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

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28 Objectives

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

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33 Methods

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

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39 Results

40 Literature search identified ten retrospective studies; following data source analysis, five studies
41 were included. Upon pooling of BT data, TAVI was significantly favoured in early mortality (odds
42 ratio [OR], 0.42; 95% confidence interval [CI], 0.19-0.92; I²=92%; p=0.03), one-year mortality
43 (OR, 0.88; CI 0.80-0.97; I²=0%; p=0.01), rates stroke/cerebrovascular events (OR, 0.71; CI 0.55-
44 0.93; I²=0%; p=0.01), and blood transfusions (OR, 0.36; CI 0.21-0.62; I²=86%; p=0.0002).

45 Pooling demonstrated fewer new pacemaker implantations in the AVR group (OR, 3.33; CI 1.94-
46 5.73; I²=74%; p=<0.0001) and no difference in the rate of vascular complications (OR, 2.27; CI
47 0.60-8.59; I²= 83%; p=0.23). Analysis including raw data revealed the length of hospital stay to
48 favour TAVI with a mean difference of -9.20 days (CI -15.58--2.82; I²=97%; p=0.005)

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50 Conclusions

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

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

58

59 Abbreviations and Acronyms:

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

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84 Introduction

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

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

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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,

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

142 Statistical Analysis

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

167 Results

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170 Search Results

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

181

182 Outcomes

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

187

188 Early mortality

189 Three BT studies involving 8163 patients reported the incidence of early postoperative mortality. One
190 study recorded early mortality 30-days following intervention, and two studies reported outcomes
191 during hospital admission. The TAVI group demonstrated a 3.9% incidence, whilst the AVR group
192 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
193 therefore a significant difference in the incidence of early mortality, favouring the TAVI group.

194

195 One-year mortality

196 Two BT studies involving 7813 patients reported the incidence of one-year postoperative mortality. The
197 TAVI group demonstrated a 28.8% incidence, whilst the AVR group reported a 31.6% incidence. OR
198 0.88 (95% CI 0.80, 0.97) $I^2= 0\%$ and $p= 0.01$. There was therefore a significant difference in the
199 incidence of one-year mortality, favouring the TAVI group.

200

201 Stroke/cerebrovascular events

202 Three BT studies involving 8163 patients reported the incidence of stroke/cerebrovascular events
203 (excluding transient ischemic attacks). Two studies recorded incidence of stroke/cerebrovascular
204 events 30-days following intervention, and one study reported outcomes during hospital admission.
205 The TAVI group demonstrated a 2.4% incidence, whilst the AVR group reported a 3.3% incidence. OR
206 0.71 (95% CI 0.55, 0.93) $I^2= 0\%$ and $p= 0.01$. There was therefore a significant difference in the
207 incidence of stroke/cerebrovascular events, favouring the TAVI group [figure 3].

208

209 Vascular complications

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

216

217 New pacemaker implantation

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

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

224

225 Blood transfusions

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

230

231 Length of admission

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

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250 Discussion

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

262

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

272

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

278 AVR for dialysis patients, clinicians must also regard the increased incidence of embolic events, the
279 increased risk of bleeding associated with life-long anticoagulation, and the possible rare relation of
280 calciphylaxis identified with warfarin therapy [31, 32]. With the increased occurrence of hospital
281 readmission for patients who received mechanical AVR – likely due to the increased valve-related
282 adverse complications – bioprosthetic valves could be considered more appropriate for higher-risk
283 dialysis-dependent patients [33]. Dialysis-dependent patients demonstrate accelerated degeneration
284 of bioprosthetic valves, with research reporting moderate to severe degeneration present in 29% of
285 patients at five years following bioprosthetic AVR [30]. The accelerated valvular prosthesis calcification
286 for both TAVI and AVR valves is a result of dialysis-dependent patients being at an increased risk of
287 developing hyperphosphatemia and hypercalcemia indicative of secondary hyperparathyroidism [34,
288 35]. Subsequent valve degeneration may deem early planning of secondary valve
289 replacement/implantation in younger dialysis patients appropriate. Despite the risk of valve-in-valve
290 TAVI-associated coronary occlusion, attributed to previous degenerated prosthetic valve leaflets
291 obstructing the left ostia, literature is demonstrating TAVI-in-TAVI to be technically feasible with
292 comprehensive pre-operative assessment and developing TAVI valves [36, 37].

293

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295 Although evidence has demonstrated that aortic valve intervention of dialysis-dependent patients with
296 AS leads to increased survival, the postoperative prognosis remains unfortunate in this subset of
297 patients [38]. A study published in 2022 retrospectively analysed the three-year survival of dialysis-
298 dependent patients who received either AVR or TAVI (1020, 1280 respectively) with a median age of
299 79.47 and 75.45, respectively. The estimated three-year mortality was 78.3% in the TAVI group and
300 60.3% in the AVR group; however, the study comments on the possible significance of selection bias,
301 with TAVI more likely to be offered to more complex and frail patients [39]. Ultimately a major
302 contributing factor to the poor prognosis of dialysis-dependent patients post-intervention is the low
303 rates of renal transplantation due to the shortage of available transplant organs and the negative impact
304 of increased co-morbidities on the likelihood of receiving renal transplantation [40].

305

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

327

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

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

340

341 Conclusion

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

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362 Conflict of Interest Statement

363 Conflict of interest: None declared.

364

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366

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369

370 Author Contributions Statement

371 Conceptualization: Sanjay Asopa

372 Data Curation: Samuel Burton, Alexander Reynolds

373 Formal Analysis: Samuel Burton, Alexander Reynolds

374 Funding acquisition: NA

375 Investigation: Samuel Burton, Alexander Reynolds, Nicola King.

376 Methodology: Alexander Reynolds, Nicola King.

377 Project administration: Samuel Burton, Alexander Reynolds.

378 Resources: NA

379 Software: Alexander Reynolds, Samuel Burton.

380 Supervision: Sanjay Asopa, Amit Modi.

381 Validation: Nicola King.

382 Visualisation: Samuel Burton, Alexander Reynolds.

383 Writing – original draft: Samuel Burton, Alexander Reynolds.

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

385

386 Data Availability Statement:

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

388

389 This review is not currently registered.

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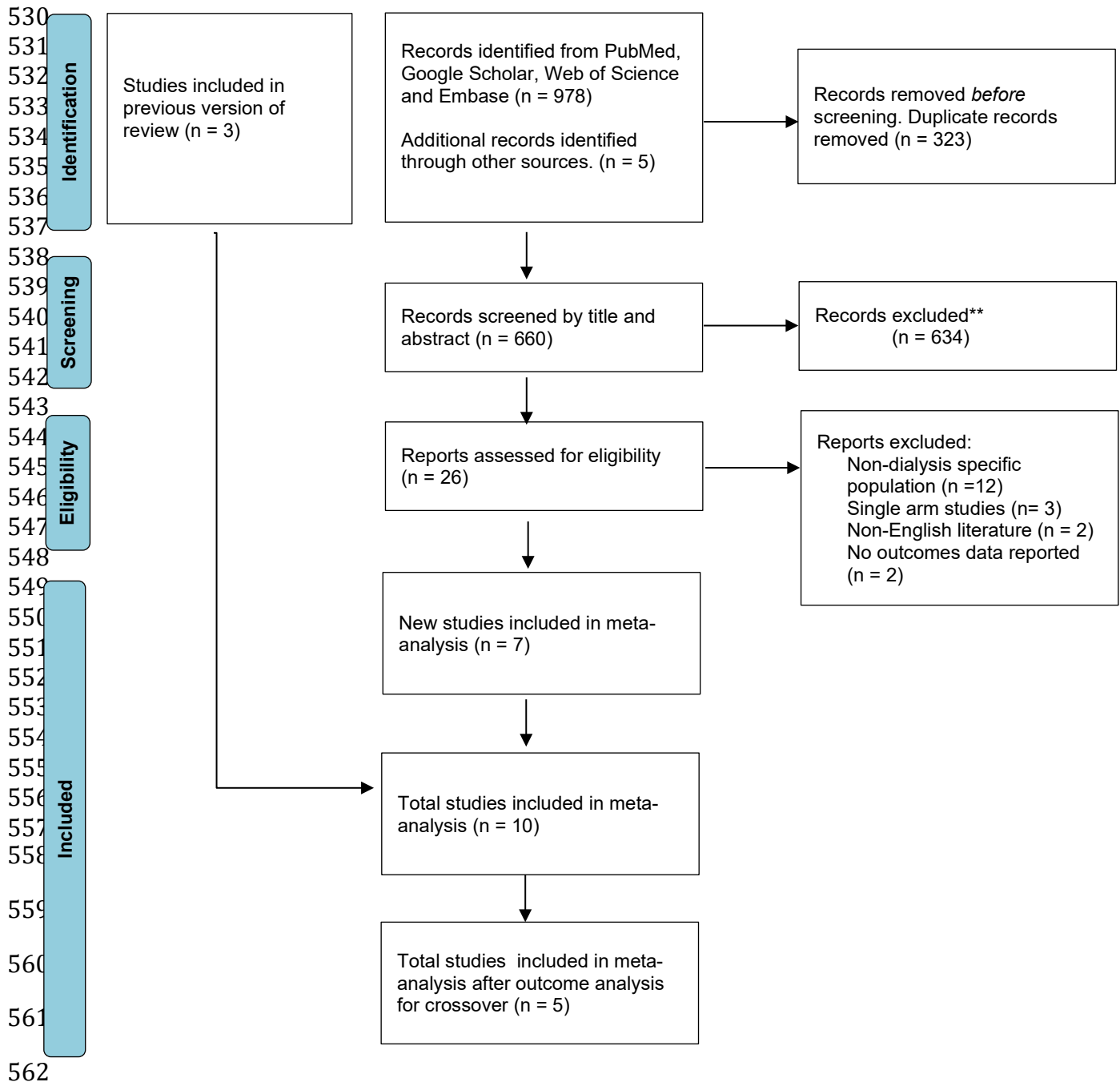
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514 [making-and-consent-english_pdf-84191055.pdf](https://www.gmc-uk.org/-/media/documents/gmc-guidance-for-doctors---decision-making-and-consent-english_pdf-84191055.pdf) (10 September 2022, date last accessed)

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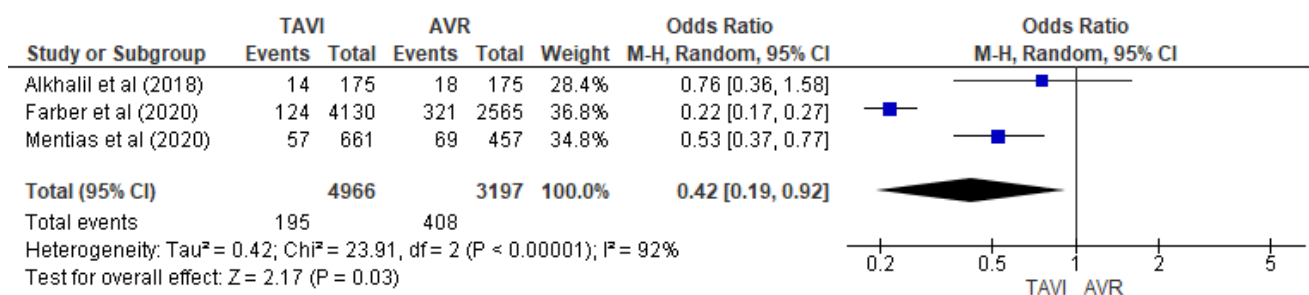
528 Figure Legend:

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

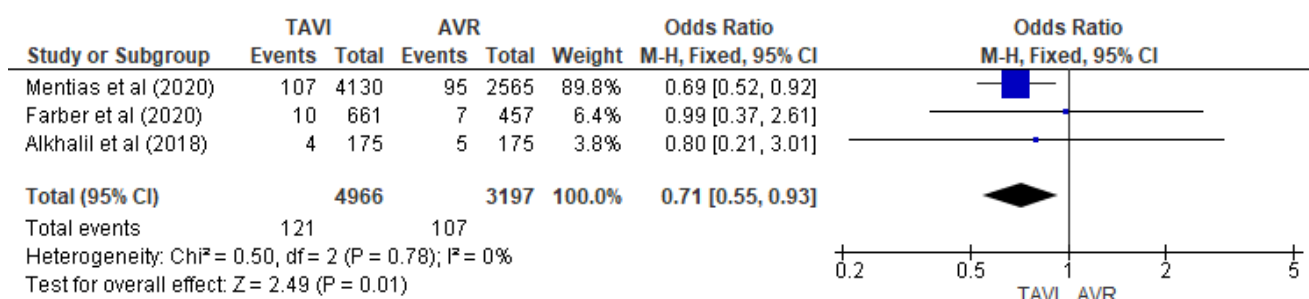
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567 [Figure 2 – Early Mortality Forest Plot.] - Review manager visualisation of meta-analysis, pooling data from
 568 included studies on rates of early mortality. Alkhalil, et al and Mentias, et al reported in-hospital
 569 mortality. Farber, et al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

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

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Table 1 – Summarizing Table

	Alkhalil, <i>et al.</i> [14]	Ando, <i>et al.</i> [15]	Farber, <i>et al.</i> [16]	Mentias, <i>et al.</i> [17]	Rau, <i>et al.</i> [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, <i>et al.</i>	Ando, <i>et al.</i>	Farber, <i>et al.</i>	Mentias, <i>et al.</i>	Rau, <i>et al.</i>
	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:

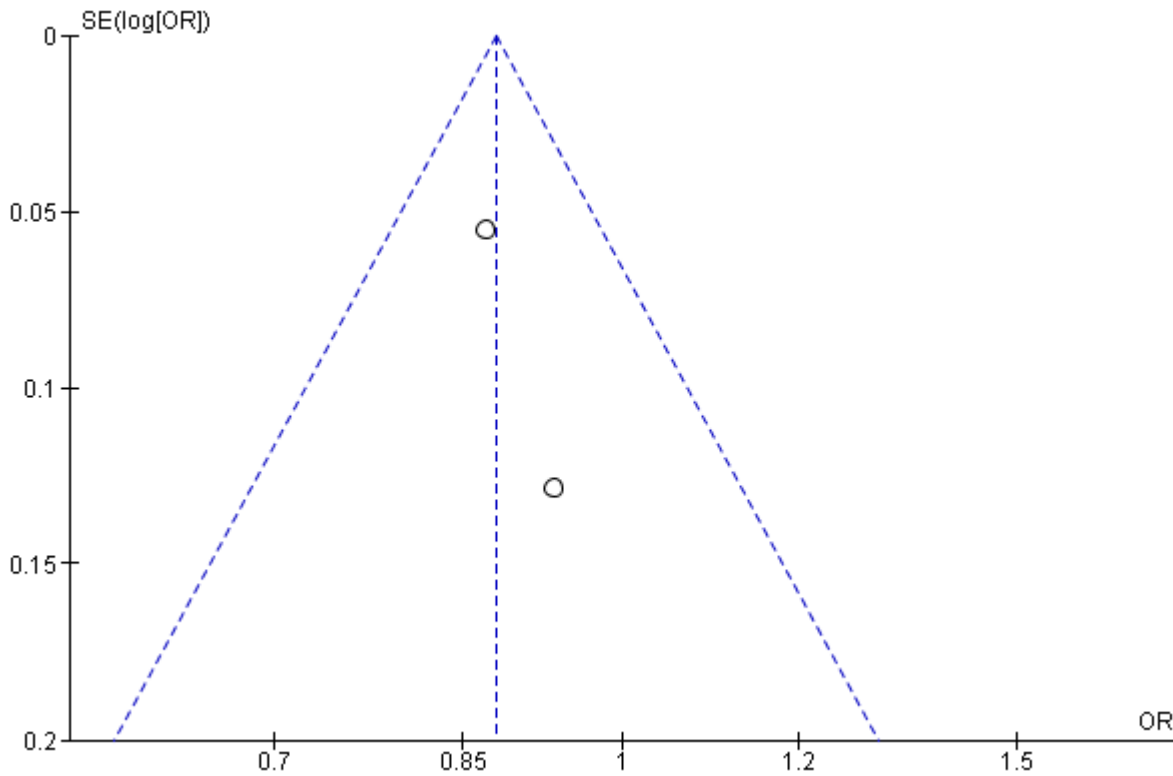
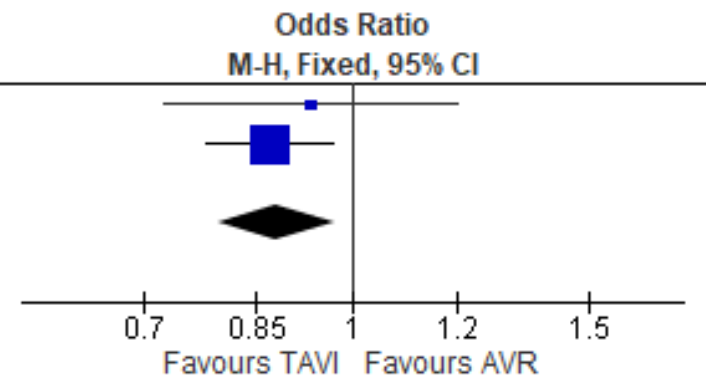
	Selection				Comparability	Outcome			
	Exposure Cohort Representative	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis **	Assessment of outcome	Was follow-up 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

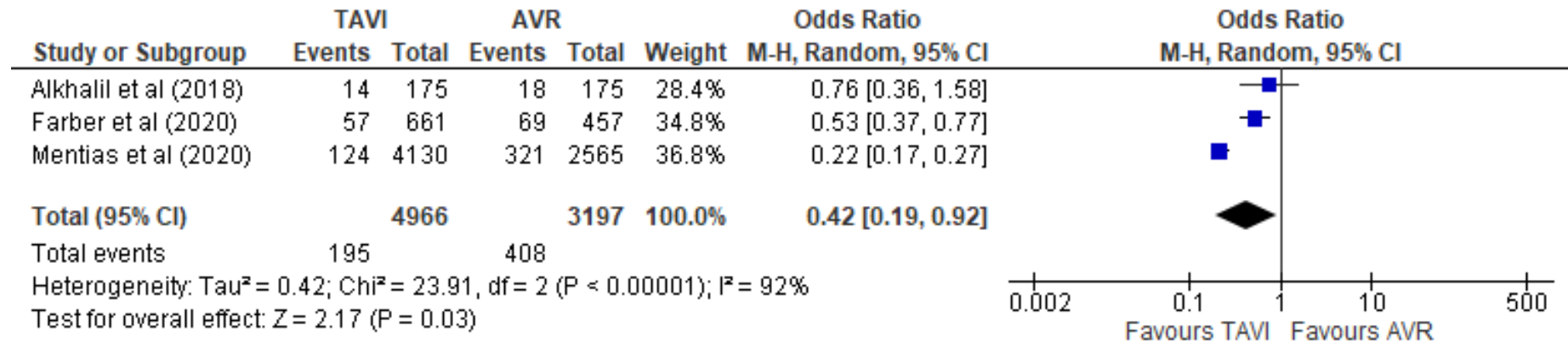
Meta-analysis Forest Plots + Funnel Plots:

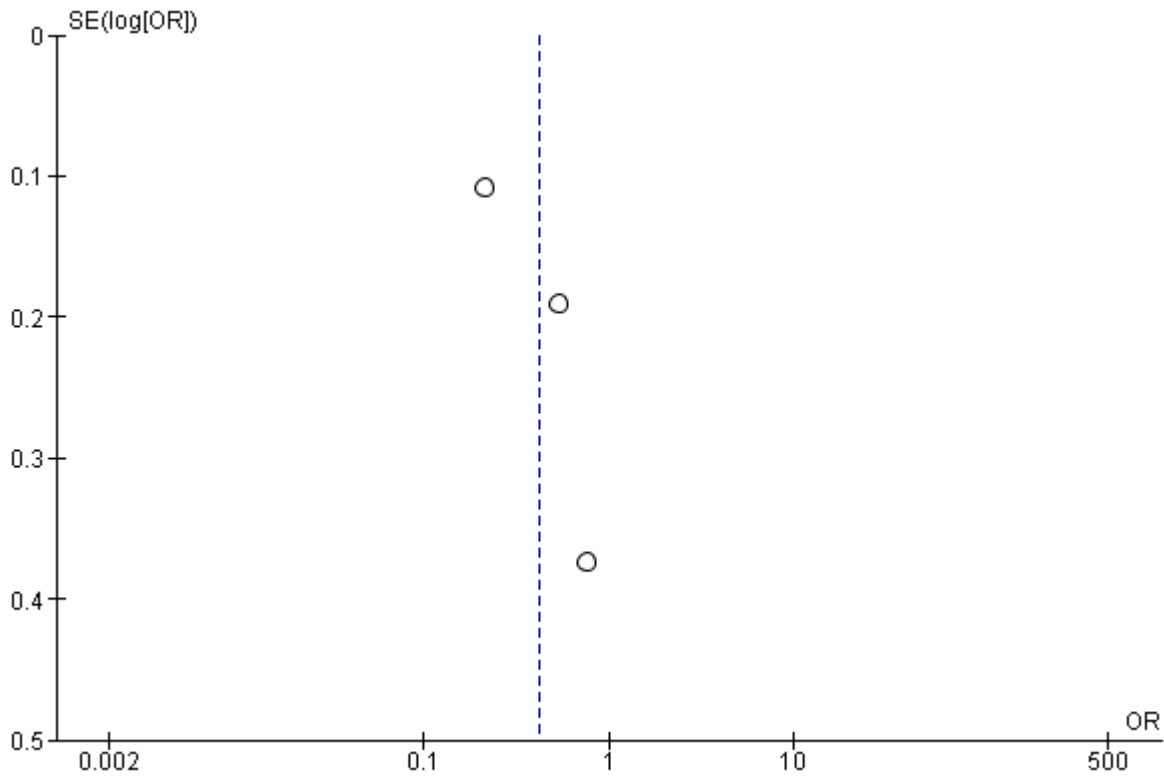
One-year mortality:

Study or Subgroup	TAVI		AVR		Weight	Odds Ratio	
	Events	Total	Events	Total		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: Chi ² = 0.25, df = 1 (P = 0.62); I ² = 0%							
Test for overall effect: Z = 2.55 (P = 0.01)							



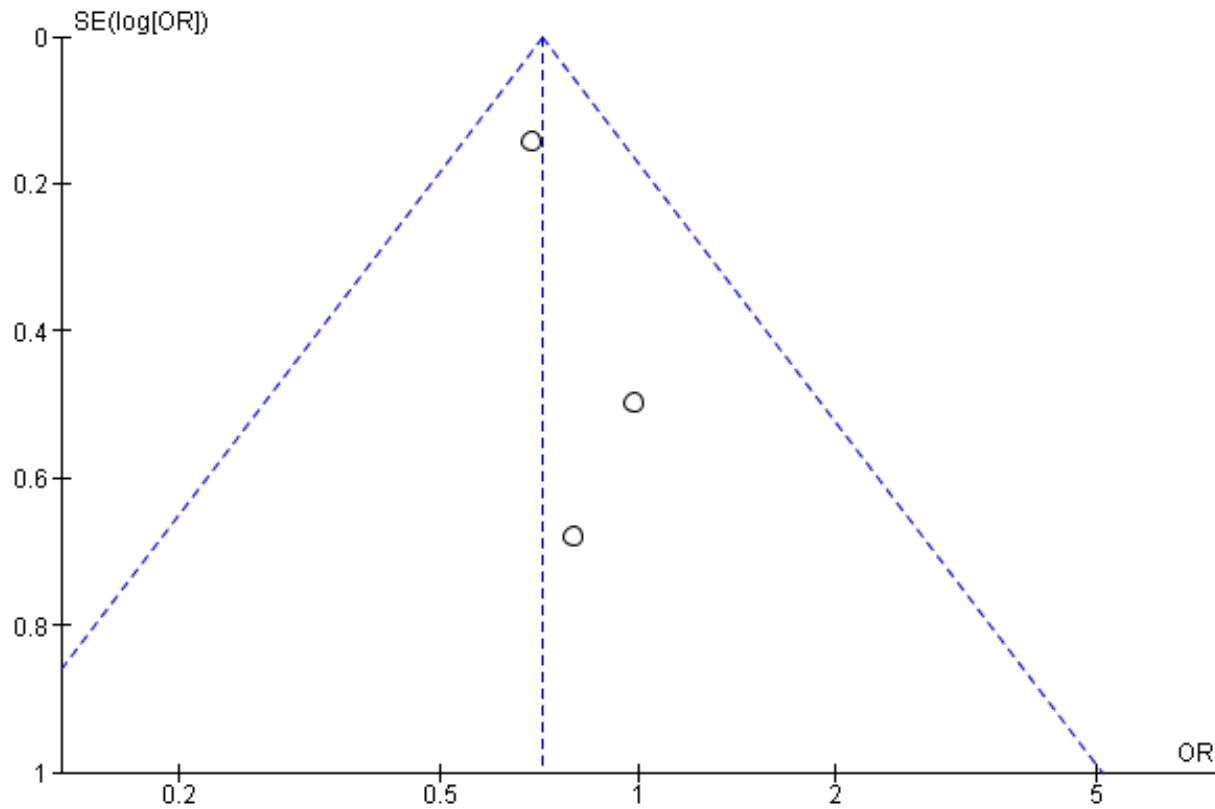
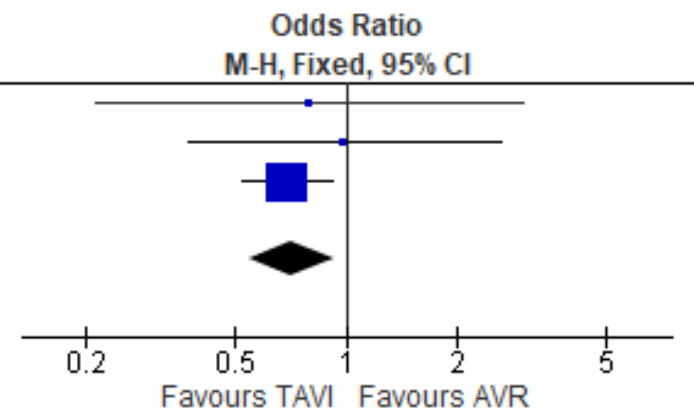
Early-mortality:



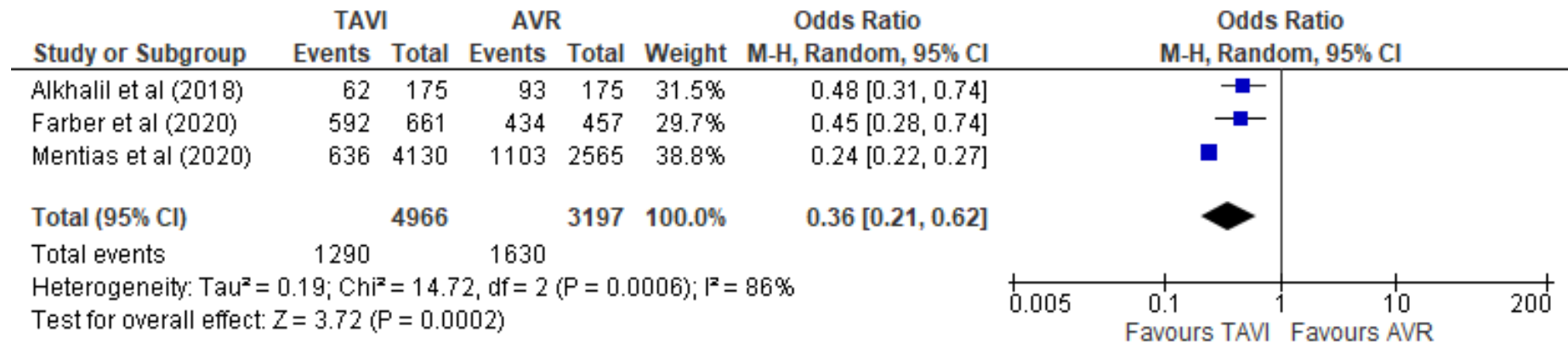


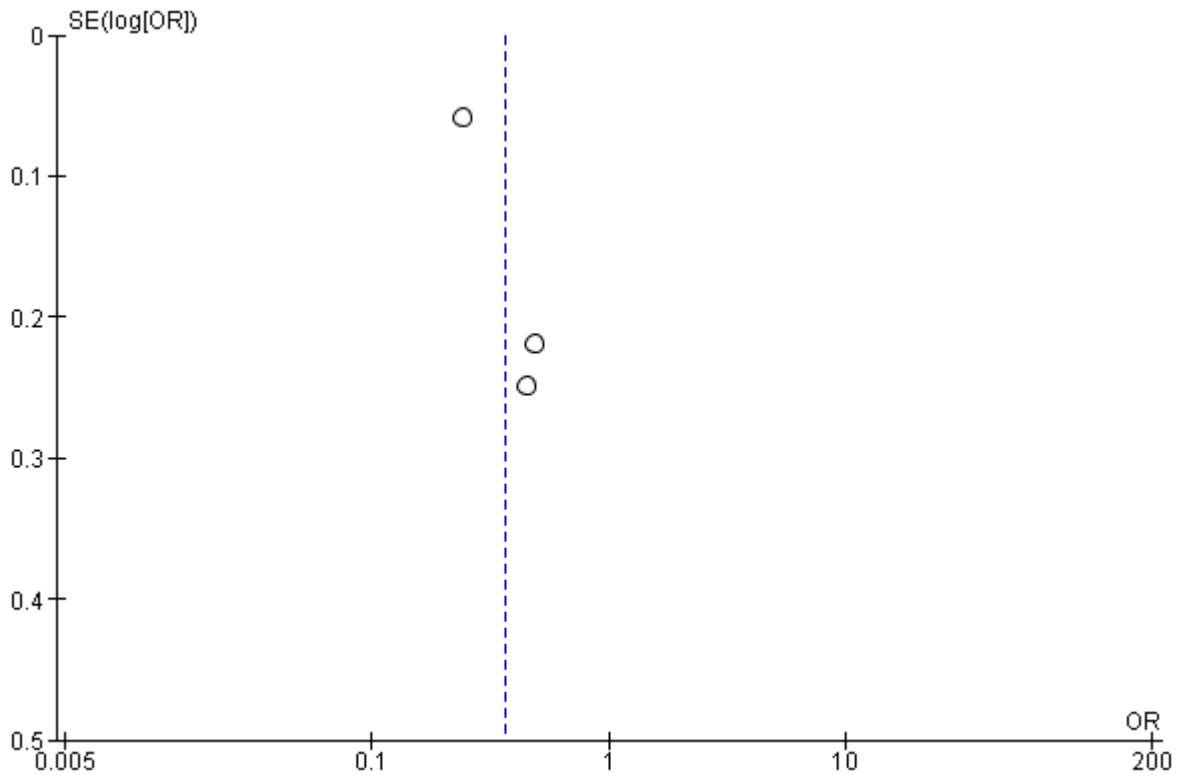
Stroke/cerebrovascular events:

Study or Subgroup	TAVI		AVR		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
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: Chi ² = 0.50, df = 2 (P = 0.78); I ² = 0%						
Test for overall effect: Z = 2.49 (P = 0.01)						



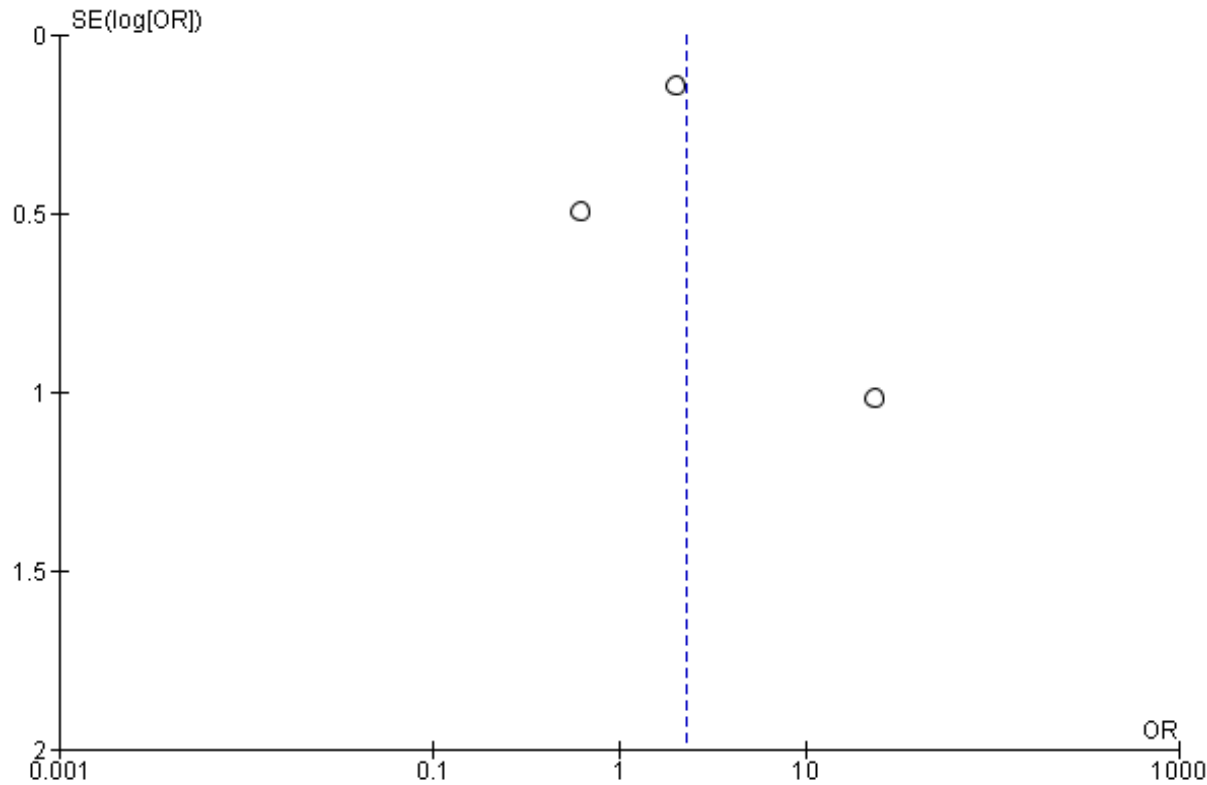
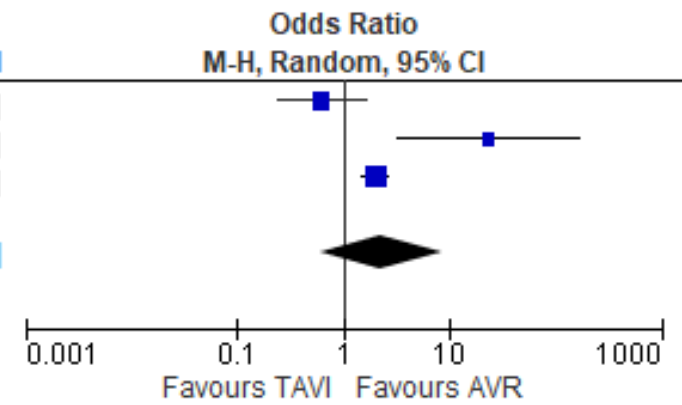
Blood transfusion:



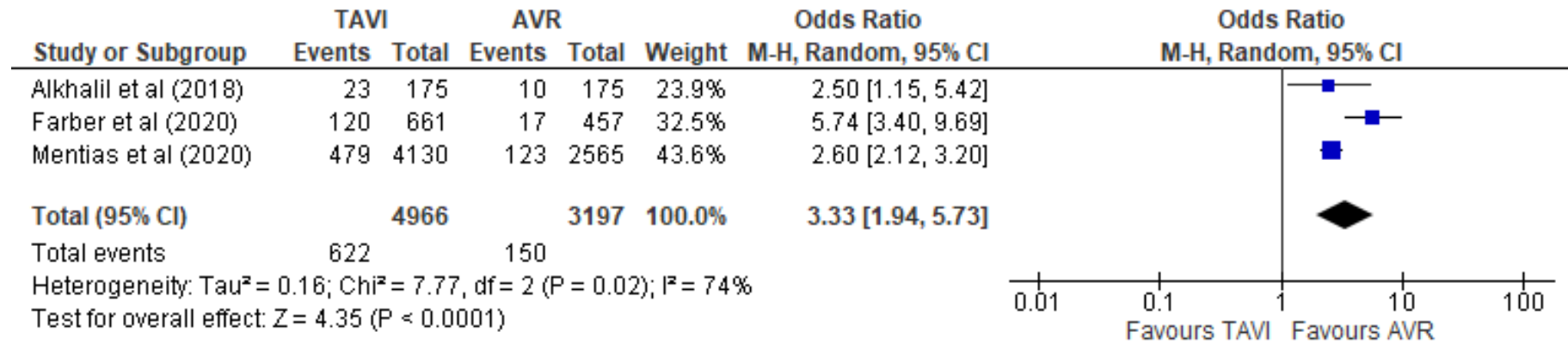


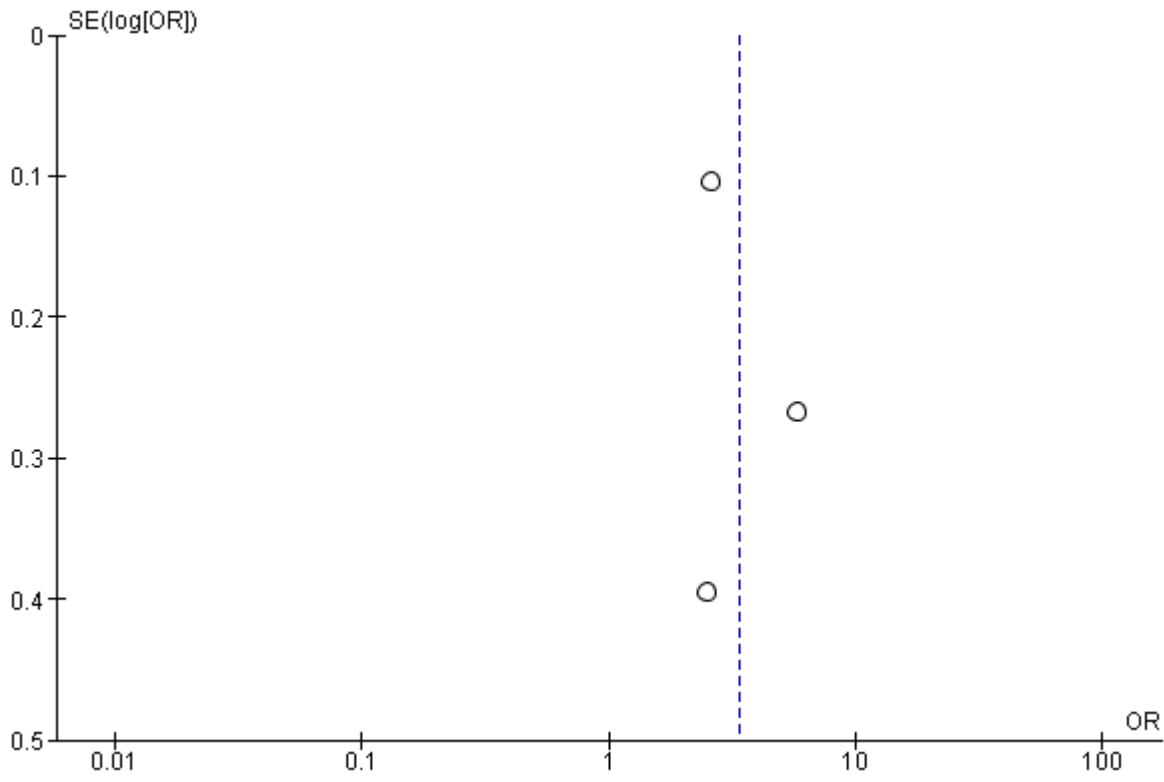
Vascular Complications:

Study or Subgroup	TAVI		AVR		Weight	Odds Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	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: Tau ² = 1.06; Chi ² = 11.77, df = 2 (P = 0.003); I ² = 83%							
Test for overall effect: Z = 1.21 (P = 0.23)							



New Pacemaker Implantation:





Length of Hospital Admission:

