Association between ICS therapy for COPD and diabetes onset and progression

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BACKGROUND

- As noted in the current GOLD (Global Initiative for Chronic Obstructive Lung Disease) 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

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.

DESIGN & METHODOLOGY

Design: Historical matched cohort study

Data sources: The Clinical Practice Research Datalink (CPRD, www.cprd.com) and Optimum Patient Care Research Database (OPCRD, opcrd.co.uk).

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

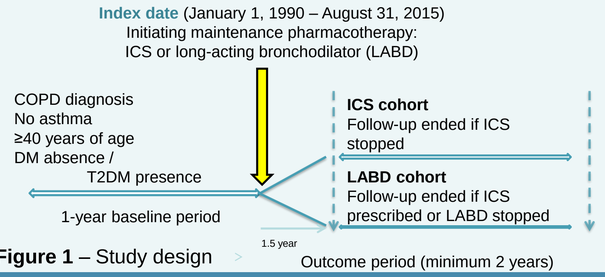


Figure 1 – Study design

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 HbA1c measurements >6.5%
- **Diabetes progression:** HbA1c increase of ≥0.5% from baseline and/or increased antidiabetic drug dose and/or new antidiabetic drug class and/or insulin initiation

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

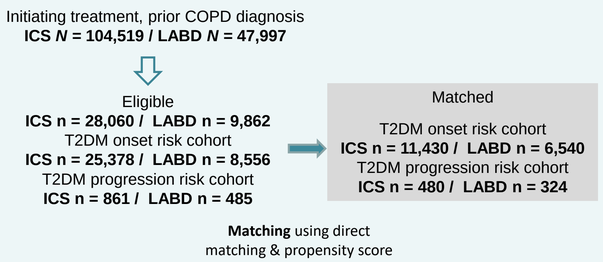


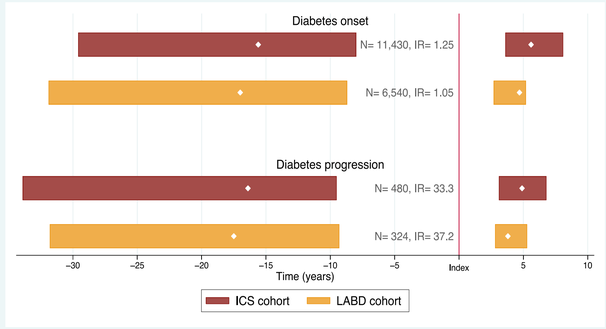
Figure 2 – Patient flow

RESULTS

Table 1 – Patient populations – matched baseline

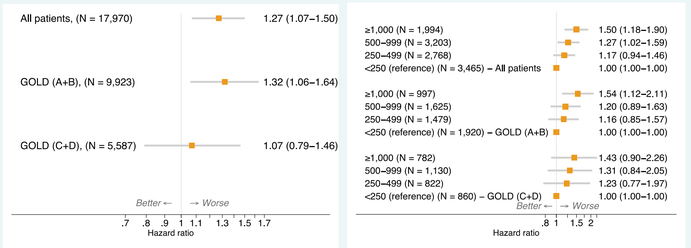
	Diabetes onset			Diabetes progression		
	ICS (n = 11,430)	LABD (n = 6,540)	SMD (%)*	ICS (*n* = 480)	LABD (*n* = 324)	SMD (%)*
Male, n (%)	6,788 (59.4)	3,835 (58.6)	1.5	319 (66.5)	214 (66.0)	0.9
Age, mean (SD)	67.7 (9.4)	68.0 (9.5)	3.9	71.1 (7.5)	70.8 (8.1)	6.1
Current smoker, n (%)	4978 (44.0)	2904 (44.8)	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



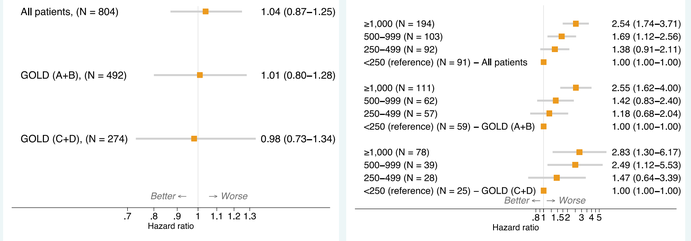
Diamond = median; Bar = interquartile range; IR, incidence rate per 100 person-years

Figure 3 – Event rates and length of baseline and outcome periods in ICS and LABD cohorts



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

Figure 4 – Diabetes onset



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

Figure 5 – Diabetes progression

STUDY STRENGTHS AND LIMITATIONS

Study strengths: Lengthy baseline and outcome observational periods. Use of highly granular UK databases with reliable prescribing information and HbA1c 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**

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

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