Study protocol: Inhaled Corticosteroids Particle Size Influence on Risk of Acquiring Pneumonia for Patients with Chronic Obstructive Pulmonary Disease. A Populations-Based Cohort Study

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This study commence from the COP:TRIN and CURE network [1].

Background

Chronic obstructive pulmonary disease (COPD) is often associated with an abnormal inflammatory response of the lungs [2]. Inhaled corticosteroids (ICS) in combinations with bronchodilators have in several randomized trials shown a reduction in exacerbation risk[3-6] but at the same time, ICS treatment has been observed in some settings, to be associated with an increased risk of pneumonia [7].

ICS particles size measured in median mass aerodynamic diameter (MMAD) ranges from 1-5um for commonly used ICS devices. Particles size has proven to play a role in distribution within the lung [8]. Smaller particles are distributed better in smaller airways and are therefore conceivably better for reaching symptom control in difficult to treat patients. In addition, It has been suggested that extra-fine particles are protective against pneumonia [9]. However, if extra-fine particle size leads to a better distribution of ICS in smaller airways, one would expect an increased risk of pneumonia for equal doses of ICS. In this study we aim to determine if extra-fine particles lead to an increased risk of pneumonia admission in COPD patients, or a similar or lower risk of this outcome.

Hypothesis

The use of devices with extra-fine particle size ICS for COPD patients is associated with an increased risk of pneumonia leading to hospitalization.

Methods

Inclusion criteria

1. Patients with outpatient clinical visits for COPD are registered in DrCOPD. Cohort entry will be defined as the date for the patients first outpatient clinic visit in DrCOPD. Patients with only in-hospital-registrations will not be included since these registrations do not hold information on essential patient characteristics (severity of airflow obstruction, degree of dyspnoea, body mass index and smoking status).
2. Imbued minimum one prescription of ICS the year prior to inclusion.

Exclusion Criteria

1. Patients with malignant neoplasm (International Classification of Disease (ICD)-10 codes: C00-C97) or immunodeficiency (ICS-10 codes: D80-84, D85, D89) 5 years prior to cohort entry
2. Prescription of disease-modifying anti-rheumatics drugs (Anatomical Therapeutic Chemical (ATC)-codes: L04AX03, L01AA01, A07EC01, L04AD01, L04AA13, L04AX01, L04AA06, P01BA02) 12 months prior to cohort entry.

Primary outcome

Hospitalization due to pneumonia (ICD-10 codes J12-18).

Study period

1/1/2008 – 31/10 2017.

Follow up:

Patients are followed 1 year from cohort entry or until the first *hospitalization due to pneumonia,* death, or 1 January 2022.

Data sources

For this study the following registries will be used:

1. The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD) to identify patients with COPD. DrCOPD is a nationwide register that holds individual patient data on demographics and all outpatient visits and hospital admissions due to exacerbation of COPD, in patients aged 30 years or above, at all hospital-based pulmonary clinics since 2010 [10].

2. The Danish National Patient Registry (DNPR) holds data on all hospital admissions since 1977 and all hospital outpatient visits since 1995 and will be used to characterize comorbidities in the study population [11].

3. The Danish National Database of Reimbursed Prescriptions (DNDRP) was used to identify prescribed and redeemed medication, including the exposure to ICS. The DNDRP is nationwide and

includes data on all reimbursed prescriptions redeemed at Danish community and hospital-based outpatient pharmacies[12].

Exposure to ICS

All prescriptions for ICS, alone or in combination inhalers, redeemed 365 days prior to cohort entry will be identified. All doses of ICS will be converted to budesonide-equivalent doses according to table 1:

	Factor
Budesonide	1:1
Momethasone	1:1
Beclomethasone	1:1
Beclomethasone HFA	1:2
Fluticasone propionate	1:2
Fluticasone furoate	1:10
Ciclesonide	1:2,5

ATC-codes:

- ICS-Mono R03BA01, R03BA02, R03BA05, R03BA07, R03BA08
- ICS-Dual: R03AK06, R03AK07, R03AK08, R03AK10, R03AK11, R03AK14
- ICS-triple therapy: R03AL08, R03AL09, R03AL11, R03AL12

ICS particle size

ICS particle size will be divided into standard particle size (MMAD >2) and extra-fine particle size (MMAD≤2)

The following devices will be categorized as extra fine particles for the analysis:

- AeroBec
- Alvesco
- Innovair
- Fostair Nexthale

- Trimbow
- Qvar Autohaler

Statistical analysis

The risk of *hospitalization due to pneumonia* associated with ICS Particle size will be estimated by using a Cox proportional hazard regression model.

Suspected confounders and markers of disease severity (to be adjusted) are: age, sex, severity of airway obstruction (percentage of predicted forced expiratory volume in the first second; FEV1), body mass index (BMI), smoking status, accumulated dose of oral corticosteroids 365 days prior to cohort entry, diagnosed with asthma, and the accumulated budesonide equivalent dose.

Patients exposed to normal particle size ICS dose will be matched 1:1 with patients exposed to extra fine particle size in a propensity match analysis.

Furthermore, we will determine if patients treated with extra-fine particles on average receives a higher ICS dose.

Missing data for the cox analysis will be handled by complete case analysis

Statistical analyses will be performed using SAS statistical software.

Timetable

The study commences in spring 2022 and analyses will take place and the manuscript will be made within a year. The manuscript will be submitted in the beginng of 2023.

Ethics

The study will be submitted for approval from Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

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