JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 5, 2019

PUBLISHED BY ELSEVIER

Renin-Angiotensin System Inhibition Following Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Several studies have demonstrated the benefits of transcatheter aortic valve replacement (TAVR) in patients with aortic stenosis, but the presence of persistent fibrosis and myocardial hypertrophy has been related to worse prognosis.

OBJECTIVES The aim of this study was to explore the potential benefits of renin-angiotensin system (RAS) inhibitors on left ventricular remodeling and major clinical outcomes following successful transcatheter aortic valve replacement (TAVR).

METHODS Patients from 10 institutions with severe aortic stenosis who underwent TAVR between August 2007 and August 2017 were included. All baseline data were prospectively recorded, and pre-specified follow-up was performed. Doses and types of RAS inhibitors at discharge were recorded, and matched comparison according to their prescription at discharge was performed.

RESULTS A total of 2,785 patients were included. Patients treated with RAS inhibitors (n = 1,622) presented similar surgical risk scores but a higher rate of all cardiovascular risk factors, coronary disease, and myocardial infarction. After adjustment for these baseline differences, reduction of left ventricular volumes and hypertrophy was greater and cardiovascular mortality at 3-year follow-up was lower (odds ratio: 0.59; 95% confidence interval: 0.41 to 0.87; p = 0.007) in patients treated with RAS inhibitors. Moreover, RAS inhibitors demonstrated a global cardiovascular protective effect with significantly lower rates of new-onset atrial fibrillation, cerebrovascular events, and readmissions.

CONCLUSIONS Post-TAVR RAS inhibitors are associated with lower cardiac mortality at 3-year follow-up and offer a global cardiovascular protective effect that might be partially explained by a positive left ventricular remodeling. An ongoing randomized trial will help confirm these hypothesis-generating findings. (Renin-Angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation [RASTAVI]; NCT03201185) (J Am Coll Cardiol 2019;74:631-41) © 2019 by the American College of Cardiology Foundation.

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Manuscript received April 8, 2019; revised manuscript received May 8, 2019, accepted May 14, 2019.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.05.055

JACC VOL. 74, NO. 5, 2019
AUGUST 6, 2019:631–41

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

LV = left ventricular

RAS = renin-angiotensin system

TAVR = transcatheter aortic valve replacement

In the past decade, transcatheter aortic valve replacement (TAVR) has dramatically changed the treatment of severe aortic stenosis (AS). TAVR is a valid option for patients with severe AS who are at intermediate to high or prohibitive surgical risk (1–5), and several trials are currently evaluating TAVR in patients at low surgical risk. In contrast to this rapid evolution, there is still a gap with respect to optimal medical therapy following TAVR that could affect mid- and long-term outcomes.

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AS is associated with progressive cellular hypertrophy, diffuse interstitial fibrosis, and focal fibrosis, which increase exponentially as the severity of AS advances. Once established, reverse remodeling seems uncertain despite valve replacement (6). The persistence of left ventricular (LV) hypertrophy and myocardial fibrosis after stenosis relief in patients with severe AS has been associated with worse prognosis in patients who underwent surgical aortic valve replacement (7–9). Renin-angiotensin system (RAS) inhibition contributes to sustained protection against LV hypertrophy and myocardial fibrosis in response to profibrotic stimuli such as AS (10). Therefore, medical strategies with RAS inhibition therapy could enhance better long-term outcomes after TAVR.

The aim of the RASTAVI (Renin-Angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation) registry is to evaluate the clinical effect of RAS inhibition in a cohort of unselected patients following successful TAVR through the comparison of both clinical outcomes and echocardiographic evolution at short- and mid-term follow-up, according to the prescription of RAS inhibitors at discharge.

METHODS

The RASTAVI registry is a multicenter, retrospective study including patients from 10 institutions. Between August 2007 and August 2017, a total of 2,866 consecutive patients undergoing TAVR were prospectively collected including any prescribed medications after obtaining permission from the patients. Following approval from the local ethic committees of all participating institutions, a retrospective analysis of all TAVR recipients was performed, dividing them into 2 groups according to medical therapy at discharge: patients who were prescribed angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers (with or without sacubitril), or spironolactone or eplerenone following TAVR (patients under RAS inhibitors; n = 1,622) and those without prescriptions for RAS inhibitors at discharge (n = 1,163; baseline medications were missing in 3 patients). Finally, 2,785 patients were analyzed as shown in Online Figure 1. The distribution according to the prescribed medications is summarized in Online Figure 2.

The selection of the TAVR device was determined by each center, including both balloon-expandable (Sapien, Sapien XT, and Sapien 3, Edwards Lifesciences, Irvine, California) and self-expandable (CoreValve and Evolut R, Accurate Neo, Allegra, and Portico, Medtronic, Minneapolis, Minnesota) systems. Procedural strategy was established according to the experience, policies, and protocols of each participating institution.

Baseline clinical, procedural, and in-hospital data were prospectively gathered within a dedicated database. However, several echocardiographic parameters were obtained later after dedicated analysis. The decision to prescribe RAS inhibition was determined by physicians on the basis of clinical criteria. At discharge, RAS inhibitor type and dose were specified, and it was assumed that patients took the medications as advised by their physicians at discharge. Short-term (1-year) and mid-term (3-year) follow-up evaluations were undertaken during clinical visits at study site according to each center's protocol. All outcomes were defined according to the Valve Academic Research Consortium-2 (11).

ECHOCARDIOGRAPHIC ASSESSMENT. Comprehensive transthoracic echocardiography was performed at baseline, before hospital discharge, and at follow-up. All transthoracic echocardiographic examinations were conducted according to American Society of Echocardiography guidelines (12) and centrally analyzed in a core laboratory. In particular, the degree of paravalvular regurgitation after TAVR was measured in accordance with current recommendations using a multiparameter integrative approach and was reported as a semiquantitative grade: none, trace, mild, moderate, or severe. Myocardial hypertrophy was assessed through the surrogate of septal width, and LV diameters were measured in the parasternal long-axis view. Changes in echocardiographic parameters between discharge and follow-up were explored according to the use or not of RAS inhibitors after adjusting for baseline differences.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or as median (interquartile range [IQR]) depending on their distribution. Normal

distribution of continuous variables was assessed using the Kolmogorov-Smirnov test and graphically tested using the Q-Q plot. The Student's *t*-test, Mann-Whitney *U* test, or paired Student's *t*-test were used to compare continuous variables as appropriate. Categorical variables are presented as numeric values and percentages. Categorical variables were compared using the chi-square test, Fisher exact test, or McNemar test as appropriate.

To evaluate the impact of RAS inhibitors on outcomes, while adjusting for baseline confounders, propensity score adjustment was performed (13). The propensity score was generated using a logistics regression model according to nonparsimonious approach. The dependent binary variable was the post-TAVR administration of RAS inhibitors (yes or no), and the independent variables were the following baseline characteristics: age, chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, dyslipidemia, hypertension, LV ejection fraction, and New York Heart Association functional class. Pairs of patients were derived using greedy 1:1 matching with a caliper width of 0.25 SDs of the logit of the propensity score.

Kaplan-Meier analysis was performed using the log-rank test to compare survival rates between the RAS inhibition and no RAS inhibition groups. Cox multivariate regression analysis was performed to identify the independent predictors of global and cardiovascular mortality in the matched population. The multivariate model was built by backward stepwise (likelihood ratio) selection, with candidate variables included if they satisfied the entry criterion of $p < 0.05$ in the univariate analysis. Verification of proportional hazard assumption was performed. Statistical analysis was performed with using IBM SPSS Statistics version 24 (IBM, Armonk, New York). All tests were 2 sided at the 0.05 significance level.

RESULTS

BASELINE, PROCEDURAL, AND IN-HOSPITAL CHARACTERISTICS. Data from 2,785 patients who underwent TAVR at 10 institutions were gathered; of them, 1,622 were under treatment with RAS inhibitors following TAVR and 1,163 were not. The main baseline and echocardiographic characteristics of the global and matched populations are summarized in **Table 1**. In the global population, there were several differences between groups. Patients taking RAS inhibitors had a higher prevalence of cardiovascular risk factors, including diabetes mellitus (36.4% vs. 31.7%; $p = 0.009$), hypertension (85.6% vs. 74.8%; $p < 0.001$), and dyslipidemia (57.0% vs. 52.2%; $p = 0.012$), compared with patients not taking RAS inhibitors, as well as a higher prevalence of comorbidities such as previous coronary artery disease (39.1% vs. 32.9%; $p = 0.002$). In contrast, patients receiving RAS inhibitors had lower rates of chronic obstructive pulmonary disease (20.5% vs. 26.8%; $p < 0.001$) and chronic kidney disease (37.3% vs. 42.5%; $p = 0.007$). Both groups of patients presented similar surgical risk as estimated by Society of Thoracic Surgeons score (5.0 [IQR: 3.5 to 8.0] vs. 5.1 [IQR: 3.4 to 7.5]; $p = 0.440$) and European System for Cardiac Operative Risk Evaluation II score (4.1 [IQR: 2.8 to 7.1] vs. 4.0 [IQR: 2.7 to 6.5]; $p = 0.135$).

Procedural characteristics and in-hospital outcomes of the global and matched population are shown in Online Table 1. TAVR was performed through the transfemoral approach in most patients (91.9% [n = 2,558]). Main periprocedural complications were comparable between groups, with the exception of a higher rate of valve embolization in patients taking RAS inhibitors (2.4% vs. 1.2%; $p = 0.031$) and a higher rate of tamponade in patients not taking RAS inhibitors (1.0% vs. 2.3%; $p = 0.013$). The in-hospital mortality rate was 3.1%.

After propensity score matching, 695 patients taking RAS inhibitors and 695 patients not taking RAS inhibitors constituted the matched population (n = 1,390). As shown in **Table 1**, baseline characteristics were well balanced between both matched groups, except for a higher prevalence of peripheral vascular disease in patients not taking RAS inhibitors (15.4% vs. 11.4%; $p = 0.0027$). Procedural and in-hospital outcomes were also similar between both matched groups except for a higher use of balloon-expandable in patients not taking RAS inhibitors (22.8% vs, 32.7%; $p < 0.001$). Regarding patient-prosthesis mismatch, transprosthetic gradients, and indexed aortic valve area, there were no differences among patients in the matched group (Online Table 1). New permanent pacemaker implantation was more frequent in patients taking RAS inhibitors (25.4% vs. 20.1%; $p = 0.025$).

SHORT- AND MID-TERM FOLLOW-UP OUTCOMES. Median follow-up was 479 days (IQR: 97 to 1,261 days). At 1-year follow-up, the rate of global mortality was 8.8% (n = 245). There were no differences in global mortality between groups, with a rate of 8.6% in patients taking RAS inhibitors compared with 9.1% in those not taking RAS inhibitors ($p = 0.562$). However, patients not taking RAS inhibitors had higher cardiovascular mortality compared with those taking RAS inhibitors (5.8% vs.

TABLE 1 Baseline Characteristics of the Study Population According to the Use of Renin-Angiotensin System Inhibitors

		Global Population			Matched Population		
	Global Study Population (n = 2,785)	RAS Inhibitors (n = 1,622)	No RAS Inhibitors (n = 1,163)	p Value	RAS Inhibitors (n = 695)	No RAS Inhibitors (n = 695)	p Value
Clinical characteristics							
Age, yrs	80.8 ± 7.1	80.8 ± 7.01	80.7 ± 7.18	0.963	80.8 ± 6.9	80.6 ± 7.4	0.644
Female	1,507 (54.1)	890 (54.9)	617 (53.1)	0.342	373 (53.7)	374 (53.8)	0.957
Body surface area, m^2	1.76 ± 0.2	1.78 ± 0.19	1.76 ± 0.2	0.041	1.8 ± 0.20	1.8 ± 0.20	0.197
Body mass index, kg/m^2	27.9 ± 5.1	27.9 ± 5.0	27.7 ± 5.1	0.107	27.9 ± 5.0	27.5 ± 4.7	0.153
Hypertension	2,257 (81.1)	1,388 (85.6)	869 (74.8)	<0.001	545 (78.4)	542 (78.0)	0.845
Dyslipidemia	1,530 (55.0)	924 (57.0)	606 (52.2)	0.012	381 (54.8)	372 (53.5)	0.628
Diabetes mellitus	959 (34.4)	591 (36.4)	368 (31.7)	0.009	232 (33.4)	246 (35.4)	0.429
NYHA functional class III or IV	1,546 (62.9)	898 (59.5)	648 (68.0)	<0.001	464 (66.8)	472 (67.9)	0.647
Atrial fibrillation	855 (30.7)	485 (29.9)	370 (31.8)	0.280	225 (32.4)	222 (31.9)	0.863
Previous pacemaker	232 (8.3)	147 (9.1)	85 (7.3)	0.102	61 (8.8)	57 (8.2)	0.706
Coronary artery disease	921 (36.6)	588 (39.1)	333 (32.9)	0.002	282 (40.6)	286 (41.2)	0.827
Previous MI	389 (15.5)	255 (16.6)	134 (13.8)	0.060	110 (15.8)	108 (15.5)	0.883
Previous PCI	514 (24.7)	325 (24.6)	189 (24.8)	0.890	150 (22.9)	163 (25.2)	0.341
Previous CABG	222 (8.9)	140 (9.1)	82 (8.5)	0.600	58 (8.4)	63 (9.2)	0.605
Previous SVR	153 (7.5)	85 (6.9)	68 (8.5)	0.193	30 (5.5)	33 (6.0)	0.742
Previous stroke/TIA	282 (11.2)	171 (11.1)	111 (11.4)	0.806	79 (11.4)	94 (13.5)	0.223
Peripheral vascular disease	298 (11.9)	168 (10.9)	130 (13.4)	0.061	79 (11.4)	107 (15.4)	0.027
COPD	644 (23.1)	333 (20.5)	311 (26.8)	<0.001	161 (23.2)	171 (24.6)	0.529
CKD (eGFR <60 ml/min)	1,080 (39.4)	599 (37.3)	481 (42.5)	0.007	291 (41.9)	298 (42.9)	0.704
Frailty	752 (28.3)	429 (27.6)	323 (29.0)	0.560	191 (27.5)	201 (28.9)	0.655
STS-PROM, %	5.1 (3.4–7.8)	5.1 (3.4–7.5)	5.0 (3.5–8.0)	0.440	5.3 (3.4–8.1)	5.3 (3.6–8.5)	0.592
EuroSCORE II, %	4.0 (2.7–6.8)	4.0 (2.7–6.5)	4.1 (2.8–7.1)	0.135	4.1 (2.9–6.9)	4.1 (2.8–6.8)	0.887
Echocardiographic findings							
Left ventricular ejection fraction, %	58.0 ± 13.8	57.4 ± 13.9	58.9 ± 13.4	0.005	58.5 ± 13.9	58.1 ± 13.7	0.544
Aortic valve area, cm^2	0.67 ± 0.19	0.68 ± 0.19	0.65 ± 0.18	<0.001	0.67 ± 0.18	0.65 ± 0.17	0.060
Mean transaortic gradient, mm Hg	47.9 ± 16.1	47.3 ± 15.7	48.9 ± 16.6	0.029	47.9 ± 15.3	48.9 ± 17.6	0.255
End-diastolic volume, ml	99 (79–112)	99 (80–113)	98 (78.5–111)	0.048	99 (80–113)	99 (79–113)	0.359
End-systolic volume, ml	41 (30–56)	41 (30–57)	41 (30–56)	0.227	42 (30–57)	41.5 (30–57)	0.450
Septal hypertrophy, mm	15.2 ± 5.5	15.1 ± 5.5	15.4 ± 5.5	0.059	14.7 ± 4.8	15.2 ± 5.4	0.140
Aortic regurgitation III or IV	337 (12.7)	194 (12.7)	143 (12.8)	0.922	71 (10.8)	80 (11.9)	0.541
Mitral regurgitation III or IV	269 (9.9)	163 (10.3)	106 (9.4)	0.422	53 (7.8)	53 (7.8)	0.999
Tricuspid regurgitation III or IV	154 (16.8)	69 (13.7)	85 (20.6)	0.005	21 (11.0)	40 (14.5)	0.264

Values are mean ± SD, n (%), or median (interquartile range).

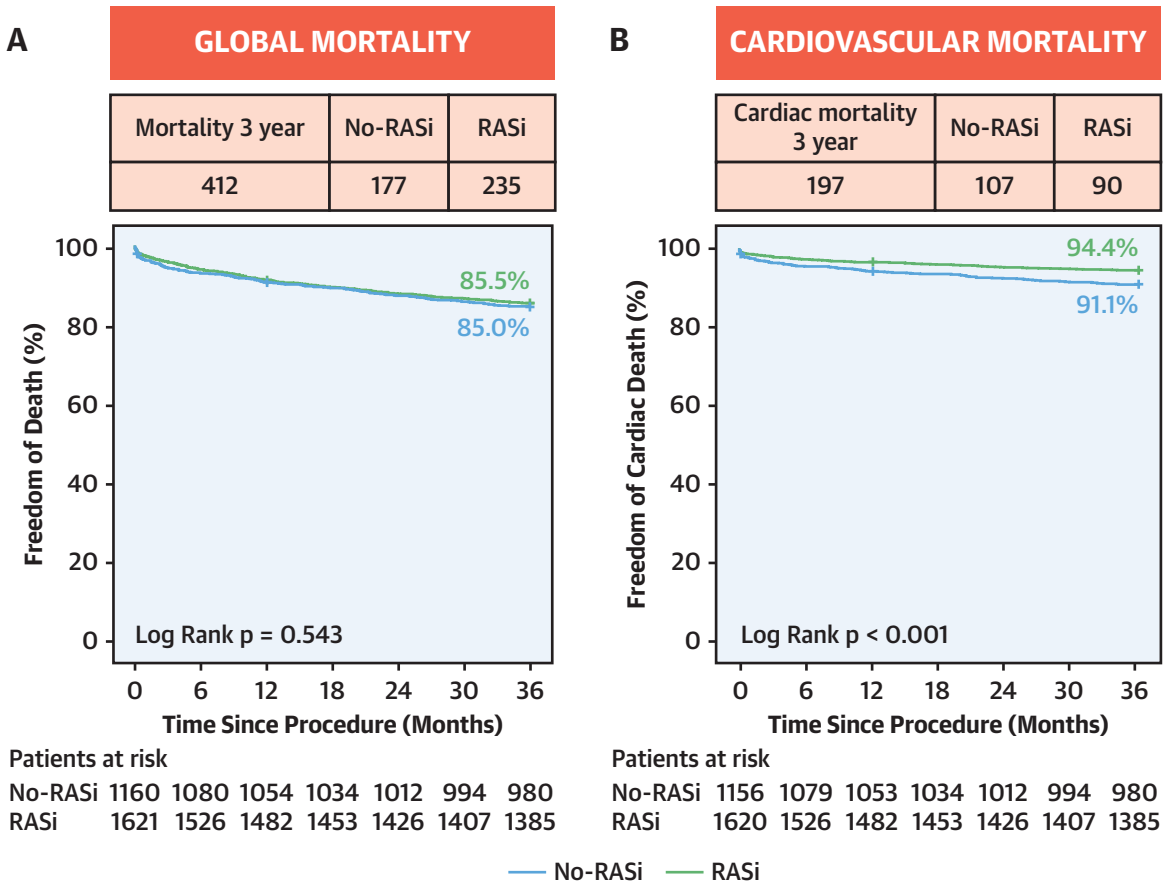
CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive coronary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RAS = renin-angiotensin system; SVR = surgical valve replacement; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TIA = transient ischemic attack.

3.5%; p = 0.003). Similar findings persisted at 3-year follow-up, with no differences in global mortality (14.5% vs. 15.3% in patients taking and not taking RAS inhibitors, respectively; p = 0.577) but higher cardiovascular mortality in those not treated with RAS inhibitors (9.3% vs. 5.6%; p < 0.001). Unadjusted Kaplan-Meier curves for global and cardiovascular mortality in the global and matched populations are shown in **Figure 1**.

The main findings regarding global and cardiovascular mortality in the matched population were comparable with those in the global population, as shown in **Figure 2**. Furthermore, at follow-up the rate of complications such as cerebrovascular events and readmissions was higher among patients not taking RAS inhibitors compared with those taking RAS inhibitors in the global and matched populations (**Table 2**).

PREDICTORS OF MORTALITY. The factors associated with cardiovascular and global mortality in the matched population are summarized in **Table 3** and Online Table 2, respectively. In a multivariate analysis, the use of RAS inhibitors at discharge following successful TAVR was the only independent protective factor against cardiovascular death (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.41 to 0.87; p = 0.007) whereas prior PCI (HR: 1.98; 95% CI: 1.35 to 2.91; p < 0.001), chronic obstructive pulmonary

FIGURE 1 Kaplan-Meier Estimates of Mortality in the Total Population at 3-Year Follow-Up



(A) Global mortality. **(B)** Cardiovascular mortality. RASi = renin-angiotensin system inhibitors.

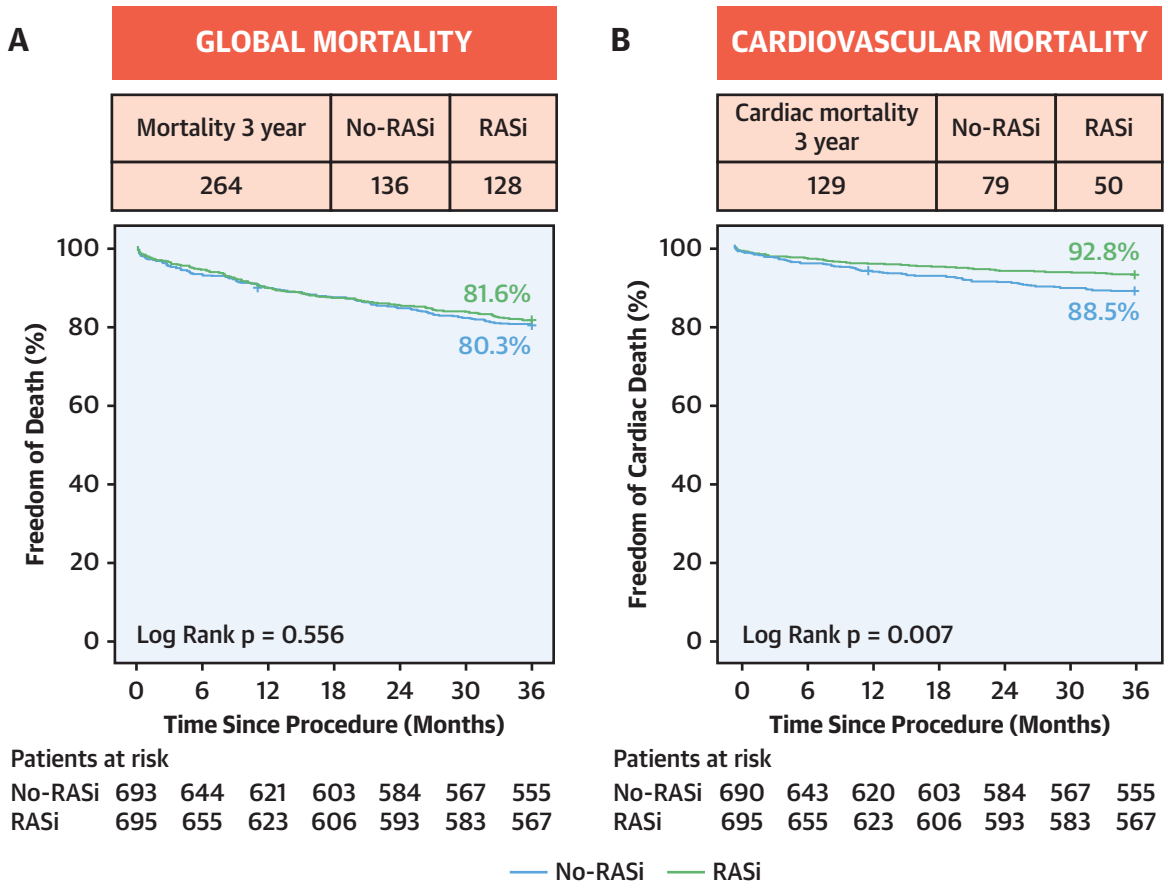
disease (HR: 1.49; 95% CI: 1.01 to 2.21; p = 0.049), advanced New York Heart Association class (HR: 1.82; 95% CI: 1.13 to 2.91; p = 0.013), post-TAVR cerebrovascular events (HR: 5.29; 95% CI: 2.87 to 9.72; p < 0.001), and moderate or severe aortic regurgitation (HR: 3.77; 95% CI: 1.73 to 8.21; p = 0.001) were associated with an increased risk for cardiovascular mortality in the matched population.

ECHOCARDIOGRAPHIC CHANGES AT FOLLOW-UP. At 3-year follow-up, 85.5% of the patients underwent echocardiographic assessment. Main changes in the echocardiographic parameters from baseline to 3-year follow-up are summarized in Table 4. In both groups, the global and matched populations, patients taking RAS inhibitors exhibited larger decrease in end-diastolic and end-systolic volumes and larger regression of septal hypertrophy compared with patients without RAS inhibitors (p < 0.001 for all). The differences in these parameters at baseline, discharge, and follow-up according to the use of RAS inhibitors in the matched population are depicted in Figure 3.

DISCUSSION

Myocardial hypertrophy and fibrosis are a final common pathway of AS that conditions the prognosis. Although TAVR is the preferred strategy in the subgroup of patients of more advanced age or those who have already developed LV dysfunction, currently the systematic use of medications that might prevent or reverse myocardial hypertrophy and fibrosis, such as RAS inhibitors, is not recommended after TAVR. Moreover, concerns regarding the risk for hypotension or renal function decline might discourage its use. The present registry represents an effort to clarify this controversial indication of RAS inhibitors

FIGURE 2 Kaplan-Meier Estimates of Mortality in the Matched Population at 3-Year Follow-Up



(A) Global mortality. **(B)** Cardiovascular mortality. RASi = renin-angiotensin system inhibitors.

and shed light on the mechanisms of their potential benefit. The main findings of this study are as follows: 1) RAS inhibition following TAVR did not affect short- and mid-term all-cause mortality but was independently associated with lower rate of cardiovascular mortality; 2) patients taking RAS inhibitors at discharge presented at mid-term follow-up more important reductions in LV volumes and hypertrophy as assessed using echocardiography; and 3) although myocardial fibrosis was not assessed, reverse

TABLE 2 Main Outcomes at 3-Year Follow-Up According to the Prescription of Renin-Angiotensin System Inhibitors at Discharge in the Global and Matched Study Populations

	Global Population			Matched Population		
	RAS Inhibitors (n = 1,622)	No RAS Inhibitors (n = 1,163)	p Value	RAS Inhibitors (n = 695)	No RAS Inhibitors (n = 695)	p Value
New-onset atrial fibrillation	352/1,129 (31.2)	177/803 (22.0)	<0.001	113/485 (23.2)	156/487 (32.0)	0.002
Cerebrovascular events	28/1,624 (1.7)	75/1,163 (6.4)	<0.001	10/695 (1.4)	41/695 (5.9)	<0.001
Readmission	317/792 (40.0)	182/339 (53.7)	<0.001	163/381 (42.8)	160/308 (51.9)	0.017
NYHA functional class III or IV	96/748 (12.8)	53/596 (8.9)	0.022	50/363 (13.8)	40/398 (10.1)	0.112
All-cause mortality	235/1,622 (14.5)	177/1,161 (15.2)	0.541	128/695 (18.4)	136/695 (19.6)	0.567
Cardiovascular mortality	90/1,622 (5.5)	107/1,158 (9.2)	<0.001	50/695 (7.2)	79/695 (11.3)	0.006

Values are n/N (%).
Abbreviations as in Table 1.

remodeling was related to reductions in atrial fibrillation, cerebrovascular events, and rate of readmissions (**Central Illustration**).

LV hypertrophy and myocardial fibrosis are key processes associated with AS. Everett et al. (6) found that cellular hypertrophy and myocardial fibrosis progress exponentially as AS severity advances, even in asymptomatic patients. After stenosis relief, a proportion of cellular hypertrophy and diffuse interstitial fibrosis reverse; in contrast, focal replacement fibrosis evaluated using late gadolinium enhancement did not show any reduction and seems to be irreversible even after 1 year of valve replacement (6,14,15). These studies emphasized the fact that AS involves not only the valve but also the myocardium, and therefore treatment strategies should also target the myocardial disease. Myocardial fibrosis occurs in response to various stimuli, including angiotensin II (10,16) that induces fibroblast activation, proliferation, and an excessive collagen production, leading to its accumulation in the extracellular matrix, hence causing myocardial fibrosis (10,17). Although myocardial fibrosis is increasingly considered an important cardiovascular therapeutic target in alternative scenarios, no standardized therapy has been proposed following TAVR.

The clinical profile of the patients included in this study shows that currently, patients treated with RAS inhibitors after TAVR are at higher cardiovascular risk. After adjustment for baseline differences, RAS inhibition shows a clear benefit in terms of cardiovascular mortality, cerebrovascular events rate, New York Heart Association functional class, and number of readmissions. These advantages of RAS inhibitors appeared in short-term (1-year) but also in mid-term (3-year) follow-up, strongly supporting that the positive effects of RAS inhibitors, such as reverse hypertrophy, are a long-standing process. Our findings are in agreement with those of a recent landmark analysis by Inohara et al. (18) including 21,312 Medicare patients that revealed, in short-term follow-up, lower risk for mortality and lower risk for heart failure in patients receiving prescriptions for RAS inhibitors at hospital discharge. With a longer follow-up period of 2 years, Ochiai et al. (19) also demonstrated, in a cohort of 560 patients who underwent TAVR, lower mortality among patients treated with RAS inhibition. In addition to former investigations, our findings also depict a positive effect in the remodeling of the left ventricle, with a comparative improvement in volumes and hypertrophy that can be induced by angiotensin II inhibition through fibroblast phenotypic alteration, cardiac fibroblast apoptosis, and reduction in blood pressure, among other

TABLE 3 Predictors of Cardiovascular Mortality at 3-Year Follow-Up in the Matched Study Population

	Univariate		Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	0.99 (0.97–1.02)	0.522		
Sex	1.33 (0.94–1.87)	0.111		
Hypertension	1.78 (1.08–2.93)	0.023		
CAD	1.49 (1.06–2.12)	0.022		
Previous PCI	1.85 (1.29–2.65)	0.001	1.98 (1.35–2.91)	<0.001
CKD	1.69 (1.20–2.40)	0.003		
COPD	1.63 (1.13–2.35)	0.009	1.49 (1.01–2.21)	0.049
Prior CABG	1.67 (1.00–2.79)	0.048		
Peripheral vascular disease	1.63 (1.05–2.51)	0.029		
Prior stroke/TIA	1.65 (1.06–2.58)	0.026		
Baseline NYHA functional class III or IV	2.19 (1.41–3.41)	0.001	1.82 (1.13–2.91)	0.013
Major bleeding	1.87 (1.07–3.26)	0.027		
Post-TAVR cerebrovascular events	5.28 (2.97–9.38)	<0.001	5.29 (2.87–9.72)	<0.001
NOAF	2.31 (1.42–4.31)	0.008		
Post-TAVR aortic regurgitation moderate or greater	3.18 (1.49–6.83)	0.003	3.77 (1.73–8.21)	0.001
Use of RAS inhibitors at discharge	0.62 (0.43–0.89)	0.008	0.59 (0.41–0.87)	0.007

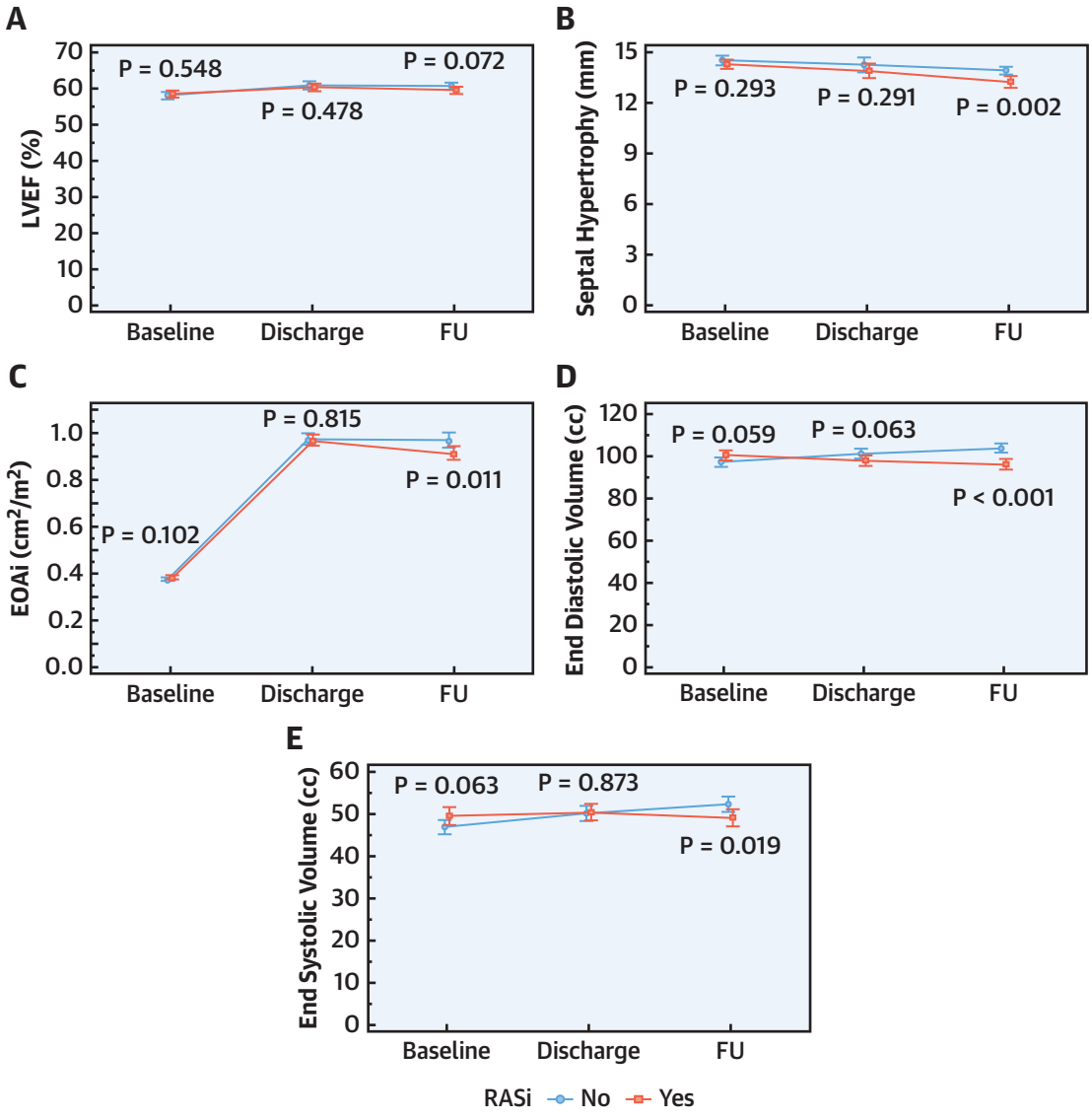
CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; NOAF = new-onset atrial fibrillation; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

TABLE 4 Changes in Echocardiographic Parameters From Baseline to Follow-Up According to the Use of Renin-Angiotensin System Inhibitors in the Global and Matched Study Populations

	Global Population			Matched Population		
	RAS Inhibitors (n = 1,622)	No RAS Inhibitors (n = 1,163)	p Value	RAS Inhibitors (n = 695)	No RAS Inhibitors (n = 695)	p Value
Δ Left ventricular ejection fraction, %	0 (−5 to 8.8)	0 (−5.8 to 9)	0.782	0 (−5 to 9)	2 (−5 to 10)	0.076
Δ Aortic valve area, cm^2	0.91 (0.6 to 1.26)	1.0 (0.73 to 1.3)	0.005	0.90 (0.6 to 1.2)	1.0 (0.73 to 1.3)	0.008
Δ Mean transaortic gradient, mm Hg	−36 (−46 to −28)	−37 (−48 to −29)	0.026	−36.8 (−47 to −28)	−37 (−48 to −29)	0.264
Δ End-diastolic volume, ml	−10 (−10 to 6)	4 (4 to 11)	<0.001	−10 (−10 to 6)	4 (4 to 11)	<0.001
Δ End-systolic volume, ml	1 (1 to 4)	3 (3 to 8)	<0.001	1 (1 to 4)	4 (3 to 8)	<0.001
Δ Septal hypertrophy, mm	−3 (−3 to −1)	0 (0 to 0)	<0.001	−3 (−3 to 0)	0 (0 to 1)	<0.001

Values are mean (95% confidence interval).
RAS = renin-angiotensin system.

FIGURE 3 **Changes in Echocardiographic Parameters From Baseline to Follow-Up According to the Use of Renin-Angiotensin Inhibitors in the Matched Study Populations**

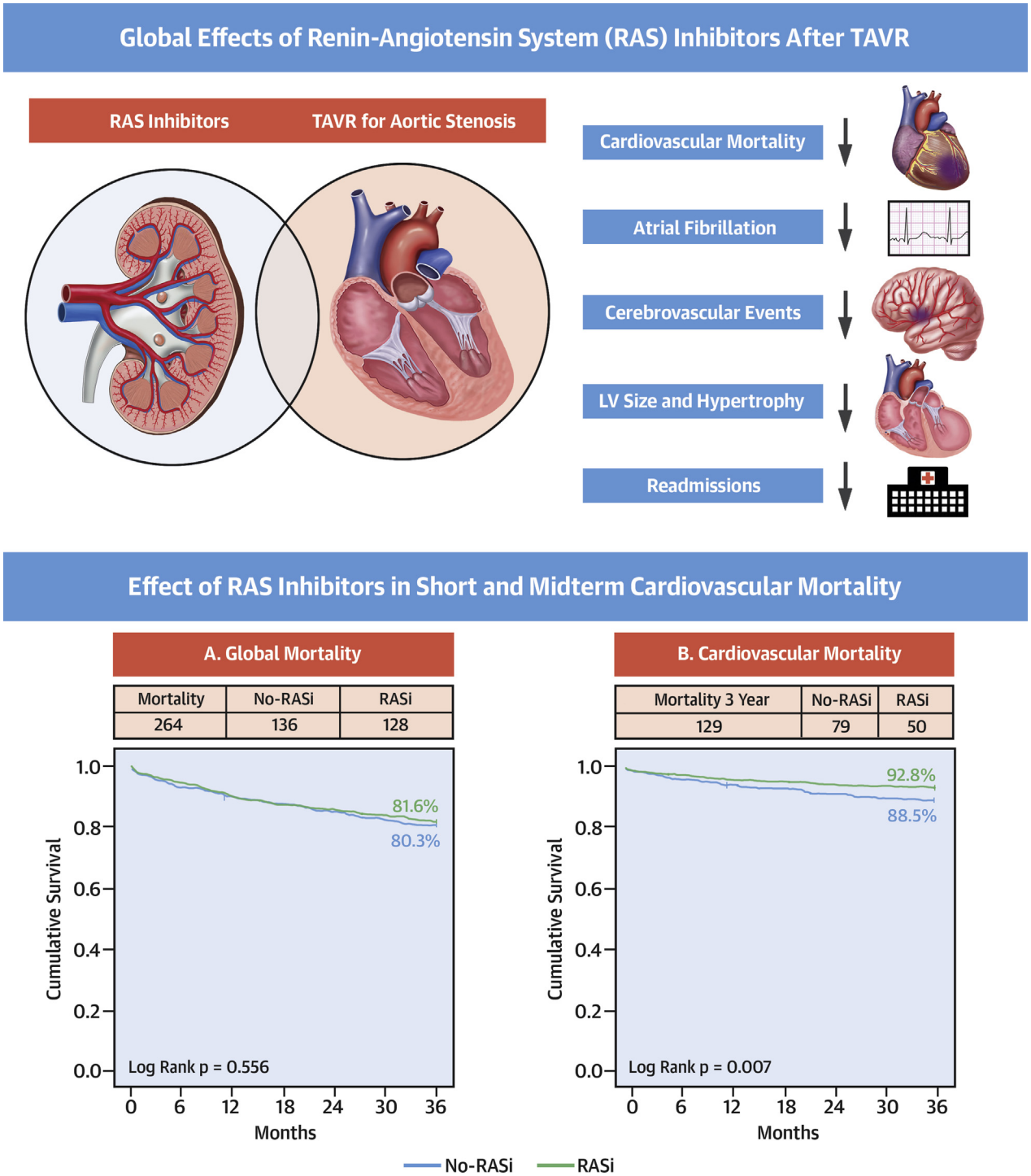


(A) Left ventricular ejection fraction (LVEF). **(B)** Septal hypertrophy. **(C)** Indexed effective orifice area (EOAi). **(D)** End-diastolic volume. **(E)** End-systolic volume. **Circles** are means, and **error bars** indicate SE. FU = follow-up; RASi = renin-angiotensin system inhibitors.

mechanisms (10). Various experimental models (20-23) have previously confirmed that RAS inhibitors reduce myocardial fibrosis (24,25), but this aspect is still under investigation in TAVR patients (26). One controversial aspect is the differential effect that alternative medications acting on the renin-angiotensin-aldosterone system might have; the subgroup analysis of our data did not show relevant differences in outcomes according to the administration of one or another drug, but, as shown in Online Figure 2, newer therapies as sacubitril are probably underrepresented in our research.

Scarce data on the echocardiographic effect of RAS inhibitors after TAVR exist. In our study, the serial echocardiographic evaluation showed an improvement in several parameters after valve replacement in both cohorts. The reduction of the LV volumes, as well as the reduction of septal width, translate the

CENTRAL ILLUSTRATION **Effects of Renin-Angiotensin System Inhibitors After Transcatheter Aortic Valve Replacement**



Rodriguez-Gabella, T. et al. J Am Coll Cardiol. 2019;74(5):631–41.

The **top panel** summarizes the cardiovascular effects driven by renin-angiotensin system (RAS) inhibitors, and the **bottom panel** includes the survival curves at 3-year follow-up for the matched population according to the use of RAS inhibitors. LV = left ventricular; RASi = renin-angiotensin system inhibitors; TAVR = transcatheter aortic valve replacement.

reverse LV remodeling expected following the afterload decrease due to the stenosis relief. However, after 3 years of follow-up, patients taking RAS inhibitors demonstrated greater reverse remodeling, with statistically lower LV volumes and smaller septal hypertrophy, compared with patients not taking RAS inhibitors at discharge.

Although the aforementioned registries (18,19) suggest a benefit of RAS blockade at 1 year, they do not give information on longer follow-up, nor do they shed light on the putative mechanistic explanations for that favorable effect. Our RASTAVI registry supports a double mechanism of RAS blockade after TAVR: 1) it bears a global protective effect, or, stated differently, it stabilizes or even reduces the cardiovascular global risk, as suggested by a decrease in new-onset atrial fibrillation, recently shown to affect mortality (27), cerebrovascular events, and readmissions; and 2) it was associated with a direct favorable effect on ventricular remodeling, as seen by the LV volumes reduction at 3 years. Whether this reverse remodeling includes a reduction in fibrosis could not be assessed in this work, because magnetic resonance imaging is lacking in most patients.

STUDY LIMITATIONS. Several limitations of the present study warrant consideration. This study was a retrospective analysis of prospectively collected data. Although statistical adjustment according to baseline differences was performed, selection bias remains possible. Although each participating center assessed frailty during patient's evaluation before the TAVR procedure, there are no standardized frailty criteria. Therefore, the impact of frailty among both groups of patients was unknown, and its confounding effect might explain why age was not an independent predictor of mortality. Complete data on patients' treatment adherence to RAS inhibitors beyond the first year of follow-up could not be assessed, because these data were not recorded in the registry. Finally, we evaluated the mid-term effect of RAS inhibitors prescribed from discharge; however, a considerable proportion of the patients who did not receive this treatment after discharge had received it previously. The degree and direction of the effect that this might have had is not fully understood.

CONCLUSIONS

RAS inhibitors following TAVR were associated with a lower rate of cardiac mortality at short- and mid-term follow-up, with global cardiovascular protective effects (lower rate of cerebrovascular events) irrespective of the baseline differences. The improved clinical outcomes in patients taking RAS inhibitors might, at least in part, be mediated by a LV positive remodeling. RASTAVI, an ongoing randomized controlled trial (NCT03201185), will help to corroborate these hypothesis-generating findings.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Inhibition of the renin-angiotensin-aldosterone system after TAVR is associated with favorable effect on ventricular remodeling, reducing LV volume, atrial fibrillation, cerebrovascular events, hospital readmission, and cardiovascular mortality over 3 years.

TRANSLATIONAL OUTLOOK: Further studies should clarify the mechanisms by which RAS inhibition improves cardiovascular outcomes in patients who have undergone TAVR and whether this differs in patients undergoing surgical valve replacement.

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KEY WORDS fibrosis, hypertrophy, RAS inhibitors, TAVR

APPENDIX For supplemental tables and figures, please see the online version of this paper.