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*a nationwide analysis from 1995 to 2015 in Denmark*

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# Beta-blocker, aspirin and statin usage after first-time myocardial infarction in patients with chronic obstructive pulmonary disease: a nationwide analysis from 1995 to 2015 in Denmark

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## ABSTRACT

### AIMS

To determine whether beta-blockers, aspirin, and statins are underutilized after first-time myocardial infarction (MI) in patients with chronic obstructive pulmonary disease (COPD) compared with patients without COPD. Further, to determine temporal trends, and risk factors for non-use.

### METHODS AND RESULTS

Using Danish nationwide registers, we performed a cross-sectional study investigating the utilization of beta-blockers, aspirin and statins after hospitalisation for first-time MI among patients with and without COPD from 1995 to 2015. Risk factors for non-use were examined in multivariable logistic regression models.

During 21 years of study, 140,278 patients were included, hereof 13,496 (9.6%) with COPD. Patients with COPD were less likely to use beta-blockers (53.2% vs. 76.2%, P<0.001), aspirin (73.9% vs. 78.8%, P<0.001), and statins (53.5% vs. 61.9%, P<0.001). Medication usage increased during the study period but in multivariable analyses, COPD remained a significant predictor for non-use: OR [95% CI] for non-use of beta-blockers 1.86 [1.76-1.97]; aspirin 1.24 [1.16-1.32]; statins 1.50 [1.41-1.59]. Analyses stratified by ST-segment elevation myocardial infarction (STEMI) and non-STEMI showed similar undertreatment of COPD patients.

Risk factors for non-use of beta-blockers in COPD included increasing age, female sex, and increasing severity of COPD (frequent exacerbations, use of multiple inhaled medications, low lung function). Similar findings were demonstrated for aspirin and statins.

### CONCLUSION

Beta-blockers, and to a lesser extent aspirin and statins, were systematically underutilized by patients with COPD following hospitalisation for MI despite an overall increase in the utilization over time. Increasing severity of COPD was a risk factor for non-use of the medications.



### KEYWORDS

Myocardial infarction; Chronic obstructive pulmonary disease; Secondary prevention; Beta-blockers; Aspirin; Statins.

## INTRODUCTION

Ischemic heart disease is a common comorbidity in chronic obstructive pulmonary disease (COPD) contributing significantly to morbidity and mortality.[1] Following myocardial infarction (MI), secondary prevention with beta-blockers, aspirin and statins reduces mortality and reinfarction.[2–4] However, it has consistently been shown that COPD patients in the period during hospitalisation for MI and up to discharge do not receive secondary prevention medication as recommended. The extent of the undertreatment varies between countries and time periods but is consistent.[5–12] In contrast, knowledge about medication usage following discharge from hospitalisation for MI is scarce. Undertreatment with beta-blockers might be related to concerns about bronchoconstriction,[13] yet few studies have investigated COPD-related factors associated with non-use of secondary prevention medications in COPD,[6,7] and data on lung function and symptom severity were available in only one study.[7]

Using Danish nationwide registers, we can study medication usage following hospitalisation, temporal trends over long time periods, and factors related to non-use of medications such as demographics, comorbidities, COPD severity, and socioeconomic status, which may explain some of the differences in treatment. We aimed to investigate the utilization of beta-blockers, aspirin and statins among Danish patients with COPD following hospitalization for first-time MI compared with patients without COPD. Furthermore, we investigated temporal trends of medication usage from 1995 to 2015, and examined factors associated with medication non-use among patients with COPD.

## METHODS

### Design and data sources

We performed a nationwide cross-sectional study using data from Danish national registers. In Denmark, a unique civil registration number is assigned to all residents at birth or immigration enabling cross-linkage between registers. We included data on prescription redemptions from The Danish Registry of Medicinal Product Statistics (a national prescription registry), hospital diagnoses from The Danish National Patient Register,[14] vital and emigration status from The Danish Civil Register,[15] and household income from Statistics Denmark.[16]

For clinical characterization of the patients, we used clinical data from the Danish Register of COPD, which is a nationwide database initiated January 1, 2008.[17] It comprises data on forced expiratory volume in 1 second expressed as percentage of predicted ($FEV_1$%), severity of dyspnoea assessed with the modified Medical Research Council (mMRC) dyspnoea score, smoking status, and body mass index (BMI) which are obtained during outpatient visits in COPD hospital clinics.

**Population and medication**

All patients hospitalised with first-time MI between 1995 and 2015 were eligible for inclusion. Diagnosis of first-time MI (ICD10 I21) have high validity in Danish registers with a positive predictive value (PPV) of 97%.[18] From the MI diagnoses we stratified the population into three groups: ST-segment elevation MI (STEMI) using the validated diagnose codes ICD10 I210B, I211B, I213;[18] non-STEMI (NSTEMI) (ICD10: I210A, I211A, I214);[18] and unspecified, which were individuals with a diagnosis of MI but where the diagnosis was not validated for type of MI. We excluded patients who died or emigrated within 90 days from discharge to obtain a homogenous population of MI-survivors accessible for secondary preventive treatment. Further, patients with missing data on income were excluded. All other variables were complete.

The utilization of secondary prevention medication after MI was determined within 90 days after discharge from hospital, and was defined as ≥1 redeemed prescriptions on beta-blockers, aspirin, and/or statins. The 90 day observation period was chosen to allow prescriptions that had been redeemed late after discharge to be included in the analysis. Prior medication usage was determined during a period of 180 days prior to first MI. ATC codes are listed in Supplementary material, Table S2.

**COPD, clinical data, and exacerbations**

The COPD population was defined as individuals with diagnosis of COPD (ICD10: J42 - J44; ICD8: 491-492) from hospital admissions or outpatient visits from 1977 to first MI. Diagnosis of COPD in Danish registers has been validated and has a PPV of 92%.[19]

Exacerbations of COPD prior to first MI were defined as ≥1 redeemed prescription of oral corticosteroids.[20] To be considered as independent exacerbations, they had to be at least 28 days apart. In accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[21] we defined frequent exacerbations as ≥2

exacerbations and/or ≥1 hospital admission with COPD one year prior to first MI as defined in Supplementary material, Table S1.

Clinical data from Danish Register of COPD prior to first MI were included in the analyses. If no observations prior to first MI were available, we allowed observations registered up to 90 days after first MI to be included. $FEV_1$% was categorised according to the GOLD classification of airflow limitation severity (GOLD 1 - mild: $FEV_1\% \geq 80$; GOLD 2 - moderate: $50 \leq FEV_1\% < 80$; GOLD 3 - severe: $30 \leq FEV_1\% < 50$; GOLD 4 - very severe: $FEV_1\% < 30$).[21]

**Comorbidities and socioeconomic status**

Comorbidities were identified during a period of 10 years prior to first MI, based on diagnoses from hospital admissions and outpatient visits. Comorbidities are listed in Table 1, and definitions, ICD and ATC codes are shown in Supplementary material, Table S1.

We included income to describe socioeconomic status of the patients. Income was calculated as the average household size adjusted disposable income of five years prior to first MI, categorised into tertiles within the study population (low, middle, and high).

**Statistical analyses**

First, we analysed the utilization of secondary prevention medications in the total study population stratified by the presence of COPD. Continuous variables were summarised using median and interquartile range (IQR) and compared using Wilcoxon rank-sum test, and categorical variables were summarised using percentages and compared using Pearson's chi-squared test. A *P* value of <0.05 was considered significant.

Second, temporal trends in medication usage from 1995 to 2015 were plotted with 95% confidence intervals while stratifying for the presence of COPD.

Third, we examined factors associated with non-use of medications using multivariable logistic regression models to estimate odds ratios and 95% confidence intervals (CI). The analyses were stratified into two time periods, 1995-2005 and 2006-2015, due to interaction between year of first MI and the association between COPD and medication non-use. Analyses from 2006 to 2015 were of primary interest, whereas analyses from 1995 to 2005 were presented in the supplemental material. We first estimated the association between COPD and

medication non-use in the total study population adjusting for the following prechosen factors: age, sex, presence of heart failure, atrial fibrillation, angina pectoris, hypertension, diabetes, peripheral vascular disease, stroke, cancer, renal failure, asthma, or depression, and income. Next, analysing patients with COPD, we identified factors associated with medication non-use using the regression model described above.

Further, in a subpopulation of patients with complete clinical data available from the Danish Register of COPD, we analysed the associations between medication non-use and GOLD class, mMRC dyspnoea score, BMI, and smoking status. This analysis was not stratified by time period, as the covariates from Danish Register of COPD were available only since 2008.

In sensitivity analyses, we stratified the population in STEMI and NSTEMI. These analyses included characteristics of patients, temporal trends of medication usage, and regression analyses of factors associated with medication non-use in COPD. These analyses were performed to account for differences in indication for beta-blockers according to type of presentation of MI.[22] Sensitivity analyses also included univariable regression analyses of factors associated with non-use of medications in patients with clinical data available from the Danish Register of COPD.

Regression models were tested for potential multicollinearity problems by estimating variance inflation factors. Data were managed with SAS 9.4 (SAS Institute, Cary, NC), and analysed with Stata/MP 15.1 (StataCorp LP, College Station, TX).

**Ethics**

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

**Role of the funding source**

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## RESULTS

### Characteristics

A total of 140,278 patients with first-time MI were included in the study. Selection of the study population is shown in Figure 1. A total of 13,496 (9.6%) had COPD (Table 1). Compared to patients without COPD, patients with COPD were older, more often women and more likely to have comorbidities, especially heart failure, atrial fibrillation, peripheral vascular disease, and depression. Medication usage prior to first MI was higher in COPD regarding aspirin and statins, however only marginally higher for beta-blockers. Income was lower in COPD. A total of 65,645 patients had a diagnosis allowing for differentiation between STEMI and NSTEMI, and among those 19,939 (30.4%) had STEMI, and 45,706 (69.6%) NSTEMI (supplementary Table S3).

### Utilization of secondary prevention medications

During the 21 year study period, a total of 53.2% patients with COPD used beta-blockers after first MI, whereas 76.2% of patients without COPD used beta-blockers (Table 1). Aspirin and statins were also underused in COPD, but to a lesser extent than beta-blockers. Sensitivity analyses of patients with validated diagnoses of STEMI and NSTEMI showed similar undertreatment in COPD (supplementary Table S3).

Characteristics of patients with COPD according to usage of secondary prevention medication are presented in Table 2. Compared to non-users, beta-blocker users were marginally younger, more likely to be male, more likely to have used cardiovascular medications including beta-blockers prior to first MI, and more likely to have concurrent cardiac disease, hypertension, diabetes, peripheral vascular disease, and renal failure. Further, beta-blocker users had less asthma and depression, fewer had frequent COPD exacerbations, and their usage of long-acting inhaled medications was lower.

The majority of beta-blockers utilized in both non-COPD and COPD were beta-1-selective and there was no distinct pattern in the usage of specific types of beta-blockers in non-COPD and COPD although the differences were statistically significant: beta-1-selective betablockers 88,705(91.8%) in non-COPD vs. 6,415(89.3%) in COPD, P<0.001; alpha-beta-blockers 6,684(6.9%) vs. 751(10.5%), P<0.001; non-selective beta-blockers 2,942(3.0%) vs. 151(2.1), P<0.001. The total percentage in this analysis adds up to more than 100% because some patients redeemed more than one prescription on beta-blockers.

**Temporal trends of secondary prevention medication**

Temporal trends of beta-blocker, aspirin, statin usage in patients with and without COPD are presented in Figures 2a - 2c. Beta-blocker usage was significantly lower in patients with COPD throughout the study period. In non-COPD the usage increased rapidly from 45.8% in 1995 to 81.6% in 2001, where it stayed consistent until 2011-2012 where it decreased slightly to 76.2% in 2015. In COPD the usage was significantly lower, starting at 18.1% in 1995 and increasing to a maximum of 70.7% in 2011, followed by a decrease to 62.7% in 2015. Aspirin usage in non-COPD increased slowly from 62.5% in 1995 to a plateau of approximately 83% from 2004 and onward. In COPD aspirin usage was slightly lower and declined from 81.2% in 2009 to 74.0% in 2015. Statin usage in non-COPD increased rapidly from 5% in 1995 to a plateau of just below 85% from 2007 and onward. In COPD statin usage was consistently lower, and stagnated at a level of around 70% from 2007 and onward.

Sensitivity analyses of patients with validated diagnoses of STEMI and NSTEMI showed overall similar trends for all three medications as for the entire study population, however undertreatment in COPD was less clear in patients with STEMI (supplementary Table S4a-c).

**Factors associated with non-use of medication in COPD**

Multivariable logistic regression analysis showed that COPD was associated with significantly increased odds for non-use of beta-blockers (OR 1.86 [95%CI 1.76-1.97; $P$<0.001]), aspirin (OR 1.24 [1.16-1.32; $P$<0.001]), and statins (OR 1.50 [1.41-1.59; $P$<0.001]) from 2006 to 2015. Analyses from 1995 to 2005 showed overall similar associations (supplementary Table S5).

Figure 3 illustrates multivariable adjusted odds ratios for non-use of medication among patients with COPD from 2006 to 2015. Risk factors for non-use of beta-blockers included increasing age, female sex, use of multiple inhaled medications, frequent exacerbations of COPD, cerebrovascular disease, asthma, and depression. In the subgroup analysis of 937 patients with complete clinical data from 2008-2015, high GOLD class, and high mMRC dyspnoea score were associated with non-use of beta-blockers (Figure 4).

Risk factors for non-use of aspirin in patients with COPD from 2006 to 2015 were atrial fibrillation, angina, hypertension, peripheral vascular disease, cerebrovascular disease, cancer, and renal failure (Figure 3), and there was a trend towards association for frequent COPD exacerbations. High mMRC dyspnoea score was also a risk factor (Figure 4), and conversely, low and medium income was associated with increased usage of aspirin (Figure 3).

In regard to statins, high age, female sex, heart failure, atrial fibrillation, cancer, renal failure, depression, frequent COPD exacerbations, low and medium income, and increasing mMRC dyspnoea score were risk factors for non-use from 2006 to 2015 (Figures 3 and 4).

Sensitivity analyses of factors associated with non-use of medications were overall consistent with the main analyses and included analyses in patients with COPD stratified by STEMI and NSTEMI from 1995 to 2005 and 2006 to 2015 (supplementary Tables S7a-d), univariable analyses in patients with COPD and clinical data available (supplementary Table S8), and multivariable analyses of factors associated with non-use of medications in patients with COPD and clinical data available stratified by STEMI vs NSTEMI (supplementary Tables S9a-b).

## DISCUSSION

### Main findings

In this large, nationwide cross-sectional study we showed that beta-blockers, and to a lesser extent aspirin and statins, were systematically underutilized by patients with COPD following hospitalization for first-time MI. Although there has been an overall increase in the utilization of secondary prevention medications during the study period, we demonstrated a consistent gap in utilization between patients with and without COPD for all three medications. Similar trends were observed in patients with STEMI and NSTEMI. While the overall uptake of beta-blockers and aspirin was already substantial by the beginning of the study period, statin usage was very low and subsequently increased rapidly. This possibly reflects the publication of the Scandinavian Simvastatin Survival Study in 1994, which was the first large trial demonstrating that lipid lowering therapy reduces mortality after MI.[23] Evidence of the effectiveness of beta-blockers and aspirin emerged during the 1980s,[24] and their use have subsequently been implemented gradually, however somewhat slowly for beta-blockers and in particular in patients with concurrent COPD. The majority of beta-blockers utilized were beta-1-selective in both COPD and non-COPD.

COPD was a significant risk factor for non-use of medications, especially beta-blockers. Additionally, when analysing patients with COPD we found that frequent exacerbations and high dyspnoea score were general risk factors for non-use of medications. These findings implicate that there is a general reluctance to prescribing secondary prevention medications to patients with COPD and that severe symptom burden of COPD increases the reluctance. Underutilization in patients with severe COPD might be particularly unfortunate as

increasing COPD severity is a risk factor for cardiovascular morbidity and mortality,[25] making secondary prevention medications particular important in these patients.

Concerning beta-blockers, we showed that multiple indicators of COPD severity and symptom burden (GOLD class, mMRC dyspnoea score, number of long-acting inhaled medications, and frequent exacerbations) were significant risk-factors for non-use. This supports the hypothesis that underutilization of beta-blockers in COPD is related to physicians concerns about bronchoconstriction. These concerns are unwarranted according to a Cochrane review updated in 2010 concluding that cardioselective beta-blockers are safe in COPD,[26] however, this have been challenged in a recent review based on new trials of beta-blockers in COPD.[13]

Patients with COPD had lower income, which is a marker of socioeconomic status. We found that low and medium income were associated with non-use of aspirin from 2006 to 2015. However, this association was not present for beta-blockers in this time period and in regard to statins low income was associated with increased statin usage, which indicate that low income is not a general risk factor for non-use of secondary prevention medications.

**Comparison with previous studies**

The present study is, to our knowledge, the first to analyse the utilization of secondary prevention medications using redeemed prescriptions following hospitalisation for MI in patients with and without COPD. Previous studies have investigated in-hospital medication and prescription rates at discharge after MI,[5–7,9–12,27] whereas one study investigated medication usage shortly (0.5 to 14 days) after admission among patients with MI and heart failure enrolled in randomised trials.[28] Thus, the results of the latter study are likely to mirror the prescribed medications at discharge, and the selection of the study population may limit the generalisability of the results. Previous studies have shown great variation in estimates of beta-blocker utilization; in early studies from 1998 and 2005 the utilization of beta-blockers among patients with MI and COPD was only 22.1% and 16.0%,[11,12] respectively - whereas studies from the past ten years indicate an increasing trend in the utilization of beta-blockers ranging from 38.6% to 84.1%.[5–7,9,10,27] The present study is in accordance with this, demonstrating an increasing utilization of beta-blockers from 1995 to 2011. However, since 2012 the utilization of beta-blockers declined in patients with and without COPD, whereas aspirin and statin utilization was fairly constant. This might reflect a current discussion about the importance of beta-blockers following MI.[22]

Our findings of risk factors for non-use of secondary prevention medications among patient with COPD confirms and extends the findings of two previous studies assessing predictors for beta-blocker usage.[6,7] We found that female sex and increasing age were risk factors for non-use of beta-blockers and statins. Underutilization in elderly might be caused by a concern about increased risk of adverse effects; however this hypothesis does not explain the underutilization among females. We found an association between various comorbidities and non-use of medications, which also is in correspondence with the previous studies.[6,7]

Concurrent asthma was a risk-factor for non-use of beta-blockers, most likely due to added fear for bronchoconstriction beyond the concerns arising from COPD. However, according to a meta-analysis of randomised controlled trials, cardio-selective beta-blockers do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease.[29]

**Strengths and limitations**

By defining medication usage as redeemed prescriptions after discharge, our results reflect the real-life utilization of the medications, in contrast to in-hospital medication or prescriptions at discharge, which might over-estimate the actual utilization because patients might not redeem submitted prescriptions. The long study period of 21 years allowed us to investigate the long term trends of medication utilization. In this period guidelines for treatment of MI have been updated a number of times, however this does not affect our conclusions as we focussed on the differences in utilization of medications between patients with and without COPD, rather than the population as a whole. We analysed several indicators of COPD severity including exacerbations, numbers of long-acting inhaled medications, GOLD class, and dyspnoea score to estimate the association with non-use of secondary prevention medications. We believe that this improves the validity of our findings.

A possible limitation of this study is that we did not have complete data on GOLD class, dyspnoea score, smoking status, and BMI on all patients with COPD where complete data were only available in 937 patients. These data are obtained during outpatient visits in COPD hospital clinics i.e. data are missing in patients with a COPD diagnosis recorded only during hospital admissions. Diagnoses of MI and COPD have shown high validity in the registries, however there is an underrecording of COPD during hospitalisations with other acute respiratory disorders than COPD with a negative predictive value of 81%.[19] Further, Danish administrative registers do not hold information on patient/physician preference or actual indication of therapy.

**Conclusions**

Secondary prevention with beta-blockers, and to a lesser extent aspirin and statins, was systematically underutilized by patients with chronic obstructive pulmonary disease (COPD) following first-time hospitalisation for myocardial infarction during years 1995-2015 despite an overall increase in the utilization. Increasing severity of COPD was a risk factor for non-use of all three medications, in particular beta-blockers. This supports the hypothesis that undertreatment with beta-blockers in COPD is related to concerns about bronchoconstriction, whereas underutilization of aspirin and statins indicate a general reluctance to prescribing secondary prevention medications to patients with COPD. COPD patients is a high risk population where adherence to treatment guidelines is of particular importance. Clinicians involved in the cardiac rehabilitation and primary care physicians overseeing the follow-up following a MI should take particular care regarding the use of secondary prevention in the COPD population. This should be ensured in order to improve the uptake of potential lifesaving medication and thus work towards increased quality of care.

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**FIGURES AND TABLES**

Figure 1. Overview of the study population.

Abbreviations: COPD = chronic obstructive pulmonary disease.

Table 1. Characteristics of 140,278 patients following myocardial infarction from 1995 to 2015 stratified by chronic obstructive pulmonary disease (COPD).

Table 2. Characteristics of 13,496 patients with chronic obstructive pulmonary disease following first-time myocardial infarction from 1995 to 2015.

Figure 2a. Temporal trends of beta-blocker usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.

Figure 2b. Temporal trends of aspirin usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.

Figure 2c. Temporal trends of statin usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.

Figure 3. Factors associated with non-use of beta-blockers, aspirin, and statins in 6,979 patients with chronic obstructive pulmonary disease (COPD) following myocardial infarction from 2006 to 2015. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Figure 4. Factors associated with non-use of beta-blockers, aspirin, and statins in 937 patients with chronic obstructive pulmonary disease and complete clinical data, following myocardial infarction from 2008 to 2015. Odds ratios are estimated by multivariable logistic regression including the presented factors. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease classification of airflow limitation severity (GOLD 1 - mild: FEV1% [forced expiratory volume in 1 second expressed as percentage of predicted] ≥ 80; GOLD 2 - moderate: 50 ≤FEV1% <80; GOLD 3 - severe: 30 ≤FEV1% <50; GOLD 4 - very severe: FEV1% <30); mMRC = modified Medical Research Council dyspnoea score; BMI = body mass index

**SUPPLEMENTARY DATA**

Table S1. Diagnoses and medicines used for definition of comorbidities.

Abbreviations: ICD10 = 10th revision of the International Classification of Diseases system. ICD8 = 8th revision of the International Classification of Diseases system. ATC = Anatomical Therapeutic Chemical Classification System.

Table S2. Definition of medications.

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification System

Table S3. Characteristics of patients following myocardial infarction (MI) from 1995 to 2015 stratified by ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI), and chronic obstructive pulmonary disease (COPD).

Figure S4a. Temporal trends of beta-blocker usage after myocardial infarction from 1995 to 2015 in patients with and without chronic obstructive pulmonary disease (COPD) and (1) ST-segment elevation myocardial infarction (STEMI) and (2) non-STEMI (NSTEMI). Bands represent 95% confidence intervals.

Figure S4b. Temporal trends of aspirin usage after myocardial infarction from 1995 to 2015 in patients with and without chronic obstructive pulmonary disease (COPD) and (1) ST-segment elevation myocardial infarction (STEMI) and (2) non-STEMI (NSTEMI). Bands represent 95% confidence intervals.

Figure S4c. Temporal trends of statins usage after myocardial infarction from 1995 to 2015 in patients with and without chronic obstructive pulmonary disease (COPD) and (1) ST-segment elevation myocardial infarction (STEMI) and (2) non-STEMI (NSTEMI). Bands represent 95% confidence intervals.

Table S5. Association between chronic obstructive pulmonary disease (COPD) and non-use of beta-blockers, aspirin, and statins in 75,087 patients following myocardial infarction from 1995 to 2005. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Table S6. Factors associated with non-use of beta-blockers, aspirin, and statins in 6,517 patients with chronic obstructive pulmonary disease (COPD) following myocardial infarction from 1995 to 2005. Odds

ratios >1.00 indicate an increased risk of non-use of medication.

* Frequent COPD exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Table S7a. Factors associated with non-use of beta-blockers, aspirin, and statins in 298 patients with chronic obstructive pulmonary disease (COPD) following ST-segment elevation myocardial infarction (STEMI) from 1995 to 2005. Odds ratios >1.00 indicate an increased risk of non-use of medication.

* Frequent COPD exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Table S7b. Factors associated with non-use of beta-blockers, aspirin, and statins in 970 patients with chronic obstructive pulmonary disease (COPD) following ST-segment elevation myocardial infarction (STEMI) from 2006 to 2015. Odds ratios >1.00 indicate an increased risk of non-use of medication.

* Frequent COPD exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Table S7c. Factors associated with non-use of beta-blockers, aspirin, and statins in 1,905 patients with chronic obstructive pulmonary disease (COPD) following non-ST-segment elevation myocardial infarction (NSTEMI) from 1995 to 2005. Odds ratios >1.00 indicate an increased risk of non-use of medication.

* Frequent COPD exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Table S7d. Factors associated with non-use of beta-blockers, aspirin, and statins in 3,449 patients with chronic obstructive pulmonary disease (COPD) following non-ST-segment elevation myocardial infarction (NSTEMI) from 2006 to 2015. Odds ratios >1.00 indicate an increased risk of non-use of medication.

* Frequent COPD exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Table S8. Factors associated with non-use of beta-blockers, aspirin, and statins in patients with chronic obstructive pulmonary disease (COPD) and clinical data available following myocardial infarction from 2008 to 2015. Odds ratios are estimated by univariable logistic regression analyses. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease classification of airflow limitation severity (GOLD 1 - mild: FEV1% [forced expiratory volume in 1 second expressed as percentage of predicted] ≥ 80; GOLD 2 - moderate: 50 ≤FEV1% <80; GOLD 3 - severe: 30 ≤FEV1% <50; GOLD 4 - very severe: FEV1% <30); mMRC = modified Medical Research Council dyspnoea score; BMI = body mass index.

Table S9a. Factors associated with non-use of beta-blockers, aspirin, and statins in 109 patients with chronic obstructive pulmonary disease (COPD) and clinical data available following ST-segment elevation myocardial infarction (STEMI) from 2008 to 2015. Odds ratios are estimated by multivariable logistic regression including the presented factors. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease classification of airflow limitation severity (GOLD 1 - mild: FEV1% [forced expiratory volume in 1 second expressed as percentage of predicted] ≥ 80; GOLD 2 - moderate: 50 ≤FEV1% <80; GOLD 3 - severe: 30 ≤FEV1% <50; GOLD 4 - very severe: FEV1% <30); mMRC = modified Medical Research Council dyspnoea score; BMI = body mass index.

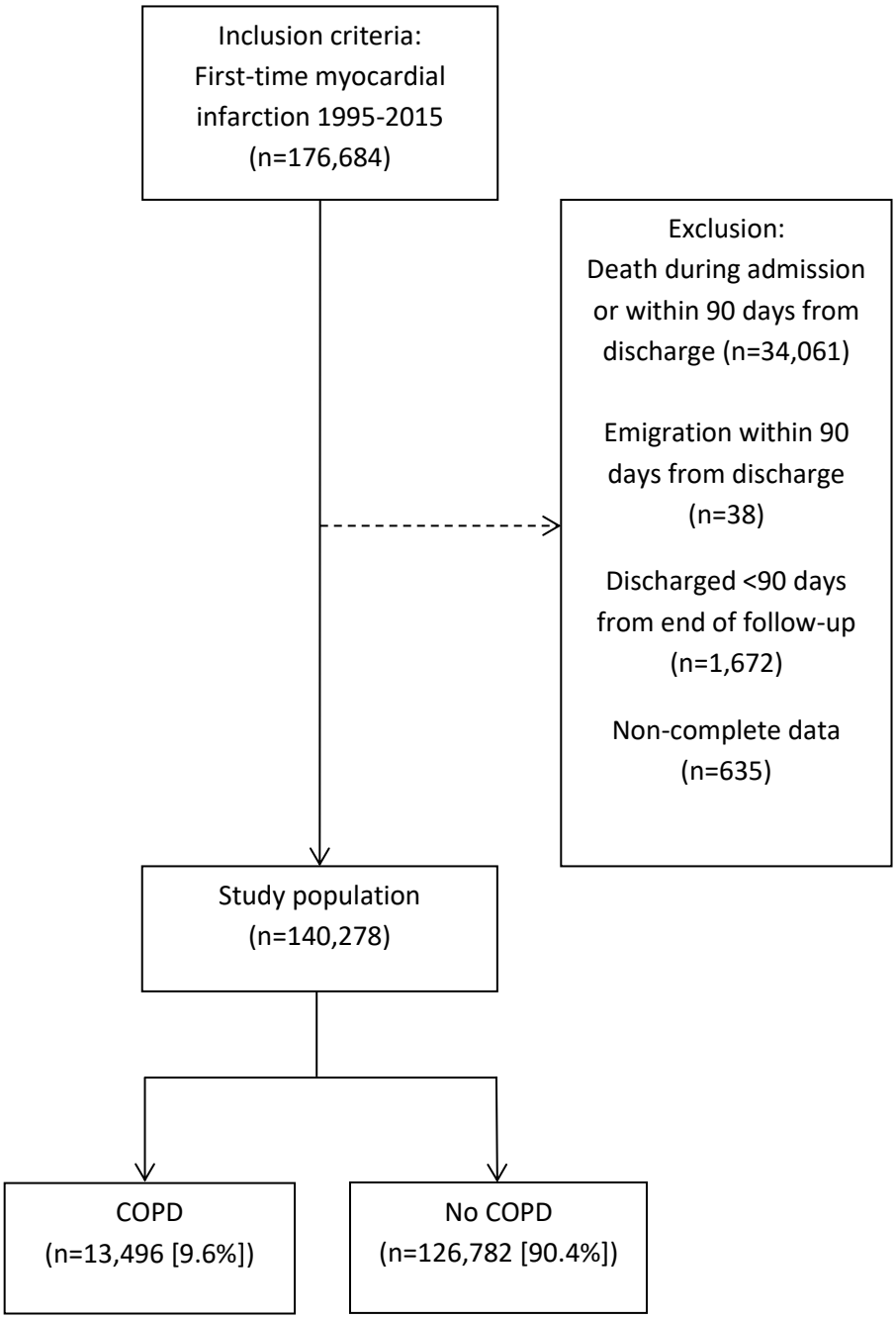
Table S9b. Factors associated with non-use of beta-blockers, aspirin, and statins in 520 patients with chronic obstructive pulmonary disease (COPD) and clinical data available following non-ST-segment elevation myocardial infarction (NSTEMI) from 2008 to 2015. Odds ratios are estimated by multivariable logistic regression including the presented factors. Odds ratios >1.00 indicate an increased risk of non-use of medication.

Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease classification of airflow limitation severity (GOLD 1 - mild: FEV1% [forced expiratory volume in 1 second expressed as percentage of predicted] ≥ 80; GOLD 2 - moderate: 50 ≤FEV1% <80; GOLD 3 -

severe: 30 ≤FEV1% <50; GOLD 4 - very severe: FEV1% <30); mMRC = modified Medical Research Council dyspnoea score; BMI = body mass index.

**TABLES AND FIGURES**

Figure 1. Overview of the study population.




Abbreviations: COPD = chronic obstructive pulmonary disease.

Table 1. Characteristics of 140,278 patients following myocardial infarction from 1995 to 2015 stratified by chronic obstructive pulmonary disease (COPD).

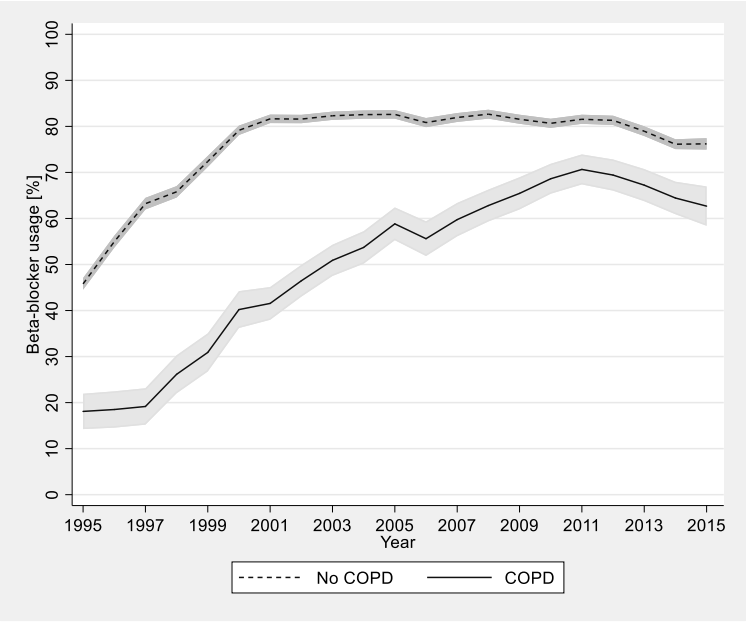
| | No COPD | COPD | *P* Value |
|---|---|---|---|
| N | 126782 | 13496 | |
| Age, median (IQR) | 67 (57, 77) | 74 (67, 80) | <0.001 |
| Male | 82257 (64.9%) | 7167 (53.1%) | <0.001 |
| Medication usage after MI | | | |
| Beta-blockers | 96592 (76.2%) | 7184 (53.2%) | <0.001 |
| Aspirin | 99902 (78.8%) | 9974 (73.9%) | <0.001 |
| Statins | 78511 (61.9%) | 7215 (53.5%) | <0.001 |
| Previous medication | | | |
| Beta-blockers | 21809 (17.2%) | 2462 (18.2%) | 0.002 |
| Aspirin | 27463 (21.7%) | 4476 (33.2%) | <0.001 |
| Statins | 19349 (15.3%) | 2812 (20.8%) | <0.001 |
| Type of MI | | | |
| STEMI | 18671 (14.7%) | 1268 (9.4%) | <0.001 |
| NSTEMI | 40352 (31.8%) | 5354 (39.7%) | |
| Unspecified | 67759 (53.4%) | 6874 (50.9%) | |
| Comorbidities | | | |
| Heart failure | 19592 (15.5%) | 4082 (30.2%) | <0.001 |
| Atrial fibrillation | 12661 (10.0%) | 2609 (19.3%) | <0.001 |
| Angina pectoris | 26911 (21.2%) | 3470 (25.7%) | <0.001 |
| Hypertension | 36159 (28.5%) | 4852 (36.0%) | <0.001 |
| Diabetes mellitus | 17883 (14.1%) | 2390 (17.7%) | <0.001 |
| Peripheral vascular disease | 7051 (5.6%) | 1569 (11.6%) | <0.001 |
| Cerebrovascular disease | 10949 (8.6%) | 1638 (12.1%) | <0.001 |
| Cancer | 9653 (7.6%) | 1609 (11.9%) | <0.001 |
| Renal failure | 4370 (3.4%) | 824 (6.1%) | <0.001 |
| Asthma | 1400 (1.1%) | 1901 (14.1%) | <0.001 |
| Depression | 12433 (9.8%) | 2710 (20.1%) | <0.001 |
| Income | | | |
| Low | 40352 (31.8%) | 6408 (47.5%) | <0.001 |
| Medium | 41910 (33.1%) | 4849 (35.9%) | |
| High | 44520 (35.1%) | 2239 (16.6%) | |

Table 2. Characteristics of 13,496 patients with chronic obstructive pulmonary disease following first-time myocardial infarction from 1995 to 2015.

| | Beta-blockers | | | Aspirin | | | Statins | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Non-user** | **User** | ***P* value** | **Non-user** | **User** | ***P* value** | **Non-user** | **User** | ***P* value** |
| N | 6312 | 7184 | | 3522 | 9974 | | 6281 | 7215 | |
| Age, median (IQR) | 74 (68, 81) | 73 (66, 80) | <0.001 | 74 (67, 80) | 74 (67, 80) | 0.160 | 76 (69, 82) | 72 (65, 79) | <0.001 |
| Male | 3072 (48.7%) | 4095 (57.0%) | <0.001 | 1842 (52.3%) | 5325 (53.4%) | 0.270 | 3234 (51.5%) | 3933 (54.5%) | 0.000 |
| Medication usage after MI | | | | | | | | | |
| Beta-blockers | 0 (0.0%) | 7184 (100.0%) | <0.001 | 1466 (41.6%) | 5718 (57.3%) | <0.001 | 2263 (36.0%) | 4921 (68.2%) | <0.001 |
| Aspirin | 4256 (67.4%) | 5718 (79.6%) | <0.001 | 0 (0.0%) | 9974 (100.0%) | <0.001 | 4088 (65.1%) | 5886 (81.6%) | <0.001 |
| Statins | 2294 (36.3%) | 4921 (68.5%) | <0.001 | 1329 (37.7%) | 5886 (59.0%) | <0.001 | 0 (0.0%) | 7215 (100.0%) | <0.001 |
| Previous medication | | | | | | | | | |
| Beta-blockers | 545 (8.6%) | 1917 (26.7%) | <0.001 | 768 (21.8%) | 1694 (17.0%) | <0.001 | 957 (15.2%) | 1505 (20.9%) | <0.001 |
| Aspirin | 1957 (31.0%) | 2519 (35.1%) | <0.001 | 1241 (35.2%) | 3235 (32.4%) | 0.002 | 1987 (31.6%) | 2489 (34.5%) | 0.000 |
| Statins | 997 (15.8%) | 1815 (25.3%) | <0.001 | 838 (23.8%) | 1974 (19.8%) | <0.001 | 539 (8.6%) | 2273 (31.5%) | <0.001 |
| Long acting inhalation therapy | | | | | | | | | |
| None | 2093 (33.2%) | 3277 (45.6%) | <0.001 | 1405 (39.9%) | 3965 (39.8%) | 0.031 | 2602 (41.4%) | 2768 (38.4%) | <0.001 |
| Mono | 993 (15.7%) | 911 (12.7%) | | 518 (14.7%) | 1386 (13.9%) | | 946 (15.1%) | 958 (13.3%) | |
| Dual | 2139 (33.9%) | 1781 (24.8%) | | 1052 (29.9%) | 2868 (28.8%) | | 1919 (30.6%) | 2001 (27.7%) | |
| Triple | 1087 (17.2%) | 1215 (16.9%) | | 547 (15.5%) | 1755 (17.6%) | | 814 (13.0%) | 1488 (20.6%) | |
| Frequent exacerbations* | 2123 (33.6%) | 1564 (21.8%) | <0.001 | 996 (28.3%) | 2691 (27.0%) | 0.140 | 1848 (29.4%) | 1839 (25.5%) | <0.001 |
| Comorbidities | | | | | | | | | |
| Heart failure | 1831 (29.0%) | 2251 (31.3%) | 0.003 | 1126 (32.0%) | 2956 (29.6%) | 0.010 | 1955 (31.1%) | 2127 (29.5%) | 0.038 |
| Atrial fibrillation | 1176 (18.6%) | 1433 (19.9%) | 0.053 | 889 (25.2%) | 1720 (17.2%) | <0.001 | 1322 (21.0%) | 1287 (17.8%) | <0.001 |
| Angina pectoris | 1443 (22.9%) | 2027 (28.2%) | <0.001 | 980 (27.8%) | 2490 (25.0%) | 0.001 | 1364 (21.7%) | 2106 (29.2%) | <0.001 |
| Hypertension | 1824 (28.9%) | 3028 (42.1%) | <0.001 | 1344 (38.2%) | 3508 (35.2%) | 0.002 | 1752 (27.9%) | 3100 (43.0%) | <0.001 |
| Diabetes mellitus | 991 (15.7%) | 1399 (19.5%) | <0.001 | 691 (19.6%) | 1699 (17.0%) | 0.001 | 944 (15.0%) | 1446 (20.0%) | <0.001 |
| Peripheral vascular disease | 646 (10.2%) | 923 (12.8%) | <0.001 | 482 (13.7%) | 1087 (10.9%) | <0.001 | 592 (9.4%) | 977 (13.5%) | <0.001 |
| Cerebrovascular disease | 776 (12.3%) | 862 (12.0%) | 0.600 | 556 (15.8%) | 1082 (10.8%) | <0.001 | 808 (12.9%) | 830 (11.5%) | 0.016 |
| Cancer | 754 (11.9%) | 855 (11.9%) | 0.940 | 472 (13.4%) | 1137 (11.4%) | 0.002 | 793 (12.6%) | 816 (11.3%) | 0.019 |
| Renal failure | 331 (5.2%) | 493 (6.9%) | <0.001 | 298 (8.5%) | 526 (5.3%) | <0.001 | 391 (6.2%) | 433 (6.0%) | 0.590 |
| Asthma | 1080 (17.1%) | 821 (11.4%) | <0.001 | 533 (15.1%) | 1368 (13.7%) | 0.038 | 889 (14.2%) | 1012 (14.0%) | 0.830 |
| Depression | 1350 (21.4%) | 1360 (18.9%) | 0.0004 | 729 (20.7%) | 1981 (19.9%) | 0.290 | 1318 (21.0%) | 1392 (19.3%) | 0.015 |
| Income | | | | | | | | | |
| Low | 3107 (49.2%) | 3301 (45.9%) | <0.001 | 1634 (46.4%) | 4774 (47.9%) | 0.230 | 3232 (51.5%) | 3176 (44.0%) | <0.001 |
| Medium | 2236 (35.4%) | 2613 (36.4%) | | 1277 (36.3%) | 3572 (35.8%) | | 2203 (35.1%) | 2646 (36.7%) | |
| High | 969 (15.4%) | 1270 (17.7%) | | 611 (17.3%) | 1628 (16.3%) | | 846 (13.5%) | 1393 (19.3%) | |

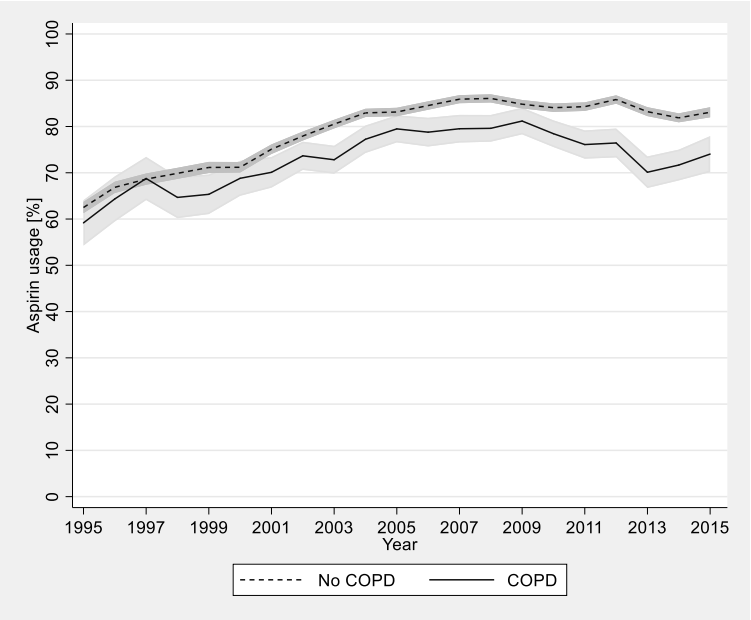
* Frequent exacerbations were defined as ≥2 exacerbations and/or ≥1 exacerbation leading to hospitalisation during last year.

Figure 2a. Temporal trends of beta-blocker usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.



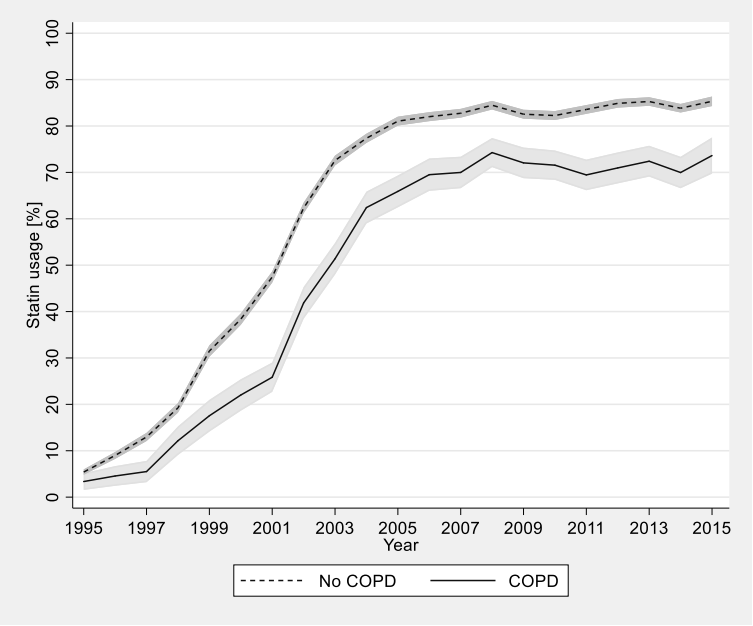

| | Year | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
| Non-COPD (% users) | 45.8 | 54.9 | 63.2 | 65.8 | 72.4 | 79.1 | 81.6 | 81.6 | 82.3 | 82.6 | 82.6 | 80.8 | 81.9 | 82.7 | 81.6 | 80.7 | 81.5 | 81.3 | 79.0 | 76.1 | 76.2 |
| COPD (% users) | 18.1 | 18.5 | 19.2 | 26.1 | 30.9 | 40.2 | 41.5 | 46.5 | 50.9 | 53.7 | 58.8 | 55.6 | 59.7 | 62.8 | 65.4 | 68.6 | 70.7 | 69.4 | 67.2 | 64.4 | 62.7 |

Figure 2b. Temporal trends of aspirin usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.




| | Year | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
| Non-COPD (% users) | 62.5 | 66.9 | 68.6 | 69.9 | 71.2 | 71.2 | 75.1 | 77.9 | 80.5 | 82.9 | 83.1 | 84.5 | 85.9 | 86.1 | 84.8 | 84.1 | 84.3 | 85.8 | 83.2 | 81.9 | 83.1 |
| COPD (% users) | 59.2 | 64.3 | 68.8 | 64.7 | 65.3 | 68.8 | 70.1 | 73.7 | 72.8 | 77.2 | 79.5 | 78.8 | 79.5 | 79.6 | 81.2 | 78.4 | 76.1 | 76.4 | 70.1 | 71.7 | 74.0 |

Figure 2c. Temporal trends of statin usage after first-time myocardial infarction in patients with and without chronic obstructive pulmonary disease (COPD) from 1995 to 2015. Bands represent 95% confidence intervals.




| | Year | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
| Non-COPD (% users) | 5.4 | 9.0 | 13.0 | 19.2 | 31.5 | 38.4 | 47.4 | 62.3 | 72.6 | 77.4 | 81.1 | 82.0 | 82.7 | 84.5 | 82.5 | 82.3 | 83.6 | 84.9 | 85.3 | 83.8 | 85.3 |
| COPD (% users) | 3.4 | 4.6 | 5.5 | 12.2 | 17.5 | 22.0 | 25.8 | 41.9 | 51.4 | 62.4 | 65.9 | 69.5 | 70.0 | 74.3 | 72.1 | 71.6 | 69.5 | 71.0 | 72.4 | 70.0 | 73.6 |

Figure 3. Factors associated with non-use of beta-blockers, aspirin, and statins in 6,979 patients with chronic obstructive pulmonary disease (COPD) following myocardial infarction from 2006 to 2015. Odds ratios >1.00 indicate an increased risk of non-use of medication.

| | Beta-blockers | | Aspirin | | Statins | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value |
| Age | | | | | | |
| 18-59 years | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |
| 60-69 years | 1.12 (0.92-1.37) | 0.246 | 1.05 (0.84-1.31) | 0.679 | 1.04 (0.84-1.29) | 0.739 |
| 70-79 years | 1.24 (1.02-1.50) | 0.028 | 1.11 (0.89-1.38) | 0.346 | 0.93 (0.75-1.14) | 0.491 |
| 80+ years | 1.49 (1.23-1.81) | <0.001 | 1.04 (0.83-1.30) | 0.743 | 1.86 (1.51-2.29) | <0.001 |
| Sex | | | | | | |
| Female | 1.30 (1.17-1.44) | <0.001 | 1.04 (0.93-1.17) | 0.502 | 1.18 (1.06-1.32) | 0.003 |
| Long acting inhaled medication | | | | | | |
| None | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | |
| Mono | 1.11 (0.93-1.32) | 0.241 | 0.94 (0.78-1.15) | 0.561 | 0.88 (0.73-1.06) | 0.190 |
| Dual | 1.37 (1.20-1.57) | <0.001 | 1.16 (1.00-1.35) | 0.054 | 1.01 (0.87-1.16) | 0.917 |
| Triple | 1.44 (1.25-1.66) | <0.001 | 1.08 (0.92-1.27) | 0.347 | 1.14 (0.98-1.32) | 0.091 |
| Frequent COPD exacerbations | 1.51 (1.34-1.70) | <0.001 | 1.14 (1.00-1.30) | 0.058 | 1.28 (1.13-1.45) | <0.001 |
| Comorbidities | | | | | | |
| Heart failure | 0.79 (0.71-0.88) | <0.001 | 0.98 (0.87-1.11) | 0.732 | 1.18 (1.05-1.32) | 0.006 |
| Atrial fibrillation | 0.93 (0.82-1.05) | 0.232 | 1.83 (1.60-2.08) | <0.001 | 1.51 (1.33-1.72) | <0.001 |
| Angina | 1.00 (0.89-1.12) | 0.983 | 1.19 (1.05-1.35) | 0.008 | 0.85 (0.75-0.96) | 0.009 |
| Hypertension | 0.73 (0.65-0.81) | <0.001 | 1.23 (1.09-1.39) | 0.001 | 0.89 (0.79-0.99) | 0.040 |
| Diabetes | 1.04 (0.91-1.19) | 0.544 | 1.10 (0.95-1.26) | 0.202 | 0.86 (0.75-0.99) | 0.041 |
| Peripheral vascular disease | 0.90 (0.77-1.04) | 0.162 | 1.19 (1.01-1.39) | 0.033 | 0.80 (0.68-0.94) | 0.007 |
| Cerebrovascular disease | 1.23 (1.05-1.43) | 0.010 | 1.41 (1.20-1.66) | <0.001 | 1.04 (0.89-1.23) | 0.608 |
| Cancer | 1.08 (0.94-1.25) | 0.281 | 1.32 (1.12-1.54) | 0.001 | 1.37 (1.18-1.59) | <0.001 |
| Renal failure | 1.13 (0.92-1.37) | 0.240 | 1.46 (1.20-1.78) | <0.001 | 1.59 (1.30-1.93) | <0.001 |
| Asthma | 1.18 (1.02-1.37) | 0.027 | 1.04 (0.88-1.23) | 0.655 | 1.01 (0.86-1.18) | 0.923 |
| Depression | 1.32 (1.17-1.48) | <0.001 | 1.07 (0.93-1.22) | 0.353 | 1.52 (1.34-1.71) | <0.001 |
| Income | | | | | | |
| Low | 0.92 (0.79-1.06) | 0.254 | 0.82 (0.69-0.97) | 0.018 | 1.36 (1.15-1.61) | <0.001 |
| Medium | 0.94 (0.81-1.09) | 0.381 | 0.90 (0.76-1.06) | 0.215 | 1.31 (1.10-1.54) | 0.002 |
| High | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |

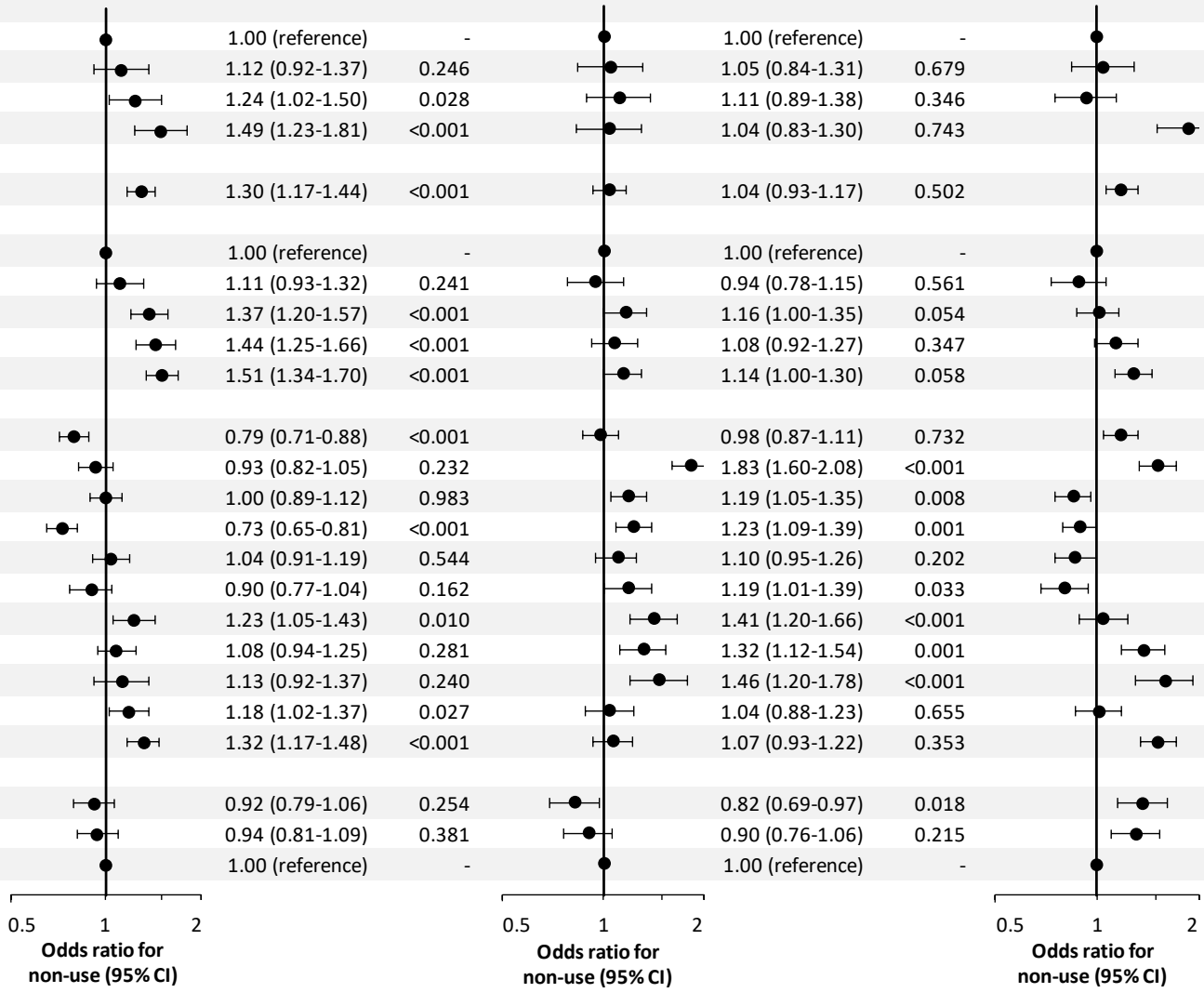
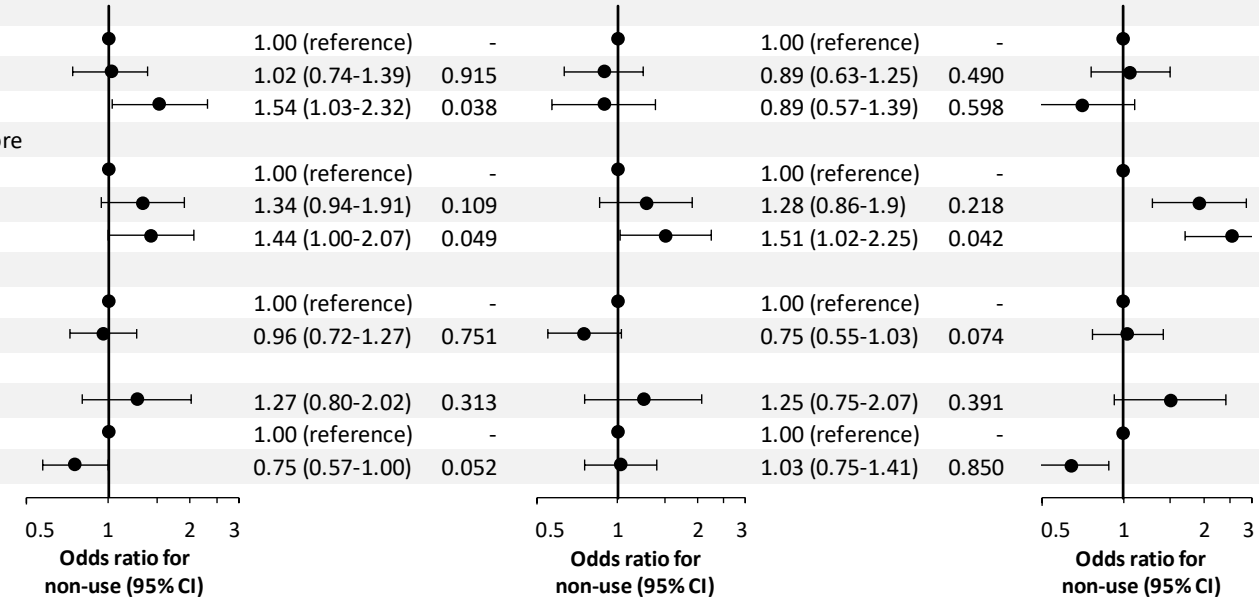


Figure 4. Factors associated with non-use of beta-blockers, aspirin, and statins in 937 patients with chronic obstructive pulmonary disease and complete clinical data, following myocardial infarction from 2008 to 2015. Odds ratios are estimated by multivariable logistic regression including the presented factors. Odds ratios >1.00 indicate an increased risk of non-use of medication.

| | Beta-blockers | | Aspirin | | Statins | |
|---|---|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value | Odds ratio (95% CI) | *P* Value |
| GOLD | | | | | | |
| GOLD 1-2 | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |
| GOLD 3 | 1.02 (0.74-1.39) | 0.915 | 0.89 (0.63-1.25) | 0.490 | 1.06 (0.76-1.49) | 0.718 |
| GOLD 4 | 1.54 (1.03-2.32) | 0.038 | 0.89 (0.57-1.39) | 0.598 | 0.70 (0.45-1.10) | 0.125 |
| mMRC dyspnoea score | | | | | | |
| mMRC 0-1 | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |
| mMRC 2 | 1.34 (0.94-1.91) | 0.109 | 1.28 (0.86-1.9) | 0.218 | 1.91 (1.28-2.86) | 0.002 |
| mMRC 3-4 | 1.44 (1.00-2.07) | 0.049 | 1.51 (1.02-2.25) | 0.042 | 2.54 (1.69-3.81) | <0.001 |
| Smoking | | | | | | |
| Non smoker | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |
| Smoker | 0.96 (0.72-1.27) | 0.751 | 0.75 (0.55-1.03) | 0.074 | 1.04 (0.77-1.41) | 0.802 |
| BMI | | | | | | |
| 10 - 18.4 | 1.27 (0.80-2.02) | 0.313 | 1.25 (0.75-2.07) | 0.391 | 1.50 (0.93-2.41) | 0.094 |
| 18.5 - 24.9 | 1.00 (reference) | - | 1.00 (reference) | - | 1.00 (reference) | - |
| 25+ | 0.75 (0.57-1.00) | 0.052 | 1.03 (0.75-1.41) | 0.850 | 0.64 (0.47-0.88) | 0.006 |




Abbreviations: GOLD = Global Initiative for Chronic Obstructive Lung Disease classification of airflow limitation severity (GOLD 1 - mild: FEV1% [forced expiratory volume in 1 second expressed as percentage of predicted] ≥ 80; GOLD 2 - moderate: 50 ≤FEV1% <80; GOLD 3 - severe: 30 ≤FEV1% <50; GOLD 4 - very severe: FEV1% <30); mMRC = modified Medical Research Council dyspnoea score; BMI = body mass index