Early and late outcomes following aortic root enlargement: A multicenter propensity score–matched cohort analysis

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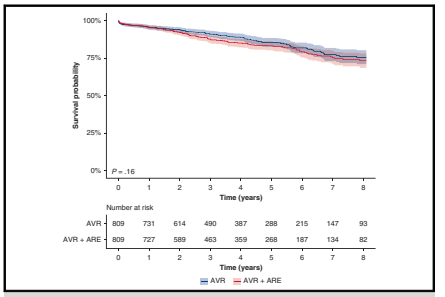
ABSTRACT

Objective: The safety and efficacy of aortic root enlargement (ARE) at the time of aortic valve replacement (AVR) remains unknown. The objective of this multicenter study was to compare AVR with ARE to AVR for early and late mortality and secondary safety outcomes.

Methods: Clinical and administrative databases in Ontario, Canada, were linked to obtain patients undergoing AVR with or without ARE from 2008 to 2017. Baseline characteristics were compared and 1:1 propensity score matching was performed to account for differences in baseline characteristics. Early outcomes were compared in the matched groups. Late mortality was compared using Kaplan-Meier survival curves and a Cox-proportional hazard model.

Results: Sixteen thousand six hundred fifty-six patients undergoing AVR in 11 Ontario institutions were reviewed. Patients who underwent ARE were younger, nonurgent, more likely to be men and had lower rates of hypertension, ischemic heart disease, and congestive heart failure. Propensity score matching yielded similar groups for comparison, with 809 pairs for AVR versus AVR with ARE. There was no difference in 30-day mortality between AVR with ARE versus AVR (2.0% vs 2.1%; $P = 1.00$). Rates of chest reopening for bleeding, permanent pacemaker implantation, and blood transfusions were similar. Late mortality over 8 years was similar between AVR with ARE and AVR ($P = .45$). In a sensitivity analysis, results were similar in 525 pairs comparing AVR with coronary artery bypass grafting and ARE to AVR with coronary artery bypass grafting, except that chest reopening for bleeding was higher with AVR with coronary artery bypass grafting and ARE (7.2% vs 3.2%; $P = .006$).

Conclusions: The addition of ARE to isolated AVR can be safely performed to increase implanted prosthesis size without compromising early mortality. Additional studies with longer follow-up are necessary. (J Thorac Cardiovasc Surg 2020;160:908-19)



Late survival comparing isolated aortic valve replacement with or without aortic root enlargement.

Central Message

The addition of ARE to isolated AVR can be safely performed to increase implanted prosthesis size without compromising early or late mortality. Additional studies with longer follow-up are necessary.

Perspective

Aortic root enlargement at the time of aortic valve replacement allows for the implantation of a larger prosthesis, potentially avoiding patient–prosthesis mismatch and facilitating future valve-in-valve transcatheter aortic valve replacement. Despite these purported benefits, the safety and efficacy of aortic root enlargement remain unknown. We show that adding aortic root enlargement to isolated aortic valve replacement is safe and does not compromise early or late mortality.

See Commentaries on pages 920, 922, and 924.

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Abbreviations and Acronyms

ARE = aortic root enlargement
AVR = aortic valve replacement
CABG = coronary artery bypass grafting
CHF = congestive heart failure
CIHI-DAD = Canadian Institute of Health Information Discharge Abstract Database
OHIP = Ontario Health Insurance Plan
PPM = patient–prosthesis mismatch
PS = propensity score
TAVR = transcatheter aortic valve replacement

Scanning this QR code will take you to the article title page to access supplementary information.

There is controversy surrounding the management of the small aortic annulus at the time of aortic valve replacement (AVR). Patients with small aortic annulus are at risk for patient–prosthesis mismatch (PPM) if a small valve relative to body surface area is implanted. When valve effective orifice area is indexed to body surface area, moderate PPM ($\leq$0.85 cm^2/m^2) or severe PPM ($\leq$0.65 cm^2/m^2) has been shown to be associated with reduced late survival in a meta-analysis of 34 observational studies with more than 27,000 patients.[1]

While aortic root enlargement (ARE) allows for the implantation of a larger valve by at least 1 labeled size, there is concern that this procedure may increase the risk of mortality and/or morbidity. A recently published meta-analysis showed that the addition of ARE was associated with increased aortic crossclamp and cardiopulmonary bypass time.[2] However, ARE may be an important adjunct in the era of valve-in-valve transcatheter AVR (TAVR) for failed biological prostheses. Studies have shown that performing valve-in-valve TAVR into a small bioprosthesis ($\leq$21 labeled size) is associated with a doubling in midterm mortality.[3] Because guidelines have changed to reduce the age threshold for a biological valve, there may be added importance of performing ARE at the time of index AVR to allow for the largest biological valve implantation possible.[4]

The literature comparing ARE at the time of AVR to AVR alone is limited to mostly observational studies that have not adequately adjusted for baseline differences in patient population. Although a large, single-center study utilizing propensity matching techniques has recently been published, this analysis only examined early outcomes.[5] Thus, there is a lack of studies utilizing statistical techniques that adjust for baseline differences in comparing both early and late outcomes. Accordingly, our primary objective was to compare early and late outcomes between AVR + ARE and isolated AVR using propensity score (PS) matching. A secondary objective is to evaluate the differences between AVR + coronary artery bypass grafting (CABG) + ARE compared with AVR + CABG.

METHODS

Study Design

A retrospective analysis of records for patients undergoing AVR from October 31, 2008, to March 31, 2017, was constructed through linkages of multiple population and clinical based databases housed at the ICES in Toronto, Ontario, Canada. ICES is Canada's largest health services research institute and holds multiple population-based health databases of the Ontario population. ICES is a prescribed entity under Ontario's Personal Health Information Protection Act, which allows for researchers to link together encoded population-based administrative databases and clinical registries for conducting approved research studies under strict privacy and security policies, procedures, and practices (see the link to Data and Privacy at www.ices.on.ca). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. The need for individual patient consent was waived. These datasets were linked using unique encoded identifiers and analyzed at ICES.

Study Population and Data Linkages

Patients undergoing AVR were first identified using the CorHealth Ontario Cardiac Registry (a repository of all patients undergoing any cardiac procedure in Ontario). We then linked the records to the Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD) to identify if they had undergone ARE using Canadian Classification of Intervention codes. Only adults (age $\geq$18 years) who underwent first time AVR with or without concomitant CABG and with or without ARE were included. Patients who underwent other concomitant cardiac or noncardiac surgery procedures were excluded. Our primary analysis included only isolated AVR patients and our secondary analysis included all patients who underwent AVR with concomitant CABG. We used a look-back period of 20 years before the index procedure date to identify patients who underwent previous cardiac surgery in the CIHI-DAD or CorHealth registry and excluded those patients. An overview of all databases involved in the linkage can be found in Appendix E1.

Baseline Demographic Characteristics

Relevant baseline demographic characteristics were compared between patients AVR + ARE and AVR. We used the Ontario Registered Persons Database to obtain sociodemographic information, including postal code, which was subsequently linked to Statistics Canada census data to obtain median neighborhood income of individuals to serve as a proxy for socioeconomic status.

Postoperative Outcomes

Thirty-day mortality was obtained using the CIHI-DAD and the Registered Persons Database. In-hospital occurrence of bleeding and chest reopening for bleeding were obtained from CIHI-DAD and the Ontario Health Insurance Plan (OHIP) billing codes respectively. New permanent pacemaker implantation was obtained through OHIP billing codes. Length of operation, hospital length of stay and 30-day readmission from date of discharge was obtained through CIHI-DAD. Our primary outcome was

late all-cause mortality ascertained from the Registered Persons Database. For other late outcomes, readmission for congestive heart failure (CHF) and aortic valve reintervention was obtained through CIHI-DAD and CorHealth. The list of clinical outcomes and their associated ICD-10, Canadian Classification of Interventions, OHIP billing code and CorHealth Ontario codes are available in Appendix E1.

Statistical Analyses

Baseline characteristics were first compared between the unmatched groups; the Student *t* test was used for normally distributed continuous variables, Wilcoxon rank-sum test for nonnormally distributed continuous variables, whereas the χ^2 test was used for categorical variables. PS matching was performed comparing AVR + ARE to isolated AVR to adjust for baseline confounders to minimize selection bias. The PS for each patient was estimated through a multivariable logistic regression model in which the intervention performed (AVR + ARE vs AVR), was regressed on 31 important baseline demographic characteristics that may influence the choice of intervention, including year of surgery and institution (Appendix E2). Subjects were matched on the logit of the PS using a 1:1 greedy nearest-neighbor with a caliper distance of 0.2 times the standard deviation of the logit of the PS.[6] Success of matching was assessed by computing the standardized difference of each covariate with a cutoff of 0.1 to denote acceptable balance.[7] The early outcomes were compared between the 2 cohorts using the McNemar test for binary outcomes and paired *t* test and the Wilcoxon signed-rank test for normally and nonnormally distributed continuous variables, respectively. All tests were 2-sided.

For late mortality, a time to event analysis using Kaplan-Meier survival curves was conducted in the matched sample, using a stratified log-rank *P* test to test the equality of the estimated survival curves.[8] In addition, hazard ratios (HRs) were estimated using a Cox-proportional hazards model, which incorporated a robust sandwich-type variance estimator to account for the matched nature of the data, which has been shown to result in more accurate estimates of standard errors compared with the conventional maximum-likelihood estimate of the standard error.[9] For CHF readmissions and late aortic valve reinterventions, we estimated cumulative incidence functions to estimate the incidence of these events after accounting for death as a competing risk. In the matched sample, both a cause-specific hazard model and a Fine-Gray subdistribution hazard model were used to regress the outcome on a single variable denoting treatment status.[10] For both models, robust variance estimators were used to estimate the standard errors.

Secondary Analysis

We repeated the above-described analysis for patients undergoing AVR + CABG + ARE to AVR + CABG (secondary analysis). Patients undergoing CABG were identified using the CorHealth Registry and CIHI-DAD. The number of distal anastomoses performed were obtained from OHIP billing codes. We excluded all other concomitant procedures.

Sensitivity Analyses

For the primary outcome of late mortality, we repeated the propensity-matched analysis for the primary (isolated AVR) and secondary analyses (AVR + CABG), matching on the 31 baseline characteristics in addition to operative characteristics. For the isolated AVR group, we matched on tissue/mechanical valve and for the AVR + CABG group, we matched on tissue/mechanical valve and number of distal coronary anastomoses. In an additional sensitivity analysis, we performed the match with up to 2 controls per exposure subjects. Finally, to address the potential for institutional effects on outcomes, we matched on the PS (as described above) and simultaneously hard matched on institution. This ensured that matched patients were treated at the same institution and operated on by a similar group of surgeon.

All analyses were conducted with SAS version 9.4 (SAS Institute Inc, Cary, NC) or R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Cohort

Out of 26,764 initial records, 1.3% (n = 363) were not linkable and thus we started with 22,679 patients who underwent a procedure of interest (Figure E1). We excluded those with concomitant procedures and a history of active infective endocarditis. The final population consisted of 8506 in the isolated AVR group and 821 in the AVR + ARE group for primary analysis; 6801 in the AVR + CABG group and 528 in the AVR + CABG + ARE group for secondary analysis.

Primary Matched Analysis

There were significant differences in important baseline characteristics in the unmatched AVR + ARE and AVR cohorts (Table 1). Those who underwent AVR + ARE were younger, more likely to be men, less likely to be from a rural area, more likely to be elective patients, had lower incidence of atrial fibrillation or ischemic heart disease, and less likely to have a history of dialysis, but more dyslipidemia and diabetes compared with isolated AVR. PS matching on 31 baseline covariates yielded 809 pairs for the AVR to AVR + ARE comparison. The match quality was adequate for both comparisons, because the standardized mean difference for all baseline characteristics were <0.1 (Table 1). We matched on valve type and extent of coronary artery disease in our sensitivity analysis. Qualitative comparison of the PS before and after matching demonstrates similar distributions of PS after matching (Figure E2).

There was no difference in 30-day mortality (2.0% vs 2.1%; $P = 1.0$) between AVR + ARE and AVR in the matched sample. Furthermore, rates of new permanent pacemaker implantation, blood transfusion, and chest reopening were similar between the 2 groups (Table 2). Although the mean (interquartile range [IQR]) length of operation was longer with AVR + ARE (272 minutes; IQR, 230-320 minutes vs 250 minutes; IQR, 210-303 minutes; $P < .001$), the total hospital length of stay was similar. There was no difference in 30-day readmission rates.

There was no difference in the rate of late mortality between AVR + ARE and AVR (Figure 1) (73.1% vs 75.4%; HR, 0.81; 95% confidence interval [CI], 0.59-1.09; $P = .17$) at 8-year follow-up. We examined the cumulative incidence function of nonfatal events (CHF readmission and aortic valve intervention) and accounting for death as a competing risk because death precludes the subsequent occurrence of the nonfatal event. We found no significant difference in the cumulative incidence of CHF

TABLE 1. Baseline characteristics before and after propensity score matching

Characteristic	Before propensity score matching			After propensity score matching		
	AVR + ARE (n = 850)	AVR (n = 8764)	SMD	AVR + ARE (n = 809)	AVR (n = 809)	SMD
Age (y)	65.64 ± 12.24	68.54 ± 11.68	0.247	65.57 ± 12.36	65.48 ± 13.38	0.007
Sex (female)	483 (56.8)	3627 (41.4)	0.325	459 (56.7)	450 (55.6)	0.022
Rurality (rural)	113 (13.3)	1597 (18.2)	0.13	111 (13.7)	108 (13.3)	0.011
Income quintile						
1	143 (16.8)	1490 (17.0)	0.057	155 (19.2)	146 (18.0)	0.029
2	163 (19.2)	1683 (19.2)	0.034	145 (17.9)	159 (19.7)	0.044
3	189 (22.2)	1841 (21.0)	0.054	156 (19.3)	147 (18.2)	0.029
4	179 (21.1)	1915 (21.9)	0.016	179 (22.1)	183 (22.6)	0.012
5	176 (20.7)	1835 (20.9)	0.016	174 (21.5)	174 (21.5)	<0.001
Charlson score	1.71 ± 1.89	1.78 ± 1.86	0.045	1.70 ± 1.90	1.76 ± 1.92	0.028
Frailty	43 (5.1)	475 (5.4)	0.011	41 (5.1)	38 (4.7)	0.017
Body surface area	1.95 ± 0.25	1.96 ± 0.26	0.119	1.92 ± 0.27	1.91 ± 0.26	0.028
Urgent	101 (11.9)	1481 (16.9)	0.148	94 (11.6)	101 (12.5)	0.027
Smoking history						
Never	486 (57.2)	4808 (54.9)	0.046	459 (56.7)	466 (57.6)	0.017
Former	261 (30.7)	2726 (31.1)	0.013	248 (30.7)	249 (30.8)	0.003
Current	103 (12.1)	1230 (14.0)	0.05	102 (12.6)	94 (11.6)	0.03
Dyslipidemia	468 (55.1)	4268 (48.7)	0.128	443 (54.8)	443 (54.8)	<0.001
Hypertension	643 (75.6)	6841 (78.1)	0.057	613 (75.8)	612 (75.6)	0.003
Diabetes	329 (38.7)	3036 (34.6)	0.09	311 (38.4)	318 (39.3)	0.018
Ischemic heart disease	299 (35.2)	3541 (40.4)	0.113	283 (35.0)	306 (37.8)	0.059
Previous PCI	6 (0.7)	131 (1.5)	0.074	6 (0.7)	9 (1.1)	0.039
CHF	354 (41.6)	4537 (51.8)	0.212	347 (42.9)	363 (44.9)	0.04
Atrial fibrillation	125 (14.7)	1696 (19.4)	0.132	119 (14.7)	122 (15.1)	0.01
PVD	24 (2.8)	332 (3.8)	0.064	21 (2.6)	26 (3.2)	0.037
CVD	34 (4.0)	484 (5.5)	0.073	33 (4.1)	40 (4.9)	0.042
CCS class						
0	382 (44.9)	4156 (47.4)	0.055	450 (55.6)	447 (55.3)	0.007
1	112 (13.2)	1228 (14.0)	0.002	126 (15.6)	146 (18.0)	0.066
2	137 (16.1)	1309 (14.9)	0.051	118 (14.6)	100 (12.4)	0.065
3	102 (12.0)	935 (10.7)	0.055	65 (8.0)	58 (7.2)	0.033
4	117 (13.8)	1136 (13.0)	0.024	50 (6.2)	58 (7.2)	0.04
NYHA functional class						0.052
1	285 (33.5)	2958 (33.8)	0.272	176 (21.8)	189 (23.4)	0.038
2	265 (31.2)	2628 (30.0)	0.182	322 (39.8)	315 (38.9)	0.018
3	253 (29.8)	2707 (30.9)	0.082	276 (34.1)	265 (32.8)	0.029
4	47 (5.5)	471 (5.4)	0.024	35 (4.3)	40 (4.9)	0.029
LV grade (%)						
≥50	692 (81.4)	7214 (82.3)	0.132	726 (89.7)	725 (89.6)	0.004
35-49	101 (11.9)	1038 (11.8)	0.116	53 (6.6)	51 (6.3)	0.01
<35	57 (6.7)	512 (5.8)	*	30 (3.7)	33 (4.1)	*
Creatinine level (mg/dL)						
≤120	752 (88.5)	7647 (87.3)	0.141	753 (93.1)	740 (91.5)	0.06
121-180	68 (8.0)	845 (9.6)	0.137	39 (4.8)	47 (5.8)	0.044
≥180	30 (3.5)	272 (3.1)	0.041	17 (2.1)	22 (2.7)	0.04
Dialysis	30 (3.5)	574 (6.5)	0.149	28 (3.5)	36 (4.4)	0.051
COPD	205 (24.1)	2044 (23.3)	0.023	194 (24.0)	181 (22.4)	0.038

(Continued)

TABLE 1. Continued

Characteristic	Before propensity score matching			After propensity score matching		
	AVR + ARE (n = 850)	AVR (n = 8764)	SMD	AVR + ARE (n = 809)	AVR (n = 809)	SMD
Cancer	94 (11.1)	1094 (12.5)	0.046	91 (11.2)	78 (9.6)	0.053
Dementia	7 (0.8)	152 (1.7)	0.08	7 (0.9)	9 (1.1)	0.025
Aortic stenosis indication	727 (85.5)	7486 (85.4)	0.005	688 (85.0)	679 (83.9)	0.031
Tissue valve	632 (77.0)	6380 (75.0)	0.052	631 (78.0)	558 (69.0)	0.185
Academic center	715 (87.1)	6624 (77.9)	0.244	700 (86.8)	700 (86.8)	<0.001
Annual volume of AVR						
Lowest tertile	110 (13.4)	1753 (20.6)	0.193	110 (13.6)	114 (14.1)	0.014
Middle tertile	136 (16.6)	2306 (27.1)	0.257	136 (16.9)	127 (15.8)	0.03
Highest tertile	575 (70.0)	4447 (52.3)	0.37	560 (69.5)	565 (70.1)	0.014

Values are presented as mean ± standard deviation or n (%). AVR, Aortic valve replacement; *ARE*, aortic root enlargement; *SMD*, standardized mean difference; *PCI*, percutaneous coronary intervention; *CHF*, congestive heart failure; *PVD*, peripheral vascular disease; *CVD*, cerebrovascular disease; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association; *LV*, left ventricular; *COPD*, chronic obstructive pulmonary disorder. *SMD not available for this category.

readmission between AVR + ARE and AVR (Figure 2) (14.9% vs 10.2%; subdistribution HR, 1.32; 95% CI, 0.92-1.90; $P = .13$) and aortic valve reintervention (Figure 3) (3.6% vs 3.7%; subdistribution HR, 0.90; 95% CI, 0.45-1.80; $P = .77$) after adjusting for death as a competing risk at 8 years. There was also no significant effect of treatment on the cause-specific hazards for CHF readmissions (cause-specific HR, 1.31; 95% CI, 0.85-2.04; $P = .22$) at 8 years and reintervention (cause-specific HR, 0.91; 95% CI, 0.39-2.14; $P = .83$).

Secondary Matched Analysis

PS matching on 31 covariates yielded 525 pairs for the AVR + CABG to AVR + CABG + ARE comparison. The match quality was adequate for both comparisons because the SMD for all baseline characteristics was <0.1 (Table E1). When AVR + CABG was compared with AVR + CABG + ARE, there was no difference in early mortality (4.0% vs 3.6%; $P = .87$). Furthermore, rates of new permanent pacemaker and any blood product transfusion were similar (Table 2). However, the rate of chest reopening was significantly higher in the AVR + CABG + ARE group (7.2% vs 3.2%; $P = .006$). There was no difference in the rate of early readmission. There was no difference in late mortality between AVR + CABG + ARE versus AVR + CABG (Figure E3) (57.3% vs 59.8%; HR, 0.97; 95% CI, 0.71-1.33; $P = .88$) at 8-year follow-up.

Sensitivity Analyses

For the sensitivity analyses in which we matched on both baseline characteristics and operative characteristics (including valve type implanted), we found no difference in late mortality for both the AVR ± ARE and AVR + CABG ± ARE analysis (Figures E4 and E5). In addition, results were robust for the outcomes of early (2.0% vs 1.4%; $P = .34$) and late mortality when 1:2 matching was performed (Figure E6). Similarly, when hard matching was performed for institution, there was no difference in early mortality (2.0% vs 1.6%; $P = .71$) and late mortality (Figure E7).

DISCUSSION

To our knowledge, this is the first multicenter, PS-matched study comparing adjunctive ARE to AVR ± CABG for both early and late outcomes. There are several pertinent findings from this study. First, the addition of ARE to isolated AVR is safe and does not

TABLE 2. Outcomes for propensity score-matched patients

Matched outcome	AVR + ARE (n = 809)	AVR (n = 809)	*P* value	AVR + CABG + ARE (n = 525)	AVR + CABG (n = 525)	*P* value
Length of stay (d)	7 (6-11)	7 (6-11)	.95	8 (7-13)	9 (7-14)	.72
Length of operation (min)	272 (230-320)	250 (210-303)	<.001	325 (285-390)	303 (265-358)	<.001
30-d Mortality	16 (2.0)	17 (2.1)	1	19 (3.6)	16 (3.0)	.731
New pacemaker	39 (4.8)	54 (6.7)	.135	28 (5.3)	28 (5.3)	1
Any blood product transfusion	540 (66.7)	510 (63.0)	.131	445 (84.8)	424 (80.8)	.102
Chest reopening	41 (5.1)	30 (3.7)	.225	38 (7.2)	17 (3.2)	.006
Early readmission	101 (12.5)	95 (11.7)	.703	72 (13.7)	83 (15.8)	.384

Values are presented as median (interquartile range) or n (%). *AVR*, Aortic valve replacement; *ARE*, aortic root enlargement; *CABG*, coronary artery bypass grafting.

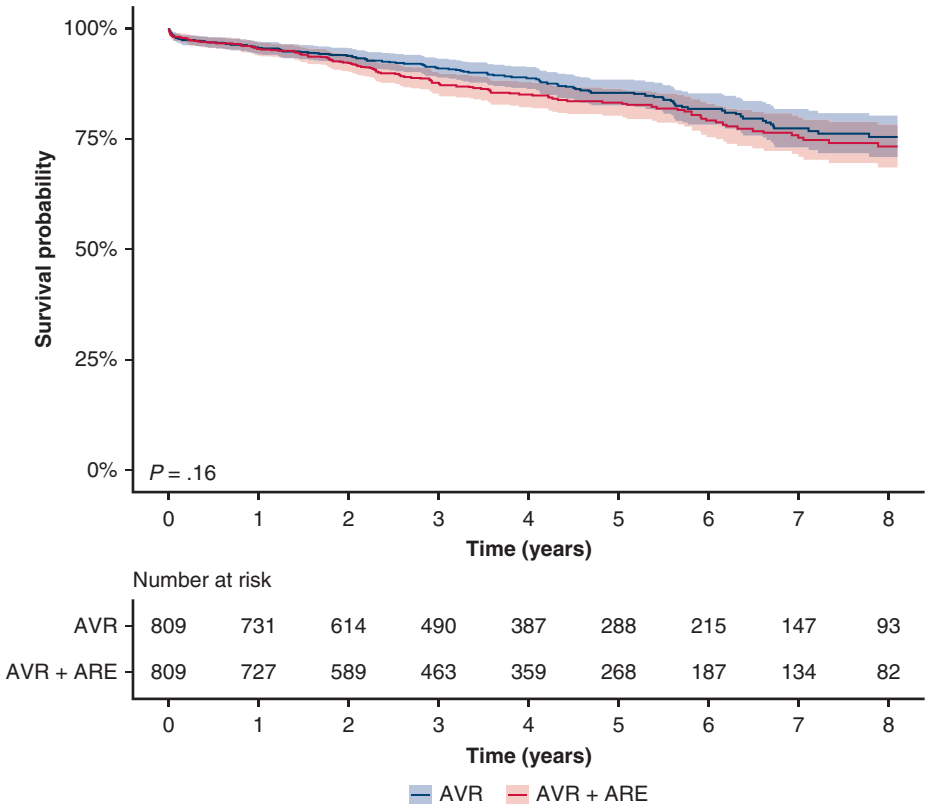

FIGURE 1. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the propensity score-matched patients undergoing aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*).

increase the risk of early mortality, permanent pacemaker implantation, or chest reopening. Second, the addition of ARE to AVR and concomitant CABG was associated with a significantly higher rate of chest reopening, although early mortality was similar between the 2 groups. Overall, there was no difference in mortality, CHF readmission, or reintervention over a long duration of follow-up (mean and maximum follow-up of 4 years and 8 years, respectively). These findings are consistent with a recent meta-analysis that showed no difference in early mortality or permanent pacemaker implantation between patients who underwent AVR and ARE to AVR alone. Although there was no difference in chest reopening when ARE was added to isolated AVR, the findings of increased chest reopening in the AVR + CABG + ARE cohort is new information and suggests that the addition of ARE to more complex procedures may precipitate more bleeding events and patients should be carefully monitored for signs of cardiac tamponade or surgical bleeding.

There are several strategies that can be used to help increase the size of valves implanted at the time of AVR. In addition to ARE, other options include the use of stentless aortic valves, full root replacements, or more aggressive ARE such as the Konno procedures.[11,12] More recently, sutureless AVR and TAVR have been shown to have superior late hemodynamic parameters when compared with conventional AVR.[13] Although recent publications of 2 randomized controlled trials demonstrated noninferiority of TAVR to surgical AVR at 1- and 2-year follow-up in low-risk patients (mean Society of Thoracic Surgeons predicted mortality <3%) at mean age 72 to 73 years, there is still uncertainty surrounding valve durability in this cohort as we await results of 10-year follow-up.[14,15] Thus, ARE remains a reasonable option for young and low-risk patients with a small annulus who require AVR.

The clinical results of PPM has been extensively studied.[16,17] Long-term follow-up of 1563 patients undergoing AVR showed that both larger prosthesis size and effective orifice area was associated with freedom from CHF and that mismatch was an independent predictor of mismatch.[18] Exercise testing in 312 AVR patients suggest that PPM was associated with poor physical capacity.[19] In addition, both left ventricle mass regression[20] and coronary flow reserve[21] may be reduced with PPM. Finally, a meta-analysis of 34 studies that included more than 27,000 patients showed that both moderate and severe PPM was associated with a modest increase in all-cause mortality.[1]

Besides reduction in PPM, the placement of a larger biological valve is particularly important in young patients (ie, those aged ≤60 years) as they are at higher risk for

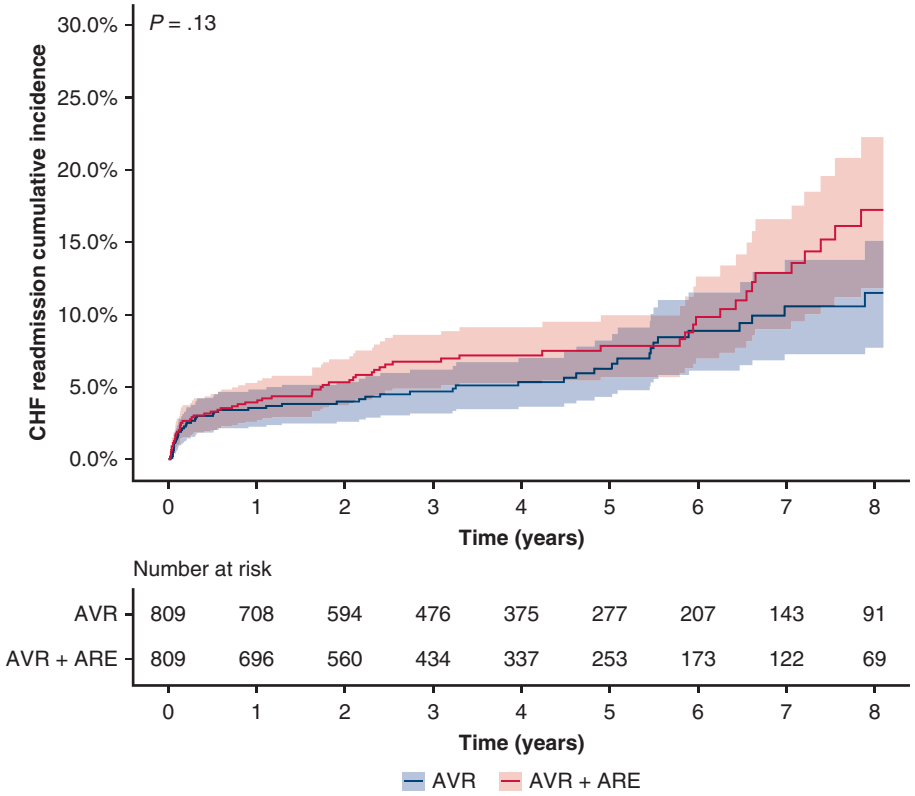

FIGURE 2. Cumulative incidence curves for 8-year congestive heart failure (CHF) readmission for the propensity-matched patients undergoing aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) adjusted for death as a competing risk.

failed biological prosthesis.[22] Recent changes in the American Heart Association guidelines have lowered the age threshold for which a biological or mechanical valve can be considered to be age 50 to 70 years based on both patient and physician preferences.[4] Trends in the literature suggest that the age threshold for biological prostheses have been decreasing in the era of TAVR.[23,24] Thus, we may expect a higher incidence of biological prosthesis failure as we continue to implant these in younger patients. Although some of these patients may have been promised an alternative reoperative strategy with TAVR, it has been recognized that the placement of TAVR prosthesis in a small bioprosthesis is associated with a doubling of late mortality.[3] Thus, ARE becomes an important adjunct at the index operation to ensure the placement of the largest possible biological prosthesis in younger patients. Our study suggests that surgeons should not shy away from this procedure because it does not increase early mortality. It is important to note that novel valves have been developed to facilitate valve fracturing, which has been shown to increase the implantation of a TAVR valve by at least 1 size at the time of the valve-in-valve procedure.[25] However, valve fracturing, as a concept, was not introduced until after the study date of our analysis and likely had no influence on surgeon decision to perform ARE in our analysis.

Limitations

This study must be interpreted in the context of some very important limitations. This was an observational study that could be biased by treatment assignment at the surgeon's discretion. We attempted to mitigate treatment allocation bias by performing PS matching on key baseline characteristics, but acknowledge that this technique only balances known confounders and is not a substitute for a randomized clinical trial. In addition, we recognize that certain surgeons may be more facile at performing ARE and thus results may be confounded by performance bias. These results must be interpreted in the context that academic centers and higher-volume AVR centers were more likely to perform adjunctive ARE and highlights the importance of surgeon expertise in performing this procedure. We performed an exact match on institution in our PS-matched analysis and showed that our findings were robust. Another key limitation is the lack of preoperative and postoperative echocardiography data such that we do not fully understand the preoperative aortic valve area and annulus size before surgery. As such, the generalizability of our findings may be limited. We can only suspect that patients undergoing ARE required it to facilitate the placement of a larger valve. There may also be heterogeneity in the type of ARE performed, we do

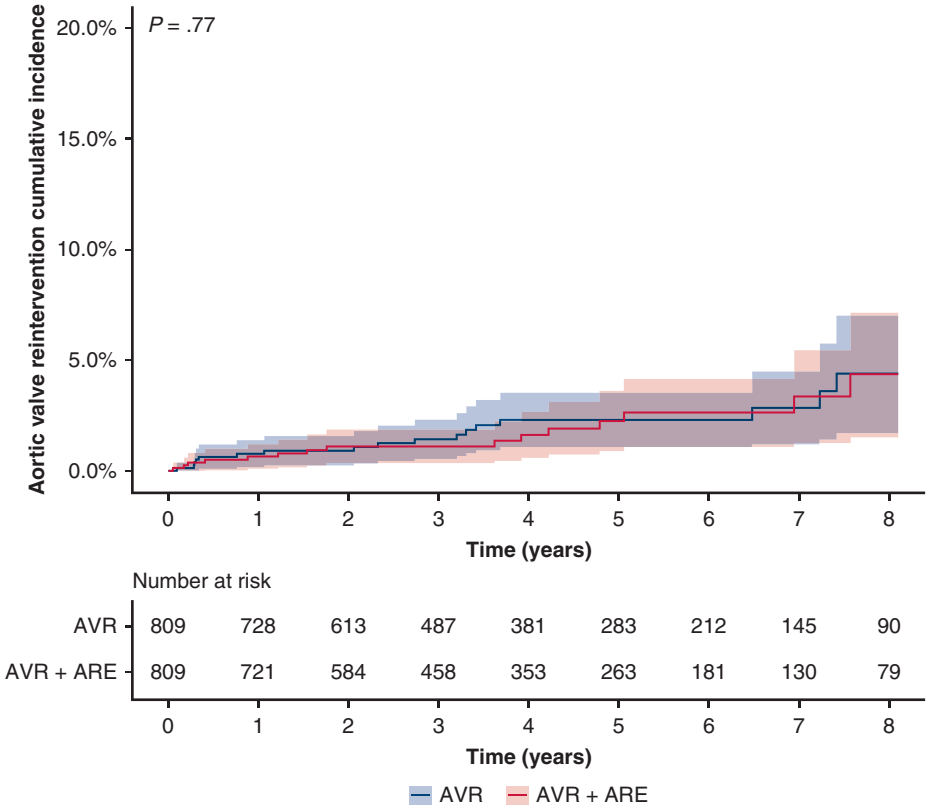

FIGURE 3. Cumulative incidence curves for 8-year any aortic valve reintervention for the propensity-matched patients undergoing aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) adjusted for death as a competing risk.

not have enough granularity to determine whether a Konno, Manougian, or Nicks was performed. Due to a lack of postoperative echocardiographic data, we do not have data on left ventricular mass regression or postoperative gradients or effective valve orifice area (measures of PPM). Instead, we measured CHF readmission; the lack of left ventricle mass regression has been shown to be associated with additional CHF readmission.[26] We recognize that a mean follow-up of 4 years may not be adequate to track late outcome differences and that further follow-up may be necessary. This analysis examined several outcomes without adjusting for multiplicity. As such, there is a risk for an inflated Type I error that must be accounted for when interpreting the significance of the results. Finally, there are the usual limitations associated with administrative database studies, including the possibility for administrative coding error, the reliance on administrative codes to track nonmortality outcomes, and data granularity.

CONCLUSIONS

In this multiple-institution, population level, PS-matched analysis, there was no difference in early mortality with adjunctive ARE to AVR ± CABG patients, although there was an increased risk of chest reopening in those undergoing ARE in addition to AVR + CABG. The addition of ARE may be an important safe adjunct to facilitate implantation of a larger valve at the time of initial aortic valve replacement.

Conflict of Interest Statement

Dr Ouzounian is a consultant for Medtronic and serves on their North American advisory board.

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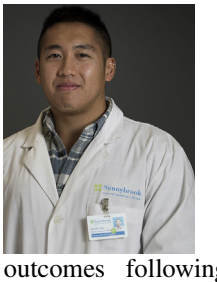
Key Words: aortic root enlargement, propensity score, aortic valve replacement

Discussion

Dr Patricia A. Thistlethwaite. So, without further ado, I'd like to open up the first Scientific Session with the opening paper, which is entitled "Early And Late Outcomes Following Aortic Root Enlargement At The Time Of Aortic Valve Replacement: A Population Based Study," and the presenter will be Derrick Tam from the University of Toronto.



Dr Derrick Y. Tam *(Toronto, Ontario, Canada)*. Dr Thistlethwaite, Dr Shemin, guests, members of the Association. On behalf of my coauthors, I would like to thank the Association for the opportunity to present this work today. Today, we will be looking at the early and late outcomes following aortic root enlargement using a population-based studied. There are no disclosures. So, the management of the small aortic annulus at the time of aortic valve replacement is controversial. We know that these patients are at risk for patient prosthesis mismatch. Large studies have demonstrated that even moderate PPN may negatively impact survival. Aortic root enlargement, or ARE, allows for the implementation of larger valves at the time of aortic valve replacement. Studies have shown that there is a longer cross time and bypass time and there are concerns for risk of additional mortality and morbidity with this procedure. However, aortic root enlargement may become important in the era of transcatheter aortic valve replacement. Several studies have shown that we are implanting more biological valves in younger and younger patients. These patients are at risk of structural valve deterioration and failure. All this is posited on the fact that these patients may receive a TAVR for their redo operation. We know the putting a valve-in-valve TAVR in these patients is associated with a doubling of mortality at one year. So, on that background, it became our research question to study at the population level is there a difference in early and late outcomes in isolated aortic valve replacement patients with or without additional aortic root enlargement. Our primary outcome was 30-day mortality and late mortality. Our secondary outcomes for those of safety related to new permanent pacemaker implantation, chest reopening, and also late congestive heart failure re admission.

So we undertook the study using the Core Health Registry located in Ontario Canada, Canada's most populous province of 11,000,000 patients. We looked at the isolated aortic valve replacement group, with our way out aortic root enlargement, as our primary analysis. We looked at patients performed in Ontario from 11 institutions from 2008 to 2017. We linked to the Discharge Abstract Database to

allow us to ascertain in hospital complication. We also linked to the Registered Persons Database to ascertain death. This allowed for 100% follow-up of all of our patients. We utilized propensity score matching to create two balanced groups to compare on the outcomes of interest, and as a sensitivity analysis, we looked at aortic valve replacement with CABG with or without aortic root enlargement. Here are our results. We started with 26,000 patients who underwent aortic valve replacement with or without CABG. After excluding those with previous cardiac surgery, active endocarditis, or non-tissue or mechanical valves, we ended up with 16,000 patients in our study. Eighty-five hundred patients underwent an isolated aortic valve replacement, 821 also had aortic root enlargement. Of the AVR with CABG cohort, we had 6800 patients, 520 also had root enlargement. Over the study period, on average, 8% of all AVRs had a root enlargement.

Here we looked at the trends overtime for aortic root enlargement as a function of aortic valve replacement. We showed that early on, around 6% of all AVRs had root enlargement and near the end of the study period it was around 10 to 12, so there seemed to be a steady increase in the number of root enlargements being performed.

Here we show that aortic root enlargement patients are different. The average age, they are younger than those who underwent isolated aortic valve replacement, and in this table or this graph here, in the blue we have aortic valve replacement patients and in the orange we have those who underwent aortic root enlargement as well. We have different baseline characteristics. Those who underwent aortic root enlargement were more likely female and also were less likely to have other comorbidities. We show these be cause the standardized mean difference was greater than 10% suggesting that they are imbalanced between the groups.

After we performed propensity score matching on about 34 variables, we showed that the patients are quite similar. The ages are similar between the group, around 65, and the standardized mean difference for these baseline characteristics were all less than 10%, denoting good balance between the groups.

Here we show the early outcomes in matched patients. The Y axis is the frequency of these outcomes and on the X axis we have the different outcomes. We show that there is no difference in 30-day mortality, new permanent pacemaker implantation, chest reopening, or 30-day re admission. We do note that the operating room time was longer. The median difference was about 20 and this was statistically significant.

Here we looked at 8-year mortality. This is on the X axis, we have year since surgery. On the Y axis, we have survival. In the red, we have aortic valve replacement. In the green, we have aortic valve replacement plus aortic root enlargement. The number at risk is on the bottom, shown here. The shading is the 95% confidence interval. We showed that at eight years, there was no difference. In the matched patients using a Cox proportional hazard model.

Here is the cumulative incidence function for congestive heart failure re admission, which is shown on the Y axis here. We adjusted for death as a competing risk factor. Again, there was no difference between the 2 groups up to 8 years.

We also looked at aortic valve reintervention, and again we adjusted for death as a competing risk factor in our model. The first thing we note is that the incidents of aortic valve re intervention up to 8 years was quite low, less than 5% and again there was no difference between the 2 groups.

As mentioned earlier, we performed a sensitivity analysis. We looked at the aortic valve replacement with CABG patients. So, in these 525 patients in the match group, there was no difference in 30-day mortality, new permanent pacemaker, or 30-day readmission. We do note that the instance of chest reopening was greater, 7% versus about 3.5%, so almost double. Again, the operating room time was longer.

However, when we looked at 8-year mortality in this Kaplan–Meier survival curve using a cost proportional hazard model, there was again no difference at 8 years between the groups.

So, we show here that the addition of aortic root enlargement to isolated aortic valve replacement is safe, there was no increase in early mortality, chest reopening or new pacemakers, late outcomes for similar between the 2 groups, and there was no difference in congestive heart failure readmission or valve reintervention. We do note that there was an increase in the risk of chest reopening with the addition of aortic root enlargement in the patients who underwent aortic valve replacement with concomitant CABG. This suggests that there is a need for more vigilant monitoring in these patient groups. However, this study must be interpreted in the context of some significant and very important limitations. First, this is an observational retrospective study design, and, as such, it may be compounded by treatment allocation bias, being that we don't know, or the treatment decision is up to the discretion of the surgeon and that we don't know the true indication for this operation in these patients. With any administrative study, there are concerns around the accuracy of relying on administrative codes to ascertain both the treatment groups and the outcomes of interest. We do note that there was a longer OR time in the patients who did undergo the procedure of interest. There is a lack of data granularity. We don't know the exact type of aortic root enlargement that was performed in these patients, and importantly we also do not have echocardiographic data on these patients, so we don't know the preoperative size of the root or the annulus or any postoperative changes at patient prosthesis mismatch.

So, in conclusion, we show that root enlargement is safe to isolated aortic valve replacement, and that the addition of aortic root enlargement to patients who underwent AVR CABG may result in more bleeding and I think we need additional follow-up for nonfatal events like valve reintervention. And with that, I'm happy to answer any questions.

Dr Tom Burdon *(Stanford, Calif).* Good morning, Derrick.

Dr Tam. Good morning.

Dr Burdon. Welcome back to the Western. Derrick is a veteran of the Western and, as you know, presented at the Samson before. Welcome to California.

Dr Tam. Thank you.

Dr Burdon. You and your coauthors do a phenomenal job in reviewing a clinical administrative database from the Province of Ontario from 2008 to 2017 identifying more than 16,000 aortic valve replacements (AVRs) from 11 hospitals in Ontario. Eleven million people and 11 hospitals; a million population per center, it sounds like. It's a phenomenal model. You identified about 809 pairs from the data that I was given for AVR and AVR plus aortic root enlargement (ARE), which demonstrates accurate codes in almost all areas of outcome. AVR and ARE in coronary artery bypass grafting, however, revealed a higher re-exploration rate for bleeding. Your conclusions, based on extremely thorough and powerful statistic modeling are that AVR and ARE do not increase surgical risk. It's tough for some of us to swallow that. Assumptions are made, the potential for patient–prosthesis mismatch is avoided and that increasing valve and valve transcatheter AVR size would be facilitated. You have identified your study's limitations as not being able to separate surgeon discretion, although propensity score matching may mitigate known confounders of this issue. We know how difficult the randomized control trial is and so we respect that. Derrick, you identified significant differences in baseline characteristics in the unmatched AVR and ARE and AVR cohorts. Those in AVR and ARE were younger, more likely men, less rural-based, more likely elective, lower rate of atrial fibrillation, and had better renal function, but had dyslipidemia and diabetes. How does propensity score matching with these issues provide you with 809 pairs for comparison? Does your study in fact violate a critical element of propensity score matching, which is the stable unit treatment value assumption, which is, number 1, no interference. Treatment of 1 patient should not influence the treatment of other patients, likely your nonrural patients were treated in centers with more or less experienced surgeons, depending on where they lived. Number 2, only 1 version should be the treatment and we know that surgeon preference will alter depending on what type of ARE is done, the vast majority probably being some form of Manougian. The Ontario Provincial Database, feeding from ICES, CorHealth, CIHI DAD, and RPDB is a veritable gold mine for data miners in administrative outcomes for researchers like yourself. However, the lack of perioperative echocardiogram data, body mass index, regression, and effective orifice area information are very important factors for patients, cardiologists, and cardiothoracic surgeons. Are you aware of any mechanisms in this Ontario database that will make this information available going forward somewhat like the Society of Thoracic Surgeons database? And lastly, in the area of broadening transcatheter AVR and sutureless surgical valves, both with single-digit gradients, how does ARE and teaching ARE factor into this? What has your experience been, and your experience as a resident with valve-in-valve procedures? Mortality for valve-in-valve, as Danny Dvir has shown us, is about 7%. It's not insignificant. Lastly, are you able to give any information on how many transcatheter AVRs are done in Ontario in relation to the number of surgical implants, and what is the budget for transcatheter AVR in a fixed budget system?

Dr Tam. Thanks Dr Burdon for the encouraging comments and those questions. I will try to do my best to answer all of them. So your first question was with regard to propensity score matching and whether or not these are indeed, or whether or not propensity score matching is indeed valid for this group. As you mentioned, propensity score matching is a great tool but it doesn't adjust for everything, just for the known confounder, the variables that we do have, and there is always concern that our findings may be compounded by unknown compounders. However, we did match on more than 30 variables and out of the 821 patients that we started with in the ARE group, which is the experimental group, we matched 809 patients. That's a lot of patients for a match. I've done other studies where I've only been able to match about 30% of patients, or 70% of patients. So to be able to match all these patients and both are isolated AVR group and our AVR/coronary artery bypass grafting group, I think it suggests that these patients are indeed quite similar. As you mentioned, we don't know their exact indication for surgery and that is a major weakness. That leads to your second question about echocardiographic data. That's something that the lead at the ICES is working on and we are planning on importing data from Toronto General first so we're going to import about 30,000 or 40,000 echocardiograms. This is going to be lots of data, so it's going to really change the way we look at some of these patients to be able to do more valve-related studies because

right now it is quite difficult to do some of these studies without the preoperative data and then also the postoperative data as well. I think we're going to be able to do it, and I think it's really going to give us a lot of interesting research questions.

And then your next question was related to transcatheter AVR in Ontario and valve-in-valve transcatheter AVR. That is something I'm looking at as part of my thesis work for my PhD; specifically, looking at valve-in-valve transcatheter AVR versus redo surgery in Ontario. From 2008 to 2016 we had about 214 patients undergo valve-in-valve surgery from our data set and I did a propensity score-matched study on this group and I'm going to present it at European Society for Cardiology in August. The early outcomes are quite different and they favor valve-in-valve transcatheter AVR. Again, we don't have a lot of echocardiographic data for late outcomes, so we can't really say what happens later because there is a concern for higher gradients with valve-in-valve procedures and we acknowledge that. I think that's also why it's so important that surgeons should not shy away from putting in larger valves in these younger patients who are the ones at risk for needing something down the road.

Dr Burdon. Do you know the ratios or what the budgets are at different hospitals?

Dr Tam. I think that's going to change quite a bit. It is center-dependent so at my center at Sunnybrook we do about 4 to 6 transcatheter AVRs a week and I think they're doing that at Saint Mike's as well. It's probably more than the number of AVRs being performed at Sunnybrook, at least for my center. I think we're going to move away from a model of AVR patients versus transcatheter AVR patients; we're going to move toward a funding model of aortic stenosis patients. I think that is among the reasons we have such a long wait list for this procedure.

Dr Richard Shemin. This is an important article in that in the minds of most surgeons who do aortic valve surgery, you know, ARE ought to become a routine part of what we can do. Better defining appropriateness besides avoiding mismatch and with the valve-in-valve is well stated and I agree with period but a clinical question that comes up is that the cardiologists love the procedure of fracturing the bioprosthetic valve to put in a larger aortic valve prosthesis and although the valve enlargement is giving you a larger prosthesis that may still be entertained and whether or not that is safe if you have gone ahead and done a root enlargement as opposed to just inserting a valve in the annulus. So do you have any data or feeling regarding how people are thinking about that clinical question?

Dr Tam. Yeah, that's a great comment, Dr. Shemin. That's something we brought up in the our article as well. The first thing to note is that during the study period not a lot of valve fracturing was performed so I don't think it really influenced whether or not people did ARE in our study period in terms of whether or not fracturing is performed, at our center we do it quite often. We did note that not all valves are fracturable and, generally, fracturing allows you to implant a slightly larger AVR and it does show that gradients are improved but I still don't think that should take away from the fact that we should be trying to, you know, put in the largest valve in our patients because even with a regular AVR in a normal-sized root the gradients are higher then what we would see in a normal valve.

Dr Shemin. And is there any way to infer from your data what is actually driving the increased rate of root enlargement?

Dr Tam. That's a good question. I don't think there's an easy answer to that using our data set.

APPENDIX E1. OVERVIEW OF ALL DATABASES INVOLVED IN THE LINKAGE. ALL DATASETS INVOLVED IN THIS ANALYSIS WERE LINKED USING A UNIQUE IDENTIFIER CODE FOR EACH PATIENT

CorHealth Ontario Registry

- Repository of all patients undergoing any cardiac procedures in Ontario
- Used for baseline characteristics and cohort derivation

Canadian Institute For Health Information—Discharge Abstract Database (CIHI-DAD)

- Administrative database containing information on all admissions to any Ontario hospitals
- Used for baseline characteristics and cohort derivation
- Used to ascertain early and late outcomes
- Used to ascertain hospital length of stay and length of procedure

Registered Persons Database

- Administrative database with information on all deaths in Ontario
- Also used to ascertain socioeconomic factors like neighborhood income quintile and rural status

Ontario Health Insurance Plan (OHIP)

- Administrative database used for billing for consultations and procedures
- Used for outcome definitions (for example chest reopening, pacemaker implantation).

Outcome definitions

Index hospitalization Safety outcomes (DXTYPE = 2).

1. 30-day postoperative mortality
2. In-hospital mortality (dischdisp = '07')
3. Chest reopening for bleeding (OHIP M134) within 7 days from date of procedure.
4. Any blood product transfusion (CIHI-DAD BTANY Flag)
5. Pacemaker implantation (CCI 1.HZ.53.GR.^^ where ^^ = NM, NK, NL, FR or 1.HZ.53.LA.^^ where ^^= NM, NK, NL, FR or OHIP fee code R752) or ICD implantation (CCI 1.HZ.53.GR.FS or 1.HZ.53.LA.FS, or OHIP fee code R761, R753). To find corresponding OHIP record during hospitalization, we searched OHIP within +7 days/–3 days since date of procedure
6. Length of operation (earliest of indur1-10 from CIHI-DADS, or Anesthesia time units in OHIP).

Late outcomes.

1. All-cause mortality (Registered Persons Database)
2. Reintervention (defined as second AVR (CorHealth off-listing detail 422 – YES) or Canadian Classification of Interventions code: 1.HV.^^ either after hospital discharge from the index episode of care OR 30 days after index procedure)
3. Readmission for congestive heart failure (ICD-10 code: I50)

31 Variables used in the main propensity score match.

1. Urgent versus elective
2. Age
3. Atrial fibrillation
4. Body surface area
5. Cancer
6. Canadian Cardiovascular Society class
7. History of smoking
8. Left ventricular function grade
9. New York Heart Association functional class
10. Creatinine group
11. Institution
12. Charlson score
13. Congestive heart failure history
14. Chronic obstructive pulmonary disease
15. Cerebrovascular disease
16. Dementia
17. Diabetes
18. Dialysis
19. Frailty
20. Hyperlipidemia
21. Hypertension
22. Income quintile
23. Ischemic heart disease history
24. Peripheral vascular disease
25. Rurality
26. Sex
27. Year of procedure
28. Previous percutaneous coronary intervention
29. Aortic stenosis
30. Severity of aortic stenosis
31. History of endocarditis

Additional covariates for matching for sensitivity analysis.

1. Tissue/mechanical valve (sensitivity analysis)
2. Distal coronary anastomosis number (sensitivity analysis)

APPENDIX E2. UNMATCHED PRIMARY ANALYSIS

When AVR + ARE was compared with AVR, there was no difference in 30-day mortality (1.8% vs 2.3%; $P = .47$), new pacemaker implantation (5.0% vs 5.0%; $P = 1.00$), or chest reopening (5.0% vs 4.2%; $P = .30$) (Table E2). Any blood product transfusion was higher with AVR + ARE compared with AVR alone (67.0% vs 55.3%; $P < .001$). Although the median (interquartile range [IQR]) length of operation was longer with AVR + ARE (272 min; IQR, 230-320 min vs

251 min; IQR, 210-302 min; $P < .001$), hospital length of stay was similar in the AVR + ARE group (7 days; IQR, 6-11 days vs 7 days; IQR, 6-12 days; $P = .60$). Thirty-day readmission was similar between groups.

In the unmatched comparison, overall survival was not statistically different in the unmatched cohort for AVR + ARE vs AVR (Figure E8) (73.3% vs 66.1%; $P = .06$). The rates of CHF readmission were similar for AVR + ARE vs AVR (14.8% vs 12.7%; $P = .99$) at 8 years (Figure E9). Similarly, there were no differences in late valve reintervention (3.6% vs 4.7%; $P = .42$) (Figure E10).

UNMATCHED SECONDARY ANALYSIS

When AVR + CABG + ARE was compared with AVR + CABG, there was also no difference in early mortality (4.0% vs 4.2%; $P = .85$) (Table 2). The rate of new pacemaker implantation and chest reopening were also similar while the need for any blood transfusion was higher following AVR + CABG + ARE compared with AVR + CABG (74.8% vs 84.7%; $P < .001$). Thirty-day readmission was similar between both groups. Late survival was higher for AVR + CABG + ARE versus AVR + CABG (60.0% vs 52.6%; $P = .02$) at 8 years (Figure E11).

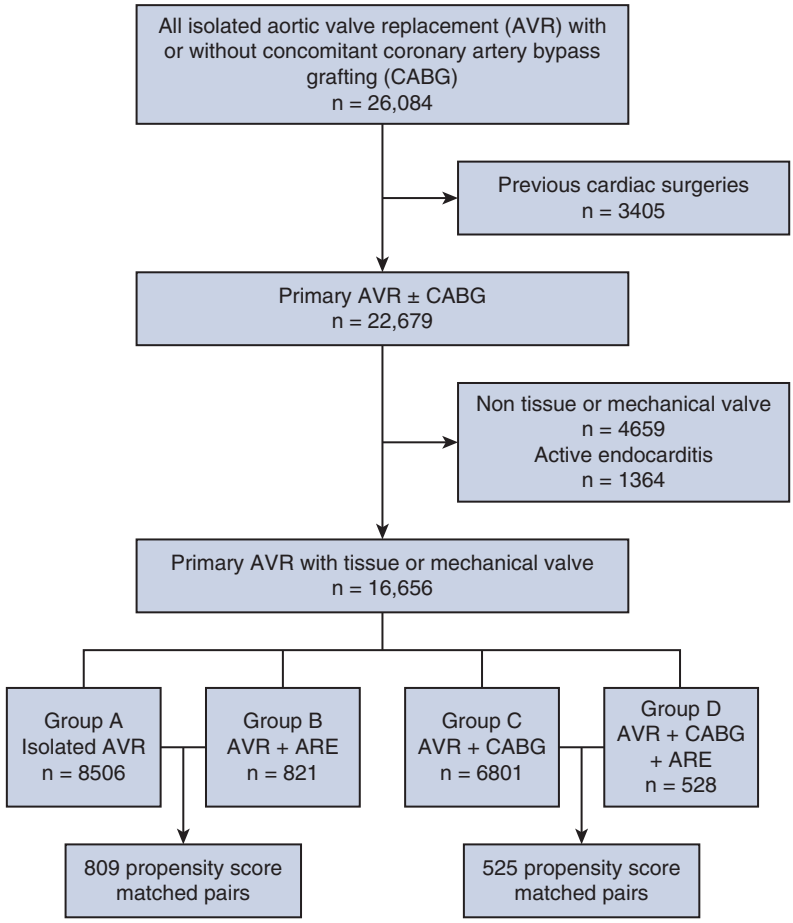


FIGURE E1. Patient flow diagram. *AVR*, Aortic valve replacement; *CABG*, coronary artery bypass grafting; *ARE*, aortic root enlargement.

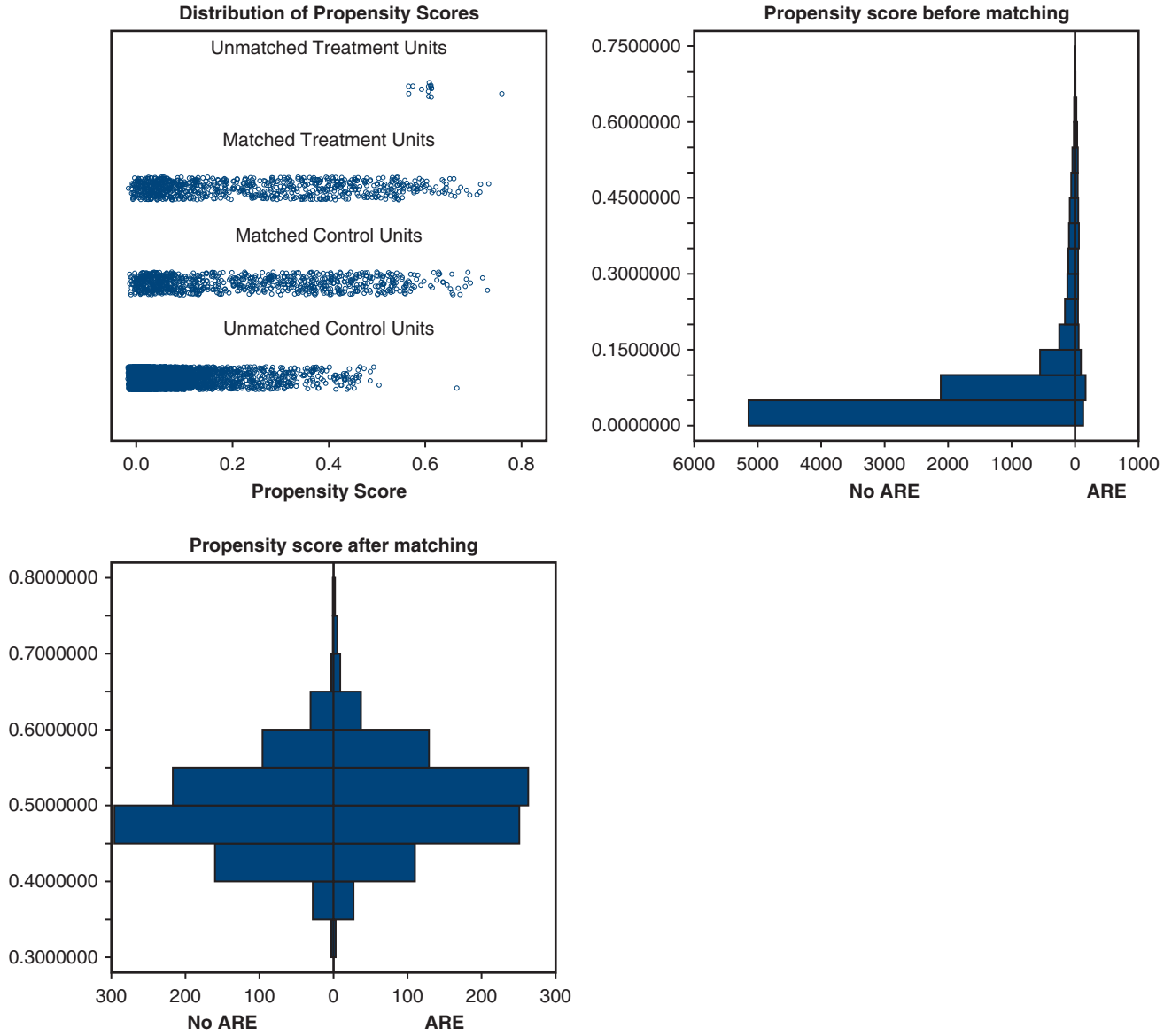


FIGURE E2. Distributions of propensity scores before and after matching for aortic valve replacement (AVR) versus AVR + aortic root enlargement (*ARE*) cohort.

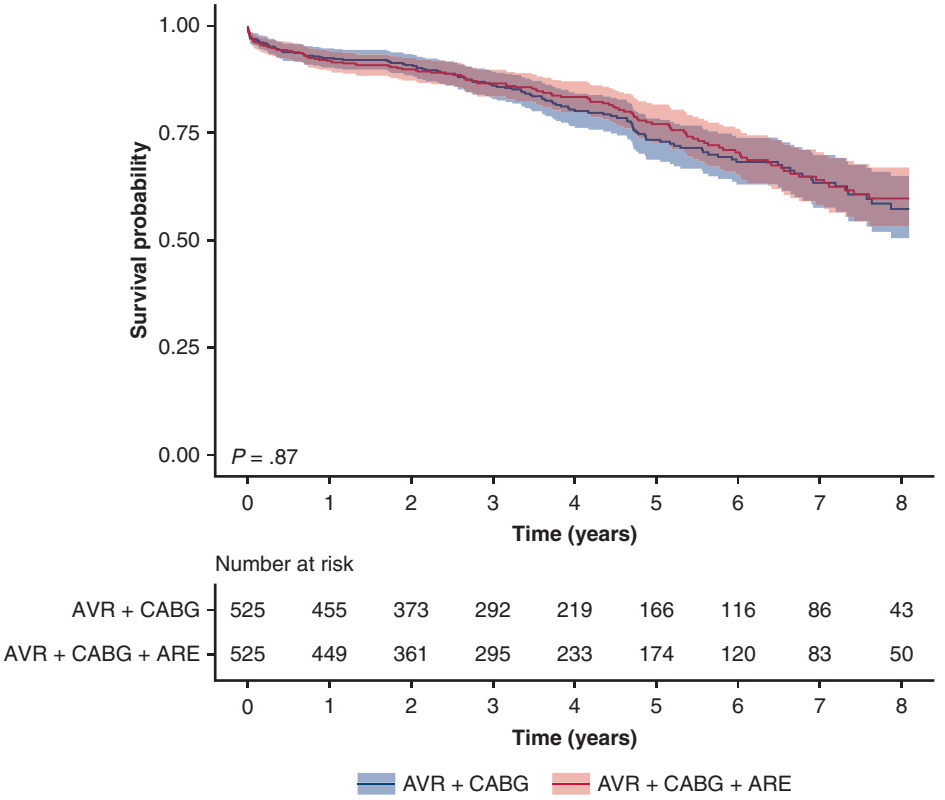


FIGURE E3. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the propensity-matched patients undergoing aortic valve replacement (*AVR*) with concomitant coronary artery bypass grafting (*CABG*) versus AVR + CABG and aortic root enlargement (*ARE*).

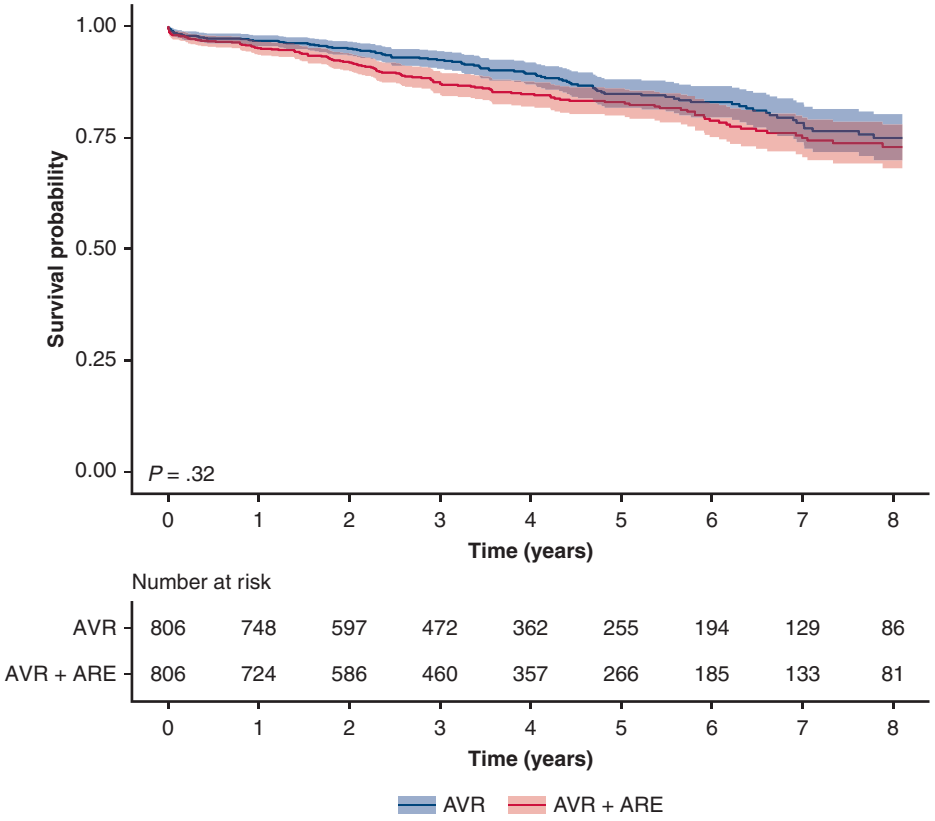


FIGURE E4. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the propensity-matched patients undergoing aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) after matching on baseline characteristics and operative characteristics.

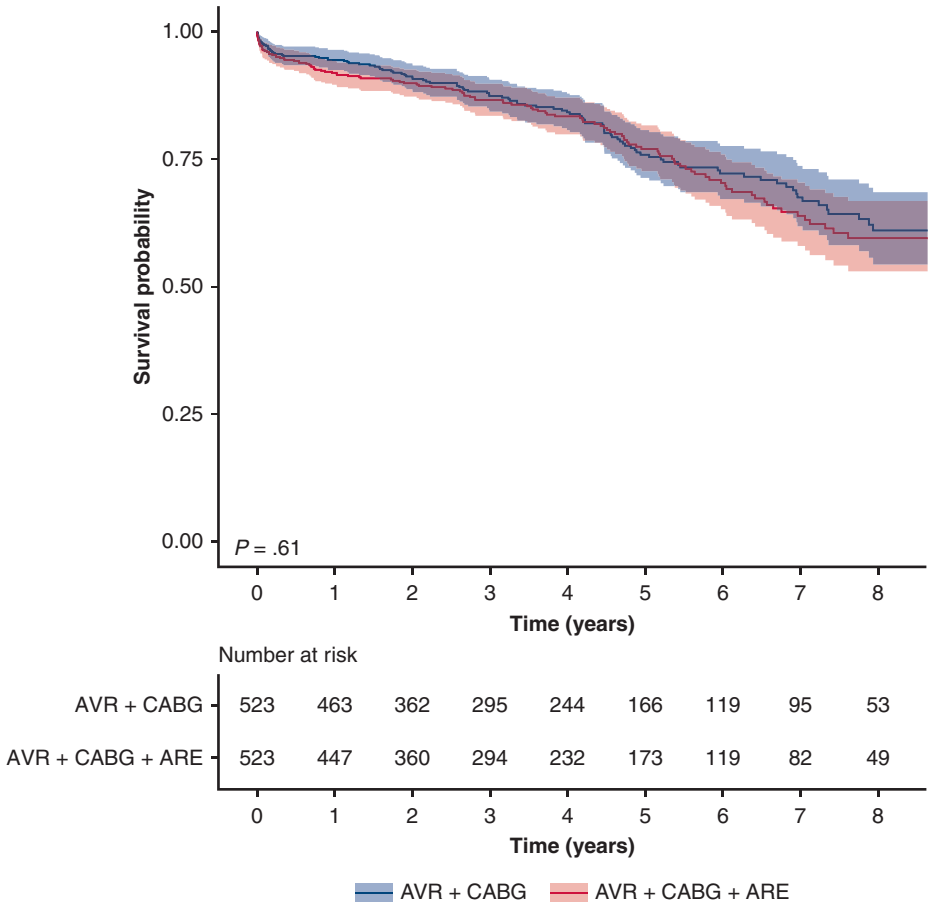


FIGURE E5. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the propensity-matched patients undergoing aortic valve replacement (*AVR*) with concomitant coronary artery bypass grafting (*CABG*) versus AVR + CABG and aortic root enlargement (*ARE*) after matching on baseline characteristics and operative characteristics.

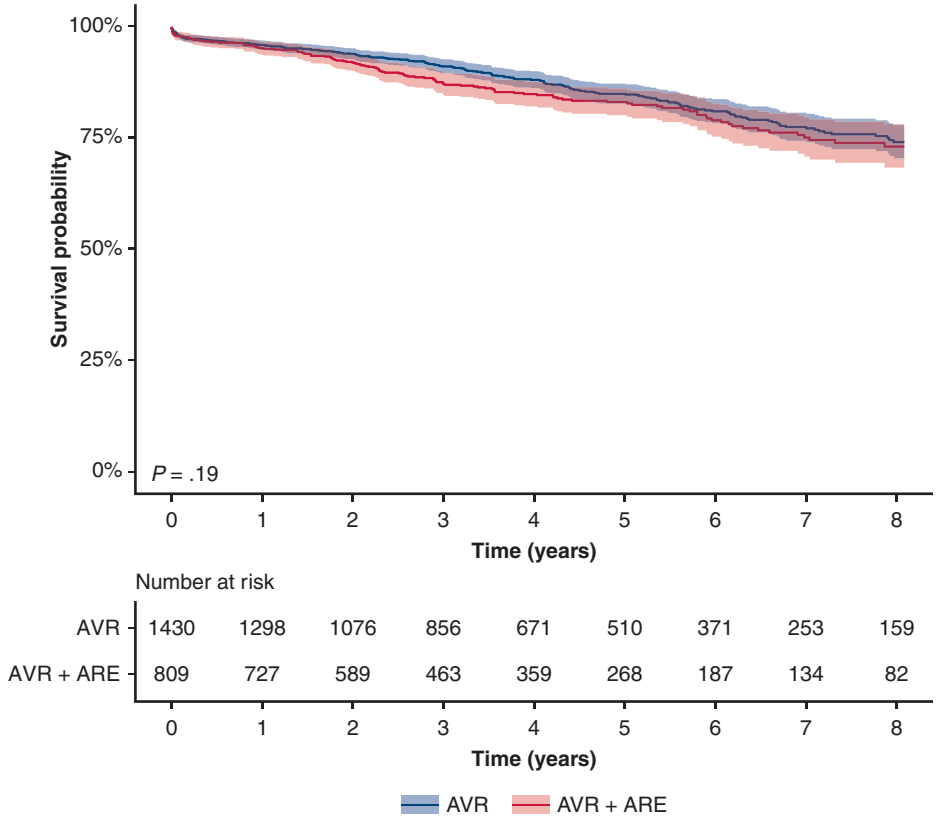


FIGURE E6. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the 1:2 propensity-matched patients undergoing aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*).

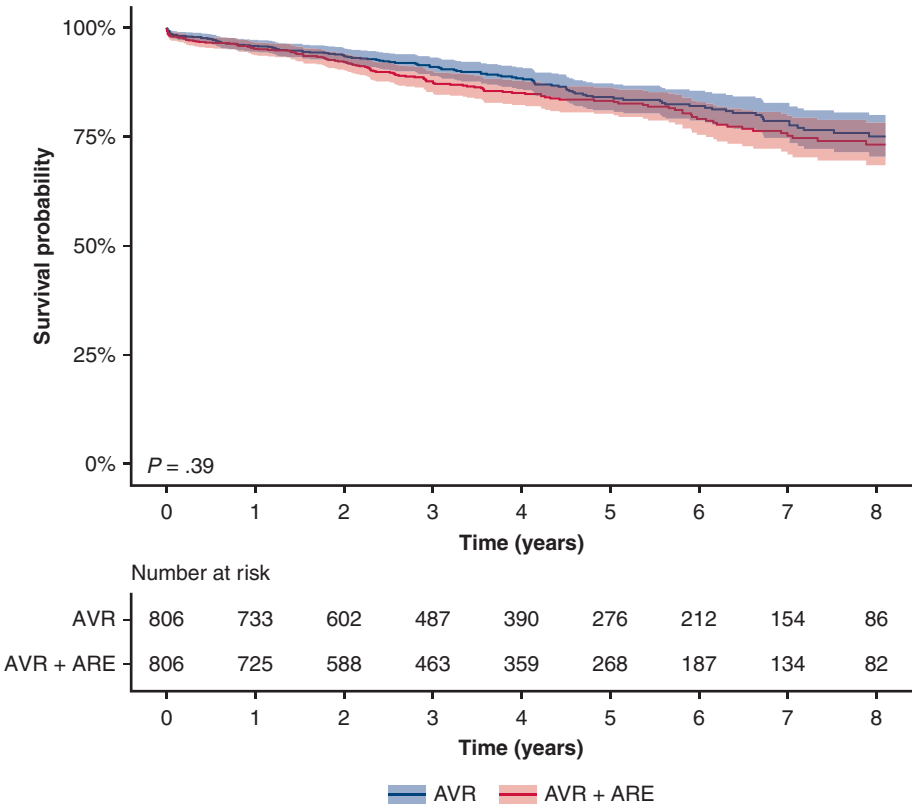


FIGURE E7. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the propensity-matched aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) patients with an exact match on institution.

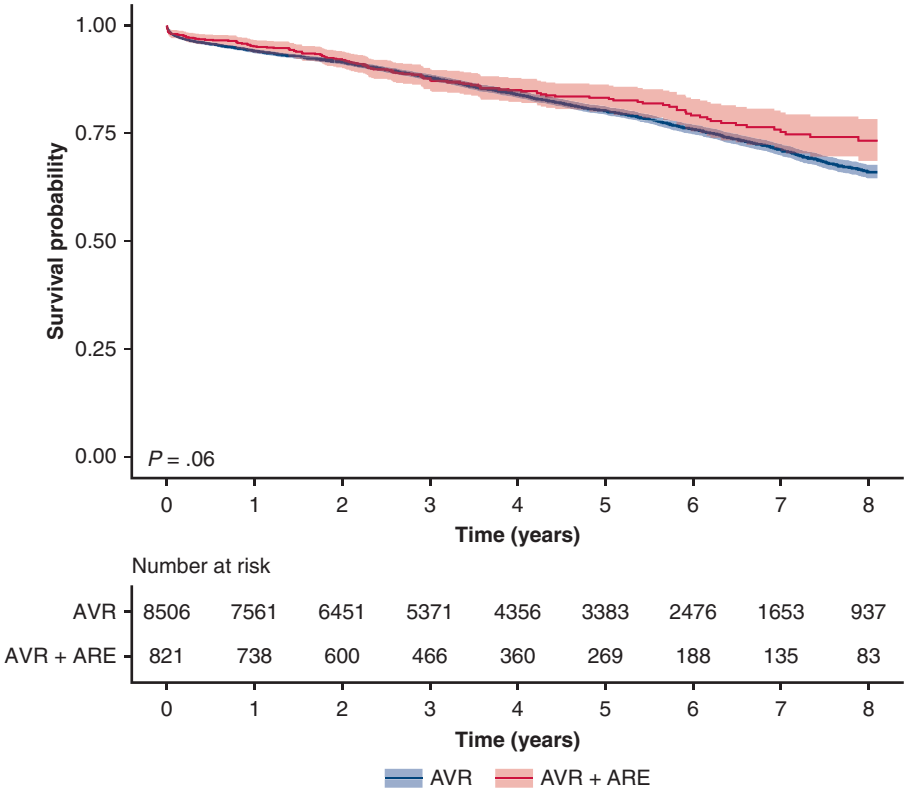


FIGURE E8. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the unmatched aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) patients.

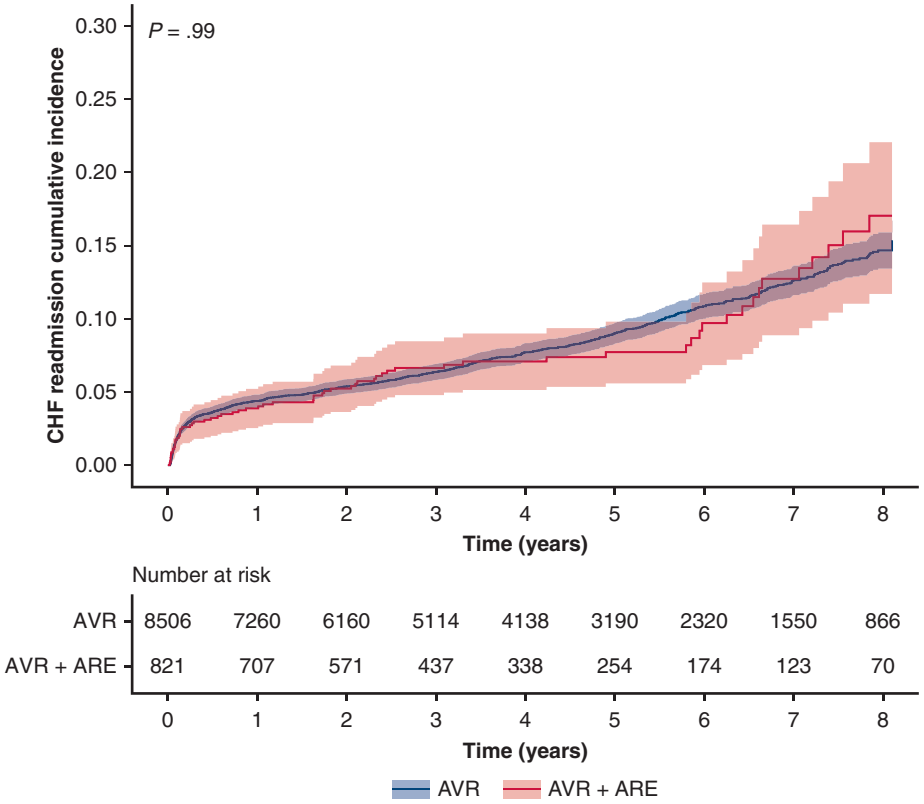


FIGURE E9. Cumulative incidence curves for 8-year congestive heart failure (*CHF*) readmission for the unmatched aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) patients adjusted for competing risk of death.

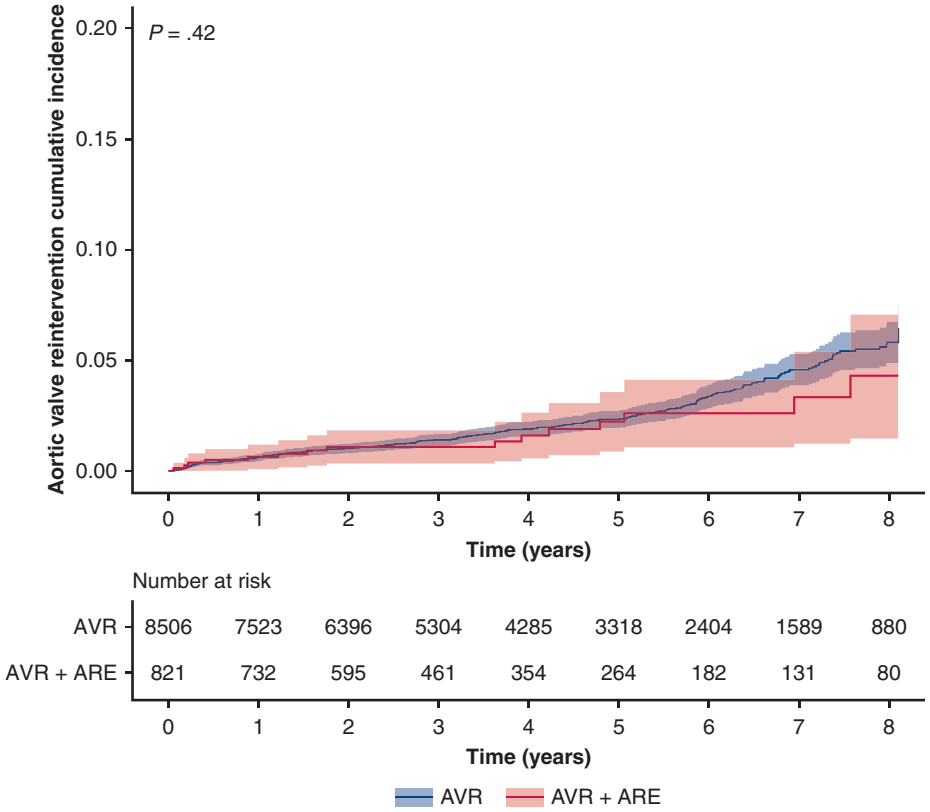


FIGURE E10. Cumulative incidence curves for 8-year valve reintervention for the unmatched aortic valve replacement (*AVR*) versus AVR and aortic root enlargement (*ARE*) patients adjusted for competing risk of death.

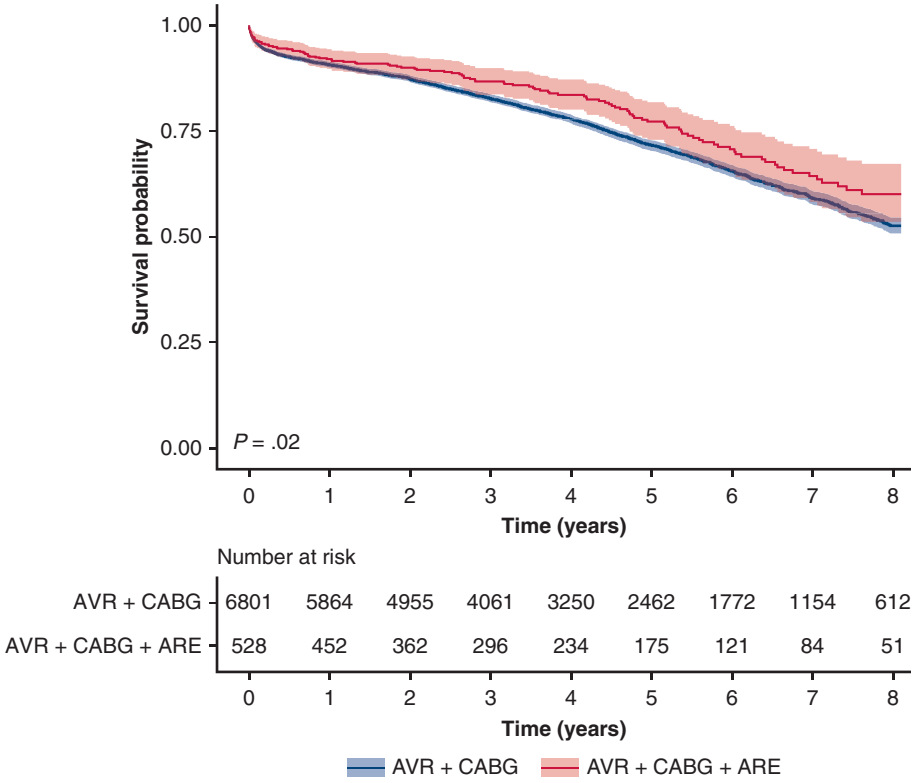


FIGURE E11. Kaplan-Meier curves for 8-year freedom from all-cause mortality for the unmatched aortic valve replacement (*AVR*) with concomitant coronary artery bypass grafting (*CABG*) versus AVR + CABG and aortic root enlargement (*ARE*) patients.

TABLE E1. Matched and unmatched baseline characteristics for secondary analysis

	Unmatched				Matched		
Characteristic	AVR + CABG + ARE (n = 546)	AVR + CABG (n = 6947)	*P* value	SMD	AVR + CABG + ARE (n = 535)	AVR + CABG (n = 525)	SMD
Age (y)	71.97 ± 9.04	73.66 ± 8.56	<.001	0.191	72.12 ± 8.80	72.36 ± 8.68	0.028
Sex (female)	246 (45.1)	1826 (26.3)	<.001	0.418	241 (45.9)	244 (46.5)	0.011
Rurality (rural)	73 (13.4)	1288 (18.5)	.003	0.134	72 (13.7)	82 (15.6)	0.054
Income quintile			.59				
1	83 (15.2)	1194 (17.2)		0.073	74 (14.1)	75 (14.3)	0.005
2	115 (21.1)	1404 (20.2)		0.027	113 (21.5)	121 (23.0)	0.037
3	125 (22.9)	1471 (21.2)		0.019	114 (21.7)	110 (21.0)	0.019
4	117 (21.4)	1425 (20.5)		0.079	97 (18.5)	95 (18.1)	0.01
5	106 (19.4)	1453 (20.9)		0.094	127 (24.2)	124 (23.6)	0.013
Charlson score	2.28 ± 1.99	2.44 ± 2.06	.075	0.099	2.25 ± 1.96	2.45 ± 2.10	0.098
Frailty	27 (4.9)	611 (8.8)	.002	0.162	25 (4.8)	23 (4.4)	0.018
Body surface area	1.96 ± 0.26	1.95 ± 0.25	.453	0.107	1.94 ± 0.24	1.94 ± 0.25	0.008
Urgent	114 (20.9)	1973 (28.4)	<.001	0.179	110 (21.0)	111 (21.1)	0.005
Smoking history			.004				
Never	259 (47.4)	3171 (45.6)		0.046	251 (47.8)	265 (50.5)	0.053
Former	240 (44.0)	2837 (40.8)		0.058	230 (43.8)	214 (40.8)	0.062
Current	47 (8.6)	939 (13.5)		0.165	44 (8.4)	46 (8.8)	0.014
Dyslipidemia	367 (67.2)	4228 (60.9)	.004	0.133	353 (67.2)	355 (67.6)	0.008
Hypertension	473 (86.6)	6211 (89.4)	.052	0.068	461 (87.8)	470 (89.5)	0.054
Diabetes	278 (50.9)	3192 (45.9)	.028	0.094	267 (50.9)	279 (53.1)	0.046
Ischemic heart disease	536 (98.2)	6844 (98.5)	.644	0.029	516 (98.3)	506 (96.4)	0.118
Previous PCI	18 (3.3)	224 (3.2)	1	0.012	18 (3.4)	20 (3.8)	0.02
CHF	260 (47.6)	3859 (55.5)	<.001	0.154	255 (48.6)	277 (52.8)	0.084
Atrial fibrillation	83 (15.2)	1404 (20.2)	.006	0.127	81 (15.4)	85 (16.2)	0.021
PVD	33 (6.0)	528 (7.6)	.213	0.062	32 (6.1)	27 (5.1)	0.041
CVD	32 (5.9)	557 (8.0)	.085	0.089	31 (5.9)	34 (6.5)	0.024
CCS class			.714				
0	263 (48.2)	3222 (46.4)		0.026	177 (33.7)	184 (35.0)	0.028
1	76 (13.9)	939 (13.5)		0.035	55 (10.5)	62 (11.8)	0.042
2	79 (14.5)	1110 (16.0)		0.091	115 (21.9)	118 (22.5)	0.014
3	63 (11.5)	752 (10.8)		0.06	94 (17.9)	86 (16.4)	0.04
4	65 (11.9)	924 (13.3)		0.155	84 (16.0)	75 (14.3)	0.048
NYHA functional class			.857				
1	185 (33.9)	2290 (33.0)		0.24	128 (24.4)	133 (25.3)	0.022
2	172 (31.5)	2135 (30.7)		0.147	182 (34.7)	176 (33.5)	0.024
3	159 (29.1)	2148 (30.9)		0.112	188 (35.8)	189 (36.0)	0.004
4	30 (5.5)	374 (5.4)		0.051	27 (5.1)	27 (5.1)	<0.001
LV grade (%)			.981				0.056
≥50	450 (82.4)	5715 (82.3)		0.259	455 (86.7)	461 (87.8)	0.034
35-49	66 (12.1)	824 (11.9)		0.172	51 (9.7)	43 (8.2)	0.053
<35	30 (5.5)	408 (5.9)		*	27 (5.1)	21 (5.0)	*

(Continued)

TABLE E1. Continued

Characteristic	Unmatched				Matched		
	AVR + CABG + ARE (n = 546)	AVR + CABG (n = 6947)	*P* value	SMD	AVR + CABG + ARE (n = 535)	AVR + CABG (n = 525)	SMD
Creatinine level (mg/dL)			.197				
≤120	484 (88.6)	5998 (86.3)		0.168	467 (89.0)	453 (86.3)	0.081
121-180	43 (7.9)	715 (10.3)		0.148	43 (8.2)	53 (10.1)	0.066
≥180	19 (3.5)	234 (3.4)		0.07	15 (2.9)	19 (3.6)	0.043
Dialysis	25 (4.6)	579 (8.3)	.003	0.159	24 (4.6)	25 (4.8)	0.009
COPD	131 (24.0)	1890 (27.2)	.114	0.096	121 (23.0)	128 (24.4)	0.031
Cancer	69 (12.6)	963 (13.9)	.462	0.043	64 (12.2)	80 (15.2)	0.089
Dementia	7 (1.3)	171 (2.5)	.11	0.101	6 (1.1)	9 (1.7)	0.048
Aortic stenosis indication	479 (87.7)	5770 (83.1)	.97	0.131	460 (87.6)	457 (87.0)	0.017
Tissue valve	454 (86.0)	5781 (85.0)	.861	0.008	452 (86.1)	446 (85.0)	0.022

Values are presented as mean ± standard deviation or mean (%). *AVR*, Aortic valve replacement; *CABG*, coronary artery bypass grafting; *ARE*, aortic root enlargement; *SMD*, standardized mean difference; *PCI*, percutaneous coronary intervention; *CHF*, congestive heart failure; *PVD*, peripheral vascular disease; *CVD*, cerebrovascular disease; *CCS*, Canadian Cardiovascular Society; *NYHA*, New York Heart Association; *LV*, left ventricular; *COPD*, chronic obstructive pulmonary disorder. *SMD not available for this category.

TABLE E2. Unmatched perioperative outcomes

Unmatched outcome	AVR + ARE	AVR	*P* value	AVR + CABG + ARE	AVR + CABG	*P* value
Length of stay (d)	7.0 (6.0-11.0)	7 (6-12)	.603	8 (6-13)	10 (7-16)	.003
Length of operation (min)	272 (230-320)	251 (210-302)	<.001	325 (285-390)	311 (263-367)	<.001
30-d Mortality	15 (1.8)	201 (2.3)	.383	21 (3.8)	294 (4.2)	.748
New pacemaker	41 (4.8)	439 (5.0)	.877	30 (5.5)	344 (5.0)	.646
Any blood product transfusion	572 (67.3)	4832 (55.1)	<.001	462 (84.6)	5191 (74.7)	<.001
Chest reopening	41 (4.8)	365 (4.2)	.411	41 (7.5)	415 (6.0)	.176
Early readmission	107 (12.6)	1047 (11.9)	.621	74 (13.6)	913 (13.1)	.836

Values are presented as median (interquartile range) or n (%). *AVR*, Aortic valve replacement; *ARE*, aortic root enlargement; *CABG*, coronary artery bypass grafting.