



Aortic valve replacement using stented or sutureless/rapid deployment prosthesis via either full-sternotomy or a minimally invasive approach: a network meta-analysis

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Background: New technologies such as sutureless or rapid deployment prosthetic valves and access via minimally invasive incisions offer alternatives to traditional full-sternotomy aortic valve replacement (SAVR). However, a comprehensive comparison of these surgical techniques along with alternative valve prosthesis has not been completed.

Methods: Electronic databases were searched for studies comparing outcomes for SAVR, minimally invasive AVR (MiAVR), sutureless/rapid-deployment AVR (SuAVR) via full-sternotomy, or minimally invasive SuAVR (MiSuAVR) from their inception until September 2018. Early postoperative outcomes and follow-up data were included in a Bayesian network meta-analysis.

Results: Twenty-three studies with 8,718 patients were identified. Compared with standard SAVR, SuAVR had significantly lower incidence of postoperative AF [odds ratio (OR) 0.33, 95% confidence interval (CI): 0.14–0.79, $P=0.013$] and MiSuAVR greater requirement for postoperative permanent pacemaker (OR 2.27, 95% CI: 1.25–4.14, $P=0.008$). All sutureless/rapid-deployment procedures had reduced cardiopulmonary bypass and cross-clamp times, by a mean of 25.9 and 25.0 min, respectively. Hospital length of stay (LOS), but not intensive care LOS, was reduced for all groups (MiAVR –1.53 days, MiSuAVR –2.79 days, and SuAVR 3.37 days). A signal towards reduced early mortality, wound infections, and acute kidney injury was noted in both sutureless/rapid-deployment and minimally invasive techniques but did not achieve significance. Sutureless/rapid-deployment procedures had favourable survival and freedom from valve related reoperation, however follow-up times were short and demonstrated significant heterogeneity between intervention groups.

Conclusions: Minimally invasive and sutureless techniques demonstrate equivalent early postoperative outcomes to SAVR and may reduce ventilation time, hospital LOS and postoperative atrial fibrillation (POAF) burden.

Keywords: Aortic valve replacement; minimally invasive; sutureless; rapid deployment; aortic stenosis (AS); hemisternotomy; right anterior thoracotomy



Submitted Feb 16, 2020. Accepted for publication May 05, 2020.

doi: 10.21037/acs-2020-surd-17

View this article at: <http://dx.doi.org/10.21037/acs-2020-surd-17>

Introduction

Aortic stenosis (AS) remains one of the most common valvular pathologies in both the developing and Western worlds. Without intervention AS progresses inexorably and once symptoms develop the life expectancy is reduced to three years on average unless the mechanical obstruction is relieved (1).

While surgical aortic valve replacement via full-sternotomy (SAVR) has for decades been the gold standard treatment for patients with severe AS, it confers additional risks to high-risk patients, particularly for those with prior cardiac surgery, renal failure, or advanced age (2,3). Minimally invasive AVR (MiAVR) (via either an upper hemisternotomy or right anterior thoracotomy) was initially utilized primarily in low-risk surgical candidates but has more recently demonstrated excellent outcomes in higher risk cohorts (4,5). These newer surgical approaches often lead to longer operation, bypass, and cross-clamp (CC) times which may expose patients to higher postoperative risk (6,7). Sutureless and rapid deployment valve technology has more recently been developed for SAVR patients to reduce operation times and therefore complications associated with cardiopulmonary bypass (CBP) and cardioplegic arrest (8-11). Subsequently, these valves have also demonstrated excellent hemodynamic profiles when compared with traditional stented valves (12-14). While many patients and the medical community alike have expectations that minimally invasive and sutureless technology will continue to expand, limited long term data is available.

With increasing options available to surgeons, the ideal choice of approach and prosthesis has become more complex. Patient factors such as age, frailty, comorbidities and unfavourable vascular anatomy may complicate the decision for minimally invasive procedures but for the large majority of surgical candidates it is left up to individual surgeon discretion. Many individual institutions have compared either rapid deployment or minimally invasive approaches to SAVR, however no single study has yet attempted to consolidate these reports and analyze the collated short and long-term outcomes.

Here we have performed a Bayesian network meta-analysis to compare short- and long-term outcomes

following SAVR, MiAVR, sutureless AVR (SuAVR) via full-sternotomy, or minimally invasive SuAVR (MiSuAVR) in the setting of severe AS.

Methods

Search strategy and study selection

Electronic searches were performed using Medline, Cochrane central register of controlled trials, Web of Knowledge and PubMed, according to the PRIMSA statement of the conduct of systematic reviews and meta-analysis (15). The terms “aortic valve”, “aortic valve replacement”, or “SAVR” were combined with “minimally invasive”, “mini”, “hemi sternotomy”, “right thoracotomy”, “sutureless”, or “rapid deployment prosthesis” as both keywords and MeSH terms. Two reviewers (KW and MD) independently screened the title and abstract of records identified in the search. Full-text publications were subsequently reviewed separately if either reviewer considered the manuscript as potentially eligible for inclusion. The reference list of all retrieved articles was reviewed for further identification of potentially relevant studies (*Table S1*). Only studies published in English were included.

Inclusion criteria

Eligible studies were those comparing separate cohorts of patients undergoing isolated aortic valve replacement via either sternotomy or a minimally invasive surgical approach (RAT or HS), using either conventional stented bioprosthesis or a sutureless/rapid deployment bioprosthesis, and reported on short- and/or long-term outcomes. Where multiple studies reported on the same patient cohort, only the most recent publication was included.

Study endpoints

Primary endpoints were early (30-day) mortality and stroke. Secondary endpoints were new postoperative atrial fibrillation (POAF), acute kidney injury (AKI), need for permanent pacemaker (PPM), major bleeding, sternal infections, intensive care unit (ICU), length of stay

(LOS), overall hospital LOS, late mortality, and need for reoperation for valve dysfunction.

Analysis

Pooled values were reported as mean \pm standard deviation or as otherwise specified. Data transformation was completed using established statistical methods when studies presented it as either median and range (16), or median and interquartile range (IQR) (17,18). Data were summarized as standard mean difference, with overall weighted mean presented where appropriate. I^2 statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. An I^2 value of greater than 50% was considered substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. All P values were 2-sided. A significant difference was defined as $P < 0.05$.

Statistical analysis was conducted with STATA Version 16 (StataCorp. 2019. Stata Statistical Software: College Station, TX: StataCorp LLC) using a program *mvmeta* to perform Bayesian network meta-analyses using Markov chain Monte Carlo stimulation as described by White (19). The number of burn-in runs was set at 10,000 for assessing the convergence of parameter estimates. The odds ratio was used as the summary statistic with 95% confidence intervals as the measure of uncertainty. Random effects modelling was used to account for heterogeneity across studies that was not accounted for by the I^2 statistic such as different surgeons, anaesthetists, and intensive care and high dependency care protocols. *Mvmeta* generates a network diagram that allows visual assessment of the connections between the different intervention groups and which are directly or indirectly connected. The size of the nodes is correlated with the sample size of each intervention group and the thickness of the edges relates to the number of comparative studies between two interventions. For each analysis a forest plot is produced with random effects modelling examining both within and between study effects. The Rankogram is a visual representation of the SUCRA score (a measure—surface under the cumulative ranking curve—that utilises both the forest plot and league table data). The SUCRA percentage gives the probability of an interventions ranking as best for the particular variable examined, and uses probability derived from the posterior distribution of all treatments (19,20) (Table S2).

Results

A total of 1,437 publications were identified through the database and bibliographic searches. After exclusion of duplicated or irrelevant publications, a total of 23 relevant articles were included and reviewed in detail (Table S1). A total of 8,718 patients were identified across 23 patient series. There were 4,717 patients who had a full-sternotomy AVR receiving either a stented prosthesis (4,421 patients) or sutureless/rapid-deployment prosthesis (296 patients). A minimally invasive approach to AVR was performed in 4,088 patients, with 2,985 patients receiving a stented prosthesis and 1,016 patients a sutureless/rapid-deployment prosthesis. Within the minimally invasive group, 1,924 patients had a hemi-sternotomy (HS) and 1,665 patients had a right anterior thoracotomy (RAT), the rest were undefined.

Baseline characteristics

Pooled data

Mean age of patients having a full sternotomy was 70.4 ± 11.4 years, while the mean age of patients undergoing a minimally invasive procedure was 70.9 ± 11.8 years. Of the 8608 patients where sex was recorded, 42.7% were female. Patients undergoing full-sternotomy procedures were less likely to be female (41.0% vs. 44.6%, $P < 0.001$), marginally but statistically significantly younger (70.4 ± 11.4 vs. 70.9 ± 11.8 years, $P < 0.044$), and significantly more likely to have New York Heart Association (NYHA) Class III/IV symptoms [52.1% (877/1,677) vs. 43.6% (724/1,661), $P < 0.0001$] compared to minimally invasive procedures. Left ventricular ejection fraction (LVEF) was similar between the two groups [$59.0 \pm 10.4\%$ [2,433] vs. $59.1 \pm 8.8\%$ [3,460], $P < 0.69$].

Data for the type of rapid deployment valve was present in 87% of the studies examined. Overall, the Livanova Perceval valve was used most commonly (84.3% of cases), followed by the Edwards Intuity (9.9%) and finally the Medtronic 3F Enable (5.8%). Although the 3F Enable valve is no longer marketed we included it in this analysis due to the heterogenous inclusion within other studies.

Further demographic details on subgroup by type of prosthesis is shown in Table 1.

Outcomes analysis

After exclusion of non-matched studies, 6,553 patients from 23 studies were included in a Bayesian network meta-analysis of propensity-matched, postoperative outcomes (Table 2).

Table 1 Baseline patient characteristics for network meta-analysis (pooled from unmatched data)

Characteristics	I. SAVR	II. MiAVR	III. SuAVR	IV. MiSuAVR	P value					
					I vs. II	I vs. III	I vs. IV	II vs. III	II vs. IV	III vs. IV
n	4,421	2,985	296	1,016						
Age (yrs)	69.7	69.1	75	76.8	0.97	<0.001	<0.001	<0.001	<0.001	<0.001
LVEF (%)	59	59.2	56.5	58.8	0.41	0.05	0.7	0.03	0.16	0.07
Female (%)	40.9	40.5	59.1	57.6	<0.001	<0.001	<0.001	0.005	<0.001	0.64
Previous stroke (%)	7.4	5.6	16.9	2.9	0.005	<0.001	<0.001	<0.001	0.02	<0.001
Peripheral vascular disease (%)	10.0	10.6	16.1	14.9	<0.001	0.96	<0.001	0.12	0.12	0.006
Diabetes (%)	21.1	20.4	25.4	27.5	0.03	0.01	<0.001	<0.001	<0.001	0.34
Hypertension (%)	66.3	70.6	76.3	88.0	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
COPD (%)	12.6	12.0	21.4	11.6	0.003	<0.001	0.01	<0.001	<0.001	<0.001
Atrial fibrillation (%)	11.3	8.6	20.1	15.3	0.45	<0.001	<0.001	<0.001	<0.001	0.26
Renal failure (%)	6.1	2.9	1.0	19.6	<0.001	0.002	<0.001	0.2	<0.001	<0.001

COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; SAVR, full sternotomy aortic valve replacement; SuAVR, sutureless aortic valve replacement via full sternotomy; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure.

Table 2 Baseline patient characteristics for network meta-analysis (pooled from matched data)

Characteristics	I. SAVR	II. MiAVR	III. SuAVR	IV. MiSuAVR	P value					
					I vs. II	I vs. III	I vs. IV	II vs. III	II vs. IV	III vs. IV
n	2,862	2,545	274	872						
Age (yrs)	70.2	69.3	74.6	75.9	0.57	0.07	0.04	0.03	0.001	0.25
LVEF (%)	57.2	57.5	56.6	58.6	0.92	0.83	0.66	0.70	0.73	0.38
Female (%)	43.7	43.4	62.4	55.3	0.93	0.05	0.05	0.05	0.04	0.40
Previous stroke (%)	7.3	4.8	13.8	3.8	0.21	0.35	0.53	0.26	0.55	0.06
Peripheral vascular disease (%)	8.3	8.7	8.6	14.1	0.85	0.96	0.04	0.98	0.07	0.40
Diabetes (%)	19.8	18.9	24.8	33.1	0.81	0.19	0.03	0.16	0.007	0.07
Hypertension (%)	66.6	68.7	76.2	78.4	0.78	0.14	0.09	0.09	0.05	0.34
COPD (%)	12.3	11.6	17.6	12.5	0.82	0.33	0.95	0.28	0.78	0.36
Atrial fibrillation (%)	13.7	10.7	20.1	15.7	0.34	0.39	0.65	0.16	0.26	0.60
Renal failure (%)	5.8	4.0	1.1	9.5	0.30	0.17	0.29	0.08	0.12	0.03

All data is expressed as proportions rather than absolute numbers. COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; SAVR, full sternotomy aortic valve replacement; SuAVR, sutureless aortic valve replacement via full sternotomy; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure.

Table 3 Perioperative outcomes

Characteristics	SAVR	SuAVR	MiAVR	MiSuAVR
Mortality (30-day)	2.8% (54/1,940)	3.7% (5/135)	1.8% (32/1,818)	1.7% (9/529)
Stroke	2.1% (32/1,508)	1.0% (1/97)	1.8% (26/1,459)	2.9% (14/488)
Bleeding (major)	3.5% (63/1,825)	5.3% (5/94)	3.7% (65/1,748)	6.2% (33/529)
New PPM	2.7% (29/1,063)	3.6% (2/56)	2.8% (32/1,156)	7.7% (44/570)
New postoperative AF	27.9% (340/1,221)	NA	21.2% (296/1,395)	15.6% (40/256)
Acute kidney injury	3.1% (66/2,129)	4.6% (9/195)	1.6% (23/1,455)	1.1% (5/453)
Surgical site infection	2.5% (11/447)	0.0% (0/56)	2.4% (13/532)	3.0% (7/235)
CPB time (min)	102.3±59.9	77.7±58.3	108.4±39.3	80.9±23.9
CC time (min)	70.0±34.7	50.3±27.0	77.1±27.0	50.8±19.1
Ventilation time (hrs)	8.7±23.1	9.0±3.3	7.3±8.7	7.4±7.6
Intensive care unit LOS (days)	1.9±1.8	3.3±3.8	1.9±2.4	1.4±1.3
Hospital LOS (days)	8.1±5.1	12.8±6.7	7.3±5.2	6.9±4.2

CPB, cardiopulmonary bypass; CC, aortic cross-clamp; PPM, permanent pacemaker; AF, atrial fibrillation; LOS, length of stay; SAVR, full sternotomy aortic valve replacement; SuAVR, sutureless aortic valve replacement via full sternotomy; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure.

Operative details

Compared with stented valve procedures, all procedures using sutureless/rapid-deployment prosthesis had significantly shorter CPB and CC times, while choice of surgical access appeared to have no effect on overall CPB or CC times (Tables 3,4 and Figures S1,S2). When comparing all procedures simultaneously SuAVR followed by MiSuAVR were ranked as most superior in terms of CPB and CC times.

Postoperative outcomes

Network meta-analysis demonstrated no significant difference in early mortality, stroke, major bleeding, AKI, surgical site complications and ICU stay between the different surgical groups. Bayesian Markov chain Monte Carlo modelling demonstrated that SuAVR had the most favorable outcomes of all AVR techniques, other than for cerebrovascular events (Figures S1,S2).

Postoperative AF was less frequent after minimally invasive surgery with either a sutureless/rapid-deployment or stented prosthesis (15.6% and 21.2%, respectively) compared to conventional full sternotomy stented AVR (27.9%). While the incidence of new complete heart block

or bradyarrhythmia requiring pacemaker insertion was significantly higher for sutureless/rapid-deployment valves (3.6% and 7.7%; SuAVR and MiSuAVR respectively) compared to stented valves (2.7% and 2.8%; AVR and MiAVR respectively). However, there was no significant difference between surgical approach within each group.

Postoperative ventilation time trended lower for all procedures compared with SAVR, however only the sutureless/rapid-deployment alternatives demonstrated a significant difference (SuAVR -2.5 hrs and MiSuAVR -3.4 hrs). Similarly, hospital LOS was significantly shorter for all surgical groups other than SAVR, however inconsistency modelling demonstrated significant heterogeneity within study groups.

Further information about peri-procedural outcomes is detailed in Tables 3,4 and Figures 1-3.

Follow-up

Late mortality

Data on mortality greater than one year following surgery was available for 1,859 patients, of which 384 had a full sternotomy (328 stented, 56 sutureless/rapid-deployment) with a mean follow-up time of 45.6 months, and 1,485 had a minimally invasive procedure (703 stented, 782 sutureless/rapid-deployment) with a mean follow-up time of 29.1 months.

Table 4 Bayesian network meta-analysis outcomes based on a consistency model using SAVR as a baseline comparator

Variable	MiAVR	MiSuAVR	SuAVR	Test for inconsistency
Mortality	0.73 (0.46–1.13), P=0.16	0.64 (0.3–1.38), P=0.25	1.49 (0.28–1.62), P=0.37	P=0.41
Stroke	0.78 (0.49–1.25), P=0.30	1.05 (0.51–2.18), P=0.89	1.4 (0.52–3.86), P=0.50	P=0.50
Bleeding	1.17 (0.79–1.77), P=0.42	1.22 (0.67–2.23), P=0.52	0.59 (0.22–1.57), P=0.29	P=0.18
AKI	0.98 (0.42–2.27), P=0.96	1.01 (0.36–2.86), P=0.98	0.82 (0.22–2.97), P=0.76	P=0.45
POAF	0.82 (0.58–1.15), P=0.25	0.61 (0.32–1.15), P=0.13	0.33 (0.14–0.79), P=0.013	–
PPM	1.05 (0.63–1.75), P=0.86	2.27 (1.25–4.14), P=0.008	0.70 (0.12–4.06), P=0.69	–
Infection	0.62 (0.29–1.34), P=0.22	0.56 (0.18–1.8), P=0.33	0.63 (0.13–3.00), P=0.56	P=0.97
CPB (min)	6.7 (–2.0–15.5), P=0.13	–24.2 (–35.1–13.4), P<0.001	–27.6 (–41.8–13.3), P<0.001	P=0.67
X-clamp (min)	5.2 (–1.1–11.5), P=0.11	–23.9 (–31.8–16.0), P<0.001	–26.1 (–36.1–16.1), P<0.001	P=0.96
Vent (hrs)	–0.91 (–2.06–0.23), P=0.12	–3.43 (–5.47–1.38), P=0.001	–2.49 (–5.14–0.17), P=0.07	–
ICU LOS (days)	–0.10 (–0.45–0.26), P=0.60	–0.27 (–0.80–0.27), P=0.33	–0.35 (–1.30–0.59), P=0.46	P=0.38
Hospital LOS (days)	–1.53 (–2.85–0.21), P=0.02	–2.79 (–4.81–0.78), P=0.007	–3.37 (–5.81–0.94), P=0.007	P=0.04

Results are shown as odds ratio (95% confidence interval) for dichotomous variables and mean difference (95% CI) for continuous variables. AKI, acute kidney injury; X-clamp, cross-clamp time; CPB, cardiopulmonary bypass time; ICU, intensive care unit; LOS, length of stay; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure; POAF, postoperative atrial fibrillation; PPM, permanent pacemaker; SuAVR, sutureless aortic valve replacement via full sternotomy; Vent, ventilation time.

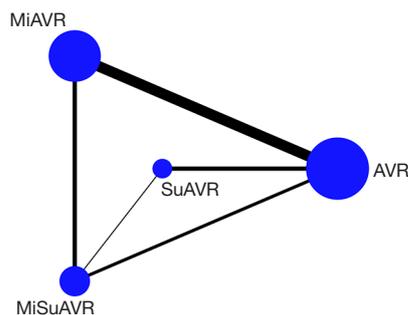


Figure 1 Network map for AVR by surgical approach and prosthesis examining postoperative outcomes. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

There were 49 late deaths (12.8%) in the full-sternotomy group and 67 (4.5%) in the minimally invasive cohort. When comparing late mortality in the network meta-analysis MiSuAVR demonstrated superiority, however there was significant heterogeneity (OR 0.26, 95% CI: 0.13–0.54, P<0.001).

Reoperation for valve dysfunction

Only four studies reported outcomes for reoperation. These studies compared sutureless versus stented valves in minimally invasive procedures (MiSuAVR *vs.* MiAVR), over a mean follow-up time of 27.5±19.0 months (MiSuAVR 13.3±14.1 months, MiAVR 42.0±17.2 months). There were 15 reoperations (2.7%) in patients who had a stented prosthesis via minimal access surgery and 5 reoperations (0.9%) in those with a sutureless/rapid-deployment prosthesis. Bayesian network meta-analysis demonstrated that sutureless prosthesis had lower overall reoperation, however there was only borderline statistical significance, and significant heterogeneity (OR 0.27, 95% CI: 0.07–1.00, P=0.05) (Tables 5,6 and Figure 4).

Discussion

The results of our network meta-analysis on propensity-matched patients show that there is no significant difference in early mortality, stroke, major bleeding, AKI, and surgical site infection for minimally invasive and sutureless/rapid-deployment aortic valve prosthesis compared to traditional full-SAVR. While patients who

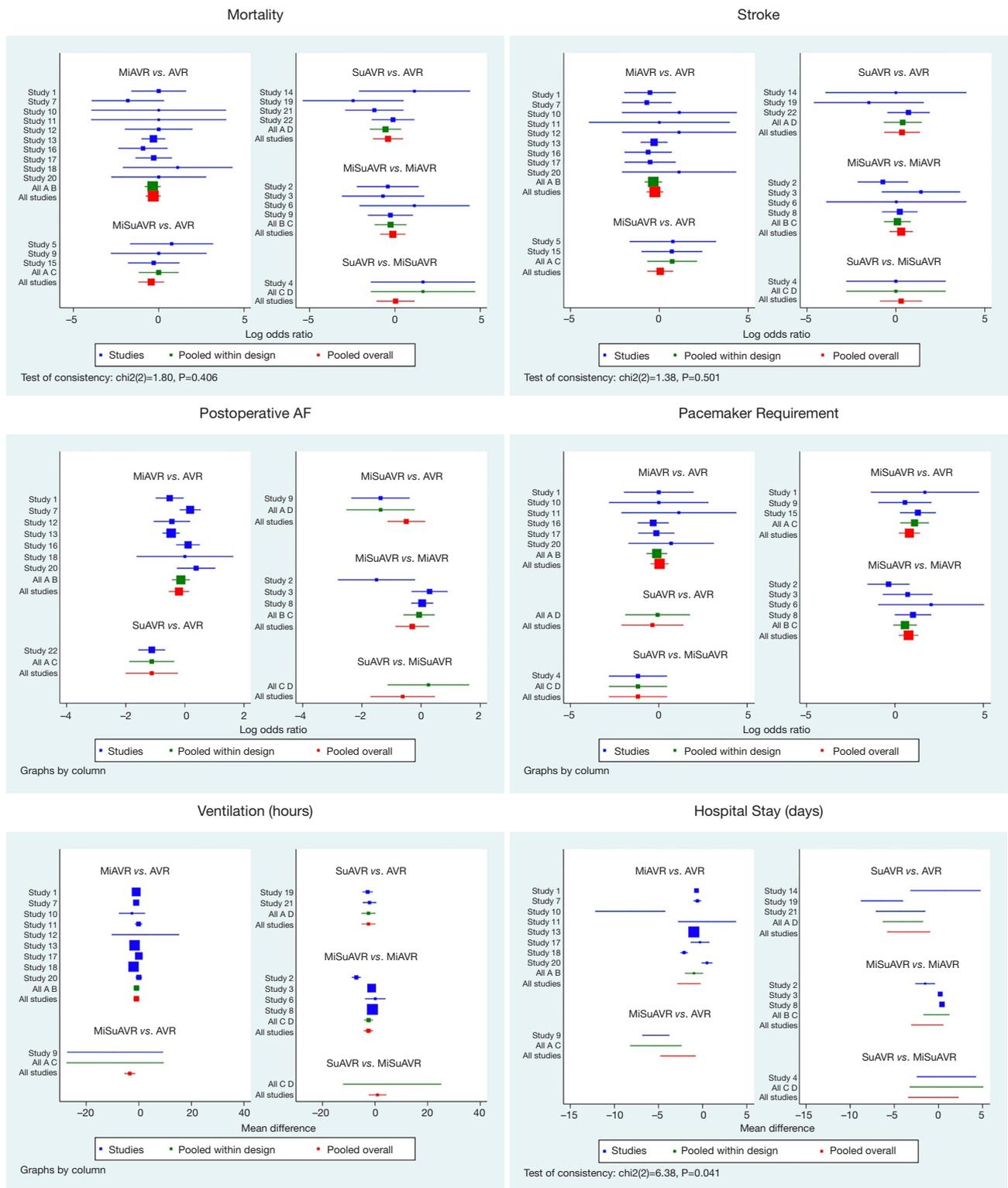


Figure 2 Forest plots for AVR by surgical approach and prosthesis examining postoperative outcomes. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

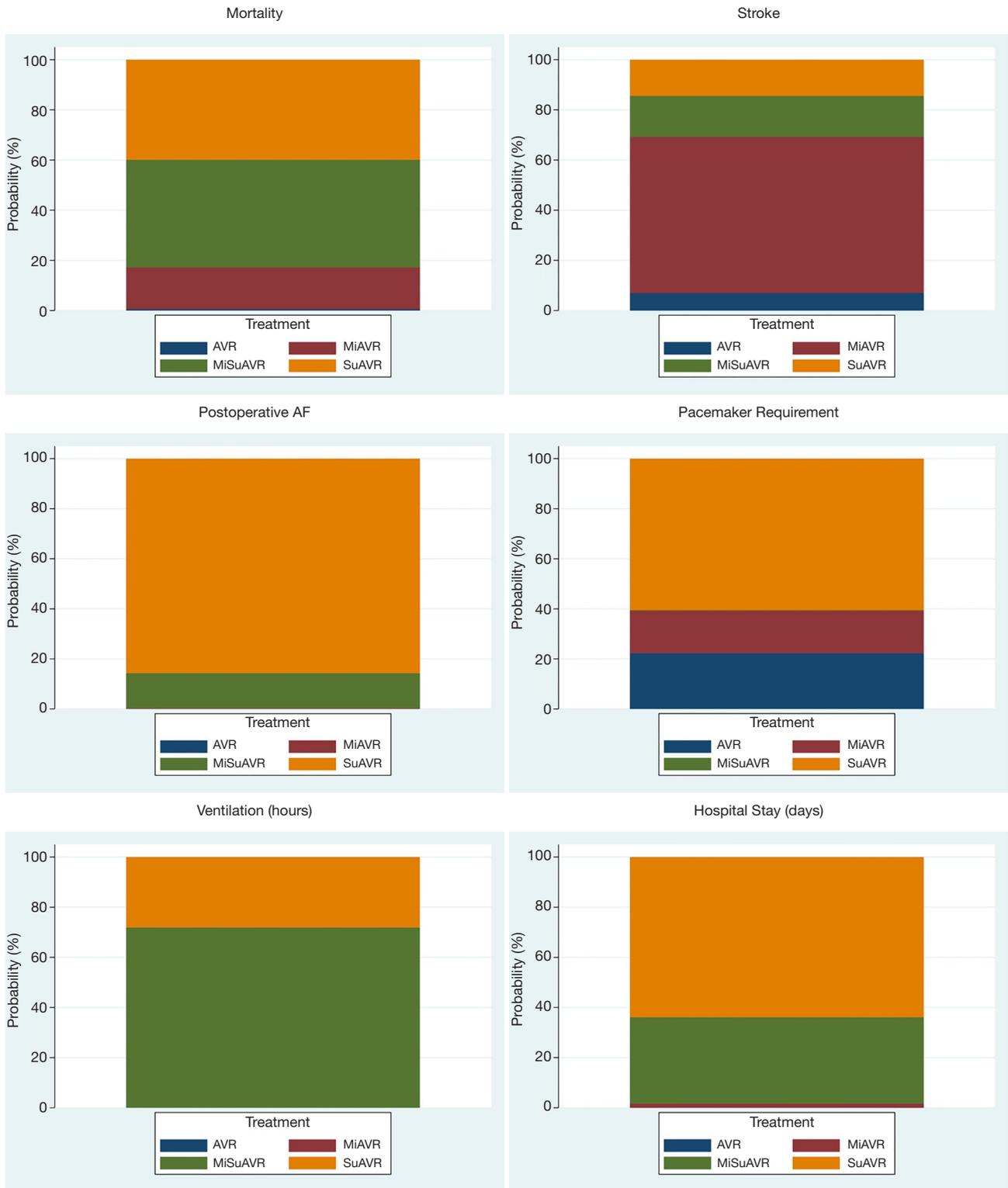


Figure 3 Rankograms for AVR by surgical approach and prosthesis examining postoperative outcomes. For example, if suAVR accounts for 40% of the rankogram, then it has a 40% probability of being the best-ranked treatment option for that particular outcome. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

Table 5 Patient outcomes at follow-up

Variable	SAVR	SuAVR	MiAVR	MiSuAVR
Follow-up (months)	51.3±19.3	16.7±20.9	44.9±17.1	13.3±11.5
Mortality (late) (n)	13.4% (44/328)	8.9% (5/56)	5.4% (38/703)	3.7% (29/782)
Valve related reoperation	NA	NA	2.7% (15/546)	0.9% (5/555)
Structural valve deteriorate			0.9% (5/546)	0
Infective endocarditis			0.9% (5/546)	0.4% (2/555)
Unknown			0.9% (5/546)	0.5% (3/555)

SAVR, full sternotomy aortic valve replacement; SuAVR, sutureless aortic valve replacement via full sternotomy; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure; NA, no data available.

Table 6 Bayesian network meta-analysis late outcomes based on a consistency model using SAVR as a baseline comparator

Variable	MiAVR	MiSuAVR	SuAVR	Test for inconsistency
Mortality	0.59 (0.25–1.38), P=0.22	0.26 (0.13–0.54), P<0.001	0.46 (0.07–2.89), P=0.41	–
Reoperation*	*	0.27 (0.07–1.00), P=0.05	–	–

Results are shown as odds ratio (95% confidence interval). *Reoperation used MiAVR as the baseline comparator.

receive sutureless/rapid-deployment prosthesis have significantly shorter CBP and CC times. Although the 3F Enable valve is no longer marketed, it was used in only 5.8% of all procedures in this analysis, and its inclusion would be unlikely to alter the findings reported here. These results are important for the modern cardiac surgeon as there is increasing demand from patients and the medical community for minimally invasive surgical approaches, particularly as these have demonstrated reductions in pain and cosmesis (21–23), while still being able to provide the same peri-operative and short term results of SAVR (24–27). As treatment options increase along with patient complexity, the incorporation of a heart team into the decision making model regarding patients' suitability for surgery will help identify the most appropriate procedure on a case-by-case basis (28).

Although our analysis demonstrated no significant difference in sternal wound complications, ranked modelling (based on the probability of the posterior distribution) suggested that minimally invasive and sutureless/rapid-deployment procedures were favored compared to traditional SAVR. Deep sternal wound infection remains a significant contributor to overall morbidity and mortality after cardiac surgery. Strategies to reduce surgical site infection may include reductions, CBP times and soft tissue

handling (29–32) which are inherent to minimally invasive and sutureless/rapid-deployment techniques. Furthermore, the use of a right anterior thoracotomy approach for SAVR, as was used in a third of the patients included in this analysis, significantly alters the profile of postoperative wound infection.

The incidence of new complete heart block or requirement for PPM was 2.8% and 7.7% for minimal access procedures (stented and sutureless/rapid-deployment, respectively), and 2.7% and 3.6% for full sternotomy procedures (stented and sutureless/rapid-deployment, respectively). This higher incidence of PPM requirement after sutureless/rapid-deployment valves is in keeping with the published literature with of PPM rates after stented AVR that are considerably lower (2.0–3.6%) than those using sutureless/rapid-deployment prosthesis (2.3% to 17%) including studies examining matched high-risk patients to TAVI (12,33–36). Large registry data has demonstrated increased all-cause long-term mortality in patients requiring PPM after SAVR and this decreased survival is also apparent in non-surgical valve replacement groups such as TAVI patients (37) thus highlighting the importance of this postoperative issue. It is worthwhile noting that recently there have been several large publications noting far lower PPM rates after sutureless/rapid-deployment prosthesis

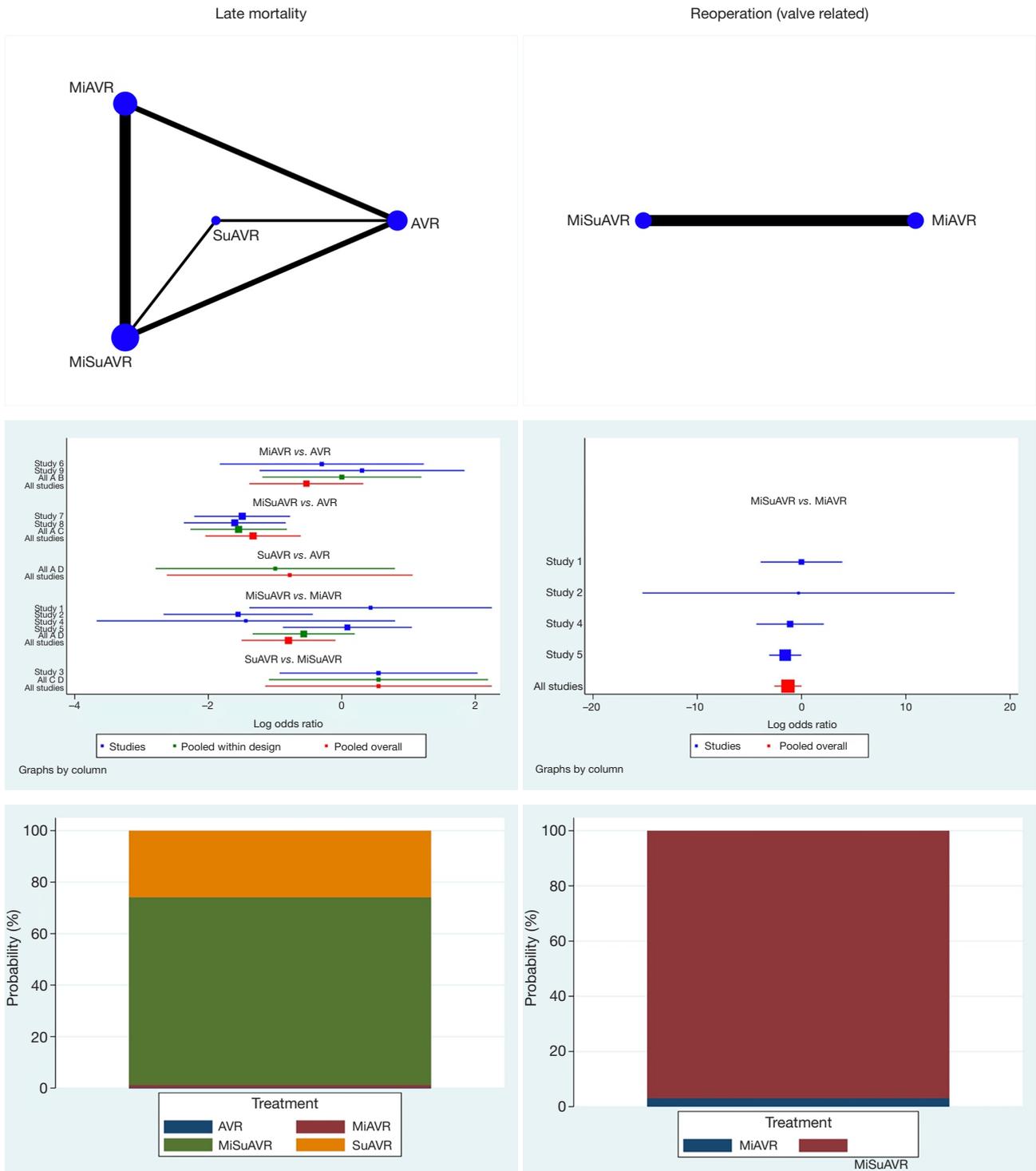


Figure 4 Network map, forest plot and rankogram for AVR by surgical approach and prosthesis examining late postoperative outcomes. For example, if suAVR accounts for 40% of the rankogram, then it has a 40% probability of being the best-ranked treatment option for that particular outcome. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

(38,39). This may be due to a greater focus on procedural modifications that reduce the incidence of conduction system injury or improved patient selection.

Sutureless/rapid-deployment prostheses rely on radial force, and often subannular components to retain the prosthetic valve in its deployed position. Reducing the subannular portion of the valve that is inserted by modifying the deployment height or by using an alternative prosthesis (with anatomical variants such as a short membranous septum) significantly reduces postoperative pacemaker requirement (40-42). Over 90% of the sutureless valves inserted in this analysis were of the self-expanding variety (Perceval or 3F Enable). Self-expanding prostheses have been shown to have significantly higher rates of postoperative conduction disturbance compared to balloon-expanded prostheses, and this is true for both surgical as well as the transcatheter literature (40,43). Finally, avoiding the use of sutureless prostheses in patients with other non-modifiable risk factors for postoperative pacemakers, such as older age and presence of pre-operative conduction abnormalities (particularly right bundle branch block), are further important considerations in the workup of any surgical candidate for aortic valve replacement.

Rates of postoperative AF (POAF) were significantly higher in full sternotomy AVR (27.9%) compared to any minimally invasive procedure (21.2% and 15.6% for stented and sutureless, respectively). The causes for POAF are multifactorial, however the systemic inflammatory response from CPB and cold ischaemia time have all been causally linked to its development in surgical AVR (44,45). POAF is linked to significant increases in hospital LOS (46), and patients who do not revert to sinus rhythm have increased risk of stroke and long-term mortality. Studies examining links between CPB and CC times in MiAVR cohorts have shown trends towards lower rates of POAF (27,47). This trend is amplified with the use of a sutureless valve via a minimally invasive incision, which further reduces CPB and CC times as well as POAF rates (5,48). Our analysis confirmed these trends, with all procedures utilizing sutureless bioprosthesis having significantly shorter CPB and CC times. The trend for worse postoperative outcomes with longer CPB times has again been demonstrated in a recent review of low-risk patients undergoing cardiac surgery (11). The reductions in CPB and CC times offer further benefits in the case of complex or multi-valve cases when operation times are expected to be long and a full sternotomy is required, or for building on benefits provided by minimally invasive surgical approaches.

The avoidance of sternotomy is important in elderly and high-risk cohorts where recovery can be significantly impaired by postoperative pain potentially leading to respiratory compromise. In our analysis, minimally invasive procedures demonstrated reduced mechanical ventilation time and overall hospital LOS compared to full sternotomy. Reduced postoperative pain and opiate analgesia requirements may contribute to decreased ventilatory support requirements (23,48). A reduction in long term survival has also been associated with prolonged postoperative mechanical ventilation time (26).

Although absolute values for late mortality were higher in full sternotomy procedures compared to minimally invasive procedures (12.8% and 4.5%, respectively) there was large heterogeneity between the groups and the results should be examined with this consideration in mind. Although studies were propensity-matched there is likely a residual effect of patient selection that particularly confounds this outcome. This was similar to the results for late valve reoperation where sutureless valves (via minimal access) demonstrated lower raw rates of late valve-related reoperations (0.9% and 2.7%, respectively). Furthermore, a third of valve-related reoperations were for infective endocarditis which is unlikely to be related to prosthesis choice at the primary operation. Variability in follow-up time and in unpublished variables are other considerations that confound these late outcomes. Limited long-term data is available for sutureless valve performance and our result may provide some reassurance that new valve technologies are at least as robust as traditional valves at mid-term follow-up. Larger studies with long-term follow-up are required to accurately answer any questions regarding long-term safety and reliability of these new prostheses. With the recent expansion of transcatheter aortic valve replacement to lower risk patients the ongoing refinements of minimally invasive aortic valve surgery, and progress in device technology have improved the range of therapeutic options available to surgeons and patients alike, overcoming some of the shortcomings of aortic valve replacement via a full sternotomy.

Limitations

Limitations of this study include the retrospective nature of the included studies, meaning that selection bias cannot be excluded. Including only propensity-matched data into the analysis reduces this risk, however as the data was collected retrospectively and is based on administrative data the effect of unregistered covariates on the clinical

outcomes cannot be accounted for. The lack of complete data on the type of sutureless or stented valve implanted also means that effect modifiers or confounding factors cannot be excluded from outcome analysis. Furthermore, as this paper relies on published case series this only reflects a small percentage of patients who develop postoperative AF, and these studies are likely from large volume or academic centres. Patient level data was not accessed for this study from each published series and this may reveal significant heterogeneity not currently evident. These issues could be addressed by accessing patient level data from each study or from registries that includes individual patient data for more detailed meta-analysis of outcomes.

Conclusions

The use of either a minimally invasive approach and/or sutureless/rapid-deployment prostheses confers equivalent very-low early mortality and stroke risk compared to AVR via full sternotomy, with a reduction in postoperative ventilation time, hospital stay and postoperative AF. When comparing all procedures SuAVR followed by MiSuAVR were associated with the greatest reductions in CBP and CC times. This reduction in perioperative morbidity requires further large, prospective trials in order to more clearly delineate which surgical approach and prosthesis choice is the most optimal for any individual patient, while also ensuring adequate long-term durability of these approaches to patients with aortic valve disease.

Expert opinion: sutureless/rapid deployment prostheses use: what are the doubts we still have?

Giuseppe Santarpino

Already from the first studies published in 2011, the sutureless/rapid deployment prostheses have been greeted with skepticism; and some weaknesses have been underlined. The presented meta-analysis highlights the strengths of these devices, but it is necessary to “work” on the potential weak points in order to further extend the use of these prostheses.

First, the minimally invasive sutureless/rapid deployment aortic valve replacement is associated with higher risk for a postoperative permanent pacemaker. This incidence is well known and published for both prosthetic models (49) but, at the same time—it should be emphasized—tips and

tricks (50) have been published to reduce this risk; and some papers have demonstrated a drastic improvement in this phenomenon over time (51).

Moreover, other studies highlight that the sutureless prostheses are associated with a higher risk of thrombocytopenia (52). In our opinion, these articles need some considerations for an “overall and integrated” choice of the prosthetic model to be used. The first consideration is that the recorded transient thrombocytopenia has no clinical impact. Conversely, the use of the sutureless prosthesis allows the implantation of a size—and therefore a better hemodynamic duration over time—significantly higher than that implantable with other prosthetic models. Therefore, there is a transitory and clinically irrelevant “disadvantage” versus a significant long-term “advantage” in hemodynamics (= patient’s quality of life).

We instead believe that we could reason on how to associate the advantages of this prosthesis (e.g., stentless profile, ease to implant) with “saving” techniques on the platelets; in other words, making the sutureless procedure “totally minimally invasive” and not only due to a “small surgical incision” (e.g., association with minimally invasive extracorporeal circulation).

Expert opinion: aortic valve replacement surgery: re-thinking clinical endpoints to further improve patient outcomes

Paolo Berretta, Marco Di Eusanio

In the recent years, the treatment of aortic valve disease has been increasingly focused towards developing and popularizing less invasive procedures. By facilitating and shortening the valve implantation process, the sutureless and rapid deployment (SURD) valves have significantly contributed to simplify and promote minimally invasive approaches (53,54). As confirmed in the present meta-analysis, minimally invasive aortic valve replacement (MI-AVR) and SURD valves have described to be associated with equivalent very low mortality and stroke risk compared to conventional AVR. These well-established excellent results raise the question of how we can further improve AVR surgery. In this respect, secondary clinical endpoints such as the incidence of minor postoperative complications, reduced trauma, rapid recovery, quality of life and cosmesis should become key elements to evaluate the results of valve interventions. Multiple studies have demonstrated that MI-AVR provides superior outcomes

in terms of reduction of postoperative complication rates and transfusion requirements, decreased length of postoperative stay, and patient satisfaction (55). In the present meta-analysis, Woldendorp *et al.* revealed that the use of either a less invasive approach and/or SURD valves is associated with reduced perioperative morbidity and faster recovery compared to conventional AVR. Patients receiving MI-AVR and/or SURD-AVR experienced a significantly lower incidence of postoperative atrial fibrillation, shorter ventilation time and reduced hospital stay. These findings confirm that less invasive approaches and SURD valves should represent essential tools in the field of modern valve surgery, and the implementation of such techniques and technologies should be considered a fundamental step to further improve patient clinical outcomes.

Expert opinion: minimally invasive and sutureless: the way to go

Bart Meuris

Surgeons and complex analyses of large data sets haven't always been a great marriage, but look...times they are a changing. In the midst of a worldwide rush towards transcatheter treatment for aortic valve disease, Woldendorp *et al.* provide excellent data on several currently existing options for surgical aortic valve replacement (SAVR). Guided by experts in minimally invasive techniques, they performed a meta-analysis gathering data from almost 9,000 patients. It is clear that both minimally invasive aortic valve surgery (MiAVR), as well as the use of sutureless valves (SuAVR), provide patients with a safe, stable and reproducible result. Looking at hard and relevant outcomes such as early mortality and postoperative stroke, the figures look far better than was obtained in the surgical arms of recent randomized trials (56). Combining both techniques (MiSuAVR) probably brings together the best of two worlds, although the volume in patients isn't there yet to demonstrate this clearly. We all should take these excellent outcomes in mind before referring all patients with aortic stenosis towards some kind of percutaneous therapy (TAVR).

Concerning sutureless valves specifically, the significantly lower rate of postoperative atrial fibrillation (AF) is important, since this will lower the overall risk of major thrombo-embolic events in the whole postoperative phase. This finding on AF has been confirmed by the results of

the PERSIST-AVR trial (data shared at the latest (online) AATS meeting). The reduced cardio-pulmonary bypass and cross-clamp times (>25 min of reduction) are important for our—increasingly older and sicker—patients, and these shorter times have many positive side-effects: less injury, less inflammation, reduced hospital stay, less wound infections, less acute kidney injury, lower ventilation times and—most relevant to all—early mortality are all reduced, but some outcomes need even larger data sets to obtain statistical significance. The issue of higher pacemaker need in sutureless valves will disappear due to better knowledge about sizing and positioning of these prostheses. And last but not least, the long-term follow is coming. We have been using sutureless valves since 2007 and the number of patients with more than a decade of follow up is growing.

Sutureless valves offer speed and safety. Clinical relevance is already there, statistical significance will be obtained in the near future. In combination with minimal access, this is the way to go.

Expert opinion: minimally invasive sutureless aortic valve replacement: on the right track

Alfredo Giuseppe Cerillo, Pierluigi Stefano, Niccolò Marchionni

The meta-analysis of Woldendorp and colleagues, based on twenty-three papers and almost 9,000 patients, demonstrates excellent outcomes and a reduced incidence of postoperative atrial fibrillation in patients receiving sutureless or rapid deployment (SURD) valves. It also suggests a benefit in terms of late mortality and freedom from valve dysfunction. Still, it fails to show significant advantages in terms of hard outcomes (mortality, disease free survival) over conventional full sternotomy aortic valve replacement.

This issue is not new: despite the fact that minimally invasive sutureless aortic valve replacement (MiSuAVR) offers improved haemodynamics and reduced surgical trauma, a definitive evidence of its superiority over conventional AVR is lacking—and this is somewhat frustrating, especially if compared with the tremendous success of transcatheter aortic valve replacement (TAVR).

Diversely from ten years ago, several therapeutic options can now be offered to patients with aortic valve disease, each having specific advantages and drawbacks. SURD valves share some advantageous features with both sutured aortic bioprostheses and transcatheter heart valves (THV). However, they also share with THV's some important

drawbacks. Being “valved stents”, their sealing relies on oversizing, and their function may be heavily dependent upon the final stent geometry. For this reason, it is logical to assume that the SURD valves may be less effective when implanted in a suboptimal anatomy, and that this could jeopardize the obvious advantages offered by MiSuAVR.

MiSuAVR might be the best alternative to TAVR for many patients with a complex anatomy (small aortic annulus, bulky annular/left ventricular outflow tract calcifications, calcific aortic root, bicuspid aortic valves, low origin of the coronary arteries, valve-in-valve in bad targets). However, it can also expose patients to specific complications. As for TAVR, only a detailed pre-operative knowledge of the patients’ anatomy can help to select the optimal candidates for MiSuAVR, and to choose the best surgical access and prosthesis size and brand for any given patient. We believe that selecting the right procedure for each individual patient according to the anatomy on cardiac CT should become mandatory: an anatomy-based approach could help to define the role of MiSuAVR compared to other treatment strategies. Large, prospective trials are needed to investigate the potential of SURD valves in specific patient subsets.

Expert opinion: sutureless valves and smaller incisions: the paradox of choice

Jacqueline K. Olive, Tom C. Nguyen

Today’s cardiac surgeons have a wide range of therapies for severe aortic stenosis, including traditional full sternotomy aortic valve replacement (SAVR), minimally-invasive aortic valve replacement (MiAVR), sutureless/rapid-deployment AVR (SuAVR) via full-sternotomy, or minimally-invasive SuAVR (MiSuAVR). In a meta-analysis with over 8,700 patients, the investigators found that sutureless and minimally-invasive techniques demonstrate similar early survival outcomes and complication rates to SAVR, with added potential for decreased cardiopulmonary bypass, aortic cross-clamping, ventilation, and hospital length-of-stay durations.

Notably, these pooled data demonstrate the newer relative success of SuAVR. Numerous studies already support the greater adoption of MiAVR, which may be associated with better outcomes than SAVR when cumulatively accounting for mortality, adverse events, and hospital costs (23-25). This study interestingly reports that SuAVR elicits nearly equivalent outcomes to MiAVR,

including 30-day mortality (3.7% *vs.* 1.8%), stroke (1.0% *vs.* 1.8%), major bleeding (5.3% *vs.* 3.7%), and late mortality (8.9% *vs.* 5.4%). Although the SuAVR cohort was small with a short follow-up period, nonetheless SuAVR, MiAVR and MiSuAVR can be considered as viable options after careful patient selection by an expert heart team.

The authors also reported that SuAVR may be most effective at reducing rates of postoperative atrial fibrillation (POAF), yet MiSuAVR actually resulted in a greater postoperative pacemaker requirement. As previously suggested, minimally-invasive surgery has demonstrated a decreased burden of POAF compared to SAVR. It is prudent not to exchange one morbidity for another by pushing for innovation in place of the standard of care or other vetted alternatives.

In summary, this study provides excellent much-needed analysis as AVR treatment options expand along with patient complexity. Individual patient selection remains critical given the significant heterogeneity between intervention groups, thus, the paradox of choice. Time will hopefully reveal critical late outcomes benefits for sutureless, minimally-invasive, and combined approaches.

Expert opinion: sutureless/rapid deployment valve foster a new era in tailored approach to aortic valve replacement

Marco Solinas, Giacomo Bianchi

In this issue of *Annals of Cardiothoracic Surgery*, Woldendorp *et al.* performed an elegant Bayesian network meta-analysis to compare the outcomes of the different surgical and valve approaches [sutureless/rapid deployment (RD) *vs.* stented] in aortic valve replacement (AVR).

The authors outline a reduction in the use of sutureless/RD valves in the sternotomy approach (6.2%), while in the minimally invasive surgery group these represent a quarter (24.8%) of the prostheses.

The use of sutureless/RD valves in a conventional approach represent the best choice in terms of reduction of post-operative atrial fibrillation, lower incidence of pacemaker implantation, acute renal failure and bleeding events, reduction of cardiopulmonary bypass and cross clamp time, intensive care and total hospital stay. On the other hand, sutureless/RD valves in a minimally-invasive approach represent the best option in terms of reduced mortality, surgical site complications, same as the aforementioned group, and are the best option in terms

of shorter mechanical ventilation time. It is important to stress the concept of pacemaker incidence in the sutureless/RD group (sutureless being 84.3% of the total), which can be determined by the very nature of self-expanding valves and an initial tendency to oversizing, as well as the implantation of these valves in patients with pre-existing conduction defects. In conclusion, this meta-analysis throws an important light on the patient selection characteristics, with the advantages of sutureless/RD valve substitutes and also that the minimally-invasive approach, which itself has a learning curve, should be used in Centers with extensive experience with a mentoring program in order not to blunt the advantages that strongly emerge from the literature and this article.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Woldendorp K, Doyle MP, Bannon PG, Misfeld M, Yan TD, Santarpino G, Berretta P, Di Eusano M, Meuris B, Cerillo AG, Stefano P, Marchionni N, Olive JK, Nguyen TC, Solinas M, Bianchi G. Aortic valve replacement using stented or sutureless/rapid deployment prosthesis via either full-sternotomy or a minimally invasive approach: a network meta-analysis. *Ann Cardiothorac Surg* 2020;9(5):347-363. doi: 10.21037/acs-2020-surd-17

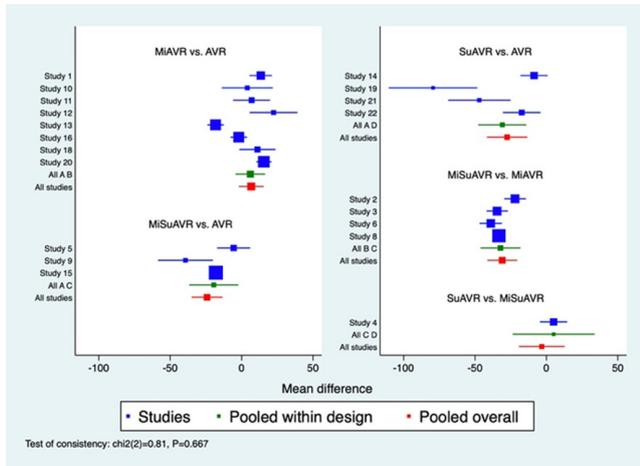
Search strategy

((((AVR) OR aortic valve replacement) OR SAVR)) AND (((((minimally-invasive) OR mini) OR hemi sternotomy) OR right thoracotomy) OR sutureless) OR rapid deployment prosthesis).

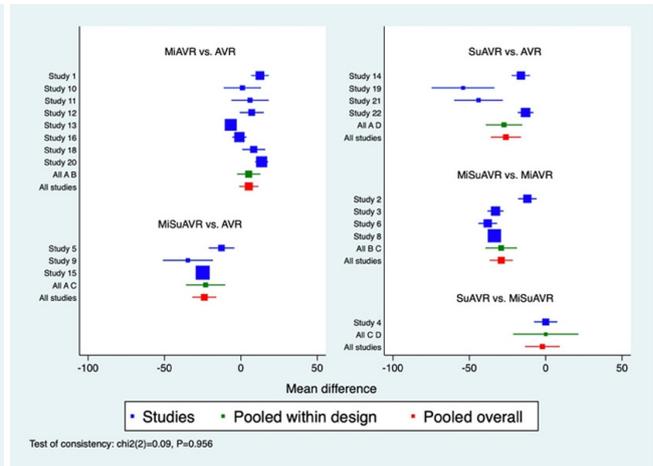
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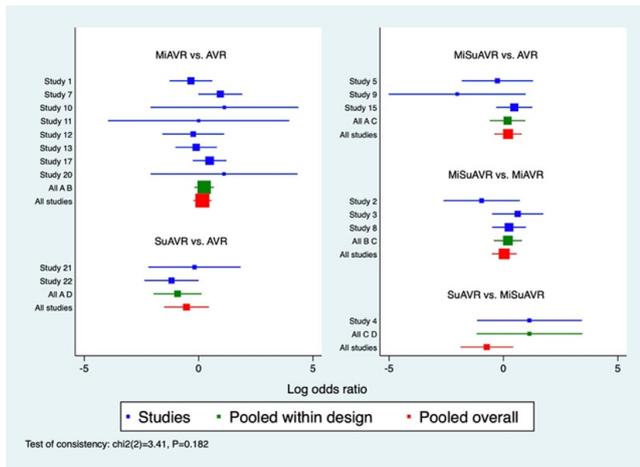
Cardiopulmonary Bypass Time



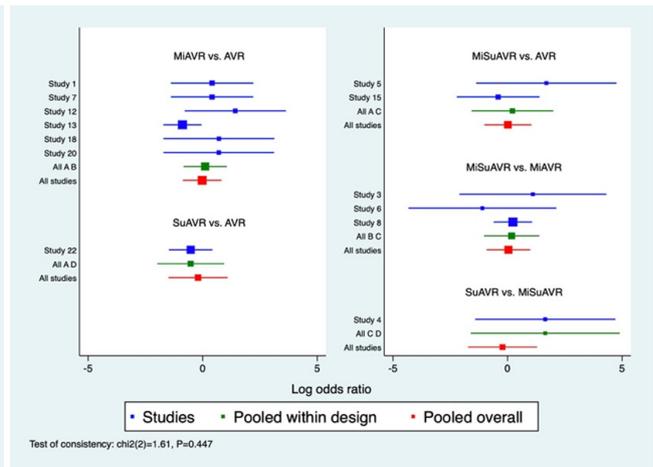
Cross-Clamp Time



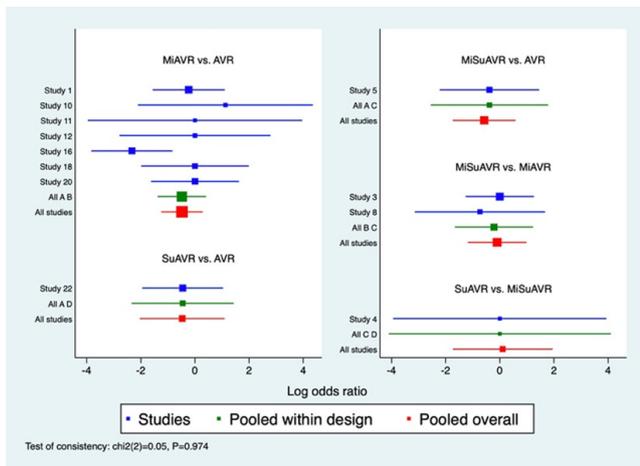
Major Bleeding



Acute Kidney Injury



Surgical Site Complication



Intensive Care Stay (days)

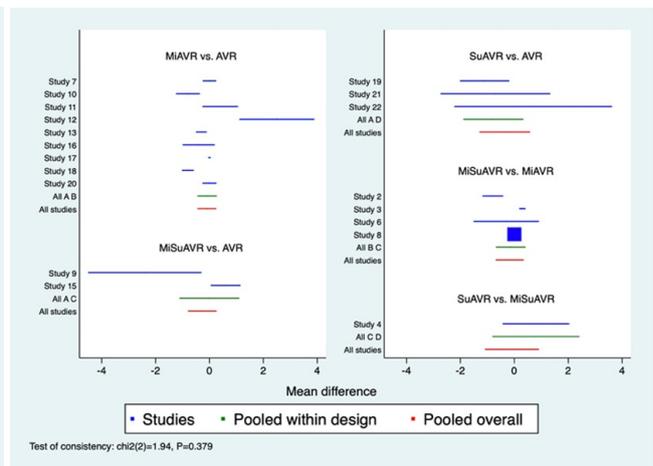


Figure S1 Forest plots for AVR by surgical approach and prosthesis examining perioperative outcomes. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

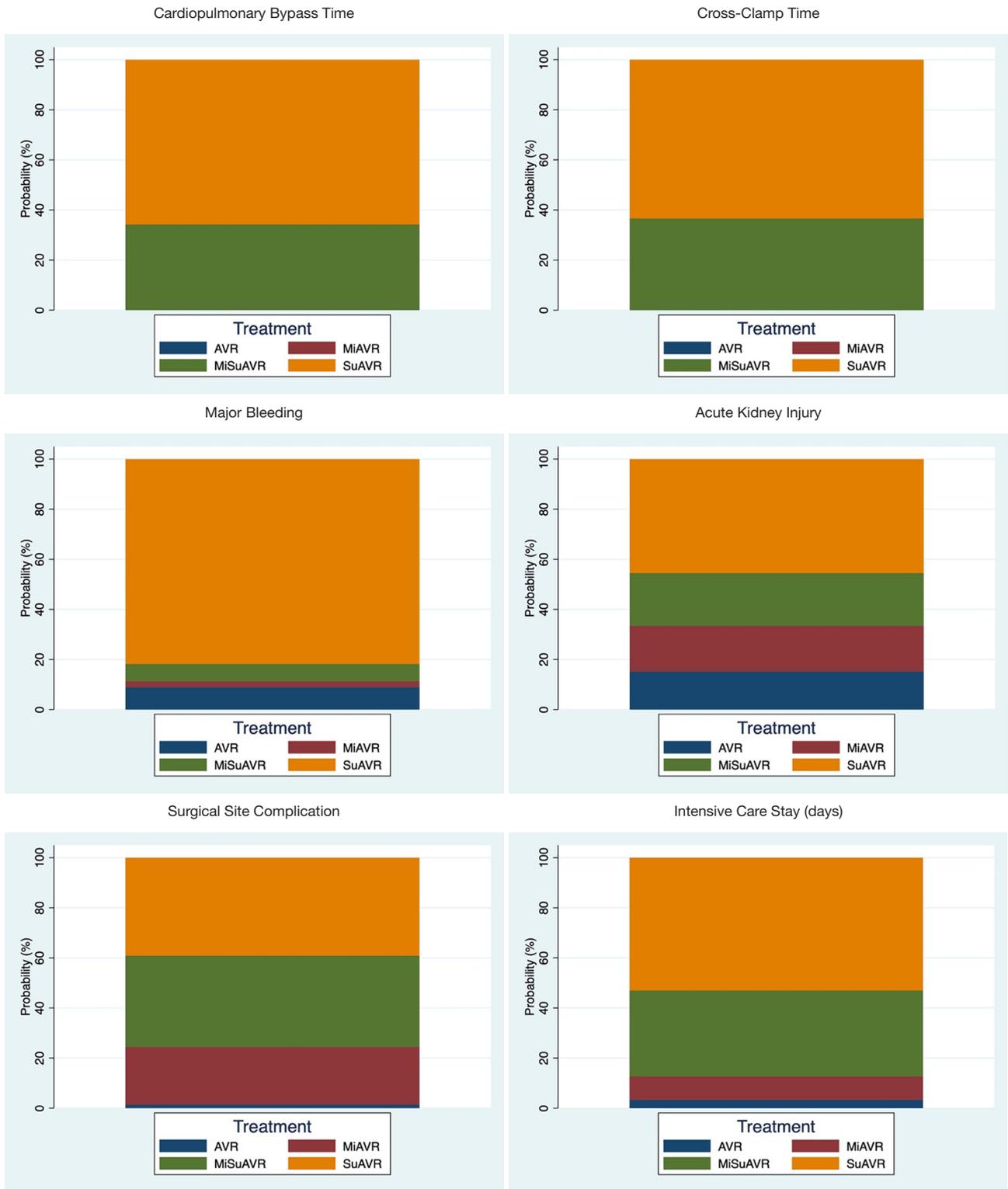


Figure S2 Rankograms for AVR by surgical approach and prosthesis examining perioperative outcomes. For example, if suAVR accounts for 40% of the rankogram, then it has a 40% probability of being the best-ranked treatment option for that particular outcome. AVR, full sternotomy aortic valve replacement; MiAVR, minimally invasive AVR; SuAVR, sutureless AVR; MiSuAVR, minimally invasive sutureless AVR.

Table S1 Study characteristics for network meta-analysis

Study	Year	Approach (n)				Location	Period	Study type	Risk score*
		SAVR	SuAVR	MiAVR	MiSuAVR				
Gilmanov (24)	2013	182	0	182	0	Italy	2004–2011	RM	Log ES I
Pollari (57)	2014	0	0	82	82	Germany	2010–2013	RM	Log ES I
Gilmanov (48)	2014	0	0	133	133	Italy	2004–2014	RM	Log ES I
Dalen (58)	2015	0	78	0	189	Sweden	2007–2014	RM	ES II
Borger (12)	2015	48	0	0	46	Germany	2012–2013	RCT	N/A
Vola (59)	2015	0	0	42	41	France	2009–2012	RM	ES I
Ghanta (23)	2015	289	0	289	0	USA	2011–2013	RM	STS PROM
Glauber (5)	2016	0	0	291	302	Italy	2004–2014	RM	Log ES I
Smith (60)	2017	556	0	0	41	Australia	2008–2015	RM	N/A
Hiraoka (61)	2014	194	0	88 [#]	0	Japan	2007–2012	RM	STS PROM
Ruttmann (62)	2010	87	0	87	0	Austria	2006–2009	RM	ES I
Neely (47)	2014	552	0	552	0	USA	2002–2014	RM	N/A
Casha (63)	2018	20	20	0	0	Malta		RM	ES I
Dalen (64)	2016	383	0	0	182	EU	2007–2014	RM	Log ES I
Bowdish (65)	2015	198	0	294	0	USA	1999–2013	RM	N/A
Giglio (27)	2018	363	0	363	0	Italy	2010–2016	RM	ES I
Aliahmed (66)	2018	356	0	70	0	Lithuania	2011–2016	RM	ES II
Mataraci (67)	2016	25	21	0	0	Turkey	2009–2014	RM	ES II
Masiello (68)	2002	100	0	100	0	Italy	1997–1999	RM	N/A
Hanedan (69)	2018	32	38	0	0	Turkey	2009–2016	RM	Log ES I
Nguyen ^a (70)	2017	35	0	35	0	USA	2011–2014	RM	STS PROM
Nguyen ^b (70)	2017	377	0	377	0	USA	2011–2014	RM	STS PROM
Mujtaba (71)	2017	624	139	0	0	Ireland	2011–2016	RM	ES II

^a, LVEF <40%; ^b, LVEF >40%; [#], divided into 62 via RT and 26 via HS; *, defines the risk score used as part of the propensity matching algorithm. LVEF, left ventricular ejection fraction; SAVR, full sternotomy aortic valve replacement; SuAVR, sutureless aortic valve replacement via full sternotomy; MiAVR, minimally invasive aortic valve replacement; MiSuAVR, sutureless aortic valve replacement via minimally invasive procedure; RCT, randomised controlled trial; RM, retrospective matched; ES I, EuroSCORE I; Log ES I, logistic EuroSCORE I; ES II, EuroSCORE II; STS PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.

Table S2 SUCRA for AVR by surgical approach and prosthesis examining perioperative outcomes

Variable	AVR	MiAVR	SuAVR	MiSuAVR
Mortality (%)	0.5	16.7	39.9	42.9
Stroke (%)	7.0	62.3	14.4	16.3
Postoperative atrial fibrillation (%)	0.0	0.3	85.7	14.0
New PPM (%)	22.3	17.1	60.5	0.1
Acute kidney injury (%)	15.2	18.2	45.5	21.1
Major bleeding (%)	9.2	2.8	81.4	6.6
Surgical site complication (%)	1.4	23.1	39.1	36.4
CPB time (min)	0.0	0.0	65.8	34.2
X-clamp time (min)	0.0	0.0	63.4	36.6
Ventilation time (hrs)	0.0	0.0	28.1	71.9
ICU LOS (days)	3.3	9.4	53.0	34.3
Hospital LOS (days)	0.0	1.7	63.9	34.4

Score represents likelihood, represented as a percentage, of the intervention being the best based on the outcome measured. AVR, aortic valve replacement; X-clamp, cross-clamp; CPB, cardiopulmonary bypass; ICU, intensive care unit; LOS, length of stay; MiAVR, minimally invasive AVR; MiSuAVR, minimally invasive sutureless AVR; SuAVR, sutureless AVR; SUCRA, surface under the cumulative ranking curve.