Association between ICS therapy for COPD and diabetes onset and progression

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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/.
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)

COPD diagnosis
No asthma
≥40 years of age
DM absence / T2DM presence

ICS cohort
Follow-up ended if ICS stopped

LABD cohort
Follow-up ended if ICS prescribed or LABD stopped

1-year baseline period

1.5 year

Outcome period (minimum 2 years)

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 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
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 $n = 485$

Matched
T2DM onset risk cohort
ICS $n = 11,430$ / LABD $n = 6,540$
T2DM progression risk cohort
ICS $n = 480$ / LABD $n = 324$

Matching using direct matching & propensity score
Patient populations – matched baseline

<table>
<thead>
<tr>
<th></th>
<th>Diabetes onset</th>
<th></th>
<th>Diabetes progression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICS (n = 11,430)</td>
<td>LABD (n = 6,540)</td>
<td>SMD (%)*</td>
<td>ICS (n = 480)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>6,788 (59.4)</td>
<td>3,835 (58.6)</td>
<td>1.5</td>
<td>319 (66.5)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>67.7 (9.4)</td>
<td>68.0 (9.5)</td>
<td>3.9</td>
<td>71.1 (7.5)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>4978 (44.0)</td>
<td>2904 (44.8)</td>
<td>2.3</td>
<td>154 (32.1)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>5823 (51.5)</td>
<td>3269 (50.5)</td>
<td></td>
<td>301 (62.7)</td>
</tr>
<tr>
<td>≥1 Exacerbation, n (%)</td>
<td>5,650 (49.4)</td>
<td>3,088 (47.2)</td>
<td>5.2</td>
<td>235 (49.0)</td>
</tr>
<tr>
<td>mMRC score ≥2, n (%)</td>
<td>3,609 (37.5)</td>
<td>2,211 (37.5)</td>
<td>0.5</td>
<td>203 (44.2)</td>
</tr>
<tr>
<td>2017 GOLD A/B, n (%)</td>
<td>6,021 (62.6)</td>
<td>3,902 (66.2)</td>
<td>6.6</td>
<td>289 (63.0)</td>
</tr>
</tbody>
</table>

*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

Diabetes onset

ICS cohort
- N = 11,430
- IR = 1.25

LABD cohort
- N = 6,540
- IR = 1.05

Diabetes progression

ICS cohort
- N = 480
- IR = 33.3

LABD cohort
- N = 324
- IR = 37.2

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients, (N = 17,970)</td>
<td>1.27 (1.07–1.50)</td>
</tr>
<tr>
<td>GOLD (A+B), (N = 9,923)</td>
<td>1.32 (1.06–1.64)</td>
</tr>
<tr>
<td>GOLD (C+D), (N = 5,587)</td>
<td>1.07 (0.79–1.46)</td>
</tr>
</tbody>
</table>

#### ≥1,000 (N = 1,994)
- 1.50 (1.18–1.90)

#### 500–999 (N = 3,203)
- 1.27 (1.02–1.59)

#### 250–499 (N = 2,768)
- 1.17 (0.94–1.46)

#### <250 (reference) (N = 3,465) – All patients
- 1.00 (1.00–1.00)

#### ≥1,000 (N = 997)
- 1.54 (1.12–2.11)

#### 500–999 (N = 1,625)
- 1.20 (0.89–1.63)

#### 250–499 (N = 1,479)
- 1.16 (0.85–1.57)

#### <250 (reference) (N = 1,920) – GOLD (A+B)
- 1.00 (1.00–1.00)

#### ≥1,000 (N = 782)
- 1.43 (0.90–2.26)

#### 500–999 (N = 1,130)
- 1.31 (0.84–2.05)

#### 250–499 (N = 822)
- 1.23 (0.77–1.97)

#### <250 (reference) (N = 860) – GOLD (C+D)
- 1.00 (1.00–1.00)
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
Back-up slides