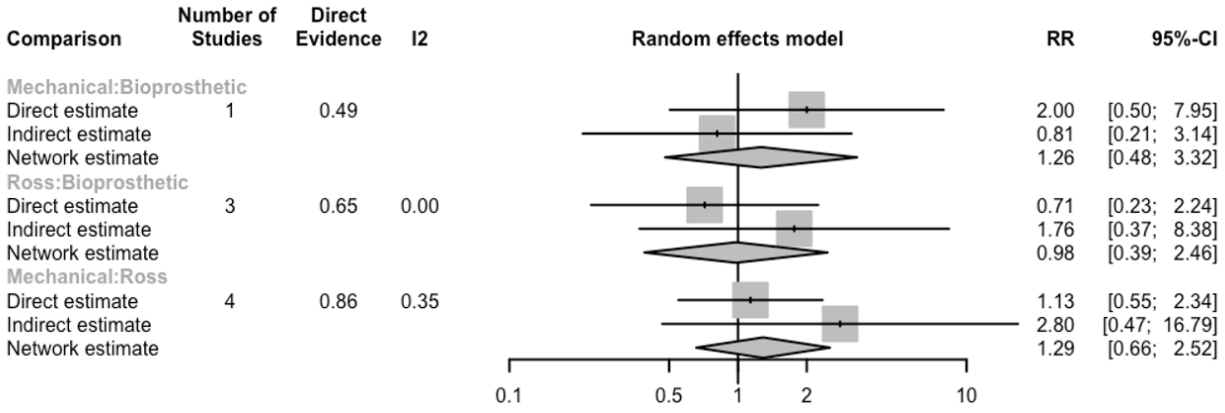
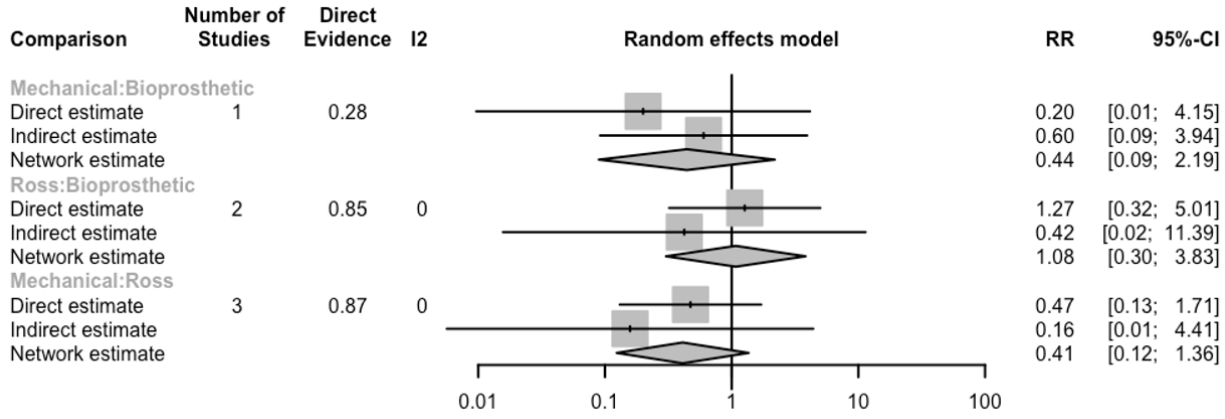

Reoperation for bleeding
95% CI
RR lower upper
Ross vs. M-AVR 0.620 0.300 1.290
Ross vs. B-AVR 1.750 0.730 4.190
M-AVR vs. B-AVR 2.810 0.900 8.770
0.1
1
10
Risk Ratio
N=216
Bioprosthetic
2
Ross
N=597
3
Mechanical
N=381

Figure S4. Direct and indirect comparisons for A) stroke, B) myocardial infarction, C) permanent pacemaker implantation, D) new onset atrial fibrillation, E) reoperation for bleeding, F) all-cause mortality, G) reintervention, H) major bleeding, I) long-term stroke, and J) infectious endocarditis.

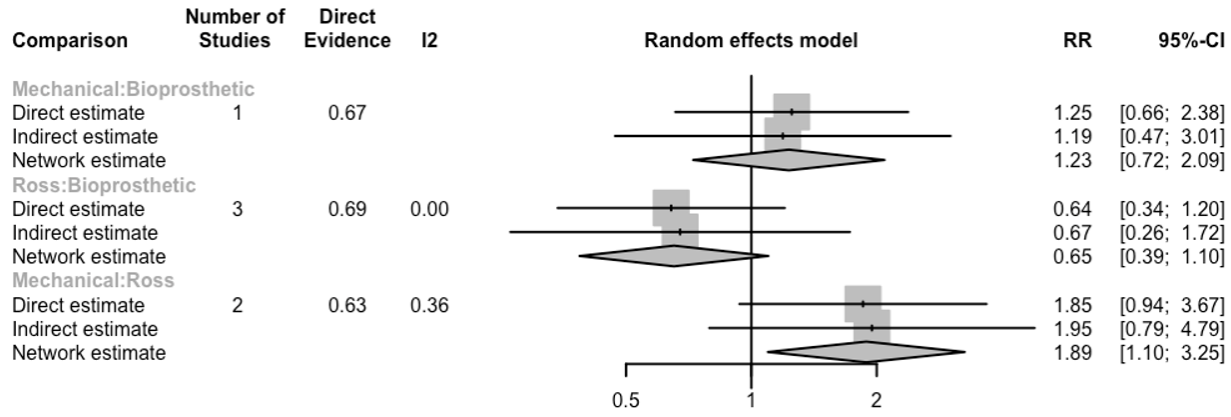
A)



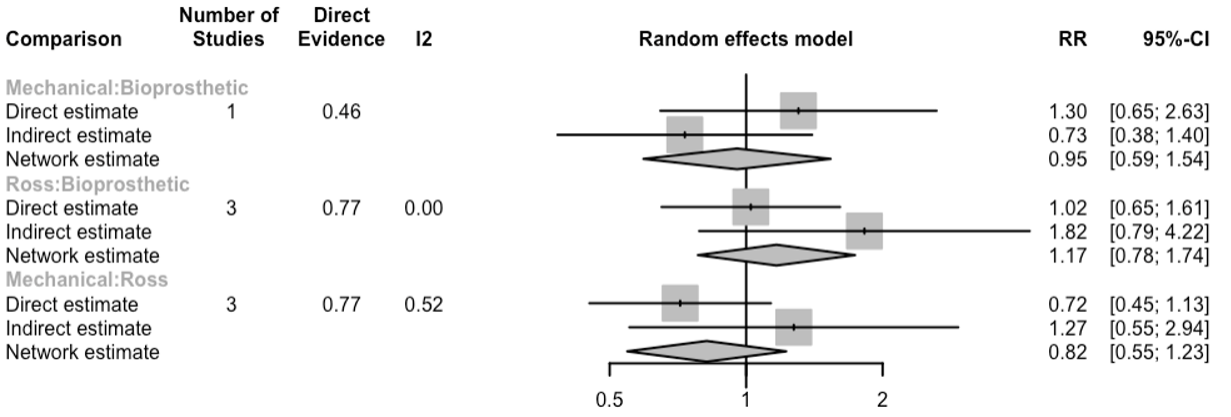
B)



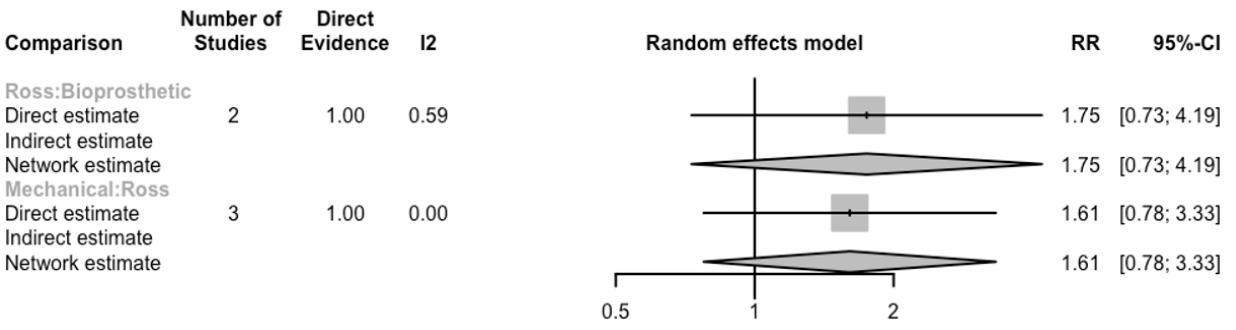
C)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
RR
95%-CI
Mechanical:Bioprosthetic
Direct estimate 1 0.67 1.25 [0.66; 2.38]
Indirect estimate 1.19 [0.47; 3.01]
Network estimate 1.23 [0.72; 2.09]
Ross:Bioprosthetic
Direct estimate 3 0.69 0.00 0.64 [0.34; 1.20]
Indirect estimate 0.67 [0.26; 1.72]
Network estimate 0.65 [0.39; 1.10]
Mechanical:Ross
Direct estimate 2 0.63 0.36 1.85 [0.94; 3.67]
Indirect estimate 1.95 [0.79; 4.79]
Network estimate 1.89 [1.10; 3.25]
0.5
1
2

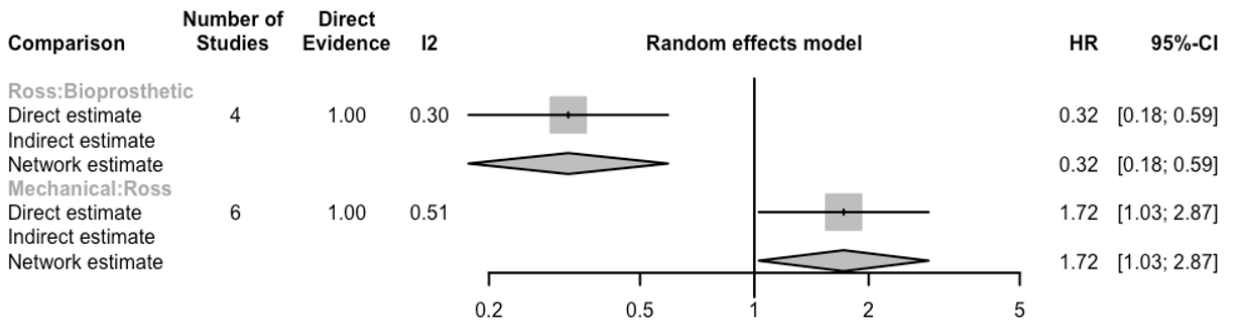
D)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
RR
95%-CI
Mechanical:Bioprosthetic
Direct estimate 1 0.46 1.30 [0.65; 2.63]
Indirect estimate 0.73 [0.38; 1.40]
Network estimate 0.95 [0.59; 1.54]
Ross:Bioprosthetic
Direct estimate 3 0.77 0.00 1.02 [0.65; 1.61]
Indirect estimate 1.82 [0.79; 4.22]
Network estimate 1.17 [0.78; 1.74]
Mechanical:Ross
Direct estimate 3 0.77 0.52 0.72 [0.45; 1.13]
Indirect estimate 1.27 [0.55; 2.94]
Network estimate 0.82 [0.55; 1.23]
0.5
1
2

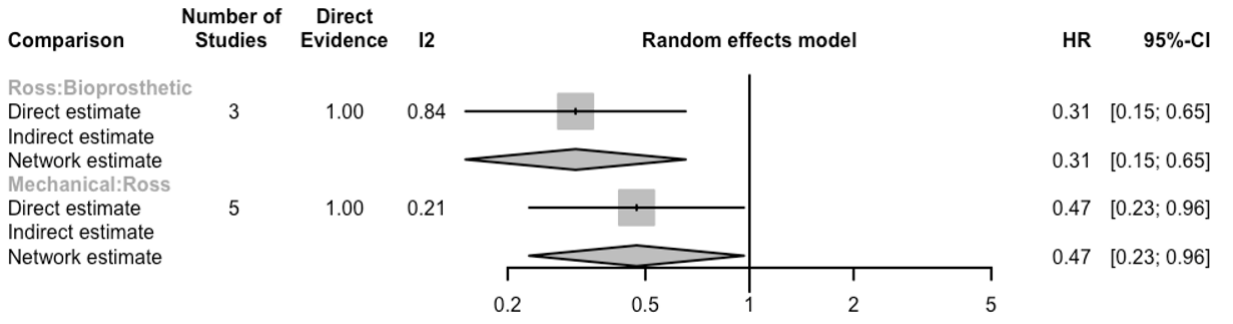
E)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
RR
95%-CI
Ross:Bioprosthetic
Direct estimate 2 1.00 0.59 1.75 [0.73; 4.19]
Indirect estimate
Network estimate 1.75 [0.73; 4.19]
Mechanical:Ross
Direct estimate 3 1.00 0.00 1.61 [0.78; 3.33]
Indirect estimate
Network estimate 1.61 [0.78; 3.33]
0.5
1
2

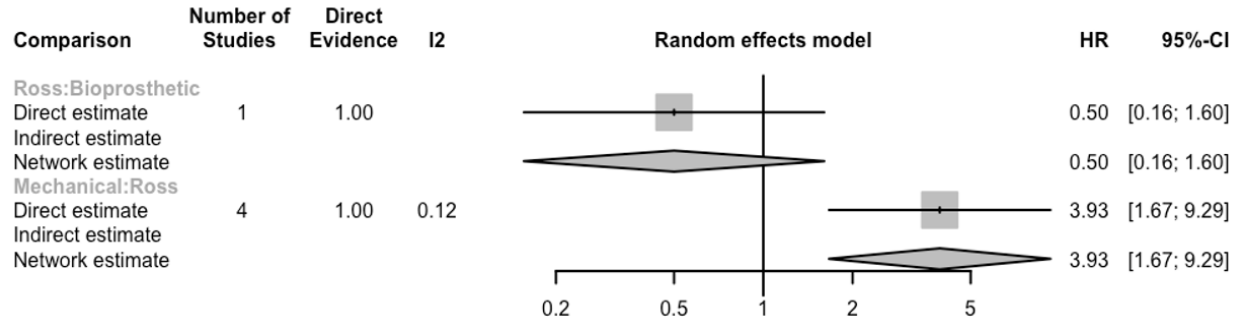
F)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
HR
95%-CI
Ross:Bioprosthetic
Direct estimate 4 1.00 0.30 0.32 [0.18; 0.59]
Indirect estimate
Network estimate 0.32 [0.18; 0.59]
Mechanical:Ross
Direct estimate 6 1.00 0.51 1.72 [1.03; 2.87]
Indirect estimate
Network estimate 1.72 [1.03; 2.87]
0.2
0.5
1
2
5

G)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
HR
95%-CI
Ross:Bioprosthetic
Direct estimate 3 1.00 0.84 0.31 [0.15; 0.65]
Indirect estimate
Network estimate 0.31 [0.15; 0.65]
Mechanical:Ross
Direct estimate 5 1.00 0.21 0.47 [0.23; 0.96]
Indirect estimate
Network estimate 0.47 [0.23; 0.96]
0.2
0.5
1
2
5

H)


Comparison
Number of Studies
Direct Evidence
I2
Random effects model
HR
95%-CI
Ross:Bioprosthetic
Direct estimate 1 1.00 0.50 [0.16; 1.60]
Indirect estimate
Network estimate 0.50 [0.16; 1.60]
Mechanical:Ross
Direct estimate 4 1.00 0.12 3.93 [1.67; 9.29]
Indirect estimate
Network estimate 3.93 [1.67; 9.29]
0.2
0.5
1
2
5

I)

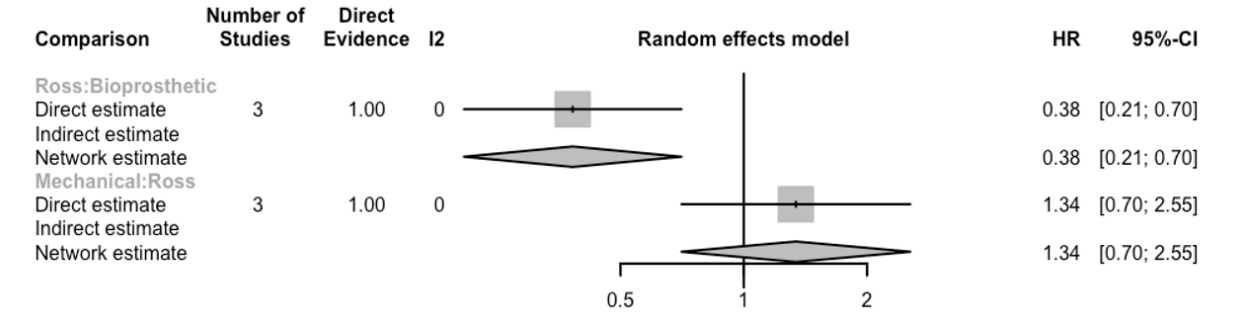
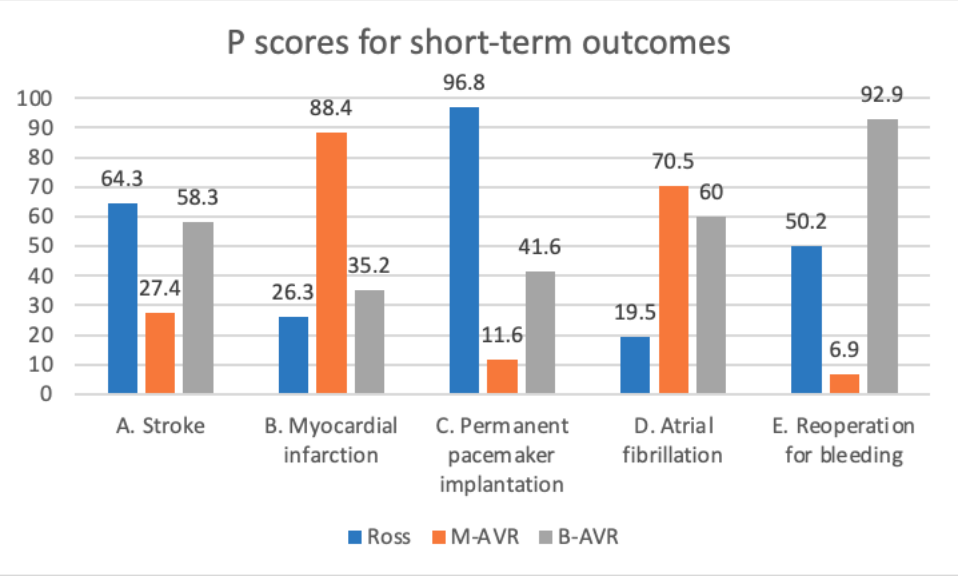
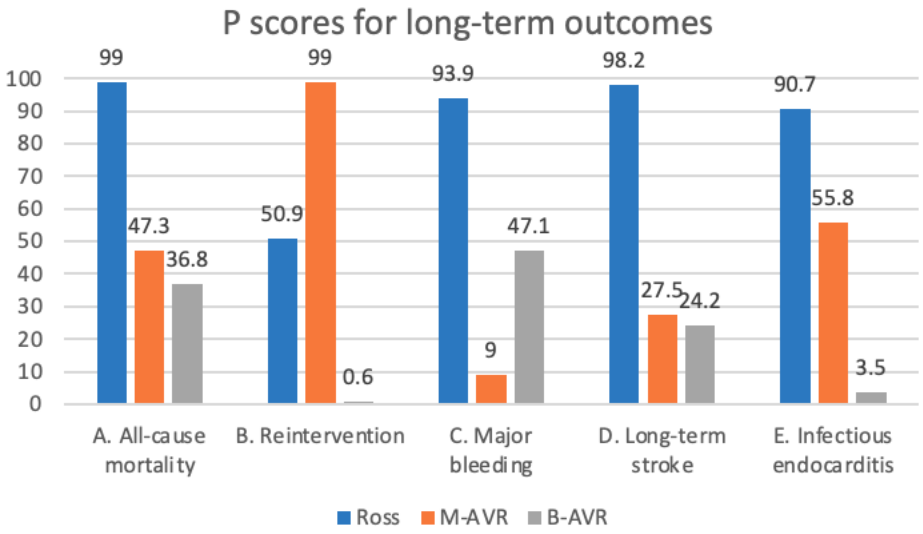

Comparison
Number of Studies
Direct Evidence
I2
Random effects model
HR
95%-CI
Ross:Bioprosthetic
Direct estimate 3 1.00 0 0.38 [0.21; 0.70]
Indirect estimate
Network estimate 0.38 [0.21; 0.70]
Mechanical:Ross
Direct estimate 3 1.00 0 1.34 [0.70; 2.55]
Indirect estimate
Network estimate 1.34 [0.70; 2.55]
0.5
1
2

Figure S5. P scores for short-term outcomes.



B-AVR, bioprosthetic aortic valve replacement; M-AVR, mechanical aortic valve replacement

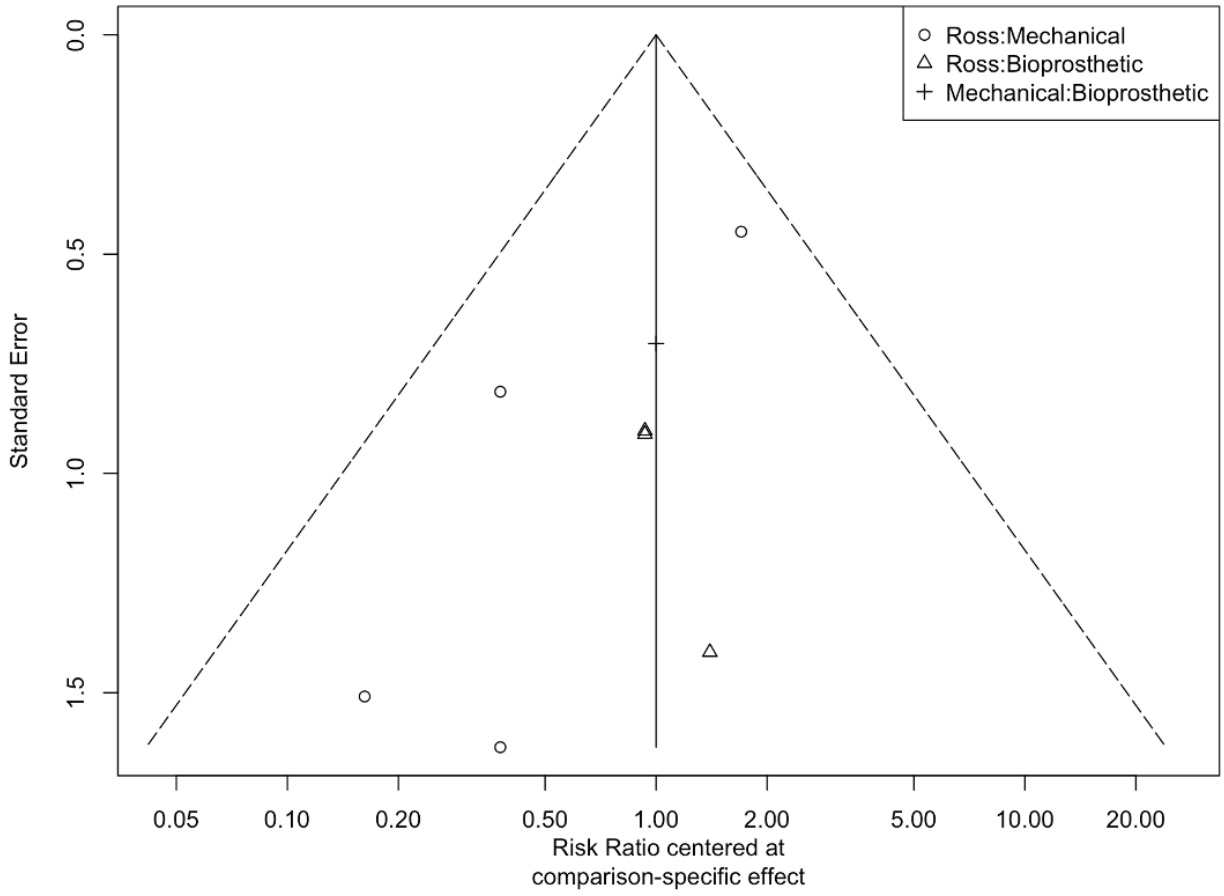
Figure S6. P scores for long-term outcomes.



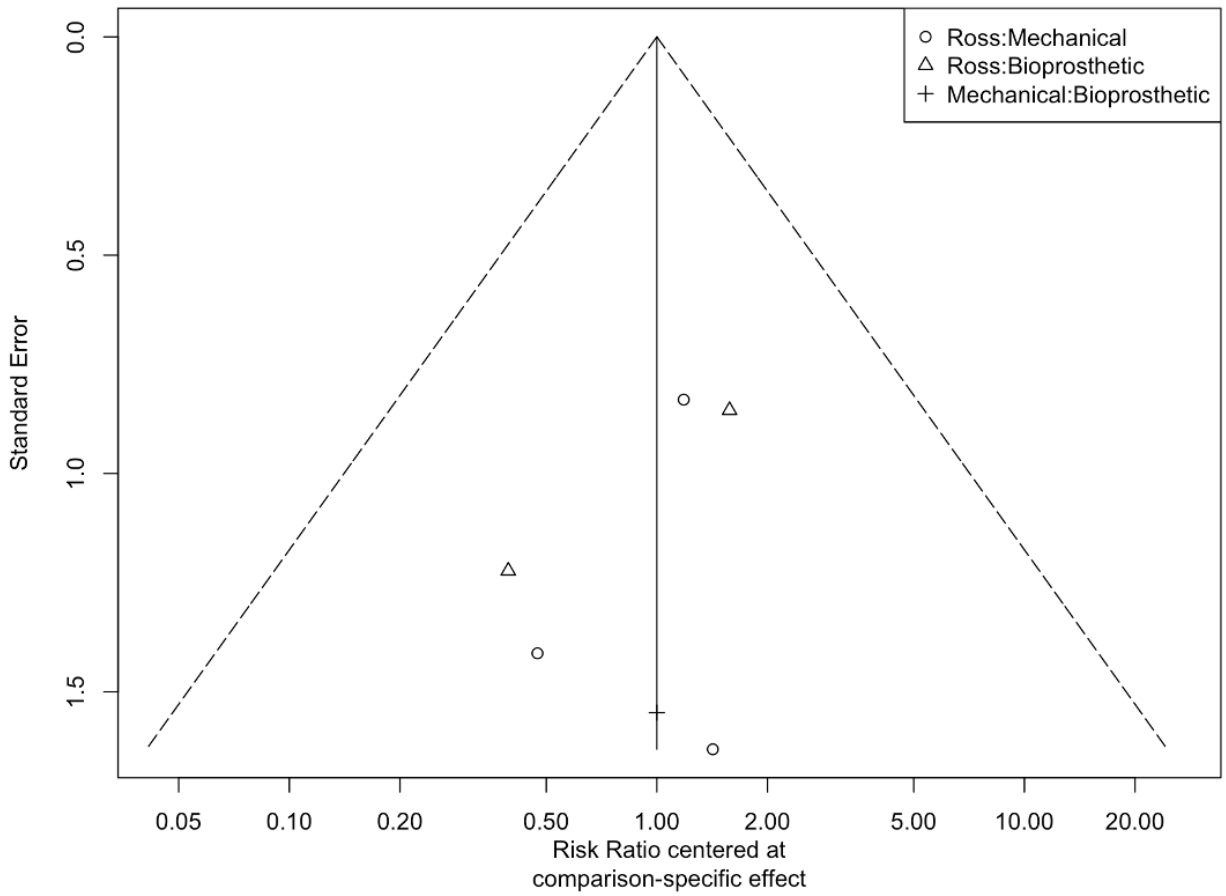
B-AVR, bioprosthetic aortic valve replacement; M-AVR, mechanical aortic valve replacement

Figure S7. Publication bias assessment using Funnel plot for A) stroke, B) myocardial infarction, C) permanent pacemaker implantation, D) new onset atrial fibrillation, E) reoperation for bleeding, F) all-cause mortality, G) reintervention, H) major bleeding, I) long-term stroke, and J) infectious endocarditis.

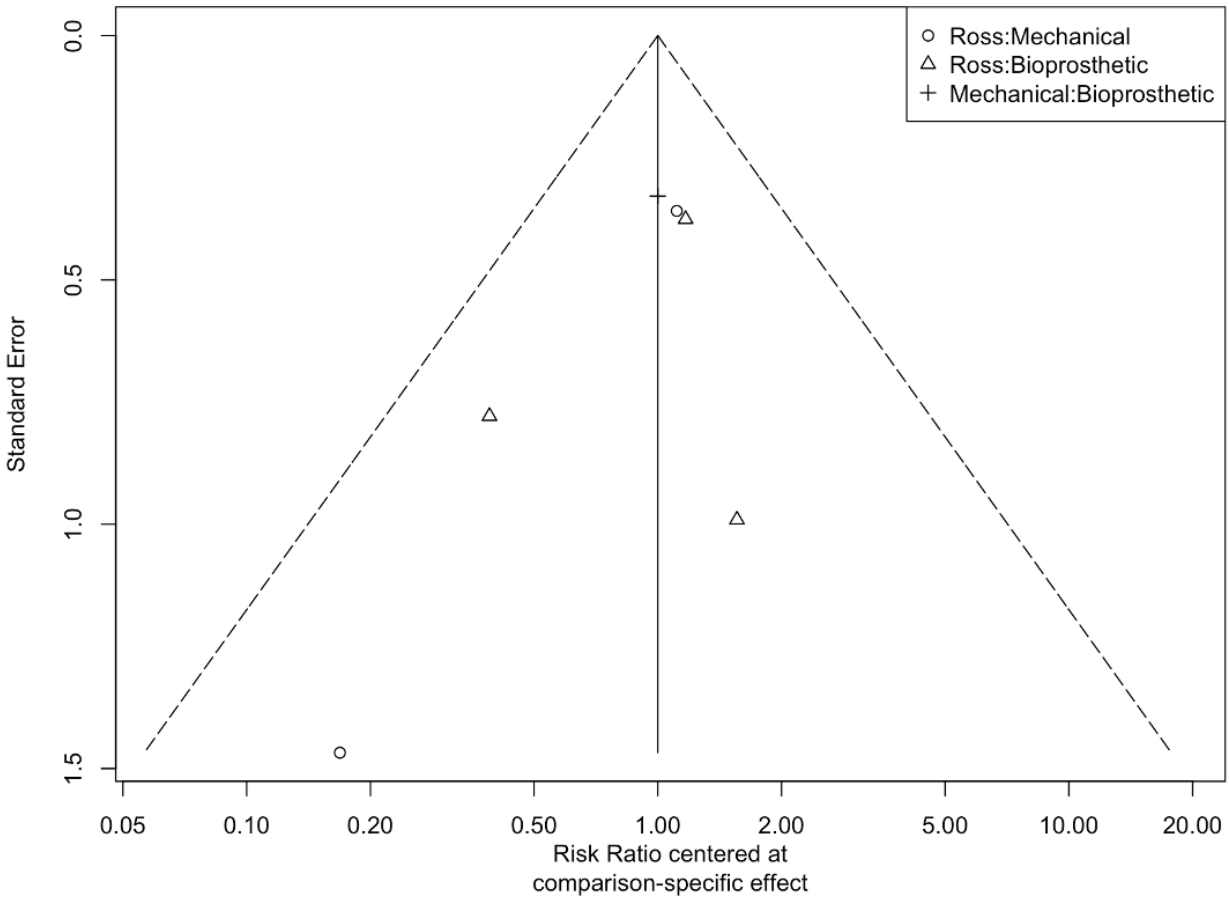
A)



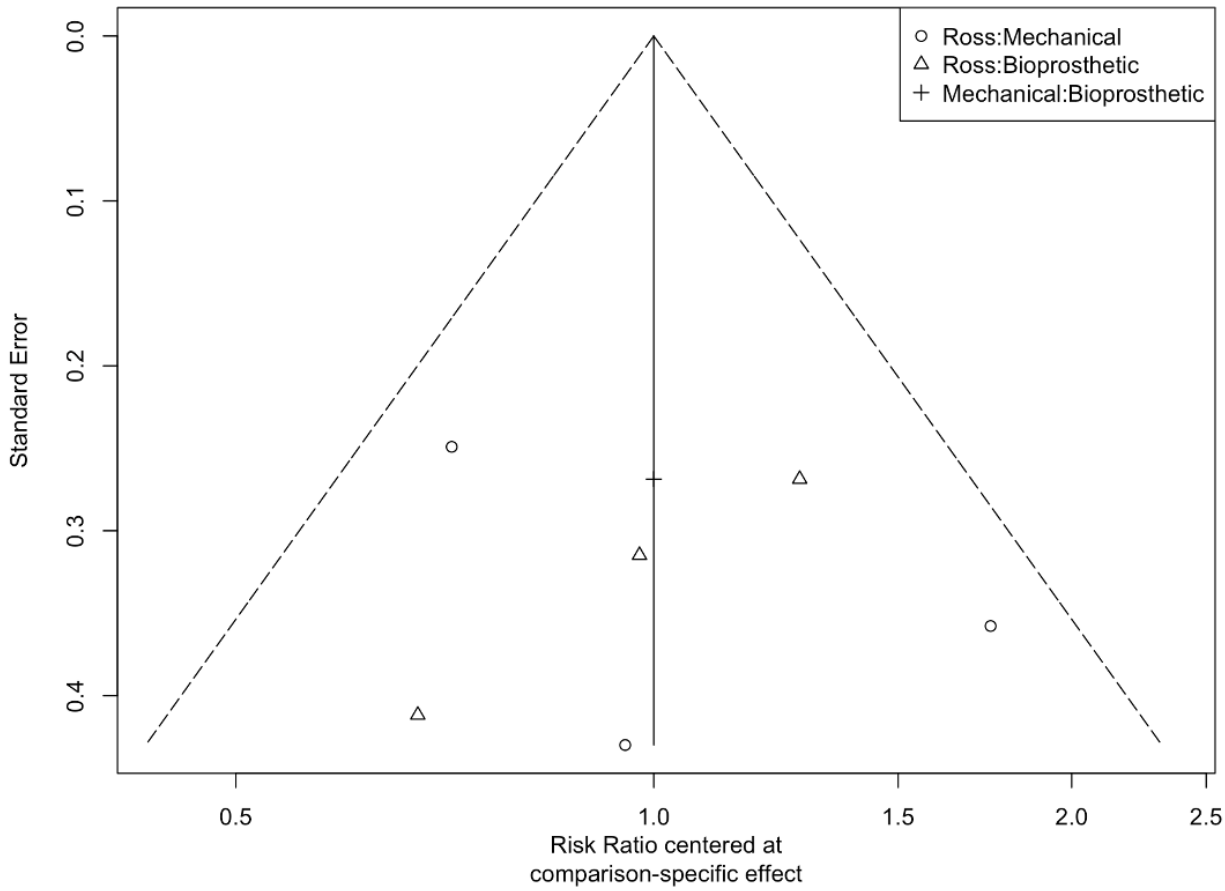
B)


Ross:Mechanical
Ross:Bioprosthetic
Mechanical:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio centered at
comparison-specific effect

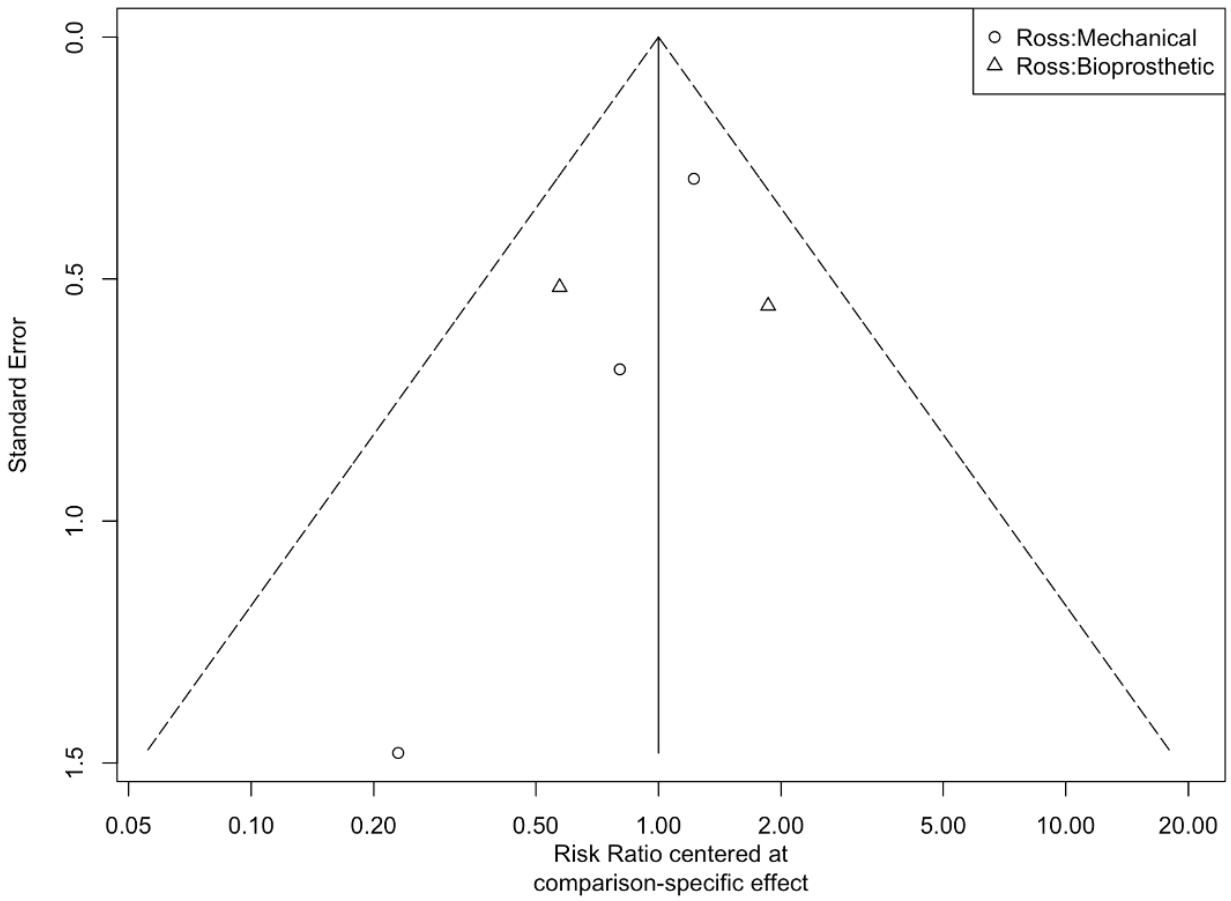
C)


Ross:Mechanical
Ross:Bioprosthetic
Mechanical:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio centered at
comparison-specific effect

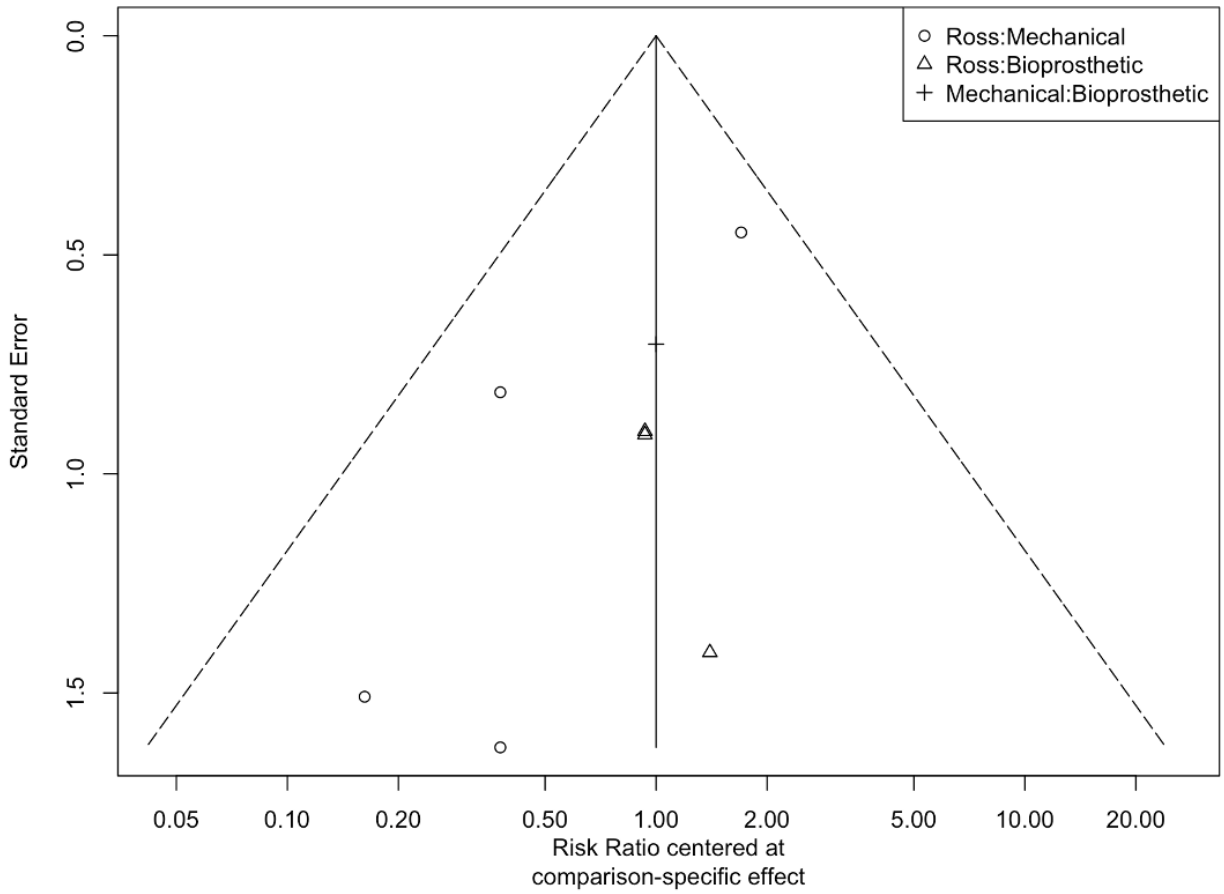
D)


Ross:Mechanical
Ross:Bioprosthetic
Mechanical:Bioprosthetic
Standard Error
0.0
0.1
0.2
0.3
0.4
0.5
1.0
1.5
2.0
2.5
Risk Ratio centered at
comparison-specific effect

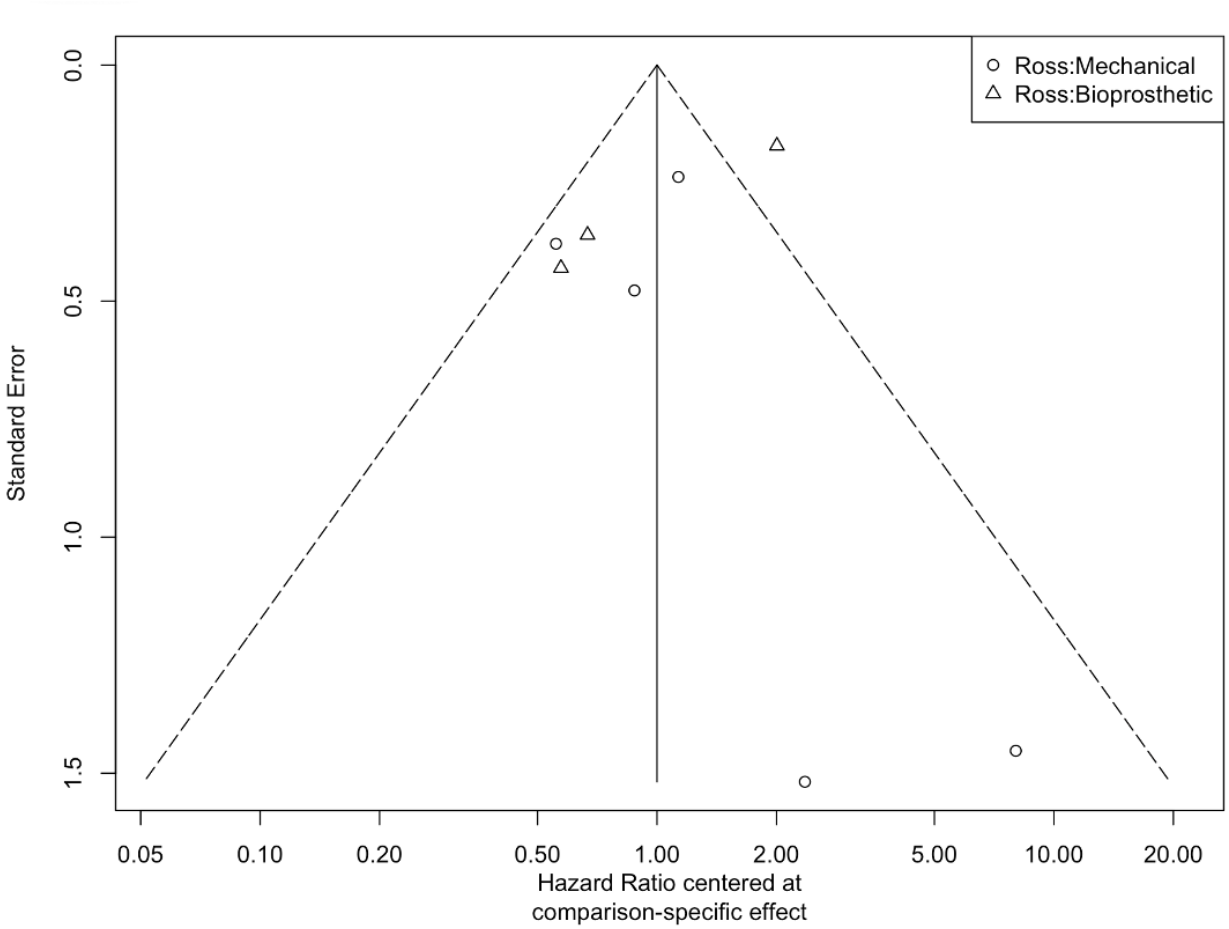
E)


Ross:Mechanical
Ross:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio centered at
comparison-specific effect

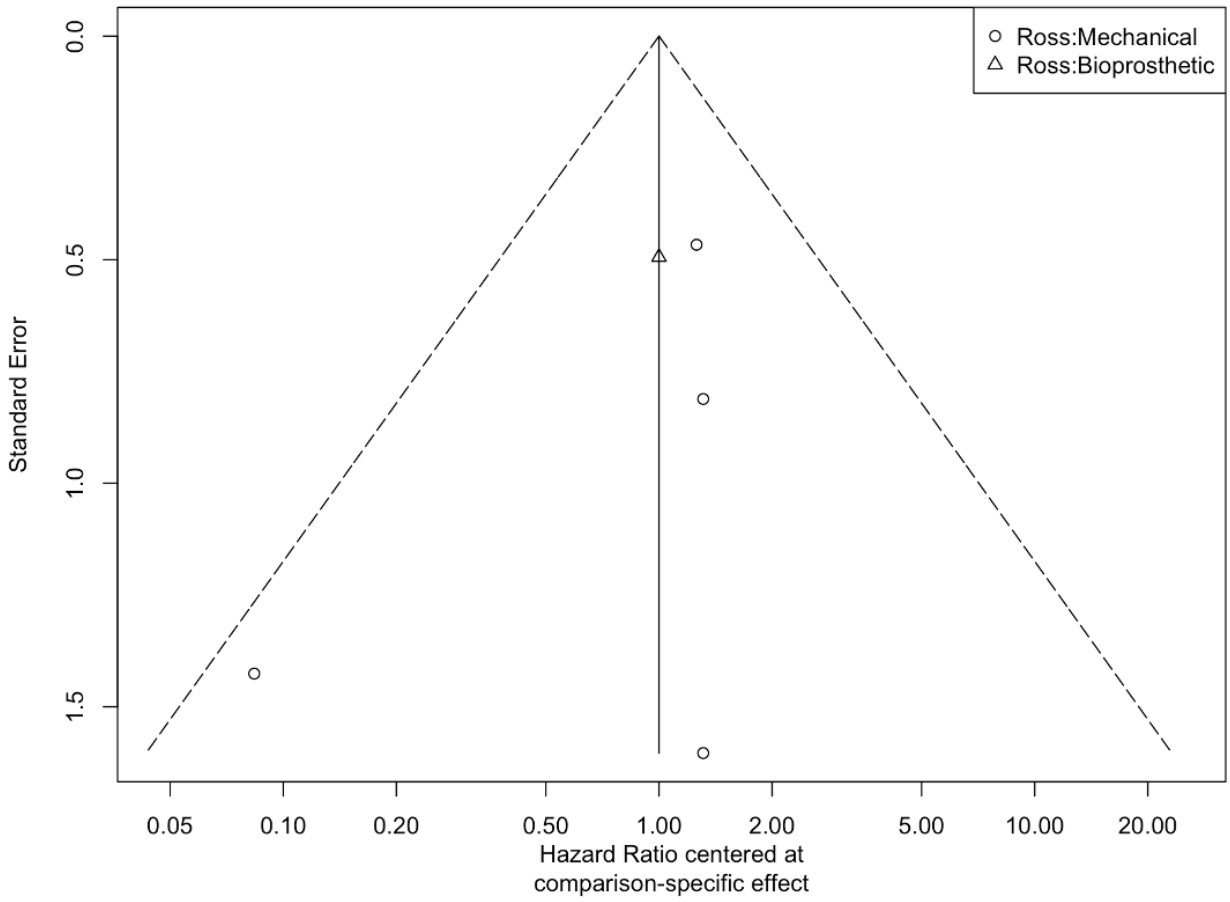
F)


Ross:Mechanical
Ross:Bioprosthetic
Mechanical:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Risk Ratio centered at
comparison-specific effect

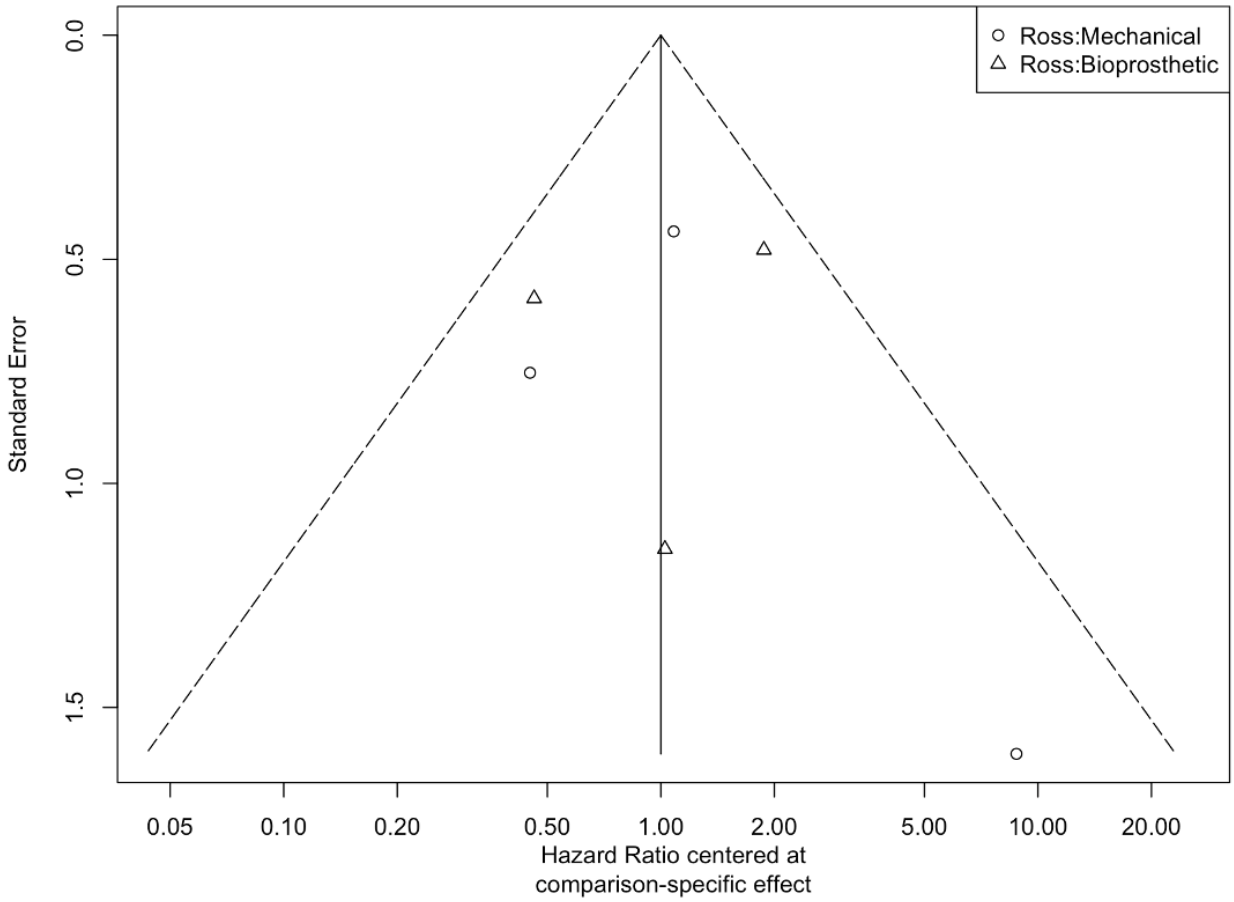
G)


Ross:Mechanical
Ross:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Hazard Ratio centered at
comparison-specific effect

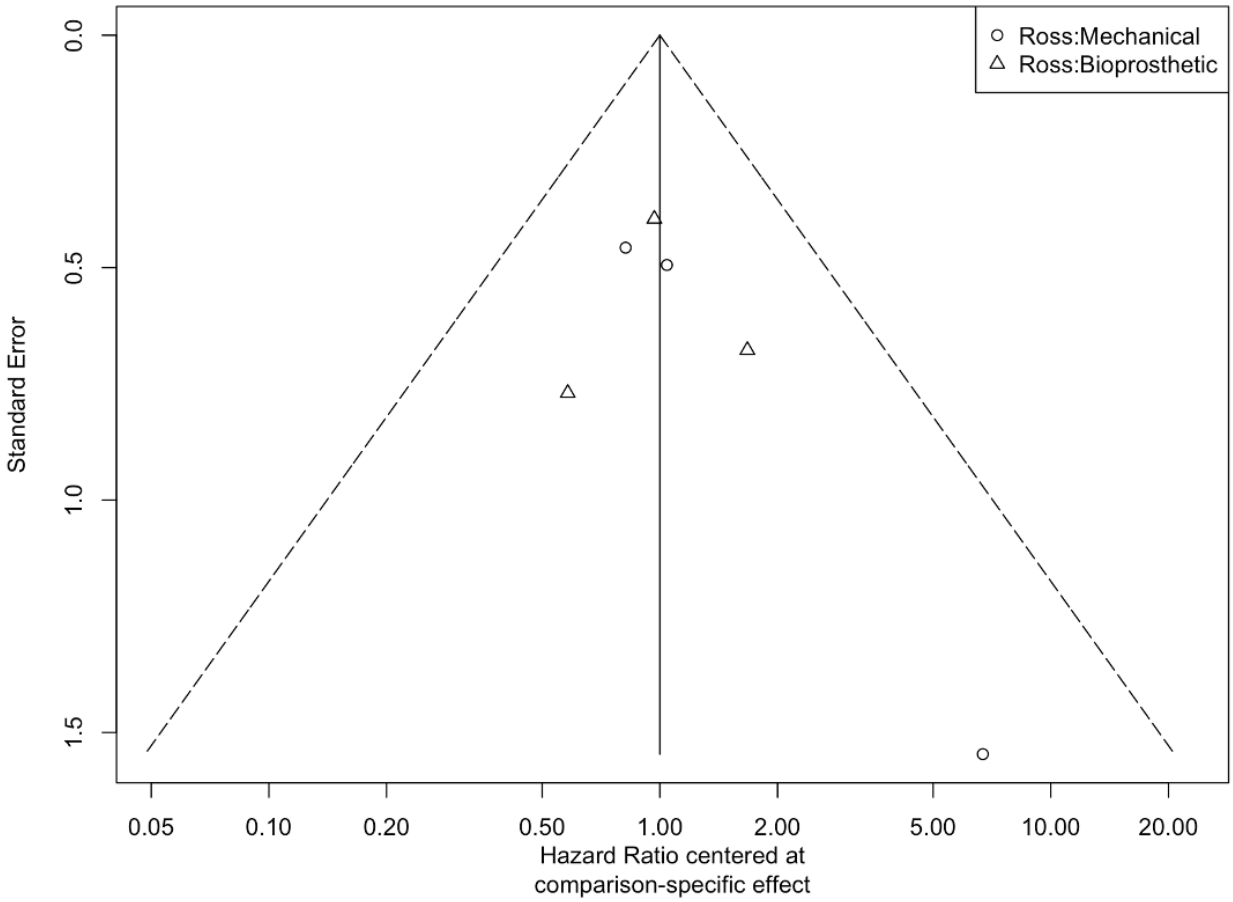
H)


Ross:Mechanical
Ross:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Hazard Ratio centered at
comparison-specific effect

I)


Ross:Mechanical
Ross:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Hazard Ratio centered at
comparison-specific effect

J)


Ross:Mechanical
Ross:Bioprosthetic
Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Hazard Ratio centered at
comparison-specific effect