Increased risk of decompensated heart failure, acute coronary syndrome, arrhythmias and ischaemic stroke following exacerbations of COPD: results from a multi-database cohort study

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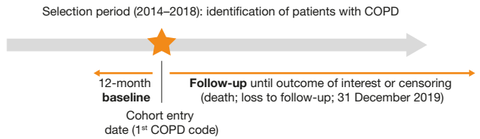
Introduction and objectives

- The risk of ACS, stroke or death is known to be increased following an exacerbation of COPD.
- However, little is known about the risk of decompensated HF or acute arrhythmias.
- Our objective was to quantify the risk of decompensated HF, ACS, acute arrhythmias and ischaemic stroke following an exacerbation of COPD.

Material and methods

- The EXACOS-CV programme is a set of observational cohort studies conducted in 10 countries including Germany, Canada, the NL and Spain.[1]
- Individuals living with COPD, <40 years old, were identified in electronic medical records and claims databases between 2014 and 2018 using validated algorithms and were followed up to the outcome of interest or censoring (**Figure 1**).

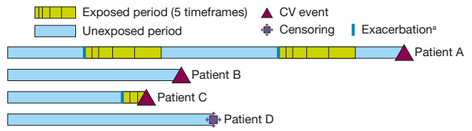
Figure 1. Study design



Exposure

- Exposure was the occurrence of an exacerbation of COPD, defined as an exacerbation managed in the outpatient setting (outpatient visit and medication adaptation) or requiring a hospitalization or emergency room visit.
- Upon the start of each exacerbation event, patients were defined as "exposed" for a maximum duration of 12 months.
- Outside of these exposed periods, patients were defined as "unexposed" (**Figure 2**). Patients could be exposed several times during the study follow-up.

Figure 2. Definition of exposure and non-exposure



[a]An exacerbation indicates the beginning of an exposure window.

Outcome

- Outcomes of interest were severe CV events, defined as a hospitalization for 1) decompensated HF, 2) ACS, 3) arrhythmias or 4) ischaemic stroke identified using (validated, where available) diagnostic codes.
- Endpoints were the time to each individual outcome of interest, explored separately, following the onset of an exacerbation of COPD.

Statistical modelling

- The 12-month exposed period was split into more granular sub-periods of time: 1–7 days, 8–14 days, 15–30 days, 31–180 days and 181–365 days.
- Time-dependent Cox regression models explored individually the risk of each endpoint following an exacerbation and were adjusted for time-invariant and time-dependent confounders.

Results

Table 1. Baseline characteristics of the study populations

	Canada N=142,787	Germany N=126,795	Spain N=24,393	The NL N=8020
Age, mean (SD)	68.1 (12.3)	66.5 (12.0)	67.9 (11.6)	65.4 (10.7)
Male, n (%)	73,777 (51.7)	76,074 (60.0)	19,085 (78.2)	4223 (52.7)
GP visits in the previous 12 months, mean (SD)	12.4 (15.5)	13.5 (14.9)	7.0 (3.5)	5.7 (7.0)
Cardiovascular risk factors and comorbid conditions[a], n (%)				
Hypertensive disease	66,462 (46.5)	95,378 (75.2)	14,576 (59.8)	3001 (37.4)
Diabetes mellitus type-2	27,527 (19.3)	39,238 (30.9)	4190 (17.2)	1076 (13.4)
Dyslipidaemia	31,346 (22.0)	71,809 (56.6)	12,263 (50.3)	1503 (18.7)
Ischaemic heart disease	36,386 (25.5)	46,341 (36.5)	4345 (17.8)	1393 (17.4)
Arrhythmias	22,126 (15.5)	35,607 (28.1)	2765 (11.3)	864 (10.8)
HF	18,649 (13.1)	35,371 (27.9)	4648 (19.1)	547 (6.8)
Cerebrovascular disease	13,276 (9.3)	29,808 (23.5)	2408 (9.9)	763 (9.5)
Pulmonary oedema	4152 (2.9)	1141 (0.9)	840 (3.4)	40 (<0.5)
Pulmonary hypertension	1654 (1.2)	6085 (4.8)	833 (3.4)	32 (<0.5)
Venous thromboembolism	3505 (2.5)	13,191 (10.4)	1833 (7.5)	310 (3.8)
Chronic kidney disease	15,184 (10.6)	26,328 (20.8)	2598 (10.7)	387 (4.8)
Medication use in the previous 12 months, n (%)				
Cardiovascular drugs[b]	87,153 (61.0)	94,112 (74.2)	22,285 (91.4)	3778 (47.1)
Metabolic drugs[c]	62,193 (43.6)	52,583 (41.5)	15,188 (62.3)	2722 (33.9)

[a]Medical conditions were explored using the entire lookback period available with a minimum of 24 months prior to cohort entry; [b]Cardiac drugs included ATC codes B01, C01-03, C07-09; [c]Metabolic drugs included ATC codes C10 and A10.

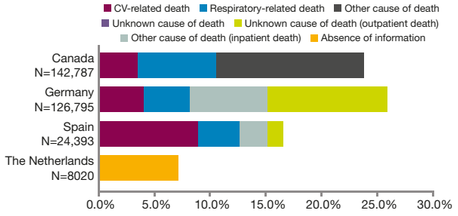
- During follow-up, between 8% of patients (NL) and 24% of patients (Spain) had at least one non-fatal CV event (**Table 2**).
- Death occurred in 26% of patients in Germany, 24% in Canada, 7% in the NL and 17% in Spain during follow-up prior to or following a non-fatal CV event (**Figure 3**).
- The risk of a non-fatal CV event was markedly increased for all four outcomes in the first 30 days and declined over time with consistent trends across countries (**Figure 4**).
- The increase in risk was the greatest for decompensated HF (**Figure 4A**).
- The risk of all four outcomes persisted out to 1-year in Canada and Spain (**Figure 4**).

Table 2. Study follow-up duration, exposure and CV outcome

	Canada N=142,787	Germany N=126,795	Spain N=24,393	The NL N=8020
Median duration of follow-up	58 months	36 months	36 months	36 months
At least one exacerbation during follow-up, n (%)	61,981 (43.4)	58,720 (46.3)	15,037 (61.6)	2234 (27.9)
At least one hospitalization for a CV event[a], n (%)	14,994 (10.5)	28,568 (22.5)	5910 (24.2)	664 (8.3)
HF decompensated	4485 (3.1)	12,779 (10.1)	2972 (12.2)	230 (2.9)
Acute coronary syndrome	5622 (3.9)	8388 (6.6)	1296 (5.3)	198 (2.5)
Cerebral ischaemia	3480 (2.4)	6447 (5.1)	653 (2.7)	163 (2.0)
New diagnosis of arrythmias	3254 (2.3)	6843 (5.4)	1847 (7.6)	177 (2.2)

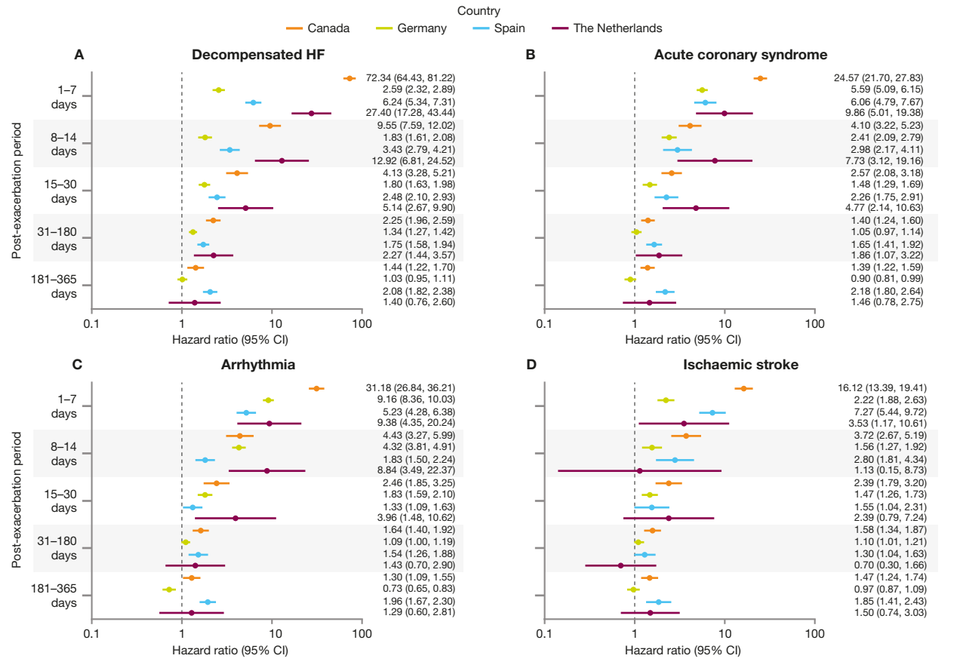
[a]The sum of each % of hospitalization is greater than the % of patients hospitalized at least once because some patients had several CV outcomes.

Figure 3. Proportion (%) of patients who died during follow-up categorized by cause of death in each country



Cause of death not available in the database used in the NL; "unknown cause" of deaths are due to death taking place outside of the hospital, or in the NL, the unavailability of cause of death in the database used; CV-related death was defined as death taking place during a hospitalization for a cardiac reason; respiratory-related death was defined as death taking place during hospitalization for a pulmonary reason.

Figure 4. Risk of a hospitalization for decompensated HF, acute coronary syndrome, arrhythmias and ischaemic stroke following the onset of an exacerbation of COPD in Canada, Germany, Spain and the NL



Take-home message

- The risk of hospitalization for HF, ACS, arrhythmias, or ischaemic stroke is substantially increased in the weeks and months following an exacerbation of COPD and may persist up to one year.
- Various pathophysiological mechanisms may explain these associations, e.g., sepsis, hypoxia, hypercoagulability, and systemic inflammation.

Implications for clinical practice

- Health-care practitioners should be aware of this heightened cardiopulmonary risk and should engage in preventative and therapeutic interventions including conducting regular risk assessments for exacerbations of COPD and CV events.
- An exacerbation of COPD should be considered as an important and preventable risk factor for cardiopulmonary events, emphasizing the need for optimized multidisciplinary management of COPD.

Abbreviations

ACS, acute coronary syndrome; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; GP, general practitioner; HF, heart failure; NL, Netherlands; SD, standard deviation.

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1. Nordon C et al. BMJ Open 2023; 13: e070022.
2. DeTora LM et al. Ann Intern Med 2022; 175: 1298–1304.

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