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Heightened long-term cardiovascular risks after exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

Objective To examine the risk of adverse cardiovascular (CV) events following an exacerbation of chronic obstructive pulmonary disease (COPD).

Methods This retrospective cohort study identified patients with COPD using administrative data from Alberta, Canada from 2014 to 2019. Exposure periods were 12 months following moderate or severe exacerbations; the reference period was time preceding a first exacerbation. The primary outcome was the composite of all-cause death or a first hospitalisation for acute coronary syndrome, heart failure (HF), arrhythmia or cerebral ischaemia. Time-dependent Cox regression models estimated covariate-adjusted risks associated with six exposure subperiods following exacerbation.

Results Among 1 42 787 patients (mean age 68.1 years and 51.7% men) 61 981 (43.4%) experienced at least one exacerbation and 34 068 (23.9%) died during median follow-up of 64 months. The primary outcome occurred in 43 564 (30.5%) patients with an incidence rate prior to exacerbation of 5.43 (95% CI 5.36 to 5.50) per 100 person-years. This increased to 95.61 per 100 person-years in the 1–7 days postexacerbation (adjusted HR 15.86, 95% CI 15.17 to 16.58) and remained increased for up to 1 year. The risk of both the composite and individual CV events was increased following either a moderate or a severe exacerbation, though greater and more prolonged following severe exacerbation. The highest magnitude of increased risk was observed for HF decompensation (1–7 days, HR 72.34, 95% CI 64.43 to 81.22).

Conclusion Moderate and severe COPD exacerbations are independent risk factors for adverse CV events, especially HF decompensation. The impact of optimising COPD management on CV outcomes should be evaluated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ People living with chronic obstructive pulmonary disease (COPD) experience higher risks of severe cardiovascular (CV) events in periods of time following an exacerbation of the disease compared with periods outside exacerbations.

WHAT THIS STUDY ADDS

⇒ In this population-based cohort study, the risk of the primary composite endpoint was increased 16 fold in the week following an exacerbation (adjusted HR 15.86, 95% CI 15.17 to 16.58). The risk of hospitalisation was increased for all CV events of interest (acute coronary syndrome, heart failure decompensation, arrhythmias or ischaemic stroke).The highest increase in risk was observed for heart failure decompensation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Exacerbations of COPD are independent and modifiable risk factors for severe CV events. The impact of optimising COPD management on CV outcomes should be evaluated.

INTRODUCTION

Cardiovascular (CV) risk factors and diseases are common in patients with chronic obstructive pulmonary disease (COPD).[1] CV mortality accounts for approximately one-third of deaths in patients with COPD, particularly in those with mild or moderate (as opposed to severe) disease severity.[2] Of the cardiac comorbidities in COPD, heart failure (HF) and arrhythmias are frequent, coexisting in up to 42% and 21% of people living with COPD, respectively.[3] There is growing evidence that exacerbations of COPD present a vulnerable, high-risk cardiac state.[4] Compared with non-exacerbating periods, periods during and following exacerbations are associated with an increased risk of adverse CV events, notably myocardial infarction (MI), stroke and CV death.[5–11] These risks are elevated following both severe and to a lesser extent moderate exacerbations and decline over time[9 10] However, how long the risk of each CV event persists is uncertain given the variable, often truncated follow-up times used across studies.[9 10 12 13] Moreover, previous studies focused on MI and stroke,[5–10 14] while only three reported risks of HF and arrhythmia measured within composite endpoints.[6 7 11]

The risk of CV events in relation to exacerbation history is also uncertain. Some studies have suggested higher,[10] similar[11 14] or even lower[9] risk of a CV event following an exacerbation in frequent versus infrequent exacerbators. Additionally, many studies used data from clinical trials[6 8 11] or a self-controlled design,[7 9 10] thereby selecting individuals

with more severe COPD. To our knowledge, no previous study examined the risk of different CV events in patients including those newly diagnosed with COPD. Altogether, the relationship between exacerbation severity and a broader range of CV outcomes is unknown in a general population with extended follow-up. Our study objectives were first, to better understand the association between the time following an exacerbation and risk of hospitalisation for acute coronary syndrome (ACS), HF decompensation, arrhythmias, cerebral ischaemia and all-cause mortality, both as a composite outcome and individually; second, to assess the risks following a moderate or severe exacerbation; and third, to assess the risks by cumulative number of exacerbations among newly diagnosed individuals.

METHODS

This observational retrospective cohort study is a part of the multi-country EXAcerbations of COPD and their OutcomeS on CardioVascular disease (EXACOS-CV) Programme; the general protocol has been published previously.[15] The STrengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist was used in writing this report.[16]

Study setting and cohort selection

The study cohort was retrieved from Alberta Health's COPD chronic disease cohort,[17] which contained sociodemographic and medical information on individuals living with COPD from multiple health administrative databases (online supplemental table S1). The cohort selection period was 1 April 2014 to 31 March 2019. Individuals with a COPD diagnosis in the outpatient or inpatient setting (online supplemental table S2) before this period were considered as prevalent and assigned a cohort entry date of 1 April 2014. Individuals diagnosed after 1 April 2014 were considered newly diagnosed (incident) and assigned the date when they first met the COPD diagnosis algorithm (online supplemental table S2) as a cohort entry date. For inclusion in the study, individuals were required to be ≥40 years old at cohort entry, residents of Alberta in the fiscal year containing the cohort entry date, have data available for at least 24 months pre-cohort entry and have no diagnosis of COPD related to alpha-1 antitrypsin deficiency. Study follow-up started at cohort entry and ended at (1) the first occurrence of the outcome of interest or (2) censoring (loss to follow-up due to moving out of Alberta, or administrative censoring on 31 March 2020).

Time-dependent exposure periods

During study follow-up, the exposure of interest was an exacerbation of COPD. All exacerbations that occurred after cohort entry were measured, thus allowing individuals to be exposed more than once. Moderate exacerbations were defined as an outpatient visit (general/family practice, respiratory medicine, cardiology, internal medicine) with a diagnosis code for COPD and a dispense of oral corticosteroids (20–60 mg prednisolone-equivalent per day) or an antibiotic for respiratory infection within 5 days of the visit (before or after) and for <15 days (medications code in online supplemental table S3). Severe exacerbations were defined as an emergency department visit with a COPD diagnosis (any position) or a hospitalisation with a 'most-responsible diagnosis' (reason for admission) code or post-admission diagnosis (complication occurring during the hospital stay) for COPD.

The exposed periods started on occurrence of each exacerbation and ended at the earliest of the event of the outcome of interest, another exacerbation or censoring. Because the risk of a first CV event was not expected to be constant over time, the exposed time periods following the onset of each exacerbation were divided *a priori* into six subperiods of 1–7, 8–14, 15–30, 31–180, 181–365 and >365 days (online supplemental figure S1). The unexposed (reference) period was defined as the time elapsed from cohort entry to a first exacerbation, or to the end of follow-up in the absence thereof.

Outcomes

Outcomes of interest were a hospitalisation of at least one night for ACS, HF decompensation, a new diagnosis of arrhythmia, or cerebral ischaemia and all-cause death. If a hospitalisation for CV events ended in mortality, the outcome was counted as death. Previously published algorithms based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) diagnosis codes were used to identify non-fatal CV outcomes (online supplemental table S4). In turn, several endpoints were considered: (1) time to a first non-fatal CV event or death (composite outcome) and (2) time to each individual non-fatal CV event or death, in order to not overestimate the incidence of events more likely to occur first (e.g., an ACS may be more likely to occur prior to a decompensation of HF).

Data analysis

Baseline characteristics of patients were summarised using means, SD and frequency distributions. The first of each outcome of interest and causes of death were summarised using frequency and percent distributions. Crude incidence rates of the composite and individual outcomes during the unexposed and exposed subperiods were expressed per 100 person-years of follow-up; 95% CIs were calculated using the exact Poisson method.

Time-dependent Cox regression models allowing for repeated exposure were used to compare the risk of outcome in the periods following an exacerbation against the reference period. Several models were fitted to estimate first the risk of the composite outcome in time following (1) an exacerbation of any severity and (2) a moderate or a severe exacerbation counted separately; and second, the risk of each individual outcome following an exacerbation of any severity. In these latter analyses, competing non-fatal events were handled as time-varying confounders and death was a censoring event. In a last model using the subpopulation of incident patients, the exposed subperiods were categorised as a first, a second or a third+exacerbation. No multiple-testing correction was applied. All models were fitted with and without adjustment for pre-specified confounders selected *a priori* based on the literature and clinical expertise (online supplemental table S5). Those included time-invariant covariates (sex, comorbidities, cohort entry year, urban/rural residence and neighbourhood income quintile) and time-varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations, winter season and time-varying age). Missing codes for a given comorbidity or healthcare event were not measurable or imputable and assumed to represent non-existent events. Statistical analyses were conducted using SAS software V.9.4 (SAS Institute, Cary, North Carolina).

Patient and public involvement

Although no patient was involved in the protocol development, pulmonologists and cardiologists were involved in the design and conduct of the study to reflect the clinical practice and maximise the relevance of this research to patients.

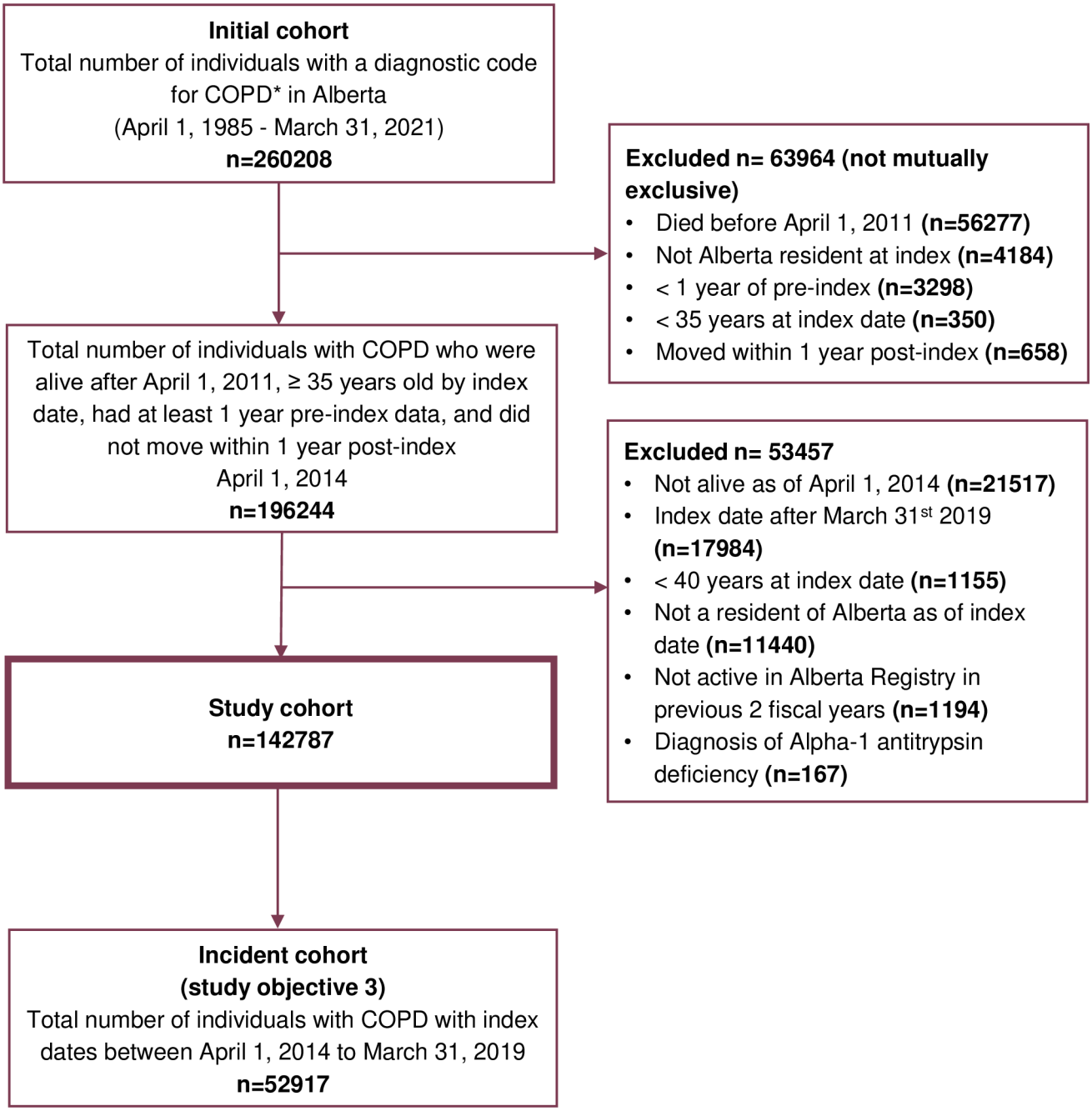

Figure 1 Flow diagram of study cohort, Alberta, Canada. COPD, chronic obstructive pulmonary disease. *An International Classification of Diseases 10th Revision (ICD-10-CA) diagnosis code for COPD (J41–J44) in any position in the Discharge Abstract Database (DAD) when discharge date was the diagnosis date or ≥2 ICD-9-CM diagnosis codes for COPD (491, 492, 496) in the primary position within a 2-year period in the Physician Claims dataset, when the second visit was the diagnosis date.

RESULTS

A total of 142 787 individuals were included in the cohort (figure 1) with baseline characteristics detailed in table 1. During a median follow-up time of 64 months (IQR, 35–72), 61 981 (43.4%) patients experienced at least one exacerbation of any severity. Overall, nearly one-quarter (n=34 068, 23.9%) of patients died with almost one-third (n=10 132, 29.7%) of those deaths being cardiac related (table 2). Crude incidence rates of outcomes are in online supplemental table S6.

The risk of the composite outcome was increased following the onset of an exacerbation of any severity (figure 2 and online supplemental table S6). The primary outcome occurred in 43 564 (30.5%) patients with an incidence rate prior to exacerbation of 5.43 (95%CI 5.36 to 5.50) per 100 person-years. This increased to 95.61 per 100 person-years in the 1–7 days post-exacerbation (adjusted HR 15.86, 95% CI 15.17 to 16.58). The risk declined over time but remained significant beyond 1-year post-exacerbation onset (incidence rate 7.35, 95% CI 7.16 to 7.55, HR 1.08, 95% CI 1.05 to 1.12). The risk of the composite outcome was increased following either a moderate or a severe exacerbation, however, with a greater and more prolonged association following a severe exacerbation (figure 3 and online supplemental table S7).

Table 1 Baseline characteristics of patients included in the cohort, Alberta, Canada

	All patients, N=1 42 787
Mean (SD) age in years at cohort entry	68.1 (12.3)
Male sex, n (%)	73 777 (51.7)
Residence, n (%)	
Urban (Calgary, Edmonton)	88 115 (61.7)
Rural (Central, North, South)	54 672 (38.3)
Neighbourhood income quintile, n (%)	
First (highest)	17 627 (12.3)
Second	24 252 (17.0)
Third	20 400 (14.3)
Fourth	38 131 (26.7)
Fifth (lowest)	42 377 (29.7)
Newly diagnosed patients, n (%)	52 917 (37.1)
Number of exacerbation in the past 12 months pre-cohort entry, n (%)	
0	116 850 (81.8)
1	20 747 (14.5)
2+	5190 (3.6)
Cardiovascular risk factors n (%)*	
Diabetes mellitus type 2	27 527 (19.3)
Dyslipidaemia†	31 346 (22.0)
Hypertensive diseases	66 462 (46.5)
Comorbidities, n (%)*	
Ischaemic heart diseases	36 386 (25.5)
Heart failure	18 649 (13.1)
Cardiomyopathy	4152 (2.9)
Pulmonary oedema	1654 (1.2)
Pulmonary hypertension	3505 (2.5)
Venous thromboembolism	14 741 (10.3)
Atrial fibrillation and other arrhythmias	22 126 (15.5)
Cerebrovascular disease	13 276 (9.3)
Current (adult) asthma	6093 (4.3)
Chronic kidney disease, renal failure	15 184 (10.6)
Severe mental illness‡	8908 (6.2)
Anxiety disorder	23 163 (16.2)
Mean (SD) number of general practitioner visits, past 12 months pre-cohort entry	12.4 (15.5)
Medication dispenses, past 12 months pre-cohort entry, n (%)§ ¶	
Cardiac medication	87 153 (61.0)
Metabolic medication	62 193 (43.6)
Long-acting inhaled COPD drug as a single therapy or combination therapy	67 262 (47.1)
Long-acting inhaled COPD drug as single therapy	44 834 (31.4)
Long-acting inhaled COPD drug as combination therapy	47 673 (33.4)
Short-acting inhaler	52 867 (37.0)
Roflumilast and/or theophylline	1241 (0.9)

*Comorbidities were based on all available lookback data except for current (adult) asthma and anxiety disorder, which were based on 24 month lookback data.
†Dyslipidaemia included hyperlipidaemia, hypercholesterolemia, dyslipidaemia.
‡Severe mental illness included recurrent and persistent depressive disorders, bipolar disorder, and schizophrenia.
§Medication dispense was defined as at least one dispensation during the 12 months pre-index.
¶Codes used to identify the medications of interest are in online supplemental table S3.
COPD, chronic obstructive pulmonary disease; CV, cardiovascular; n, sample size.

Table 2 Proportion of patients with an outcome of interest during study follow-up

	Patients with at least one CV event or death N=1 42 787
	n (%)
At least one outcome of interest, composite measure	43 564 (30.5)
Type of CV event or death	
Hospitalisation for acute coronary syndrome*	5622 (3.9)
Acute myocardial infarction	4894 (3.4)
Unstable angina	943 (0.7)
Hospitalisation for heart failure decompensation*	4485 (3.1)
(Congestive) heart failure	4201 (2.9)
Acute pulmonary oedema	321 (0.2)
Hospitalisation for cerebral ischaemia*	3480 (2.4)
Cerebral infarction	2640 (1.8)
Transient ischaemic attack (transient cerebral ischaemic attacks and related syndromes)	941 (0.7)
Hospitalisation with a new diagnosis of arrhythmia*†	3254 (2.3)
Atrial fibrillation and flutter	2538 (1.8)
Other cardiac arrhythmias	539 (0.4)
Cardiac arrest	283 (0.2)
Death during study follow-up*	34 068 (23.9)
COPD-related death‡	4973 (3.5)
CV-related death§	10 132 (7.1)
Multiple cause (COPD and CV) death	81 (0.1)
Death due to other or unknown causes	18 882 (13.2)

*Patients with a first CV event of each type or death are counted; the sum of percentages for each type of event (or death) is greater than 100% due to some patients experiencing several types of outcomes.
†New diagnosis of atrial fibrillation defined as the absence of code I48 or I49 in the medical history of the patient prior to cohort entry date.
‡COPD-related death was defined using reason codes or diagnosis codes of J41, J42, J43 or J44 from Vital Statistics or the Discharge Abstract Database (DAD).
§CV-related death was defined using International Classification of Diseases 10th Revision (ICD-10-CA) codes of I00-I99 from Vital Statistics or the Discharge Abstract Database (DAD).
COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

The risks of all individual types of severe CV events increased significantly following the onset of an exacerbation of any severity (figure 4 and online supplemental table S6), with the greatest risk in the earlier periods. For all types of severe CV events, the increase in risk persisted for the entire year following an exacerbation. After 1 year, the associations remained significantly elevated only for ACS and all-cause death. During the first 6 months following an exacerbation, the adverse risk was particularly elevated for HF decompensation relative to the other CV outcomes. The incidence rate for HF decompensation prior to a first exacerbation was 0.56 (95% CI 0.53 to 0.58) per 100 person-years. This increased to 21.45 (95% CI 20.07 to 22.90) in the 1 to 7-day period (adjusted HR 72.34 (95% CI 64.43 to 81.22)) and remained significantly elevated at 31 to 180 days (incidence rate 0.68 (95% CI 0.61 to 0.76), adjusted HR 2.25 (95% CI 1.96 to 2.59)).

The increased risk of ACS, arrythmias and cerebral ischaemia were of comparable magnitude except during the very early exacerbation period (1–7 days post onset).

In the incident cohort, the risk of the composite outcome was significantly increased after a first, a second or a third+exacerbation with similar magnitude of associations (figure 5 and online supplemental table S8).

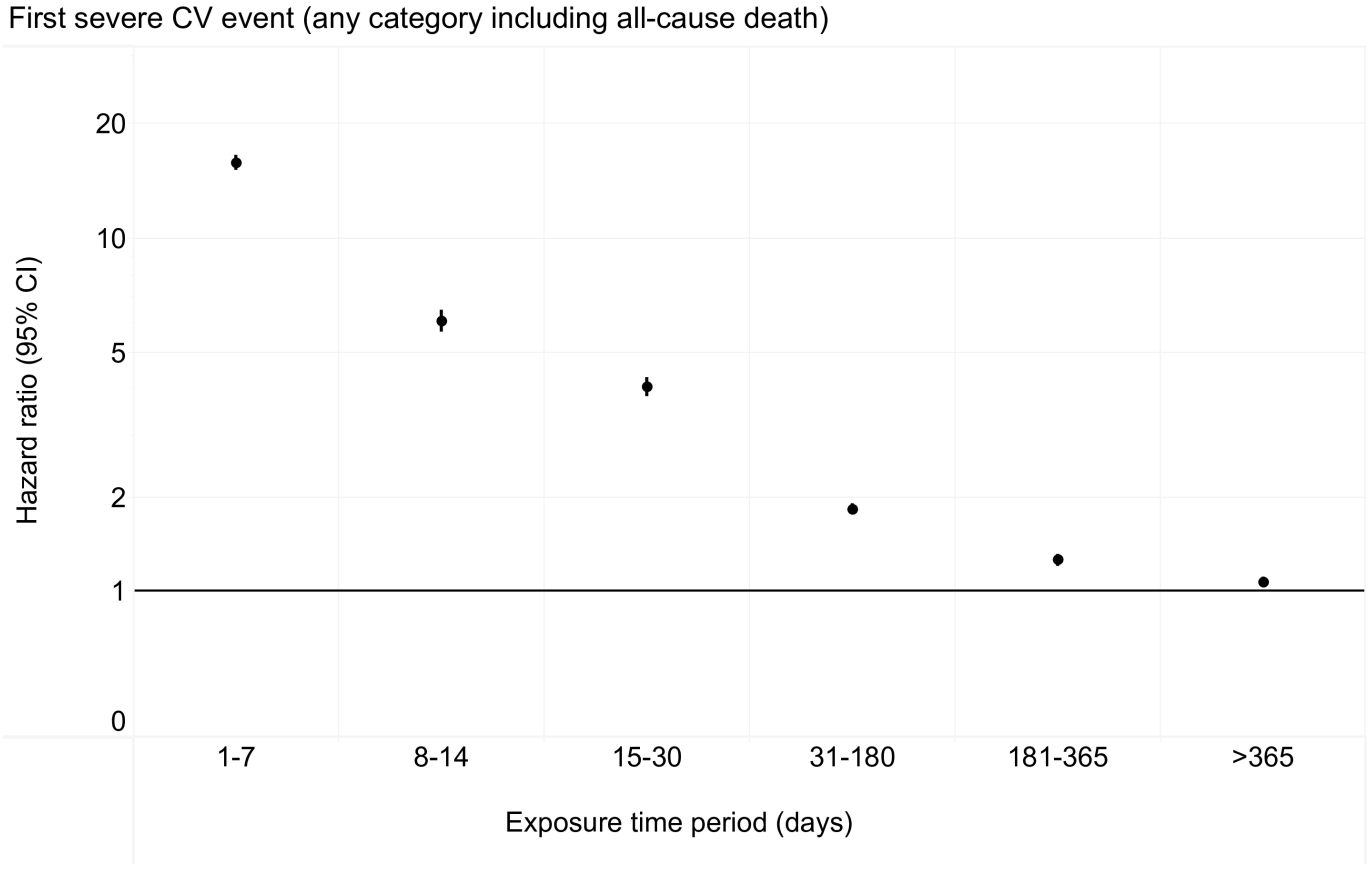

Figure 2 Risk of a first cardiovascular event or all-cause death following an exacerbation of any severity; covariate-adjusted hazard ratios from fitted Cox model with 95% CIs. Note: Fully adjusted models included sex, comorbidities, year of index, residence at index, neighbourhood income quintile and time varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits and number of exacerbations in last 12 months, winter season and time-varying age). Note: Reference category was the unexposed period. COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

DISCUSSION

Key findings

In this population-based cohort study of nearly 143 000 individuals living with COPD in Canada, exacerbations of COPD were associated with an increased risk for all-cause death and hospitalisation for ACS, HF decompensation, arrhythmia and cerebral ischaemia. Among these four major CV outcomes, the risk was greatest for HF and arrhythmias, which are the outcomes least studied to date. Although the risk declined over time, it persisted up to 1 year for all the outcomes, and beyond 1 year for ACS and all-cause mortality. Similar to prior studies, the risk was markedly increased in both magnitude and duration following severe exacerbations,[9–11] but even moderate exacerbations were significantly associated with adverse CV outcomes. CV events were common, as nearly half (43%) of patients exacerbated at least once during an average follow-up of 5 years.

Only two prior studies have examined HF and arrhythmia as individual outcomes in relation to exacerbations. In the Understanding potential long-term impacts on function with tiotropium (UPLIFT) trial,[6] incidence rate ratios up to 180 days after an exacerbation (vs before) were notably higher for HF than for MI and stroke, supporting our findings. By contrast, in a self-controlled case series using Medicare administrative data, the magnitude of risk was comparable for HF, arrhythmias and MI.[7] In UPLIFT, only moderate exacerbations served as exposure, while the US study included only patients with one single severe exacerbation, excluding frequent exacerbators. We extend these findings by evaluating both short-term and long-term risk of CV outcomes following both moderate and severe exacerbation events in a broad and generalisable population. The risk of HF and arrhythmia was markedly elevated in the initial 7 days (HRs 72.3 and 31.2, respectively) but was also very high at 8–14 days (HR 9.6 for HF).

There are several plausible explanations for the increased risk of HF decompensation following an exacerbation of COPD. Airway infection and inflammation can directly inhibit myocardial contraction, while hypoxia increases pulmonary artery pressure and right heart strain.[18 19] Concurrently, dynamic hyperinflation and increased thoracic pressure may compromise ventricular filling, leading to diastolic dysfunction and potentially HF decompensation in the short and longer-term.[20] Regarding cardiac arrhythmias, the biventricular impairment of preload, afterload and contractility not only reduces cardiac output but also increases atrial strain. Hypercapnia, acidosis and sympathetic activation increase automaticity and exacerbate these atrial haemodynamic effects to precipitate atrial fibrillation. Drug prescribing patterns may further compound these pathophysiological disturbances. For instance, beta-blockers may be discontinued following an exacerbation of COPD due to unfounded concerns regarding respiratory side effects.[21 22]

The considerable elevation in the risk of HF decompensation during the exacerbating period (1–7 days) may be partially explained by misclassification where HF decompensation is initially misdiagnosed as an exacerbation before the correct

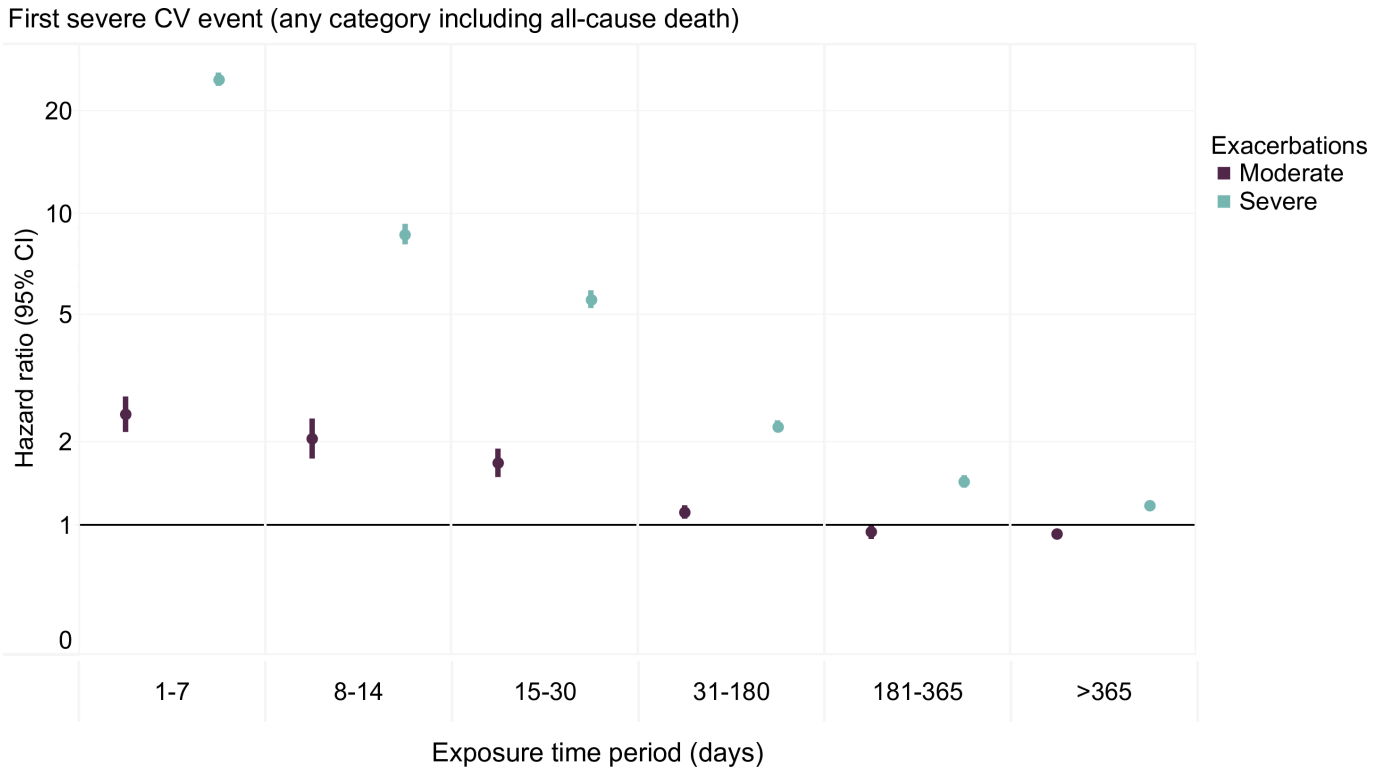

Figure 3 Risk of a first severe cardiovascular event or all-cause death following a severe, or a moderate exacerbation of COPD; covariate-adjusted hazard ratios from fitted Cox model with 95% CIs. Note: Fully adjusted model included sex, comorbidities, year of index, residence at index, neighbourhood income quintile and time-varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age). Note: Reference category was the unexposed period. COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

diagnosis is made, because symptoms, signs and radiological findings overlap.[23] Airflow obstruction is common in decompensated HF due to interstitial and alveolar oedema compressing airways along with bronchial hyper-responsiveness. In a multinational study, only one-third of patients with COPD had HF correctly identified in the emergency department.[24] In clinical practice, a diagnostic algorithm combining, for example, natriuretic peptides and cardiac imaging is essential to confirm or refute concurrent HF in patients with suspected exacerbations.[25] However, misclassification would not explain our observed longer term increased risk of HF.

The association of atherosclerotic events with both moderate and severe exacerbations has been recognised for durations ranging from 30 days to 1 year.[5–9] However, previous analyses have been restricted to severe patients included in clinical trials[6 8 11] or using self-controlled design studies.[7 9 10] We extend these findings to a large, contemporary, population-based cohort with more granular division of the early exacerbation period and longer follow-up. Similar to HF and arrhythmia, the risk was more than five-fold higher in the first 7 days compared with days 8–14. Moreover, the increased risk of ACS and all-cause death persisted beyond 1 year. The early increased risk for any CV event, particularly after severe as opposed to moderate exacerbations, likely in part reflects access to diagnostics while hospitalised or attending the emergency department (e.g., troponin, natriuretic peptide, imaging).

Acute atherosclerotic events are likely precipitated by 'spillover' of pulmonary inflammation into the systemic circulation.[26] Inflammatory cytokines such as tumour necrosis factor-α and interleukins 1, 6 and 8 promote vascular endothelial dysfunction, leucocyte and macrophage signalling, C reactive protein and complement activation and rupture of susceptible plaques. In parallel, mediators increase fibrinogen levels, platelet activation and impair fibrinolysis. The resulting hypercoagulability leads to both thrombosis at endothelial injury and increased thromboembolic risk, particularly in patients with atrial fibrillation, highlighting the complex interplay between those mechanisms.[27] The persistent, although small, long-term elevated risk beyond 1 year may suggest an acceleration of atherosclerosis, although unadjusted confounding may contribute.

Another important finding of our study is the increased risk of severe CV events and all-cause death following even a first post-diagnosis exacerbation. Exacerbation history has become a focus of attention since triple compared with dual inhaled therapy reduced the secondary endpoint of all-cause mortality in the IMPACT[11] and ETHOS trials,[28] whose inclusion criteria required exacerbations in addition to airflow limitation.[11] Five studies have assessed CV risk—mainly MI and stroke—in patients categorised by number of exacerbations or dichotomised as <2 versus ≥2 exacerbations ('frequent exacerbators') in the preceding year.[9–11 13 14] The associated risk was found higher,[10 13] similar[11 14] or lower[9] in frequent compared with infrequent exacerbators. Our study further explored the effect of exacerbation history as a cumulative exposure (first, second or third exacerbation) in a broader range of CV outcomes with more granular post-exacerbation time periods. Our results do not suggest incremental risk in frequent exacerbators, highlighting the impact of exacerbation beyond the lungs even at an early stage of disease management.

Strength and limitations

The large population-based administrative health datasets included comprehensive data on hospital, ambulatory and pharmacy-level claims from all hospitals and outpatient settings in Alberta. This minimised missing information on exposure and outcome, enabled

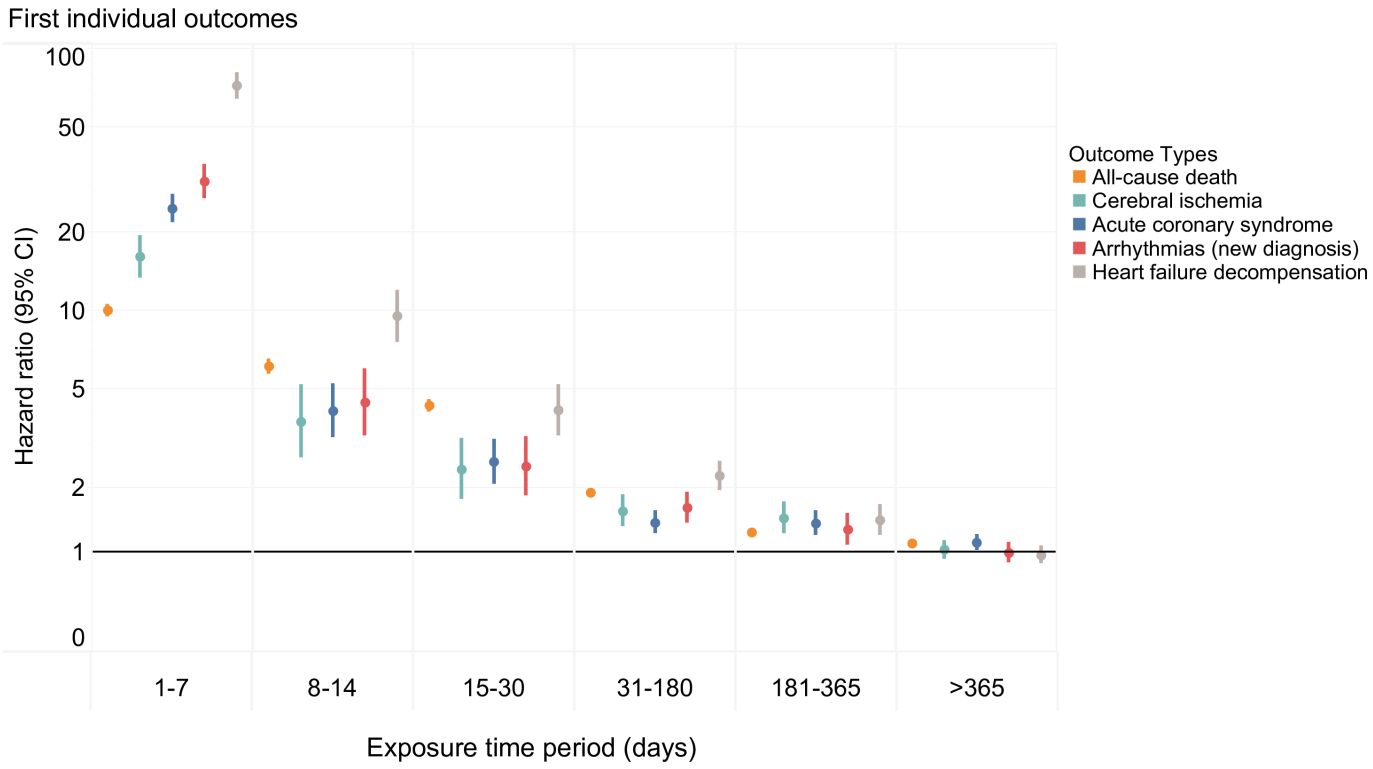

Figure 4 Risk of a first severe cardiovascular event or all-cause death (individual endpoints) following an exacerbation of any severity; covariate-adjusted hazard ratios from fitted Cox model with 95% CIs. Note: Fully adjusted model included sex, comorbidities, year of index, residence at index, neighbourhood income quintile and time varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age). Note: Reference category was the time prior to the earliest of (1) a first exacerbation or (2) end of follow-up due to experiencing the outcome or right censoring. COPD, chronic obstructive pulmonary disease.

risk estimation over a long period and the differentiation between incident and prevalent patients. Compared with clinical trial data, our results are more generalisable to a broader population of real-world patients living with COPD with varying disease severity and comorbidities. Our multivariable models accounted for time-varying patient characteristics and exposure status. However, the accuracy and reporting of medical codes in claims databases can vary, due to, for example, diagnosis errors with misclassification of exposure and outcome. Unfortunately, behavioural risk factors such as smoking, diet, alcohol consumption, and body weight are not captured in the database. Unmeasured confounding may result in overestimating the strength of association.

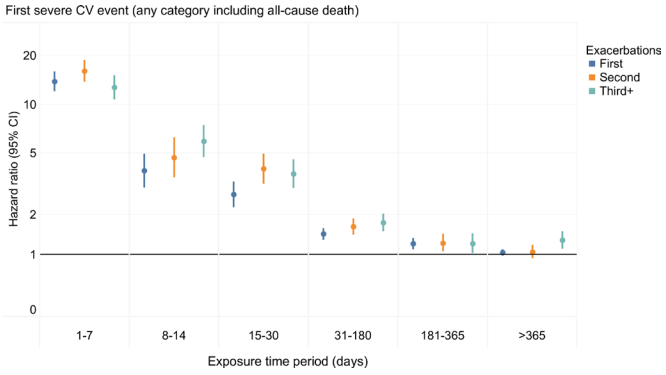

Figure 5 Risk of a first severe cardiovascular event or all-cause death following a first, or a second, or a third exacerbation of any severity in the incident cohort (N=52 917); covariate-adjusted hazard ratios from fitted Cox model with 95% CIs. Note: Fully adjusted model included sex, comorbidities, year of index, residence at index, neighbourhood income quintile and time-varying covariates (cardiac/metabolic agents, COPD medication use, general practitioner visits, number of exacerbations in last 12 months, season and time-varying age). Note: Reference period was the time prior to the earliest of (1) a first exacerbation or (2) end of follow-up due to experiencing the outcome or right censoring. COPD, chronic obstructive pulmonary disease; CV, cardiovascular.

Clinical implication

Our real-world findings of elevated risk for a broad range of cardiac events and all-cause death, persisting for 1 year or more, including first and subsequent exacerbations, emphasise the burden of cardiopulmonary risk in patients living with COPD. Patients who experience exacerbations are treated across diverse medical specialities including primary care, respirology, cardiology and internal medicine. All healthcare professionals managing patients with COPD should optimise strategies to prevent exacerbations and mitigate this heighted CV risk, which includes minimising exposure to potential triggers (e.g., clean air strategies, smoking cessation and vaccination), self-management, inhaled maintenance therapies, along with CV risk factor screening and treatment.[29 30] In addition, the GOLD guidelines recommend cardiologists become familiar with the pharmacological therapies for COPD to initiate therapy in the absence of a pulmonary specialist, for example, at diagnosis.[31] Once exacerbations occur, therapies and risk stratification for both cardiac and pulmonary disease should be revisited and intensified. Multidisciplinary team-based approaches are needed to address the complex interaction

between lung and cardiac dysfunction. Together, these findings can help healthcare professionals identify patients at risk of CV events or death, to initiate timely preventive care and monitoring, reduce the risk of first and future exacerbations and improve patient outcomes.

Contributors This study is based in part by data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions are those of the researchers and do not represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health express any opinion in relation to this study. NMH and DDS were involved in the study design, interpretation, and writing of the manuscript. SM and PE accept full responsibility, as guarantors, for the conduct of the study, had access to the data, and controlled the decision to publish. SM and PE were involved in the study design, acquisition of data, analysis, interpretation, and writing of the manuscript. TP was involved in the study design, acquisition of data, interpretation, and writing of the manuscript. KR and AKR contributed to the conceptualisation, study design, analysis plan, results interpretation and writing of the manuscript. All authors provided their approval of the final version to be published. The authors wish to thank Professor Edeltraut Garbe for her guidance in the methodology of the study. We acknowledge Heather Neilson for contributing to manuscript writing and Aaron Gelfand and Phongsack Manivong for developing the figures. The findings from this study were accepted for presentation by NMH at the European Society of Cardiology Congress in Amsterdam, Netherlands in August 2023 and by Prof Vogelmeier at the European Respiratory Society International Congress in Milan, Italy in September 2023.

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Competing interests SM, PE and TP are employed by Medlior Health Outcomes Research Ltd. which received funding for the study from AstraZeneca UK. NMH participated on advisory boards for Bayer, BI, and Servier. He also received honoraria for speakers bureau from AZ, Novartis, and Servier and grants/research support from AZ and Novartis and consulting fees from AZ. DDS received honoraria for speaking engagements on the topic of COPD from AZ, GSK and BI. AKR, MT, CN, KR are the employees of AstraZeneca and may hold shares/stock options.

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

Patient consent for publication Not applicable.

Ethics approval Research Ethics Board approval was obtained from Health Research Ethics Board of Alberta–Community Health Committee (HREBA.CHC-22-0006). A waiver of consent was granted due to the population-based and retrospective nature of the study.

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