ORIGINAL RESEARCH

Beta-blocker use and acute exacerbations of COPD following myocardial infarction: a Danish nationwide cohort study

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ABSTRACT

Introduction Patients with chronic obstructive pulmonary disease (COPD) are undertreated with beta-blockers following myocardial infarction (MI), possibly due to fear for acute exacerbations of COPD (AECOPD). Is beta-blocker use associated with increased risk of AECOPD in patients following first-time MI?

Methods Danish nationwide study of patients with COPD following hospitalisation for MI from 2003 to 2015. Multivariable, time-dependent Cox regression accounting for varying beta-blocker use based on claimed prescriptions during up to 13 years of follow-up.

Results A total of 10 884 patients with COPD were discharged after first-time MI. The 1-year rate of AECOPD was 35%, and 65% used beta-blockers at 1 year. Beta-blocker use was associated with a lower risk of AECOPD (multivariable-adjusted HR 0.78, 95% CI 0.74–0.83). This association was independent of the type of MI (HR 0.70, 95% CI 0.59–0.83 in ST-elevation MI (STEMI) and HR 0.80, 95% CI 0.75–0.84 in non-STEMI), presence or absence of heart failure (HR 0.82, 95% CI 0.74–0.90 and HR 0.77, 95% CI 0.72–0.82, respectively), beta-blocker dosage and type, as well as exacerbation severity. Results were similar in 1118 patients with full data on COPD severity and symptom burden (median forced expiratory volume in 1 s as percentage of predicted was 46 and majority had moderate dyspnoea), and in 1358 patients with severe COPD and frequent AECOPD with a high 1-year rate of AECOPD of 70%.

Discussion Beta-blocker use was not associated with increased risk of AECOPD following MI. This finding was independent of COPD severity, symptom burden and exacerbation history, and supports the safety of beta-blockers in patients with COPD, including high-risk patients with severe disease.

Key messages

What is the key question?

► Is beta-blocker use following myocardial infarction (MI) associated with increased risk of acute exacerbations of chronic obstructive pulmonary disease (COPD)?

What is the bottom line?

► This large nationwide cohort study using time-dependent variables shows that beta-blocker use, defined as claimed prescriptions, is not associated with increased risk of acute exacerbations following MI, suggesting that beta-blockers are safe in patients with COPD.

Why read on?

► Analyses also suggest that beta-blocker use is safe in patients with a very high risk of exacerbations, and the results were independent of the type of MI, presence or absence of heart failure, COPD severity and symptom burden, as well as dosage and type of beta-blocker.

INTRODUCTION

Beta-blockers are recommended following myocardial infarction (MI) to reduce mortality and morbidity.[1 2] However, patients with chronic obstructive pulmonary disease (COPD) are undertreated, in particular those with severe airflow limitation, high symptom burden or frequent exacerbations.[3] Concerns about the safety of beta-blockers in patients with COPD may contribute to the observed undertreatment.

Although non-selective beta-blockers are poorly tolerated in COPD due to adverse blockage of airway beta-2-receptors causing bronchoconstriction,[4] the evidence for the safety of beta-1-selective beta-blockers in patients with COPD is less clear. On one hand, a Cochrane review updated in 2010[5] concluded that beta-1-selective beta-blockers do not decrease lung function significantly, and in contemporary observational studies, beta-blockers (primarily beta-1-selective) were associated with unaffected[6–10] or even reduced[11–14] risk of acute exacerbations of COPD (AECOPD). On the other hand, Baker and Wilcox[15] in a 2016 review of clinical and observational studies concluded that despite being tolerated by many patients with COPD, beta-1-selective beta-blockers cause a significant reduction in lung function and efficacy of inhaled beta-2-agonists. This may increase the risk of AECOPD, particularly in patients with severe COPD and frequent AECOPD.[16] This is supported by the recently published BLOCK COPD trial of metoprolol versus placebo for patients with COPD with increased risk of AECOPD.[17] Here, hospitalisation for AECOPD was more common in the beta-blocker group, whereas time until the first AECOPD was similar in the two groups.

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Further evidence is needed on the safety of beta-blockers in patients with COPD following MI, in particular long-term studies, as beta-blockers are a mainstay of secondary prevention medication following MI, and patients with COPD and MI constitute a high-risk group for exacerbations.[18] In previous observational studies,[6–14] beta-blocker use was assessed as sent prescriptions at baseline and analyses did not account for changes in use during follow-up, which potentially could lead to misclassification of beta-blocker users.[19] Also, this approach can overestimate beta-blocker use as not all prescriptions are being claimed. Optimally, beta-blocker use should be assessed continuously and as true to life as possible during follow-up and included as a time-dependent variable in time-to-event analyses. This can be achieved by using data on claimed prescriptions from the Danish National Prescription Registry.

We, therefore, investigated whether time-dependent beta-blocker use was associated with increased risk of AECOPD in patients following first-time MI from 2003 to 2015 including subgroups of patients with complete clinical characteristics and with a high risk of exacerbations. Also, we investigated the potential dose-dependent relationship between beta-blocker use and AECOPD, as well as differences between beta-1-selective and non-selective beta-blockers, and moderate and severe AECOPD.

METHODS

Data sources

In Denmark, all residents are assigned a unique personal identifying number. Through this number, we linked data on hospital diagnoses from The Danish National Patient Register[20] and claimed prescriptions from The National Prescription Registry, vital status from The Danish Civil Register,[21] household income from Statistics Denmark and clinical COPD data from Danish Register of COPD.[22] The latter was established in 2008 and collects lung function (forced expiratory volume in 1 s as a percentage of predicted (FEV_1%)), dyspnoea score (modified Medical Research Council (mMRC)), smoking status and body mass index (BMI) during outpatient visits in all Danish hospital COPD clinics.

Study population and beta-blocker usage

We included all patients discharged with a first-time diagnosis of MI and concurrent COPD from 1 January 2003 to 31 December 2015. Patients who died during hospitalisation were not included. Diagnosis codes for MI and COPD have high validity in the Danish National Patient Registry[23 24] and are listed in the online supplementary table S1. Follow-up started at the date of discharge (baseline).

Beta-blocker exposure was evaluated using information from the Danish National Prescription Registry by claimed prescriptions on beta-blockers (ATC C07) including strength and number of pills dispensed. From these data, the average daily dosage and treatment duration was calculated at each new prescription claim as previously described.[25 26] This method allows for beta-blocker exposure status, dosage and type of beta-blocker to change through time and data were included as time-dependent variables in the time-to-event analyses.

Outcome and follow-up

The outcome of interest was first moderate or severe AECOPD following MI. Moderate AECOPD was defined by a claimed prescription of oral corticosteroids (ATC H02AB06), which has been validated and found to be a robust method,[27] and severe AECOPD as hospitalisation for COPD (ICD10 J44 as a primary diagnosis; or J44 as secondary diagnosis along with a primary diagnosis of DJ96 or DJ13–DJ18). Patients were followed from baseline until first moderate AECOPD, first severe AECOPD, death, emigration or the end of the study.

Characterisation of the study population

Comorbidities were identified up to 10 years prior to baseline according to definitions listed in the online supplementary table S1. To account for new-onset comorbidities during follow-up, comorbidities were included as time-dependent variables in the analyses.

We identified the history of frequent AECOPD and the number of inhaled long-acting medications prior to baseline. Frequent AECOPD is a strong predictor for future AECOPD[16 28] and was defined as two or more claimed prescriptions of oral corticosteroids at least 28 days apart[27] and/or one or more hospital admission for COPD[29] within 1 year prior to baseline. The number of different classes of long-acting inhaled medications (online supplementary table S2) used within 180 days was identified and use of all three classes of inhaled medications ('triple therapy') was used as a proxy for severe COPD associated with a higher risk of AECOPD than patients using dual, mono or no inhalation therapy.

Complete clinical characteristics from the Danish Register of COPD were available in a subgroup of patients (n=1118) including severity of airflow limitation, Global Initiative for Chronic Obstructive Lung Disease classification (GOLD stages 1–4 equalling FEV_1%≥80% of predicted value, 50%–79%, 30%–49% and <30%, respectively),[29] severity of dyspnoea (mMRC dyspnoea score), smoking status and BMI.

We identified the type of MI (ST-elevation MI (STEMI) and non-STEMI (NSTEMI)) because this can be a potential confounder due to differences in prognosis[30 31] and treatment recommendations.[1 2] STEMI was defined according to diagnosis codes validated for STEMI[23] (online supplementary table S1) and the remainder were classified as NSTEMI. Revascularisation procedures during hospitalisation for first MI were identified using the International Classification of Diseases and Related Health Problems (ICD) procedure codes. Income (adjusted for household size) was included as a marker of socioeconomic status. Income was missing in an insignificant number of patients (n=16), whereas all other variables were complete. The loss to follow-up was negligible (n=11; all due to emigration).

Statistical analyses

Baseline characteristics were tabulated using frequencies and percentages for categorical variables, and median and IQR for continuous variables. For comparison between subgroups, we used Pearson's χ^2 test and Wilcoxon rank-sum test, respectively. A p value<0.05 was considered significant.

We estimated HRs with 95% CIs for the association between beta-blocker use and first moderate or severe AECOPD following MI using Cox proportional hazards regression models. Adjusting variables were predetermined by using directed acyclic graphs[32] (online supplementary figure S1) and included age, sex, history of AECOPD, inhaled therapy, comorbidities (heart failure, atrial fibrillation, angina pectoris, hypertension, diabetes mellitus, peripheral vascular disease, cerebrovascular disease, cancer, renal failure, asthma and depression), type of MI, revascularisation procedures, income (categorised in tertiles for this cohort) and calendar year of baseline. We avoided conditioning on future exposure by including beta-blocker use, comorbidities and age as continuously updated time-dependent variables,

and the remainder were time-fixed variables defined by baseline exposure, thereby preventing immortal time and selection bias.[33] The proportional hazards assumption in the Cox models was inspected graphically using log-minus-log plots. Potential clinically relevant interactions were tested and none were found, unless otherwise stated.

In stratified Cox analyses, we investigated potential differences in patients with STEMI versus NSTEMI and with and without heart failure at baseline. This was done to account for differences in prognosis[30 31] and treatment recommendations[1 2] in STEMI and NSTEMI and because acute decompensated heart failure may be misinterpreted as AECOPD.[34]

In secondary analyses, we analysed first moderate and first severe AECOPD separately. When analysing moderate AECOPD, patients were censored in case of any prior severe AECOPD during follow-up as this was considered to have higher importance.

A potential dose-dependent relationship was analysed by including beta-blocker dosage as a time-dependent categorical variable in the multivariable Cox model with no beta-blocker exposure as reference. Dosages were categorised into thirds of the recommended maximum dosage for each type of beta-blocker. Detailed definitions are shown in the online supplementary table S3.

Next, beta-blockers were categorised into beta-1-selective (metoprolol, atenolol, bisoprolol) and non-selective (carvedilol, sotalol, propranolol) and we analysed their association with AECOPD in the multivariable Cox model. Uncommon beta-blocker types were not included due to a negligible low number of users. Dosage and type of beta-blockers used in patients alive and free of AECOPD were analysed at specified times during follow-up.

To investigate the influence of COPD severity, symptom burden and a history of frequent exacerbations, two subgroup analyses were performed: (1) patients with complete clinical characteristics from Danish Register of COPD in a Cox model adjusting for sex, age, GOLD stage, mMRC dyspnoea score, smoking status, BMI, history of AECOPD, inhaled therapy, heart failure, asthma and calendar year; (2) high-risk patients defined as a history of frequent AECOPD and use of triple therapy as defined above. In the latter, we used the same Cox model as in the primary analysis. In these subgroups, we also analysed moderate and severe AECOPD separately. In a sensitivity analysis of new beta-blocker users, we excluded patients who had used beta-blockers 180 days prior to the first MI to investigate potential healthy adherer bias. Subsequently, we excluded patients with major medical conditions other than MI at baseline for which beta-blockers are indicated (ie, heart failure, angina and hypertension) to assess potential confounding by indication.

To address potential unaccounted behavioural bias, that is, patients not using beta-blockers may have other adverse behaviours that can impact AECOPD, we investigated the influence of the use of other secondary prevention medications. This was done by performing Cox analyses stratified by whether patients had used both aspirin and statins, and angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARBs) within 90 days after MI. To avoid conditioning on future exposure, these analyses started at 90 days of follow-up.[33]

To investigate the influence of death as a competing risk, we analysed a composite outcome of death and AECOPD in the Cox model. Competing risks regression was not performed as they have shown to be inappropriate with time-dependent variables.[35]

Landmark analyses at 90 days and 1 year, respectively, were performed to investigate potential short-term and long-term associations of beta-blockers with AECOPD.

Table 1 Baseline characteristics of 10 884 patients with chronic obstructive pulmonary disease following first-time MI from 2003 to 2015

Characteristic	Value
N	10 884
Age, median (IQR)	74 (68–81)
Sex, n (%)	
Male	5659 (52.0)
Frequent exacerbations, n (%)	3148 (28.9)
Long-acting inhalation therapy, n (%)	
None	4034 (37.1)
Mono	1368 (12.6)
Dual	2943 (27.0)
Triple	2539 (23.3)
Type of MI, n (%)	
ST-segment elevation MI (STEMI)	1255 (11.5)
Non-STEMI	9629 (88.5)
Comorbidities, n (%)	
Heart failure	3610 (33.2)
Atrial fibrillation	2449 (22.5)
Angina pectoris	2837 (26.1)
Hypertension	4828 (44.4)
Diabetes mellitus	2211 (20.3)
Peripheral vascular disease	1520 (14.0)
Cerebrovascular disease	1439 (13.2)
Cancer	1534 (14.1)
Chronic kidney disease	858 (7.9)
Asthma	1406 (12.9)
Depression	2588 (23.8)

MI, myocardial infarction.

Data management and statistical analyses were performed with SAS V.9.4 (SAS Institute) and Stata/MP V.15.1 (StataCorp LP).

Ethics

The Danish Data Protection Agency approved the study (reference no. 2008-58-0020/REG-11-2016). Ethical approval is not required for register-based studies in Denmark. Data were made available such that individuals could not be identified.

RESULTS

Patient characteristics

Of a total of 96 567 patients discharged after first-time MI, 10 884 (11.3%) had a diagnosis of COPD and were included in the study. The median age was 75 years (IQR 68–81), 52.0% were male individuals, and comorbidities were common, in particular cardiac comorbidities (table 1).

Follow-up was up to 13 years, and the median follow-up time was 278 days. A total of 5829 had one or more AECOPD during follow-up, and 1-year and 5-year rates of AECOPD were 34.9% and 50.1%, respectively. At baseline, 3298 (30.3%) used beta-blockers (of those were 2234 (67.7%) beta-blocker users prior to MI), and among patients alive and free from exacerbations at 90 days and 1 year the number of users were 4693 (65.0%) and 2994 (61.5%), respectively (online supplementary table S4).

Table 2 Association of beta-blocker use with AECOPD following MI

	HR	95% CI	*P* value
Total study population	0.78	0.74–0.83	<0.0001
Stratified by type of MI			
STEMI	0.7	0.59–0.83	<0.0001
NSTEMI	0.8	0.75–0.84	<0.0001
Stratified by the presence of heart failure			
Heart failure	0.82	0.74–0.9	0.0001
No heart failure	0.77	0.72–0.82	<0.0001
Aspirin and statin use after MI			
Yes	0.84	0.77–0.92	0.0002
No	0.87	0.78–0.97	0.015
ACEi or ARB use after MI			
Yes	0.84	0.76–0.93	0.0005
No	0.85	0.76–0.94	0.0012
Subgroup of patients with complete clinical data*	0.82	0.71–0.96	0.0113
Subgroup of patients with a history of frequent exacerbations and triple therapy	0.77	0.67–0.87	<0.0001
Landmark analyses			
0–90 days	0.72	0.66–0.78	<0.0001
91 days to maximum follow-up	0.84	0.78–0.9	<0.0001
0–1 year	0.75	0.7–0.8	<0.0001
1 year to maximum follow-up	0.87	0.8–0.96	0.003
Beta-1-selectivity of beta-blockers			
No beta-blocker exposure	1	Reference	–
Beta-1-selective beta-blockers	0.78	0.74–0.82	<0.0001
Non-selective beta-blockers	0.82	0.73–0.91	0.0002
Dosage of beta-blockers			
No beta-blocker exposure	1	Reference	–
Low dosage	0.81	0.77–0.86	<0.0001
Medium dosage	0.73	0.67–0.79	<0.0001
High dosage	0.74	0.64–0.85	<0.0001

HR were estimated using time-dependent multivariable Cox regression adjusting for age, sex, history of AECOPD, inhaled therapy, comorbidities, type of MI, revascularisation procedures, income and calendar year unless otherwise stated.
*Adjusted for sex, age, Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, modified Medical Research Council dyspnoea score, smoking status, body mass index, history of AECOPD, inhaled therapy, heart failure, asthma and calendar year.
ACEi, angiotensin-converting enzyme inhibitors; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; ARB, angiotensin II receptor blocker; MI, myocardial infarction; NSTEMI, Non-STEMI; STEMI, ST-elevation myocardial infarction.

Association of beta-blockers with AECOPD

In the total study population, beta-blocker use was associated with lower risk of AECOPD (multivariable-adjusted HR 0.78, 95% CI 0.74–0.83, p<0.0001) as shown in table 2.

The stratified analyses showed overall similar estimates for beta-blocker use across all strata including STEMI and NSTEMI, and patients with and without heart failure. Statistical interaction was noted between heart failure and beta-blocker use (interaction term HR 1.16, 95% CI 1.04–1.29, p=0.007), however, as shown in table 2, the estimates had the same direction and similar magnitude. There was no significant interaction between the type of MI and beta-blocker use (HR 0.89, 95% CI 0.75–1.05, p=0.16). Baseline characteristics according to strata are found in the online supplementary table S5.

Table 3 Association of beta-blocker use with moderate and severe AECOPD following MI

	HR	95% CI	*P* value
Total study population			
Moderate AECOPD	0.81	0.75–0.86	<0.0001
Severe AECOPD	0.76	0.71–0.82	<0.0001
Subgroup of patients with complete clinical data*			
Moderate AECOPD*	0.77	0.63–0.95	0.014
Severe AECOPD*	0.90	0.75–1.08	0.27
History of frequent exacerbations and triple therapy			
Moderate AECOPD	0.78	0.66–0.93	0.006
Severe AECOPD	0.78	0.67–0.90	0.0006

HR were estimated using time-dependent multivariable Cox regression adjusting for age, sex, history of AECOPD, inhaled therapy, comorbidities, type of MI, revascularisation procedures, income and calendar year unless otherwise stated.
*Adjusted for sex, age, GOLD stage, mMRC dyspnoea score, smoking status, BMI, history of AECOPD, inhaled therapy, heart failure, asthma and calendar year.
ACEi, angiotensin-converting enzyme inhibitors; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DrCOPD, Danish Register of COPD; MI, myocardial infarction; mMRC, modified Medical Research Council; NSTEMI, non-STEMI; STEMI, ST-segment elevation myocardial infarction.

Analyses of secondary outcomes showed that 3495 had one or more moderate AECOPD during follow-up and 3684 had a severe AECOPD. There was a similar beneficial association of beta-blocker use with moderate and severe AECOPD (HR 0.81, 95% CI 0.75–0.86, p<0.0001; HR 0.76, 95% CI 0.71–0.82, p<0.0001, respectively) (table 3).

When investigating beta-blocker dosage, we found that majority of beta-blocker users were on low dosage throughout the follow-up period (online supplementary table S6). There was no significant dose-dependent relationship between beta-blocker dosage and AECOPD, yet, a tendency towards lower HRs for medium and high dosage compared with low as shown in table 2.

The majority of beta-blocker users used beta-1-selective beta-blockers, particularly metoprolol (online supplementary table S7). Multivariable Cox regression showed a similar association between beta-1-selective and non-selective beta-blockers and AECOPD with no beta-blocker exposure as the reference (table 2).

Subgroup analyses

A total of 1118 patients had complete clinical characteristics (the Danish Register of COPD). In this subgroup, a history of frequent exacerbations and use of triple therapy was more prevalent compared with patients without complete clinical data (online supplementary table S8). Median FEV_1% was 46% and the majority had mMRC dyspnoea score 2, corresponding to moderate symptom burden (online supplementary table S9), and rates of AECOPD during follow-up were higher (1-year rate 54.3% and 5-year rate 65.3%) than in the total study population. Similar to primary analyses, beta-blocker use was associated with a lower risk of AECOPD in this subgroup after adjustment for the GOLD stage, mMRC dyspnoea score and other important potential confounders (table 2). Analyses of secondary outcomes showed similar association for moderate AECOPD, yet no significant association for severe AECOPD (table 3). Among the total study population 3148 patients had a history of frequent exacerbations and 2539 were on triple inhalation therapy. Of

these, 1358 were high-risk patients fulfilling both criteria. Baseline characteristics are shown in the online supplementary table S8. AECOPD incidence during follow-up was high: 1-year rate 70.0% and 5-year rate 79.8%. Cox regression showed similar results for the association of beta-blockers with AECOPD in this subgroup (table 2). The results were similar for the secondary outcomes (table 3).

Sensitivity and landmark analyses

The new-user analysis and the analysis excluding patients with another indication for beta-blockers showed similar results as the main analysis (HR 0.79, 95% CI 0.74–0.84, p<0.0001 and HR 0.75, 95% CI 0.68–0.82, p<0.0001, respectively).

Analysing a composite outcome of death and AECOPD also showed a beneficial association of beta-blocker exposure (HR 0.74, 95% CI 0.70–0.77, p<0.0001) suggesting no significant influence of death as a competing risk. Stratifying for the use of aspirin and statins and ACEi/ARBs within 90 days did not change the results significantly (table 2). Number of users of these medications are shown in the online supplementary table S10. Landmark analyses were overall consistent with the main analysis yet showed a particularly strong association between beta-blocker use a reduced with AECOPD in the first 90 days following MI (table 2).

DISCUSSION

In this Danish nationwide study comprising almost 11 000 patients with COPD discharged after first-time MI from 2003 to 2015, we demonstrated that beta-blocker use was not associated with increased risk of AECOPD. Using data on claimed prescriptions, this is the first cohort study to assess beta-blocker exposure continuously during follow-up and include as a time-dependent variable. The association was consistent regardless of the type of MI, presence or absence of heart failure and the severity of COPD, including high-risk patients on triple therapy and with frequent exacerbations. Also, we found no increased risk of AECOPD with high beta-blocker dosage or with non-selective beta-blockers, and analyses of moderate and severe AECOPD were similar. These are encouraging results suggesting that beta-blockers are safe in COPD and may even reduce the risk of exacerbations.

The present study is, to our knowledge, the first to investigate the association between beta-blockers and AECOPD following MI. This is an important topic as beta-blockers are a mainstay of secondary prevention medication following MI,[1 2] and patients with COPD and MI have increased risk of AECOPD.[18] Most previous observational studies have investigated unselected groups of patients with COPD without known indications for beta-blockers[7 11–14] showing reduced or similar risk of AECOPD with beta-blockers. Studies investigating patients with COPD with cardiovascular disease (CVD) or risk factors for CVD include Au *et al*[10] (hypertension), Stefan *et al*[9] (hypertension, ischaemic heart disease or heart failure), Angeloni *et al*[8] (following CABG) and Dransfield *et al*[6] (heightened CVD risk), which all showed no difference in AECOPD between patients with and without beta-blockers. The present study population consisted of survivors after the first-time MI, and we had detailed information about comorbidities and use of beta-blockers throughout the entire follow-up period. As shown in the online supplementary table S4, only 6 out of 10 claimed a beta-blocker prescription within 6 months, and only about half of the population did so after 10 years. These numbers are lower than in a contemporary Swedish study where beta-blocker use was defined as sent prescriptions at hospital discharge.[36]

In the present study, we also investigated a subgroup of patients with a high risk of exacerbations and found a similar beneficial association of beta-blockers with AECOPD as in the total study population, suggesting that beta-blockers are safe even in patients at highest risk. This finding is supported previous observational studies of patients with frequent exacerbations,[7 12] however, it is in contrast to the BLOCK COPD trial where patients treated with metoprolol had a higher risk of severe AECOPD, although the overall risk of AECOPD in this trial was similar to placebo.[17] In the present study, we did not find significant differences for moderate and severe AECOPD except in a subgroup analysis of patients with complete clinical data showing no significant association of beta-blocker use and severe AECOPD. Importantly, patients with an established indication for beta-blockers were excluded from BLOCK COPD, whereas patients in the present study had accepted indications for beta-blockers. This might contribute to the different findings as patients with MI have a high risk of recurrent ischaemic events and other cardiac conditions, particularly heart failure and arrhythmia, which are often unrecognised in COPD.[34] As these conditions may be misinterpreted as AECOPD,[34] a beneficial effect of beta-blockers can be a result of their cardioprotective properties. In contrast, several benefits of beta-blockers in COPD have been proposed, including lowering background adrenergic and inflammatory states[15] and protection against downregulation of beta-2-receptors in the airways,[37] thus preserving the efficacy of inhaled beta-2-agonists and reducing the risk of AECOPD.

The major strengths of this study are the nationwide design and a homogeneous study population with MI as an indication for beta-blocker treatment that minimises selection bias and confounding by indication. Importantly, true-to-life beta-blocker usage and comorbidities were continuously assessed during follow-up and included as time-dependent variables. In addition, the large study population allowed for adjustment for a wide range of possible confounders as well as stratified analyses. Subgroup analyses adjusting for COPD severity and symptom burden and of high-risk patients were consistent with the main analyses, suggesting minimal bias arising due to physicians might being reluctant to prescribe beta-blockers to patients with severe COPD, that is, confounding by selective prescribing.[38] Sensitivity analyses were also consistent suggesting that other potential biases, in particular confounding by indication,[38] are unlikely to explain our findings. Nonetheless, residual confounding cannot be excluded due to the observational nature of the study. Another possible limitation is that detailed clinical data were not available in all patients, allowing only for adjustment for COPD severity in a subgroup. To account for this, we used proxies for COPD severity (history of AECOPD and inhaled therapy) that were available on all patients.

CONCLUSIONS

In this large, nationwide cohort study we demonstrated that beta-blocker use defined as claimed prescriptions following MI was not associated with increased risk of acute exacerbations of COPD. The association was independent of the type of MI, presence or absence of heart failure, COPD severity and symptom burden, as well as dosage and type of beta-blocker suggesting that beta-blockers are safe in patients with COPD including high-risk patients with severe disease.

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Contributors DBR, MTJ, UB, ML and PL conceptualised and designed the study. Statistical analyses were done by DBR with assistance from ML. DBR wrote the first draft of the manuscript with input from MTJ, UB, ML and PL. All authors critically revised the manuscript and approved the submitted version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work.

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