Study Protocol **27.02.26**

Title

Risk of Pneumonia Hospitalization After Initiation of DPP-4 Inhibitors Versus Sulfonylureas Among Patients With COPD and Type 2 Diabetes Treated With Metformin: A Nationwide Register-Based Cohort Study

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Background

Metformin is a widely used first-line therapy for type 2 diabetes. In addition to its glucose lowering effects, metformin has been shown to possess immunomodulatory and anti-inflam matory properties, which could theoretically reduce systemic inflammation and potentially lower the risk of infections, including respiratory infections as pneumonia.

Among patients already treated with metformin, the choice of additional antidiabetic therapy is clinically important, as different drug classes may have varying effects on immune function. Dipeptidyl peptidase-4 inhibitors (DPP-4i) and sulfonylureas (SU) are in this study used as add-on treatments.

Access to nationwide Danish registries, including the Danish Register for COPD (DrKOL), the Danish National Prescription Registry (LSR), and the National Patient Register (LPR), linked with laboratory data, provides an opportunity to investigate the risk of pneumonia hospitalization among patients initiating DPP-4i versus SU as add-on therapy to metformin. Using a new-user, active-comparator design, with adjustment for glycemic control (HbA1c), inhaled corticosteroid use (ICS), renal function (eGFR), and other relevant clinical factors, allows for a robust assessment of whether the choice of additional antidiabetic therapy affects pneumonia risk in patients with COPD and type 2 diabetes.

Design

Metformin users initiating DPP-4 inhibitor vs metformin users initiating sulfonylurea (alternativt SGL2 og GLP1)

Hypothesis: Among adults ≥40 years with COPD and type 2 diabetes treated with metformin, initiation of a DPP-4 inhibitor versus a sulfonylurea is associated with a different risk of pneumonia hospitalization.

Index: date of first redeemed prescription for a DPP-4 inhibitor or sulfonylurea among patients receiving metformin.

Primary Outcome: Hospitalization for pneumonia, ICD-10 codes DJ12.0–DJ18.9, occurring within 12 months of follow-up.

Secondary outcomes: Pneumonia within 365 days, intubation during hospitalization (proce dure codes in LPR), all-cause mortality within 30 days, time to first COPD exacerbation within 12 months

Comparator:

Exposure: DPP-4 inhibitor initiation

Comparator: sulfonylurea initiation

Registers

DrKOL: COPD diagnosis, FEV1, GOLD classification, smoking status, BMI, and MRC score.

LSR: metformin, other oral antidiabetic medications (DPP-4 inhibitors, sulfonylureas), ICS, and respiratory antibiotics (e.g., amoxicillin, amoxicillin/clavulanate).

LPR: Hospitalizations, ICD-10 diagnoses (pneumonia, COPD exacerbation), and procedures (intubation).

Laboratory data: HbA1c, renal function (eGFR, creatinine) available at baseline and, where possible, as time-dependent measurements.

Inclusion and exclusion criteria:

Inclusion: Adults ≥40 years with COPD registered in DrKOL and type 2 diabetes who:

have ongoing metformin treatment

initiate either a DPP-4 inhibitor or sulfonylurea between 2010–2023

have no prescription for DPP-4 inhibitors or sulfonylureas in the previous 12 months

Exclusion: Adults with type 1 diabetes, chronic dialysis, eGFR <30 mL/min/1.73 m^2, recent pneumonia hospitalization (within 30 days before index)

Exposure:

The index date is defined as the date of the first redeemed prescription for DPP4 inhibitors or SU following a ≥12-month washout period.

Covariates (baseline):

Age, sex, BMI, smoking status, FEV1% predicted / GOLD grade, prior COPD exacerbations within 12 months, , baseline HbA1c trajectory, eGFR, ICS use (categorized by defined daily doses), oral corticosteroids, pneumonias 12 months before, and comorbidities (Charlson comorbidity index). number of metformin prescriptions prior to index, prior insulin use

Statistics:

Descriptive: baseline characteristics (metformin vs comparator).

Primary analysis: Cause specific cox proportional hazards model for time to pneumonia hospitalization accounting for death as a competing risk.

Sensitivity Analyses

Inverse propensity of treatment weighted model. The propensity model will include all covariates listed above, plus year.

Time-dependent analysis (Inverse Probability of Censoring Weighting).

Stratified analyses: eGFR ≥60 vs 30–59, ICS use (yes/no), HbA1c tertiles.

Negative control outcome (e.g., non-respiratory hospitalization) to assess residual confounding.

Missing data: multiple imputation for laboratory variables if >30% missing; otherwise, a complete case analysis will be included.