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Exacerbation history and risk of myocardial infarction and pulmonary embolism in chronic obstructive pulmonary disease

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Conflicts of Interest

Lowie Vanfleteren reports relationships with GSK, AstraZeneca, Boehringer Ingelheim Pharmaceuticals Inc, Novartis, Chiesi, Resmed and Pulmonx that includes: speaking and lecture fees.

Caroline Stridsman reports relationships with AstraZeneca, Chiesi, Boehringer Ingelheim, TEva that includes: consulting or advisory and speaking and lecture fees.

Anne Lindberg reports relationships with Boehringer Ingelheim, Novartis, GlaxoSmithKline and AstraZeneca that includes: consulting or advisory and speaking and lecture fees.

Fredrik Nyberg was previously an employee of AstraZeneca until 2019 and owns stock in the company.

Oskar Wallström reports no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Acknowledgement of all authors' contribution(s) to the research and manuscript :

Conceived and designed the analysis: OW, LEGWV

Collected the data: OW, CS, LEGWV

Contributed data or analysis tools: OW, FN

Performed the analysis: OW

Wrote the paper: OW, LEGWV

Critically reviewed the manuscript: All authors

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Key Words List

- Acute exacerbations of chronic obstructive pulmonary disease
- Comorbidity
- Cardiovascular adverse events
- Retrospective nationwide registry cohort
- Myocardial infarction
- Pulmonary embolism

Abbreviation List

- AECOPD- Acute Exacerbation of Chronic Obstructive Pulmonary Disease
- MI – Myocardial Infarction
- PE- Pulmonary Embolism
- COPD – Chronic Obstructive Pulmonary Disease
- GOLD - Global Initiative for Obstructive Lung Disease
- SNAR - Swedish National Airway Register
- FEV_1 - Forced Expiratory Volume in the 1 second
- NPR - The National Patient Register
- NCDR - The National Cause of Death Register
- NPDR - The National Prescribed Drug Register
- ATC - Anatomical Therapeutic Chemical Classification System
- ICD-10 - International Classification of Diseases tenth revision
- BMI – Body-mass index
- FVC- Forced Vital Capacity (FVC)
- mMRC- Modified Medical Research Council dyspnoea-scale
- CAT- COPD-assessment test
- SAMA - Short acting antimuscarinic agent
- SABA - Short acting beta2 agonist
- LAMA - Long acting antimuscarinic agent
- LABA - Long acting beta2 agonist
- ICS - Inhaled corticosteroid
- CI – Confidence Interval

- **ABSTRACT**

Background: Acute exacerbations of COPD (AECOPDs) are increasingly recognized as episodes of heightened risk of cardiovascular events. It is not known whether exacerbation history is differentially associated with future myocardial infarction (MI) or pulmonary embolism (PE).

Research Question: Is the number and severity of AECOPDs associated with increased risk of MI or PE in a real-life cohort of patients with COPD?

Study Design and Methods: We identified a cohort of 66422 patients (≥30yr) with a primary diagnosis of COPD in the Swedish National Airway Register January 2014 to June 2022, with complete data on lung function. Patients were classified by moderate (prescription of oral corticosteroids) and severe (hospitalization) exacerbations the year before index date and were followed until Dec 2022 for hospitalization or death from MI or PE, corresponding to >265 000 patient-years, with a maximum follow-up time of 9 years. Competing-risk regression, according to Fine-Gray, was used to calculate subdistribution hazard ratios (SHRs) with 95% confidence intervals (CI).

Results: Compared with no AECOPDs in the baseline period, AECOPD number and severity was associated with increased long term risk of both MI and PE in a gradual fashion, ranging from a SHR of 1.10 (0.97-1.24) and 1.33 (1.11-1.60), respectively, for one moderate exacerbation, to 1.82 (1.36-2.44) and 2.62 (1.77-3.89), respectively, for two or more severe exacerbations. In a time-restricted follow-up sensitivity analysis, the associations were stronger during the first year of follow up and diminished over time.

Interpretation: The risk of MI and PE increases with the frequency and severity of AECOPD in this large real life cohort of patients with COPD.

263 Words

Key words: Acute exacerbations of chronic obstructive pulmonary disease, comorbidity, cardiovascular adverse events, retrospective nationwide registry cohort, myocardial infarction, pulmonary embolism

Acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) are important events in the natural course of COPD, associated with accelerated decline in lung function, increased morbidity, lower quality of life and, increased risk of future exacerbations and mortality [1-8]. The risk of having a new AECOPD and the risk of mortality increase in a gradual fashion, based on the frequency and severity of prior exacerbations [6].

In the presence of an AECOPD, the risk of myocardial infarction (MI) and pulmonary embolism (PE) is greatly elevated and importantly, both of these diagnoses contribute to higher mortality among patients with COPD [9, 10]. The time-dependent risk of cardiovascular events in the period immediately after an AECOPD has been studied [11-15]. However, only some studies have specifically addressed the long-term risk of cardiovascular events related to the number and severity of exacerbations in the last year, which is the method the Global Initiative for Obstructive Lung Disease (GOLD) currently recommends to determine the risk of future exacerbations in order to guide treatment strategies [16-19].

Therefore, we conducted a register-based cohort study using the Swedish National Airway Register (SNAR) [20], with the aim to investigate the association between exacerbation frequency and severity in the last year with future risk of MI and PE in patients with COPD.

Methods

Study Population

SNAR was initiated in 2013 and includes data on patients with obstructive lung diseases, from primary and secondary care, registered in over 1000 clinics across Sweden [20]. In this study, patients with a physician-assessed primary diagnosis of COPD registered in SNAR from January 2014 to June 2022, and aged 30 years or older on the index date, were included. The choice of January 2014 as the start of the study period reflects the earliest possible date with SNAR-data. The index date was defined as the latest health care visit with a registered Forced Expiratory Volume in the 1 second (FEV_1) in SNAR within the predefined period. This ensures that all participants start the follow-up with relevant recent data on this important covariate.

Patient characteristics and definitions

Figure 1 provides an overview of the cohort covariate assessment in the different registers and follow-up periods. For covariates pertaining to cardiovascular comorbidities and outcome variables, we used data linkage between SNAR, the National Patient Register (NPR), the National Cause of Death Register (NCDR) and the National Prescribed Drug Register (NPDR) to obtain relevant data.

To create exacerbation history strata, we used previously validated methods to identify moderate and severe exacerbations [21]. Moderate exacerbations were defined as pharmacy prescriptions of short-term oral corticosteroids captured by Anatomical Therapeutic Chemical Classification System (ATC)-code H02AB, retrieved from NPDR. A list of corticosteroid treatments was manually reviewed to identify treatments prescribed for the COPD exacerbation indication. Severe exacerbations were defined as respiratory hospitalizations captured by the

International Classification of Diseases tenth revision (ICD-10) codes J41-J44, J96, J12-J18 or J20-J22 retrieved from NPR used as the main or secondary diagnosis in the electronic medical record.

In the main analysis, the exposure of patients with COPD was classified into 5 categories based on exacerbation history in the year prior to the index date: 1. No exacerbations; 2. One moderate exacerbation, no severe exacerbations; 3. Two or more moderate exacerbations; no severe exacerbations; 4. One severe exacerbation; 5. Two or more severe exacerbations *(Figure 2).* In the case of exposure to both moderate and severe exacerbations, the classification was done on the highest severity meaning the exposure category was the number of severe exacerbations, similar to a previously developed method [22].

Primary outcome and follow-up

The primary outcomes were MI (ICD-10 I21-I22) and PE (ICD-10 I26), defined as the first of either [date of admission for] hospitalization (main or secondary diagnosis code from the NPR) or [date of] out-of-hospital-death from a MI or PE (underlying cause of death from NCDR) during follow-up. Patients were followed from the index date for a maximum of 9 years to the occurrence of the outcome of interest (MI or PE), death from another cause, or the end of follow-up on 30 November 2022. The minimum amount of follow-up was 6 months for patients registered on 1 June 2022.

Sensitivity analyses were conducted, with the follow up time restricted to one, two, and five years, respectively, for the main outcomes. The same competing risk regression model and covariates were used.

Covariates

Covariates extracted from SNAR included sex, age, Body-Mass-Index (BMI), smoking status and spirometry values (FEV_1, Forced Vital Capacity (FVC) and ratio FEV_1/FVC), modified Medical Research Council dyspnoea-scale (mMRC)-score and COPD-Assessment Test (CAT)-score. The latest registered datapoint in the period 18 months before the index date was used for smoking and BMI, since such more stable covariates with more observations in the dataset can be well accounted for in this way. Smoking status was categorized as patients who never smoked, patients who previously smoked (smoking-free for at least 6 months) and patients who currently smoke. BMI was categorized as normal weight (18.5-24.9), underweight (<18.5), overweight (25-29.9) and obese (>30). Swedish reference values were used to calculate the percent of predicted FEV_1 as well as Forced Vital Capacity (FVC) [23, 24]. Lung function was divided into the GOLD grades based on FEV_1 % of predicted: GOLD 1; FEV_1 ≥80%, GOLD 2; ≥50% FEV_1 <80%, GOLD 3; ≥30% FEV_1 <50% and GOLD 4; FEV_1 <30% [16].

Maintenance COPD and cardiovascular pharmacological treatment were retrieved from the NPDR and defined as at least 1 dispensation within 1 year before the index date, (see Table E1 and E2 in the online data supplement for the ATC-codes and definitions). All COPD inhaler combination therapies were defined by dispensations of ATC-codes for fixed single inhaler treatment.

The cardiovascular comorbidities selected as covariates were a previous history of: MI: I21-I24, stroke: I61, I63, heart failure: I50, atrial fibrillation: I48, coronary artery disease: I20-I25, hypertension: I10 or I109, peripheral artery disease: I702, I739, diabetes type 2: E11, and PE: I26, captured by ICD-10 codes as the main or

concomitant diagnosis in the NPR at any time prior to the index date but after 2007-01-01 .

Socioeconomic status (SES) was based on the indicators education and income, obtained from the Longitudinal integrated database for health insurance and labour market studies (LISA) Statistics Sweden from the registered value in the year prior to the index date. Income was levelled into 4 quartiles based on the median salary in Sweden. Educational level was levelled into 3 categories: low (less than nine years), medium (9 to 12 years) and high (more than 12 years).

Ethical approval

The study was approved by the Swedish Ethical Review Authority (2019-04915).

Statistical Analysis

We used descriptive statistics to present the baseline characteristics of the analysed study participants. Normally distributed continuous values were described using mean and standard deviation. Categorical variables were described using counts and percentages.

Competing risk regression, specifically the Fine-Gray proportional hazards model for subdistribution, was used to estimate subdistribution hazard ratios (SHRs) for the occurrence of MI and PE among patients with COPD, classified by their exacerbation history (*Figure 3 & 4).* In this model death from all other-causes was considered as a competing risk [25]. Crude and adjusted SHRs with 95% confidence intervals (CIs) were computed for MI and PE, with the group with no exacerbations in the year prior to the index date as the reference. We adjusted both models for sex, age, BMI, smoking status, FEV_1 % of predicted at baseline, any previous cardiovascular comorbidity, cardioprotective medications, income and educational level. Cumulative

incidence function curves were constructed to complement our regression analysis in accordance with the recommendations for reporting Fine-Gray competing regression analyses (*Online Supplement E-Figure 1 & 2)* [26].

The choice of covariates was made on their clinical relevance but also on their availability within our datasets. Of note we did not adjust the model for CAT-score or mMRC because of limited data on these variables.

To handle the small percentage of missing data on BMI (2.2%) and smoking (6.7%), we used multiple imputations by chained equations to impute the missing data on smoking and BMI for the main analysis in order to avoid introducing selection bias into the results. To account for the potential of misclassified asthma among patients who never smoked in our cohort of COPD patients, we conducted a sensitivity analysis where we excluded patients who never smoked. We also conducted another sensitivity analysis including sleep apnea as a covariate in the competing risk regression model, treating missing on this variable as a factor level. Results from these sensitivity analyses, one including only patients who currently or previously smoked and one adding sleep apnea as a covariate, are presented in the Online Supplementary (E-Tables E5-E6).

The baseline data were defined using SAS (version 15.2) and R (version 4.3.1) was used for further data management. The mice-package (version 3.16.0) was used for imputation and the cmprsk-package (version 2.2-11) was used for the competing risk regression analyses according to Fine-Gray.

RESULTS

Characteristics of the study population

Figure 2 shows a flow diagram of the study population, in total, 66 422 unique patients with COPD aged >30 years on index date with data on FEV_1 were included in the cohort.

The baseline characteristics of cohort are presented in *Tables 1-3.* Mean FEV_1 percent of predicted was 60.3, 37.6% were patients who currently smoke, 77.2% used bronchodilation therapy and 50.2% were on ICS. While 71.1% had no AECOPD in the year before the index date, 13.0% had 1 moderate, 8.8% ≥2 moderate, 5.8% 1 severe, and 1.3% ≥2 severe AECOPD. With increasing frequency and severity of AECOPD, patients were more often female, older, more often underweight and had more often a history of smoking . They also had lower lung function, were more frequently on combination treatment with ICS, LABA and LAMA i.e. triple therapy and had a higher prevalence of cardiovascular comorbidity at baseline.

Outcome of MI

For the outcome of MI, patients were followed for a median of 3.94 years (interquartile range [IQR] 2.26-5.60), for a total of 265 849 patient-years. There were 2260 cases of MI during the follow-up; of these 19.9% (n=450) were out-of-hospital fatal events. In the crude model, the number of AECOPDs at baseline increased the risk of MI in a gradual fashion (*Online Supplement Table E3).* The observed pattern was only slightly attenuated when adjusted for covariates. The adjusted SHR of MI in patients with 1 moderate exacerbation was not significantly elevated 1.10 (95% CI 0.97-1.24), however for patients with 2 or more moderate exacerbations without severe exacerbations, the SHR of MI was elevated 1.57 (95% CI 1.38-1.78). For the group with one severe exacerbation, the SHR of MI was 1.47 (95% CI 1.26-1.71) and

for the group with two or more severe exacerbations, 1.82 (95% CI 1.36-2.44) (*Figure 3)*. The cumulative incidence function curves for MI is displayed in *Supplementary E-Figure 1.*

Outcome of PE

For PE the median follow-up time was 3.72 years (IQR 2.32-5.62), for a total of 268 473 patient-years. There were 961 cases of PE during the follow-up, of which 5.4% (n=52) were out-of-hospital fatal events. In both the crude and adjusted model, the risk of PE was elevated in all exacerbation history strata compared to the reference group with zero exacerbations (*Figure 4 and Supplementary-Table E3-E4)*. The adjusted SHR ranged from 1.33 (95% CI 1.11-1.60) in patients with 1 moderate exacerbation without severe exacerbations, to an adjusted SHR of 2.62 (95% CI 1.77-3.89) in the group with 2 or more severe exacerbations (*Figure 4)*. The cumulative incidence function curve for PE is displayed in *Supplementary E-Figure 2.*

Both model findings were supported by similar results in the sensitivity analysis excluding patients who never smoked and the sleep apnea sensitivity-analysis. (*Online Supplement E-Tables E5-E6)*. Of the 30% of patients with recorded data on the sleep apnea variable, 7.2% had a sleep apnea diagnosis.

In our time-restricted sensitivity analysis, the association between the exposure categories and the main outcomes of MI and PE were the strongest in the first year of follow up. The results are presented in (*Tables 4-5*). The associated risk increases diminished over time but was still significant and a bit more pronounced after 5 years compared to the maximum follow up time of nine years.

DISCUSSION

This is the first study to investigate the association across both number and severity of exacerbations among patients with COPD with the risk of MI and PE in a large real life cohort with disease-specific register data. We found that an exacerbation history with more frequent and/or severe exacerbations was independently associated with increasing risk of future MI and PE during a median of almost 4 years of follow-up, in total ~ 265 000 patient-years. In our time-restricted sensitivity analyses, the associated risk increase was most pronounced the first year of follow-up and then diminished slightly over time.

The current GOLD document recommends to evaluate the number and severity of exacerbations during the last 12 months as an estimate of the risk of future exacerbations [16]. In our, clinically representative COPD cohort, a detailed exacerbation history could indeed independently identify patients at differential increased risk for cardiovascular and pulmonary embolic events.

Although long-term cardiovascular risk based on exacerbation history in the prior year has not been previously studied, increased cardiovascular risk during and shortly after an exacerbation of COPD has been reported before. In a UK cohort based on medical records, the authors reported a 2.27-fold higher risk of MI in the 5 days after the start of pharmacological treatment for an exacerbation, and patients with MI had higher rates of exacerbations [15]. A post-hoc analysis of the SUMMIT trial found a near 10 times increased risk of CVD-events (stroke, transient ischemic attacks and unstable angina) in the 30 days following hospitalization for an AECOPD [13]. Similarly, a recent post-hoc analysis of the IMPACT trial found a higher risk of CVD-events (new or worsened cardiac arrhythmia, cardiac failure, ischemic heart disease, hypertension, and central nervous system haemorrhages and

cerebrovascular conditions) during and in the 30 days following the resolution of an exacerbation [11]. Furthermore, in a self-controlled case series studying different time periods after the incidence of an AECOPD, found a risk increase for both MI and ischemic stroke in the 1-91 days after the onset of an acute exacerbation [10].

Previous studies have also identified a substantial prevalence of PE during AECOPDs in hospitalized patients within 48 hours after admittance for AECOPD with pooled prevalence estimates in meta analyses ranging from 11.0% – 19.9% [27-29]. PE is associated with increased mortality, and in patients with COPD the risk of death when diagnosed with PE might be twice as high compared to patients without COPD [9, 30, 31]. Further larger cohort studies are needed in order to establish potential new screening algorithms for PE in the setting of hospitalisation for AECOPD [32]. Our study adds to this previous knowledge by highlighting an important longer-term longitudinal association between AECOPDs and MI and PE, respectively, and the utility of a detailed exacerbation history in the assessment of these life threatening events.

Prevention of exacerbations is a key objective of COPD management, and our results further emphasise its importance for cardiovascular risk. Interestingly, in two large randomized controlled trials evaluating the effects of LABA/LAMA/ICS versus LABA/LAMA on exacerbation risk, a reduction of all-cause mortality, as well as cardiovascular mortality specifically, was demonstrated [33, 34]. The potential prevention of cardiovascular and thromboembolic events by antiplatelet therapy in frequent exacerbators is promising, but remains to be studied in randomized controlled trials.

The results also serve to further emphasize the importance of cardiovascular and other comorbidity in COPD, which is often unassessed and undiagnosed [28, 35]. It is

important to carefully consider differential diagnoses of a suspected COPD exacerbation in patients with COPD presenting with worsening dyspnoea in the acute care setting, and this includes particularly MI and PE [27, 28, 32, 36, 37].

Sleep apnea is an important comorbidity in COPD and a potential confounder between COPD exacerbations and cardiovascular disease. Although we excluded it from the main model due to the large portion of missing data, our sensitivity analysis, where sleep apnea was included as a covariate in our competing risk regression model, indicated that the risk of the main outcomes was of similar magnitude even when adjusting for sleep apnea.

Two main strengths of this study are the size of the study cohort, with an estimated observation time of ~ 265,000 person-years and the real-life setting reflecting clinical COPD practice in Sweden. Additionally, SNAR provides a comprehensive and detailed assessment of demographic and clinical characteristics of the patients with COPD studied. A further strength is the linkage with population-based health registries through the unique national personal identity number [38, 39]. These registers provided 100% complete data for the prescription of COPD treatments and cardioprotective medications, hospitalization, and mortality for the patients in our study. By using the latest registered FEV_1-value for cohort selection, we ensured complete data on this important variable which has previously been linked to cardiovascular disease outcomes and increased mortality in patients with COPD [40, 41].

One study limitation is that we used a definition of moderate exacerbations which did not include exacerbations treated with antibiotics alone, which may lead to an underestimation of moderate exacerbations. However, this bias is likely to be small and a prescription-based definition only using oral corticosteroids has been shown to

be a robust definition of moderate COPD exacerbations [21]. Additionally, MIs can have different aetiologies, the most common being plaque-rupture and thrombosis causing acute coronary artery occlusion (type 1 infarction). But it can also be caused by a mismatch in blood oxygen supply and demand in the heart (type 2 infarction), a mechanism which could be important and potentially more common in patients with COPD hospitalized for AECOPD, who often are affected by hypoxemia [42]. However, a limitation of ICD-10 codes for MI is that they do not differentiate between these types.

Further, the registered diagnosis in the NCDR collected from death certificates are most often based on clinical diagnosis, since clinical autopsies are rarely performed in Sweden unless the individual died unnaturally or under unclear circumstances calling for a forensic autopsy. While this procedure is similar to other countries, death certificates based on clinical diagnosis nonetheless represents a possible source of inaccuracy and bias compared to cause of death based autopsies. Likewise, the SNAR diagnosis of COPD relies on a physician-registered primary diagnosis of COPD. It is not possible to validate an individual COPD-diagnosis within SNAR, due to the nature of the real-life register data, and some patients might therefore be misdiagnosed asthma-patients, (although asthma has its own physician-defined diagnosis variable within SNAR). Fixed airflow obstruction in patients who never smoked could be misclassified asthma. However, our sensitivity analysis excluding patients who never smoked yielded results that were reassuringly to our main analysis.

In summary, we found that patients who had severe or frequent exacerbations had a long-term increased risk of MI and PE. We conclude that the stratification of patients with COPD based on their exacerbation history in the last year can be a valuable

assessment of the future risk of MI and PE. A detailed assessment of cardiovascular comorbidity is warranted in patients with COPD and frequent or severe exacerbations, in a stable phase but also during worsening of dyspnoea. Future studies should evaluate primary cardiovascular prevention strategies in frequent exacerbators.

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Table 1. Baseline characteristics among 66 422 patients with COPD aged 30 years or older in the Swedish National Airway Register from 2014 to 2022, overall and by pre-baseline exacerbation categories.

		Number of exacerbations, moderate/severe (n/n)				
Characteristics	Total study population	0/0	1/0	≥2/0	0/1	0/≥2
Patients, n (%)	66422	47236 (71.1)	8652 (13.0)	5825 (8.8)	3853 (5.8)	856 (1.3)
Male sex, n (%)	29180 (43.9)	21546 (45.6)	3439 (39.7)	2250 (38.6)	1614 (41.9)	331 (38.7)
Age, mean (SD)	70.3 (9.4)	70.0 (9.4)	69.7 (9.5)	70.9 (9.1)	73.2 (8.9)	74.1 (8.3)
BMI‡, mean (SD)	26.9 (5.7)	26.8 (5.3)	27.1 (5.8)	27.2 (5.7)	26.3 (6.5)	25.8 (6.8)
BMI category†, n (%)						
Patients who are obese	16187 (24.4)	11309 (23.9)	2254 (26.1)	1520 (26.1)	902 (23.4)	202 (23.6)
Patients who are normalweight	22992 (34.6)	16438 (34.8)	2883 (33.3)	1909 (32.8)	1454 (37.7)	308 (36.0)
Patients who are underweight	3473 (5.2)	2271 (4.8)	453 (5.2)	251 (4.3)	377 (9.8)	121 (14.1)
Patients who are overweight	22276 (33.5)	16175 (34.2)	2830 (32.7)	1996 (34.3)	1062 (27.6)	213 (24.9)
Smoking status†, n (%)						
Patients who currently smoke	24963 (37.6)	18403 (39.0)	3169 (36.6)	1718 (29.5)	1394 (36.2)	279 (32.6)
Patients who previously smoked	29763 (44.8)	20444 (43.3)	3947 (45.6)	3016 (51.8)	1900 (49.3)	456 (53.3)
Patients who never smoked	7225 (10.9)	5244 (11.1)	939 (10.9)	664 (11.4)	319 (8.3)	59 (6.9)
Spirometry values, mean (SD)						
FEV_1‡	1.7 (0.7)	1.8 (0.7)	1.6 (0.7)	1.5 (0.6)	1.3 (0.6)	1.0 (0.5)
FEV_1 % predicted	60.3 (18.5)	62.4 (17.8)	58.6 (18.6)	55.9 (18.5)	49.4 (18.6)	41.0(17.7)
FVC‡	2.8 (0.9)	2.9 (0.9)	2.7 (0.9)	2.6 (0.9)	2.4 (0.8)	2.1 (0.8)
FVC % predicted	76.2 (17.5)	77.4 (17.2)	75.1 (17.3)	73.3 (17.3)	69.5 (18.8)	64.2 (18.9)
FEV_1/FVC	0.6 (0.2)	0.6 (0.1)	0.6 (0.2)	0.6 (0.17)	0.6 (0.2)	0.5 (0.2)
GOLD grade, n (%)						
GOLD 1	9721 (14.6)	7731 (16.4)	1116 (12.9)	587 (10.1)	257 (6.7)	30 (3.5)
GOLD 2	37801 (56.9)	28326 (60.0)	4733 (54.7)	3024 (51.9)	1524 (39.6)	194 (22.7)
GOLD 3	15574 (23.4)	9597 (20.3)	2305 (26.6)	1775 (30.5)	1519 (39.4)	378 (44.2)
GOLD 4	3326 (5.0)	1582 (3.3)	498 (5.8)	439 (7.5)	553 (14.4)	254 (29.7)
Symptomatic burden, mean (SD)						
CAT† score	13.4 (7.1)	12.5 (6.6)	14.5 (7.4)	15.5 (7.8)	16.3 (7.8)	19.4 (7.9)
mMRC† score	1.6 (1.2)	1.4 (1.1)	1.8 (1.2)	2.0 (1.2)	2.4 (1.2)	3.0 (1.1)
GOLD class ABE†, n (%)						
GOLD A	14800 (29.0)	12962 (36.2)	1838 (27.4)	0 (0.0)	0 (0.0)	0 (0.0)
GOLD B	27725 (54.4)	22846 (63.8)	4879 (72.6)	0 (0.0)	0 (0.0)	0 (0.0)
GOLD E	8458 (16.6)	0 (0.0)	0 (0.0)	4583 (100.0)	3152 (100)	723 (100.0)

† Footnote: Body mass Index (BMI) available for 64 928 patients, smoking status available for 61 951 patients, COPD assessment test (CAT)-score available for 46214 patients, Modified Medical Research Council (mMRC)-score available for 31970 patients, Global Initiative for Chronic Obstructive Lung Disease (GOLD)-classification A-E available for 50 983 patients.

Table 2. Primary endpoints and cardiovascular comorbidity at baseline among 66 422 patients with COPD aged 30 years or older in the Swedish National Airway Register from 2014 to 2022.

		Number of exacerbations, moderate/severe (n/n)				
Cardiovascular event outcomes and baseline comorbidities	Total study population N= 66422	0/0 N = 47236	1/0 N = 8652	≥2/0 N = 5825	0/1 N = 3853	0/≥2 N = 856
Myocardial infarction						
Person years	265849	190480	35876	23565	13462	2466
No. Events	2260	1434	291	289	197	49
Events/100 000 person years	850	753	811	1226	1463	1987
Pulmonary Embolism						
Person years	268473	192354	36182	23796	13639	2502
No. Events	961	558	147	126	102	28
Events/100 000 person years	358	290	406	529	748	1119
Comorbidities, n (%)						
Myocardial infarction	2080 (3.1)	1287 (2.7)	249 (2.9)	228 (3.9)	250 (6.5)	66 (7.7)
Stroke	1620 (2.4)	1085 (2.3)	190 (2.2)	143 (2.5)	158 (4.1)	44 (5.1)
Heart failure	5132 (7.7)	2778 (5.9)	656 (7.6)	513 (8.8)	872 (22.6)	313 (36.6)
Atrial fibrillation	6817 (10.3)	4144 (8.8)	881 (10.2)	700 (12.0)	861 (22.3)	231 (27.0)
Coronary heart disease	7574 (11.4)	4717 (10.0)	984 (11.4)	783 (13.4)	851 (22.1)	239 (27.9)
Hypertension	19044 (28.7)	12082 (25.6)	2398 (27.7)	1934 (33.2)	2088 (54.2)	542 (63.3)
Peripheral artery disease	2044 (3.1)	1336 (2.8)	243 (2.8)	204 (3.5)	208 (5.4)	53 (6.2)
Diabetes mellitus type 2	6135 (9.2)	3946 (8.4)	744 (8.6)	576 (9.9)	690 (17.9)	179 (20.9)
Deep vein thrombosis	1050 (1.6)	673 (1.4)	138 (1.6)	143 (2.5)	66 (1.7)	30 (3.5)
Pulmonary Embolism	831 (1.3)	462 (1.0)	123 (1.4)	108 (1.9)	101 (2.6)	37 (4.3)
Any cardiovascular disease‡	24919 (37.5)	16031 (33.9)	3112 (36.0)	2450 (42.1)	2650 (68.8)	676 (79.0)

‡ Any cardiovascular disease: Any of the comorbidities presented in the table.

Table 3. Baseline COPD and cardioprotective medications among 66 422 patients with COPD aged 30 years or older in the Swedish National Airway Register from 2014 to 2022. All combination therapies were fixed single inhaler combination therapies

		Number of exacerbations, moderate/severe (n/n)				
	Total study population N= 66422	0/0 N = 47236	1/0 N = 8652	≥2/0 N = 5825	0/1 N = 3853	0/≥2 N = 856
COPD medication, n (%)						
ICS‡	3139 (4.7)	2360 (5.0)	467 (5.4)	215 (3.7)	89 (2.3)	8 (0.9)
LABA‡	1226 (1.8)	982 (2.1)	128 (1.5)	80 (1.4)	34 (0.9)	2 (0.2)
LAMA‡	8710 (13.1)	6881 (14.6)	935 (10.8)	456 (7.8)	407 (10.6)	31 (3.6)
SABA‡ or SAMA‡	2885 (4.3)	2150 (4.6)	469 (5.4)	145 (2.5)	116 (3.0)	5 (0.6)
ICS/LABA ‡	8306 (12.5)	5832 (12.3)	1304 (15.1)	817 (14.0)	295 (7.7)	58 (6.8)
ICS/LABA/LAMA ‡	20017 (30.1)	10871 (23.0)	3369 (38.9)	3003 (51.6)	2111 (54.8)	663 (77.5)
ICS/LAMA ‡	1894 (2.9)	1327 (2.8)	293 (3.4)	179 (3.1)	78 (2.0)	17 (2.0)
LABA/LAMA‡	5086 (7.7)	3628 (7.7)	654 (7.6)	390 (6.7)	357 (9.3)	57 (6.7)
No inhalation treatment	15159 (22.8)	13205 (28.0)	1033 (11.9)	540 (9.3)	366 (9.5)	15 (1.8)
Cardioprotective medication, n (%)						
Anticoagulation	25851 (38.9)	17447 (36.9)	3322 (38.4)	2464 (42.3)	2100 (54.5)	518 (60.5)
Anti-arrhythmic	7421 (11.2)	4510 (9.5)	1089 (12.6)	900 (15.5)	717 (18.6)	205 (23.9)
Diuretics	731 (1.1)	459 (1.0)	120 (1.4)	77 (1.3)	69 (1.8)	6 (0.7)
Betablocker	16170 (24.3)	9881 (20.9)	2215 (25.6)	1870 (32.1)	1676 (43.5)	528 (61.7)
Calcium channel-blocker	23244 (35.0)	15750 (33.3)	2993 (34.6)	2192 (37.6)	1853 (48.1)	456 (53.3)
ACE/ARB	16967 (25.5)	11890 (25.2)	2070 (23.9)	1545 (26.5)	1202 (31.2)	260 (30.4)
Statin	29630 (44.6)	20882 (44.2)	3719 (43.0)	2671 (45.9)	1933 (50.2)	425 (49.6)
Diabetes	24136 (36.3)	17215 (36.4)	2935 (33.9)	2093 (35.9)	1534 (39.8)	359 (41.9)
Any cardiac agent ‡	8906 (13.4)	6278 (13.3)	1032 (11.9)	792 (13.6)	642 (16.7)	162 (18.9)
Any metabolic ‡	46460 (69.9)	32149 (68.1)	5999 (69.3)	4423 (75.9)	3135 (81.4)	754 (88.1)
Any cardiometabolic ‡	26404 (39.8)	18791 (39.8)	3198 (37.0)	2319 (39.8)	1693 (43.9)	403 (47.1)

Footnote:
‡ Abbreviations: SAMA = Short acting antimuscarinic agent, SABA = short acting beta2 agonist, LAMA = Long acting antimuscarinic agent, LABA = Long acting beta2 agonist, ICS = Inhaled corticosteroid
‡ Any cardiac agent, Any metabolic, Any cardiometabolic; see supplementary table E2 for definitions

Table 4. Table of adjusted[1] subdistribution hazard ratios (SHRs) for myocardial infarction on baseline exacerbation history, from competing risk regression analysis for 66 422 Swedish patients diagnosed with COPD, registered in the Swedish National Airway Register January 2014 - June 2022, with follow-up time restricted to one, two and five years respectively.

Exacerbation History	Adjusted[1] results on 66 422 patients, adjusted SHR 95% CI for Myocardial infarction		
Follow up time maximum	1 year	2 years	5 years
0 Exacerbations	Ref	Ref	Ref
1 moderate 0 hosp	1.28 (1.01-1.63)	1.12 (0.93-1.35)	1.13 (0.99-1.29)
>2 moderate 0 hosp	1.80 (1.41-2.29)	1.77 (1.48-2.11)	1.61 (1.40-1.84)
1 severe	1.68 (1.27-2.21)	1.68 (1.37-2.05)	1.51 (1.29-1.77)
2+ severe	2.88 (1.88-4.42)	2.30 (1.62-3.27)	1.87 (1.38-2.52)
Event rate per 100 000 patient years	941	923	870

Footnote: 1= Adjusted for sex, age, BMI, smoking status, FEV1 % predicted, the presence of baseline cardiovascular comorbidity, cardioprotective medications and socioeconomic factors. Abbreviations: SHR = Subdistribution hazard ratio, CI = Confidence Interval

Table 5. Table of adjusted[1] subdistribution hazard ratios (SHRs) for pulmonary embolism on baseline exacerbation history, from competing risk regression analysis for 66 422 Swedish patients diagnosed with COPD, registered in the Swedish National Airway Register January 2014 - June 2022, with follow-up time restricted to one, two and five years respectively.

Exacerbation History	Adjusted[1] results on 66 422 patients, adjusted SHR 95% CI for pulmonary embolism		
Restricted maximum follow up time	1 year	2 years	5 years
0 Exacerbations	Ref	Ref	Ref
1 moderate 0 hosp	1.59 (1.07-2.34)	1.49 (1.13-1.98)	1.34 (1.10-1.63)
>2 moderate 0 hosp	2.76 (1.91-3.98)	1.89 (1.40-2.55)	1.60 (1.30-1.98)
1 severe	3.12 (2.10-4.63)	2.58 (1.89-3.50)	2.11 (1.67-2.66)
2+ severe	4.54 (2.45-8.44)	3.71 (2.24-6.15)	2.63 (1.73-3.99)
Event rate per 100 000 patient years	364	340	355

Footnote: 1 = Adjusted for sex, age, BMI, smoking status, FEV1 % predicted, the presence of baseline cardiovascular comorbidity, cardioprotective medications and socioeconomic factors. Abbreviations: SHR = Subdistribution hazard ratio, CI = Confidence Interval

Figure 1: Cohort design, covariate assessment and follow-up period.

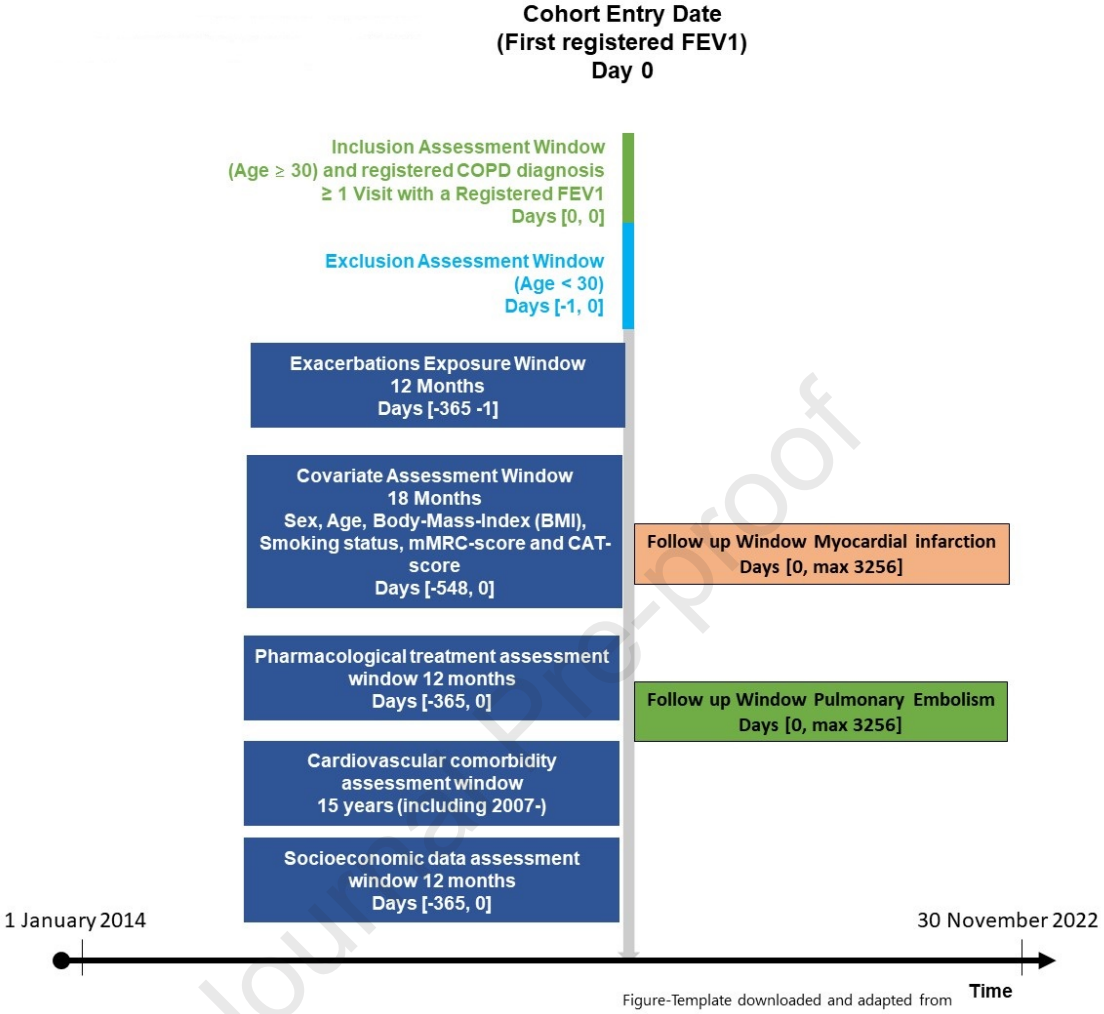
Figure 2: Flow diagram for Distribution of exacerbation history groups.

Figure 3. Forest plot of adjusted[1] subdistribution hazard ratios (SHRs) for myocardial infarction depending on baseline exacerbation history, from competing risk regression analysis for 66 422 Swedish patients diagnosed with COPD, registered in the Swedish National Airway Register January 2014 - June 2022 and followed for up to 9 years.

1 *Adjusted for sex, age, BMI, smoking status, FEV_1 % predicted, the presence of baseline cardiovascular comorbidity, cardioprotective medications and socioeconomic factors. Abbreviations: SHR = Subdistribution hazard ratio, CI = Confidence Interval*

Figure 4. Forest plot of adjusted[1] subdistribution hazard ratios (SHRs) for pulmonary embolism depending on baseline exacerbation history, from competing risk regression analysis for 66 422 Swedish patients diagnosed with COPD, registered in the Swedish National Airway Register January 2014 - June 2022 and followed for up to 9 years.

1 *Adjusted for sex, age, BMI, smoking status, FEV_1 % predicted, the presence of baseline cardiovascular comorbidity, cardioprotective medications and socioeconomic factors. Abbreviations: SHR = Subdistribution hazard ratio, CI = Confidence Interval*



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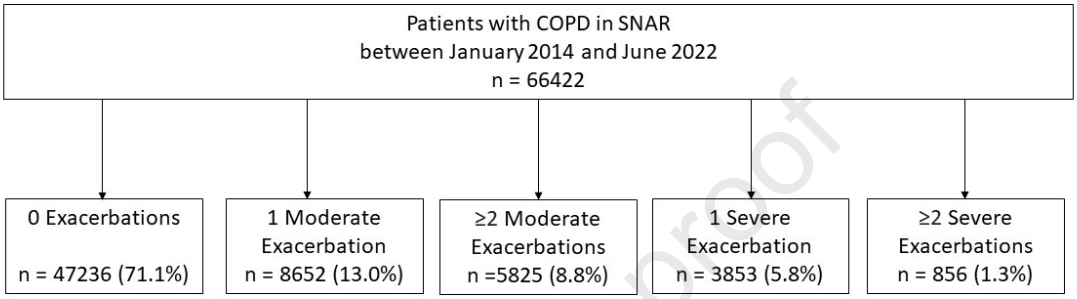
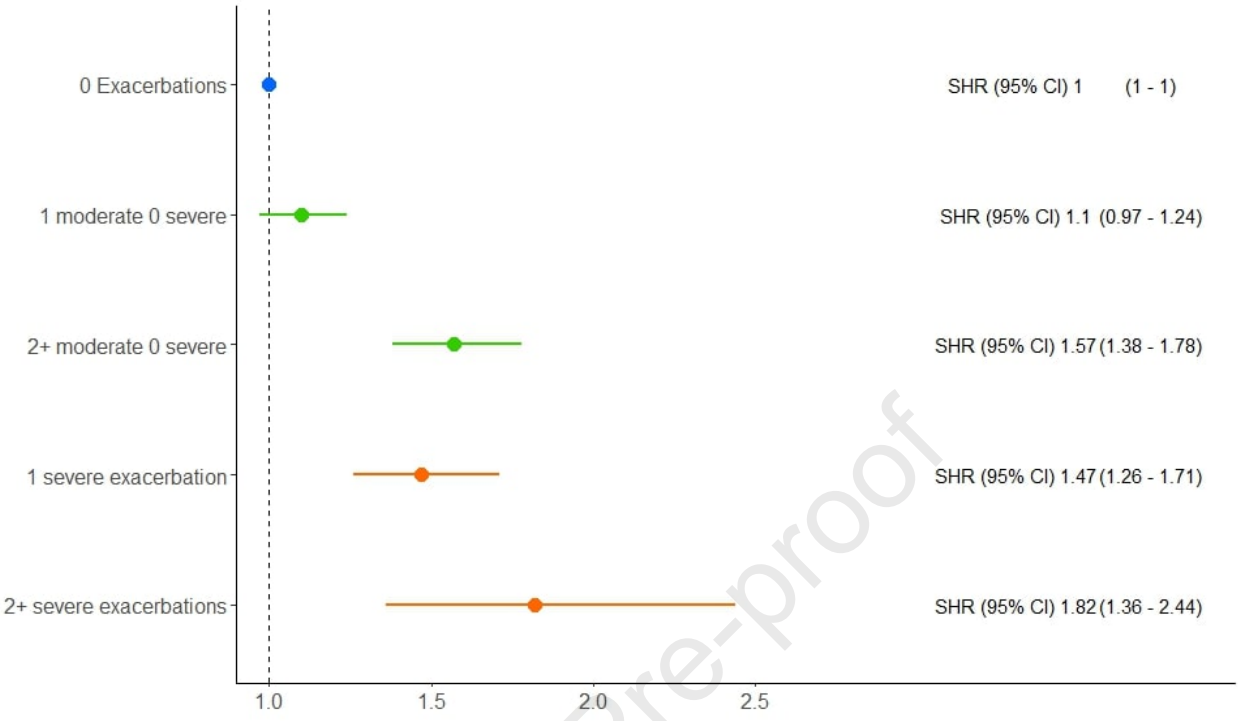
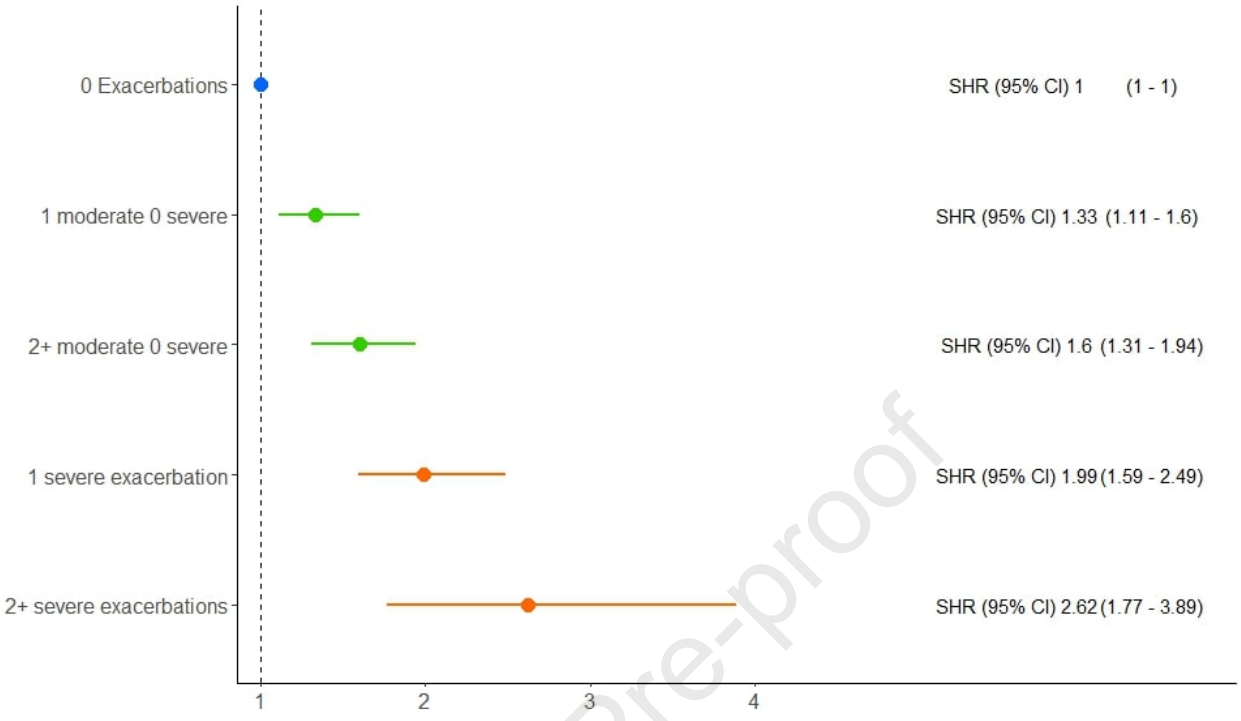




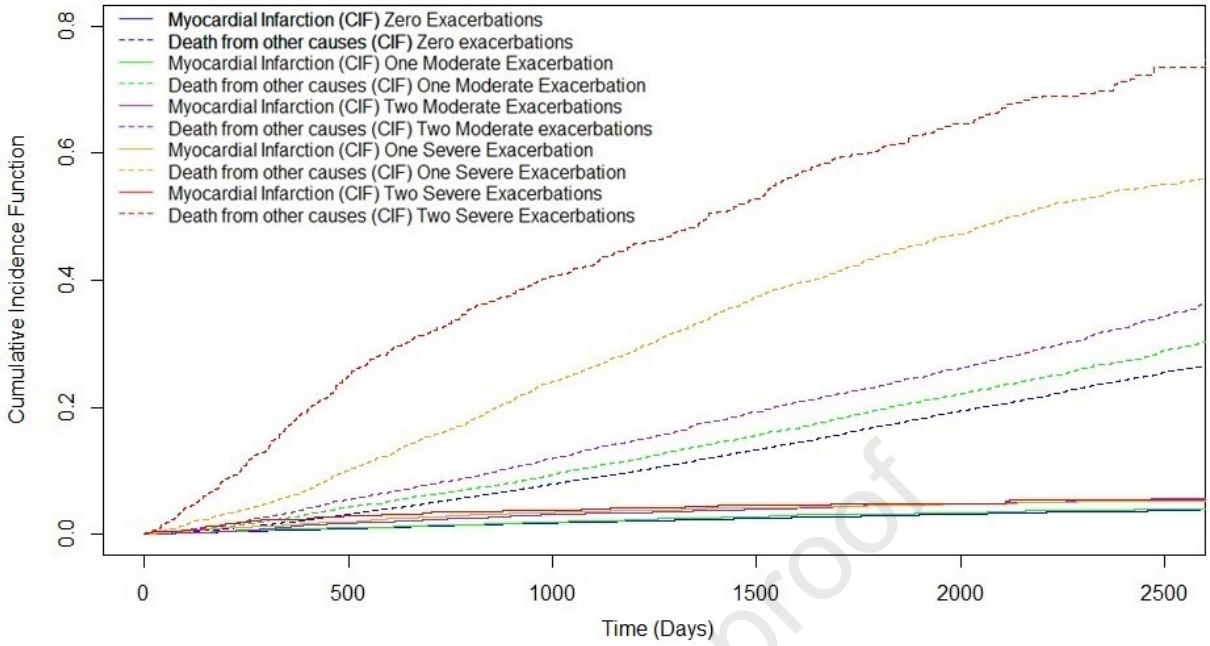


Take-Home Point pullout

- Study question: Is the number and severity of AECOPDs associated with increased risk of MI or PE in a real-life cohort of patients with COPD?
- Results: Exacerbation number and severity was associated with the future long-term rate of both MI and PE in a gradual fashion
- Interpretation: The risk of MI and PE increases with the frequency and severity of AECOPD in this large real life cohort of patients with COPD.

E-Figure 2. CIF-plot of cumulative incidence functions for outcome of pulmonary embolism with death from other causes as a competing risk, 66422 Patients with COPD divided by baseline exacerbation history

E-Figure 1. CIF-plot of cumulative incidence functions for outcome of myocardial infarction with death from other causes as a competing risk, 66422 Patients with COPD divided by baseline exacerbation history



Supplementary

LIST OF ATC CODES FOR INHALER THERAPY

Table E1: Drug therapy classes and ATC codes for respiratory inhaler therapy used in this study from the Swedish Prescribed Drug Register.

Drug therapy class	ATC codes for respiratory inhaler therapy
SABA and/or SAMA	• R03AC02, Salbutamol • R02AC03, Terbutalin • R03BB01, Ipratropiumbromid • R03AL02, Salbutamol and ipratropiumbromid
LAMA	• R03BB01, Ipratropiumbromid • R03BB04, Tiotropiumbromid • R03BB05, Aclidiniumbromid • R03BB06, Glycopyrroniumbromid • R03BB07, Umeclidiniumbromid
LABA	• R03AC12, Salmeterol • R03AC13, Formoterol • R03AC18, Indacaterol • R03AC19, Olodaterol
ICS	• R03BA01, Beclometason • R03BA02, Budesonide • R03BA04, Betametason • R03BA05, Fluticason • R03BA07, Mometason • R03BA08, Ciklesonid
LABA/LAMA	• R03AL03, Vilanterol and Umeclidiniumbromid • R03AL04, Indacaterol and Glycopyrroniumbromid • R03AL05, Formoterol and Aclidiniumbromid • R03AL06, Olodaterol and Tiotropiumbromid • R03AL07, Formoterol and Glycopyrroniumbromid • R03AL10, Formoterol and Tiotropium
LABA/ICS	• R03AK06, Salmeterol and Fluticason • R03AK07, Formoterol and Budesonid • R03AK08, Formoterol and Beclometason • R03AK09, Formoterol and Mometason • R03AK10, Vilanterol and Fluticasonfuroat • R03AK11, Formoterol and Fluticason • R03AK12, Salmeterol and Budesonid • R03AK13, Salmeterol and Budesonid • R03AK14, Indakaterol and Mometason
LABA/LAMA/ICS	• R03AL08, Vilanterol, umeklidiniumbromid and flutikasonfuroat • R03AL09, Formoterol, Glycopyrroniumbromid and Beclometason • R03AL11, Formoterol, Glykopyrroniumbromid, Budesonide • R03AL12, Indakaterol, Glukopyrronium, Mometason

Table E2: Drug therapy classes and ATC codes for cardioprotective medications used in this study from the Swedish Prescribed Drug Register.

Drug therapy class	**ATC code groups**
Anticoagulation	B01
Anti-arrhythmic	C01
Diuretics	C03
Betablocker	C07
Calcium channel-blocker	C08
ACE/ARB	C09
Statin	C10
Diabetes	A10
Any cardiac drug	B01 C01 C02 C03 C07 C08 C09
Any Metabolic drug	C10 A10
Any Cardiometabolic drug	B01 C01 C02 C03 C07 C08 C09 A10

Table E3. Crude subdistribution hazard ratios (SHRs) from competing risk regression analysis of risk of myocardial infarction (left) and pulmonary embolism (right) side-by-side comparison in 66 422 Swedish COPD patients stratified by baseline exacerbation history

Exacerbation history	**Main results crude SHR 95% CI for myocardial infarction**	**Main results crude SHR 95% CI for pulmonary embolism**
0 Exacerbations	Ref	Ref
1 Moderate	1.08 (0.95-1.22)	1.40 (1.17-1.68)
>2 Moderate	1.63 (1.44-1.85)	1.83 (1.50-2.22)
1 Severe	1.92 (1.65-2.23)	2.59 (2.09-3.19)
2+ Severe	2.58 (1.94-3.44)	3.87 (2.65-5.67)

Table E4. Adjusted subdistribution hazard ratios (SHRs) from competing risk regression analysis of risk of myocardial infarction (left) and pulmonary embolism (right) side-by-side comparison in 66 422 Swedish COPD patients stratified by baseline exacerbation history

Exacerbation history	**Main results adjusted SHR 95% CI for myocardial infarction**	**Main results adjusted SHR 95% CI for pulmonary embolism**
0 Exacerbations	Ref	Ref
1 Moderate	1.10 (0.97-1.24)	1.33 (1.11-1.60)
>2 Moderate	1.57 (1.38-1.78)	1.60 (1.31-1.94)
1 Severe	1.47 (1.26-1.71)	1.99 (1.59- 2.49)
2+ Severe	1.82 (1.36-2.44)	2.62 (1.77-3.89)

1 *Adjusted for sex, age, BMI, smoking status, FEV_1 % predicted, the presence of baseline cardiovascular comorbidity and cardioprotective medications, income and educational level*

Table E5 Adjusted[1] subdistribution hazard ratios (SHRs) for myocardial infarction and pulmonary embolism depending on baseline exacerbation history, from competing risk regression analysis for 54 726 Swedish patients diagnosed with COPD who previously or currently smoked, registered in the Swedish National Airway Register January 2014 - June 2022 and followed for up to 9 years.

Exacerbation history	**Adjusted[1] SHR 95% CI for myocardial infarction**	**Adjusted[1] SHR 95% CI for Pulmonary Embolism**
0 Exacerbations	Ref	Ref
1 Moderate	1.08 (0.94-1.24)	1.33 (1.08-1.63)
>2 Moderate	1.57 (1.37-1.80)	1.62 (1.30-2.02)
1 Severe	1.43 (1.21-1.69)	2.14 (1.68 -2.73)
2+ Severe	1.59 (1.14-2.20)	2.89 (1.91-4.38)

1 *Adjusted for sex, age, BMI, FEV_1 % predicted, the presence of baseline cardiovascular comorbidity and cardioprotective medications, income and educational level.*

Table E6 Adjusted[1] subdistribution hazard ratios (SHRs) for myocardial infarction and pulmonary embolism depending on baseline exacerbation history, from competing risk regression analysis for 66 422 Swedish patients diagnosed with COPD, with added adjustment for sleep apnea with missing as a factor level, registered in the Swedish National Airway Register January 2014 - June 2022 and followed for up to 9 years.

Exacerbation history	**Adjusted[1] SHR 95% CI for myocardial infarction**	**Adjusted[1] SHR 95% CI for Pulmonary Embolism**
0 Exacerbations	Ref	Ref
1 Moderate	1.11 (0.98-1.27)	1.24 (1.02-1.51)
>2 Moderate	1.60 (1.41-1.83)	1.64 (1.33-2.02)
1 Severe	1.45 (1.23-1.70)	2.05 (1.62-2.58)
2+ Severe	1.64 (1.19-2.27)	2.84 (1.90-4.25)

1 *Adjusted for sex, age, BMI, smoking status, FEV1 % predicted, the presence of baseline cardiovascular comorbidity, cardioprotective medications and sleep apnea*

Supplementary

LIST OF ATC CODES FOR INHALER THERAPY

Table E1: Drug therapy classes and ATC codes for respiratory inhaler therapy used in this study from the Swedish Prescribed Drug Register.

Drug therapy class	ATC codes for respiratory inhaler therapy
SABA and/or SAMA	• R03AC02, Salbutamol • R02AC03, Terbutalin • R03BB01, Ipratropiumbromid • R03AL02, Salbutamol and ipratropiumbromid
LAMA	• R03BB01, Ipratropiumbromid • R03BB04, Tiotropiumbromid • R03BB05, Aclidiniumbromid • R03BB06, Glycopyrroniumbromid • R03BB07, Umeclidiniumbromid
LABA	• R03AC12, Salmeterol • R03AC13, Formoterol • R03AC18, Indacaterol • R03AC19, Olodaterol
ICS	• R03BA01, Beclometason • R03BA02, Budesonide • R03BA04, Betametason • R03BA05, Fluticason • R03BA07, Mometason • R03BA08, Ciklesonid
LABA/LAMA	• R03AL03, Vilanterol and Umeclidiniumbromid • R03AL04, Indacaterol and Glycopyrroniumbromid • R03AL05, Formoterol and Aclidiniumbromid • R03AL06, Olodaterol and Tiotropiumbromid • R03AL07, Formoterol and Glycopyrroniumbromid • R03AL10, Formoterol and Tiotropium
LABA/ICS	• R03AK06, Salmeterol and Fluticason • R03AK07, Formoterol and Budesonid • R03AK08, Formoterol and Beclometason • R03AK09, Formoterol and Mometason • R03AK10, Vilanterol and Fluticasonfuroat • R03AK11, Formoterol and Fluticason • R03AK12, Salmeterol and Budesonid • R03AK13, Salmeterol and Budesonid • R03AK14, Indakaterol and Mometason
LABA/LAMA/ICS	• R03AL08, Vilanterol, umeklidiniumbromid and flutikasonfuroat • R03AL09, Formoterol, Glycopyrroniumbromid and Beclometason • R03AL11, Formoterol, Glykopyrroniumbromid, Budesonide • R03AL12, Indakaterol, Glukopyrronium, Mometason

Table E2: Drug therapy classes and ATC codes for cardioprotective medications used in this study from the Swedish Prescribed Drug Register.

Drug therapy class	**ATC code groups**
Anticoagulation	B01
Anti-arrhythmic	C01
Diuretics	C03
Betablocker	C07
Calcium channel-blocker	C08
ACE/ARB	C09
Statin	C10
Diabetes	A10
Any cardiac drug	B01 C01 C02 C03 C07 C08 C09
Any Metabolic drug	C10 A10
Any Cardiometabolic drug	B01 C01 C02 C03 C07 C08 C09 A10

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