Beta blockers and long-term outcome after coronary artery bypass grafting: a nationwide observational study

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Aims	Beta blockers are associated with improved outcomes for selected patients with cardiovascular disease. We assessed long-term utilization of beta blockers after coronary artery bypass grafting (CABG) and its association with outcome.
Methods and results	All 35 184 patients in Sweden who underwent first-time isolated CABG between 1 January 2006 and 31 December 2017 and were followed for at least 6 months were included in a nationwide observational study. Multivariable Cox regression models using time-updated data on dispensed prescriptions were used to assess associations between different types of beta blockers and outcomes. The primary outcome was major adverse cardiovascular events (MACEs), a composite of all-cause mortality, stroke, and myocardial infarction (MI). Subgroup analyses were performed in patients with and without previous MI, heart failure, and reduced left ventricular ejection fraction (LVEF). Median follow-up was 5.2 years (range 0–11). At baseline, 33 159 (94.2%) patients were dispensed beta blockers, 30 563 (92.2%) of which were cardioselective beta blockers. After 10 years, the dispensing of cardioselective beta blockers had declined to 73.7% of all patients. Ongoing treatment with cardioselective beta blockers was associated with a slight reduction in MACEs [hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.89–0.98, $P = 0.0063$]. The reduction was largely driven by a reduced risk of MI (HR 0.83, 95% CI 0.75–0.92, $P = 0.0003$), while there was no significant reduction in all-cause mortality (HR 0.99, 95% CI 0.93–1.05) and stroke (HR 0.96, 95% CI 0.87–1.05). The reduced risk for MI was consistent in all the investigated subgroups.
Conclusion	Ongoing treatment with cardioselective beta blockers after CABG is associated with a reduction in MACEs, mainly because of reduced long-term risk for MI. The association between cardioselective beta blockers and MI was consistent in patients with and patients without previous MI, heart failure, atrial fibrillation, or reduced LVEF.
Keywords	CABG • Secondary prevention • Beta blockers

Introduction

Myocardial revascularization by coronary artery bypass grafting (CABG) is still the most common open cardiac surgical procedure performed worldwide.[1] Long-term outcome after CABG is dependent on prevention of progressive native artery disease and maintained graft patency.[2–5] Secondary prevention medication, with platelet inhibitors, beta blockers, renin–angiotensin system (RAS) inhibitors, and lipid-lowering drugs, is recommended in current guidelines to patients with previous myocardial infarction (MI) to reduce the risk of adverse events.[6–9]

Beta blockers have been shown to improve outcomes for patients with reduced left ventricular function and/or previous MI.[10,11] Recent data have questioned the benefit for patients with previous

MI but without reduced left ventricular ejection fraction (LVEF).[12] European and North American guidelines recommend lifelong medication with beta blockers after CABG for patients with reduced LVEF and a recent MI.[13,14] However, the evidence for this treatment is sparse and primarily based on studies of patients with reduced LVEF and a recent MI who had not had CABG.[14] Previous studies on beta-blocker therapy after CABG have consistently reported a suboptimal prescription rate and insufficient adherence to guidelines.[15,16] Only one randomized trial studying beta blockers after CABG has been published and it failed to show a reduction in cardiac events or mortality associated with treatment.[17] Most of the existing studies are limited by restricted study populations and/or single-centre designs[14]; large contemporary observational studies on beta-blocker therapy after CABG are still lacking.

Recently, our group reported on the use of secondary prevention medication and its association with all-cause mortality after CABG.[18] That study, partly based on the same study cohort as in the present study, showed that the use of secondary prevention medication after CABG is suboptimal and that time-updated treatment with statins, RAS inhibitors, and platelet inhibitors, but not beta blockers, is associated with lower all-cause mortality. However, the study neither investigated subgroups of beta blockers nor investigated endpoints other than all-cause mortality.

The aim of the current study was therefore to investigate the association between long-term beta-blocker therapy and major adverse cardiovascular events (MACEs), defined as all-cause mortality, MI, and/or stroke, and further to investigate whether the association varied between cardioselective beta blockers and any beta blockers and between different subgroups of CABG patients.

Methods

Data sources

Data were collected from four Swedish nationwide registries: the Swedish Cardiac Surgery Registry[19] (part of the SWEDEHEART Registry), the National Patient Registry, the Cause of Death Registry, and the Swedish Prescribed Drug Registry. Individual patient data were linked across the four registers using the Swedish personal identification number, which is unique to each individual and given to all Swedish inhabitants at birth or immigration.[20] The resulting database was anonymized and used for analyses. The National Patient Registry[21] contains information on comorbid conditions from in- and outpatient visits. Financial compensation to the departments is based on these reports and reporting is mandatory. Mortality status and cause of death were obtained from the Cause of Death Registry. Records of dispensed prescriptions of beta blockers, RAS inhibitors, statins, and platelet inhibitors were collected from the Swedish Prescribed Drug Registry and updated every third month as previously described.[18] The registry includes all dispensed prescriptions in Sweden and was established in July 2005. Medication data were based on the Anatomical Therapeutic Chemical (ATC) classification as presented in the Supplementary material online, *Table S1*. All patients who undergo open heart surgery in Sweden are included in the Swedish Cardiac Surgery Registry. The registry includes pre-operative patient characteristics, such as LVEF, comorbid conditions, and complications, and has excellent coverage and validity.[22]

Study cohort

Between 1 January 2006 and 31 December 2017, all patients in Sweden who underwent first-time isolated CABG were screened for inclusion ($n = 37\,520$). Patients who had <6 months of follow-up (i.e. who were discharged after 30 June 2017, emigrated within 6 months of discharge, or did not survive until 6 months after discharge) were excluded. Patients with an MI or stroke during the first 6 months were also excluded. The exclusion criteria were based on the assumption that early postoperative mortality and morbidity are related to periprocedural events and are unlikely to be preventable by secondary prevention medication. The stepwise exclusion of patients is illustrated in the Supplementary material online, *Figure S1*. Follow-up lasted until 31 December 2017, until an event occurred, or until emigration.

Statistical analyses

Outcome variables

The primary outcome was a composite of all-cause mortality, MI, and stroke (MACE). The individual constituents of MACE were considered secondary outcome variables. Outcome data were based on a primary or secondary diagnosis of codes I21.0–I21.4 (MI) or I61–I64 (stroke, which includes both haemorrhagic and ischaemic stroke) of the 10th revision of the International Classification of Diseases (ICD-10). Because of the severity of these diagnoses, they have very high validity in the National Patient Registry.[21] A full list of comorbid conditions and their associated ICD codes can be found in the Supplementary material online, *Table S1*.

Treatment indication and subgroups

Beta blockers are a cornerstone in the medical treatment of chronic heart failure. In addition, beta blockers are often dispensed after MI, although this has recently been questioned for patients without reduced LVEF.[23] Since the treatment effect was presumed to differ between patient subgroups, selected subgroups were analysed separately. The subgroups included patients with known heart failure and/or previous MI, patients with atrial fibrillation, and patients with reduced LVEF. For these indications, cardioselective beta blockers are used, and therefore cardioselective beta blockers were used when evaluating the association with treatment and outcome. Treatment with any beta blocker was explored as a secondary analysis.

Statistics

Calculation of crude incidence rates was performed by dividing the number of events by 100 person-years. Differences between groups were analysed using Fisher's exact test for dichotomous variables and χ^2 or Mantel–Haenszel χ^2 for categorical variables. For continuous variables, the Mann–Whitney U test was used. Medication data were updated at 3-month intervals during follow-up and patients were considered off treatment if they had no dispensed prescription during two consecutive 3-month periods, as described previously.[18] Adjusted Cox proportional hazard regression models were used to obtain adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs). Beta blockers were analysed as cardioselective beta blockers or, separately, as any beta blocker. These groups were decided a priori on the basis of their different pharmacological effects.

Three levels of adjustments were used and, unless otherwise stated, results reported are from the fully adjusted model. The minimally adjusted model included age and sex. At the next level of adjustment, comorbidities and patient characteristics were included. The following variables were adjusted for: year of CABG, acute coronary

Table 1 Baseline characteristics of patients with no beta-blocker treatment and with cardioselective and non-cardioselective beta-blocker treatment

	No treatment with beta blockers (n = 2025)	Treatment with cardioselective beta blockers (n = 30 563)	Treatment with non-cardioselective beta blockers (n = 2596)	P-value
Men	1674 (82.7%)	24 468 (80.1%)	2106 (81.1%)	**0.009**
Women	351 (17.3%)	6095 (19.9%)	490 (18.9%)	
Age (years)	69.3 (9.2)	67.9 (9.2)	69.4 (8.2)	0.39
Body mass index	27.0 (4.1)	27.5 (4.1)	27.4 (4.1)	**0.007**
Left ventricular ejection fraction				
Normal	1521 (75.1%)	20 776 (68.0%)	1877 (72.3%)	**<0.001**
<50%	486 (24.0%)	9565 (31.3%)	686 (26.4%)	
Unknown	18 (0.9%)	222 (0.7%)	33 (1.3%)	
Comorbidities				
Previous MI	832 (41.1%)	16 808 (55.0%)	1255 (48.3%)	**<0.001**
Heart failure	337 (16.6%)	6870 (22.5%)	537 (20.7%)	**<0.001**
Atrial fibrillation	484 (23.9%)	8740 (28.6%)	1410 (54.3%)	**<0.001**
Hypertension	1360 (67.2%)	21 802 (71.3%)	1836 (70.7%)	**<0.001**
Diabetes	607 (30.0%)	9412 (30.8%)	771 (29.7%)	0.40
Previous stroke	194 (9.6%)	2691 (8.8%)	239 (9.2%)	0.41
Renal failure	103 (5.1%)	1632 (5.3%)	119 (4.6%)	0.24
Chronic obstructive pulmonary disease	127 (6.3%)	1792 (5.9%)	93 (3.6%)	**<0.001**
Medications				
Statins	1814 (89.6%)	29 418 (96.3%)	2438 (93.9%)	**<0.001**
RAS inhibitors	1323 (65.3%)	23 170 (75.8%)	1834 (70.6%)	**<0.001**
Platelet inhibitors	1817 (89.7%)	28 907 (94.6%)	2426 (93.5%)	**<0.001**

Categorical variables are presented as numbers (%) and continuous variables are presented as mean (standard deviation).
MI, myocardial infarction; RAS, renin–angiotensin system.

syndrome [ST-segment elevation MI (STEMI)/non-ST-segment elevation MI (NSTEMI)/unstable angina] or stable angina as indication for CABG, left ventricular function, body mass index (BMI), diabetes mellitus, hypertension, hyperlipidaemia, previous stroke, atrial fibrillation, heart failure, previous MI, chronic obstructive pulmonary disease, history of cancer, peripheral arterial disease, pulmonary hypertension, chronic kidney disease (CKD) and CKD stage, marital status, education, and income. The Chronic Kidney Disease Epidemiology Collaboration formula[24] was used to estimate the glomerular filtration rate (eGFR) for CKD staging. These comorbidities were selected a priori based on the assumption that they would have an effect on outcomes and treatment status. In the model with the most comprehensive adjustments, time-updated other secondary prevention medications (RAS inhibitors, statins, and platelet inhibitors) were added to the model, under the assumption that they could be associated with outcome and treatment with other medications. The comorbidities, sex, age, and treatment status had no missing data. However, 273 (0.8%) patients had missing data on LVEF and 2903 (8.3%) patients had missing data for BMI. Patients with missing LVEF or BMI data were included in a separate category when adjusting for these covariates. To evaluate the validity of the analysis and to investigate whether the association between treatment and MACE varied over time, a sensitivity analysis was performed in which follow-up was restricted to 1 year and medical dispensation at the start of the year was considered as being under treatment for the full 1-year period. The fully adjusted model was used for this sensitivity analysis. A P-value of <0.05 was con-

sidered statistically significant and all tests were two-tailed. The analyses were carried out using SAS version 9.4 (SAS Institute, Cary, NC, USA).
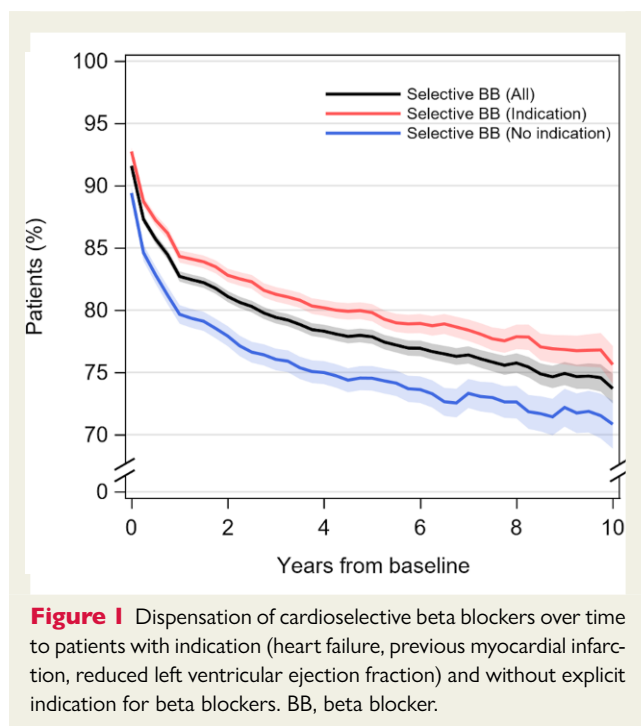
Ethics

The study was evaluated and approved, and the need for individual patient consent waived, by the regional research ethics committee in Gothenburg (registration number 139-16). Patients included in the SWEDEHEART Registry are informed, before inclusion, about their participation in the registry and the right to opt out. The study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Results

Baseline characteristics

A total of 35 184 patients were included in the study; out of these 174 patients emigrated during follow-up and were censored at the time of emigration. Among this group of patients, a total of 9320 MACEs occurred during a median follow-up of 5.2 years. Altogether 6363 (18.1%) patients died, 2293 (6.5%) suffered an MI, and 3022 (8.6%) had a stroke. At baseline, 33 159 (94.2%) patients were treated with beta blockers, the vast majority (n = 32 225, 91.6% of all patients) with cardioselective beta blockers. Baseline characteristics are presented in Table 1. A higher proportion of patients who

Figure 1 Dispensation of cardioselective beta blockers over time to patients with indication (heart failure, previous myocardial infarction, reduced left ventricular ejection fraction) and without explicit indication for beta blockers. BB, beta blocker.

received cardioselective beta-blocker treatment were female; they also had a lower age and higher BMI than patients without cardioselective beta-blocker treatment. They were also more likely to have had a previous MI or heart failure, and to have a low LVEF, atrial fibrillation, and hypertension. Other medications also differed between the groups; patients treated with cardioselective beta blockers were also treated with antiplatelet therapy, statins, and RAS inhibitors to a greater extent than patients without beta blockers or on non-cardioselective beta blockers. In total, of all patients, 7744 (22.0%) had a prior diagnosis of heart failure, 10 634 (30.2%) had a prior diagnosis of atrial fibrillation, 18 895 (53.7%) had had a previous MI, and 10 737 (30.5%) had reduced LVEF at the time of surgery.

Use over time
The dispensation of cardioselective beta blockers declined considerably during follow-up (*Figure 1*), falling from 91.6% at baseline to 77.9% and 73.7%, respectively, at 5 and 10 years after baseline. A higher percentage of patients with a history of MI and/or heart failure were dispensed cardioselective beta blockers at baseline than of those without clear indication (92.7% vs. 89.4%, $P < 0.001$). By 10 years, the difference had increased: 75.6% of patients with an indication and 70.8% without indication at baseline were dispensed cardioselective beta blockers. For any beta blocker, the dispensation declined from 94.2% at baseline to 80.4% and 76.2%, respectively, at 5 and 10 years after baseline.

Association between cardioselective beta blockers and outcome
During follow-up, patients with ongoing treatment with cardioselective beta blockers had a lower crude MACE rate, 4.8 (95% CI 4.7–4.9) vs. 5.8 (95% CI 5.5–6.0) per 100 patient-years. Treatment with cardioselective beta blockers was associated with a reduction

in MACEs, both in the analysis adjusted for patient characteristics and comorbidities (aHR 0.81, 95% CI 0.78–0.86, $P < 0.001$) and in the fully adjusted analysis (aHR 0.93, 95% CI 0.89–0.98, $P = 0.0063$) (*Figure 2*). The results from the age- and sex-adjusted models and the model with adjustments for comorbid conditions can be found in the Supplementary material online, *Table S2*. In the fully adjusted analyses, there was a significant association between treatment and risk for MI (aHR 0.83, 95% CI 0.75–0.92, $P < 0.001$) but not for all-cause mortality (aHR 0.99, 95% CI 0.93–1.05, $P = 0.63$) or stroke (aHR 0.96, 95% CI 0.87–1.05, $P = 0.33$).

The results of the subgroup analyses are presented in *Figure 2*. There was a significant interaction for patients with compared with patients without previous MI (aHR 0.96, 95% CI 0.90–1.03 vs. aHR 0.90, 95% CI 0.83–0.97, interaction *P*-value 0.042) when looking at MACE as outcome. For all-cause mortality, MI, and stroke, there were no interactions for any of the subgroups (all interaction *P*-values >0.05, *Figure 3*A–C). The association between treatment with cardioselective beta blockers and MI therefore remained robust in all subgroups, including patients without heart failure, atrial fibrillation, or previous MI and in patients with normal LVEF. In a sensitivity analysis with each year of follow-up analysed separately, similar findings as in the main analysis were observed (Supplementary material online, *Figure S2*).

## Association between any beta blocker and outcome
In the model adjusted for patient characteristics and comorbidities, treatment with any beta blocker was associated with a decreased risk of MACEs (HR 0.81, 95% CI 0.77–0.85, $P < 0.001$), while in the analysis additionally adjusted for time-updated use of other secondary prevention medications (platelet inhibitors, RAS inhibitors, and statins) treatment with any beta blocker was not significantly associated with a reduced MACE rate (aHR 0.95, 95% CI 0.90–1.00, $P = 0.055$) (Supplementary material online, *Figure S3*). There was a significant association between any beta-blocker treatment and MI (aHR 0.85, 95% CI 0.76–0.94, $P = 0.003$). No associations between any beta-blocker treatment and all-cause mortality (aHR 1.01, 95% CI 0.95–1.08, $P = 0.69$) or stroke (aHR 0.97, 95% CI 0.87–1.07, $P = 0.49$) were observed. The associations did not differ for patients with previous MI, heart failure, and atrial fibrillation in the fully adjusted models (Supplementary material online, *Figure S2*).

Non-cardioselective beta blockers
Treatment with sotalol was neither associated with a reduction in MACEs (aHR 1.13, 95% CI 0.95–1.35, $P = 0.17$) in any of the adjusted models nor associated with all-cause mortality, MI, or stroke (Supplementary material online, *Table S3*). Treatment with other non-cardioselective beta blockers had similar results, i.e. no association in the fully adjusted analysis between MACE rate (aHR 1.12, 95% CI 0.99–1.28, $P = 0.078$), all-cause mortality, MI, and stroke.

Discussion
The main findings of this large nationwide study, comprising all patients undergoing CABG in Sweden from 2006 to 2017 and surviving 6 months or more, were that treatment with cardioselective beta
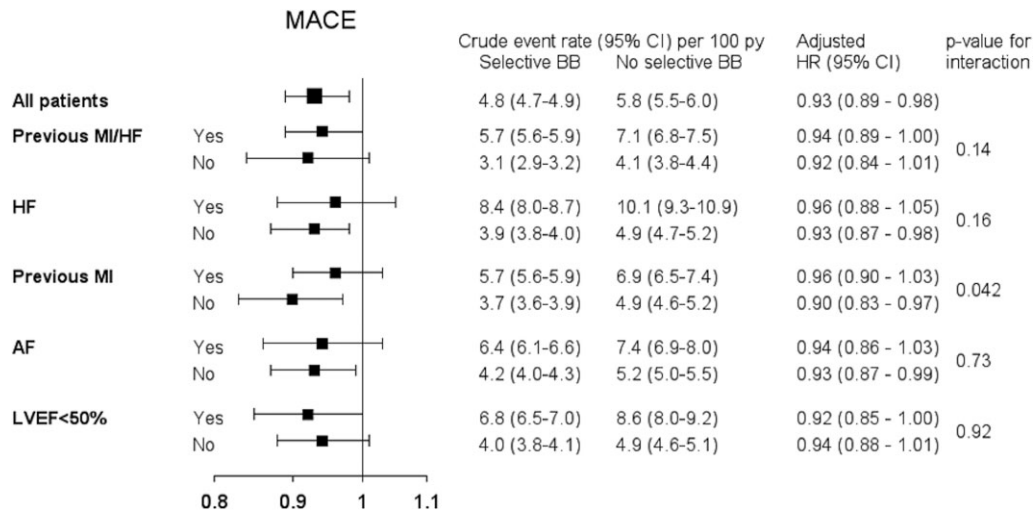
Figure 2 Forest plot in different subgroups of patients with major adverse cardiovascular events receiving cardioselective beta blockers, showing results from the fully adjusted Cox regression model. AF, atrial fibrillation; HF, heart failure; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; and MI, myocardial infarction.

blockers was associated with a slightly lower risk of MACEs and that this association was driven by reduced risk of MI.

The proportion of patients prescribed beta blockers at the time of discharge after CABG was high regardless of whether the patients did or did not have an explicit indication for beta-blocker treatment, i.e. heart failure, previous MI, or reduced LVEF (95% vs. 92%). Notably, the degree of continued use of beta-blocker therapy gradually decreased over time and was 76% at 10 years of follow-up. Part of this decline could be explained by a reduced need for symptomatic treatment for angina pectoris after revascularization. However, assuming the treatment reduces the risk for adverse events, the decline in secondary prevention therapy over time is alarming. This underlines the importance of persistent follow-up of secondary prevention treatment measures among post-CABG patients. An interesting finding of the current study is that there were no significant interactions between cardioselective beta blockers and MACEs, with the exception of previous MI. This implies that the association with a reduction in MACEs was similar across a wide spectrum of cardiac diseases, which is interesting as the benefit of beta blockers after MI has recently been questioned.[23] The finding that patients without previous MI had a larger associated benefit from beta-blocker treatment is interesting, but the present study design cannot explain these results.

Our group has previously reported on the associations between secondary prevention medication after CABG and all-cause mortality.[18] In that study, which was partly based on the same study cohort as in the present study, no association was found between any beta-blocker therapy and all-cause mortality. These results were confirmed in the present study. However, ongoing cardioselective beta-blocker therapy after CABG was in the present study associated with reduced risk of MACEs and reduced risk of new or recurrent MI during follow-up. The dissimilarity in the clinical profile of different beta blockers motivates the stratification used in the cur-

rent study, as treatment effect would be expected to differ between cardioselective and non-cardioselective beta blockers. As expected, baseline characteristics and outcomes were statistically different for patients treated with non-cardioselective beta blockers, highlighting the difference in use. Treatment with non-cardioselective beta blockers was not associated with any benefit; in fact, the HRs suggest an increase in MACEs, albeit without statistical significance.

In a single-centre study, Zhang *et al.* found that, during a median follow-up of 3 years, adherence to beta-blocker therapy after CABG was associated with significantly lower risk of a composite MACE outcome, as well as lower all-cause mortality.[25] Subgroup analysis showed that the association was independent of the presence of preceding MI but was not observed in patients with a heart failure diagnosis. These results agree with the observed outcomes in the present study, in the patients treated with cardioselective beta blockers, although the present study found no association between beta blockers and reduced mortality. There are methodological differences between the studies, which are worth mentioning, including adherence to medication (68.8% at baseline in the study by Zhang *et al.*[25] vs. 94.2% in the present study) and the length of follow-up, which was longer in the current study (median 5.2 years).

In Booij *et al.*'s study of 2553 low-risk coronary artery disease patients undergoing CABG, continued beta-blocker therapy was not associated with reduced risk of the primary outcome, a composite of cardiovascular events, or its individual components, at a median follow-up of 33 months.[26] The authors conclude that, while insufficient power due to low event rates may have affected the results, the benefit of prolonged beta-blocker treatment may be limited in low-risk patients. Post-operative beta blockers for patients with heart failure or reduced LVEF have previously been found to increase short-term survival in non-CABG patients, with the exception of patients with severely reduced LVEF, among whom beta-blocker treatment has been associated with increased mortality.[27] A
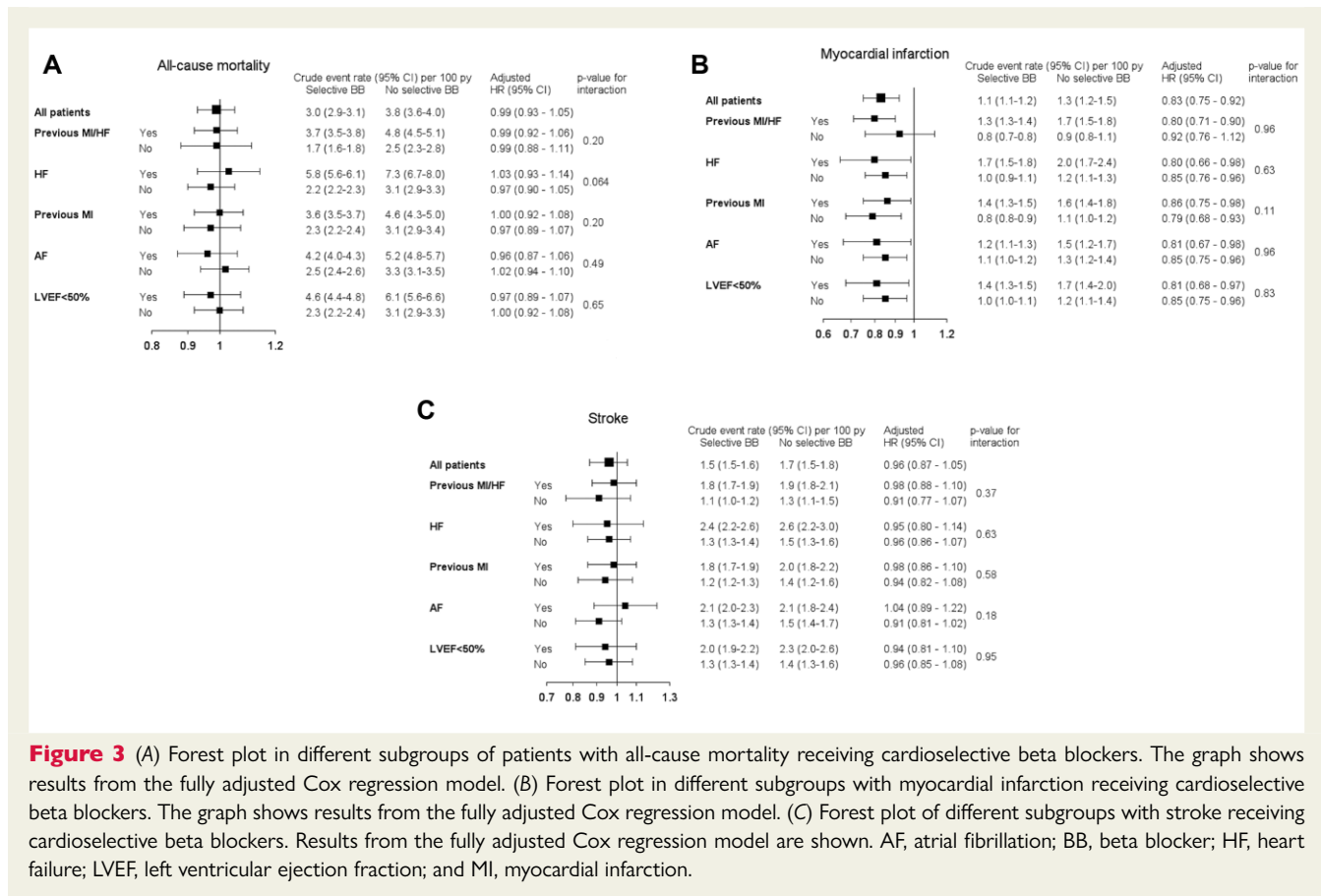
Figure 3 (*A*) Forest plot in different subgroups of patients with all-cause mortality receiving cardioselective beta blockers. The graph shows results from the fully adjusted Cox regression model. (*B*) Forest plot in different subgroups with myocardial infarction receiving cardioselective beta blockers. The graph shows results from the fully adjusted Cox regression model. (*C*) Forest plot of different subgroups with stroke receiving cardioselective beta blockers. Results from the fully adjusted Cox regression model are shown. AF, atrial fibrillation; BB, beta blocker; HF, heart failure; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

systematic review and meta-analysis did not show any clear benefit from pre-operative beta blockers.[28] In the current study of CABG patients mainly treated with cardioselective beta blockers, we did not find an association between long-term beta-blocker therapy and reduced mortality in patients with heart failure. Even so, prolonged therapy was firmly associated with decreased risk of MACEs and MI among patients treated with beta blockers, giving support to current guideline recommendations.

The only randomized controlled trial on beta-blocker therapy after CABG we have found, the MACB trial, included 967 patients and did not show any significant reduction in cardiovascular events or death over a total follow-up of two years between patients treated with metoprolol and patients receiving placebo.[17] The discrepancies between previous studies and the current study highlight the need for careful patient evaluation and selection before starting beta blockers in patients after CABG, but it is worth noting that the MACB trial[17] was conducted prior to contemporary medical therapy. The current results suggest that there is an association between beta-blocker treatment and a reduced risk for MACEs and MI, but in the light of the previously mentioned studies, this may not be applicable to all patients after CABG.

It is notable that the addition of other secondary preventive medications to our statistical models attenuated the association between MACE and treatment with beta blockers. This suggests that the beneficial effect of beta blockers may be less pronounced if other, potentially more effective, medications can be initiated. The optimal secondary prevention medication strategy after CABG is still un-

known. It is possible, and even likely, that different combinations of therapies could have different synergistic effects depending on the specific combination and patient characteristics.

Strengths and limitations

The study's strengths include the use of a large, nationwide cohort with complete registry coverage. Use of national health registries allows for complete follow-up over an extended period. Access to time-updated data on dispensed prescriptions limits the risk of recollection bias associated with self-reported data. Regarding limitations, we did not have information pertaining to the reasons for non-adherence or non-subscriptions of secondary prevention medications; this may have been a source of confounding. Furthermore, it should be noted that the cut-off for low LVEF is 50% in the Swedish Cardiac Surgery Registry, which is higher than the most commonly used LVEF cut-off (40%). Treatment strategies and adherence to treatment may differ between countries; hence, the results of the present study may not be directly transferable to all countries. Finally, as with all observational studies, selection bias and residual confounding may have been present, affecting our results.

Conclusions

Ongoing use of cardioselective beta blockers after CABG was associated with reduced risk of MACEs, driven by a reduced risk of MI. The association with a reduced risk of MACEs was found in all

subgroups except for patients with previous MI. Non-cardioselective beta blockers were not associated with a reduced risk of MACEs.

Supplementary material

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

Funding

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 permission of SWEDEHEART and the National Board of Health and Welfare.

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