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ORIGINAL ARTICLE

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Betablockers and clinical outcome after surgical aortic valve replacement: a report from the SWEDEHEART registry

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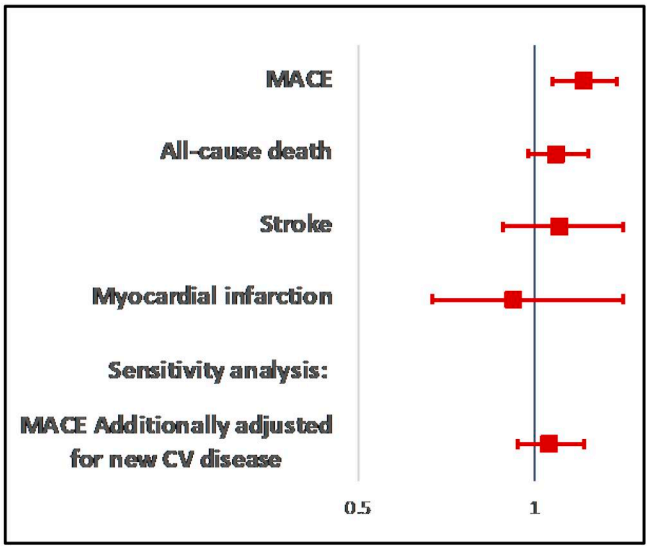
Betablockers and clinical outcome after surgical aortic valve replacement – a report from the SWEDEHEART registry

Summary

Patients with surgical aortic valve replacement due to aortic stenosis (n=11 894) were identified in mandatory national registries. MACE during follow-up (median 5.4 years [range 0-13.5]) was compared depending on betablocker treatment, defined as continuing time-updated dispense. Patients with betablockers had higher risk of MACE, but the effect was diminished when adjusting for new cardiovascular comorbidities during follow up.



Legend: MACE: Major adverse cardiovascular events

Abstract

OBJECTIVES: Previous reports suggest that betablockers appear non-beneficial after surgical aortic valve replacement (SAVR). This study aims to clarify the associations between betablockers and long-term outcome after SAVR.

METHODS: All patients with isolated SAVR due to aortic stenosis in Sweden between 2006 and 2020, alive at 6 months after surgery, were included. Patients were identified in the SWEDEHEART registry, and records were merged with data from 3 other mandatory national registries. Association between dispensed betablockers and major adverse cardiovascular events (MACE) (all-cause mortality, myocardial infarction and stroke) was analyzed using Cox proportional hazards models, with time-updated data on medication and adjusted for age, sex and comorbidities at baseline.

RESULTS: In total, 11 849 patients were included [median follow-up 5.4 years (range 0–13.5)]. Betablockers were prescribed to 79.7% of patients at baseline, decreasing to 62.2% after 5 years. Continuing treatment was associated with higher risk of MACE [adjusted hazard ratio 1.14 (95% confidence interval, CI 1.05–1.23)]. The association was consistent over subgroups based on age, sex and comorbidities except atrial fibrillation [hazard ratio (HR) 1.05 (95% CI 0.93–1.19)]. A sensitivity analysis including time-updated data on comorbidites attenuated the difference between the groups [HR 1.04 (95% CI 0.95–1.14, $P = 0.33$)].

CONCLUSIONS: Treatment with betablockers did not appear to be associated with inferior long-term outcome after SAVR, when adjusting for new concomitant diseases. Thus, it is likely that it is the underlying cardiac diseases that are associated with MACE rather than betablocker treatment.

Keywords: Aortic stenosis • Cardiac surgery • Surgical aortic valve replacement • Secondary prevention • Beta blocker

ABBREVIATIONS

AF	Atrial fibrillation
aHR	Adjusted hazard ratio
CABG	Coronary artery bypass grafting
CI	Confidence interval
HR	Hazard ratio
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
RAS	Renin–angiotensin system
SAVR	Surgical aortic valve replacement

BACKGROUND

Severe and symptomatic aortic stenosis is a malignant condition with high risk of mortality if left untreated. Nowadays, the prognosis and life expectancy after surgical aortic valve replacement (SAVR) as well as after transcatheter aortic valve implantation is excellent, even in patients of advanced age [1]. In addition to successful surgical results, the life expectancy after SAVR may potentially be even further improved if optimal and continuing secondary prevention of further cardiovascular diseases is offered.

In patients undergoing coronary artery bypass grafting (CABG), early start of secondary prevention medication after the initial event has been identified as an important target to improve patient care [2], and current guidelines recommend statins and antiplatelet therapy to all patients with established coronary artery disease, and renin–angiotensin system (RAS)-inhibitors and betablockers in selected subgroups. This combination of secondary prevention medication has been shown to reduce mortality after CABG [2], although the benefit from betablockers is increasingly being questioned [3–5].

In patients undergoing isolated SAVR, current guidelines are less clear regarding the benefits of secondary prevention medication and which drugs to use [6, 7]. Compared to coronary artery disease, there are no clear recommendations regarding medical treatment after SAVR. In addition to any need for anticoagulation, treatment of comorbidities, such as hypertension and heart failure, is recommended [7]. An American study from 2019 [5] reported that preoperative use of betablockers was associated with worse survival after SAVR in a large retrospective registry using data from the Society of Thoracic Surgeons database. However, patients with betablockers had more comorbidities and the paper reports only short-term outcome and had no information on postoperative medication. A recent publication from our group detailing medical treatment after SAVR in Sweden [8], reports that postoperative use of RAS inhibitors and statins was associated with improved survival after SAVR, whereas use of betablockers was associated with reduced survival. However, the report described only all-cause mortality and did not distinguish type of betablocker. This study aims to further investigate the use of betablockers after SAVR, associations with major adverse cardiovascular events (MACE) and explore whether any specific subgroup, based on preoperative comorbidities, may benefit from betablocker treatment.

METHODS

All cardiac surgery patients in Sweden since 1992 are recorded in the Swedish Cardiac Surgery Registry [9], as a part of the SWEDEHEART (Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) registry [10]. Data from this registry have been merged with data from other mandatory national Swedish registries (the National Patient Register, the National Cause of Death Register and the Swedish Prescribed Drug Register) using the unique personal identification number given to every Swedish citizen at birth or immigration. The National Patient Register contains information on International Classification of Diseases version 10 (ICD-10) diagnoses from every hospitalization in Sweden since 1987, the National Cause of Death Register records date and cause of death and the Swedish Prescribed Drug Register has information on prescribed and dispensed drugs using the Anatomical Therapeutic Classification (ATC).

Ethical statement

The study was approved by the regional research ethics committee (registration number 2021–00122), waiving individual consent, and was written according to Strengthening the Reporting in Observational studies in Epidemiology recommendations [11].

Patients and definitions

All patients undergoing SAVR due to aortic stenosis with a biological or mechanical valve prosthesis between 2006 and 2020

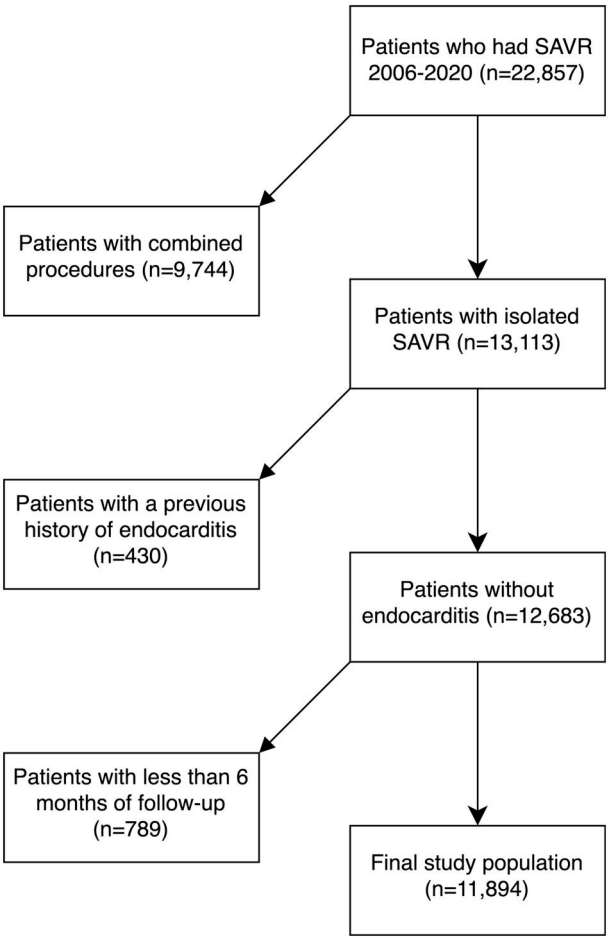


Figure 1: Flowchart of included patients.

were identified from the Cardiac Surgery Registry and included in the dataset. Patients with infectious endocarditis or concomitant procedures were excluded. Patients who died within 6 months after surgery were excluded as early mortality was deemed unlikely to be affected by long-term pharmacological treatment, similarly, patients with less than 6 months of follow-up were also excluded. Otherwise, patients were followed until death, emigration or until closure of the database at 31 December, 2020. Comorbidities were taken from the Cardiac Surgery Registry and supplemented with diagnoses from the National Patient Register, defined as present at baseline if they were present at discharge after surgery. Betablocker treatment was defined as dispense of any prescribed betablocker (ATC C07) at 6 months after surgery. Cardioselective betablockers were defined as ATC C07AA, while patients with non-selective betablockers (ATC C07AB and C07AG, i.e. propranolol, carvedilol or sotalol) represented a minority of patients ($n = 532$, 4.5%, Figs 1 and 2) and were excluded from the outcome analysis. Adherence to treatment over time was updated every 3 months during follow-up and non-adherence was defined as failure to retrieve prescribed medication over 2 consecutive 3-month periods. Only dispensed prescriptions were considered in the analyses.

The primary endpoint was major cardiovascular adverse events (MACE), defined as a composite endpoint of either all-cause mortality, or a new diagnosis of stroke or myocardial infarction (MI) starting at 6 months after surgery. Secondary endpoints were the individual endpoints included in the composite endpoint. A priori determined subgroups of interest for analysis were patients with previous MI, heart failure, hypertension, atrial fibrillation (AF) and low left ventricular ejection fraction (LVEF). A sensitivity analysis adjusting for emerging comorbidities possibly confounding the analysis by an

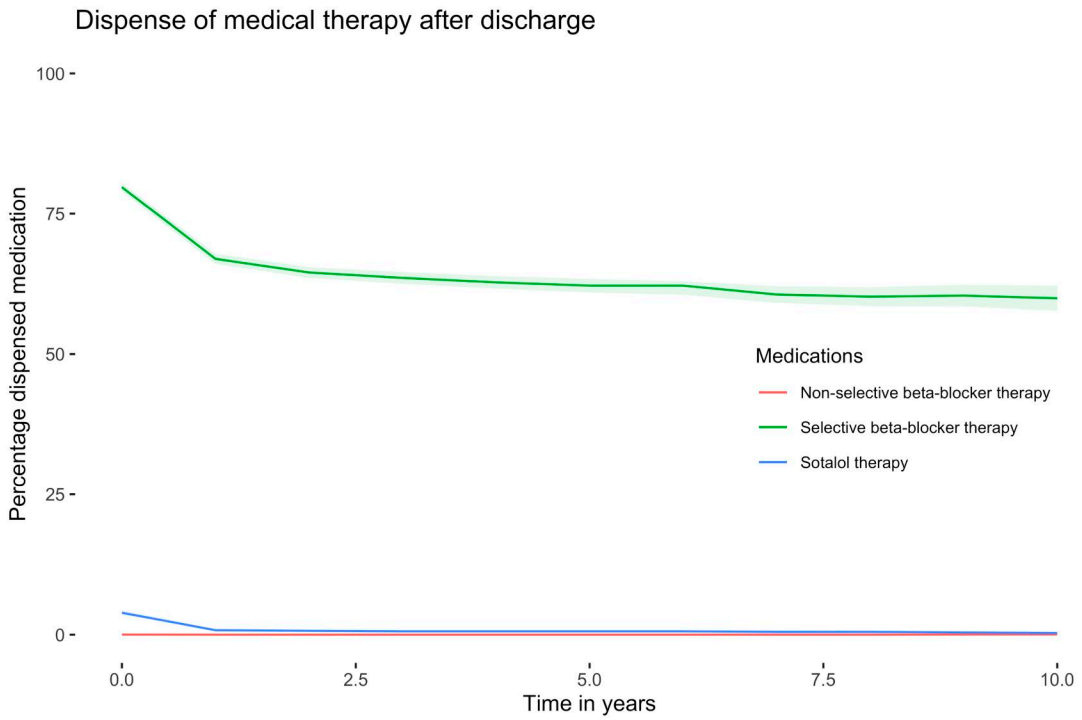


Figure 2: Dispense of betablockers at baseline 6 months after surgical aortic valve replacement, and during follow-up. Shaded area represents 95% confidence interval.

association with both treatment and outcome (i.e. heart failure, new MI, hypertension or AF) during follow-up was also conducted.

Statistics

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 Chi-square test for categorical variables. Whether the variables satisfied the normal distribution were evaluated by graphical evaluation using histograms and QQ-plots. A time-dependent Cox proportional hazards model was used to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for potential associations between treatment with betablockers and MACE. The model was adjusted for age, sex, year of surgery, mechanical/biological valve prosthesis, prior stroke, peripheral vascular disease, previous MI, prior heart failure, hypertension, hyperlipidaemia, diabetes mellitus, AF, LVEF over or under 50%, estimated glomerular filtration rate calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula [12], use of statins, use of renin-angiotensin-system-inhibitors and use of acetylsalicylic acid. The adjustments were determined prior to analyses. Several variables had missing data, body mass index ($n = 308$, 2.6%), LVEF ($n = 46$, 0.4%) and type of prosthesis ($n = 34$, 0.3%). Missing data were handled by multiple imputation by polytomous regression or logistic regression, as appropriate. Formal interaction analysis was performed for the previously mentioned clinically relevant subgroups. The proportional hazards assumption was evaluated using Schoenfeld residuals and the model did not meet the assumption. The variables with a time-varying effect were age at operation and year of surgery. This was handled by using a time-interaction term for these variables. Collinearity was assessed by variance inflation factor. Collinearity was considered non-significant as all variables had a variance inflation factor below 2.0. As a sensitivity analysis, the primary outcome was evaluated using propensity score matching. The variables as described above were used to calculate the propensity score. Logistic regression was used to predict the use of betablockers, and patients were matched 1:1 using nearest-neighbor matching with a caliper of 0.1. Matching was evaluated using standardized difference for each variable, and adequate matching was achieved.

For outcomes which did not include all-cause mortality (i.e. stroke and myocardial infarction), cause-specific hazards were calculated to account for competing risks as the aim of the study was to evaluate the impact of the treatment rather than survival probability.

Data are presented as median with 25th—75th percentiles or number with percent. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

In total, 11 894 patients were identified and ultimately included in the study. Median follow-up time was 5.4 years (range 0–13.5 years). A flowchart of excluded patients can be found in Fig. 1. Baseline comorbidities are summarized in Table 1. Patients who were prescribed betablockers at baseline were older and had significantly more comorbidities. AF was present in 47.0% of patients on betablockers compared to 27.2% of patients without betablockers, and 65.7% of patients had hypertension compared to 51.2% in the group without treatment. Additionally, previous MI, heart failure and diabetes mellitus were more common among patients treated with betablockers.

Dispense of betablockers

Betablockers were dispensed to 79.7% of patients at baseline, and decreased over the following years (Fig. 2) to 62.2% after

Table 1: Baseline characteristics

	Patients on betablockers at baseline ($n = 9610$)	Patients not on betablockers at baseline ($n = 2284$)	*P*-value
Age (years)	69.9 (SD 10.7)	67.7 (SD 12.4)	<0.001
Female (%)	3946 (41.1%)	865 (37.9%)	0.004
Left ventricular ejection fraction <50%	2085 (21.7%)	301 (13.2%)	<0.001
BMI (kg/m^2)	27.0 (IQR 21.0–33.0)	26.3 (IQR 20.7–31.9)	<0.001
eGFR (ml/min/m^2)	76.5 (29.4)	79.8 (29.1)	<0.001
Previous MI	825 (8.6%)	122 (5.3%)	<0.001
Atrial fibrillation	4520 (47.0%)	622 (27.2%)	<0.001
Heart failure	1167 (12.1%)	134 (5.9 %)	<0.001
Diabetes	1839 (19.1%)	345 (15.1%)	<0.001
Renal failure	564 (5.9%)	89 (3.9%)	0.003
Previous stroke	358 (3.7%)	65 (2.8%)	0.040
Hypertension	6316 (65.7%)	1169 (51.2%)	<0.001
Peripheral artery disease	1859 (19.3%)	380 (17.0%)	0.021
Hyperlipidaemia	2911 (30.3%)	565 (24.7%)	<0.001
Biological valve prosthesis	7585 (80.0%)	1810 (74.9%)	<0.001
Statin treatment	4974 (52.4%)	1032 (42.8%)	<0.001
RAS-inhibitor treatment	5334 (56.2%)	1043 (43.3%)	<0.001
ASA treatment	4499 (47.4%)	1143 (47.4%)	0.99

Comparison between patients with or without betablockers.

ASA: acetyl salicylic acid; BMI: body mass index; eGFR: estimated glomerular filtration; IQR: interquartile range; MI: myocardial infarction; RAS: renin–angiotensin–system.

5 years. A smaller proportion of patients (3.9%) were prescribed sotalol and this proportion decreased to close to zero over the first years after surgery. Between 2007 and 2020, the prescription of sotalol has dwindled to almost nonexistent (Fig. 3). Patients with non-selective betablockers were excluded from outcome analysis.

Outcomes

Crude event rate of MACE was 6.5 vs 5.1 events per 100 patient-years in patients with and without betablockers, respectively. In the adjusted model (Table 2), treatment with betablockers at baseline was associated with a higher risk of MACE [aHR 1.14 (95% CI 1.05–1.23)]. MACE probability over time depending on betablocker treatment is illustrated in Fig. 4. The results from the sensitivity analysis using propensity score matching resulted in a similar estimate [hazard ratio (HR) 1.13, 95% CI 1.03–1.24, $P = 0.014$]. There were no significant differences in the individual outcomes; death from any cause [aHR 1.06 (95% CI 0.98–1.15)], stroke [aHR 1.07 (95% CI 0.91–1.25)] or MI [aHR 0.94 (95% CI 0.71–1.25)]. Crude event rate of MACE was numerically higher in older patients and patients with previously diagnosed comorbidities (Supplementary Material, Table S1). The association between risk for MACE and ongoing betablocker treatment was similar and remained unchanged in all prespecified subgroups (Fig. 5), except for the group with preoperative atrial fibrillation in which there was no increased risk of MACE with betablocker treatment [aHR 1.05 (95% CI 0.93–1.19) for patients with AF and HR 1.24 (95% CI 1.11–1.38) for patients without AF, *P* for interaction = 0.038].

In a sensitivity analysis, we also included new comorbidities emerging during follow-up as a time-updated factor effect, 9.2% of patients had a new diagnosis of hypertension, 6.0% a new diagnosis of atrial fibrillation and 2.9% a new diagnosis of heart failure. After adding these to the model, the association between betablocker treatment and MACE was attenuated and there was no association between treatment and risk of MACE (HR 1.04, 95% CI 0.95–1.14, $P = 0.38$, Table 2).

DISCUSSION

This population-based study shows a high rate of long-term use of betablockers after isolated SAVR due to aortic stenosis. It also demonstrates a correlation between ongoing use of betablockers after SAVR and a worsened prognosis, expressed as a higher risk for MACE. This negative association was present also after extensive adjustments for concomitant diseases at baseline, and remained robust in all prespecified clinically interesting subgroups except for patients with atrial fibrillation.

Patients on betablocker treatment are clearly older and have more comorbidities compared with patients without betablockers, which may be one reason for the inferior outcome. Still, the difference in MACE between these groups was present also after adjustments for baseline factors. Nevertheless, the difference was mitigated after adjustments for additional diagnoses emerging during the follow-up period.

Betablockers have for long been a cornerstone in the treatment of heart failure with reduced ejection fraction. However, it has come in to question in the treatment of other cardiac diseases in the later years [4], as reflected by a number of new studies re-evaluating the use of betablockers in coronary artery disease [13]. After cardiac surgery, secondary prevention with RAS inhibitors and statins have shown consistently positive results both after SAVR [8] and coronary artery bypass grafting [14], whereas the benefits of betablockers are more ambiguous [2, 3]. Our report strengthens the initiative to evaluate

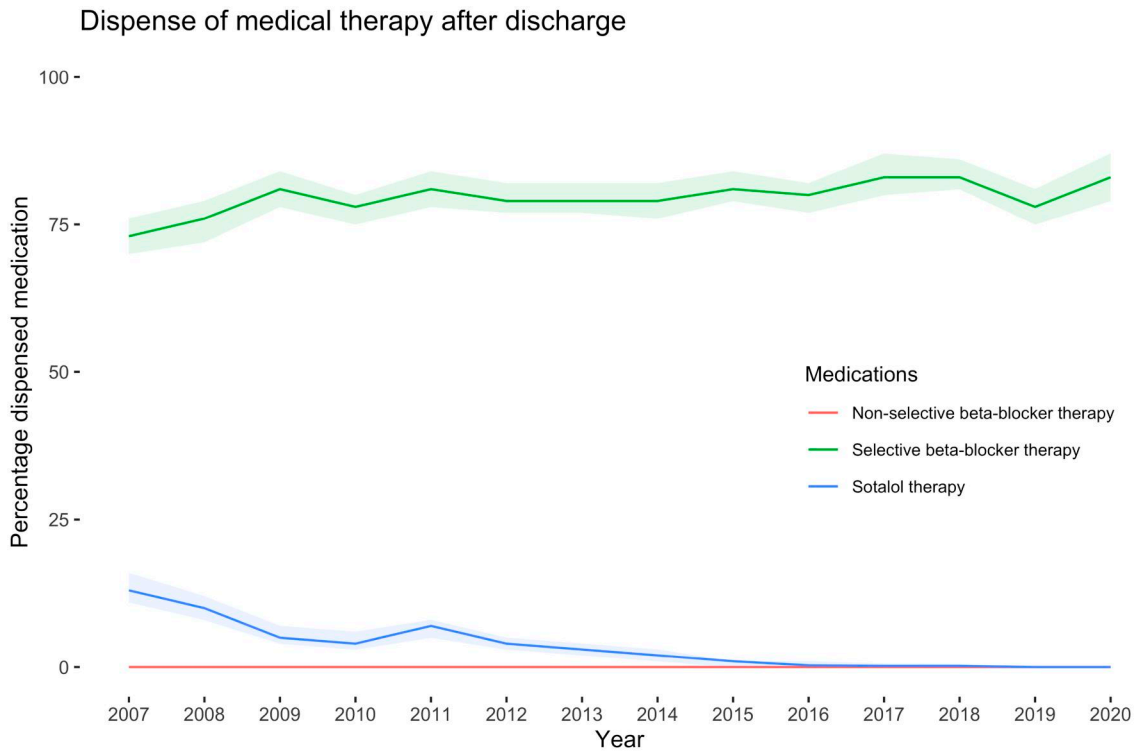


Figure 3: Change in dispense of different types of betablockers after surgical aortic valve replacement over time.

Table 2: Primary and secondary endpoints

	Patients on betablockers at baseline ($n = 9610$) Event rate (per 100 patient years)	Patients not on betablockers at baseline ($n = 2284$) Event rate (per 100 patient years)	Adjusted[a] hazard ratio aHR (95% CI)
MACE	6.5 (6.3–6.8)	5.1 (4.8–5.6)	1.14 (1.05–1.23)
All-cause death	4.9 (4.7–5.1)	3.9 (3.6–4.3)	1.06 (0.98–1.15)
Stroke	2.1 (1.9–2.2)	1.5 (1.3–1.8)	1.07 (0.91–1.25)
Myocardial infarction	0.5 (0.4–0.6)	0.5 (0.4–0.6)	0.94 (0.71–1.25)
Sensitivity analyses			
Additionally adjusted for cardiovascular disease occurring during follow-up[b]			
MACE			1.04 (0.95–1.14)
All-cause death			0.92 (0.84–1.00)
Stroke			0.92 (0.79–1.05)
Myocardial infarction			0.92 (0.69–1.22)

[a]Hazard ratio from Cox regression analysis. Adjusted for age, sex, year of surgery, mechanical/biological valve prosthesis, prior stroke, peripheral vascular disease, previous MI, prior heart failure, hypertension, hyperlipidaemia, diabetes mellitus, atrial fibrillation, LVEF over or under 50%, estimated glomerular filtration rate (eGFR) calculated according to the Chronic Kidney Disease Epidemiology Collaboration formula [12], use of statins, use of renin–angiotensin–system inhibitors and use of acetylsalicylic acid.

[b]Additionally adjusted for new diagnosis of heart failure, myocardial infarction, hypertension or atrial fibrillation.

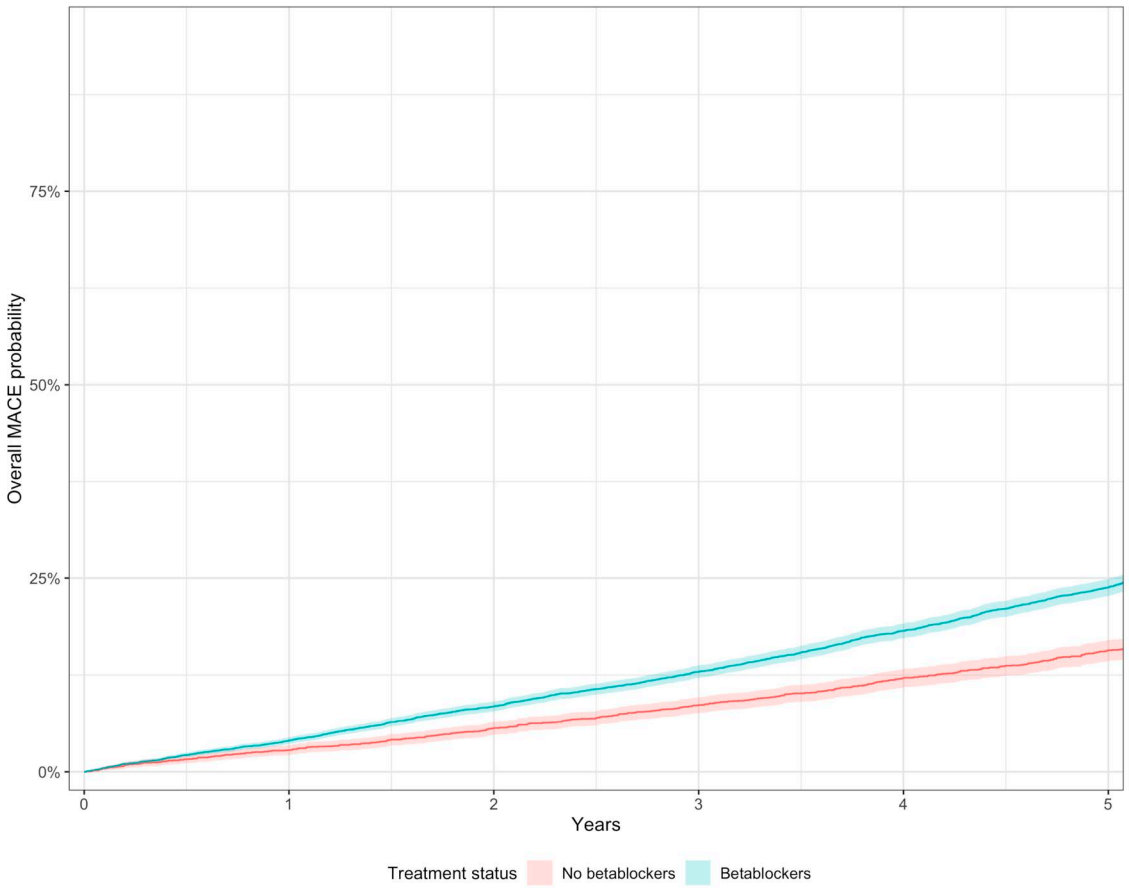


Figure 4: Major adverse cardiovascular events over time in patients with and without betablocker treatment after surgical aortic valve replacement. The curves start at start of follow-up at 6 months after surgery. Shaded areas represent 95% confidence intervals.

betablocker treatment anew in this era of cardiology with far more therapeutical options, such as RAS inhibitors, which were not present in the early studies showing beneficial effects of betablockers. Newer treatments for heart failure such as sodium-glucose cotransporter-2 inhibitors were not prevalent during the studied period and have not been considered in this paper.

In this study, the models were controlled not only for concomitant diagnoses at baseline but also for the use of other secondary prevention medications (i.e. platelet inhibitors, statin

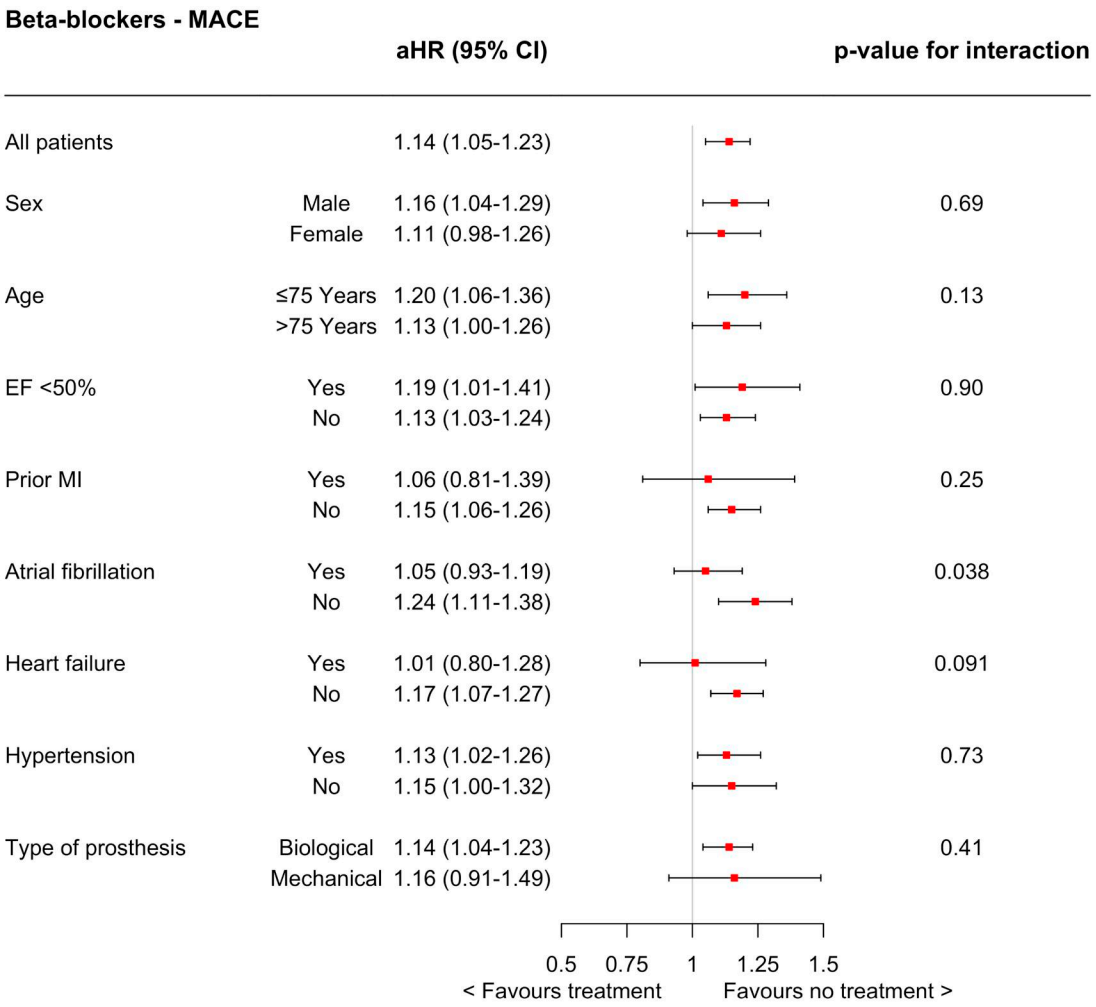


Figure 5: Effect of betablockers after surgical aortic valve replacement in prespecified subgroups.

treatment and RAS inhibitors) during follow-up. As previously reported from our group [8], patients use of RAS inhibitors was beneficial both before and after adjustments for confounding factors. In the current study, there was no trend toward a more positive effect in any of the subgroups with traditionally strong indications for betablockers, such as heart failure or previous MI. It should be noted that information describing the exact indication for use of betablocker treatment in each patient was not noted in the registries. It is therefore not possible to separate patients on betablocker treatment due to heart failure from those who have it mainly as an adjunct in antihypertensive treatment if both diagnoses are present.

This cohort does not include patients with coronary artery disease requiring surgical intervention, as only isolated SAVR was included. Hence, it is possible that a number of SAVR patients who would benefit more from betablocker treatment were excluded in this study design.

The present data confirm and expand previously reported studies [5, 8]. Schubert *et al.* reported that patients on betablockers prior to surgery had worse short-term prognosis after SAVR, when compared to patients without betablockers. Another study has shown similar results for betablocker treatment after transcatheter aortic valve implantation, where no effect, positive or negative, could be seen on midterm outcome [15]. Our data confirm this absence of effect also after SAVR in long-term follow-up with continuing betablocker treatment.

Patients with AF is a group with a normally strong indication for treatment with betablockers. In this study, we were not able to ascertain a beneficial effect in these patients. However, the negative association in the main analysis was not present in patients with AF. Also, most patients with AF have an indication for treatment with anticoagulants, which we have not studied in this paper, but may impact morbidity and mortality during the follow-up.

The sensitivity analysis of emerging comorbidities which may impact the indication for use of betablockers and also possibly affect outcomes included hypertension, AF and heart failure. Hypertension was the most common cardiac comorbidity to appear during follow-up, with 9.2% of patients receiving a new diagnosis. A new diagnosis of AF was less common, 6.0% in total during follow-up. It is important to note that postoperative AF presenting in the first period after surgery is included in baseline comorbidities and were therefore not included in the sensitivity analysis. Development of heart failure was rather uncommon, which is encouraging, as it confirms that SAVR alleviates the increased strain on the heart and prevents the expected deterioration of heart function if the valve would have been left untreated. When adjusted for these factors, the negative

association was no longer significant, indicating that it is not the betablocker treatment *per se*, but instead the underlying worsening of cardiac disease that is causing the increase in MACE.

This report represents a retrospective registry study, which comes with well-known strengths and limitations. The study setup carries an inherent risk for residual confounding, as it is only possible to correct for factors which we have measured. There is also a risk for confounding by indication as all prescriptions were made by clinicians evaluating all aspects of the individual patient. It is therefore possible that prescription of betablockers were made mainly to patients who were in a more advanced stage of their cardiac disease, or have individual indications for use of betablockers which we have not been able to include in the present adjustments in the statistical analysis.

However, as randomized controlled studies of pharmaceutical agents with already established indications in cardiac surgery patients are very hard to conduct due to lack of funding and the sheer number of patients necessary for interpretable results, retrospective analyses may be the only way to answer such questions. Nevertheless, that renders it necessary to ensure the highest quality possible in the included data. Our data sources are robust, well validated and show real-world data from an entire nation with virtually no loss of follow-up. The registries are mandatory and include both public and private caregivers and pharmacies, and data on medication are not only from prescription, but actual dispense of medication to the patient. Another strength of this study setup is that data on medication was time-updated every 3 months during the entire follow-up, meaning that each patient contributes risk to the treatment group in which they belong throughout follow-up, and not to the group they represented at the start of the study. Lastly, the results remained consistent after using different statistical analyses, indicating that the associations are robust. However, reasons for interruption of treatment were not registered, so we are unable to report on reasons for discontinuation. Furthermore, we are not able to ascertain cause of death with sufficient resolution, and are thus forced to report only on all-cause mortality instead of cardiovascular mortality.

To conclude, this retrospective registry study shows that betablocker treatment is common after SAVR due to AS. An initial non-beneficial association between long-term betablocker treatment after SAVR and MACE was found, but this was attenuated after adjustment for emerging comorbidites. We therefore suggest, due to lack of prospective randomized clinical studies in this specific population, that betablockers should be used to treat concomitant cardiac disease such as heart failure with reduced LVEF or cardiac arrythmias as per current guidelines, but not given generally to patients after SAVR without other indications for treatment.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

FUNDING

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DATA AVAILABILITY

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

Author contributions

Emma C. Hansson: Conceptualization; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing—original draft; Writing—review & editing. **Andreas Martinsson:** Conceptualization; Data curation; Formal analysis; Methodology; Visualization; Writing—review & editing. **Julia Baranowska:** Conceptualization; Writing—review & editing. **Charlotta Törngren:** Writing—review & editing. **Emily Pan:** Writing—review & editing. **Erik Björklund:** Writing—review & editing. **Martin Karlsson:** Conceptualization; Methodology; Writing—review & editing.

Reviewer information

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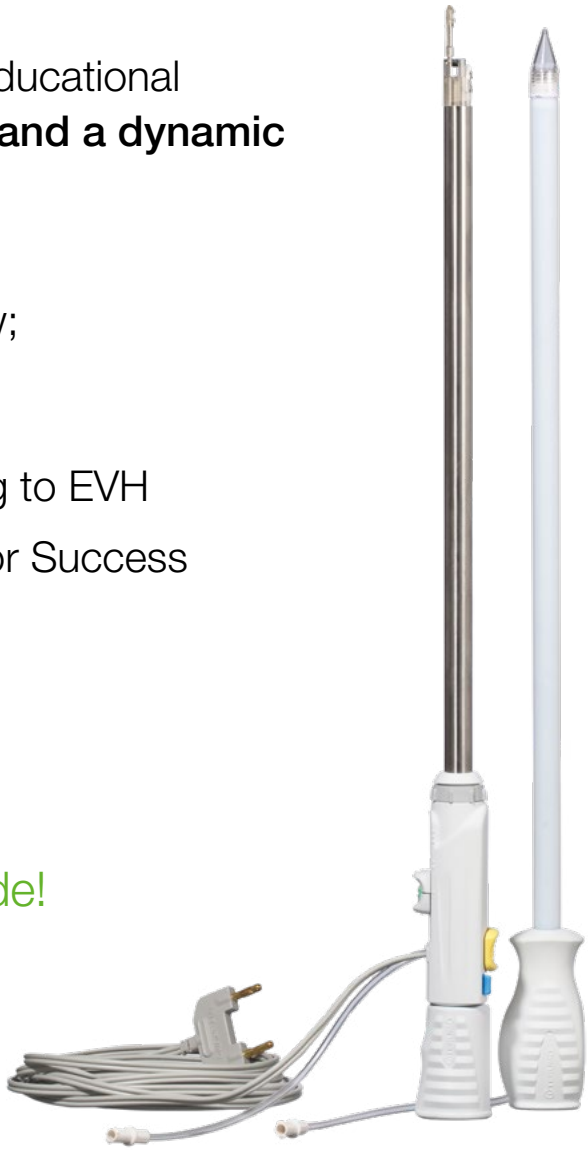

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