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Systematic Review/Meta-analysis

Aortic Root Enlargement Is Safe and Reduces the Incidence of Patient-Prosthesis Mismatch: A Meta-analysis of Early and Late Outcomes

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See editorial by Lazar, pages 707–709 of this issue.

ABSTRACT

Background: Aortic root enlargement (ARE) may be an important adjunct to aortic valve replacement (AVR) to prevent patient-prosthesis mismatch and facilitate future valve-in-valve transcatheter AVR (TAVR). However, the early safety and late benefits of adding surgical ARE to AVR remain controversial.

Methods: MEDLINE and EMBASE were searched from 1946 to 2018 for articles comparing patients undergoing AVR+ARE with those undergoing AVR alone. A random-effects meta-analysis was performed to compare early and late clinical outcomes.

Results: A total of 2570 AVR+ARE and 5,991 AVR patients were included from 9 observational studies. There was no difference in early mortality (relative risk [RR] 1.21; 95% confidence interval [CI], 0.94-1.54; $P = 0.13$). Both cardiopulmonary bypass (mean difference [MD] 20 minutes; 95% CI, 15-25; $P < 0.01$) and aortic cross-clamp time (MD 14 minutes; 95% CI, 11-17, $P < 0.01$) were higher following

RÉSUMÉ

Introduction : La dilatation de la racine aortique (DRA) peut être un complément important au remplacement valvulaire aortique (RVA) pour prévenir la disproportion patient-prothèse et faciliter le RVA de type *valve-in-valve* par cathéter (RVAC). Toutefois, l'innocuité initiale et les avantages tardifs de l'ajout de la DRA au RVA demeurent controversés.

Méthodes : Nous avons consulté MEDLINE ET EMBASE pour trouver des articles entre 1946 et 2018 qui portaient sur la comparaison des patients qui subissaient des RVA+DRA aux patients qui subissaient seulement un RVA. Nous avons réalisé une méta-analyse à effets aléatoires pour comparer les résultats précoces et tardifs.

Résultats : Nous avons retenu un total de 2570 RVA+DRA et 5991 patients ayant subi un RVA qui provenaient de 9 études observationnelles. Nous n'avons observé aucune différence dans la mortalité précoce (risque relatif [RR] 1,21; intervalle de confiance [IC] à 95 %,

The management of patients with a small aortic annulus at the time of aortic valve replacement (AVR) remains controversial. These patients are at risk for patient-prosthesis mismatch (PPM) if a small valve prosthesis is implanted.[1] Reduced effective orifice area (EOA) indexed to body surface area ≤ 0.85 cm^2/m^2 (ie, moderate PPM) or ≤ 0.65 cm^2/m^2 (ie, severe PPM) following AVR has been associated with adverse postoperative outcomes such as incomplete left ventricular mass regression, lower freedom from heart failure, and reduced late survival.[2]

Aortic root enlargement (ARE) at the time of AVR allows for the implantation of a larger valve prosthesis of at least 1 labelled size. A number of studies have shown reduced postoperative gradients and a lower incidence of PPM in patients undergoing AVR+ARE compared with AVR alone.[2,3] Furthermore, in the era of valve-in-valve transcatheter aortic valve replacement (TAVR), AVR+ARE may become increasingly important as valve-in-valve TAVR in small bioprostheses have less favourable outcomes compared with valve-in-valve TAVR in larger bioprostheses.[4] Thus, further benefits of ARE include facilitating future valve-in-valve interventions by enlarging the aortic annulus and allowing for placement of a larger valve at the index operation. Nevertheless, some studies raise concerns for additional mortality and morbidity with ARE, and uptake of this technique by the surgical community has been limited.[5]

The body of literature regarding the risks and benefits of ARE is controversial and unclear. Therefore, the purpose of

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AVR+ARE. There was no difference in the risk of permanent pacemaker implantation (RR 1.02; 95% CI, 0.83-1.25; $P = 0.86$), reoperation for bleeding (RR 1.05; 95% CI, 0.84-1.32; $P = 0.64$), or stroke (RR 0.93; 95% CI, 0.68-1.27; $P = 0.65$). The risk of moderate (indexed effective orifice area [iEOA] < 0.85 cm^2/m^2) and severe (iEOA < 0.65 cm^2/m^2) patient-prosthesis mismatch (PPM) was lower with AVR+ARE (RR 0.65; 95% CI, 0.51-0.83; $P < 0.01$) and RR 0.36; 95% CI, 0.16-0.82; $P = 0.01$, respectively). There was no difference in late mortality (incidence rate ratio [IRR] 1.05; 95% CI, 0.87-1.27; $P = 0.59$) at mean 7.8-year follow-up in 5 studies.

Conclusions: Surgical ARE is a safe adjunct to AVR in selected patients that does not increase early adverse events and results in less patient-prosthesis mismatch. This strategy allows for a larger valve size at the time of implantation, an important consideration for potential future valve-in-valve procedures in the era of TAVR.

0,94-1,54; $P = 0,13$). La durée du pontage cardiopulmonaire (différence moyenne [DM] de 20 minutes; IC à 95 %, 15-25; $P < 0,01$) et la durée de clampage aortique (DM de 14 minutes; IC à 95 %, 11-17, $P < 0,01$) étaient plus élevées après les RVA+DRA. Nous n'avons noté aucune différence dans le risque d'implantation permanente d'un stimulateur cardiaque (RR 1,02; IC à 95 %, 0,83-1,25; $P = 0,86$), de réintervention chirurgicale en raison d'hémorragie (RR 1,05; IC à 95 %, 0,84-1,32; $P = 0,64$) ou d'accident vasculaire cérébral (RR 0,93; IC à 95 %, 0,68-1,27; $P = 0,65$). Le risque de disproportion patient-prothèse (DPP) modérée (surface fonctionnelle de l'orifice indexée [SFOi] $< 0,85$ cm^2/m^2) et de DPP importante (SFOi $< 0,65$ cm^2/m^2) était plus faible lors de RVA+ DRA (RR 0,65; IC à 95 %, 0,51-0,83; $P < 0,01$) et RR 0,36; IC à 95 %, 0,16-0,82; $P = 0,01$, respectivement). Nous n'avons noté aucune différence dans la mortalité tardive (rapport de taux d'incidence [RTI] 1,05; IC à 95 %, 0,87-1,27; $P = 0,59$) au suivi moyen de 7,8 ans de 5 études.

Conclusions : La DRA chirurgicale est un complément au RVA chez les patients sélectionnés qui ne fait pas augmenter les événements indésirables précoces et entraîne moins de disproportion patient-prothèse. Cette stratégie permet une taille valvulaire plus grande au moment de l'implantation, un aspect important pour les interventions éventuelles de type *valve-in-valve* à l'ère du RVAC.

this study is to conduct a quantitative meta-analysis to determine the safety of ARE as a surgical adjunct to AVR and evaluate early and late outcomes.

Methods

Systematic review of the literature

The Ovid versions of 2 databases, MEDLINE and EMBASE, were searched for articles published between 1946 and 2018. The key search terms used were *aortic root enlargement* and *aortic annular enlargement*. Studies that compared patients undergoing AVR+ARE with those undergoing isolated AVR and contained at least 1 outcome of interest were eligible for inclusion. Conference abstracts and proceedings, non-English publications, case reports, and noncomparative study designs were ineligible and excluded. In addition to the database search, all references and articles on the topic were manually reviewed to ensure that all relevant studies were identified. Titles and abstracts of studies were independently screened by 2 investigators (D.Y.T. and A.M.), and articles that potentially met the inclusion criteria were retrieved for further review. Disagreements among investigators were resolved through discussion.

Quality assessment and data abstraction

The quality of evidence from the observational studies was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Supplemental Table S1).[6] Data from the studies were abstracted by 2 independent investigators (D.Y.T. and W.Y.) and included baseline demographics and risk factors, operative details, and study outcomes (Table 1). The primary outcome was defined as late mortality. Secondary outcomes were perioperative endpoints and included early mortality, myocardial infarction, permanent pacemaker implantation, reoperation for bleeding, stroke, moderate PPM (defined as an indexed EOA ≤ 0.85 cm^2/m^2), and severe PPM (defined as an indexed EOA < 0.65 cm^2/m^2). Okamoto et al. used *in vivo* echocardiography to calculate the EOA from the continuity equation[7] whereas all other studies that reported indexed EOA (iEOA) obtained the EOA values from the published literature or the manufacturer's specification, which was then divided by the patient's body surface area to obtain an indexed EOA.

Analysis

A random-effects meta-analysis was performed using *Meta* and *Metafor* packages on RStudio (R version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria). For binary outcomes, weighted risk ratios (RRs) based on sample sizes were calculated from event rates using the Mantel-Haenszel method. Crude event rates for binary outcomes were also tabulated. For continuous outcomes, weighted mean differences were calculated using the inverse variance method. We also performed a meta-analysis of baseline demographics and risk factors to assess for potential differences in baseline characteristics in our included studies.

For late mortality with potentially different follow-up times among groups, natural logarithms of the incidence rate ratios (IRRs) were calculated using the generic inverse variance method.[8] IRRs were estimated using 1 of 2 methods: by comparing events over cumulative group-specific person-years of follow-up or by using hazard ratios from time-to-event curves. The standard errors for IRRs estimated from events were calculated as the square root of the sum of the inverses of the number of events in each group. Alternatively, the standard errors for IRRs were estimated from time-to-event curves from the log rank P value. For cases in which mean and standard deviation were not provided, they were estimated using the median and range, as described previously.[9,10] We reported heterogeneity as low ($I^2 = 0\%$ to

Table 1. Baseline demographics and risk factors

First author, year	Number		Age (years)		Male sex (%)		Cerebrovascular disease (%)		Chronic renal failure (%)		Coronary artery disease (%)	
	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE
Adjusted observational												
Rocha, 2018	1625	1625	66.20 ± 13.7	66.20 ± 13.30	55.5	56.7	-	-	0.9	1.2	2.3	2.2
Okamato, 2016	58	58	73.40 ± 11.90	74.70 ± 8.50	19.0	19.0	0.0	0.0	6.9	10.3	10.3	10.3
Unadjusted observational												
Beckmann, 2016	36	92	63.20 ± 13.00	71.50 ± 10.90	16.7	18.5	-	-	19.4	16.3	27.2	24.1
Correia, 2016	239	767	70.40 ± 12.50	69.90 ± 9.60	18.4	12.0	5.0	6.3	29.3	30.8	-	-
Penaranda, 2014	30	87	85.05 ± 3.20	85.25 ± 2.50	13.3	2.3	20.0	12.6	0.0	3.4	-	-
Prakash, 2010	47	162	36.40 ± 12.40	38.80 ± 13.70	61.7	62.3	-	-	4.3	5.6	-	-
Kulik, 2008	172	540	66.80 ± 12.30	69.10 ± 11.80	30.8	25.2	-	-	-	-	-	-
Dhareshwar, 2007	249	2117	64.30 ± 19.60	70.10 ± 12.20	28.9	66.5	-	-	-	-	-	-
Castro, 2002	114	543	72.50 ± 11.00	72.50 ± 12.40	38.6	65.0	-	-	-	-	-	-

First author, year	COPD (%)		Smoking (%)		Diabetes mellitus (%)		Hypertension (%)		Urgent or emergent status (%)		Prior cardiac operations (%)	
	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE
Adjusted observational												
Rocha, 2018	4.6	4.6	8.6	8.7	23.8	23.4	55.8	56.7	4.4	4.8	17.4	16.9
Okamato, 2016	0.0	3.4	12.1	13.8	22.4	17.2	67.2	63.8	0.0	1.7	5.2	0.0
Unadjusted observational												
Beckmann, 2016	8.3	5.4	-	-	22.0	32.6	66.7	72.8	-	-	13.9	2.2
Correia, 2016	6.7	5.7	-	-	17.6	12.9	57.7	44.1	-	-	8.8	6.9
Penaranda, 2014	26.7	12.6	-	-	16.7	16.1	76.7	74.7	6.7	6.9	10.0	8.0
Prakash, 2010	4.3	6.2	-	-	10.6	12.3	19.1	21.6	-	-	-	-
Kulik, 2008	-	-	7.0	10.4	-	-	-	-	-	-	-	-
Dhareshwar, 2007	-	-	-	-	-	-	-	-	-	-	31.3	5.6
Castro, 2002	-	-	-	-	-	-	-	-	-	-	27.2	25.0

First author, year	Ejection fraction (< 35%) (%)		NYHA 3/4 (%)		Con CABG (%)		Con valve replacement (%)		Con other procedure (%)		Mechanical valve (%)	
	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE	ARE	No ARE
Adjusted observational												
Rocha, 2018	-	-	-	-	-	-	-	-	-	-	-	-
Okamato, 2016	0.0	3.4	0.0	0.0	10.3	10.3	22.4	24.1	24.1	24.1	31.0	36.2
Unadjusted observational												
Beckmann, 2016	-	-	27.8	83.7	-	-	-	-	5.6	32.6	-	-
Correia, 2016	-	-	49.4	57.9	17.2	13.7	9.2	18.8	-	-	23.8	47.7
Penaranda, 2014	-	-	80.0	78.2	43.3	50.6	100.0	100.0	-	-	-	-
Prakash, 2010	14.9	15.4	21.3	22.2	-	-	-	-	-	-	-	-
Kulik, 2008	14.0	12.2	38.4	40.9	43.6	39.6	7.6	18.9	-	-	43.0	40.2
Dhareshwar, 2007	5.6	10.3	79.9	73.1	34.1	49.0	-	-	6.8	3.2	42.2	38.1
Castro, 2002	14.9	10.3	80.7	73.7	50.0	35.9	21.1	19.9	11.4	16.9	-	-

First author, year	Body surface area (mean)		Ejection fraction (mean)		Labelled size of valve (mean)	
	ARE	No ARE	ARE	No ARE	ARE	No ARE
Adjusted observational						
Rocha, 2018	1.87 ± 0.20	1.87 ± 0.20	-	-	-	-
Okamato, 2016	1.45 ± 0.16	1.38 ± 0.16	63.10 ± 7.80	62.70 ± 7.20	19.40 ± 1.60	19.30 ± 1.30

Unadjusted observational						
Beckmann, 2016	1.80 ± 0.20	1.80 ± 0.20	58.00 ± 6.60	58.70 ± 13.10	19.00 ± 0.94	19.75 ± 1.01
Correia, 2016	1.59 ± 0.15	1.57 ± 0.13	65.30 ± 15.90	64.60 ± 16.00	21.80 ± 1.00	20.70 ± 0.50
Penaranda, 2014	1.75 ± 0.14	1.62 ± 0.18	59.00 ± 1.10	54.20 ± 1.30	-	-
Prakash, 2010	1.64 ± 0.10	1.65 ± 0.14	55.10 ± 14.70	54.70 ± 14.30	20.79 ± 1.33	19.39 ± 0.80
Kulik, 2008	-	-	-	-	19.40 ± 1.60	18.00 ± 1.30
Dhareshwar, 2007	1.92 ± 1.20	1.98 ± 0.25	-	-	21.50 ± 1.60	23.20 ± 2.30
Castro, 2002	1.78 ± 0.26	1.85 ± 0.23	49.50 ± 13.40	50.50 ± 13.20	23.20 ± 1.70	23.90 ± 2.20

ARE, aortic root enlargement; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft; Con, concomitant; NYHA, New York Heart Association.

25%), moderate (I^2 = 26% to 50%), and high (I^2 > 50%).[11] All analyses were performed as a pooled analysis of all included studies and then separately in 2 sub-groups: adjusted observational and unadjusted observational. We reported all individual and pooled results with 95% confidence intervals (CIs). A mean follow-up time weighted by the number of patients in each study was calculated from studies that reported late mortality. Finally, as a sensitivity analysis, we conducted a meta-regression to examine the impact of the mean study patient age in the AVR+ARE group on late mortality.

Results

Description of included studies and quality assessment

The initial search yielded 389 unique citations from MEDLINE and EMBASE (Supplemental Fig. S1). Of these citations, 9 articles were included in the analysis after reviewing titles, abstracts, and full articles. Articles were primarily excluded based on inappropriate study design or lack of reporting outcomes of interest. For perioperative outcomes, the 9 articles consisted of 2 adjusted observational studies (n = 3366)[7,12] and 7 unadjusted observational studies (n = 5195)[2,3,13-17] for a total of 8561 patients. There were no randomized controlled trials (RCTs). For late mortality, 5 studies were included. Although 3 studies used regression to adjust for confounders, only 1 study reported the hazard ratio for mortality associated with the ARE, and thus unadjusted results were used from the other 2 studies. One other study used propensity score matching to adjust for potential confounders, and 1 study did not perform any adjustment. Overall, for the outcome of late mortality, we included 3 unadjusted studies (n =1251)[13-15] and 2 adjusted studies (n = 828)[2,7] for a total of 2079 patients.

A meta-analysis of baseline demographics and risk factors was performed. The crude event rates/means and relative risk (95%) are summarized in Supplemental Tables S2 and S3. Most observational studies had comparable baseline demographics and risk factors. Study patients' conditions were generally nonurgent, with normal ejection fraction but otherwise hypertensive with poor New York Heart Association functional class status in both AVR and AVR+ARE groups. Patients in the AVR+ARE group were 1.63 years younger than patients in the AVR-alone group (68.5 years vs 70.1 years, 95% CI, −3.05 to −0.22). The mean body surface area (BSA) (1.71 vs 1.69 m^2) and mean labelled valve size implanted (20.7 vs 20.6) were similar in patients undergoing AVR+ARE and those undergoing AVR alone.

Early and late mortality

The crude event rates and relative risk (95% CI) for early mortality are summarized in Table 2. There was no significant difference in early (in-hospital or 30-day) mortality in the pooled results for AVR+ARE vs AVR (4.1% vs 3.4%; RR 1.21; 95% CI, 0.94-1.54; P = 0.13; I^2 = 0%; Fig. 1). Moreover, there was no significant difference between the adjusted (4.1% vs 3.9%; RR 1.06; 95% CI, 0.76-1.48; P = 0.72; I^2 = 0%) and unadjusted (4.1% vs 3.2%; RR 1.40; 95% CI, 0.96- 2.04; P = 0.08; I^2 = 2%) subgroups for AVR + ARE vs AVR, respectively. Similarly, there was no

Table 2. Pooled outcome rates and relative risk ratios from meta-analysis

	ARE event Rate	No ARE event rate	RR (95% CI)	*P* value
Mortality (n = 9 studies)				
Adjusted	69/1683 (4.10%)	65/1683 (3.86%)	1.06 (0.76, 1.48)	0.72
Unadjusted	36/887 (4.06%)	136/4308 (3.16%)	1.40 (0.96, 2.04)	0.08
Pooled	105/2570 (4.09%)	201/5991 (3.36%)	1.21 (0.94, 1.54)	0.13
Myocardial infarction (n = 4 studies)				
Adjusted	17/1683 (1.01%)	17/1683 (1.01%)	1.01 (0.52, 1.96)	0.98
Unadjusted	3/363 (0.83%)	8/2660 (0.30%)	3.12 (0.42, 23.43)	0.27
Pooled	20/2046 (0.98%)	25/4343 (0.58%)	1.30 (0.54, 3.13)	0.56
Permanent pacemaker implantation (n = 6 studies)				
Adjusted	145/1683 (8.62%)	141/1683 (8.38%)	0.93 (0.41, 2.12)	0.86
Unadjusted	13/362 (3.59%)	95/2458 (3.86%)	0.93 (0.53, 1.63)	0.80
Pooled	158/2045 (7.73%)	236/4141 (5.70%)	1.02 (0.83, 1.25)	0.86
Reoperation (n = 7 studies)				
Adjusted	95/1625 (5.85%)	91/1625 (5.60%)	1.04 (0.79, 1.38)	0.76
Unadjusted	34/648 (5.25%)	170/3541 (4.80%)	1.07 (0.74, 1.55)	0.71
Pooled	129/2273 (5.68%)	261/5166 (5.05%)	1.05 (0.84, 1.32)	0.64
Stroke (n = 7 studies)				
Adjusted	48/1683 (2.85%)	53/1683 (3.15%)	1.08 (0.35, 3.32)	0.90
Unadjusted	17/612 (2.78%)	107/3449 (3.10%)	1.00 (0.60, 1.68)	0.99
Pooled	65/2295 (2.83%)	160/5132 (3.12%)	0.93 (0.68, 1.27)	0.65
Moderate PPM < 0.85 cm^2/m^2 (n = 5 studies)				
Adjusted	15/58 (25.86%)	12/58 (20.69%)	1.25 (0.64, 2.43)	0.51
Unadjusted	149/555 (26.85%)	798/1937 (41.20%)	0.60 (0.30, 0.69)	< 0.01
Pooled	164/613 (26.75%)	810/1995 (40.60%)	0.65 (0.51, 0.83)	< 0.01
Severe PPM < 0.65 cm^2/m^2 (n = 5 studies)				
Adjusted	0/58 (0%)	3/58 (5.17%)	0.14 (0.01, 2.71)	0.19
Unadjusted	5/352 (1.42%)	52/1108 (4.69%)	0.39 (0.16, 0.91)	0.03
Pooled	5/410 (1.22%)	55/1166 (4.72%)	0.36 (0.16, 0.82)	0.01

ARE, aortic root enlargement; CI, confidence interval; PPM, patient prosthesis mismatch; RR, risk ratio.

significant difference in late mortality (IRR 1.05; 95% CI, 0.87-1.27; $P = 0.59$; $I^2 = 0\%$) at a mean follow-up of 7.8 years across 5 studies (Fig. 2).

Operative data

The crude event rates and relative risk (95% CI) for the following operative data are summarized in Table 3. Compared with the AVR+ARE, the AVR group showed significantly shorter pooled aortic cross clamp (MD 14 minutes; 95% CI, 11-17; $P < 0.01$; $I^2 = 71\%$) and cardiopulmonary bypass times (MD 20 minutes; 95% CI, 15-25; $P < 0.01$; $I^2 = 80\%$) during the operation (Supplemental Figures S2 and S3). This pattern was also observed when specifically analyzing adjusted and unadjusted subgroups.

Postoperative outcomes

The crude event rates and relative risk (95% CI) for the following early postoperative outcomes are summarized in Table 2. There was no significant difference in the pooled risk of myocardial infarction (Supplemental Fig. S4), permanent pacemaker implantation (Supplemental Fig. S5), reoperation for bleeding (Supplemental Fig. S6), and stroke (Supplemental Fig. S7) for AVR+ARE compared with AVR alone, respectively. In addition, there were no significant differences among the subgroups of adjusted and unadjusted studies.

There was no significant difference in the pooled iEOA between the AVR+ARE and AVR-alone cohorts (MD −0.05 cm/m^2; 95% CI, −0.01 to 0.11; $P = 0.08$; $I^2 = 97\%$; Supplemental Fig. S8). Although no difference was seen in the adjusted subgroup (MD −0.05 cm/m^2; 95% CI, −0.12 to 0.01; $P = -0.11$; $I^2 = 62\%$), the iEOA was significantly higher after AVR + ARE in the unadjusted subgroup analysis (MD 0.08 cm/m^2; 95% CI, 0.03-0.13; $P < 0.01$; $I^2 = 92\%$).

Although there was no difference in the pooled iEOA results, the analyses showed a significant difference between groups regarding pooled risk of PPM. The AVR+ARE group had a significantly lower risk of moderate (26.8% vs 40.6%; RR: 0.65; 95% CI, 0.51-0.83; $P < 0.01$; $I^2 = 46\%$) and severe PPM (1.2% vs 4.7%; RR 0.36; 95% CI, 0.16-0.82; $P < 0.01$; $I^2 = 0\%$) compared with the AVR group (Supplemental Figs. S9 and S10). Subgroup analyses showed a similar pattern of results for unadjusted studies in moderate (26.9% vs 41.2%; RR 0.60; 95% CI, 0.30-0.69; $P < 0.01$; $I^2 = 0\%$) and severe PPM (1.4% vs 4.7%; RR 0.39; 95% CI, 0.16-0.91; $P = 0.03$; $I^2 = 0\%$). However, a significant difference between AVR+ARE and AVR was not seen in adjusted studies for moderate (25.9% vs 20.7%; RR 1.25; 95% CI, 0.64-2.43, $P = 0.51$) and severe PPM (0% vs 5.2%; RR 0.14; 95% CI, 0.01-2.71; $P = 0.19$).

Meta-regression

We found no impact of mean study patient's age in the AVR+ARE group on late mortality (Supplemental Fig. S11, $P = 0.71$).

Discussion

This is the first meta-analysis examining the short- and long-term safety of ARE in patients undergoing AVR. Most published outcomes comparing AVR+ARE with AVR alone were derived from single centres and may have been

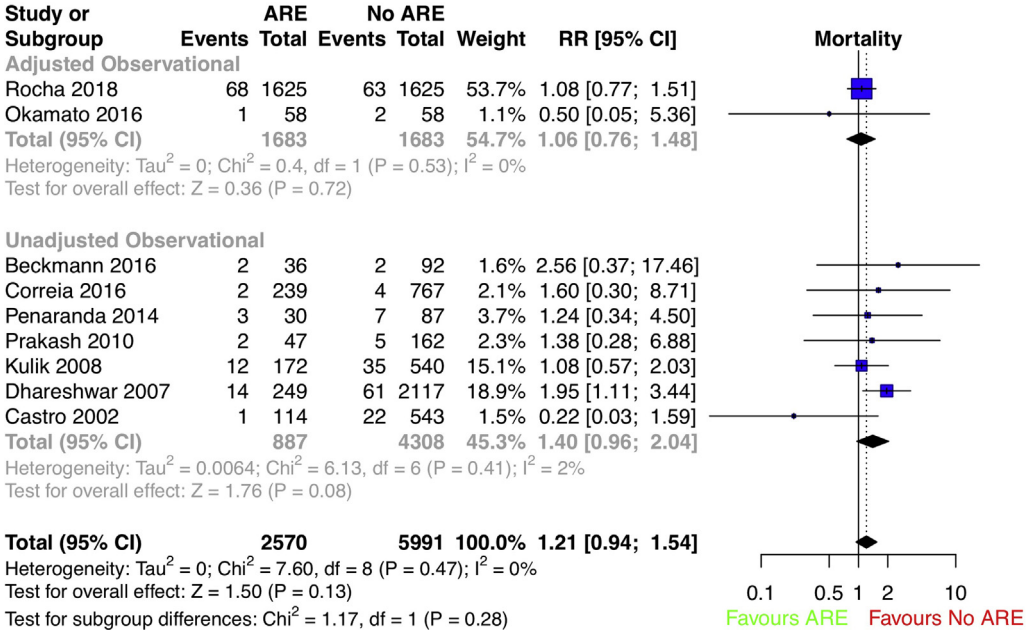

Figure 1. Forest plot for relative risk of 30-day or in-hospital mortality for ARE vs no ARE at the time of an aortic valve replacement subgrouped according to study design. ARE, aortic root enlargement; CI, confidence interval; RR, risk ratio.

underpowered to detect for differences in clinically important endpoints. By aggregating published studies from the global literature, our study provides several important findings with a larger sample size and experiences from centres around the world. The addition of surgical ARE to AVR does not increase early mortality or increase complications such as myocardial infarction, permanent pacemaker implantation, reoperation for bleeding, or stroke. Importantly, AVR with ARE was associated with less moderate and severe PPM following AVR alone at early echocardiography. We note that there were small trade-offs to performing adjunctive ARE: namely, a modest increase in both cardiopulmonary bypass and aortic cross clamp times. However, although a previous multivariable regression of more than 20,000 patients showed an association of late mortality with increased aortic cross-clamp time,[18] we found no difference in late mortality between the 2 groups with an observed mean difference of 15 minutes.

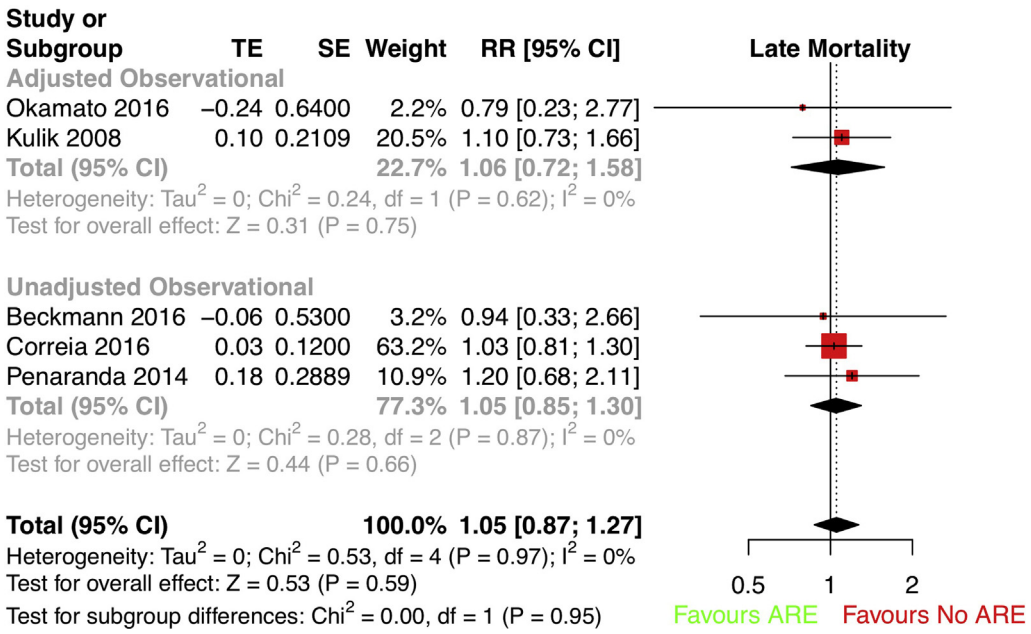

Figure 2. Forest plot for incident rate ratio of late mortality for ARE vs no ARE at the time of an aortic valve replacement subgrouped according to study design. The mean reported length of follow-up was 7.8 years across 2 adjusted observational studies and 3 unadjusted observational studies. ARE, aortic root enlargement; CI, confidence interval; RR, rate ratio.

Table 3. Pooled means and mean differences from meta-analysis

	ARE mean	No ARE mean	MD (95% CI)	*P* value
Aortic cross-clamp time (min) (n = 9 studies)				
Adjusted	109.05	95.48	13.13 (10.64, 15.62)	< 0.01
Unadjusted	72.11	58.02	14.23 (10.67, 17.79)	< 0.01
Pooled	79.57	65.59	13.98 (11.30, 16.66)	< 0.01
Cardiopulmonary bypass time (min) (n = 9 studies)				
Adjusted	145.60	128.45	16.18 (13.08, 19.28)	< 0.01
Unadjusted	104.69	83.75	21.64 (15.20, 28.09)	< 0.01
Pooled	113.69	93.58	20.11 (15.45, 24.77)	< 0.01
iEOA (cm^2/m^2) (n = 8 studies)				
Adjusted	0.87	0.88	-0.05 (-0.12, 0.01)	0.11
Unadjusted	0.97	0.89	0.08 (0.03, 0.13)	< 0.01
Pooled	0.94	0.89	0.05 (-0.01, 0.11)	0.08

ARE, aortic root enlargement; CI, confidence interval; iEOA, indexed effective orifice area; MD, mean difference

Patient-prosthesis mismatch has been shown to be an independent predictor of early and late mortality.[19,20] There are several surgical strategies that can be employed to help increase the size of valves being implanted at the time of AVR. These options include the use of stentless aortic valves, full root replacements, or by performing different techniques such as the Konno procedure.[21-23] Here, we focus on adjunctive ARE with a patch enlargement of the aortic annulus as a strategy to avoid patient-prosthesis mismatch owing to its ease of reproducibility when compared with the other options. Other technological advances that can also improve postoperative hemodynamics include sutureless AVR and TAVR, which have been shown to have improved long-term hemodynamics in clinical trials when compared with conventional AVR with stented or mechanical valves. Although reports have shown a decreased incidence of PPM when compared with standard AVR,[24,25] there remains a lack of evidence to support the use of TAVR in low-risk and young patients as a primary strategy to address a small aortic root, unless standard AVR is deemed high risk.

Work from the Valve-in-Valve International Database (VIVID) has shown that performing valve-in-valve TAVR in a small prosthesis ($\leq$ 21mm) is associated with a doubling of mortality at 1 year.[26] Thus, there has been an increasing amount of interest in the cardiovascular community regarding the use of ARE at the time of aortic valve replacement to place a larger prosthesis and potentially facilitate future valve-in-valve TAVR. Although some surgeons have shied away from liberally performing ARE, our data provide justification for offering this technique in certain patients receiving bioprosthetic aortic valves who would otherwise receive small prostheses. This may be particularly important in young patients, as there is a global trend in placing biological valves in younger patients,[27-29] which is reflected in recent changes in the American Heart Association guidelines for the age thresholds for biological vs mechanical valves.[30] Valve fracturing at the time of TAVR has been described and shown to be effective in the placement of larger TAVR prosthesis. However, its use has been limited to some centres, and there are certain valves that cannot be fractured.[31] Thus, in young patients undergoing AVR with bioprosthetic valves who are at risk for future reintervention, placing the largest possible valve at the time of the index procedure may improve future valve-in-valve outcomes.

Limitations

This study must be interpreted in the context of some important limitations. There were no RCTs published comparing AVR+ARE with AVR alone, and thus this meta-analysis was informed entirely from observational studies. As such, there is the concern for treatment allocation bias, as surgical strategy was at the surgeon's discretion. This meta-analysis was not designed to determine which patients are ideally suited for AVR+ARE, and we recognize that there are select patient groups in which adjunctive ARE may be less beneficial: advanced age, calcific aortic annulus, multiple comorbidities that limit long-term survival, and those patients with other concomitant procedures that may significantly increase cross-clamp time. There were no data available regarding the incidence of left ventricular fibrosis or massive left ventricular hypertrophy, 2 situations in which it has been shown that ARE is not beneficial and should be avoided. Furthermore, baseline differences in the nonrandomized samples may account for differences in outcome. To address potential known confounders, a comprehensive list of baseline characteristics were assessed in this meta-analysis and were similar in the groups, with the exception of age. Meta-analyses on surgical technique are often limited by heterogeneity in study definitions for surgical procedures; we addressed this by employing a random-effects model, which yields larger and more conservative confidence intervals. There was variability in the selection of patients into the ARE arm, whereby some studies chose patients with an estimated projected iEOA < 0.85 cm^2/m^2, and others considered a small root as one that could not accept a 19-mm prosthesis. Similarly, there was variability between studies in the surgical technique chosen to carry out root enlargement, such as the Nicks, Manouguian, or Nunez. The outcomes of the study were limited to mostly early safety outcomes and late mortality, as only 1 study reported readmissions due to congestive heart failure, and no studies reported late aortic valve reintervention. There were no late echocardiography data reported, and thus it is not known whether the initial decline in early PPM was maintained and may be a factor in explaining the lack of late benefit with AVR+ARE. Finally, late survival was based on only 5 studies with differential long-term follow-up periods, which we adjusted for by calculating IRRs that were estimated from Kaplan–Meier curves to incorporate the length of follow-up. A lack of difference in

late mortality may be related to both power (ie, sample size) and length of follow-up in the 5 studies.

Conclusions

Overall, our analysis suggests that adjunctive aortic root enlargement to surgical AVR is a safe strategy to help facilitate the implantation of larger valve prostheses in selected patients. This is a particularly important consideration in light of the growing trend toward bioprosthetic valve implantation in younger patients, which may necessitate future valve-in-valve TAVR procedures.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.02.004.