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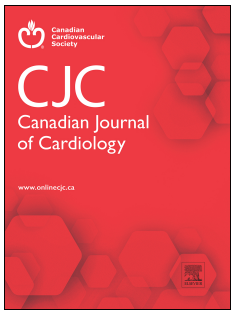

Renin-Angiotensin System Inhibition and Cardiac Damage in Patients Undergoing Transcatheter Aortic Valve Replacement

Daijiro Tomii, MD, Taishi Okuno, MD, Masaaki Nakase, MD, Fabien Praz, MD, Stefan Stortecky, MD, MPH, David Reineke, MD, Stephan Windecker, MD, Jonas Lanz, MD, MSc, Thomas Pilgrim, MD, MSc

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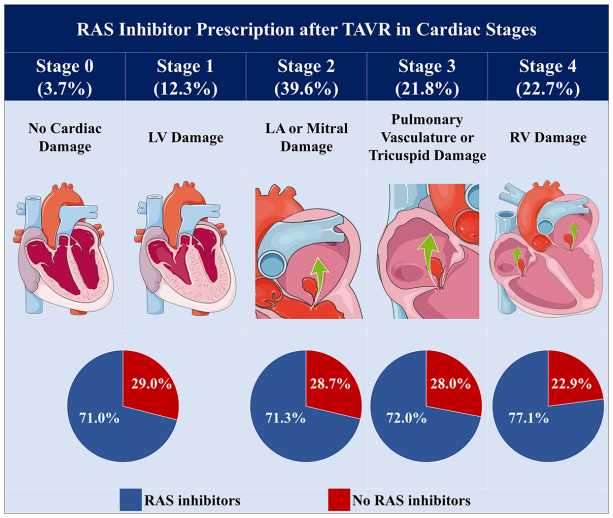

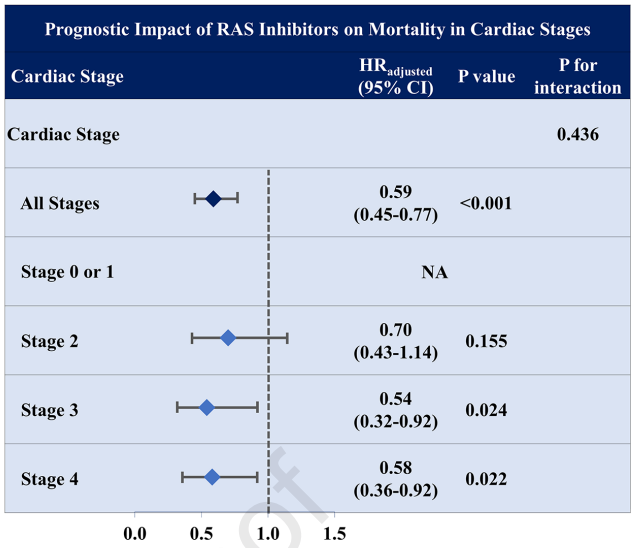

Renin-Angiotensin System Inhibition and Cardiac Damage in Patients Undergoing Transcatheter Aortic Valve Replacement

Daijiro Tomii, MD[a]; Taishi Okuno, MD[a]; Masaaki Nakase, MD[a]; Fabien Praz, MD[a]; Stefan Stortecky, MD[a], MPH; David Reineke, MD[b]; Stephan Windecker, MD[a]; Jonas Lanz, MD, MSc[a#]; Thomas Pilgrim, MD, MSc[a#]

[a]Department of Cardiology, Inselspital, University of Bern, Bern, Switzerland;
[b]Department of Cardiac Surgery, Inselspital, University of Bern, Bern, Switzerland
#Dr. Pilgrim and Dr. Lanz contributed equally to this work and are joint last authors.

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Twitter handle: Thomas Pilgrim (@ThomPilgrim), Daijiro Tomii (@DaijiroTomii)

Corresponding Author:
Thomas Pilgrim, MD, MSc
Department of Cardiology
Inselspital
Bern University Hospital
CH-3010 Bern
Phone: 0041 31 632 21 11
Fax: 0041 31 632 47 70
Mail: thomas.pilgrim@insel.ch

Abstract

Background: The optimal medical treatment strategy after transcatheter aortic valve replacement (TAVR) has not been established, and may be impacted by the extent of extra-valvular cardiac damage. We aimed to investigate the prognostic effect of renin-angiotensin system (RAS) inhibitors in TAVR patients stratified by the extent of extra-valvular cardiac damage.

Methods: In a prospective TAVR registry, patients were retrospectively evaluated for baseline cardiac damage and classified into five stages of cardiac damage (0-4) according to established criteria. Clinical outcomes at 1 year were compared according to RAS inhibitor prescription at discharge.

Results: Among 2,247 eligible patients undergoing TAVR between August 2007 and June 2021, 1,634 (72.7%) were prescribed RAS inhibitors at discharge. Eighty-three patients (3.7%) were classified as Stage 0, 276 (12.3%) as Stage 1, 889 (39.6%) as Stage 2, 489 (21.8%) as Stage 3, and 510 (22.7%) as Stage 4. RAS inhibitor prescription after TAVR was associated with a reduced risk of 1-year mortality ($HR_{adjusted}$ 0.59, 95% CI 0.45–0.77). The protective effect was accentuated among patients with cardiac stage 3 and 4 ($HR_{adjusted}$ 0.54, 95% CI 0.32–0.92 and $HR_{adjusted}$ 0.58, 95% CI 0.36–0.92, respectively), but not statistically significant in stages 2 ($HR_{adjusted}$ 0.70, 95% CI 0.43–1.14).

Conclusions: In patients undergoing TAVR, we found a strong association of RAS inhibitor prescription and improved clinical outcome in the overall population, and there were no signs of heterogeneity across stages of cardiac damage.

Clinical Trial Registration: https://www.clinicaltrials.gov. NCT01368250.

Keywords: Aortic stenosis, cardiac damage staging classification, renin-angiotensin system inhibitors, transcatheter aortic valve replacement

Abbreviations

AS = aortic stenosis

RAS = renin-angiotensin system

TAVR = transcatheter aortic valve replacement

Introduction

Aortic stenosis (AS) is a progressive disease that causes chronic pressure overload. Current guidelines recommend the timing of aortic valve replacement (AVR) based mainly on valve-related factors and symptoms(1,2). However, recent evidence suggests that extra-aortic valve cardiac remodeling is an important determinant of prognosis in patients with AS. Consequently, there is growing interest to improve patient management and therapeutic decision-making by focusing on extra-valvular damage(3). An integrated staging system to quantify the extent of cardiac damage associated with AS has shown that advanced cardiac stages are strongly associated with an increased risk of adverse events after AVR, irrespective of treatment modality(4). Although the prognostic implications of the staging system have been validated in several independent cohorts(5,6), the optimal medical management after AVR in patients with AS related advanced cardiac damage remains unclear.

Renin-angiotensin system (RAS) inhibition is an established medical therapy that attenuates myocardial hypertrophy and fibrosis, improving outcomes in patients with heart failure and coronary artery disease(7). Observational and registry data support the use of RAS inhibitors after AVR in patients with severe AS(8-12); however, there is limited data on the association between RAS inhibitor prescription and clinical outcome in AS patients with advanced cardiac damage. Therefore,

the present study aimed to investigate the prognostic effect of RAS inhibitors according to the extent of cardiac damage in AS patients undergoing transcatheter aortic valve replacement (TAVR).

Methods

Study design and population

Between August 2007 and June 2021, consecutive patients with severe symptomatic AS who underwent TAVR at Bern University Hospital (Bern, Switzerland) were enrolled into an institutional prospective registry, which forms part of the nationwide SwissTAVI registry (registered at clinicaltrials.gov with NCT01368250)(13) and were considered eligible for the present analysis. For the purpose of this study, patients with inadequate information to assess cardiac stage, missing data on RAS inhibitor prescription at discharge after TAVR, patients underwent TAVR for pure aortic regurgitation, or patients with in-hospital death were excluded. The registry was approved by the Bern cantonal ethics committee (SwissTAVI Kantonale Ethikkommission number 2021-01738), and patients provided written informed consent for participation.

Cardiac damage staging classification and prescription of RAS inhibitors

Patients were categorized into the following 5 stages according to the proposed classification (**Figure 1**)(4): Stage 0—no cardiac damage; Stage 1—left ventricular (LV) damage (LV ejection fraction [LVEF] <50%, LV mass index >95 g/m^2 for women, >115 g/m^2 for men, or E/e' ≥14); Stage 2—left atrium (LA) or mitral valve damage (LA volume index [LAVI] >34 mL/m^2, moderate or severe mitral regurgitation, or presence of atrial fibrillation [AF]); Stage 3—pulmonary vasculature or tricuspid valve damage (pulmonary systolic artery pressure (PASP) ≥60 mmHg, or moderate or severe tricuspid regurgitation); Stage 4—right ventricular (RV) damage (the presence of RV dysfunction). RV dysfunction was documented in the presence of at least one of the following parameters: tricuspid annular plane systolic excursion (TAPSE) <1.7 cm, S' <9.5 cm/s and fractional area change (FAC) <35%(14). If more than two parameters were available and discrepant, RV dysfunction was defined by prioritizing in the order of TAPSE, S' and FAC(15). Patients were hierarchically classified into the most advanced cardiac damage stage if at least one of the criteria was met within that stage(6). Comprehensive transthoracic echocardiography using Philips iE33 equipment (Philips Healthcare, Andover, Massachusetts) was performed by a board-certified cardiologist and an echocardiography specialist at baseline in accordance to the current guidelines(16,17). We also assessed cardiac damage at 1 year in patients for whom 1-year echocardiography was available. Acquired images were transferred to a dedicated workstation

(Syngo Dynamics Workplace version 9.5) and re-evaluated by independent, experienced imaging specialists blinded to clinical outcome in the Corelab(14).

Patients were stratified according to the prescription of RAS inhibitors, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or angiotensin receptor-neprilysin inhibitors, at the time of discharge after TAVR.

Data collection and clinical endpoints

All baseline clinical, procedural, and follow-up data were prospectively recorded in a dedicated database, held at the Clinical Trials Unit of the University of Bern. Clinical follow-up data at 1 year after TAVR were obtained by standardised interviews, documentation from referring physicians, and hospital discharge summaries as previously described(18). All adverse events were systematically collected and adjudicated by a dedicated clinical event committee on the basis of the Valve Academic Research Consortium (VARC) criteria applicable at the time of the procedure(19-21). The outcomes of interest in the present study was the evaluation of clinical outcomes at 1 year after TAVR according to the prescription of RAS inhibitors and extent of cardiac damage.

Statistical analysis

Categorical data are represented as frequencies and percentages, and the differences between groups were evaluated with the chi-square test or Fisher's exact test. Continuous variables are

presented as mean ± standard deviation (SD) and were compared between groups using Student's t-test. Cumulative time-to-event curves were constructed using the Kaplan-Meier method. Multivariable cox proportional hazards models were used to calculate adjusted hazard ratios ($HR_{adjusted}$) and 95% confidence intervals (CI) for the clinical outcomes. Multivariable adjustment was performed with predefined baseline variables and in-hospital outcomes potentially related to prescription of RAS inhibitors and clinical outcomes, including age, sex, body mass index (BMI), Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), diabetes, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), anemia, peripheral artery disease, aortic valve area, impaired LV systolic function (LVEF ≤40%), prescription of beta-blockers and statins at discharge, discharge site, and in-hospital complications (cerebrovascular events, major or life-threatening bleeding, and acute kidney injury). All statistical tests were 2-sided and *p*-values of <0.05 were considered significant. Statistical analyses were performed using R for Windows 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population and baseline characteristics

Among 3,245 consecutive patients who underwent TAVR between August 2007 and June 2021, 2,247 patients met the inclusion criteria (**Figure 2**). At baseline, 83 patients (3.7%) were classified as Stage 0, 276 (12.3%) as Stage 1, 889 (39.6%) as Stage 2, 489 (21.8%) as Stage 3, and 510 (22.7%) as Stage 4. The specific components of cardiac damage for patients in each stage at baseline are summarized in **Table 1**. Among 2,247 patients, 1,289 (57.4%) were on RAS inhibitor therapy prior to TAVR, and 1,634 (72.7%) were prescribed RAS inhibitors at discharge (73.5% [N = 1,201] had a continued prescription and 26.5% [n = 433] had a new prescription): 255 (71.0%) in Stage 0 or 1, 634 (71.3%) in Stage 2, 352 (72.0%) in Stage 3, and 393 (77.1%) in Stage 4 (**Figure 1**).

Table 2 shows baseline characteristics according to RAS inhibitor prescription and cardiac stages. In the overall cohort, patients with RAS inhibitors had a higher prevalence of hypertension (79.4% vs. 90.0%; P <0.001), diabetes (28.2% vs. 23.8%, P = 0.038), coronary artery disease (51.9% vs. 62.2%; P <0.001), history of myocardial infarction (10.9% vs. 16.6%; P = 0.001) and history of cardiac surgery (11.1% vs. 15.9%; P = 0.005) compared with those without RAS inhibitors. Systolic blood pressure, diabetes, CKD, anemia, and hypoalbuminemia were comparable between groups. Patients on RAS inhibitors had a lower mean aortic valve gradient (38.7 ± 16.6 mmHg vs. 40.3 ± 17.1 mmHg; P = 0.039) and LVEF (53.4 ± 14.2% vs. 56.7 ± 12.3 mmHg; P <0.001), and a higher prevalence of impaired LVEF (≤40%) (17.2% vs. 9.7%; P <0.001) at baseline. Beta-blockers, statins,

and diuretics for fluid retention were more frequently prescribed at discharge in patients with RAS inhibitors than in those without RAS inhibitors (60.5% vs. 54.0%; P = 0.006, 62.9% vs. 53.2%; P <0.001, and 68.6% vs. 58.9%; P <0.001, respectively). When comparing the prescription of RAS inhibitors in each cardiac stage, patients on RAS inhibitors had a higher prevalence of cardiovascular risk factors compared to those not on RAS inhibitors (hypertension: 89.8% vs. 68.3%, P <0.001 in Stage 0 or 1; 90.4% vs. 80.8%, P <0.001 in Stage 2; 91.2% vs. 83.2%, P = 0.016 in Stage 3, coronary artery disease: 59.6% vs. 46.2%, P = 0.026 in Stage 0 or 1; 61.0% vs. 50.0%, P = 0.013 in Stage 2).

In-hospital outcomes

In-hospital outcomes are shown in **Table 3**. Patients with prescribed RAS inhibitors had a shorter total hospital length of stay compared with those without RAS inhibitor prescription (8.2 ± 3.9 days vs. 8.7 ± 6.3 days, P = 0.029) while length of stay after TAVR was comparable between groups. Compared to patients without RAS inhibitor prescription, patients with RAS inhibitor prescription were more frequently discharged to home more frequently (31.1% vs. 26.2%). Cerebrovascular events, major or life-threatening bleeding, and acute kidney injury were less frequently observed in patients on RAS inhibitors (2.8% vs. 5.7%, P = 0.001, 12.7% vs. 16.5%, P = 0.023, and 4.5% vs. 7.8%, P = 0.002).

Changes in cardiac damage after TAVR

Evaluation of cardiac damage at 1 year after TAVR was available in 478 patients (24.0% of the alive patients). In the analysis, improvements in cardiac damage in patients with baseline stage 1-4 were observed in 26.0% of patients (N = 87) with RAS inhibitors and 24.4% of patients (N = 30) without RAS inhibitors at discharge (P = 0.809).

Clinical outcomes

Clinical outcomes at 1 year after TAVR are summarized in **Table 4** and **Supplemental Table S1** and **S2**. There was a stepwise increase in all-cause and cardiovascular mortality rates at 1 year according to increasing stages of cardiac damage, and advanced cardiac damage was associated with a progressively increasing risk of all-cause mortality compared with cardiac stage 0 or 1 (**Supplemental Table S1** and **Supplemental Figure S1**).

Table 4 summarizes clinical outcomes at 1 year after TAVR stratified by RAS inhibitor prescription and cardiac stage. In the entire cohort, patients with RAS inhibitor prescription at discharge had a reduced risk of all-cause and cardiovascular death compared with those without ($HR_{adjusted}$ 0.59, 95% CI 0.45–0.77, P <0.001 and $HR_{adjusted}$ 0.58, 95% CI 0.41–0.82, P = 0.002, respectively) (**Supplemental Figure S2**). There was no significant interaction between the protective effect of RAS inhibitors on mortality and cardiac damage stage (p for interaction = 0.436). When patients were stratified according to the extent of cardiac damage and prescription of RAS inhibitors,

all-cause death occurred less frequently in patients with versus without RAS inhibitors; 3.1% vs. 7.7% in Stage 0 or 1, 7.4% vs. 12.2% in Stage 2, 10.8% vs. 20.4% in Stage 3, and 16.5% vs. 28.2% in Stage 4, respectively After adjustment, the use of RAS inhibitors after TAVR was associated with a reduced risk of all-cause death in patients in cardiac stage 3 and 4 ($HR_{adjusted}$ 0.54, 95% CI 0.32–0.92 and $HR_{adjusted}$ 0.58, 95% CI 0.36–0.92, respectively), while the risk of all-cause death in patients with RAS inhibitors in the group of cardiac stage 2 was not statistically reduced compared to those without RAS inhibitors ($HR_{adjusted}$ 0.70, 95% CI 0.43–1.14) (**Figure 3**). There was no significant difference in residual heart failure symptoms (NYHA III or IV) between patients with and without RAS inhibitors at each cardiac stage.

Sensitivity analysis

It was anticipated that patients with serious complications would be unlikely to be prescribed RAS inhibitors after TAVR. To account for the potential cofounder, we performed a sensitivity analysis including only patients with technical success (N = 1,955). In the analysis, the protective effect of RAS inhibitors on mortality was consistent with the overall population without a significant interaction between the protective effect of RAS inhibitors on mortality and cardiac stage ($HR_{adjusted}$ 0.59, 95% CI 0.45–0.79, p for interaction = 0.802) (**Supplemental Table S2** and **Supplemental Figure S2**).

Discussion

The salient findings of this study are as follows: 1) in a prospective TAVR registry, 20-30% of patients with severe AS were not prescribed RAS inhibitors even after TAVR regardless of the extent of cardiac damage; and 2) prescription of RAS inhibitors was associated with a reduced risk of 1-year mortality after TAVR, with an accentuated protective effect in patients with advanced stages of cardiac damage.

Several independent registries have validated the staging classification and have shown that baseline cardiac damage has substantial prognostic implications in patients with severe AS who undergo TAVR(5,6). Consistent with these findings, patients with advanced cardiac damage had a worse prognosis in the present analysis. Despite the usefulness of the staging system for risk stratification, there has yet to be an established post-AVR management strategy based on the classification of cardiac damage. RAS blocker therapy after AVR is associated with a relative risk reduction in mortality(8-12), and current guidelines recommend the prescription of RAS inhibitors in patients with severe AS treated by TAVR (Class 2b, Level of Evidence: B-NR)(1). Although previous studies have evaluated the protective effect in various patient subgroups, they mainly focused on atherosclerotic comorbidities(8,10,11). To our knowledge, this is the first study to

investigate the effect of RAS inhibitors in patients with severe AS according to the extent of extra-aortic valvular damage. In the present study, we found that the prescription of RAS inhibitors was associated with a reduced risk of mortality in patients with extra-valvular cardiac damage. These findings suggest that prescribing RAS inhibitors after intervention based on the assessment of baseline cardiac stage may have a protective effect in patients undergoing TAVR. Of note, the accentuated effect of RAS inhibitors was observed within the first 60 days. Previous studies in various populations, including heart failure, myocardial infarction, and TAVR, have suggested that the protective effect of RAS inhibitors on cardiovascular outcomes occurs early and persists through long-term follow-up(8,22-24). These findings support the early initiation of RAS inhibitors after TAVR.

Intriguingly, more than 20% of patients undergoing TAVR were not prescribed RAS inhibitors after the procedure, which is consistent with previous TAVR studies(8,9,12,25). This considerable undertreatment of TAVR patients with RAS inhibitors across different reports may reflect the high prevalence of elderly patients in these studies. The Euro Heart Failure Survey II reported that patients aged ≥80 years were less commonly prescribed heart failure medications than those <80 years of age(26). The high prevalence of comorbidities, frailty, aversion toward polypharmacy, less specialist care, and social circumstances may complicate adherence to heart

failure medications in an elderly population(27). Therefore, the observation of an accentuated effect of RAS inhibitors in the present analysis may be biased by the presence of a residual confounder. In order to minimize confounding potentially associated with prescription of RAS inhibitors after TAVR, we adjusted for discharge status and in-hospital complications and performed a sensitivity analysis considering only patients with procedural success. Nevertheless, the protective effect of RAS inhibitors remained consistent. A tailored approach, including a careful assessment of patient status and identification of the tolerability of RAS inhibitors, continues to be key in this population.

Chronic pressure overload due to AS causes various degrees of anatomical and functional remodeling of the myocardium, ultimately leading to extra-valvular damage. Although relief of pressure overload by AVR has been shown to improve remodeling, persistent pressure overload may cause advanced myocardial damage in some patients, at which point cardiac damage may not improve even after treatment of AS(28). RAS inhibitors attenuate the residual cellular hypertrophy and myocardial fibrosis and favorably influence the prognosis of patients with severe AS undergoing TAVR. Indeed, previous studies have reported that patients on RAS inhibitors had a greater reduction in LV end-diastolic and end-systolic volumes and a more significant regression of LV hypertrophy after TAVR compared with patients without RAS inhibitors and that regression of left ventricular mass occurs as early as 30 days after TAVR(9,10,25,29). Although there was no

interaction of the protective effect of RAS inhibitors on mortality as a function of cardiac damage in the present study, the prescription of RAS inhibitors was not associated with a reduced risk of mortality in patients with early cardiac damage. One possible reason for the non-significant finding is the low event rate in patients with early cardiac stages in the present analysis. Indeed, mortality at 1 year in patients with cardiac stage 0 or 1 was only 4.5%. Despite the beneficial effects on reverse remodeling and the favorable effect on mortality with RAS inhibitors, only 20% of patients in the present analysis improved cardiac stage at 1 year after TAVR, and there was no difference in the improvement between patients with and without RAS inhibitors. These findings suggest that irreversible myocardial damage is established at the time of intervention and is not ameliorated even by the combination of TAVI and RAS blockade therapy. In the analysis of the PARTNER 2 and 3 trials, more than 80% of cardiac damage remained pathological or even worsened after AVR, and lack of improvement in cardiac stage at 1 year after AVR was significantly associated with adverse events at 2 years after AVR(28). Further studies are warranted to evaluate the long-term safety and efficacy of RAS inhibitors in TAVR patients with extra-valvular cardiac damage, to investigate the optimal medical management after TAVR, and to determine the clinical benefit of early intervention in patients with AS (RASTAVI [NCT03201185], PROGRESS [NCT04889872], and EXPAND TAVI [NCT05149755]).

It should be noted that the prescription of RAS inhibitors may not improve functional outcomes in patients with severe AS undergoing TAVR. The STS/ACC TVT registry demonstrated that patients with RAS inhibitors after TAVR had statistically greater improvement in Kansas City Cardiomyopathy Questionnaire score compared to those without RAS inhibitor, while the effect size did not reach the minimal clinically important difference of 5 points(8). Similarly, in the present study, the prevalence of residual worse functional status (NYHA III or IV) was comparable between patients with and without RAS inhibitors. Survival alone does not fully reflect the treatment goal of TAVR, particularly in elderly patients, for whom improvement in quality of life may be just as important as prognostic considerations(21). The pooled analysis of the PARTNER 2 and 3 trials showed that patients with extra-aortic valve damage had a poor health status at 1 year after AVR(30). Consistent with previous studies, a non-negligible proportion of stage 2-4 patients in the present study still had advanced heart failure symptoms (NYHA III or IV) after TAVR. In order to prevent the development of advanced cardiac damage, timely intervention, identification and treatment of cardiac comorbidities (concomitant valvular disease, amyloidosis, and arrhythmias), as well as the use of guideline directed medical heart failure therapy may be a key to obtain an optimal benefit from AVR(31-33).

Study Limitations

The results of our study should be interpreted in light of several limitations. First, more than 20% of the patients were excluded because of inadequate echocardiographic quality for the assessment of cardiac damage and lack of information on RAS inhibitor prescription after TAVR, which may have introduced a degree of selection bias. In return, we provide comprehensive data on more than 2,200 patients with granular assessment of cardiac stage from a large prospective registry with high data quality standards, and independent event adjudication. Second, information on dose and adherence of RAS inhibitors during follow-up was unknown. High doses of RAS inhibitors provide more beneficial effects, and nonadherence to medication may lead to suboptimal effects of RAS inhibitors(12). In addition, we did not have information on the reasons why RAS inhibitors were or were not prescribed. Patients who were not expected to benefit from RAS inhibitors because of their short life expectancy, comorbidity, frailty, or intolerance may have been included in the present analysis. Therefore, the results of the present analysis may overestimate the protective effect of RAS inhibitors because healthier patients may be more likely to receive RAS inhibitors. Third, the present cohort included predominantly octogenarians, and the results may not be generalizable to younger patients with less comorbidities and longer life expectancy. Fourth, the number of patients with echocardiography at 1 year was modest; therefore, the assessment of changes in cardiac damage according to RAS inhibitor prescription must be interpreted with caution. Given the difficulty of

serial follow-up echocardiography in elderly population, the follow-up echocardiography may be performed more frequently in patients with unstable conditions (e.g., decompensated heart failure). Finally, since this was a retrospective analysis based on a prospective registry, the possibility of residual confounding cannot be excluded despite rigorous statistical techniques. Our findings need to be validated in other TAVR cohorts.

Conclusion

In patients undergoing TAVR, we found a strong association of RAS inhibitor prescription and improved clinical outcome in the overall population, and there were no signs of heterogeneity across stages of cardiac damage.

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Patient consent for publication:

The authors confirm that a patient consent form(s) has been obtained for this article.

Ethics approval:

This study involves human participants and was approved by Bern Cantonal Ethics Committee (SwissTAVI Kantonale Ethikkommission number 2021-01738). The study was conducted in compliance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Data availability:

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure 1. Renin-angiotensin system inhibition and cardiac damage in patients undergoing TAVR

Aortic stenosis staging classification based on the extent of cardiac damage and prescription rate of RAS inhibitors in patients undergoing TAVR.

LA = left atrium; LV = left ventricular; RAS = renin-angiotensin system; RV = right ventricular; TAVR = transcatheter aortic valve replacement.

Figure 2. Study flowchart

RAS = renin-angiotensin system; TAVR = transcatheter aortic valve replacement.

Figure 3. Kaplan-Meier curves for all-cause mortality according to RAS inhibitor in each cardiac stage

$HR_{adjusted}$ = adjusted hazard ratio; RASI = renin-angiotensin system inhibitor; TAVR = transcatheter aortic valve replacement.

14 **Table 1. Prevalence of cardiac stages and its individual components**

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	All patients	**No RASI**	**RASI**
	N = 2247	**N = 613**	**N = 1634**
Stage 0			
Stage 1	83 (3.7)	27 (4.4)	56 (3.4)
Increased left ventricular mass index	276 (12.3)	77 (12.6)	199 (12.2)
E/e' >14	1353/1814 (74.6)	347/486 (71.4)	1006/1328 (75.8)
Left ventricular ejection fraction <50%	792/1184 (66.9)	191/309 (61.8)	601/875 (68.7)
Stage 2	609/2240 (27.2)	123/610 (20.2)	486/1630 (29.8)
Atrial fibrillation	889 (39.6)	255 (41.6)	634 (38.8)
Left atrium volume index >34 ml/m2	825/2247 (36.7)	233/613 (38.0)	592/1634 (36.2)
Moderate or severe mitral regurgitation	1371/1954 (70.2)	368/527 (69.8)	1003/1427 (70.3)
Stage 3	510/2218 (23.0)	138/555 (22.7)	372/1609 (23.1)
Pulmonary artery systolic pressure ≥60 mmHg	489 (21.8)	137 (22.3)	352 (21.5)
Moderate or severe tricuspid regurgitation	441/2097 (21.0)	121/567 (21.3)	320/1530 (20.9)

Stage 4	394/1611 (17.7)	109/609 (17.9)	285/1611 (17.7)
Right ventricular dysfunction	510 (22.7)	117 (19.1)	393 (24.1)

Values are n/N (%).

*left ventricular mass index >95 g/m^2 for women and >115 g/m^2 for men.

RASI = renin-angiotensin system inhibitor.

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17 **Table 2. Baseline characteristics**

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	Entire cohort			Stage 0 or 1			Stage 2			Stage 3			Stage 4		
	No RASI N = 613	**RASI N = 1,634**	**P value**	**No RASI N = 104**	**RASI N = 255**	**P value**	**No RASI N = 255**	**RASI N = 634**	**P value**	**No RASI N = 137**	**RASI N = 352**	**P value**	**No RASI N = 117**	**RASI N = 393**	**P value**
Age, years	81.9 ± 6.9	81.8 ± 6.2	0.646	79.8 ± 8.0	80.4 ± 5.5	0.385	82.3 ± 5.9	82.2 ± 5.8	0.827	83.5 ± 6.0	82.9 ± 6.1	0.269	81.2 ± 8.1	81.1 ± 7.1	0.875
Female, n (%)	318 (51.9)	786 (48.1)	0.118	56 (53.8)	130 (51.0)	0.643	128 (50.2)	292 (46.1)	0.266	86 (62.8)	218 (61.9)	0.917	48 (41.0)	146 (37.2)	0.45
Body mass index, kg/m^2	26.2 ± 5.5	26.7 ± 5.2	0.025	26.1 ± 5.8	26.9 ± 5.2	0.20	26.3 ± 5.1	27.1 ± 5.2	0.053	26.4 ± 5.4	26.6 ± 5.2	0.745	25.5 ± 6.2	26.1 ± 5.1	0.272
STS-PROM, %	5.4 ± 4.1	5.3 ± 3.8	0.672	3.9 ± 2.7	4.0 ± 2.4	0.873	5.3 ± 4.6	4.9 ± 3.2	0.11	6.1 ± 3.7	6.0 ± 4.4	0.823	6.3 ± 4.0	6.4 ± 4.6	0.704
NYHA III or IV, n (%)	414 (67.5)	1127 (69.1)	0.507	55 (52.9)	149 (58.4)	0.349	164 (64.3)	410 (64.8)	0.938	100 (73.0)	262 (74.4)	0.732	95 (81.2)	306 (78.1)	0.521
Systolic blood pressure, mmHg	120.2 ± 24.1	122.0 ± 26.6	0.199	126.5 ± 26.0	127.3 ± 26.9	0.813	123.2 ± 25.0	123.3 ± 27.2	0.971	116.6 ± 22.4	121.5 ± 24.5	0.085	111.6 ± 18.9	117.0 ± 26.4	0.076
Comorbidities															
Hypertension, n (%)	487 (79.4)	1470 (90.0)	<0.001	71 (68.3)	229 (89.8)	<0.001	206 (80.8)	573 (90.4)	<0.001	114 (83.2)	321 (91.2)	0.016	96 (82.1)	347 (88.3)	0.087
Diabetes, n (%)	146 (23.8)	461 (28.2)	0.038	21 (20.2)	73 (28.6)	0.113	50 (19.6)	168 (26.5)	0.031	34 (24.8)	95 (27.0)	0.65	41 (35.0)	125 (31.8)	0.574

CKD (eGFR <60 mL/min/1.73 m^2), n (%)	436 (71.4)	1109 (68.0)	0.125	62 (59.6)	145 (56.9)	0.64	171 (67.3)	416 (65.7)	0.695	109 (79.6)	263 (74.7)	0.289	94 (81.0)	285 (72.7)	0.089
Coronary artery disease, n (%)	318 (51.9)	1016 (62.2)	<0.001	48 (46.2)	152 (59.6)	0.026	127 (49.8)	384 (60.6)	0.003	72 (52.6)	203 (57.7)	0.312	71 (60.7)	277 (70.5)	0.054
COPD, n (%)	68 (11.1)	199 (12.2)	0.51	7 (6.7)	30 (11.8)	0.183	24 (9.4)	65 (10.3)	0.805	14 (10.2)	47 (13.4)	0.366	23 (19.7)	57 (14.5)	0.194
Anemia, n (%)	399 (65.1)	1074 (65.7)	0.803	68 (65.4)	157 (61.6)	0.548	158 (62.0)	419 (66.1)	0.245	89 (65.0)	228 (64.8)	1.00	84 (71.8)	270 (68.7)	0.569
Hypoalbuminemia, n (%)	257/448 (57.4)	615/1156 (53.2)	0.146	42/81 (51.9)	85/193 (44.0)	0.288	101/196 (51.5)	239/474 (50.4)	0.80	52/94 (55.3)	138/237 (58.2)	0.712	62/77 (80.5)	153/252 (60.7)	0.002
Past medical history															
History of myocardial infarction, n (%)	67 (10.9)	271 (16.6)	0.001	7 (6.7)	29 (11.4)	0.245	27 (10.6)	94 (14.8)	0.105	15 (10.9)	53 (15.1)	0.308	18 (15.4)	95 (24.2)	0.057
History of cardiac surgery, n (%)	68 (11.1)	259 (15.9)	0.005	9 (8.7)	23 (9.0)	1.00	13 (5.1)	87 (13.7)	<0.001	13 (9.5)	32 (9.1)	0.863	33 (28.2)	117 (29.8)	0.817
Peripheral artery disease, n (%)	72 (11.7)	241 (14.7)	0.075	9 (8.7)	33 (12.9)	0.283	25 (9.8)	88 (13.9)	0.119	21 (15.3)	49 (13.9)	0.669	17 (14.5)	71 (18.1)	0.406
Previous pacemaker	55 (9.0)	140 (8.6)	0.801	1 (1.0)	9 (3.5)	0.292	21 (8.2)	47 (7.4)	0.677	18 (13.1)	32 (9.1)	0.187	15 (12.8)	52 (13.2)	1.00

implantation, n (%)														
Echocardiography														
Aortic valve area, cm^2	0.73 ± 0.24	0.75 ± 0.24	0.125	0.75 ± 0.21	0.76 ± 0.21	0.68	0.74 ± 0.25	0.76 ± 0.22	0.40	0.70 ± 0.25	0.73 ± 0.24	0.293	0.73 ± 0.23	0.75 ± 0.29	0.457
Mean gradient, mmHg	40.3 ± 17.1	38.7 ± 16.6	0.039	42.2 ± 15.1	40.5 ± 14.8	0.324	42.0 ± 16.9	39.3 ± 16.5	0.027	40.7 ± 18.7	41.2 ± 18.0	0.79	34.4 ± 16.1	34.2 ± 16.0	0.916
LVEF, %	56.6 ± 12.3	53.4 ± 14.2	<0.001	61.0 ± 7.9	59.8 ± 9.7	0.231	59.0 ± 11.5	55.9 ± 12.3	0.001	55.9 ± 11.5	54.2 ± 13.4	0.203	48.4 ± 13.9	44.5 ± 15.9	0.019
LVEF <40%, n (%)	59 (9.7)	271 (17.2)	<0.001	2 (1.9)	14 (5.5)	0.167	18 (7.1)	71 (11.2)	0.065	13 (9.6)	49 (14.0)	0.226	26 (22.2)	147 (37.5)	0.003
Medication at discharge														
ACE inhibitor, n (%)	0	1039 (63.6)	-	0	150 (58.8)	-	0	388 (61.2)	-	0	238 (67.6)	-	0	263 (66.9)	-
ARB, n (%)	0	589 (38.0)	-	0	105 (43.4)	-	0	249 (40.7)	-	0	113 (34.7)	-	0	122 (32.8)	-
ARNI, n (%)	0	17 (2.6)	-	0	1 (1.1)	-	0	4 (1.5)	-	0	2 (1.4)	-	0	10 (6.3)	-
ßeta blocker, n (%)	331 (54.0)	988 (60.5)	0.006	37 (35.6)	130 (51.0)	0.01	136 (53.3)	367 (57.9)	0.232	84 (61.3)	213 (60.5)	0.918	74 (63.2)	278 (70.7)	0.139
Statin, n (%)	326 (53.2)	1028 (62.9)	<0.001	64 (61.5)	169 (66.3)	0.396	143 (56.1)	398 (62.8)	0.068	68 (49.6)	200 (56.8)	0.158	51 (43.6)	261 (66.4)	<0.001
Diuretics, n (%)	361 (58.9)	1121 (68.6)	<0.001	35 (33.7)	142 (55.7)	<0.001	142 (55.7)	421 (66.4)	0.003	93 (67.9)	242 (68.8)	0.914	91 (77.8)	316 (80.4)	0.515
Values are mean ± SD or n (%).															

ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitors; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RASI = renin-angiotensin system inhibitor; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

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Table 3. In-hospital outcomes according to RAS inhibitor prescription in each cardiac stage

	Entire cohort			Stage 0 or 1			Stage 2			Stage 3			Stage 4		
	No RASI N = 613	**RASI N = 1,634**	**P value**	**No RASI N = 79**	**RASI N = 210**	**P value**	**No RASI N = 180**	**RASI N = 454**	**P value**	**No RASI N = 103**	**RASI N = 278**	**P value**	**No RASI N = 125**	**RASI N = 426**	**P value**
Total length of hospital stay, days	8.7 ± 6.3	8.2 ± 3.9	0.029	7.6 ± 3.4	7.5 ± 3.3	0.874	8.7 ± 7.3	7.9 ± 3.7	0.027	8.9 ± 5.6	8.5 ± 3.9	0.378	9.2 ± 6.5	8.7 ± 4.7	0.401
Length of hospital stay after TAVR, days	6.3 ± 5.5	6.1 ± 3.2	0.201	5.8 ± 2.6	5.7 ± 3.0	0.759	6.4 ± 6.8	6.0 ± 3.0	0.158	6.47 ± 4.1	6.2 ± 3.0	0.615	6.4 ± 5.5	6.3 ± 3.6	0.894
Discharge location, n (%)															
Home	158 (26.2)	500 (31.1)	0.04	29 (27.9)	81 (32.3)	0.653	69 (27.5)	208 (33.1)	0.155	33 (4.6)	95 (27.5)	0.184	27 (23.9)	116 (30.2)	0.388
Rehabilitation facility	432 (71.8)	1089 (67.7)		74 (71.2)	166 (66.1)		177 (70.5)	413 (65.8)		96 (71.6)	247 (71.4)		85 (75.2)	263 (68.5)	
Other	12 (2.0)	20 (1.2)		1 (1.0)	4 (1.6)		5 (2.0)	7 (1.1)		5 (3.7)	4 (1.2)		1 (0.9)	5 (1.3)	
In-hospital complications															
Cerebrovascular events, n (%)	35 (5.7)	45 (2.8)	0.001	6 (5.8)	4 (1.6)	0.038	12 (4.7)	20 (3.2)	0.319	9 (6.6)	12 (3.4)	0.138	8 (6.8)	9 (2.3)	0.034

Major or life-threatening bleeding, n (%)	101 (16.5)	207 (12.7)	0.023	12 (11.5)	25 (9.8)	0.702	41 (16.1)	77 (12.1)	0.126	30 (21.9)	45 (12.8)	0.017	18 (15.4)	60 (15.3)	1
Acute kidney injury, n (%)	48 (7.8)	73 (4.5)	0.002	5 (4.8)	5 (2.0)	0.161	19 (7.5)	26 (4.1)	0.044	13 (9.5)	18 (5.1)	0.097	11 (9.4)	24 (6.1)	0.216
Values are mean ± SD or n (%). RASI = renin-angiotensin system inhibitor; TAVR = transcatheter aortic valve replacement.															

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Table 4. Clinical outcomes according to RAS inhibitor prescription in each cardiac stage

	Entire cohort				Stage 0 or 1				Stage 2				Stage 3				Stage 4			
	No RASI	RASI	RASI vs. No RASI		No RASI	RASI	RASI vs. No RASI		No RASI	RASI	RASI vs. No RASI		No RASI	RASI	RASI vs. No RASI		No RASI	RASI	RASI vs. No RASI	
	N = 613	N = 1,634	$HR_{adjusted}$ (95% CI)	Adjusted P value	N = 104	N = 255	$HR_{adjusted}$ (95% CI)	Adjusted P value	N = 255	N = 634	$HR_{adjusted}$ (95% CI)	Adjusted P value	N = 137	N = 352	$HR_{adjusted}$ (95% CI)	Adjusted P value	N = 117	N = 393	$HR_{adjusted}$ (95% CI)	Adjusted P value
At 1 year																				
All-cause death, n (%)	100 (16.3)	158 (9.7)	0.59 (0.45-0.77)	<0.001	8 (7.7)	8 (3.1)	NA	NA	31 (12.2)	47 (7.4)	0.70 (0.43-1.14)	0.155	28 (20.4)	38 (10.8)	0.54 (0.32-0.92)	0.024	33 (28.2)	65 (16.5)	0.58 (0.36-0.92)	0.022
Cardiovascular death, n (%)	63 (10.3)	96 (5.9)	0.58 (0.41-0.82)	0.002	2 (1.9)	3 (1.2)	NA	NA	19 (7.5)	28 (4.4)	0.69 (0.36-1.30)	0.257	16 (11.7)	24 (6.8)	0.58 (0.29-1.17)	0.128	26 (22.2)	41 (10.4)	0.45 (0.26-0.78)	0.005
NYHA III or IV, n (%)*	66 (13.3)	156 (11.0)	0.82 (0.59-1.15)	0.255	11 (11.8)	19 (7.9)	0.48 (0.18-1.26)	0.137	20 (9.1)	57 (10.1)	1.17 (0.65-2.11)	0.599	18 (17.3)	34 (11.5)	0.77 (0.36-1.65)	0.496	17 (21.2)	46 (14.8)	0.64 (0.3-1.28)	0.209

Values are n (%), unless otherwise indicated. *Described risk ratios (95% CIs) from robustified Poisson regression are reported, with corresponding P values.

CI = confidence interval; $HR_{adjusted}$ = adjusted hazard ratio; NYHA = New York Heart Association; RASI = renin-angiotensin system inhibitor.