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ORIGINAL ARTICLE

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Impact of surgical aortic root enlargement on the outcomes of aortic valve replacement: a meta-analysis of 13 174 patients

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Key question

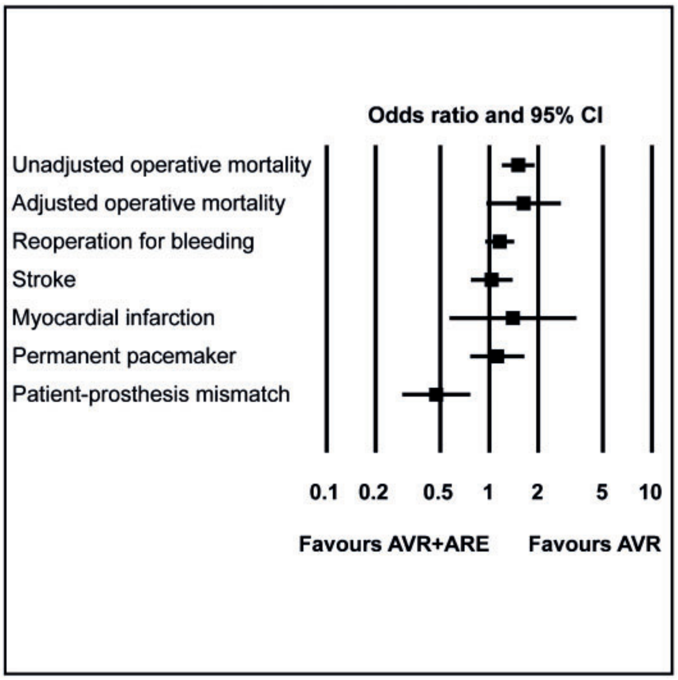
What is the impact of surgical aortic root enlargement on the outcomes of surgical aortic valve replacement?

Key finding(s)

Increased perioperative mortality.
Lower risk for patient-prosthesis mismatch (PPM).

Take-home message

The benefit of lower risk for PPM must be balanced against the higher risk for perioperative mortality.



Abstract

OBJECTIVES: This study sought to evaluate the impact of surgical aortic root enlargement (ARE) on the perioperative outcomes of aortic valve replacement (AVR).

METHODS: Databases were searched for studies published until April 2018 to carry out a systematic review followed by meta-analysis of results.

RESULTS: The search yielded 1468 studies for inclusion. Of these, 10 articles were analysed and their data extracted. A total of 13 174 patients (AVR with ARE: 2819 patients; AVR without ARE: 10 355 patients) were included from studies published from 2002 to 2018. The total rate of ARE was 21.4%, varying in the studies from 5.7% to 26.3%. The overall odds ratio (OR) [95% confidence interval (CI)] for perioperative mortality showed a statistically significant difference between the groups (among 10 studies), with a higher risk in the 'AVR with ARE' group (OR 1.506, 95% CI 1.209–1.875; $P < 0.001$), but not when adjusted for isolated AVR + ARE without any concomitant procedures such as mitral valve surgery, coronary artery bypass surgery, etc. (OR 1.625, 95% CI 0.968–2.726; $P = 0.066$—among 6 studies). The 'AVR with ARE' group showed an overall lower risk of significant patient–prosthesis mismatch among 9 studies (OR 0.472, 95% CI 0.295–0.756; $P = 0.002$) and a higher overall difference in means of indexed effective orifice area among 10 studies (random-effect model: 0.06 cm^2/m^2, 95% CI 0.029–0.103; $P < 0.001$).

CONCLUSIONS: Surgical ARE seems to be associated with increased perioperative mortality but with lower risk of patient–prosthesis mismatch.

Keywords: Aortic stenosis • Aortic valve replacement • Heart valve prosthesis • Meta-analysis • Prosthesis–patient mismatch

INTRODUCTION

Rationale

Patient–prosthesis mismatch (PPM) after surgical aortic valve replacement (AVR) increases all-cause and cardiac-related overall mortality [1]. An adequate prosthetic valve size should match the patient's body surface area to allow proper blood flow and promote left ventricular (LV) mass regression [2, 3]. Surgical aortic root enlargement (ARE) during AVR allows for larger prosthesis implantation, consequently minimizing PPM [2, 3]. Despite these potential benefits, surgical ARE has not been widely adopted by cardiovascular surgeons, likely owing to concerns regarding the possible increased risk of perioperative mortality and morbidity. As far as we know, there is no meta-analysis published in the medical literature on this subject. We therefore conducted a systematic review with meta-analysis to assess the impact of ARE on the outcomes after AVR.

Objectives

We aimed to determine the impact of surgical ARE on the outcomes of surgical AVR. This analysis was planned in accordance with current guidelines for performing comprehensive systematic reviews and meta-analysis, including the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [4] guidelines.

METHODS

Eligibility criteria

With the population, intervention, comparison, outcomes, study design (PICOS) strategy, studies were considered if: (i) the population comprised patients who underwent AVR; (ii) there was a group of patients who underwent AVR with ARE; (iii) there was a group of patients who underwent AVR without ARE; (iv) outcomes studied included any of the following: perioperative mortality, myocardial infarction, stroke, complete heart block or permanent pacemaker implantation, reoperation for bleeding, postoperative PPM, postoperative indexed effective orifice area (iEOA), cardiopulmonary bypass (CPB) time, aortic cross-clamp time; and (v) studies were retrospective, prospective, randomized or non-randomized.

Information sources

The following databases were used (until April 2018): MEDLINE, EMBASE, CENTRAL/CCTR (Cochrane Controlled Trials Register), ClinicalTrials.gov, SciELO (Scientific Electronic Library Online), LILACS (Literatura Latino Americana em Ciências da Saúde), Google Scholar and reference lists of relevant articles.

Search

We conducted the search with the following terms: 'aortic root enlargement OR aortic annulus enlargement' AND 'AVR OR aortic valve replacement'.

Study selection

The following steps were taken as conducted in our previous studies [5, 6]: (i) identification of titles of records through databases searching, (ii) removal of duplicates, (iii) screening and selection of abstracts, (iv) assessment for eligibility through full-text articles and (v) final inclusion in the study. One reviewer followed steps 1–3. Two independent reviewers followed step 4 and selected studies. Inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer made the final decision.

Data items

The end points were perioperative death, myocardial infarction, stroke, complete heart block or permanent pacemaker implantation, reoperation for bleeding, postoperative PPM, mean postoperative iEOA, mean CPB time and mean aortic cross-clamp time.

Data collection process

Two independent reviewers extracted the data as conducted in our previous studies [5, 6]. When there was a disagreement about the data, a third reviewer checked them and made the final decision. From each study, we extracted patient characteristics, study design and outcomes. When the data were not clearly available in the articles, we contacted the authors of the original articles by email.

Risk of bias in individual studies

Included studies were assessed for the following characteristics: retrospective or prospective; randomized or non-randomized; multicentric or not; and selection bias, performance bias, detection bias, attrition bias and adequacy of multivariable adjustment for possible confounders. Taking these characteristics into account, the papers were classified into A (low risk of bias), B (moderate risk of bias) or C (high risk of bias). Two independent reviewers assessed the risk of bias. An agreement between the 2 reviewers was assessed with kappa statistics for full-text screening and rating of relevance and risk of bias. When there was disagreement about the risk of bias, a third reviewer checked the data and made the final decision as conducted in our previous studies [5, 6].

Summary measures

The principal summary measures were odds ratio (OR) with 95% confidence interval (CI) for non-parametric outcomes and difference in means with 95% CI for parametric outcomes (considered statistically significant when $P < 0.05$). The meta-analysis was completed with the software Comprehensive Meta-Analysis (version 2, Biostat, Inc., Englewood, NJ, USA).

Synthesis of results

Forest plots were generated for graphical presentations of clinical outcomes, and we performed the I^2 test and the χ^2 test for the assessment of heterogeneity across the studies [7]. The inter-study heterogeneity was explored using the χ^2 statistic, but the I^2-value was calculated to quantify the degree of heterogeneity across the studies that could not be attributable to chance alone. When I^2 was more than 50%, significant statistical heterogeneity was considered to be present. Each study was summarized by the OR or difference in means, whose values were combined across studies using a weighted DerSimonian–Laird random-effects model [8].

Risk of bias across studies

To assess the publication bias, a funnel plot was generated for each outcome, statistically assessed by the Begg and Mazumdar's test [9] and the Egger's test [10], as conducted in our previous studies [5, 6].

Sensitivity analysis

We analysed the pool data regarding perioperative mortality for AVR without concomitant procedures (coronary artery bypass grafting, mitral valve surgery, etc.). We also investigated the influence of each study on the overall effect—by sequentially removing 1 study—to test the robustness of the main results, so that we could verify whether any study had an excessive influence on the overall results.

Meta-regression analysis

Meta-regression analyses were performed to determine whether the effects of ARE were modulated by prespecified factors. Meta-regression graphs describe the effect of ARE on the outcome (plotted on the *y* axis) as a function of a given factor (plotted as a mean or proportion of that factor on the *x*-axis).

The pre-determined modulating factors to be examined were age, sex, hypertension, diabetes, renal failure, smoker, left ventricular ejection fraction (LVEF) (%), previous cardiac surgery, concomitant procedures, CPB time and aortic cross-clamp time.

RESULTS

Study selection

A total of 1468 citations were identified, of which 15 studies were potentially relevant and retrieved as full-text. Ten publications [11–20] fulfilled our eligibility criteria. Interobserver reliability of study relevance was excellent (Kappa = 0.85). Agreement for decisions related to study validity was very good (Kappa = 0.86). The search strategy can be seen in Fig. 1.

Study characteristics

A total of 13 174 patients (AVR with ARE: 2819 patients; AVR without ARE: 10 355 patients) were included from studies published from 2002 to 2018. The total rate of ARE was 21.4%, varying in the studies from 5.7% to 26.3%. The studies consisted of patients whose mean age varied from 37.5 to 83.9 years (except for 1 study [15], the mean age was above 65 years). Other characteristics are described in the Supplementary Material, Table. The overall internal validity was considered as a moderate risk of bias (Table 1).

Synthesis of results

The OR for perioperative mortality in the 'AVR with ARE' group compared with the 'AVR without ARE' group in each study is reported in Fig. 2. There was evidence of low statistical heterogeneity of the treatment effect among 10 studies for perioperative mortality. The overall OR (95% CI) of perioperative mortality showed a statistically significant difference between the groups, with a higher risk in the 'AVR with ARE' group (random-effect model: OR 1.506, 95% CI 1.209–1.875; $P < 0.001$).

The ORs for myocardial infarction (4 studies), stroke (8 studies), complete heart block/permanent pacemaker implantation (7 studies) and reoperation for bleeding (9 studies) in the 'AVR with ARE' group compared with the 'AVR without ARE' group in each study are reported in Fig. 3. The overall OR (95% CI) for these outcomes showed no statistically significant difference between the groups.

The differences in means for CPB time (9 studies) and aortic cross-clamp time (9 studies) in the 'AVR with ARE' group compared with the 'AVR without ARE' group in each study are reported in Fig. 4. There was evidence of high statistical heterogeneity of the treatment effect among the studies for these outcomes. The overall differences in means for these outcomes were statistically significantly higher in the 'AVR with ARE' group.

The OR for PPM in the 'AVR with ARE' group compared with the 'AVR without ARE' group in each study is reported in Fig. 5A. There was evidence of high statistical heterogeneity of the treatment effect among 9 studies for PPM. The overall OR (95% CI) of PPM showed a statistically significant difference between the groups, with lower risk in the 'AVR with ARE' group (random-effect model: OR 0.472, 95% CI 0.295–0.756; $P = 0.002$).

The difference in means for iEOA in the 'AVR with ARE' group compared with the 'AVR without ARE' group in each study is

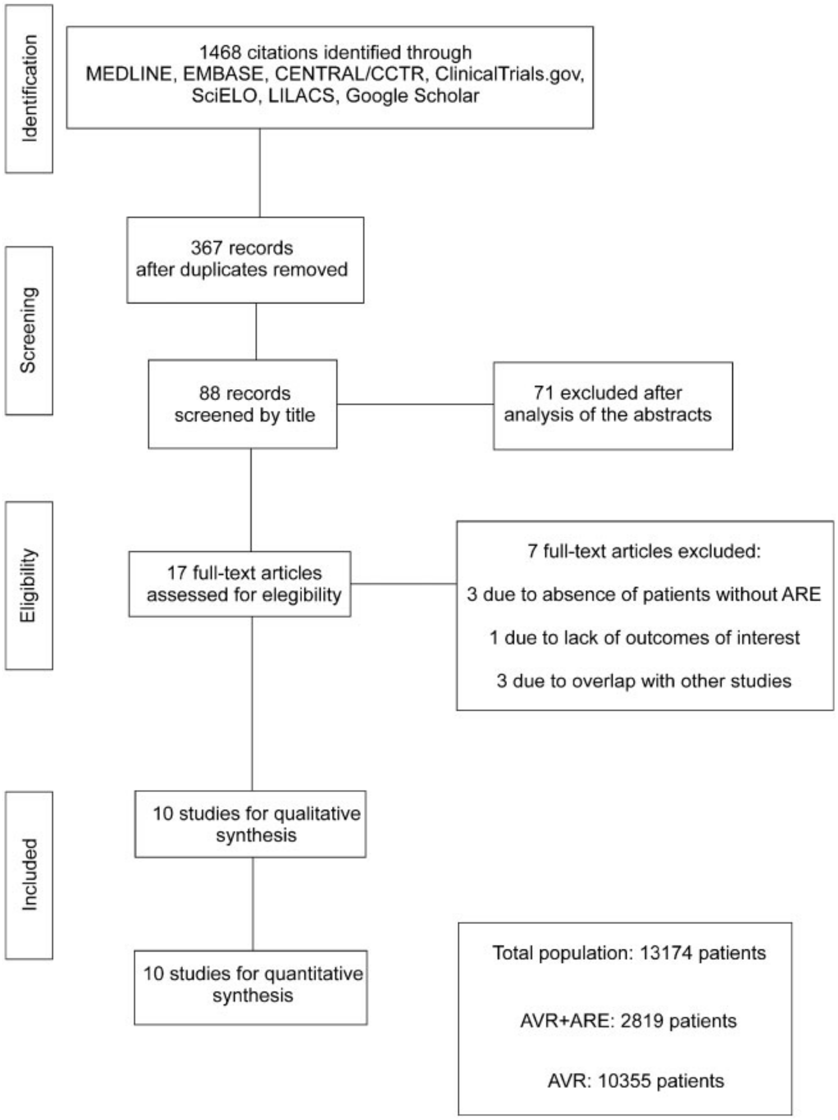


Figure 1: Flow diagram of studies included in data search. ARE: aortic root enlargement; AVR: aortic valve replacement; CCTR: Cochrane Controlled Trials Register; LILACS: Literatura Latino Americana em Ciências da Saúde; SciELO: Scientific Electronic Library Online.

Table 1: Analysis of risk of bias: internal validity

Study	*N* (AVR + ARE/AVR)	Design	Selection bias	Performance bias	Detection bias	Attrition bias	Multivariable adjustment
Rocha *et al.* [11]	1854/5185	NR, P, NM	B	B	A	A	Probably adequate
Beckmann *et al.* [12]	36/92	NR, NP, NM	B	B	A	A	Probably adequate
Correia *et al.* [13]	239/767	NR, NP, NM	B	B	A	A	Probably adequate
Ghoneim *et al.* [14]	20/259	NR, P, NM	C	B	A	A	None
Okamoto *et al.* [15]	58/531	NR, P, NM	A	B	A	A	Propensity match
Penaranda *et al.* [16]	30/87	NR, NP, NM	C	B	A	A	None
Prakash *et al.* [17]	47/162	NR, NP, NM	B	B	A	A	Probably adequate
Kulik *et al.* [18]	172/540	NR, NP, NM	B	B	A	A	Probably adequate
Dhareshwar *et al.* [19]	249/2117	NR, NP, NM	B	B	A	A	Probably adequate
Castro *et al.* [20]	114/543	NR, NP, NM	B	B	A	A	Probably adequate

A: risk of bias is low; ARE: aortic root enlargement; AVR: aortic valve replacement; B: risk of bias is moderate; C: risk of bias is high; D: incomplete reporting; M: multicentric; NM: non-multicentric; NP: non-prospective; NR: non-randomized; P: prospective; R: randomized.

Study name	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight (%)
Rocha 2018	1.454	1.104	1.914	0.008	63.63
Beckmann 2016	2.647	0.358	19.545	0.340	1.20
Correia 2016	1.610	0.293	8.843	0.584	1.66
Ghoneim 2016	3.511	1.081	11.404	0.037	3.47
Okamoto 2016	4.640	0.414	51.974	0.213	0.82
Penaranda 2014	1.270	0.307	5.259	0.742	2.38
Prakash 2010	1.396	0.262	7.436	0.696	1.72
Kulik 2008	1.082	0.549	2.135	0.820	10.42
Dhareshwar 2007	2.008	1.106	3.645	0.022	13.52
Castro 2002	0.210	0.028	1.571	0.128	1.19
Overall effect	1.506	1.209	1.875	<0.001	

Statistics for each study; Weight (Random)

Test for heterogeneity: Chi² = 8.74; df = 9 (P = 0.461); I² = 0.0%
Test for overall random effect: Z = 3.66 (P < 0.001)

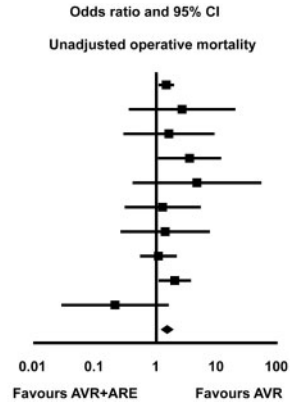


Figure 2: Odds ratio and conclusions plot of unadjusted operative mortality. The summary effect of AVR + ARE versus AVR alone is shown. ARE: aortic root enlargement; AVR: aortic valve replacement; CI: confidence interval.

reported in Fig. 5B. There was evidence of high statistical heterogeneity of the treatment effect among 9 studies for iEAO. The overall difference in means of iEOA was statistically significantly higher in the 'AVR with ARE' group (random-effect model: +0.06 cm^2/m^2, 95% CI 0.029–0.103, $P < 0.001$).

Risk of bias across studies

The funnel plot analysis (Supplementary Material) disclosed no asymmetry around the axis for the outcomes (except for complete heart block/permanent pacemaker implantation), which means that we have low risk of publication bias related to the outcomes.

Sensitivity analysis

We observed in the sensitivity analysis (Fig. 6) that the risk for mortality between the groups was not statistically significantly different when adjusted for isolated AVR (without any concomitant procedures such as mitral valve surgery, coronary artery bypass surgery, etc.) with or without ARE (among 6 studies).

Sensitivity analyses performed by removing each single study from the meta-analysis to determine the influence of individual data sets to the pooled results (ORs or difference in means) showed that none of the studies had a particular impact on the summary measures.

Meta-regression analysis

Meta-regression coefficients were not statistically significant for age, sex, hypertension, diabetes, renal failure, smoker, LVEF (%), previous cardiac surgery, concomitant procedures, CPB time and aortic cross-clamp time, which indicates that none of these evaluated factors had any modulation influence on the final effect with regard to the analysed outcomes.

DISCUSSION

Summary of evidence

To the best of our knowledge, this is the first meta-analysis of studies performed to date that provides incremental value by demonstrating that, overall, patients who underwent AVR with ARE have a statistically significant higher risk for perioperative mortality in comparison to those without ARE, but not when without concomitant procedures (actually, we also observed a higher risk, but the difference was statistically non-significant). We also observed that, despite longer CPB time and aortic cross-clamp time, patients who underwent AVR with ARE did not experience higher rates of myocardial infarction, stroke, complete heart block/permanent pacemaker implantation and reoperation for bleeding. On the other hand, patients who underwent AVR with ARE had higher overall mean of iEOA and lower overall rate of PPM.

The problem of patient–prosthesis mismatch

The main purpose of AVR is to relieve the pressure and/or volume overload of the left ventricle. There are many ways to avoid PPM, being surgical ARE one of the options available. Several studies have been published since the inclusion period of the latest published meta-analysis, which was between 1965 and 2014. Until now, 4 meta-analyses have been published addressing mainly the long-term survival in patients with PPM [1, 21–23]. The largest published meta-analysis by Dayan *et al.* [1] included 58 studies with a total number of 40 381 patients (39 568 surgical aortic valve replacement (SAVR) and 813 transcatheter aortic valve replacement (TAVR)). They agree that overall PPM and severe PPM are associated with reduced long-term survival. There are, however, discrepancies among these studies with regard to the impact of moderate PPM. Dayan *et al.* [1] found that even a moderate PPM is associated with a significant increase in the risk of perioperative mortality (but not in the risk of overall mortality), which they explained by the fact that, in the perioperative period, the LV function would be highly vulnerable to residual afterload even if it is moderate.

Surgical aortic root enlargement: the solution to the problem

There is no easy solution to this problem, but we find that ARE would allow for larger prosthesis implantation and might be a useful adjunct to AVR. Some surgeons (maybe most of them) are reluctant to perform such surgical procedures because they think that it implies higher operative mortality rates, although the medical literature has given evidence to the contrary in some selected scenarios.

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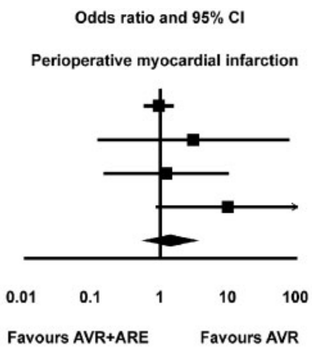
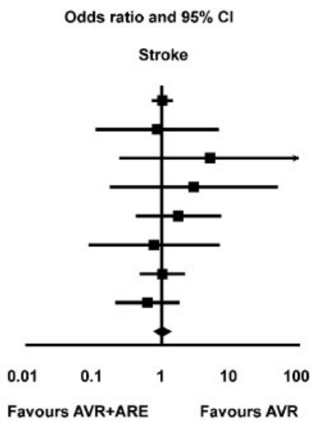
Study name	Statistics for each study				Weight (Random)	
	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight	(%)
Rocha 2018	0.947	0.575	1.557	0.829	66.58	
Okamoto 2016	3.023	0.122	75.050	0.500	7.00	
Dhareshwar 2007	1.215	0.149	9.920	0.855	14.74	
Castro 2002	9.679	0.870	107.660	0.065	11.69	
Overall effect	1.398	0.576	3.395	0.459		

Test for heterogeneity: Chi² = 3.86; df = 3 (P = 0.277); I² = 22.3%
Test for overall random effect: Z = 0.74 (P = 0.459)



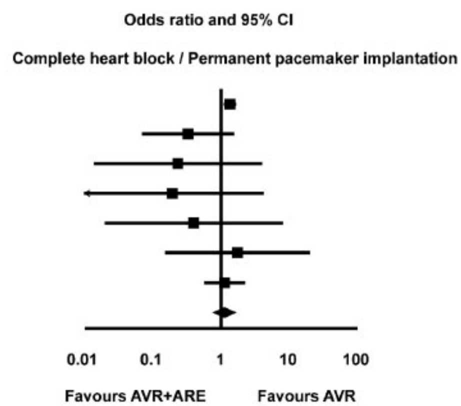
Study name	Statistics for each study				Weight (Random)	
	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight	(%)
Rocha 2018	1.030	0.732	1.451	0.864	68.92	
Ghoneim 2016	0.864	0.110	6.805	0.890	1.90	
Okamoto 2016	5.177	0.243	110.224	0.292	0.86	
Penaranda 2014	2.966	0.180	48.942	0.447	1.03	
Prakash 2010	1.773	0.426	7.376	0.431	3.97	
Kulik 2008	0.784	0.087	7.059	0.828	1.67	
Dhareshwar 2007	1.032	0.489	2.175	0.935	14.51	
Castro 2002	0.622	0.215	1.801	0.381	7.14	
Overall effect	1.033	0.777	1.372	0.823		

Test for heterogeneity: Chi² = 3.13; df = 7 (P = 0.873); I² = 0.0%
Test for overall random effect: Z = 0.22 (P = 0.823)



Study name	Statistics for each study				Weight (Random)	
	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight	(%)
Rocha 2018	1.352	1.117	1.637	0.002	65.71	
Beckmann 2016	0.328	0.071	1.522	0.154	5.43	
Ghoneim 2016	0.233	0.014	3.940	0.312	1.68	
Okamoto 2016	0.193	0.009	4.113	0.292	1.44	
Penaranda 2014	0.396	0.020	7.886	0.544	1.50	
Prakash 2010	1.739	0.154	19.612	0.654	2.27	
Dhareshwar 2007	1.124	0.573	2.202	0.734	21.97	
Overall effect	1.121	0.774	1.623	0.547		

Test for heterogeneity: Chi² = 7.02; df = 6 (P = 0.321); I² = 14.3%
Test for overall random effect: Z = 0.60 (P = 0.547)



Study name	Statistics for each study				Weight (Random)	
	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight	(%)
Rocha 2018	1.148	0.914	1.443	0.236	71.98	
Beckmann 2016	2.647	0.358	19.545	0.340	0.94	
Ghoneim 2016	3.060	0.951	9.850	0.061	2.75	
Okamoto 2016	1.000	0.026	38.780	1.000	0.28	
Penaranda 2014	0.716	0.077	6.666	0.769	0.75	
Prakash 2010	1.810	0.587	5.583	0.302	2.96	
Kulik 2008	0.848	0.398	1.810	0.670	6.53	
Dhareshwar 2007	1.066	0.576	1.972	0.839	9.92	
Castro 2002	0.950	0.356	2.538	0.919	3.89	
Overall effect	1.159	0.955	1.407	0.134		

Test for heterogeneity: Chi² = 4.97; df = 8 (P = 0.760); I² = 0.0%
Test for overall random effect: Z = 1.49 (P = 0.134)

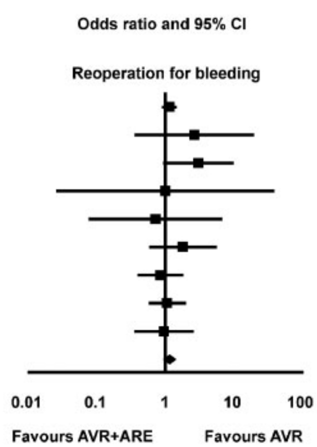


Figure 3: Odds ratio and conclusions plot of perioperative complications. The summary effect of AVR + ARE versus AVR alone is shown. ARE: aortic root enlargement; AVR: aortic valve replacement; CI: confidence interval.

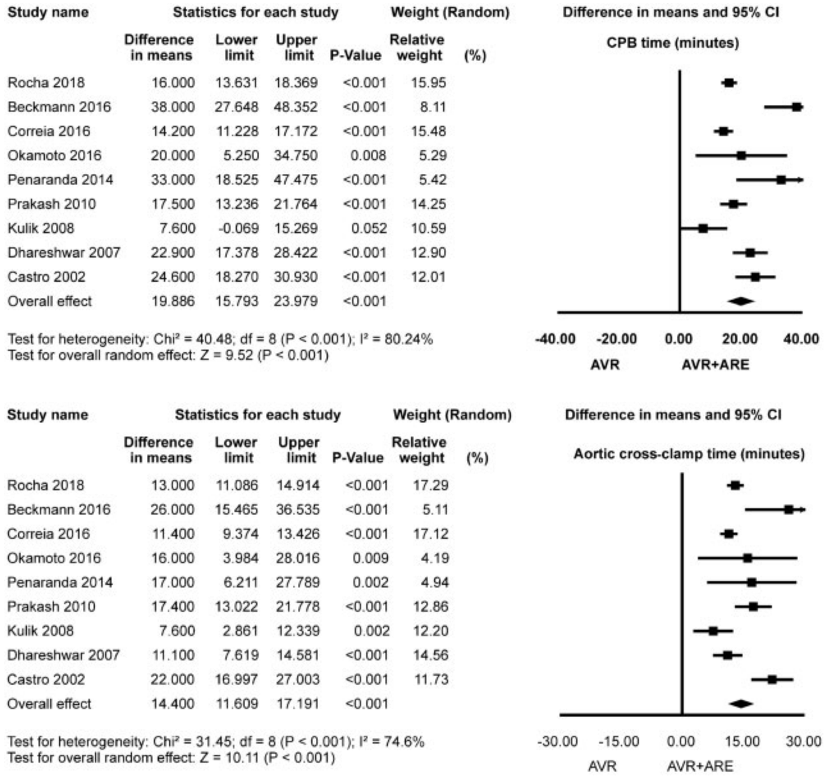


Figure 4: Difference in means and conclusions plot of intraoperative times. The summary effect of AVR + ARE versus AVR alone is shown. ARE: aortic root enlargement; AVR: aortic valve replacement; CI: confidence interval; CPB: cardiopulmonary bypass.

Rocha *et al.* [11] stated that ARE does not increase the operative mortality of surgical AVR among 7039 patients (AVR, $n = 5185$; AVR + ARE = 1854). In-hospital mortality was actually higher in the latter group (3.0% vs 4.3%, $P = 0.008$), but when the cohort was restricted to isolated AVR with or without ARE, mortality was not statistically significantly different (1.1% vs 1.7%, $P = 0.290$). Following adjustment baseline characteristics, AVR + ARE was not associated with an increased risk of in-hospital mortality when compared with AVR (OR 1.030, $P = 0.850$). Results were also similar when propensity matching was used for baseline characteristics. Correia *et al.* [13], Penaranda *et al.* [16] and Dhareshwar *et al.* [19] also found that ARE does not increase mortality in the context of AVR.

A crucial question remains: 'Is the modest gain in iEOA worth a procedure that prolongs CPB times and might contribute to higher mortality?' In the real-world practice, the answer might be centre-specific: experienced ones with higher surgical volumes might be more likely to successfully implement the procedure in selected cases, whereas other centres should hold to a more conservative approach.

Furthermore, it is worth mentioning that some studies included in our meta-analysis [13, 15, 16, 18] reported their 5-year survival rates, showing no statistically significant difference between the groups.

The Konno–Rastan procedure: a forgotten technique

We did not observe, among the studies, any report of anterior aortic annular enlargement: the Konno–Rastan procedure (also known as aortoventriculoplasty). This technique was first described in 1975 for congenital aortic stenosis secondary to small annular size, relieving subvalvar, valvar and supravalvar stenosis [24]. Furthermore, it is an option in patients who have already undergone a mitral valve replacement and are no longer candidates for a Nicks or Manougian procedure, offering also the advantage of not having to mobilize the coronaries. It is demanding, because the aortic annulus is enlarged by the implantation of a patch into the incised ventricular septum and another patch is required for the closure of the right ventricular incision, which might well explain why it is not widely applied.

Sutureless valves as an option

Usual aortic valve prostheses narrow the effective orifice area owing to their suturing ring. Sutureless valve prostheses, on the other hand, are stentless and offer the advantage of a larger effective orifice area, hence lower rates of PPM. Beckmann *et al.* [12] carried out a study with 128 patients to compare the perioperative and mid-term outcomes of patients undergoing surgery for aortic valve stenosis with a small annulus that received either conventional AVR with ARE (36 patients) or implantation of a sutureless valve (92 patients). Albeit comprised older patients, the group that received sutureless valves had a 30-day mortality and survival rates comparable to those of the other group. The authors concluded that sutureless valve implantation might be a valuable alternative to conventional AVR with ARE to treat patients with a small aortic annulus, especially in elderly patients.

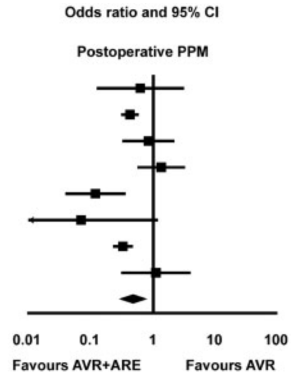
Risk of bias and limitations of the present study

As we described in our previous meta-analytical studies [5, 6], there are inherent limitations with meta-analyses, including the use of cumulative data from summary estimates. Patient data

Study name	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight (%)
Beckmann 2016	0.618	0.125	3.059	0.555	6.46
Correia 2016	0.422	0.309	0.576	<0.001	22.91
Ghoneim 2016	0.833	0.324	2.142	0.704	12.57
Okamoto 2016	1.337	0.563	3.177	0.511	13.69
Penaranda 2014	0.117	0.039	0.352	<0.001	10.68
Prakash 2010	0.069	0.004	1.166	0.064	2.51
Kulik 2008	0.324	0.228	0.462	<0.001	22.27
Castro 2002	1.102	0.309	3.931	0.881	8.91
Overall effect	0.472	0.295	0.756	0.002	

Statistics for each study; Weight (Random)

Test for heterogeneity: Chi² = 20.11; df = 7 (P = 0.005); I² = 65.2%
Test for overall random effect: Z = -3.12 (P = 0.002)



Study name	Difference in means	Lower limit	Upper limit	P-Value	Relative weight (%)
Rocha 2018	0.030	0.022	0.038	<0.001	14.30
Beckmann 2016	0.080	0.019	0.141	0.010	10.32
Correia 2016	0.060	0.047	0.073	<0.001	14.17
Ghoneim 2016	0.040	-0.074	0.154	0.492	6.06
Okamoto 2016	-0.100	-0.184	-0.016	0.019	8.30
Penaranda 2014	0.290	0.218	0.362	<0.001	9.31
Prakash 2010	0.120	0.100	0.140	<0.001	13.81
Kulik 2008	0.100	0.072	0.128	<0.001	13.29
Castro 2002	-0.060	-0.120	<0.001	0.050	10.43
Overall effect	0.066	0.029	0.103	<0.001	

Statistics for each study; Weight (Random)

Test for heterogeneity: Chi² = 150.78; df = 8 (P < 0.001); I² = 94.7%
Test for overall random effect: Z = 3.49 (P < 0.001)

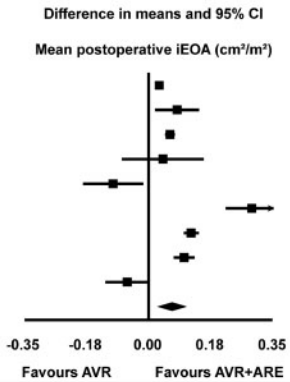


Figure 5: Odds ratio, difference in means and conclusions plot of PPM and iEOA. The summary effect of AVR + ARE versus AVR alone is shown. ARE: aortic root enlargement; AVR: aortic valve replacement; CI: confidence interval; iEOA: indexed effective orifice area; PPM: patient–prosthesis mismatch.

Study name	Odds ratio	Lower limit	Upper limit	P-Value	Relative weight (%)
Rocha 2018	1.580	0.687	3.632	0.281	38.69
Ghoneim 2016	4.500	0.449	45.083	0.201	5.05
Okamoto 2016	0.491	0.043	5.589	0.567	4.53
Prakash 2010	1.396	0.262	7.437	0.696	9.58
Dhareshwar 2007	2.106	0.888	4.994	0.091	35.96
Castro 2002	0.567	0.071	4.540	0.593	6.19
Overall effect	1.625	0.968	2.726	0.066	

Statistics for each study; Weight (Random)

Test for heterogeneity: Chi² = 3.05; df = 5 (P = 0.693); I² = 0.0%
Test for overall random effect: Z = 1.84 (P = 0.066)

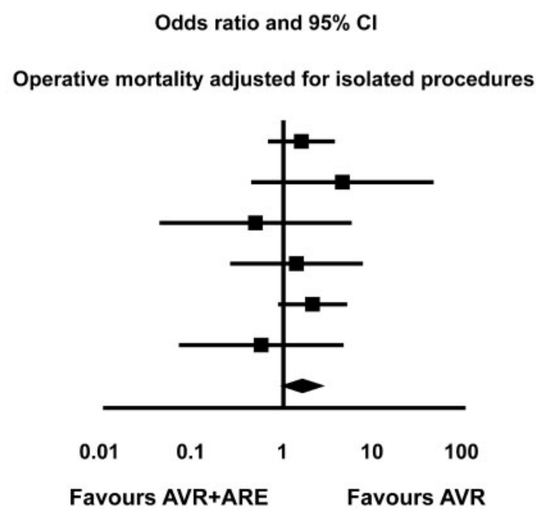


Figure 6: Odds ratio and conclusions plot of operative mortality adjusted for isolated procedures. The summary effect of AVR + ARE versus AVR alone is shown. ARE: aortic root enlargement; AVR: aortic valve replacement; CI: confidence interval.

were gathered from published data, not from individual patient follow-up. Access to individual patient data would have enabled us to conduct further subgroup analysis and propensity analysis to account for differences between the treatment groups. This meta-analysis included data from studies that reflect the 'real world', mostly with multivariable adjustment. On the other hand, these studies are more limited by selection bias, publication bias, treatment bias, confounders and a certain tendency to overestimate treatment effects. All these aspects have some impact on the results of our meta-analysis.

Moreover, considerable statistical heterogeneity was observed in some analyses, but we used the random-effects model to counterbalance this aspect. We also observed some publication bias in the outcomes. We must remind the readers of the fact that research with statistically significant results is more likely to be submitted to medical journals and published than work with null or non-significant results, being the former also more likely to appear more prominently in English, in higher impact journals. All of the aforementioned aspects lead to the appearance of publication biases, but, in this case, we cannot state that the impact of ARE on the outcomes observed in our study is only because of such biases.

CONCLUSIONS

Surgical ARE seems to be associated with an increased risk of perioperative mortality, but with a lower risk of PPM. Therefore, the benefit of the lower risk for PPM with ARE must be balanced against the higher risk for perioperative mortality. The surgeons must weigh up all the pros and cons of carrying out this surgical procedure.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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