Systematic Review

Early and mid-term outcomes of aortic annular enlargement: a systematic review and meta-analysis

Dustin Tanaka[1], Dominique Vervoort[1], Amine Mazine[1], Lina Elfaki[1], Jennifer C. Y. Chung[1,2], Jan O. Friedrich[3], Maral Ouzounian[1,2]

[1]Division of Cardiac Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada; [2]Division of Cardiovascular Surgery, Peter Munk Cardiac Center, Department of Surgery, University of Toronto, Toronto, ON, Canada; [3]Department of Medicine and Interdepartmental Division of Critical Care, University of Toronto and Unity Health Toronto-St. Michael's Hospital, Toronto, ON, Canada

Correspondence to: Maral Ouzounian, MD, PhD. Division of Cardiovascular Surgery, Peter Munk Cardiac Center, University Health Network-Toronto General Hospital, 200, Elizabeth Street, Eaton North, Room 4-464, Toronto, ON M5G 2C4, Canada. Email: maral.ouzounian@uhn.ca; Jan O. Friedrich, MD, DPhil. Critical Care and Medicine Departments, Unity Health Toronto-St. Michael's Hospital, 30 Bond Street, Room 4-015 Bond, Toronto, ON M5B 1W8, Canada. Email: jan.friedrich@unityhealth.to.

Background: There is mounting evidence at experienced centers that aortic annular enlargement (AAE) procedures are safe adjuncts to surgical aortic valve replacement (SAVR) that do not increase perioperative morbidity and mortality. This systematic review and meta-analysis aims to assess the impact of AAE procedures on mid-term outcomes after SAVR.

Methods: OVID MEDLINE, OVID Embase, and Cochrane Library were searched comprehensively. Comparative studies examining adult patients undergoing SAVR with and without AAE were eligible for inclusion. Studies involving aortic root replacement, Ross procedures, and Ozaki procedures were excluded. The risk of bias was assessed according to Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I), and the quality of evidence was evaluated according to Grading of Recommendations Assessment, Development and Evaluation (GRADE). Random effects meta-analysis facilitated the quantitative synthesis.

Results: A total of 2,765 records were retrieved. After full-text review, 15 eligible studies were identified for data extraction and synthesis. The dataset included a total of 216,654 patients (AAE: 7,967; no AAE: 208,687). Only mid-term outcomes were available. In unmatched and unadjusted studies, perioperative mortality was noted to be higher in the AAE group. However, this difference was not observed in studies with matching or adjusted outcomes. In both the unmatched and unadjusted studies, and the matched and adjusted studies, there were no statistically significant differences identified regarding perioperative stroke, myocardial infarction, or permanent pacemaker implantation. Similarly, there were no statistically significant differences identified in mid-term mortality [hazard ratio (HR), 1.03; 95% confidence interval (CI): 0.95 to 1.11; P=0.49; I^2=20% (matched/adjusted studies)], aortic valve reintervention [HR, 0.98; 95% CI: 0.75 to 1.27; P=0.86; I^2=0% (matched/adjusted studies)], or heart failure [HR, 1.06; 95% CI: 0.86 to 1.30; P=0.58; I^2=25% (matched/adjusted studies)].

Conclusions: SAVR with AAE does not appear to be associated with increased perioperative morbidity or mortality. There is no conclusive indication that AAE enhances mid-term survival, freedom from reoperation, or freedom from heart failure after SAVR.

Keywords: Aortic annular enlargement (AAE); aortic root enlargement; small aortic annulus; systematic review; meta-analysis

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Introduction

Patient-prosthesis mismatch (PPM) is widely recognized as a significant factor impacting clinical outcomes following prosthetic valve implantation. In the context of surgical aortic valve replacement (SAVR), PPM, whether moderate or severe, has been shown to increase both all-cause mortality and cardiac-related mortality (1). In the current era, patients with PPM continue to have reduced long-term survival, as well as an increased risk of rehospitalizations for heart failure (2,3), with some studies also suggesting an increased risk of re-replacement of the aortic valve (3).

To minimize the risk of PPM, the largest possible prosthetic valve should be implanted in each patient. When the native aortic root is small, i.e., at increased risk of PPM, an important approach is to enlarge the aortic annulus before implanting a prosthetic valve. This technique is referred to as aortic annular enlargement (AAE) and includes a variety of techniques, each differing in terms of either the location of the annular incision or the extent of the incision. These techniques include the posterior incisions of Nicks (4,5), Manouguian (5,6), the Nunez modification to the Manouguian (5,7), and the Y-incision described by Yang *et al.* (8). Additionally, the anterior annular incision with a right ventricular outflow tract (RVOT) incision, the Konno procedure (9), is often reserved for congenital heart disease and adult congenital heart disease applications. Despite the increasing importance of addressing PPM, the most recent valvular heart disease guidelines do not address when or if AAE should be performed (10,11).

There is mounting evidence at experienced centers (8,12,13) that AAE procedures are safe adjuncts to SAVR that do not increase perioperative morbidity and mortality (8,12-15). Despite the increasing experience with AAE at high-volume centers, there is an absence of high-quality evidence related to the long-term results of AAE. There are no comparative studies of AAE versus SAVR without AAE that report mean follow-up periods of 10 years or more. With the literature available, it is unclear how AAE influences the mid- and long-term outcomes of SAVR (14,16).

The most recent meta-analysis examining mid-term survival after AAE was completed by Sá *et al.* in 2022 (16). Kaplan-Meier curves were required for their quantitative synthesis to generate individual patient data (IPD) using one method of IPD extraction by Liu and colleagues (17). Therefore, their review excluded seven studies due to the absence of Kaplan-Meier curves (16). The other relevant meta-analyses were completed by Yu *et al.* in 2019 (14) and Sá *et al.* in 2021 (15). While Yu *et al.* (14) examined mid-term mortality with five studies published up to 2018, Sá *et al.* (15) limited their analysis to the perioperative outcomes of AAE. Thus, this systematic review features the most up-to-date and inclusive meta-analysis on the impact of AAE on both the perioperative and mid-term outcomes after SAVR.

Methods

This systematic review is based on a protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD 42023461543). The protocol was developed according to the Cochrane Handbook for Systematic Reviews of Interventions (18), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) statement (19), with consultation from a health sciences librarian at the Gerstein Science Information Centre at the University of Toronto.

Literature search strategy

OVID MEDLINE, OVID Embase, and Cochrane Library were searched comprehensively with no limits on the publication time period or language. The search was completed on August 3, 2023. Search terms included "aortic annular enlargement, aortic root enlargement, and aortic valve replacement", along with relevant synonyms. The reference lists of included studies were reviewed to retrieve additional eligible studies. Grey literature sources were not searched. The search strategy was developed in collaboration with a health sciences librarian at the Gerstein Science Information Center.

Eligibility criteria

Randomized controlled trials (RCTs), controlled (non-randomized) clinical trials, and comparative observational studies were eligible for inclusion. Non-comparative observational studies, case reports, conference proceedings, abstracts, commentaries, letters to the editor, and unpublished work were excluded. The population was limited to adult patients, 18 years or older, who underwent SAVR. Studies that included concurrent procedures were eligible for inclusion, except those that included aortic root replacement with bioprosthetic or mechanical valves, homograft root replacement, the Ozaki procedure, and the Ross procedure. Any study that included patients with a prior aortic root replacement or Ross procedure was also excluded. To be eligible for inclusion, each comparative study needed to have a clearly defined intervention group that underwent SAVR with AAE, and a clearly defined comparator group that underwent SAVR without AAE. Eligible AAE procedures included the following techniques: Nicks (4,5), Manouguian (5,6), Nunez modification to the Manouguian (5,7), Y-incision (8), Konno (9), and any other aortic annular incision that did not require coronary button mobilization and reimplantation. To be eligible for inclusion, each study needed to report on at least one of the outcomes of interest through at least 5 years of follow-up. This was confirmed through a full-text review of the potentially eligible studies by two independent reviewers. The primary outcome of interest was all-cause mortality. Relevant secondary outcomes included cardiac mortality, aortic valve reintervention, structural valve deterioration and non-structural valve dysfunction, valve thrombosis, infective endocarditis, major bleeding, stroke, and rehospitalization for heart failure. While this review intended to examine the long-term results following AAE, due to the absence of studies with mean follow-up lengths beyond 10 years, only mid-term outcomes were assessed.

Data extraction and critical appraisal

Search results were de-duplicated in EndNote (Berkeley, California, USA) and were uploaded to Covidence (Covidence, Melbourne, Australia), an online platform that facilitates de-duplication, record screening, and data extraction for systematic reviews. Title and abstract screening were performed in Covidence by two independent reviewers. Disagreements were resolved by consensus, involving a third reviewer if consensus could not be reached. The records that remained after title and abstract screening underwent a full-text review by two independent reviewers. Data were extracted by two independent reviewers and included study design, patient demographics, surgical techniques, perioperative surgical outcomes, and long-term outcomes of interest. The data extraction form is available on request. Two of the included studies contained Kaplan-Meier curves that required digitization (20,21). This was performed using a web-based Shiny application previously developed by Liu and colleagues to facilitate the digitization and reconstruction of IPD from published Kaplan-Meier curves (17). Risk of bias was assessed in duplicate according to the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, as all the eligible studies were of non-randomized design (18,22,23). An overall rating of low risk of bias is uncommon within the ROBINS-I methodology as this would mean that the observational study being evaluated would be comparable to a well-designed RCT examining the same question. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to determine the overall quality of evidence (24,25). This was completed by two reviewers based on consensus. Results are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (26).

Statistical analysis

Analyses were performed using Review Manager (RevMan version 5.4; Cochrane Collaboration, Oxford, UK) and random effects models, which incorporated between-trial heterogeneity and provided wider and more conservative confidence intervals (CIs) when heterogeneity was present (27). We assessed statistical heterogeneity among trials using I^2, which is defined as the percentage of total variability across studies attributable to heterogeneity rather than chance. Published guidelines categorized I^2 values as low (25% to 49%), moderate (50% to 74%), and high (≥75%) heterogeneity (28). For peri-operative outcomes, relative risks (RRs) were used to pool binary outcomes, and the mean difference (MD) was employed for continuous outcomes. When required, the method of Wan *et al.* (29) was used to convert continuous variables reported as medians and interquartile ranges, or ranges to means and standard deviations. For mid-term outcomes with different follow-up periods between groups, we pooled hazard ratios (HRs) or, if not provided, incidence rate ratios (IRRs) as approximations of the HR on the logarithmic scale using the generic inverse variance method in Review Manager. IRRs for each study were calculated either (I) as the ratio of the Kaplan-Meier survival-curve mortality estimates for each group, with standard error estimated using either the log-rank survival curve P value when available, or alternatively using the standard errors of the survival-curve mortality estimates and the ratio of means method (30,31); or otherwise (II) as the ratio of reported events divided by the group-specific patient-years of follow-up when the group-specific mean follow-up durations were provided,

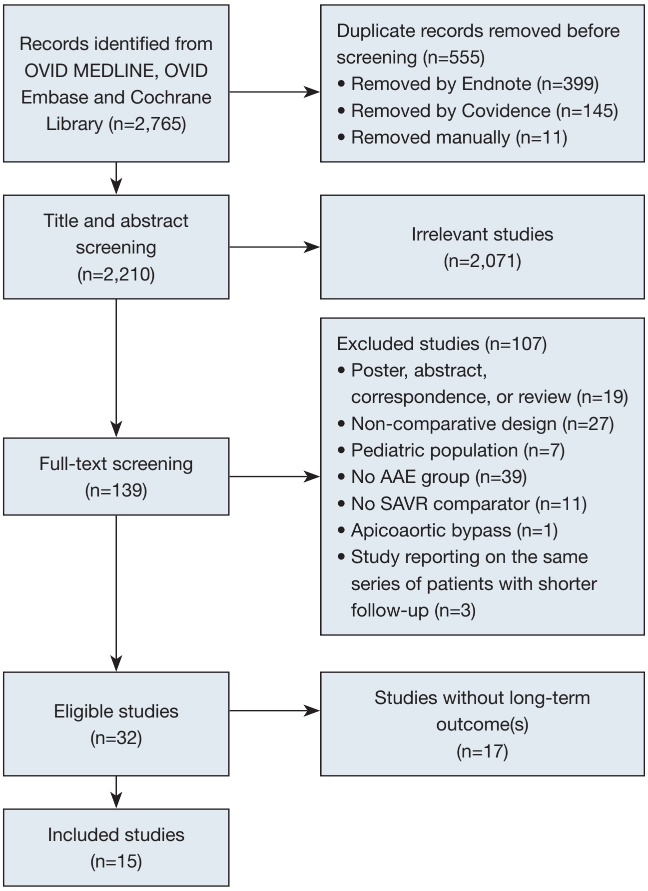

Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement.

with standard error on the logarithmic scale estimated as the square root of the sum of the reciprocals of the event rates (32). Individual trial and pooled summary results were reported with 95% CIs. Separate sub-groups were created for propensity-score matched or risk-adjusted observational data and unmatched/unadjusted observational data. The *a priori*-determined sensitivity analyses included studies at moderate versus serious and critical risk of bias, studies with both moderate and serious risk of bias versus critical risk of bias, and studies with and without concomitant procedures. An additional sensitivity analysis was performed to assess the impact of the Rao *et al.* study, as the procedures used in the AAE cohort were markedly heterogeneous (12). Uncertainty for the pooled binary and continuous outcomes is represented by 95% CIs. Differences between subgroups were assessed using *Z*-tests. P<0.05 was taken as statistically significant.

Results

Literature search

The search strategy retrieved 2,765 records. After de-duplication, 2,210 unique records remained. Title and abstract screening were performed in duplicate, identifying 139 potentially eligible studies that underwent full-text review by two independent reviewers. Overall, 32 potentially eligible studies (12,13,20,21,33-51) were identified (52-60), including 17 studies (13,45-60) that were excluded because they did not include any information on at least one of the mid-term outcomes of interest through 5 years of follow-up. Consequently, 15 unique studies (12,20,21,33-44) remained and were included in data extraction and quantitative synthesis. The screening process is summarized in the PRISMA trial flow diagram (*Figure 1*).

Quality of evidence

All 15 included studies are observational and non-randomized (12,20,21,33-44). Of the included studies, five compared propensity-matched groups (34,36,38,41,43), two employed case-control designs to define their reference SAVR groups (34,42), and four reported adjusted mid-term outcomes of interest (21,37,43,44). Notably, Tam and colleagues described two distinct cohorts of patients within the same study—patients who underwent isolated SAVR with or without AAE, and patients who underwent SAVR combined with coronary artery bypass grafting (CABG) with or without AAE (43). As a result, these cohorts were extracted independently, and then combined in the pooled analyses. Only three studies were based on multicentre patient data (12,21,43); the rest reported single-center outcomes (20,33-42,44).

Risk of bias was assessed for each outcome of interest within the included studies according to the ROBINS-I framework (*Figure 2* and Figure S1, and Appendix 1) (18,22,23). None of the included studies within our systematic review were deemed to have an overall low risk of bias. Only three included studies reported on outcomes at moderate risk of bias (38,41,43). Mid-term mortality was deemed to be at moderate risk of bias in the studies by Shih *et al.*, Tam *et al.*, and Okamoto *et al.* (38,41,43). Cumulative incidence of aortic valve reintervention was assessed to be at moderate risk of bias in the study reported by Tam and colleagues (43). All five studies that reported on heart failure-related endpoints were at serious or critical risk of bias for that outcome (12,21,37,38,43). The

First author	Year	Domain 1-confounding	Domain 2-selection	Domain 3-classification of interventions	Domain 4-deviations from intended interventions	Outcome-specific domains	Domain 5-missing data	Domain 6-outcome measurement	Domain 7-reported results	Overall risk of bias	Outcome
Matched or adjusted observational studies											
Yousef	2023	S	L	M	L	Mortality	M	L	M	S	Mortality
						AoV reintervention	M	M	M	S	AoV reintervention
Shih	2022	M	L	M	L	Mortality	L	L	M	M	Mortality
						AoV reintervention	L	M	M	M	AoV reintervention
Mehaffey	2021	S	L	S	L	Mortality	L	L	M	S	Mortality
						AoV reintervention	L	M	M	S	AoV reintervention
						CHF rehospitalization	L	S	M	S	CHF rehospitalization
Chauvette	2020	S	L	L	NI	Mortality	L	L	M	S	Mortality
Tam	2020	M	L	L	L	Mortality	L	L	M	M	Mortality
						AoV reintervention	L	M	M	M	AoV reintervention
						CHF rehospitalization	L	S	M	S	CHF rehospitalization
Tam*	2020	M	L	L	L	Mortality	L	L	M	M	Mortality
Haunschild	2019	M	L	L	M	Mortality	S	L	M	S	Mortality
Okamoto	2016	M	L	L	L	Mortality	NI	L	M	M	Mortality
						CHF	NI	S	NI	S	CHF
Kulik	2008	S	L	L	C	Mortality	M	L	M	C	Mortality
						CHF composite	M	S	M	C	CHF composite
Sommers	1997	S	L	L	NI	Mortality	L	L	M	S	Mortality
Unmatched/unadjusted observational studies											
Rao	2023	C	L	S	C	Mortality	S	L	L	C	Mortality
						AoV reintervention	S	M	L	C	AoV reintervention
						NYHA III–IV	S	S	L	C	NYHA III–IV
Beckmann	2016	S	L	L	C	Mortality	S	L	M	C	Mortality
Correia	2016	S	L	S	C	Mortality	L	L	M	C	Mortality
Prifti	2015	C	L	L	M	Mortality	NI	L	S	C	Mortality
						AoV reintervention	NI	M	S	C	AoV reintervention
Penaranda	2014	S	L	L	S	Mortality	M	L	M	S	Mortality
Sakamoto	2006	C	L	L	NI	Mortality	NI	NI	M	C	Mortality
						Reoperation**	NI	M	M	C	Reoperation**

Figure 2 ROBINS-I assessment for mortality, aortic valve reintervention, and heart failure. *, distinct secondary cohort reported within the same publication; **, long-term reoperation outcome was assumed to be related to aortic valve reintervention. L, low risk of bias; M, moderate risk of bias; S, serious risk of bias; C, critical risk of bias; NI, no information; AoV, aortic valve; CHF, congestive heart failure; NYHA, New York Heart Association; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions.

remaining studies and their other reported outcomes of interest were at serious or critical risk of bias (12,20,21,33-37,39,40,42,44).

Publication bias was assessed with visual analysis of the funnel plot for the primary outcome, mid-term mortality (*Figure 3*), with no indication of significant asymmetry.

Baseline demographics

Meta-analyses of baseline characteristics (*Table 1* and Table S1)

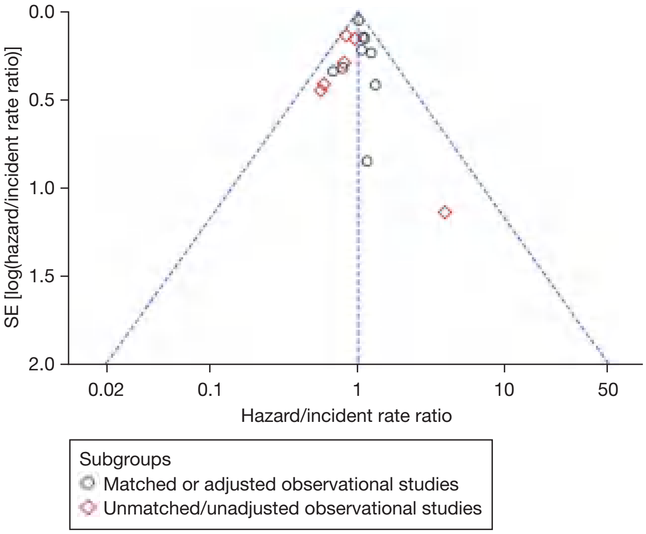

Figure 3 Funnel plot for mid-term mortality. SE, standard error.

were performed to assess for differences between groups and the effectiveness of matching in the relevant studies (Figures S2-S31). Prior to adjustment or matching, patients who underwent AAE at the time of SAVR were younger (MD, −1.72 year; 95% CI: −2.61 to −0.82), less likely to be male sex (RR, 0.72; 95% CI: 0.63 to 0.81), and had higher body mass index (BMI; MD, 1.80 kg/m^2; 95% CI: 0.44 to 3.16), at the same body surface area (BSA; MD, −0.01 m^2; 95% CI: −0.03 to 0.01). They were less likely to have chronic renal failure (RR, 0.87; 95% CI: 0.77 to 0.99), coronary artery disease (RR, 0.92; 95% CI: 0.86 to 0.98), and preoperative atrial fibrillation (RR, 0.77; 95% CI: 0.69 to 0.86). They were more likely to have diabetes (RR, 1.13; 95% CI: 1.10 to 1.16), and a history of prior SAVR (RR, 4.54; 95% CI: 2.45 to 8.44). Despite having a slightly higher preoperative left ventricular ejection fraction (LVEF; MD, 0.87%; 95% CI: 0.11% to 1.62%), they tended to have a smaller preoperative aortic valve area (MD, −0.05 cm^2; 95% CI: −0.08 to −0.02), including when indexed to BSA [indexed effective orifice area (iEOA); MD, −0.03 cm^2/m^2, 95% CI: −0.05 to −0.01], a smaller aortic annular diameter (MD, −1.36 mm; 95% CI: −2.12 to −0.59), and were more likely to present with predominantly stenotic aortic valve disease (RR, 1.03; 95% CI: 1.01 to 1.05). There were no significant differences regarding BSA, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), smoking, dialysis, hypertension, dyslipidemia, peripheral vascular disease, congestive heart failure/reduced LVEF, New York Heart Association (NYHA) class III–IV, mean NYHA class, elective versus urgent/emergent surgery, Society of Thoracic Surgeons (STS) risk score, prior cardiac surgery, peak aortic gradient, mean aortic gradient, or bicuspid aortic valve. When examining only the studies with matching or adjusted outcomes, almost all significant baseline differences disappeared, with the only exceptions being that patients undergoing AAE had higher preoperative BMI (MD, 1.24 kg/m^2; 95% CI: 0.18 to 2.31), with no significant difference in their BSA, and were less likely to have a bicuspid aortic valve (RR, 0.64; 95% CI: 0.43 to 0.95).

Of the 15 included studies, only five described attempting to standardize the size of the native aortic annulus between the SAVR with AAE and SAVR without AAE groups, including two matched/adjusted studies (37,41) and three unmatched and unadjusted studies (33,35,39). Kulik *et al.* described both groups as having a native annulus that would have necessitated a size 21 prosthesis or smaller (37). Shih *et al.* incorporated the aortic valve area into their propensity score matching model (41). Beckmann *et al.* defined both groups as having a projected iEOA ≤0.89 cm^2/m^2 when measured intraoperatively (33). Correia *et al.* defined both groups as having an implanted prosthesis size of 21 mm or smaller (35). Penaranda *et al.* defined both groups as having an annulus that would only accept a maximum valve size of 19 mm prior to any annular enlargement being performed (39).

Intraoperative details

AAE was performed through a variety of techniques (*Table 2*). The most common approaches were the Nicks, and the Manouguian procedures. Only one study (20) described the use of the Nunez technique in combination with the Nicks root enlargement. None of the included studies described the use of the Konno or Y-incision techniques. Importantly, two of the three largest multicentre studies did not capture the AAE technique within their study data (21,43). In both cases, this was due to limitations of the databases used in each of these studies; Mehaffey and colleagues used the STS Adult Cardiac Surgery Database (21), while Tam and colleagues used the CorHealth Ontario Cardiac Registry in combination with the Canadian Institute of Health Information Discharge Abstract Database to collect procedural data for each patient (43). Finally, in the multicentre study reported by Rao and colleagues, there was marked heterogeneity within the proposed aortic root

Table 1 Characteristics of included studies (brief)

First author	Year	Cohort size	Group		Group number		Age (year)		Male sex (%)		Body surface area (m^2)	
			AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies												
Yousef	2023	2,371	AAE + AVR	Isolated AVR	131 (5.5%)	2,240 (94.5%)	62.0 [55.0–70.0]	68.0 [60.0–76.0]	32.1	63.6	1.99±0.27	2.03±0.27
Shih	2022	216	AAE + AVR	Isolated AVR	54 (25%)	162 (75%)	63.92±12.63	64.94±10.84	29.6	29.0	1.89±0.28	1.91±0.25
Mehaffey	2021	189,268	AAE + AVR	AVR	5,412 (2.9%)	183,856 (97.1%)	75 [70–79]	76 [71–81]	40.0	62.0	–	–
Chauvette	2020	125	AAE + Redo AVR	Redo AVR	21 (16.8%)	104 (83.2%)	63±3	63±3	28.6	42.3	–	–
Tam	2020	1,618	AAE + AVR	Isolated AVR	809 (50%)	809 (50%)	65.57±12.36	65.48±13.38	43.3	44.4	1.92±0.27	1.91±0.26
Tam*	2020	1,050	AAE + AVR + CABG	AVR + CABG	525 (50%)	525 (50%)	72.12±8.80	72.36±8.68	54.1	53.5	1.94±0.24	1.94±0.25
Haunschild	2019	338	AAE + AVR	AVR	169 (50%)	169 (50%)	67.48±10	67.58±9	34.0	34.0	1.9±0.2	1.9±0.2
Okamoto	2016	116	AAE + AVR	AVR	58 (50%)	58 (50%)	73.4±11.9	74.7±8.5	19.0	19.0	1.45±0.16	1.38±0.16
Kulik	2008	712	AAE + AVR	AVR in SAR	172 (24.2%)	540 (75.8%)	66.8±12.3	69.1±11.8	30.8	25.2	–	–
Sommers	1997	530	AAE + Medtronic Hancock II bioAVR	Medtronic Hancock II bioAVR	98 (18%)	432 (82%)	64±13	64±12	55.0	87.0	1.79±0.22	1.83±0.19
Unmatched/unadjusted observational studies												
Rao	2023	602	Aortic root, STJ, or annular enlargement + Medtronic Avalus AVR	Medtronic Avalus AVR	90 (15.0%)**	512 (85.0%)	67.9±7.2	69.3±8.9	62.2	78.3	2.00±0.21	2.00±0.22
Beckmann	2016	128	AAE + bioAVR in SAR	Corcym Perceval bioAVR in SAR	36 (28.1%)	92 (71.9%)	62 (37–92)	79 (37–91)	16.7	18.5	1.8±0.2	1.8±0.2
Correia	2016	1,006	AAE + AVR in SAR	AVR in SAR	239 (23.8%)	767 (76.2%)	70.4±12.5	69.9±9.6	18.4	12.0	1.59±0.15	1.57±0.13
Prifti	2015	55	AAE + 19 mm supraannular AVR	17 mm supraannular AVR	35 (63.6%)	20 (36.4%)	67.6±10	69.75±7.4	17.0	10.0	1.68±0.16	1.67±0.2
Penaranda	2014	117	AAE + 21 mm AVR	19 mm AVR	30 (25.6%)	87 (74.4%)	83.8 (80.2–93.4)	84.1 (80.1–92.7)	13.0	2.0	1.7 (1.5–2.1)	1.6 (1.2–2.1)
Sakamoto	2006	128	AAE + St Jude mechAVR	St Jude mechAVR	24 (18.75%)	104 (81.25%)	52.6±11.9†		72.7†		1.60±0.15†	

Continuous variables are presented as n (%), percentage, mean ± standard deviation, median (range), or median [interquartile range]. *, distinct secondary cohort reported within the same publication; **, of 90 patients within the intervention arm, only 27 patients (30%) had a confirmed AAE and 3 patients (3.3%) within the intervention arm had an aortic root replacement; †, demographic information derived from the overall cohort of the respective study. AAE, aortic annular enlargement; AVR; aortic valve replacement; CABG, coronary artery bypass graft; bioAVR, bioprosthetic aortic valve replacement; STJ, sinotubular junction; SAR, small aortic root; mechAVR, mechanical aortic valve replacement.

Table 2 Aortic annular enlargement techniques

First author	Year	Cohort size	AAE group		No AAE group		Concomitant procedure(s)	AAE technique
			N	Description	N	Description		
Matched or adjusted observational studies								
Yousef	2023	2,371	131	AAE + AVR	2,240	Isolated AVR	No	55% Nicks; 45% Manouguian
Shih	2022	216	54	AAE + AVR	162	Isolated AVR	No	57.4% Nicks; 33.3% Manouguian; 9.3% unknown
Mehaffey	2021	189,268	5,412	AAE + AVR	183,856	AVR	Yes	NR
Chauvette	2020	125	21	AAE + redo AVR	104	Redo AVR	NR	24% Nicks; 71% Manouguian; 5% unknown
Tam	2020	1,618	809	AAE + AVR	809	Isolated AVR	No	NR
Tam*	2020	1,050	525	AAE + AVR + CABG	525	AVR + CABG	CABG	NR
Haunschild	2019	338	169	AAE + AVR	169	AVR	Yes	Nicks
Okamoto	2016	116	58	AAE + AVR	58	AVR	Yes	Nicks
Kulik	2008	712	172	AAE + AVR	540	AVR in SAR	Yes	28.5% Nicks; 71.5% Manouguian
Sommers	1997	530	98	AAE + Medtronic Hancock II bioAVR	432	Medtronic Hancock II bioAVR	NR	Nicks
Unmatched/unadjusted observational studies								
Rao	2023	602	90**	Aortic root, STJ, or annular enlargement + Medtronic Avalus bioAVR	512	Medtronic Avalus bioAVR	Yes	Of patients with confirmed ARE**: 70% Nicks; 15% Manouguian; 15% other
Beckmann	2016	128	36	AAE + bioAVR in SAR	92	Corcym Perceval bioAVR in SAR	Yes	Nicks
Correia	2016	1,006	239	AAE + AVR in SAR	767	AVR in SAR	Yes	Nicks
Prifti	2015	55	35	AAE + 19 mm supraannular AVR	20	17 mm supraannular AVR	Yes	77% Nicks-Nunez; 23% Manouguian
Penaranda	2014	117	30	AAE + 21 mm AVR	87	19 mm AVR	Yes	Nicks
Sakamoto	2006	128	24	AAE + St Jude mechAVR	104	St Jude mechAVR	NR	25% Nicks; 75% Manouguian

*, distinct secondary cohort reported within the same publication; **, only 27 patients had a confirmed AAE, and 3 patients had an aortic root replacement. AAE, aortic annular enlargement; AVR, aortic valve replacement; bioAVR, bioprosthetic aortic valve replacement; CABG, coronary artery bypass grafting; NR, not reported; SAR, small aortic root; STJ, sinotubular junction; mechAVR, mechanical aortic valve replacement.

enlargement group (12). Only 27 of the 90 patients in the group underwent a confirmed AAE, with three other patients undergoing an aortic root replacement within the group, and others within the group undergoing either a sinotubular junction (STJ) enlargement or a sinus of Valsalva patch augmentation.

The indication(s) for AAE were infrequently reported within the included studies (*Table 3*). When indications were

Table 3 Indications for and results of aortic annular enlargement

First author	Year	Cohort size	AAE group	AAE indication	AAE technique	Annular size increase
Matched or adjusted observational studies						
Yousef	2023	2,371	131	Surgeon discretion	55% Nicks; 45% Manouguian	NR
Shih	2022	216	54	NR	57.4% Nicks; 33.3% Manouguian; 9.3% unknown	NR
Mehaffey	2021	189,268	5,412	NR	NR	NR
Chauvette	2020	125	21	NR	24% Nicks; 71% Manouguian; 5% unknown	NR
Tam	2020	1,618	809	NR	NR	NR
Tam*	2020	1,050	525	NR	NR	NR
Haunschild	2019	338	169	Surgeon discretion: smaller annulus than expected; inability to close aortotomy	Nicks	NR
Okamoto	2016	116	58	Surgeon discretion: avoidance of severe PPM	Nicks	NR
Kulik	2008	712	172	Surgeon discretion	28.5% Nicks; 71.5% Manouguian	At least 1 valve size larger than native annulus
Sommers	1997	530	98	Surgeon discretion: sizing table for Hancock II relative to BSA	Nicks	1–2 valve sizes larger than native annulus
Unmatched/unadjusted observational studies						
Rao	2023	602	90**	Surgeon discretion	Of patients with confirmed ARE**: 70% Nicks; 15% Manouguian; 15% other	NR
Beckmann	2016	128	36	Surgeon discretion: small EOA relative to BSA	Nicks	At least 1 valve size larger than native annulus
Correia	2016	1,006	239	Surgeon discretion: SAR relative to BSA; at least 21 mm prosthesis could not be used	Nicks	1–2 valve sizes larger than native annulus
Prifti	2015	55	35	Surgeon discretion: SAR <19 mm; severe LVH; severe LVH in LVOT; extensively calcified SAR	77% Nicks-Nunez; 23% Manouguian	1 valve size larger (supraannular implantation)
Penaranda	2014	117	30	NR	Nicks	NR
Sakamoto	2006	128	24	Small aortic annulus (<21 mm when measured with valve sizer)	25% Nicks; 75% Manouguian	Manouguian technique gained 2 valve sizes

*, distinct secondary cohort reported within the same publication; **, only 27 patients had a confirmed AAE, and 3 patients had an aortic root replacement. AAE, aortic annular enlargement; NR, not reported; PPM, patient-prosthesis mismatch; BSA, body surface area; EOA, effective orifice area; SAR, small aortic root; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract.

reported, they were often listed as possible considerations that could be weighed at the surgeon's discretion at the time of the operation. Only the study by Sakamoto and colleagues described an objective criterion, aortic annulus smaller than a size 21 valve sizer, without indicating that the decision could also be influenced by surgeon preference (40). Correspondingly, the intraoperative results of the AAE procedures, i.e., the extent of annular enlargement achieved, were also infrequently described. The studies that did report the extent of annular enlargement described an implanted valve, at most, one-to-two valve sizes larger than the initial intraoperative measurement of the aortic root (20,33,35,37,40,42).

Operative details, including valve type, sizing, and rates of concomitant procedures, were pooled (Figures S32-S39). In the matched or adjusted studies, there were notable procedural differences between the AAE and SAVR groups. The patients undergoing AAE were less likely to receive a mechanical valve (RR, 0.80; 95% CI: 0.68 to 0.93), and required both longer cardiopulmonary bypass (MD, 21.33 min; 95% CI: 9.69 to 32.97) and aortic cross-clamp (MD, 19.25 min; 95% CI: 10.17 to 28.33) times. In the unmatched and unadjusted studies, patients receiving AAE were less likely to receive both concomitant mitral valve surgery (RR, 0.55; 95% CI: 0.39 to 0.78) and concomitant tricuspid valve surgery (RR, 0.27; 95% CI: 0.10 to 0.73). Implanted valve size in the AAE group was lower, but only in the matched/adjusted studies (MD, −0.67 mm; 95% CI: −1.09 to −0.25). Only one matched study described concomitant mitral and tricuspid valve surgeries, and these were well-balanced after propensity matching (38). Notably, there was no significant difference in the rate of concomitant CABG observed between groups, in either the matched/adjusted studies or the unmatched/unadjusted studies.

Perioperative outcomes

Perioperative outcomes were also assessed via meta-analyses (Figures S40-S55). In the unmatched and unadjusted studies, AAE patients were less likely to have severe PPM (iEOA ≤0.65 cm^2/m^2; RR, 0.61; 95% CI: 0.40 to 0.93), moderate or severe PPM (defined as iEOA ≤0.85 cm^2/m^2 in most studies; RR, 0.70; 95% CI: 0.58 to 0.84), and were at increased risk of chest reopening (RR, 1.10; 95% CI: 1.01 to 1.20). Notably, they were also at increased risk of perioperative mortality (RR, 1.34; 95% CI: 1.02 to 1.76), and prolonged mechanical ventilation/other respiratory complications (RR, 1.67; 95% CI: 1.23 to 2.26). However, when only the matched or adjusted studies were considered, the risks of perioperative mortality (RR, 1.06; 95% CI: 0.69 to 1.61), and prolonged ventilation/other respiratory complications (RR, 1.61; 95% CI: 0.75 to 3.47) were not significantly higher in the AAE group. In both the unadjusted/unmatched and the matched/adjusted studies, there were no significant differences identified regarding the risk of perioperative stroke, myocardial infarction, permanent pacemaker implantation, intensive care unit (ICU) length of stay, hospital length of stay, deep sternal wound infection, postoperative iEOA, moderate PPM, peak/mean transprosthetic gradient at discharge or paravalvular leak. The only perioperative complication that was found to be statistically significant in the matched and adjusted studies, was an increased risk of chest reopening in the AAE group (RR, 1.58; 95% CI: 1.13 to 2.21). This was primarily due to the results of Tam *et al.* (43), which accounted for 89% of the weighting for this matched/adjusted pooled outcome. Without the study from Tam *et al.* (43), the pooled outcome for the risk of chest reopening in the remaining matched/adjusted studies was no longer statistically significant (RR, 0.97; 95% CI: 0.36 to 2.65).

Assessment of primary and secondary endpoints

The only outcomes of interest with sufficient data to allow for pooled analysis were the mid-term mortality (*Figure 4*), aortic valve reintervention (*Figure 5*), and heart failure (*Figure 6*). The other outcomes of interest were reported by too few studies to provide meaningful pooled estimates of effect (Figures S56-S61).

Mid-term mortality was reported by nine studies with matched groups or adjusted outcomes (21,34,36-38,41-44) and six studies without matching or adjustment (12,20,33,35,39,40). The unmatched/unadjusted cohorts within six of the studies with matching/adjustment were also available and were included in the synthesis of unmatched/unadjusted studies (21,36,37,42-44). Of note, the study by Tam and colleagues yielded an independent secondary cohort, SAVR with CABG both with and without AAE, that contained both matched/adjusted and unmatched/unadjusted outcome data for mid-term mortality (43). The estimates from the primary and secondary cohorts were combined in the pooled analyses for mid-term mortality. The study by Mehaffey and colleagues, with a median follow-up of 3.3 years, provided two separate HRs for mid-term mortality, up to 3 years of follow-up, and greater than 3 years of follow-up (21). As the primary interest of the review was mid-term mortality, we elected to consolidate the two HRs into an average HR. Importantly, the pooled HR was unchanged when the two HRs were replaced by the average HR. Overall, there was no significant difference in the mid-term mortality observed between groups in either the unmatched/unadjusted (HR, 0.91; 95% CI: 0.80 to 1.03; P=0.12; I^2=63%) or matched/adjusted (HR, 1.03; 95% CI:

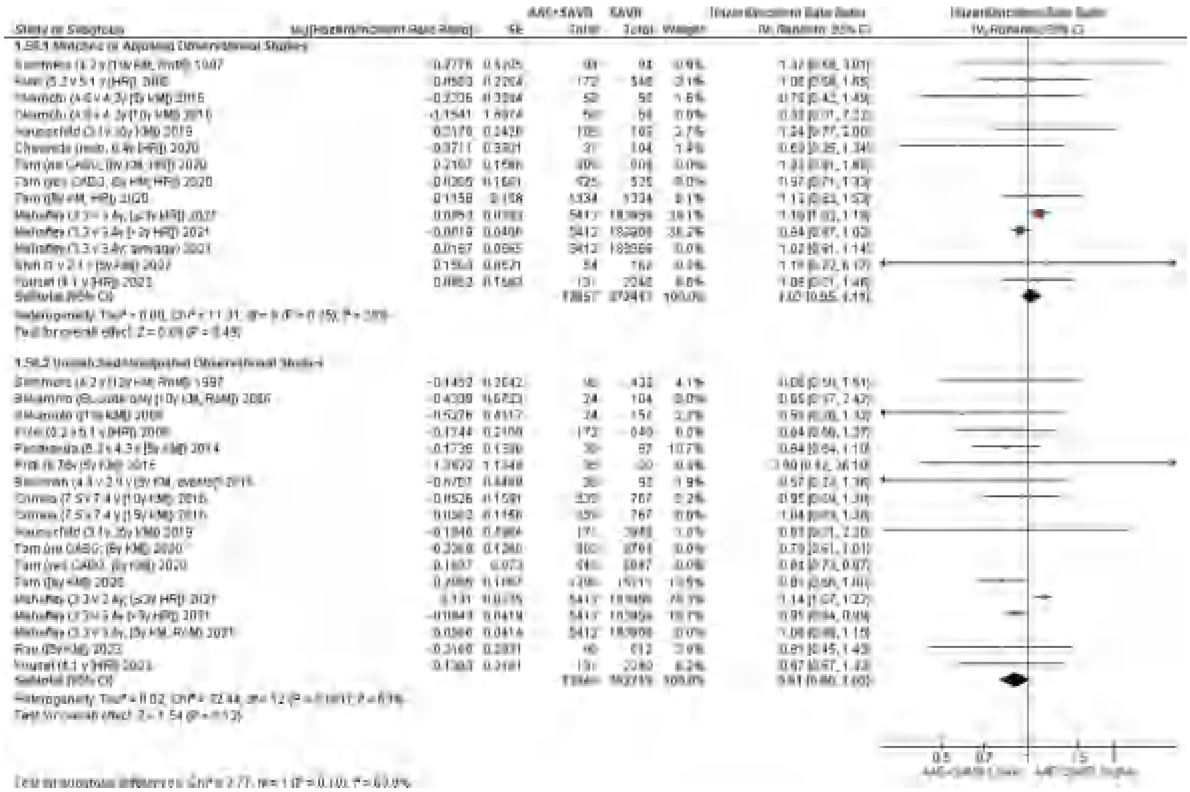

Figure 4 Meta-analysis for mid-term mortality. Mean duration of follow-up in round brackets for AAE + SAVR *vs.* SAVR groups; method used to calculate hazard ratio or incident rate ratio in square brackets. The ≤3 and >3 years HRs provided in Mehaffey *et al.* were replaced with an average HR as the pooled HR is essentially unchanged. AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement; SE, standard error; IV, inverse variance; CI, confidence interval; KM, Kaplan-Meier; HR, hazard ratio; CABG, coronary artery bypass graft; RoM, ratio of means.

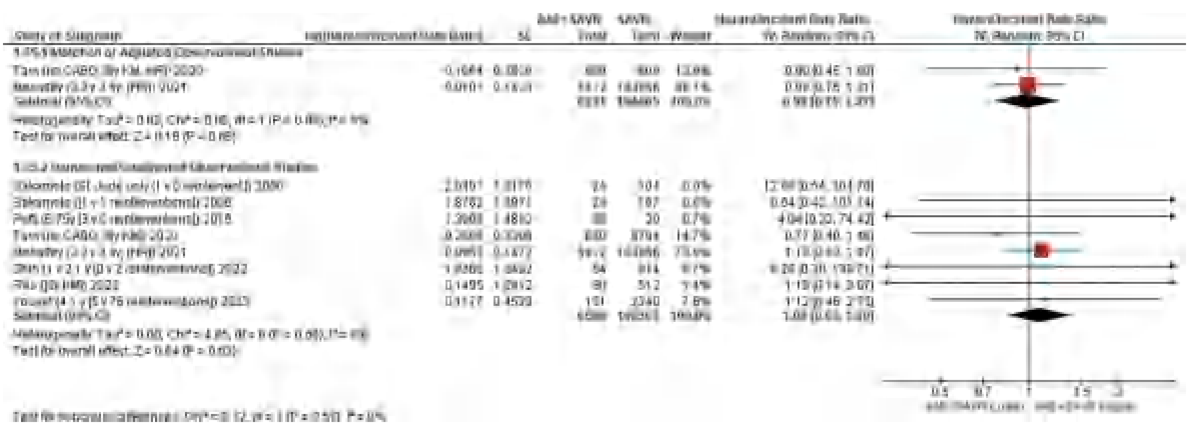

Figure 5 Meta-analysis for aortic valve reintervention. Mean duration of follow-up in round brackets for AAE + SAVR *vs.* SAVR groups; method used to calculate hazard ratio or incident rate ratio in square brackets. Tam *et al.*, Mehaffey *et al.*, and Rao *et al.* provided hazard ratios, and Shih *et al.* provided group-specific follow-up. For Sakamoto *et al.*, Prifti *et al.*, and Yousef *et al.*, where no group-specific follow-up or hazard ratio was provided, equal follow-up was assumed to calculate incident rate ratios. AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement; SE, standard error; IV, inverse variance; CI, confidence interval; CABG, coronary artery bypass graft; KM, Kaplan-Meier; HR, hazard ratio.

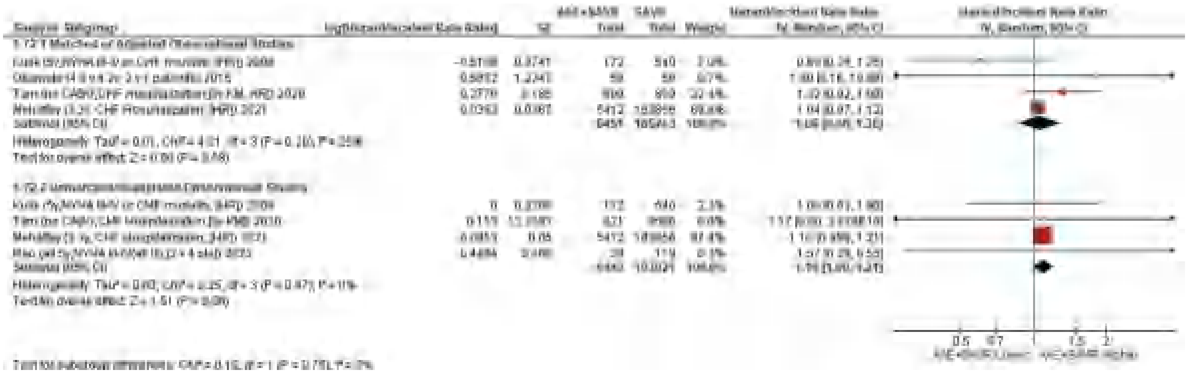

Figure 6 Meta-analysis for heart failure. Mean duration of follow-up in round brackets for AAE + SAVR *vs.* SAVR groups; method used to calculate hazard ratio or incident rate ratio in square brackets. AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement; SE, standard error; IV, inverse variance; CI, confidence interval; NYHA, New York Heart Association; CHF, congestive heart failure; HR, hazard ratio; CABG, coronary artery bypass graft; KM, Kaplan-Meier; pts, patients.

0.95 to 1.11; P=0.49; I^2=20%) studies.

Unmatched/unadjusted aortic valve reintervention was reported by seven studies (12,20,21,40,41,43,44). Two of the seven studies also reported matched or adjusted results (21,43). There was no significant difference in aortic valve reintervention observed between groups in either the unmatched/unadjusted studies (HR, 1.08; 95% CI: 0.85 to 1.39; P=0.53; I^2=0%) or the matched/adjusted studies (HR, 0.98; 95% CI: 0.75 to 1.27; P=0.86; I^2=0%).

Unadjusted/unmatched congestive heart failure was reported by four studies (12,21,37,43). Three of the four studies also reported matched or adjusted results (21,37,43), along with another study that reported only propensity-matched results (38). There was no significant difference in heart failure observed between groups in either the unmatched/unadjusted studies (HR, 1.10; 0.998 to 1.21; P=0.06; I^2=0%) or the matched/adjusted studies (HR, 1.06; 95% CI: 0.86 to 1.30; P=0.58; I^2=25%).

The overall quality of evidence for each outcome of interest was assessed using the GRADE methodology and is presented in the summary of findings table (*Table 4*) (24,25). For both mid-term mortality and aortic valve reintervention, the quality of evidence was low and very low in the matched/adjusted and the unmatched/unadjusted subsets, respectively. For heart failure, the quality of evidence was very low in both the matched/adjusted and the unmatched/unadjusted subsets. In the case of the matched or adjusted subsets, their ratings resulted from the inherent limitations of unblinded and non-randomized study designs. While for the unmatched and unadjusted subsets, the serious and critical risk of bias associated with multiple included studies warranted an additional downgrade to very low-quality evidence. Importantly, the matched/adjusted subset for heart failure was also downgraded to very low quality due to the presence of studies at serious and critical risk of bias (*Table 4* and Table S2).

Sensitivity analyses

Sensitivity analyses were performed to assess the impact of the Rao 2023 study (12), the inclusion of concomitant procedures, and the studies at various risk of bias levels (*Tables 5*,*6* and Figures S62,S63). The sensitivity analyses were limited to mid-term mortality and aortic valve reintervention, as there were too few included studies in the heart failure outcome to warrant additional hypothesis testing. The pooled results for both mid-term mortality and aortic valve reintervention did not differ with regards to the presence or absence of the Rao 2023 study (12), concomitant procedures, or the removal of either studies only at critical risk of bias or studies at both serious and critical risk of bias.

Discussion

As is consistent with the current understanding of AAE procedures, the results of this meta-analysis attest to their perioperative safety. The findings of no increased risk of perioperative mortality, myocardial infarction, permanent pacemaker implantation, or stroke when AAE is performed

Table 4 GRADE summary of findings table for pooled mid-term mortality, aortic valve reintervention, and heart failure outcomes

Outcome	SAVR + AAE group	SAVR group	Studies	Pooled estimate, HR (95% CI)	P value	Heterogeneity (I^2)	GRADE quality
Mid-term mortality—matched or adjusted	7,445	188,557	9*	1.03 (0.95, 1.12)	0.45	20%	Low[a]
Mid-term mortality—unmatched/unadjusted	7,834	208,363	12*	0.91 (0.80, 1.03)	0.12	63%	Very low[a,b]
Aortic valve reintervention—matched or adjusted	6,221	184,665	2	0.98 (0.75, 1.27)	0.86	0%	Low[a]
Aortic valve reintervention—unmatched/ unadjusted	6,596	196,363	7	1.08 (0.85, 1.39)	0.53	0%	Very low[a,b]
Heart failure—matched or adjusted	6,451	185,263	4	1.06 (0.86, 1.30)	0.58	25%	Very low[a,b]
Heart failure—unmatched/unadjusted	6,443	193,021	4	1.10 (0.998, 1.21)	0.06	0%	Very low[a,b]

GRADE Working Group grades of evidence—high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate. [a], quality limited by the absence of randomized and blinded study designs; [b], quality limited by the inclusion of studies at critical risk of bias; *, separate estimate from a secondary cohort of Tam *et al.* counted as the same study. GRADE, Grading of Recommendations Assessment, Development and Evaluation; SAVR, surgical aortic valve replacement; AAE, aortic annular enlargement; HR, hazard ratio; CI, confidence interval.

in appropriately matched patients, align with the previous work of Yu *et al.* (14) and Sá *et al.* (15). Similarly, this synthesis is aligned with the previous work of Yu *et al.* (14) and Sá *et al.* (16) that did not demonstrate a difference in mid-term mortality in appropriately matched patients. However, this review is the first to describe the mid-term risks of aortic valve reintervention and heart failure after AAE. It is also the first synthesis to identify an increased risk of chest reopening after AAE procedures that were present within matched groups. This finding was primarily driven by the increased risk of chest reopening in the secondary cohort of one study, i.e., SAVR with CABG with or without AAE (43). While Tam *et al.* (43) have theorized that this may have been due to the addition of AAE to a more complex operation, i.e., SAVR with CABG, this finding warrants further exploration, ideally through well-matched comparative studies with detailed descriptions of concomitant procedures.

Despite the increasing use of AAE during SAVR, there remains a paucity of long-term data concerning the impact of AAE on SAVR. For the studies that do have a mid-term follow-up, the reported outcome domains are sparse, with only enough data at this time to derive pooled estimates for all-cause mortality, aortic valve reintervention, and heart failure. A few of the many mid- and long-term outcomes that can factor into the decision to perform an AAE include cardiac mortality, stroke, and structural valve deterioration. Outcomes such as these are not available to patients and their surgeons in the context of AAE. At best, there is indirect evidence of the long-term viability of AAE procedures. When performed in high-volume centers of expertise or examined in syntheses (14,15) with appropriate adjustment to account for meaningful differences in baseline risks between patient populations, there appears to be no added perioperative morbidity or mortality due to AAE (8,12-15). When these procedures are successfully performed, the iEOA is either restored to that of a comparator group with a native annulus that can accommodate the same valve size without requiring augmentation, or the annular enlargement cohort exceeds the iEOA of a comparator group that received a valve that was sized too small relative to their BSA. Given the growing understanding of the risks posed by PPM, i.e., increased risk of mortality (2,3), heart failure rehospitalization (2,3), and aortic valve reintervention (3), a successful AAE cohort would be expected to either reach the equivalent survival to a comparator group with an appropriately sized valve or superior survival versus one with significant PPM.

The overall literature regarding AAE is poorly defined. Most studies do not report preoperative aortic annular dimensions, including the high-powered database studies that are often limited in that they lack the granularity of

Table 5 Sensitivity analyses for subgroup differences in mid-term mortality

Mid-term mortality	RR (95% CI)	N	Interaction P value
Matched/adjusted studies			
Primary analysis	1.03 (0.95, 1.11)	9	
Subgroup analyses: risk of bias			
Moderate *vs.* serious/critical	1.05 (0.80, 1.38) *vs.* 1.03 (0.93, 1.14)	3 *vs.* 6	0.89
Moderate/serious *vs.* critical	1.03 (0.94, 1.13) *vs.* 1.06 (0.68, 1.65)	8 *vs.* 1	0.90
Subgroup analysis: concomitant procedures			
Yes *vs.* not reported *vs.* no	1.02 (0.92, 1.13) *vs.* 0.91 (0.49, 1.71) *vs.* 1.16 (0.94, 1.43)	5 *vs.* 2 *vs.* 3	0.51 (0.28*)
Unmatched/unadjusted studies			
Primary analysis	0.91 (0.80, 1.03)	12	
Subgroup analyses: excluding Rao 2023 (reported only unmatched/unadjusted data)			
Excluding Rao 2023 *vs.* Rao 2023 only	0.91 (0.80, 1.04) *vs.* 0.81 (0.45, 1.43)	11 *vs.* 1	0.69
Subgroup analyses: risk of bias			
Moderate *vs.* serious/critical	0.81 (0.66, 1.00) *vs.* 0.99 (0.91, 1.08)	1 *vs.* 11	0.08
Moderate/serious *vs.* critical	0.92 (0.80, 1.06) *vs.* 0.85 (0.69, 1.06)	6 *vs.* 6	0.55
Subgroup analysis: concomitant procedures			
Yes *vs.* not reported *vs.* no	0.92 (0.81, 1.04) *vs.* 0.76 (0.48, 1.21) *vs.* 0.81 (0.65, 1.00)	9 *vs.* 2 *vs.* 2	0.50 (0.31*)
All studies (prioritizing matched/adjusted if unmatched/unadjusted also reported)			
Primary analysis (all studies)	1.00 (0.92, 1.08)	15	
Subgroup analyses: risk of bias			
Moderate *vs.* serious/critical	1.05 (0.80, 1.38) *vs.* 0.99 (0.90, 1.09)	3 *vs.* 12	0.67
Moderate/serious *vs.* critical	1.02 (0.93, 1.11) *vs.* 0.88 (0.72, 1.08)	8 *vs.* 7	0.21
Moderate *vs.* serious *vs.* critical	1.05 (0.80, 1.38) *vs.* 1.02 (0.91, 1.13) *vs.* 0.88 (0.72, 1.08)	3 *vs.* 5 *vs.* 7	0.44
Subgroup analysis: concomitant procedures			
Yes *vs.* not reported *vs.* no	0.99 (0.90, 1.08) *vs.* 0.79 (0.50, 1.25) *vs.* 1.16 (0.94, 1.43)	10 *vs.* 3 *vs.* 3	0.23 (0.17*)

*, interaction P value for yes *vs.* no concomitant procedures only (i.e., excluding studies in which concomitant procedures were not reported). RR, relative risk; CI, confidence interval.

individual patients' echocardiographic data. Matching patients in the annular enlargement and comparator groups by their native aortic annular dimensions is also rarely described. As such, it is rarely possible to determine whether the expected outcome is for the annular enlargement cohort to reach equivalence to an appropriately sized comparator or exceed the performance of a group with a significant PPM. The decision of when to perform AAE is similarly unclear. Although the adverse effects of PPM continue to be recognized, most studies either do not list objective decision-making criteria, such as predicted PPM, or when they do, they qualify the criteria with the decision remaining subject to surgeon discretion. When even the best available studies are subjected to this uncertainty, the possibility of unmeasured known and unknown confounders multiplies. The finding that patients undergoing AAE are less likely to receive mechanical valves within the matched and adjusted studies is perhaps a signal that alternate means of avoiding the unfavorable hemodynamics of a mismatched bioprosthesis are being employed in comparator groups,

Table 6 Sensitivity analyses for subgroup differences in aortic valve reintervention

Aortic valve re-intervention	RR (95% CI)	N	Interaction P value
Matched/adjusted studies			
Primary analysis	0.98 (0.75, 1.27)	2	
Unmatched/unadjusted studies			
Primary analysis	1.08 (0.85, 1.39)	7	
All studies (prioritizing matched/adjusted if unmatched/unadjusted also reported)			
Primary analysis (all studies)	1.03 (0.80, 1.31)	7	
Subgroup analyses: excluding Rao 2023 (reported only unmatched/unadjusted data)			
Excluding Rao 2023 *vs.* Rao 2023 only	1.03 (0.80, 1.31) *vs.* 1.16 (0.14, 9.67)	6 *vs.* 1	0.91
Subgroup analyses: risk of bias			
Moderate *vs.* serious/critical	1.32 (0.29, 6.04) *vs.* 1.03 (0.79, 1.34)	2 *vs.* 5	0.75
Moderate/serious *vs.* critical	1.00 (0.78, 1.28) *vs.* 2.58 (0.60, 11.01)	4 *vs.* 3	0.21
Moderate *vs.* serious *vs.* critical	1.32 (0.29, 6.04) *vs.* 1.00 (0.77, 1.31) *vs.* 2.58 (0.60, 11.01)	2 *vs.* 2 *vs.* 3	0.43
Subgroup analysis: concomitant procedures			
Yes *vs.* not reported *vs.* no	1.01 (0.76, 1.32) *vs.* 6.54 (0.42, 101) *vs.* 1.04 (0.61, 1.78)	3 *vs.* 1 *vs.* 3	0.41 (0.92*)

*, interaction P value for yes *vs.* no concomitant procedures only (i.e., excluding studies in which concomitant procedures were not reported). RR, relative risk; CI, confidence interval.

thereby diminishing the potential benefits seen with AAE procedures. Finally, the definition of a successful AAE is equally uncertain. In the rare studies where the annular increase is reported, it is often conservative, with one to two valve sizes at most (20,33,35,37,40,42). With new techniques (8,61) yielding annular enlargement to the extent of three to five valve sizes, one must wonder whether a single valve size increase is enough, and whether the studies that do not report their annular dimensions are achieving any annular increase at all. An illustration of this technical variability can be seen wherein patients undergoing AAE in the matched or adjusted studies were more likely to receive a smaller valve size. Importantly, the same AAE methods were described in both subsets. Despite the numerous techniques described for AAE, their central principle is the alleviation of PPM, and it is this principle that is often unable to be assessed within the existing literature.

There are inherent methodologic limitations within this systematic review. Firstly, all the included studies were non-randomized, leaving a significant possibility of confounding, particularly with regard to the selection of patients undergoing AAE. While some studies reported mid-term secondary outcome data for stroke, structural valve deterioration, non-structural valve dysfunction, infective endocarditis, or major bleeding, they lacked the specificity in terms of the outcome descriptions and the requisite breadth of data across the dataset to be able to enter quantitative syntheses. As the included studies were published from 1997 to 2023, there is additionally an era effect that can be expected in terms of both the evolution of prosthetic aortic valve technologies, as well as the surgical volumes and technical developments with the various AAE techniques at both the center and surgeon levels.

The quality of available observational studies remains poor and randomized trials are unlikely. Collaborative multicentre prospective studies with clear decision-making criteria for AAE and *a priori* determined benchmarks of technical success, including the number of valve sizes gained, and the expected post-operative transprosthetic gradients, would be able to better assess the impact of AAE procedures on the long-term outcomes of SAVR. It is likely that the exact technique of AAE is less important than the successful upsizing of the prosthetic valve and avoidance of PPM. With regards to propensity matching, selecting comparator patients based on preoperative annular size may yield a much more informative comparison than matching based on the size of the prosthetic valve implanted. Patients matched by implanted valve size would also likely be matched to BSA, and thus would not be expected to have a meaningful difference in PPM, a potential driver of their mid- and long-term outcomes (2,3).

Conclusions

Despite the variability in technical success amongst the studies reviewed and inherent issues with generalizability from single-center, non-randomized, observational studies, particularly those that select patients for AAE without formal criteria, AAE remains an important technique to address the challenge of SAVR in the small aortic root. SAVR with AAE does not appear to be associated with increased perioperative morbidity or mortality. There is no conclusive indication that AAE enhances mid-term survival, freedom from reoperation after SAVR, or freedom from heart failure. When considering mid- to long-term outcomes, it is important to consider what the definition of success would be for AAE procedures. It is critical to be able to understand whether an AAE has succeeded in alleviating PPM, and what the natural history of a particular comparator group is, to contextualize the technical innovations and refinements of AAE to come.

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Footnote

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References

1. Head SJ, Mokhles MM, Osnabrugge RL, et al. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. Eur Heart J 2012;33:1518-29.
2. Dismorr M, Glaser N, Franco-Cereceda A, et al. Effect of Prosthesis-Patient Mismatch on Long-Term Clinical Outcomes After Bioprosthetic Aortic Valve Replacement. J Am Coll Cardiol 2023;81:964-75.
3. Fallon JM, DeSimone JP, Brennan JM, et al. The Incidence and Consequence of Prosthesis-Patient Mismatch After Surgical Aortic Valve Replacement. Ann Thorac Surg 2018;106:14-22.
4. Nicks R, Cartmill T, Bernstein L. Hypoplasia of the aortic root. The problem of aortic valve replacement. Thorax 1970;25:339-46.
5. Nezić D, Knezević A, Borović S. Surgical techniques for posterior aortic root enlargement. J Thorac Cardiovasc Surg 2008;135:1401-2; author reply 1402-4.
6. Manouguian S, Seybold-Epting W. Patch enlargement of the aortic valve ring by extending the aortic incision into the anterior mitral leaflet. New operative technique. J Thorac Cardiovasc Surg 1979;78:402-12.
7. Nuñez L, Aguado MG, Pinto AG, et al. Enlargement of the aortic annulus by resecting the commissure between the left and noncoronary cusps. Tex Heart Inst J 1983;10:301-3.
8. Yang B, Ghita C, Makkinejad A, et al. Early outcomes of the Y-incision technique to enlarge the aortic annulus 3 to 4 valve sizes. J Thorac Cardiovasc Surg 2024;167:1196-1205.e2.
9. Konno S, Imai Y, Iida Y, et al. A new method for prosthetic valve replacement in congenital aortic stenosis associated with hypoplasia of the aortic valve ring. J Thorac Cardiovasc Surg 1975;70:909-17.
10. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart

disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Rev Esp Cardiol (Engl Ed) 2022;75:524.
11. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227.
12. Rao V, Linick JA, Reardon MJ, et al. Early and late effects of aortic root enlargement: Results from the Pericardial Surgical Aortic Valve Replacement Pivotal Trial: A multicenter, prospective clinical trial. JTCVS Open 2023;13:54-74.
13. Rocha RV, Manlhiot C, Feindel CM, et al. Surgical Enlargement of the Aortic Root Does Not Increase the Operative Risk of Aortic Valve Replacement. Circulation 2018;137:1585-94.
14. Yu W, Tam DY, Rocha RV, et al. Aortic Root Enlargement Is Safe and Reduces the Incidence of Patient-Prosthesis Mismatch: A Meta-analysis of Early and Late Outcomes. Can J Cardiol 2019;35:782-90.
15. Sá MPBO, Zhigalov K, Cavalcanti LRP, et al. Impact of Aortic Annulus Enlargement on the Outcomes of Aortic Valve Replacement: A Meta-analysis. Semin Thorac Cardiovasc Surg 2021;33:316-25.
16. Sá MP, Van den Eynde J, Amabile A, et al. Late Outcomes After Aortic Root Enlargement During Aortic Valve Replacement: Meta-Analysis With Reconstructed Time-To-Event Data. J Cardiothorac Vasc Anesth 2022;36:3065-73.
17. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2021;21:111.
18. Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. February 2022. Available online: www.training.cochrane.org/handbook [accessed 15 June 2023].
19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
20. Prifti E, Bonacchi M, Baboci A, et al. Hemodynamics of 17-mm vs. 19-mm St. Jude Medical Regent and annulus enlargement. Asian Cardiovasc Thorac Ann 2015;23:670-83.
21. Mehaffey JH, Hawkins RB, Wegermann ZK, et al. Aortic Annular Enlargement in the Elderly: Short and Long-Term Outcomes in the United States. Ann Thorac Surg 2021;112:1160-6.
22. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
23. Sterne JAC, Higgins JPT, Elbers RG, et al. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance. 20 October 2016. Available online: http://www.riskofbias.info [accessed 16 January 2024].
24. Schünemann HJ, Brennan S, Akl EA, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE - A statement by the GRADE guidance group. J Clin Epidemiol 2023;159:79-84.
25. Schünemann H, Brożek J, Guyatt G, et al., editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. October 2013. Available online: https://gdt.gradepro.org/app/handbook/handbook.html [accessed 1 February 2024].
26. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
27. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45:139-45.
28. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
29. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
30. Friedrich JO, Adhikari NK, Beyene J. Ratio of means for analyzing continuous outcomes in meta-analysis performed as well as mean difference methods. J Clin Epidemiol 2011;64:556-64.
31. Friedrich JO, Adhikari NK, Beyene J. The ratio of means method as an alternative to mean differences for analyzing continuous outcome variables in meta-analysis: a simulation study. BMC Med Res Methodol 2008;8:32.
32. Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Section 6.7.1 Effect Measures for Counts and Rates. Available online: www.training.cochrane.org/handbook [accessed 20 February 2024].
33. Beckmann E, Martens A, Alhadi F, et al. Aortic valve

replacement with sutureless prosthesis: better than root enlargement to avoid patient-prosthesis mismatch? Interact Cardiovasc Thorac Surg 2016;22:744-9.
34. Chauvette V, Sénéchal M, Barrette V, et al. Annulus root enlargement during redo aortic valve replacement: Perioperative results and hemodynamic impact. J Card Surg 2020;35:2158-64.
35. Correia PM, Coutinho GF, Branco C, et al. Long-term follow-up of patients undergoing aortic root enlargement for insertion of a larger prosthesis. Eur J Cardiothorac Surg 2016;50:82-8.
36. Haunschild J, Scharnowski S, Mende M, et al. Aortic root enlargement to mitigate patient-prosthesis mismatch: do early adverse events justify reluctance? Eur J Cardiothorac Surg 2019. doi: 10.1093/ejcts/ezz016.
37. Kulik A, Al-Saigh M, Chan V, et al. Enlargement of the small aortic root during aortic valve replacement: is there a benefit? Ann Thorac Surg 2008;85:94-100.
38. Okamoto Y, Yamamoto K, Sugimoto T, et al. Early and Late Outcomes of Aortic Valve Replacement with Aortic Annular Enlargement: A Propensity Analysis. Thorac Cardiovasc Surg 2016;64:410-7.
39. Penaranda JG, Greason KL, Pislaru SV, et al. Aortic root enlargement in octogenarian patients results in less patient prosthesis mismatch. Ann Thorac Surg 2014;97:1533-8.
40. Sakamoto Y, Hashimoto K, Okuyama H, et al. Prevalence and avoidance of patient-prosthesis mismatch in aortic valve replacement in small adults. Ann Thorac Surg 2006;81:1305-9.
41. Shih E, DiMaio JM, Squiers JJ, et al. Outcomes of aortic root enlargement during isolated aortic valve replacement. J Card Surg 2022;37:2389-94.
42. Sommers KE, David TE. Aortic valve replacement with patch enlargement of the aortic annulus. Ann Thorac Surg 1997;63:1608-12.
43. Tam DY, Dharma C, Rocha RV, et al. Early and late outcomes following aortic root enlargement: A multicenter propensity score-matched cohort analysis. J Thorac Cardiovasc Surg 2020;160:908-919.e15.
44. Yousef S, Brown JA, Serna-Gallegos D, et al. Impact of Aortic Root Enlargement on Patients Undergoing Aortic Valve Replacement. Ann Thorac Surg 2023;115:396-402.
45. Aka SA, Orhan G, Unal S, et al. Functional results in aortic root enlargement. Heart Surg Forum 2004;7:E160-3.
46. Castro LJ, Arcidi JM Jr, Fisher AL, et al. Routine enlargement of the small aortic root: a preventive strategy to minimize mismatch. Ann Thorac Surg 2002;74:31-6; discussion 36.
47. Dhareshwar J, Sundt TM 3rd, Dearani JA, et al. Aortic root enlargement: what are the operative risks? J Thorac Cardiovasc Surg 2007;134:916-24.
48. Fouad A, Hassan M, Maged M, et al. Aortic Valve Replacement in Patients with Small Aortic Annulus: New Pericardial Stented Valves vs Aortic Root Enlargement Procedures. Authorea 2021. doi: 10.22541/au.163943224.41477072/v1.
49. Ghoneim A, Bouhout I, Demers P, et al. Management of small aortic annulus in the era of sutureless valves: A comparative study among different biological options. J Thorac Cardiovasc Surg 2016;152:1019-28.
50. Shibata Y, Abe T, Sekine S, et al. Supraannular aortic root enlargement in patients with small aortic annulus: efficacy and safety. Ann Thorac Cardiovasc Surg 1998;4:262-5.
51. Takakura H, Kurosawa H, Nakano M, et al. Enlarging procedure for small aortic annulus. J Cardiol 1995;26(Suppl I):105-8.
52. Kitamura M, Yamazaki K, Ohta T, et al. Left ventricular function on exercise after surgical treatment of small aortic annuli. Cardiovasc Surg 1995;3:583-5.
53. Mubarak Y, Abdel Jawad AAR. Aortic Root Enlargement in patients with small aortic annulus undergoing double valve replacement. Is it justified? A retrospective Comparative cohort study. Heart Surg Forum 2021. doi: 10.1532/hsf.3401.
54. Oshima H, Usui A, Akita T, et al. Aortic valve replacement for the small aortic annulus. Kyobu Geka 2006;59:269-75.
55. Prakash S, Agarwal S, Dutta N, et al. A comparative study of surgical treatment of small aortic root with or without aortic root enlargement using a single prosthesis type. J Cardiovasc Med (Hagerstown) 2010;11:836-42.
56. Sant'anna JR, de Bacco FW, Santánna RT, et al. Aortic valve replacement with anterior and posterior enlargement of small aortic annulus is comparable to surgery with normal annulus. Rev Port Cardiol 2006;25:593-602.
57. Sim EK, Orszulak TA, Schaff HV, et al. Influence of prosthesis size on change in left ventricular mass following aortic valve replacement. Eur J Cardiothorac Surg 1994;8:293-7.
58. Stoger GI, Marenchino RG, Rosi E, et al. Aortic annulus enlargement vs. Conventional surgery in patients with small aortic annulus undergoing aortic valve replacement. Rev Argent Cardiol 2017;85:30-4.
59. Wang R, Chen X, Xu M, et al. Clinical research of aortic

valve replacement in small aortic annulus. Zhonghua Wai Ke Za Zhi 2014;52:131-4.
60. David TE, Uden DE. Aortic valve replacement in adult patients with small aortic annuli. Ann Thorac Surg 1983;36:577-83.
61. Yang B, Ghita C, Palmer S. Y-incision Aortic Root Enlargement With Modified Aortotomy Upsizing the Annulus by 5 Valve Sizes. Ann Thorac Surg 2022;114:e479-81.

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Supplementary

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Appendix 1

References

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Supplemental Figures:

First author	Year	Domain 1-Confounding	Domain 2-Selection	Domain 3-Classification of Interventions	Domain 4-Deviations from Intended Interventions	Outcome-Specific Domains	Domain 5-Missing Data	Domain 6-Outcome Measurement	Domain 7-Reported Results	Overall Risk of Bias	Outcome
Matched or Adjusted Observational Studies											
Yousef	2023	S	L	M	L	Mortality	M	L	M	**S**	Mortality
						AoV Reintervention	M	M	M	**S**	AoV Reintervention
						Non-Structural Valve Dysfunction-PVL	S	S	M	**S**	Non-Structural Valve Dysfunction-PVL
Shih	2022	M	L	M	L	Mortality	L	L	M	**M**	Mortality
						AoV Reintervention	L	M	M	**M**	AoV Reintervention
Mehaffey	2021	S	L	S	L	Mortality	L	L	M	**S**	Mortality
						AoV Reintervention	L	M	M	**S**	AoV Reintervention
						Stroke Hospitalization	L	M	M	**S**	Stroke Hospitalization
						CHF Rehospitalization	L	S	M	**S**	CHF Rehospitalization
Chauvette	2020	S	L	L	NI	Mortality	L	L	M	**S**	Mortality
Tam	2020	M	L	L	L	Mortality	L	L	M	**M**	Mortality
						AoV Reintervention	L	M	M	**M**	AoV Reintervention
						CHF Rehospitalization	L	S	M	**S**	CHF Rehospitalization
Tam*	2020	M	L	L	L	Mortality	L	L	M	**M**	Mortality
Haunschild	2019	M	L	L	M	Mortality	S	L	M	**S**	Mortality
Okamoto	2016	M	L	L	L	Mortality	NI	L	M	**M**	Mortality
						Cardiac Mortality	NI	M	M	**M**	Cardiac Mortality
						SVD	NI	S	NI	**S**	SVD
						IE	NI	S	NI	**S**	IE
						Major Bleeding	NI	S	NI	**S**	Major Bleeding
						Stroke	NI	S	NI	**S**	Stroke
						CHF	NI	S	NI	**S**	CHF
Kulik	2008	S	L	L	C	Mortality	M	L	M	**C**	Mortality
						CHF Composite	M	S	M	**C**	CHF Composite
Sommers	1997	S	L	L	NI	Mortality	L	L	M	**S**	Mortality
						Cardiac Mortality	L	M	M	**S**	Cardiac Mortality
Unmatched/Unadjusted Observational Studies											
Rao	2023	C	L	S	C	Mortality	S	L	L	**C**	Mortality
						AoV Reintervention	S	M	L	**C**	AoV Reintervention
						SVD	S	M	L	**C**	SVD
						Non-Structural Dysfunction	S	M	L	**C**	Non-Structural Dysfunction
						Valve Thrombosis	S	M	L	**C**	Valve Thrombosis
						NYHA III-IV	S	S	L	**C**	NYHA III-IV
						IE	S	S	L	**C**	IE
						Major Anticoagulant-Related Hemorrhage	S	S	L	**C**	Major Anticoagulant-Related Hemorrhage
						Thromboembolism	S	S	L	**C**	Thromboembolism
Beckmann	2016	S	L	L	C	Mortality	S	L	M	**C**	Mortality
Correia	2016	S	L	S	C	Mortality	L	L	M	**C**	Mortality
Prfiti	2015	C	L	L	M	Mortality	NI	L	S	**C**	Mortality
						AoV Reintervention	NI	M	S	**C**	AoV Reintervention
Penaranda	2014	S	L	L	S	Mortality	M	L	M	**S**	Mortality
Sakamoto	2006	C	L	L	NI	Mortality	NI	NI	M	**C**	Mortality
						Reoperation**	NI	M	M	**C**	Reoperation**
						Prosthetic Valve IE	NI	S	M	**C**	Prosthetic Valve IE
						Thromboembolism	NI	S	M	**C**	Thromboembolism

Figure S1 ROBINS-I assessment for all reported outcomes within each of the included studies.

Legend for ROBINS-I assessment: L, low risk of bias; M, moderate risk of bias; S, serious risk of bias; C, critical risk of bias; NI, no information.

Abbreviations: AoV, aortic valve; CHF, congestive heart failure; IE, infective endocarditis; NYHA, New York Heart Association functional class; PVL, paravalvular leak; SVD, structural valve deterioration.

* Distinct secondary cohort reported within the same publication.

** Long-term reoperation outcome was assumed to be related to aortic valve reintervention.

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Figures S2-S31. Meta-analyses for baseline characteristics

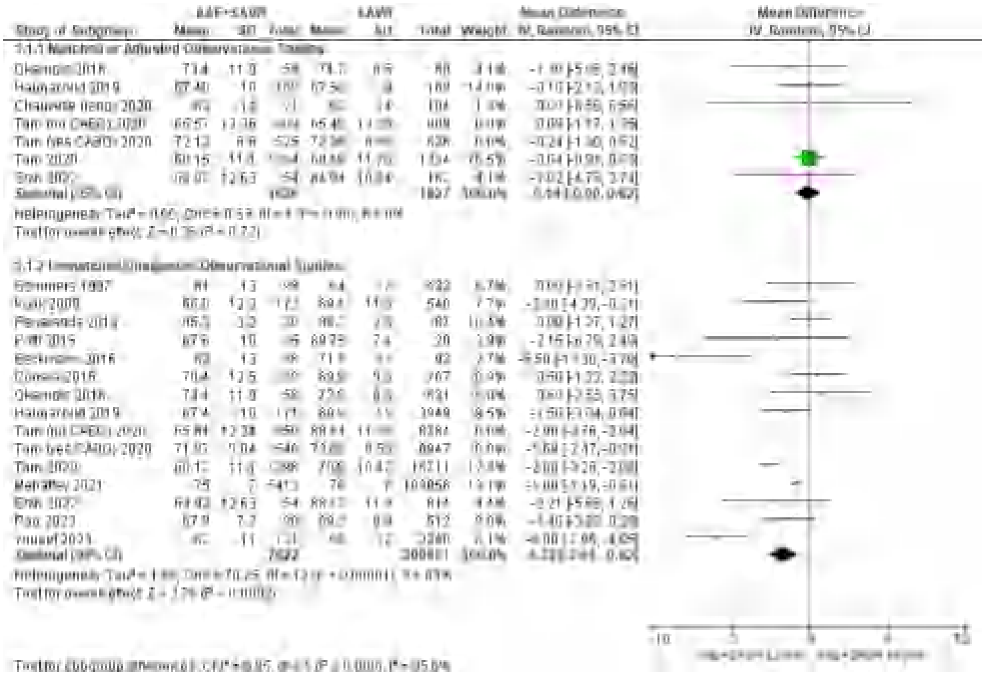

Figure S2 Forest plot for age at time of operation (years).

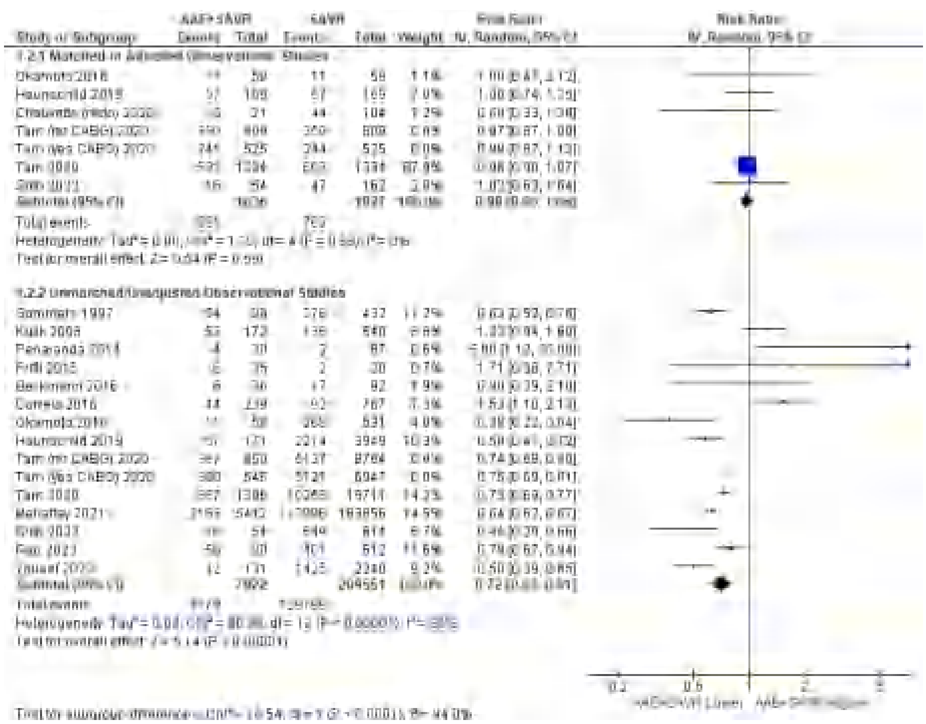

Figure S3 Forest plot for male sex.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

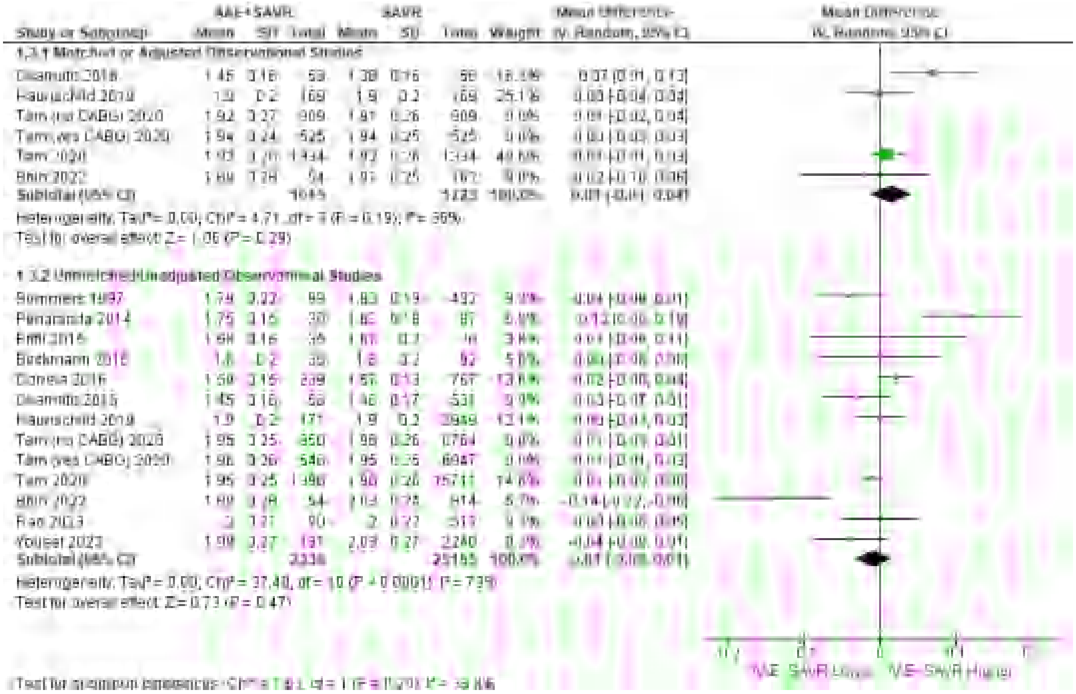

Figure S4 Forest plot for preoperative body surface area (m^2).

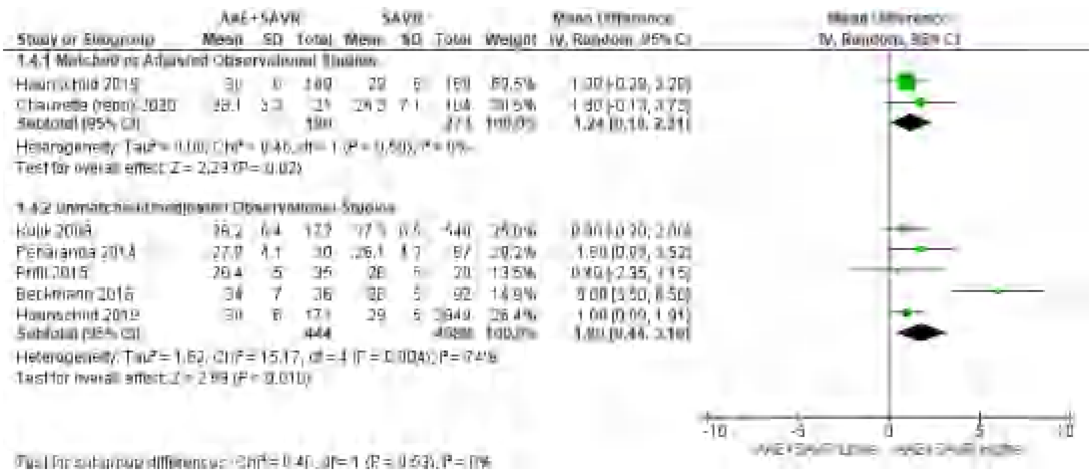

Figure S5 Forest plot for preoperative body mass index (kg/m^2).

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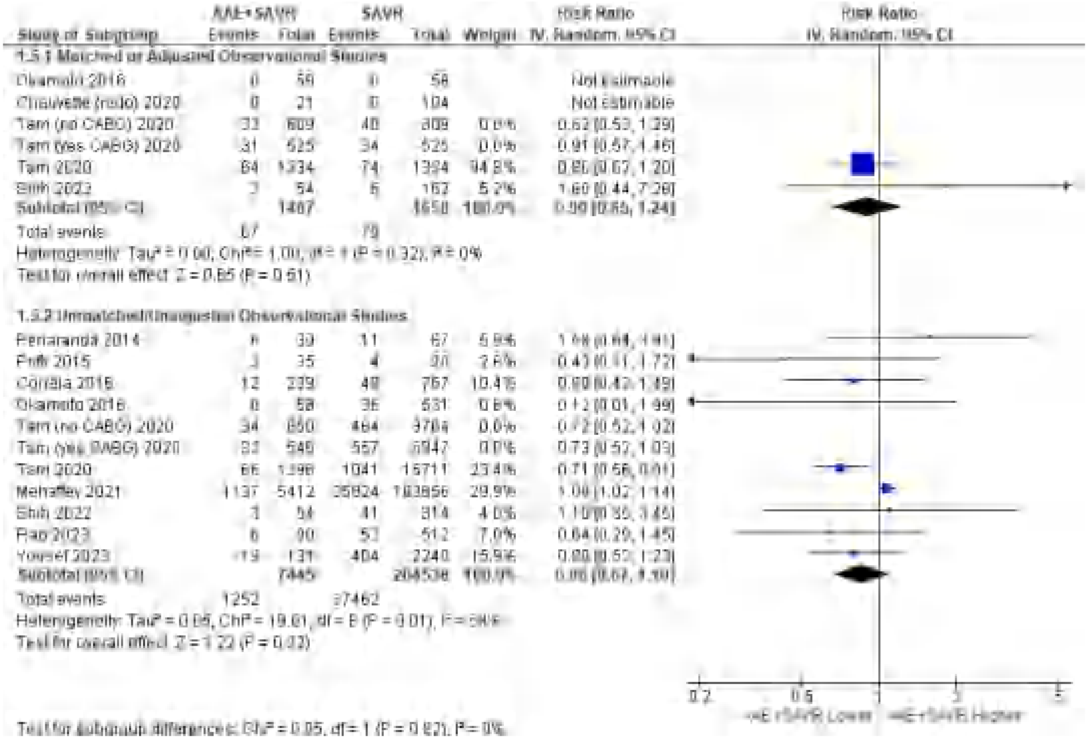

Figure S6 Forest plot for cerebrovascular disease.

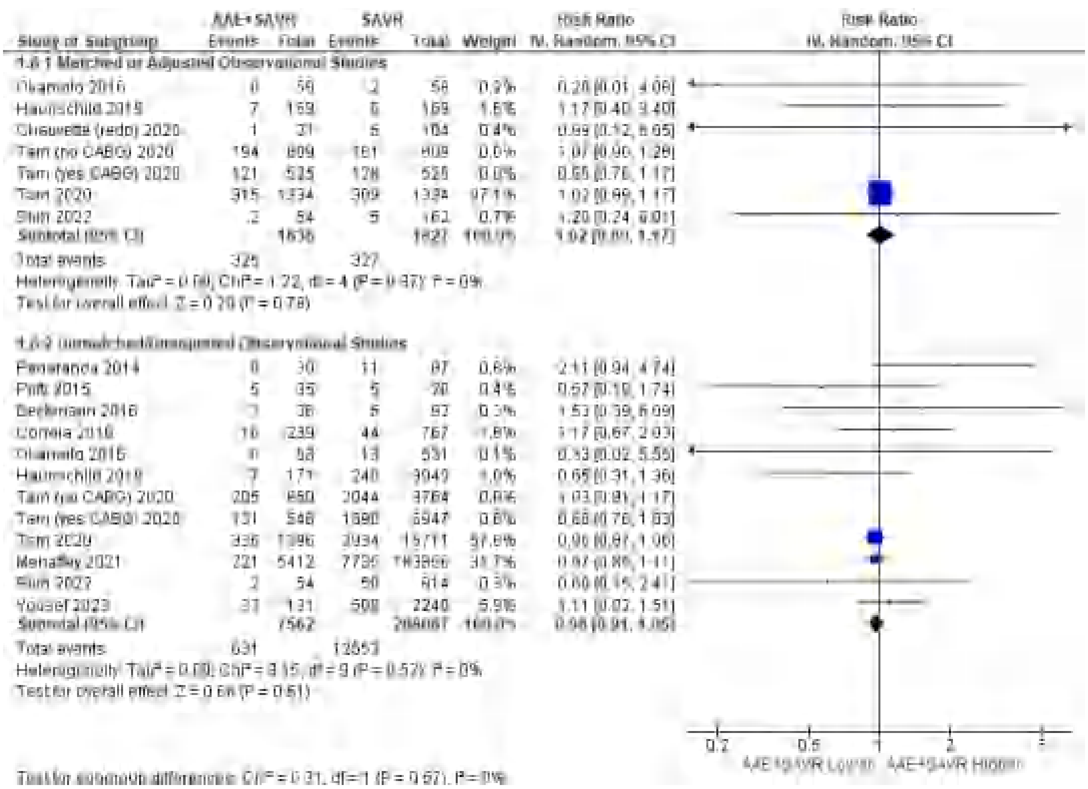

Figure S7 Forest plot for chronic obstructive pulmonary disease (COPD).

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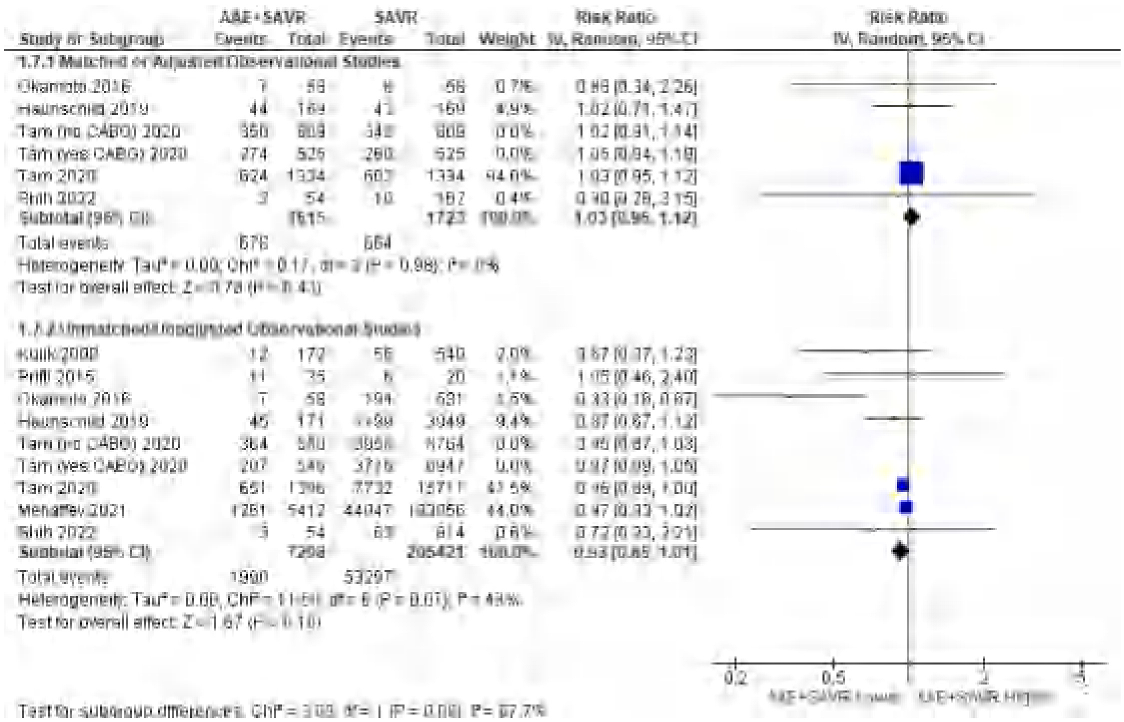

Figure S8 Forest plot for smoking.

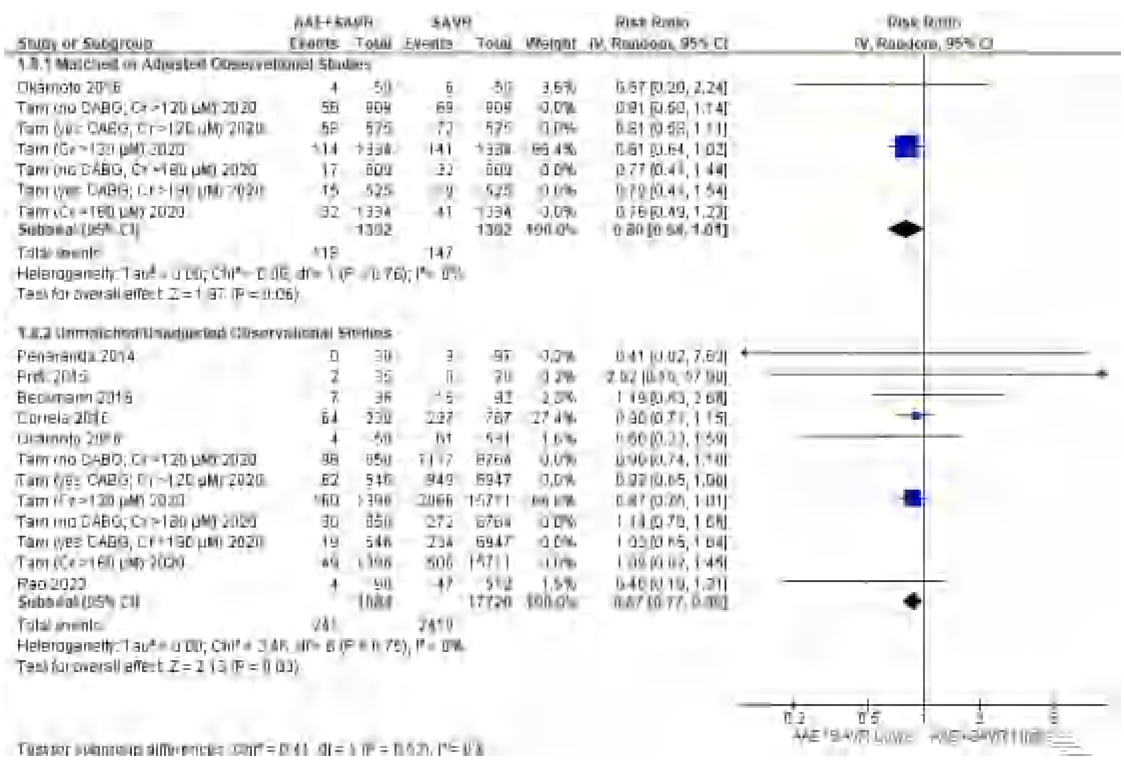

Figure S9 Forest plot for chronic renal failure.

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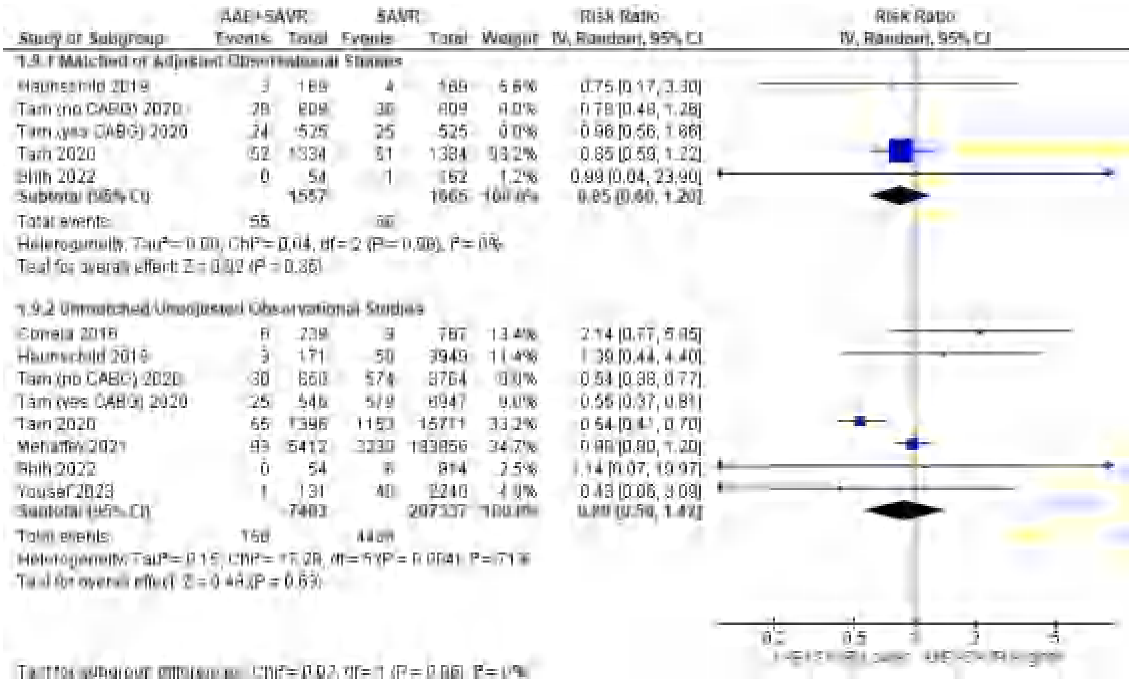

Figure S10 Forest plot for dialysis.

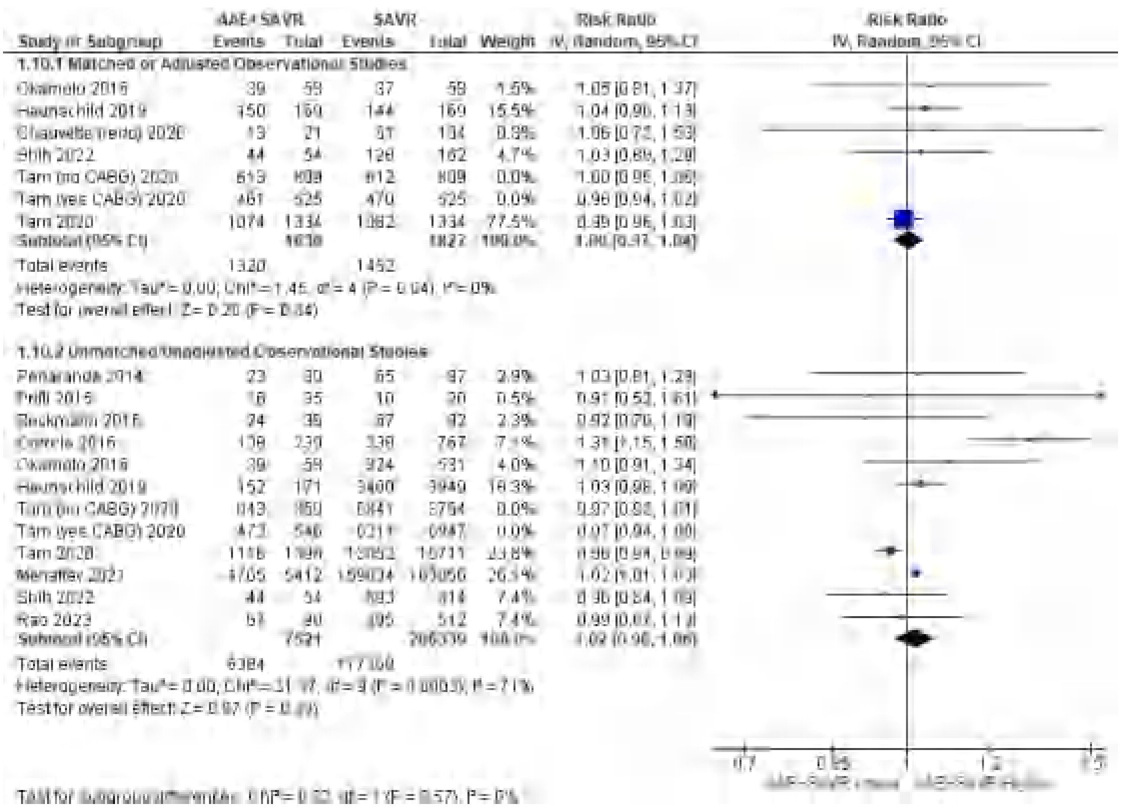

Figure S11 Forest plot for hypertension.

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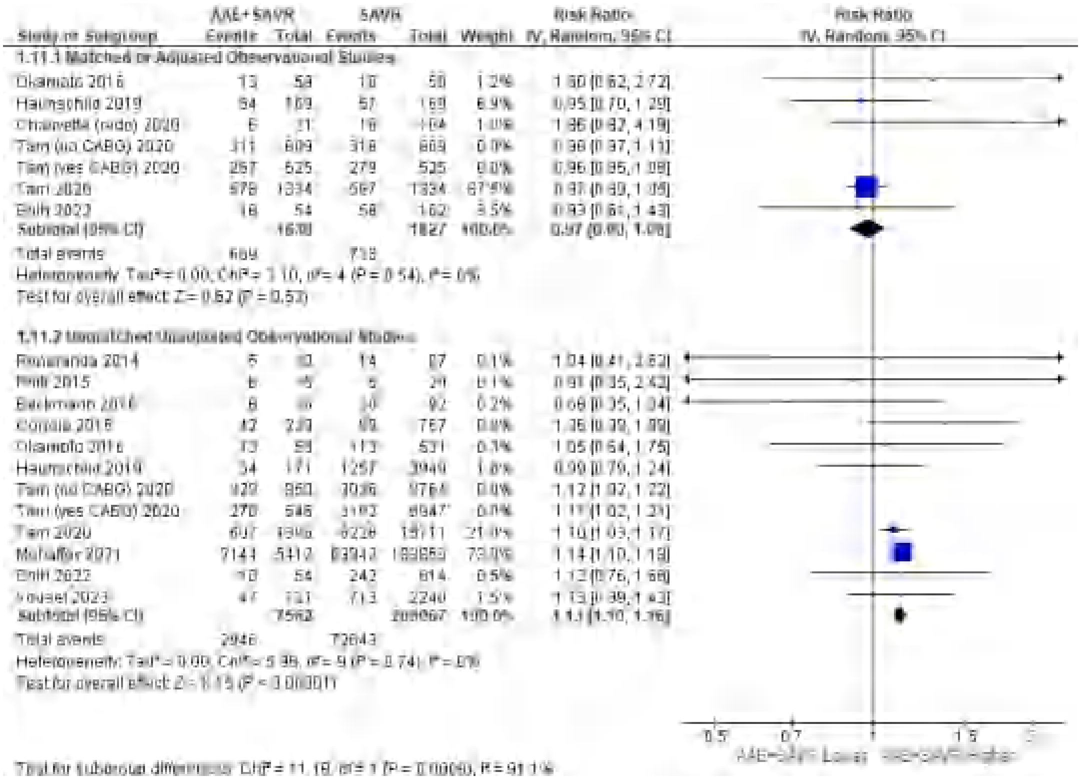

Figure S12 Forest plot for diabetes.

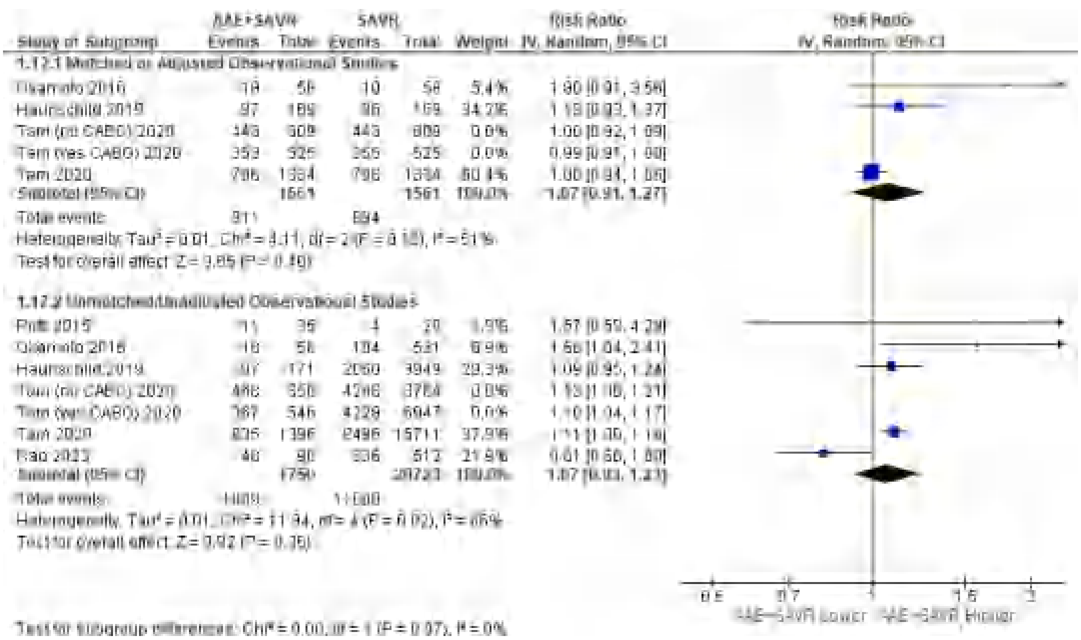

Figure S13 Forest plot for dyslipidemia.

https://dx.doi.org/10.21037/acs-2024-aae-0023

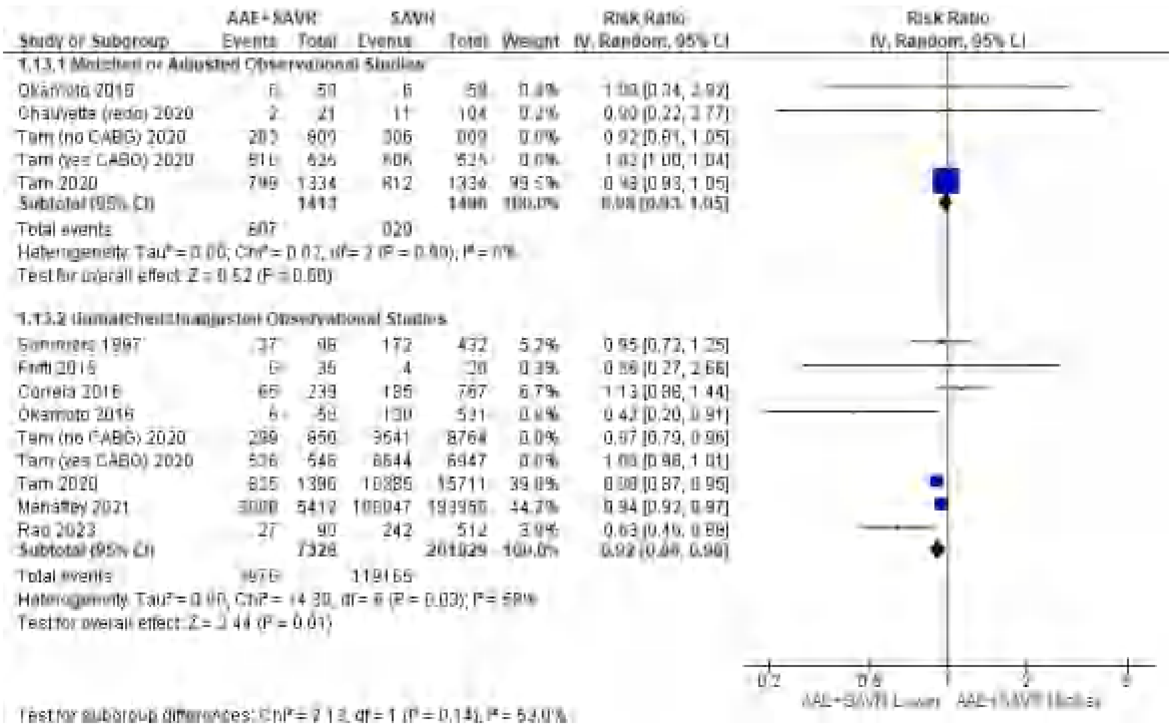

Figure S14 Forest plot for coronary artery disease.

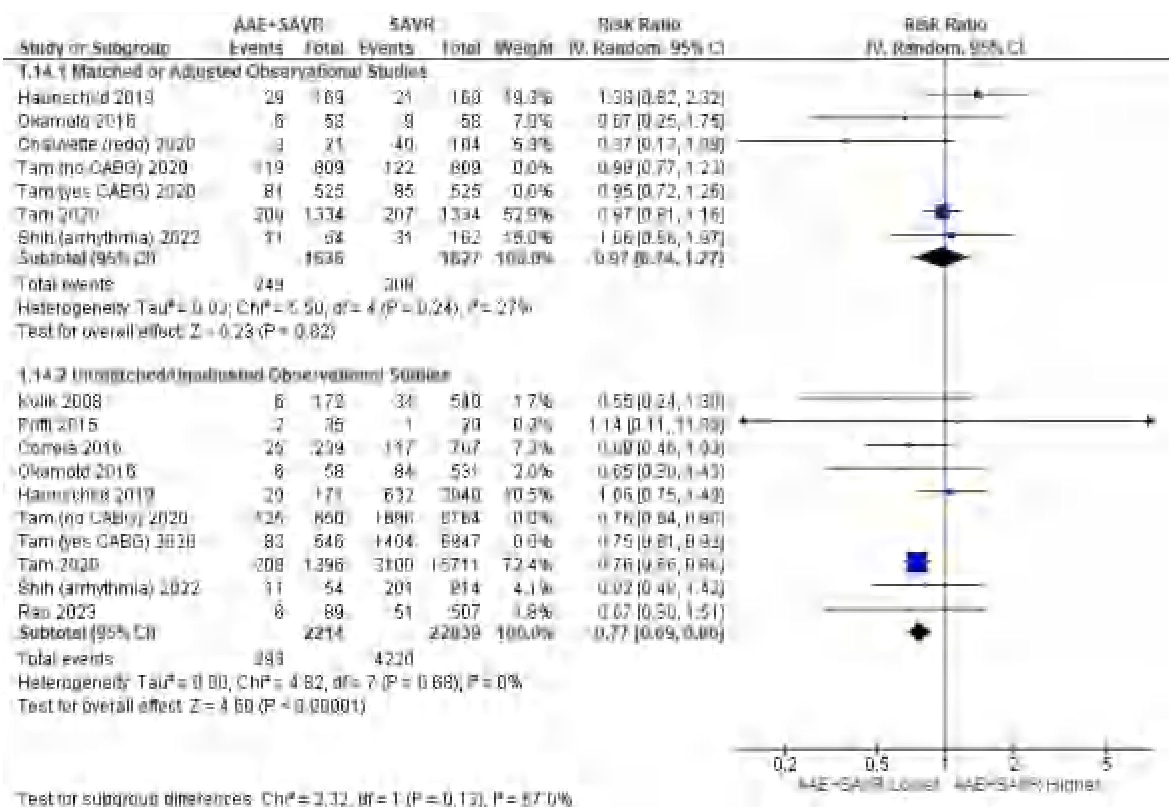

Figure S15 Forest plot for preoperative atrial fibrillation.

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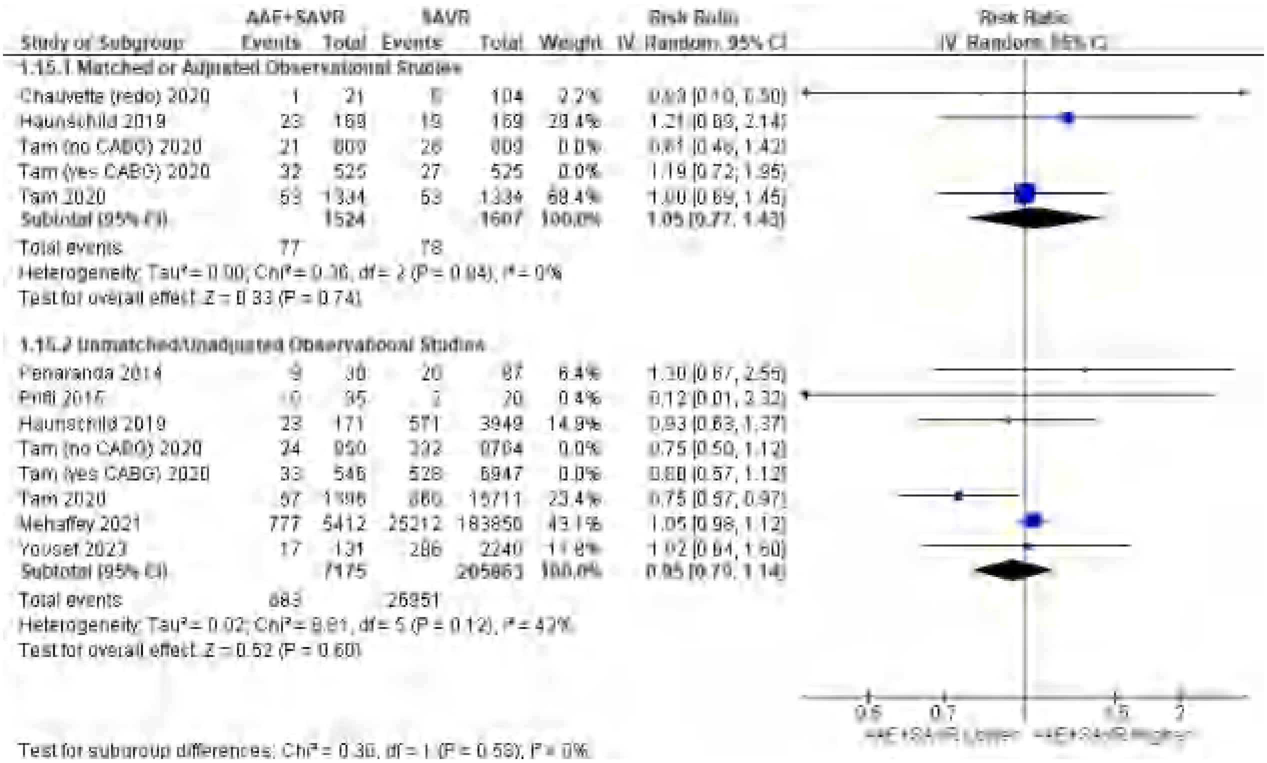

Figure S16 Forest plot for peripheral vascular disease.

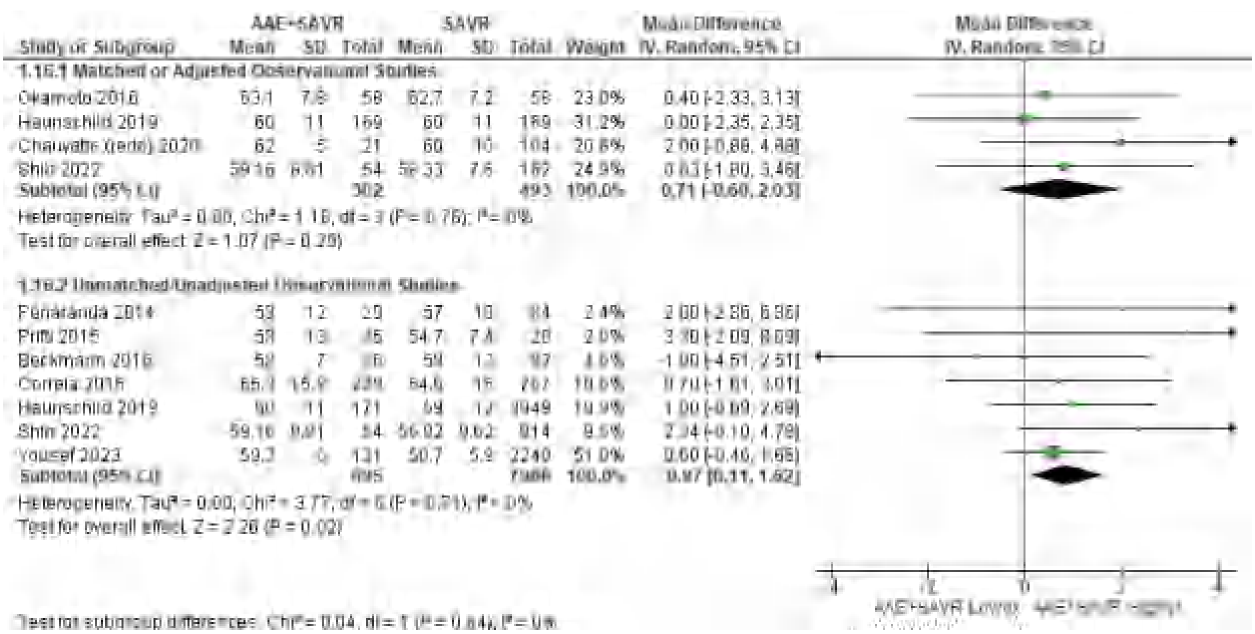

Figure S17 Forest plot for left ventricular ejection fraction (LVEF, %).

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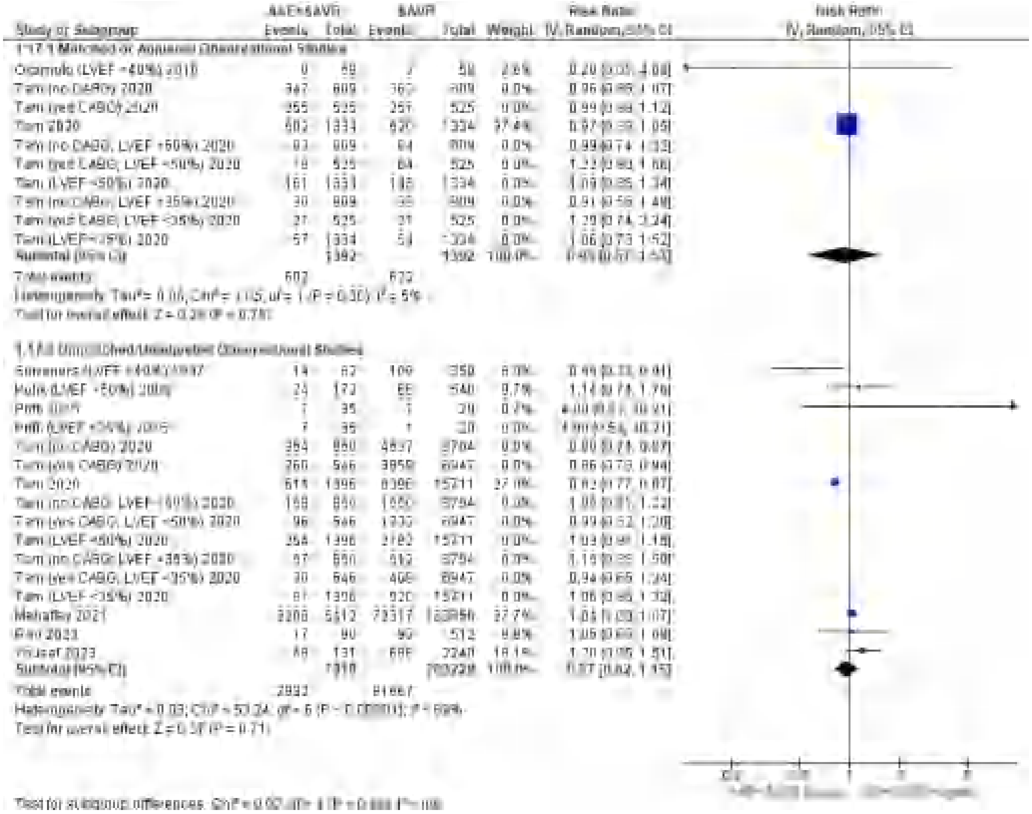

Figure S18 Forest plot for CHF or low LVEF.

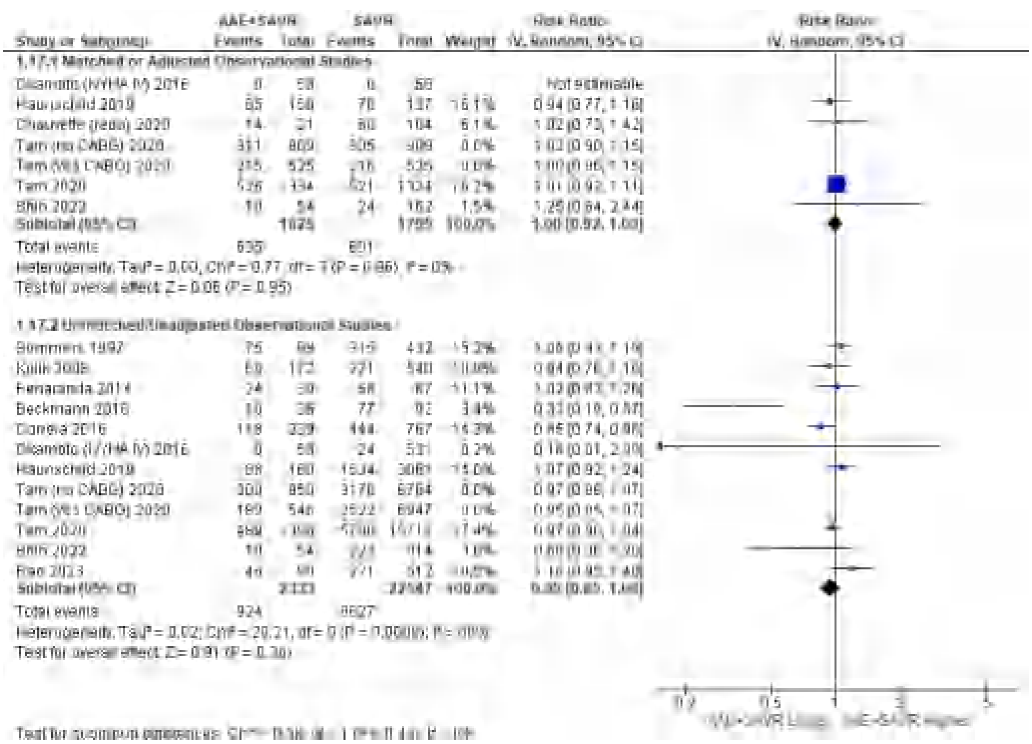

Figure S19 Forest plot for NYHA III or IV.

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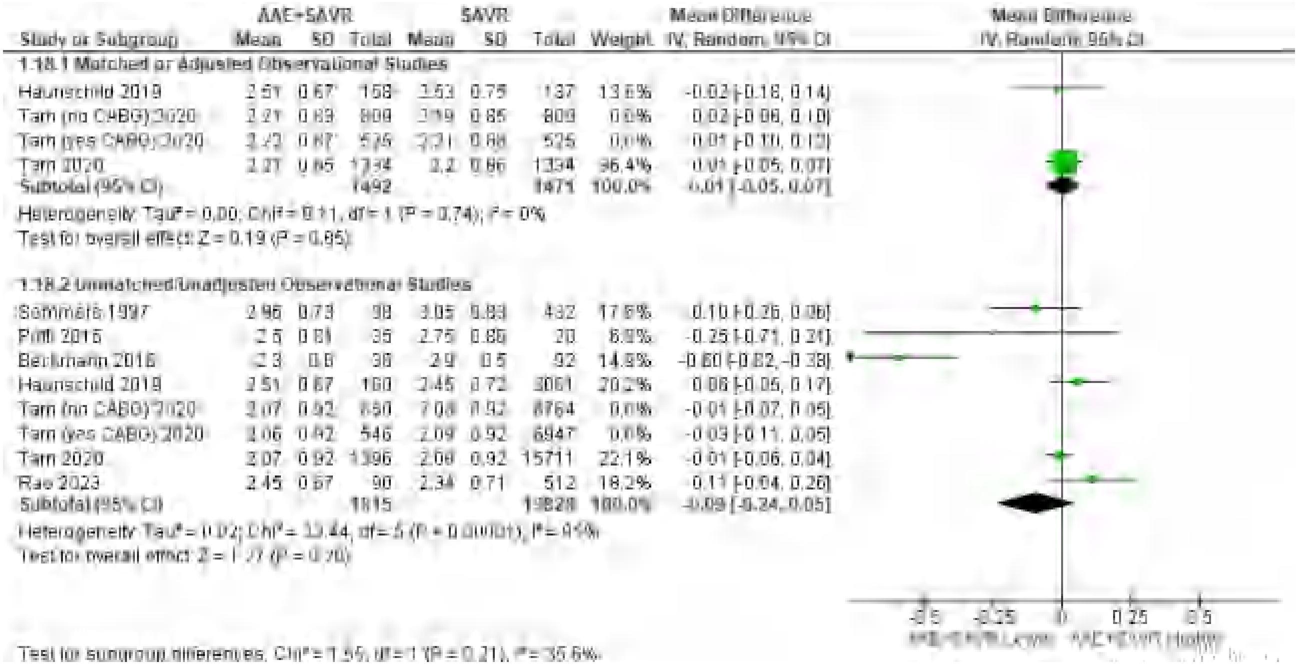

Figure S20 Forest plot for mean NYHA grade.

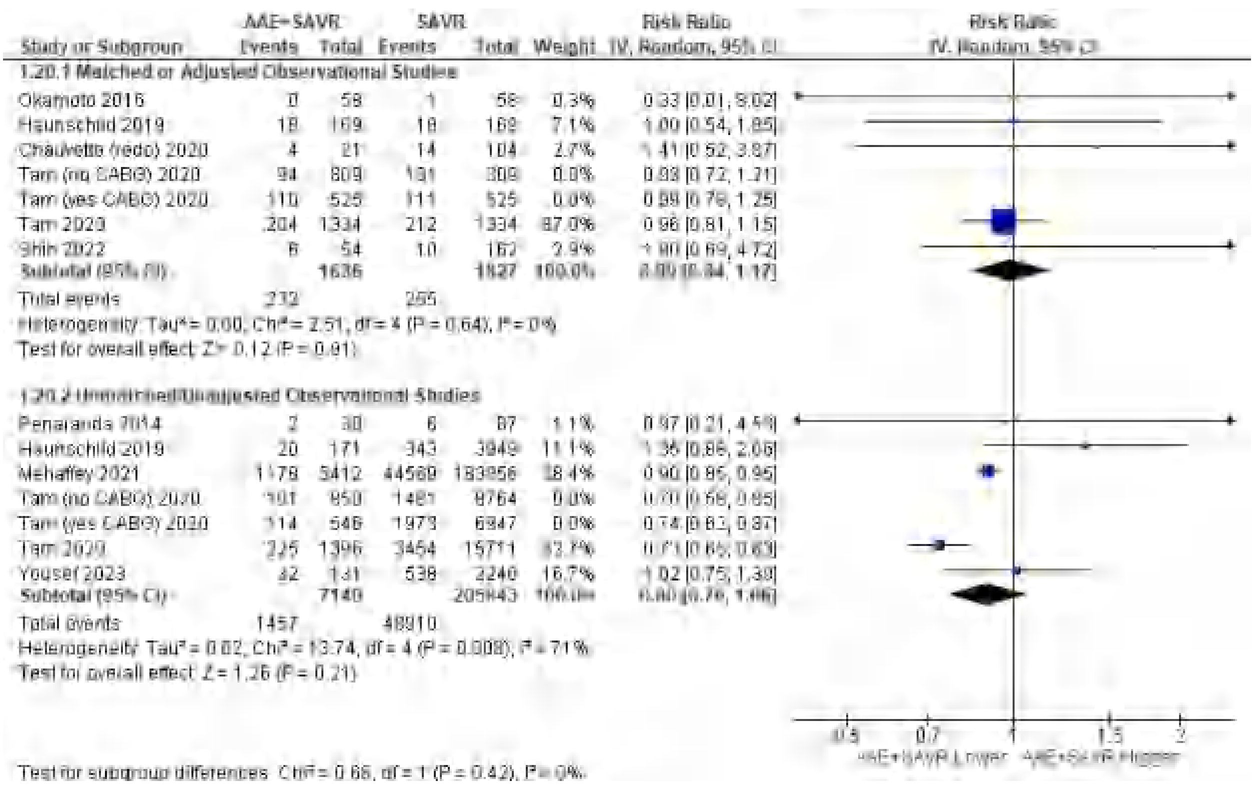

Figure S21 Forest plot for non-elective surgery.

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Study or Subgroup	AAE+SAVR Mean	AAE+SAVR SD	AAE+SAVR Total	SAVR Mean	SAVR SD	SAVR Total	Weight	Mean Difference IV, Random, 95% CI
1.22.1 Matched or Adjusted Observational Studies								
Shih 2022	2.1	1.6	54	2	2.1	162	100.0%	0.10 [-0.44, 0.64]
Subtotal (95% CI)			**54**			**162**	**100.0%**	**0.10 [-0.44, 0.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.37 (P = 0.71)								
1.22.2 Unmatched/Unadjusted Observational Studies								
Mehaffey 2021	2.99	4.1	5412	2.97	4.2	183856	53.5%	0.02 [-0.09, 0.13]
Shih 2022	2.1	1.6	54	1.9	1.7	814	6.8%	0.20 [-0.24, 0.64]
Rao 2023	1.6	1	90	1.8	1.2	512	20.0%	-0.20 [-0.43, 0.03]
Yousef 2023	1.9	1.35	131	1.97	1.48	2240	19.8%	-0.07 [-0.31, 0.17]
Subtotal (95% CI)			**5687**			**187422**	**100.0%**	**-0.03 [-0.15, 0.09]**
Heterogeneity: Tau² = 0.00; Chi² = 3.94, df = 3 (P = 0.27); I² = 24%								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%								

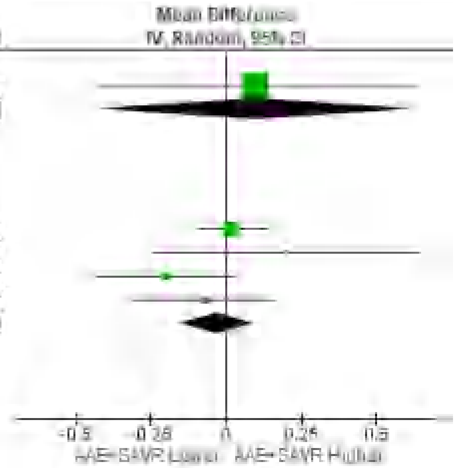

Figure S22 Forest plot for Society of Thoracic Surgeons (STS) score (%).

Study or Subgroup	AAE+SAVR Events	AAE+SAVR Total	SAVR Events	SAVR Total	Weight	Risk Ratio IV, Random, 95% CI
1.23.1 Matched or Adjusted Observational Studies						
Okamoto 2016	3	58	0	58	0.0%	7.00 [0.37, 132.50]
Haunschild 2019	0	169	0	169		Not estimable
Chauvette (redo) 2020	21	21	104	104	99.2%	1.00 [0.94, 1.07]
Shih 2022	8	54	26	162	0.8%	0.92 [0.44, 1.92]
Subtotal (95% CI)		**302**		**493**	**100.0%**	**1.00 [0.94, 1.07]**
Total events	32		130			
Heterogeneity: Tau² = 0.00; Chi² = 1.74, df = 2 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.23.2 Unmatched/Unadjusted Observational Studies						
Frith 2015	6	35	0	20	0.7%	7.58 [0.45, 127.94]
Beckmann 2016	5	36	2	92	2.0%	6.39 [1.30, 31.45]
Correia 2016	21	239	53	767	15.7%	1.27 [0.78, 2.06]
Haunschild 2019	0	171	0	3949		Not estimable
Mehaffey 2021	705	5412	21380	183856	49.4%	1.12 [1.04, 1.20]
Shih 2022	8	54	125	814	9.8%	0.96 [0.50, 1.87]
Rao 2023	1	90	21	512	1.3%	0.27 [0.04, 1.99]
Yousef 2023	23	131	341	2240	21.2%	1.15 [0.79, 1.69]
Subtotal (95% CI)		**6168**		**192250**	**100.0%**	**1.17 [0.93, 1.47]**
Total events	769		21922			
Heterogeneity: Tau² = 0.03; Chi² = 8.76, df = 6 (P = 0.19); I² = 31%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Chi² = 1.59, df = 1 (P = 0.21), I² = 37.0%						

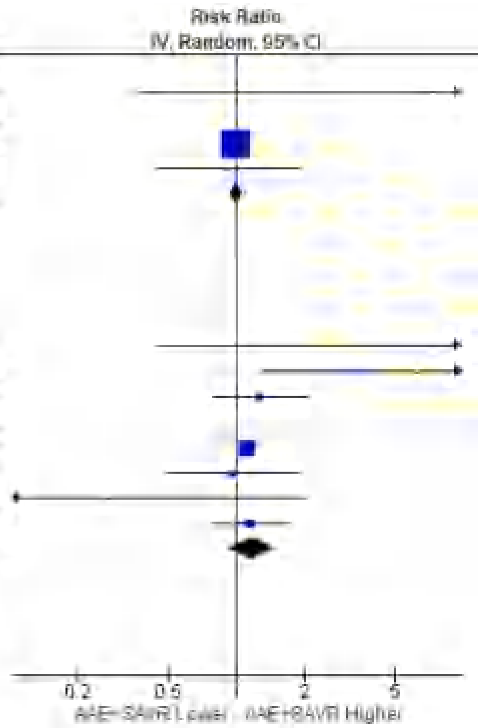

Figure S23 Forest plot for prior cardiac surgery.

https://dx.doi.org/10.21037/acs-2024-aae-0023

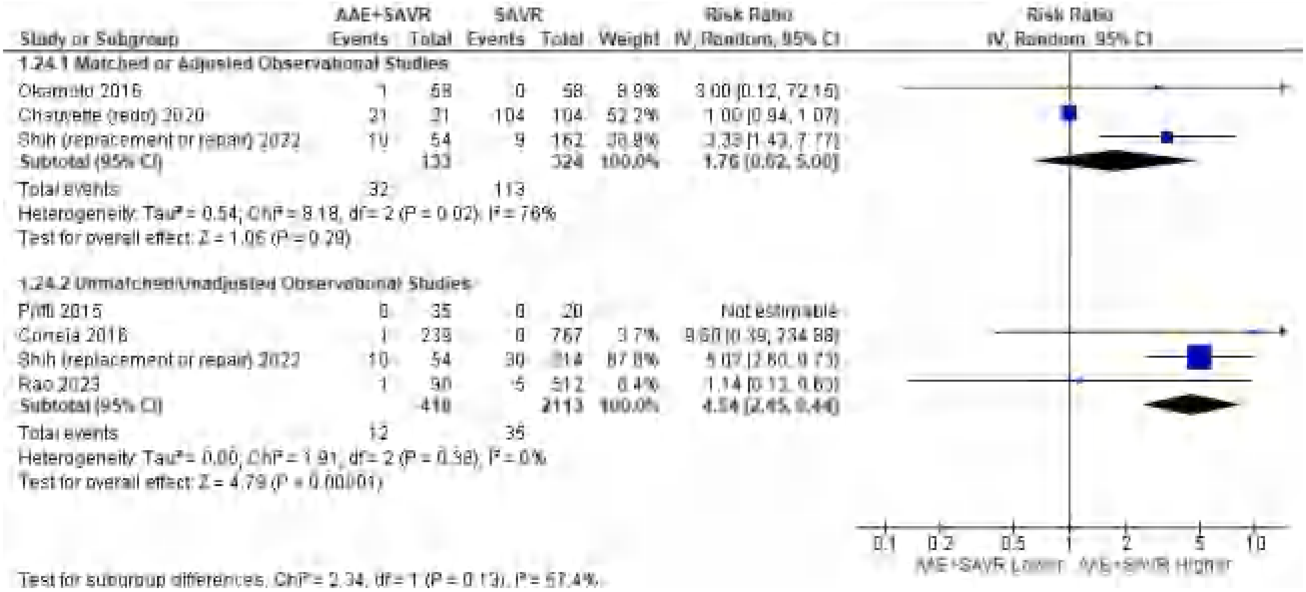

Figure S24 Forest plot for prior SAVR.

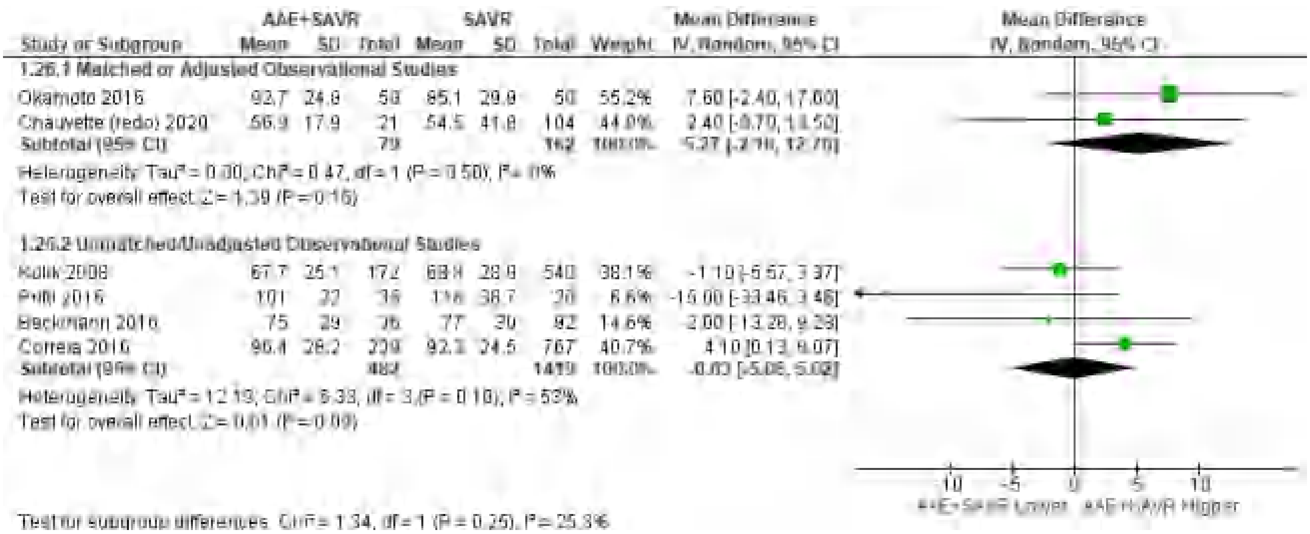

Figure S25 Forest plot for peak aortic gradient (mm Hg).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

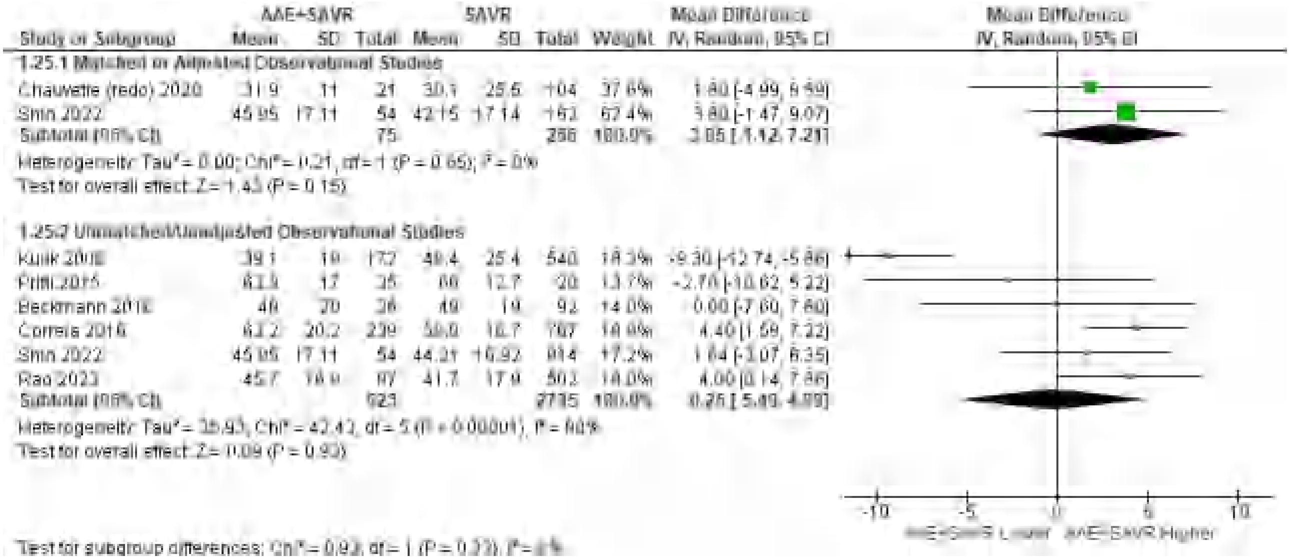

Figure S26 Forest plot for mean aortic gradient (mm Hg).

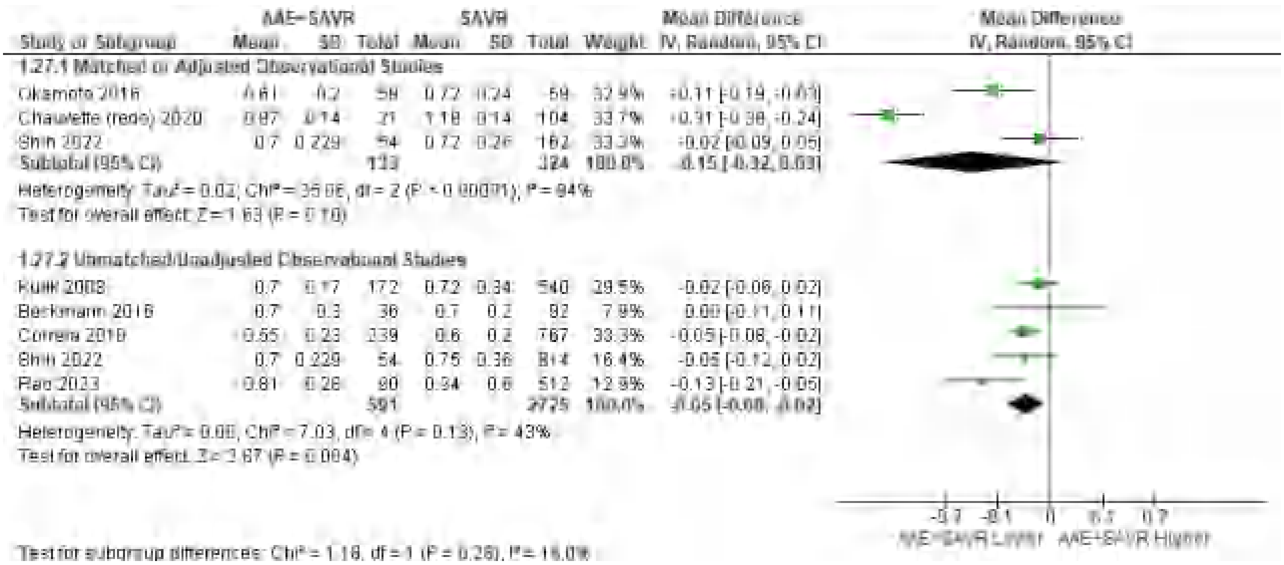

Figure S27 Forest plot for aortic valve area (cm^2).

https://dx.doi.org/10.21037/acs-2024-aae-0023

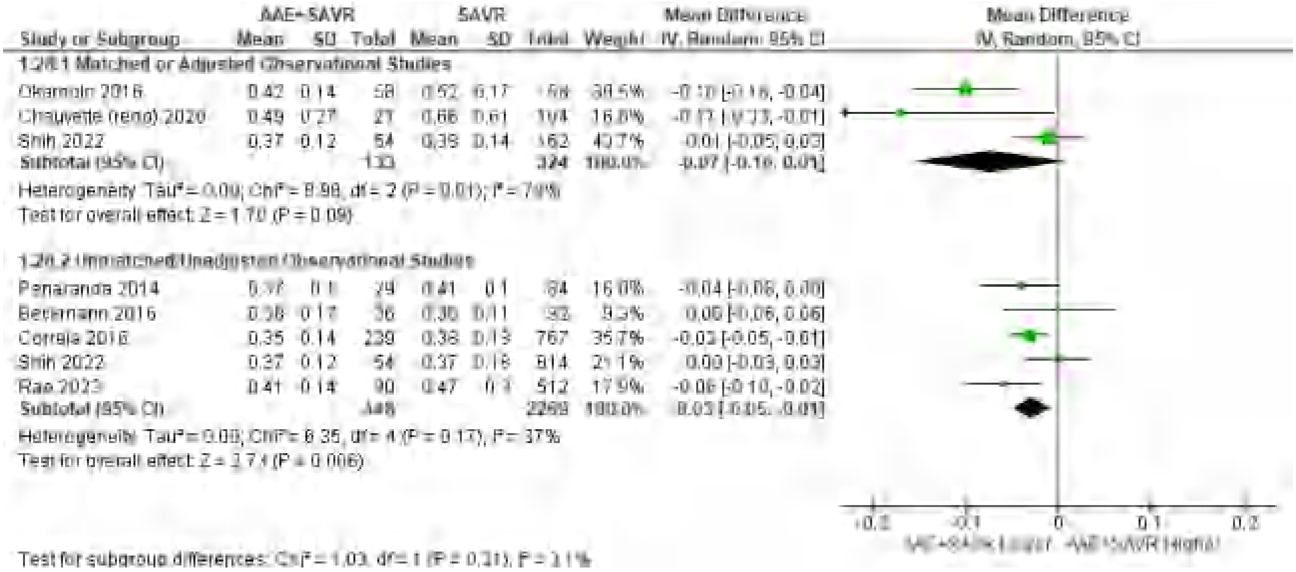

Figure S28 Forest plot for indexed effective orifice area (cm^2/m^2).

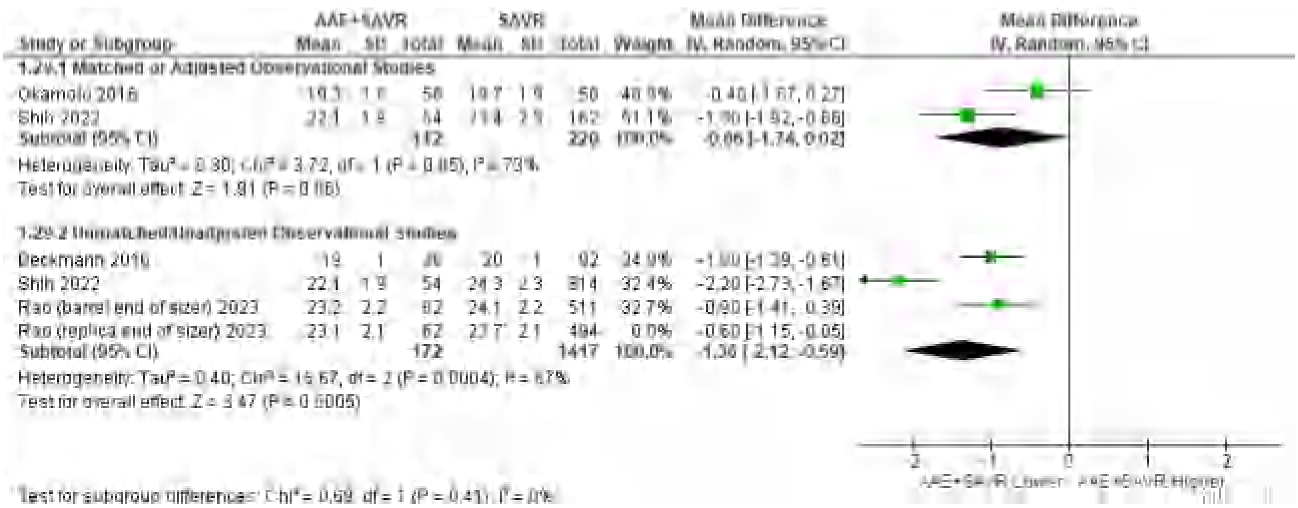

Figure S29 Forest plot for aortic annular diameter (mm).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

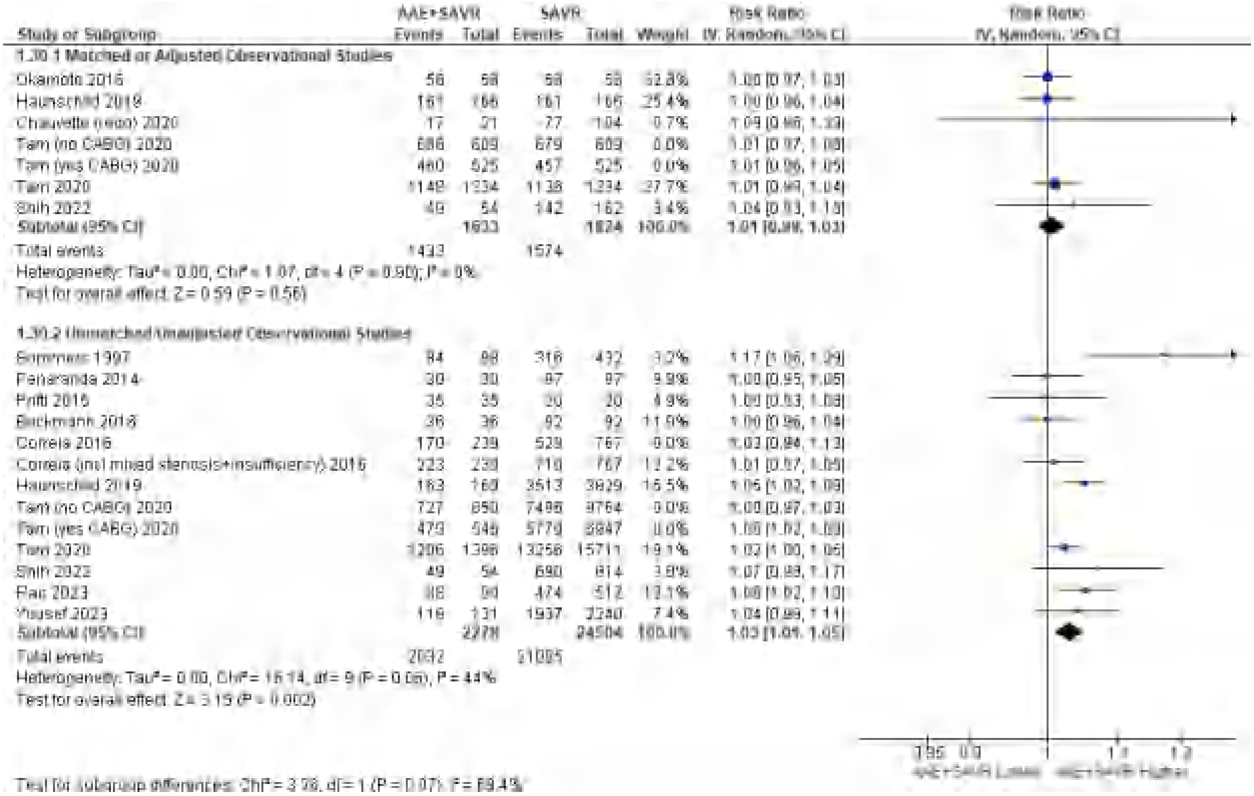

Figure S30 Forest plot for aortic stenosis [including mixed stenosis and insufficiency] vs insufficiency.

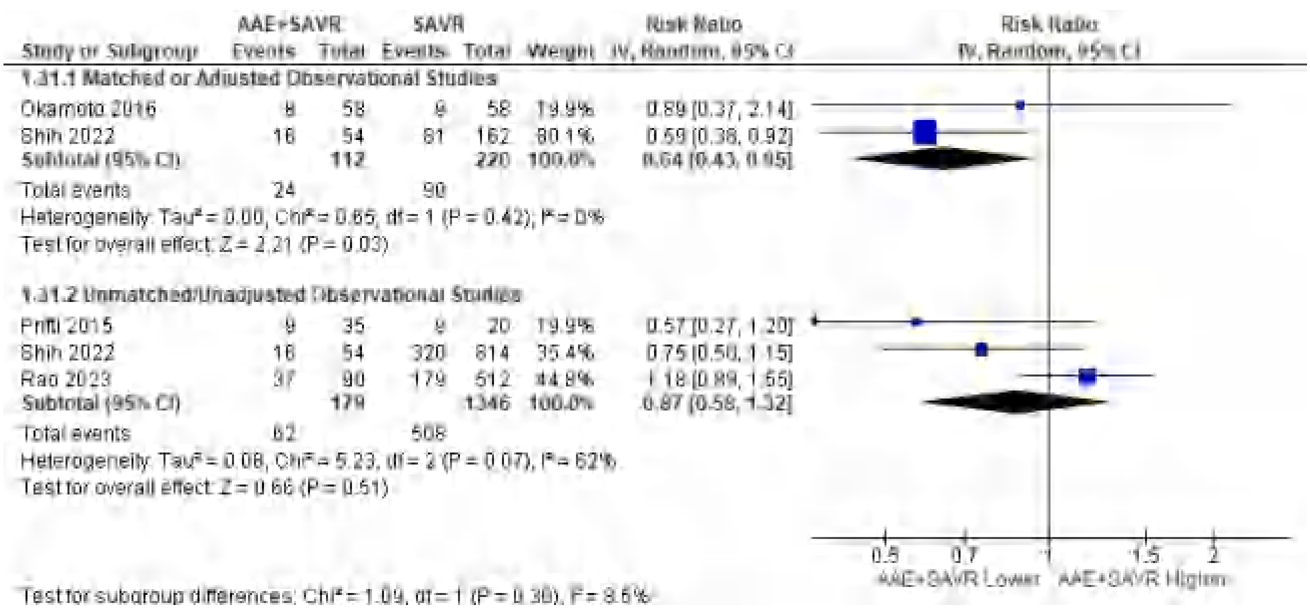

Figure S31 Forest plot for bicuspid aortic valve.

Figures S32-S39. Meta-analyses for operative outcomes

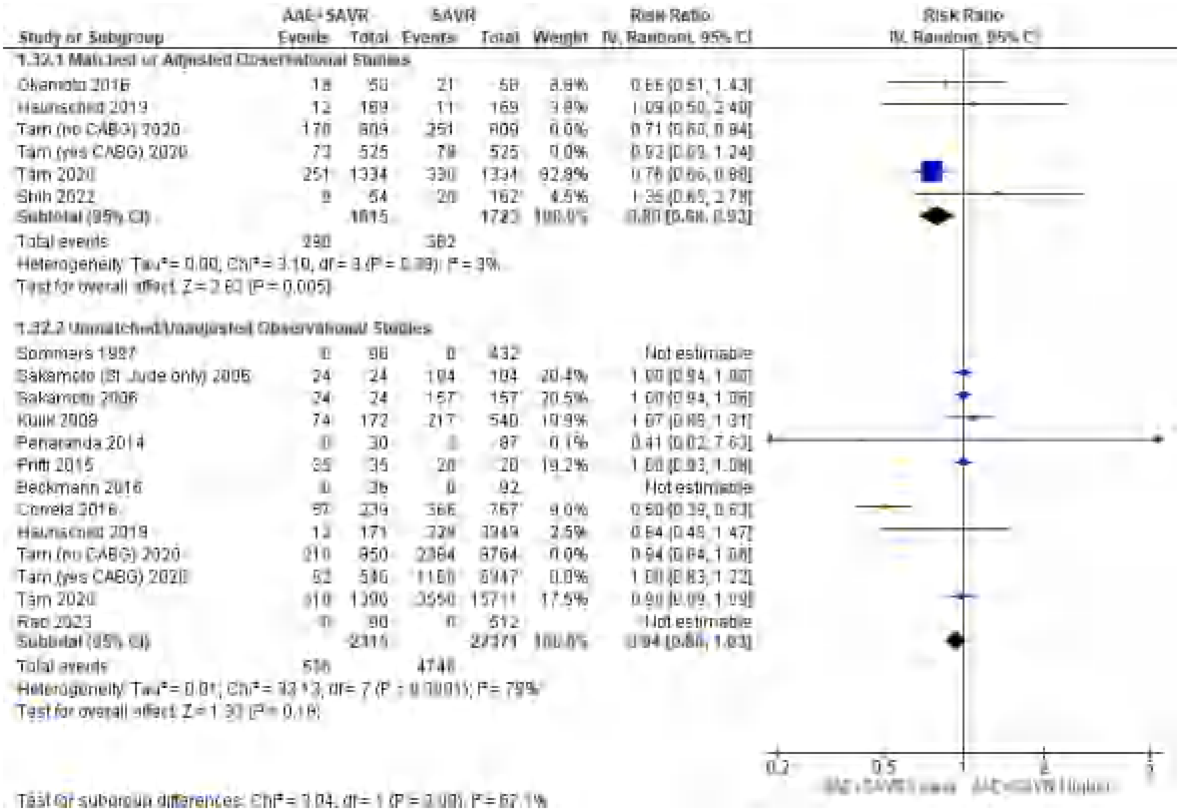

Figure S32 Forest plot for mechanical *vs.* bioprosthetic aortic valve replacement.

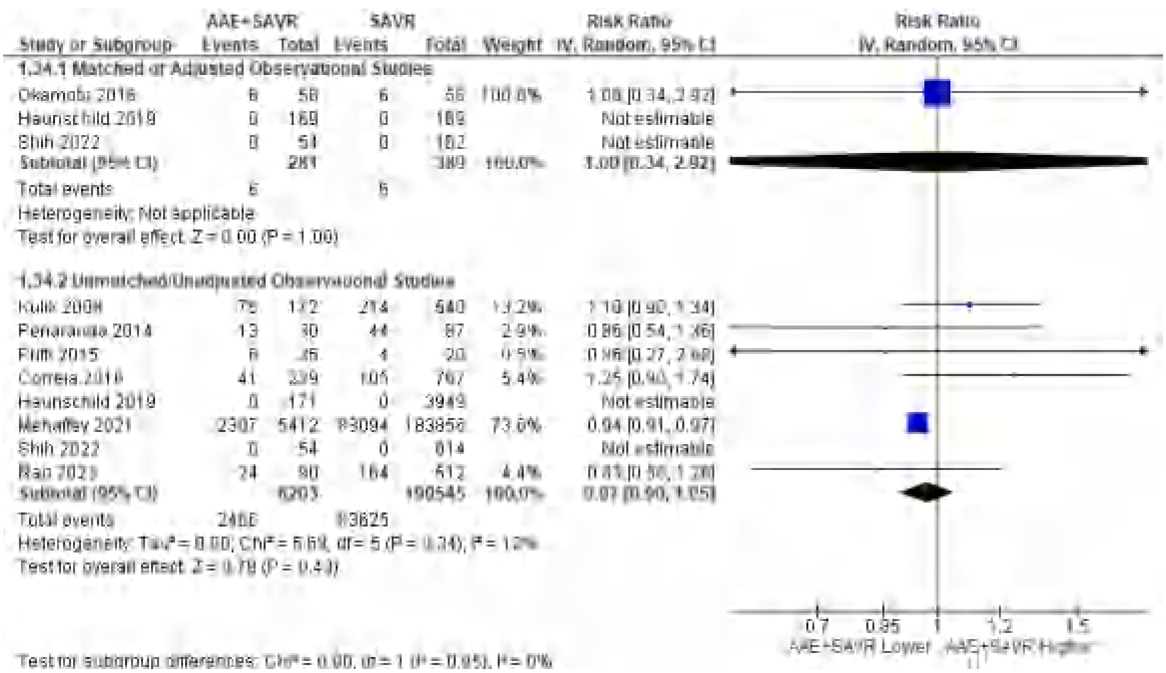

Figure S33 Forest plot for concomitant CABG.

https://dx.doi.org/10.21037/acs-2024-aae-0023

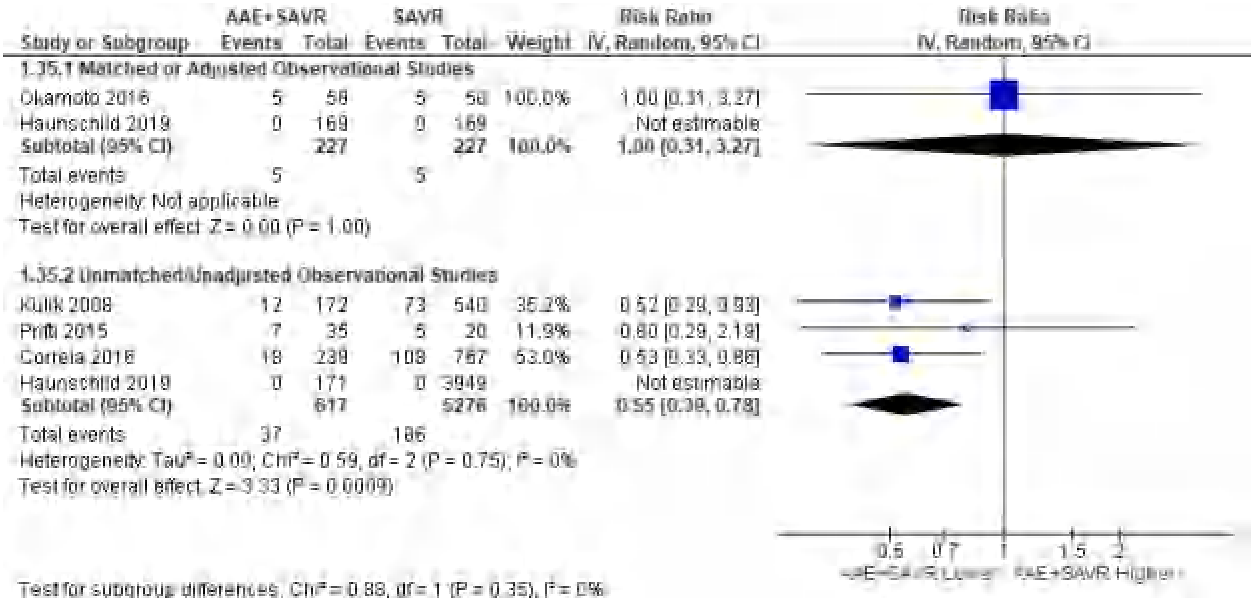

Figure S34 Forest plot for concomitant mitral valve surgery.

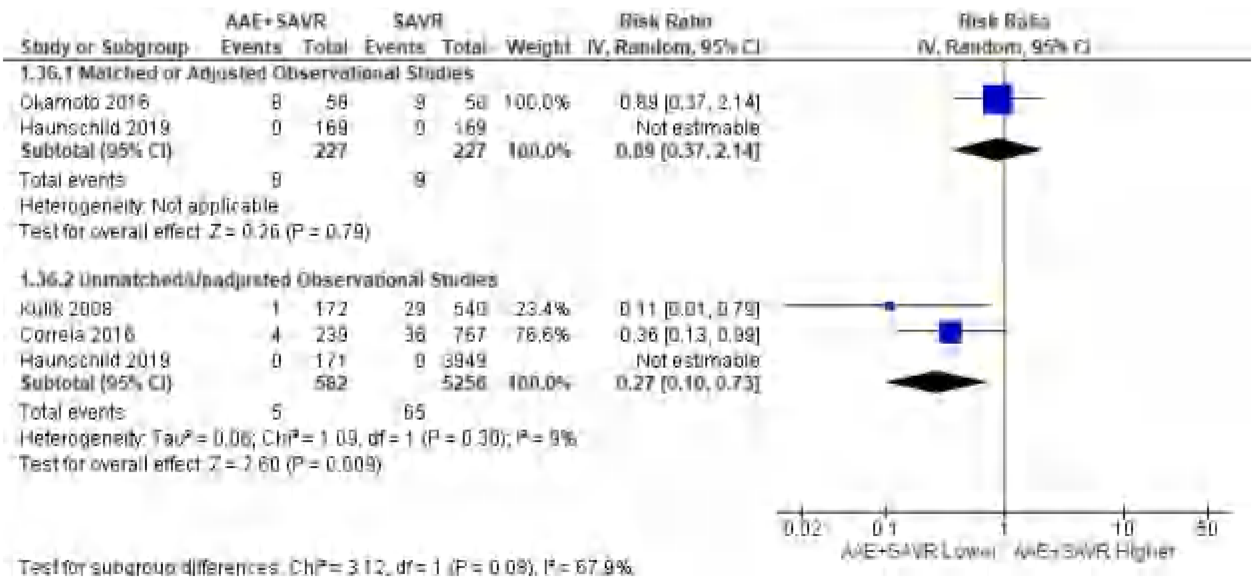

Figure S35 Forest plot for concomitant tricuspid valve surgery.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

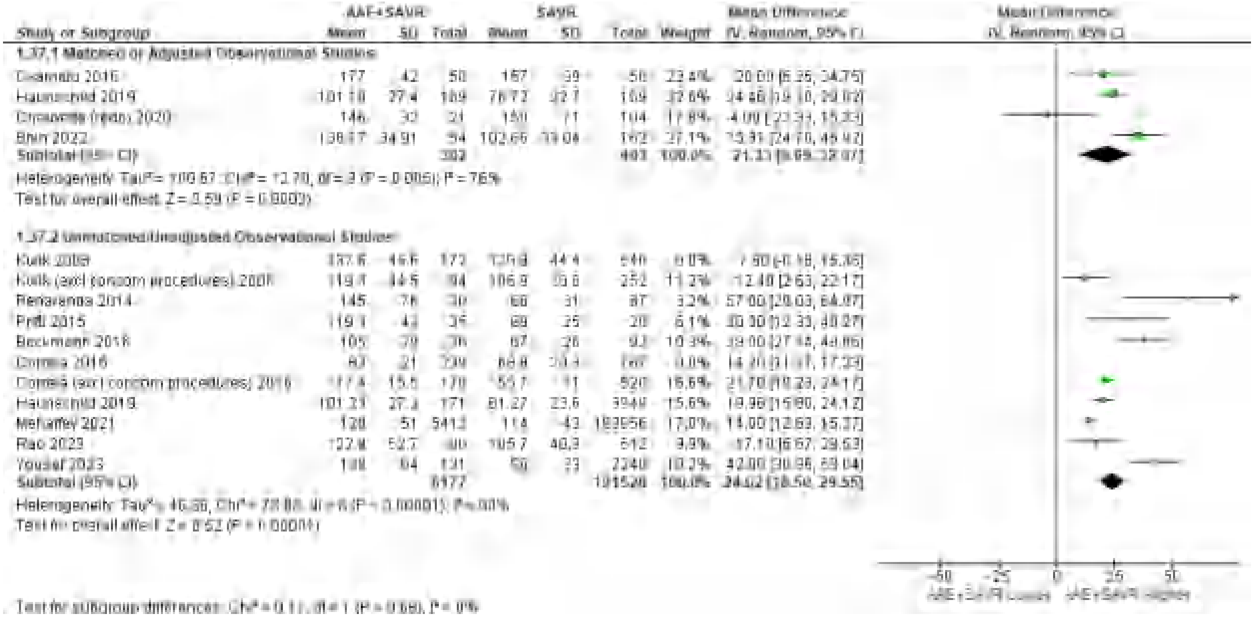

Figure S36 Forest plot for cardiopulmonary bypass time (min).

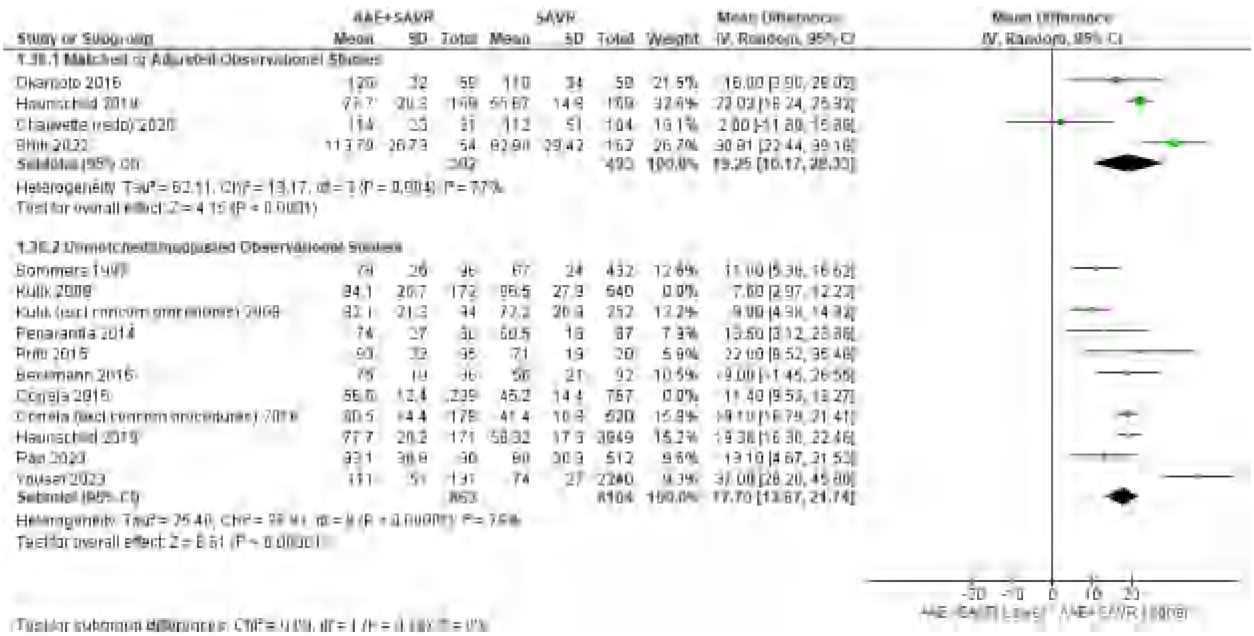

Figure S37 Forest plot for aortic cross clamp time (min).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

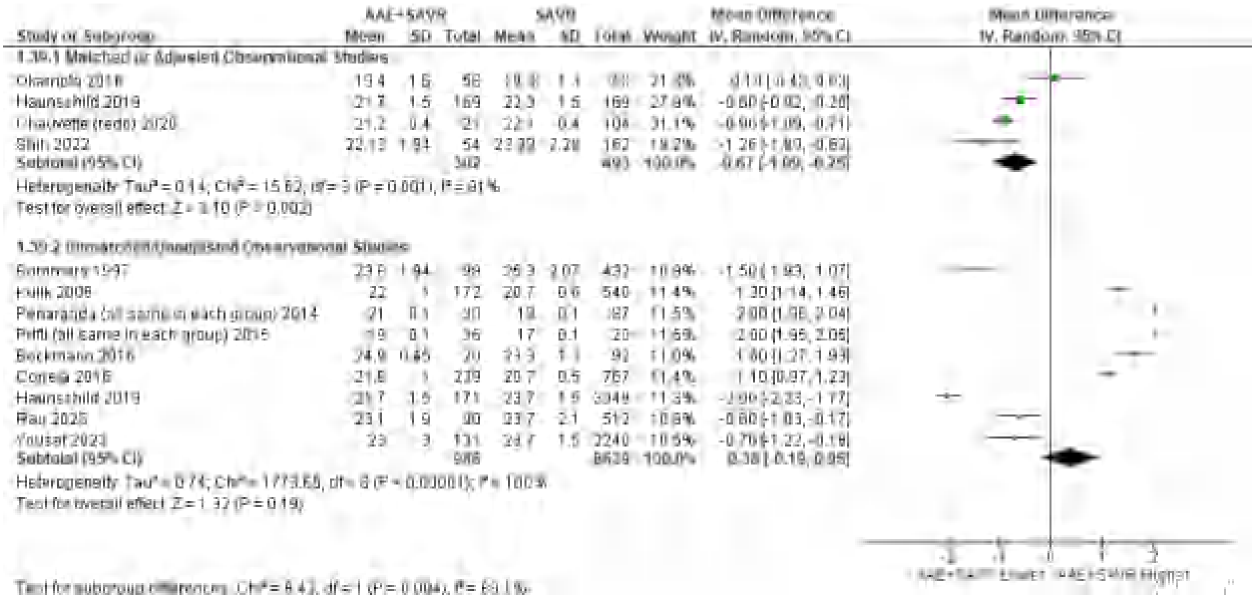

Figure S38 Forest plot for aortic prosthesis size (mm) with arbitrary small standard deviation of 0.1 imputed for Penaranda 2014 and Prifti 2015 to allow inclusion in the pooled analysis. These studies would otherwise be excluded in the pooled analysis as each group received only one prosthesis size for these two studies resulting in zero standard deviations.

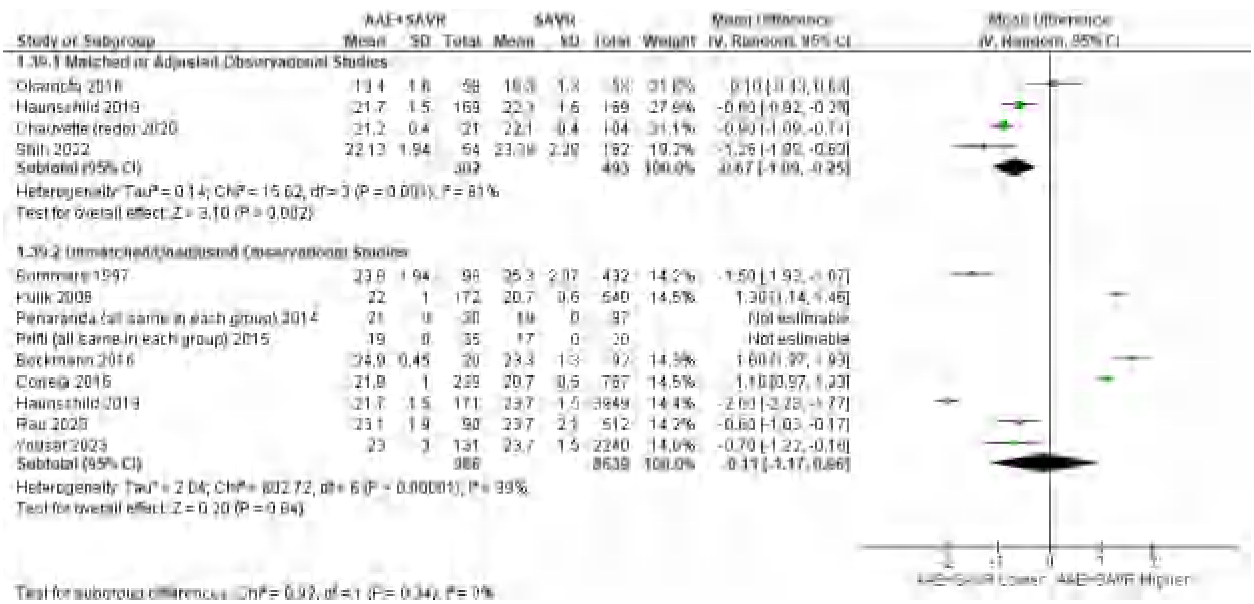

Figure S39 Forest plot for aortic prosthesis size (mm) without imputed standard deviations from (thereby excluding) Penaranda 2014 and Prifti 2015.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

Figures S40-S55. Meta-analyses for early postoperative outcomes

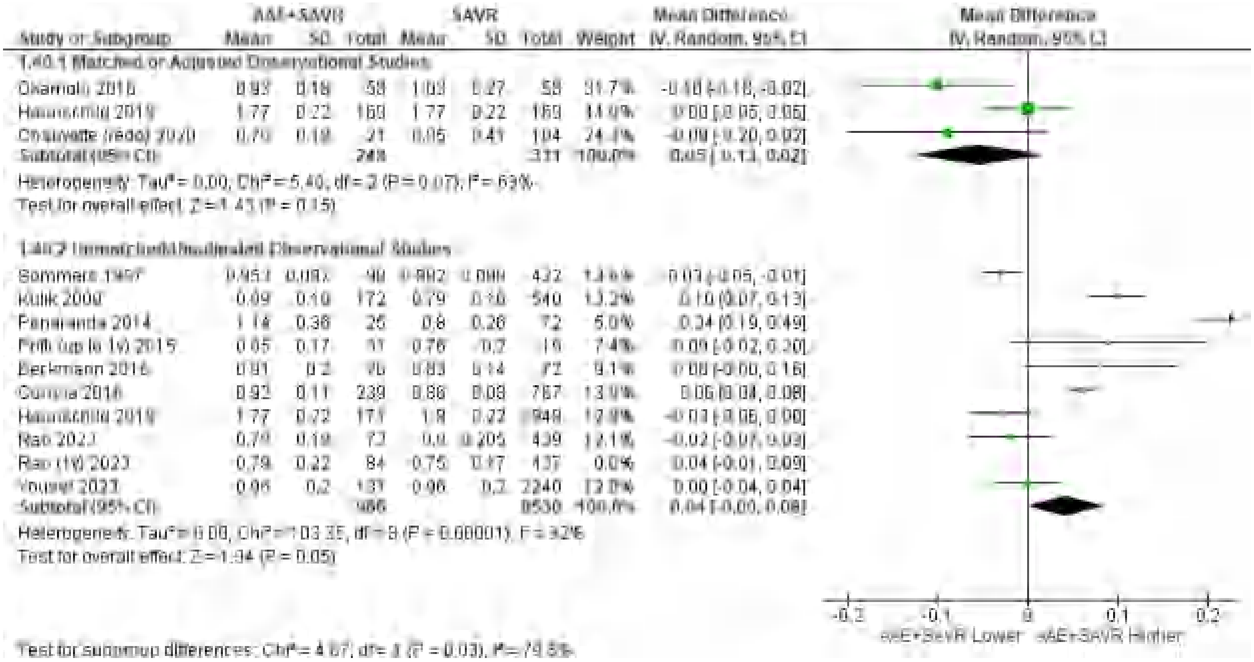

Figure S40 Forest plot for postoperative indexed effective orifice area (cm^2/m^2).

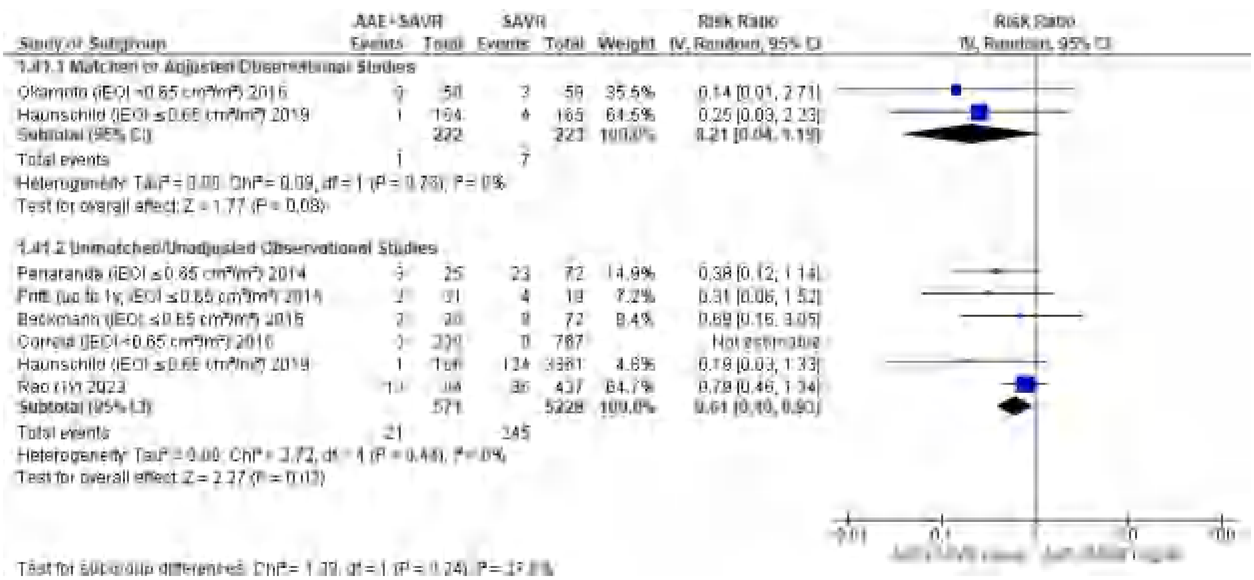

Figure S41 Forest plot for severe patient-prosthesis mismatch (PPM).

https://dx.doi.org/10.21037/acs-2024-aae-0023

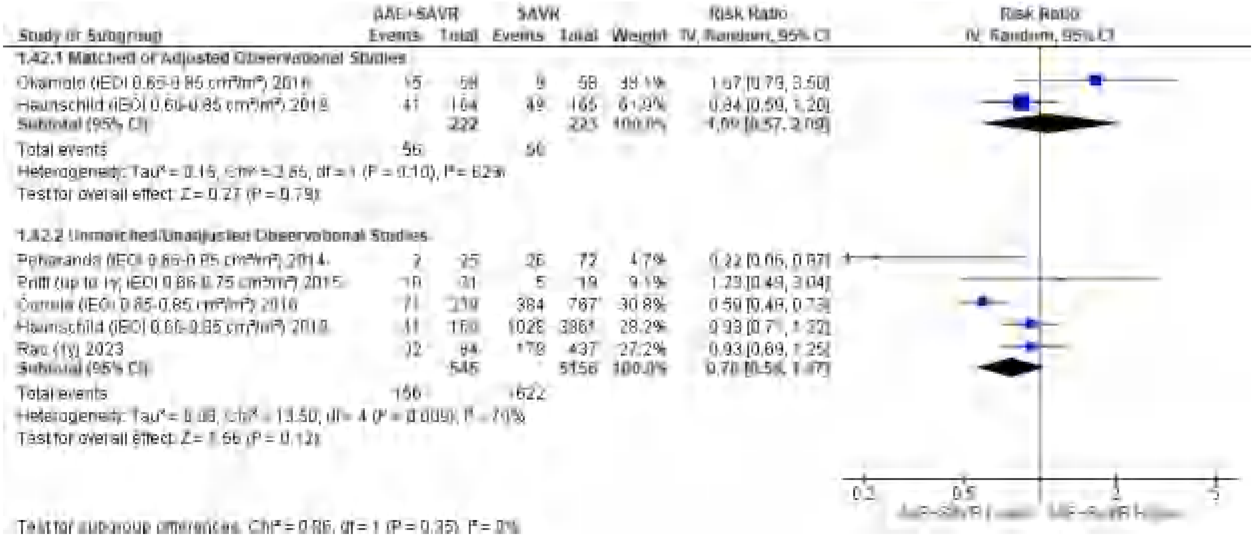

Figure S42 Forest plot for moderate patient-prosthesis mismatch (PPM).

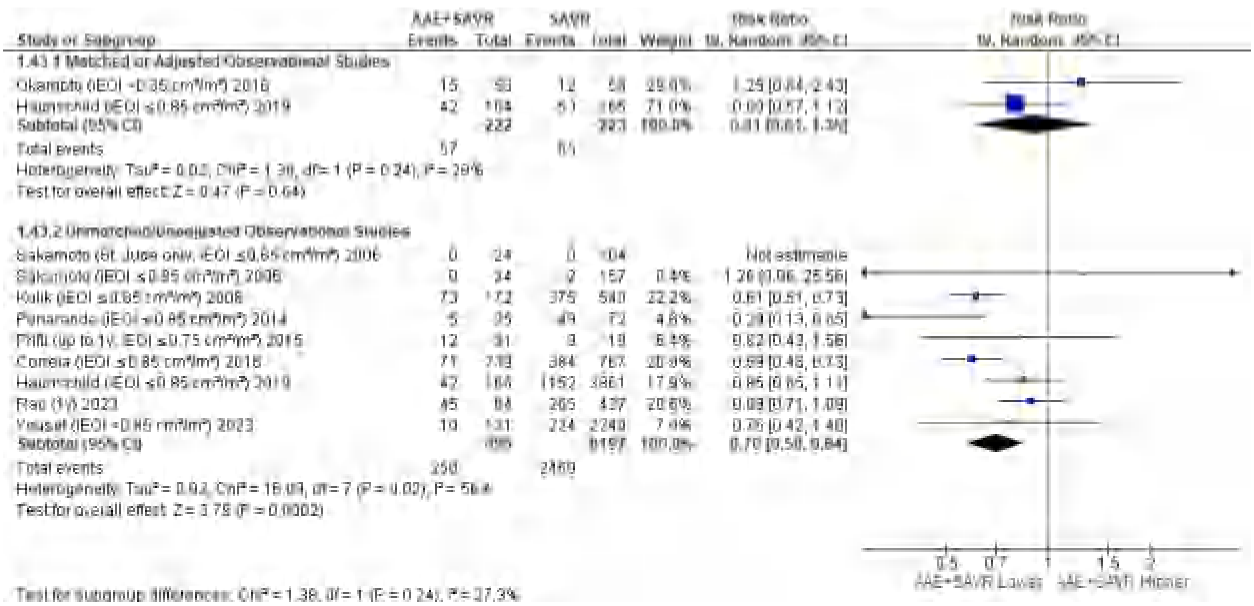

Figure S43 Forest plot for moderate or severe patient-prosthesis mismatch (PPM).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

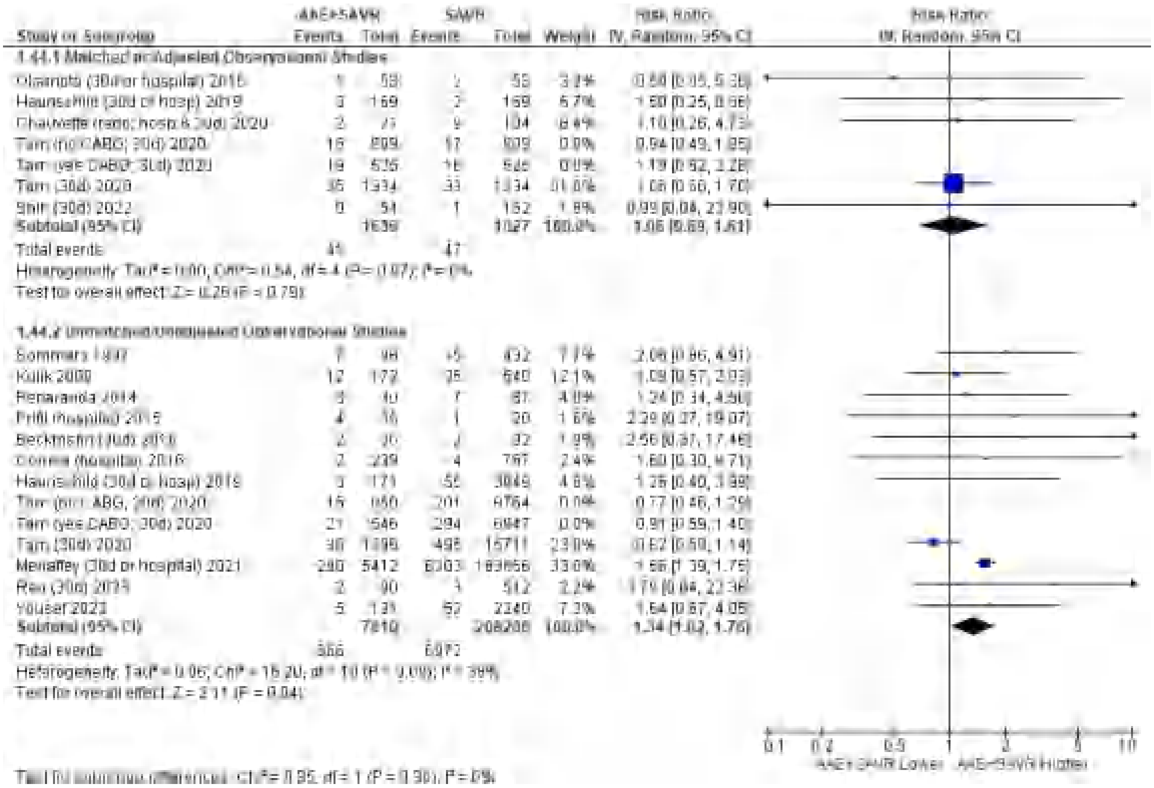

Figure S44 Forest plot for perioperative mortality.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

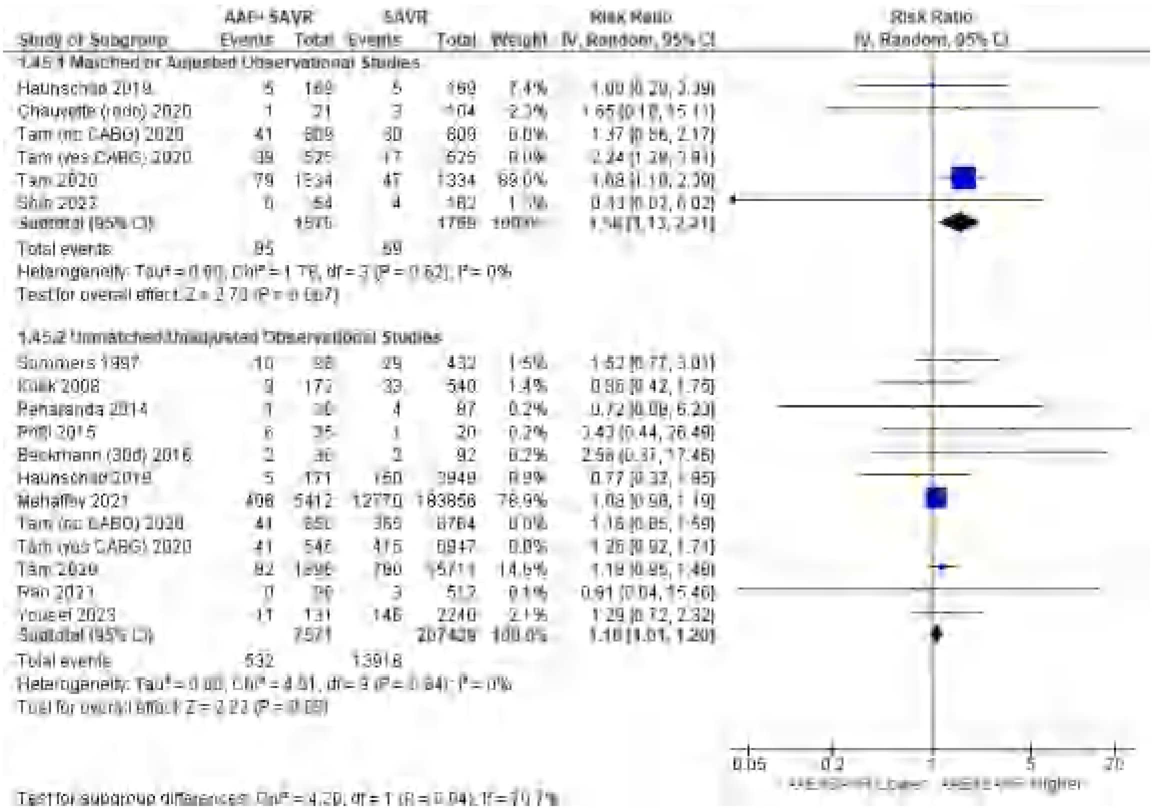

Figure S45 Forest plot for perioperative chest reopening. Increased risk of perioperative chest reopening among the matched/adjusted studies was primarily due to the results of Tam 2020 which accounted for 89% of the weighting. Excluding Tam 2020, the pooled risk of chest reopening in the remaining matched/adjusted studies was no longer statistically significant (RR 0.97 [0.36, 2.65]).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

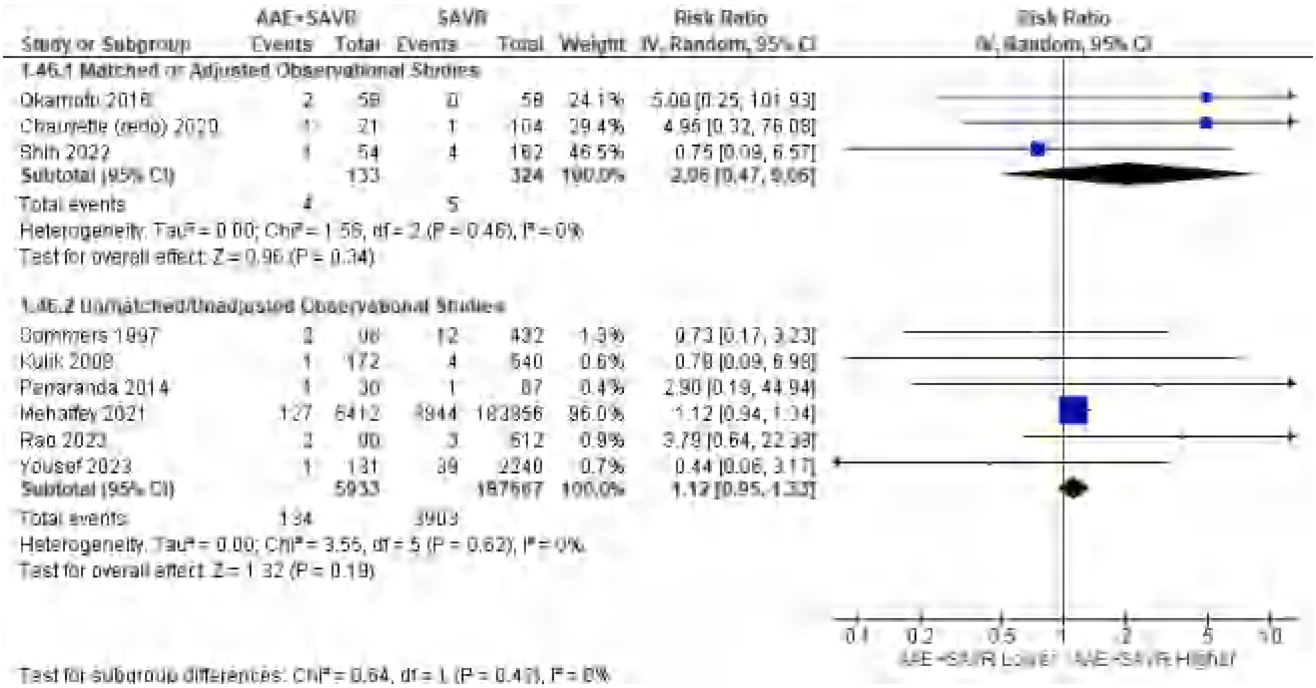

Figure S46 Forest plot for perioperative stroke.

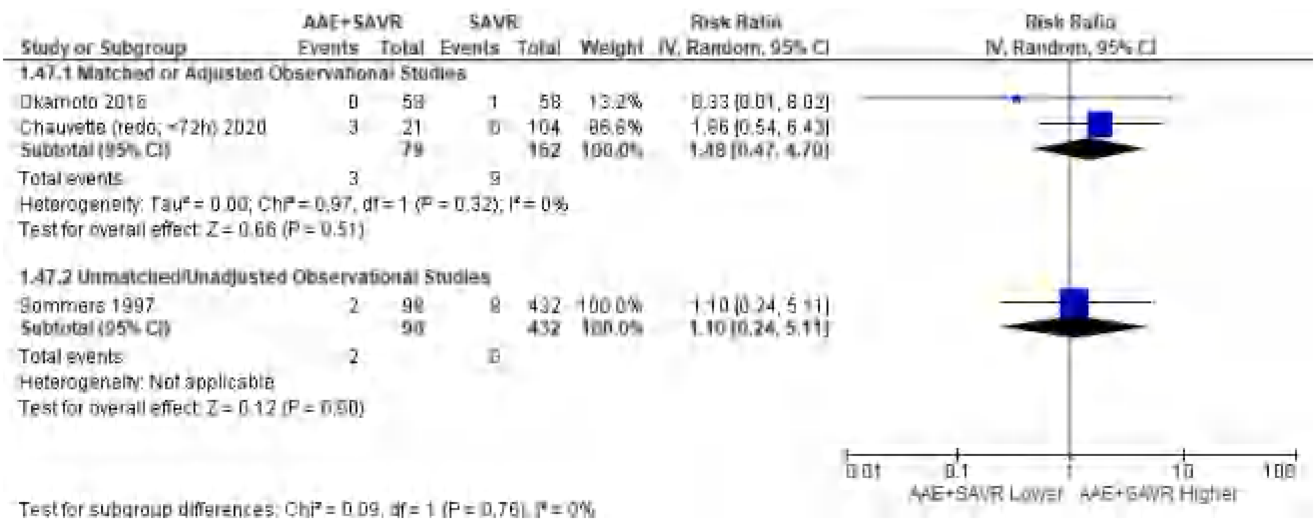

Figure S47 Forest plot for perioperative myocardial infarction.

https://dx.doi.org/10.21037/acs-2024-aae-0023

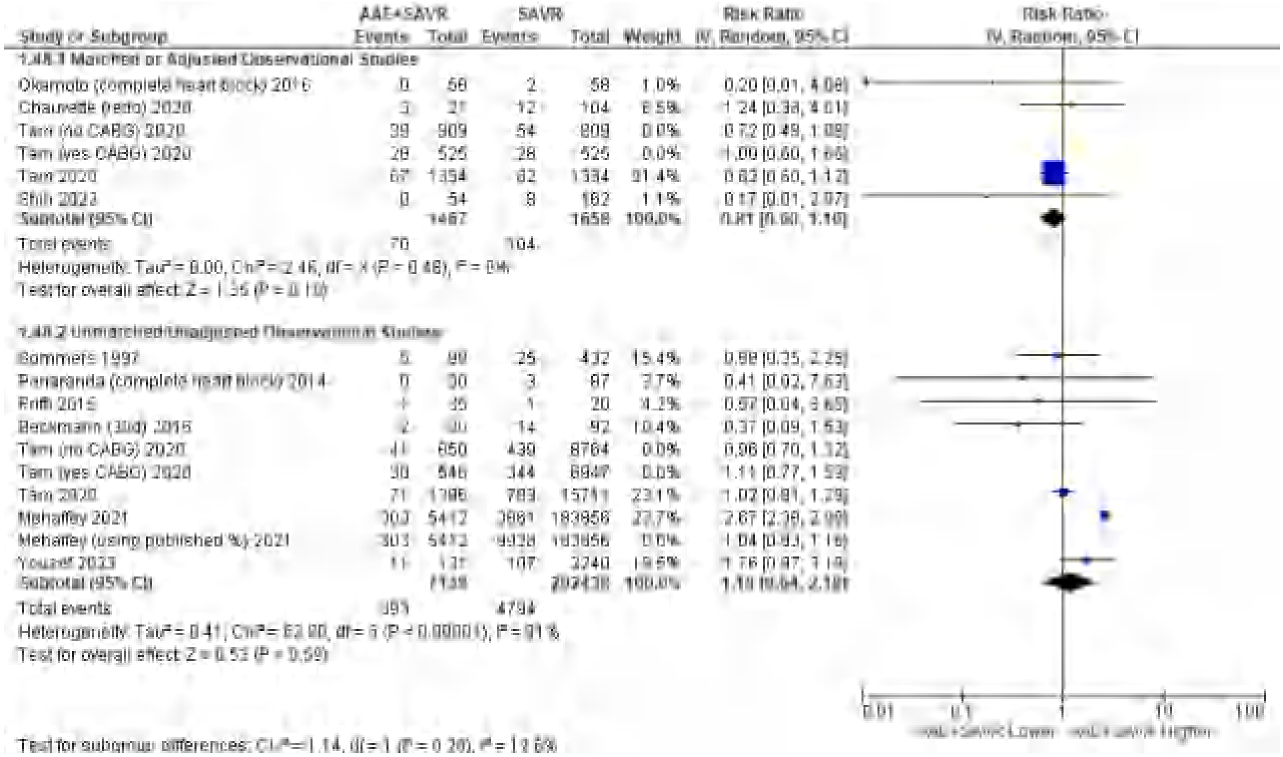

Figure S48 Forest plot for perioperative new permanent pacemaker.

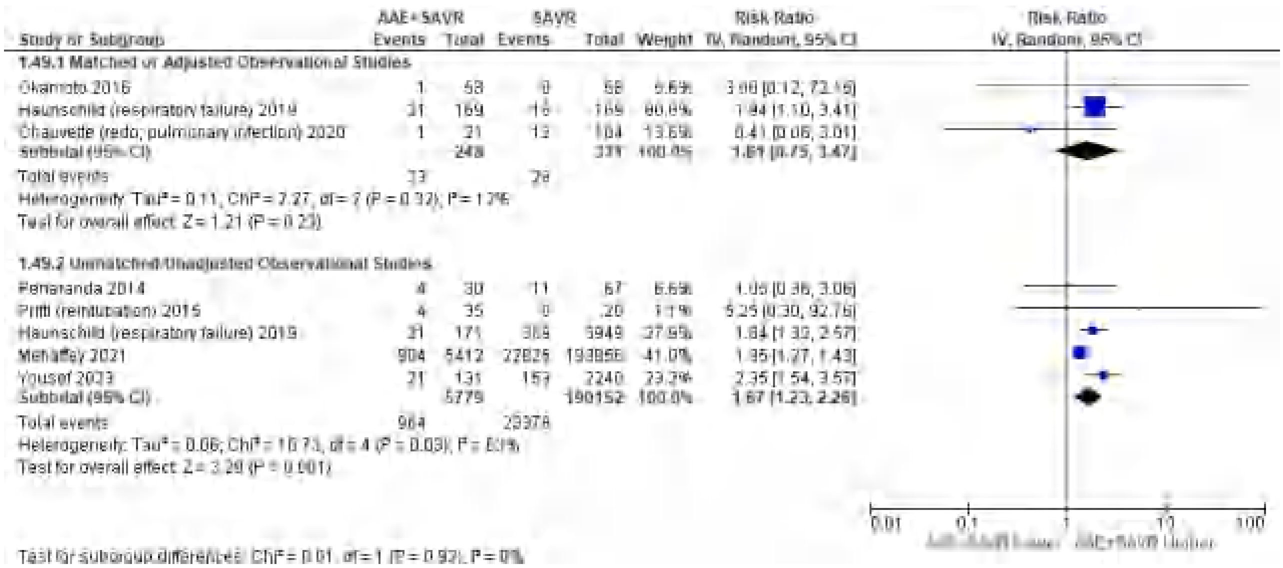

Figure S49 Forest plot for prolonged mechanical ventilation (>24 hours) or other respiratory complications.

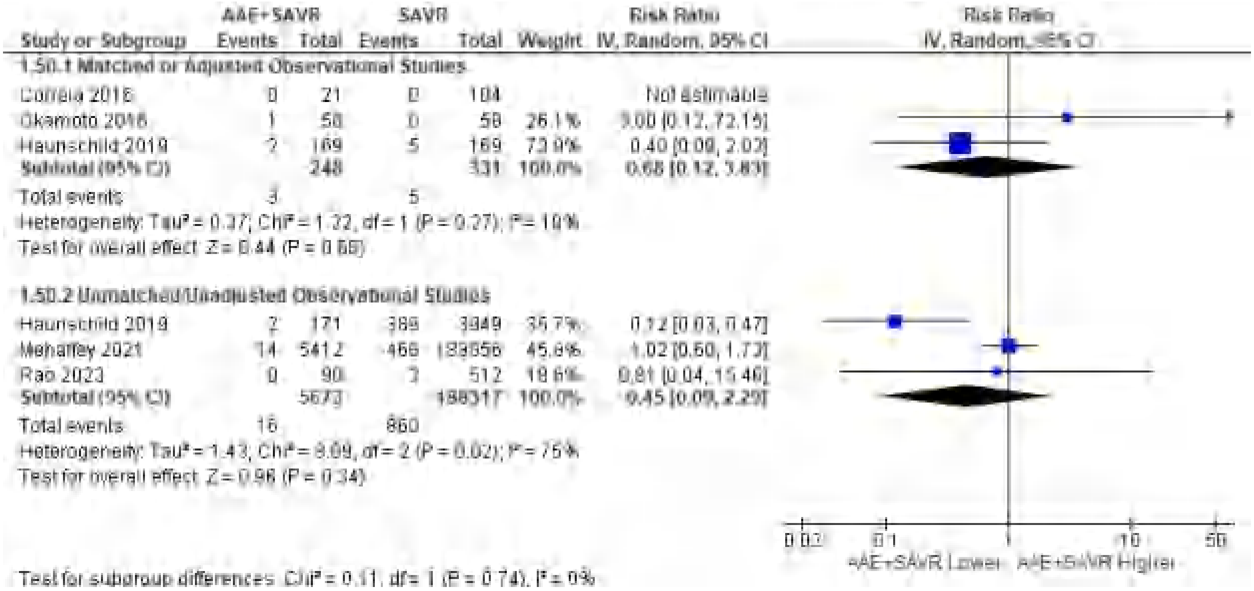

Figure S50 Forest plot for deep sternal wound infection.

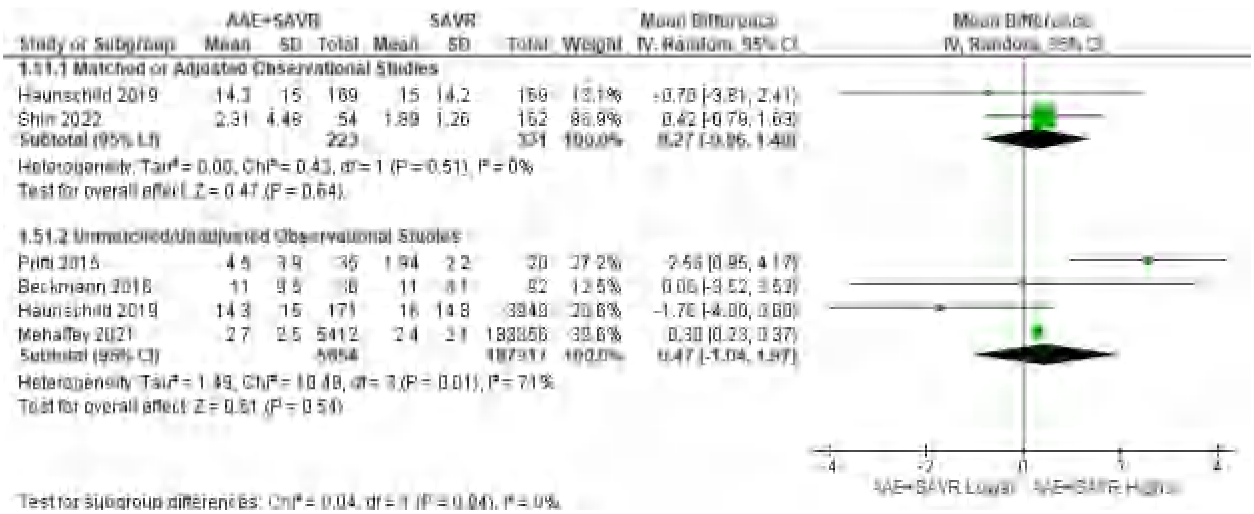

Figure S51 Forest plot for ICU length of stay (days).

 https://dx.doi.org/10.21037/acs-2024-aae-0023

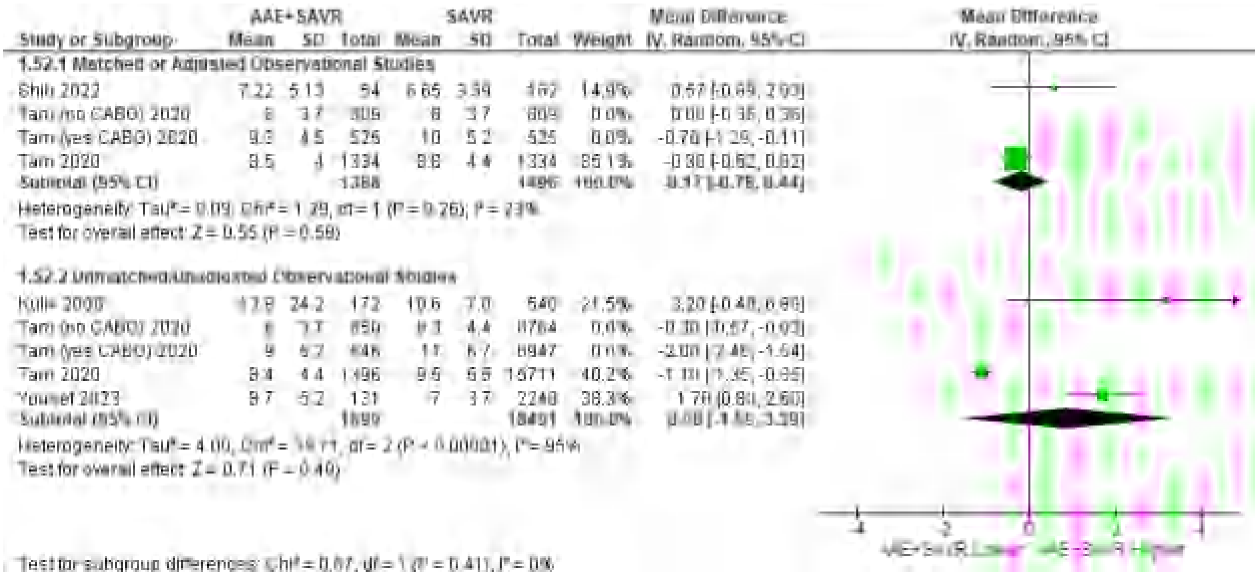

Figure S52 Forest plot for hospital length of stay (days).

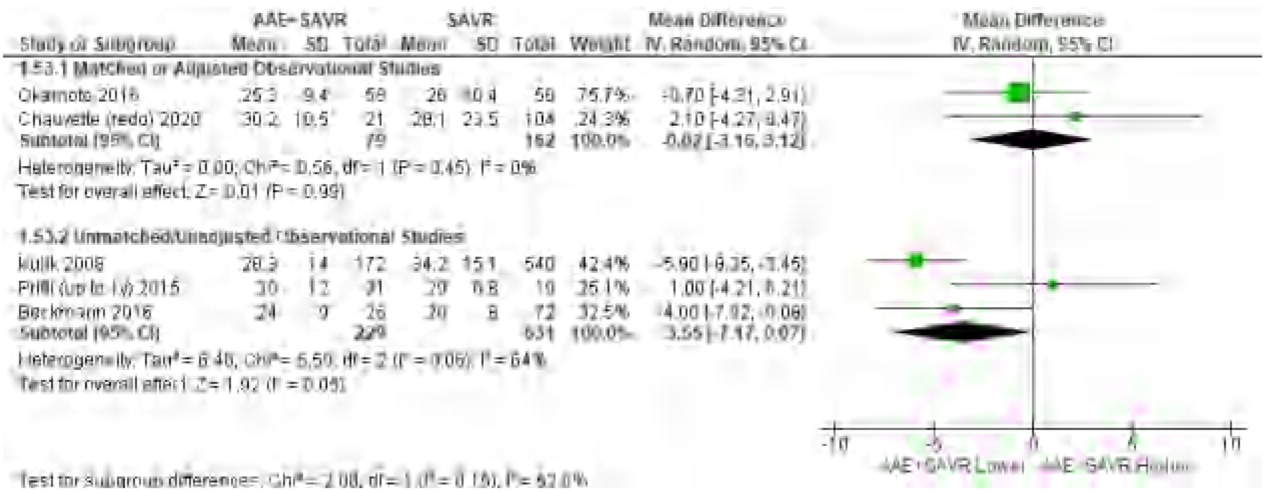

Figure S53 Forest plot for peak transprosthetic gradient at discharge (mm Hg).

https://dx.doi.org/10.21037/acs-2024-aae-0023

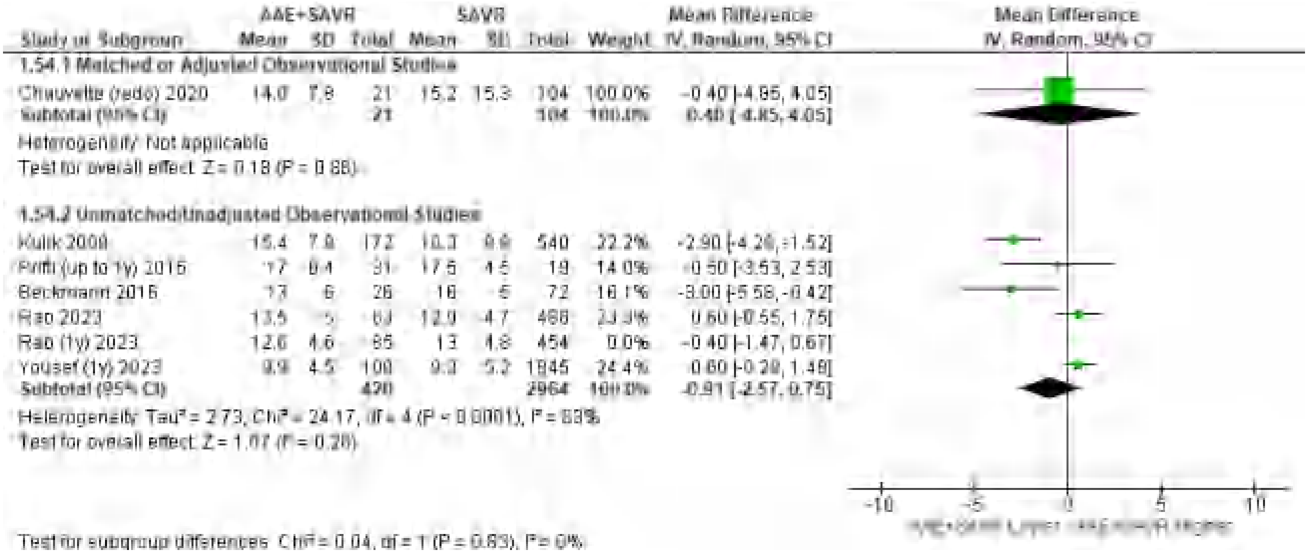

Figure S54 Forest plot for mean transprosthetic gradient at discharge (mm Hg).

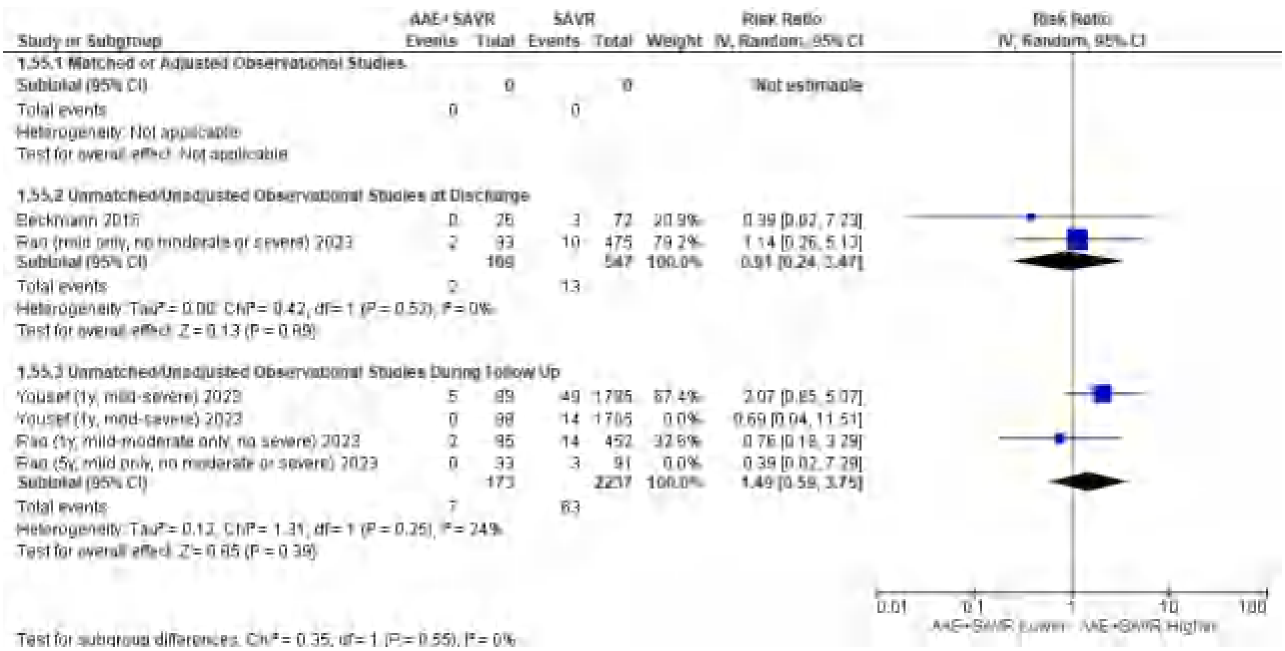

Figure S55 Forest plot for paravalvular leak at discharge and during follow up.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

Figures S56-S61. Meta-analyses of secondary outcomes lacking sufficient data

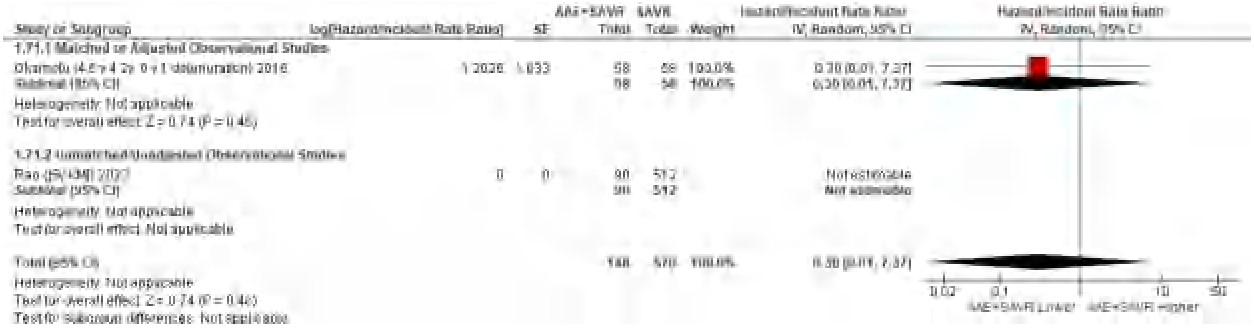

Figure S56 Forest plot for structural valve deterioration during follow-up.

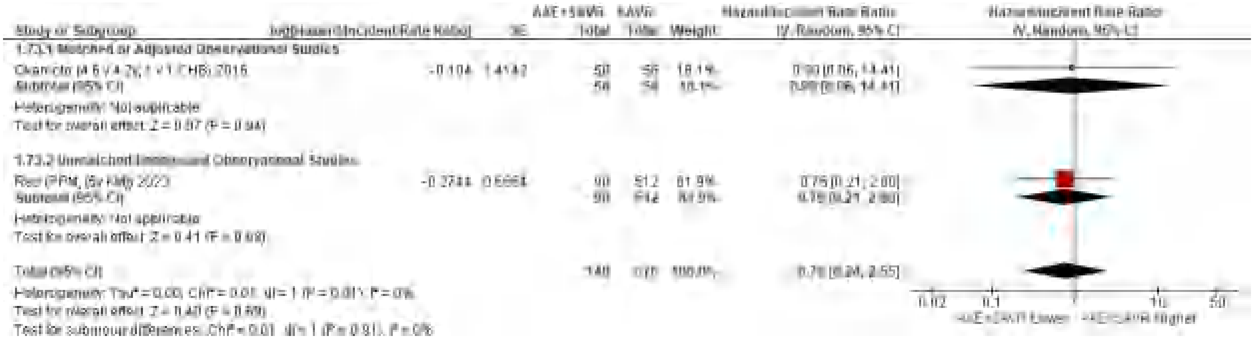

Figure S57 Forest plot for complete heart block or permanent pacemaker insertion.

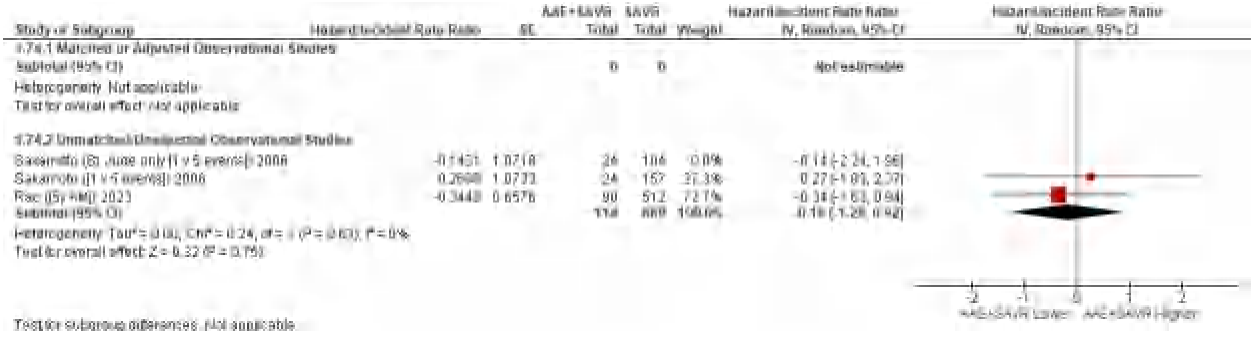

Figure S58 Forest plot for thromboembolism during follow-up. Assumed equal follow-up lengths between groups if only overall follow-up was provided.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

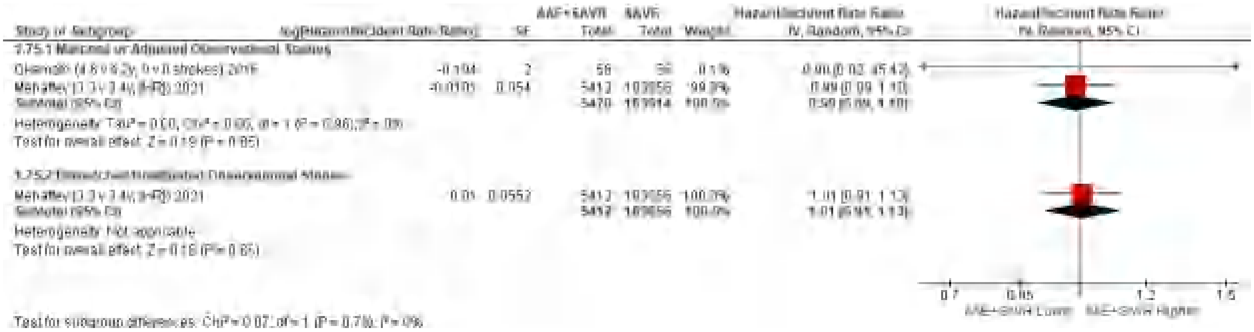

Figure S59 Forest plot for stroke during follow-up.

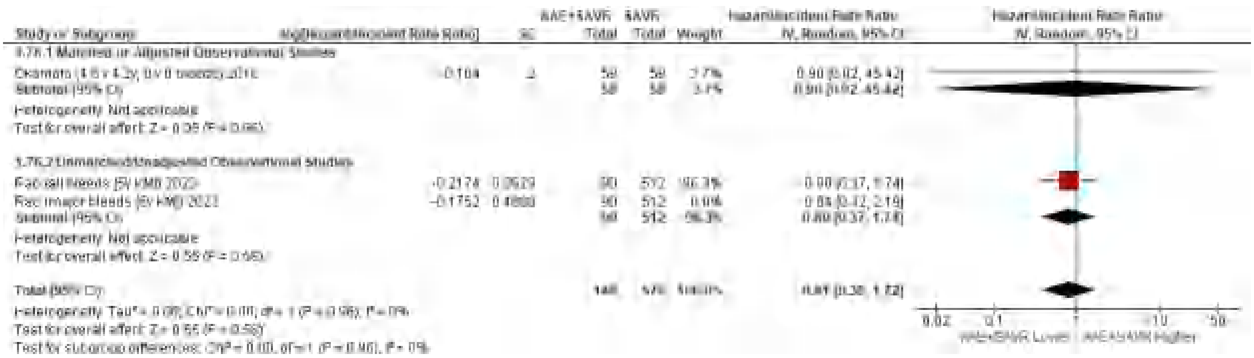

Figure S60 Forest plot for bleeding during follow-up.

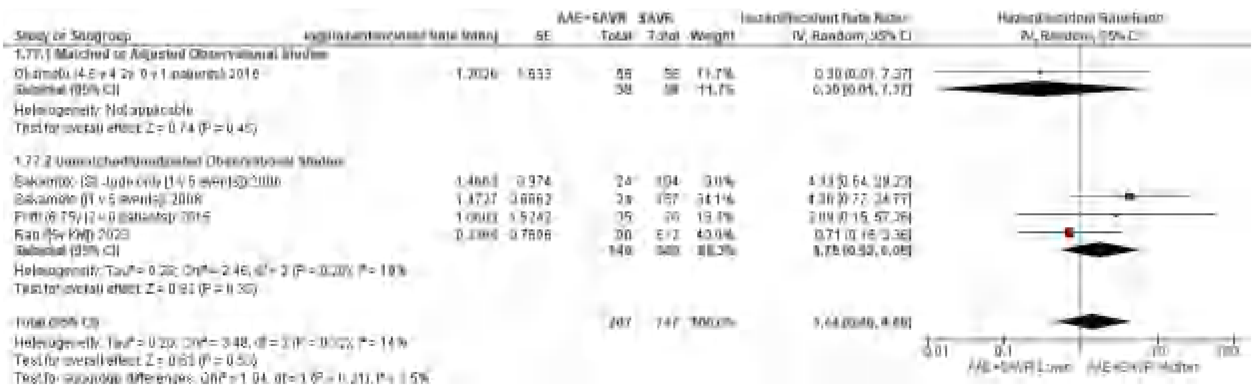

Figure S61 Forest plot for endocarditis during follow-up.

Figures S62-S63. Summaries of sensitivity analyses

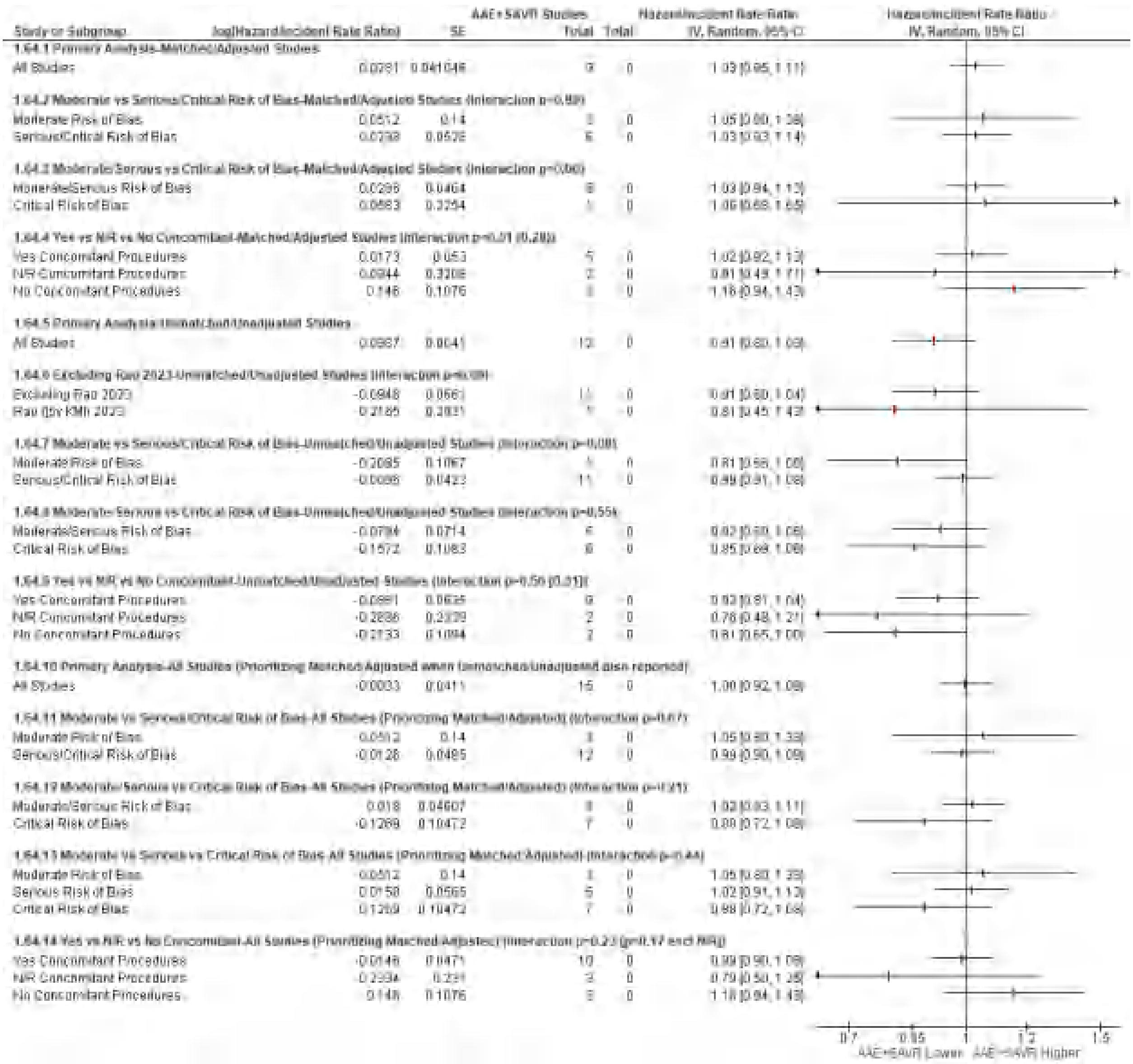

Figure S62 Sensitivity analyses for mid-term mortality.

 https://dx.doi.org/10.21037/acs-2024-aae-0023

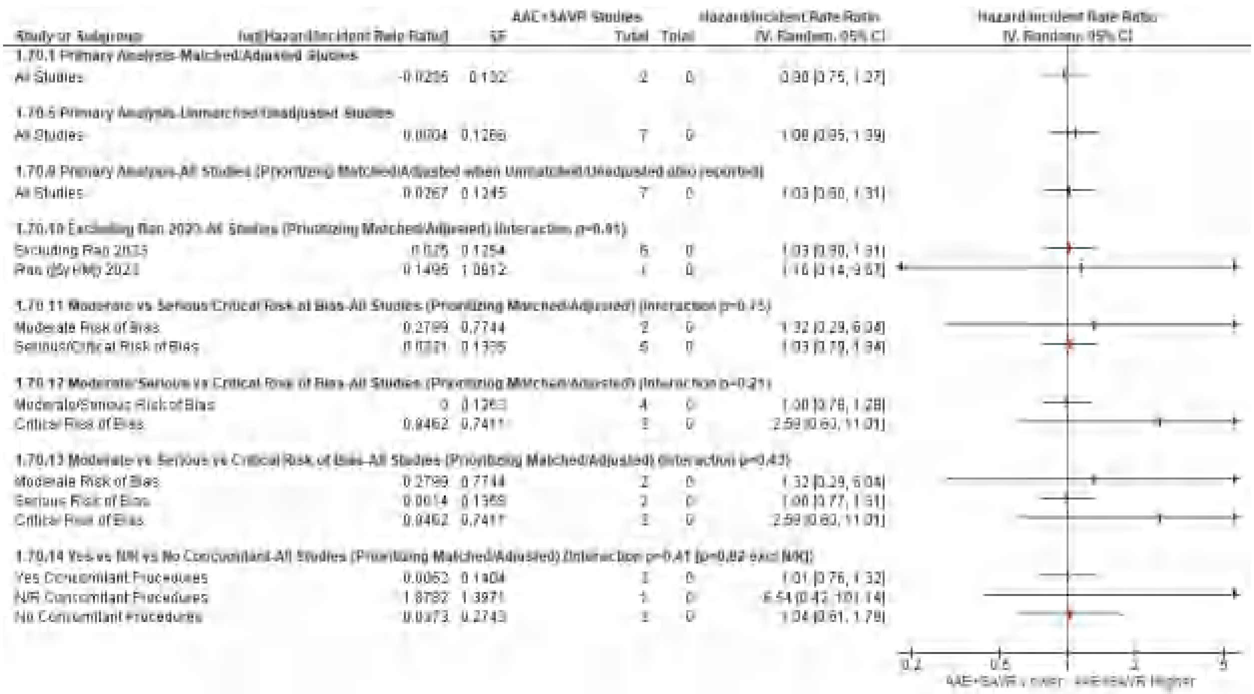

Figure S63 Sensitivity analyses for aortic valve reintervention.

https://dx.doi.org/10.21037/acs-2024-aae-0023

Supplemental Tables:

Table S1 Characteristics of included studies (detailed)

First author	Year	Cohort size	Group		Group number, n (%)		Age (year)		Male sex (%)		Body surface area (m²)		Cerebrovascular disease (%)	
			AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies														
Yousef	2023	2371	AAE + AVR	Isolated AVR	131 (5.5%)	2240 (94.5%)	62.0 [55.0–70.0]	68.0 [60.0–76.0]	32.1	63.6	1.99±0.27	2.03±0.27	14.5	18.0
Shih	2022	216	AAE + AVR	Isolated AVR	54 (25%)	162 (75%)	63.92±12.63	64.94±10.84	29.6	29.0	1.89±0.28	1.91±0.25	5.6	3.1
Mehaffey	2021	189268	AAE + AVR	AVR	5412 (2.9%)	183856 (97.1%)	75 [70–79]	76 [71–81]	40.0	62.0	–	–	21.0	19.4
Chauvette	2020	125	AAE + Redo AVR	Redo AVR	21 (16.8%)	104 (83.2%)	63±3	63±3	28.6	42.3	–	–	0.0	0.0
Tam	2020	1618	AAE + AVR	Isolated AVR	809 (50%)	809 (50%)	65.57±12.36	65.48±13.38	43.3	44.4	1.92±0.27	1.91±0.26	4.1	4.9
Tam*	2020	1050	AAE + AVR + CABG	AVR + CABG	525 (50%)	525 (50%)	72.12±8.80	72.36±8.68	54.1	53.5	1.94±0.24	1.94±0.25	5.9	6.5
Haunschild	2019	338	AAE + AVR	AVR	169 (50%)	169 (50%)	67.48±10	67.58±9	34.0	34.0	1.9±0.2	1.9±0.2	–	–
Okamoto	2016	116	AAE + AVR	AVR	58 (50%)	58 (50%)	73.4±11.9	74.7±8.5	19.0	19.0	1.45±0.16	1.38±0.16	0.0	0.0
Kulik	2008	712	AAE + AVR	AVR in SAR	172 (24.2%)	540 (75.8%)	66.8±12.3	69.1±11.8	30.8	25.2	–	–	–	–
Sommers	1997	530	AAE + Medtronic Hancock II bioAVR	Medtronic Hancock II bioAVR	98 (18%)	432 (82%)	64±13	64±12	55.0	87.0	1.79±0.22	1.83±0.19	–	–
Unmatched/unadjusted observational studies														
Rao	2023	602	Aortic root, STJ, or annular enlargement + Medtronic Avalus AVR	Medtronic Avalus AVR	90 (15.0%)**	512 (85.0%)	67.9±7.2	69.3±8.9	62.2	78.3	2.00±0.21	2.00±0.22	1.1	4.7
Beckmann	2016	128	AAE + bioAVR in SAR	Corcym Perceval bioAVR in SAR	36 (28.1%)	92 (71.9%)	62 (37–92)	79 (37–91)	16.7	18.5	1.8±0.2	1.8±0.2	–	–
Correia	2016	1006	AAE + AVR in SAR	AVR in SAR	239 (23.8%)	767 (76.2%)	70.4±12.5	69.9±9.6	18.4	12.0	1.59±0.15	1.57±0.13	5.0	6.3
Prifti	2015	55	AAE + 19 mm supraannular AVR	17 mm supraannular AVR	35 (63.6%)	20 (36.4%)	67.6±10	69.75±7.4	17.0	10.0	1.68±0.16	1.67±0.2	8.6	20.0
Penaranda	2014	117	AAE + 21 mm AVR	19 mm AVR	30 (25.6%)	87 (74.4%)	83.8 (80.2–93.4)	84.1 (80.1–92.7)	13.0	2.0	1.7 (1.5–2.1)	1.6 (1.2–2.1)	20.0	13.0
Sakamoto	2006	128	AAE + St Jude mechAVR	St Jude mechAVR	24 (18.75%)	104 (81.25%)	52.6±11.9†		72.7†		1.60±0.15†		–	–

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Table S1 (*continued*)

First author	Year	Renal failure (%)		Dialysis (%)		Coronary artery disease (%)		COPD (%)		Smoking (%)		Diabetes (%)		Hypertension (%)		Urgent status (%)		Emergent Status (%)		Urgent/Emergent Status (%)	
		AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies																					
Yousef	2023	–	–	0.8	1.8	–	–	–	–	–	–	35.9	31.8	–	–	–	–	–	–	24.4	24.0
Shih	2022	–	–	0.0	0.6	–	–	3.7	3.1	5.6	6.2	33.3	35.8	81.5	79.0	11.1	6.2	0	0	11.1	6.2
Mehaffey	2021	–	–	1.7	1.8	55.4	58.8	–	–	23.3	24.0	39.6	34.7	88.1	86.5	21.7	24.2	0	0	21.7	24.2
Chauvette	2020	–	–	–	–	10.0	11.0	3.0	5.0	–	–	28.0	15.0	62.0	59.0	–	–	–	–	19.0	13.0
Tam	2020	–	–	3.5	4.4	35.0	37.8	24.0	22.4	43.3	42.4	38.4	39.3	75.8	75.6	11.6	12.5	0	0	11.6	12.5
Tam*	2020	–	–	4.6	4.8	98.3	96.4	23.0	24.4	52.2	49.5	50.9	53.1	87.8	89.5	21.0	21.1	0	0	21.0	21.1
Haunschild	2019	–	–	2.0	2.0	–	–	4.0	4.0	26.0	25.0	32.0	34.0	89.0	85.0	11.0	11.0	0	0	11.0	11.0
Okamoto	2016	6.9	10.3	–	–	10.3	10.3	0.0	3.4	12.1	13.8	22.4	17.2	67.2	63.8	–	–	–	–	0.0	1.7
Kulik	2008	–	–	–	–	–	–	–	–	12.8	10.4	–	–	–	–	–	–	–	–	–	–
Sommers	1997	–	–	–	–	38.0	40.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Unmatched/unadjusted observational studies																					
Rao	2023	4.4	9.2	–	–	30.0	47.3	–	–	–	–	–	–	74.4	75.2	–	–	–	–	–	–
Beckmann	2016	19.0	16.0	–	–	–	–	8.0	5.0	–	–	22.0	33.0	66.0	73.0	–	–	–	–	–	–
Correia	2016	26.8	29.6	2.5	1.2	27.2	24.1	6.7	5.7	–	–	17.6	12.9	57.7	44.1	–	–	–	–	–	–
Prifti	2015	5.7	0.0	–	–	17.1	20.0	14.3	25.0	31.4	30.0	23.0	25.0	46.0	50.0	–	–	–	–	–	–
Penaranda	2014	0.0	3.0	–	–	–	–	–	–	–	–	17.0	16.0	77.0	75.0	–	–	–	–	7.0	7.0
Sakamoto	2006	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

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Table S1 (*continued*)

First author	Year	EuroSCORE II (%)		STS score (%)		Previous cardiac surgery (%)		Previous SAVR (%)		Preoperative LVEF (%)		Preoperative LVEF (< 35%) (%)		Preoperative NYHA ≥3 (%)	
		AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies															
Yousef	2023	–	–	1.7 [1.1–2.9]	1.7 [1.1–3.1]	17.6	15.2	–	–	60.0 [55.0–63.0]	58.0 [55.0–63.0]	–	–	–	–
Shih	2022	–	–	2.1±1.6	2.0±2.1	14.8	16.1	–	–	59.16±8.81	58.33±7.6	–	–	18.5	14.8
Mehaffey	2021	–	–	2.99±4.1	2.97±4.2	13.0	11.6	–	–	–	–	–	–	–	–
Chauvette	2020	13.8±1.6	10.4±1.6	–	–	100.0	100.0	100.0	100.0	62±1	60±1	–	–	67.0	65.0
Tam	2020	–	–	–	–	0.0	0.0	0.0	0.0	–	–	4	4	38.4	37.7
Tam*	2020	–	–	–	–	0.0	0.0	0.0	0.0	–	–	5	5	40.2	41.1
Haunschild	2019	–	–	–	–	0.0	0.0	0.0	0.0	60±11	60±11	–	–	51.0	47.0
Okamoto	2016	–	–	–	–	5.2	0.0	1.7	0.0	63.1±7.8	62.7±7.2	–	–	–	–
Kulik	2008	–	–	–	–	–	–	–	–	–	–	–	–	38.4	40.9
Sommers	1997	–	–	–	–	–	–	–	–	–	–	–	–	77.0	73.0
Unmatched/unadjusted observational studies															
Rao	2023	–	–	1.6±1.0	1.8±1.2	1.1	4.1	1.1	1.0	–	–	–	–	51.1	43.1
Beckmann	2016	–	–	–	–	14.0	2.0	–	–	60 (42–70)	60 (25–90)	–	–	28.0	84.0
Correia	2016	–	–	–	–	8.8	6.9	0.4	0.0	65.3±15.9	64.6±16.0	–	–	49.4	57.9
Prifti	2015	–	–	–	–	17.1	0.0	0.0	0.0	58±13	54.7±7.4	20	5	–	–
Penaranda	2014	–	–	NS		10.0	8.0	–	–	64 (30–78)	63 (13–78)	–	–	80.0	78.0
Sakamoto	2006	–	–	–	–	–	–	–	–	–	–	–	–	–	–

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Table S1 *(continued)*

First author	Year	Preoperative mean aortic gradient (mmHg)		Preoperative iEOA (cm^2/m^2)		Preoperative aortic annulus diameter (mm)		Aortic stenosis (%)		Aortic insufficiency (%)		Mixed aortic valve disease (%)	
		AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies													
Yousef	2023	–	–	–	–	–	–	90.1	86.5	32.1	37.1	–	–
Shih	2022	45.95±17.11	42.15±17.14	0.37±0.12	0.38±0.14	–	–	90.7	87.7	–	–	–	–
Mehaffey	2021	–	–	–	–	–	–	–	–	–	–	–	–
Chauvette	2020	31.9±2.4	30.1±2.5	0.49±0.06	0.66±0.06	–	–	82.0	74.0	–	–	–	–
Tam	2020	–	–	–	–	–	–	85.0	83.9	–	–	–	–
Tam*	2020	–	–	–	–	–	–	87.6	87.0	–	–	–	–
Haunschild	2019	–	–	–	–	–	–	95.0	95.0	4.0	4.0	–	–
Okamoto	2016	–	–	0.42±0.14	0.52±0.17	19.3±1.8	19.7±1.9	74.1	74.1	0.0	0.0	25.9	25.9
Kulik	2008	39.1±18.0	48.4±25.4	–	–	–	–	–	–	–	–	–	–
Sommers	1997	–	–	–	–	–	–	57.0	42.0	14.0	27.0	29.0	31.0
Unmatched/unadjusted observational studies													
Rao	2023	46±17	42±18	0.41±0.14	0.47±0.30	23.2	24.1	88.9	82.2	2.2	7.0	8.9	10.4
Beckmann	2016	48±20	48±19	0.38±0.17	0.38±0.11	19 (17–21)	20 (17–22)	100.0	100.0	–	–	–	–
Correia	2016	63.2 ±20.2	58.8±16.7	0.35±0.14	0.38±0.13	–	–	71.1	68.8	6.3	7.4	22.2	23.7
Prifti	2015	63.3±17	66±12.7	–	–	–	–	100.0	100.0	–	–	–	–
Penaranda	2014	–	–	0.40 (0.14–0.53)	0.41 (0.16–0.64)	19	19	100.0	100.0	–	–	30.0	17.0
Sakamoto	2006	–	–	–	–	–	–	8.6[†]		50[†]		33.6[†]	

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Table S1 (*continued*)

First author	Year	BAV (%)		Mechanical valve (%)		Mean implanted valve size (mm)		Concomitant valve surgery (%)		Concomitant CABG (%)		Concomitant other procedure(s) (%)	
		AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies													
Yousef	2023	–	–	25[†]		23.0 [21.0–25.0]	25.0 [23.0–25.0]	0.0	0.0	0.0	0.0	0.0	0.0
Shih	2022	30.2	50.0	19.6	12.4	22.13±1.94	23.39±2.28	0.0	0.0	0.0	0.0	0.0	0.0
Mehaffey	2021	–	–	–	–	23.0[‡]	23.0[‡]	0.0	0.0	42.6	45.2	0.0	0.0
Chauvette	2020	–	–	–	–	21.2±0.4	22.1±0.4	–	–	–	–	–	–
Tam	2020	–	–	22.0	31.0	–	–	0.0	0.0	0.0	0.0	0.0	0.0
Tam*	2020	–	–	13.9	15.0	–	–	0.0	0.0	100.0	100.0	0.0	0.0
Haunschild	2019	–	–	7.0	6.5	21 [21–23]	23 [21–23]	0.0	0.0	0.0	0.0	33.0	17.0
Okamoto	2016	13.8	15.5	31.0	36.0	19.4±1.6	19.3±1.3	22.4	24.1	10.3	10.3	24.1	31.0
Kulik	2008	–	–	43.0	40.2	22.0	20.7	7.6	18.9	43.6	39.6	–	–
Sommers	1997	–	–	0.0	0.0	23.8±1.94	25.2±2.07	–	–	–	–	–	–
Unmatched/unadjusted observational studies													
Rao	2023	41.1	35.0	0.0	0.0	23.1±1.9	23.7±2.1	0.0	0.0	26.7	32.0	46.7	31.6
Beckmann	2016	–	–	0.0	0.0	–	23.07	–	–	–	–	6.0	33.0
Correia	2016	15.3[†]		23.8	47.7	21.8±1.0	20.7±0.5	9.2	18.8	17.2	13.7	59.0	68.2
Prifti	2015	25.7	45.0	100.0	100.0	19	17	20.0	25.0	17.1	20.0	–	–
Penaranda	2014	–	–	0.0	3.0	21	19	–	–	43.0	51.0	16.7	21.8
Sakamoto	2006	–	–	100.0	100.0	24.1[†]		28.9[†]		0.0	0.0	3.1[†]	

Continuous variables are presented as mean ± standard deviation, median (range), or median [interquartile range]. *, distinct secondary cohort reported within the same publication; **, of 90 patients within the intervention arm, only 27 patients (30%) had a confirmed AAE and 3 patients (3.3%) within the intervention arm had an aortic root replacement; †, demographic information derived from the overall cohort of the respective study; ‡, median implanted valve size. AAE, aortic annular enlargement; BAV, bicuspid aortic valve; bioAVR, bioprosthetic aortic valve replacement; AVR; aortic valve replacement; COPD, chronic obstructive pulmonary disease; iEOA, indexed effective orifice area; LVEF, left ventricular ejection fraction; mechAVR, mechanical aortic valve replacement; NS, no statistically significant difference in STS score between ARE and no ARE groups; SAR, small aortic root; SAVR, surgical aortic valve replacement; STJ, sinotubular junction.

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Table S2 GRADE domain-specific judgements for midterm mortality, aortic valve reintervention, and heart failure

Outcome	AAE + SAVR	SAVR	Studies	Design	Risk of bias	Unexplained heterogeneity	Indirectness	Imprecision	Publication bias	Large effect	Dose response	Plausible residual confounding	Overall quality
Midterm mortality													
Matched or adjusted	7445	188,557	9*	Low quality	–	–**	–	–	–	N/A	N/A	N/A	Low
Unmatched/unadjusted	7834	208,363	12*	Very low quality	Downgrade	–**	–	–	–	N/A	N/A	N/A	Very low
Aortic valve reintervention													
Matched or adjusted	6221	184,665	2	Low quality	–	–**	–	–	–	N/A	N/A	N/A	Low
Unmatched/unadjusted	6596	196,363	7	Very low quality	Downgrade	–**	–	–	–	N/A	N/A	N/A	Very low
Heart failure													
Matched or adjusted	6451	185,263	4	Low quality	Downgrade	–**	–	–	–	N/A	N/A	N/A	Very low
Unmatched/unadjusted	6443	193,021	4	Very low quality	Downgrade	–**	–	–	–	N/A	N/A	N/A	Very low

GRADE Working Group grades of evidence—high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate. *, separate estimate from secondary cohort of Tam *et al.* considered as same study; **, the vast majority of heterogeneity was felt to be explained by the risk of bias observed within each of the subsets of examined studies. GRADE, Grading of Recommendations Assessment, Development and Evaluation; AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement; N/A, not applicable; –, no change to overall quality rating.

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Appendix 1: Detailed risk of bias assessment

Only three included studies reported on outcomes at moderate risk of bias (1-3). All three studies were designed with extensive propensity score matching that addressed the relevant a priori-specified baseline confounders that could bias the selection of patients for or against receiving an AAE procedure at the time of SAVR. The remaining studies and their reported outcomes of interest were either at severe or critical risk of bias (4-15). These ratings were primarily driven by unclear or incomplete accounting methods for confounding variables or the complete absence of matching or adjustment of outcomes. Notably, in the studies by Rao et al. (12) Beckmann et al., (4) Correia et al. (6), and Kulik et al. (8), there were also critical issues regarding the composition of the intervention group (12) and the imbalance of important concomitant procedures (4,6,8,12).

The study by Sakamoto et al. did not provide information regarding baseline characteristics, intraoperative details and perioperative outcomes to be able to compare the characteristics of the St. Jude mechanical AVR with AAE versus St. Jude mechanical AVR without AAE groups (13). However, the data regarding mid-term mortality and aortic valve reintervention are described by Sakamoto et al. These outcomes are reported for the distinct groups of interest, i.e., AAE and St. Jude mechanical AVR and St. Jude mechanical AVR without AAE (13). As such, these estimates remain in the mid-term outcomes syntheses.

References

1. Shih E, DiMaio JM, Squiers JJ, et al. Outcomes of aortic root enlargement during isolated aortic valve replacement. J Card Surg 2022;37:2389-94.
2. Tam DY, Dharma C, Rocha RV, et al. Early and late outcomes following aortic root enlargement: A multicenter propensity score-matched cohort analysis. J Thorac Cardiovasc Surg 2020;160:908-919.e15.
3. Okamoto Y, Yamamoto K, Sugimoto T, et al. Early and Late Outcomes of Aortic Valve Replacement with Aortic Annular Enlargement: A Propensity Analysis. Thorac Cardiovasc Surg 2016;64:410-7.
4. Beckmann E, Martens A, Alhadi F, et al. Aortic valve replacement with sutureless prosthesis: better than root enlargement to avoid patient-prosthesis mismatch? Interact Cardiovasc Thorac Surg 2016;22:744-9.
5. Chauvette V, Sénéchal M, Barrette V, et al. Annulus root enlargement during redo aortic valve replacement: Perioperative results and hemodynamic impact. J Card Surg 2020;35:2158-64.
6. Correia PM, Coutinho GF, Branco C, et al. Long-term follow-up of patients undergoing aortic root enlargement for insertion of a larger prosthesis. Eur J Cardiothorac Surg 2016;50:82-8.
7. Haunschild J, Scharnowski S, Mende M, et al. Aortic root enlargement to mitigate patient-prosthesis mismatch: do early adverse events justify reluctance? Eur J Cardiothorac Surg 2019. doi: 10.1093/ejcts/ezz016.
8. Kulik A, Al-Saigh M, Chan V, et al. Enlargement of the small aortic root during aortic valve replacement: is there a benefit? Ann Thorac Surg 2008;85:94-100.
9. Mehaffey JH, Hawkins RB, Wegermann ZK, et al. Aortic Annular Enlargement in the Elderly: Short and Long-Term Outcomes in the United States. Ann Thorac Surg 2021;112:1160-6.
10. Penaranda JG, Greason KL, Pislaru SV, et al. Aortic root enlargement in octogenarian patients results in less patient prosthesis mismatch. Ann Thorac Surg 2014;97:1533-8.
11. Prifti E, Bonacchi M, Baboci A, et al. Hemodynamics of 17-mm vs. 19-mm St. Jude Medical Regent and annulus enlargement. Asian Cardiovasc Thorac Ann 2015;23:670-83.
12. Rao V, Linick JA, Reardon MJ, et al. Early and late effects of aortic root enlargement: Results from the Pericardial Surgical Aortic Valve Replacement Pivotal Trial: A multicenter, prospective clinical trial. JTCVS Open 2023;13:54-74.
13. Sakamoto Y, Hashimoto K, Okuyama H, et al. Prevalence and avoidance of patient-prosthesis mismatch in aortic valve replacement in small adults. Ann Thorac Surg 2006;81:1305-9.
14. Sommers KE, David TE. Aortic valve replacement with patch enlargement of the aortic annulus. Ann Thorac Surg 1997;63:1608-12.
15. Yousef S, Brown JA, Serna-Gallegos D, et al. Impact of Aortic Root Enlargement on Patients Undergoing Aortic Valve Replacement. Ann Thorac Surg 2023;115:396-402.

 https://dx.doi.org/10.21037/acs-2024-aae-0023