Study title: Prevalence and healthcare utilization of eosinophilic chronic obstructive pulmonary disease in the UK

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Background: Chronic obstructive pulmonary disease (COPD) is a common, treatable, and largely preventable lung disease. It includes two main conditions: emphysema, which damages the air sacs in the lungs, and chronic bronchitis, which involves long-term inflammation of the airways. A subset of patients with COPD display evidence of Type 2 inflammation, which is associated with an increased blood eosinophil count and exhaled nitric oxide concentration, and an increased frequency of exacerbations requiring antibiotic or steroid treatment or hospitalisation. COPD patients with evidence of Type 2 inflammation could potentially benefit from treatment with biological treatment targeting the inflammation (biologicals), and in 2024 the UK Medicine Regulation Agency (MHRA) has granted the first marketing authorisation for a biological (dupilumab) as an add-on maintenance treatment for adults with uncontrolled COPD. The MHRA approval was based on results from two replicate phase 3 BOREAS and NOTUS studies, which evaluated the efficacy and safety of dupilumab in adults with uncontrolled COPD with evidence of type 2 inflammation. Specifically, the approval covers patients already on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

Based on the Quality Outcome Framework (QOF), there were 1.2 million (1.9%) patients with diagnosed COPD in England in 2023/2024. Estimates of the proportion of COPD patients with evidence of Type 2 inflammation is highly variable between studies, depending on the demographics of the study population and the definition of Type 2 inflammation. A systematic review using blood eosinophil counts to define Type 2 inflammation found the proportion ranging from 19 to 67% (https://doi.org/10.3389/fmed.2019.00282), which would translate to 0.3 to 0.8 million patients in England. It is unknown how many of these would qualify for biological treatment based on other eligibility criteria for biologic treatment (uncontrolled COPD).

Objectives:

The primary objective of this study is to compare patients with diagnosed eosinophilic COPD with patients with diagnosed non-eosinophilic COPD in the UK.

Objective 1a) To estimate the prevalence and the number of patients with active eosinophilic COPD and active non-eosinophilic COPD in the UK on January 1st, 2024.

Objective 1b) To estimate the potential prevalence and the number of patients with bio-eligible eosinophilic COPD on January 1st, 2024, under different eligibility criteria.

Objective 2) To determine risk factors for (2a) eosinophilia and (2b) bio-eligibility in patients with active COPD.

Objective 3) To compare disease progression and healthcare utilization of (3a) patients with active eosinophilic COPD compared to patients with active non-eosinophilic COPD and of (3b) patients with active eosinophilic bio-eligible COPD compared to non-eligible patients in a 1-year follow-up period from January 1st to December 31st, 2024.

Study Design: The study design is a retrospective data linkage study. It will be conducted according to STARD guidelines (7).

Data Resource: Primary care data from the OPCRD.

Study population and study period: The study population are people continuously registered in the OPCRD research data base between 2021 and the end of 2023, older than fifteen on January 1st, 2021, and alive on January 1st, 2024.

Classifications (Figure 1):

Classification of COPD: To identify patients with COPD, all GP records of patients in the study population for a period from 01.01.2021 to 31.12.2023 will be interrogated for a COPD-related code. All remaining patients with at least one COPD-related code will be classified as having COPD on 1.1.2024. COPD will be classified using code lists from OpenCodelist.

Classification of active COPD: To classify active COPD, prescription records of people with COPD will be interrogated for a COPD-related prescription between 01.01.2023 and 31.12.2023. Patients with at least one prescription will be classified as having active COPD on 1.1.2024.

Classification of eosinophilic COPD / Type 2 inflammation: To classify COPD subtype in patients with active COPD on 1.1.2024, all GP records from patients with active COPD on 1.1.2024 will be interrogated for a period from 01.01.2021 to 31.12.2023 for results from blood tests. Patients with at least 1 eosinophil count >= 300 cells/µL will be classified as eosinophilic COPD; those with at least 1 eosinophil count <300 cells/µL and no eosinophil count >= 300 cells/µL will be classified as non-eosinophilic COPD and those with no eosinophil count as status unknown. For objective 3, patients will not be re-classified with additional information from tests during the follow-up period.

Classification of asthma: To identify patients with asthma-COPD overlap and to reflect patient selection in randomized control trials, records of patients with eosinophilic COPD will be interrogated for an asthma-related code for a period from 01.01.2021 to 31.12.2023. Asthma will be classified in the records using code lists from OpenCodelist.

Classification of bio-eligible patients with eosinophilic COPD: To classify bio-eligibility, health records of people with active eosinophilic COPD will be interrogated for distinct episodes of exacerbation related codes between 1.1.2023 and 31.12.2023. Distinct episodes will be defined as exacerbation-related diagnostic codes and/or prescriptions for Prednisolone or specific antibiotics at least 4 weeks apart. Prescription records will then be interrogated for exposure to triple therapy (LAMA+LABA+ICS) at the time of exacerbation. All patients with at least two distinct exacerbations while exposed to triple therapy (szenario 1) and all patients with at least three distinct exacerbations while exposed to triple therapy (szenario 2) will be classified potentially bio-eligible. COPD-related exacerbations will be classified using code lists from OpenCodelist.

Classification of covariates: To describe the population of patients with eosinophilic COPD in the UK on 1.1.2024, we will stratify the population by age, sex, BMI, ethnicity, geography, IMD and smoking history. All covariates will be classified using information from OPCRD.

Classification of health care utilization and disease progression: To classify health care utilization we will interrogate GP records and prescription records for all patients with active

COPD in January 1st 2024 for a period of 1 year from January 1st, 2024, to December 31st, 2024. GP records and prescription records will be used to classify distinct episodes of exacerbations, hospital admissions, mortality, COPD-medication use and comorbidities.

Analysis:

All data management and statistical analysis will be done using MS SQL-Server, Stata V19 and R 4.5.0.

Objective 1a and 1b) To calculate the prevalence of active eosinophilic COPD, active non-eosinophilic COPD and potentially bio-eligible COPD on 1.1.2024 in the study population, we divide the respective number of patients by the number of patients in the study population. Under the assumption that the OPCRD patient population reflects the population of the UK, we can then use census data to calculate the number of patients on 1.1.2024 in the UK. To describe patients with active eosinophilic COPD, active non-eosinophilic COPD and potentially bio-eligible COPD we will use descriptive statistics (frequency counts/median + IQR).

Objective 2) To determine risk factors for eosinophilia in patients with active COPD we will use multivariable logistic regression models. For the models we will categorise all continuous variables; statistical significance of co-variates will be determined using Likelihood ratio tests.

Objective 3) To compare clinical outcomes and treatment patterns we will use Cox proportional hazard models to calculate the hazard of (all cause) mortality, exacerbation, co-morbidity and (all cause) hospital admission during follow-up. In all models, estimates will be adjusted for the effect of age and gender.

Power calculations[1]: An initial analysis of data in OPCRD indicates that the number of patients in OPCRD with diagnosed active COPD and at least one eosinophile count on January 1st, 2024 was approximately 85,000. Of those, 35,000 (41%) were eosinophilic and 50,000 (59%) were non-eosinophilic. Ignoring the potential effect of covariates and the random practice effect, if the patient population of patients with diagnosed active COPD split into 50% males and 50% females, the sample size of 85,000 patients is large enough to have >80% power to detect a difference of 1% (e.g., 41% of males being eosinophilic and 42% of females being eosinophilic). If the 1-year mortality rate was 5%, the sample size of 85,000 patients is large enough to have >80% power to detect a Hazard ratio of 1.1 (a 10% difference in morality risk between males and females).

[1] Using R, package survivalpwr and pwrss

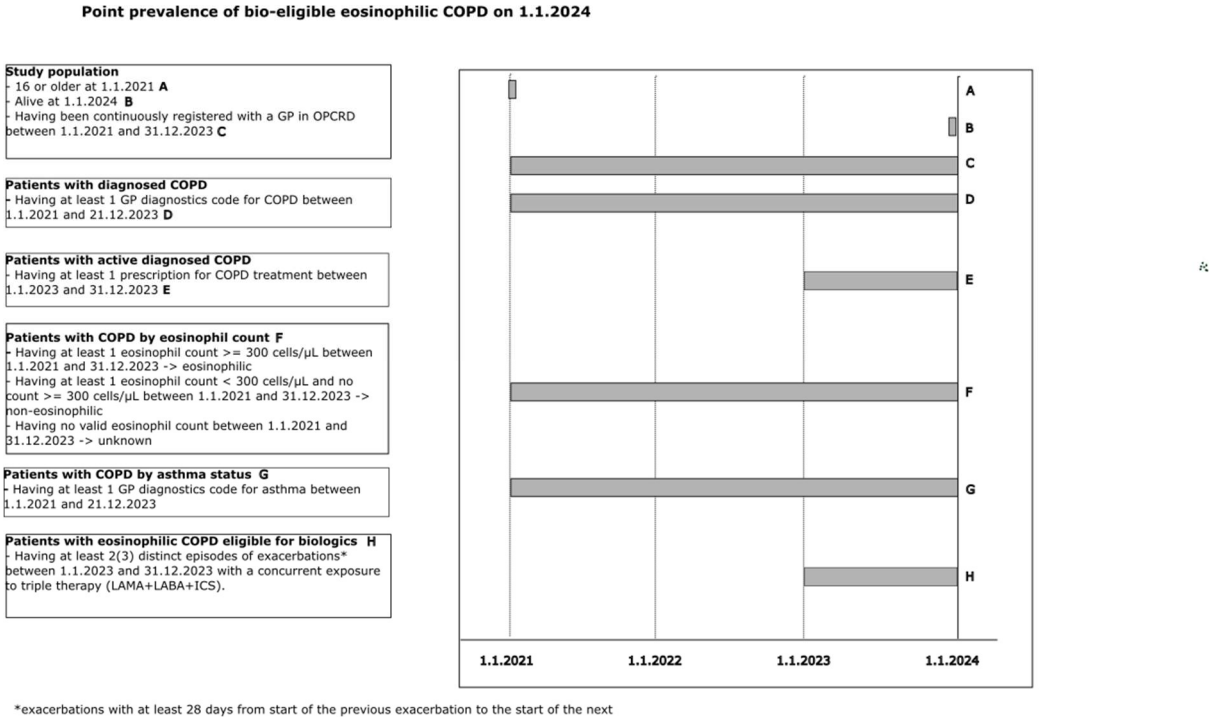

Figure 1 Classification of patients with bio-eligible eosinophilic COPD in the UK 1.1.2024.