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ORIGINAL ARTICLE

# Associations between medical therapy after surgical aortic valve replacement for aortic stenosis and long-term mortality: a report from the SWEDEHEART registry

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**Aims** The association between the use of statins, renin–angiotensin system (RAS) inhibitors, and/or $\beta$-blockers and long-term mortality in patients with aortic stenosis (AS) who underwent surgical aortic valve replacement (SAVR) is unknown.

**Methods and results** All patients with AS who underwent isolated first-time SAVR in Sweden from 2006 to 2017 and survived 6 months after discharge were included. Individual patient data from four mandatory nationwide registries were merged. Cox proportional hazards models, with time-updated data on medication status and adjusted for age, sex, comorbidities, type of prosthesis, and year of surgery, were used to investigate associations between dispensed statins, RAS inhibitors, and $\beta$-blockers and all-cause mortality. In total, 9553 patients were included, and the median follow-up time was 4.9 years (range 0–11); 1738 patients (18.2%) died during follow-up. Statins were dispensed to 49.1% and 49.0% of the patients within 6 months of discharge from the hospital and after 10 years, respectively. Corresponding figures were 51.4% and 53.9% for RAS inhibitors and 79.3% and 60.7% for $\beta$-blockers. Ongoing treatment was associated with lower mortality risk for statins {adjusted hazard ratio (aHR) 0.67 [95% confidence interval (95% CI) 0.60–0.74]; $P < 0.001$} and RAS inhibitors [aHR 0.84 (0.76–0.93); $P < 0.001$] but not for $\beta$-blockers [aHR 1.17 (1.05–1.30); $P = 0.004$]. The associations were robust in subgroups based on age, sex, and comorbidities ($P$ for interactions $>0.05$).

**Conclusions** The results of this large population-based real-world study support the use of statins and RAS inhibitors for patients who underwent SAVR due to AS.

**Keywords** Aortic valve replacement • Medical therapy • Statins • Renin–angiotensin inhibitors • $\beta$-Blockers

## Introduction

Aortic stenosis (AS) is the most common valvular heart disease and has an abysmal prognosis, if untreated, when severe and symptomatic.[1–3] No general recommendations for medications, apart from antithrombotic medication, are given in the guidelines for the management of valvular heart disease after surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI),[4,5] This contrasts with myocardial revascularization guidelines, which give explicit recommendations including statins and platelet inhibitors for all patients without contraindications; and renin–angiotensin system (RAS) inhibitors and $\beta$-blockers for patients with heart failure, previous myocardial infarction (MI), or reduced left ventricular ejection fraction (LVEF).[6] This difference reflects the lack of robust evidence from randomized trials or large population-based observational studies to show that any medical

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therapy after SAVR/TAVI improves outcomes. Limited data from single-centre studies,[7] smaller cohort studies,[8,9] and randomized studies with surrogate endpoints[10] indicate that long-term treatment with RAS inhibitors after SAVR is beneficial, but no data are available for statins and $\beta$-blockers after SAVR. Studies of medical treatment after TAVI, which focused on statins and RAS inhibitors, are more extensive and consistently show an association with reduced mortality risk.[10–15]

Despite the absence of general recommendations for medical therapy, medical treatment is indicated in AS patients with hyperlipidaemia, hypertension, and/or heart failure after valvular replacement. Accordingly, a substantial proportion of AS patients are dispensed statins, RAS inhibitors, and/or $\beta$-blockers after surgery. These circumstances allow us to study potential associations between ongoing treatment with statins, RAS inhibitors, and/or $\beta$-blockers and long-term mortality after SAVR in AS patients.

The aims of this large population-based study in AS patients were as follows: (i) To determine the extent of treatment with statins, RAS inhibitors, and $\beta$-blockers over time after SAVR; (ii) to evaluate potential associations between ongoing treatment with statins, RAS inhibitors, and/or $\beta$-blockers and long-term mortality after SAVR; and (iii) to examine potential associations between treatment and mortality in subgroups of patients based on age, sex, and co-morbidities.

# Methods

## Data sources

The study population was selected from the Swedish Cardiac Surgery Registry, a part of SWEDEHEART.[16] The registry has an inclusion rate of >99% of all cardiac surgery procedures performed in Sweden since 1992.[17] Pre-operative patient characteristics, comorbid conditions, and surgical details are entered at the time of surgery. Individual patient data from SWEDEHEART were linked to three other validated national registries: the Cause of Death Registry, the Swedish Prescribed Drug Registry, and the National Patient Registry,[18,19] by using the unique personal identification number assigned to all Swedish inhabitants at birth or immigration. Since 1997, diagnoses in the Cause of Death Registry and the National Patient Registry are based on the International Classification of Disease version 10 (ICD-10). Data on dispensed medications were based on the Anatomical Therapeutic Classification as listed in Supplementary material online, *Table S1*, which also displays the ICD-10 codes used for the identification of comorbidities and events in the study. The manuscript has been written according to recommendations in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

## Study population

All patients in Sweden who underwent SAVR due to AS for the first time from January 2006 to December 2017 were considered for inclusion. Patients with endocarditis, concomitant coronary artery bypass grafting (CABG), multiple valve interventions, or concomitant aortic surgery were excluded. Patients who emigrated within the first 6 months or who did not survive to 6 months after surgery were excluded based on the assumption that early post-operative mortality is commonly related to the intervention itself and is unlikely to be modifiable by medical therapy. Patients who received either a bioprosthesis or a mechanical prosthesis were included. Follow-up started at 6 months after SAVR. Patients who emigrated during follow-up were censored at the time of emigration.

Medication status was updated every third month from the time of surgery. Patients were considered off-treatment if they were not dispensed medication during two consecutive 3-month periods as previously described.[21] Estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula.[22]

## Statistical analysis

Continuous variables are presented as means with standard deviation (SD) or medians with interquartile range (IQR). Categorical variables are presented as numbers and frequency (percentage). Crude incidence rates were calculated by dividing the number of events by follow-up years; associated 95% CIs were calculated assuming a Poisson distribution. Time-updated Cox proportional hazards models were used to calculate adjusted hazard ratios (aHRs) with 95% CIs for potential associations between treatment with RAS inhibitors, $\beta$-blockers, or statins with all-cause mortality, which was the primary outcome. The models had two levels of adjustments: one with adjustments for age and sex only; and one with adjustments for age, sex, previous MI, hypertension, diabetes, heart failure, hyperlipidaemia, kidney function, LVEF, type of prosthesis, year of surgery, and ongoing treatment with statins, RAS inhibitors, and $\beta$-blockers. The adjustments were decided prior to the analysis. Two variables had missing data: LVEF ($n = 95$) and kidney function ($n = 213$). Patients with missing data were handled as a separate category in the statistical analyses. Robust standard errors were used to account for the invalid hazard proportionality.[23]

Several clinically relevant subgroup analyses were decided upon a priori. These included sex, age (</≥75 years), diabetes, heart failure, previous MI, previous stroke, LVEF (</≥50%), hyperlipidaemia, hypertension, and atrial fibrillation. Formal interaction analyses were performed to evaluate differences between the subgroups. Heart failure was defined as a clinical diagnosis of heart failure; thus, it includes both patients with preserved and reduced LVEF.

Sensitivity analyses were also performed. To evaluate the possible influence of new events on the time-updated treatment, analyses were performed with time-updated data on common indications for the medical therapy investigated, i.e. heart failure, atrial fibrillation, hypertension, and MI. To assess the validity of the statistical analysis, each year was separated into 1-year of follow-up, and patients who were dispensed medicine at the start of the year were considered as being under treatment for the full 1-year period, using the fully adjusted model. Additionally, EurSCORE I and II were added to the model to further adjust for comorbid conditions. Patients were stratified into low, intermediate, and high risk according to their EuroSCORE I/II score, <10%/<4%, 10–20%/4–8%, >20%/>8%, for low, intermediate, and high risk, respectively. The results of the sensitivity analyses were compared with the results from the primary analysis.

All tests were two-tailed and interpreted at the 0.05 significance level. All analyses were performed using the R version 4.03 (R Foundation for Statistical Computing, Vienna, Austria).

### Ethics

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 in this retrospective, population-based study was waived by the committee.

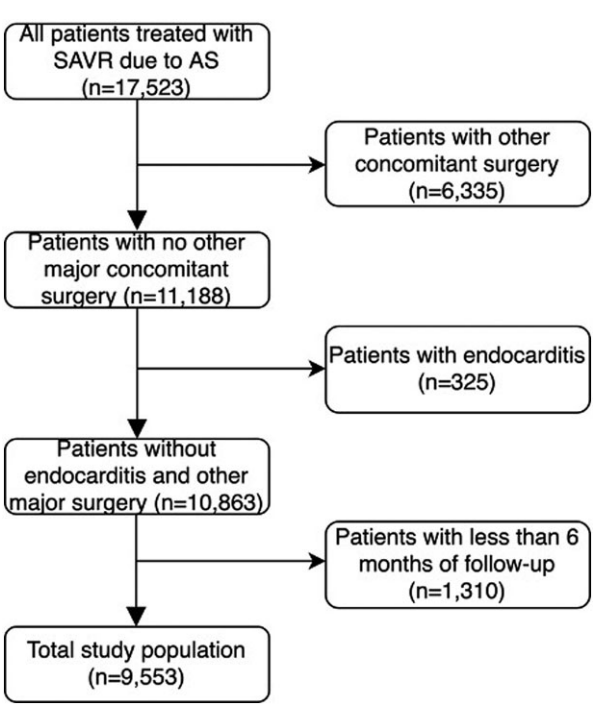


**Figure 1** Exclusion criteria in the study. Flowchart of the stepwise approach to the final selection of study population.

# Results

## General

A total of 17 523 patients were considered for inclusion; of these, 5645 (32.2%) were excluded due to concomitant CABG, 690 (3.9%) were excluded because they had multiple valves implanted or concomitant surgery of the aorta, 325 (1.9%) were excluded due to recent endocarditis, and 1310 (7.5%) did not have 6 months of follow-up. *Figure 1* illustrates the stepwise exclusion of patients in the study. After exclusions, 9533 patients were included, of whom, 4092 (42.8%) were women, and the mean age was 69.7 (SD 11.1) years. The median follow-up time was 4.9 years (range 0–11 years).

At baseline, 60.5% of the patients had a diagnosis of hypertension, 18.1% had diabetes, 20.8% had heart failure, 7.8% had previous MI, and 27.5% had hyperlipidaemia. Patient characteristics for all patients and patients stratified by treatment status for statins, RAS inhibitors, and $\beta$-blockers at baseline are presented in *Table 1*. At baseline, patients with medical therapy had a higher prevalence of all investigated comorbidities than patients without medical therapy (Supplementary material online, *Tables S2–S4*).

A total of 1738 (18.2%) patients died during follow-up. In addition, 493 (5.2%) patients developed new-onset heart failure, 899 (9.4%) got a new diagnosis of atrial fibrillation, 1249 (13.1%) had hypertension, 262 (2.7%) suffered a stroke, and 171 (1.8%) had an MI. Besides medical therapy, the following variables were associated with mortality: advanced age, male sex, early year of operation, previous stroke, previous MI, peripheral artery disease, heart failure, low LVEF, hypertension, diabetes, reduced kidney function, and biological prosthesis.

## Statin therapy

### Utilization

The extent of statins, RAS inhibitors, and $\beta$-blockers dispensed over time is presented in *Figure 2*. Statins were dispensed to 4686 (49.1%) patients at baseline, a proportion that remained stable during follow-up (49.0% at 10 years after SAVR). The extent of statins dispensed in relation to sex is presented in Supplementary material online, *Figure S1A*. Fewer female than male patients were dispensed statins, but the proportions did not change over time.

### Associations between statins and long-term mortality

Crude mortality rates and aHRs are presented in *Table 2* for all studied medications. Ongoing treatment with statins was significantly associated with lower long-term mortality risk in both the age- and sex-adjusted model and the fully adjusted model (aHR 0.67, 95% CI 0.60–0.74; $P < 0.001$, *Table 2* and *Figure 3*). The fully adjusted associations between medical therapy and mortality for subgroups based on age, sex, and comorbidities are presented in *Figures 4–6*. For statins, there was no interaction for any of the investigated subgroups, i.e. an association between treatment and a lower risk of mortality was found in all studied subgroups (*Figure 4*).

### Sensitivity analyses

The aHR when adding time-updated data on comorbid conditions (heart failure, atrial fibrillation, hypertension, and MI) was 0.69 (95% CI 0.62–0.76), similar to that from the main analysis for statins. The results from the analyses of individually updated comorbid conditions were the same as in the main analysis and are presented in Supplementary material online, *Table S5*. Results from the consecutive 1-year analyses with a 1-year stepwise increase in follow-up confirmed the results in the main analysis (Supplementary material online, *Figure S2*).

## RAS inhibitor therapy

### Utilization

RAS inhibitors were dispensed to 4946 (51.8%) of the patients at baseline, and the proportion remained stable during follow-up with 53.9% of the patients dispensed RAS inhibitors after 10 years (*Figure 2*). The use of RAS inhibitors in relation to sex was similar to that of statins, with fewer RAS inhibitors dispensed to female patients than to male patients and without an increased difference over time (Supplementary material online, *Figure S1B*).

### Associations between RAS inhibitor therapy and long-term mortality

Ongoing treatment with RAS inhibitors was not significantly associated with lower mortality risk in the age- and sex-adjusted model, but in the fully adjusted model, there was a significant association (aHR 0.84, 95% CI 0.76–0.93; $P = 0.004$, *Table 2*). In subgroup analyses (*Figure 5*), there was a significant interaction with diabetes, with a stronger association observed between treatment and reduced mortality risk in patients with diabetes than in those without diabetes (interaction *P*-value 0.018). For the other subgroups, including heart failure, previous MI, low LVEF,

**Table 1** Baseline characteristics of 9553 SAVR patients combined and divided by treatment status at baseline

| | All patients ($n = 9553$) | Patients on $\beta$-blockers at baseline ($n = 7601$) | Patients on RAS-inhibitors at baseline ($n = 4946$) | Patients on statins at baseline ($n = 4686$) |
|---|---|---|---|---|
| Age (years, SD) | 69.7 (11.1) | 70.3 (10.7) | 70.9 (9.9) | 71.3 (8.7) |
| Female (%) | 4092 (42.8%) | 3291 (43.3%) | 2008 (40.6%) | 1941 (41.4%) |
| *Left ventricular ejection fraction* | | | | |
| <50% | 1894 (19.8%) | 1644 (21.6%) | 1329 (26.9%) | 937 (20.0%) |
| BMI (IQR) | 27.0 (IQR 6.3) | 27.1 (IQR 6.3) | 27.5 (IQR 6.6) | 27.5 (IQR 6.4) |
| eGFR (mL/min, SD) | 76.3 (29.6) | 75.5 (29.5) | 74.0 (29.0) | 73.8 (28.8) |
| Previous MI | 746 (7.8%) | 652 (8.6%) | 487 (9.8%) | 568 (12.1%) |
| Atrial fibrillation | 4195 (43.9%) | 3639 (47.9%) | 2422 (49.0%) | 2138 (45.6%) |
| Heart failure | 1990 (20.8%) | 1729 (22.7%) | 1435 (29.0%) | 1039 (22.2%) |
| Diabetes | 1730 (18.1%) | 1449 (19.1%) | 1247 (25.2%) | 1228 (26.2%) |
| Renal failure | 441 (4.6%) | 377 (5.0%) | 267 (5.4%) | 242 (5.2%) |
| Previous stroke | 790 (8.3%) | 657 (8.6%) | 477 (9.6%) | 519 (11.1%) |
| Hypertension | 5784 (60.5%) | 4844 (63.7%) | 3788 (76.6%) | 3327 (71.0%) |
| Hyperlipidaemia | 2629 (27.5%) | 2183 (28.7%) | 1591 (32.2%) | 2195 (46.8%) |
| Mechanical prosthesis | 2049 (21.4%) | 1553 (20.4%) | 931 (18.8%) | 833 (17.8%) |

Treatment status was stratified on statins, RAS inhibitors, and $\beta$-blockers. Mean and standard deviation or numbers (percentage). BMI, body mass index; GFR, glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; RAS, renin–angiotensin system; SAVR, surgical aortic valve replacement; SD, standard deviation.

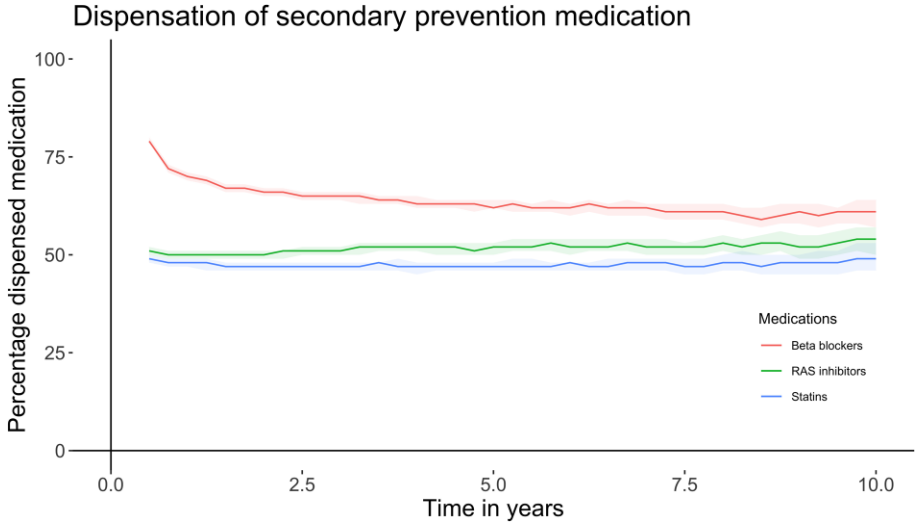


**Figure 2** Dispense of medical therapy over time. Line plot illustrating the medical therapy dispensed over time after SAVR.

and hypertension, there were no interactions for RAS inhibitor treatment.

### Sensitivity analyses

When time-updated data on all comorbid conditions were added to the model, the aHR for RAS inhibitors was 0.79 (95% CI 0.71–0.87), consistent with the main analyses, and no differences were observed in the 1-year stepwise model (Supplementary material online, *Figure S2*), nor for the individually updated comorbidities (Supplementary material online, *Table S5*).

## $\beta$-Blocker therapy

### Utilization

At baseline, 7601 (79.6%) of the patients were dispensed $\beta$-blockers. This proportion declined rapidly during the first year after SAVR and continued to slowly decline over time; after 10 years 60.7% were dispensed $\beta$-blockers (*Figure 2*). More $\beta$-blockers were dispensed to female patients than to male patients; the trends over time, however, were similar for both sexes (Supplementary material online, *Figure S1C*).

**Table 2 Crude mortality rates with a 95% confidence interval based on time-updated exposure and adjusted effects of time-updated use of medical therapy on mortality evaluated by Cox regression**

| | Crude mortality rate without treatment per 100 person-years (95% CI) | Crude mortality rate with treatment per 100 person-years (95% CI) | Age- and sex-adjusted model aHR (95% CI) *P*-value | Full model[a] aHR (95% CI) *P*-value |
|---|---|---|---|---|
| Statins | 3.67 (3.43–3.91) | 3.50 (3.27–3.74) | 0.60 (0.50–0.73) $P < 0.001$ | 0.67 (0.60–0.74) $P < 0.001$ |
| RAS inhibitors | 3.13 (2.92–3.35) | 4.43 (4.16–4.72) | 0.85 (0.71–1.02) $P = 0.088$ | 0.84 (0.76–0.93) $P = 0.004$ |
| $\beta$-Blockers | 3.07 (2.75–3.42) | 3.83 (3.64–4.04) | 1.12 (0.91–1.37) $P = 0.30$ | 1.17 (1.05–1.30) $P < 0.001$ |

aHR, adjusted hazard ratio; CI, confidence interval; RAS, renin–angiotensin system.
[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.

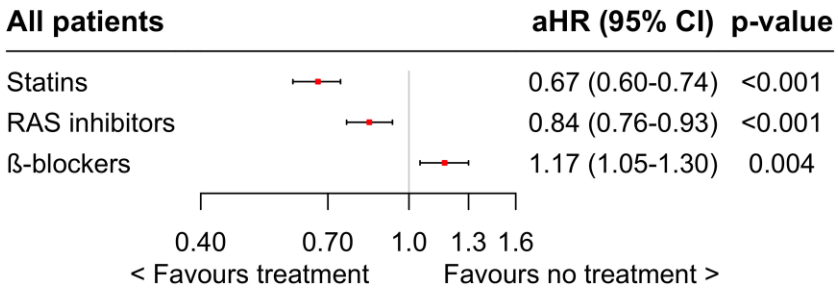


**Figure 3** Association between all-cause mortality and different medical therapies for all patients. Forest plot illustrating the adjusted association between ongoing medical treatment and mortality. Presented aHRs are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of other medical therapies. aHR, adjusted hazard ratio; CI = confidence interval.

### Associations between $\beta$-blocker therapy and long-term mortality

Ongoing $\beta$-blocker treatment was not significantly associated with a higher mortality risk in the age- and sex-adjusted model, but in the fully adjusted model, a significant association was observed (aHR 1.17, 95% CI 1.05–1.30; $P < 0.001$, *Table 2*). There were no interactions for $\beta$-blockers in any of the studied subgroups (*Figure 6*).

### Sensitivity analyses

In the analysis with the addition of time-updated data on all comorbid conditions, the point estimate for $\beta$-blockers was lower compared to the main analysis and did not meet statistical significance; aHR 1.11 (95% CI 1.00–1.26), $P = 0.057$. The point estimates were also lowered in analyses of the individual comorbid conditions, but the results remained similar to the main analysis (Supplementary material online, *Table S5*). In the consecutive 1-year analyses with 1-year stepwise increases, no differences were observed compared to the main analysis for all the 1-year analyses (Supplementary material online, *Figure S2*).

### General sensitivity analyses

The exclusion of patients with previous PCI ($n = 450$) and previous MI ($n = 448$) did not change the results of the main analysis. In an additional sensitivity analysis, an incremental effect of the combination of RAS inhibitors and statins was explored. There was a stronger association when patients used both drugs simultaneously, aHR 0.54 (95% CI 0.46–0.62), compared to one of them, aHR 0.79 (95% CI 0.71–0.89). When additional adjustment with a risk score (EuroSCORE I/II) was added to the fully adjusted model, the results remained the same, 0.65 (95% CI 0.58–0.73), HR 0.83 (95% CI 0.75–0.92), and 1.17 (95% CI 1.05–1.31) for statins, RAS inhibitors, and $\beta$-blockers, respectively.

## Discussion

The main finding of this large population-based study is that ongoing use of statins and RAS inhibitors was independently associated with lower long-term mortality risk in patients who had undergone isolated SAVR due to AS. Statin use was associated with lower mortality risk both in SAVR patients with and without a diagnosis of hyperlipidaemia, previous stroke, or previous MI at baseline.

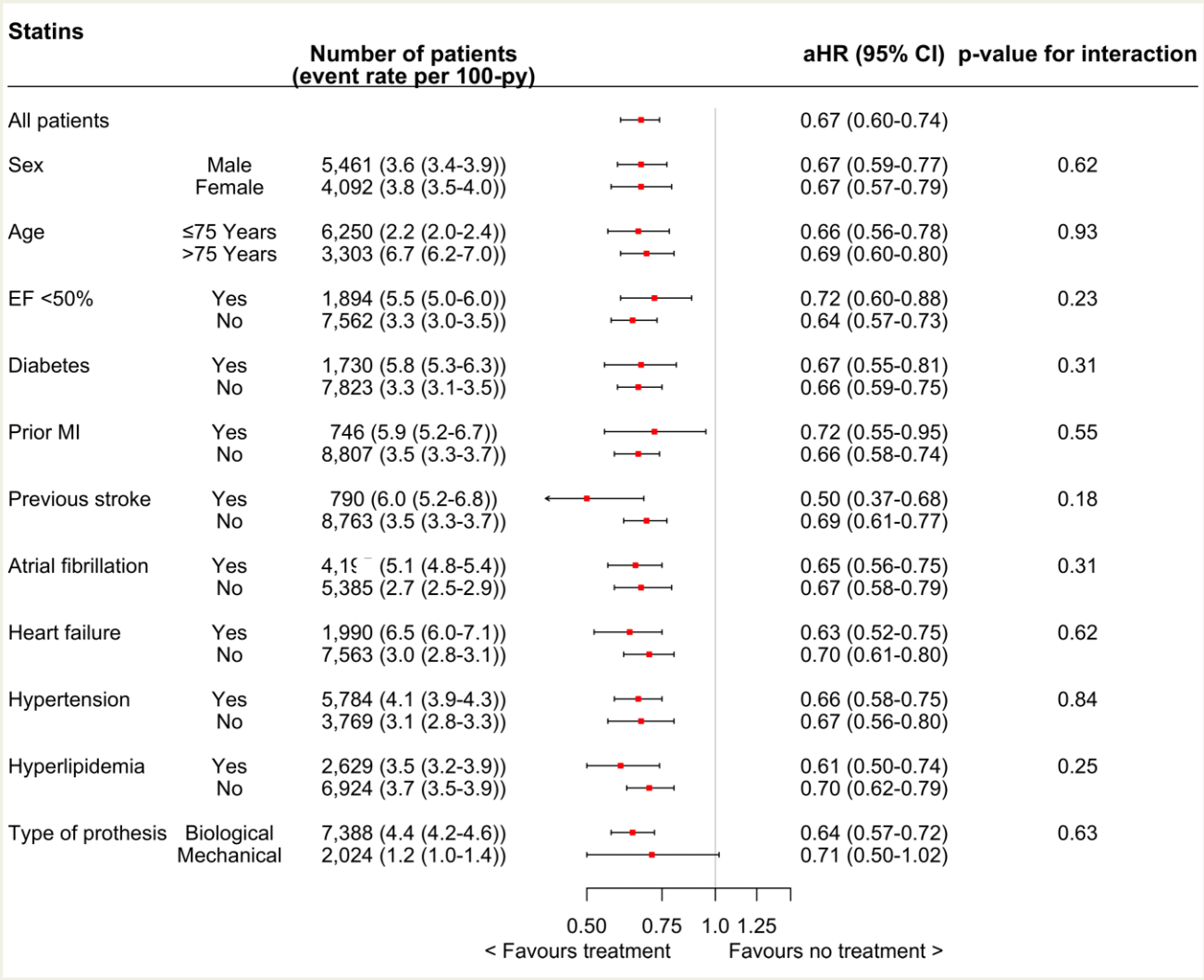


**Figure 4** Association between all-cause mortality and statin treatment. Forest plot illustrating the adjusted association between ongoing statin treatment and mortality stratified on different subgroups. Presented aHRs are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of other medical therapies. The event rate is presented with a 95% CI. Py, person-years; HR,hazard ratio; CI, confidence interval; EF, ejection fraction; MI, myocardial infarction.

The association between RAS inhibition and lower mortality risk was significant in patients with and without a diagnosis of hypertension, heart failure, previous MI, and reduced LVEF at baseline. $\beta$-Blocker therapy was associated with an increased mortality risk.

Current American and European valve guidelines lack clear recommendations for medical therapy in SAVR patients, except for antithrombotic medications. However, medical treatment is indicated in patients with hyperlipidaemia, hypertension, and heart failure after SAVR. In this study, 27.5% of the patients had hyperlipidaemia, 60.5% had hypertension, 20.8% had heart failure, 19.8% had reduced LVEF at baseline, and 7.8% had a previous MI, while only 26.5% of the patients had none of these conditions at baseline. Accordingly, a substantial proportion of the SAVR patients in this study were dispensed statins, RAS inhibitors, and/or $\beta$-blockers during follow-up, allowing us to study the associations between ongoing use of statins, RAS inhibitors, and $\beta$-blockers and long-term mortality after SAVR in AS patients. Optimizing the post-surgical medical therapy after SAVR is of utmost importance as these patients have substantial life expectancy after surgery.[24]

We are unaware of any previous study that has evaluated the association between statin treatment and outcome after SAVR. However, meta-analyses of observational studies and sub-studies of randomized trials have shown significant associations between statin treatment and better long-term survival in TAVI patients.[14,15,25] The mechanism is unclear, but it has been speculated that statin therapy reduces the risks of mortality through a reduction of ischaemic events.[25] The results of studies in TAVI populations cannot be directly translated to SAVR patients given that most TAVI patients are markedly older and have more comorbidities than SAVR patients. In this study, 27.5% of the patients had a diagnosis of hyperlipidaemia and 49.1% were treated with statins at baseline, indicating that a

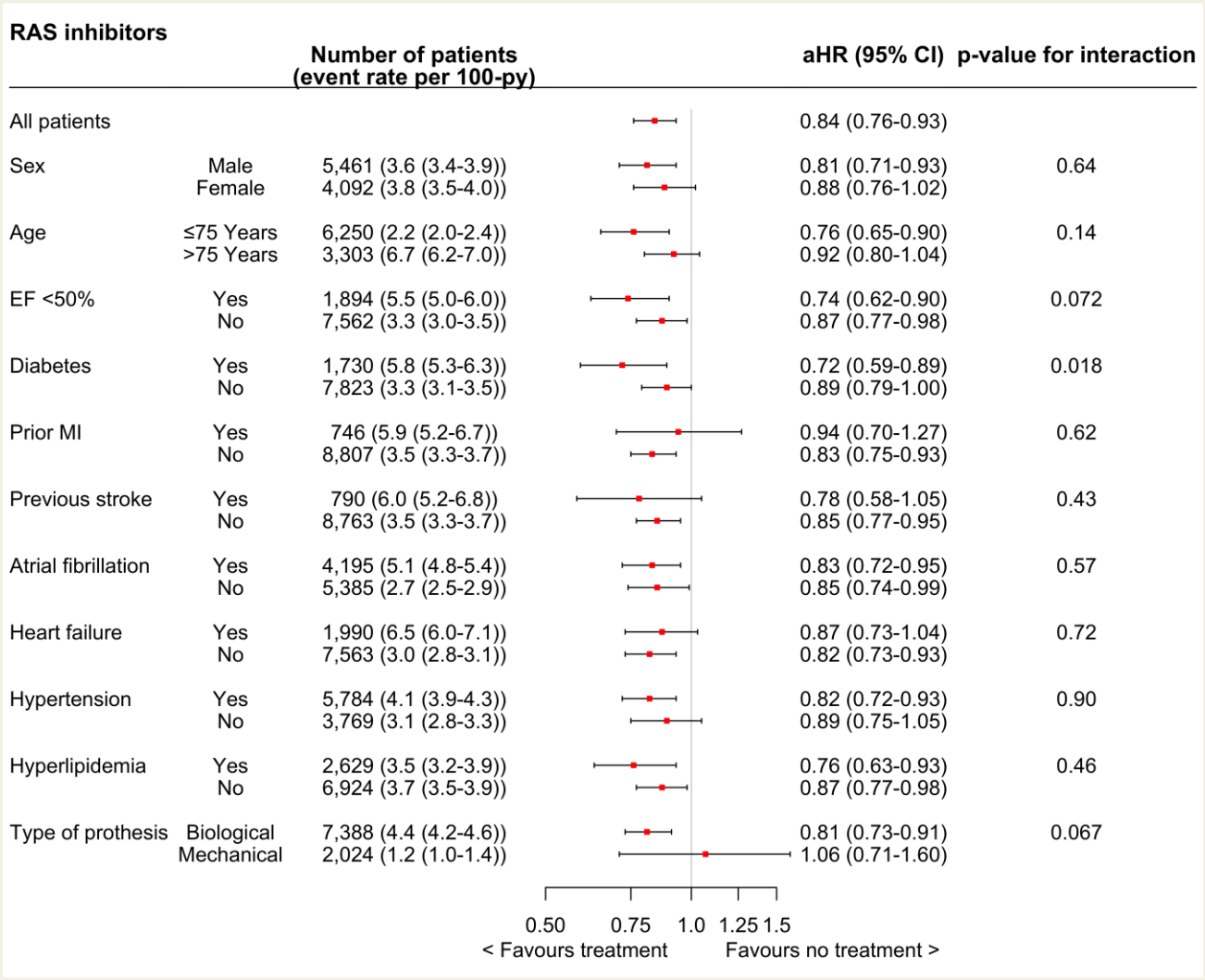


**Figure 5** Association between all-cause mortality and RAS inhibitor treatment. Forest plot illustrating the treatment effect of RAS inhibitors stratified on different subgroups. Presented aHRs are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of other medical therapies. The event rate is presented with a 95% CI. Py, person-years; HR, hazard ratio; CI, confidence interval; EF, ejection fraction; MI, myocardial infarction.

substantial number of patients were prescribed statins because of risk factors and comorbidities other than hyperlipidaemia. Accordingly, previous MI and previous stroke were more common in statin-treated patients. We observed a strong association between ongoing statin treatment and lower mortality risk (aHR 0.67), and the findings were consistent in all subgroups of patients, including patients without hyperlipidaemia, previous stroke, and previous MI at baseline (*Figure 4*). Sensitivity analyses confirmed the association with a reduction in mortality in all additional analyses. Although an observational study, such as the present one, cannot establish causality, the results suggest that statin treatment may be considered in all SAVR patients without contraindications, even in the absence of hyper/ dyslipidaemia, previous stroke, or MI.

Observational studies have shown that the RAS inhibition is associated with reduced mortality after TAVI, but there are limited data after SAVR.[12,13] In SAVR patients, RAS inhibitors target several pathways that may be beneficial. RAS blockade reduces inflammation, fibrosis, and calcification, thereby enhancing reverse remodelling and improving myocardial contractility, and diastolic function, which may result in an improved outcome after SAVR.[11,26] Goel *et al.* showed in an observational single-centre study in 1752 SAVR patients, 741 of whom received RAS inhibitors, that the medication was associated with greater adjusted survival at 10 years.[7] Smaller observational single-centre studies, from Magne *et al.* ($n = 508$) and Yiu *et al.* ($n = 150$), also showed greater long-term survival in SAVR patients treated with RAS inhibitors.[8,9] In this study, approximately half of the patients were dispensed RAS inhibitors at baseline. During follow-up, this proportion remained stable even though more patients developed an indication for treatment. As expected, patients treated with RAS inhibitors had a lower LVEF and a higher prevalence of heart failure, previous MI, diabetes, and hypertension at baseline. RAS inhibition was associated with significantly lower adjusted

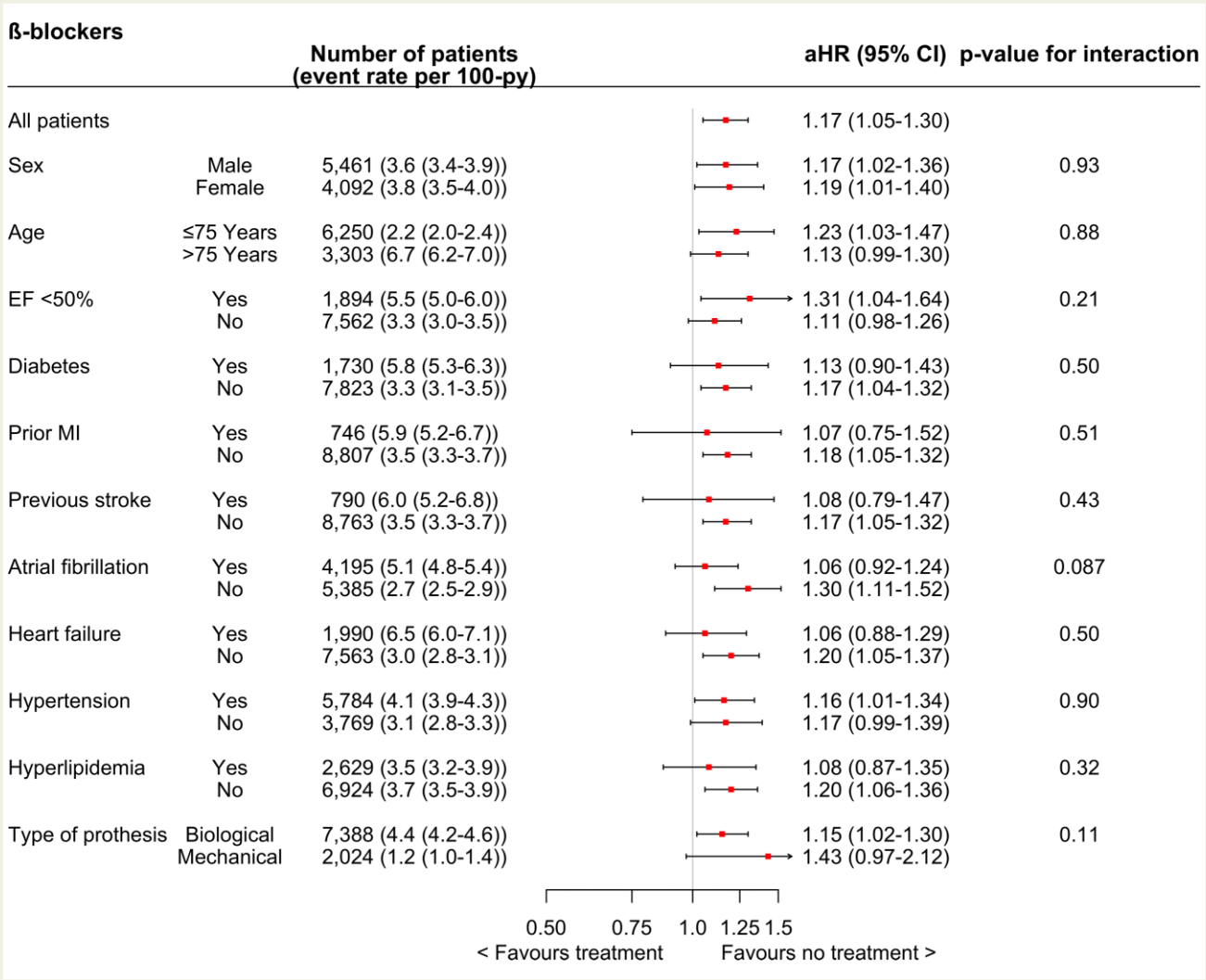


**Figure 6** Association between all-cause mortality and $\beta$-blocker treatment. Forest plot illustrating the treatment effect of $\beta$-blockers stratified on different subgroups. Presented aHRs are from Cox regression models, adjusted for age, sex, comorbid conditions, and time-updated use of other medical therapies. The event rate is presented with a 95% CI. Py, person-years; HR, hazard ratio; CI, confidence interval; EF, ejection fraction; MI, myocardial infarction.

mortality risk during follow-up, which confirms the results of the previously published smaller observational studies.[7–9] Notably, the association between treatment and lower mortality was also present in patients without a diagnosis of hypertension, heart failure, previous MI, or reduced LVEF. The association with lower mortality was consistent in all subgroups of patients (interaction *P*-values $>$ 0.05), except for those without diabetes (*Figure 5*). Whether the interaction in the diabetes subgroup is a chance finding or reflects a stronger association in patients with diabetes remains unclear. In Goel *et al.*'s study, the association between RAS inhibition and better survival was consistent in those with and without diabetes.[7] Interestingly, patients treated with concomitant RAS inhibition and statin therapy had the strongest association with reduced mortality, indicating that treatment has an incremental effect and that there is potential for optimizing post-interventional medical treatment.

Interestingly, almost 80% of the patients were dispensed $\beta$-blockers at baseline even though only a minority of patients had any of the established indications for $\beta$-blockade, i.e. previous MI (with reduced LVEF) or heart failure with reduced LVEF. However, a large proportion had atrial fibrillation (44%) or hypertension (61%), for which $\beta$-blockers are commonly prescribed. The use of $\beta$-blockers declined over time, most notably during the first year of follow-up, but over 60% of patients were still prescribed these drugs after 10 years.

We were unable to find any previous prospective or observational studies analysing the association between $\beta$-blockade and long-term outcome after SAVR. There is also a paucity of studies on $\beta$-blockers in TAVI patients. One recent observational study reported that (i) the incidence of all-cause mortality and re-hospitalization was higher in $\beta$-blocker-treated TAVI patients than in patients treated with RAS inhibitors; (ii) $\beta$-blocker treatment at discharge was not

associated with a lower risk for death or heart failure hospitalization at 2 years, aHR 0.94 (95% CI 0.71–1.25); and (iii) the addition of $\beta$-blockade to RAS inhibition was not associated with lower risk compared to RAS inhibition alone.[27] In this study, ongoing $\beta$-blocker therapy was associated with a small, but statistically significant increase in mortality risk, aHR 1.17 (95% CI 1.05–1.30). This finding should, however, be interpreted cautiously for at least two reasons. First, $\beta$-blockade was not stratified on selective vs. non-selective $\beta$-blockers, which may have different indications. Thus, the observed association may rather be a marker for higher risk in patients treated with $\beta$-blockers, not captured by the adjustments. Second, the observational study design infers a risk of residual confounding. To minimize confounding, we performed a sensitivity analysis and showed that the point estimate of the hazard ratio was attenuated (from 1.17 to 1.11) when time-updated information on heart failure, MI, hypertension, and atrial fibrillation was added to the model.

Taken together, our results warrant further investigations of the efficacy and safety of $\beta$-blocker therapy in AS patients after SAVR. In agreement with our findings, the benefit of $\beta$-blockers as a general cardioprotective treatment has been brought into question lately.[28] The current evidence indicates that the beneficial effects of $\beta$-blockers, reported mainly in patients with MI prior to the era of effective revascularization and findings in patients with heart failure with reduced LVEF, might not be applicable to the whole range of cardiac patients.[29]

This study has both strengths and limitations. Strengths include the large nationwide study cohort, the real-world setting, the complete follow-up, the time-updated information on dispensed medication, and the use of validated and monitored registries. Only a small proportion of patients developed new indications for treatment with statins, RAS inhibitors, or $\beta$-blockers during follow-up. Requiring 2–3 months' period without a dispensed prescription to count as off-treatment reduces the risk of reverse causality (i.e. that terminally ill patients stop using medications). However, there are also important inherent limitations in observational studies, including residual confounding and selection bias, and the results presented in the current study should therefore not be interpreted as establishing a causal link between treatment and outcome. The adherence to medical therapy in Sweden may differ from other countries. Furthermore, we do not have information on reasons for not being dispensed medications nor information about patients' compliance to the prescribed medications. The analyses were, however, based on dispensed medications, not just prescriptions.

# Conclusions

The results of this large population-based real-life study in AS patients treated with SAVR suggest that treatment with statins and RAS inhibitors is associated with reduced all-cause mortality risk, while the use of $\beta$-blockers was associated with an increased risk of all-cause mortality. Randomized controlled trials are necessary to establish causal treatment effects.

# Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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## 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 National Board of Health and Welfare.

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