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Transcatheter Aortic Valve Implantation versus surgical Aortic Valve Replacement in dialysis-dependant patients: A meta-analysis

Samuel Burton[1], Alexander Reynolds BSc (Hons)[2], Nicola King PhD[3], Amit Modi FRCS(CTh)[4], Sanjay Asopa FRCS(CTh)[5],

1. Faculty of Medicine and Dentistry, University of Plymouth, UK.
2. Swansea University Medical School, Wales, UK.
3. Faculty of Health, University of Plymouth, UK.
4. Wessex Cardiac Centre, Southampton, UK.
5. Southwest Cardiothoracic Centre, Plymouth, UK.

Corresponding Author: Samuel Burton, +44 7572719515, s.burton11@nhs.net,

Address for correspondence: John Bull Building, Plymouth Science Park, Plymouth, PL6 8BU

Objectives

This meta-analysis aims to compare the clinical outcomes of transcatheter aortic valve implantation (TAVI) versus aortic valve replacement (AVR) for aortic stenosis in dialysis-dependent patients.

Methods

Literature searches employed PubMed, Web of Science, Google Scholar and Embase to identify relevant studies. Bias-treated (BT) data was prioritised, isolated, and pooled for analysis; raw data utilised where BT data was unavailable. Outcomes were analysed to assess for study data crossover.

Results

Literature search identified ten retrospective studies; following data source analysis, five studies were included. Upon pooling of BT data, TAVI was significantly favoured in early mortality (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.19-0.92; I2=92%; p=0.03), one-year mortality (OR, 0.88; CI 0.80-0.97; I2=0%; p=0.01), rates stroke/cerebrovascular events (OR, 0.71; CI 0.55-0.93; I2=0%; p=0.01), and blood transfusions (OR, 0.36; CI 0.21-0.62; I2=86%; p=0.0002). Pooling demonstrated fewer new pacemaker implantations in the AVR group (OR, 3.33; CI 1.94-5.73; I2=74%; p=<0.0001) and no difference in the rate of vascular complications (OR, 2.27; CI 0.60-8.59; I2= 83%; p=0.23). Analysis including raw data revealed the length of hospital stay to favour TAVI with a mean difference of -9.20 days (CI -15.58--2.82; I2=97%; p=0.005)

Conclusions

Bias-treated meta-analysis comparing surgical AVR and TAVI favoured TAVI in early mortality, one-year mortality, rates of stroke/cerebrovascular events and blood transfusions. There was no difference in the rates of vascular complications; however, TAVI required more pacemaker implantations. Data pooling including raw data revealed that the length of hospital admission favours TAVI.

Keywords: Transcatheter aortic valve implantation, Surgical aortic valve replacement, End-stage renal disease, Dialysis, Aortic stenosis.

Abbreviations and Acronyms:

Acute kidney injury (AKI), Aortic stenosis (AS), Aortic valve replacement (AVR), Bias-treated (BT), chronic kidney disease (CKD), Chronic obstructive pulmonary disease (COPD), Confidence interval (CI), End-stage renal disease (ESRD), General Medical Council (GMC), Inverse probability weighting (IPTW), Mean difference (MD), Multi-variable regression model (MVRM), Newcastle-Ottawa Scale (NOS), Overlap propensity score matched (OPSM) Reporting Items for Systematic Review and Meta-Analysis (PRISMA), Propensity score matched (PSM), Randomised control trial (RCT), Transcatheter aortic valve implantation (TAVI).

Introduction

As the incidence of chronic kidney disease (CKD) and the use of dialysis continues to increase globally, owing to increased rates of hypertension and diabetes [1], the occurrence of dialysis-associated aortic stenosis (AS) is becoming more regular due to prolonged increased uraemic milieu and inflammatory mediators [2]. As well as the increased predisposition of progressive AS in dialysis-dependent patients, literature reports accelerated progression and a higher incidence of cardiovascular and all-cause mortality associated with AS in dialysis versus non-dialysis-dependent patients [3-5]. Although CKD is considered a significant co-morbidity for surgical intervention, compounding the pre-existing significant risk of acute kidney injury (AKI), data suggests that the consideration of end-stage renal disease (ESRD) in dialysis patients should not preclude surgeons from aortic intervention [2, 6], as intervention leads to an improvement of prognosis [7, 8]. The question of whether surgical aortic valve replacement (AVR) or the less invasive transcatheter aortic valve implantation (TAVI) produces better outcomes for patients on dialysis remains uncertain due to ESRD patients being excluded from all performed randomised control trials (RCTs) comparing TAVI versus AVR. All data comparing AS interventions in dialysis patients is obtained via observational and retrospective studies. In addition, there is a global insufficient quantity of long-term outcome data. Both TAVI and AVR require complex strategies to reduce risk and/or manage complications perioperatively for dialysis patients, with current guidelines favouring reduced contrast technique for TAVI in high-risk AKI patients [2].

This meta-analysis aims to pool all existing data comparing short-term clinical outcomes of AVR versus TAVI in dialysis-dependent patients, utilising the recent increase in relevant studies.

Materials and Methods

Search Strategy

Electronic databases PubMed, Web of Science, Google Scholar and Embase were consulted using preliminary search terms (“TAVI” AND “AVR" AND ("chronic kidney disease” OR “dialysis-dependent”)). Articles were further reviewed for relevant study identification and previous meta-analyses were consulted. Literature searching was conducted in adherence with Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [9]. Inclusion and exclusion criteria were applied to identify studies selected for review.

Selection Criteria

Previous meta-analyses were consulted, and relevant studies were selected for review and inclusion. Inclusion criteria were as follows: English language double-arm studies comparing TAVI versus AVR in dialysis-dependent patient populations only for AS. Conference presentations, abstracts, case series, case reports, expert opinions and editorials were omitted from screening.

Study Selection and Data Extraction

Search results from the noted databases and additional sources were screened using title and abstract by two independent researchers (S.B and A.R); full manuscripts were further evaluated by applying the inclusion criteria. Any variation in study selection by investigators was resolved by discussion. The quality of all studies was assessed independently by S.B using the Newcastle-Ottawa Scale (NOS). Studies were considered high quality with a score equal to or more than 6 out of 9. Reporting and publication bias was assessed via funnel plots [10]. Data was obtained via extraction of the study text, figures, and table; percentages were converted to raw figures where necessary. Extracted data included study methodology, data source and study period, in addition to adjusted and raw demographic and clinical outcomes data. The reported clinical outcomes extracted and pooled include early mortality (in-hospital and 30-day mortality), one-year mortality,

stroke/cerebrovascular events, vascular complications, new pacemaker implantation, blood transfusions, and length of hospital stay.

Statistical Analysis

This meta-analysis employed the Mantel-Haenszel test, calculating the Odds Ratio (OR) for dichotomous outcomes and Mean Difference (MD) for continuous data, with a 95% confidence interval (CI), and the fixed effects model for outcomes with a calculated heterogeneity (I^2) of <50%, the random-effects model was implemented where I^2= >50%. Statistical analyses were produced where clinical outcomes were reported by three or more of the included studies, with the exception of two large BT sample studies. BT data such as propensity score-matched, inverse probability weighting, and multi-variable regression models were prioritised with raw data employed where BT data was insufficient. Each outcome was independently assessed for data crossover by assessing all study data sources and study periods. In the case of potential crossover by both data source and study period, the more recently studied article was prioritised, and other data samples were excluded from the outcome analysis. Statistical significance was determined by a p-valve of <0.05 for all meta-analyses. Review Manager 5.3 was utilised to produce all meta-analyses and forest plots [11].

Results

Search Results

Databases PubMed, Web of Science, Google Scholar and Embase identified 978 articles using the selected search terms; five articles were identified from other sources including bibliographic searching. The remaining 660 articles were screened by title and abstract after removing duplicate records. Twenty-six articles were reviewed via full manuscript for eligibility, of which 19 studies were omitted based on exclusion criteria. Additionally, three out of the four studies from a previous meta-analysis were selected for inclusion [12]; the remaining excluded study possessed a mixed population of dialysis and non-dialysis CKD patients [13]. A total of 10 observational studies were selected for inclusion in the meta-analysis. However, after study analysis of data source and study period, five studies were included in the meta-analyses [figure 1]. All studies included scored high on quality assessment (NOS), as seen in table 1. NOS scoring can be observed in the supplementary material.

Outcomes

The selected studies contained sufficient data to produce BT statistical analyses for early mortality, one-year mortality, stroke/cerebrovascular events, vascular complications, new pacemaker implantation, and blood transfusions. Raw data was therefore employed for outcomes regarding the length of admission.

Early mortality

Three BT studies involving 8163 patients reported the incidence of early postoperative mortality. One study recorded early mortality 30-days following intervention, and two studies reported outcomes during hospital admission. The TAVI group demonstrated a 3.9% incidence, whilst the AVR group reported a 12.8% incidence. OR 0.42 (95% CI 0.19, 0.92) I^2= 92% and p= 0.03 [figure 2]. There was therefore a significant difference in the incidence of early mortality, favouring the TAVI group.

One-year mortality

Two BT studies involving 7813 patients reported the incidence of one-year postoperative mortality. The TAVI group demonstrated a 28.8% incidence, whilst the AVR group reported a 31.6% incidence. OR 0.88 (95% CI 0.80, 0.97) I^2= 0% and p= 0.01. There was therefore a significant difference in the incidence of one-year mortality, favouring the TAVI group.

Stroke/cerebrovascular events

Three BT studies involving 8163 patients reported the incidence of stroke/cerebrovascular events (excluding transient ischemic attacks). Two studies recorded incidence of stroke/cerebrovascular events 30-days following intervention, and one study reported outcomes during hospital admission. The TAVI group demonstrated a 2.4% incidence, whilst the AVR group reported a 3.3% incidence. OR 0.71 (95% CI 0.55, 0.93) I^2= 0% and p= 0.01. There was therefore a significant difference in the incidence of stroke/cerebrovascular events, favouring the TAVI group [figure 3].

Vascular complications

Three BT studies involving 8163 patients reported the incidence of vascular complications. One study recorded incidence of vascular complications 30-days following intervention, and two studies reported outcomes during hospital admission. The TAVI group demonstrated a 4.9% incidence, whilst the AVR group reported a 2.4% incidence. OR 2.27 (95% CI 0.60, 8.59) I^2= 83% and p= 0.23. There was therefore no significant difference in the incidence of vascular complications between the TAVI and the AVR group.

New pacemaker implantation

Three BT studies involving 8169 patients reported the incidence of new pacemaker implantation. One study recorded rates of new pacemaker implantation 30-days following intervention, and two studies reported outcomes during hospital admission. The TAVI group demonstrated a 12.5% incidence, whilst the AVR group reported a 4.7% incidence. OR 3.33 (95% CI 1.94, 5.73) I^2= 74% and p= <0.0001.

There was therefore a significant difference in the incidence of new pacemaker implantation, favouring the AVR group.

Blood transfusions

Three BT studies involving 8169 patients reported the incidence of blood transfusion. The TAVI group demonstrated a 26.0% incidence, whilst the AVR group reported an 51.0% incidence. OR 0.36 (95% CI 0.21, 0.62) I^2= 86% and p= 0.0002. There was therefore a significant difference in the incidence of blood transfusions, favouring the TAVI group.

Length of admission

Three studies that employ raw data involving 13379 patients reported the length of hospital admission. Mean difference (MD) -9.20 (95% CI -15.58, -2.82) I^2= 97% and p= 0.005. There was therefore a significant difference in the length of hospital admission, favouring the TAVI group.

Discussion

Dialysis-dependent patients have demonstrated increased incidence, acceleration, and worse prognosis, of AS. Although intervention has shown to improve prognosis, dialysis-dependent patients present a higher surgical and postoperative risk for both TAVI and AVR [2, 19]. Previous RCTs comparing TAVI to AVR for treatment of severe aortic stenosis in the intermediate surgical risk group have reported TAVI one-year survival to be similar if not superior to AVR [20-23]. However, all completed RCTs have excluded patients with end-stage renal failure (ESRD) resulting in a present lack of data on the surgical risk and post-operative complications associated with dialysis-dependent patients receiving aortic intervention. Patients with ESRD present with a specific aetiology, as they are more likely to experience co-morbidities, including ischemic heart disease, atrial fibrillation, and hypertension leading to prolonged recovery and possible different clinical outcomes [24].

Multiple studies have identified blood transfusions as an adverse prognostic factor for both TAVI and AVR due to the subsequent increased risk of AKI associated with increased mortality and longer length of admission [25-27]. In patients awaiting renal transplantation, transfusion increases the risk of sensitisation to human leukocyte antigen (HLA) by development of anti-HLA antibodies which may limit time to transplant and have an increased incidence of early or late graft rejection [28]. This current meta-analysis revealed a significantly higher rate of new permanent pacemaker implantation in the TAVI group; a 2020 meta-analysis has demonstrated the negative prognostic value of new pacemaker implantation with increased risk of one-year all-cause mortality in TAVI groups [29]. In contrast, this meta-analysis has shown one-year mortality to be lower in patients receiving TAVI.

Surgical AVR provides the opportunity to employ either bioprosthetic or mechanical valve replacement. The most recent meta-analysis and systematic review comparing mechanical and bioprosthetic AVR in dialysis patients state that mechanical valves demonstrated lower mortality and higher rates of bleeding and stroke. However, the review notes the poor data quality due to suspected selection bias and therefore justified the recommendation of bioprosthetic AVR [30]. When considering mechanical

AVR for dialysis patients, clinicians must also regard the increased incidence of embolic events, the increased risk of bleeding associated with life-long anticoagulation, and the possible rare relation of calciphylaxis identified with warfarin therapy [31, 32]. With the increased occurrence of hospital readmission for patients who received mechanical AVR – likely due to the increased valve-related adverse complications – bioprosthetic valves could be considered more appropriate for higher-risk dialysis-dependent patients [33]. Dialysis-dependent patients demonstrate accelerated degeneration of bioprosthetic valves, with research reporting moderate to severe degeneration present in 29% of patients at five years following bioprosthetic AVR [30]. The accelerated valvular prosthesis calcification for both TAVI and AVR valves is a result of dialysis-dependent patients being at an increased risk of developing hyperphosphatemia and hypercalcemia indicative of secondary hyperparathyroidism [34, 35]. Subsequent valve degeneration may deem early planning of secondary valve replacement/implantation in younger dialysis patients appropriate. Despite the risk of valve-in-valve TAVI-associated coronary occlusion, attributed to previous degenerated prosthetic valve leaflets obstructing the left ostia, literature is demonstrating TAVI-in-TAVI to be technically feasible with comprehensive pre-operative assessment and developing TAVI valves [36, 37].

Although evidence has demonstrated that aortic valve intervention of dialysis-dependent patients with AS leads to increased survival, the postoperative prognosis remains unfortunate in this subset of patients [38]. A study published in 2022 retrospectively analysed the three-year survival of dialysis-dependent patients who received either AVR or TAVI (1020, 1280 respectively) with a median age of 79.47 and 75.45, respectively. The estimated three-year mortality was 78.3% in the TAVI group and 60.3% in the AVR group; however, the study comments on the possible significance of selection bias, with TAVI more likely to be offered to more complex and frail patients [39]. Ultimately a major contributing factor to the poor prognosis of dialysis-dependent patients post-intervention is the low rates of renal transplantation due to the shortage of available transplant organs and the negative impact of increased co-morbidities on the likelihood of receiving renal transplantation [40].

There is currently limited evidence relating to the longevity of TAVI valves in comparison to bioprosthetic AVR in dialysis-dependent patients. The NOTION trial in low risk patients but a mean age of 79.1 years– not including patients with ESRD – although with higher total aortic regurgitation and pacemaker rates in the TAVI group at 1 year, has shown no statistical difference for composite of major clinical outcomes after TAVI with self-expanding valve compared to surgical AVR [41, 42]. Although increased rates of valvular calcification result in a decreased durability of bioprosthetic valves, the poor prognosis following aortic intervention in dialysis-dependent patients without renal transplantation may bring into question the considered significance of valve longevity. With a study reporting five-year mortality of 91.2% [43], consideration must be given to the implication on the quality of life for patients receiving TAVI versus AVR. This meta-analysis has demonstrated an increased length of stay and more frequent surgical and postoperative complications leading to prolonged surgical recovery in the AVR group as well as a decrease in one-year survival in the surgical AVR group. Due to the varied aetiology and complex nature of patients with ESRD, clinicians should employ personalised care via discussion with a multidisciplinary Heart Valve Team in consultation with nephrology physicians to offer treatments in congruence with patient-centred care. The United Kingdom General Medical Council guidelines on professional standards stress the importance of informed consent in ethical decision-making [44]. Medical practitioners should employ counselling to provide dialogue on the current uncertainty of TAVI versus AVR in dialysis-dependent aortic stenosis patients. To facilitate decision-making in line with patient values, counselling must allow for the consideration of patient prognosis, the likelihood of receiving renal transplantation, and the impact on the quality of life that both interventions provide.

Despite sufficient sample size, limitations to the conducted meta-analyses include the small number of studies included and therefore reduced reliability of performed funnel plots. Notwithstanding the prioritisation of BT data, the significance of selection bias is unclear due to the lack of available randomised data. Due to the nature of database analyses, included studies did not report the cause of patient mortality, generations of TAVI devices used, rates of device success, rates of reduced contrast procedures, or the impact of vascular complications concerning dialysis access. Owing to the

heterogeneous aetiology of the patient group and the nature of aortic intervention, as opposed to definitive management of ESRD with renal transplantation, the authors question the reliability/relevance of long-term survival data and emphasise the intervention implications on the length of hospital stay and quality of life. In the absence of randomised studies, the authors believe the conducted analysis provides the highest quality available data relevant to informed patient decision-making.

Conclusion

The findings of this meta-analysis suggest that TAVI may offer better short-term clinical outcomes compared to AVR for aortic stenosis in dialysis-dependent patients. Further research is necessary as to the long-term durability of TAVI prostheses for the dialysis population. However, considering the patient quality of life and the poor prognosis of dialysis-dependent patients following the aortic intervention, TAVI could be offered following patient counselling (with respect to uncertain durability) to adopt an intervention in line with the patient's values.

Conflict of Interest Statement

Conflict of interest: None declared.

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Author Contributions Statement

Conceptualization: Sanjay Asopa

Data Curation: Samuel Burton, Alexander Reynolds

Formal Analysis: Samuel Burton, Alexander Reynolds

Funding acquisition: NA

Investigation: Samuel Burton, Alexander Reynolds, Nicola King.

Methodology: Alexander Reynolds, Nicola King.

Project administration: Samuel Burton, Alexander Reynolds.

Resources: NA

Software: Alexander Reynolds, Samuel Burton.

Supervision: Sanjay Asopa, Amit Modi.

Validation: Nicola King.

Visualisation: Samuel Burton, Alexander Reynolds.

Writing – original draft: Samuel Burton, Alexander Reynolds.

Writing – review & editing: Samuel Burton, Alexander Reynolds, Sanjay Asopa, Amit Modi.

Data Availability Statement:

The data underlying this article are available in the article and in its online supplementary material.

This review is not currently registered.

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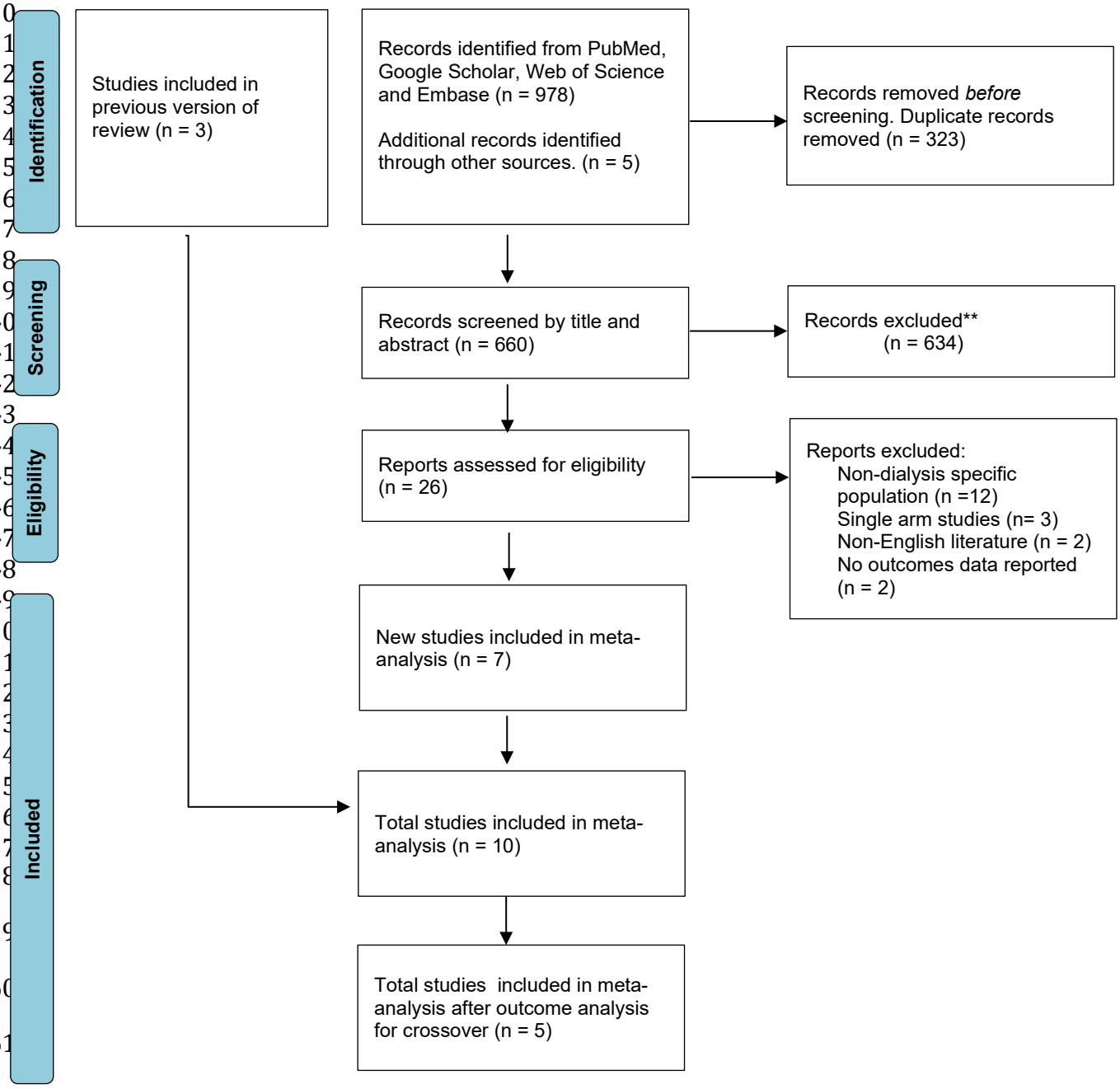
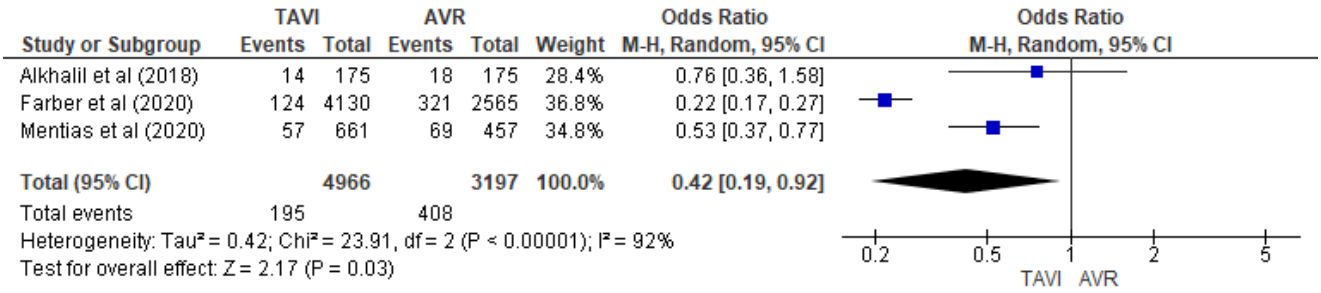
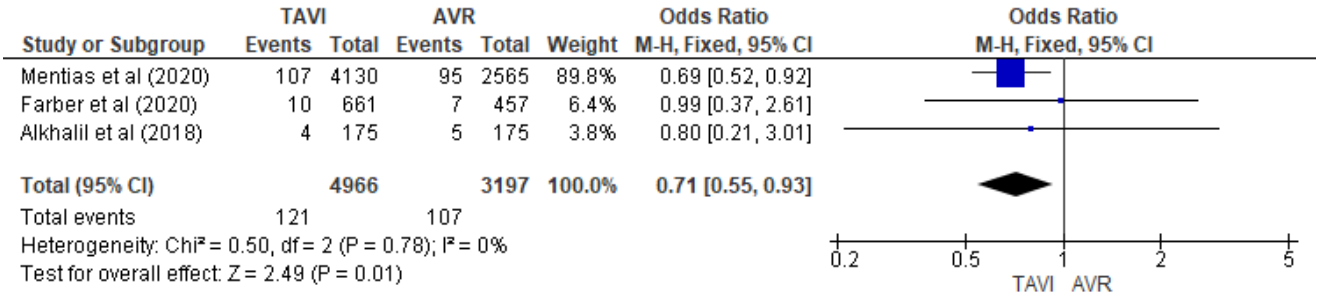
Figure Legend:



[Figure 1 – PRISMA flowchart] - Systematic Review and Meta-Analysis (PRISMA) flowchart of study selection via the process of study screening, applying inclusion and exclusion criteria.



[Figure 2 – Early Mortality Forest Plot.] - Review manager visualisation of meta-analysis, pooling data from included studies on rates of early mortality. Alkhalil, et al and Mentias, et al reported in-hospital mortality. Farber, et al reported 30-day mortality.



[Figure 3 – Stroke/Cerebrovascular Event Forest Plot.] - Review manager visualisation of meta-analysis, pooling data from included studies on stroke/cerebrovascular events. Farber, et al and Mentias, et al recorded incidence of stroke/cerebrovascular events 30-days post-intervention, and Alkhalil, et al reported in-hospital events.

Table 1 – Summarizing Table

	Alkhalil, *et al.* [14]	Ando, *et al.* [15]	Farber, *et al.* [16]	Mentias, *et al.* [17]	Rau, *et al*. [18]
Year of Publication	2018	2020	2021	2020	2012
Study Period	2012-2014	2013-2017	2012-2015	2015-2017	2005-2010
Type of Study	Retrospective Database Analysis	Retrospective Database Analysis	Retrospective Database Analysis	Retrospective Database Analysis	Multi-Centre Retrospective Analysis
Bias Control	PSM	MVRM	IPTW	OPSM	
NOS Score	8	7	8	7	6
TAVI (n)	175	5731	661	4130	15
AVR (n)	175	6491	457	2565	24
TAVI Access (% endovascular)	80	92.1	69 - All transfemoral		80 - 60% transfemoral, 20% axillary
% of bioprosthetic AVR prosthesis					83.3
Outcomes Employed in Analysis (% TAVI, AVR):					
Early Mortality	8.0, 10.3		3.0, 12.5	8.6, 15.1	
One-Year Mortality			33.4, 35.0	28.1, 31.0	
Stroke/Cerebrovascular Event	2.3, 2.9		1.5, 1.5	2.6, 3.7	
Blood Transfusion	35.4, 53.1		89.7, 95.3	15.4, 43.0	
Pacemaker Implantation	13.1, 5.7		18.2, 3.7	11.6, 4.8	
Vascular Complications	4.0, 6.3		4.8, 0.2	4.9, 2.5	
Length of Hospital Stay (Mean)		12, 18	10, 23.2		22.5, 24

Propensity score matched (PSM), Overlap propensity score matched (OPSM), Inverse probability weighting (IPTW), Multi-variable regression model (MVRM)
Adjusted data employed where possible.
Endovascular approach was defined as non-apical access.

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Table 2 – Demographics [a]

		Alkhalil, *et al.*	Ando, *et al.*	Farber, *et al.*	Mentias, *et al.*	Rau, *et al.*
	TAVI (n)	175	5731	661	4130	15
	AVR (n)	175	6491	457	2565	24
Age (Mean)	TAVI	70.63	74.00	78.00	63.18	69.5
	AVR	70.46	63.5	76.00	63.18	66.5
Male Gender	TAVI	67.40	61.90	69.10	67.00	73.00
	AVR	67.40	68.30	74.30	67.00	79.00
Diabetes	TAVI	27.40	54.10	45.20	66.00	40.00
	AVR	26.90	45.60	49.30	66.00	26.00
Hypertension	TAVI	88.60	94.70	87.20	99.00	87.00
	AVR	86.90	92.80	49.30	99.00	88.00
Heart Failure	TAVI	9.70	81.60		82.00	
	AVR	9.70	65.50		82.00	
COPD/Chronic Pulmonary Disease	TAVI	22.30	38.00	27.70	38.00	14.00
	AVR	22.30	30.50	25.60	38.00	13.00
Atrial Fibrillation / Atrial Flutter	TAVI		42.40	36.80	38.00	46.00
	AVR		43.00	36.70	38.00	35.00

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[a] Adjusted Demographic data was employed where possible.

Section and Topic	Item #	Checklist item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5

Section and Topic	Item #	Checklist item	Reported on Page #
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-12
	23b	Discuss any limitations of the evidence included in the review.	12-13
	23c	Discuss any limitations of the review processes used.	10-13
	23d	Discuss implications of the results for practice, policy, and future research.	10-13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

PRISMA – Abstract Checklist:

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes to source.
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes (not participants)
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Section and Topic	Item #	Checklist item	Reported (Yes/No)
OTHER			
Funding	11	Specify the primary source of funding for the review.	NA
Registration	12	Provide the register name and registration number.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Newcastle-Ottawa Scale:

	Selection				Comparability	Outcome			
	Exposure Cohort Representive	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis **	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total
Alkhalil et al.	+	+		+	++	+	+	+	8
Ando et al.	+	+			++	+	+	+	7
Farber et al.	+	+		+	++	+	+	+	8

Mentias et al.	+	+			++	+	+	+	7
Rau et al.	+	+		+		+	+	+	6

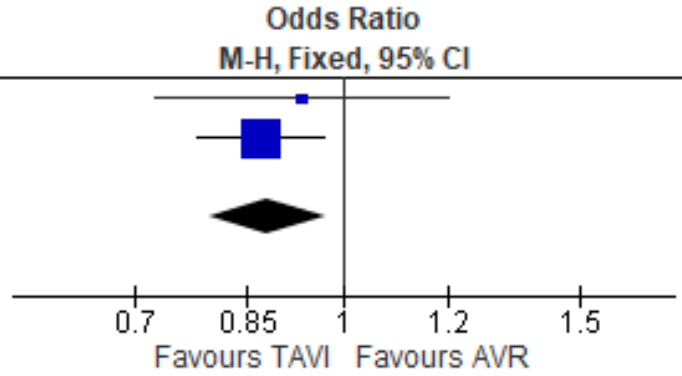
Meta-analysis Forest Plots + Funnel Plots:

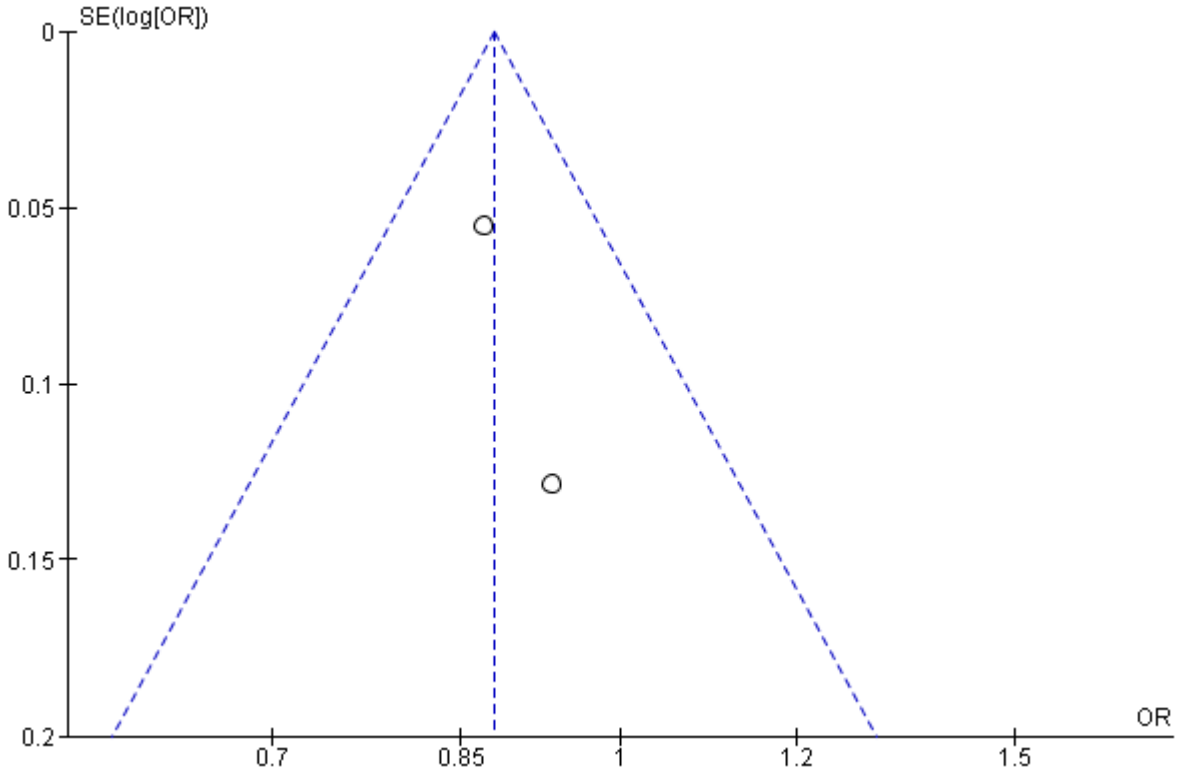
One-year mortality:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Farber et al (2020)	221	661	160	457	15.1%	0.93 [0.73, 1.20]
Mentias et al (2020)	1160	4130	795	2565	84.9%	0.87 [0.78, 0.97]
Total (95% CI)		**4791**		**3022**	**100.0%**	**0.88 [0.80, 0.97]**
Total events	1381		955			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%

Test for overall effect: Z = 2.55 (P = 0.01)

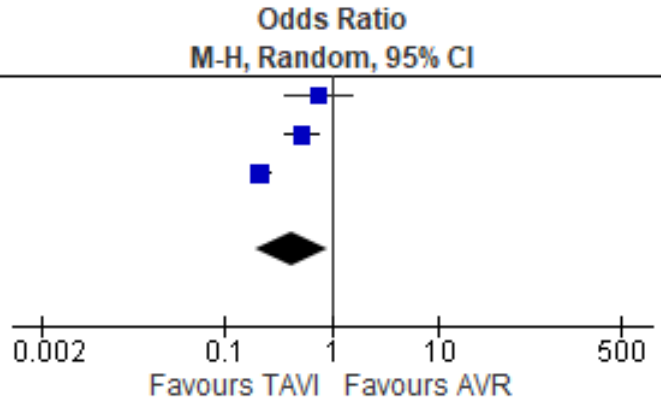


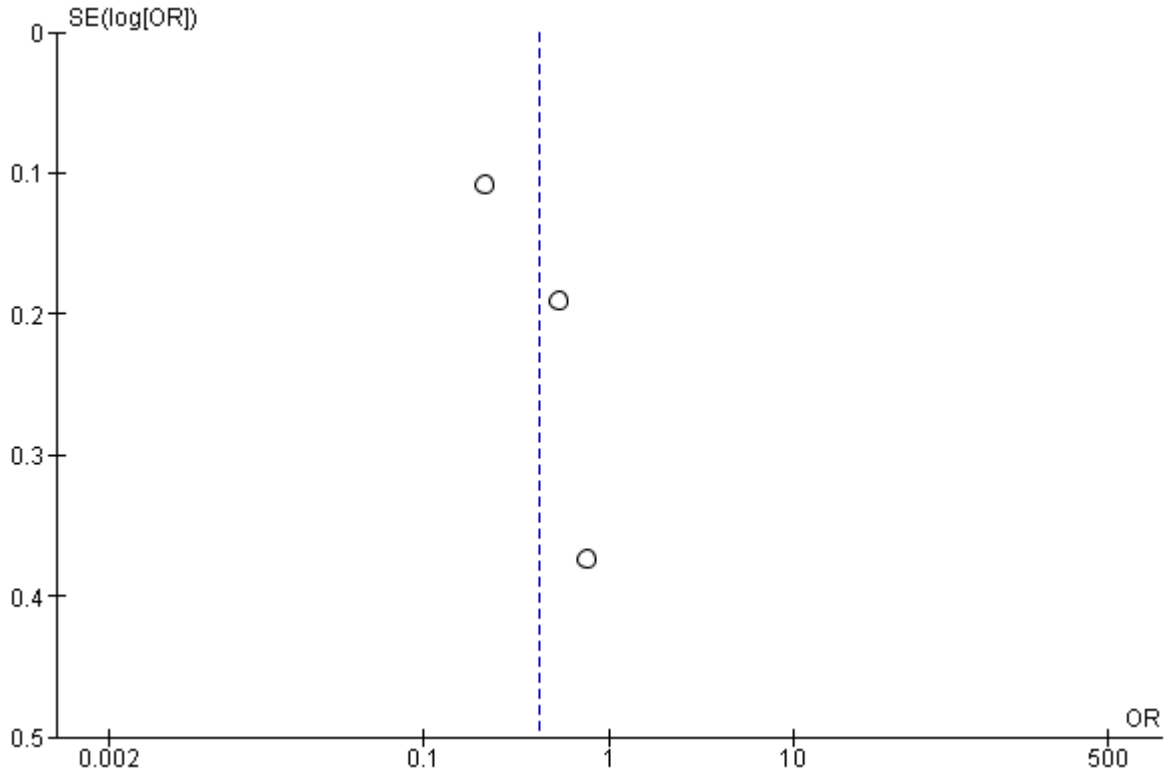


Early-mortality:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Alkhalil et al (2018)	14	175	18	175	28.4%	0.76 [0.36, 1.58]
Farber et al (2020)	57	661	69	457	34.8%	0.53 [0.37, 0.77]
Mentias et al (2020)	124	4130	321	2565	36.8%	0.22 [0.17, 0.27]
Total (95% CI)		**4966**		**3197**	**100.0%**	**0.42 [0.19, 0.92]**
Total events	195		408			

Heterogeneity: Tau² = 0.42; Chi² = 23.91, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.17 (P = 0.03)



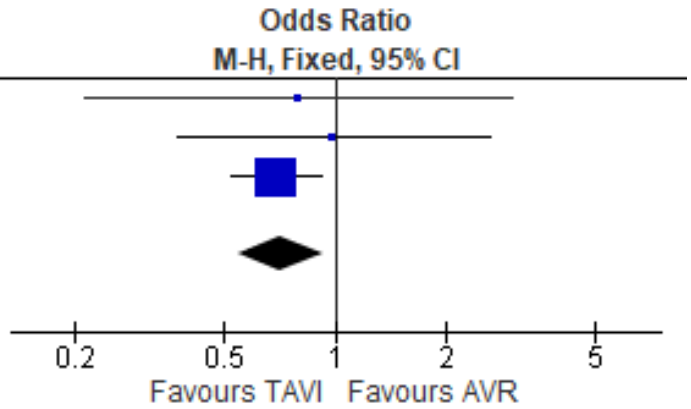


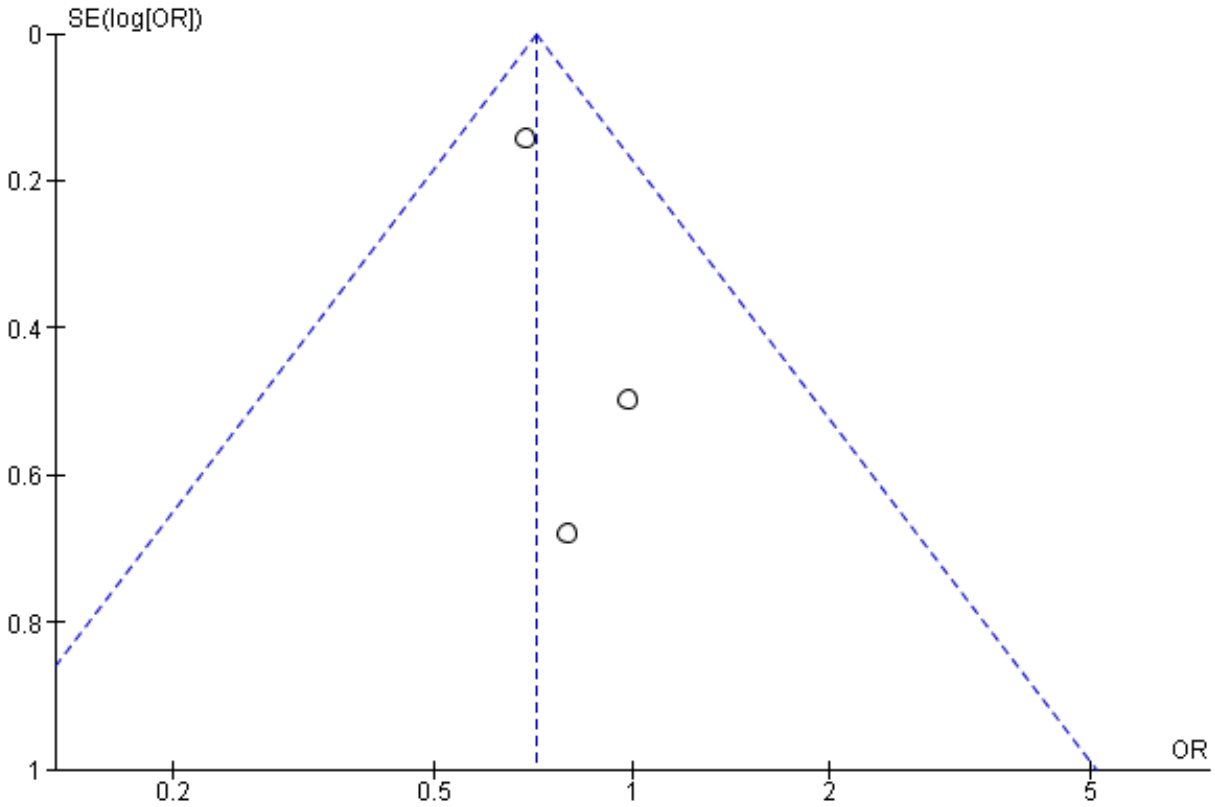
Stroke/cerebrovascular events:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alkhalil et al (2018)	4	175	5	175	3.8%	0.80 [0.21, 3.01]
Farber et al (2020)	10	661	7	457	6.4%	0.99 [0.37, 2.61]
Mentias et al (2020)	107	4130	95	2565	89.8%	0.69 [0.52, 0.92]
Total (95% CI)		**4966**		**3197**	**100.0%**	**0.71 [0.55, 0.93]**
Total events	121		107			

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² = 0%

Test for overall effect: Z = 2.49 (P = 0.01)



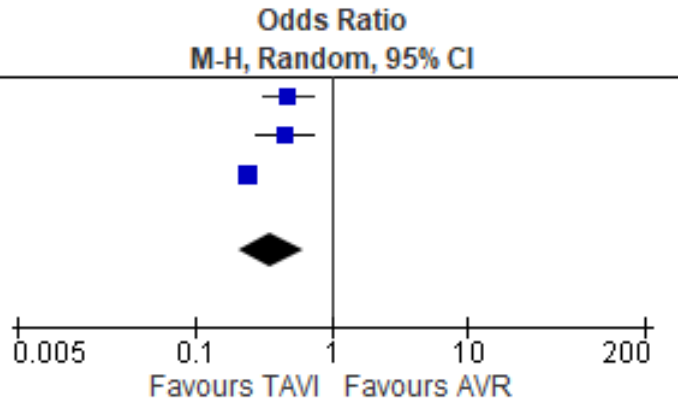


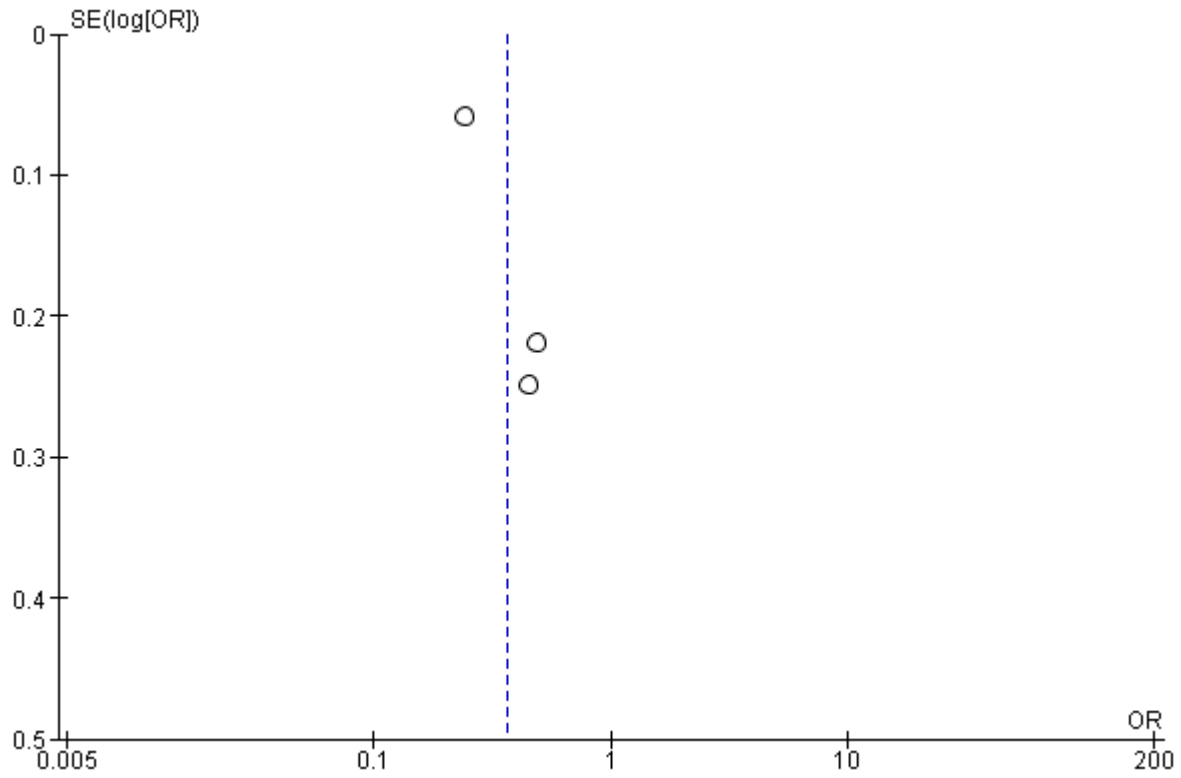
Blood transfusion:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Alkhalil et al (2018)	62	175	93	175	31.5%	0.48 [0.31, 0.74]
Farber et al (2020)	592	661	434	457	29.7%	0.45 [0.28, 0.74]
Mentias et al (2020)	636	4130	1103	2565	38.8%	0.24 [0.22, 0.27]
Total (95% CI)		**4966**		**3197**	**100.0%**	**0.36 [0.21, 0.62]**
Total events	1290		1630			

Heterogeneity: Tau² = 0.19; Chi² = 14.72, df = 2 (P = 0.0006); I² = 86%

Test for overall effect: Z = 3.72 (P = 0.0002)

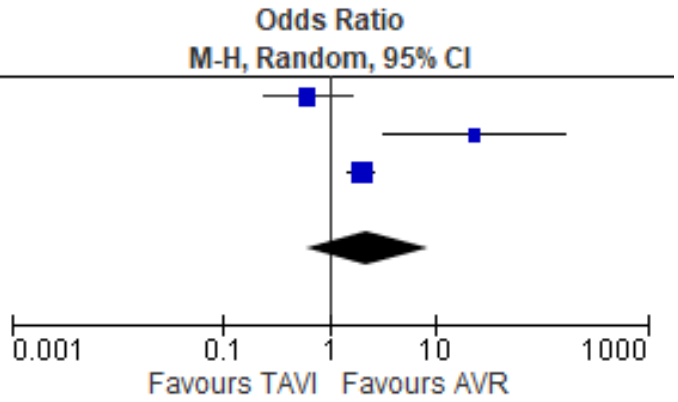


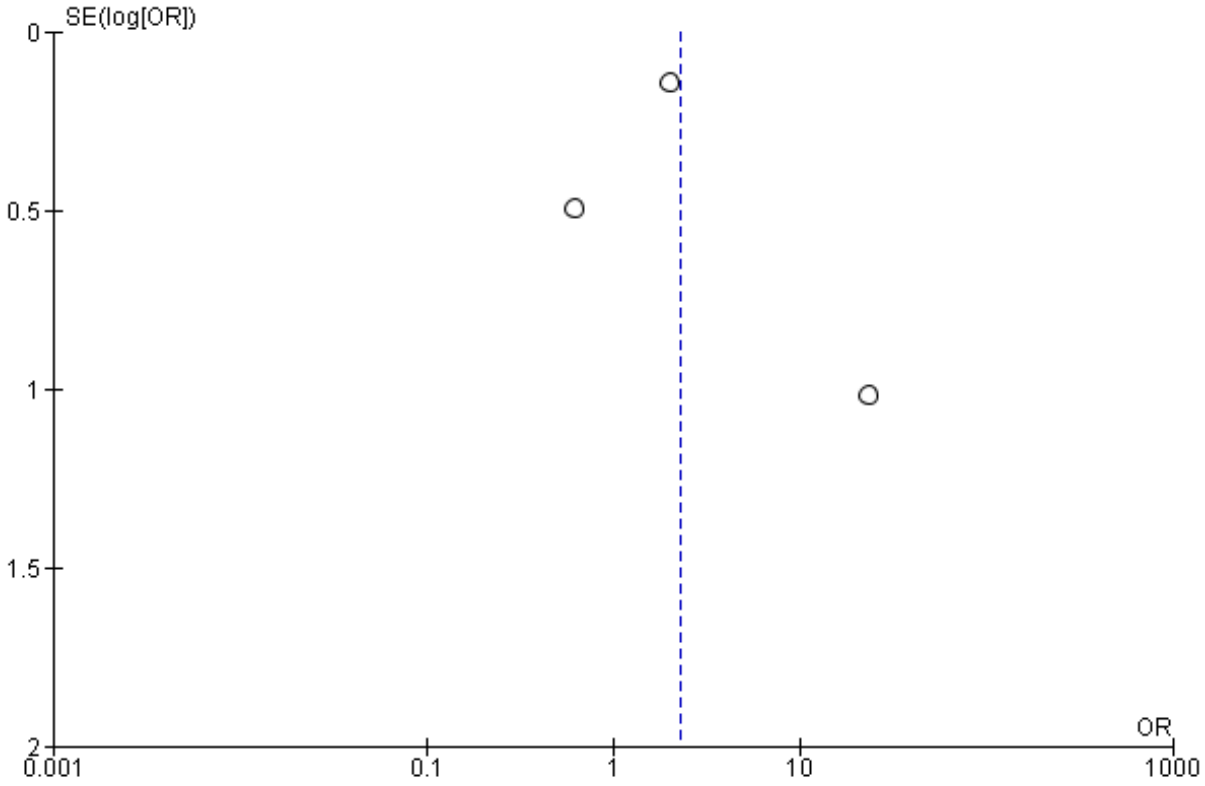


Vascular Complications:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Alkhalil et al (2018)	7	175	11	175	35.3%	0.62 [0.24, 1.64]
Farber et al (2020)	32	661	1	457	22.0%	23.20 [3.16, 170.39]
Mentias et al (2020)	202	4130	64	2565	42.7%	2.01 [1.51, 2.67]
Total (95% CI)		**4966**		**3197**	**100.0%**	**2.27 [0.60, 8.59]**
Total events	241		76			

Heterogeneity: Tau² = 1.06; Chi² = 11.77, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 1.21 (P = 0.23)



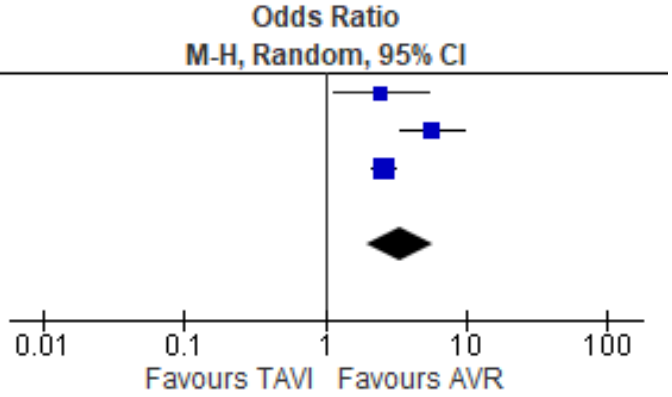


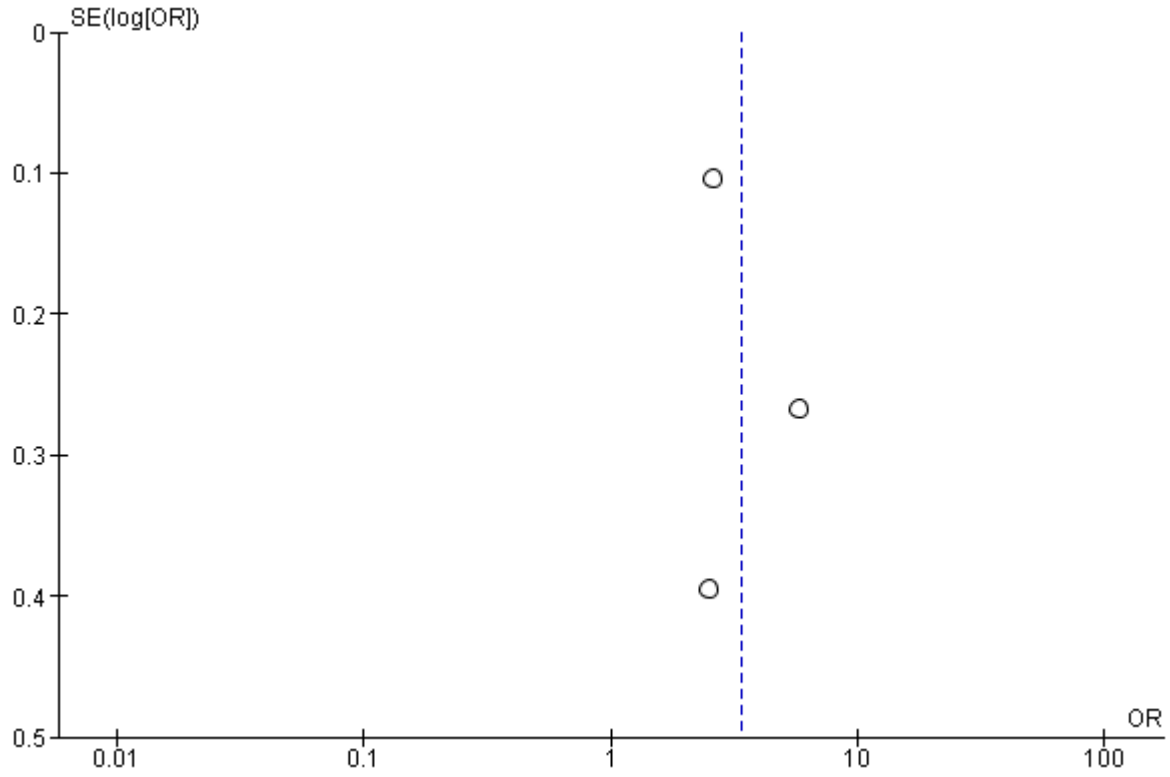
New Pacemaker Implantation:

Study or Subgroup	TAVI Events	TAVI Total	AVR Events	AVR Total	Weight	Odds Ratio M-H, Random, 95% CI
Alkhalil et al (2018)	23	175	10	175	23.9%	2.50 [1.15, 5.42]
Farber et al (2020)	120	661	17	457	32.5%	5.74 [3.40, 9.69]
Mentias et al (2020)	479	4130	123	2565	43.6%	2.60 [2.12, 3.20]
Total (95% CI)		**4966**		**3197**	**100.0%**	**3.33 [1.94, 5.73]**
Total events	622		150			

Heterogeneity: Tau² = 0.16; Chi² = 7.77, df = 2 (P = 0.02); I² = 74%

Test for overall effect: Z = 4.35 (P < 0.0001)





Length of Hospital Admission:

Study or Subgroup	TAVI Mean	TAVI SD	TAVI Total	AVR Mean	AVR SD	AVR Total	Weight	Mean Difference IV, Random, 95% CI
Rau et al (2012)	22.5	13.1	15	29.5	25.8	24	16.5%	-7.00 [-19.27, 5.27]
Farber et al (2020)	10	12.9	5731	23.2	22.2	6491	42.2%	-13.20 [-13.83, -12.57]
Ando et al (2020)	12	10.28	661	18	14.97	457	41.3%	-6.00 [-7.58, -4.42]
Total (95% CI)			**6407**			**6972**	**100.0%**	**-9.20 [-15.58, -2.82]**

Heterogeneity: Tau² = 25.00; Chi² = 69.33, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.83 (P = 0.005)