Original Article

Transcatheter, sutureless and conventional aortic-valve replacement: a network meta-analysis of 16,432 patients

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Background: Minimally invasive surgical techniques pose alternatives to conventional surgery for the treatment of aortic stenosis (AS). We present a Bayesian network analysis comparing Valve Academic Research Consortium-2 clinical outcomes between transcatheter aortic valve implantation (TAVI), sutureless (SL-AVR) and conventional aortic valve replacement (CAVR).

Methods: Electronic searches of databases were conducted and seven two-arm randomized-controlled trials and 25 propensity-score-matched studies comparing clinical outcomes of TAVI, SL-AVR and CAVR for treatment of AS were identified. Bayesian Markov chain Monte Carlo modelling was used to analyze clinical outcomes.

Results: The analysis included 16,432 patients who underwent TAVI [7,056], SL-AVR [1,238] or CAVR [8,138]. Compared to CAVR, TAVI and SL-AVR were associated with reduced postoperative major bleeding of 59% (OR 0.41, 95% CI: 0.28–0.59) and 44% (OR 0.56, 95% CI: 0.30–0.99) respectively. TAVI had a 41% reduction in postoperative myocardial infarction (OR 0.59, 95% CI: 0.40–0.86) and SL-AVR had a 40% reduction in postoperative acute kidney injury (AKI) (OR 0.62, 95% CI: 0.42–0.86). Compared to TAVI, CAVR and SL-AVR had a reduction in moderate/severe paravalvular regurgitation of 89% (OR 0.11, 95% CI: 0.07–0.16) and 92% (OR 0.08, 95% CI: 0.03–0.17). CAVR had a 67% decreased postoperative permanent pacemaker (PPM) implantation compared to TAVI (OR 0.33, 95% CI: 0.24–0.45) and a 63% reduction compared to SL-AVR (OR 0.37, 95% CI: 0.22–0.61). There were no differences in 30-day mortality or postoperative stroke between the groups.

Conclusions: In selected patients, minimally invasive surgical interventions including TAVI and SL-AVR for severe AS are viable alternatives to conventional surgery. However, TAVI is associated with increased paravalvular regurgitation, whereas TAVI and SL-AVR are associated with increased conduction disturbances compared to CAVR.

Keywords: Transcatheter aortic valve implantation (TAVI); sutureless aortic valves; surgical aortic valve replacement, Bayesian network analysis; aortic stenosis (AS)

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Introduction

Aortic stenosis (AS) is a valvular cardiac disease with an increasing incidence in an aging population (1). Conventional aortic valve replacement (CAVR) has historically been the gold standard for surgical intervention of AS, however approximately a third of patients with AS present with a high degree of co-morbidities (2) rendering them unsuitable for CAVR.

Technological advances have focused on the development of minimally invasive techniques to expand interventions to patients with AS who are deemed inoperable. These new treatment alternatives include sutureless aortic valve replacement (SL-AVR) and transcatheter aortic valve implantation (TAVI) (3-6). Recent randomised controlled trials (RCTs) have found outcomes of TAVI (7) and SL-AVR to be non-inferior to CAVR amongst high-risk patients (8). Multi-arm analyses comparing perioperative outcomes amongst TAVI, SL-AVR and CAVR, which could potentially lend support to particular recommendations, are currently lacking.

We present a Bayesian network analysis comparing Valve Academic Research Consortium-2 clinical outcomes between TAVI, SL-AVR and CAVR. Findings from this study are of particular importance given the drive towards use of TAVI and SL-AVR in place of CAVR amongst all-comers in the treatment of AS.

Methods

Literature search strategy

Five electronic databases were searched including PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club and the Database of Abstracts of Review of Effectiveness (DARE). To minimise the risk of overlooking relevant studies and given the wide variety of procedural nomenclature, it was necessary to combine a large number of key words and MeSH terms. This constituted the terms "*sutureless*" or "*transcatheter*" or "*transfemoral*" or "*transapical*" or "*trans-subclavian*" or "*conventional*" or "*standard*" or "*minimally invasive*" and "*aortic valve*" or "*aortic-valve*" and "*implantation*" or "*replacement*" or "*procedure*" or "*treatment*" and "*aortic stenosis*" and "*randomised*" or "*propensity*" or "*trial*". Reference lists of relevant literature were examined for any further studies. *Figure 1* depicts a PRISMA flow diagram highlighting the overall search strategy.

Outcome measures

Baseline characteristics for both pre- and post-propensity score matching cohorts were recorded, as well as all postoperative outcomes within the given timeframes. For each postoperative outcome published, criteria from the Valve Academic Research Consortium-2 (VARC-2) (9) were applied to maintain consistency and validity of results. In line with VARC-2 recommendations, mortality was only recorded if it was 30-day postoperative all-cause mortality. The VARC-2 guideline does not place similar 30-day time periods on the reporting of other postoperative complications, as such, this data was retained.

Eligibility criteria

Only propensity score matching studies and RCTs published in English were deemed eligible to be included in the analysis. Studies were included if they recorded specific postoperative outcomes following an AVR. Selection criteria was non-discriminant towards studies focusing on patient populations deemed low, medium or high surgical risk; however, a publication was excluded if the authors focused on AVR outcomes in the presence of one or more specific co-morbidities. If there were multiple studies published on the same patient population, only the most recent literature was included. All case reports, expert opinions, singe-arm studies and presentations were excluded. All studies on non-human subjects were removed.

Data extraction

Two reviewers independently appraised studies using a standard form and extracted data on methodology and outcome measures. Additionally, quality of studies was appraised using assessment criteria recommended by the Centre for Evidence Based Medicine (University of Oxford) (*Table S1*). For quantitative baseline characteristics, only data given as a mean and standard deviation or as a median and range were recorded. Discrepancies between reviewers were resolved by discussion and consensus.

Statistical analysis

Baseline patient characteristics were assessed through pairwise analysis of odds ratios for dichotomous data and the difference of means for continuous data.

Clinical postoperative outcomes were examined using

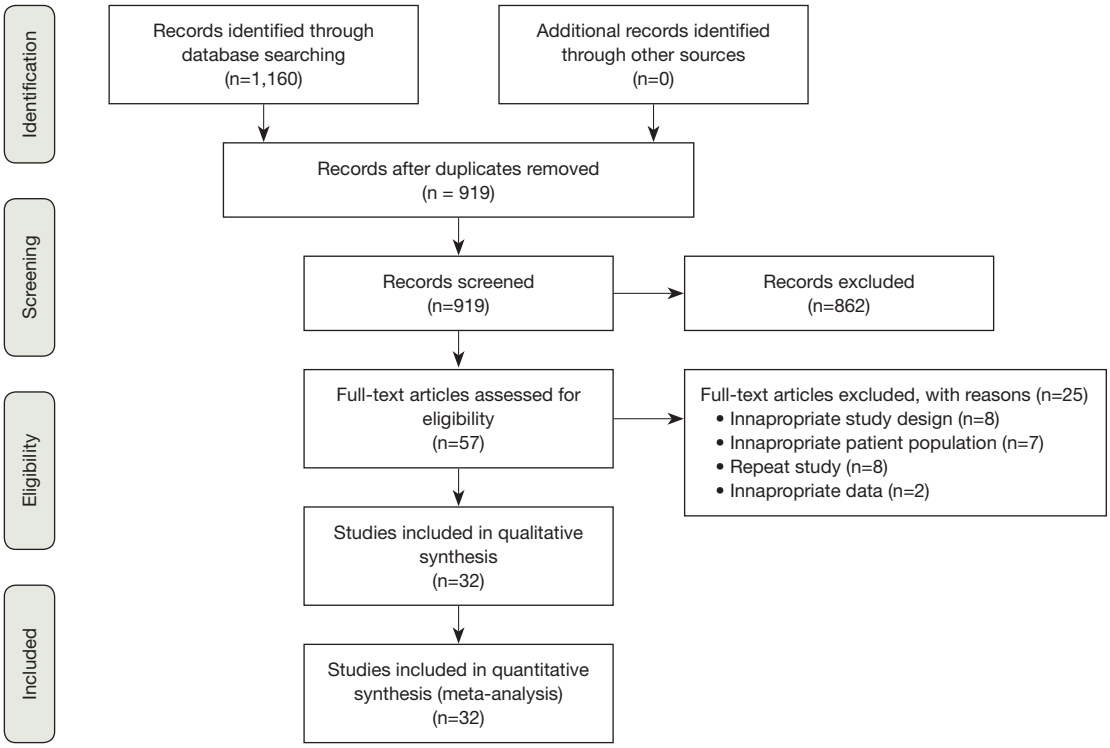

Figure 1 PRISMA flowchart depicting the search strategy.

odds ratios, specifically random effects with informative priors to best minimise the impact of the diversity of the assorted patient populations and designs for each study. Bayesian analysis was implemented due to its ability to simultaneously compare multiple treatment options and for its greater flexibility. The analyses were executed using the Bayesian Markov Chain Monte Carlo method in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) through the conduit of the Microsoft Excel based macro NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health) (10). A convergence test for each analysis was conducted by checking whether the Monte Carlo error was less than 5% of the standard deviation of the effect estimates or the variance between the studies. Convergence was achieved for all analyses at 20,000 "burn in" runs and 30,000 model runs. Furthermore, NetMetaXL allows for rank probabilities to be plotted against the possible ranks for a treatment to result in the production of a graphical "rankogram" (11). This method of visually representing probabilities was combined with a surface under the cumulative ranking line for each surgical intervention (SUCRA). For example, a SUCRA of 0.5 means that there is a 50% chance that the respective intervention is the best option in achieving the lowest rate of an undesirable clinical outcome. The forest plots and rankograms generated from the analysis are presented in *Figures 2* and *3* respectively.

Results

Of the 32 studies that met inclusion criteria, seven were RCTs and 25 propensity matched studies; recording outcomes for 16,432 patients (*Table 1*).

Of these patients, 8,138 patients underwent CAVR, 7,056 received TAVI and 1,238 received SL-AVR. Various routes (transfemoral, subclavian, transapical) of transcatheter access were reported in the literature, however this data was not comprehensively published. Of note, two studies focused entirely on transapical transcatheter approaches (n=201) (24,32).

Eight postoperative outcomes were identified from the VARC-2 consensus document to be suitable for the network analysis due to their consistent reporting across the range of studies. These included 30-day all-cause mortality, major bleeding or bleeding requiring surgical re-exploration, postoperative cerebrovascular accident (CVA), transient

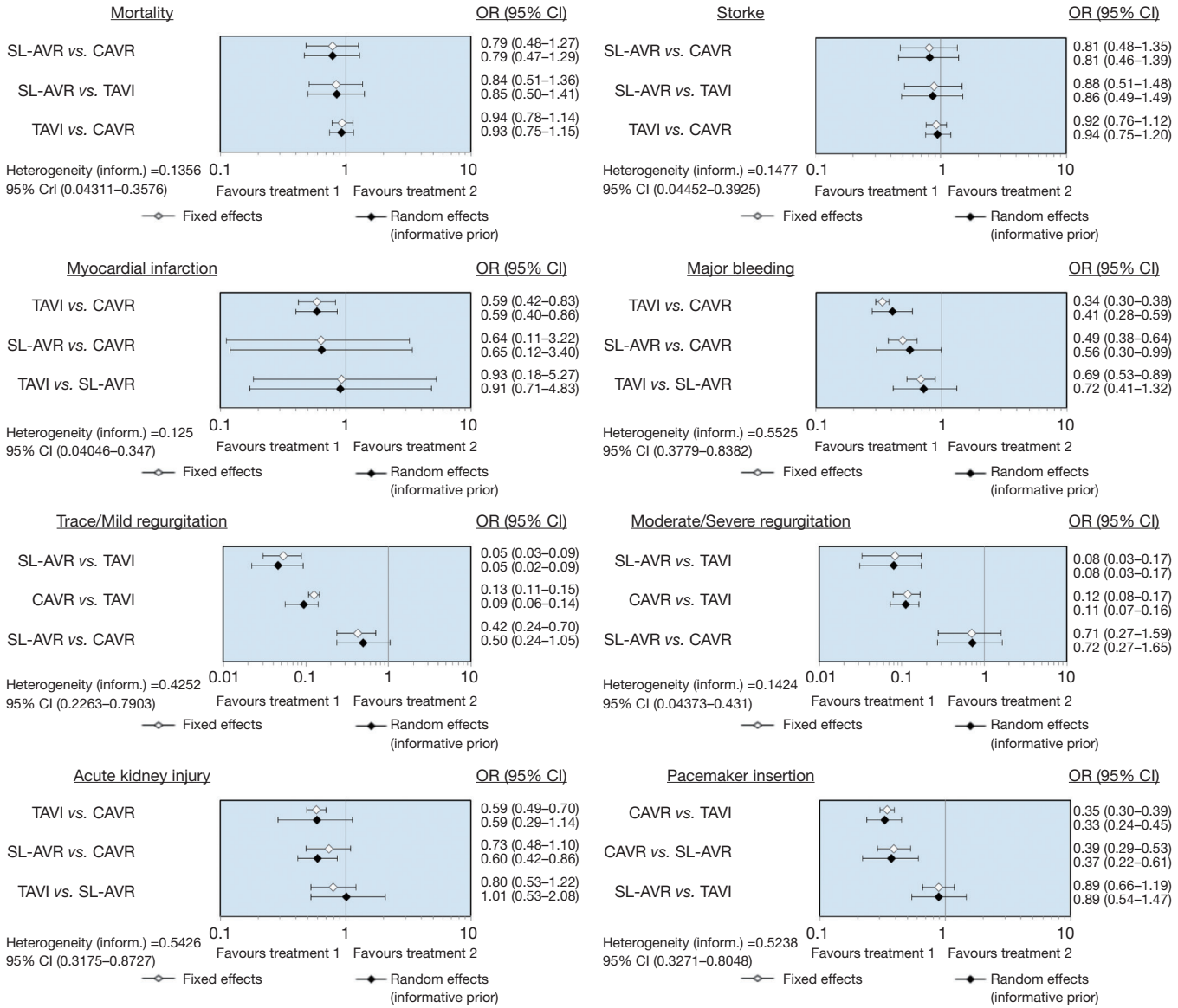

Figure 2 Forest plots from the Markov chain Monte Carlo model. Y axes are given as "Treatment 1 *vs.* Treatment 2". A significant result means Treatment 1 reduces the rate of that complication against Treatment 2. OR, odds ratio; CI, confidence interval.

ischaemic attack (TIA), acute kidney injury (AKI), renal failure, rates of mild/trace paravalvular leakage, rates of moderate/severe paravalvular leakage, myocardial infarction and permanent pacemaker (PPM) implantation.

Baseline characteristics

Patients who received SL-AVR in studies compared against CAVR had significantly higher rates of diabetes mellitus (OR 0.64, 95% CI: 0.44–0.93, P=0.02). No other differences were found in the baseline characteristics for any matched patient population (*Table 2*).

Mortality

The network meta-analysis yielded no significant differences. The modelling suggested that SL-AVR had the highest probability of producing the lowest rate of 30-day mortality of the three interventions with a SUCRA of 78.20%. Heterogeneity was low (τ^2=0.1356).

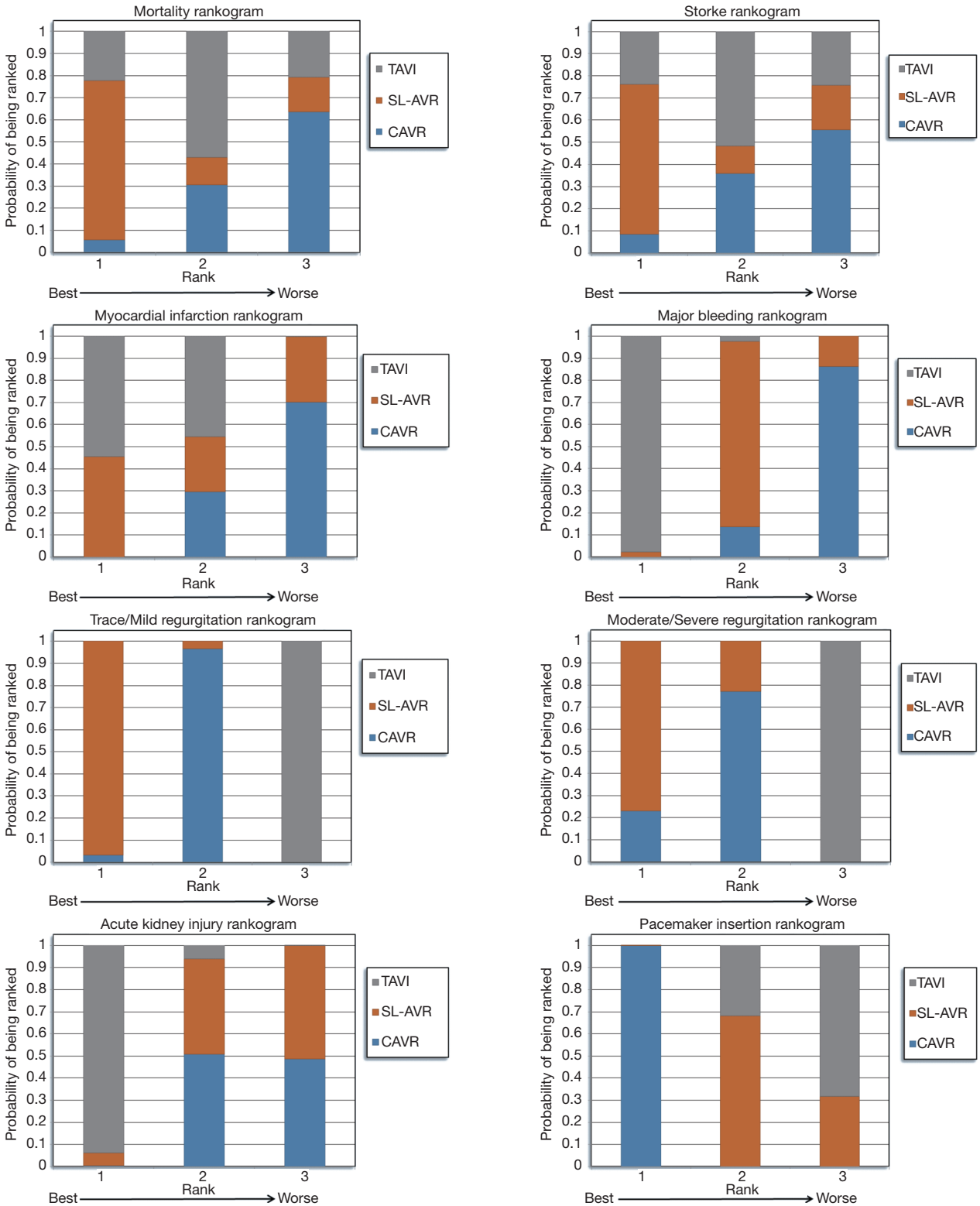

Figure 3 Rankograms from the Markov chain Monte Carlo model. Each intervention is ranked on a probability that it will cause a certain outcome. For example, TAVI has the highest probability of causing moderate/severe regurgitation postoperatively and the modelling reflects this. It is extremely likely that TAVI will be placed. TAVI, transcatheter aortic valve implantation.

Table 1 Characteristics of included studies

First author	Year	Study design	Study period	Country	Total (n)	TAVI (n)	SL-AVR (n)	CAVR (n)	Specific risk profiles targeted by the authors
Adams (12)	2014	RCT (CoreValve)	2011–2012	USA	747	390	–	357	Increased risk
Ailawadi (13)	2016	PSM	2011–2013	USA	680	340	–	340	Intermediate and high risk
Biancari (14)	2016	PSM	2007–2014	Italy	288	144	144	–	–
Borger (8)	2015	RCT (CADENCE-MIS)	2012–2013	Germany	94	–	46	48	Low to moderate risk
Calle-Valda (15)	2018	PSM	2011–2015	Spain	100	50	–	50	Low to intermediate risk
Castrodeza (16)	2016	PSM	2009-2014	Spain	140	70	–	70	Low to intermediate risk
Conradi (17)	2012	PSM	2009–2010	Germany	164	82	–	82	High risk
D'Onofrio (18)	2016	PSM	2007–2014	Italy	428	214	214	–	–
Dalén (19)	2016	PSM	2007–2014	Sweden	342	–	171	171	Previous cardiac surgery excluded
Forcillo (20)	2016	PSM	2011–2015	Canada	195	–	65	130	Patients aged 80 years or older
Fusari (21)	2012	PSM	2008–2009	Italy	60	30	–	30	–
Gilmanov (22)	2014	PSM	2004–2014	Italy	266	–	133	133	–
Hannan (23)	2016	PSM	2011–2012	USA	810	405	–	405	–
Holzhey (24)	2012	PSM	2001–2010	Germany	334	167	–	167	–
Johansson (25)	2016	PSM	2008–2014	Sweden	291	166	–	125	–
Kamperidis (26)	2015	PSM	2007–2013	The Netherlands	80	40	40	–	High risk
Latib (27)	2012	PSM	2003–2011	Italy	222	111	–	111	Intermediate risk
Leon (28)	2016	RCT (PARTNER 2)	2011–2013	USA	2,032	1,011	–	1,021	Intermediate risk
Miceli (29)	2016	PSM	2008–2013	Italy	74	37	37	–	High risk
Minutello (30)	2015	PSM	2011–2011	USA	2,380	595	–	1,785	–
Muneretto (31)	2015	PSM	2007–2014	Italy	612	204	204	204	Intermediate to high risk
Nielsen (32)	2012	RCT (STACCATO)	2003–2011	Denmark	70	34	–	36	–
Piazza (33)	2013	PSM	2006–2010	Germany	810	405	–	405	Intermediate risk
Pollari (34)	2014	PSM	2010–2013	Germany	164	–	82	82	–
Reardon (35)	2017	RCT (SURTAVI)	2012–2016	USA, Europe, Canada	1,660	864	–	796	Intermediate risk
Santarpino (36)	2015	PSM	2010–2015	Germany	204	102	102	–	–
Schymik (37)	2015	PSM	2008–2012	Germany	432	216	–	216	Less than high risk
Saxena (38)	2011	RCT (PARTNER)	2007–2009	USA	699	348	–	351	High risk
Tamburino (39)	2015	PSM	2010–2012	Italy	1,300	650	–	650	–
Thongprayoon (40)	2016	PSM (OBSERVANT)	2008–2014	USA	390	195	–	195	–
Thyregod (41)	2015	RCT (NOTION)	2009–2013	Nordic	276	142	–	134	–
Zweng (42)	2016	PSM	2009–2015	Australia	88	44	–	44	High risk
Total					16,432	7,056	1,238	8,138	

TAVI, transcatheter aortic valve implantation; SL-AVR, sutureless aortic valve replacement; CAVR, conventional aortic valve replacement; PSM, Propensity Score Matched Study; RCT, randomized controlled trial.

Table 2 Analysis of baseline patient characteristics

Variables	CAVR *vs.* TAVI		CAVR *vs.* SL-AVR		SL-AVR *vs.* TAVI	
	95% CI	P	95% CI	P	95% CI	P
Age*	−0.18 (−0.69, 0.32)	0.48	0.39 (−0.25, 1.04)	0.23	−0.37 (−2.09, 1.35)	0.67
Male	1.00 (0.93, 1.07)	0.93	0.79 (0.50, 1.24)	0.31	0.91 (0.74, 1.13)	0.41
log Euroscore*	0.36 (−0.15, 0.86)	0.16	−0.34 (−1.19, 0.52)	0.44	−0.43 (−1.44, 0.58)	0.40
STS PROM*	0.07 (−0.03, 0.17)	0.17	0.13 (−0.12, 0.38)	0.29	−0.30 (−1.02, 0.42)	0.42
LVEF%*	−0.14 (−0.67, 0.39)	0.60	−0.23 (−1.21, 0.75)	0.64	0.84 (−0.56, 2.24)	0.24
DM	0.98 (0.88, 1.10)	0.77	0.64 (0.44, 0.93)	0.02 (significant)	1.02 (0.79, 1.32)	0.90
HT	1.03 (0.89, 1.20)	0.66	0.86 (0.65, 1.14)	0.30	1.30 (0.68, 2.47)	0.43
CAD	0.99 (0.91, 1.08)	0.91	1.20 (0.77, 1.88)	0.42	0.81 (0.54, 1.21)	0.31
Prior MI	1.01 (0.90, 1.12)	0.90	3.74 (0.47, 29.55)	0.21	0.94 (0.47, 1.87)	0.85
COPD	0.96 (0.88, 1.05)	0.35	1.83 (0.51, 6.61)	0.36	0.95 (0.74, 1.22)	0.70
PVD	1.07 (0.98, 1.17)	0.13	0.97 (0.71, 1.32)	0.83	0.98 (0.74, 1.30)	0.88
Prior PM	0.99 (0.84, 1.15)	0.86	0.11 (0.01, 2.02)	0.14	1.01 (0.84, 1.21)	1.00
Prior CVA/TIA	0.98 (0.88, 1.09)	0.70	0.82 (0.47, 1.43)	0.49	0.88 (0.49, 1.56)	0.66

*, mean difference, 95% CI. All other data presented as odds ratios, 95% CI. TAVI, transcatheter aortic valve implantation; SL-AVR, sutureless aortic valve replacement; CAVR, conventional aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; LVEF, left ventricular ejection fraction; DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; PM, pacemaker; CVA/TIA, cerebrovascular accident/transient ischemic attack.

CVA/TIA

The network meta-analysis yielded no significant differences. SUCRA was highest for SL-AVR at 73.83% and heterogeneity was low (τ^2=0.1477).

Myocardial infarction

TAVI was significantly associated with a 41% reduction in incidence of postoperative myocardial infarction when compared to CAVR (OR 0.59, 95% CI: 0.40–0.86). There were no other significant associations. SUCRA was highest for TAVI at 77.13%. Heterogeneity was low (τ^2=0.125).

Major bleeding

TAVI was significantly associated with a 59% reduced incidence of postoperative major bleeding compared to CAVR (OR 0.41, 95% CI: 0.28–0.59). Similarly, SL-AVR was significantly associated with a 44% reduction in major bleeding compared to CAVR (OR 0.56, 95% CI: 0.30–0.99). The modelling indicated that TAVI had the highest probability of producing the lowest rates of bleeding. SUCRA for TAVI was 98.83% and heterogeneity was high (τ^2=0.5525).

Trace/mild paravalvular regurgitation

SL-AVR and CAVR were significantly associated with a reduction in the occurrence of trace or mild levels of regurgitation when compared to TAVI, 95% (OR 0.05, 95% CI: 0.02–0.09) and 91% (OR 0.09, 95% CI: 0.06–0.14) respectively. The highest SUCRA was for SL-AVR at 98.37% and heterogeneity was high (τ^2=0.4252).

Moderate/severe paravalvular regurgitation

SL-AVR and CAVR were significantly associated with a reduction in the occurrence of moderate to severe postoperative aortic paravalvular regurgitation when compared to TAVI, 92% (OR 0.08, 95% CI: 0.03–0.17) and 89% (OR 0.11, 95% CI: 0.07–0.16) respectively. The highest SUCRA was for SL-AVR at 88.53% and

heterogeneity was low (τ^2=0.1424).

Acute kidney injury

SL-AVR was associated with a 40% reduction in postoperative AKI rates compared to CAVR (OR 0.60, 95% CI: 0.42–0.86). No other significant associations were reported. However, the modelling indicated that TAVI had the highest SUCRA of 96.89%. Heterogeneity was high (τ^2=0.5426).

Pacemaker implantation

CAVR was significantly associated with a 67% reduction in postoperative PPM when compared to TAVI (OR 0.33, 95% CI: 0.24–0.45) and a 63% reduction when compared to SL-AVR (OR 0.37; 95% CI: 0.22–0.61). The highest SUCRA was for CAVR at 99.99% and heterogeneity was high (τ^2=0.5238).

Discussion

In the present study, we sought to compare postoperative outcomes of TAVI, SL-AVR and CAVR by means of a network meta-analysis using Bayesian Markov chain Monte Carlo modelling. Our analysis has several significant findings. TAVI was associated with reduced rates of postoperative myocardial infarction and major bleeding when compared to CAVR but had higher rates for all grades of paravalvular regurgitation when compared to SL-AVR and CAVR. SL-AVR was associated with reduced rates of postoperative major bleeding and AKI when compared to CAVR. However, compared to CAVR, both TAVI and SL-AVR had significantly higher rates of conduction disturbance requiring PPM. There were no differences with regards to 30-day all-cause mortality or postoperative stroke between the groups. The pairwise analysis found little difference between the preoperative patient populations.

Compared to other meta-analyses, our network analysis differs in rates of clinically relevant perioperative complications. Whereas Khan *et al.* (43) found no difference in bleeding when TAVI was compared with CAVR, our findings of reduced rates of major bleeding with TAVI are consistent with findings from Tam *et al.* (44). These differences may be attributed to variance in sample size and study type, when comparing the meta-analysis of observational studies by Khan *et al.* with a sample size of 420, to the meta-analysis of RCTs by Tam *et al.*, total sample size 8,234, and our study of 16,432 patients.

Our study demonstrates that compared to CAVR, the TAVI cohort experienced a 41% reduction in postoperative myocardial infarction. However, the VARC-2 criteria for diagnosis of myocardial infarction may overestimate this outcome due to direct procedural related myocardial injury confounding findings of increased cardiac troponins and creatine kinase MB (45). Furthermore, compared to CAVR, SL-AVR was significantly associated with reduced rates of postoperative AKI grade 2 or 3, however AKI had the highest level of heterogeneity, likely secondary to discrepancies in grading between studies.

We observed significantly higher rates of all grades of paravalvular regurgitation for TAVI when compared to SL-AVR or CAVR. Three studies (24,26,27) included rates for aortic regurgitation but were excluded from analysis as they did not specify type of leakage (transvalvular, paravalvular or both). Conflicting data exists in regards to the long-term outcomes for postoperative aortic regurgitation (46). Results of the PARTNER trial at 2 years suggest that even a mild degree of aortic regurgitation significantly decreases patient survival (47). Aortic regurgitation following TAVI implantation may be secondary to non-uniform calcified native valve compression against the aortic wall following TAVI deployment or suboptimal balloon inflation. In contrast, the ability to remove valve leaflets, decalcify the annulus and size and implant under direct vision have been attributed as reasons for reduced postoperative aortic regurgitation for SL-AVR and CAVR (48). Heterogeneity exists in the grading schemes of paravalvular regurgitation (49) and it is unclear whether VARC-2 definitions were universally used. Technological developments in TAVI technology include the introduction of a polyethylene terephthalate outer skirting in the SAPIEN 3 prosthesis (Edwards Lifesciences, Irvine, California) with the goal of increasing contact and adhesion of the valve against the aortic annulus (50). Clinical results suggest that the SAPIEN 3 prosthesis is associated with a lower incidence of paravalvular leak compared to SAPIEN XT (Edwards Lifesciences) and CoreValve EvolutR (Medtronic, Minneapolis, Minnesota) (51). Future larger studies with longer follow-up will be required to demonstrate whether these differences have a significant clinical effect.

Significant heterogeneity for PPM exists between studies with 34.1% of TAVI patients in the NOTION trial receiving a PPM (41) in contrast to 3.8% in the PARTNER trial (52). Variance in studies may be attributed to the

different devices implanted and implantation technique (53). Other meta-analyses of newer generation TAVI valves appear to still indicate relatively high rates of PPM of approximately 16.2% (54). In the present study, there was a 67% reduction in the rate of PPM with CAVR compared to SL-AVR. It is suggested that excessive removal of calcified cusps during the implantation of a SL-AVR is predictive of PPM (55). Overall, the higher risk of PPM presents an important consideration in balancing the risks and benefits of minimally invasive approaches.

The results of the original PARTNER trial and the CoreValve US Pivotal Trial have led to the recognition of TAVI as the procedure of the choice for inoperable patients and an alternative to CAVR in high risk patients (52). However, when considering intermediate risk patients, Muneretto *et al*. (56) demonstrate in a retrospective multicohort study that TAVI significantly increased early and late morbidity and mortality when compared with SL-AVR and CAVR; moreover, use of TAVI was identified as an independent predictor for all-cause mortality in intermediate risk patients.

Currently, multiple trials are underway including the PARTNER 3 (Placement of Aortic Transcatheter Trial 3, NCT02675114) to investigate SAPIEN 3 TAVI as compared to CAVR for low risk patients as well as the PERSIST-AVR trial (Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement, NCT02673697). It is with anticipation that we await the long-term outcomes from these multicentre, randomised trials which we hope will provide new insight into the role of TAVI and SL-AVR, if any, in intermediate and low risk patients.

Limitations

Pooling of data from trials with different inclusion criteria, eras, design, patient surgical risks, concomitant procedures, follow-up duration with variable attrition rates and variable definition and validation of endpoints contributes to the heterogeneity observed between the studies. Additionally, we refined the multitude of techniques for AVR into the three broad categories of TAVI, SL-AVR and CAVR which were not able to account for variable practices between centres, differences in vascular access and types of valves implanted. We acknowledge that this heterogeneity in study population and different indications for each type of valve is a fundamental limitation that cannot be addressed due to inability to extract sufficient detail from the pooled data.

Conclusions

The inclusion of RCTs and propensity-matched studies are strengths in the present meta-analysis. However, there are several key limitations that merit consideration. This network meta-analysis demonstrates no differences in perioperative mortality or stroke between patients who received TAVI, SL-AVR or CAVR interventions for their AS. Minimally invasive surgical and percutaneous interventions for severe AS are a viable alternative to CAVR in selected patients. However, TAVI is associated with increased paravalvular regurgitation, whereas TAVI and SL-AVR are associated with increased conduction disturbances compared to CAVR.

Acknowledgements

None.

Footnote

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

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Supplementary

Table S1 Quality assessment of studies

First author	Population	Outcomes	Independent evaluation	Follow-up?	No loss	Confounders identified
Adams	Yes	Yes	Unknown	Yes	Yes	Yes
Ailawadi	Yes	Yes	No	No	Unknown	Yes
Biancari	Yes	Yes	No	Yes	Yes	Yes
Borger	Yes	Yes	Unknown	Yes	Yes	Yes
Calle-Valda	Yes	Yes	No	Yes	Unknown	Yes
Castrodeza	Yes	Yes	No	Yes	Yes	Yes
Conradi	Yes	Yes	No	Yes	Yes	Yes
D'Onofrio	Yes	Yes	No	Yes	Unknown	Yes
Dalén	Yes	Yes	No	Yes	Unknown	Yes
Forcillo	Yes	Yes	No	Yes	Unknown	Yes
Fusari	Yes	Yes	Yes	Yes	Yes	Yes
Gilmanov	Yes	Yes	No	Yes	Yes	Yes
Hannan	Yes	Yes	No	Yes	Yes	Yes
Holzhey	Yes	Yes	No	Yes	Yes	Yes
Johansson	Yes	Yes	No	Yes	Unknown	Yes
Kamperidis	Yes	Yes	No	Yes	Unknown	Yes
Latib	Yes	Yes	No	Yes	Unknown	Yes
Leon	Yes	Yes	Unknown	Yes	Yes	Yes
Miceli	Yes	Yes	No	Yes	Unknown	Yes
Minutello	Yes	Yes	No	No	N/A	Yes
Santarpino	Yes	Yes	No	Yes	Unknown	Yes
Muneretto	Yes	Yes	No	Yes	Unknown	Yes
Nielsen	Yes	Yes	Unknown	Yes	Yes	Yes
Piazza	Yes	Yes	No	Yes	Yes	Yes
Reardon	Yes	Yes	Yes	Yes	Yes	Yes
Schymik	Yes	Yes	No	Yes	Yes	Yes
Smith	Yes	Yes	Unknown	Yes	Yes	Yes
Tamburino	Yes	Yes	Yes	Yes	Yes	Yes
Thongprayoon	Yes	Yes	No	Yes	Yes	Yes
Thyregod	Yes	Yes	Yes	Yes	Yes	Yes
Zweng	Yes	Yes	No	Yes	Unknown	Yes

Population: is there a clear definition of the study population? Outcomes: is there a clear definition of outcomes and subsequent assessment? Independent evaluation: were the outcome parameters independently assessed? Follow-up: was there a sufficient duration of follow-up? Loss: was there no selective loss of patients? Confounders identified: were important confounders and prognostic founders identified? N/A, not applicable.