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Original research

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

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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

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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

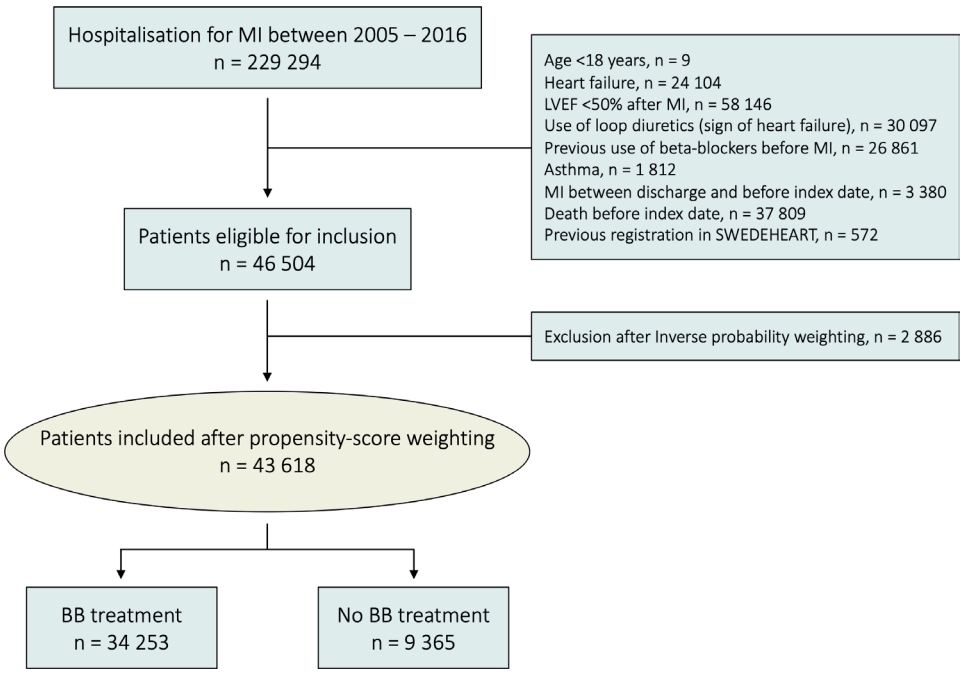

Figure 1 CONSORT diagram illustrating inclusion and exclusion of patients. BB, beta-blockers; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended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

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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

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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, determining whether

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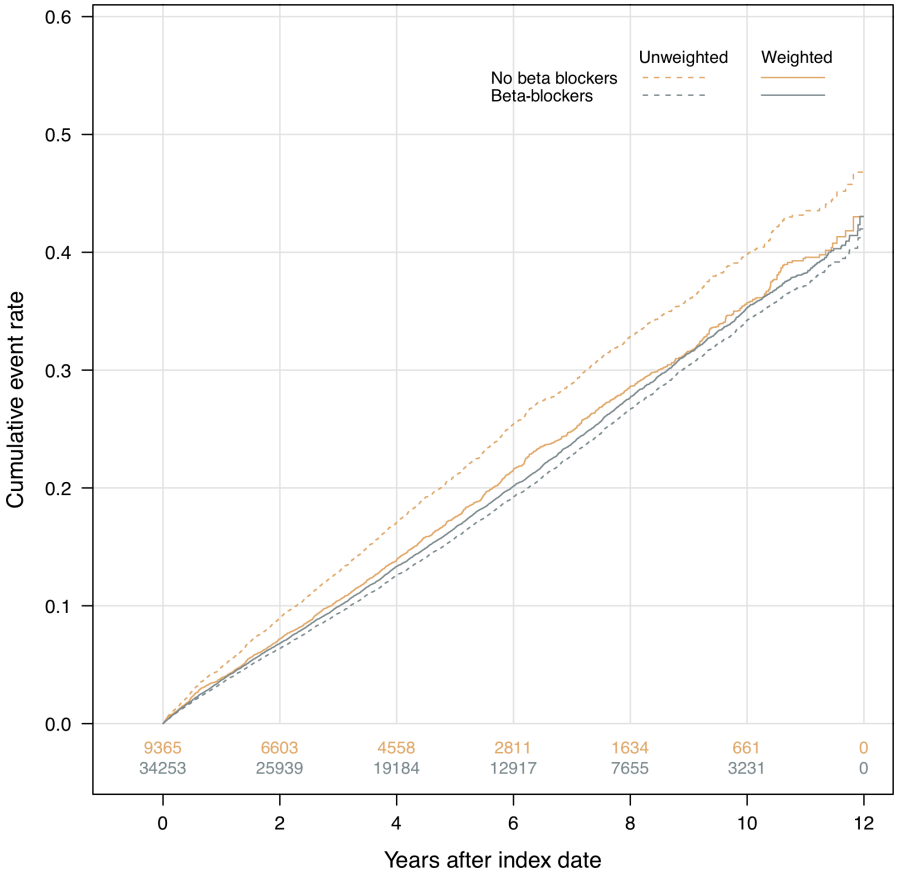

Figure 2 Kaplan–Meier plot of the primary composite outcome.

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 control

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.

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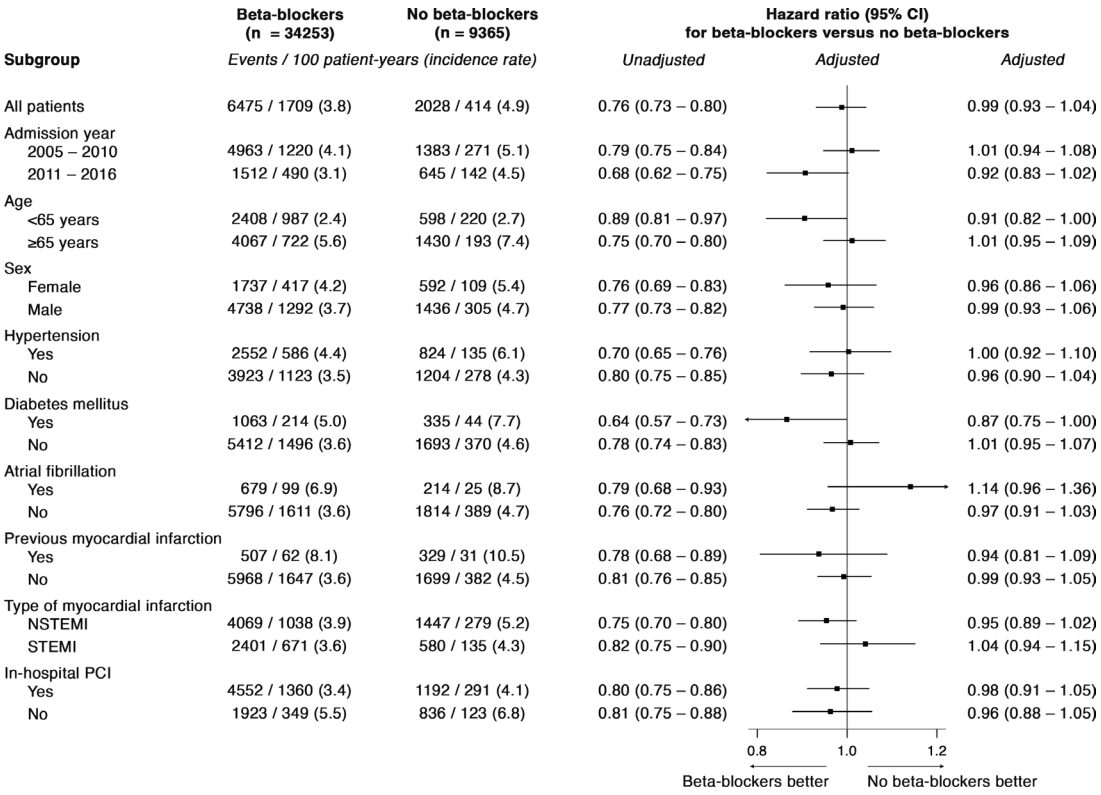

Figure 3 Primary composite outcome for subgroups in the intention-to-treat analysis. CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

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.

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