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ORIGINAL ARTICLE

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Medical therapy after surgical aortic valve replacement for aortic regurgitation

Charlotta Törngren[a,b], Kristjan Jonsson [a,b], Emma C. Hansson[a,b], Amar Taha[b,c], Anders Jeppsson [a,b] and Andreas Martinsson [b,c,*]

[a] Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden
[b] Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[c] Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden

* Corresponding author. Department of Cardiology, Sahlgrenska University Hospital, 41345 Gothenburg, Sweden. Tel: +46-709841884; e-mail: andreas.s.martinsson@vgregion.se (A. Martinsson).

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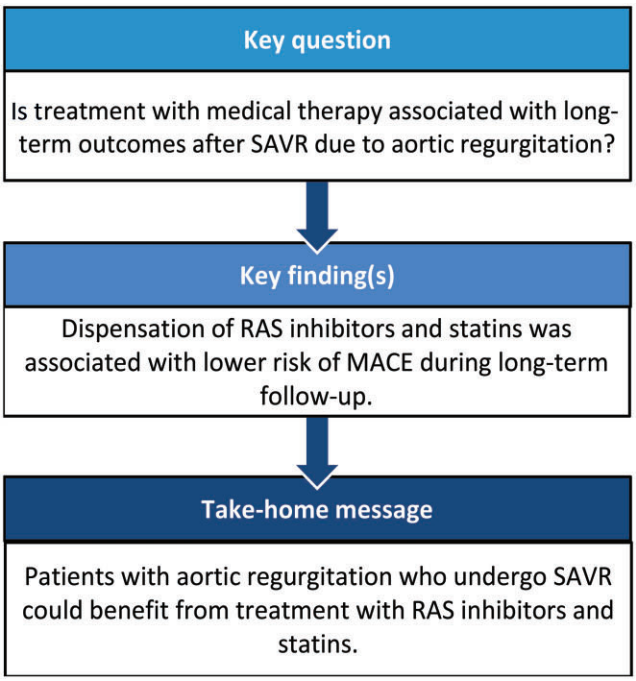

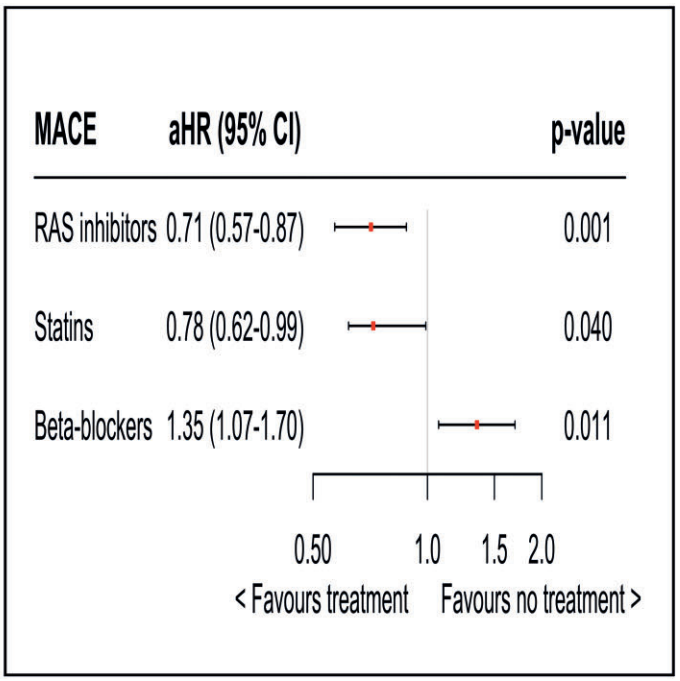

Abstract

OBJECTIVES: Current clinical guidelines have no specific recommendations regarding medical therapy after surgical aortic valve replacement in patients with aortic regurgitation (AR). We studied the association between medical therapy with renin–angiotensin system (RAS) inhibitors, statins and β-blockers and long-term major adverse cardiovascular events.

METHODS: All patients undergoing valve replacement due to AR between 2006 and 2017 in Sweden and alive 6 months after discharge were included. Time-dependent multivariable Cox regression models adjusted for age, sex, patient characteristics, comorbidities, other medications and year of surgical aortic valve replacement were used. Primary outcome was a composite of all-cause mortality, myocardial infarction and stroke. Subgroup analyses based on age, sex, heart failure, low ejection fraction, hyperlipidaemia and hypertension were performed.

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RESULTS: A total of 2204 patients were included [median follow-up 5.0 years (range 0.0–11.5)]. At baseline, 68% of the patients were dispensed RAS inhibitors, 80% β-blockers and 35% statins. Dispense of RAS inhibitors and β-blockers declined over time, especially during the first year after baseline, while dispense of statins remained stable. Treatment with RAS inhibitors or statins was associated with a reduced risk of the primary outcome [adjusted hazard ratio (aHR) 0.71, 95% confidence interval (CI) 0.57–0.87 and aHR 0.78, 95% CI 0.62–0.99, respectively]. The results were consistent in subgroups based on age, sex and comorbidities. β-Blocker treatment was associated with an increased risk for the primary outcome (aHR 1.35, 95% CI 1.07–1.70).

CONCLUSIONS: The results indicate a potential beneficial association of RAS inhibitors and statins as part of a secondary preventive treatment regime after aortic valve replacement in patients with AR. The role of β-blockers needs to be further investigated.

Keywords: Medical therapy • Aortic regurgitation • Renin–angiotensin system inhibitors • Statins • β-Blockers • surgical aortic valve replacement

ABBREVIATIONS

aHR	Adjusted hazard ratio
AR	Aortic regurgitation
CIs	Confidence intervals
LVEF	Left ventricular ejection fraction
MACE	Major cardiovascular adverse events
MI	Myocardial infarction
RAS	Renin–angiotensin system
SAVR	Surgical aortic valve replacement

INTRODUCTION

Aortic regurgitation (AR), with its reversal of blood flow through the aortic valve and volume overload of the left ventricle, may lead to development of clinical heart failure with reduced ejection fraction [1]. Moderate-to-severe AR has an estimated prevalence of 0.5% in the general population, increasing to 1.6% in the elderly [2, 3]. Severe AR is associated with substantial morbidity and mortality if not treated with surgical intervention [4]. Medical therapy, which is widely used to mitigate morbidity in other cardiac surgery patient cohorts [5], has a smaller role in clinical guidelines for AR patients. Current recommendations include renin–angiotensin system (RAS) inhibitors for patients with severe symptomatic AR but who are unsuitable for surgery, or in anticipation of intervention [6, 7]. In patients with aortic disease, use of statins may have beneficial actions due to improvement of inflammation, oxidative stress, endothelial dysfunction and stabilization of atherosclerotic plaque [8]. There are no randomized controlled trials evaluating medical therapy after surgical aortic valve replacement (SAVR) for AR. This is reflected in the lack of clear recommendations on secondary medical treatment after aortic valve surgery in current guidelines, except for recommendations regarding anticoagulation and for specific subgroups such as Marfan patients [9, 10]. Potentially, RAS inhibitors, statins and β-blockers could have beneficial effects on cardiac and vascular remodelling in patients after surgical intervention [11–13]. Currently, the only 2 medications recommended in the postoperative phase in European guidelines are RAS inhibitors and β-blockers, both only for selected patients [9]. Statins are also recommended but only based on the overall cardiovascular risk of the individual patient and not specifically for patients after surgery. The contemporary use of these medications after surgery has not previously been reported and it is unlikely that large, randomized studies will be performed in the postoperative patient cohort.

Therefore, this study aimed to evaluate the associations between long-term major cardiovascular adverse events (MACE, consisting of all-cause mortality, myocardial infarction and stroke) and time-updated use of RAS inhibitors, statins and β-blockers in a large nationwide cohort of patients. The medications were selected on the basis on their well-established cardiovascular benefit, specifically inhibiting adverse remodelling and protective vascular effects. Secondary aims were to evaluate if subgroups of patients have different associations with treatment and to describe the use of RAS inhibitors, statins and β-blockers over time after SAVR due to AR.

MATERIALS AND METHODS

Ethical statement

The study was performed in accordance with the 1975 Declaration of Helsinki and was approved by the regional research ethics committee in Gothenburg (registration number 139-16). The need for individual patient consent was waived by the committee.

Data sources

Patients were collected from the Swedish Cardiac Surgery Registry, which is a part of the SWEDEHEART registry [14]. The cardiac surgery registry includes all patients who had cardiac surgery in Sweden since 1992 and have excellent coverage (99%) [15]. The registry contains information on the type of surgery performed, periprocedural details and preoperative patient characteristics. Data from SWEDEHEART were merged with data from 3 mandatory nationwide registries—the Swedish National Patient Registry, the Cause of Death Registry and the Prescribed Drug Registry [16, 17]. The linkage was based on the unique, personal identification number that all Swedish inhabitants obtain at immigration or birth. Sweden employs a single-payer system with healthcare reimbursed by the state. Financial compensations to the departments are based on the same International Classification of Disease codes as are entered into the registries and all medications evaluated in the study are partly or fully paid for by the Swedish state. International Classification of Disease-10 codes were used to identify previous diagnoses of comorbid conditions and the Anatomical Therapeutical Classification was

used when collecting data on medication. The codes used can be found in Supplementary Material, Table S1.

The article has been composed according to recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology statement [18].

Study population

All patients surviving the first 6 months after first-time SAVR due to AR, with either mechanical or biological prostheses from January 2006 to December 2017 in Sweden were considered for inclusion. Patients with valve repair, other concomitant procedures or endocarditis were excluded. Baseline was set at 6 months after surgery based on the assumption that early postoperative mortality is less likely to be preventable by medical therapy and is frequently related to the intervention itself. Patients with <6 months of follow-up (due to death, emigration or surgery within the last 6 months before the end of follow-up) were therefore excluded. Patients who emigrated contributed with follow-up time until their emigration, at which time point they were censored. Excluding 9 patients who emigrated during study period, follow-up was complete for all patients, medication and events during the study period.

Medication status was updated every third month from the time of surgery. Patients were considered off treatment if they were not dispensed medication during 2 consecutive 3-month periods as previously described [5, 19]. Estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula [20].

Statistical analysis

Categorical variables are presented as numbers and frequency. Continuous variables are presented as medians with interquartile range or means with standard deviation, as appropriate based on distribution. Distribution was checked by visual inspection of histograms. Incidence rates were calculated as the number of events divided by follow-up time and presented per 100 person-years. A Poisson distribution was assumed when calculating the associated 95% confidence intervals (CIs). Multivariable time-dependent Cox proportional hazards models were used to estimate hazard ratios with 95% CI. Medication data were the time-updated variables and were updated with 3-month intervals; patients were considered on or off treatment based on the updated medication data. Each interval had an unique row in the database, which was setup in a counting process style, with clustering according to each individuals unique, anonymized identification number. The Cox regression model was adjusted for age, sex, previous myocardial infarction (MI), hypertension, prior stroke, diabetes, heart failure, hyperlipidaemia, kidney function, left ventricular ejection fraction (LVEF), type of prosthesis, year of surgery and ongoing treatment with statins, RAS inhibitors and β-blockers. The adjustments were decided on prior to the analysing phase of the study. The proportional hazards assumption was tested based on scaled Schoenfeld residuals and was fulfilled for all analyses. To assess if there was collinearity in the model variance inflation factor was used. No included variables, including medications, had a variance inflation factor above 2.5 and the collinearity of the model thus was considered non-significant. All analyses were performed using R version 4.22 (R Foundation for Statistical Computing, Vienna, Austria).

Subgroups based on patient characteristics and comorbidities were analysed separately. These subgroups were sex, age </≥75 years, heart failure, LVEF (</≥50%), diabetes, atrial fibrillation, previous MI, previous stroke, hyperlipidaemia and hypertension. In addition, a sensitivity analysis with cardiovascular indications as a subgroup was performed. In the analysis each medication had separate indications. Indications for RAS inhibitors were hypertension, previous MI and heart failure, statins were considered indicated in patients with previous MI, stroke or hyperlipidaemia. Indications for β-blockers were hypertension, previous MI, atrial fibrillation and heart failure. Interaction analyses were performed to evaluate differences between the groups. Heart failure was defined as a clinical diagnosis of heart failure; thus, it includes both patients with preserved and reduced LVEF.

RESULTS

General

A total of 4197 patients were eligible for inclusion. 930 patients were excluded due to concomitant coronary artery bypass grafting. In addition, 415 patients were excluded because they had other simultaneous valvular interventions and 494 patients were excluded due to current or previous endocarditis. Finally, 154 were excluded due to <6 months of follow-up. After exclusions, the final study population was 2204. Figure 1 illustrates the inclusion and exclusion of patients to arrive at the final study population.

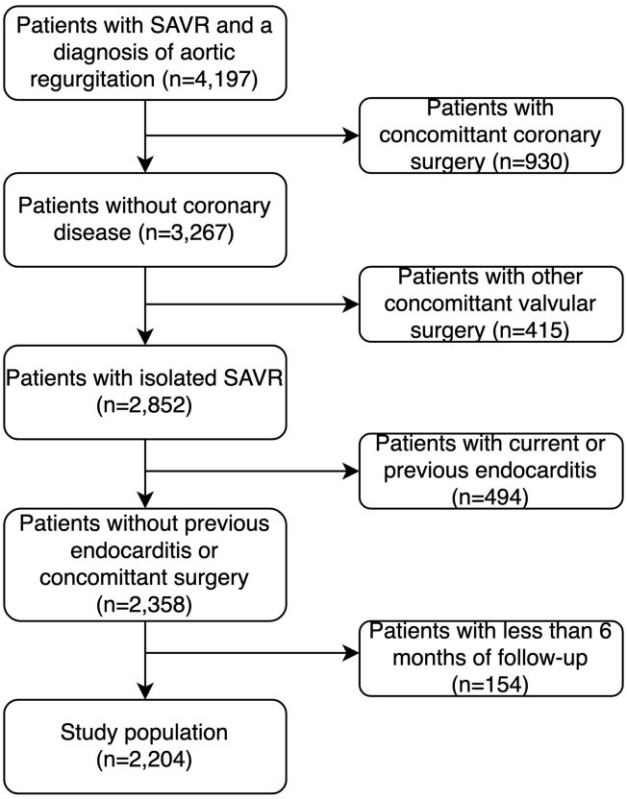

Figure 1: Flowchart of excluded patients to arrive at final study population.

Baseline characteristics

The mean age was 62.7 years, 72.9% were male and 38.2% had an LVEF <50% (see Table 1). Patients treated with RAS inhibitors (68.1%) more often had a previous diagnosis of all comorbid condition except for previous MI (Supplementary Material, Table S2). Patients treated with statins (35.3%), similarly, more frequently had all comorbid conditions apart from low EF (Supplementary Material, Table S3). Heart failure, low LVEF, atrial fibrillation, hypertension, hyperlipidaemia and renal failure were more common among patients treated with β-blockers (80.5%, Supplementary Material, Table S4). In patients on RAS inhibitors, 38.3% was on statins and 85.7% was on β-blockers at baseline. Patients on statins were frequently treated with RAS inhibitors (73.9%) and β-blockers (85.0%). Patients on β-blockers were often treated with RAS inhibitors (72.5%) and 37.3% were also treated with statins. During follow-up (median 5.0, range 0.0–11.5 years), 391 (17.7%) patients had any MACE, 289 (13.1%) died, 26 (1.2%) had an MI and 147 (6.7%) suffered a stroke. A total of 1723 (78.2%) patients had at least 1 indication for RAS inhibitors, 589 (26.7%) patients had at least 1 indication for statin treatment and 1850 (83.9%) had at least 1 indication for β-blockers.

Utilization of medical therapy after surgical aortic valve replacement *due to* aortic regurgitation

The dispensation of RAS inhibitors, statins and β-blockers over time is shown in Fig. 2. RAS inhibitors were dispensed to 1502 (68.1%) at baseline. Dispensation declined during follow-up and 60.1% were dispensed RAS inhibitors at 10 years. Statins were dispensed to 778 (35.3%) at baseline, increasing over time to 40.6%. β-Blockers were dispensed to 1774 (80.5%) at baseline but declined over the first year to 64.8%, after 10 years 59.4% of patients were dispensed β-blockers.

Association between medical therapy and long-term outcomes. *RAS inhibitors*

The MACE rate was 4.3 (95% CI 3.8–4.9) per 100 person-years for patients treated with RAS inhibitors at baseline and 3.7 (95% CI 3.1–4.4) for patients without RAS inhibitors at baseline. The event rate for the individual components of MACE is reported in Table 2, event rates for all-cause mortality and stroke were slightly higher while event rates for MI was similar for patients on or off treatment. In the fully adjusted model, RAS inhibitors were associated with a reduced risk of MACE [adjusted hazard ratio (aHR) 0.71 (95% CI 0.57–0.87), $P = 0.001$, central image]. Most of the studied subgroups had similar results as the main analysis; however, patients with diabetes seemed to have a stronger association between RAS inhibitors and reduced risk of MACE [aHR 0.48 (95% CI 0.27–0.86) vs 0.76 (95% CI 0.60–0.96), P for interaction 0.029] compared to non-diabetic patients

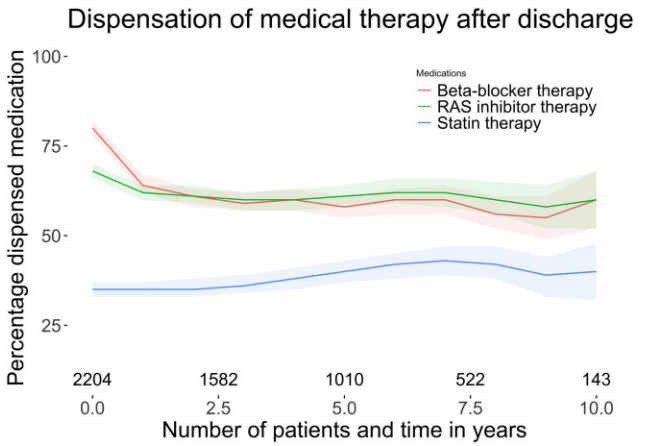

Figure 2: Dispensation over time of the different medical therapies in the study. Line plot illustrating the medical therapy dispensed over time after surgical aortic valve replacement. Shaded areas denote 95% confidence intervals.

Table 1: Baseline characteristics of 2204 surgical aortic valve replacement patients combined and divided by treatment at baseline with renin–angiotensin system inhibitors, statins and β-blockers

	All patients ($n = 2204$)	Patients on RAS inhibitors at baseline ($n = 1502$, 68.1%)	Patients on statins at baseline ($n = 778$, 35.3%)	Patients on β-blockers at baseline ($n = 1774$, 80.5%)
Age (years), mean (SD)	62.7 (14,5)	64.0 (13.1)	67.9 (10.1)	63.7 (13.7)
Male	1606 (72.9%)	1143 (76.1%)	530 (68.1%)	1287 (72.5%)
BMI (IQR)	26.2 (5.3)	26.5 (5.5)	26.6 (5.3)	26.4 (5.4)
LVEF <50%	842 (38.2%)	685 (45.6%)	281 (36.1%)	723 (40.8%)
eGFR (ml/min), mean (SD)	81.1 (31.5)	79.5 (29.6)	73.4 (29.5)	79.4 (30.8)
Diabetes	201 (9.1%)	152 (10.1%)	129 (16.6%)	172 (9.7%)
Prior MI	127 (5.8%)	89 (5.9%)	88 (11.3%)	116 (6.5%)
Previous stroke	162 (7.4%)	123 (8.2%)	98 (12.6%)	128 (7.2%)
Atrial fibrillation	966 (43.8%)	712 (47.4%)	388 (49.9%)	855 (48.2%)
Heart failure	684 (31.0%)	574 (38.2%)	285 (36.6%)	598 (33.7%)
Hypertension	1245 (56.5%)	991 (66.0%)	558 (71.7%)	1058 (59.6%)
Hyperlipidaemia	414 (18.8%)	299 (19.9%)	325 (41.8%)	349 (19.7%)
Renal failure	106 (4.8%)	75 (5.0%)	51 (6.6%)	99 (5.6%)
Biological prosthesis	1464 (66.4%)	1011 (67.3%)	587 (75.4%)	1201 (67.7%)
RAS inhibitor therapy	1502 (68.1%)	–	575 (73.9%)	1287 (72.5%)
Statin therapy	778 (35.3%)	575 (38.3%)	–	661 (37.3%)
β-Blocker therapy	1774 (80.5%)	1287 (85.7%)	661 (85.0%)	–

Values are represented as mean and standard deviation or numbers and percentage.

BMI: Body mass index; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; RAS: renin–angiotensin system; SD: standard deviation.

Table 2: Event rates and adjusted hazard ratio for the components of major cardiovascular adverse events stratified by medical therapy (at baseline)

	RAS inhibitors	Statins	β-Blockers
Event rates (per 100 person-years) (95% CI)			
Crude mortality rate without treatment	2.7 (2.1–3.3)	2.4 (3.27–3.74)	2.0 (1.5–2.7)
Crude mortality rate with treatment	3.0 (2.6–3.5)	3.8 (3.2–4.5)	3.2 (2.8–3.6)
Crude myocardial infarction rate without treatment	0.3 (0.1–0.6)	0.2 (0.1–0.4)	0.3 (0.1–0.7)
Crude myocardial infarction rate with treatment	0.3 (0.2–0.4)	0.4 (0.2–0.6)	0.2 (0.1–0.4)
Crude stroke rate without treatment	1.3 (1.0–1.8)	1.2 (0.9–1.5)	1.1 (0.7–1.7)
Crude stroke rate with treatment	1.7 (1.4–2.0)	2.3 (1.8–2.9)	1.7 (1.4–2.0)
Cox regression analyses[a] (fully adjusted model, aHR) (95% CI), *P*-value			
All-cause mortality	0.66 (0.51–0.85), 0.001	0.68 (0.52–0.90), 0.006	1.20 (0.92–1.57) 0.19
Myocardial infarction	0.59 (0.29–1.21), 0.15	1.51 (0.64–3.59), 0.35	1.00 (0.54–1.84), 0.99
Stroke	0.78 (0.53–1.15), 0.21	0.93 (0.64–1.35), 0.70	1.52 (1.01–2.31), 0.046

[a]Adjusted for the following variables at baseline: age, sex, previous MI, hypertension, diabetes, heart failure, kidney function, LVEF, type of prosthesis, year of surgery and use of the other time-updated medical therapy other than the main effect variable.
aHR: adjusted hazard ratio; CI: confidence interval; LVEF: left ventricular ejection fraction; MI: myocardial infarction; RAS: renin–angiotensin system.

(Fig. 3). The reduced risk associated with RAS inhibitors was mainly driven by all-cause mortality [aHR 0.66 (95% CI 0.51–0.85), $P = 0.001$] while RAS was not independently associated with a reduced risk of MI and stroke (Table 2).

Statins. Patients dispensed statins at baseline had an MACE rate of 5.7 (95% CI 4.9–6.6) per 100 person-years while patients without statins at baseline had an event rate of 3.4 (95% CI 2.9–3.9) per 100 person-years. Overall, patients on statin treatment at baseline had higher event rates for the individual components of MACE. As with RAS inhibitors, statins were associated with reduced risk of MACE in the fully adjusted model [aHR 0.78 (95% CI 0.62–0.99), $P = 0.040$]. The results remained consistent in all studied subgroups (Fig. 4). Statin treatment was associated with a reduced risk of all-cause mortality [aHR 0.68 (95% CI 0.52–0.90), $P = 0.006$] but not with MI or stroke.

β-Blockers. The MACE rate was 4.5 (95% CI 4.0–5.0) per 100 person-years for patients on β-blockers at baseline and 3.0 (95% CI 2.3–3.8) for those without treatment at baseline. Event rates for all-cause mortality and stroke were higher for patients on β-blockers at baseline, but there was no difference between patients on and off β-blocker treatment for MI. β-Blockers were associated with MACE in the fully adjusted model [1.35 (95% CI 1.07–1.70), $P = 0.012$]. There was a significant interaction between having an indication for treatment and outcomes associated with β-blocker treatment (Fig. 5). The analysis suggests that patients with a prior indication for treatment with β-blockers did not have a significant association with increased risk of MACE, while those without an indication did (P for interaction = 0.043). Patients on β-blockers had an association with a higher risk of stroke [aHR 1.52 (95% CI 1.01–2.31), $P = 0.046$] but not all-cause mortality or MI.

DISCUSSION

The main finding of this large, real-world, population-based study was an association between ongoing use of RAS inhibitors and statins and a reduced risk of MACE in patients who had SAVR due to AR. The associations were robust in all the prespecified subgroups. In contrast, β-blocker treatment was associated with an increased risk of MACE, except in patients with an indication for β-blocker treatment, in which the results were not statistically significant. The association between RAS inhibitors and statins with a reduced risk of MACE was mainly driven by a lower risk for all-cause mortality.

Among AR patients, studies evaluating the use of medical therapy after SAVR are scarce. The current guidelines on valvular heart disease do not give any recommendations about medical therapy after SAVR in patients with AR, unless to treat comorbidities such as heart failure and hypertension [9, 10]. In the current study, hypertension (56.5%), heart failure (31.0%) and reduced LVEF (38.2%) were frequent, and hyperlipidaemia (18.8%) was not uncommon. Consequently, there was a high degree of dispensation of RAS inhibitors, statins and β-blockers in the present population, allowing us to evaluate the use of these medications after SAVR. As AR patients are relatively young (mean age 62.7 years), a substantial life expectancy can be anticipated in this cohort and long-term optimization of treatment is of great importance.

Renin–angiotensin system *inhibitors*

RAS inhibitors were dispensed to most patients after SAVR and remained dispensed at a high rate during follow-up. There was a strong association between treatment with RAS inhibitors and a reduced risk of MACE ($P = 0.001$). The association was independent of existing comorbidities considered an indication for RAS inhibitors (hypertension, heart failure, reduced LVEF and previous myocardial infarction). One earlier retrospective study has indicated a similar benefit from treatment with RAS inhibitors in patients with untreated AR, but studies in SAVR patients are lacking [7]. There are several potential mechanisms that could lead to the findings in the current study. RAS inhibitors improve contractility and diastolic function and enhance reverse remodelling [21]. Speculatively, patients treated surgically due to AR often have early signs of left ventricular dysfunction such as left ventricular dilatation and slightly reduced LVEF even if they do not have a clinical heart failure diagnosis and these patients could benefit from RAS inhibition. Bicuspid aortic valve is a risk factor for the development of AR, and it is a common underlying diagnosis in patients who have SAVR [22]. There are no randomized controlled trials evaluating medical therapy in patients with

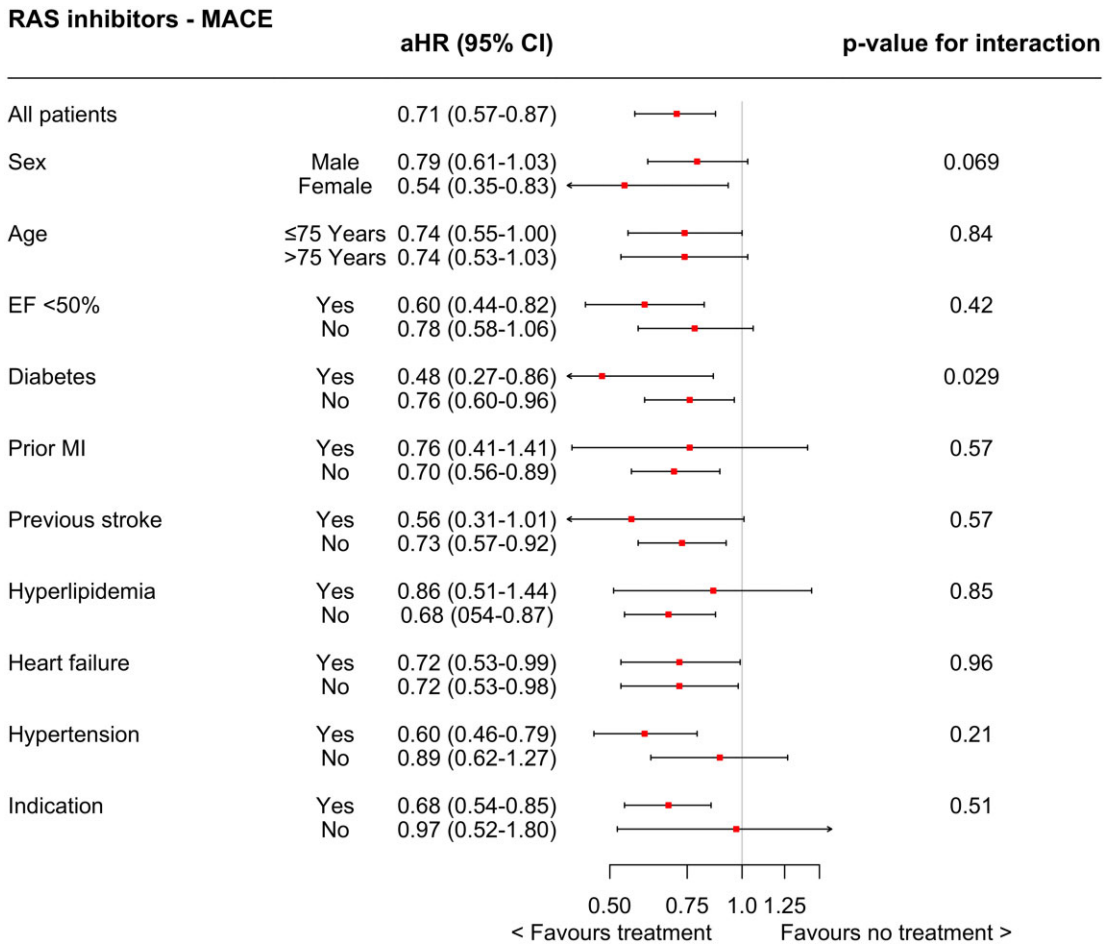

Figure 3: Forest plot illustrating the treatment effect of renin–angiotensin system inhibitors stratified by different subgroups. Presented adjusted hazard ratio are from Cox regression models, adjusted for age, sex, comorbid conditions and time-updated use of other medical therapies. CI: confidence interval; EF: ejection fraction; HR: hazard ratio; MI: myocardial infarction.

bicuspid aortic valves and AR. With the current study design, it is not possible to evaluate the morphologic qualities of the individual valves, but there is no indication that the results could not be applied to the bicuspid aortic valve population with AR. Previous studies have indicated that RAS inhibitors may reduce aortic dilation rate [23], and it is possible that the current findings could possibly be due to a reduction in aortic dilatation rate in addition to the above-mentioned possible beneficial cardiac effects.

Statins

The pleiotropic effects of statins are well-established, and they have proven benefits in a wide variety of patients [8, 24, 25]. The effects include endothelial benefits and immune-modulatory properties in addition to its primary mechanism of lowering cholesterol. There are several patient cohorts with a predisposition towards AR that potentially benefit from statin use. First, the cholesterol-lowering effects likely contribute substantially to a reduction in vascular events. Secondly, patients with bicuspid aortic valve have abnormalities leading to aortic dilatation, commonly including defects in the aortic media layer with matrix disruption potentially leading to atherosclerotic aortic aneurysm. Potentially some of the beneficial effects of continuous statin therapy in the current study could be due to a reduction in aortic dilatation rate [13, 26, 27].

Interestingly, statin therapy was associated with a reduced risk for all-cause mortality but not for MI and stroke. The cardiovascular benefit of statin treatment is well-established and the neutral results for MI and stroke are likely caused by a strong correlation between vascular disease and statin treatment that is not fully adjusted for in the models. The robust association with reduced all-cause mortality is likely still related to cardiovascular benefits, possibly by reducing myocardial infarction and stroke size, and is in agreement with a previous study in patients with aortic stenosis who had SAVR [28].

β-*Blockers*

β-Blockers were associated with an increase in long-term risk of MACE in the current study. The associated risk increase was only significantly increased for stroke when evaluating the individual components of MACE. These results persisted in most individual subgroups, including heart failure and hypertension. However, importantly, if patients had any indication for β-blockers, the association with increased risk was attenuated and did not meet statistical significance. In agreement with our findings, 1 previous randomized study assessed the effect of β-blockers in preventing excessive ventricular dilatation in response to AR. The study could not show a difference in change of left ventricular volume over 6 months between patients treated with metoprolol and

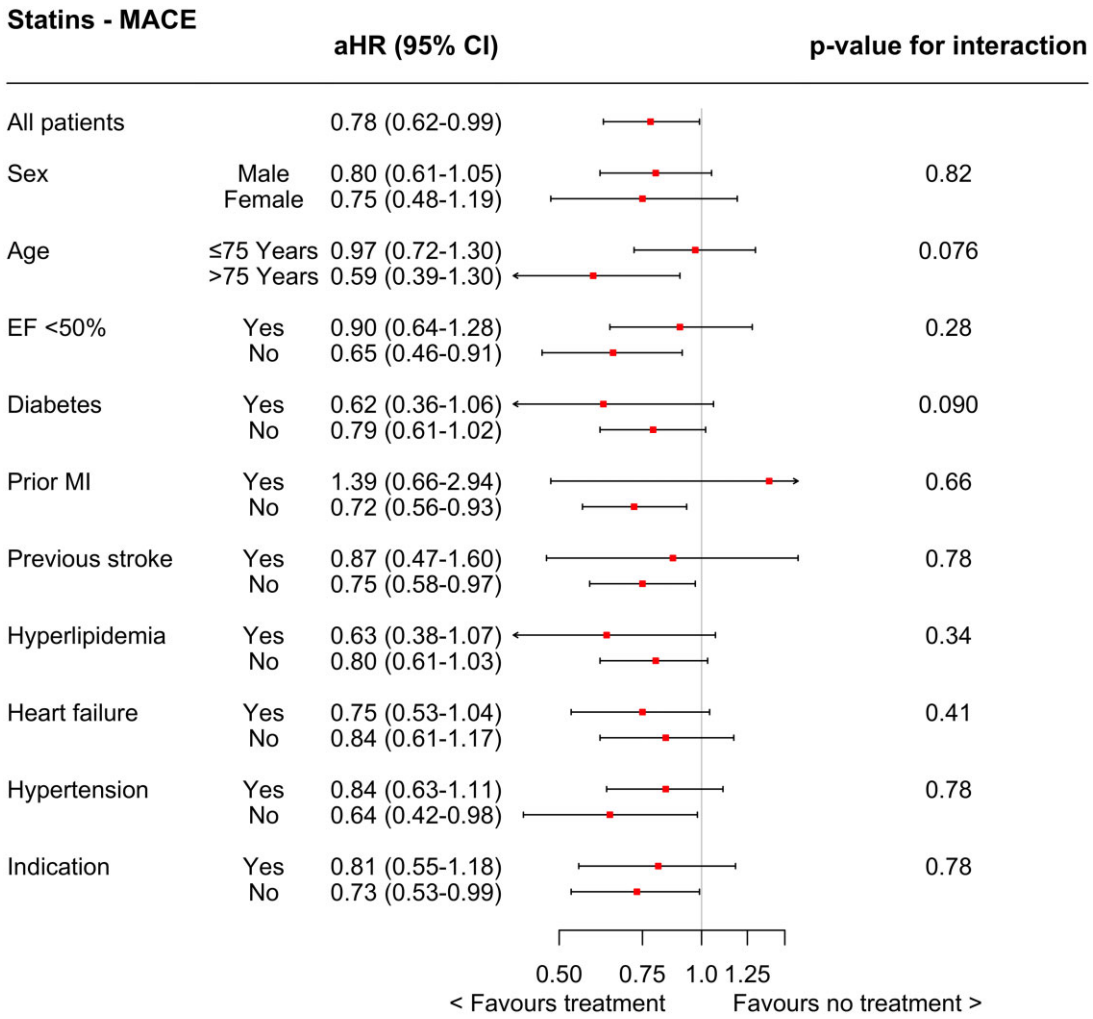

Figure 4: Forest plot illustrating the treatment effect of statins stratified by different subgroups. Presented adjusted hazard ratio are from Cox regression models, adjusted for age, sex, comorbid conditions and time-updated use of other medical therapies. CI: confidence interval; EF: ejection fraction; HR: hazard ratio; MI: myocardial infarction.

placebo [29]. It is possible that the effect of β-blockers in patients with heart failure due to AR after surgical replacement is less pronounced than for patients with heart failure due to other aetiologies in which there is no resolution for the underlying pathophysiology. Finally, the current study lacked information on the type of β-blockers and previous studies on patients after cardiac surgery have shown that the results differ between selective and non-selective β-blockers [30].

Strengths and limitations

There are important limitations to consider in the current study, but it also has merits that should be emphasized. Strengths of the study include that the results are from a real-world, nationwide setting, indicating that the results are applicable to the general population of AR patients after SAVR. The study was large compared to other contemporary retrospective studies and the dispensation of medications was time updated throughout the study period. The data collected were from high-quality registries with nationwide coverage. Limitations are inherent to the study design; residual confounding cannot be ruled out, patients' compliance with dispensed medication is unknown and there was a lack of echocardiographic data other than LVEF. The first 6 months after surgery was excluded and thus no conclusions can be drawn regarding treatment during the early postoperative period and survival bias cannot be ruled out. Causal treatment effects cannot be ascertained with the current study design and the results should be interpreted as such.

CONCLUSIONS

The results in this real-world population-based study suggest that there is an association between the ongoing dispensation of RAS inhibitors and statins and reduced MACE for patients with AR who underwent SAVR. The associations were robust in all investigated subgroups of patients and driven by all-cause mortality. This suggests that AR patients could benefit from treatment with RAS inhibitors and statins after SAVR. β-Blocker use after SAVR in patients with AR needs to be further evaluated. Randomized trials are warranted to confirm our findings.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

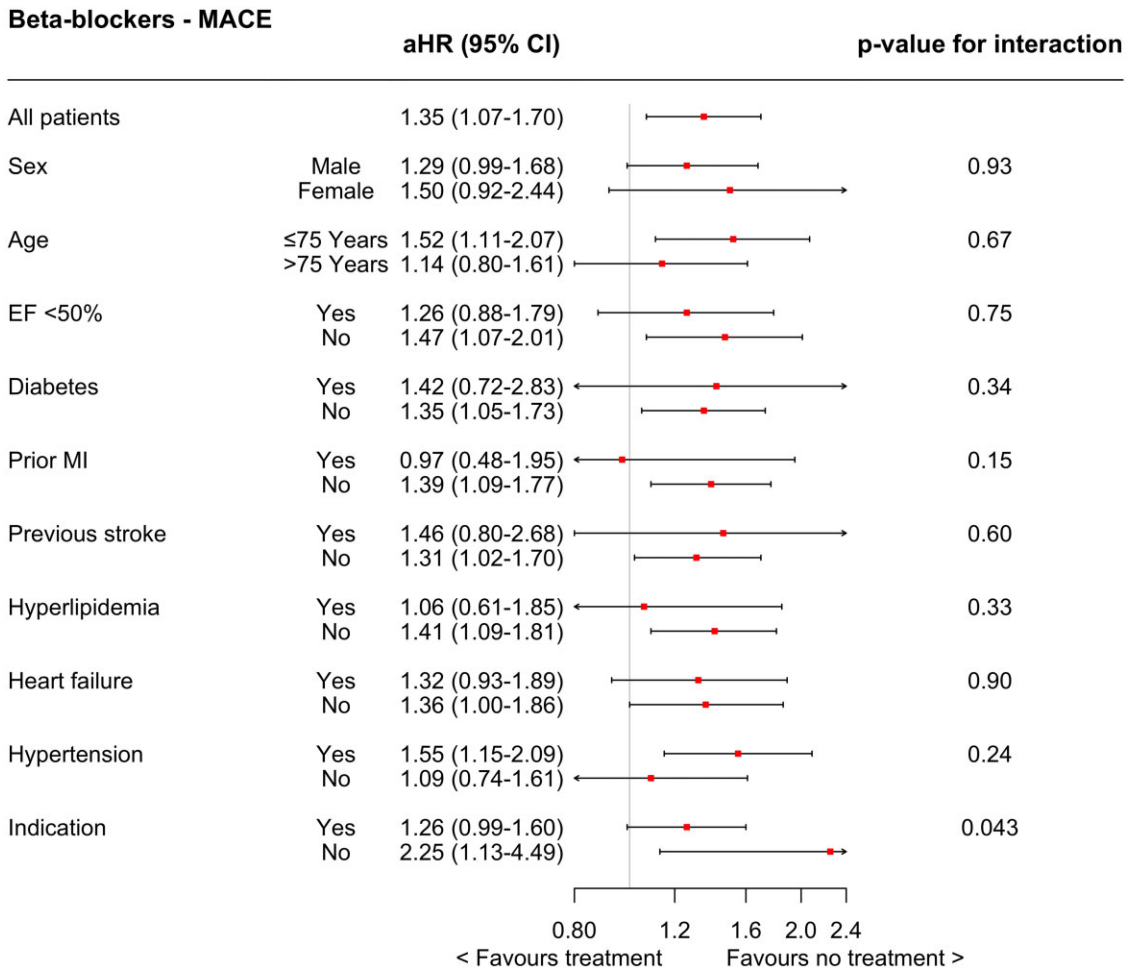

Figure 5: Forest plot illustrating the treatment effect of β-blockers stratified by different subgroups. Presented adjusted hazard ratio are from Cox regression models, adjusted for age, sex, comorbid conditions and time-updated use of other medical therapies. CI: confidence interval; EF: ejection fraction; HR: hazard ratio; MI: myocardial infarction.

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Conflict of interest: Anders Jeppsson has received fees for consultancy from AstraZeneca, LFB Biotechnologies and Werfen, all unrelated to the present work. None of the other co-authors have anything to disclosure.

DATA AVAILABILITY

The data underlying this article were provided by SWEDEHEART and national healthcare registries in Sweden. Data will be shared on reasonable request to the corresponding author with the permission of SWEDEHEART and the Swedish National Board of Health and Welfare.

Author contributions

Charlotta Törngren: Conceptualization; Formal analysis; Validation; Writing—original draft. **Kristjan Jonsson:** Validation; Writing—review & editing. **Emma C. Hansson:** Formal analysis; Validation; Writing—review & editing. **Amar Taha:** Formal analysis; Validation; Writing—review & editing. **Anders Jeppsson:** Conceptualization; Formal analysis; Funding acquisition; Validation; Writing—review & editing. **Andreas Martinsson:** Conceptualization; Formal analysis; Funding acquisition; Validation; Writing—original draft.

Reviewer information

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