OPEN ACCESS

Original research

Association of beta-blockers beyond 1 year after myocardial infarction and cardiovascular outcomes

Divan Ishak,[1] Suleman Aktaa,[2,3] Lars Lindhagen,[4] Joakim Alfredsson,[5,6] Tatendashe Bernadette Dondo ,[3] Claes Held,[1,4] Tomas Jernberg,[7] Troels Yndigegn ,[8] Chris P Gale,[2,3] Gorav Batra [1,4]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2022-322115).

For numbered affiliations see end of article.

Correspondence to
Dr Gorav Batra, Department of Medical Sciences, Cardiology, Uppsala University, Uppsala 751 05, Sweden;
gorav.batra@ucr.uu.se

Received 8 November 2022
Accepted 14 February 2023
Published Online First
2 May 2023

ABSTRACT

Objective Beta-blockers (BB) are an established treatment following myocardial infarction (MI). However, there is uncertainty as to whether BB beyond the first year of MI have a role in patients without heart failure or left ventricular systolic dysfunction (LVSD).

Methods A nationwide cohort study was conducted including 43 618 patients with MI between 2005 and 2016 in the Swedish register for coronary heart disease. Follow-up started 1 year after hospitalisation (index date). Patients with heart failure or LVSD up until the index date were excluded. Patients were allocated into two groups according to BB treatment. Primary outcome was a composite of all-cause mortality, MI, unscheduled revascularisation and hospitalisation for heart failure. Outcomes were analysed using Cox and Fine–Grey regression models after inverse propensity score weighting.

Results Overall, 34 253 (78.5%) patients received BB and 9365 (21.5%) did not at the index date 1 year following MI. The median age was 64 years and 25.5% were female. In the intention-to-treat analysis, the unadjusted rate of primary outcome was lower among patients who received versus not received BB (3.8 vs 4.9 events/100 person-years) (HR 0.76; 95% CI 0.73 to 1.04). Following inverse propensity score weighting and multivariable adjustment, the risk of the primary outcome was not different according to BB treatment (HR 0.99; 95% CI 0.93 to 1.04). Similar findings were observed when censoring for BB discontinuation or treatment switch during follow-up.

Conclusion Evidence from this nationwide cohort study suggests that BB treatment beyond 1 year of MI for patients without heart failure or LVSD was not associated with improved cardiovascular outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Beta-blockers (BB) are an established treatment following myocardial infarction (MI). However, it is unknown whether BBs beyond the first year of MI have a secondary preventive role in patients without heart failure or left ventricular systolic dysfunction (LVSD).

WHAT THIS STUDY ADDS

⇒ In this nationwide cohort study including 43 618 patients with first MI presentation, 78.5% patients received BB and 21.5% did not at the index date 1 year following MI. After inverse propensity score weighting and multivariable adjustment, the risk of the composite cardiovascular outcome of all-cause mortality, recurrent MI, unscheduled revascularisation and hospitalisation for heart failure did not differ among patients treated with or without BB during a median follow-up of 4.5 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In patients with MI without heart failure or LVSD, long-term treatment with BB should be reassessed.

INTRODUCTION

Clinical outcomes following acute myocardial infarction (MI) have improved in recent years, partly due to the implementation of evidence-based therapies including timely reperfusion and secondary prevention medications.[1 2] As such, more patients are surviving MI with no heart failure or left ventricular systolic dysfunction (LVSD).[3] Beta-blockers (BB) have been established as a strongly recommended therapy for patients with heart failure and/or LVSD because they reduce morbidity and mortality.[4] For those without heart failure or LVSD, evidence supports the use of BB in the early phase after MI, but there is uncertainty as to whether BB should be continued beyond the first year after MI in the absence of other clinical indications.[5–9]

The longer-term use of BB following MI has been evaluated in historical randomised controlled trials (RCTs) in which BB therapy reduced mortality rates.[10 11] These trials were conducted prior to the integration of invasive reperfusion strategies and antithrombotic agents into routine MI care.[12–14] More recently, a number of studies have examined the association between BB therapy and clinical outcomes in MI survivors who have no heart failure or LVSD.[15–21] However, the generalisability of these studies is limited by the inclusion of a subset of MI patients, relatively small sample size or short follow-up.[15–21]

Presently, there is an unmet need to determine whether BB therapy is indicated beyond the first year of MI in patients with no other indication for BB. While RCTs are in the process of studying BB therapy after discharge or 6 months after MI in patients with no heart failure (ClinicalTrials.gov

Linked

► http://dx.doi.org/10.1136/heartjnl-2023-322544

Check for updates

To cite: Ishak D, Aktaa S, Lindhagen L, *et al*. *Heart* 2023;**109**:1159–1165.

Identifier: NCT03646357, NCT03278509, NCT03778554, NCT03596385 and NCT03498066), the benefit with BBs in the chronic phase beyond the first year might remain unknown and the long follow-up required to draw firm conclusions may be challenging to achieve in traditional RCTs. Therefore, we aimed to investigate the association between BB therapy and cardiovascular (CV) outcomes beyond the first year of MI in patients without heart failure or LVSD using real-world data. We hypothesised that BB therapy was associated with a lower risk of all-cause mortality, recurrent MI, unplanned revascularisation or hospitalisation for heart failure in patients with no heart failure or LVSD beyond the first year after MI.

METHODS

Study population, data sources, and patient and public involvement

We included consecutive patients registered for the first time with an MI between 1 January 2005 and 31 December 2016 from the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register, the national register for coronary heart disease in Sweden. The study included all patients aged ≥18 years with ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI) who had been hospitalised at one of the 74 cardiac care units in Sweden. The index date for start of follow-up was defined as 1 year after hospitalisation with MI. The exclusion criteria comprised death, recurrent MI, diagnosis of heart failure, left ventricular ejection fraction <50%, treatment with loop diuretics (surrogate marker of heart failure) and asthma up until the index date 1 year after MI. Patients with a history of BB therapy within 6 months prior to the MI were also excluded (figure 1).

Data from SWEDEHEART were used to identify the analytical cohort. These data were further complemented by linkage with the National Patient Register, the National Prescribed Drug Register and the National Cause of Death Register in Sweden. The National Patient Register is a mandatory nationwide database that collects discharge date with primary and secondary diagnoses for all patients based on the International Classification of Disease, 10th revision (ICD-10). The National Prescribed Drug Register is a mandatory nationwide database that captures information about prescribed drug dispenses based on the Anatomical Therapeutic Chemical classification. Data linkage between registries was performed by the National Board of Health and Welfare using the 10-digit personal identification number applicable to all Swedish citizens.

All patients included in SWEDEHEART were informed about their participation in the register and were given the option to opt out. This research was done without patient involvement. The study was registered and approved by the SWEDEHEART board and by the Ethical Review Board in Sweden (application number 2012/60-13/2).

Beta-blocker exposure

We defined two treatment cohorts (BB and no BB therapy) 1 year after hospitalisation with an MI. Information about exposure to BB at the index date and during follow-up was obtained from the National Prescribed Drug Register based on dispensing history over the preceding 4 months (online supplemental table 1). This period was determined based on the Swedish reimbursement system which encourages the prescription of medications for 3-month periods, with an extra month added to compensate for different prescribing patterns and stockpiling.[22] Also, for patients in the BB treatment arm, the median time observed between two successive dispensations of BB was approximately 4 months (data not shown) in accordance with the Swedish reimbursement system.

Patient characteristics

Information about patient characteristics and in-hospital treatment was obtained from SWEDEHEART with complementary

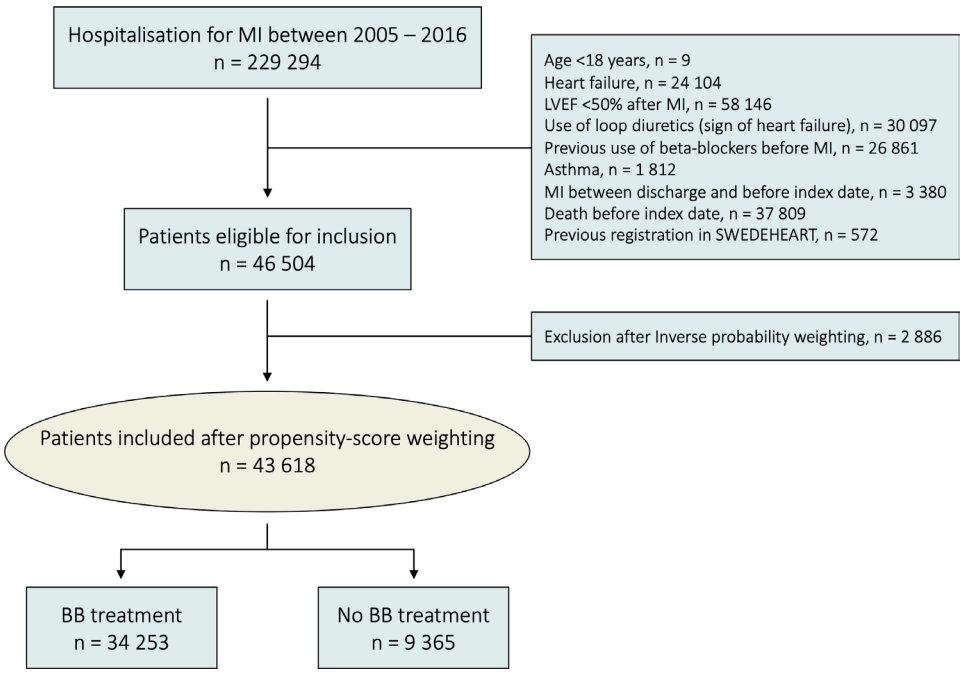


Figure 1 CONSORT diagram illustrating inclusion and exclusion of patients. BB, beta-blockers; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

data from the National Patient Register up to the index date (online supplemental table 1). Data pertinent to other prescribed medications within the 4-month period preceding the index date were extracted from the National Prescribed Drug Register (online supplemental table 1).

Outcomes

The primary outcome was a composite of all-cause mortality, recurrent MI, unscheduled revascularisation or hospitalisation for heart failure. Secondary outcomes included the separate components of the composite outcome in addition to CV death and stroke. We used an unrelated diagnosis (pneumonia) as a negative control in a sensitivity analysis. Outcomes were derived from SWEDEHEART, the National Patient Register and the National Cause of Death Register (online supplemental table 2).

Statistics

This study is reported in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (online supplemental figure 1). Patient characteristics, in-hospital treatment and medications at index date were reported as medians with 25th–75th percentiles for continuous variables and as frequencies with percentages for categorical variables. Follow-up started at the index date (1 year after MI) at which point patients were divided into two groups based on BB therapy. Patients were followed until 31 December 2017 with a minimum follow-up of 1 year. For CV death, last date of follow-up was 31 December 2016 based on data availability for underlying cause of death from the National Cause of Death Register. In the main intention-to-treat analysis, patients were censored at the end of follow-up or at the occurrence of mortality (if not part of the outcome), whichever came first. We conducted a sensitivity per-protocol analysis in which patients were also censored at the time of first BB therapy switch (in either direction).

Inverse probability weighting propensity scores were estimated using logistic regression to balance treatment assignment using the prespecified variables through weighting on the index date (age, sex, calendar year, smoking status, diabetes mellitus, hypertension, cerebrovascular disease, peripheral arterial disease, atrial fibrillation/flutter, chronic obstructive pulmonary disease, previous MI, previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft (CABG) surgery, type of MI (STEMI or NSTEMI), concomitant treatment with antithrombotic therapy, renin-angiotensin-aldosterone system inhibitors and statins) (online supplemental figure 2). Based on the findings from the inverse probability weighting, some patients were excluded from further analysis due to lack of contrast (figure 1). Time-to-event for the primary composite CV outcome was illustrated using Kaplan–Meier survival plots and adjusted survival curves. All secondary outcomes were presented using cumulative incidence plots. The primary composite outcome and the secondary outcome of all-cause mortality were analysed using Cox regression models. All remaining secondary outcomes were analysed using Fine–Grey models accounting for competing risk of mortality. Cox proportional hazards and Fine–Grey models were analysed without adjustment and after adjustment for prespecified covariates defined on the index date (age, sex, calendar year, smoking status, diabetes mellitus, hypertension, cerebrovascular disease, peripheral arterial disease, atrial fibrillation/flutter, chronic obstructive pulmonary disease, previous MI, previous PCI, previous CABG, type of MI, concomitant treatment with antithrombotic therapy, renin-angiotensin-aldosterone system inhibitors and statins). The proportional hazards' assumption was assessed using Schoenfeld residuals with no significant violations observed. Missing data were present for two confounders (type of MI (0.02%) and smoking status (1.8%)) and were handled using the multiple imputation method of chained equations and logistic regression generating five imputed datasets. Consistency of the primary composite outcome was tested among eight prespecified subgroups (year of admission for MI, age <65 or ≥65 years, sex, hypertension, diabetes mellitus, atrial fibrillation, previous MI, type of MI and in-hospital PCI). All statistical analyses were performed in R version 4.2.1 (R Foundation for Statistical Computing). Information about the relevant R packages used for the analyses is available in the online supplemental file.

RESULTS

Patient characteristics and comorbidities

Between 1 January 2005 and 31 December 2017, a total of 46 504 patients met the inclusion criteria (figure 1). Complete data were available for most variables with some missing data for the type of MI, renal function and smoking status (online supplemental table 3). After inverse probability weighting, 43 618 (93.8%) patients were included (figure 1). Of those, 34 253 (78.5%) patients were on a BB therapy at the index date and 9365 (21.5%) were not. Median age was 64 years and 11 131 (25.5%) of the patients were women. The demographics were well balanced between the two treatment groups in terms of baseline characteristics and comorbidities including hypertension, diabetes mellitus and atrial fibrillation/flutter (table 1). However, in the non-BB group there were approximately twice as many patients with a prior history of MI, PCI or CABG compared with the BB group. Patients in the BB group were more likely to have STEMI, undergo in-hospital revascularisation and to be on statin therapy compared with the non-BB group (table 1).

Outcomes

In an intention-to-treat analysis, the primary composite outcome of all-cause mortality, recurrent MI, unscheduled revascularisation and hospitalisation for heart failure occurred in 6475 (18.9%) patients on BB and in 2028 (21.7%) patients not on BB during a median follow-up of 4.5 years (unadjusted hazard ratio (HR) 0.76; 95% confidence interval (CI) 0.73 to 0.80) (figure 2 and table 2). After adjustment for demographics, relevant comorbidities and with inverse probability weighting, BB versus no BB therapy was associated with a similar rate of the primary composite outcome (HR 0.99; 95% CI 0.93 to 1.04). A similar finding was observed when censoring for discontinuation or switch of treatment strategy during follow-up in per-protocol analysis (HR 0.98; 95% CI 0.90 to 1.06) (online supplemental table 4).

An analysis of the individual components of the composite outcome resulted in similar associations with BB therapy and all-cause mortality (HR 1.00; 95% CI 0.92 to 1.09), recurrent MI (HR 1.00; 95% CI 0.91 to 1.09), unscheduled revascularisation (HR 0.96; 95% CI 0.85 to 1.09) and hospitalisation for heart failure (HR 1.05; 95% CI 0.85 to 1.31). Comparable findings were observed for CV mortality (HR 0.98; 95% CI 0.83 to 1.14) and stroke (HR 1.02; 95% CI 0.89 to 1.17) (table 2, online supplemental figure 3 and online supplemental table 4).

The association between BB therapy and the primary composite outcome was consistent across the prespecified subgroups, including sex, hypertension, diabetes mellitus, atrial

Table 1 Demographics and characteristics after propensity score weighting

Parameters	Beta-blockers (n=34 253)	No beta-blockers (n=9365)
Demographics		
Age, years, median (IQR)	64 (56–71)	65 (57–74)
Sex, female, n (%)	8595 (25.1)	2536 (27.1)
Smoking, n (%)	10 820 (32.0) [483]	2494 (27.4) [256]
Medical history 1 year after MI, n (%)		
Hypertension	13 152 (38.4)	3530 (37.7)
Diabetes mellitus	4601 (13.4)	1108 (11.8)
Atrial fibrillation/flutter	2250 (6.6)	635 (6.8)
Prior MI*	1501 (4.4)	806 (8.6)
Prior PCI*	882 (2.6)	546 (5.8)
Prior CABG*	418 (1.2)	244 (2.6)
Cerebrovascular disease	1765 (5.2)	659 (7.0)
Peripheral vascular disease	824 (2.4)	329 (3.5)
COPD	957 (2.8)	367 (3.9)
Index event, n (%)		
NSTEMI	21 310 (62.2) [6]	6511 (69.5) [1]
STEMI	12 937 (37.8)	2853 (30.5)
In-hospital course and medication at discharge		
eGFR, median (IQR)	77 (67–89) [1388]	78 (68–90) [335]
PCI, n (%)	27 383 (79.9)	6637 (70.9)
CABG, n (%)	1236 (3.6)	218 (2.3)
Beta-blockers, n (%)	32 757 (95.7) [28]	4848 (51.8) [5]
Concomitant medication 1 year after MI, n (%)		
Acetylsalicylic acid	32 548 (95.0)	8555 (91.4)
$P2Y_{12}$ inhibitors	5808 (17.0)	1421 (15.2)
Oral anticoagulants	539 (1.6)	142 (1.5)
ACE inhibitors	11 448 (33.4)	2349 (25.1)
ARB	4050 (11.8)	1095 (11.7)
Statins	31 154 (91.0)	7493 (80.0)

*Data about prior MI, PCI and CABG were collected at the time of hospitalisation for MI. Values are in median (IQR) for continuous variables and numbers (%) for categorical variables. Numbers within square brackets indicate number of missing values. eGFR levels are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and are presented in ml/min/1.73 m^2.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

fibrillation/flutter, previous MI, type of MI and in-hospital PCI (figure 3 and online supplemental table 5).

Sensitivity analysis

The incidence rate of pneumonia was similar across the two treatment arms with no differences observed in the adjusted analysis (HR 1.07; 95% CI 0.94 to 1.22) (table 2 and online supplemental table 4).

DISCUSSION

In this nationwide cohort study of patients who survived MI beyond 1 year, we included 43 618 patients without heart failure or LVSD 1 year after first MI and found that long-term BB therapy was not associated with improved CV outcomes during median follow-up of 4.5 years. These findings were consistent across individual secondary endpoints and across patient subgroups.

The results of our study address an existing gap in the current evidence and provide an insight into long-term optimal secondary prevention strategies for a large proportion of MI survivors,[9] namely patients with no heart failure or LVSD who may have longer survival compared with those who develop such complications after an MI.[23 24] As such, understanding the association between long-term BB use and CV outcomes in this group of patients has important implications in determining health policies and developing Clinical Practice Guidelines, but also has an impact on patients' health-related quality of life and compliance with other CV preventive therapies.[1 2]

Following MI, heart failure is a major determinant of long-term morbidity and mortality for which several prognostic therapies including BB have been shown to improve outcomes.[4] While Clinical Practice Guidelines state that it is reasonable to initiate and continue BB therapy following MI in patients without heart failure or LVSD, these recommendations are based on RCTs that predate the reperfusion and potent antiplatelets era.[1 2] The current clinical practice of routine long-term use of BB is based on historical data which might not be extrapolated to patients with MI without heart failure or LVSD. As such, recent Clinical Practice Guidelines for myocardial revascularisation have questioned the routine use of chronic BB in patients with chronic coronary syndrome.[25]

Here we present the largest study evaluating BB therapy in patients without heart failure or LVSD following MI. Among 43 618 patients, long-term BB therapy was not associated with improved CV outcomes. Until recently, no RCT had tested the efficacy of BB on long-term CV outcomes among patients with MI without heart failure or LVSD. In a contemporary small RCT, patients with STEMI without heart failure or LVSD were randomised to long-term carvedilol therapy or placebo.[15] The trial reported that BB had no beneficial effect on CV outcomes. However, this RCT was underpowered and employed an open-label approach. In addition, the study included only a subset of MI patients thus limiting the generalisability of the results.

A number of observational studies have reported contradicting results about the associations between BB therapy and CV outcomes in patients with MI without heart failure.[15–21] Some studies reported that BB treatment was associated with improved CV outcomes while others suggest no association.[15–21] Although our study design is observational, it encompasses a large sample of patients, has a median follow-up of 4.5 years and implements causal inference techniques. Contrary to our study, the aforementioned studies were limited to only subgroups of MI patients, small sample sizes or short follow-up.[15–21] Also, the findings of our study align with the results of a recent meta-analysis of contemporary trials evaluating the role of BB after MI in patients with no heart failure or LVSD.[7 8]

The potential mechanism of BB in improving CV outcomes following MI is attributed to the inhibition of the sympathetic overdrive, lowering heart rate and thus reducing myocardial oxygen consumption.[9] However, routine and timely coronary reperfusion, as well as usage of potent antiplatelet therapy, reduces infarct size, minimising the upregulation of sympathetic activity, particularly in those individuals who do not sustain substantial myocardial damage.[26] As such, long-term BB therapy in concurrent MI patients without heart failure or LVSD may not have a role in improving CV outcomes as shown in the current study.

Health-related quality of life has been increasingly used as an important measure of medical interventions. Given their adrenergic blocking effect, BB have been associated with several side effects (eg, depression and fatigue).[27] Thus,

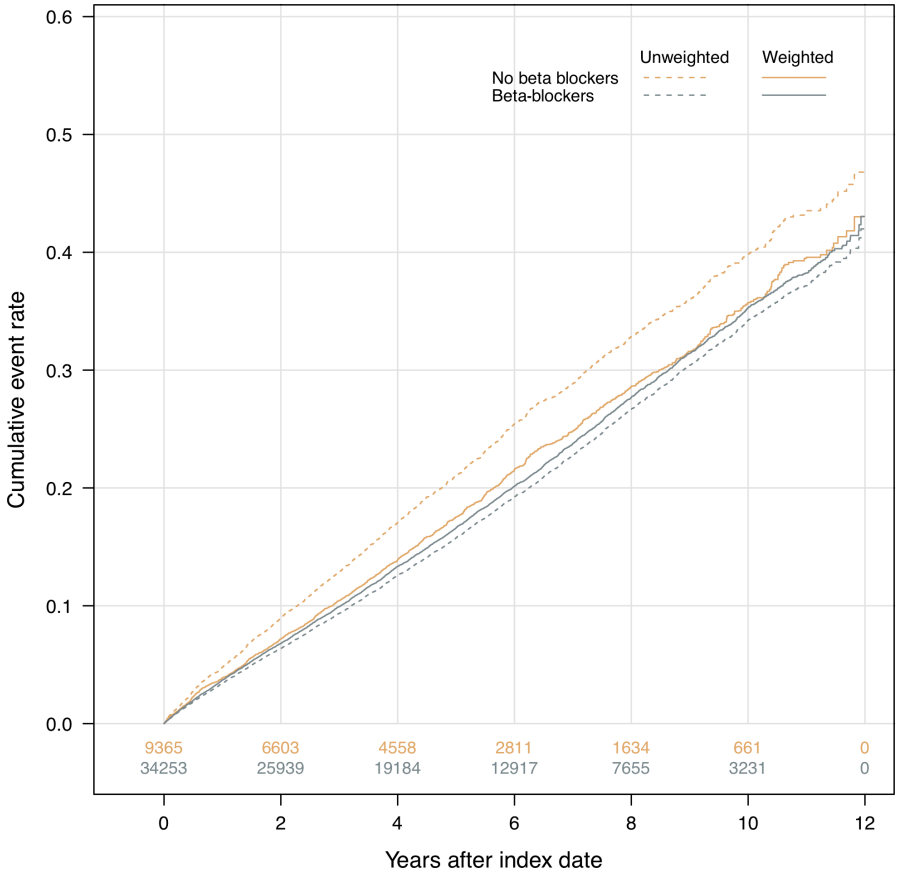


Figure 2 Kaplan–Meier plot of the primary composite outcome.

determining whether BB are indicated beyond the first year of MI may have an impact on patient health-related quality of life. While robust ascertainment of such a question is difficult to conclude from an observational study like ours, the need for long follow-up when assessing this relationship might limit the feasibility of an RCT. Ongoing RCTs (ClinicalTrials.gov Identifier: NCT03646357, NCT03278509, NCT03778554, NCT03596385 and NCT03498066) will be able to address some important questions regarding BB directly after MI; however, the long-term benefit with BB therapy in the chronic phase after MI might remain unknown.

Limitations

Even though this is one of the largest studies based on real-life data analysing the association between long-term BB therapy and CV outcomes beyond 1 year of MI in patients without heart failure or LVSD, the findings should be viewed in the context of some limitations. Due to the observational cohort design, this study reports associations between BB therapy and CV outcomes, and causation cannot be inferred given treatment allocation was not randomised. To avoid selection bias, inverse propensity score weighting, Cox regression and Fine–Grey analysis were applied; nonetheless, residual confounding cannot be discounted. However, pneumonia was used as a negative

Table 2 Primary and secondary outcomes in the intention-to-treat analysis

Outcome	Beta-blockers (n=34 253) Events/100 patient-years (incidence rate)	No beta-blockers (n=9365) Events/100 patient-years (incidence rate)	Hazard ratio (95% CI) for beta-blockers (unadjusted)	Hazard ratio (95% CI) for beta-blockers (adjusted)
Primary composite outcome	6475/1709 (3.8)	2028/414 (4.9)	0.76 (0.73 to 0.80)	0.99 (0.93 to 1.04)
All-cause mortality	2872/1733 (1.7)	945/420 (2.3)	0.72 (0.67 to 0.78)	1.00 (0.92 to 1.09)
Myocardial infarction	2598/1733 (1.5)	787/420 (1.9)	0.82 (0.76 to 0.89)	1.00 (0.91 to 1.09)
Unscheduled revascularisation	1415/1709 (0.8)	372/414 (0.9)	0.95 (0.84 to 1.06)	0.96 (0.85 to 1.09)
Heart failure hospitalisation	462/1733 (0.3)	145/420 (0.4)	0.78 (0.65 to 0.94)	1.05 (0.85 to 1.31)
Other secondary outcomes				
Cardiovascular mortality	760/1481 (0.5)	270/355 (0.8)	0.68 (0.59 to 0.78)	0.98 (0.83 to 1.14)
Stroke	1136/1704 (0.7)	318/412 (0.8)	0.88 (0.78 to 1.00)	1.02 (0.89 to 1.17)
Negative control outcome				
Pneumonia	1314/1707 (0.8)	375/414 (0.9)	0.86 (0.77 to 0.97)	1.07 (0.94 to 1.22)

The primary composite outcome was a composite of all-cause mortality, myocardial infarction, hospitalisation for heart failure and unscheduled coronary revascularisation. Person time and incidence rate is given in 100 person-years. Hazard ratios are given with 95% confidence intervals. The no beta-blockers group is the reference group.

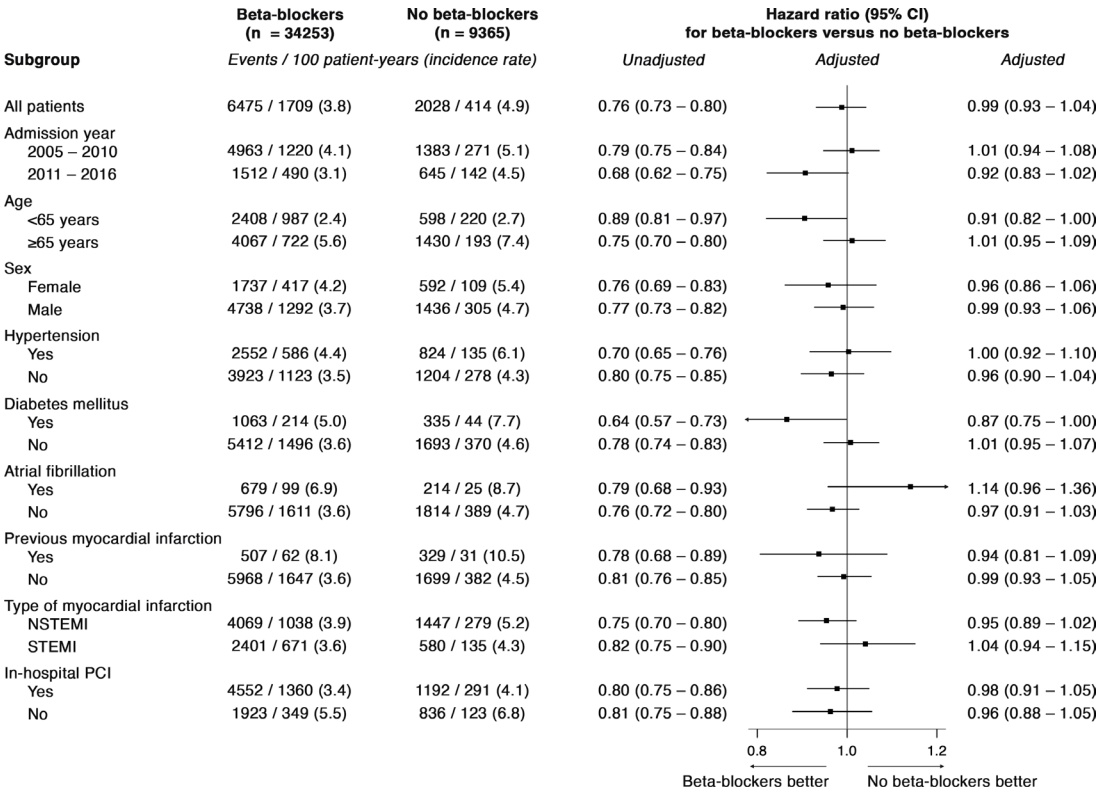


Figure 3 Primary composite outcome for subgroups in the intention-to-treat analysis. CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

control outcome for sensitivity analysis which resulted in no association between BB therapy and pneumonia, which was expected but also reassuring. The CV outcomes in this study were restricted to hospitalisation for MI, unscheduled revascularisation, hospitalisation for heart failure and stroke which are well validated, and information on mortality has previously been shown to be accurate.[28 29] For medical therapy 1 year after discharge for MI, filled prescriptions of BB in the National Prescribed Drug Register was utilised as it has previously been shown to be an adequate measure for medication use.[22] Nevertheless, adherence to prescribed and collected BB cannot be ascertained. Also, the formal indication for BB therapy was unknown despite patients receiving the therapy post-MI. To avoid other indications for BB therapy, we excluded cases with BB therapy prior to MI as well as patients with a diagnosis of heart failure or reduced/mid-range left ventricular ejection fraction (LVEF) before the index date for which BB was indicated. In the main analysis, an intention-to-treat approach was employed. However, patients may have commenced or discontinued BB therapy during follow-up. As such, in the per-protocol sensitivity analysis, we censored for discontinuation or switch of treatment strategy during follow-up because cessation of BB may have been due to side effects, and treatment initiation due to indications such as hypertension, heart failure or arrythmias. Nonetheless, it is reassuring that the sensitivity per-protocol analysis resulted in similar findings as in the main intention-to-treat analysis. Finally, we were not able to assess the association between health-related quality of life and BB therapy, which is increasingly important from a patient's perspective.[27]

CONCLUSIONS

In this large nationwide cohort study, long-term BB therapy beyond the first year of MI was not associated with lower risk of CV outcomes in patients without heart failure or LVSD. The results of ongoing RCTs will provide much-needed evidence about the role of long-term BB therapy in this group of patients.

Author affiliations
[1]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden
[2]Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[3]Division of Epidemiology and Biostatistics, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[4]Uppsala Clinical Research Center, Uppsala, Sweden
[5]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
[6]Department of Cardiology, Linköping University, Linköping, Sweden
[7]Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd University Hospital, Stockholm, Sweden
[8]Department of Cardiology, Lund University, Lund, Sweden

Twitter Tatendashe Bernadette Dondo @bernadetteTDond, Chris P Gale @cpgale3 and Gorav Batra @goravbatra

Acknowledgements We thank all staff members at all coronary care units in Sweden for their contribution to the SWEDEHEART register. We also thank Ida Björkgren (Uppsala Clinical Research Center, Uppsala, Sweden) for editorial support. An abstract with preliminary findings from this study were presented at the European Society of Cardiology (ESC) Congress 2022.

Contributors GB and CPG conceived and designed the study. GB, JA, CH, TJ and TY contributed to acquiring the data. LL curated the data and conducted the analysis. TBD verified the analytical methods. GB verified the underlying data. DI, SA and GB drafted the article. All authors provided critical interpretation and revision of the article. All authors had full access to all the study data and accept responsibility for submitting the article for publication. GB is the guarantor.

Funding This work was supported by grants from the Swedish State under the agreement between the Swedish Government and the County Councils (the ALF-agreement).

Competing interests JA reports, outside the submitted work, honoraria for lectures from Boehringer Ingelheim, AstraZeneca, MSD and Bayer; advisory board from AstraZeneca and Novartis. CH reports, outside the submitted work, institutional research grants from Pfizer, GlaxoSmith Kline, AstraZeneca, Bristol Myers Squibb;

advisory board from AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and Coala Life; personal fees from event adjudication for Uppsala Clinical Research Center. CPG reports, outside the submitted work, consultancy/advisory (AstraZeneca, AINexus, Bayer, Bristol Myers Squibb, Boehringer-Ingelheim, Chiesi, Daiichi Sankyo, GPRI Research B.V., iRhythm Menarini, Novartis, Organon), international advisory board member (*BMJ Heart*), speaker fees (AstraZeneca, Bayer, Menarini, Raisio Group, Wondr Medical, Zydus), editorship (Deputy Editor: *European Heart Journal Quality of Care and Clinical Outcomes*, Oxford University Press), grants (British Heart Foundation, National Institute for Health Research, Horizon 2020, Abbott Diabetes, Bristol Myers Squibb), leadership (NICE Indicator Advisory Committee, Chair ESC Quality Indicator Committee). GB reports, outside the submitted work, institutional research grants from Pfizer; expert committee and consulting fees to his institution from Bayer; honoraria for lectures and scientific advice from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Pfizer and Sanofi.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. SWEDEHEART does not allow individual data sharing to third parties. Access to aggregated data may be granted following review by the SWEDEHEART steering committee. Such requests can be submitted to the SWEDEHEART steering committee for consideration.

ORCID iDs
Tatendashe Bernadette Dondo http://orcid.org/0000-0002-8337-8425
Troels Yndigegn http://orcid.org/0000-0002-8960-2125
Gorav Batra http://orcid.org/0000-0002-2480-9547

REFERENCES

1 Ibanez B, James S, Agewall S, *et al*. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–77.
2 Collet J-P, Thiele H, Barbato E. The 'Ten Commandments' for the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;41:3495–7.
3 Seferović PM, Vardas P, Jankowska EA, *et al*. The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *Eur J Heart Fail* 2021;23:906–14.
4 McDonagh TA, Metra M, Adamo M, *et al*. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599–726.
5 Bangalore S, Steg G, Deedwania P, *et al*. β-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;308:1340–9.
6 Bangalore S, Bhatt DL, Steg PG, *et al*. β-Blockers and cardiovascular events in patients with and without myocardial infarction: post hoc analysis from the CHARISMA trial. *Circ Cardiovasc Qual Outcomes* 2014;7:872–81.
7 Kim Y, Byun S, Kim H-Y, *et al*. Long-term beta-blocker therapy after myocardial infarction without heart failure in the reperfusion era-systemic review and meta-analysis. *J Cardiovasc Pharmacol* 2022;79:650–4.
8 Bangalore S, Makani H, Radford M, *et al*. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. *Am J Med* 2014;127:939–53.
9 Safi S, Sethi NJ, Nielsen EE, *et al*. Beta-blockers for suspected or diagnosed acute myocardial infarction. *Cochrane Database Syst Rev* 2019;12:CD012484.
10 Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med* 1981;304:801–7.
11 The β-Blocker Heart Attack Trial. *JAMA* 1981;246:2073–4.
12 Grines CL, Browne KF, Marco J, *et al*. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1993;328:673–9.
13 Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. *N Engl J Med* 1997;336:1621–8.
14 Wallentin L, Becker RC, Budaj A, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361:1045–57.
15 Watanabe H, Ozasa N, Morimoto T, *et al*. Long-term use of carvedilol in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *PLoS One* 2018;13:e0199347.
16 Holt A, Blanche P, Zareini B, *et al*. Effect of long-term beta-blocker treatment following myocardial infarction among stable, optimally treated patients without heart failure in the reperfusion era: a Danish, nationwide cohort study. *Eur Heart J* 2021;42:907–14.
17 Joo S-J, Kim S-Y, Choi J-H, *et al*. Effect of beta-blocker therapy in patients with or without left ventricular systolic dysfunction after acute myocardial infarction. *Eur Heart J Cardiovasc Pharmacother* 2021;7:475–82.
18 Kim J, Kang D, Park H, *et al*. Long-term β-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. *Eur Heart J* 2020;41:3521–9.
19 Puymirat E, Riant E, Aissaoui N, *et al*. β blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. *BMJ* 2016;354:i4801.
20 Dondo TB, Hall M, West RM, *et al*. β-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. *J Am Coll Cardiol* 2017;69:2710–20.
21 Neumann A, Maura G, Weill A, *et al*. Clinical events after discontinuation of β-blockers in patients without heart failure optimally treated after acute myocardial infarction: a cohort study on the French healthcare databases. *Circ Cardiovasc Qual Outcomes* 2018;11:e004356.
22 Lesén E, Sandström TZ, Carlsten A, *et al*. A comparison of two methods for estimating refill adherence to statins in sweden: the RARE project. *Pharmacoepidemiol Drug Saf* 2011;20:1073–9.
23 Steg PG, Dabbous OH, Feldman LJ, *et al*. Determinants and prognostic impact of heart failure complicating acute coronary syndromes. *Circulation* 2004;109:494–9.
24 Hung J, Teng T-H, Finn J, *et al*. Trends from 1996 to 2007 in incidence and mortality outcomes of heart failure after acute myocardial infarction: a population-based study of 20,812 patients with first acute myocardial infarction in Western Australia. *J Am Heart Assoc* 2013;2:e000172.
25 Lawton JS, Tamis-Holland JE, Bangalore S, *et al*. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol* 2022;79:e21–129.
26 Bonnemeier H, Hartmann F, Wiegand UK, *et al*. Heart rate variability in patients with acute myocardial infarction undergoing primary coronary angioplasty. *Am J Cardiol* 2000;85:815–20.
27 Kramer JM, Hammill B, Anstrom KJ, *et al*. National evaluation of adherence to beta-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance. *Am Heart J* 2006;152:454.
28 Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450.
29 Brooke HL, Talbäck M, Hörnblad J, *et al*. The Swedish cause of death register. *Eur J Epidemiol* 2017;32:765–73.
30 Ishak D, Aktaa S, Lindhagen L, *et al*. Association of beta-blockers beyond 1 year after myocardial infarction for patients without heart failure or left ventricular systolic dysfunction and cardiovascular outcomes: nationwide cohort study. *Eur Heart J* 2022;43:ehac544.2724.

Supplemental material

Association of beta-blockers beyond one year after myocardial infarction and cardiovascular outcomes

Supplementary Figure 1. STROBE statement

STROBE Statement – checklist of items that should be included in reports of observational studies

	Item No	Recommendation
✓ **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
✓ **Introduction**		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
✓ **Methods**		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Supplementary Figure 1 (continued). STROBE statement

✓	**Results**		
	Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
	Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
			(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
	Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
			Cross-sectional study—Report numbers of outcome events or summary measures
	Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
			(*b*) Report category boundaries when continuous variables were categorized
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
✓	**Discussion**		
	Key results	18	Summarise key results with reference to study objectives
	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
	Generalisability	21	Discuss the generalisability (external validity) of the study results
✓	**Other information**		
	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Statistical analyses software and data packages

All statistical analyses were performed at Uppsala Clinical Research Center (UCR) with the use of R version 4.2.1 (R Foundation for Statistical Computing). Following relevant R packages were utilised during the analyses:

- dplyr 1.0.10
- rms 6.3-0
- survival 3.3-1
- mice 3.14.0

Supplementary Table 1. Data sources and the International Code of Disease, tenth revision (ICD-10) and the Anatomical Therapeutic Chemical (ATC) codes applied to identify comorbidities and comedication

Variable	Data source	ICD-10 / ATC code
Calendar year	SWEDEHEART	-
Age	SWEDEHEART	-
Sex	SWEDEHEART	-
Smoking	SWEDEHEART	-
Hypertension	SWEDEHEART, NPR	I10, I11, I12, I13, I15
Diabetes mellitus	SWEDEHEART, NPR	E10, E11, E12, E13, E14
Atrial fibrillation/flutter	SWEDEHEART, NPR	I48
Previous MI	SWEDEHEART, NPR	I21, I22, I252
Previous PCI	SWEDEHEART, NPR	Z951
Previous CABG	SWEDEHEART, NPR	Z955
Heart failure	SWEDEHEART, NPR	I42, I50, I110, I255, I130, I132, K761
Cerebrovascular disease	SWEDEHEART, NPR	I60, I61, I63, I64, I672, I678, I679, G45
Peripheral arterial disease	NPR	I70, I71, I72, I73
COPD	NPR	J43, J44
Asthma	NPR	J45, J46
Type of MI	SWEDEHEART	-
Creatinine/eGFR	SWEDEHEART	-
Blood pressure	SWEDEHEART	-
In-hospital PCI	SWEDEHEART	-
In-hospital CABG	SWEDEHEART	-
Left ventricular ejection fraction	SWEDEHEART	-
Beta-blockers	Prescribed Drug Register	C07
Acetylsalicylic acid	Prescribed Drug Register	B01AC06
$P2Y_{12}$ inhibitor	Prescribed Drug Register	B01AC04, B01AC05, B01AC22, B01AC24
Oral anticoagulants	Prescribed Drug Register	B01AA03, B01AE07, B01AF
ACE inhibitors	Prescribed Drug Register	C09A, C09B
ARB	Prescribed Drug Register	C09C, C09D
Statins	Prescribed Drug Register	C10AA
Diuretics	Prescribed Drug Register	C03C

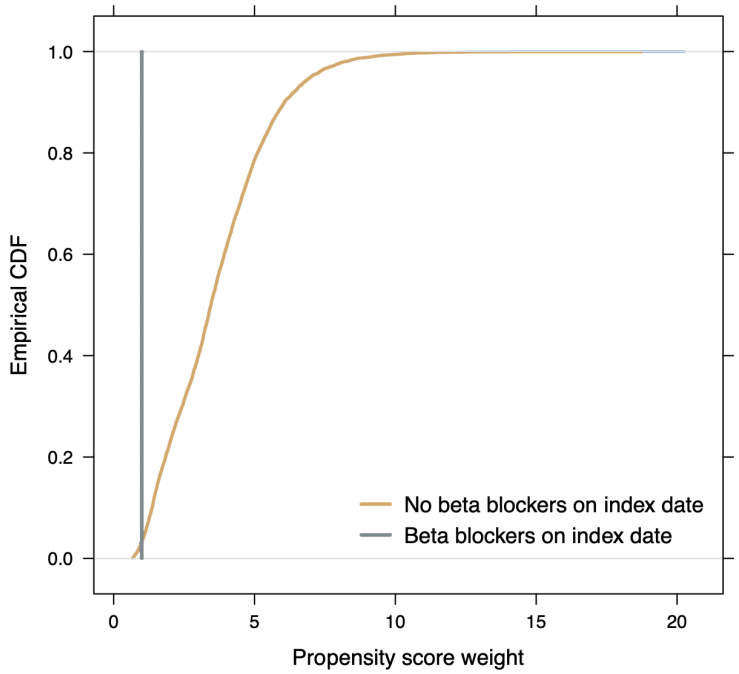
eGFR levels are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MI, myocardial infarction; NPR, National Patient Register; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TTR, time in therapeutic range.

Supplementary Table 2. Data sources and the International Code of Disease, tenth revision (ICD-10) codes applied to identify outcomes

Variable	Data source	ICD-10 code
Primary composite outcome		
All-cause mortality	Population register	-
Myocardial infarction	NPR	I21, I22
Unscheduled revascularisation	SWEDEHEART	-
Heart failure hospitalisation	NPR	I42, I50, I110, I255, I130, I132, K761
Secondary outcomes		
Cardiovascular mortality	Cause of death register	I00 – I99
Stroke	NPR	I60, I61, I63, I64
Negative control outcome		
Pneumonia	NPR	J12, J13, J14, J15, J16, J17, J18

Abbreviations: NPR, National Patient Register.

Supplementary Figure 2. Empirical cumulative distribution function plot illustrating the weights in the inverse propensity score weighting model

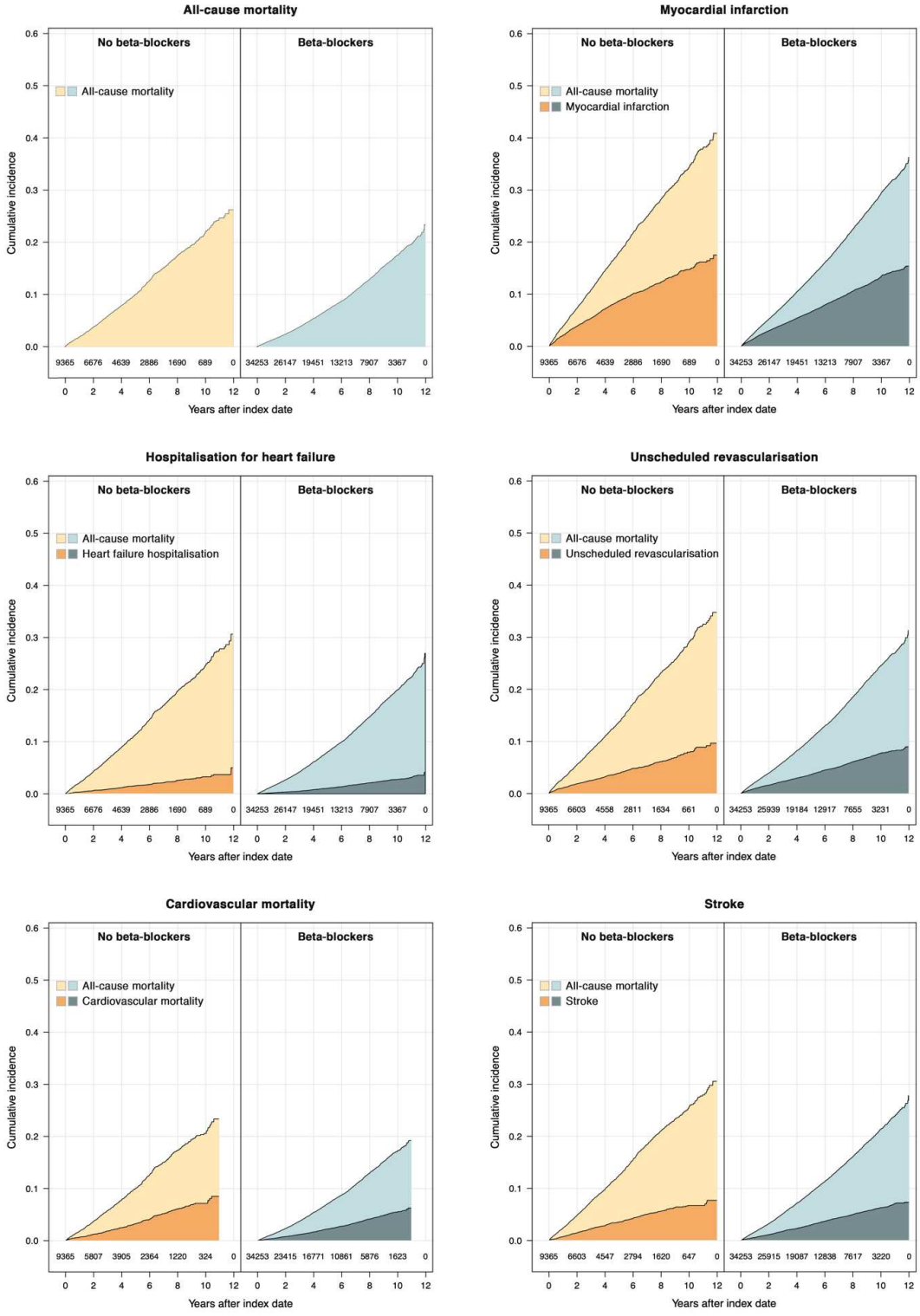


Supplementary Table 3. Demographics and characteristics before propensity score weighting

Characteristic	Beta-blockers (n = 34900)	No beta-blockers (n = 11604)
Demographics		
Age, years, median (IQR)	64 (56 – 71)	65 (56 – 74)
Sex, female, n (%)	8871 (25.4)	3181 (27.4)
Smoking, n (%)	10973 (31.9) [516]	3299 (29.3) [340]
Medical history 1 year after MI, n (%)		
Hypertension	13455 (38.6)	4250 (36.6)
Diabetes mellitus	4694 (13.4)	1380 (11.9)
Atrial fibrillation/flutter	2347 (6.7)	765 (6.6)
Prior MI	1626 (4.7)	1083 (9.3)
Prior PCI	966 (2.8)	746 (6.4)
Prior CABG	458 (1.3)	327 (2.8)
Cerebrovascular disease	1833 (5.3)	814 (7.0)
Peripheral vascular disease	854 (2.4)	404 (3.5)
COPD	997 (2.9)	484 (4.2)
Index event, n (%)		
NSTEMI	21816 (62.5) [6]	8104 (69.9) [2]
STEMI	13078 (37.5)	3498 (30.1)
In-hospital course and medication at discharge		
eGFR, median (IQR)	77 (67 – 89) [1408]	78 (67 – 90) [446]
PCI, n (%)	27706 (79.4)	7845 (67.6)
CABG, n (%)	1245 (3.6)	252 (2.2)
Beta-blockers, n (%)	33344 (95.6) [28]	6426 (55.4) [9]
Concomitant medication 1 year after MI, n (%)		
Acetylsalicylic acid	32595 (93.4)	8610 (74.2)
$P2Y_{12}$ inhibitors	5880 (16.8)	1501 (12.9)
Oral anticoagulants	540 (1.5)	145 (1.2)
ACE inhibitors	11541 (33.1)	2499 (21.5)
ARB	4111 (11.8)	1181 (10.2)
Statins	31164 (89.3)	7513 (64.7)

*History about prior MI, prior PCI and prior CABG is before hospitalisation for MI. Values are in median (interquartile range [IQR]) for continuous variables and numbers (%) for categorical variables. Numbers within square brackets indicate number of missing values. eGFR levels are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and presented in mL/min/1.73m^2. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Supplementary Figure 3. Unadjusted cumulative incidence plot of all secondary outcomes considering competing risk by all-cause mortality



Supplementary Table 4. Primary and secondary outcomes in the per-protocol analysis

	Beta-blockers (n = 34253) Events/100 patient-yr (incidence rate)	**No beta-blockers (n = 9365)** Events/100 patient-yr (incidence rate)	**Hazard ratio (95% CI) for beta-blockers** (unadjusted)	**Hazard ratio (95% CI) for beta-blockers** (adjusted)
Primary composite outcome	1856 / 541 (3.4)	1427 / 296 (4.8)	0.72 (0.67 – 0.78)	0.98 (0.90 – 1.06)
All-cause mortality	772 / 544 (1.4)	678 / 298 (2.3)	0.70 (0.62 – 0.78)	1.01 (0.90 – 1.14)
Myocardial infarction	801 / 544 (1.5)	567 / 298 (1.9)	0.73 (0.65 – 0.82)	0.95 (0.84 – 1.07)
Unscheduled revascularisation	418 / 541 (0.8)	250 / 296 (0.9)	0.84 (0.72 – 0.99)	0.88 (0.74 – 1.06)
Heart failure hospitalisation	104 / 544 (0.2)	80 / 298 (0.3)	0.72 (0.53 – 0.98)	0.91 (0.64 – 1.27)
Other secondary outcomes				
Cardiovascular mortality	271 / 495 (0.6)	200 / 255 (0.8)	0.78 (0.65 – 0.95)	1.10 (0.89 – 1.36)
Stroke	342 / 540 (0.6)	228 / 294 (0.8)	0.84 (0.70 – 1.00)	1.01 (0.84 – 1.22)
Negative control outcome				
Pneumonia	385 / 540 (0.7)	254 / 294 (0.9)	0.88 (0.74 – 1.04)	1.09 (0.91 – 1.31)

The primary composite outcome was a composite of all-cause mortality, myocardial infarction, hospitalisation for heart failure or unscheduled coronary revascularisation. Person time and incidence rate is given in 100 person-years. Hazard ratios are given with 95% confidence intervals. The no beta-blockers group is the reference group. In the per-protocol analysis, treatment with beta-blockers is defined as a time-varying variable and patients are censored at their first treatment switch (regardless of direction). In total, 8401 (24.5%) of the patients in the beta-blockers group and 6441 (68.8%) of the patients in the no beta-blockers group did not switch treatment during follow-up for the primary composite outcome.

Supplementary Table 5. Primary composite outcome for subgroups in the per-protocol analysis

	Beta-blockers (n = 34253) Events/100 patient-yr (incidence rate)	**No beta-blockers (n = 9365)** Events/100 patient-yr (incidence rate)	**Hazard ratio (95% CI) for beta-blockers** (unadjusted)	**Hazard ratio (95% CI) for beta-blockers** (adjusted)
All patients	1856 / 541 (3.4)	1427 / 296 (4.8)	0.72 (0.67 – 0.78)	0.98 (0.90 – 1.06)
Admission year				
2005 – 2010	1176 / 323 (3.6)	933 / 188 (5.0)	0.75 (0.68 – 0.82)	1.00 (0.90 – 1.10)
2011 – 2016	680 / 219 (3.1)	494 / 108 (4.6)	0.67 (0.59 – 0.75)	0.94 (0.82 – 1.07)
Age				
Age <65 years	583 / 292 (2.0)	407 / 155 (2.6)	0.76 (0.67 – 0.87)	0.77 (0.66 – 0.89)
Age ≥65 years	1273 / 249 (5.1)	1020 / 140 (7.3)	0.73 (0.67 – 0.80)	1.06 (0.96 – 1.16)
Sex				
Female	544 / 134 (4.1)	423 / 78 (5.4)	0.78 (0.68 – 0.89)	0.96 (0.83 – 1.11)
Male	1004 / 217 (4.6)	1312 / 407 (3.2)	0.70 (0.64 – 0.76)	0.97 (0.88 – 1.07)
Hypertension				
Yes	784 / 194 (4.1)	570 / 93 (6.2)	0.67 (0.60 – 0.75)	1.03 (0.91 – 1.17)
No	1072 / 348 (3.1)	857 / 203 (4.2)	0.75 (0.68 – 0.82)	0.92 (0.83 – 1.02)
Diabetes mellitus				
Yes	328 / 64 (5.2)	233 / 30 (7.9)	0.67 (0.56 – 0.81)	0.94 (0.77 – 1.15)
No	1528 / 478 (3.2)	1194 / 266 (4.5)	0.73 (0.67 – 0.79)	0.98 (0.90 – 1.07)
Atrial fibrillation				
Yes	241 / 33 (7.4)	157 / 15 (10.2)	0.70 (0.57 – 0.87)	1.11 (0.87 – 1.43)
No	1615 / 508 (3.2)	1270 / 280 (4.5)	0.72 (0.67 – 0.78)	0.96 (0.88 – 1.05)
Previous myocardial infarction				
Yes	163 / 18 (9.0)	240 / 23 (10.2)	0.82 (0.66 – 1.00)	1.04 (0.84 – 1.29)
No	1693 / 523 (3.2)	1187 / 272 (4.4)	0.77 (0.71 – 0.83)	0.98 (0.90 – 1.06)
Type of myocardial infarction				
NSTEMI	1239 / 334 (3.7)	1023 / 204 (5.0)	0.74 (0.68 – 0.81)	0.98 (0.89 – 1.07)
STEMI	614 / 207 (3.0)	404 / 91 (4.4)	0.70 (0.62 – 0.80)	0.96 (0.83 – 1.12)
In-hospital PCI				
Yes	1172 / 432 (2.7)	790 / 203 (3.9)	0.72 (0.66 – 0.79)	0.91 (0.82 – 1.01)
No	684 / 109 (6.3)	637 / 93 (6.9)	0.89 (0.80 – 1.00)	1.05 (0.93 – 1.19)

The primary composite outcome was a composite of all-cause mortality, myocardial infarction, hospitalization for heart failure or unscheduled coronary revascularisation. Person time and incidence rate is given in 100 person-years. Hazard ratios are given with 95% confidence intervals. The no beta-blockers group is the reference group. In the per-protocol analysis, treatment with beta-blockers is defined as a time-varying variable and patients are censored at their first treatment switch (regardless of direction).