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Minimally invasive surgery versus transcatheter aortic valve replacement: a systematic review and meta-analysis

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) has recently been approved for use in patients who are at intermediate and low surgical risk. Moreover, recent years have witnessed a renewed interest in minimally invasive aortic valve replacement (miAVR). The present meta-analysis compared the outcomes of TAVR and miAVR in the management of aortic stenosis (AS). We conducted an electronic search across six databases from 2002 (TAVR inception) to December 2019. Data from relevant studies regarding the clinical and length of hospitalisation outcomes were extracted and analysed using R software. We identified a total of 11 cohort studies, of which seven were matched/propensity matched. Our analysis demonstrated higher rates of midterm mortality (≥1 year) with TAVR (risk ratio (RR): 1.93, 95% CI: 1.16 to 3.22), but no significant differences with respect to 1 month mortality (RR: 1.00, 95% CI: 0.55 to 1.81), stroke (RR: 1.08, 95% CI: 0.40 to 2.87) and bleeding (RR: 1.45, 95% CI: 0.56 to 3.75) rates. Patients undergoing TAVR were more likely to experience paravalvular leakage (RR: 14.89, 95% CI: 6.89 to 32.16), yet less likely to suffer acute kidney injury (RR: 0.38, 95% CI: 0.21 to 0.69) compared with miAVR. The duration of hospitalisation was significantly longer in the miAVR group (mean difference: 1.92 (0.61 to 3.24)). Grading of Recommendations Assessment, Development and Evaluation assessment revealed ≤moderate quality of evidence in all outcomes. TAVR was associated with lower acute kidney injury rate and shorter length of hospitalisation, yet higher risks of midterm mortality and paravalvular leakage. Given the increasing adoption of both techniques, there is an urgent need for head-to-head randomised trials with adequate follow-up periods.

INTRODUCTION

Aortic stenosis (AS) is a progressive age-related disease with a prevalence of up to 7.2% in the elderly.[1] The stenotic aortic valve increases the ventricular afterload, leading to initial compensatory left ventricular hypertrophy and eventual progression to left-sided heart failure, if not treated.[2] The 5-year mortality rates are as high as 50% in medically managed patients.[3] Traditionally, surgical aortic valve replacement (SAVR) was the standard of care; however, the advent of transcatheter aortic valve replacement (TAVR) has gained appreciable momentum, with a nearly ninefold increase in utilisation between 2012 and 2016.[4–6] Until recently, TAVR was reserved for high-risk patients unfit for surgery; however, following the landmark PARTNER 3 and Evolut Low Risk trials,[7 8] the Food and Drug Administration approved TAVR for low-risk patients as well.

In addition, recent years have witnessed a renewed interest in minimally invasive aortic valve replacement (miAVR) in selected patients.[9] This approach involves either a mini-sternotomy or a right anterior mini-thoracotomy, as opposed to the full median sternotomy in traditional surgical approaches. The outcomes of miAVR in recent studies have been favourable, including decreased blood loss, shorter intensive care unit stay durations, and lower acute kidney injury (AKI) and perioperative mortality rates.[10 11] Potential concerns with this approach are the increased cardiopulmonary bypass and aortic cross-clamp durations,[12] which carry greater risks of adverse outcomes.[13 14] The adoption of sutureless or rapid deployment valves, however, has mitigated these concerns to some extent.[15]

Potential advantages of miAVR over TAVR include the ability to directly observe the valve during the operation, removal of annular calcifications and lower incidence of paravalvular leakage.[16] However, these may come at the cost of longer hospital stay durations and higher risk of AKI.[17] Aside from these differences, recent studies that compared the two approaches were controversial with regard to the superiority of either approach for stroke,[17–22] atrial fibrillation (AF),[17–20 22 23] and AKI[16–18 20] outcomes. To that end, we conducted the present systematic review and meta-analysis to compare the

outcomes of TAVR and miAVR in the treatment of AS in the contemporary era.

MATERIALS AND METHODS

The protocol for this systematic review was prospectively registered on PROSPERO (CRD42020170176) and the meta-analysis was reported in compliance with the MOOSE checklist[24] (online supplemental appendix 1).

Literature search

We searched the following databases: MEDLINE via PubMed, Embase, Web of Science, CENTRAL, the WHO clinical trials registry (WHO ICTRP) and clinicaltrials.gov during December 2019. The main terms included in the search strategy were free-text and MeSH combinations of 'TAVR', 'TAVI', 'Transcatheter Aortic Valve Replacement', 'percutaneous', 'Minimally Invasive Surgical Procedures', 'Heart valve prosthesis implantation', 'Aortic valve stenosis/Surgery', 'Replace*', 'Implant*' and 'Aortic Stenosis'. The details of our search strategy used can be found in online supplemental appendix 2. A starting date restriction was placed at 2002 (first TAVR procedure in humans).[25] No restrictions by language were employed. We inspected the reference lists of the included studies to ensure that no relevant studies were missed.

Inclusion/exclusion criteria

All randomised controlled trials (RCTs) or cohort studies comparing the outcomes in patients with symptomatic AS[26] who underwent either TAVR (regardless of access route) or miAVR (regardless of whether a sternotomy or a mini-thoracotomy was used, and regardless of sutureless valve use) were eligible. We excluded studies which adopted the traditional SAVR technique solely or those from which relevant data could not be extracted.

Selection and data extraction

Two reviewers (KW and SA) independently screened the titles and abstracts of all citations identified by the search strategy. Full-text articles were then obtained for studies that met our inclusion criteria, or studies which were inconclusive and required further review. The full-text articles were thoroughly examined for eligibility. Disagreements between authors regarding the inclusion of a particular study were resolved by an independent third reviewer (AS).

Data extraction was performed using a standardised spreadsheet. We collected data from eligible studies regarding the baseline characteristics, sample sizes, study designs and outcome measures. The main outcomes included all-cause mortality (both short-term and midterm ≥1 year), stroke, paravalvular leakage, AKI, AF, major bleeding and hospitalisation durations.[27] The data extraction was performed by two independent reviewers (KW and SA) and the conflicts were resolved by a third reviewer (AS). When insufficient details were provided in

the published articles, we attempted to contact the study authors.

Two reviewers (KW and SA) used the Newcastle-Ottawa scale (NOS) to assess the risk of bias in the included cohort studies. We planned to use the Cochrane risk of bias-2 tool to assess RCTs; however, we did not identify any RCTs that met our inclusion criteria. Conflicts were resolved by a third author (MM). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to assess the certainty of evidence (very low, low, moderate and high) based on the following: risk of bias as assessed by NOS, imprecision, indirectness, inconsistency and publication bias. We considered large effect sizes as a possible upgrading factor.

Data synthesis

We used the random-effects model (DerSimonian and Laird method) to obtain pooled estimates of the risk ratio (RR) or mean difference (MD) due to the anticipated high heterogeneity. We only pooled data from studies where baseline matching was performed since including studies without baseline matching would have introduced confounding by indication/selection bias. Additionally, a number of studies reported only the pooled results for their entire surgical cohort rather than for miAVR specifically. In such cases, we only included their outcome if it did not occur at all (event rate=0) in the surgical group. Heterogeneity quantification was performed using the I^2. We used R meta package (V.3.5.1., R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses.

RESULTS

Characteristics of the included studies

We identified 1666 records of which 1370 remained after duplicates were removed. After initial title/abstract screening, 26 articles remained of which 14 were excluded due to ineligible interventions, lack of separate outcome reporting and studies being only available as abstracts. Finally, we included 11 studies (12 reports) in our qualitative analysis,[9 16–23 28–30] 7 of which were eligible for meta-analysis[16–22] (figure 1). Among the included studies, there were no clinical trials, one unmatched,[9] one matched,[20] three where adjustment was made via a multivariate model[23 28–30] and six propensity-matched[16–19 21 22] cohort studies. The included studies comprised a total sample size of 4674 patients, of which 2346 underwent TAVR, while 2328 patients underwent miAVR. The average reported follow-up among the included studies was 26.7 months (range: 13–46.7 months; table 1).

PATIENT BASELINE CHARACTERISTICS

The mean pooled age across the included studies is 82.08 years (range: 63–85.6 years), and most studies reported nearly equal numbers of males and females. There was variable reporting of baseline comorbidities in the
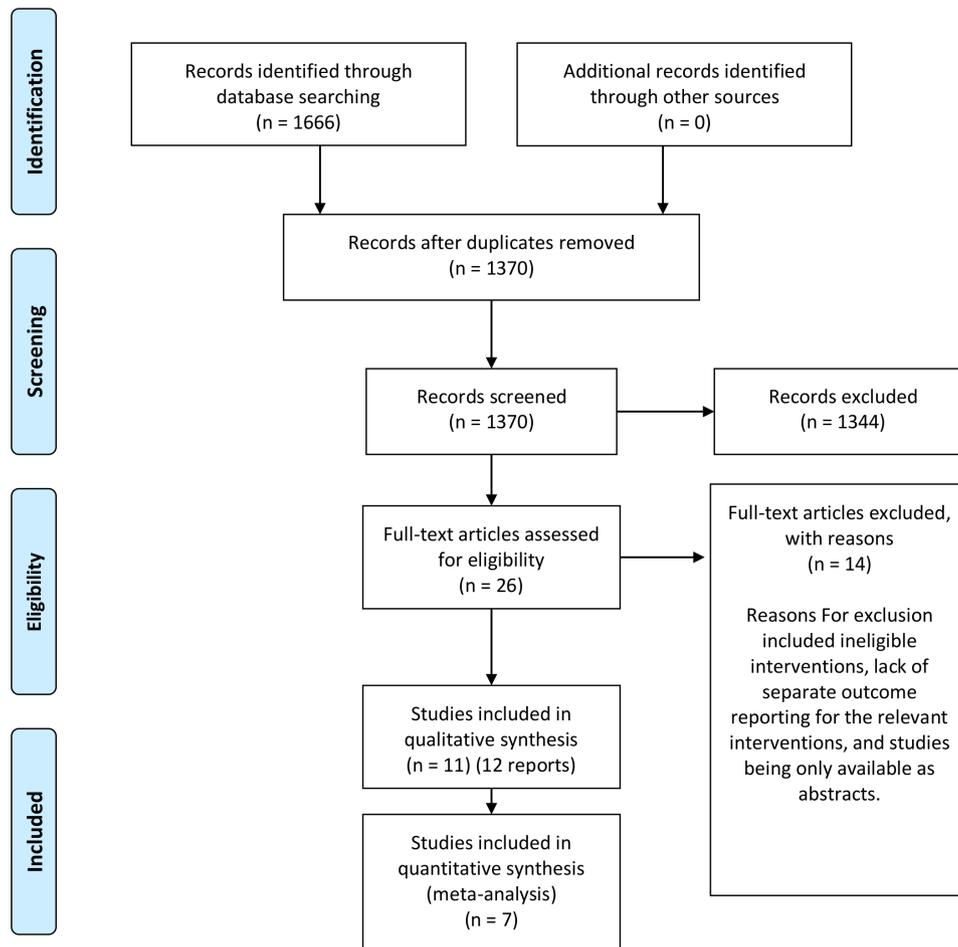
Figure 1 Flow diagram of literature search and study selection.

included studies. Of the studies that reported on diabetes, none had a proportion <20%. The majority of studies reporting on hypertension had rates >75%.[18 19 21–23 30] AF was reported in three studies, with an overall prevalence <20% (table 2).

Furukawa et al[18] and Hirji et al[30] were the only studies to report STS scores (3.4 and 5.95, respectively). Six studies used EuroScore II for risk stratification, with propensity-matched cohorts including patients with a low-to-moderate surgical risk (defined as a EuroScore II<6%). Five of the included studies reported logEuroScore with risks ranging from 38% in Zierer et al's[20] cohort to 3.77% in Tokarek et al's study.

Risk of bias in included studies

A summary of the risk of bias assessment is illustrated in figure 2. Overall, the majority of included studies were at low risk of bias, aside from two studies in which the risk of bias was moderate due to inadequate adjustment for baseline factors[9] or inadequate reporting on attrition rates.[23 28] Across all outcomes, no evidence of significant publication bias was detected. GRADE assessment revealed ≤moderate quality of evidence in all outcomes. GRADE assessment results for each outcome are reported in table 3.

Selection

All included studies had a low risk of selection bias. The use of a central/hospital database to select patients and retrieve information by all studies meant that selection of the non-exposed cohort was adequate in all studies and that the studies were representative of the exposed cohort. The ascertainment of exposure among all studies was done through medical records. Finally, given that our primary outcome was mortality and acute postoperative complications, we can ensure that the outcome of interest was not present at the start of the study in all patients.

Comparability

All of the included studies, except for one,[9] adjusted for comparability between the intervention groups, either by propensity-score matching or multiregression analysis.

Outcome

All studies had at least a 30-day follow-up period (which we considered sufficient based on our primary outcome of 30-day mortality). Nine out of the 11 studies either had a complete follow-up or minimal attrition rates suggesting a low risk of attrition bias.

Table 1 Characteristics of the included studies

Study	Country	Study design	Intervention (N)	Type of valve	Duration of follow-up (days or months)	Outcomes	Main finding
Paparella 2019[17]	Italy	Retrospective cohort	miAVR (386)	Mechanical (Bicarbon and CarboMedics); Biological (Hancock II and Mosaic)*	–	30-day ACM, stroke, repeat intervention, AF, AKI, hospitalisation duration	► The miAVR arm required more blood transfusion, longer hospitalisation, and had a higher incidence of AKI. ► The TAVI arm had more permanent pacemakers. ► No differences in terms of 30-day mortality or stroke.
			TAVI (386)(98% TF; 2% TA)†	CoreValve (93.2%), Lotus (6.8%)†			
Furukawa 2018[18]	Germany	Retrospective cohort	miAVR (177)	miAVR: Perimount Magna (74%), Perimount Magna Ease (14.1%), Hancock II (2.8%), Trifecta (7.9%), Perceval (1.1%)	766 days	30-day ACM, bleeding, stroke, AMI, AF, AKI, paravalvular leakage, hospitalisation duration	► Longer hospitalisation in the transapical arm. ► The transapical arm trended towards worse midterm survival. ► No differences in terms of 30-day mortality, stroke or myocardial infarction.
			TA–TAVI (177)	TA–TAVI: Sapien XT (41.8%), Sapien 3 (32.2%), Accurate TA (26%)			
			TF–TAVI (177)	CoreValve (55.9%), Sapien XT 15.8%, Sapien 3 (14.7%), Accurate TF neo (2.3%), Direct Flow (11.3%)			
Calle-Valda 2017[19]	Spain	Retrospective cohort	miAVR (50)	NA	46.7 months	30-day ACM, repeat intervention (re-exploration for bleeding), bleeding (postoperative bleeding mL/24 hours), stroke (30 days), AF, 30-day readmission, hospitalisation duration (days)	The TAVI arm required more pacemakers and had higher rates of paravalvular leakage. The TAVI arm required shorter hospitalisation. No statistically significant differences in terms of survival.
			TF–TAVI (50)	CoreValve (100%)			
Bruno 2017[22]	Italy	Retrospective cohort	miAVR (19)	Intuity Valve (100%)	29.1 months	ACM, bleeding, stroke, AMI, AF, paravalvular leakage (early and midterm), hospitalisation duration	► The TAVI arm required more pacemakers and had higher rates of paravalvular leakage. ► No significant differences in terms of mortality.
			TF–TAVI (30)	CoreValve (100%)	27.7 months		
Hijri 2017[30]	USA	Retrospective cohort	SAVR (722)	Bioprosthetic (92%), Mechanical (8%)	35 months	Operative mortality, AKI, hospitalisation duration	The TAVI (irrespective of approach), miAVR and conventional surgical arms had comparable rates of intraoperative and midterm mortality.
			TAVI (306)	Sapien (28.4%), Sapien XT (23.9%), Sapien 3 (30.7%), CoreValve (15%)			

Continued

Table 1 Continued

Study	Country	Study design	Intervention (N)	Type of valve	Duration of follow-up (days or months)	Outcomes	Main finding
Nguyen 2017[9]	USA	Retrospective cohort	miAVR (699) TF–TAVI (727) TA–TAVI (303)	NA NA NA	–	30 day ACM, stroke, AF, dialysis, hospitalisation duration	▶ The results showed an increasing rate of adoption for TF–TAVI and miAVR, but a decrease in TA–TAVI and conventional surgery. ▶ 30-day mortality was highest for TA–TAVR, followed by TF–TAVR, SAVR and miAVR.
Tokarek 2015/2016[23]	Poland	Retrospective cohort	TF–TAVI (39) MT (50) MS (44)	Sapien XT (79%), CoreValve (21%) NA NA	583.5 days	ACM (30 days, 6 months, 1 year), bleeding, stroke, AMI, AF, paravalvular leakage QoL (EQ-5D-3L and MLHFQ 24 M)	▶ The TAVI arm had a higher ejection fraction, but there were no differences in mortality (2015). ▶ The TAVI arm had better QoL for up to 1 year, but no differences persisted at 2 years (2016).
Miceli 2016[21]	Italy	Retrospective cohort	RT (37) TAVI (37)(51.6% TF; 48.3% TA)**	Perceval S (100%) Sapien (100%)	13 months	Mortality, bleeding, stroke, paravalvular leakage, AKI, hospitalisation duration	▶ The TAVI arm had a significantly higher rate of paravalvular leakage. ▶ No significant differences in terms of stroke, 1 year and 2 year survival.
Santarpino 2014[16]	Germany	Retrospective cohort	MIS (37) TAVI (37) (59% TA; 40.2% TF; 0.8% transaortic)†	Perceval (100%) Sapien, Sapien XT*	18.9 months	In-hospital mortality, stroke, paravalvular leakage, AKI	▶ In high-risk patients, cumulative survival was higher in the miAVR arm compared with the TAVI arm. ▶ TAVI had significantly higher rates of paravalvular leakage, which was significantly associated with mortality.
Haldenwang 2014[29]	Germany	Retrospective cohort	miAVR (77) TA–TAVI (56)	Perimount, Trifecta* SAPIEN (100%)	–	AKI	▶ TA–TAVI carried a higher risk of AKI.
Zierer 2009[20]	Germany	Retrospective cohort	TA–TAVI (21) PUS-AVR (30)	Cribier-Edwards (100%) Perimount (100%)	–	ACM (30 days, 1 year), repeat intervention, stroke, AMI, AF, hospitalisation duration	▶ TA–TAVI had shorter postoperative recovery. ▶ There were no significant differences in terms of morbidity or mortality.

*Insufficient data provided to specify the percentages used for each valve type.
†Percentages given for overall cohort rather than the propensity-matched cohort used for analysis, as data for the latter were not available.
ACM, all-cause mortality; AF, atrial fibrillation; AKI, acute kidney injury; ; AMI, acute myocardial infarction; miAVR, minimally invasive aortic valve replacement; MIS, minimally invasive sutureless; MS, ministernotomy; MT, mini-thoracotomy; NA, not available; PUS-AVR, partial upper sternotomy-aortic valve replacement; RD-AVR, rapid-deployment aortic valve replacement; RT, right anterior mini-thoracotomy; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement; TF, transfemoral.

Table 2 Baseline characteristics of enroled patients in the included studies

Study	Demographics		Comorbidities (%)									Surgical Risk Score		
	Age mean/ med (SD/ range)	Males (%)	Diabetes	Hyper-tension	AF	Kidney disease	Prior MI	Prior stroke	Prior CS	Prior PCI	STS score	Euro Score II	Log EuroScore (%)
Paparella 2019[17]													
miAVR	81 (5)	43	29.5	87.5	19.6	14.4	–	1.0	9.9	–	–	3.0 (2.0–4.8)*	
TAVI	81 (7)	40.9	26.8	85.9	20.2	14.0		1.8	10.9			2.9 (2.2–4.4)*	
Furukawa 2018[18]													
miAVR	78 (75–82)	46.9	29.9	89.3	12.4	–	8.5	4.0	0.6	–	3.2 (2.7)†	3.0 (2.3)†	–
TA–TAVI	80 (75–84)	49.1	28.8	88.7	10.7	–	6.2	5.7	1.1	–	3.6 (2.4)†	3.4 (3)†	–
TF–TAVI	79 (75–83)	50.8	28.3	89.3	11.3	–	7.3	5.7	0.6	–	3.4 (2.2)†	2.9 (0.5)†	–
Calle-Valda 2017[19]													
miAVR	82.3 (4.8)	56.0	22.0	82.0	8.0	2.0	6.0	10.0	–	–	–	–	8.3±3.4*
TAVI	85.6 (4.9)	46.0	32.0	92.0	32.0	18.0	16.0	20.0					15.8±5.4*
Bruno 2017[22]													
RD-AVR‡	79.9 (3.6)	50.0	20.0	83.3	–	10.0	10.0	–	–	–	–	5.01±0.87*	–
TAVI	81.1 (3.3)	56.7	31.0	73.3	–	16.7	6.9	–	–	–	–	5.19±1.15*	–
Hijri 2017[30]													
SAVR	84.1 (3.2)	47.8	19.3	79.5	–	5.1	9.0	5.7	18.6	–	5.58 (3.48)§	–	–
TAVI	86.2 (3.9)	47.4	35.0	80.1		13.1	24.2	12.7	31.7		6.81 (4.54)§	–	–
Nguyen 2017[9] ¶													
Tokarek 2015/2016[23]													
TF–TAVI	80 (73–83)	35.9	–	–	–	–	10.5	–	15.4	46.2	–	3.4 (1.8–5.4)*	9.5 (7–4)*
MT	63 (54–73)	66.0	–	–	–	–	16.0		0.0	10.0		1 (0.7–1.4)*	2.7 (1.8–3.8)*
MS	67 (57–77)	45.4	–	–	–	–	13.6		2.3	11.4		1.2 (0.9–1.6)*	4 (2.2–7)*
Miceli 2016[21]													
RT	79 (4.5)	30.1	27	86.5	–	–	–	–	–	–	–	–	16.1±11§
TAVI	78.8 (7.4)	40.5	18.9	83.8									15.7±8.5§
Santarpino 2014[16]													
MIS	81.5 (5.1)	40.5	–	73.0	–	13.5	27	–	–	–	–	–	18.1±1.9*
TAVI	84.5 (5.1)	48.6		59.5		13.5	37.8						20.6±2.2*
Haldenwang 2014[29]													
miAVR	81.9 (4.5)	57.1	31.2	–	–	–	–	–	–	–	–	8.7±(6.9)§	–
TA–TAVI	78.5 (3.4)	41.1	26.8									4.5±(5.7)§	–
Zierer 2009[20]													
TA–TAVI	85.0 (6)	29.0	29.0	–	–	19.0	–	14.0	14.0	–	–	–	38.0 (14)*
PUS–AVR	82.0 (4)	37.0	23.0			10.0		5.0	0.0				35.0 (9)*

*Reported as % (range).
†Reported as median % (IQR).
‡Baseline characteristics reported here represent the rapid deployment cohort as a whole, however only 19 patients underwent the procedure through a minimally invasive approach thus were included in the analysis.
§Reported as mean % (SD).
¶Authors did not report baseline characteristics for the cohort.
AF, atrial fibrillation; CS, cardiac surgery; miAVR, minimally invasive aortic valve replacement; MIS, minimally invasive sutureless; MS, ministernotomy; MT, mini-thoracotomy; PCI, percutaneous coronary intervention; PUS, partial upper sternotomy; RD-AVR, rapid-deployment aortic valve replacement; RT, right anterior mini-thoracotomy; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral.

Outcomes

All-cause mortality

One month

Five studies[17–21] reported on 30-day all-cause mortality. We found no significant difference between TAVR and miAVR (RR: 1.00, 95% CI: 0.55 to 1.81, n=1528, I^2=0%) with no evidence of heterogeneity. Even after excluding

the high surgical-risk cohort by Zierer *et al*[20] from the analysis, the pooled effect estimate showed no significant difference (RR: 1.23, 95% CI: 0.57 to 2.64, I^2=23%). This difference remained non-significant after limiting the analysis to studies that adopted a transapical approach (RR: 0.57, 95% CI:0.15 to 2.15, I^2=0%), studies which (partially) employed newer generation valves (RR:
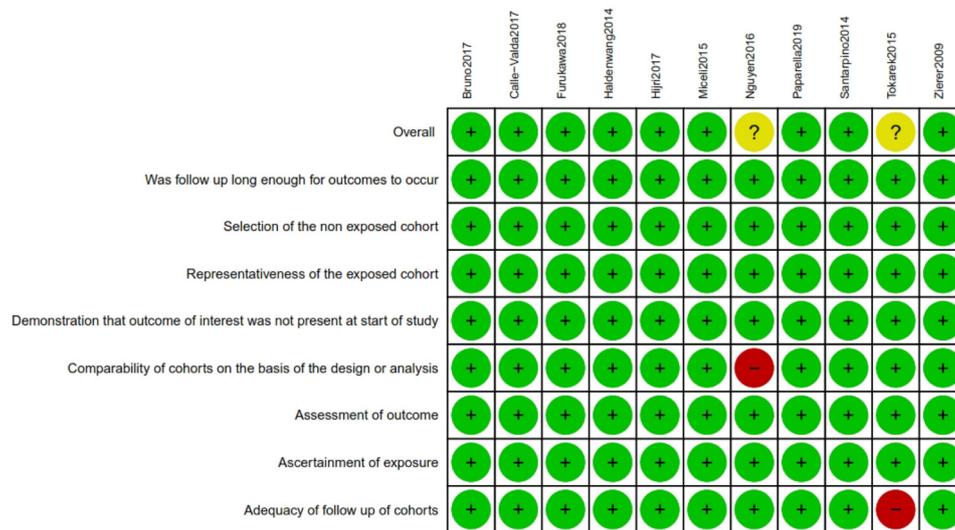
Figure 2 Risk of bias assessment results as per the Newcastle-Ottawa scale.

0.88, 95% CI: 0.45 to 1.73, $I^2=0\%$) and recent studies, published no earlier than 2015 (RR: 0.96, 95% CI: 0.48 to 1.91, $I^2=6\%$; figure 3A).

Midterm mortality
Four studies[19–22] contributed to the effect estimate of midterm mortality (as defined by a minimum follow-up of 1 year). Patients undergoing TAVR had a significantly higher rate of midterm mortality than those undergoing miAVR (RR: 1.93, 95% CI: 1.16 to 3.22, n=211, $I^2=0\%$). Challenging our results, we included Bruno *et al*'s[22] results on the worst-case assumption that both patients who died in the surgical arm were in the miAVR group as separate data were not made available for the miAVR arm; figure 3B. A similar finding was obtained when analysing only recent studies (published no earlier than 2015, RR: 1.85, 95% CI: 1.05 to 3.26, $I^2=0\%$). However, subgroup

analysis of the two studies that exclusively employed the transfemoral (TF) approach revealed a non-significant difference (RR: 1.71, 95% CI: 0.86 to 3.43, $I^2=0\%$), which could be due to either better results with TF approach or a significant reduction in the analysis power when excluding the other two studies.

Stroke
Six studies[17–22] reported the outcome of stroke. We found no significant differences between TAVR and miAVR (RR: 1.08, 95% CI: 0.40 to 2.87, n=1588, $I^2=5\%$) with little evidence of heterogeneity; figure 4A. Similar results were obtained after limiting analysis to studies (partially) employing newer generation valves (RR: 0.67, 95% CI: 0.17 to 2.61), recent studies published no earlier than 2015 (RR: 1.18, 95% CI: 0.42 to 3.31, $I^2=0\%$) or studies

Table 3 Summary of findings and GRADE assessment results

Outcome	No of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Total number of patients	Effect size* (95% CI)	Quality of evidence
30-Day mortality	5	Low	Low	Low	High†	Low	1528	1.00 (0.55 to 1.81)	Very low
One-year mortality	4	Low	Low	Low	Low	Low	211	1.93 (1.16 to 3.22)	Low
Stroke	6	Low	Low	Low	High†	Low	1588	1.08 (0.40 to 2.87)	Very low
Paravalvular leakage	5	Low	Low	Low	Low	Low	1537	14.89 (6.89 to 32.16)	Moderate‡
Kidney injury	4	Low	Low	Low	Low	Low	1428	0.38 (0.21 to 0.69)	Moderate‡
AF	5	Low	High§	Low	High†	Low	1514	0.37 (0.10 to 1.32)	Very low
Major bleeding	4	Low	Low	Low	High†	Low	716	1.24 (0.46 to 3.35)	Very low
Hospitalisation duration	6	Low	High§	Low	Low	Low	1588	1.92 (0.61 to 3.24)	Very low

*All effect sizes, with the exception of hospitalisation durations (presented as mean differences), are presented as relative risk ratios.
†Crosses threshold of no difference.
‡Upgraded due to large effect size.
§High I^2 and non-overlapping confidence intervals.
AF, atrial fibrillation; GRADE, Grading of Recommendations Assessment, Development and Evaluation.
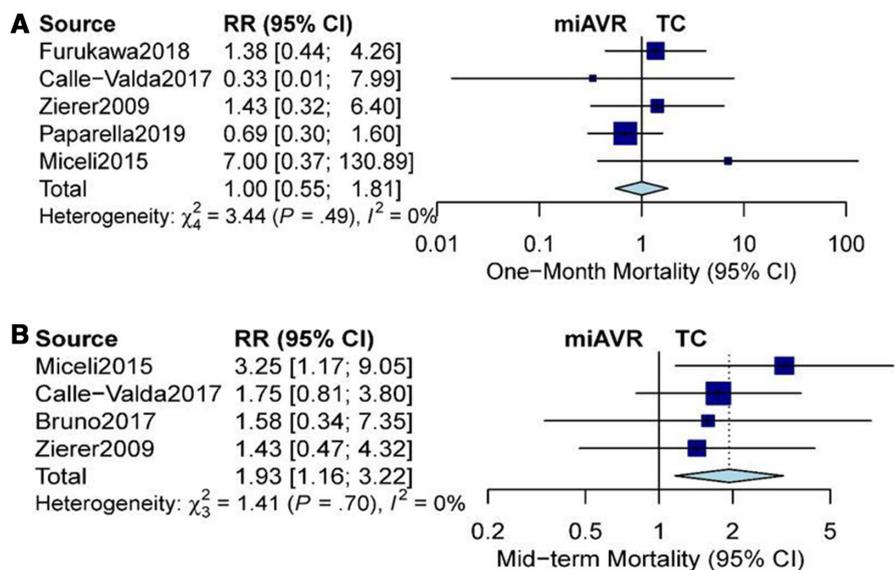
Figure 3 Forest plot comparing TC and miAVR (RR, 95% CI). (A) One month all-cause mortality and (B) midterm all-cause mortality. miAVR, minimally invasive aortic valve replacement; RR, risk ratio; TC, transcatheter.

that used the TF approach (RR: 1.70, 95% CI: 0.47 to 6.23, I^2=0%).

Paravalvular leakage

Five studies[16 18–21 23] reported on paravalvular leakage. Our results show an increased incidence of paravalvular leakage with TAVR (RR: 14.89, 95% CI: 6.89 to 32.16, n=1537, I^2=0%; figure 4B). This result was persistent after excluding the study by Santarpino et al[16] where data were not provided separately for the miAVR group but was included in the main analysis as paravalvular leakage did not occur at all in the entire surgical cohort (RR: 15.24, 95% CI: 6.85 to 33.92, I^2=0%). Similar results were obtained after limiting analysis to studies published

no earlier than 2015 (RR: 15.79, 95% CI: 6.87 to 36.27, I^2=0%) or employing newer generation valves (RR: 16.18, 95% CI: 5.21 to 50.22).

Acute kidney injury

Four studies[16–18 20] reported on AKI. We showed a significantly lower incidence of AKI with TAVR compared with miAVR (RR 0.38, 95% CI: 0.21 to 0.69, n=1428, I^2=35%), with moderate evidence of heterogeneity. On excluding Santarpino et al's[16] results where miAVR outcomes were not reported separately, the heterogeneity was resolved (RR: 0.34, 95% CI: 0.23 to 0.51, I^2=0%) with more of an advantage for TAVR.
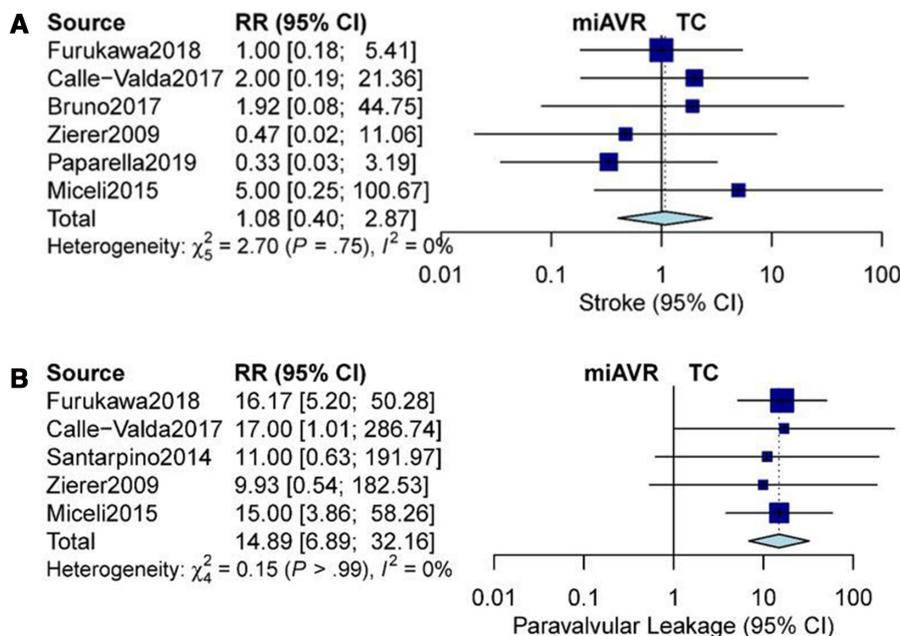

Figure 4 Forest plot comparing transcatheter and miAVR (RR, 95% CI). (A) Stroke and (B) paravalvular leakage. miAVR, minimally invasive aortic valve replacement; RR, risk ratio; TC, transcatheter.

Atrial fibrillation

Six studies[17–20 22 23] reported on AF outcome. Initially, our results showed no significant differences between the two groups in terms of the incidence of postoperative AF (RR: 0.37, 95% CI: 0.10 to 1.32, n=1514, I^2=89%). However, the significant heterogeneity prompted us to probe further; we found that when considering only TF–TAVR procedures where some of the patients received newer generation valves, the reduction in postoperative AF became statistically significant in favour of TAVR, though heterogeneity was still high (RR: 0.14, 95% CI: 0.04 to 0.48, I^2=88%).

Major bleeding

Four studies reported on major postoperative bleeding,[18 20–23] with no significant difference between the two approaches (RR: 1.24, 95% CI: 0.46 to 3.35, n=716, I^2=0%).

Hospitalisation duration

Six studies[17–22] reported on hospitalisation duration, with miAVR showing significantly longer durations as compared with TAVR (MD: 1.92, 95% CI: 0.61 to 3.24, n=1588, I^2=95%), though high heterogeneity was observed. On excluding the TA cohorts of Zierer et al[20] and Bruno et al,[22] both of which had extreme values (the former in favour of TAVR and the latter in favour of miAVR), heterogeneity was resolved (MD: 2.00, 95% CI: 1.61 to 2.40, I^2=0%).

DISCUSSION

Despite the promising short-term results of the PARTNER trials,[7 31] long-term outcomes after TAVR remain an ongoing concern. For instance, 2 to 5 year follow-up analysis of the PARTNER 2 trial[31] demonstrated a higher incidence of all-cause mortality in the TAVR cohort. Many have postulated that the underlying reasons may include the increased likelihood of structural valve degeneration and paravalvular leakage associated with TAVR. Consistent with this hypothesis, the TAVR cohort in the PARTNER 2 trial had a greater need for repeat intervention and valve-in-valve TAVR. Unfortunately, the PARTNER trials did not separately compare TAVR with miAVR (as the surgical arm was inclusive of all approaches); therefore, leaving an important gap in the literature.

In our pooled analysis, the 30-day all-cause mortality did not differ significantly between both groups; however, midterm mortality was significantly higher in the TAVR cohort. It should be noted that none of the included studies independently demonstrated a survival difference, likely due to the lack of statistical power, a common issue with propensity-matched studies (owing to the smaller sample size produced by the matching process). We could not include the study by Tokarek et al,[23] which found no significant differences between the two approaches because rather than matching patients at baseline, the authors only adjusted for confounders by inserting the propensity score as a variable in their logistic regression model. Their results contrasted with ours in that they trended towards (but were not significant for) higher survival rates with TAVI; however, the small sample size and consequently wide confidence intervals limit our ability to draw solid conclusions. The study by Hirji et al[30] investigated the same question in octogenarians and after adjustment for a number of important variates in a Cox model, none of the approaches (TF/TA–TAVI, miAVR or conventional surgery) seemed to be statistically significant determinants of survival. Further studies, especially RCTs, are warranted to better delineate the outcome differences between the two procedures.

Our finding that TAVR is associated with a greater degree of paravalvular leakage is consistent with previous studies.[7 31] The PARTNER 2A trial suggested that moderate-to-severe regurgitation may be associated with higher mortality on extended follow-up, which may explain our previous finding. The lower risk of paravalvular leakage with miAVR may be due to a number of factors, including the ability to resect the previously calcified native valve,[32] and the relatively lower degree of mechanical stress on valve leaflets.[33]

In addition, our analysis demonstrated a lower risk of AF with TF–TAVR when newer generation valves were utilised. This finding is in agreement with previous studies which have reported a lower risk of AF with TAVR procedures, and others which suggest that the TF approach and newer generation valves are associated with a lower risk of AF.[34–38] This is particularly important as AF has been shown to be associated with a higher incidence of mortality, stroke, bleeding and pacemaker placement post-TAVR.[39–43]

Our analysis also demonstrated that TAVR was associated with a lower risk of AKI compared with miAVR. This contrasts with a previous study by Haldenwang et al,[29] which showed a higher incidence of AKI with TAVR; however, in Haldenwang et al's study, the TAVR arm only employed the TA approach, which was shown to be associated with higher rates of AKI than TF approach.[44] A possible explanation may be the non-pulsatile blood flow provided by cardiopulmonary bypass and aortic cross-clamping, which may either increase ischaemic times or increase the risk for embolic events to the kidney, causing reversible ischaemic renal damage.

As previously reported in the literature, TAVR was associated with shorter hospitalisation durations. This finding is understandable if we consider the relatively greater degree of surgical trauma and invasiveness inherent to miAVR. The heterogeneity in our result was explained by the utilisation of TA–TAVR in one study[20] and an increased incidence of pacemaker implantation in the TAVR cohort in the other.[22] The only study to report on quality of life was an unmatched cohort that showed better quality of life with TAVI on the short term (1 month and 1 year), but no differences on the long term (2 years).[28]

Our study has some limitations. First, we could not conduct separate subgroup long-term mortality

analysis for the TF cohort or different surgical risk strata given the lack of sufficiently detailed data within the included studies. Second, many of the studies used older-generation valves, which may have hampered or confounded TAVR's longer-term effectiveness over miAVR. Further, some eligible studies did not provide data on important outcomes such as long-term mortality and AKI; therefore future studies should employ longer follow-up periods in addition to a more comprehensive reporting of outcomes. Finally, though we only included propensity-matched studies in our analyses, we were still unable to completely rule-out the possible confounding by variables not accounted for in the matching process. An individual patient data meta-analysis approach could be valuable in this regard.

The recent results of the PARTNER 2A and 3[7 31] trials seem to have placed TAVR in the driving seat for most AVR procedures. Nevertheless, long-term valvular dysfunction and consequent mortality remain valid concerns. Likewise, miAVR has also seen a considerable increase in uptake over the past few years along with the general preference for less invasive approaches dominating the realm of AVR in selected patients. The use of miAVR may retain the superior haemodynamic outcomes usually associated with surgery, while minimising the downsides of the highly invasive SAVR; all while providing better long-term survival outcomes than TAVR. Yet, the higher risks of AKI and prolonged hospitalisation deserve attention. Nevertheless, these findings need to be confirmed in future RCTs, as the current state of the literature does not allow a definitive statement in this regard. In addition, our findings suggest an urgent need to develop comprehensive evidence-based criteria to determine which patients, especially the younger population, may benefit most from either of the two procedures.

CONCLUSION

According to our meta-analysis of matched cohort studies, miAVR may be associated with a lower risk of midterm mortality, while TAVR was associated with shorter hospitalisation durations and a lower risk of AKI. Given the increasing adoption of both techniques, there is an urgent need for head-to-head randomised trials with adequate follow-up periods.

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Supplementary File II: Literature Search Strategies

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1. MEDLINE via PubMed

((((aortic stenosis[MeSH Terms]) OR ((aort*[Text Word]) AND stenos*[Text Word]))) AND ((((minimal*[Text Word])

OR Minimally Invasive Surgical Procedures[MeSH Terms])) AND (((((Surg*[Text Word] OR Operat*[Text Word] OR

Replace*[Text Word] OR Implant*[Text Word]))) OR Aortic Valve Stenosis/surgery*[MeSH Terms]) OR Aortic Valve

Stenosis/surgery*))) AND ((((Transcatheter Aortic Valve Replacement[MeSH Terms]) OR ((tavi[Text Word] OR ta-

tavi[Text Word] OR tavr[Text Word] OR pavi[Text Word] OR pavr[Text Word]))) OR (((((((((implant*[Text Word] OR

insert*[Text Word] OR replace*))) AND valve*[Text Word]) AND aort*[Text Word]))) AND ((transcutan*[Text Word]

OR transarterial*[Text Word] OR percutan*[Text Word] OR transcatheter*[Text Word] OR transkatheter*[Text

Word] OR transapical*[Text Word] OR transfemor*[Text Word] OR transsubclav*[Text Word] OR transaort*[Text

Word] OR trans- cutan*[Text Word] OR trans-arterial*[Text Word] OR trans-catheter*[Text Word] OR trans-

katheter*[Text Word] OR trans-apical*[Text Word] OR trans-femor*[Text Word] OR transsubclav*[Text Word] OR

trans-aort*[Text Word])))))))) Filters: Publication date from 2002/01/01

2. Embase

1 exp clinical article/ (2283463)

2 exp controlled study/ (7251218)

3 exp major clinical study/ (3268487)

4 exp prospective study/ (569399)

5 exp cohort analysis/ (533602)

6 cohort.ti,ab. (858241)

7 compared.ti,ab. (4606972)

8 groups.ti,ab. (2721585)

9 'case control'.ti,ab. (156659)

10 multivariate.ti,ab. (473641)

11 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 (13292388)

12 ('crossover procedure':de or 'double-blind procedure':de or 'randomized controlled trial':de or 'singleblind

procedure':de).mp. or (((random* or factorial* or crossover* or cross) adj over*) or placebo* or

doubl* adjn blind* or singl* adjn blind* or assign* or allocat* or volunteer*).de,ti,ab. [mp=title, abstract,

heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade

name, keyword, floating subheading word, candidate term word] (1162557)

13 11 or 12 (13637171)

14 exp Transcatheter Aortic Valve Replacement/ (19756)

15 tavi.ti,ab. (9219)

16 ta-tavi.ti,ab. (190)

17 tavr.ti,ab. (5800)

18 pavi.ti,ab. (51)

19 pavr.ti,ab. (99)

20 14 or 15 or 16 or 17 or 18 or 19 (21586)

21 implant*.ti,ab. (508724)

22 insert*.ti,ab. (332115)

23 replace*.ti,ab. (477445)

24 21 or 22 or 23 (1236539)

25 valve*.ti,ab. (180183)

26 aort*.ti,ab. (343946)

27 25 and 26 (78101)

28 24 and 27 (47240)

29 20 or 28 (51334)

30 transcutan*.ti,ab. (17530)

31 transarterial*.ti,ab. (10475)

32 percutan*.ti,ab. (207285)

33 transcatheter*.ti,ab. (37952)

34 transkatheter*.ti,ab. (3)

Supplemental material

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Open Heart

35 transapical*.ti,ab. (3353)

36 transfemor*.ti,ab. (8644)

37 transsubclav*.ti,ab. (81)

38 transaort*.ti,ab. (2331)

39 trans- cutan*.ti,ab. (127)

40 trans-arterial*.ti,ab. (1006)

41 trans-catheter*.ti,ab. (1125)

42 trans-katheter*.ti,ab. (0)

43 trans-apical*.ti,ab. (271)

44 trans-femor*.ti,ab. (841)

45 trans-subclav*.ti,ab. (108)

46 trans-aort*.ti,ab. (409)

47 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46

(272714)

48 exp Minimally Invasive Surgical Procedures/ (40013)

49 minimal*.ti,ab. (478272)

50 48 or 49 (490361)

51 Surg*.ti,ab. (2386161)

52 Operat*.ti,ab. (1341159)

53 Replace*.ti,ab. (477445)

54 Implant*.ti,ab. (508724)

55 51 or 52 or 53 or 54 (3854674)

56 Aortic valve stenosis.ti,ab. (4885)

57 surgery.ti,ab. (1479628)

58 56 and 57 (1193)

59 55 or 58 (3854674)

60 50 and 59 (168721)

Supplemental material

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Open Heart

61 exp aortic stenosis/ (8979)

62 exp aortic valve stenosis/ (2671)

63 aort*.ti,ab. (343946)

64 stenos*.ti,ab. (208478)

65 63 and 64 (45623)

66 61 or 62 or 65 (48421)

67 13 and 29 and 47 and 60 and 66 (374)

68 29 or 47 (302390)

69 13 and 60 and 66 and 68 (642)

70 limit 69 to yr="2002 -Current" (584)

3. Cochrane Central

#1 (((transcutan* or transarterial* or percutan* or transcatheter* or transkatheter* or transapical* or transfemor* or transsubclav* or transaort* or trans-cutan* or trans-arterial* or trans-catheter* or transkatheter* or trans-apical* or trans-femor* or trans-subclav* or trans-aort*) and aort* and valve* and (implant* or insert* or replace*))):ti,ab,kw (Word variations have been searched) 1002
#2 MeSH descriptor: [Transcatheter Aortic Valve Replacement] explode all trees 143
#3 ((tavi or ta-tavi or tavr or pavi or pavr)):ti,ab,kw (Word variations have been searched) 859
#4 #1 OR #2 OR #3 1083
#5 MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees 27216
#6 minimal* 38392
#7 #5 OR #6 63188
#8 (Surg* OR Operat* OR Replace* OR Implant*):ti,ab,kw (Word variations have been searched) 311776
#9 MeSH descriptor: [Heart Valve Prosthesis Implantation] explode all trees 757
#10 MeSH descriptor: [Aortic Valve] explode all trees 452
#11 MeSH descriptor: [Aortic Valve Stenosis] explode all trees 867
#12 #9 AND (#10 OR #11) 411
#13 #7 AND (#8 OR #12) 28250
#14 MeSH descriptor: [Aortic Valve Stenosis] explode all trees 867
#15 (aort*):ti,ab,kw (Word variations have been searched) 12126
#16 (stenos*):ti,ab,kw (Word variations have been searched) 12755
#17 #15 AND #16 1947
#18 #14 OR #17 2151
#19 #4 AND #13 AND #18 43

The search strategies were adapted for Clinicaltrials.gov, The WHO trials registry and Web of Science.