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Increased risk of major adverse cardiac events following the onset of acute exacerbations of COPD

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Summary at a glance

We aimed to determine whether acute COPD exacerbations may trigger major adverse cardiac events and found an almost 4-fold increased risk of myocardial infarction, stroke and cardiovascular death in the period following the exacerbation onset. The risk was particularly high for exacerbations requiring hospitalization and among the oldest individuals.

Abstract

Background and objective

Acute exacerbations in chronic obstructive pulmonary disease (COPD) may trigger major adverse cardiac events. We aimed to determine whether the risk of having major adverse cardiac events was transiently increased following the onset of an acute COPD exacerbation.

Methods

We conducted a nationwide, register-based study from 1997 to 2014 comprising individuals with an acute COPD exacerbation followed by a major adverse cardiac event (acute myocardial infarction, stroke, or cardiovascular death). Using the case-crossover design, we estimated odds ratios (OR) for the association between acute exacerbations of COPD and major adverse cardiac events as well as for single outcomes (acute myocardial infarction, stroke, and cardiovascular death), different levels of severity of exacerbations, and within patient subgroups.

Results

We identified 118,807 cases with a major adverse cardiac event preceded by an exacerbation. Overall, the risk of major adverse cardiac events increased almost 4-fold following the onset of an acute exacerbation compared to periods without exacerbations in the same individuals (OR 3.70; 95% CI 3.60-3.80). The associations were consistent for single outcomes (acute myocardial infarction, OR 3.57; cardiovascular death, OR 4.33; and stroke, OR 2.78) and particularly strong associations were demonstrated for severe exacerbations (OR 5.92) and the oldest individuals (OR 4.18).

Conclusion

The risk of major adverse cardiac events increased substantially following the onset of an acute exacerbation. This highlights that prevention of cardiac events is an important goal in the

management of COPD. Attention should be paid to detecting cardiovascular disease following acute COPD exacerbations.

Key words: COPD, acute COPD exacerbations, Myocardial Infarction, Stroke, Epidemiologic Studies

Short title: MACE following COPD exacerbations

Introduction

Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of cardiovascular diseases,[1] which are also frequent causes of death in this population.[2–5] Further, the disease trajectory is often characterized by episodes of acute exacerbations that may be serious and recurring for some COPD patients.[6] Over time, exacerbations can result in decreased lung function with lowered quality of life and increased mortality.[7,8] On a short-term basis, levels of systemic inflammatory markers such as fibrinogen and interleukin-6 elevate at the onset of acute exacerbations. These markers are potent pro-thrombotic stimuli[9,10] and may trigger cardiovascular events.[11–13] Additionally, exacerbations may trigger type-II myocardial infarctions (MIs) secondary to an imbalance in oxygen supply and demand.[14,15] Consequently, prevention of both exacerbations and comorbidities are key components in the treatment strategies for COPD.[16]

It has been investigated whether exacerbations per se trigger cardiovascular events, such as acute MI, stroke, and cardiovascular death.[17–20] An association would imply more focus on preventive cardiovascular treatment strategies for the management of exacerbations. However, it is unclear whether the association is explained by exacerbations per se or by mutual causes (e.g., smoking history), or patient characteristics (e.g., family predisposition).[17–20] We used a very large dataset based on nationwide Danish sources and employed a self-controlled, case-crossover design, thereby resolving some of the limitations caused by smoking and other potential confounders. The aim of this study was to address whether the risk of major adverse cardiac events (MACE) (i.e., acute MI, stroke, or cardiovascular death) increased in the period following the onset of an acute exacerbation in COPD.

Methods

Using Danish nationwide health registries, we performed a case-crossover study including Danish COPD exacerbators from 1997 to 2014. We investigated if the risk of MACE was increased following the onset of an acute COPD exacerbation. The case-crossover design allowed us to perform a strictly within-person comparison of each individual's exacerbation status at the time of the outcome event and at previous points in time, thereby eliminating the influence of time-invariant confounding.[21] The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board.[22] A thorough description of the Danish health registries and the case-crossover design can be found in **Appendix S1** in Supplementary Information.

Study population

By design, only individuals with COPD who had both an outcome (i.e., MACE) and were exposed (i.e., had an acute COPD exacerbation) in either the case- or control window prior to the outcome event contribute to the results of a case-crossover study (**Figure 1**).[21] Thus, we included all Danish COPD patients who were ≥50 years old, had a first-occurrence of MACE from January 1, 1997 to December 31, 2014, and had an acute COPD exacerbation within a 42-week period prior to the MACE. Thereby, our study population would contribute to the most comprehensive sensitivity analysis (see below). MACE was defined as 1) non-fatal acute MI, 2) non-fatal stroke, 3) cardiovascular death, or 4) any MACE (composite outcome of 1, 2, and 3).

Exposure definition

COPD exacerbations were defined by two events; filling a short-term course of oral corticosteroids [OCS] or having a hospital admission due to COPD. This definition is considered valid and robust in epidemiological studies [23] and has been used in other registry-based studies.[23–25]

In a case-crossover study, individuals are considered exposed on a given index- or control date if the date is covered by the assumed exposed period of an exacerbation (**Figure 1**). The duration of exacerbations (i.e., the length of the exposed period) was defined as the 4-week period starting from the date of the exacerbation onset. This was based on the assumption that recovery is reached within this time window in the majority of patients.[26] Based on the 4-week exposure period, we divided the 24-week period prior to a MACE for each case into a 4-week case window (exposure status at the time of the outcome event), a 4-week washout period, and finally, 4 x 4-week control windows (exposure status at earlier points in time).

A detailed account of the study population, exposure and outcomes, and the validity hereof is provided in **Appendix S2 and Table S1-S5** in Supplementary Information**.**

Analysis

We used conditional logistic regression to calculate odds ratios (OR) associating MACE with the onset of acute COPD exacerbations. Since the case-crossover analysis inherently controls for all time-invariant confounders[27], no further confounder adjustment was performed.

First, we evaluated the association between MACE (any MACE, acute MI, stroke, and cardiovascular death) and exacerbations (regardless of severity) and between any MACE and different severities of exacerbations. To further investigate the timing of exacerbation onsets in relation to a MACE, we performed a post-hoc analysis in which we calculated the number of exacerbations on each day prior to the MACE (Figure 2).

Next, to investigate if any subgroups of COPD exacerbators were at particularly high or low risk of MACE following acute COPD exacerbations, we restricted the analysis to individuals with different risk profiles (e.g., individuals with ischemic heart disease).

Finally, we performed several sensitivity analyses on critical definitions used in our study. First, acknowledging that the duration of an exacerbation is questionable, we performed sensitivity analyses in which we compared exacerbation status in case- and control windows of 2 and 7 weeks, respectively. Second, since exacerbations are sometimes treated with antibiotics alone, we performed sensitivity analyses in which we included the recommended first-line antibiotic in the treatment of exacerbations, i.e., amoxicillin with enzyme inhibitors. However, as we were unable to separate antibiotic prescriptions targeted at exacerbations from those targeted at other infections, we repeated the analysis including all the most frequently used antibiotics in the treatment of exacerbations. Finally, to address that the management of COPD exacerbations may have changed over time, we evaluated the association between MACE and exacerbations in equally sized sub-periods (1997-2002, 2003-2008, 2009-2014). Stata Version 14.1 (StataCorp, College Station, TX, USA) was used for all analyses.

Results

We identified 118,807 cases with a first-occurrence of a MACE from 1997 to 2014 that was preceded by an acute COPD exacerbation. Patients had a median age of 71 years and 48% were male (**Table 1**). Acute MI was the most frequently experienced outcome (53.0%, n=62,966) followed by cardiovascular death and stroke (24.8% and 22.2%, respectively).

Association between exacerbations and MACE

Overall, COPD exacerbations were associated with an increased risk of any MACE during a 4-week risk period after the onset of the exacerbation (OR 3.70; 95% CI: 3.60-3.80) (**Table 2**). When stratifying by type of MACE, we found the strongest association between exacerbations and cardiovascular death (OR 4.33; 95% CI: 4.15-4.52). The association was also clear for acute MI and stroke (OR 3.57; 95% CI: 3.43-3.71 and OR 2.78; 95% CI: 2.60-2.97, respectively) (**Table 2**). The risk of MACE was markedly higher among individuals hospitalized due to COPD exacerbations (OR 5.92; 95% CI: 5.92-6.14), compared with non-hospitalized individuals treated with oral corticosteroids (OR 2.50; 95% CI: 2.40-2.61) (**Table 3**) and individuals treated with amoxicillin with enzyme inhibitors (OR 2.08; 95% CI: 1.91-2.26) (**Supplementary Table S6**). Varying the length of the risk period to 2 and 7 weeks, as in our sensitivity analysis, the risk of MACE became slightly less pronounced when extending the risk period (**Supplementary Table S6 and S7**). This is supported by the post-hoc analysis showing that the number of exacerbations increased steadily until the MACE; though, this finding was particularly pronounced for acute MI and cardiovascular death (**Figure 2**).

Subgroup analysis

Within all subgroups, we consistently found an increased risk of MACE following the onset of any acute exacerbation (**Table 4**). Stratification by age groups revealed a 2.31-fold increase in the risk of MACE in individuals younger than 55 years. The association became increasingly pronounced in the older age groups (OR 3.34-4.18). A particularly strong association was observed among COPD patients with at least one hospitalization due to a COPD exacerbation within the 12-month period prior to the MACE (OR 5.38) (**Table 4**). Of note, this association was influenced by hospitalizations due to COPD being strongly associated with the risk of MACE. Restricting the analysis to subgroups at high risk of MACE revealed consistently high ORs (OR 2.88-3.81), though comparable to the risk among individuals without any cardiovascular antecedents (OR 3.64) (**Table 4**).

Discussion

We observed an almost 4-fold increased risk for MACE in the period following the onset of an acute COPD exacerbation compared to periods without exacerbations in the same individuals. The association was strongest for cardiovascular death; though, it was also evident for nonfatal acute MI and stroke. Individuals whose exacerbations resulted in hospitalization were at especially high risk of developing MACE. The subgroup analysis showed a strong association in the older age groups. Apart from this, we did not identify any other subgroups at a particularly high or low risk of developing MACE following the onset of acute exacerbations.

Our study has important strengths. First and foremost, the study is based on nationwide data from the general population. The Danish health care offers full tax-funded coverage of all Danish citizens, which provides a unique opportunity to investigate associations in a large-scale, real-life setting while minimizing the risk of selection bias. Second, our self-controlled study design eliminates the influence of known and unknown confounders that are stable over time. Thereby, our findings are not biased by the baseline severity of disease, genetic predispositions, and life style factors e.g., smoking history, which are shared risk factors for both COPD exacerbations and cardiovascular events.

The indication for prescribing OCS and antibiotics is not available from the Danish health registries. Despite this, we consider the risk and impact of misclassified exacerbations to be minor, mainly because the use of short-term treatment with OCS for indications other than COPD exacerbations is minimal.[23] Even if some of our exacerbations are not valid, this would most likely cause non-differential misclassification that only biases the OR towards the null value. Further, we did not have information on lung function and patient symptomatology. Thus, additional variation

in the disposition to MACE in subgroups of COPD patients with certain severities of disease cannot be ruled out.

Since COPD exacerbations of a certain severity are treated with prednisolone, it may be discussed whether our study is confounded by treatment, i.e., that the increased risk of MACE is caused by therapy with OCS rather than the exacerbation itself. An association between OCS and MACE has been discussed in several papers. However, these studies had difficulties eliminating the opposite effect, i.e., confounding by indication.[28,29] Treatment with an OCS can induce dyslipidemia, hypertension, and hyperglycemia, which plausibly affect the development of cardiovascular events in the long-term.[30] On the other hand, the acute increase in systemic inflammatory markers and the increased cardiac work load during an acute exacerbation seem plausible biological mechanisms behind an immediate increased risk. This is supported by the suggested increased risk of acute MI and stroke following respiratory tract infections.[31]

Though the case-crossover design elegantly eliminates the influence of time-invariant confounding, it does not adjust for time-dependent confounding. For example, individuals may initiate or intensify use of bronchodilators during an exacerbation.[16] Since these drugs stimulate sympathetic control and suppress the parasympathetic nervous system, their use may imply a short-term increased cardiovascular risk.[32,33] Similarly, exacerbations are often also treated with antibiotics. Though some antibiotics may increase the risk of cardiac events,[34,35] it is the site of infection more than the choice of antibiotic causing the increased risk.[36] Altogether, the influence of time-dependent confounding caused by these drugs cannot be ruled out.

The symptomatology of acute COPD exacerbations and acute MI are often difficult to distinguish. Thus, it may be argued that our results reflect reverse causation i.e., that early symptoms of an MI are misinterpreted as a COPD exacerbation and treated accordingly. As the MI diagnosis is made after initiation of treatment for a COPD exacerbation, this will produce a spurious association

between COPD and MI. Such interpretation is compatible with the remarkably short induction time observed in our study. However, COPD may also cause a discrepancy between coronary oxygen supply and demand, precipitating a so-called type 2 MI.[14] Such a mechanism would be expected to have an equally short induction time. Notably, we also found a clear association between stroke and COPD exacerbations. As strokes are rarely if ever confused with COPD exacerbations, we can conclude that our result is unlikely to be explained in its entirety by reverse causation.

To our knowledge this is the first truly population-based study that investigates the association between the timing of COPD exacerbations and MACE in a large-scale, real-life setting. Only a few previous studies have investigated this specific association.[17–20] In a nested case-control study by Huiart et al., including 371 cases with MI, the risk of first-time MI was increased 2-fold among COPD patients within 15 days after the onset of an exacerbation (defined by initiation of OCS therapy).[18] Similarly, in a study based on 3,960 COPD exacerbators from the UPLIFT study (of whom 14 had MI and 11 had stroke), the results indicated an increased risk of extra-pulmonary manifestations following exacerbations, in particular regarding cardiac events.[19] In a self-controlled case series study by Donaldson et al., including 426 patients with MI and 482 patients with stroke, the risk of MI increased 2.27-fold on days 1-5 following the onset of an exacerbation. Though the association was not consistent, this study further indicated that the risk of stroke was slightly increased in the weeks following an exacerbation.[17] Finally, a recent observational cohort study based on the SUMMIT trial, demonstrated a 3.8-fold increase in the risk of cardiovascular disease in the 30-day period following an acute COPD exacerbation. Though this study included 16,485 COPD patients, the number of cases was low; 32 COPD patients with a cardiovascular event within a 30-day period from the exacerbation onset. The risk of cardiovascular disease had returned to baseline level one year after the exacerbation. They further reported a substantially higher risk among patients hospitalized due to COPD (based on 24 cases).[20] In general, all these studies have

a relatively small number of outcomes. Since the precision of an observational study is ultimately dependent on the number of exposed outcomes, all of their estimates had wide confidence intervals. Apart from the self-controlled study by Donaldson et al., a limitation of these studies is the difficulty in eliminating confounding within individuals, such as the impact of life style, smoking status and history, and family predisposition.

Our study raises the question whether cardiovascular prevention strategies should be added to treatment recommendation for COPD. In addition, meticulous prevention of COPD exacerbations would be justified solely on the grounds of cardiovascular risk. Studies investigating the effect of cardiovascular treatment on the course of disease among COPD exacerbators are extremely scarce.[1,37] Thus, it is currently unknown how to optimize treatment and mitigate the increased risk of MACE following the onset of exacerbations.

In conclusion, the risk of major adverse cardiac events (acute MI, stroke, and cardiovascular death), increased substantially following the onset of an acute exacerbation. The association between acute COPD exacerbations and MACE highlights that the prevention of cardiac events is an important goal in the management of COPD. Attention should be paid to detecting cardiovascular disease following acute COPD exacerbations.

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Figure legends

Figure 1. Schematic presentation of the case-crossover design. The case window in the main analysis was the 4-week exposure period prior to the outcome event; while, the exposure period in the sensitivity analysis was 2 or 7 weeks. The blue lightning indicates the index date of the outcome event; the orange arrow indicates the onset of treatment for an exacerbation. The first four individuals are discordant while individuals five and six are fully concordant. Individual seven has not developed a MACE and is therefore not included in the study. Since the case-crossover study provides a within person comparison between exposure status in the case window and each of the 4 control windows, individuals who either have exacerbations in all case- and control windows or zero exacerbations in all case- and control windows, fully concordant individuals do not contribute to the analysis.

Figure 2. Overall count of exacerbations in case-, washout-, and control windows. Illustration of the overall count of exacerbations at each day in the 24-weeks preceding the outcomes: A) acute myocardial infarction, B) cardiovascular death, and C) stroke. Black and grey dots represent exacerbations in case and washout windows, whereas the black circles are exacerbations in control windows. The x-axis represents days from the index date.

Tables

Table 1. **Baseline characteristics.** Characteristics of the study population, i.e., individuals with MACE and at least one COPD exacerbation in the 42-week period prior to the MACE.

	Cases n=118,807 (%)
Male	57,368 (48.3%)
Median age, years [IQR]	71 (60-80)
Exposure by severity:	
Infrequent exacerbators [a]	104,378 (87.9%)
Frequent exacerbators [b]	14,429 (12.1%)
Severe exacerbators [c]	22,922 (19.3%)
First-occurring outcome event:	
Stroke	26,427 (22.2%)
Acute myocardial infarction	62,966 (53.0%)
Cardiovascular death	29,414 (24.8%)
Prior hospital diagnosis of:	
COPD hospitalization	47,632 (40.1%)
Obesity	5,550 (4.7%)
Diabetes	12,907 (10.9%)
Ischemic heart disease	20,112 (16.9%)
Cerebrovascular disease	11,274 (9.5%)
Peripheral vascular disease	11,332 (9.5%)
Malignant disease	17,112 (14.4%)
Prior use of (within 24 months):	
ICS	50,052 (42.1%)
LAMA	15,770 (13.3%)

LABA	26,210 (22.1%)
SABA	81,000 (68.2%)
SAMA	8,140 (6.9%)
SAMA+SABA comb	27,358 (23.0%)
LAMA+LABA comb	75 (0.1%)
LABA+ICS comb	22,455 (18.9%)
Acetylsalicylic acid	43,947 (37.0%)
Antihypertensive agents	65,112 (54.8%)
Statins	21,496 (18.1%)
Antidiabetic agents	13,769 (11.6%)

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; LAMA: long-acting muscarinic antagonists; LABA: long-acting beta-agonists, SAMA: short-acting muscarinic antagonists; SABA: short-acting beta-agonists; [a] One Exacerbation within 12 months prior to the outcome event; [b] Two or more exacerbations within 12 months prior to the outcome event; [c] At least one exacerbation requiring hospitalization within 12 months prior to the outcome event.

Table 2. Results from the main case-crossover analysis of the association between any MACE (composite outcome including acute myocardial infarction, stroke, and cardiovascular death) and exacerbations.

Outcome	Cases (n=118,807)		No. of fully concordant individuals [a]	Case-crossover estimate
	No. of exposed /unexposed case windows	No. of exposed / unexposed control windows		OR (95% CI)
Composite	12577 / 106230	17073 / 458155	80.3%	3.70 (3.60 - 3.80)
MI	5444 / 57522	7502 / 244362	83.5%	3.57 (3.43 - 3.71)
Stroke	1702 / 24725	2808 / 102900	86.0%	2.78 (2.60 - 2.97)
CV death	5431 / 23983	6763 / 110893	68.4%	4.33 (4.15 - 4.52)

MI: myocardial infarction; CV: cardiovascular; [a] Individuals who had same exposure (either exposed (0.04% of the study population) or non-exposed) in all time windows.

Table 3. Results from the main case-crossover analysis of the association between different levels of severity of exacerbations and any MACE (composite outcome including acute myocardial infarction, stroke, and cardiovascular death).

Exposure level	Cases (n=118,807)		No. of fully concordant individuals [a]	Case-crossover estimate
	No. of exposed/ unexposed case windows	No. of exposed/ unexposed control windows		OR (95% CI)
Exacerbations requiring:				
All levels				
OCS	4170 / 85593	8897 / 406178	90.6%	2.50 (2.40 - 2.61)
Hospitalization	8407 / 85593	8176 / 406178	88.3%	5.92 (5.71 - 6.14)

OCS: oral corticosteroids; [a] *Individuals who had same exposure (either exposed or non-exposed) in all time windows.*

Table 4. Results from subgroup analysis of the association between exacerbations and any MACE (composite outcome including acute myocardial infarction, stroke, and cardiovascular death).

Subgroup	Cases (n=118,807)		No. of fully concordant individuals[a]	Case-crossover design
	No. of exposed/ unexposed case windows	No. of exposed/ unexposed control windows		OR (95% CI)
Total	12577 / 106230	17073 / 458155	80.3%	3.70 (3.60 - 3.80)
Sex				
Male	6113 / 51255	8254 / 221218	80.3%	3.72 (3.58 - 3.87)
Female	6464 / 54975	8819 / 236937	80.4%	3.67 (3.54 - 3.81)
Age group, years				
<55	507 / 17889	966 / 72618	93.2%	2.31 (2.05 - 2.59)
55-69	3004 / 33290	4432 / 140744	84.0%	3.34 (3.17 - 3.53)
70-79	4949 / 28798	6641 / 128347	73.3%	3.82 (3.66 - 3.98)
80+	4117 / 26253	5034 / 116446	76.0%	4.18 (3.98 - 4.38)
Infrequent exacerbators [b]	5985 / 98393	5700 / 411812	88.9%	4.26 (4.11 - 4.42)
Frequent exacerbators [c]	6592 / 7837	11373 / 46343	18.1%	3.17 (3.05 - 3.29)
Severe exacerbators [d]	9532 / 13390	11148 / 80540	31.7%	4.78 (4.63 - 4.94)
History of:				
Ischemic heart disease	2435 / 17677	3476 / 76972	77.4%	3.54 (3.34 - 3.76)
Cerebrovascular disease	1052 / 10222	1527 / 43569	81.8%	3.36 (3.07 - 3.67)
Atrial fibrillation	1768 / 9790	2531 / 43701	71.6%	3.57 (3.33 - 3.83)
Heart failure	2675 / 11630	3649 / 53571	66.3%	3.81 (3.60 - 4.04)
Diabetes or use of antidiabetic agents	1511 / 14454	2179 / 61681	81.7%	3.41 (3.16 - 3.67)
Use of low-dose aspirin	4721 / 39226	6731 / 169057	79.4%	3.45 (3.31 - 3.60)
Use of statin	1627 / 19869	2627 / 83357	83.9%	2.88 (2.69 - 3.09)

Hypertension or use of antihypertensive agents	7585 / 60130	10837 / 260023	78.7%	3.48 (3.36 - 3.59)
No cardiovascular antecedent	10967 / 85951	15166 / 372506	78.9%	3.64 (3.53 - 3.74)
Case period				
1997-2002	5796 / 43125	7147 / 184709	85.7%	4.18 (4.01 - 4.36)
2003-2008	3664 / 34622	5120 / 145555	87.2%	3.37 (3.21 - 3.54)
2009-2014	3117 / 28483	4413 / 115764	80.7%	3.18 (3.02 - 3.36)

[a] *Individuals who had same exposure (either exposed or non-exposed) in all time windows.* [b] *Exacerbation within 12 months prior to the outcome event.* [c] *Two or more exacerbations within 12 months prior to the outcome event.* [d] *At least one exacerbation requiring hospitalization within 12 months prior to the outcome event*