STUDY PROTOCOL

Oral corticosteroid and the risk for major cardiovascular events among patients with chronic obstructive pulmonary disease, a Danish registry-based cohort study

Version 5.0

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Background:

Exacerbations in chronic obstructive pulmonary disease (COPD) are often treated with oral corticosteroid (OCS) prescribed by healthcare providers in various settings such as general practitioner, emergency rooms or outpatient clinics. The recommended dosage for such a regimen is up to 40 mg of prednisolone equivalent administered for up to 5 days[1]. Additionally, patients may possess so-called rescue home-treatment of OCS at home, enabling them to promptly initiate treatment and prevent further deterioration of lung function before consulting a medical doctor[2 3]. Current guidelines recommend the use of systemic corticosteroid in treating acute exacerbations of chronic pulmonary disease (AECOPD)[4] due to their proven efficacy in improving lung function, lowering the risk of relapse, and expediting recovery after exacerbations[5 6]. However, concerns have been raised regarding the long-term effects and potential adverse outcomes associated with prolonged or cumulative use of OCS, even short-term use has been associated with increase in rates of sepsis, venous thromboembolism and fractures[7]. Studies indicate that adverse effects exhibit a dose-response relationship with OCS exposure in the treatment of patients with asthma. Intake of OCS is associated with an increased risk of type 2 diabetes, obesity, osteoporosis, gastrointestinal bleeds, cataracts, and hypertension.[8 9] While this association is not as extensively studied in the context of COPD treatment, research reveals that prolonged exposure to OCS is an independent predictor of all-cause mortality in patients with COPD, and reducing the recommended treatment duration from 14 to 5 days has proven noninferior in terms of reexacerbation within 6 months[10 11 12]. This emphasizes the importance of carefully considering the potential risks when employing long-term treatment for patients with COPD, as the advantages of using OCS must be taken into context.

COPD itself is associated with an increased risk of cardiac events, sharing major risk factors such as age, smoking, and physical inactivity. Treatment with OCS has been linked to hypertension and hyperlipidemia, which are known risk factors for events such as acute myocardial infarction (AMI).[13] A few observational studies have explored the relationship between OCS and myocardial infarction in patients with COPD, these studies suggest a correlation between OCS dosage and cardiac risk[14 15 16].In the absence of systematic investigation within a large, well-characterized population of patients with COPD, the comparative impact of short-term oral corticosteroids versus respiratory antibiotics on major cardiovascular events (MACE) remains unclear. The current study aims to determine whether patients with COPD administered dosages of ≤250 mg OCS (short term) for AECOPD have a higher risk of MACE compared to those treated with respiratory antibiotics. By selecting respiratory antibiotics as the control group, this approach aims to mitigate bias by indication. The results of this study are important in advancing the understanding of COPD management, particularly regarding the use of OCS in patients with underlying cardiac risk factors We hypothesize that increased cumulative use of OCS is associated with an increased risk of MACE in patients with COPD compared to the use of respiratory antibiotics.

Methods:

Design
We will conduct a cohort study using nationwide registered data from the following Danish registers:

1. The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD). Established in 2008 it is a nationwide database containing information on the quality of treatment of all patients with COPD who are treated by a respiratory medicine specialist at a Danish Hospital[17]. Covariates included in the study were age, lung function assessed as forced expiratory volume in first second as percent of predicted (FEV%), BMI (body mass index) assessed as kilograms per square meter, dyspnea assessed using the Medical Research Council (MRC) Dyspnea Scale and smoking status.

2. All citizens in Denmark acquire a unique personal identification number at birth or immigration. This unique personal identification number links individual information for each resident to information on name, sex, date of birth and vital status. The data is registered in the Danish Civil Registration System.[18]

3. The Danish National Health Service Prescription Database holds information on all prescriptions dispensed by Danish pharmacies since 2004 (coded according to ATC classification), including date on dispensation, quantity dispensed, strength and formulation. All pharmacies are required by Danish legislation to provide information that ensures complete and accurate registration.[19]

4. The Danish National Patient Registry holds information on all admissions to Danish hospitals since 1977, and hospital outpatient clinic visits since 1995. Each visit is coded by physicians with one primary diagnosis and one or more secondary diagnoses, according to the International Classification of Diseases, eighth revision (ICD-8) codes until 1994 and ICD-10 thereafter.[20]

5. Danish register of death (DAR) dates to 1970 and holds information of causes of death on all deaths in Denmark. All deaths in Denmark are registered by a doctor and both the manner and cause of death is registered in DAR.[21]

Cohort
Data from the DrCOPD register will be used to form a cohort consisting of all Danish patients diagnosed with COPD, who meet the specified criteria.

Inclusion criteria are as followed:
- Specialist verified diagnosis of COPD
- Treatment in a hospital out-patient clinic
- Age >30 years

Exclusion criteria are as followed:
- Collection of prescriptions of prednisolone or prednisone 2,5, 5 or 10 mg
- Cancer within 5 years

There will be conducted analysis of interactions involving patients with previously confirmed AMI. If any interactions are proven, the groups will be stratified accordingly.

Timeline and exposure

The research duration spans from January 1st, 2010, to January 1st, 2022, during which each enrolled patient will be monitored for exposure and events.
The patients exposed to the defined parameters will be followed for the occurrences of events or death within the follow-up period.

The first prescription of OCS of at least 25 mg or respiratory antibiotics (see below) after inclusion in DrCOPD will be used as an exposure variable.

Respiratory antibiotics (defined as amoxicillin (J01CA04), amoxicillin with clavulanic acid (J01CR02), ciprofloxacin (J01MA02), doxycycline (J01AA02), azithromycin (J01FA10), roxithromycin (J01FA06), clarithromycin (J01FA09) and moxifloxacin (J01MA14)).
Comparing patients with COPD treated with OCS versus treated with respiratory antibiotics aims to prevent bias by indication in treating with OCS, and thus patients treated only with antibiotics act as the control group.
If the patient is treated with both OCS and respiratory antibiotics at index date, the patient will be considered as part of the OCS-treated group.
The index date for defining exposure is determined as the date of beginning treatment with OCS or respiratory antibiotics.
The patients will be followed for events within 20 days from collection of prescription.

Outcomes

Evaluation will include the following outcomes:

Primary:

- All MACE within 20 days following exposure registered as lethal cardiovascular events (DG45, DI20, DI21, DI22, DI23 or DI24), cardiovascular events requiring revascularization (surgery diagnosed as KFNA00. KFNA20, KFNC10-30, KFNE00, KFNG02A, KFNG05 or KFNG05A) cardiovascular events requiring admission (hospitalization diagnosed as DG45, DI20, DI21, DI22, DI23 or DI24) and cardiovascular events requiring prescriptions of ADP receptor inhibitors or nitrates.

Secondary:

- Lethal cardiac events (DI20, DI21, DI22, DI33 or DI24), cardiac events requiring revascularization (surgery diagnosed as KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02A, KFNG05 or KFNG05A), cardiac events requiring admission (hospitalization diagnosed as DI20, DI21, DI22, DI23 or DI24) and cardiac events requiring prescriptions of ADP receptor inhibitors or nitrates.

- Lethal cardiac events (DI20, DI21, DI22, DI33 or DI24).
- Cardiac events requiring revascularization (surgery diagnosed as KFNA00, KFNA20, KFNC10-30, KFNE00, KFNG02A, KFNG05 or KFNG05A).
- Cardiac events requiring admission (hospitalization diagnosed as DI20, DI21, DI22, DI23 or DI24).
- Cardiac events requiring prescriptions of ADP receptor inhibitors or nitrates.
- Cardiac arrhythmias and bundle branch blocks (DR001, DI440-7, DI450-9, DI480-9, DI490-9, DI470-9 excluding DI472E).

All secondary outcomes are considered within 20 days following exposure.

Statistics

Continuous data will be analyzed with non-parametric tests (Mann–Whitney-U-test. Categorical data were compared by using Chi-square or Fischer's exact tests where appropriate. The patients were followed for 30 days after they had redeemed a prescription for OCS or respiratory antibiotics at the pharmacy.

Patients treated with OCS will be propensity score matched to patients treated with respiratory antibiotics using the Greedy Match algorithm from the Mayo clinic[22] by the following possible confounders:

- Age at entry
- Sex (male/female)
- Body Mass Index (group 1: 10.0–18.4, group 2: 18.5–24.9, group 3: 25.0–29.9)
- MRC 1-4
- FEV1% (1: FEV1 ≥ 80%, 2: 50% ≤ FEV1 ≤ 80%, 3: 30% ≤ FEV1 ≤ 50%, 4: FEV1 ≤ 30%)
- Tobacco exposure (1: Non-smoker, 2: Former-smoker, 3: Smoker, 4: Unknown)
- Calendar year
- Exacerbations within the previous year (0, 1, ≥ 2)
- Charlson comorbidity index

Results will be presented as hazard ratios (HR) with 95% confidence intervals (CI) and cause specific HRs with 95% CI, analyzed by unadjusted Cox analysis.
HRs will be visualized as cumulative incidence curves and as forest plots.

Sensitivity analysis:

Multivariable analysis will be performed using Cox proportional hazards models while adjusting for the above-mentioned possible confounding variables. Models will be controlled for proportional hazards, interactions and linearity. Stratification is performed when appropriate.

Publication of results
The study findings will be published regardless of their outcome being positive, negative or inconclusive. We intend to publish the results in international peer-reviewed scientific journals. If

securing publication in such a peer-reviewed scientific journal is not possible, the study outcomes will be presented as a report on an online platform.

Ethical statement/approval

The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

References:

[1] 'Global Initiative for Chronic Obstructive Lung Disease [Homepage on the Internet]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Updated 2024].', n.d.

[2] 'KOL - Lægehåndbogen På Sundhed.Dk', accessed 17 February 2024, https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/lunger/tilstande-og-sygdomme/obstruktive-lungesygdomme/kol/.

[3] 'The Appropriate Use of Rescue Packs | Primary Care Respiratory Society', accessed 17 February 2024, https://www.pcrs-uk.org/resource/current/appropriate-use-rescue-packs.

[4] 'Global Initiative for Chronic Obstructive Lung Disease [Homepage on the Internet]. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Updated 2024].'

[5] Shawn D. Aaron et al., 'Outpatient Oral Prednisone after Emergency Treatment of Chronic Obstructive Pulmonary Disease', *The New England Journal of Medicine* 348, no. 26 (26 June 2003): 2618–25, https://doi.org/10.1056/NEJMoa023161.

[6] Julia A. E. Walters et al., 'Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease', *The Cochrane Database of Systematic Reviews*, no. 9 (1 September 2014): CD001288, https://doi.org/10.1002/14651858.CD001288.pub4.

[7]Waljee A K, Rogers M A M, Lin P, Singal A G, Stein J D, Marks R M et ak. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study *BMJ* 2017; 357 :j1415 doi:10.1136/bmj.j1415

[8] Patrick W. Sullivan et al., 'Oral Corticosteroid Exposure and Adverse Effects in Asthmatic Patients', *The Journal of Allergy and Clinical Immunology* 141, no. 1 (January 2018): 110-116.e7, https://doi.org/10.1016/j.jaci.2017.04.009.

[9] Marlene Bloechliger et al., 'Adverse Events Profile of Oral Corticosteroids among Asthma Patients in the UK: Cohort Study with a Nested Case-Control Analysis', *Respiratory Research* 19, no. 1 (27 April 2018): 75, https://doi.org/10.1186/s12931-018-0742-y.

[10] Pradeesh Sivapalan et al., 'COPD Exacerbations: The Impact of Long versus Short Courses of Oral Corticosteroids on Mortality and Pneumonia: Nationwide Data on 67 000 Patients with COPD Followed for 12 Months', *BMJ Open Respiratory Research* 6, no. 1 (30 March 2019): e000407, https://doi.org/10.1136/bmjresp-2019-000407.

[11] Jörg D. Leuppi et al., 'Short-Term vs Conventional Glucocorticoid Therapy in Acute Exacerbations of Chronic Obstructive Pulmonary Disease: The REDUCE Randomized Clinical Trial', *JAMA* 309, no. 21 (5 June 2013): 2223–31, https://doi.org/10.1001/jama.2013.5023.

[12] Pradeesh Sivapalan et al., 'Effect of Different Corticosteroid Regimes for Hospitalised Patients with Exacerbated COPD: Pooled Analysis of Individual Participant Data from the REDUCE and CORTICO-COP Trials', *Respiratory Research* 22 (2021): 155, https://doi.org/10.1186/s12931-021-01745-5.

[13] Carol Bazell et al., 'A 4-Year Retrospective Claims Analysis of Oral Corticosteroid Use and Health Conditions in Newly Diagnosed Medicare FFS Patients with COPD', *International Journal of Chronic Obstructive Pulmonary Disease* Volume 17 (October 2022): 2635–52, https://doi.org/10.2147/COPD.S373590.

[14] Cristina Varas-Lorenzo et al., 'Use of Oral Corticosteroids and the Risk of Acute Myocardial Infarction', *Atherosclerosis* 192, no. 2 (1 June 2007): 376–83, https://doi.org/10.1016/j.atherosclerosis.2006.05.019; Laetitia Huiart et al., 'Oral Corticosteroid Use and the Risk of Acute Myocardial Infarction in Chronic Obstructive Pulmonary Disease', *Canadian Respiratory Journal* 13, no. 3 (April 2006): 134–38, https://doi.org/10.1155/2006/935718.

[15] Bazell et al., 'A 4-Year Retrospective Claims Analysis of Oral Corticosteroid Use and Health Conditions in Newly Diagnosed Medicare FFS Patients with COPD'.

[16] Gary Tse et al., 'A Long-Term Study of Adverse Outcomes Associated With Oral Corticosteroid Use in COPD', *International Journal of Chronic Obstructive Pulmonary Disease* 18 (15 November 2023): 2565–80, https://doi.org/10.2147/COPD.S433326.

[17] Peter Lange et al., 'Danish Register of Chronic Obstructive Pulmonary Disease', *Clinical Epidemiology* Volume 8 (October 2016): 673–78, https://doi.org/10.2147/CLEP.S99489.

[18] Morten Schmidt, Lars Pedersen, and Henrik Toft Sørensen, 'The Danish Civil Registration System as a Tool in Epidemiology', *European Journal of Epidemiology* 29, no. 8 (August 2014): 541–49, https://doi.org/10.1007/s10654-014-9930-3.

[19] Vera Ehrenstein, Sussie Antonsen, and Lars Pedersen, 'Existing Data Sources for Clinical Epidemiology: Aarhus University Prescription Database', *Clinical Epidemiology* 2 (2 December 2010): 273–79, https://doi.org/10.2147/CLEP.S13458.

[20] Morten Schmidt et al., 'The Danish National Patient Registry: A Review of Content, Data Quality, and Research Potential', *Clinical Epidemiology* 7 (17 November 2015): 449–90, https://doi.org/10.2147/CLEP.S91125.

[21] 'Dødsårsagsregisteret (DAR) - Sundhedsdatastyrelsen', accessed 8 February 2024, https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/doedsaarsager-og-biologisk-materiale/doedsaarsagsregisteret.

[22] Research, D.o.Q.H.S.M.C. http://bioinformaticstools.mayo.edu/research/gmatch/. 2024 [cited 2024 21.3].