Study Protocol

Title: Association Between Inhaled Corticosteroid (ICS) Dose and Risk of cardiovascular events (CVE) in the Danish COPD Register.

Hypothesis

Among patients included in the Danish COPD Register, higher cumulative exposure to inhaled corticosteroids (ICS) is associated with an increased risk of CVE [1] compared with no/moderate/low exposure, after adjustment for confounders [2].

Background and Rationale

High-dose inhaled corticosteroids (ICS) may produce systemic effects [3] through increased absorption leading to fluid retention [4] and electrolyte disturbances that can predispose to heart failure and atrial arrythmias. In addition, metabolic alterations such as weight gain, insulin resistance, and diabetes along with modulation of systemic inflammation, may elevate the risk of ischemic heart disease [2, 5]. Together, these mechanisms provide biological plausibility for a dose-dependent association between ICS and adverse cardiovascular outcomes [2].
Although prior studies have suggested an association between systemic corticosteroids and AF [6, 7], evidence regarding ICS is inconsistent, and few studies have investigated new-onset CVE in large, unselected COPD populations with detailed prescription data. Denmark's nationwide registers offer a unique opportunity to address this gap.

Study Design

- **Type:** Register-based retrospective cohort study
- **Exposure modeling:** ICS exposure

Data sources:

- **Danish COPD Register:** Inclusion criteria, baseline lung function, clinical covariates (e.g., FEV1, exacerbation history).
- **National Prescription Registry:** Dispensed ICS prescriptions (ATC codes, package details, defined daily doses [DDD]).
- **National Patient Registry:** AF diagnoses (ICD-10 I48.x) and comorbidities.
- **Civil Registration System:** Vital status, emigration, and censoring.
- **Optional linkage:** Laboratory databases, primary care data, socioeconomic registries (if accessible).

Study Population

- **Inclusion criteria:** All patients registered in the Danish COPD Register between 2010–2021.
- **Exclusion criteria:** History of CVE before cohort entry; missing key identifiers; age <40 years.
- **Follow-up:** From cohort entry (first COPD registration during study window) until incident AF, death, emigration, or end of follow-up.

Exposure Definition

- **ICS exposure:** ICS exposure will be defined as all prescriptions in the 1 year prior to cohort entry converted into budesonide-equivalent doses[3]. Time-varying exposure will be based on cumulative dispensed DDDs over the past 6–12 months.
- **Categories:** None, low, medium, high dose (cutoffs to be defined by clinical guidelines).

Outcomes

- CVE *including acute coronary syndrome (ICD-10: I24.9), heart failure (ICD-10: I50.x), arrhythmia (ICD-10: I49.x)(e.g. AF* (ICD-10: I48.x)*,* AF requiring intervention (cardioversion/ablation) (ICD-10: KFPD) and ischemic heart disease (ICD-10: DI20-DI25)

Covariates

- **Demographics:** Age, sex
- **Disease severity:** FEV1 (% predicted), GOLD stage, exacerbation frequency, BMI, smoking status, MRC.
- **Comorbidities (baseline):** The following comorbidities, all of which are included in the Charlson Comorbidity Index; myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease, cerebrovascular disease, dementia, connective tissue disease, ulcer disease, mild, moderate, or severe liver disease, diabetes mellitus, hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any solid tumor (non-metastatic), leukemia, lymphoma, metastatic solid tumor, acquired immunodeficiency syndrome (AIDS).
- **Medications:** Oral corticosteroids (H02), β-blockers (C07), antiarrhythmic drugs (C01B, C01BA, C01BB, C01BC, C01BD, C01BG), bronchodilators (R03), antithrombotic (B01)[8].

Statistical Analysis

1. **Descriptive statistics:** Baseline characteristics by ICS exposure category. Categorical variables will be summarized by count and percentages. Continuous variables will be computed as mean and standard deviation, if the variable is deemed normal, otherwise median and interquartile ranges will be reported.

2. **Primary analysis:** Cox regression proportional hazards models with ICS exposure as cumulative DDDs. Death will be handled as a competing risk.
    - Adjustments:
      a) Demographics
      b) FEV1, exacerbations and charlson comorbidity index
      c) Medications
    - Test proportional hazards assumption (Schoenfeld residuals). Stratification or time-interaction terms if violated.
    - Unadjusted cumulative incidence plot (log rank test).
3. **Secondary analyses:**
    - Subgroups: Age (<65 vs. ≥65), prior cardiovascular disease, FEV1 strata.
    - Sensitivity: Lag periods (30/90 days) to reduce reverse causation; stricter CVE definitions (hospital-confirmed only). Cox regression with time varying exposure.
    - Negative control outcomes (e.g., unrelated conditions) to assess residual confounding.
4. **Handling confounding by indication:**
    - Propensity score weighting or marginal structural models with inverse probability of treatment weighting (IPTW) to account for time dependent confounding (e.g.,exacerbations, systemis steroid use).

Missing Data

- Use multiple imputation for missing covariates (e.g., FEV1, BMI) if missingness is non-trivial.
- Most register-based variables (diagnoses, prescriptions) are expected to be complete.

Power and Sample Size (sketch)

- CVE incidence in COPD populations is estimated at 10–20 per 1,000 person-years [9].
- For an expected hazard ratio (HR) of 1.20 (high vs. no ICS), α=0.05, and 80% power, several hundred to a few thousand AF events are required.
- Given nationwide coverage, Danish registers are expected to provide sufficient statistical power. A precise calculation will be made once incidence and cohort size are defined.

Bias and Limitations

- **Confounding by indication:** Addressed through time-varying modeling and IPTW.
- **Exposure misclassification:** Prescriptions reflect dispensed, not consumed drugs.
- **Outcome misclassification:** CVE diagnosed only in hospital settings may miss primary care cases; mitigated by using validated hospital codes.
- **Residual confounding:** Lifestyle factors (alcohol, exercise) not captured; addressed through negative control analyses and discussion.

Ethics and Data Access

- Approvals required from the Danish Data Protection Agency and the Danish Health Data Authority.
- Regional ethical committee approval depending on local requirements.
- Data linkage performed via Statistics Denmark and the Danish Health Data Authority, with secure data handling in compliance with GDPR.

References

1. von Bülow, A., et al., *Use of High-Dose Inhaled Corticosteroids and Risk of Corticosteroid-Related Adverse Events in Asthma Findings From the NORDSTAR Cohort.* J Allergy Clin Immunol Pract, 2025. **13**(7): p. 1609-1619.e5.
2. Bloom, C.I., et al., *Association of Dose of Inhaled Corticosteroids and Frequency of Adverse Events.* Am J Respir Crit Care Med, 2024. **211**(1): p. 54-63.
3. Lee, H. and H.Y. Yoon, *Inhaled corticosteroid increased the risk of adrenal insufficiency in patients with chronic airway diseases: a nationwide population-based study.* Sci Rep, 2024. **14**(1): p. 28831.
4. Myers, A. and C. Godden, *Peripheral oedema as a side-effect of fluticasone.* BMJ Case Rep, 2010. **2010**.
5. Savas, M., et al., *Associations Between Systemic and Local Corticosteroid Use With Metabolic Syndrome and Body Mass Index.* J Clin Endocrinol Metab, 2017. **102**(10): p. 3765-3774.
6. van der Hooft, C.S., et al., *Corticosteroids and the risk of atrial fibrillation.* Arch Intern Med, 2006. **166**(9): p. 1016-20.
7. Christiansen, C.F., et al., *Glucocorticoid use and risk of atrial fibrillation or flutter: a population-based, case-control study.* Arch Intern Med, 2009. **169**(18): p. 1677-83.
8. Laegemiddelstyrrelsen. *ATC-codes*. 2025; Available from: https://www.medicinpriser.dk/Default.aspx?id=65&letter=B.
9. Groenewegen, A., et al., *Sex-specific and age-specific incidence of ischaemic heart disease, atrial fibrillation and heart failure in community patients with chronic obstructive pulmonary disease.* BMJ Open Respir Res, 2022. **9**(1).