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Renin–angiotensin system inhibition after surgical aortic valve replacement for aortic stenosis

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ABSTRACT

Objective The optimal medical therapy after surgical aortic valve replacement (SAVR) for aortic stenosis remains unknown. Renin–angiotensin system (RAS) inhibitors could potentially improve cardiac remodelling and clinical outcomes after SAVR.

Methods All patients undergoing SAVR due to aortic stenosis in Sweden 2006–2020 and surviving 6 months after surgery were included. The primary outcome was major adverse cardiovascular events (MACEs; all-cause mortality, stroke or myocardial infarction). Secondary endpoints included the individual components of MACE and cardiovascular mortality. Time-updated adjusted Cox regression models were used to compare patients with and without RAS inhibitors. Subgroup analyses were performed, as well as a comparison between angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Results A total of 11 894 patients (mean age, 69.5 years, 40.4% women) were included. Median follow-up time was 5.4 (2.7–8.5) years. At baseline, 53.6% of patients were dispensed RAS inhibitors, this proportion remained stable during follow-up. RAS inhibition was associated with a lower risk of MACE (adjusted hazard ratio (aHR) 0.87 (95% CI 0.81 to 0.93), p<0.001), mainly driven by a lower risk of all-cause death (aHR 0.79 (0.73 to 0.86), p<0.001). The lower MACE risk was consistent in all subgroups except for those with mechanical prostheses (aHR 1.07 (0.84 to 1.37), p for interaction=0.040). Both treatment with ACE inhibitors (aHR 0.89 (95% CI 0.82 to 0.97)) and ARBs (0.87 (0.81 to 0.93)) were associated with lower risk of MACE.

Conclusion The results of this study suggest that medical therapy with an RAS inhibitor after SAVR is associated with a 13% lower risk of MACE and a 21% lower risk of all-cause death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with severe aortic stenosis planned for surgical aortic valve replacement (SAVR) commonly suffer from the effects of cardiac remodelling due to strain caused by the valvular disease. Renin–angiotensin system (RAS) inhibition could potentially have positive effects on the cardiac remodelling after surgery.

WHAT THIS STUDY ADDS

⇒ This study shows an association between treatment with RAS inhibitors and improved outcomes after SAVR. Randomised controlled trials are necessary to establish a causal relationship.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides estimates that could be used to plan for a randomised controlled trial for RAS inhibitors after SAVR, to establish causality.

INTRODUCTION

The long-term prognosis for patients with severe, symptomatic valvular aortic stenosis (AS) is dismal.[1–3] The only curative treatment is aortic valve replacement (AVR), which can be achieved either by surgical aortic valve replacement (SAVR) or transcatheter intervention (TAVI).[4 5] Despite substantial life expectancy, little focus has been placed on optimising medical therapy after intervention.[6 7]

Renin–angiotensin system (RAS) inhibitors include both angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs), which have similar properties. RAS inhibitors is a well-established treatment for heart failure with reduced ejection fraction and hypertension.[8 9] RAS inhibitors improve cardiac remodelling, reduce afterload and improve left ventricular ejection fraction (LVEF), which all may be advantageous after SAVR.[10–12] RAS inhibitors have been shown to be associated with improved outcome after TAVI,[13] but there are no large long-term studies after SAVR, except a recent study where associations between different secondary prevention medications and mortality were investigated.[14] In that study, an association between RAS inhibition and lower all-cause mortality was observed. In the current study, partly based on the same patient cohort, we aimed to evaluate if there is an association between RAS inhibition and major adverse cardiovascular events (MACEs) after SAVR, if there are subgroups of SAVR patients with more noticeable associations for any of the endpoints and if potential associations with long-term outcomes differ between ACE inhibitors and ARBs.

METHODS

Data sources

The study population was collected from the Swedish Cardiac Surgery Registry which is a part of the SWEDEHEART Registry.[15 16] All patients who had undergone cardiac surgery in Sweden

since 1992 are included in this registry, which has full coverage since the start of the study period. The registry contains information on the details of the surgery performed, comorbid conditions of note and preoperative patient characteristics. All Swedish inhabitants receive a unique identification number at time of birth or immigrations, and after pseudonymisation, this unique identification number was used to link data from the Swedish Cardiac Surgery Registry to three other national registries, the Swedish Prescribed Drug Register, the National Patient Register and the Cause of Death Register.[17 18] These registries also have full coverage and excellent validity for cardiovascular diseases.[17 18] Financial reimbursement to the hospitals is based on reporting to these registries. Dispensed medications were extracted from the Swedish Prescribed Drug Register; the data were based on the Anatomical Therapeutic Classification (ATC). The National Patient Register and the Cause of Death Register used the International Classification of Disease version 10 (ICD-10) codes during the study period. ATC and ICD-10 codes used in the current study are listed in online supplemental table 1, only diagnoses requiring hospitalisation were considered for all endpoints, for details see online supplemental table 1.

The manuscript was written in accordance with the recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19]

Study population

All patients in Sweden who underwent SAVR due to valvular AS between January 2006 and December 2020 were initially included. Exclusion criteria included concomitant coronary artery bypass grafting, other valve intervention, aortic surgery or endocarditis. Follow-up started at 6 months after discharge date since early postoperative events are most often related to the surgery and is thus unlikely to be affected by secondary medical therapy. Patients who emigrated later during follow-up contributed to follow-up time until their emigration at which time they were censored. Follow-up was complete for dispensed medication and events during the study period.

In Sweden, chronic medications are usually prescribed in 3-month intervals. Individual patient's medication status was therefore updated every third month as previously described.[20] In short, patients who were not dispensed medication during two consecutive 3-month periods were considered off treatment and patients with a dispensed medication during the current 3-month interval were considered on treatment. Patients were considered on treatment based only on medications dispensed at a pharmacy. A sensitivity analysis to compare the interruption of dispense of ACE inhibitors and ARBs was performed. In this analysis, a 3-month interval with dispensed treatment followed by an interruption of dispense the following 3-months interval was considered as end of treatment. Estimations of the glomerular filtration rate (eGFR) was based on the algorithm proposed by the Chronic Kidney Disease Epidemiology Collaboration formula.[21]

Statistical analysis

Continuous variables are presented as means with SD or medians with IQR depending on their distribution. Categorical variables are presented as numbers and frequency (percentage). Statistical comparison between baseline characteristics was evaluated using Student's t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables and χ^2 test for categorical variables. Crude incidence rates were calculated by dividing the number of events by follow-up years; associated 95% CIs were calculated assuming a Poisson distribution. Dispense of medication was illustrated with line plots per operation year and per year after follow-up. These dispense charts illustrate the dispense during the first 6 months after surgery stratified per year of surgery and the first 3 months each follow-up year, respectively.

Time-updated Cox proportional hazards models were used to calculate adjusted hazard ratios (aHRs) with 95% CI for associations between treatment with RAS inhibitors and MACE. The primary outcome was MACE, defined as a composite of all-cause mortality, myocardial infarction (MI) or stroke. Secondary outcome was the individual components of MACE and cardiovascular mortality. Adjustments were decided on prior to the analyses phase of the study based on prior studies. The model was adjusted for age, sex, previous MI, hypertension, diabetes, heart failure, hyperlipidaemia, kidney function, LVEF, type of prosthesis, year of surgery and ongoing treatment with RAS inhibitors, beta-blockers and statins. Missing data were handled as a separate category in the statistical analyses based on the assumption that the data was missing at random. The proportional hazards assumption was tested using scaled Schoenfeld residuals. The model did not meet the assumption, and therefore robust standard errors were used to account for the invalid hazard proportionality.[22] Variance inflation factor was used to assess collinearity in the model.

Several clinically relevant subgroup analyses were decided on a priori. These included sex, age (</≥75 years), diabetes, heart failure, previous MI, previous stroke, LVEF (</≥ 50%) and hypertension. Formal interaction analyses were performed to evaluate differences between the subgroups. Heart failure includes both patients with preserved and reduced LVEF. ACE inhibitors and ARBs were analysed separately as secondary analyses. Furthermore, the use of RAS inhibitors within 3 months before surgery was explored in a sensitivity analysis using the same adjustments as the main analysis. As RAS inhibitors are highly correlated to certain comorbid conditions, these conditions (heart failure, hypertension and MI) were also included as time-updated variables in the analysis of the primary and secondary outcomes as a sensitivity analysis. As an additional sensitivity analysis, both primary and secondary outcomes were evaluated using propensity score matching to limit the influence of potential confounding factors and to select appropriate controls. The same variables as described above were used in the propensity score with time-updated use of medications, heart failure, hypertension and MI. Logistic regression was used to predict the use of RAS inhibitors and patients were matched 1:1 using nearest-neighbour matching with a calliper of 0.1. Matching was evaluated using standardised difference for each variable.

All tests were two-tailed and interpreted at the 0.05 significance level. All analyses were performed using R V.4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patients and public involvement

The current study did not have any patient involvement.

Ethics and data sharing statement

The study was approved by the Swedish Ethical Review Authority. The need for individual patient consent was waived by the committee. The study was performed in accordance with the Declaration of Helsinki. The data underlying this article were provided by national healthcare registries in Sweden and SWEDEHEART. Data will be shared on reasonable request to

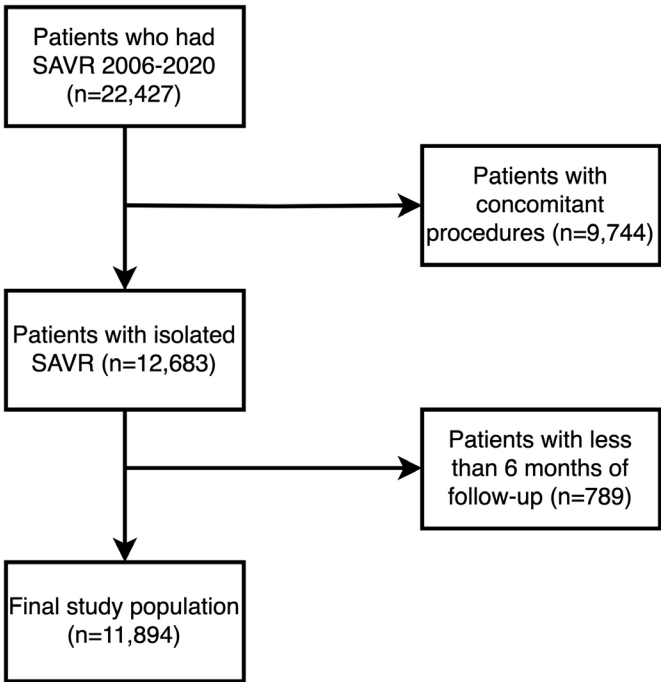

Figure 1 Flow-chart of excluded patients to arrive at final study population. SAVR, surgical aortic valve replacement.

the corresponding author if permission can be obtained from SWEDEHEART and the Swedish National Board of Health and Welfare.

RESULTS

General

A total of 22427 adult patients were eligible for inclusion. Of these, 9744 had other concomitant procedures and 789 had less than 6 months of follow-up. After exclusions, 11894 patients were included in the analysis. The exclusions are illustrated in figure 1. The median follow-up time was 5.4 (IQR 2.7–8.5) years.

Baseline characteristics

Mean age (SD) at the time of operation was 69.5 (11.1) years and 6377 (53.6%) of patients were dispensed RAS inhibitors at baseline. Patients on RAS inhibitor treatment at baseline were more frequently men and had more comorbid conditions, as shown in table 1. The most substantial differences between baseline characteristics for patients with or without RAS inhibitors were low LVEF, heart failure, hypertension and diabetes. Patients on RAS inhibitors were also to a higher degree dispensed statins and beta-blockers. The dispense of RAS inhibitors remained stable during follow-up, with similar proportions of patients being dispensed ACE inhibitors and ARBs (figure 2). There was an increase in dispense of ARBs after surgery in later years (figure 3). Patients ended their treatment with ACE inhibitors more frequently than with ARBs, 15.1% per person-year compared with 10.4% per person-year (p<0.001), respectively. Three variables had missing data, LVEF (n=46, 0.4%), BMI (n=308, 2.6%) and type of prosthesis (n=34, 0.3%). All other data used for adjustment were complete.

Major adverse cardiovascular event

The crude MACE event rate was 6.4 (6.2–6.7) per 100 person-years for patients treated with RAS inhibitors at baseline, while patients without RAS inhibitors had a crude MACE event rate of 5.3 (5.0–5.5) per 100 person-years (online supplemental table 2). There were marginally higher crude event rates for secondary endpoints for patients on RAS inhibitors.

Ongoing treatment with RAS inhibitors were in the adjusted analyses associated with a lower risk of MACE (aHR 0.87 (95% CI 0.81 to 0.93, p<0.001) as shown in figure 4. The association remained robust in most subgroups, patients with heart failure and diabetes had a stronger association than patients without these conditions, but patients without heart failure and diabetes still had a significant association with lower risk of MACE. Patients who had mechanical prostheses implanted did not have the same association with lower risk of adverse outcomes as patients with biological prostheses (p for interaction=0.040). No included variables had a variance inflation factor above 2.0, thus collinearity was considered non-significant in the model.

Table 1 Baseline characteristics

	Patients on RAS inhibitors at baseline (n=6377)	Patients not on RAS inhibitors at baseline (n=5517)	P values
Age (years)	70.7 (SD 9.7)	68.0 (SD 12.3)	<0.001
Female (%)	2439 (38.2%)	2372 (43.0%)	<0.001
Left ventricular ejection fraction <50%	1665 (26.1%)	675 (12.2%)	<0.001
BMI	27.4 (IQR 21.1–33.7)	26.3 (IQR 20.8–31.8)	<0.001
eGFR	74.7 (SD 28.9)	79.9 (SD 29.6)	<0.001
Previous MI	610 (9.6%)	337 (6.1%)	<0.001
Atrial fibrillation	3021 (47.4%)	2121 (38.4%)	<0.001
Heart failure	1014 (15.9%)	287 (5.2%)	<0.001
Diabetes	1588 (24.9%)	596 (10.8%)	<0.001
Renal failure	391 (6.1%)	263 (4.8%)	0.001
Previous stroke	259 (4.1%)	164 (3.0%)	0.001
Hypertension	5030 (78.9%)	2455 (44.5%)	<0.001
Beta-blocker treatment	5415 (84.9%)	4195 (76.0%)	<0.001
Statin treatment	3638 (57.0%)	2368 (42.9%)	<0.001
Biological prosthesis	5204 (81.8%)	4165 (75.8%)	<0.001

Statistical comparison between baseline characteristics was evaluated using Student's t-test for normally distributed continuous variables, Mann-Whitney U test for non-normally distributed continuous variables and χ^2 test for categorical variables.
BMI, body mass index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; RAS, renin–angiotensin system.

Secondary outcomes

The individual components of MACE were also explored in a secondary analysis. RAS inhibitor treatment was associated with a lower risk of all-cause mortality (aHR 0.79 (95% CI 0.73 to 0.86, p<0.001)) but had no significant association with stroke (aHR 1.04 (95% CI 0.91 to 1.18, p=0.57)), MI (aHR 1.04 (95% CI 0.82 to 1.34, p=0.73)) nor cardiovascular mortality (aHR 1.01 (95% CI 0.89 to 1.14, p=0.91)), table 2.

The associations did not differ between ACE inhibitors (aHR 0.89 (95% CI 0.82 to 0.97)) and ARBs (aHR 0.87 (95% CI 0.81 to 0.93)), online supplemental figures 1 and 2, respectively. There was no significant interaction between ACE inhibitors and ARBs (p for interaction 0.32). The results were similar in most studied subgroups. However, patients without hypertension did not seem to derive the same benefit from treatment with ACE inhibitors as patients with hypertension ((aHR 0.85 (95%

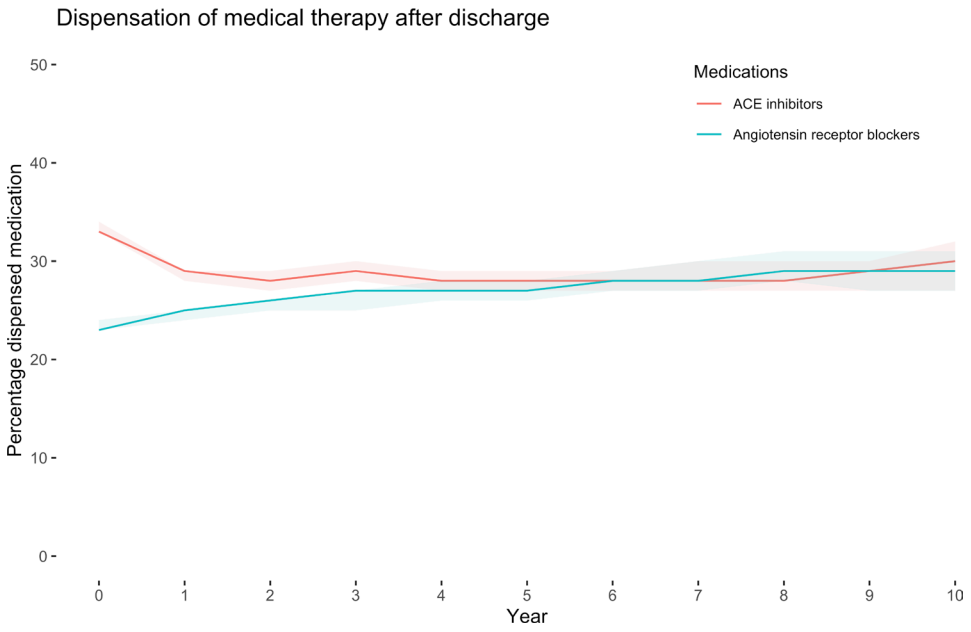

Figure 2 Dispensation over time of ACE inhibitors and ARBs. Line plot illustrating the medical therapy dispensed over time after surgical aortic valve replacement. Shaded areas denote 95% CIs. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

CI 0.77 to 0.94)) vs (aHR 1.00 (95% CI 0.86 to 1.16), p for interaction=0.035). There was also a significant interaction for patients without heart failure, although there was still an association between ACE inhibitors and lower risk of adverse outcomes in patients without heart failure. Online supplemental table 3 displays the secondary outcomes for both ACE inhibitors and ARBs.

Sensitivity analysis

There was no association between RAS inhibitor treatment prior to SAVR and MACE in an adjusted analysis (aHR 1.01 (95% CI 0.92 to 1.11, p=0.83)). After propensity score matching 1:1, a total of 61.8% of treated patients and 72.0% of controls were included in the analysis. After matching, the standardised mean differences for included variables were all <0.1 (online supplemental table 4). In the propensity score matched analysis, there was an association between treatment with RAS and a lower risk of MACE (HR 0.82 (95% CI 0.75 to 0.88, p<0.001)) and all-cause mortality (HR 0.70 (95% CI 0.64 to 0.77, p<0.001)). There were no significant associations with RAS inhibition and stroke (HR 1.01 (95% CI 0.88 to 1.17, p=0.87)), MI (HR 0.93 (95% CI 0.71 to 1.22, p=0.60)) or cardiovascular mortality (HR 0.90 (95% CI 0.79 to 1.03, p=0.14)) (table 2).

In an additional sensitivity analysis, time-updated use of events was added. These point estimates of these analyses supported the results of the main analysis (table 2).

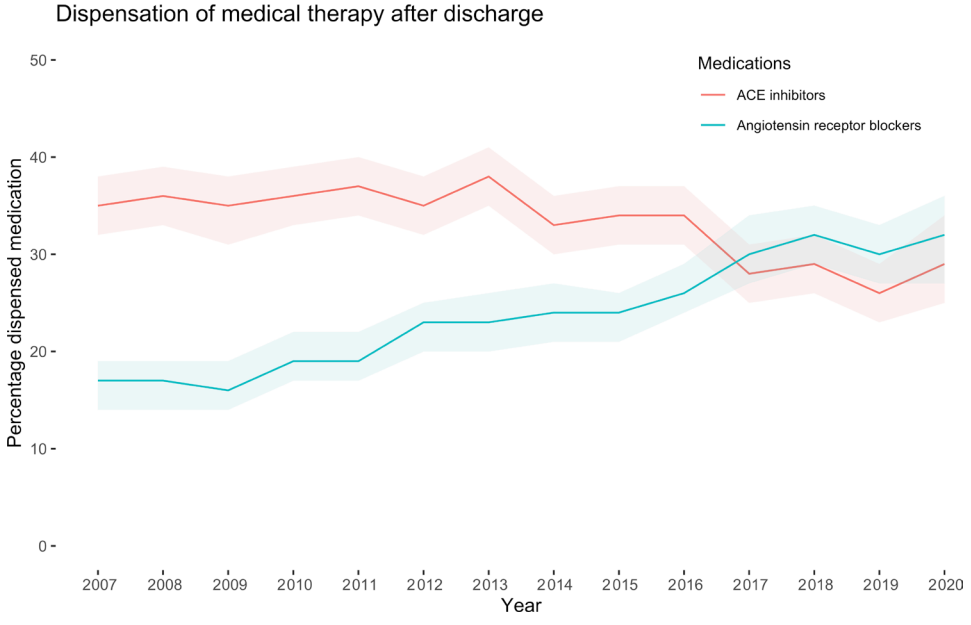

Figure 3 Dispensation over time of ACE inhibitors and ARBs at baseline stratified by year of surgery. Line plot illustrating the medical therapy dispensed after surgical aortic valve replacement stratified by year of surgery. Shaded areas denote 95% CIs. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

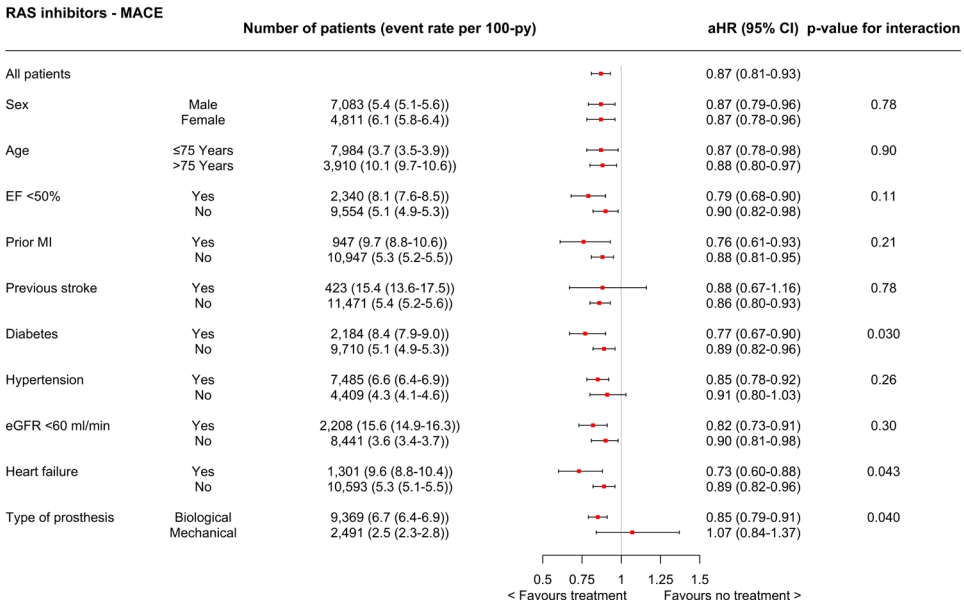

Figure 4 Forest plot illustrating the association between ongoing treatment with RAS inhibitors and MACE stratified by different subgroups. Presented aHRs are from Cox regression models, adjusted for age, sex, comorbid conditions at baseline and time-updated use of other medical therapies. aHR, adjusted hazard ratio; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction; RAS, (renin–angiotensin system.

DISCUSSION

The main findings of this large real-world study were that ongoing treatment with RAS inhibitors was associated with a lower risk of MACE after SAVR in patients with aortic valve stenosis. The lower risk was present in most investigated subgroups; the lone exception was patients with mechanical prostheses and the association was driven by a lower risk of all-cause death. Finally, the association with lower risk of MACE did not differ between ACE inhibitors and ARBs.

In the present study, RAS inhibition was associated with a lower risk of MACE in SAVR patients with aortic valve stenosis. There are several different mechanisms that may explain the lower risk. First, myocardial remodelling in patients with outflow obstruction associated with AS leads to progressive myocardial fibrosis resulting in impaired diastolic function.[23] The negative remodelling and myocardial fibrosis reverses after aortic valve replacement and are accompanied by improvements in New York Heart Association functional class and N-terminal pro-B-type natriuretic peptide levels.[24] RAS inhibitors have been found to improve both fibrosis and remodelling in other cardiovascular diseases.[25] Therefore, one of the potential benefits for RAS inhibitors could be that it further augments the cardiac remodelling seen after AVR which consequently would improve functional class and diastolic function. The findings are in line with one smaller randomised trial and one retrospective study on the use of ARBs after aortic valve replacement which showed a larger improvement in systolic function and LV mass in patients on treatment versus controls.[26 27] In addition, RAS inhibitor is an effective treatment for hypertension, which is a common driver of cardiac remodelling and is associated with systolic and diastolic heart failure as well as arrhythmias which have well-known effects on long-term survival.[28] It is important to note that the findings were consistent among both time-updated Cox regression analysis and propensity score matched analysis, indicating a robust statistical association. The analysis of cardiovascular mortality had point estimates indicating an association with lower risk but the findings did not meet statistical significance.

Interestingly, we did not find an association between RAS inhibitors and improved long-term outcomes in patients with mechanical prostheses. Studies have shown that ACE and angiotensin II are present in stenotic native aortic valves and that they are likely to contribute to disease progression.[28 29] There are several risk factors for faster disease progression in native AS that could be attenuated by RAS inhibitors treatment.[29] This includes a reduction in blood pressure, improved endothelial integrity and inhibition of atherosclerotic changes, speculatively these changes could be beneficial for patients with biological valve prosthesis.

The lower MACE risk in the present study was attributed to a lower risk of all-cause mortality, but the current study did not capture any association between RAS inhibition and incidence of stroke or MI. Likely, there are other pathophysiological aspects

Table 2 Results from Cox regression analysis, propensity score matched analysis and Cox regression analysis with time-updated comorbidities

	Adjusted HRs and 95% CI	Propensity score matched analysis	Adjusted HRs after addition of time-updated comorbidites
MACE	0.87 (0.81 to 0.93), p<0.001	0.82 (0.75 to 0.88), p<0.001	0.78 (0.73 to 0.84), p<0.001
All-cause mortality	0.79 (0.73 to 0.86), p<0.001	0.70 (0.64 to 0.77), p<0.001	0.72 (0.66 to 0.79), p<0.001
Stroke	1.04 (0.91 to 1.18), p=0.57	1.01 (0.88 to 1.17), p=0.87	1.00 (0.88 to 1.14), p=0.98
Myocardial infarction	1.04 (0.82 to 1.34), p=0.73	0.93 (0.71 to 1.22), p=0.60	0.98 (0.77 to 1.27), p=0.91
Cardiovascular mortality	1.01 (0.89 to 1.14), p=0.91	0.90 (0.79 to 1.03), p=0.14	0.89 (0.79 to 1.01), p=0.061

MACE, major adverse cardiovascular event.

which have a more profound effect on these diseases than what could be mitigated by RAS inhibitor therapy.

More patients dispensed ACE inhibitors than ARBs had an interruption in their dispense. This finding is in line with previous studies in that ACE inhibitors tend to cause more adverse events. Interestingly, patients who had surgery late in the study period had a larger proportion of ARBs dispensed after discharge compared with earlier in the study period. This is most likely due to the introduction of generic brands of ARBs during follow-up with an improved cost-to-benefit ratio. The association between RAS inhibitors and MI differed between ACE inhibitors and ARBs, but neither medication had a statistical association with a change in MI risk.

There are studies on TAVI patients which have shown similar results as the current study.[13 30] TAVI and SAVR cohorts differ based on surgical risk, but the underlying pathophysiology is equivalent, as is the remodelling due to the severe left ventricular outflow obstruction. Thus, it is expected that both TAVI and SAVR patients have comparable benefit from RAS inhibition despite the difference in patient characteristics. Speculatively, due to the younger age of SAVR patients, optimising their medical therapy after discharge could have an even greater impact on long-term outcomes.

Strengths and limitations

The current study has merits that should be considered and also important limitations. The study includes data from a nationwide, real-world setting which improves the external validity of the findings in similar settings. The data is contemporary, and a significant part of the inclusion and follow-up includes an era with TAVI as an alternative to SAVR. The study is markedly larger than previous observational studies, and the time-updated data on dispensed medications allows for improved confidence that patients were on the treatment studied. However, the study is retrospective in its design and therefore residual confounding is possible. Furthermore, the first 6 months after surgery was excluded and therefore, we could not evaluate the effect of early postoperative RAS inhibition. In addition, despite the time-updated nature of the data, the registry lacks resolution about the exact time of the diagnosis of heart failure in relation to medication dispense. Any hospitalisation with heart failure could thus overlap with dispense of RAS indicating that patients were on treatment at the hospitalisation, when in reality the dispense might have been after hospitalisation. Only diagnoses leading to hospitalisation were considered, potentially leading to underdiagnosis of incident events. Causal association cannot be ascertained with the current study design.

CONCLUSIONS

The results of this contemporary, population-based study show an association between the ongoing treatment with RAS inhibitors and lower risk of MACE for patients with AS who underwent SAVR. The association was consistent in all subgroups except for patients who had mechanical prostheses and was driven by a lowered risk of all-cause mortality. The beneficial association with outcome was similar for ACE inhibitors and ARBs. These findings provide support for the realisation of larger randomised controlled trials to evaluate the effect of RAS inhibition on clinical outcomes after SAVR.

Contributors AM and AJ conceptualised the work and contributed to all parts of data acquisition, analysis and interpretation of data. AM and AJ authored the first draft. CT, EP, ECH and AT contributed to interpretation of the data. SJN contributed substantially to data acquisition and critical interpretation of data. All authors contributed to critical revising for important intellectual content, approved the final version of the manuscript and agree to be accountable for all aspects of the work. AM and AJ accept full responsibility for the work and conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests AJ has received fees for consultancy from AstraZeneca, Werfen and LFB Biotechnologies, all unrelated to the present work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Swedish Ethical Review Authority (registration number 2021-00122).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data underlying this article were provided by national healthcare registries in Sweden and SWEDEHEART. Data will be shared on reasonable request to the corresponding author if permission can be obtained from SWEDEHEART and the Swedish National Board of Health and Welfare.

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RAS inhibition after surgical aortic valve replacement and long-term outcomes – A report from the SWEDEHEART Registry.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. ICD and ATC codes for different diseases and medications used in the study.

Supplementary Table 2. Crude event rates per 100 person-years for different outcomes stratified on baseline RAS inhibition.

Supplementary Table 3. Secondary outcomes and their associations with ACE inhibitors and ARBs.

Supplementary Table 4. Standardized mean differences before and after propensity score matching.

Supplementary Figure 1. Forest plot illustrating the association between ongoing treatment with ACE inhibitors and MACE stratified by different subgroups. Presented aHR are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of

other medical therapies. HR=hazard ratio, CI=confidence interval, EF=ejection fraction, MI=myocardial infarction.

Supplementary Figure 2. Forest plot illustrating the association between ongoing treatment with ARBs and MACE stratified by different subgroups. Presented aHR are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of other medical therapies. HR=hazard ratio, CI=confidence interval, EF=ejection fraction, MI=myocardial infarction.

Supplementary Table 1. ICD and ATC codes used in the study.

Clinical conditions	**ICD-10 codes (from 1997)**	**Type of diagnosis considered**
Myocardial infarction	I21.0-I21.4	Diagnosis with hospitalization
Diabetes	E10-E14 (any diagnosis)	Any diagnosis
Hypertension	I10.0-I15.9 (any diagnosis)	Any diagnosis
Heart failure	I50, I42-143.8, I11.0, I13.0, I13.2, I25.5	Diagnosis with hospitalization
Atrial fibrillation	I48	Any diagnosis
Stroke	I61.0-I64	Diagnosis with hospitalization
Chronic respiratory disease	J40-J47	Any diagnosis
Renal failure	N17-N19	Any diagnosis
Hyperlipidemia	E78	Any diagnosis
Peripheral artery disease	I70, I73.9, I74, I77	Any diagnosis
Left ventricular ejection fraction	Data collected from SWEDEHEART	
Medication groups	**ATC code**	
B-blockers	C07 (excluding C07AA07)	
RAS inhibitors	C09	
Statins	C10AA, C10BA02, C10BX06	

Supplementary Table 2. Crude event rates per 100 person-years for different outcomes stratified on baseline RAS inhibition.

	Patients on RAS inhibitors at baseline (n=6,377)	**Patients not on RAS inhibitors at baseline (n=5,517)**
MACE	6.4 (6.2-6.7)	5.3 (5.0-5.5)
All-cause mortality	5.4 (5.2-5.7)	3.9 (3.7-4.2)
Stroke	2.3 (2.1-2.5)	1.6 (1.5-1.7)
Myocardial infarction	0.6 (0.5-0.7)	0.4 (0.4-0.5)
Cardiovascular mortality	2.1 (1.9-2.2)	1.4 (1.3-1.5)

HR=Hazard ratio, CI=Confidence interval, RAS=Renin-angiotensin system inhibitors.

Supplementary Table 3. Secondary outcomes and their associations with ACE inhibitors and ARBs

	ACE inhibitors	ARBs	p for interaction
All-cause mortality	0.84 (95% CI 0.77-0.93, p<0.001)	0.78 (95% CI 0.71-0.86, p<0.001)	0.18
Stroke	1.00 (95% CI 0.87-1.16, p=0.98)	1.09 (95% CI 0.94-1.26, p=0.26)	0.29
Myocardial infarction	0.83 (95% CI 0.62-1.11, p=0.22)	1.24 (95% CI 0.95-1.61, p=0.11)	0.014
Cardiovascular mortality	1.06 (95% CI 0.92-1.21, p=0.42)	1.02 (95% CI 0.89-1.18, p=0.75)	0.92

Supplementary Table 4. Standardized mean differences before and after propensity score matching.

	SMD before matching	SMD after matching
Age	0.23	-0.02
Sex	-0.07	0.02
Year of surgery	0.04	0.03
BMI	0.20	0.01
Reduced LVEF	0.26	0.04
eGFR	0.09	0.02
Stroke	0.04	0.02
Myocardial infarction	0.08	0.03
Heart failure	0.15	0.06
Hypertension	0.57	0.07
Hyperlipidemia	0.22	0.03
Diabetes	0.29	0.07
Atrial fibrillation	0.15	-0.00
Peripheral vascular disease	-0.02	-0.00
Betablocker therapy	0.43	-0.02
Statin therapy	0.38	-0.01
Type of prosthesis	0.11	0.00

SMD=Standardized mean difference.

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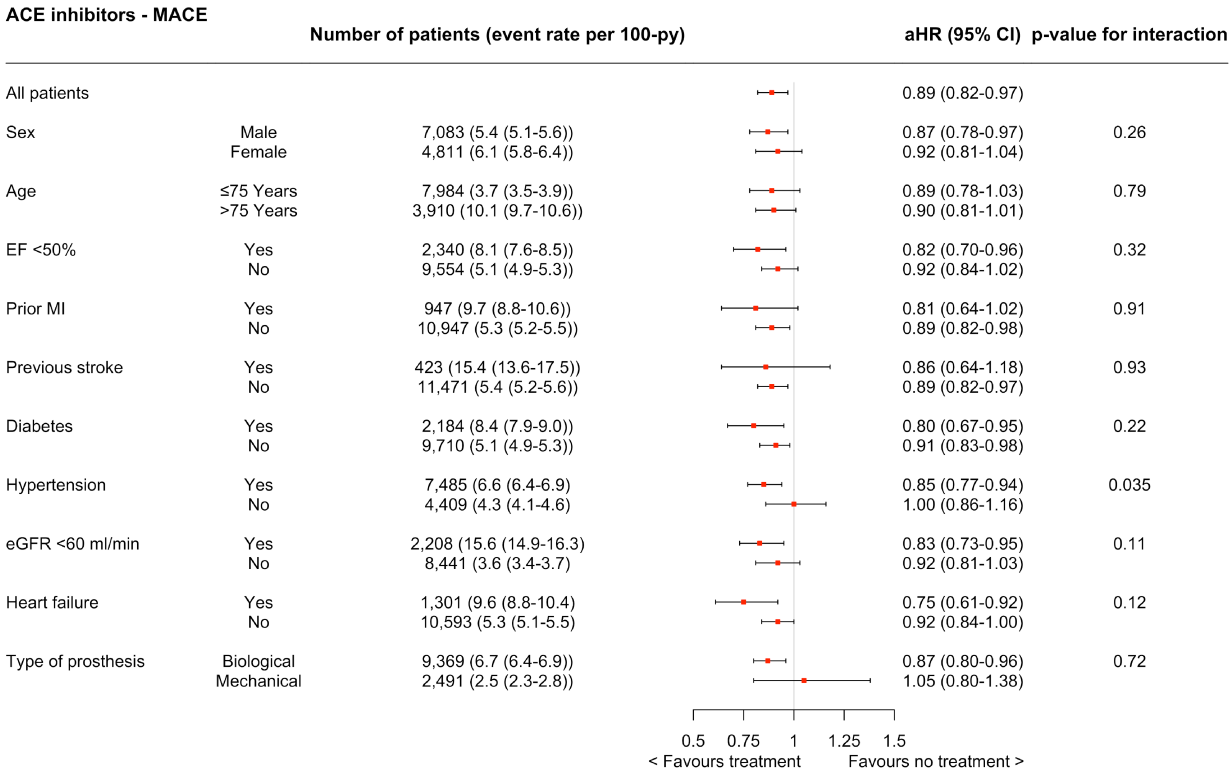

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