Annals of Internal Medicine | ORIGINAL RESEARCH

Renin–Angiotensin System Blockade Therapy After Surgical Aortic Valve Replacement for Severe Aortic Stenosis

A Cohort Study

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Background: Data are lacking on the effect of renin–angiotensin system (RAS) blockade therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers after surgical aortic valve replacement (SAVR) for severe aortic stenosis (AS).

Objective: To investigate the association between RAS blockade therapy and outcomes after SAVR for severe AS.

Design: Retrospective study.

Setting: Single tertiary referral care center.

Patients: Patients who were prescribed angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers after SAVR for severe AS between 1991 and 2010 who had at least 2 refills 90 days apart and at least a 6-month follow-up constituted the RAS blockade group ($n = 741$). Patients who did not receive these prescriptions were in the untreated group ($n = 1011$). Unadjusted and propensity-matched analyses (594 matched pairs of treated and untreated patients) were performed.

Measurements: The primary outcome was survival rates after SAVR. Secondary end points were changes in left ventricular mass index, left ventricular ejection fraction, and left atrial size.

Results: Overall unadjusted estimated survival rates at 1, 5, and 10 years were significantly greater in the RAS blockade group than in the non–RAS blockade group (99%, 90%, and 60% vs. 99%, 81%, and 53%, respectively; $P < 0.001$). Among propensity-matched patients, estimated survival rates at 1, 5, and 10 years remained significantly greater in the RAS blockade group than in the non–RAS blockade group (99%, 90%, and 71% vs. 96%, 78%, and 49%, respectively; $P < 0.001$). For the matched cohorts, the groups did not significantly differ in the change in left ventricular mass index ($P = 0.37$), left ventricular ejection fraction ($P = 0.67$), or left atrial size ($P = 0.43$) after SAVR on echocardiographic analysis.

Limitation: Retrospective, single-center analysis.

Conclusion: Renin–angiotensin system blockade therapy is associated with increased survival rates in patients after SAVR for severe AS. A randomized trial of RAS blockade therapy after SAVR should be considered.

Primary Funding Source: None.

Ann Intern Med. 2014;161:699-710. doi:10.7326/M13-1505 www.annals.org
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Aortic stenosis (AS) is a common valve disease in the aging population (1). Surgical aortic valve replacement (SAVR) is the gold standard therapy for operable patients with severe symptomatic AS (2). Severe AS is associated with progressive left ventricular hypertrophy (LVH) and diastolic dysfunction. Persistence of LVH and diastolic dysfunction after SAVR are associated with reduced long-term survival (3–5). Inhibition of the renin–angiotensin system (RAS) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) is associated with modulation of adverse left ventricular (LV) remodeling and reduction in myocardial hypertrophy and fibrosis, resulting in clinical improvement in patients with heart failure; however, this has not been studied in patients with severe AS. In addition, the role of RAS blockade therapy after SAVR for severe AS is unknown. We hypothesize that RAS inhibition may improve outcomes in patients after SAVR and that the mechanism may be related to LV remodeling secondary to regression of LVH and LV mass. Therefore, we sought to investigate the association between RAS blockade therapy and outcomes after SAVR for severe symptomatic AS.

METHODS

Patients

The study population consisted of adult patients who had primary SAVR for severe AS at the Cleveland Clinic Foundation (Cleveland, Ohio) from 1 January 1991 through 31 December 2010. Severe AS was defined as an aortic valve area of less than 1 cm^2. Patients with predominant aortic regurgitation, infective endocarditis, rheumatic valve disease, or indications for SAVR other than AS were excluded. This cohort was then stratified on the basis of postoperative usage of RAS blockade therapy with ACE inhibitors or ARBs. Patients who were discharged with prescriptions for ACE inhibitors or ARBs after SAVR and had at least 2 confirmed refills (that is, the prescription was dispensed to the patient twice, 90 days apart) constituted the RAS blockade group, and those not prescribed any ACE inhibitor or ARB were in the control group. A patient had to be alive long enough to have had a prescription

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Supplement

Context

Although angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers improve survival rates in heart failure, whether renin–angiotensin system (RAS) blockade therapy is associated with improved survival rates after surgical aortic valve replacement (SAVR) for severe aortic stenosis is unknown.

Contribution

This retrospective cohort study found that prescribing RAS blockade therapy after SAVR for severe aortic stenosis was associated with improved survival rates.

Caution

Patient treatments were not randomly assigned, so whether RAS blockade therapy caused the observed improved survival rates cannot be determined.

Implication

A randomized trial is needed to evaluate the use of RAS blockade after SAVR for severe aortic stenosis.

—The Editors

refilled 90 days after discharge after SAVR to be qualified to be in the ACE inhibitor or ARB group. Therefore, a patient had to survive 90 days after discharge to be eligible for this study. Patients who did not have at least 90 days of follow-up were excluded. It is assumed that the patient filled the prescription and consumed the medication as advised when the prescription was dispensed. The duration of treatment with ACE inhibitors or ARBs was ascertained by reviewing the electronic medical chart for refills ordered by the managing health provider. We excluded patients who did not have at least a 6-month follow-up in our health system after SAVR and patients who were not treated with ACE inhibitors or ARBs after SAVR but were prescribed them at some point during follow-up (crossover patients) (**Figure 1**). Preoperative, operative, and postoperative variables were retrieved from the computerized, prospective Cleveland Clinic Cardiovascular Information Registry and echocardiographic variables from the Echocardiography Database. Both databases were approved for research by the Institutional Review Board at the Cleveland Clinic Foundation, with patient consent waived.

Echocardiography

Preoperative measurements were retrieved from the transthoracic echocardiography performed nearest to, but preceding, the date of SAVR. Left ventricular mass was calculated using the formula validated by Devereux and colleagues (6). Peak instantaneous aortic valve gradients were calculated from Doppler velocity, and aortic valve area was calculated using the continuity equation. Echocardiography was done routinely before discharge and at the discretion of referring physicians during follow-up. Identical measurements were made on all available postoperative transthoracic echocardiographies. Postoperative echocardiography reports were used to assess the intermediate and long-term changes in LV mass, left ventricular ejection fraction (LVEF), and left atrial (LA) size. Follow-up echocardiography was evaluated at as many time points as possible for each patient.

Follow-up

Follow-up was obtained through the Cleveland Clinic Cardiovascular Information Registry at the Cleveland Clinic Foundation and supplemented with Social Security Death Index data. The Social Security Death Index was last run on 27 October 2011 with a lag time of 6 months and the closing date set for 27 April 2011.

Outcomes

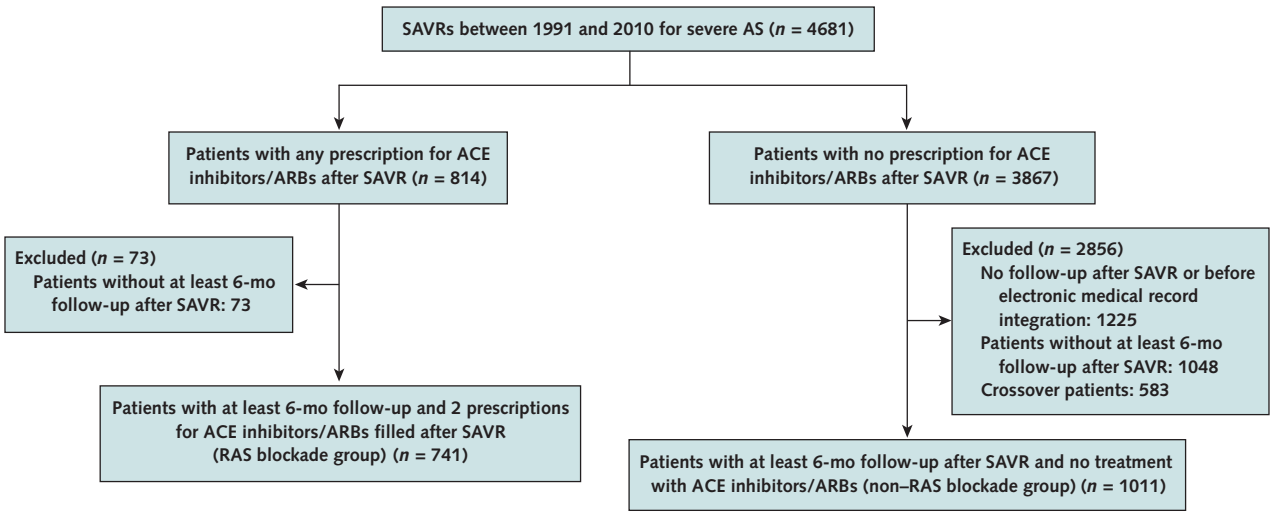
All-cause mortality was the primary outcome we assessed. Secondary outcomes were regression of LV mass and changes in LVEF and LA size after SAVR.

Statistical Analysis

Group Differences and Propensity Score Matching

To reduce or eliminate bias between the RAS blockade and non–RAS blockade groups, differences between these groups were determined and a propensity score was formed to adjust for group differences in subsequent analyses. Multivariable logistic regression was first performed to identify preoperative factors associated with RAS blockade therapy after SAVR. Variables that were considered in this analysis are listed in the **Supplement** (available at www.annals.org). We used bootstrap bagging with automated analysis of 500 resampled data sets, followed by tabulating the frequency of occurrence at a P value of 0.05 or less of both single factors and closely related clusters of factors (7, 8). A parsimonious model was then constructed, retaining factors that occurred in 50% or more of the bootstrap models. Thereafter, this model was augmented with all other available preoperative variables (or a single representative factor from every cluster of highly correlated variables) in an attempt to account for any unrecorded selection factors and to form a saturated model (9). By solving this equation, we estimated a propensity score, which represents the probability of the patient receiving RAS blockade therapy with ACE inhibitors or ARBs, for each patient. Propensity scores were used for matching to evaluate the outcomes between more comparable groups. Using the propensity score on the probability scale, we matched patients receiving RAS blockade therapy to those who were not receiving it by using a greedy matching strategy (10). Greedy matching obtains matches patient by patient, finding the nearest neighbor; once a match is formed, that patient is not reused. Patients receiving RAS blockade therapy whose propensity scores deviated more than 0.10 from those of patients who were not receiving RAS blockade therapy were considered unmatched. This caliper was chosen because it provided a sufficient set of matches (80%) and matches across the range of propensity scores. In this

Figure 1. **Study flow diagram.**



ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AS = aortic stenosis; RAS = renin–angiotensin system; SAVR = surgical aortic valve replacement.

retrospective observational study, many variables had small amounts of missing values. Therefore, we used 5-fold multiple imputation (11) applying Markov chain Monte Carlo technique to impute the missing values (SAS PROC MI, SAS Software, SAS Institute). On the basis of each imputed complete data set, we estimated propensity scores for each patient. We then used the average of the propensity scores over the 5 imputed complete data sets as the final estimate of the propensity score for each patient (12).

Survival

Overall and stratified nonparametric survival estimates were obtained by the Kaplan–Meier method. A parametric method was used to resolve the number of phases of instantaneous risk for death (hazard function) and to estimate the shaping variables (13, 14). The effects of RAS therapy and concomitant coronary artery bypass grafting (CABG) were analyzed in the overall and matched cohorts. Adjusted survival rates comparing the RAS blockade and non–RAS blockade groups were evaluated by using the propensity score as a continuous variable and forcing it into each phase of the hazard model and by using the matched groups and forcing the group variable only into each hazard phase. In addition, subgroup analyses were done using simple Cox proportional hazard models (SAS PROC PHREG) containing RAS group, the subgroup factor, and the corresponding interaction term. Hazard ratios and 95% CIs are provided for several subgroups that were defined a priori and investigated. Time zero for all analyses was the date of SAVR.

Left Heart Reverse Remodeling Time Course

To assess the temporal trend of the LV mass index, LVEF, and LA size, we analyzed follow-up transthoracic echocardiograms longitudinally for patterns of change across time, from time of SAVR. Nonlinear mixed model regression analysis (15–17) was used to resolve many time phases to form a temporal decomposition model and to estimate the shaping variables at each phase (18). Mixed model regression for continuous repeated measurements (SAS PROC NLMIXED) was used to implement the temporal decomposition model. A normal distribution was assumed for the patient-specific random effect (intercept) and error term. After the underlying time course for each measure was characterized, use of RAS blockade therapy was added into the longitudinal model to compare the propensity-matched groups with respect to these changes over time.

Presentation of Data

Continuous variables are presented as means (SDs) and as 15th, 50th (median), and 85th percentiles; comparisons were made using the Wilcoxon rank-sum test. Categorical data are described using frequencies and percentages; comparisons were made using the chi-square test or Fisher exact test when frequency was less than 5. All analyses were done using SAS software, version 9.2. Because transformation of the scale of continuous variables was often necessary to meet statistical model assumptions, results of multivariable logistic regression model are presented with their coefficients rather than less interpretable odds ratios. Uncertainty is expressed by 95% confidence limits.

Table 1. **Baseline Characteristics of Patients After SAVR**

Characteristic	All Patients Receiving RAS Blockade Therapy (n = 741)		All Patients Not Receiving RAS Blockade Therapy (n = 1011)		*P* Value	Propensity-Matched Patients Receiving RAS Blockade Therapy (n = 594)		Propensity-Matched Patients Not Receiving RAS Blockade Therapy (n = 594)		*P* Value
	Patients, *n*	Value	Patients, *n*	Value		Patients, *n*	Value	Patients, *n*	Value	
Mean age (SD), *y*	741	72 (9)	1011	72 (10)	0.65	594	72 (9)	594	72 (9)	0.89
Female, *n (%)*	741	294 (39.7)	1011	394 (39.0)	0.77	594	242 (40.7)	594	237 (39.9)	0.77
Mean preoperative BMI (SD), *kg/m²*	728	30 (7)	992	28 (6)	<0.001	583	29 (6)	588	29 (6)	0.65
Symptom, *n (%)*										
NYHA functional class	726	–	993	–	0.062	581	–	587	–	0.44
I	–	131 (18.0)	–	228 (23.0)	–	–	112 (19.3)	–	136 (23.2)	–
II	–	408 (56.2)	–	532 (53.6)	–	–	323 (55.6)	–	310 (52.8)	–
III	–	161 (22.2)	–	192 (19.3)	–	–	124 (21.3)	–	118 (20.1)	–
IV	–	26 (3.6)	–	41 (4.1)	–	–	22 (3.8)	–	23 (3.9)	–
Syncope	577	82 (14.2)	861	118 (13.7)	0.79	468	67 (14.3)	488	64 (13.1)	0.59
Coronary anatomy, *n (%)*										
Number of diseased vessels	693	–	933	–	0.072	551	–	562	–	0.78
0	–	285 (41.1)	–	444 (47.6)	–	–	236 (42.8)	–	227 (40.4)	–
1	–	180 (26.0)	–	216 (23.2)	–	–	132 (23.9)	–	148 (26.3)	–
2	–	138 (19.9)	–	159 (17.0)	–	–	107 (19.4)	–	107 (19.0)	–
3	–	90 (13.0)	–	114 (12.2)	–	–	76 (13.8)	–	80 (14.2)	–
Left main coronary artery disease ≥50%	637	44 (6.9)	834	62 (7.4)	0.72	504	38 (7.5)	499	38 (7.6)	0.96
LAD coronary artery system disease ≥50%	683	281 (41.1)	907	350 (38.6)	0.31	544	220 (40.4)	549	240 (43.7)	0.27
LCX coronary artery system disease ≥50%	673	202 (30.0)	876	222 (25.3)	0.041	535	156 (29.2)	528	160 (30.3)	0.68
RCA system disease ≥50%	741	229 (30.9)	1011	273 (27.0)	0.074	594	185 (31.1)	594	184 (31.0)	0.95
Echocardiography										
Mean AV area (SD), *cm²*	642	0.69 (0.13)	858	0.66 (0.14)	<0.001	514	0.68 (0.14)	506	0.68 (0.14)	0.35
Mean peak AV gradient (SD), *mm Hg*	657	78 (25)	883	82 (26)	0.008	526	79 (25)	515	78 (24)	0.44
Mean AV gradient (SD), *mm Hg*	665	46 (15)	881	49 (17)	0.010	525	47 (15)	516	46 (15)	0.33
LV dysfunction (LVEF), *n (%)*	725	–	980	–	0.051	581	–	578	–	0.95
None (≥50%)	–	565 (77.9)	–	819 (83.6)	–	–	461 (79.3)	–	464 (80.3)	–
Mild (40%–49%)	–	57 (7.9)	–	64 (6.5)	–	–	48 (8.3)	–	44 (7.6)	–
Moderate (35%–39%)	–	54 (7.4)	–	48 (4.9)	–	–	40 (6.9)	–	35 (6.1)	–
Moderately severe (26%–34%)	–	26 (3.6)	–	26 (2.7)	–	–	19 (3.3)	–	20 (3.5)	–
Severe (≤25%)	–	23 (3.2)	–	23 (2.3)	–	–	13 (2.2)	–	15 (2.6)	–
Mean LVIDD (SD), *cm*	654	4.6 (0.8)	845	4.6 (0.8)	0.28	525	4.6 (0.8)	491	4.6 (0.7)	0.57
Mean LVISD (SD), *cm*	650	3.0 (0.9)	837	2.9 (0.8)	0.002	521	3.0 (0.8)	487	2.9 (0.8)	0.102
Mean LVEDV (SD), *mL*	654	102 (41)	845	100 (40)	0.28	525	101 (41)	491	99 (37)	0.58
Mean LVESV (SD), *mL*	650	41 (30)	837	37 (27)	0.002	521	40 (29)	487	37 (25)	0.102
Mean LV mass index (SD), *g/m²*	634	128 (39)	813	128 (40)	0.74	509	129 (40)	479	126 (39)	0.21
Mean LA volume index (SD), *mL/m²*	608	20.7 (9.6)	765	21 (13)	0.152	492	21 (10)	460	20 (10)	0.141
Comorbid condition, *n (%)*										
History of MI	741	135 (18.2)	1011	193 (19.1)	0.64	594	102 (17.2)	594	117 (19.7)	0.26
Atrial fibrillation/flutter	628	33 (5.3)	843	78 (9.3)	0.0041	495	31 (6.3)	488	28 (5.7)	0.73
Smoking	738	406 (55.0)	1002	550 (54.9)	0.96	591	323 (54.7)	589	321 (54.5)	0.96
Peripheral arterial disease	741	67 (9.0)	1011	89 (8.8)	0.86	594	50 (8.4)	594	58 (9.8)	0.42
Stroke/cerebral vascular accident	741	55 (7.4)	1011	63 (6.2)	0.33	594	45 (7.6)	594	42 (7.1)	0.74
Carotid disease	741	311 (42.0)	1011	424 (41.9)	0.99	594	244 (41.1)	594	277 (46.6)	0.054
COPD	741	93 (12.6)	1011	137 (13.6)	0.54	594	72 (12.1)	594	93 (15.7)	0.078

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Table 1—**Continued**

Characteristic	All Patients Receiving RAS Blockade Therapy (*n* = 741)		All Patients Not Receiving RAS Blockade Therapy (*n* = 1011)		*P* Value	Propensity-Matched Patients Receiving RAS Blockade Therapy (*n* = 594)		Propensity-Matched Patients Not Receiving RAS Blockade Therapy (*n* = 594)		*P* Value
	Patients, *n*	Value	Patients, *n*	Value		Patients, *n*	Value	Patients, *n*	Value	
Hypertension	741	626 (84.5)	1011	643 (63.6)	<0.001	594	483 (81.3)	594	478 (80.5)	0.71
Insulin-treated diabetes	719	53 (7.4)	977	56 (5.7)	0.17	574	37 (6.4)	570	40 (7.0)	0.69
Non–insulin-treated diabetes (including diet)	719	160 (22.3)	977	131 (13.4)	<0.001	574	111 (19.3)	570	101 (17.7)	0.48
Pharmacologically treated diabetes	721	187 (25.9)	979	150 (15.3)	<0.001	576	128 (22.2)	572	121 (21.2)	0.66
Renal disease	741	18 (2.4)	1011	53 (5.2)	0.0032	594	18 (3.0)	594	21 (3.5)	0.63
Preoperative renal dialysis	681	8 (1.2)	887	18 (2.0)	0.189	536	8 (1.5)	539	10 (1.9)	0.64
Medication										
β-Blocker, *n (%)*	741	660 (89.1)	1011	568 (56.2)	<0.001	594	524 (88.2)	594	343 (57.7)	<0.001
Aldosterone antagonist, *n (%)*	741	104 (14.0)	1011	46 (4.5)	<0.001	594	74 (12.5)	594	24 (4.0)	<0.001
ACE inhibitor, *n (%)*	741	598 (80.7)	1011	0 (0)	–	594	482 (81.1)	594	0 (0)	–
ARB, *n (%)*	741	306 (41.3)	1011	0 (0)	–	594	243 (40.9)	594	0 (0)	–
Duration of therapy with ACE inhibitors after SAVR*, *y*	598	1.2/4.8/10.7	–	–	–	482	1.2/5.2/11.0	–	–	–
Duration of therapy with ARBs after SAVR*, *y*	306	1.4/5.1/10.8	–	–	–	243	1.3/5.3/10.9	–	–	–
Laboratory result										
Mean preoperative BUN level (SD)	730	–	995	–	0.123	583	–	586	–	0.82
mmol/L	–	7.5 (3.2)	–	7.5 (3.6)	–	–	7.5 (3.2)	–	7.5 (3.6)	–
mg/dL	–	21.1 (9.0)	–	21.1 (10.0)	–	–	21.0 (9.0)	–	21.0 (10.0)	–
Mean preoperative creatinine level (SD)	727	–	991	–	0.149	580	–	582	–	0.67
μmol/L	–	96.36 (45.08)	–	97.2 (44.2)	–	–	97.2 (44.2)	–	97.2 (44.2)	–
mg/dL	–	1.09 (0.51)	–	1.1 (0.5)	–	–	1.1 (0.5)	–	1.1 (0.5)	–
Mean preoperative hematocrit level (SD), *%*	697	38 (6)	938	38.3 (5.5)	0.36	556	38 (6)	556	38 (5)	0.85
Procedural										
Concomitant CABG, *n (%)*	741	392 (52.9)	1011	454 (44.9)	0.001	594	300 (50.5)	594	316 (53.2)	0.35
Concomitant mitral valve surgery, *n (%)*	741	5 (0.7)	1011	16 (1.6)	0.085	594	4 (0.7)	594	2 (0.3)	0.41
Concomitant tricuspid valve surgery, *n (%)*	741	4 (0.5)	1011	13 (1.3)	0.115	594	3 (0.5)	594	7 (1.2)	0.20
Mean aortic prosthetic valve size (SD), *mm*	741	22.4 (2.2)	1011	22.5 (2.1)	0.46	594	22.3 (2.2)	594	22.4 (2.1)	0.30
Mean total myocardial ischemia (SD), *min*	733	73 (31)	994	71 (28)	0.164	586	72 (31)	590	73 (27)	0.52
Mean total cardiopulmonary bypass (SD), *min*	733	91 (35)	994	90 (36)	0.49	586	90 (35)	590	92 (37)	0.43
Management										
ICU length of stay, *h**	741	23/27/74	1011	24/26/72	0.28	594	24/28/76	594	24/26/72	0.172
Operative length of stay, *d**	741	5.0/6.3/10.1	1011	4.9/6.3/10.1	0.66	594	5.0/6.9/10.1	594	5.0/6.8/10.3	0.97
Hospital length of stay, *d**	741	5.3/7.3/14.0	1011	5.3/7.3/14.0	0.18	594	5.3/7.4/14.0	594	5.3/7.3/15.0	0.63
Interval from surgery to death or follow-up, *y*	741	2.1/6.1/11.3	1011	1.9/6.04/10.9	–	594	1.9/6.3/11.1	594	1.4/5.4/10.1	–
Postoperative complication, *n (%)*										
Stroke	741	8 (1.1)	1011	14 (1.4)	0.57	594	7 (1.2)	594	9 (1.5)	0.61
Perioperative MI	741	2 (0.3)	1011	1 (0.1)	0.39	594	2 (0.3)	594	1 (0.2)	0.56
Reoperation for bleeding/tamponade	741	24 (3.2)	1011	35 (3.5)	0.83	594	23 (3.9)	594	21 (3.5)	0.76
Atrial fibrillation	741	238 (32.1)	1011	337 (33.3)	0.59	594	186 (31.3)	594	201 (33.8)	0.35

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Table 1—Continued

Characteristic	All Patients Receiving RAS Blockade Therapy (*n* = 741)		All Patients Not Receiving RAS Blockade Therapy (*n* = 1011)		*P* Value	Propensity-Matched Patients Receiving RAS Blockade Therapy (*n* = 594)		Propensity-Matched Patients Not Receiving RAS Blockade Therapy (*n* = 594)		*P* Value
	Patients, *n*	Value	Patients, *n*	Value		Patients, *n*	Value	Patients, *n*	Value	
Prolonged ventilation >24 h	502	40 (8.0)	578	42 (7.3)	0.66	383	29 (7.6)	362	28 (7.7)	0.93
Renal failure requiring dialysis	741	2 (0.3)	1011	9 (0.9)	0.104	594	1 (0.2)	594	6 (1.0)	0.058
Renal failure	741	21 (2.8)	1011	48 (4.7)	0.042	594	14 (2.4)	594	28 (4.7)	0.028
Septicemia	741	10 (1.3)	1011	14 (1.4)	0.95	594	7 (1.2)	594	10 (1.7)	0.46
Deep sternal wound infection	741	3 (0.4)	1011	5 (0.5)	0.78	594	3 (0.5)	594	5 (0.8)	0.48

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; AV = aortic valve; BMI = body mass index; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; LA = left atrial; LAD = left anterior descending; LCX = left circumflex; LV = left ventricular; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; LVIDD = left ventricular internal diastolic dimension; LVISD = left ventricular internal systolic dimension; MI = myocardial infarction; NYHA = New York Heart Association; RAS = renin–angiotensin system; RCA = right coronary artery; SAVR = surgical aortic valve replacement.
* Presented as 15th percentile/median/85th percentile because of the skewed distribution of this variable.

Role of the Funding Source

This study did not receive external funding.

RESULTS

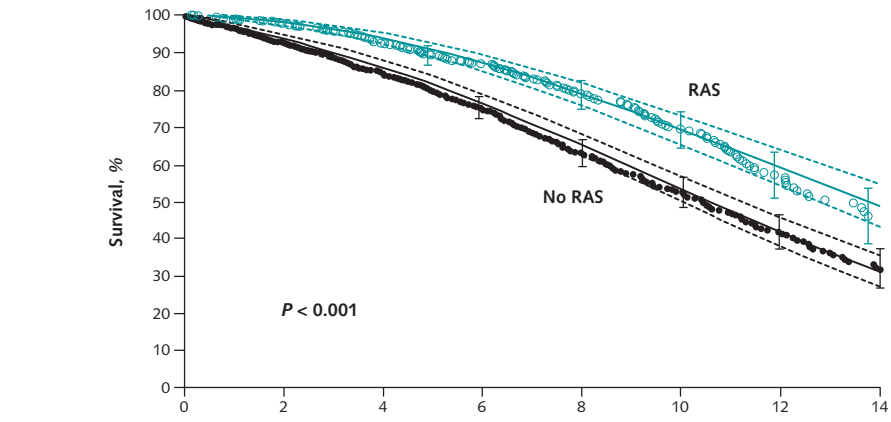
Patient Characteristics

Between 1991 and 2010, a total of 4681 patients had SAVR at the Cleveland Clinic Foundation. After we applied the exclusion criteria, 1752 patients were in our study, with 741 (42%) in the RAS blockade group and 1011 (58%) who were never treated with ACE inhibitors or ARBs after SAVR (non–RAS blockade group) (**Figure 1**). Baseline characteristics of unmatched patients in the RAS blockade and non–RAS blockade groups are shown in **Table 1**. Mean age was similar in both groups (72 years [SD, 9] vs. 72 years [SD, 10]; $P = 0.65$), and 60% of patients were men. In the RAS blockade group, 598 patients (80.7%) were treated with ACE inhibitors for a median of 4.8 years (range, 1.2 to 10.7 years) and 306 patients (41.3%) were treated with an ARB for a median of 5.1 years (range, 1.4 to 10.8 years). A total of 846 patients (48%) had concomitant CABG at the time of SAVR. Patients in the RAS blockade group were more likely to have history of hypertension, LV dysfunction, greater preoperative body mass index, and concomitant CABG. Patients in the non–RAS blockade group were more likely to have history of chronic kidney disease and concomitant mitral or tricuspid valve surgery. In the multivariable logistic regression model, factors associated with RAS blockade therapy in more than 50% of the bootstrap models included the more recent surgery date, history of hypertension, greater body mass index, and more severe LV dysfunction. The final parsimonious model retaining all factors that occurred in 50% or more of the bootstrap models is presented in **Table 1** of the **Supplement**. After augmenting this model with all other available factors, such as sex, NYHA (New York Heart Association) class, preoperative echocardiographic data, and other comorbid conditions, we formed the saturated propensity model to further adjust the groups and reduce bias in our comparison. Greedy matching based on propensity scores yielded 594 well-matched pairs of patients (**Table 1**).

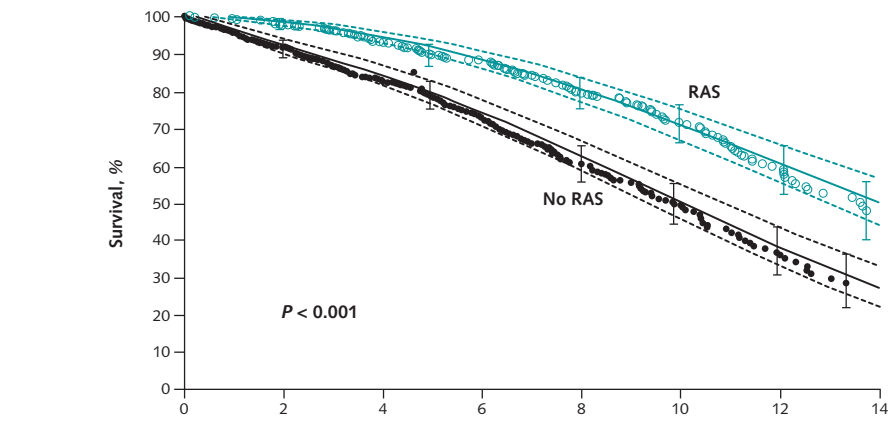
Survival

There were 11 002 patient-years of follow-up. Median follow-up was 5.8 years (15th and 85th percentiles, 1.7 and 11.0 years, respectively) with 10% of the patients followed for more than 12 years. There were 562 all-cause deaths: 170 in the RAS blockade group and 392 in the non–RAS blockade group. The hazard function resolved to 2 phases with an early phase in the first year, accounting for less than 10% of the 562 deaths, and a late increasing phase thereafter. The unadjusted survival rates at 6 months and 1, 5, 10, and 12 years in the RAS blockade group were 99%, 99%, 90%, 69%, and 58%, respectively, compared with 99%, 99%, 81%, 53%, and 42% in the non–RAS blockade group ($P < 0.001$) (**Figure 2** [*top*] and **Table 2**). When stratified by concomitant CABG status, survival rates were significantly better in the RAS blockade group ($P < 0.001$). Adjustment for the propensity score in the model gave similar results as comparison between matched groups (see **Table 2**). Among propensity-matched patients, survival rates at 6 months and 1, 5, 10, and 12 years were significantly better in the RAS blockade group (99%, 99%, 90%, 71%, and 60% vs. 97%, 96%, 78%, 49%, and 37%, respectively; $P < 0.001$) (**Figure 2**, [*middle*] and **Table 2**). In matched patients stratified by concomitant CABG status, survival rates were still significantly greater in the RAS blockade group (**Figure 2**, *bottom*). The difference in survival rates between the RAS blockade and non–RAS blockade groups after SAVR was consistent across various subgroups (**Figure 3**). We found very similar results to the

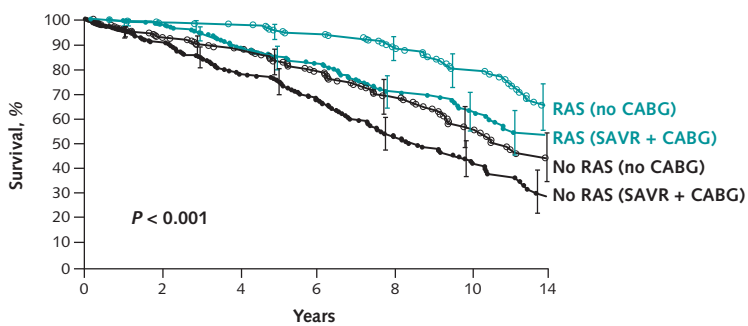
Figure 2. **Survival curves.**



Persons at risk, *n*								
RAS	741	643	496	378	264	157	87	42
No RAS	1011	853	680	512	336	215	105	53



Persons at risk, *n*								
RAS	594	520	407	323	228	142	85	42
No RAS	594	482	373	284	181	107	48	20



Persons at risk, *n*							
RAS (no CABG)	294	248	221	176	121	84	49
RAS (SAVR + CABG)	300	255	190	149	101	58	41
No RAS (no CABG)	278	218	167	126	91	51	27
No RAS (SAVR + CABG)	316	259	193	144	90	53	20

Each symbol represents a death, and vertical bars represent 95% CIs estimated by Kaplan–Meier method. Solid lines are parametric estimates enclosed within a 95% confidence band. CABG = coronary artery bypass grafting; RAS = renin–angiotensin system; SAVR = surgical aortic valve replacement. **Top.** Unadjusted survival stratified by RAS blockade therapy. **Middle.** Survival in the propensity-matched groups stratified by RAS blockade therapy. **Bottom.** Survival in the propensity-matched groups stratified by RAS blockade therapy and CABG.

Table 2. **Risk for Death After SAVR With RAS Blockade Therapy Compared With No RAS Blockade Therapy**

Model*	Early (Approximately 1 Year)		Late (>1 Year)	
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Unadjusted (n = 1752)	0.12 (0.02–0.78)	0.024	0.66 (0.52–0.83)	<0.001
Propensity-adjusted† (n = 1752)	0.16 (0.04–0.71)	0.012	0.64 (0.47–0.87)	0.002
Propensity-matched (n = 1188)	0.11 (0.02–0.61)	0.009	0.58 (0.44–0.75)	<0.001

RAS = renin–angiotensin system; SAVR = surgical aortic valve replacement.
* Parametric multiphase hazard model for mortality with RAS group variable.
† Propensity score included in the model for adjustment.

significantly improved survival rates in the RAS blockade group when we included all patients who had SAVR without excluding those who were not followed at the Cleveland Clinic Foundation (**Figures 1** to **5** of the **Supplement**). In the first 90 days after SAVR, 251 deaths occurred in the non–RAS blockade group compared with 60 deaths in the RAS blockade group (log-rank $P = 0.07$) (**Figure 6** of the **Supplement**). The propensity scores differed insignificantly across the 5 imputed data sets. When matching separately within the imputed data sets (rather than averaging the 5 propensity scores and matching), with the same 0.10 caliper, we obtained similar numbers of matches (1196, 1190, 1196, 1204, and 1198) compared with our 1188 matches using the combined score. Comparisons of matched survival yielded similar results if matches were used within imputed data sets rather than averaging the propensity score across the data sets.

Change in LV Mass, LVEF, and LA Size

The distribution of the number of echocardiograms with data on LV mass, LVEF, and LA size during follow-up after SAVR is shown in **Tables 2** to **4** of the **Supplement**. On the basis of these distributions, we could reliably assess overall temporal trend of LV mass, LVEF, and LA size up to 10 years in the matched patients. The estimated mean LV mass index of the overall matched population after SAVR sharply decreased in the first 6 months followed by a slight increase at 10 years. Estimated mean LV mass index of this study population was 120 g/m^2 on the first day, sharply decreased to 107 g/m^2 by the third month, and gradually increased to 115 g/m^2 after 10 years. There was no significant difference in the RAS blockade and non–RAS blockade groups with respect to change in LV mass index ($P = 0.37$) (**Figure 4**, *top*). The temporal decomposition trend of the estimated mean LVEF of this study population had an early increase in the first year to approximately 0.56 and then a slowly decreasing, nearly constant phase thereafter, with LVEF of roughly 0.55. The change in LVEF did not differ significantly between the RAS blockade and non–RAS blockade groups ($P = 0.67$) (**Figure 4**, *middle*). The temporal decomposition trend of LA size yielded an early peaking phase immediately after surgery followed by a decreasing phase in the first year to approximately 4.3 cm. A late, slow increase in LA diameter was seen over the next years, increasing to greater than 4.5 cm by 10 years. The change in LA diameter did not significantly differ between the groups ($P = 0.43$) (**Figure 4**, *bottom*).

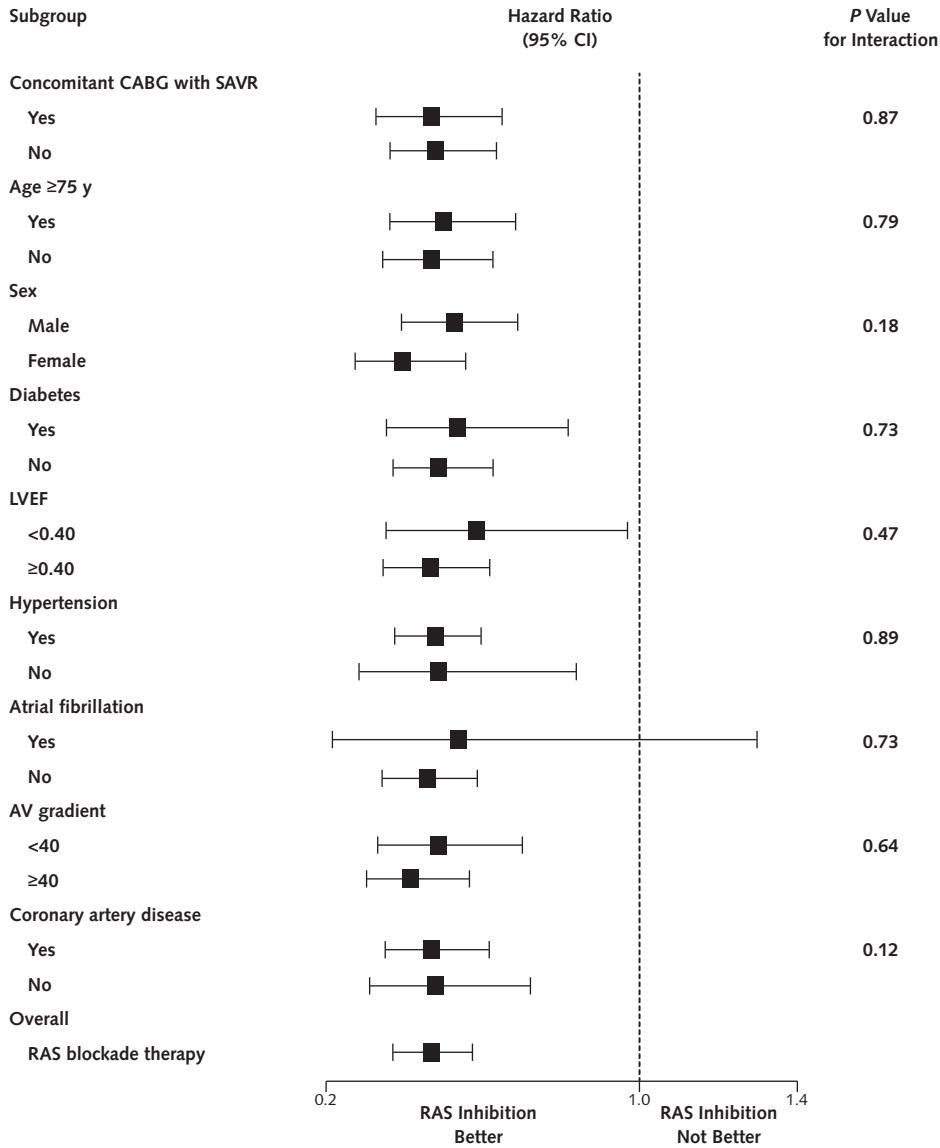
DISCUSSION

In a large consecutive group of patients having SAVR for severe AS, we saw improved survival rates in patients treated with RAS blockade therapy with ACE inhibitors or ARBs over long-term follow-up. In this cohort, changes in LV mass, LVEF, and LA size did not seem to explain the association between RAS blockade therapy and improved survival rates.

Aortic stenosis is associated with LVH to compensate for increased afterload and to maintain adequate cardiac output. Progressive myocardial hypertrophy is associated with reduced myocardial perfusion, particularly in the subendocardium, leading to interstitial fibrosis (19, 20). In turn, interstitial fibrosis associated with a decline in ventricular function (systolic and diastolic), progressive heart failure, arrhythmogenicity, and sudden death (20). Previous studies have shown that LVH associated with severe AS persists after SAVR and is associated with worse long-term outcome and mortality rates (3–5). Existing data demonstrate beneficial effects of RAS blockade therapy with ACE inhibitors or ARBs in patients with hypertension (6) and heart failure (21–24) and those at high risk for vascular events (25). A large observational study recently suggested that ACE inhibitor or ARB therapy is associated with improved survival rates and lower risk for cardiovascular events (cardiovascular death or hospitalizations) in 2117 patients with varying degrees of AS (26). To our knowledge, this is the first study to evaluate the association between RAS blockade therapy with ACE inhibitors or ARBs and survival rates in patients with severe AS after SAVR and to demonstrate significantly lower all-cause mortality in patients treated with ACE inhibitors or ARBs after SAVR in a propensity-matched analysis. The significant survival benefit associated with RAS blockade therapy was present even when patients were stratified by concomitant CABG status.

Risk factors for AS and atherosclerosis have been shown to be similar (27). Renin–angiotensin system blockade therapy has been proven to be beneficial in patients at high risk for cardiovascular events, such as those with evidence of atherosclerosis or diabetes with other risk factors for atherosclerosis (as in the Heart Outcomes Prevention Evaluation trial [25]). A meta-analysis of studies evaluating the role of ACE inhibitors in patients with stable vascular disease without overt heart failure or LV dysfunction showed that ACE inhibitors significantly reduced mortality

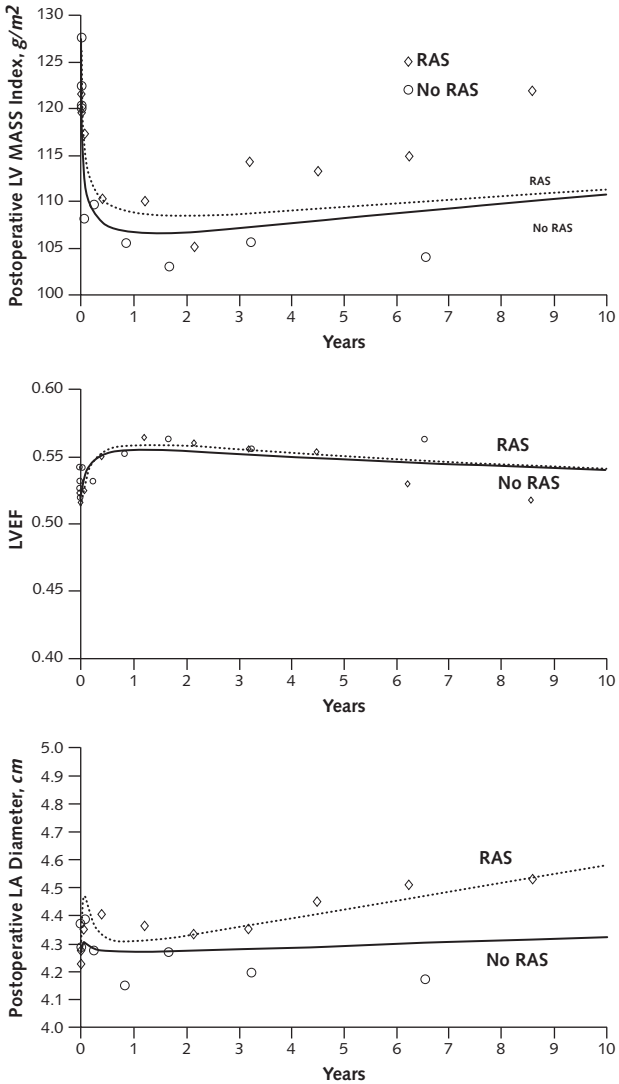
Figure 3. **Subgroup analysis of survival after SAVR with RAS blockade therapy.**



CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; RAS = renin–angiotensin system; SAVR = surgical aortic valve replacement.

rates and cardiovascular events (28). In the present study, in addition to having SAVR for severe AS, more than 80% patients had hypertension, more than 50% had evidence of coronary artery disease, more than 40% had evidence of carotid atherosclerosis, and 30% had diabetes mellitus. This clearly represents a patient population at high risk for atherosclerotic cardiovascular events. Therefore, one possible explanation of increased survival rates associated with the use of RAS blockade therapy in our study may be related to the cardioprotective effects of ACE inhibitor or ARB therapy in the form of inhibition of vasoconstriction, atherosclerotic plaque stabilization leading to reduction in plaque rupture and improvement in endothelial function (25, 29). Another explanation is that the increased survival rates associated with RAS blockade therapy after SAVR may be related to regression of myocardial fibrosis that occurred as part of adverse LV remodeling with AS (30). A recent small, unblinded, randomized study found significant reverse LV and LA remodeling after SAVR in patients treated with candesartan compared with conventional management (31). We hypothesized that regression of LV mass after SAVR may be the mechanism of improved survival rates associated with RAS blockade therapy in this population; however, the results of our echocardiographic analysis suggests that this may not be the case because the magnitude of change in these variables was similar in pa-

Figure 4. **Temporal trends of echocardiographic changes in propensity-matched patients.**



Lines represent parametric estimates of temporal trend. Symbols represent raw data grouped by decile (without regard to repeated measurements) and plotted at mean time within the decile to provide a crude verification of model fit in RAS blockade and non–RAS blockade groups. LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; RAS = renin–angiotensin system; SAVR = surgical aortic valve replacement. **Top.** Temporal trend of LV mass index after SAVR. **Middle.** Temporal trend of LVEF after SAVR. **Bottom.** Temporal trend of LA diameter after SAVR.

tients treated with and without ACE inhibitors or ARBs. Echocardiography has some limitations in assessing LV mass. The Devereux formula for measurement of LV mass by echocardiography uses geometric assumptions validated in normal hearts (32); however, LV mass may be inaccurately measured by this method in the presence of asymmetric LVH (33, 34), which is often seen in patients with AS. In addition, interstitial fibrosis cannot be directly quantified by echocardiography. Data from histologic and cardiac magnetic resonance imaging studies demonstrate the prognostic value of myocardial fibrosis in patients with severe AS (35, 36). Weidemann and colleagues (36) showed that myocardial fibrosis in patients with AS as assessed by cardiac magnetic resonance imaging was not completely reversible in the 9 months after SAVR and that LVEF was normal despite abnormalities seen on magnetic resonance imaging. It is possible that RAS blockade therapy may lead to regression of myocardial fibrosis in patients with AS after SAVR, similar to hypertensive heart disease, regardless of LVH regression (30). Last, RAS blockade therapy may also lead to reduction in arrhythmogenic sudden cardiac death secondary to its potassium-sparing effects (37). These potential mechanisms of increased survival rates associated with RAS blockade therapy in patients with AS after SAVR are speculative, and it is not possible to infer the actual mechanism from this retrospective analysis. A randomized trial in the near future is needed, with careful evaluation of LV and LA remodeling by echocardiography or magnetic resonance imaging to help clarify the association between RAS blockade therapy after SAVR and outcomes.

Our study has important potential clinical implications. Most patients with AS having SAVR are at high risk for cardiovascular events, given concurrent presence of coronary or peripheral atherosclerosis and risk factors, such as hypertension, hyperlipidemia, and diabetes mellitus. The abundance of data suggests benefit of RAS blockade therapy in preventing death and illness in these patients. Our data identify yet another high-risk patient population in which the use of RAS blockade therapy is associated with increased survival rates. Patients with SAVR remain at high risk for rehospitalization secondary to persistent diastolic (or systolic) ventricular dysfunction. Although we did not compare rates of rehospitalization secondary to decompensated heart failure with and without RAS blockade therapy in this population, existing data showed marked benefit of this therapy in preventing rehospitalization and reducing health care costs (38, 39).

To our knowledge, this is the first study in this patient population with severe AS after SAVR, demonstrating a significant association between RAS blockade therapy and improved outcomes. However, this study has limitations inherent to any retrospective, nonrandomized, observational analysis. This study could not determine the association (positive or negative) between RAS blockade therapy and very short-term outcomes because patients who died within 90 days after SAVR were excluded from the study. We have attempted to account for the baseline differences in patients by performing a propensity score–matched analysis (**Figure** 7 of the **Supplement**). Post-SAVR echocardiographic data were not available in all propensity-matched patients. However, baseline characteristics were similar between propensity-matched patients treated with and without ACE inhibitors or ARBs in whom echocardiographic data were available for analysis of changes in LV

mass and LVEF (data not shown). Oversampling of echocardiography in patients with persistent heart failure symptoms after SAVR (and consequently more adverse LV remodeling) could possibly have washed out any beneficial effect of RAS inhibition on changes in LV mass and LVEF. It is still possible that receipt of RAS blockade therapy is indicative of overall better care administered to these patients in our study; however, this would be impossible to prove or disprove, short of a randomized trial. Data on blood pressure during follow-up were not consistently available. It is possible that the association between RAS blockade therapy after SAVR and improved outcomes may be related in part to the antihypertensive effects of this therapy.

To our knowledge, this is the first study evaluating the association between RAS blockade therapy and survival rates in patients with severe AS after SAVR. Renin–angiotensin system blockade therapy with ACE inhibitors or ARBs is associated with improved survival rates in patients with severe AS after SAVR. In this cohort, changes in LV mass, LVEF, and LA size do not seem to explain this association. Treatment with ACE inhibitors or ARBs should be considered in patients after SAVR if proven beneficial in randomized, controlled trials.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M13-1505.

Reproducible Research Statement: *Study protocol:* Available from Dr. Goel (e-mail, sachinsgoel@gmail.com). *Statistical code and data set:* Available from Ms. Houghtaling (e-mail, houghtp@ccf.org).

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