

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

# Dustin Tanaka<sup>1</sup>, Dominique Vervoort<sup>1</sup>, Amine Mazine<sup>1</sup>, Lina Elfaki<sup>1</sup>, Jennifer C. Y. Chung<sup>1,2</sup>, Jan O. Friedrich<sup>3</sup>, Maral Ouzounian<sup>1,2</sup>

<sup>1</sup>Division of Cardiac Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada; <sup>2</sup>Division of Cardiovascular Surgery, Peter Munk Cardiac Center, Department of Surgery, University of Toronto, Toronto, ON, Canada; <sup>3</sup>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<sup>2</sup>=20% (matched/adjusted studies)], aortic valve reintervention [HR, 0.98; 95% CI: 0.75 to 1.27; P=0.86; I<sup>2</sup>=0% (matched/adjusted studies)], or heart failure [HR, 1.06; 95% CI: 0.86 to 1.30; P=0.58; I<sup>2</sup>=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 midterm 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 (nonrandomized) 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<sup>2</sup> values as low (25% to 49%), moderate (50% to 74%), and high  $(\geq 75\%)$  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,

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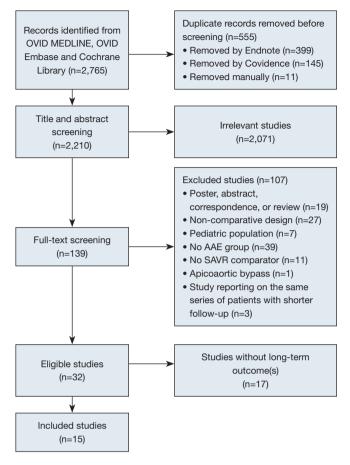


Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram. AAE, aortic annular enlargement; SAVR, surgical aortic valve replacement.

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 deduplication, 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 followup. 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 nonrandomized (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 midterm 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

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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 ad	justed ob	servational studie	s								
Yousef	2023	S	L	М	L	Mortality	м	L	м	S	Mortality
						AoV reintervention	м	м	м	S	AoV reintervention
Shih	2022	М	L	М	L	Mortality	L	L	м	м	Mortality
						AoV reintervention	L	М	м	м	AoV reintervention
Mehaffey	2021	S	L	S	L	Mortality	L	L	м	S	Mortality
						AoV reintervention	L	м	м	S	AoV reintervention
						CHF rehospitalization	L	S	м	S	CHF rehospitalization
Chauvette	2020	S	L	L	NI	Mortality	L	L	м	S	Mortality
Tam	2020	М	L	L	L	Mortality	L	L	м	м	Mortality
						AoV reintervention	L	м	м	м	AoV reintervention
						CHF rehospitalization	L	S	м	S	CHF rehospitalization
Tam*	2020	М	L	L	L	Mortality	L	L	м	м	Mortality
Haunschild	2019	М	L	L	М	Mortality	S	L	м	S	Mortality
Okamoto	2016	М	L	L	L	Mortality	NI	L	м	м	Mortality
						CHF	NI	S	NI	S	CHF
Kulik	2008	S	L	L		Mortality	м	L	м	С	Mortality
						CHF composite	м	S	м	С	CHF composite
Sommers	1997	S	L	L	NI	Mortality	L	L	м	S	Mortality
Unmatched/un	adjusted	observational stu	dies								
Rao	2023		L	S		Mortality	S	L	L		Mortality
						AoV reintervention	S	м	L		AoV reintervention
						NYHA III–IV	S	S	L		NYHA III–IV
Beckmann	2016	S	L	L		Mortality	S	L	м	С	Mortality
Correia	2016	S	L	S	С	Mortality	L	L	м	С	Mortality
Prifti	2015		L	L	м	Mortality	NI	L	S		Mortality
						AoV reintervention	NI	м	S		AoV reintervention
Penaranda	2014	S	L	L	S	Mortality	М	L	М	S	Mortality
Sakamoto	2006		L	L	NI	Mortality	NI	NI	м	С	Mortality
						Reoperation**	NI	м	м	С	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)



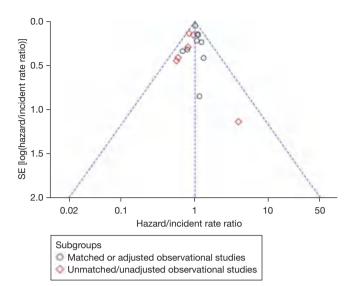


Figure 3 Funnel plot for mid-term mortality. SE, standard error.

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<sup>2</sup>; 95% CI: 0.44 to 3.16), at the same body surface area (BSA; MD,  $-0.01 \text{ m}^2$ ; 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,  $-0.05 \text{ cm}^2$ ; 95% CI: -0.08 to -0.02), including when indexed to BSA [indexed effective orifice area (iEOA); MD, -0.03 cm<sup>2</sup>/m<sup>2</sup>, 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

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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<sup>2</sup>; 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  $\leq 0.89 \text{ cm}^2/\text{m}^2$  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 Chara	acteristic	s of include	Table 1 Characteristics of included studies (brief)									
Eirot outbor		Cohort	Group		Group number	-	Age (year)		Male s	Male sex (%)	Body surface area $(m^2)$	e area (m²)
FIISL duti 101	ובמו	size	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or adjusted observational studies	djusted (	observation	tal 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	I	I
Chauvette	2020	125	AAE + Redo AVR	Redo AVR	21 (16.8%)	104 (83.2%)	63±3	63±3	28.6	42.3	I	1
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	I	1
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	Inadjuste	ed observat	ional 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	<b>1.8±0.2</b>	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 <sup>†</sup>		72.7 <sup>†</sup>		1.60±0.15 <sup>†</sup>	
Continuous v the same put replacement; artery bypass	/ariables olication; <sup>†</sup> , demo graft; bi	are preser **, of 90 p graphic infr oAVR, biop	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; <sup>†</sup> , 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.	<ul> <li>mean ± standar</li> <li>mtion arm, only 27</li> <li>e overall cohort of</li> <li>acement; STJ, sinc</li> </ul>	d deviation, me patients (30%) h the respective tubular junction	dian (range), or had a confirmed study. AAE, aor ; SAR, small aor	median [interq I AAE and 3 pa tic annular enl tic root; mechA	uartile rangej. *, tients (3.3%) wit argement; AVR; VR, mechanical	distinc thin the aortic v aortic v	t secondar interventio alve replac alve replac	y cohort repo on arm had ar cement; CAB	orted within I aortic root 3, coronary

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Table 2 Aortic	c annula	r enlargeme	ent techr	iiques				
First author	Year	Cohort	AAE gi	roup	No AAE g	group	Concomitant	
First author	rear	size	N	Description	Ν	Description	procedure(s)	AAE technique
Matched or a	djusted	observatio	nal stud	ies				
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/u	nadjust	ed observa	tional st	udies				
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 Indica	tions for	r and result	s of aortic :	annular enlargement		
First author	Year	Cohort size	AAE group	AAE indication	AAE technique	Annular size increase
Matched or ac	djusted	observatio	nal studies	3		
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/u	nadjuste	ed observa	tional stuc	lies		
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	gained 2 valve sizes
*, distinct sec	ondary	cohort repo	orted with	in the same publication; **, only 27	patients had a confirmed AAE, a	and 3 patients had an aortic

\*, 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  $\leq 0.65 \text{ cm}^2/\text{m}^2$ ; RR, 0.61; 95% CI: 0.40 to 0.93), moderate or severe PPM (defined as iEOA  $\leq 0.85 \text{ cm}^2/\text{m}^2$ 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 midterm 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<sup>2</sup>=63%) or matched/adjusted (HR, 1.03; 95% CI:

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**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  $\leq$ 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.

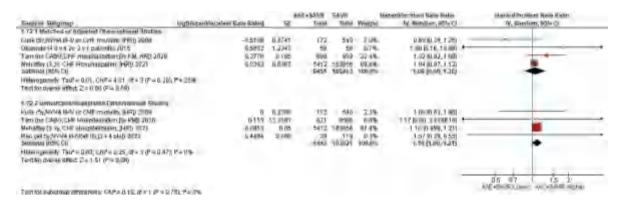
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Figure 5 Meta-analysis for aortic valve reintervention. Mean duration of follow-up in round brackets for AAE + SAVR vs. SAVR groups; method used to calculate hazard ratio or incident rate ratio in square brackets. Tam *et al.*, Mehaffey *et al.*, and 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.

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**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<sup>2</sup>=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<sup>2</sup>=0%) or the matched/adjusted studies (HR, 0.98; 95% CI: 0.75 to 1.27; P=0.86; I<sup>2</sup>=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

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Table 4 GRADE summary of findings table for	pooled mid-te	rm mortality	y, aortic val	lve reintervention, an	d heart fai	ilure outcomes	
Outcome	SAVR + AAE group	SAVR group	Studies	Pooled estimate, HR (95% Cl)	P value	Heterogeneity (I²)	GRADE quality
Mid-term mortality-matched or adjusted	7,445	188,557	9*	1.03 (0.95, 1.12)	0.45	20%	Low <sup>a</sup>
Mid-term mortality-unmatched/unadjusted	7,834	208,363	12*	0.91 (0.80, 1.03)	0.12	63%	$\text{Very low}^{a,b}$
Aortic valve reintervention – matched or adjusted	6,221	184,665	2	0.98 (0.75, 1.27)	0.86	0%	Low <sup>a</sup>
Aortic valve reintervention—unmatched/ unadjusted	6,596	196,363	7	1.08 (0.85, 1.39)	0.53	0%	Very low <sup>a,b</sup>
Heart failure-matched or adjusted	6,451	185,263	4	1.06 (0.86, 1.30)	0.58	25%	Very low <sup>a,b</sup>
Heart failure-unmatched/unadjusted	6,443	193,021	4	1.10 (0.998, 1.21)	0.06	0%	Very low <sup>a,b</sup>

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. <sup>a</sup>, quality limited by the absence of randomized and blinded study designs; <sup>b</sup>, 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 wellmatched 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

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Table 5 Sensitivity analyses for subgroup difference	nces in mid-term mortality		
Mid-term mortality	RR (95% CI)	Ν	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 (rep	ported 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 <i>vs.</i> 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 un	matched/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*)
* false of Dealer factors	the structure of the structure structure is subject a		

\*, 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 differ	ences in aortic valve reintervention		
Aortic valve re-intervention	RR (95% CI)	Ν	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 un	nmatched/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 <i>vs.</i> 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 procedu	res		
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 ves vs. no concomit	ant procedures only (i.e., excluding studies in which concom	itant procedu	res 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) vielding 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 202

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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# Supplementary

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Appendix 1

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# **Supplemental Figures:**

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
ljusted	Observational S	tudies								
					Mortality	М	L	М	S	Mortality
2023	S	L	М	L	AoV Reintervention	М	М	М	S	AoV Reintervention
					Non-Structural Valve Dysfunction-PVL	S	S	М	S	Non-Structural Valve Dysfunction-PVL
2022	м	т	м	т	Mortality	L	L	М	М	Mortality
2022	M	1	NI	L	AoV Reintervention	L	М	М	М	AoV Reintervention
					Mortality	L	L	М	S	Mortality
2021	e		s	T T	AoV Reintervention	L	М	М	S	AoV Reintervention
2021	3	L	3	L	Stroke Hospitalization	L	М	М	S	Stroke Hospitalization
					CHF Rehospitalization	L	S	М	S	CHF Rehospitalization
2020	S	L	L	NI	Mortality	L	L	М	S	Mortality
					Mortality	L	L	М	М	Mortality
2020	М	L	L	L	AoV Reintervention	L	М	М	М	AoV Reintervention
					CHF Rehospitalization	L	S	М	S	CHF Rehospitalization
2020	М	L	L	L	Mortality	L	L	М	М	Mortality
2019	М	L	L	М	Mortality	S	L	М	S	Mortality
					Mortality	NI	L	М	М	Mortality
					Cardiac Mortality	NI	М	М	М	Cardiac Mortality
					SVD	NI	S	NI	S	SVD
2016	М	L	L	L	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
					Mortality	М	L	М	С	Mortality
2008	8	L	L	C	CHF Composite	М	S	М	С	CHF Composite
1005				27	Mortality	L	L	М	S	Mortality
1997	8	L	L	NI	Cardiac Mortality	L	М	М	S	Cardiac Mortality
nadjust	d Observational	Studies			• •					
					Mortality	S	L	L	С	Mortality
					AoV Reintervention	S	м	L	С	AoV Reintervention
					SVD	S		L	с	SVD
					Non-Structural Dysfunction	S		L	c	Non-Structural Dysfunction
2023	с	L	s	с	Valve Thrombosis			L	c	Valve Thrombosis
					NYHA III-IV			L		NYHA III-IV
					IE	S	S	L	С	IE
					Major Anticoagulant-Related Hemorrhage	S	S	L	c	Major Anticoagulant-Related Hemorrhag
								L		Thromboembolism
2016	S	L	L	С	Mortality	S	I	М	c	Mortality
1		L	S	c	Mortality	L.	L	M	c	Mortality
2016	S				Mortality	NI	L	S	c	Mortality
2016	S									
2016 2015	s C	L	L	М	AoV Reintervention	NI	м	S	с —	AoV Reintervention
2015	С	L	L		AoV Reintervention Mortality	NI	М	S M	C	AoV Reintervention Mortality
		L L		M S	Mortality	М	L	М	S	Mortality
2015 2014	C S	L	L	S	Mortality Mortality	M NI	L NI	M M	S C	Mortality Mortality
2015	С	L L L			Mortality	М	L	М	S	Mortality
	justed 2023 2022 2021 2020 2020 2020 2019 2016 2008 1997 adjust	Year         Confounding           justed         Observational Si           2023         S           2024         M           2025         S           2020         S           2020         M           2021         M           2020         S           2020         S           2020         S           2020         S           adjust         Observational           2021         S           adjust         Observational           2023         C	Year     Oranomia     Selection       juster     Selection     Juster       2023     AS     L       2024     AS     L       2025     AS     L       2020     AS     L       2021     AS     L       2020     AS     L       2021     AS     L       2021     AS     L	YeaDomain 1 ConfoundingDomain 2 Classification of Interventions2021SLMA2022MLM2023SLM2024SLM2025SLL2020MLL2021MLL2020MLL2020MLL2020MLL2020MLL2020MLL2021MLL2020MLL2030MLL2041SLL2052SLL2053SLL2054SLS2055SLS2056SLS2057SLS2058SLS	YenDomain 1- constructionsDomain 2- constructionsChastication of interventionsFrom Intended interventions2021SLML2022MLML2023SLML2020SLSL2021SLSL2022MLSL2023MLLNI2020MLLNI2020MLLNI2020MLLNI2021MLLNI2023MLLL2030MLLNI2041MLLNI2052MLLNI2053SLLNI2054SLLNI2053SLLNI2054SLSS2055SLSS2053CISS2053CISS2053CISS2054SSS2055SSS2054SSS2054SSS2055SSS2055SSS2055SSS2056SSS20	Yead     Domain 1/2 Interventions     Domain 2/2 Interventions     Classification of Interventions     from Intended Interventions     Outcome-Specific Domains       2023     S     L     Interventions     Interventions     Interventions       2024     S     L     Morality     Adv Reintervention       2021     M     L     Morality     Non-Structural Valve Dysfunction-PVL Non-Structural Valve Dysfunction-PVL       2021     M     L     Morality     Adv Reintervention       2031     M     L     Intervention     Morality       2041     M     Morality     Adv Reintervention       2051     M     L     Intervention     Morality       2061     M     Intervention     Morality       2071     M     Intervention     Morality       2081     M     Intervention     Morality       2091     M     Intervention     Intervention       2010     M     Intervention     Intervention       2021     M     Intervention     Intervention       2022     M     Intervention     Intervention       2031     M     Intervention     Intervention       2041     M     Morality     Intervention       2041     Intervention	Year     Ormain-homain-homain-homani-homanin-homani-homanin-homanin-homanin-homanin-homanin-	Yead control 	YearDomain or longing basisDomain or longing basisDomain or longing basisDomain or longing basisRespect or longing basis3001000000000000000000000000000000000000	Year         Domain bin         Ordenity of the sector of

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.

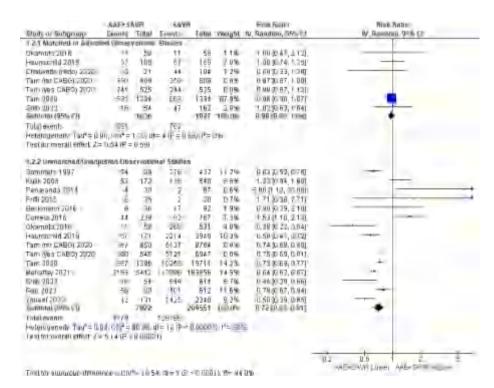
\* Distinct secondary cohort reported within the same publication.

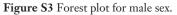
\*\* Long-term reoperation outcome was assumed to be related to aortic valve reintervention.

### Figures S2-S31. Meta-analyses for baseline characteristics

		FISAU			LAWE			Minary Conference	Mean Diduring
itary of Subgroup.	Mana	- 1817	Pollat	A	ALT	Total	WHOM	W, Rammuni, 956, 13	19 Rombers, 95%-(1
d.1 Nanchrill or Attive	ed com	www.titmi	a 1as	ins -	-		-		
Hendin 301K	714	11 0	58	78.77		- 76	3.10	-1.0015/6.21%	
aun annud Sitt 9	177-40	10	1.822	17.5	- 14	7.69	1.1.000	-310F211,1/09	
hauvene manor 2020	illine.	1.18	- vI.	100	1.6	ITA	1.06	2007 (-1) 26, 656	
aro ma CaEdo 1030	66.57	17.16	100.04	15.4	1100	HIIM	111190	0.04117,175	
Tum friks CRaftin 2020	7213	0.0	575	-7258	- n	638	711%	-9.26 (-1.10) 0.52	
am 2020	10115	11.1	A local	<b>BILME</b>	44,70	1.04	15.5%	-164 -0.98, 8-9	+
000 B002	100.07	12 63	-54	10.48	30.04	In.	110	-7021476, 374	
incomity structure			(CP)			1827	Annaly	0.0410.00.0421	•
relengenets Tell <sup>4</sup> - 0.0	C, DHE	emisel	il = i i	- 11.00	), Perm	4 ×			
inition month etwork 2 -	1175.18	- 11 7.7							
121-material One		in a sub-	inui S	unites.					
CHIMPIS 1997		13	0.9	11.4	1.0	+22	8.7%	1000 (Hilling 2001)	
0.0070000	67.0		17.5	89.4	11.1	540	7791	-11014 39,-0.11	the second se
while shreakers	15.1	3.2	10	198.2	1.10	(82	10.5%	3700 1-1 27, 1-27	the second se
100 2015	87.5	10	-9	8973	7.4	20	1.995	-215kn 29, 249	
Strom JOTE	102	13	18	71.0	1.0	#2	2.7%	-550 (-1 + 30, - 170)	
1009-0 2016	76.4	175	- 10	895	9.0	267	6.0%	0.601132,2.22	
Henoir Dith.	7.84	11.0	-58	724	0.0	(82)	10.104	1060 (0.53, 9.75)	
P PDC Mid/remier	174	10	171	80%	1.5	1949	8.5%	EC 50 ED 704, 0 /041	
ANY MULTIPECT 2020	7-5 84	12.38	-50	88.84	11	8384	71.108	-2.000-1.762.04	
am bealt Alloy 2020	71.85	1.04	540	71/	0.55	0947	iñ hw	-* 68 2 17,-0.11	
am (1020)	and the	316	C MR	702	1042	FRZ11	12.09	-21011-3282200	-
letrattey 2021	74	. 7	-413	76	1.1	101058	1.5.190	-5105739,-061	-
70h 1077	开户项目	1263	54	8842	11.0	812	18.836	-0.21 (5.68) 4.26	
00.2023	67.9	7.7	201	09.0	0.0	512	Ϋ́ ŊΨι	-1401301.0.20	
runner2003	- Min	-11	1.11	148	112	CODER	0.1%	-0.0012.05.4.05	and the second s
Continued COVPL C.D.			7622			300#E1	100.0%	A.228.244 0.400	•
		1.20.00	21 - F	100.00	Description & C.	11107			

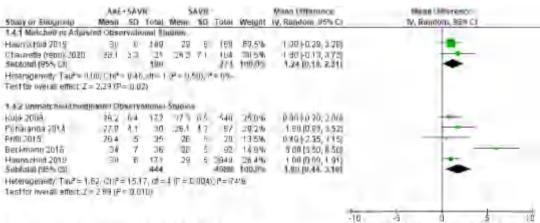
Figure S2 Forest plot for age at time of operation (years).





	AA3	+5A4	H.		ANR			Minuri Unificiturita-	Mush Entrenet isc
study or Soliginup	Mail 10	511	Intal	Mintre	50	Totto	waight	IV Random, 22Ve F3	W. Handings (199 £)
1,3 * Matchiel or Adjust	and filmsa	CVID/C	01650	diné		-			
Cisamuno 2016	1.45	T16	59	138	016	50	18.69	10 107 (0 H), 11 F3	
Hawwohld 2014	1.9	02	165	19	0.2	(69)	25.1%	0.001004004 0.04	
Tam (na CVBG) 2020	1.92	3.27	909	1.91	0.26	909	0.046	9 00 (D 02, D 04)	
Tamilies CABO (2020	154	0.24	525	1 94	11.25	525	10 m/m	ELD DUTIED	
Tam 2020	1.123	1.00	1114	1.92	0.2%	10134	40.5%	mmr jarmi, hinaj	-
Enin 2022	5 HM	176	- 64-	1.97	1.75	107	10.0%	0.0240.10.0.16	
Subicital (USH CI)			1085			1123	100,05	0.07 (-0.04) 0.047	*
Heterogiereity, Taute 0,	to; chr:	= 4,71	11=1	(F) = 11.1	9); Pa	36%		1 M M M M	
Telshin overall effect Z =	1-06 (P	= E 73	4)						
132 Ummiched-Linady	usted Tot	SMIVE	m al l	Hudies					
Sommers: 1997	1.74	3.22	69	1.83	(E19)	497	9.0%	-ULU-4 FOX-048 (0.371)	
Penaminta 2014	1.75	115	30	1.BC	bi 1 B	HT	0.44	0.1210.00.010	the second se
Emilante	1 51	116	- 56	1.875	11.7	10	3.8%	0.011000 0011	
Birdkmann 2016	1.8	12	350	1.8	32	92	5 17.	0.0.14T 08 0.000	
Clonela 2016	1.50	315	239	1 5%	013	767	128.0	10.02 10.00,0000	++-
Chianmitto 2015	145	diñ.	60	1.46	017	531	9.0%	0.03+0.07.0.011	
Laurischild 2019	1.9	12	171	19	0.2	3949	1210	0.00100.000	
Tarry (my CABIE) 2028	1 95	1 25	âŝtr	1 98	0.26	1764	0.0%	um para adu	
Tam (yes CABO) 2000	1.5%	0.26	546	1 95	0.26	6947	0.046	man am, man	
Tamy 2020	195	0.25	1 3917	1.90	11-24	75711	74 64	0.01 (0.02) 0.00	-
HBID 2022	1.609	U./R	54	11.4	11-28	BT4	5.71	-0.341-0.22,-0.96	
Field 20013	- 3	177	90	2	0.72	317	H P90	100110.05.0.19	
Youset 2021	1 519	3.17		2,09	0 27	2280	1.196	-0.04 (0.00.0.01)	
Sublaini (66%, CIT			2338			25155	100.0%	-ALF ( 2011-0/01)	•
heterogeneity, TayP = 0.				0 (P )	a cinic i	1 [*=7]	9		
Test for overall effect Za	W Li (W	= (1) 4)							
									the de to the to
						r=			WE SHIRLING WE SWE HIM ISI

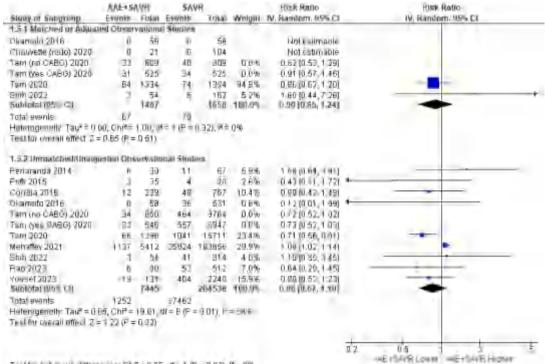
Figure S4 Forest plot for preoperative body surface area (m<sup>2</sup>).



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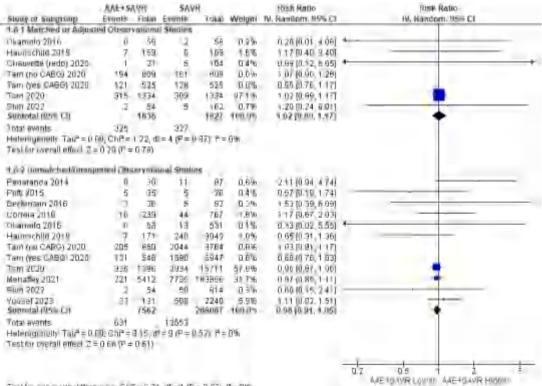
Figure S5 Forest plot for preoperative body mass index (kg/m<sup>2</sup>).

The LET sub-proper difference  $Chi^2 = 0.46$ , dr = 1.(R = 0.53), P = 0.94



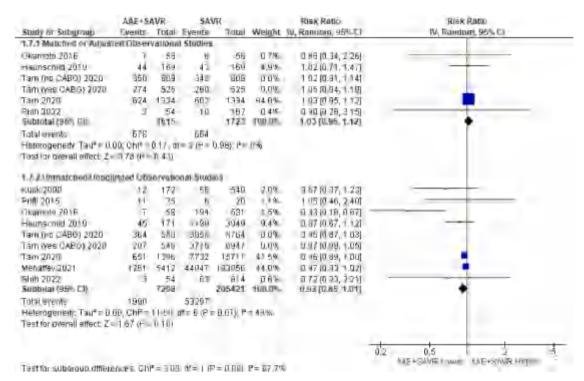
To it for a obtaining difference  $(0,0)^{2} = 0.05$ , df = 1 (P = 0.02), P = 0%.

#### Figure S6 Forest plot for cerebrovascular disease.



To all on a observed difference of  $C_{1} = 0.31$ , df = 1.(P = 0.67),  $P = DW_{1}$ 

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



#### Figure S8 Forest plot for smoking.

	. AAE+A	HAN	SAV	/11		Risk Ratio	Days Dames
Study of Subgroup	CENTS	Totili	Ellerite	Total	triple/W	IV. Rundom, 95% Cl	IV, Random, 95% CI
1.1.1 Matcheil in Adjusted Observe	numel Sta	dies		_			A Design of the second s
Okamoto 2016	+	-50	6	-50	3,6%	6.57 [0.20, 2.24]	
Time the CABG; Cr >120 LMY 2020	56	809	69	804	-0.0%	0.91 (0.60, 1.14)	
fam (vel: CAEG, Cr>17E aM0 2020	58	575	17	575	11 1146	D.ET (0.5E, 1 11)	
fam (Gr =138 pM) anzu	11.0	11338.	141	1338	89.4%	0.61 (0.64, 1.02)	
Fam (no CABG, Cr -TED pM) 2020	17	604	.22	6614	0.0%	0.77 (0.41, 1.44)	
Terrive: CAB(9; Cr >190 ptt) 702/1	-15	525	- y	5,22	10.0%	079 (0.44, 1.54)	
Familie TED UNY 2020	32	1334	41	1334	3,0%	0.76 (0.49, 1.27)	
Subbrial (JeSA C1)		1302		1302	100.0%	0 80 [0 54, 1.01]	•
faitair ann an tr	419		147				
lelerogeneity: Tau <sup>4</sup> = u cu; Chi <sup>4</sup> - C i	IE dr= 11	P-076	5); P= 03	N			
Tesh for overall effect $Z = 1.87$ (P = 0)	06)						
LE2 Unmaiched Unweiselind Closer	valornel	mins					
Peneranda 2014	D	30	3	97	0.2%	0.41 (0.02, 7.60)	-
Pret 2015	ĩ	35	ñ.		0.2%	2.02 (0.50, 57 190)	
Beckmann 2016	ž	36	5		2.7%	1 19 (0, #3, 2 670)	
Correla 2016	64	234	297		27.4%	0.00.0071.115	
Jictumoto 2011 0	4	- 50	BI	5-11	1.6%	0.66(0.23, 1:59)	
Tam (no CABO; Cr = 120 UM 2020	98	850	1117	BZEIA	0.0%	0.90-0.74, 1.300	
am Ves CABO; Fri-120 gMr 2020	E7	546	949	6947	0.0%	0.0210.05, 1.001	
Fam (Fe>120 pM) 2020	160	> 398	2066	15711	80.178	0.87 (0.25, 1.01)	
fain mo DABG; Cri>180 pMy 2020	đu	850	272	6764	0.0%	1.13(0.70,168)	
Tam mes CABIS, C1+190 LMI 2020	19	546	734	6947		1 0010 65,1 04	
Cam (Ce =160 LIND 2020	44	1395	506	14711	11.078	1 09 00 02, 1 451	
Rep 2020		MIL	47	512	1.5%	646 pt 19, 1, 21	
Subbilial (05% C1)		-Inke		17720			•
fols/ mento	241		2410				
Heleroganeth: Tau*= 0 00; Chif = 3 (		Pen7					
Heleroganeth: Tau*+ u DDr, Chif + 3 / Tan) for oversil effect $\vec{Z}$ = 2 (5 (P = 0		Pen7	5); I* = 0**				12 15 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Testar weaten tille pricks carf -	P41 81=	117 = 1	15h/PE	U.N.			the sector Power ANE readable Inter-

Figure S9 Forest plot for chronic renal failure.

	AAE+5/	AVR	5A	VR		RISH Ratio	RISK RADO
Study or Subgroup	Events	Total	Evenie	Tatal	Weight	IV, Randowri, 95% CI	W, Random, 95% CJ
1.9.1 MAtched of Adjus	int Otrer	Pridtom #	i Shows			and a second descent of	
Haunssmid 2019	3	189	4	169	6.6%	0.75 [0 17, 3.30]	
Tam (no CARG) 2070	28	608	36	609	可且能	0.78(0.48, 1.28)	
T Im Jyna CABG) 2020	24	:525	25	525	0.11%	0.96 [0.56, 1.66]	
Tam 2020	52	1334	51	1384	982%	0.85 [0.59, 1.22]	
Bith 2022 Subtroal (95% CU	0	54 1557	1	162	1.2%	0.99 (0.04, 23,90) 0.85 (0.60, 1.20]	
Total events:	55		1000				
Helerogamelly, 7-au*=0.	till, ChP=	0.04.10	=2 (P=	0.000 P=	APR-		
Teul for overally effect Z:							
1.9.2 Unmutched (Unio)	usuul ühe	arvatic	mai Stud	149			-
Correla 2016	Ð	239		787	13.4%	2.14 (0.77, 5.85)	
Haunschild 2019	÷.	171	-50	3949		1 39,10.44, 4,401	
Tam (no CABO) 2020	30	660	574	3764	010%	0 54 (0.38, 0 77)	
Tam was 0,4800 2020	25	545	5/9	1947	9.078	0.5510.37, 0.811	
Tam 2020	65	1396	1153	15711	33.2%	0 54 [0 41, 0 70]	
Mehattey 2021	493	5412	3230	183856	34.7%	0.98(0.90, 1.20)	
Bbih 2022	- Ô	54	8	814	2.5%	1.14 [0.07, 19.97]	+
Youser 2023	1.1	131	40	12240	1 11%	0 43 (0 06, 3 09)	the second se
Suntonai (95% CI)		7403		207337	100.0%	LAN (U.50, 1.47)	-
Tohn evenis	160		4400			10.00	
Heletogereity, Tail*= 0	15 CHP=	TE ZR.	T= SYP:	= R (7R4) 1	P= 71 T		
Tail for overal office 2:							

To fifte subgroup difference with P = 0.02, n = 1.07 = 0.06, P = 0.9.

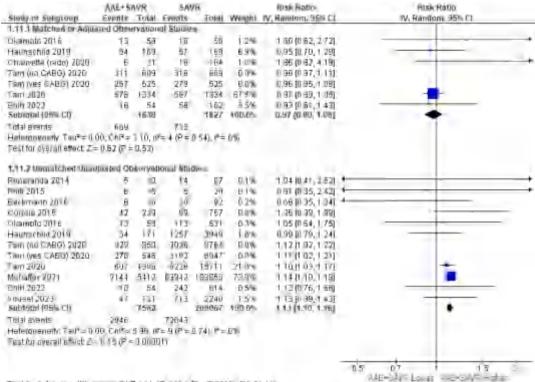
# Figure S10 Forest plot for dialysis.

	AAE+ SI	AVR	SAV	R-		Risk Raup	RISK Ratio
Study (ir Subgroup)	Events	Tulai	Evenis	i dial	Weight	W, Random, 95%-CT	W, Random 96% Cl
1.10.1 Matched or Adrus	sted Obse	rvation	al Studies	1			
Jkamelo 2016	39	-59	37	-59	1.5%	1.05 (0.91, 1.37)	
-aumschild 2019	150	159	154	169	15.5%	1.04 (0.90, 1.1.3)	
Chauwette mento) 2026	13	21	ΞŦ	1.54	0.3%	1.06 [0.7.1, 1.53]	
9bih 2022	4.4	54	126	162	4.7%	1.03 (0.89, 1.20)	
am (mp CABG) 2020	613	HOP	#12	809	0.0%	1.00 (0.95, 1.06)	
am IVer CABG) 2020	461	525	470	525	0.0%	0.96 [0.94, 1.0.2]	
am 2020	1074	1334	1.062	1334	77.5%	1.39 (0.96, 1.03)	
intitutari (95% Ct)		1010		1822	109.0%	1.04.0.97.1.04)	+
atal events	1320		1452				
ieterogennity: Tau*= 0.1			= 4 (P= 6	(14) ME	19		
est far iwernil effert Z=	0.20 (F=	D-34)	1.1				
10.2 Unmatched/Unpd	Hand Co	sen/all	orial Stud	ie ie			
emarande 2014	23	E.	65	-97	2.99	1.03 (0.81, 1.29)	
105 (Nr	1.6	35	10	20	11.5%	0.91 (0.52, 1.61)	
leckmann 201E	74	35	87	172	2.39	0.92 [0.76, 1.19]	
averia 2016	108	2.39	1.36	767	7.4%	1.31 (0,15, 1.50)	
Vkamato 2016	39	-59	324	531	4.0%	1 10 0 91, 1 34	
immachild 2019	152	171	9400	3949	18:39	1 03 (0.98, 1 09)	
im on CABGy 2020	1743	1155	EH4Y	8754	0.0%	9.97 [0.94, 1 [11]	
Am lyes (CABG) 2020	47.3	546	0211	0.987	0.0%	0.07 [0.94, 1.00]	-
am 2020	1116	1.1997	10053	10711	43.69	11 55 [0 54, 5 m3]	+
Kernattiev 2021	\$7.65	5412	1.59034	303056	26.546	1.0219.01.1.0.0	•
bih 2022	44	- 54	193.5	814	7.4%	0 35 (0 54, 1 03)	
Rab 2023	57	30	105	512	7.4%	0.99 (0.02, 1 1 2)	
iubmani (95% Ci)		7521		206339	100.0%	1.02 (0.96, 1.06)	
otal events	6384		117100				p-
leterogeneoy: "au"= 0 i	00, Ch#=	31 17.1	1=3(F=	O LODAN,	F=71%		
festfor over all effects Z =	E 87 (P =	1.175					
							07 118 1 12
			and a list				MERINE, MERINE

TAM for two product  $d^{m}$  which  $f \in D^{m} = 0$  and  $f \in T = 0.57$ ,  $P = D^{m}$ .

Figure S11 Forest plot for hypertension.

NEISTREAM UE - CARA



To differ tubberoug differences: "Lh# = 11, (E, er = 1 /P = 110006), R = 91 1 %

Figure S12 Forest plot for diabetes.

SAVE RAFFSAUR Risk Ratio Risk Batto Slavy or Subgroup Trisa' Weight IV, Hanilom, 99% CI IV, Random, 059-Cl Evenis Talai Evenis 1.12.1 Motchind on Augusted Class-ryoticinal Striffics Thamato 2016 1 80 10 91, 3 561 TH .50 5.4% 10 Havinschild 2019 169 1 19 [0.93, 1.97] 87 IT EIST NG. 34.7% Tami (nº CABO) 2020 1500 345 **FIDA** 145 0.0% 1.00 [0.92, 1.69] Tern (Ves CABO) 2020 353 976 355 575 17.01% 0.99 (0.91, 1.00) Tem 2020 706 1684 796 1314 50 1-5 1.00 (r B1, 1 bit) Similatel (\$5% CI) 109,0% 1561 1561 1.07 (0.91, 1.27) Total events: 811 **EB/4** Heterogeneibr Tau<sup>2</sup> = 0.01,  $Ch^4$  = 0.01, df = 2 (F = 0.10), P = 51 % Test for overall effect Z = 9.85 (P = 0.40) 1.17.2 Linmatched/ImAdiluated Conervational Studies Point (015) 10.5 36 1.5 20 1.5% 1.57 10 55, 4 200 Diamino 2016 110 58 1774 581 696 1 56 [1 04, 2 41] Haumschlidt, 019 MY 171 2050 3949 29,3% 1.09 (0.95, 1.24) 488 650 Tour (for CAE (r) 2020) 4206 3764 0.0% 1 13 11 118, 1 21 Tinte (well CABO) 2020 167 545 4229 6947 0.0% 1.40 11.04, 1.171 11110.110 TanA 2020 876 1396 2496 15711 37,916 Rao 2023 21.8% 0.01 (0.60, 1.80) 1413 AD 1936 517 Innointial (05= CI) 1750 201721 110.0% 1.07 [0.03, 1.23] Tolar overils. 11600 100151 Haterequently,  $T a a^4 = (hT)^4$ ,  $(Th^2 = \frac{1}{2}1, \frac{94}{94}, m = \frac{1}{4}(F = \hat{h}, \hat{h}_2), \hat{h}^2 = n\hat{h}\hat{h}^2$ To show over all effect: Z = 0.92 (P = 0.36) E E 10.7 治 LLE--S-VFLOWER WE-S-WF Hener

Tass for subgroup enterenzas: Chi# = 0.00, IF = 17P = 0.07; # = 0%

Figure S13 Forest plot for dyslipidemia.

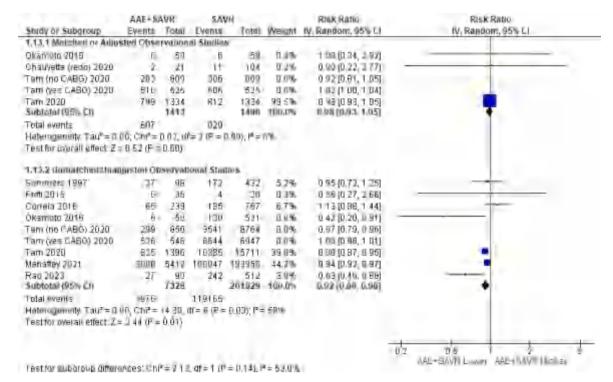


Figure S14 Forest plot for coronary artery disease.

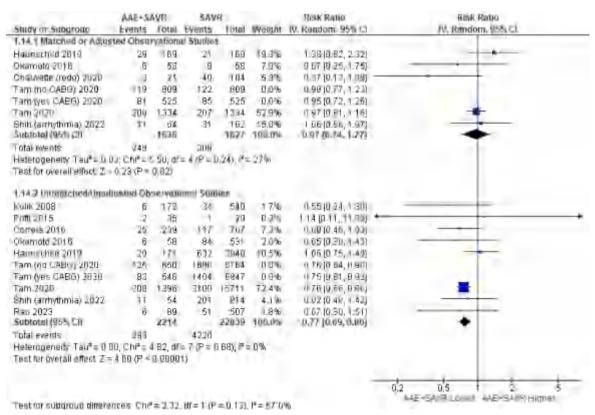


Figure S15 Forest plot for preoperative atrial fibrillation.

	AAE+S	AVR	54	NN I		Brok Balin	Risk Ratio
Study of Subgroup	Events	Total	Events	Total	Weight	IV Random 95% CI	IV Random 15% G
1.15.1 Matched or Auju	sted Dbae	TABLET	ini Stude	14		1.00	
Chauvette (redo) 2020	1	21		104	2.2%	0.83 (010, 530)	
Haunschild 2019	23	169	15	159	29.4%	1.21 (0 89, 2.14)	
Tam (no CADO) 2020	21	809	26	009	0.0%	0.61 [0.46, 1.42]	
Tam (yes CABO) 2020	32	525	27	525	五0%	1.19 [0.72; 1.95]	
Tam 2020	53	1334	53	1334	68.49	1.00 [0.69, 1.45]	
Subinial (95% (1))		1524		1607	100,0%	1.05 (0.77, 1.43)	
Total events	77		18				
Heterogeneity: Tau?= 1)	00; ChI*=	0.16, d	1=2(P=	0.84); #=	0.06		
Test for overall effect Z	= E 33 (P =	0.741					
1.15.2 Unmatched/Una	djuanted (Dr	servat	ional Stu	diné .			
Penaranda 2014	9	30	20	87	6.4%	1.10 (0.67, 2.55)	
Pn81 2015	1.0	35	1.1	20	0 4%	0,12 [0.01, 2.32]	
Haunschild 2019	23	171	571	3949	14.9%	D.93 (0.63, 1, 37)	
Tam (no CABO) 2020	24	950	332	0764	0.0%	0.75 [0.50, 1.12]	
Tam (Ves CABG) 2020	33	546	528	6947	0.0%	0.80 (0.57, 1.12)	
Tam 2020	.97	1396	580	15711	23.4 %	0,75 [0.57, 0.97]	
Mehaffey 2021	777	5412	25212	183850	431%	1.05 [0.98, 1.12]	-
Youset 2023	17	131	286	2240	1181	102(064,160)	
Subtotal (95% (J)		7175		205863	100.0%	0.95 (0.79, 1.14)	-
Total events	685		26951				
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect. Z			f=5(P=	0.12), P=	429		
	and the						
							0/5 0/7 1/5 2 ##F+S4#R1.base ##F+S4#R #cdram
Test for subornin differ	ances' Chi	e - 0 30	1. 10 - 1. 0	787.0 ± 9	P = 196		The column belles and counter and as

Test for subaroup differences;  $Chi^2 = 0.30$ , df = 1 (P = 0.58); P = 0%.

Figure S16 Forest plot for peripheral vascular disease.

5AVR Mida Difference AAE+SAVR Moán Difference Menh SD Total Menh SD Total Weight IV. Random, 95% CI Shidy of Slibgroup IV. Random: 151 CI 1.15.1 Matched or Adjusted Observational Studies Okamoto 2018 7.8 58 58 23 0% 0.401-2.33, 3.131 63/1 62.7 7.2 189 31.2% Haunschild 2019 60 159 60 11 0.001/2,35, 2,35[ 11 Chauyatre (renti) 2020 62 ÷, 21 60 10 104 20.5% 2 00 1 0,86, 4,881 54 59.33 Shib 2027 5916 8.51 7.6 182 74.9% 0 A361 BU. 3.460 502 Subtotal (95% L.I) 493 100.0% 0,71 [-0.60, 2.03] Heteromeneity  $Tau^{2} = 0.00$ ,  $Chr^{2} = 1.16$ , dt = 3.(P = 0.76); P = 0.95Test for overall effect 2 = 1.07 (P = 0.25) 1.16.2 Unmatched/Unadjusted Umarvaliuma Shulles Ferraranda 1014 53 12 ĉŋ, 57 ١B 184 2.4% 2 00 1 2 36, 6 361 Prift 2015 2.0% 3 70 1 2 09, 6 69 58 13 15 547 7Aास Beckmann 2016 52 II FL 51 117 1.5% 1 001451,2511 7 13 23% 262 1741-1 81, 3011 Correla 2015 65.1 15.P B4.0 用版 11.0% Haunschlid 2019 ψŪ. 11 171 64 11 1949 10.9% 1 D0 (-0 D9; 2.69) Shin 2022 59.10 D.01 54 56.02 0.02 014 8.5% 2.04(-0.10, 4.78) Youse(2023 59.7 /131 50.7 5.9 2240 51 D% D.60 (-D.46, 1.65) - 9 Subtotul (95% CJ) 1115 71406 100.0% 0.97 [0.11, 1.62] Heterogenetty, Tau? = 0.00; Ohi? = 3.77; d/ = 5.(P = 0.71), P = D% Test for overall effect Z = 2 26 (P = 0.02) 26 w AVE+PAVE FORMA HEIR RICH The strain subtracting differences. Chill = 0.04, di = 1 (P = 0.04), P = 0.04

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

	ALENS		8.4			Risk Baller	faish Romin		
Study of Subproup			EvenL	Fylai	Werahi	IV. Raniforn, SMs Ct	N, Hanstorn, Dhis Cl.		
1177 1 Matched or Annual Ethente	attornal 5th								
Disamolo (LVEF =4090 ar010	0	68		31	2.25%	0.20 (2005) 4.040	•		
1207 (no D490) 2020	347	903	360	-111	8.0%	0.95 49 85 1.071			
Familyed CHBICh251211	265	525	257	525	11 11 11	1 99 (0 se 1.1.2)			
fam 2020	602	1334	620	1334	37.4%	1.97-10.39 1.051			
Tem Inc DABO, LVEF +509(v 2020	03	869	84	DIN	0.0%	0.994074 133			
Fam true LABC; LVEF ~5105) 2020	18	525	64	525	0.09	1.22 (2.83 1.68)			
Tan: ILVEF - 50%1 2020	161	last	i i i i i i i i i i i i i i i i i i i	1334	0.05	1 09 10.25 1 141			
Tem Invoc ABoy, LVEF + 365ex 2020	30	809		5//14	0.0%	0.9140.56 + 440			
Fam Init CABE, LVEF <35% 2020	27.	525	21	575	0.0*	1 20 (0 74 1 24)			
Fem ILVEF- 15%1 2020	57	1004	- ŝi	- 334	0.0%	06 (073 1:52)	1 A A		
Summital (With Cit		\$592		1392	100.0				
Coheb-monthly	607		672						
useruperarby Tau?= 0.05, Chife 1.0		e=030							
Control everal effects Z = 0.28 (P = 0.7		1.00							
1.5.6. Blance USheed Manufaceboot Grave	entitional i	Shi lee							
Summars HAFF + 40.474097	14	87	100	350	ê TIN.	11-00-00-11-0-041			
Autor duties + Ecolog 200m	24	177	EE	-540	9.7%	1.12 (0.74, 1.70)	1 m m		
Potto autory	1	35		211	0.7%	# 00 (0.0 ) TO \$11			
PHIL OLIVET + DATAL VIEWS	7	35		30	0.00	1 100 (0.5%, 10.71)			
- m ho - c ABO) 2020	364	850	40.37	370A	0.0%	0.00 (0.74.0.07)			
Carry John CABISO 2020	260	546	3858	ENAT.	0.0%	0.86 (0.78, 0.94)			
Fieri 2020	615	1396	9966	15711	27.00	0.020077.0.071			
Care included LVEF-16015 2020	168	830.	1000	3754	0.05				
2010 CABIO, L//ET <50103 2020	96	546	1230	TARS	8.0%				
FamilityEE +50%i 2020	25.6	1396	2160	15711	11.00				
Com inc. CASG: LVEF + 3530 2010	97	650	512	3754	0.03				
Tem (ve+ CABG, LVET - 35%) 2020	30	646	465	ENAT	0.0%	0.94 (0)65 1.340			
Cam (LVEF <35%) 2020	Br		920	15711	0.0**_				
Vehatley 2021	2200	5512	70317	123850	2774		+		
Pag 2023	17	80	-90	512	0.0%	1.05 (0.65 1.00)			
muser 2073	Å H	151	68F	77A1	18.18				
Sunnotal (MSA- C))		1010	444	70372#			+		
Table events	2992		BIEE/						
Hatermanety Tau" = 0.03; Chil = 50				H EISH-					
Fear for overall effect: Z = G ST (P = 0)				Aw at					
control ferring succession of the - h-									
							X12 11 1 1 1		

Test for subgroup officiences. Chille 0.02 after 1 Te - 0 and Period.

#### Figure S18 Forest plot for CHF or low LVEF.

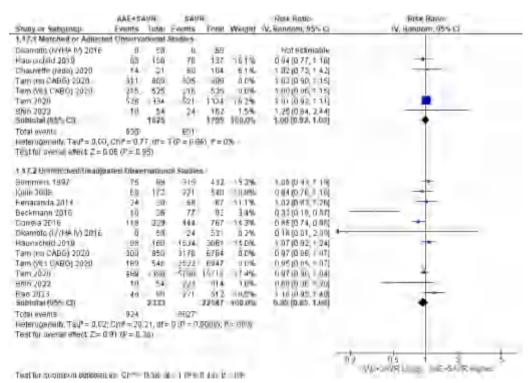


Figure S19 Forest plot for NYHA III or IV.

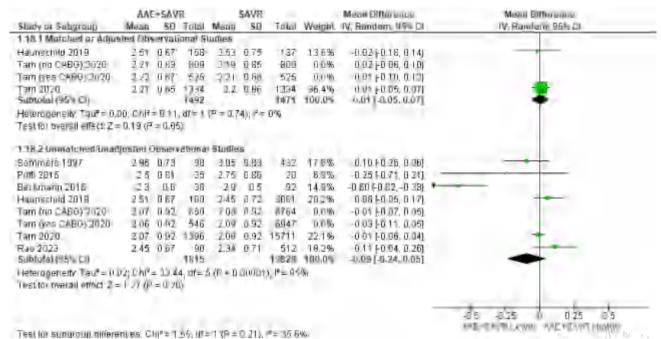
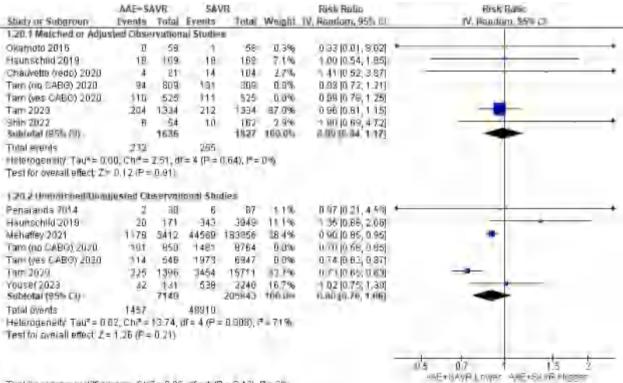


Figure S20 Forest plot for mean NYHA grade.



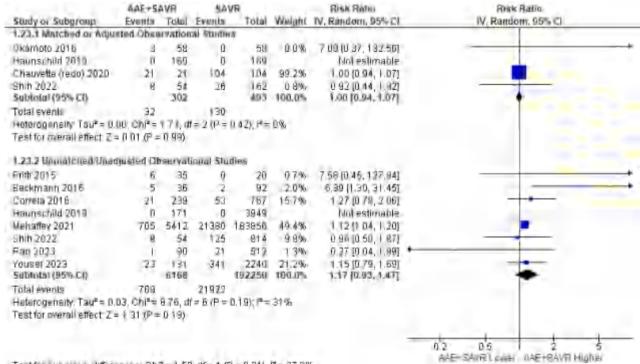
Test for subgroup differences C trif = 0.66, of = 1 (P = 0.42), P = 0%.

Figure S21 Forest plot for non-elective surgery.

	AAE	+SAV	R		SAVE			Mean B/Merunice	Mean Bifferun-
Study of Subgroup	Menn	50	<b>Töläl</b>	Meán	-50	Total	Waght	W. Random: 951 Cl.	IV, Random, 95% Cl
1.22.1 Matchied or Ad	fjilsteit (	Nhàián	vittiorià	Studie	÷.				
Shih 2022 Subtotal (95% 6.0	.2.1	1.6	54 54	2	2.1	162 162	100.0%	0.10[-0.44, 0.64] 0.10[-0.44, 0.64]	
Haterogenalty Not ap	plicable	c						- A. S. M. B. B.	
Test for overall effect	Z = 0.37	(F=)	8.715						
1.22.2 Unmatched/Un	attiuste	d obs	ervalio	nal Su	oles				
Mehattey 2021	2.99	4.1	6412	2 97	4.7	183855	\$2.5W	6 02 (-0 05, 0 1 3)	
Shih 2027	21	16	54	1.9	1.7	814	ā 8%	0 20 (-0 24, 0 0.4)	
Flag 2023	1.6	11	<b>BB</b>	1.9	12	512	20.0%	-0.20(-0.43), 0.09]	
Yousef 2023 Subilitial (95 - CI)	19	1.35	131	1 97	1.48	2248	19.8%	-0.07 +0.31 0 17].	-
Heteropensity Tau#=				3 (P =	0.27);	(*= 24%			
Test for overall effect	Z = 0.51	(P=)	60)						
								-	to the dealer
and the state of the state of the					1.01	1.			-0's 0'ze A 0.24 0.5 -AE-SAVR Lunci AAE-SAVR Hultur

Test for subgroup differences:  $(5h)^{6} = 0.22$ ,  $a_{1} = 1$  (P = 0.04), P = 0.96

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



Test for subaroup differences: ChP = 1.59, dP = 1 (P = 0.21), P = 37.0%

Figure S23 Forest plot for prior cardiac surgery.

	AAE+S	AVR	5AV	R		Risk Ratio	Risk Ratio
Sludy or Subgroup	Events	Total	Events	Total	Weight	N, Random, 95% CI	IV, Random 95% C1
1.24.1 Matched or édjusied Obser	vational 5	tudies					
Okameto 2016	1	58	0	58	9.9%	3 00 (0.12, 72 15)	
Chauvette (redo) 2020	21	21	104	104	52 294	1 00 [0.94, 1 07]	
Shih (repracement or repair) (2022 Subtotal (95% CI)	ΤŲ	54 133	à	162 324	38.9%	1,33 [1,47, 7,77] 1,76 (0.62, 5,00]	
Tota/ events	32		113				
Heterogeneity: Tau? = 0.54; Chi? = 8	18, df= 2	(P = 0)	(2)  #=7	6%			
Test for overall effect: $I = 1.06$ (P = (	29)	0					
1.24.2 Unmatched/Unadjusted Obs	ervalona	Studie	15				
P/m 2015	0	-35	0	20		Not estimable	
Coneia 2016	1	235	0	767	3.7%	9 60 (0 39, 734 88)	
Shih (replacement or repair) 2022	10	54	30	110	87 日%	5 07 (2 80. 0 73)	
Rao 2023	1	30	-5	\$1Z	0.4%	1.14 (0.12, 0.60)	
Subtotal (95% CI)		-410		2113	100.0%	4.54 (2.45, 0.44)	-
Totai events	12		36				
Heterogeneity Tau <sup>2</sup> = $0.00$ ; $Ch^2$ = $1$ Test for overall effect: $Z = 4.79$ (P = $1$		(P = 1)	98); (*= 0	ж.			
							01 02 05 1 2 5 10
Test for suburbup differences, Chi?	= 2,34, dfs	1 (P=	0.13). P	= 67.45	K		MEHSAVR LOW T MEHSWIR HIGHT

Figure S24 Forest plot for prior SAVR.

	AAE	+SAV	R	6	AVR			More Difference	Mean Difference
Study or Subgroup	Меал	50	Intel	Mean	50	Intal	Weigshi	IV, Nandoni, 955 Cl	IV, Bondam, 95% CL
1.26.1 Malched or Adjust	sled Obs	servali	લાસ ડા	udjas		-	-		
Okamoto 2016	92,7	24.8	.58	85,1	29.0	50	55,2%	7.60 [-2.40, 17.60]	
Chauvette (redo) 2020	.56.9	17.9	21	54.5	41.8	104	44.0%	2.40[-0.70, 11.50]	
Subtotal (95+ CI)			79			16.2	TENS OF	527 1.2 11, 12 701	
Helerogeneity Tau <sup>a</sup> = 0	00, Ch?	= 0.47.	df=1	(P=115	D), P=	11%			
Test for overall effect Z =	= 1.39 /P	=0.16	ù -						
1.26.2 Unmatched/Unad	busted C	lisery	aliena	Studie	6				
KONK 2006	67.7	25.1	171	68-11	28.8	540	38.1%	-1 107-5 57, 3 37]	
PHIL 2016	101	22	36	1.98	38.7	20	6.6%	-15.00 [-33.46, 3.46]	•
Electronianon 2010	75	79	75	77	30	82	14.6%	2 00 113 28, 9 281	
Correra 2016	95.4	28.2	229	92.1	24.5	767	40.7%	410 0 13 9.07]	
Subrotal (96+ CI)			482			1419	100.0%	190.2, 30.2.] CND-	
Hoterogeneity Tau#= 12	1 19; Ghi	* 63	3, <i>ill</i> = 3	3,(P = 0)	10); 1	= 53%			
Test for overall effect 1=	- D.D.I. (P	=0.09	Ŋ						
									ALE-SALE LOWER ALE HAVE HIDDED
Testror subgroup differe	sques C	107=1	34, UF-	1 (F=	0.25).	P= 25.	3%		The second

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

	AA	E+S/IVE			SAVE			Mean Différence	Mean Effetence
Study or Subgroup	Mean	50	Total	Mean	50	Total	Weight	IV, Random, 95% EI	IV, Random, 95% El
1.25.1 Matched on Ailyn	About Dos	ervatm	nal Ste	adres				and the second s	
Chauvette (redo) 2020	119		21	3D.V	25.6	+04	37 69	1 80 (-4 99, 9 99)	
Smn 2022	45 95	17.11	54	4215	17.14	+61	67.49	380 (-1 47, 9.07)	
Subtratial (FIRE), Ch			75			256	100.0%	3 05 [ 4.42, 7.21]	
kieterogeneity Tau'= 0.	00; Ch/%	-0.21,6	n'= † 1)	P=0.65	$\hat{u}_i \hat{r} = \hat{u}_i$	00			
Test for overall effect Z:									
1.25.7 Unmali heil/Unm									
KURK 2001	19.1	10	17.2		25.4	540	18.39		+
Print 2015	ALP	17	- 25		12.7	20	1.3.798		
Beckmann 2016	48	70	- 36	19	14	92	14 D%	0.00 (-7.60, 7.60)	
Correia 2016	612	20.2	2.39	50,0	10.7	747	1.0 6.90	4.40 (1.69, 7.22)	
Smn 2022	45 115	17.11	54	44.21	16.92	114	+7.2%	164 (-107, 6.35)	
Rao 2023	457	76.0	W	41.7	17.6	507	14.0%	4.00 (0.14, 7.86)	
SUDADINI (DIRT, Ch			129			2715	100.0%	8.26[5.49.4.99]	
kieterogeneit/ Tau*= 1	.g.j. Chil	= 42.43	) dt = !	5 (11 + 0	000015	$\mathbf{P} = \mathbf{\hat{P}} \hat{0}$	15		
Test for overall effect 2:					0.00.04				
	A STREET								
									-10 -5 0 6 10
Test for subgroup differe	ances m	- 0.9	100-	LID-T	53.2	14			E-S S L V F ANE SAVR Higher
the state of a second rate h which a	CONCERCION OF	100	10 M P	1.11.100.0					

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

	0.4	E-SAVE	3		5AVR			Mean Différence	Mean Difference
Study or Subgroup	Мыца	50	Total	Moun	50	Total	Weight.	IV, Random, 95% CI	IV, Random, 95% Cl
1.27.1 Matched or Adju	sted Dis	auryatia	na) 511	nties		-	-	the second second	
Okamoto 2016	661	-02	DH.	0.72	11.74	-59	32.9%	+0.11 F0.19; +0.61	
Chauvette (rede) 2020	0.87	0.74	-21	118	014	104	33.7%	0.911-0.98 +0.24	
Shih 2022 Sublatal (95% CI)	87	0 229	94 113	072	0.26	162		+0.02 p0.09, 0.05j 0.15 [-0.32, 0.03]	-
Heterogeneity Tau <sup>2</sup> = 0.	ar che	= 36.66		(P = 0.0	indines s				
Test for overall effect Z=				hards	ind if		1		
1.27.2 Utimatched/Boad	jusied (	bserva	hoani.	Studies					
KUHK 2003	0.7	6.17	172	0.72	0.34	540	29.5%	-0.02 (-0.06, 0.02)	-
Beckmann 2016	0.7	0.3	36	0.7	0.2	92	79%	0.00 (-0.11, 0.11)	
Correra 2019	0.55	0.23	139	0.6	0.2	767	33.3%	-0.05 [-0.08, -0.02]	-
Bhill 2022	0.7	0.229	54	0.75	0.36	Bi4	16.4%	-0.05 [-0.12, 0.02]	
Rao 2023 Sebbatal (95% CI)	0.81	0.26	90 591	0.34	0.0	512	12.3%	-0.13 [-0.21, -0.05] -0.05 [-0.00, -0.07]	•
Helerogeneity: Tau? = 0.	OE, Chr	-7.03.0	dfi= 4 (f	P = 0.13	S, Paul	13%		1.00100000000	
Test for overall effect. Za									
									AZ AL 1 - 12
									HAR HEAVE I WART ANT SAVE HUMAN
Test for subgroup differe	mcee C	bi* = 1.1	8. df =	1 (P = 0)	28), P	= 15.0	10		The maintenance of the second control

**Figure S27** Forest plot for aortic valve area (cm<sup>2</sup>).

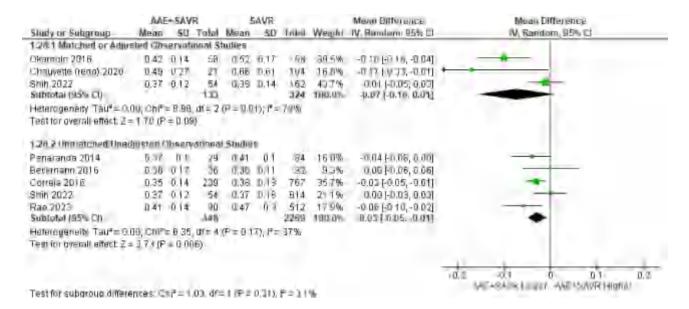


Figure S28 Forest plot for indexed effective orifice area  $(cm^2/m^2)$ .

	AAF	+1AV	R	3	AVE			Mann Infference	Mean Difference
Study or Subgroup-	Mean	511	Hotat	Mean	811	Total	Whight.	IV. Random, 95%CI	IV, Random, 95% (3
1.2%1 Matched or Adjusted Ob	ervation	nat Sta	otties						
Okamolo 2016	19.3	1.1	58	10.7	11	50	40.9%	-0.40   1 67, 0.27]	-
Shih 2022	224	1 8	- 84	114	-23	162	61.1%	-1.00 [-1 52,-0 86]	
Subroual (95% CI)			112			220	100.0%	-0.05 ]-1.74, 0.02]	
Heteromenally, Tau <sup>2</sup> = 0.30; r.h. <sup>4</sup>	3.72.0	F= 10	F D II	5), 12 = 7	12				
Test for avenual effect Z = 1.81 (P	= 0 ((6)								
1.29.2 Unmatched Unadjusten L	nserval	in mail	smille						
Deckmann 2010	19	1	10	20	11	02	24.9%	-1.00 E1 39, -0.61)	-8
Shih 2022	22.1	19	54	243	23	814	32.4%	-2,201-2,73, -1 67	• • • • •
Rao (barrel end of sizer) 2023	23.2	2.2	82	24.1	22	511	32.7%	-0/90 E1 41: 0.39]	
Rap (teplica end of sizer) 2023	23.1	21	67	237	21	494	0.0%	-0.60[115,-0.05]	
Subtotal (95% CI)			172			1417	100,0%	1,36 2,12 -0.59)	
Heterogeneity: TauP = 0.40; ClnP	= 16 57,	dt = 2	(P=1)	0004);	R = 11	29.			the second se
Test for overall effect Z = 3 47 (P	= 0 600	5)							
									ALE+SHUR LOWER ARE ISAVE HIGHER
Test for subgroup differences' C	$hl^* = 0.61$	9 df =	1 (P =	0.41) 1	$= D\dot{\eta}$	6			The second residence of the

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

	MAE+5	AVR	SAN			FDSK Retto	fille Rete-
Study of Subgroup	Events	Total	Events	Total	Wright	IV: Sandon, 15% El	IV, Bendom, 1975 CI
1.30 1 Motched or Adjusted Observational Studie	19						the second se
Okamote 2016	56	68	58	58	52.3%	1.00 (0 97; 1.03)	
Haunsen d 2019	161	766	167	166	25.4%	7 00 (0.96, 1.04)	
Charavette (redo) 2020	17	.21	-7.7	1.04	0.7%	1.09 (0.46, 1.19)	
Tam (no CABG) 2020	686	609	679	603	0.0%	1.01 (0.17, 1.00)	
Tam (yes CABG) 2020	480	525	457	525	0.0%	1.01 (0.96, 1.05)	
Twn 2020	1148	1234	1138	1234	27.7%	1.01.03.99, 1.04	
Shih 2022	49	54	142	162	34%	1.04 (0.13, 1.15)	
Suprotal (95% CI)		1633		1824	106.0%	1.01 (0.99, 1.03)	•
Total events	1433		1574				
Heterogenety: Tau*= 0.00, Ch#= 1.07, pt=4 (P =	0.90); P =	19					
Tright for overall effect, Z = 0.59 (P = 0.56)							
1.39.2 (Immerched Unavjusted Observational Sta	dint						
Sommers 1997	B4	98	316	492	3.2%	117 (106, 1.29)	
Fenaranda 2014	30	30	87	87	9.9%	1.00 (0.95, 1.05)	
Pntt 2016	35	-35	20	-20	4.9%	1.03 (0.53, 1.08)	
Eluckmann 2018	36	36	92	92	11.9%	1 00 (0 96, 1 04)	
Correls 2016	170	239	529	767	0.036	1.03 (0.94, 1.13)	
Correla (inc) mixed stenosis+insufficiency) 2016	223	230	710	767	112%	1.01 (0.57, 1.05)	
Haunschild 2019	183	160	3513	3929	15.5%	1 06 (1 02, 1 09)	
Tanhino CABOI 2020	727	850	7496	8764	0.01%	1.00 (0.97, 1.03)	
Fam (yes CAEG) 2020	479	545	5779	3947	110%	1.00 (1.02, 1.00)	
Turn 2020	1206	1396	13256	15711	191%	1 07 1 00, 1 06	
Shih 2022	49	54	690	814	3 61%	1.07 (0.88, 1.17)	
Fac 2023	NE.	0.0	474	312	17.1%	1.00 (1.02, 1.10)	
Yousef 2023	116	131	1937	7240	74%	1 04 (0.99, 114)	
Subtaial (95% Ci)		2278		24504	100.0%	1.03 [1.04. 1.05]	•
Folal events	2092		51005				
Heterogeneov: Tau <sup>4</sup> = 0.00, $Chi^4$ = 1.5.14, $dt$ = 9 (P Test for overall effect. Z = 3.15 (P = 0.002)	= 0 0m), P	= 44%					
							gins uig i th the the synchronic and the Human
Test for Jubgroup differences. Chi#= 3 78, df= 1 (	P = 0.075	F= 69,4	19				APTICAL TOTAL OF LOUD LOUD

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

AAE+SAVR SAVR Risk Natio Risk Hallo Study or Subgroup Events Total Events Total Weight IV, Random, 05% IV, Rambon, 95% C 1.31.1 Matched or Adjusted Observational Studies Okamoto 2016 H 58 8 58 19.9% 0.89 (0.37, 2.14) Shih 2022 16 54 81 162 80.1% 0.59 (0.38, 0.92) Sublotal (95% Ch 112 220 100.0% 0.64 [0.43, 0.95] Total events 24 90 Heterogeneity: Tau<sup>2</sup> = 0.00, Chi<sup>e</sup> = 0.65, dt = 1 (P = 0.42); P = D% Test for overall effect: Z = 2.21 (P = 0.03) 1.31.2 Unmatched/Unadjusted Diservational Studies Pnfti 2015 9 35 8 20 19.9% 0.57 (0.27, 1.20) 075 (0.50, 115) Shih 2022 16 54 320 814 35.4% Rao 2023 90 512 #4.9% 1 18 [0 89, 1 55] 38 179 Subtotal (95% CI) 179 1346 100.0% 0.87 (0.58, 1.32] Total events 62 508 Heterogeneity, Tau? = 0.08, Chi? = 5.23, df = 2 (P = 0.07), (\* = 62%) Test for overall effect: Z = 0.66 (P = 0.51) 0.5 0.7 15 AAE+SAVR LOWER AAE+SAVR Higton Test for subaroup differences, Chi#=1.09, at=1 (P=0.30), F=3.6%

Figure S31 Forest plot for bicuspid aortic valve.

#### Figures S32-S39. Meta-analyses for operative outcomes

	Marce 3	AVR	541			Rid# Ratio	Risk Ratio
tudy of Subgroup	Evente	Total	Events	Tetal	Weight	NV, Rannoni, 95% Cl	IV. Random, 95% C
32.1 Matubest or Attynsted Oper	erhidonu	el Stutte	85				
kanioto 2016	18	58	21	- 58	3.日%	0.66 (0.51, 1.43)	
sunsched 2019	12	169	11	169	3.8%	1 09 (0 50, 2 40)	
am (no CABG) 2020	170	ana	251	FI09	0.0%	0 71 (6 68, 0 84)	
am (yes CABG) 2020	73	525	76	525	0.0%	0.92 [0.69.1.24]	
2020	251	1334	330	1331	92.9%	0.78 (0.86, 0.88)	-
hih 2622	1	54	20	162	4.5%	1.36 (0.65, 3.78)	
ubtotal (95% CI)		4695		1723	108.0%	11.RT [D.GH. 1.93]	•
stal events	290		382				
eterogeneity Tau*= 0.00, Chi*=	3.10, 40	= 3 (P =	E. 119) (*	/VE =			
est for overall offers Z=2.03 (P:							
32.7 Ummitched Unaujustei 0	bacryala	unit St	illes.				
ommers 1927	D.	96	0	432		Not estimable	
akamoto (Bt Jude only) 2005	24	24	104	104	20.4%	1 00 10 94 1 001	+
akametu 2006	24	24	157	157	70.5%	1 601 (6) 94, 1 061	+
UIIK 2009	74	172	217	540	10.9%	1 07 (0 89, 1 31)	
anatanda 2014	-0	30	1.1	97	0.1%	0.41 (0.02.7.63)	ti contra
rift 2015	35	35	20	20	19.2%	1 60 (0.03, 1.08)	- +
eckmann 2016	D.	36	0	.82		Hot estimate	
ometa 2016.	57	239	365	757	9.0%	0 60 (0 39, 0 63)	
striscond 2019	1.1	171	734	1949	2.59	0.64 (0.45 1.47)	
am (no CÁEG) 2020	210	850	2364	8764	10%	0.94 (0.84, 1.08)	
arn (yes CABG) 2020	52	506	1150	8947	0.0%	1 80 (8 83, 1 72)	
am 2020	010	1396	3550	15711	17.5%	0.90 (0.09, 1.09)	-
80 2023		90	n.	512		Not estimable	
ublintari (05% CJ)		-2116			108.0%	1 94 (0.80, 1.03)	•
alial avenue	518		4748				
eterogeneity' Twa*= El Bt; Chi*= est for overall effect Z = 1 30 (P	1313,1	lf= 7 (P		); P= 79	d,		

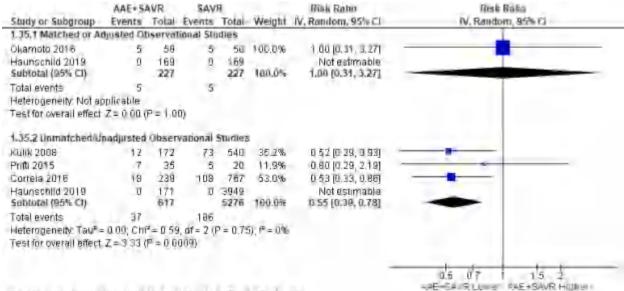
Tast or subgroup differences:  $Chi^2 = 1.04$ , dt = 1.07 = 2.09, P = 67.1%

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

AAE+SAVR SAVR RISK RATIO **Risk Ratio** Study or Subgroup Events Total Events Fotal Weight IV, Random, 95% L IV. Random, 95% CJ 1,34.1 Matched or Adjusted Observational Studies Okamobi 2016 55 100.0% Ð 58 6 1 00 [0 34, 2 92] Haunschild 2619 Ð 189 Ø 189 Notestimable 102 Shih 2022 51 Not estimable Ð 0 Subinial (954 CI) 281 389 100.0% 1.00 [0.34, 2.92] Total events E 6 Heterogeneity; Not applicable Test for overall effect Z = 0.00 (P = 1.00) 1.54.2 Unmutched/Unexpected Observeruonal Studies Kullik 200H 75 13.2% 110 (0 90, 1 34) 172 214 540 Penaranna 2014 87 2.9% 0.96 (0.54, 1.36) 13 30 44 Film 2015 Ð .15 4 20 0.94 0 H6 [0 27, 2 6P] Correta.2018 239 767 7.25 [0.90, 1.74] 41 105 5.4% Haunschild 2019 л 171 0 3949 Not estimable. Methalfey 2021 2307 5412 P3094 83858 73.0% 0.94 [0.91, 0.97] Shih 2022 Nol estimable π -54 -10 1014 Ran 7023 80 612 4.4% 1783(0.50,1.20) 24 164 190545 0.07 [0.90, 1.05] Subinial (95%, CI) 6203 100.0% 13625 Total events 2466 Heterogeneity: Tave = 0.00; Chi# = 6.69, dr = 5 (P = 0.24); # = 12% Test for overall effect Z = 0.78 (P = 0.4.)) 07 0.95 1.5 AVE+SAVR Lower AS+S+VF H

Test for subarpup offerences: G(n) = 0.00, m = 1 (n = 0.05), h = 0.05

Figure S33 Forest plot for concomitant CABG.



Test for subgroup differences,  $Ch^{\mu} = 0.88$ , df = 1 (P = 0.35),  $f^{\mu} = 0.%$ 

Figure S34 Forest plot for concomitant mitral valve surgery.

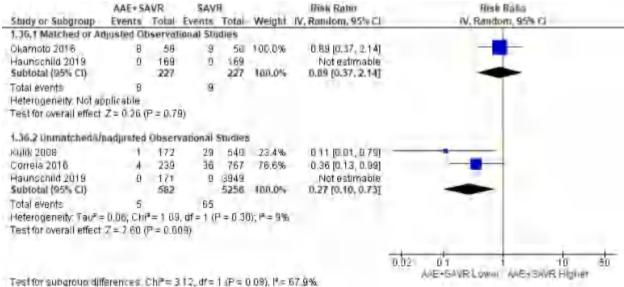


Figure S35 Forest plot for concomitant tricuspid valve surgery.

	AAF	+ SAVIR	D1		SATE			Million Differences	Mudar Distance
Shudy or Subgroup	Altern	-50	Total	<b>WALKER</b>	50	Total	Weight	IV, Randolm, 95% FL	D. Hentflinter, 9299 (3
1.37,1 Matched or Adjusted Doseryation	al Stuans	2							
Cisaming 2016	177	42	50	167	39	58	224%	20.00 (6.26, 04.75)	
Haunurchied 2019	10110	27 4	109	7672	421	10.9	12 646	94 46 79 0, 29 02	-
Chemperine (rests) 2020	140.	30	24	1.50	21	104	17 84.	-4.00[[21:33, 15,25]]	
Bhin 2022	138.17	34 91	34	102.66	19.04	162	27.1%	13.31 [24 70, 45 47]	
Subinitation (1991) C1)			302			401	100.0%	71.13 (9.69.32.0/)	-
leterogeneity Taur= 700 67 :01#= 12 7	0, 61 = 3 (7	= D EN	5)) (F=1	76%				and the second s	
Test for overall effect Z = 3.59 (F = 0.900)	12								
1.37.2 Limmaterreal limitigipated Observati	ionai Situd	inter							
Kunik zater	137.6	46.6	172	125.8	44.4	640	0.0%	/ 90 (-0.48, 45,36)	
Kullk (excl concorn wacedwes) 2001	1147	145	- 54	106.9	5 B B	252	112%	12,40 [2:63, 22:17]	
Renavanda 2014	145	28	30	66	31	37	3.2%	57 00 [28 03, 64.07]	
Prelizată	1191	-43	36	69	.25	-20	ā1%	10 10 11 2 31, 30 271	
Beckmann 2018	105	-79		67	-26	9.1	10 3%	JB 00 [27 14, 44 mb]	
Comma 2016	-AJ	-21	224	NÓ H	20.4	(11)	0.0%	14 20 21 1, 17, 23	
Come a least concorn procedures; 2016	117.8	15.5	170	557	1.91	520	15,6%	21.70 (19.23, 24.17)	
Haunechild 2019	101.21	27.3	171	E1.27	23,6	3944	15,6%	19,96 [15 80, 24,17]	-
Met wittey 20/21	120	51	541.3	114	-43	183656	17.0%	14,00 [12:63, 15:37]	
Rao 2023	122.4	52.7	-MD	7057	48,3	612	3,9%	17.10.16.67. 29.63)	
Yousef 2023 Subtrite (95% CI)	108	-64	121	E.I	23	2340	10.7%	42.00 (30.96, 55.04) 24.02 (38.56, 29.55)	
Helerogeneth: Tau <sup>2</sup> + 46.59, Chr <sup>a</sup> + 78 Mil	in a state	2.000		10110		191244	Indiana	same line a road	-
Tent for prenal alliel I 2 = 0.52 (P + 0.000)		- at filling	arxis	100.00					
									the second
								-	- 10 - 15 - 15 - 15 - 15 - 15 - 15 - 15
Test for subgroup differences. Chat a 11	WHAT W	► 0.5 m	P= 03						WEATHING WEATHING

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

	AAF	+SAM			SAVE			Mont Difference	Mison Utfornace
Study or Supproval	Mean	- SD	Total	Mesui	5D	Total	Weight	(V. Random, 95%, C/	IV, Randoro, 19% Ci
1.31.1 Matchell og Adureteil Observation	el Shatines	1							
Divariato 2016	120	32	55	110	34	50	21.5%	16,00 (3 50, 26 02)	
Haumschild 2018	77.7	70.3	199	55.67	14-6	150	32.6%	72 03 (16 24, 75 32)	+
Chawette wedp) 2020	184	35	21	112	51	104	101%	2 00 11 80 15 86	
Bhitt 20.22	11370	2673	54	62.9/	29.42	162	26.70	30 81 [22 44, 39 16]	
Selifolul (95% Of)			307	1.11	110	-490	100.0%	19.25 [16.17, 28.33]	-
Helarogenéity Tau*= 62.11. ChF= 13.17. Tost far ovorall e fact Z = 4 15 (P < 0.000)		= D,CID 4	)  *=7	7%					
1.3E.2 UnmotchedEmulguisted Observall	ound Soud								
Ecromers 1997	(74)	26	Jt.	67	24	432	12.6%	11 00 (5 36, 16 62)	
KUIIK ZODE	34.1	2017	172	96.5	27.9	640	0.0%	7.60 [2.97, 12.27]	
Kulik (saci rimcorri amminioner) 2008	82.1	21.3	94	72.2	20 8	292	12.2%	9.00 (4.9), 14 92	
Penarantia 2014	74	27	âL	60.5	1a	37	7.3%	13:50 [3 12, 23 36]	
Finite 261 5	90	112	95		19	20	5.9%	22 (00 (8 52, 36 46)	
Berlimann 2016	75	14	36	56	21	92	10.5%	(9.00 p+1.45, 26:55)	
Conela 2015)	5E 17	1.12.4	.239	45.2	14.4	757	0.0%	11.40 (9.53, 18.27)	
Coneta (axci commini procedures) //01e	3D 5.	14.4	175	41.4	10 8	570	15.8%	+9 10 [1E 74, 21 41]	-
Haunschild 2019	777	-28.2	171	58 32	17 5	3949	15.2%	1938 [16 30, 22.46]	
Pag 2020	83.1	311.0	- 30	90	00.9	512	9.6%	1910 467, 2153	
VIIIVISEV 2023	111	- 51	135	TA	27	2240	14.3%	3/ 00 [28 20, 45 80]	
Subinial (Ath. Ct)			863			8104	100.0%	17.70 [11.87, 24.74]	•
Helenageneite Taut= 7540, chris 20 en Techtoroverall effect 2 = 661, P ~ 0 diluo		11111	RTY P=	764					
									6 5 6 8 4
									-20 -10 0 (0 2) ANE CALIFICATION AND AND AND AND AND AND AND AND AND AN
Turbler submon difference Chi?= 1016	IT=1/F	= (1.10)	m = 0.0						Lote include Failed - Mare 200,6010806

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

		H-SAY			499	and a		Moun Officiance	Mean Difference
Study or Subgroup	Meen		Lotal.	Mehit	- ND	1.01.04	Weight	W, Bandom, 95% Cl	ty, Random, 95%-Cl
1.39.) Maiched or Adjusient Obsummional									
Okannolo 2014	19.4	15	56	化肥料	114	- 16.02	21.8%	410 (0 A) 0 D)	
launschild 2019	21.7	1.5	169	22,3	15	169	27.8%	-0.60 (-0.92, -0.20)	
ha(wette (redit) 2020	21,2	0.4	21	220	0.4	104	. 31.1%	-0.90551.09, 0.711	-
Shih 2022	22/13	1.91	54	22.72	7.21	167	19.2%	-1 26 t 40, -0.60	
Subrianii (95% CI)			2015			493	100.0%	4.67 (-1.09, -0.25)	•
Heterogenalty TruP = 0.14; ChP = 15.62; if =	= 9 (P = )	1000	P= Bt	No					1.C.
Test for overall effect $\mathcal{I} = 1$ fo (P = 0.002)									
1.39.2 Ulmatroell/Unit/Band Observation	ni Sinii	ne -							
Sotomate 1997	23.8	1.94	- 99	26.3	2.07	432	10.9%	1.50(1.93, 1.07)	
Allik 2006	22	. 5	172	20.7	0.6	540	11.4%	1.30 (1.14, 1.46)	-
Penaranda (all same in each group) 2014	-21	E 1	-90	151	0.1	187	11.5%	2 00 (1.9E, 2.04)	
Prifti (bil same in each group) 2015	19	01	36	17	0.1	20	11.6%	2 00 (1.95, 2.06)	
Bockmann 2016	24.9	0.45	- 20	23.5	- 84	- 92	11.0%	1 80 (1:27.1.93)	
Coneia 2016	21,8	1.5	219	20.7	0.5	767	61.4%	1 10 (0.97, 1.23)	-
Hawasshild 2019	217	1.5	171	23.7	1.5	3348	11.3%	-1005233,-177	+-
Rau 2025	231	19	90	237	-21	512	10.6%	-0.80(-1.03,-0.17)	
Yousat 2023	23	3	131	247	1.5	7240	10.5%		
Subtaint (95% CI)			9/6	- 21		B639	100.0%	0.38 [ 0.19, 0.95]	-
Heterogeneity Tau" = 0.74; Ch*= 1773.65,	st = B (F	- 0.00	IOB IS: P	· 1003	ň				
Test for twefail effect Z=1 32 (P=0.19)			and and						
Contraction of the second s									
								-	
									1 1 1 1 2
Tent for subproup cimerences. Chi#= 8.42, d	f=1 Pa	= 0.00	$i_{1} P = i_{1}$	81195					ALT A LINET AAEASAVA HIGTAT

**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.

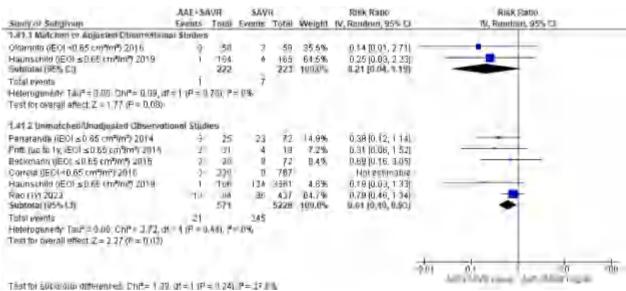
	(hA)	H5AV	11		AVR			Party (Imposition	Addall Little	OFFICE STREET
Study or Subgroup	Mean	୍ରାର	Total	Mean	- 80	LOTH.	Welant	IV, Random, 195% CI	iV, Hansterr	.95% CI
1.39.1 Matched or Adjusted Obsorvacional	Studies	0.00	11.1					A		
Okamphy 2016	119.4	1.8	-58	46.8	1.8	- 58	018%	0.101040.43, 0.6.0	-	-
Haunschild 2019	21.7	1.5	169	22.3	16	69	27.9%	-0.00(0.82,-0.20)		
Chauvette (redo) 2020	21.2	-0.4	21	22.1	0.4	104	31.1%	-0.901-1.090.141	+	
Shih 2022 Sabiahi (95% CI)	22.13	1.94	64 302	23,79	2.29	182	10.2%	-1.261-1.020.63	-	
Heterogen elter Tau <sup>a</sup> = 0.14; Ch $^{a}$ = 16.62; dr Fest for overall effect: $\mathcal{I}$ = 3.10 (P = 0.002)	= ) (P = )	i in the	P = 81	<b>%</b>						
1.39.2 Unmatched/Unadjusted Observation	ini Snici	res								
Sommers 1997	23.8	1.94	98	25.3	2.117	432	14.2%	1.50   1.92 -0.07]	-	
SUIK 2006	22	1	172	20.7	0.6	540	14,5%	1.3011.14, 1.45]		-
Penaranda (all same in each group) 3014	.21	U.	-30	1.14	D	97		Mol westimable		
Prifti (all same in each group) 2015	19	0	35	17	0	20		Not estimable		
Biockmann 2016	24.9	0.45	20	23.3	13	92	14,3%	1-60 / 1.97, 1-931		
Coneia 2015	Z1,8	1	2.89	20.7	0,5	707	14.5%	1.10.03.97.1.201		-
Haunschild 2019	21.7	15	171	237	1.5	3949	144%	-2101[-223,-177]		
Pau 2028	231	19	90	297	21	512	14.2%	-0.60 (-1.03 -0.17)		
YnUsat 2025 Sebtelal (95% CI)	53	3	131	23.7	15	2240 8639	14,0%	-0.70 [-1.22, -0.10] -0.17 [-1.17, 0.86]		-
Hetwogeneity Twu" = 2 D4; Chr" = 802 72, d Teol for twetnil effect Z = 0 20 (P = 0 84)	t= 6 (P -	0.000	01), (*i	39%						

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

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

108-43		1+5AVI	1		SAVR			Mean Dittelence	Mean Difference		
Study of Subgroup	Milder	50	Fotal	Miller	50.	Fothi	Weight	IV. Random, 955, EL	IV, Random, 95% (.)		
1.40.1 Matched or Adlut	Direct Direct	#IVatio	nul Sta	idents.		_					
Okamolo 2016	0.93	0.18	-58	10.9	1.27	55	31.7 .	-0.10(+0.18, -0.02)			
Hauros6mild 2019	1.77	0.22	160	177	D.22	169	11.0%	1 DO 1 0 05, 0.051			
Chiliwette (rédo) 3070 Sabtatut (US=Ct)	0.70	0.18	21	0.05	11.49	104	24.1%	-0.00 ( 0.20, 0.07] 0.05 [ 0.11, 0.02]			
Hetorogene &' Tau* = D.)	00; DhF:	=5.40.4	f=20	P=0.07	$3.1^{2} = 63$	- 30 E					
Test for overall effect Z =											
1.462 Demaiplicefolia	inaleri (	Sector	tumal	Madary							
Sommers 1997	0.451	0.087	-90	0.992	LL FIMM	432	1.109	0.01(-0.05,-0.01)			
Kutik 2000	0.09	0.10	172	0.79	1140	-540	1.5.2%	010(007.013)			
Paperente 2014	114	0.36	25	0.8	0.26	7.2	- 5.0%	0.04 (0.19, 0.49]			
Frith (up to 1v) 2015	0.05	0.17	157	0.76	-D.Z	10	7.4%	m m 10 ( 0 0 Z, 0 20)			
Berkmann 2016	0.81	02	14	L H J	1114	82	9.1 %	0.001-0.00, 0.16[			
Currera 2016	0.92	0.11	239	0.86	0.03	767	13.0%	0.06 (0.04, 0.08)			
Hammichille 2019	177	6 72	17.5	1.8	0.72	949	17.9%	-0.03 (0.06, 0.06)			
Rao 202.1	0.70	0.19	72	0,0	0.205	439	12.1%	-0.02(-0.07, 9.03)			
Rap (19) 2023	0.79	0.22	84	0.75	11.87	137	0.0%	D.04 (-0.01, 2.09)			
Vousief 2023 Subtotal (95% Cf)	0.96	0,2	137	0.96	D,7		12.0%	0.001-004,0041 0.041-0.00,0.081	-		
Helenogene &. Tau°≡ B l				9 (F = 6	666001)	F= 32	16				
Test for overall effect: Z=	=1:94 (P	= 0.05)									
									-0.2 -0.1 0 0.1 0.2		
Test for submup differe	nene-C	10.00	dian-	8 10 - 1	nn in	20.20			eveE+SeVR Lower HAE+SAVR Hinter		

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



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

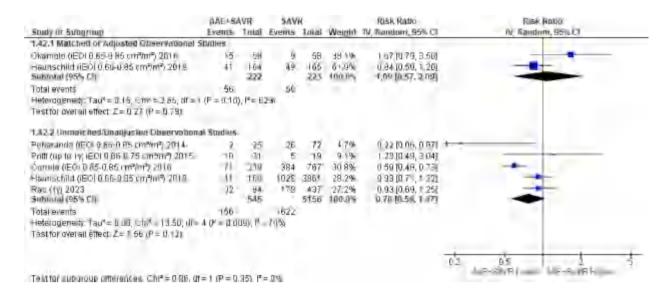


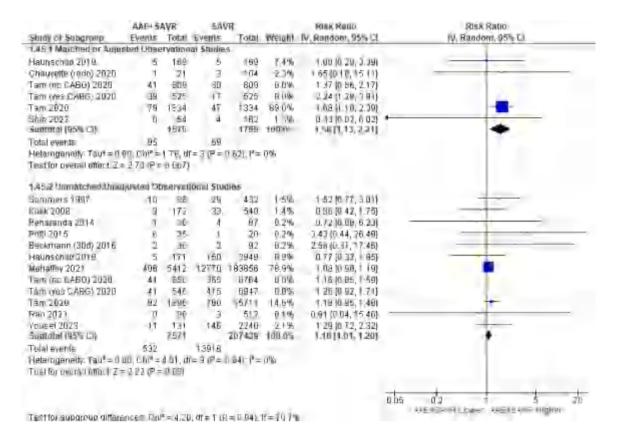
Figure S42 Forest plot for moderate patient-prosthesis mismatch (PPM).

	AAE+57	AVR.	SAV	57		105K Rebo	Persia Provisio
Study or Subgroup	Events.	Total	EVIDITA	(one)	Weight	W. Kantom Jon Cl	W. Random, JSP-E1
1.43 1 Matched or Adjusted Observational Studies						COLUMN THE OWNER	
0kampto (IEO) -b 35.cm*/m* 2016	15	- 53	12	68	25.0%	25 [0 84, 2 43]	
H summoniad 0€ 0.1 ≤ 0.85 cm/d/m²) 201.9 Subfetal (95% C0	42	164	-57	105	71.0%	0.0010.57, 1.12	
Total events	57		8.5				
Hoteromeneity $Tau^{\mu} = 0.02$ , $CmP = 1.30$ , $df = 1.(P = 0.2)$	(4), F = 26	116					
Test for overall effect: $Z = 0.47$ (P = 0.64)							
1.43,2 Unmatching/Union/Justed Observational Studie	is .						
Sakamoto (St. Juse only, EOI ≤0,65 cm/lm/5 2006	.0	24	Ő.	104		Not estimable	
Sakamoto (IEO) <0.85 on?/m?) 2006	D.	- 34	2	157	₽.\$/E		
Kulik ()EOI \$1785 :m3m3 2008	73	172	375	540	22.2%	0.61 [0.51, 6.73]	
Punarande (IEO) = 0.85 cm?m? 2014	5	-05	49	72	48%	0 20 10 13, 0 65	
PARL (up to 1V. EDI ≤0.75 cm=m=5 2015	12	- 31	18.	19	五字祭	0.82 (0.43, 1.56)	
Coneia (IEO) > 0 85 cm*lm*) 2016	74	7.13	384	757	20.9%	0.59 [0.48, 6.73]	
Haumschild (EDI <0 85 cm²/m²) 2010	47	185	1152	3861	17.9%	0.86 (0.85,11)	
Rep (3)/3 2023	45	80	265	\$27	卫星有限	0.09 (0.71, 1.09)	
Yinusef (IEO) = D H5 rm?/m*) 2023. Sectotal (95% Ct)	10	131	224	2240	7 0%	0.76 [0.42, 1.40] 0.70 [0.50, 0.84]	•
Potal events Hotorogéneity Tau <sup>2</sup> = 0.03, Chi <sup>2</sup> = 16.03, di = 7 ( $P$ = 0 Festforoverall effect Z = 3.75 ( $P$ = 0.0002)	250 .02), P= 5	50 A	5940Đ				

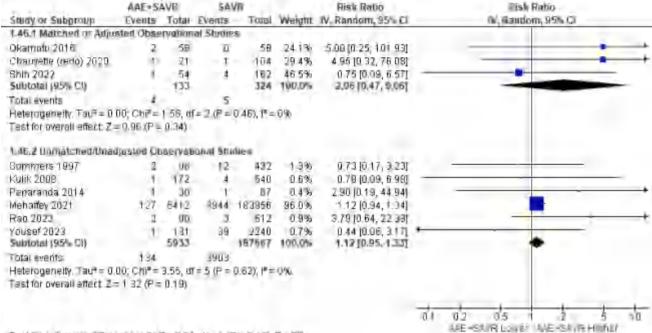
Figure S43 Forest plot for moderate or severe patient-prosthesis mismatch (PPM).

	dAEA5	AVH	54	MH		HISH, HINDO	HILES Harboy
Study or Seleptote	Eventa	Toba	Exemite	Tole	Weight	IV, Rambon, 95% Ct.	th, Random, S5m CI
1.44.1 Maiched ar Adjusted Observ	a lianni Sh	ndias				1.	
Otempts (30/For hospilar) 2016		538	2	-53	-31%	0.60 (0.15, 5.36)	
Haunsemin (300 ci hose) 3019	6	169	- 2	169	67%	1 60 (0.25, 0.66)	
Thatweffe (red); hosh & Judi 2020	-2	15	9	104	8.09	1.10 (0.26, 4.75	
Terr (no < ABO) 2020	15	1205	17	1079	0.0%	0.9410.49, 1.851	
Tarr yee DABGE SLd) 2020	19	515	18	546	007	1 19 (0 82, 1 ZB)	
Tam (308) 2020		1994	êÉ.	1.134	UI Die	06 (0 56, 1 70)	
9hit (303) 2022	0	51	1	152	1.8%	0,09 (0,04, 23,90)	•
Subtain1 (95% CI)		1636	C	1/127	100.0%	1.05 (0.69, 1.61)	-
Trital events	41		47				
Henrogenetty Tau? = 1:00; OHP > 0.3	14. H= 4 (	P= 0.07	77.0=04	6			
Test to overall effect $I = 0.76$ (F = 0.							
1.44.2 Unmotched/Unputpeeded Option	HINGDOM N	Station					
Sommara 1847	7	MH4	+5	492	714	2.08 (0.86, 4.91)	
Kulik 2000	12	172	75	640	1219	1.09 (0.57, 2.03)	-
Fienavanola 2014		10	1	67.	4.0%	1 24 [0 34, 4.50]	
Prifit Prospiller) 2015	4	57	1	20	1 676	2 29 (0 27, 19 07)	
Beckmann i Judy all? 6	4	10	- 1	32	1.9%	2.56 (0.57, 17.46)	
Conres (housitan 2016	2	239	- 4	767	2.494	1.60 [0.30, # 71)	
Hauris hild (30.1 p. hpsp) 2019	3	129	55	3049	4.8%	1 25 (0.40, 1 89)	
Thir (6111 ABG, 2000 2020	15	050	201	6764	n n44	0 77 [0 46, 1 29]	
Terr (yee CAEO; 30d) 2020	27	1546	294	6647	10.0%	0.91 (0.59.1.40)	
Tam (304) 2020	36	1195	498	15711	23 11%	0162 (0.50, 1.14)	
Memalitey (30d or hospital) 2021	-240	5412	E003	183856	33.0%	1 66 (1 39, 1.76)	
Rea (30a) 2024	- 2	90	- 4	- 502	2.24	179 [0.64, 22:36]	
Yöuser 2021	5	7.35	57	2240	7.3%	1.64 [0.67, 4.05]	
Subtanul (95% CI)		7810		208205	100.0%	1.34 (1.112, 1.76)	*
Tubal evends	356		6972			0.000	
Heferogeneity, Tau <sup>a</sup> = 0.06; ChP = 15 Tent for overall effect, $Z = 2.11$ (F = 0.		û têre û	(UN); Pre-	384			
							61 nz es 1 2 1 1
Ta Hiti Jaka may america i chi*=	1.12	1 10 -1	THE R.	1980			AAE+ CANTR LOAKE AAE-SAVE HIDTEN
The state of the s	1 27 1 4	116.41	3010.0	1.24			

Figure S44 Forest plot for perioperative mortality.



**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]).



Test for subdroup differences: Chi#= 0.64, df = 1 (P = 0.4)), P = 0%

Figure S46 Forest plot for perioperative stroke.

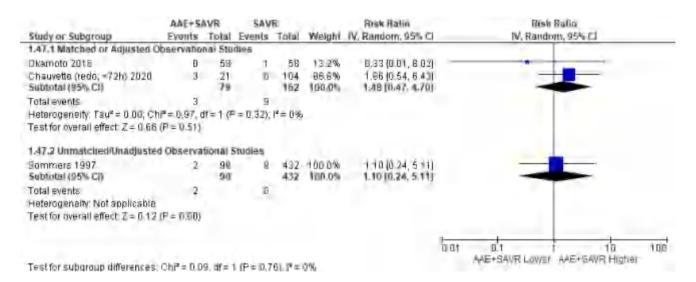


Figure S47 Forest plot for perioperative myocardial infarction.

	AAEAS	WR.	SA			RISK RAND	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	IV, Ravidom, 95%-Ci	IV, Rannom, 95-L
1.43.1 Maichen or Adjusied Closervation	nal Studies						
Okamoto (complete haart block) 2016	D.	50	2	58	1.0%	0.20 (0.01, 4 08)	· · · · · · · · · · · · · · · · · · ·
Chauvette (retto) 2020	3	25	12	104	E 59.	1 24 (0.38, 4 01)	
Fami (nd CAEG) 2020	39	909	54	809	0.0%	0 7.2 [0 49, 1 09]	
Fam lives CABG) 2020	28	525	28	525	0.0%	1.00 (0.60, 1.66)	
Tam 2020	67	1354	82	1 3 3 4	91.4%	0 62 [0 60, 1 12]	-
Bhilir 2023	0	54	9	162	11%	0 17 [0.01, 2.07]	
Sumoter (95% CI)		1467		1658	106.0%	D.RT [0.60, 1.10]	
Fonel events	70		104.				
Helerogeneity, Tau <sup>2</sup> = 8.00, Ch <sup>2</sup> = 2.46, 6	IF= X (足 = 0	46), =	= 0 My				
Test for overall effect $Z = 1.55 (P = 0.10)$							
AN 2 Unmarchedrithadjisted filmerve	mman Stud	100					
Sommers 1997	5	89	25	432	15.4%	0.00 (0.35, 2.25)	the second se
Penaranda (complete near block) 2014	π	00	3	87	3.7%	0.41 [0.02, 7.63]	
Rriffi 2015	-	35	1	20	4.2%	0.57 (0.04, 6 6.5)	
Beckmann (30d) 2016	2		14	47	10.4%	0.37 (0.09, 1.53)	
Fami (mi CABG) 2020	-44	650	439	8764	0.0%	0.96 (0.70, 1.12)	
Fam (yes CABG) 2020	30	546	344	6947	0.0%	1.11 (0.77, 1.53)	
Tâm 2020	71	1706	783	15711	23.1%	1.02(0.81, 1.29)	+
lishaffey 2021	20.7	5412	2661	183856	27.7%	2.67 [2.36, 2.99]	
dehatey (using published %) 2021	303	5482	9928	103656	0.0%	1 04 (0.9.1, 1 16)	
YOURM 2023	11	131	107	3740	19.5%	1 76 [0 97; 1 19]	+
Subrotal (95% Ch		11.35		702418	100.0%	1.10 (0.54, 2.18)	*
Total events	197		4734				
Heterogeneity: Taiv= 8.41, CmP= 63.90, Fest for overall effect: Z = 0.53 (P = 0.59)	dr=i(P⊰	ה ממחה	(), (* = 17)	8			
							1
							101 11 10 11
Fest for subarrow afferences; CL*=1.1	4. @=1 @	= 0 20)	e=126	36			wat + Sayord Literary wat + Layore + Hittory

Figure S48 Forest plot for perioperative new permanent pacemaker.

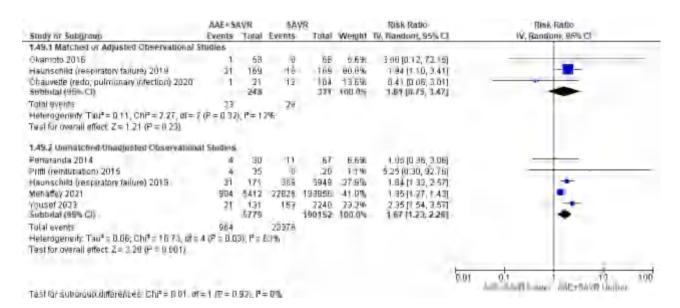


Figure S49 Forest plot for prolonged mechanical ventilation (>24 hours) or other respiratory complications.

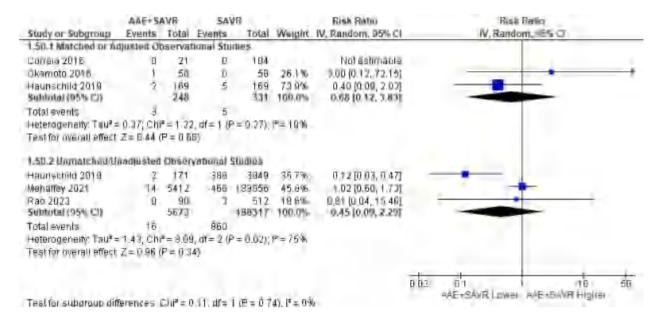


Figure S50 Forest plot for deep sternal wound infection.

	A4E+SAVB		11		SAVE			Moun Enflurgence	Moun EMPLIC SCL
Study of Subgroup	Minan	6D	Total	Meán	50	TOTAL	Weight	IV: Ramforn 15% Ct	IV, Randora 38*, 5
1.51.1 Matched of A	quasting (	Ohser	<i>intiona</i>	1.511idie	15				
Haunschild 2019	14.3	15	189	15	14.2	159	12,195	:0.78 (-3.81, 2.41)	
Shin 2022	2.31	4.46		1.89	1.26	162	86.9%	8.42 10 79, 1,63	
Subtotal (95% Lf)			223			331	100.0%	11.27 1-0.36. 1-401	
Heletogeneity, Tau*=	0.00, C	hP=0	43, 07=	= 1 (P=	0.511	P= 0%			
Test for overall effect	2=0.47	.(F = 1	0.64).						
1.51.2 Ummucred/d	nativita	d Obs	IN THE OWNER	11a) 510	otes				
Print 2015	44	14	35	1.94	22	20	27.2%	2.55 [0.95, 4 17]	
Beckmann 2016	11	9.5	i Li	11	181	52	125%	(105  -3 52, 3 53)	
Haunsphild 2019	143	15	171	18	14.8	3249	20.6%	-1.70 [-4.80, 0.60)	
MehalTey 2021	27	2.5	5412	24	-21	193356	32.6%	0.30 (0.28, 0.37)	
Submital (95% CI)			-5854			187917	100.00	1.47 [-1.04, 1.97]	
Heteropensity Tair#=	1.49.0	NP=1	0 10, 01	= 1.(P	= 0.01)	[P=71笑			
To it for overall effect	Z = 0.61	$(F^i = )$	150						
									AAE+SAVR LOWER AAE-SATE HUND
Test for Subdroup diff	lerences.	Confe	± 0.04.1	df = 1.1	F=0.0	<ol> <li>P = 0.9</li> </ol>	h.		the second second second second second

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

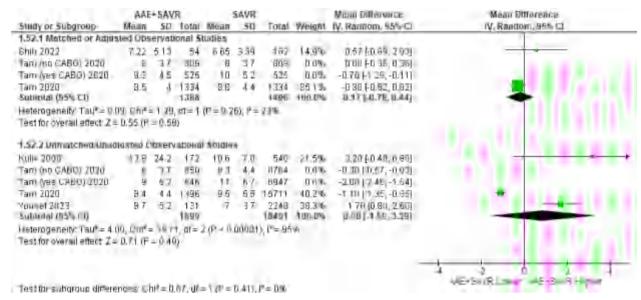


Figure S52 Forest plot for hospital length of stay (days).

	AAE-SAVR SA		AVR			Mean Difference	Mean Difference		
Study of Silborodo	Mean	-50	Tüfál	Mean	SD	Total	Weight	N. Random, 95% Ct.	IV, Random, 95% Cl
1.53.1 Mitched or Alipu	sted Dbs	<i>ervati</i>	onial St	lifles			111	and the second sec	
Okarnote 2016	25.3	9.4	58	26	04	50	75.7%	+0.70 [-4.21, 2.91)	
Chauvetle (redo) 2020 Subtotal (95%, Cl)	30.2	10.5	21	20.1	23.5	104	.24.3% 100.0%	2.10 [-4.27, 0.47] -0.07 [-3.16, 3.12]	
Hateronametty: Tau <sup>2</sup> = 0.	00; Ch7;	0.56	df= 1	(P=0.4	5) 1=	1196			
Test for overall effect, Z =									
1.53.2 Linmatched/Linux	justed (	baary	otiona	5tudie	ŝ				
kullk 2008	28.3	34	172	34.2	151	540	42:4%	-5.90   0.15, -1.46]	
Prill (up to 1 / 2015	30	12	-21	29	<b>BB</b>	10	25.1%	1.00 (-4.21, 8.21)	
Beckmann 2016 Subtotal (95% CI)	24	9	220	20	8	72 631	32.5%	4.001-7.02; 0.061	
) leterogen : ity: $Tau^{4} = 6$ Test for overall effect $Z$ =				$(\Gamma = 0.0$	6), (*=	64%			
den er en der		1	1.1						-10 -5 A A A IN

Lest for subgroup differences,  $Ch^{\mu} = 1.00$ , dl = 1.01 = 0.15),  $l^{\mu} = 52.0\%$ 

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

	AAE+SAVE			5648				Mean Rillerence	Mean Enfference		
Slady in Subgroup	Mean	30	Total	Mean	- BH	Testal.	Weight	TV, Randum, 95% CI	IV, Random, 地色 CT		
1.54.1 Matched or Adjus	ded Obs	ANY VILLA	ional 5	itutti-a		_					
Chauvette (redo) 2020 Subtotal (Mills Cl)	14.0	1,8	21	15,2	15,3	104	100.0%	-0 40 [-4.85, 4.05] 0.40 (-4.85, 4.05]			
Heterogeneity Not applie	able										
Test for overall effect Z=	018 (P	= 0 88	(B								
1.54.2 Unmatchoditinad	usted D	baer	ations	1.51401							
Kulik 2009	15.4	7.6	172	10.1	8.6	540	22.2%	-2.90 [-4.20,=1.52]			
Prifti (up to 1y) 2015	.77	0.4	31	17.5	45	19	14.0%	0 50 [-3.53, 2 53]			
Beckmann 2016	23	6	26	16	- 5	72	161%	-3.00 [-5 58, -6 42]			
R#0 2023	13.5	-5	6.1	12.0	47	468	21.14	0.60 [-0.55, 1.75]			
Rao (1y) 2023	12.6	4.6	86	13	1.8	454	0.0%	-0.40[-1.47, 0.67]			
Yousef (1y) 2023 Subtotal (95% CI)	8.8	4.5	100	9.3	-5.2	1845 2964	24.4%	0.60  -0.28, 1.49] -0.91 [-2.57, 0.75]	-		
Helerogeneily Tau* = 27	73, Ch?.	24.1	7. 01-	4 (F <sup>1</sup> ~ B	0001	), (* = 15)	3%	the particular			
Test for overall effect Z =											
									the second se		
									-10 -5 0 5 10		
Tott in algoriants differen									WEARING LIVET AND MARKED AND		

Test for subgroup differences  $C\,h^{-1} \simeq 0.04,\, di = 1 \,\,(P \simeq 0.83),\, P \simeq 0\%$ 

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

	AAE 1 SI	AVR	5AV	R		RIEK Retto	FOIBIK RUTICI
Study or Subgroup	Evenis	Tuial.	Events	Total	Weight	N, Random, 95% Cl	IV; 6 and pm, 95%-C1
1.55.1 Matched or Adjusted Observational Studie	5	_		_			
Sublatial (95% CI)		0		0		Not estimate	
Total events	0		0				
letirogeneity Not applicable							
Test for overall effect. Not applicable							
1,55,2 Unmatched/Unpdjusted Observational Stu	dies at Di	scharg	e				-
Beckmann 2016	p.	26	3	72	20.9%	n 39 (b.07, 7 73)	
Rad (mild prily, no moderate or severe) 2023	- 2	93	10	475	79 2%	1 14 [0.26, 5.13]	
Sublinial (95% CI)		105		547	100.0%	0.91 [0.24, 3.47]	
Total events	2.		13				
Hetarogeneity Tau*= 0.00 CAP= 0.42, df= 1 (P=)	0.57) P=	WD #					
Test for overall effect Z = 0.13 (P = 0.89)							
1,55,3 Unmatched/Unpdjusted Observational Stu	dies Duni	to Folio	WUp				
rousef (1y, mild-selvere) 2023	5	89	49	1786	87.4%	2.07 (D.E5 5.07)	
rousef (ity, mod-severe) 2023	0	96	114	1705	0.0%	0.69 (0.04, 11.51)	
Rea (ty, mild-moderate only, no severe) 2023	2	95	14	452	37.6%	0.76 [0.18, 3.29]	
Fao (5y, mild only, no moderate or severe) 2029	0	.93	3	91	0.0%	0 39 [0 02, 7 29]	
Subbielal (95% CI)		173		2237	100.0%	1.49 [0.59, 3.75]	-
Total events	7		63				
Helorogeneity Tau? = 0.13, ChP= 1.31, df= 1 (P=)	0.25), P=	249					
Test for overall effect $Z = 0.85$ (P = 0.39)							
						D	101 01 1 1 10 10
Test for subgroup differences, Cin#= 0.35, df= 1 (F	= 0.55).	F = 0%					ANE+SIME LUWIN ANE+SAVE HIghin

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

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

Snuey bri Sabgroup	log[Hazard/hcidutt Rate Ratio]	st	AAs=SAWA Tobal		Weight	Indiad President Path Patho N, Random, 55% C	Regional Net Ideal Bala Balth W. Randoni, 1995 Ci
1.71.1 Maiched or Adjusted Obtervalianal St					1.11		
Okamolu (4.6 y 4 2y 0 y 1 doluniuration) 2016. Robinsul (10% CI)	1 2026	1.833	58	69 54	100.0%	0.30(0.0), 7.37	
Hele openeity Not applicable Trainfor overall effect $Z = 0.74~(P=0.45)$							
1.71.2 Unmatched Unadjested Observational	Studies						
Rao ((5(14)4) (70) Summer (55% Cit	Ū	0	90	517 512		Notestimatie Net estimatio	
Heterogeneity that approable Test (or overall effect Not sportcable							
Total (#5% C)) Heterogenetity 7401 appscable			140	570	THEOS.	u zo ferua <sup>1</sup> s'931	
Test for overall effect Z = 0.74 (P = 0.46) Test for subcroun differences (vot spp14 aco							WE+BWELING WE+BWE+BR

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

Study or Subgroup	hethiaan Uncident Rate Kabo)		AAE+SEVA Total	+AVG +AVG		Hagand Top Rate Ratio 19. Raudom, 95% Cl	NATURATION AND A STREET
1.7.3.1 Motohed or Adjusted Descryot	and Sudias						
Chanicle (4.6 y 4.2 y, 1 y 1.0 HB) 2016. Submar (15% C)	-0.104	14132	50 50	45.0	18.19		
Hotenigement Notesupercable Tout for overall effect $\mathcal{I}=0.97~(\Phi=0.94)$							100 100
1.73.2 Unstalched Imma d Observ	ational Studies.						
Red (PPM, (5v KM)y 2020 Subtemil (95% Cit	-0 2744	0.6668	90	\$12 File	81 9%. Rr 9%	075 (0.21, 200) 0.75 (0.21, 200)	-
Heteropenalty not applicable Test ice overall offert Z = 0.41 (F = 0.02	7						
Total (195% Cit	·		140	070	100.05	0.71 [0.24, 2.55]	-
Followignmenty: Thut = 0.00, Chit = 0.01. This if the relation of out $\mathcal{J} = 0.471$ (F = 0.471 Test for submound (Beneficien, es., Chit = 0.	1.			-		No. Contraction	ากไทย กล่า เหมืองมีสามารถเหลืองมีการเป็นเป็นเป็นกลายเป็นกลายเป็นกลายเป็นเป็นเป็นเป็นเป็นเป็นเป็นเป็นเป็นเป็น

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

Study or Subgroup Hea	er et to-ciclaint Rato Ratio Si	AAE+EAVA Total	MAVIE Total	Weight	Huzaritämettent Plate Batte IV, Rondon, MSh-CF	Huzani Incident Run- Ratio IV, Random, 95% Cl
1.74.1 Marchea ur Alfonsteri Observational Strates			-			and the second sec
Sabiotal (85% CI)		D	D		Mot eautrinible	
Heterogeneity Nut applicable						
That for averall effect visy applicable						
174.2 Unmatched Uneigenni Chervatenai Stud	ina .					
Sacemitto (St. Juge only 1) v 5 events): 2006	-0:1401 1:071	8 26	106	0.0%	-1114-224, 1-961	
Sakamoto (j1 v 5 merks) 2006	0.2668 1.077			27.3%	0 27 1-1 81, 2 371	
Rac ((5) + M)/ 2023	-0.3448 0.657	5 90 114	517	727%	-0.3#(-+63,0.94)	
Saltimetal (95% CI)		114	689	100.05	0.18(-1.28, 0.92)	
returogeneity Taure Diau, Chire B 24, dre 1 (Pe D	101); P=0%					
Twel for overall effect Z = 0.32 (F = 0.75)						
					-	<u> </u>
						ALLISAN LONG ANCALAVALISTOT
est the subproup offerences, fulbil annucable						

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

Strucy of Samproup-	Placent Marcident Rate Ratio	SF	AAF+EAVR TOAM	SAVE Total	Winch	Hazanilischent flate Kase IV, Bandom, 1955 Ex	Hazand Incition Facto Factor PA Relations, 95% C1
1751 Marchell or Administ Obertystenal (to		-		_			
Okempile (# 8 9 % 2y, 0 v II shokes) 201F	-0.104		59	- 58	.0.5%	0.00.00.02.45426.4	
Men affec (17.3 + 7.4%, H-Fg) 2021 Summate (1995) Con	-0.0105	0.054		103056	99 79) 101 79		
Heterogenetik Tau² = 0.00, Ctr/* + 0.00, ot + 1.6 Test for menali effect 2 = 0.19 (P+ 0.85)	$^{2} = (0.9.6), 3^{4} = 0.90$						
12521 model threat under Differenting	stan						
Methattey (3, 3 y 3 4% 3+R)/ 2021 Services rists Em	0.05	0.0552		103056	100.7%	1.01(0.01.1.13)	-
Heterogeneity Not approache Test for overall effect Z = 0 16 (Pi= 0 65)							
							07 10 10 12 15
Test for subgroup differences. Čhi?=0.071.0f=	1 (P=0.710; P=09)						MEASING LOW MEASING HIGHL

## Figure S59 Forest plot for stroke during follow-up.

Study or Subgroup	Ng[Nounthincount Rate Rate]		AAE+SAVE Tidal	SAVE Total	Wooght	Hustaniime ideni Fiate Natio N, Rondom, 95% Ct	Mizaritincident Rate Rate W. Random, 95% 1
1.78.1 Marchea or Allpister Observation				1.1	1.1	a dama a la co	
Ckamata (4 6 v 4 2y, 0 v 8 twoody 2010. Settotal (95% C)	0104		50 50 58	58 58	37%	0.90 (0.82, 45.42) 0.90 (0.82, 45.42)	
Hetaloganetty Nintaccillabile							
Tast & roweral affert Z = 0.05 /F = 0.061							
1.76.7 Linmatched Unidusted Observerts	mail Shidan						
Facial meets (5) kMB 2020	-0:2178	0.09525		592	106.3%	0.00 /5:17, 1.741	
Rac imager bleeds (Ev FW) 2021 Sectional (95% Cit	-01752	0.4800	1 30 50	512 512			+
retargeneity higi uschicatule							
Test is revenal effect Z = 0.55 (F = 0.65).							
Total (55% Dy			140	570	Sources.	0.07 (0.30, 1.72)	· · · · · · · · · · · · · · · · · · ·
i-steingenetty Tau*= 0.00; Ch/*=0.00; dt	+ 1 (P + 0 56); P = 096						10 z ut - 10 z0.0
Test for overall affect: Z + 0.55 (F + 0.56)	the local states in 1994						WHAT WE SHIR LOVE AVEASAIN Higher
Fest for subarcap offerences: On®+ 0.00	0[=1 0 <sup>2</sup> =0.46], P=09						

# Figure S60 Forest plot for bleeding during follow-up.

Snury of Stagroup anglinitantmeter	und funde ferine)	68		SAVE 7 chail	Weight	N. Random, 35% Li	Hadings in Endown Harm Frank
1.77.1 Matched or Adjusted Obtervational Intellem	_						
Ohamatu (4.6 y 4 2y 0 y 1 analusratu) 2016 Subarnut (95% Cil	1.2026	1.633	46	50	11.7%		
Hele openeity Not applicable Trist for overall effect $\mathcal{I} = 0$ 74 (P = 0.45)							
1.7? 2 Unmatched Unidential Ober (rational Madam							
Sakamor (Stude only [14 5 events); 2000	1.466.2	8.974	24	194	3.0%	4 11 10 64 29 23	
Bekamieln ()1 v 5 evente) 2008	1.8727	36662	2.0	1087	1041%	1.0630-72-34.791	
Print @ 79/12 - 0 matiants(r 2014	1 CRAFE	1.5242	- 39	- 69	19.7%	2111/07/15 57:26	
Fran (Ser KMI) 2028	D T med	0.7606		E12			
Refering (35% C)			140	140	0825	1.75 (0.52, c.ot)	
Helessgensity Tau <sup>n</sup> = 0.28; Ch <sup>n</sup> = 2.46; d <sup>2</sup> + 2 (P = 0.20); P = 103 Test to overall effect Z = 0.92 (P = 0.36)							
Tube dish Co			101	747	100.cm	5,64 (0040), 4 460	-
Helenogenetik, final = 0.20, $(0.4^{\circ} - 3.48, 0.5 - 2.48) = 0.723$ (* = 0.723) (* = 14.9) Test for overall effect Z = 0.63 (* = 0.50) Test for accuracy, differences, $(0.4^{\circ} - 1.04, 0.5 - 1.47) = 0.213$ (* =							401 ALL-DAVELLINE AVENENT Hotor

Figure S61 Forest plot for endocarditis during follow-up.

# Figures S62-S63. Summaries of sensitivity analyses

			AVIT Studies		continuations flate fiallin	inageoincident Rate fiato
andy or Subgroup. log/Hazard Incident	Rate Rate)	SE	Total	Telal	IV, Random, MS-C	IV, Handom, US% CI
64.1 Primary Amilysis-Mintched Adjusted Studies	-					
I Studies	0.0791	0.041046	13	0	1.03(0.65, 1.11)	-++
64.J Motomin vs Snitows Critical Risk of East-Male	ched/Aquatio	ti Stuties (Internic	ion p-0,839			
pilerate Pisk of Elas	0.0512	0.14		0	1.05(0.00, 1.08)	
ericive/Cotical Fish of Bias	0.0798	0.0576	E.	0	1.0310.03 1 149	
					Love be shit W	
64.1 Moderate Sorrays vs Critical Risk of East-Mak	chud Adjusio	d Studies (Intervo	tion p=cobco			
pnerstelSen nus Risk of Bras	0.0298	0.0464	8	0	1.03 (0.94, 1.10)	
ritical Fick of Bian	0.0563	0.3254		0	1.0510.65.1.651	
the at the set of the set	0.000.00				Loss Speed a such	
64.4 Yes vs NR vs No Cutcomilani-Malched Adjust	led Studies I	menucion p-0.51	10,200			
es Concornitaril Procedures	0.0173	0.053	4	0	1.0210.92.1130	
R Concumitant Procedures	0.0944	0.3206	10	-0	0.0110.45.1711	
a Conconstant Procedures	D.148	0.1076		0	1.18(0.94, 1.43)	
n of a number of an ones	0.140	0.1010		v	1.10.5/34/1.434	
64.5 Primary Analysia Unimat/Jud/Unadjusted Stud	lies					
(Sudiet	0.0967	0.0041	10	0	ID:41 (0.60, 1.06)	
Constant a	Press/	in a first	14	N.	man Bren i hali	
64.0 Excluding Ray 2523-Unimatched/Unadjusted 5	Califies Hiller	COUR DOD TOTAL				
ciuding Fag 2073	-0.0948	0.0561	14	0	TO GHI SO GD. 1 OAS	
au ((5v KMh 2023)	-0.0948	0.2021	1.0	0	0.811245 1 431	
AN ITSE CHILL PARTY	0.1103	M-418-21		-0	10.01 (4.42) 1 421 4	
64.7 Moderate vs Serious/Critical Risk of Envi-Umi	ate faith the side	and the second structures	Income States and In	nus.		
nierate Firse of Eles.	-0/2085	0.1067	toking the of	0.00	minutes in a set	
				0	II R1 (0.58), 1 CO)	
ensus/Collical Frisk of Elias	0.0008	0.0423	11	0	0.49 (0.61, 1.08)	
64.8 Moderate Serious vs. Critical Risk of Bas-Dim	and a Reach of Lorenty	instant Providence and	In contract on the	E.C.N.		
					at the set of a line	
Diferats/Sensus Fish of Blas	-0.0784	0.0714	6	0	d us lo eu 1 cel	
rilical Risk of Blas	01572	10.11/83	10	-0	0.85 (0.69, 1.06)	
64.5 Yea ve MR vs No Concomitaint-Unmatched Un	distant and	the last sector in the	in the lot with			
the first state of the state of				1.1	and the second second	
es Concomitant Pinceduren	- 0.0881	0.0625	0	0	n up to st. i vy)	
R Cuncumstant Procedures	-0.2838	0.2329	2	0	0.78 (0.48 1.21)	
n Cohenhilart Procedures	-0.1133	0.1084	7	- 0	0.81 (0.65, 7.00)	
A REAL PROPERTY AND A REAL		a la construction de		and in the local sectors		
64.10 Primery Analysis-AU Studies (Prioritizing Mon					the second se	
Studies	-0.00033	0:0411	16	0	1.00 (0.92, 1.08)	
Ca ad Manhamphi (c) Classical Protocol Data in Sec. 14	Charles and	anima bereta a	design and the start	and the second second	net.	
54.11 Moderate Vis Schous Ontical Risk of Basi-All			diagonal topo			
adurate Pilair of Elion.	0.050 2	0.14	1	-0	1.05 (0.80 1.38)	
enous/Critical Risk of Blas	0.01.28	0.0485	12	0	D 99 (0 90, 1 09)	
	-	Sec.	and the second second	1.00		
64,17 Model up / Second VE Critical Risk of Euro-All						
udensta/Serious Hick of Base	0.018	0.04607		0	1.02 (0.03.1.11)	
rttical Risk of Ellars	01269	0.10472	T	-0	0.88 (0.72.1.08)	
and the second se	a state of the	in the second			Laboration Providence	
64.13 Moderate Ve Served ve Critical Risk of Bas-						
udurate Rink of Eine.	0.0512	0.14	1	0	1.05 (0.83, 1.35)	
erious Risk of Bras	0.0158	0.0565	5	0	1.02 (0.91, 1.1.2)	
nte al Risk of Blas	01269	11.111472	Ť	- 0	0.88 0.72, 7.68	
64.14 Yes vs RIR vs ha Enricomitani Ali Santins (P)	sarding Ma	cited Antostect (II	ненасван р~б	23 (p=0.1	7 end MRD	
es Concornitant Proceduras	-DID14R	0.0471	10	0	0.30 (0.90, 1.06)	
R Concomitant Procedures	0.2994	0.281	3	0	0.79 (0.50, 1.25)	
a Concombant Princeriures	0.148	0 1076	8	0	1 10 00 04 1 450	
					and the second	
						the star of the
						07 0.15 1 12

Figure S62 Sensitivity analyses for mid-term mortality.

Budy or Subarran	furt Hazon Lincident Rule Flatud	1F	AAE 15AVE Studies	Tolai		IV. Familient 05% Cl	Hazard Incident Bate Actor IV. Random: 05% Cl	
70.1 Primary Analysis-Mi		. v	1000	CUM	_	CA PRIMITING A24 PT	Dr. Partitionity of the Ca	
Studies	-0.0215	0 102	2	۵	1	0 90 (0 75, ( 27)		
70.5 Primary Analysis-Lie	imarched/Unadjusted Studies							
a Stridles	0.00764	0,1266	7	0	-	1 00 (0.05, 1.39)		
70.9 Prenary American Alt	Studies (Prioritize o Mintched) Adjuste	d when	Unmatched the dpush	ed alter	iepint	243)		
# Studies	0.0267	0 1245	7	0		rica (ciao, i 31)		
70.40 Excelling fian 202	AK Studies (Principality Matchedi Ad)	naied) (heren	deraction (r=0.05)					
voluting Rati 2015	n 0.25	0.1254	5	0	t	103 (0.90, 1.91)		
na ((Sy e10() 2021	01495	1 0912	-4	0	0.00	1256,410,471	1	
70 11 Moderato vs Serior	us Critical Risk at Blas-All Studies (Pro	milling	Marcheel-Adjusted) (in	neras	tion (p=1	175)		
luderate Frisk of Bras.	0.2799	0,7744	2	0	10.00	1 32 (0 29, 6 04)		_
ennus/Critical Risk of Blas	5 IN 11 24	01995	5		·	1 (03 (0,79, 1 34)		
70 17 Moderate Sellove	Ve Entited Rose of Bire All Studies (Pre	pointing	Mitchen/Aducated) (In	aturac	non p-6	231		
Inderate/Sumous Risk of B	ias 0	01763	4	- 0	. · · · ·	1.00 10 78, 1.28		
inflictal Frick of Blass	0.9462	0,7411	1	0	£	2,59 (0.60, 11,01)		-
70/13 Moderale ve Serve	us ye Critical Risk of Using All Studies (	Priorities	Matched/Adjusted	) Civiter	actions	(C.A.C	the second se	
foderale Risk of Bas	0.2799	07744	1	0		1 32 0.29, 6 04		_
erious Fisic of Elina	0.0014	0.1369	2	0	×	1.00 10 77, 1 61		
inflicar Free of Erias	0.0462	0.7411	1	Ū		2,59 (0,80, 11,01)		-
70/14 Yes ve full ys No C	concumitant-All Studies (Providuing Ma	Kined/A	divisited) /Interaction p	-0.41	10-0,87	Pexic M(KD)	the second se	
es Concomilant Frucedure	85 0.0052	0 1 1004	1	0		(01 076, 132)		
UR Consomitant Procedure	es 1.8782	1 3971	1	0	× .	E 54 (0.42 10) 14		
ia Concomitant Frucedure	u U.U.u73.	0.2743	1	0	F	1 04 (0.61, 1.78)	_	
							1 4 4	-
						0.2	ALE+SAVE UNAFT HEREAVE HERE	. 3

Figure S63 Sensitivity analyses for aortic valve reintervention.

# Supplemental Tables:

First author	Year	Cohort	Group		Group number, r	ו (%)	Age (year)	Male sex (%)		Body surface a	rea (m²)	Cerebro disease	ovascular e (%)	
		size ·	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or a	djusted o	observatio	nal 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/u	nadjuste	d observa	ational 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%)	$52.6 \pm 11.9^{\dagger}$		$72.7^{+}$		$1.60 \pm 0.15^{\dagger}$		_	_

Table S1 (con	tinued)																				
First author	Year	Renal fa	ailure (%)	Dialysis	(%)	Coronar disease	, ,	COPD (9	%)	Smoking	g (%)	Diabete	s (%)	Hyperte	nsion (%)	Urgent status (9	%)	Emerge Status (		Urgent/ Status (	/Emergent (%)
		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 a	ldjusted	observati	onal 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/u	unadjust	ed observ	ational studi	ies																	
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	_	_	_	_	-	_	_	_	_	_	-	-	_	-	_	-	_	-	_	_

Table S1 (contin	nued)														
First author	Year	EuroSCORE	II (%)	STS score (%)		Previous surgery (		Previous	SAVR (%)	Preoperative LVEF	(%)	Preoperative LVEF (< 35%) (%)		Preopera 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 adj	justed observ	vational 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/un	adjusted obs	ervational studie	es												
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	_	_	_	_	_	-	-	-	_	_	_	_	_	-

Table S1 (cont	tinued)												
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 a	djusted ob	servational 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/L	unadjusted	observational studies	S										
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	_	-	_	_	_	_	$8.6^{\dagger}$		$50^{\dagger}$		$33.6^{\dagger}$	

Table S1 (contin	nued)												
First suth su	No or	BAV (%)		Mechanical valve (%)		Mean implanted valve size (mm)		Concomitant valve surgery (%)		Concomitant CABG (%)		Concomitant other procedure(s) (%)	
First author	Year	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE	AAE	No AAE
Matched or ad	justed obser	vational studi	es										
Yousef	2023	-	-	$25^{\dagger}$		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 <sup>‡</sup>	23.0 <sup>‡</sup>	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/un	adjusted ob	servational stu	udies										
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	$15.3^{\dagger}$		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 <sup>†</sup>		28.9 <sup>†</sup>		0.0	0.0	$3.1^{\dagger}$	

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; <sup>†</sup>, demographic information derived from the overall cohort of the respective study; <sup>‡</sup>, 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.

Table S2 GRADE domain-specie	fic judgements	for midterm mo	ortality, aortic va	lve 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; moderate 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.

### 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.

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