Study protocol

A Cohort study of two propensity scored cohorts of patients with COPD and asthma, and with COPD without asthma

Estimating the risk of ischemic stroke and ischemic heart disease in patients with COPD and asthma compared to patients with COPD without asthma

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Scientific Project Sponsor

Chronic Obstructive Pulmonary Disease Trial Network: COP: TRIN - A network of independent COPD researchers in Denmark: www.coptrin.eu.

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Background

COPD with asthma is a clinical presentation of chronic airways disease in which patients show both features usually associated with COPD; and features usually associated with asthma. The COPD traits comprise chronic airway obstruction without reversibility, and the asthmatic traits may comprise features such as reversibility, wheezing and airway hyper-responsiveness (1-6). Patients with concomitant COPD and asthma seem to have a higher risk of mortality, hospitalizations and morbidity than patients with COPD without asthma, however the underlying mechanisms are not yet clear (1-4, 6, 7). Patients with both COPD and asthma also seem to have different and inhomogeneous inflammatory and metabolic profiles, distinct from both patients with COPD without asthma and from patients with asthma without COPD. The clinical implications and importance of these differences in metabolites and immunological mediators is still unknown (8).

Studies have pointed toward a systemically elevated level of chronic low-grade inflammation in patients with asthma with chronically elevated pro-inflammatory biomarkers such as high sensitivity C-reactive protein (hsCRP). This low-grade inflammation may be present even during stable disease, but it may also increase with the severity of the asthmatic disease (9-22). This elevated level of local and systemic inflammation may play a role in inducing the prothrombotic stage, which has been shown in asthmatics including enhanced thrombogenesis and impaired fibrinolysis, which may similarly to hsCRP reflect the severity of disease (23-27). The chronic inflammation may be associated with and even predict coronary artery disease and myocardial infarction (28-34). Treatment with direct and indirect inhibitors of chronic, systemic inflammation such as monoclonal antibodies targeting IL-1β, inhaled corticosteroids, colchicine, tiotropium bromide and exercise have been proposed (19, 22, 35).

Cardiovascular diseases share many risk factors with COPD, and not surprisingly the two are frequently found together (36-41). Asthma also seems associated with cardiovascular disease, coronary heart disease and ischemic heart disease (42-47), as well as with more severe outcomes such as myocardial infarction, stroke, cardiovascular death (43, 48-53), and an increased risk of mortality in patients with myocardial infarction (54). Some asthma subtypes also seem to predict cardiovascular disease and stroke (46, 55, 56) or atherosclerosis (57) and coronary artery disease (58).

A few studies have examined cardiovascular comorbidity in patients with concomitant COPD and asthma. They point to a possibly higher risk for cardiovascular, however many of the studies lacked adjustment for confounders such as gender, diabetes, obesity, tobacco exposure, and length of education. (59-61). Finally, there is the question of side-effect of oral corticosteroids, which is a common treatment for asthma, and which may in itself increase the risk of acute myocardial infarction (62).

In general, patients with concomitant COPD and asthma are a poorly studied group of patients, and in the area of cardiovascular diseases, previous studies leave room for further investigation. As the underlying inflammation and metabolic status of patients with both COPD and asthma may differ from patients with COPD without asthma, we propose that the degree of cardiovascular comorbidity may also differ regardless of underlying confounders. Hence, we intend to evaluate the differences in prevalence of cardiovascular diseases between patients with both COPD and asthma compared to patients with COPD without asthma. The underlying inflammatory mechanisms will not be addressed in this study.

Objectives

The project aims to study:

Whether the presence of a concomitant asthma diagnosis increases the risk of fatal and non-fatal ischemic cardiovascular events*.

Hypothesis

The presence of a concomitant asthma in patients with COPD increases the risk of fatal and non-fatal ischemic cardiovascular events*.

*fatal and non-fatal ischemic cardiovascular events are defined as: i) Death from myocardial infarction (any type) or death from ischemic stroke (any type), ii) Admission to hospital under the diagnoses of acute myocardial infection (any type), acute ischemic stroke (any type), transitory cerebral ischemia, first time admittance to hospital or worsening of ischemic heart disease , iii) de novo prescription of any type of nitroglycerin (fast-acting or protracted effect), adenosine diphosphate (ADP)-receptor inhibitors or nicotinamide derivates.

Method

Study design

A multi-center retrospective cohort study will be conducted with Danish residents registered with a diagnosis of COPD between 1. January 2017 and 31 December 2017 identified in the DrCOPD database. The study cohort was formed by identifying all patients with asthma in addition to COPD and the control cohort was formed by propensity score matching each patient with both COPD and asthma to two patients with COPD without asthma on known and likely confounders including age, gender, tobacco exposure and BMI.

Patients with concomitant asthma were defined as patients diagnosed with asthma. This has previously been verified as

Patient population: The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD) is a nationwide database that contains information on the quality of treatment of all patients with COPD in Denmark. All Danish hospitals, since 2008, that treat patients with COPD report to the register (63). Covariates included in this study were age, lung function—assessed as FEV_1% predicted, body mass index—assessed as kilograms per square meter, dyspnea—assessed using the Medical Research Council (MRC) Dyspnea Scale, smoking status, ICS, and long-acting β2-agonist (LABA) or long-acting muscarinic antagonist use.

The Danish Civil Registration System (CRS) includes individual information on the unique personal identification number, name, sex, date of birth and vital status (64).

Inclusion criteria

- Diagnosed with COPD by a specialist
- Affiliated with a specialized pulmonary outpatient clinic
- Age ≥18 years

Exclusion criteria

Active cancer within 5 years

Analysis software:

All analyses will be performed using SAS® software version 9.4.

Descriptive analysis:

The following baseline characteristics of the study population will be summarized separately within the study cohort with COPD and asthma and the control group with COPD without asthma:

- Age, median (IQR), y
- Male sex, n (%)
- Essential hypertension, n (%)
- Diabetes Mellitus, n (%)
- Chronic renal insufficiency, n (%)
- Hypercholesterolemia, n (%)
- Atrial fibrillation, n (%)
- Osteoporosis, n (%)
- Malignancy, n (%)
- Liver failure, n (%)
- Body mass index, median (IQR), kg/m2
- Medical Research Council dyspnea scale, n (%)
- Active smoker ≤6 months
- Never and former >6 months
- COPD assessment test score, median (IQR)
- COPD GOLD class
- Disease symptoms duration, median (IQR), y
- Number of exacerbations previous year, n (%)
- Atopy, n (%)
- Mean cumulative systemic corticosteroid dose 4 weeks before study entry, median (IQR), mg
- Use of noninvasive mechanical ventilation, n (%)
- FEV1, median (IQR), L
- FEV1, median (IQR), % predicted

For each variable, the percent of missing values will be reported. For categorical values, chi-square, Fisher´s exact test, Cox regression and log-rank test will be calculated and for the latter, a corresponding Kaplan-Meier plot will be presented.

Primary endpoint:

Fatal cardiovascular event measured as death from myocardial infarction (any type) or death from ischemic stroke (any type). Please see diagnostic codes included below.

Secondary endpoints:

1. MACE-event (65) defined as the composite of death, myocardial infarction as mentioned below under ii) and revascularization
2. Cardiovascular event requiring hospital admission. Please see diagnostic codes included below.
3. Cardiovascular event requiring de novo prescription of ischemia-related medication. Please see list of included medication below.

Diagnostic codes:

Cerebral ischemia as measured by de novo diagnosis of G45.9 Transient cerebral ischemic attack or G45.8 Other transient cerebral ischemic attacks and related syndromes.

Cardiac ischemia as measured by de novo diagnosis of i) any kind of angina: I20.0 unstable angina, I20.8 Other forms of angina pectoris, I20.9 Angina pectoris, unspecified; ii) any kind of acute myocardial infarction: I21.0 ST elevation (STEMI) myocardial infarction of anterior wall, I21.1 STEMI of inferior wall, I21.3 STEMI of unspecified site, I21.4 Non-STEMI, I 21.9 AMI, unspecified; iii) any kind of ischemic heart disease: I24 Other acute ischemic heart diseases, I24.0 Acute coronary thrombosis not resulting in myocardial infarction, I24.1 Dressler's syndrome, I24.8 Other forms of acute ischemic heart disease, I24.9 Acute ischemic heart disease, unspecified.

Medical treatment:

De novo prescription of any type of i) nitroglycerin (fast-acting or protracted effect); all formulations of glycerylnitrat, isosorbiddinitrat or isosorbidmononitrat; or ii) any type of ADP-receptor inhibitors; all formulations of ticagrelor, clopidogrel, cangrelor, plasugrel and prasugrel; or iii) any kind of nicotineamid derivates; all formulations of nicorandil.

The Danish National Patient Registry (DNPR), which holds information on all admissions to Danish hospitals, since 1977, and hospital outpatient clinic visits, since 1995. Each hospital 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 (66). Covariates included all the below mentioned diagnostic codes.

The Danish National Health Service Prescription Database (DNHSPD) holds information on all prescriptions that have been dispensed in Danish pharmacies, since 2004 (coded according to the Anatomical Therapeutic Chemical (ATC) classification system), including the following information in terms of OCS: the date of dispensation, the quantity dispensed as well as the strength and formulation of all prescriptions that have been dispensed from Danish Pharmacies. All pharmacies are required by Danish legislation to provide information that ensures complete and accurate registration. (67)

Statistical analysis

Patients with concomitant COPD and asthma will be propensity score (using Greedy Match from the Mayo Clinic) matched to patients with COPD without asthma by known and suspected confounders including age, gender, tobacco exposure, BMI and FEV1 at inclusion. The propensity score method aims to control for confounding by balancing confounders between patients with COPD and asthma and patients with COPD without asthma (68) . We will use an unadjusted Cox proportional hazard model to conduct the survival analyses on the matched population. A two-sided 95%- confidence interval will be considered statistically significant. All statistical analyses will be performed using SAS 9.4, Cary, NC, USA.

Sensitivity analysis:

Cox regression model will be used to assess the risk of the fatal cardiovascular events between the two different groups, adjusting for the beforementioned confounders. Appropriate formal tests will be performed to test the proportional hazards assumption, linearity of continuous variables and interaction

Cardiovascular mortality and time to first non-lethal cardiac event

Differences in time to death and time to first non-lethal cardiac event (hospitalization due to above mentioned diagnoses or prescription of abovementioned medications) will be calculated using the Kaplan-Meier method in combination with the log-rank test.

Figures and tables

The first table will include baseline characteristics of the study cohort with COPD and asthma and the control cohort with COPD without asthma (also the propensity matched baseline). The second table will be of the primary and secondary outcomes according to the two groups and pairwise comparisons.

The first figure will be a Kaplan-Meier plot to describe the process of fatal cardiovascular events in the two cohorts.

Ethics

The study was approved by the Danish Data Protection Agency (Journal number: HGH-2017-091, with I-Suite number: 05884). In Denmark retrospective use of register data does not require ethical approval or patient consent.

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