# Association between ICS therapy for COPD and diabetes onset and progression

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# Disclosures

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  - This work was supported by Novartis
- Jaco Voorham
  - Employee of the Observational and Pragmatic Research Institute, which conducted this study and which has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine; AKL Ltd.; Almirall; AstraZeneca; British Lung Foundation; Boehringer Ingelheim; Chiesi; GlaxoSmithKline; Mylan; Mundipharma; Napp; Novartis; Orion; Respiratory Effectiveness Group; Takeda; Teva; and Zentiva, a Sanofi company

# Background

- As noted in the current GOLD strategy document[1]:
  - "Results of observational studies **suggest** that **ICS treatment could also be associated with increased risk of diabetes/poor control of diabetes**[2]…"
- Limitations of prior studies:
  - Most RCTs: not sufficiently powered or long enough to evaluate adverse effects, do not evaluate diabetes progression
  - Prior observational studies: include patients with concomitant asthma and/or suffer from patient selection or time-related biases

GOLD = Global Initiative for Chronic Obstructive Lung Disease

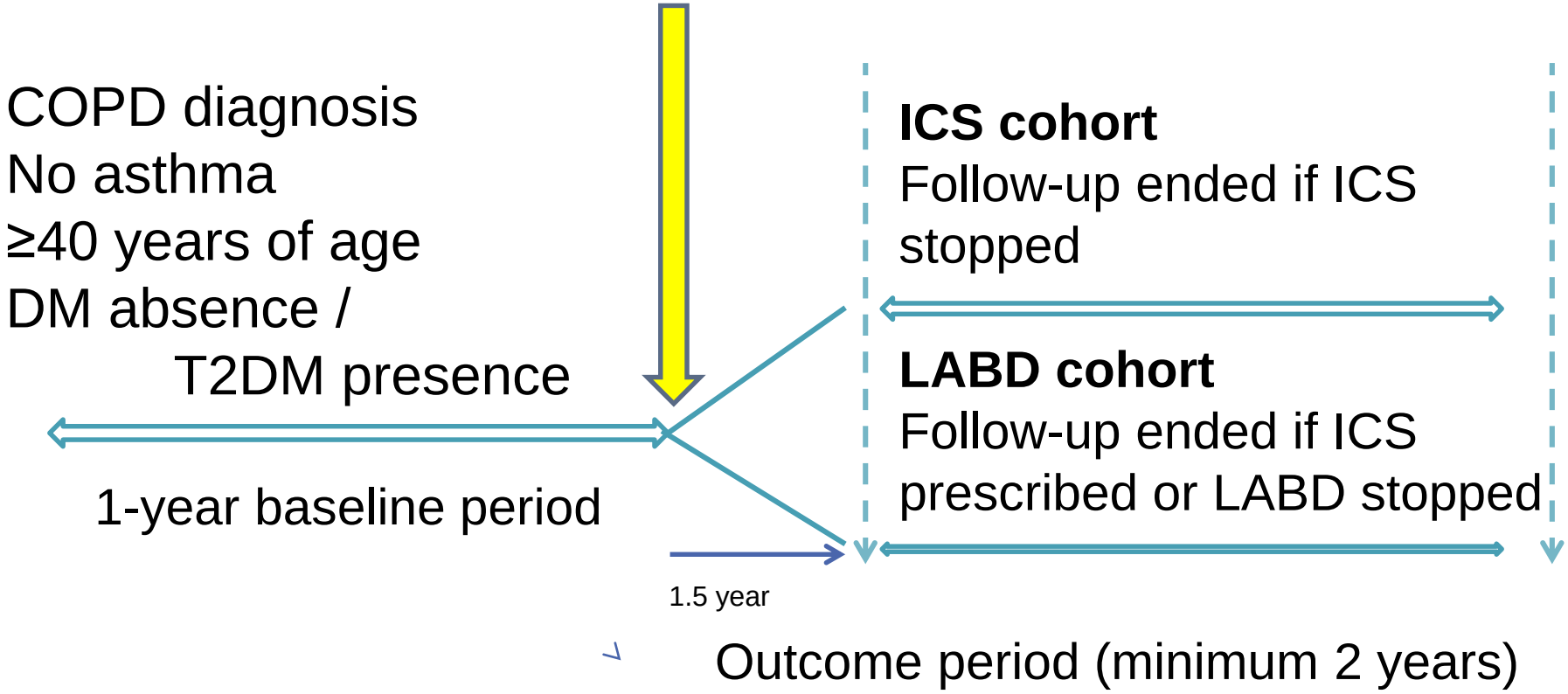
[1] http://goldcopd.org/gold-reports/. [2] Suissa et al. Am J Med 2010; 123:1001-6.

# Study objective

To evaluate whether ICS therapy for patients with COPD is associated with an increased incidence rate or accelerated progression of type 2 diabetes mellitus

# Historical matched cohort study

**Index date** (January 1, 1990 – August 31, 2015)
Initiating maintenance pharmacotherapy:
ICS or long-acting bronchodilator (LABD)




**CPRD:** Clinical Practice Research Datalink

- ~5 million patients
- >600 subscribing practices

**OPCRD:** Optimum Patient Care Research Database

- >5.4 million patients
- >600 subscribing practices

Only <5 oral corticosteroid (OCS) prescriptions during each study year allowed

# Exposure and outcomes

## ICS exposure

- ICS versus LABD-only
- Average daily exposure: cumulative amount of ICS prescribed (fluticasone eq. dose), divided by number of days since ICS initiation. Updated at each prescription.

## Endpoints

- **Incident diabetes:** type 2 diabetes diagnosis and/or antidiabetic drug prescription and/or 2 $HbA_{1c}$ measurements >6.5%
- **Diabetes progression:** $HbA_{1c}$ increase of ≥0.5% from baseline and/or increased antidiabetic drug dose and/or new antidiabetic drug class and/or insulin initiation

# Analyses

## Approaches to handle confounding

1. **Matching of ICS and LABD cohorts:** mixed (1 up to 3) matching on year of index date, age, sex, smoking status, BMI, number of baseline year exacerbations, propensity score
2. **Adjusted models** included variables showing (residual) confounding plus age, sex, and two time-varying covariates representing exposure to OCS over time
3. **Restriction** of non-maintenance OCS users

**Proportional hazards regression** used to compare

1. ICS vs. LABD
2. Mean daily ICS exposure vs. reference value of <250 µg/day

# Patient flow

Initiating treatment, prior COPD diagnosis

**ICS *N* = 104,519 / LABD *N* = 47,997**

Eligible

**ICS n = 28,060 / LABD n = 9,862**

T2DM onset risk cohort

**ICS n = 25,378 / LABD n = 8,556**

T2DM progression risk cohort

**ICS n = 861 / LABD n = 485**

**Matching** using direct matching & propensity score

Matched

T2DM onset risk cohort

**ICS n = 11,430 / LABD n = 6,540**

T2DM progression risk cohort

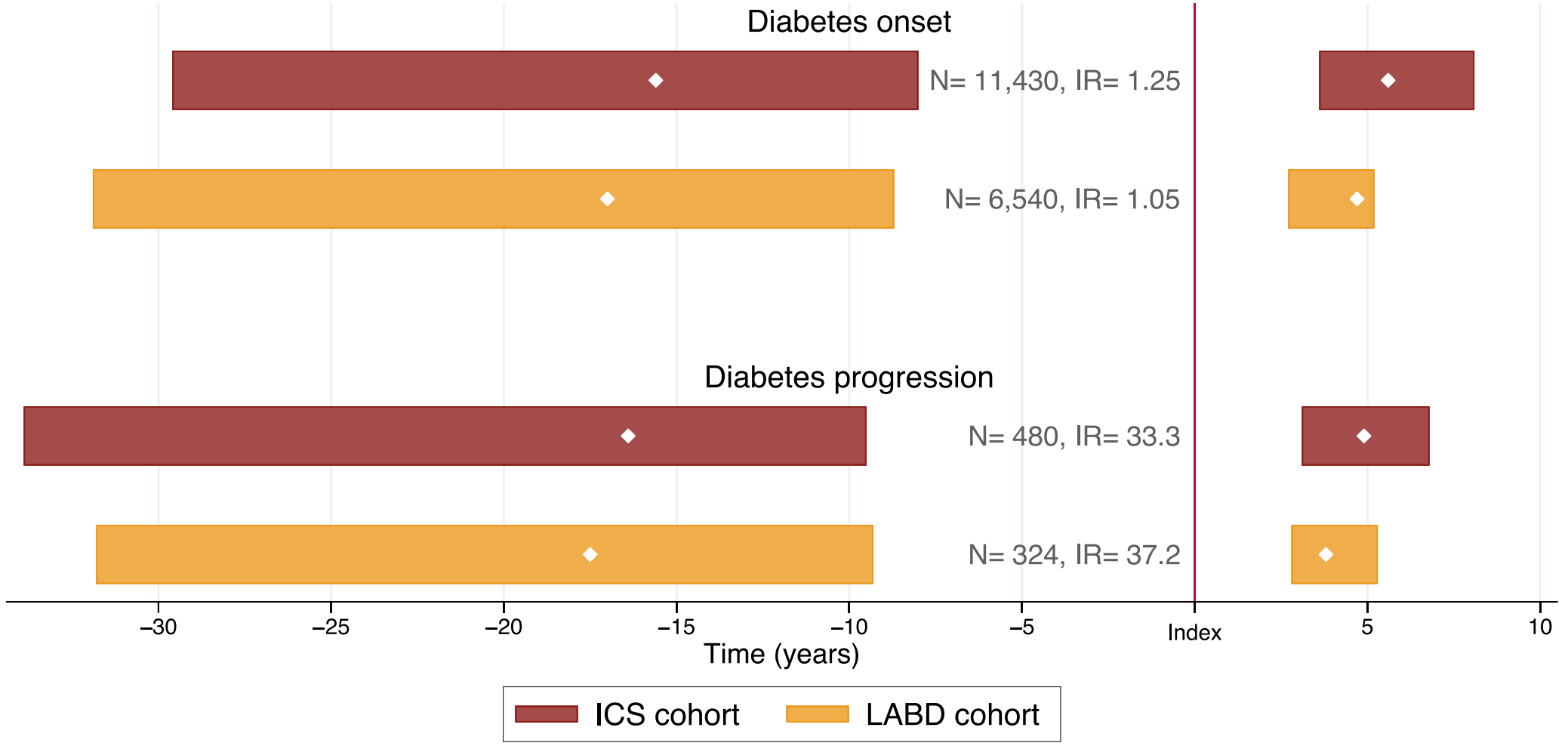
**ICS n = 480 / LABD n = 324**

# Patient populations – matched baseline

| | Diabetes onset | | | Diabetes progression | | |
|---|---|---|---|---|---|---|
| | ICS (n = 11,430) | LABD (n = 6,540) | SMD (%)* | ICS (*n* = 480) | LABD (*n* = 324) | SMD (%)* |
| Male, n (%) | 6,788 (59.4) | 3,835 (58.6) | 1.5 | 319 (66.5) | 214 (66.0) | 0.9 |
| Age, mean (SD) | 67.7 (9.4) | 68.0 (9.5) | 3.9 | 71.1 (7.5) | 70.8 (8.1) | 6.1 |
| Current smoker, n (%) | 4978 (44.0) | 2904 (44.8) | 2.3 | 154 (32.1) | 119 (36.7) | 10.0 |
| Ex-smoker | 5823 (51.5) | 3269 (50.5) | | 301 (62.7) | 188 (58.0) | |
| ≥1 Exacerbation, n (%) | 5,650 (49.4) | 3,088 (47.2) | 5.2 | 235 (49.0) | 149 (46.0) | 8.8 |
| mMRC score ≥2, n (%) | 3,609 (37.5) | 2,211 (37.5) | 0.5 | 203 (44.2) | 134 (43.6) | 5.5 |
| 2017 GOLD A/B, n (%) | 6,021 (62.6) | 3,902 (66.2) | 6.6 | 289 (63.0) | 203 (66.1) | 6.9 |

*An SMD ≤10% indicates sufficient balance between groups.
mMRC = modified Medical Research Council dyspnoea scale

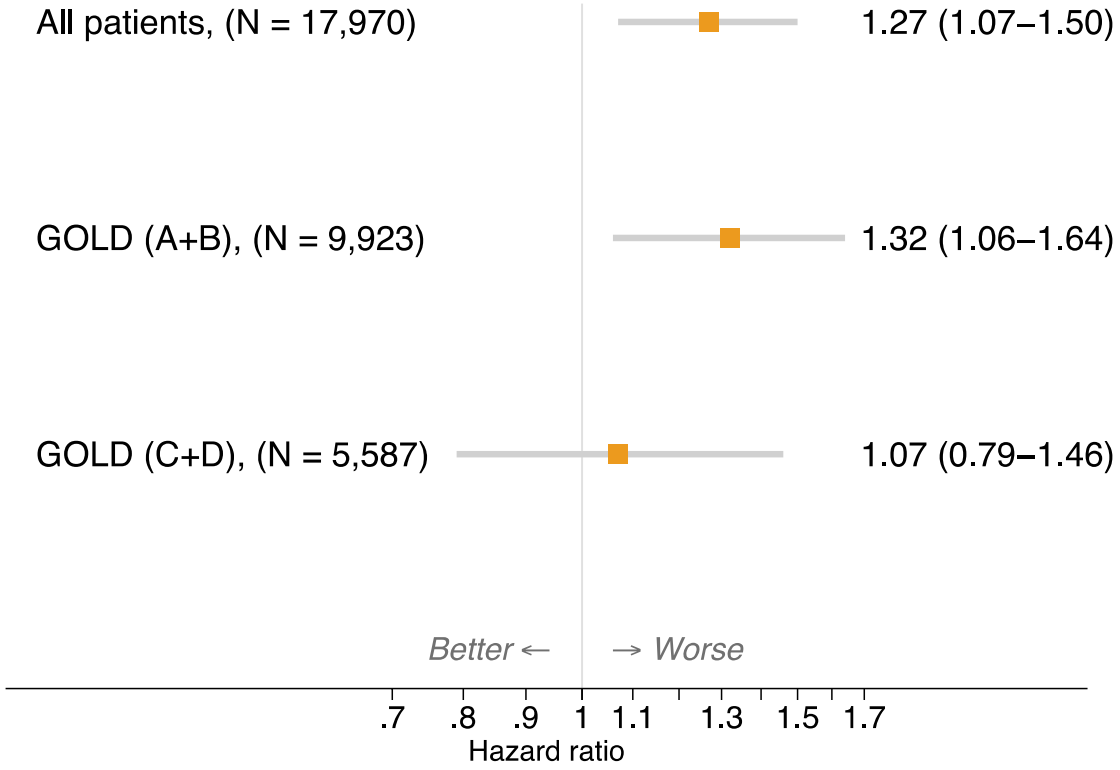
# Event rates and length of baseline and outcome periods in ICS and LABD cohorts

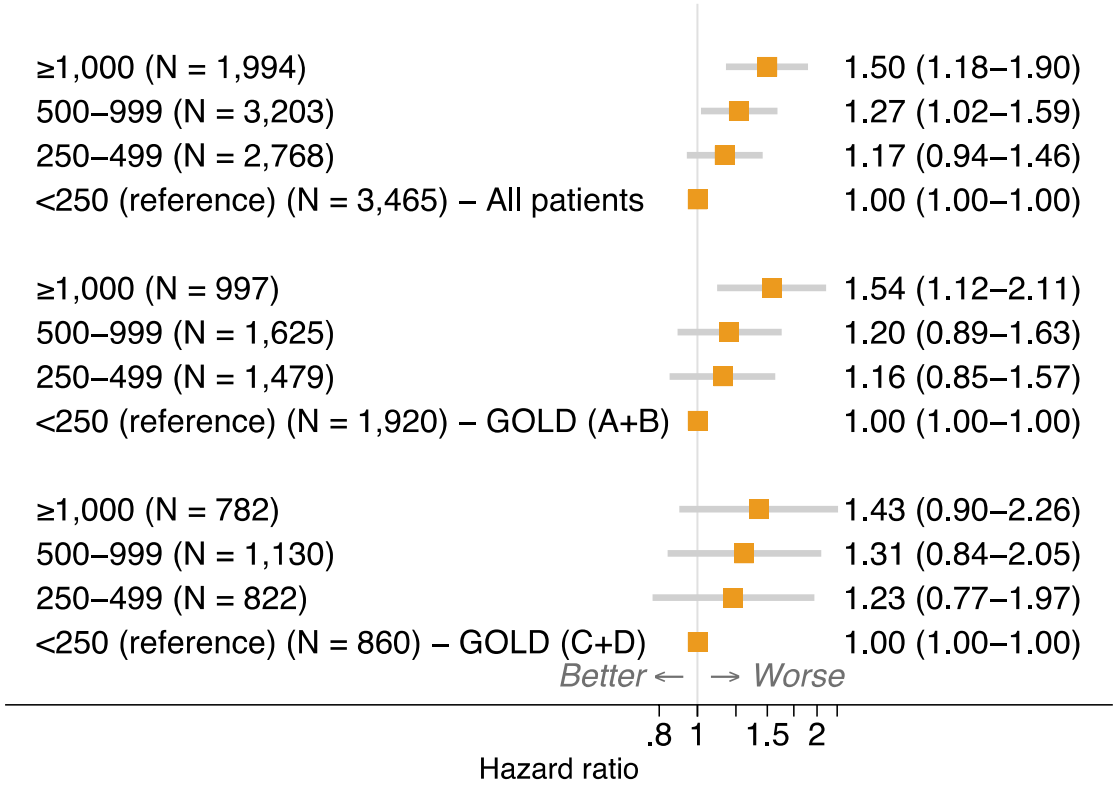



Diamond = median; Bar = interquartile range; IR, incidence rate per 100 person-years

# Diabetes onset

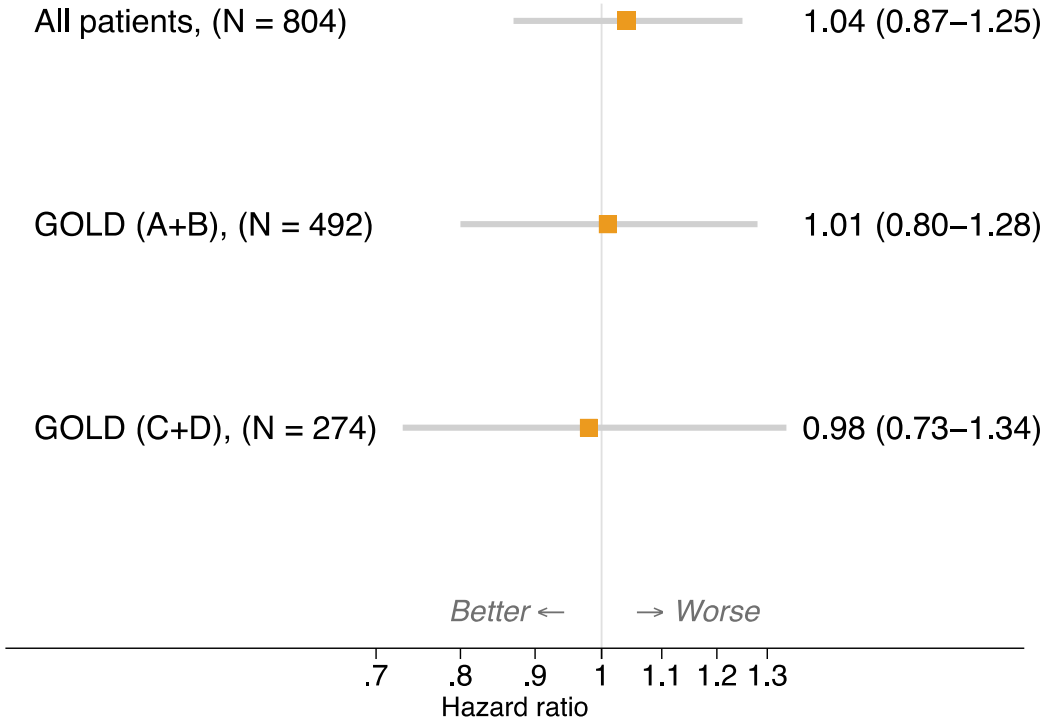
- **Increased risk overall** (vs. LABD) and **dose response** (ICS only)

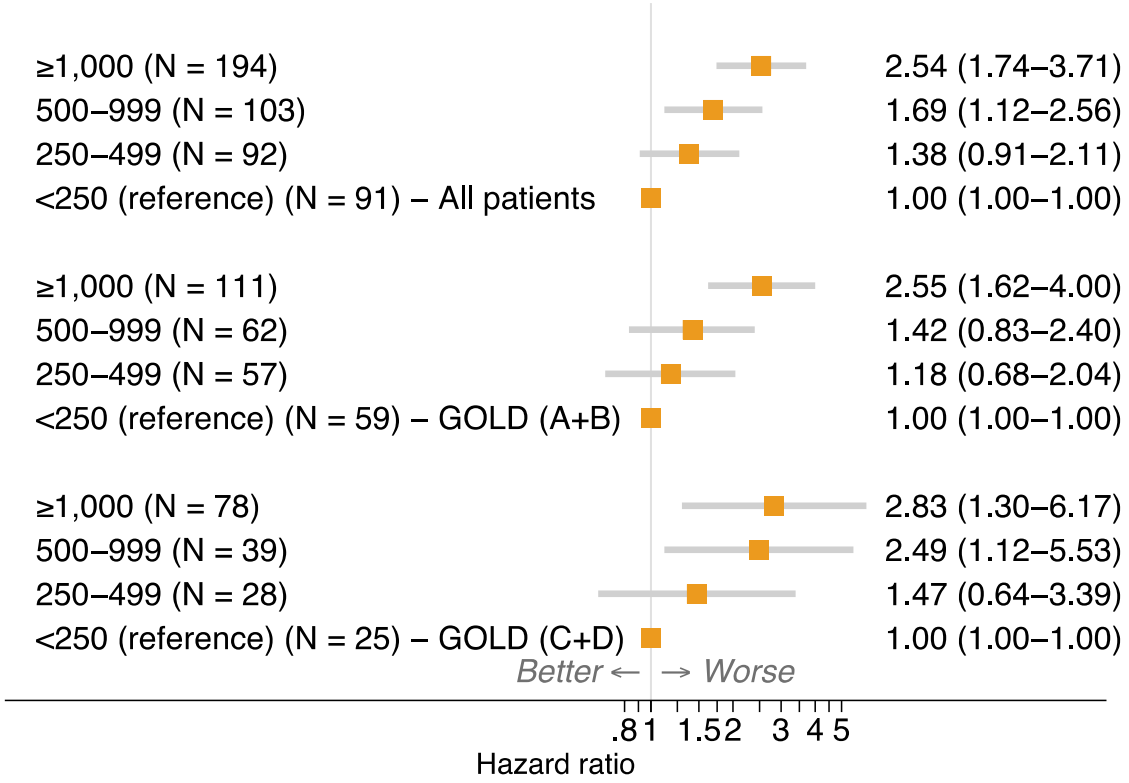


# Diabetes progression

- No increase in risk overall but **dose response** (ICS only)



# Study strengths & limitations

## Study strengths

- Lengthy baseline and outcome observational periods
- Use of highly granular UK databases with reliable prescribing information and $HbA_{1c}$ recording
- Real-world patients with COPD, no recorded asthma
- Multiple approaches to handle confounding

## Study limitations

- Database information is recorded for clinical, not research, purposes
- Potential for unmeasured confounding
- Small diabetes progression population

# Conclusions

- ICS (vs. LABD) initiation as the first COPD maintenance treatment is associated with greater risk of developing type 2 diabetes mellitus
- An ICS dose response was evident for both diabetes onset and diabetes progression: with significantly greater risks at **mean daily ICS exposures of ≥500 µg/day**

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# Back-up slides