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Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: effect of drug, dose, and device

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CONFLICTS OF INTEREST

PNRD and/or his department have received unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Takeda and Teva; consulting and advisory fees from AstraZeneca, Boehringer Ingelheim, Takeda, Chiesi, Zambon, Novartis and Teva.

MB & AC are employees of Research in Real Life, which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd, and which conducted this study and has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva, a Sanofi company.

LW was an employee of Research in Real Life, which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd, at the time of the study.

SBA sits on an advisory board for TEVA and has consulted for TEVA, GSK, Mundipharma.

HC has no shares in any pharmaceutical companies. He has received sponsorship to carry out studies, together with Board Membership, consultant agreements and honoraria for

presentation, from several pharmaceutical companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, Napp Pharmaceuticals, Mundipharma, NorPharma, Norvartis, Orion, Sanofi, Teva, Truddell Medical International, UCB and Zentiva. Research sponsorship has also been received from grant awarding bodies (EPSRC and MRC). He is the owner of Inhalation Consultancy Ltd. He is also an employee of Research in Real Life, which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd, and which conducted this study and has conducted paid research in respiratory disease on behalf of the following other organizations in the past 5 years: Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Orion, Takeda, Teva, and Zentiva, a Sanofi company.

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MF has received travel/educational grants from Astra Zeneca and TEVA. She has received no personal funding for advisory boards or consultancy activities but her institution has received funding from Teva, Almirall, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Orion for such activities.

JBS was employed by Research in Real Life, which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd, at the time of the study. He has received received pharmaceutical company grants from GSK in 2011 and Chiesi in 2012 via CIMERA his

former home institution, and in 2014 and 2015 from Linde via Hospital Universitario de La Princesa; he participated in speaking activities, advisory committees and consultancies during the period 2011-2016 sponsored by: Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, ERS, GEBRO, Grifols,GSK, Linde, Lipopharma, Mundipharma, Novartis, Pfizer, RiRL, Rovi, SEPAR, Takeda, and Teva.

LB has received over the past 3 years (i) fees for speaking, or participation in advisory boards for Aerocrine, Arsonette, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sandoz, Sanofi, Takeda and Teva.

DP has board membership with Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; consultancy with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer, and Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Research in Real-Life Ltd, which is subcontracted by Observational and Pragmatic Research Institute Pte Ltd [OPRI], and OPRI) from UK National Health Service, British Lung Foundation, Aerocrine, AKL Ltd, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, and Zentiva; payments for lectures/speaking from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; patents (planned, pending or issued) from AKL Ltd; payment for the development of educational materials from GlaxoSmithKline and Novartis; stock/stock options from AKL Ltd which produces phytopharmaceuticals; owns 80% of Research in Real

Life Ltd, which is subcontracted by OPRI, 75% of the social enterprise Optimum Patient Care Ltd, and 75% of OPRI; received payment for travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Almirral, Chiesi, Teva Pharmaceuticals, and Zentiva; and peer reviewer for grant committees of the Medical Research Council (2014), Efficacy and Mechanism Evaluation programme (2012), HTA (2014).

Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: effect of drug, dose, and device

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Key words: oral candidiasis, chronic obstructive pulmonary disease, inhaled corticosteroid, spacer, dry powder inhaler, pressurised metered-dose inhaler

ABSTRACT

Background and aims

Little information is available on real-life occurrence of oral thrush in COPD patients treated with ICS. We investigated oral thrush incidence in COPD patients prescribed FDC ICS/LABA therapies and assessed whether it is modulated by the ICS type, dose, and delivery device.

Methods

We conducted a historical, observational, matched cohort study (one baseline year before and one outcome year after initiation of therapy) using data from the UK Optimum Patient Care Research Database. We assessed oral thrush incidence in patients initiating long-acting bronchodilators or FDC ICS/LABA therapy. We then compared different combination therapies (budesonide/formoterol fumarate dihydrate [BUD/FOR] and fluticasone propionate/salmeterol xinafoate [FP/SAL]) and devices (DPI and pMDI).

Results

Patients prescribed FDC ICS/LABA had significantly greater odds of experiencing oral thrush than those prescribed long-acting bronchodilators alone (adjusted OR 2.18 [95% CI 1.84–2.59]). Significantly fewer patients prescribed BUD/FOR DPI developed oral thrush compared with FP/SAL DPI (OR 0.77 [0.63–0.94]) when allowing for differences in prescribed doses between the drugs. A significantly smaller proportion of patients developed oral thrush in the FP/SAL pMDI arm than in the FP/SAL DPI arm (OR 0.67 [0.55–0.82]). Additionally, in the FP/SAL cohort (both DPI and pMDI), increased risk of oral thrush was significantly associated with high ICS daily dose (OR 1.97 [1.22–3.17] vs low daily dose).

Conclusions

ICS use increases oral thrush incidence in COPD and this effect is dose-dependent for FP/SAL therapies. Of the therapies assessed, FP/SAL pMDI and BUD/FOR DPI may be more protective against oral thrush.

INTRODUCTION

Oral thrush, also known as oral candidiasis, is a well-documented local side-effect associated with regular inhaled corticosteroid (ICS) use in patients with asthma[1-4]. It is thought to be caused by a reduced local immune response[5] or an increase in salivary glucose (which stimulates growth of *Candida albicans*[6]) after deposition of ICS in the oropharyngeal cavity. Many factors have been reported to influence the incidence of oral thrush in asthma, including type and dose of ICS used, mode of drug delivery, and patient compliance with medication instructions[7-11]. Although generally associated with temporary symptoms, ICS local side-effects, including oral thrush, can be clinically significant, and may affect patient quality of life and therapy adherence[3,12,13].

ICS are also prescribed for the treatment of chronic obstructive pulmonary disease (COPD) in patients with severe airflow limitation and/or at high risk of exacerbations, and are generally recommended in combination with long-acting β_2-agonists (LABAs)[14,15]. However, recent studies have found that ICS are being prescribed in COPD even more widely and frequently than would be expected from current management guidelines, particularly among less severe patients[16,17]. Despite the widespread use of ICS in this disease, there is little information on real-life occurrence and distribution of oral thrush in patients with COPD who are prescribed ICS[18-21]. The objective of this study was to investigate the incidence of oral thrush in COPD patients receiving ICS as part of their ICS/LABA combination therapy. In particular, we sought to assess whether oral thrush incidence is modulated by the type of ICS, the ICS dose, and the delivery device (dry powder inhaler [DPI] vs pressurised metered-dose inhaler [pMDI]).

METHODS

Study design and data source

This was a historical, observational, matched cohort study utilising healthcare records from the Optimum Patient Care Research Database (OPCRD)[22]. The OPCRD is a bespoke database with focus on patient-reported outcomes that, at the time of this study, contained anonymous data for over 2.4 million patients from over 550 UK primary care practices across England, Scotland, Wales, and Northern Ireland. It contains two types of data: (1) routinely recorded clinical data and (2) questionnaire responses from over 40,000 patients with respiratory conditions. We examined data during a one-year baseline period (prior to the index date, defined below) for patient characterisation, and a one-year outcome period after initiation of a new or additional COPD therapy. The index date was defined as the date of first prescription for either a fixed dose combination (FDC) ICS/LABA (therapies assessed described below) or long-acting bronchodilator therapy (LABA, long-acting muscarinic antagonist [LAMA], or their combination; addition of an alternative long-acting bronchodilator was also considered as first prescription). This study design was necessary to determine the incidence of oral thrush, compared with a reference group without ICS exposure, and allow for seasonal changes in respiratory disease symptoms and related conditions. The study was conducted to standards suggested for observational studies, including an independent advisory group, use of an *a priori* analysis plan, study registration with commitment to publish, and a well-maintained and monitored study database[23].

Ethical approval

The study was conducted and is reported in compliance with the criteria of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP;

registration number: ENCEPP/SDPP/12762). OPCRD received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Its governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee (http://optimumpatientcare.org/our-database/), an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG, http://www.effectivenessevaluation.org/) to govern the standard of research conducted on internationally recognised databases (ADEPT approval reference for this study: ADEPT1416).

Inclusion and exclusion criteria

Patients eligible for inclusion in the study received a quality outcomes framework (QOF) code for COPD diagnosis[24], were aged ≥40 years at the index date, had at least 2 years of continuous practice data (1 year of baseline and 1 year of outcome data), and received ≥2 prescriptions of FDC ICS/LABA or long-acting bronchodilator during the outcome period (including prescriptions at the index date). Patients were excluded if in the baseline period they received ≥1 prescription for ICS, ≥1 prescription for both LABA and LAMA, maintenance oral corticosteroid prescription, or if they had a diagnostic code for any chronic respiratory disease other than COPD, asthma, or bronchiectasis.

Cohorts and treatment arms

We initially studied two cohorts of patients with COPD. The first cohort included patients that were prescribed FDC ICS/LABA combination therapy at the index date. Combination therapy included the following: budesonide/formoterol fumarate dihydrate (BUD/FOR) administered via a DPI device (Symbicort® Turbohaler®); fluticasone propionate/salmeterol xinafoate (FP/SAL; Seretide®) administered via DPI (Accuhaler®) or pMDI (Evohaler®) device; and beclometasone dipropionate/formoterol fumarate

dihydrate (BDP/FOR; Fostair®) administered via a DPI (NEXThaler®) or pMDI device. Patients prescribed BDP/FOR DPI were not included in the subsequent analyses owing to their low number. The second cohort included patients who were prescribed non-ICS therapy (any long-acting bronchodilator) at the index date, namely LABA, LAMA or their combination. The two cohorts were matched 1:1 (see below and Table S1). Before matching, in the non-ICS therapy cohort, patients could have been included more than once with different first prescriptions for LABA, LAMA or their combination.

We then conducted subset analyses dividing patients of the unmatched FDC ICS/LABA cohort according to different combination therapies (BUD/FOR DPI and FP/SAL DPI) and devices (FP/SAL pMDI and FP/SAL DPI) and matched them 1:1 (see below and Figure S1A, B). Finally, in the FP/SAL pMDI treatment arm, we conducted a subgroup analysis of patients who were prescribed a spacer in the period comprising the baseline year, the index date, and two weeks after the index date (ensuring that spacer device use preceded the occurrence of oral thrush), and compared them with patients who were not prescribed a spacer in the same period.

Exact matching

We used matching with statistical adjustment for residual confounders (exact matching, as described in previous studies[25,26]) in order to ensure that we analysed comparable groups of patients. We compiled a list of potential matching criteria informed by expert clinical advice and previous research experience, including variables predictive of outcomes and the key baseline clinical characteristics differing between unmatched cohorts (identified using t-test, and Chi-Squared and Mann-Whitney U tests, as appropriate). The matching criteria (described in Table S1 and Figure S1A, B) were then applied sequentially to

produce two matched cohorts containing all possible pairings; bespoke software was used to randomly select final unique matched pairs.

ICS daily doses

To better capture the relationship between ICS dose and oral thrush, we used the intended daily dose of ICS, defined as the dose prescribed at the index date. Doses are expressed in FP equivalent units (FP: BUD, 1:2 dose ratio; see Table 10 in British Thoracic Society [BTS]/Scottish Intercollegiate Guidelines Network [SIGN] British Guideline on the Management of Asthma, 2014[27]) and were categorised in low (<500 µg/day), moderate (500–999 µg/day), and high (≥1000 µg/day) dose categories based on previous studies[28]. BUD/FOR DPI and FP/SAL DPI are licensed for use in COPD in the UK at recommended daily doses of 400 (FP equivalents) and 1000 µg/day, respectively[29]. FP/SAL pMDI is not licensed for use in COPD in the UK, however, as this study indicates, it is widely prescribed off-licence for the treatment of COPD.

Outcomes

The primary outcome was the incidence of oral thrush, defined as the proportion of patients with a diagnosis of oral thrush and/or prescribed antifungal medication for the treatment of oral thrush within the outcome period (occurring at distinct dates). Because oral thrush is generally successfully treated with antifungal medications (http://www.nhs.uk/conditions/Oral-thrush---adults/Pages/Introduction.aspx), different episodes can be regarded as independent cases/diagnosis.

Statistical analysis

All analyses were carried out using SAS version 9.3[30], SPSS Statistics version 22[31], and R version 3.2.3[32]. The study was powered on the primary outcome, incidence of oral thrush. The sample size required for a 90% power to reject the null hypothesis (no difference in

oral thrush incidence between the study cohorts) estimated a minimum of 360 patients in each of the cohorts. This calculation assumed an expected difference in proportions of 0.05 (π_1 = 0.020 and π_2 = 0.070; two-group Chi-squared test with 0.05 two-sided significance level) based on results from a similar study by Calverley et al. (2007)[19].

For matched data, we used conditional logistic regression to compare oral thrush incidence between cohorts and treatment arms. For unmatched data, we used logistic regression. Outcomes were adjusted for any residual non-collinear baseline confounders and for those demographic and baseline variables predictive of the outcome through full multivariable analysis. Results are reported both as number (and percentage) of patients who had a diagnosis of oral thrush and/or medication prescribed for oral thrush in the outcome period and as odds ratios (OR) with 95% confidence intervals (CI), unadjusted and adjusted for confounders. When CI does not contain 1.00, results are statistically significant at the 5% level. We used the Chi-Squared test for unmatched comparisons (results are statistically significant when $p < 0.05$).

RESULTS

In the unmatched cohorts, we analysed observations from 13,647 patients who were prescribed FDC ICS/LABA and 10,043 observations from 9,161 patients who were prescribed non-ICS therapy (Figure 1A, B). Matching procedure (Table S1) resulted in a final population of 8,255 uniquely matched patients per cohort. We characterised unmatched and matched patients according to baseline demographic and clinical features. Overall characteristics of the unmatched populations were retained in the matched cohorts (Table 1). In the matched cohorts, the mean age was 69 years (SD 10), 57% of patients were male, the majority were ex-smokers (50%) or current-smokers (40%), and the mean BMI was 27 (SD 6), indicating that the majority of patients were overweight or obese. Diabetes (18%), eczema (14-15%), and asthma (7-10%) were the most frequent comorbidities. Finally, Table 1 shows that oral thrush prevalence was low in the baseline period both in the matched (1%) and in the unmatched cohorts (3%).

Incidence of oral thrush in patients prescribed ICS

In the outcome period, the incidence of oral thrush was higher in patients prescribed FDC ICS/LABA compared with those prescribed non-ICS therapy (Table 2; 456 [5.5%] vs 227 [2.7%] patients; adjusted OR 2.18 [95% CI 1.84–2.59]). Among the total patients with oral thrush, 493 (72.2%) and 118 (17.3%) experienced one episode and two episodes, respectively, of oral thrush in the outcome period.

Incidence of oral thrush by ICS drug and inhaler device

To carry out subset analyses we used matching (Figure S1A, B), which resulted in 3,465 uniquely matched patients per treatment in the cohort comprising BUD/FOR DPI and FP/SAL DPI, and in 3,800 uniquely matched patients per treatment in the cohort

comprising FP/SAL pMDI and FP/SAL DPI. Baseline characteristics of these matched cohorts are summarised in Table 3.

Significantly fewer patients prescribed BUD/FOR DPI developed oral thrush compared with patients prescribed FP/SAL DPI (Figure 2, top; 196 [5.7%] patients with oral thrush vs 244 [7.0%]; OR 0.77 [95% CI 0.63–0.94] after adjusting for baseline confounders). However, the majority of patients who were on BUD/FOR DPI therapy were prescribed the medication at low ICS dose, whereas most patients on FP/SAL DPI therapy were prescribed the medication at higher ICS doses (Table S2). After adjusting for intended ICS daily dose, we found no significant difference in the incidence of oral thrush between the treatment arms (Figure 2, top; fully adjusted OR 1.04 [95% CI 0.54–2.00]). The ICS dose was an expected *a priori* confounder in this cohort, given that the daily dose recommended for use in COPD is different between BUD/FOR and FP/SAL[29].

A significantly smaller proportion of patients developed oral thrush in the FP/SAL pMDI arm than in the FP/SAL DPI arm (Figure 2, bottom; adjusted OR 0.67 [95% CI 0.55–0.82]; 208 [5.5%] patients with oral thrush vs 279 [7.3%]).

A subgroup analysis revealed that oral thrush incidence was lower among patients prescribed FP/SAL pMDI with a spacer device compared with those prescribed FP/SAL pMDI without a spacer (Table S3; 35 [4.2%] vs 173 [5.8%]); however, this difference did not reach statistical significance (Table S3; adjusted OR 0.74 [95% CI, 0.51–1.07]).

Incidence of oral thrush by ICS dose

In the cohort comprising FP/SAL pMDI and FP/SAL DPI a significantly higher number of patients prescribed high daily dose of ICS (≥1000 µg/day FP equivalent units) developed oral thrush compared with those prescribed low daily dose of ICS (<500 µg/day) (Table 4; number [%] of patients with oral thrush: low dose, 35 [4.7%]; high dose, 329 [7.2%];

adjusted OR 1.97 [95% CI, 1.22–3.17]). An exploratory analysis within treatment arm indicated that the main driver of this difference was FP/SAL pMDI (Table S2; number [%] of patients with oral thrush: low dose, 14 [3.6%]; high dose, 132 [6.5%]; unadjusted OR 1.85 [95% CI, 1.05–3.25] for high vs low comparison; no significant differences were detected in the FP/SALDPI arm [Table S2]).

A similar pattern of increasing odds for oral thrush with increasing ICS dose was observed in the cohort comprising BUD/FOR DPI and FP/SAL DPI, however this difference did not reach statistical significance (Table 4; number [%] of patients with oral thrush: low dose, 210 [5.6%]; high dose, 169 [7.4%]; adjusted OR 1.42 [95% CI, 0.70–2.88]). Our exploratory analysis within treatment arms confirmed no significant effect of dose for either treatment, which for BUD/FOR DPI was due to heavy prescribing at a low daily dose (3,411 patients [98.4%], Table S2).

DISCUSSION

There is limited research on the real-life incidence of oral thrush in patients with COPD who are prescribed ICS. Here, we showed that ICS therapy increases the risk of developing oral thrush in real-life patients with COPD and this effect is modulated by the delivery device and, for some ICS therapies, by dose.

We observed a significant reduction in the risk of oral thrush among patients prescribed BUD/FOR DPI compared with those prescribed FP/SAL DPI, which was likely attributable to the ICS dose prescribing patterns: in UK, the daily dose of FP/SAL DPI that is recommended for use in COPD is more than double the FP-equivalent dose of BUD/FOR DPI[29]. After adjusting for this *a priori* confounder, we observed no significant difference in the incidence of oral thrush between the two therapies, suggesting that if the drugs were prescribed at the same dose the risk of developing oral thrush would be

similar. However, BUD/FOR DPI may represent a better therapeutic option to reduce the risk of oral thrush given that it is generally prescribed at lower doses (and thus associated with less amount of ICS being deposited in the oropharynx). We considered whether the difference in the prescribing patterns could be confounded by the selection of ICS therapy by general practitioners, with milder patients being prescribed BUD/FOR DPI and more severe patients being prescribed FP/SAL DPI. However, patients were matched on COPD exacerbations in the baseline period and other variables related to disease severity (COPD therapy, FEV_1 % predicted, acute oral corticosteroid courses, and lower respiratory consultations in the baseline period) were balanced between the treatment arms. Therefore, it is unlikely that disease severity was systematically different between the groups.

Several studies reported that the incidence of oral thrush is positively associated with the ICS dose among patients with asthma[7,8,10,11]. Overall, we observed that a higher number of patients developed oral thrush when prescribed high daily dose of ICS compared with those prescribed low daily dose of ICS. However, this difference was only significant in the cohort comprising FP/SAL DPI and FP/SAL pMDI and, according to our exploratory analyses, it was likely driven by FP/SAL pMDI (for which the odds of developing oral thrush was 85% higher when the drug was prescribed at a high dose). The lack of dose effect in the BUD/FOR DPI arm was likely due to the fact that, as mentioned above, most patients (over 98%) were prescribed this therapy at low daily dose.

In our study, we found that delivery of FP/SAL via a pMDI device was protective against oral thrush compared with delivery via a DPI device. This may reflect differential drug deposition in the respiratory tract between the two devices. Research has shown that FP delivered via a pMDI device produces a stronger bronchodilatory effect[33] and achieves better disease control[34] than FP delivered via a DPI device, likely because of greater ICS delivery to the lung[35] and consequently less deposition in the throat. This may also explain

why we did not observe a significant effect of dose for FP/SAL DPI, as the amount of drug deposited in the throat may already saturate the tissue with ICS at low dose. With the pMDI device, instead, as our results indicate, the reduced oropharyngeal deposition of ICS would make the effect of different doses more quantifiable and clinically relevant. However, oropharyngeal deposition is influenced but many factors, including inhalation speed, inhaler technique, particle size, and pharyngeal and lower airway anatomy, among others[36], which makes it challenging to truly assess differences in drug deposition between different drugs and inhalers. Thus, this hypothesis should be investigated further.

Both drug deposition in the upper airways[37,38] and oral candidiasis[39] are reduced when using a pMDI with a spacer device, likely because the portion of the dose that usually impacts in the oropharynx is left in the spacer[40]. Accordingly, we found that fewer patients developed oral thrush when using FP/SAL pMDI with a spacer than without a spacer. This result was not statistically significant, however studying this association in a larger population could result in a statistically significant outcome. As poor inhaler and spacer technique is an issue in COPD[41,42], it is possible that the occurrence of oral thrush could be further reduced by improving knowledge of proper use of spacers.

In our study, approximately 40% of patients in each cohort were current smokers, in line with typical estimates of smoking prevalence in COPD[43]. Smoking is a known risk factor for developing oral thrush[44]. Thus, smoking may contribute to increased risk of oral thrush in patients with COPD who are smokers and are treated with ICS. However, because smoking status was a matching criterion in our study, it is unlikely that smoking habits introduced bias in our results.

We found high rates of diabetes and eczema comorbidities among patients with COPD in this study (in the study cohorts and arms, diabetes was present in approximately 20% of

patients and eczema in approximately 15% of patients). We observed that incidence of oral thrush was significantly higher in patients with COPD and diabetes prescribed ICS compared with patients with COPD and diabetes prescribed non-ICS therapy (5.9% vs 3.2%; p = 0.001). Because eczema can be caused by *Candida albicans* and diabetes is known to increase the risk of oral infections (owing to increased concentrations of glucose in saliva[6,11]), oral thrush may be a substantial issue for individuals with COPD and coexisting diabetes and/or eczema who are prescribed ICS. In these patients, a more careful consideration of which ICS should be prescribed, and at which dosage, may be appropriate. This aspect warrants further research.

Study strengths and limitations

This is one of a few studies exploring real-life incidence and determinants of oral thrush in COPD. A strength of this study is the cohort design; exposure to specific COPD therapies preceded the outcome measure, which allowed a stronger assessment of the causal association between ICS therapy, dose, and device type, and oral thrush. Our findings are also strengthened by the large sample sizes and by the use of data from primary care practices, particularly since the population investigated here is more representative of real-life patients and of the clinical setting faced by practitioners than clinical trial populations [23]. However, observational database studies may be limited by selection bias and residual confounding. Our goal in using a matching approach was to minimise cohort baseline differences and identify treatment cohorts of similar baseline COPD severity and other relevant determinants, as would occur with the randomisation process in a clinical trial. However, we cannot entirely exclude the possibility of systematic differences between patient cohorts due to some unobserved baseline characteristics. Another study limitation is the possibility of misdiagnosis or miscoding of oral thrush in routine primary care practice.

In the study cohorts, the incidence of oral thrush never exceeded 10%. In the literature, there is a high variability in the reported incidence of oral thrush with ICS use, with rates ranging from <1% to >70%, likely reflecting differences in diagnostic criteria, as reviewed elsewhere[3,4]. Although a true diagnosis of oral thrush would require confirmation by culture for *Candida albicans*, the infection is routinely diagnosed by visual examination of the oral lesions without further confirmation, with the exception of immunocompromised or hospitalised patients. Therefore, here and in other studies, misclassification of oral thrush cannot be excluded. It is also plausible that some patients would self-diagnose oral thrush, using previous experience, and visit community-based pharmacies to treat oral infections with over-the-counter medications without visiting their general practitioner. Thus, the incidence of oral thrush in this study may be underestimated and future research could be improved by collection of pharmacy data.

Another explanation for the relatively low rate of oral thrush in our study may be poor adherence to therapy. Although adherence is difficult to assess using primary care prescribing data, poor adherence to inhaled treatment is a well-documented issue in chronic diseases, including asthma[45] and COPD[41]. Cooper et al. (2015)[12] found that patients who are more adherent to ICS experience more side-effects (including oral thrush). OPCRD, which was used in this study, collects data on prescriptions but it does not collect data on dispensing or actual use of drugs (or spacers); therefore, we cannot determine whether all patients effectively took their medications as prescribed. On the other hand, local side-effects of ICS may be the cause of poor compliance with therapy[12,13]. A clinical trial assessing long-term effects of ICS in COPD found that local side-effects, namely oral thrush and local irritation of the throat, were specified reasons for withdrawing from the trial[20]. This underlines the importance of investigating strategies to

reduce oral thrush with robust study designs, as good adherence is required to achieve appropriate disease control.

CONCLUSIONS

This study indicates that ICS treatment increases the incidence of oral thrush in patients with COPD and that this effect is dose-dependent for FP/SAL therapies. Of the therapies assessed in this study, and considering real-life prescribing patterns, FP/SAL pMDI and BUD/FOR DPI may represent more protective therapies against the local ICS side-effect oral thrush. In addition, our findings support implementation of guideline recommendations on spacer use, as additional reduction in oral thrush incidence may be achieved using spacer devices, especially for COPD patients with inhaler technique coordination problems. However, both device-related and patient-related factors can influence disease outcome when using inhaler medications. Therefore, the risk of side-effects should be carefully balanced against therapeutic outcomes, patients' preference, and patients' inhaler technique when choosing the most appropriate inhaler therapy for individual patients.

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Figure legends

Fig. 1. Flow chart of participation in the study. This figure shows the number of patients in the FDC ICS/LABA (A) and non-ICS (B) cohorts at different stages of the study, including the number of potentially eligible individuals at the start of the study, the number of individuals lost after screening for inclusion/exclusion criteria, and the final eligible patients.

Abbreviations: COPD = chronic obstructive pulmonary disease; FDC = fixed dose combination; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; QOF = quality and outcomes framework

*FDC ICS/LABA therapy included initiation of budesonide/formoterol fumarate dihydrate (BUD/FOR) DPI, fluticasone propionate/salmeterol xinafoate (FP/SAL) (DPI or pMDI) or beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FOR) (DPI or pMDI) at the index date

†Non-ICS therapy included initiation of LABA, LAMA, or their combination at the index date

Fig.2. Incidence of oral thrush by therapy and device. This figure shows the unadjusted and adjusted odds ratio (OR; 95% CI) for oral thrush for BUD/FOR DPI and FP/SAL pMDI arms (comparators) vs FP/SAL DPI arm (reference). In the comparison between FP/SAL pMDI and FP/SAL DPI, the intended inhaled corticosteroid (ICS) daily dose was not an *a priori* confounder and when added to the model the variable did not change the treatment effect, thus the fully adjusted OR is not shown for this cohort.

Abbreviations: BUD/FOR = budesonide/formoterol fumarate dihydrate; DPI = dry powder inhaler; pMDI = pressurised metered-dose inhaler; FP/SAL = fluticasone propionate/salmeterol xinafoate

*Adjusted for gastroesophageal reflux disease (GERD) in the baseline period

†Adjusted for GERD in the baseline period and for intended ICS daily dose in the outcome period

‡Adjusted for spacer device use in the outcome period

Tables

Table 1: Baseline demographic and clinical characteristics of unmatched and matched cohorts (patients prescribed FDC ICS/LABA or non-ICS therapies)

	Unmatched		Matched*	
	ICS/LABA† (n = 13,647)	**Non-ICS**‡ (n = 10,043)	**ICS/LABA**† (n = 8,255)	**Non-ICS**‡ (n = 8,255)
Age, mean (SD)	68.6 (10.1)	69.2 (9.9)	68.7 (9.9)	68.9 (9.7)
Sex§, male, n (%)	7,597 (55.7)	5,754 (57.3)	4,699 (56.9)	4,699 (56.9)
BMI§,¶				
N (% non-missing)	13,211 (96.8)	9,778 (97.4)	8,076 (97.8)	8,076 (97.8)
Mean (SD)	27.0 (5.9)	27.3 (5.7)	27.1 (5.8)	27.2 (5.7)
Smoking Status§, n (%)				
N (% non-missing)	13,184 (96.6)	9,706 (96.6)	8,056 (97.6)	8,056 (97.6)
Non-smoker	1,205 (9.1)	798 (8.2)	612 (7.6)	612 (7.6)
Current smoker	5,160 (39.1)	3,925 (40.4)	3,288 (40.8)	3,288 (40.8)
Ex-smoker	6,819 (51.7)	4,983 (51.3)	4,156 (51.6)	4,156 (51.6)
FEV_1 % predicted				
N (% non-missing)	12,541 (91.9)	9,400 (93.6)	7,574 (91.8)	7,739 (93.7)
Mean (SD)	57.0 (19.4)	59.4 (18.8)	56.9 (19.2)	59.4 (18.8)
mMRC score#, n (%)				
N (% non-missing)	12,199 (89.4)	9,146 (91.1)	7,326 (88.7)	7,524 (91.1)
0 - 1	6,411 (52.6)	5,140 (56.2)	3,913 (53.4)	4,291 (57.0)
≥ 2	5,788 (47.4)	4,006 (43.8)	3,413 (46.6)	3,233 (43.0)
COPD exacerbations**, n (%)				
0	5,996 (43.9)	5,403 (53.8)	4,026 (48.8)	4,450 (53.9)
1	3,905 (28.6)	2,683 (26.7)	2,597 (31.4)	2,173 (26.3)

2	2,067 (15.1)	1,192 (11.9)	941 (11.4)	1,014 (12.3)
≥ 3	1,679 (12.3)	765 (7.6)	691 (8.4)	618 (7.5)
Acute oral corticosteroid courses[††], n (%)				
0	9,136 (66.9)	7,640 (76.1)	5,969 (72.3)	6,305 (76.4)
1	2,887 (21.2)	1,688 (16.8)	1,650 (20.0)	1,371 (16.6)
2	1,035 (7.6)	462 (4.6)	413 (5.0)	380 (4.6)
≥ 3	589 (4.3)	253 (2.5)	223 (2.7)	199 (2.4)
Antibiotic courses (lower resp. consult.[‡‡]), n (%)				
0	7,596 (55.7)	6,257 (62.3)	4,978 (60.3)	5,135 (62.2)
1	3,196 (23.4)	2,245 (22.4)	1,950 (23.6)	1,843 (22.3)
2	1,582 (11.6)	941 (9.4)	763 (9.2)	790 (9.6)
≥ 3	1,273 (9.3)	600 (6.0)	564 (6.8)	487 (5.9)
GOLD grade[§§], n (%)				
N (% non-missing)	12,199 (89.4)	9,146 (91.1)	7,326 (88.7)	7,524 (91.1)
A	3,054 (25.0)	3,073 (33.6)	2,069 (28.2)	2,562 (34.1)
B	2,396 (19.6)	2,102 (23.0)	1,565 (21.4)	1,663 (22.1)
C	3,357 (27.5)	2,067 (22.6)	1,844 (25.2)	1,729 (23.0)
D	3,392 (27.8)	1,904 (20.8)	1,848 (25.2)	1,570 (20.9)
COPD therapy[§], n (%)				
None	3,232 (23.7)	2,532 (25.2)	2,628 (31.8)	2,139 (25.9)
SABA and/or SAMA	6,138 (45.0)	6,342 (63.1)	4,816 (58.3)	5,305 (64.3)
LABA (± SABA or ± SAMA)	1,459 (10.7)	674 (6.7)	422 (5.1)	422 (5.1)
LAMA (± SABA or ± SAMA)	2,818 (20.6)	495 (4.9)	389 (4.7)	389 (4.7)
Oral thrush[§], n (%)	373 (2.7)	234 (2.3)	84 (1.0)	84 (1.0)
Asthma[¶¶], n (%)	1,342 (9.8)	719 (7.2)	800 (9.7)	591 (7.2)

Rhinitis[¶¶], n (%)	1,043 (7.6)	807 (8.0)	592 (7.2)	630 (7.6)
Pneumonia, n (%)	253 (1.9)	99 (1.0)	149 (1.8)	84 (1.0)
GERD[¶¶], n (%)	1,069 (7.8)	853 (8.5)	590 (7.1)	691 (8.4)
Eczema, n (%)	1,979 (14.5)	1,561 (15.5)	1,175 (14.2)	1,255 (15.2)
Diabetes[§,¶¶], n (%)	2,729 (20.0)	2,043 (20.3)	1,516 (18.4)	1,516 (18.4)
Charlson comorbidity index score[##]				
Mean (SD)	1.9 (3.9)	1.7 (3.8)	1.90 (3.9)	1.7 (3.8)

Abbreviations: BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; GERD = gastroesophageal reflux disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC score = modified Medical Research Council score; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist

[*]Cohorts matched on the following baseline variables: sex, age (±5 years), smoking status, BMI, COPD exacerbations (categorised), COPD therapy, nasal corticosteroids, oral thrush diagnosis and/or medication, and diabetes diagnosis and/or medication (see Table S1)

[†]Fixed dose combination (FDC) ICS/LABA therapy, which included initiation of budesonide/formoterol fumarate dihydrate (BUD/FOR) DPI, fluticasone propionate/salmeterol xinafoate (FP/SAL) (DPI or pMDI) or beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FOR) (DPI or pMDI) at the index date

[‡]Non-ICS therapy included initiation of LABA, LAMA, or their combination at the index date; 10,043 are observations from 9,161 unique patients (patients may be included more than once with different first prescriptions for LABA, LAMA or their combination).

[§]Matching variable

[¶]Measured as kg/m^2

[#]mMRC score is used to assess the severity of breathlessness; both mMRC scores recorded in routine medical practice and patient mMRC scores were used, with the most recent score taking precedence

[**]Moderate/severe exacerbations within the baseline period included occurrence of any of the following: (a) acute course of oral corticosteroids; (b) antibiotics prescribed with a lower respiratory consultation; (c) COPD-related hospital admission to emergency department or hospital for COPD; (d) recorded hospitalisation admission on same day as a lower respiratory consultation (excluding the cases in which the only lower respiratory code recorded on that day was for a lung function test)

[††]Defined as all courses that are not maintenance therapy and/or all courses for which dosing instructions suggest exacerbation treatment (e.g. tapering doses from 6 to 1, or 30 mg as directed) and/or all courses with no dosing instructions but unlikely to be maintenance therapy owing to prescription strength or frequency of prescriptions

[‡‡]Lower respiratory consultation refers to lower respiratory diagnostic codes (including asthma, COPD, and lower respiratory tract infection [LRTI] read codes), or asthma/COPD review codes excluding any monitoring letter codes, or lung function and/or asthma monitoring AND any additional respiratory examinations, referrals, chest x-rays, or events. When >1 oral corticosteroid courses/antibiotic prescriptions occurred within 2 weeks of each other, these events were considered to be the result of the same course

[§§]GOLD grades based on 2011 GOLD guidelines[14]: **A** = Low risk, low symptom burden, mMRC = 0-1 and $FEV_1 \geq 50\%$ and/or low exacerbation rate (0-1/year); **B** = Low risk, higher symptom burden, mMRC ≥ 2 and $FEV_1 \geq 50\%$ and/or low exacerbation rate (0-1/year); **C** = High risk, low symptom burden, mMRC = 0-1 and

FEV_1 < 50% and/or high exacerbation rate (≥ 2/year); **D** = High risk, higher symptom burden, mMRC ≥ 2 and FEV_1 < 50% and/or high exacerbation rate (≥ 2/year)

[¶¶]With a diagnostic code recorded at any time prior to or at the index date; asthma patients with asthma resolved codes were excluded

[##]Calculated for the year prior to index date

Table 2: Incidence of oral thrush in patients prescribed FDC ICS/LABA or non-ICS therapy in the matched cohorts

n = 8,255 matched pairs[*]	Baseline		Outcome	
	ICS/LABA[†]	Non-ICS[‡]	ICS/LABA[†]	Non-ICS[‡]
Oral thrush, n (%)	84 (1.0)	84 (1.0)	456 (5.5)	227 (2.7)
Unadjusted OR (95% CI)	-	-	2.07 (1.76, 2.43)	1.00
Adjusted OR (95% CI)[§]	-	-	2.18 (1.84, 2.59)	1.00

Abbreviations: ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; OR = odds ratio

*Cohorts matched on the following baseline variables: sex, age (±5 years), smoking status, body mass index (BMI), COPD exacerbations (categorised), COPD therapy, nasal corticosteroids, oral thrush diagnosis and/or medication, and diabetes diagnosis and/or medication (see Table S1)

[†]Fixed dose combination (FDC) ICS/LABA therapy, which included initiation of budesonide/formoterol fumarate dihydrate (BUD/FOR) DPI, fluticasone propionate/salmeterol xinafoate (FP/SAL) (DPI or pMDI) or beclometasone dipropionate/formoterol fumarate dihydrate (BDP/FOR) (DPI or pMDI) at the index date

[‡]Non-ICS therapy included initiation of LABA, long-acting muscarinic agonist (LAMA), or their combination at the index date

[§]Adjusted for baseline confounders: categorised COPD-related consultations, categorised Charlson comorbidity index score, and categorised antibiotic courses

Table 3: Baseline demographic and clinical characteristics of patients in the matched BUD/FOR DPI + FP/SAL DPI and FP/SAL DPI + FP/SAL pMDI cohorts

	Matched cohorts*			
	BUD/FOR DPI (n = 3,465)	**FP/SAL DPI** (n = 3,465)	**FP/SAL pMDI** (n = 3,800)	**FP/SAL DPI** (n = 3,800)
Age, mean (SD)	68.1 (9.7)	68.2 (9.6)	68.8 (10.0)	68.6 (9.8)
Sex†, male, n (%)	1,994 (57.5)	1,994 (57.5)	2,157 (56.8)	2,157 (56.8)
BMI‡				
N (% non-missing)	3,368 (97.2)	3,344 (96.5)	3,686 (97.0)	3,667 (96.5)
Mean (SD)	26.9 (5.9)	27.0 (6.0)	27.0 (5.8)	27.0 (5.9)
Smoking Status†, n (%)				
N (% non-missing)	3,414 (98.5)	3,414 (98.5)	3,690 (97.1)	3,690 (97.1)
Non-smoker	249 (7.3)	249 (7.3)	297 (8.0)	297 (8.0)
Current smoker	1,323 (38.8)	1,323 (38.8)	1,470 (39.8)	1,470 (39.8)
Ex-smoker	1,842 (54.0)	1,842 (54.0)	1,923 (52.1)	1,923 (52.1)
FEV_1 % predicted				
N (% non-missing)	3,216 (92.8)	3,181 (91.8)	3,501 (92.1)	3,481 (91.6)
Mean (SD)	56.8 (19.1)	56.1 (19.4)	57.0 (19.1)	56.1 (19.3)
mMRC score§				
N (% non-missing)	3,172 (91.5)	3,114 (89.8)	3,361 (88.4)	3,401 (89.5)
0 - 1	1,692 (53.3)	1,581 (50.8)	1,768 (52.6)	1,742 (51.2)
≥ 2	1,480 (46.7)	1,533 (49.2)	1,593 (47.4)	1,659 (48.8)
COPD exacerbations†¶, n (%)				
0	1,546 (44.6)	1,546 (44.6)	1,676 (44.1)	1,676 (44.1)
1,	993 (28.7)	993 (28.7)	1,092 (28.7)	1,092 (28.7)
2	522 (15.1)	522 (15.1)	571 (15)	571 (15)

≥ 3	404 (11.7)	404 (11.7)	461 (12.1)	461 (12.1)
Acute oral corticosteroid courses[#], n (%)				
0	2,299 (66.3)	2,346 (67.7)	2,592 (68.2)	2,567 (67.6)
1	759 (21.9)	710 (20.5)	772 (20.3)	774 (20.4)
2	265 (7.6)	260 (7.5)	280 (7.4)	291 (7.7)
≥ 3	142 (4.1)	149 (4.3)	156 (4.1)	168 (4.4)
Antibiotic courses (lower resp. consult.[**]), n (%)				
0	1,932 (55.8)	1,951 (56.3)	2,113 (55.6)	2,125 (55.9)
1	828 (23.9)	808 (23.3)	889 (23.4)	882 (23.2)
2	404 (11.7)	397 (11.5)	443 (11.7)	442 (11.6)
≥ 3	301 (8.7)	309 (8.9)	355 (9.3)	351 (9.2)
GOLD grade[††], n (%)				
N (% non-missing)	3,172 (91.5)	3,114 (89.9)	3361 (88.4)	3401 (89.5)
A	792 (25.0)	731 (23.5)	876 (26.1)	804 (23.6)
B	633 (20.0)	624 (20.0)	658 (19.6)	675 (19.8)
C	900 (28.4)	850 (27.3)	892 (26.5)	938 (27.6)
D	847 (26.7)	909 (29.2)	935 (27.8)	984 (28.9)
COPD therapy, n (%)				
None	841 (24.3)	846 (24.4)	876 (23.1)	926 (24.4)
SABA and/or SAMA	1,622 (46.8)	1,441 (41.6)	1,741 (45.8)	1,584 (41.7)
LABA (± SABA or ± SAMA)	317 (9.1)	332 (9.6)	488 (12.8)	359 (9.4)
LAMA (± SABA or ± SAMA)	685 (19.8)	846 (24.4)	695 (18.3)	931 (24.5)
Oral thrush[†], n (%)	13 (0.4)	11 (0.3)	13 (0.3)	14 (0.4)
Asthma[§§], n (%)	320 (9.2)	313 (9)	391 (10.3)	344 (9.1)
Rhinitis[§§], n (%)	277 (8)	266 (7.7)	268 (7.1)	288 (7.6)

Pneumonia, n (%)	48 (1.4)	74 (2.1)	71 (1.9)	82 (2.2)
GERD[§§], n (%)	303 (8.7)	247 (7.1)	279 (7.3)	278 (7.3)
Eczema, n (%)	493 (14.2)	519 (15)	511 (13.4)	581 (15.3)
Diabetes[†§§], n (%)	651 (18.8)	651 (18.8)	746 (19.6)	746 (19.6)
Charlson comorbidity index score[¶¶]				
Mean (SD)	1.9 (3.8)	1.8 (3.9)	1.9 (4.0)	1.9 (4.0)

Abbreviations: BMI = body mass index; BUD/FOR = budesonide/formoterol fumarate dihydrate; DPI = dry powder inhaler; FEV_1 = forced expiratory volume in 1 second; FP/SAL = fluticasone propionate/salmeterol xinafoate; GERD = gastroesophageal reflux disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC score = modified Medical Research Council score; pMDI = pressurised metered-dose inhaler; SABA = short-acting β_2-agonist; SAMA = short-acting muscarinic antagonist

*Cohorts matched on the following baseline variables: sex, age (±5 years), smoking status, COPD exacerbations (categorised), oral thrush diagnosis and/or medication, and diabetes diagnosis and/or medication (see Figure S2)

[†]Matching variable

[‡]Measured as kg/m^2

[§]mMRC score is used to assess the severity of breathlessness; both mMRC scores recorded in routine medical practice and patient mMRC scores were used, with the most recent score taking precedence

[¶]Moderate/severe exacerbations within the baseline period included any of the following: (a) acute course of oral corticosteroids; (b) antibiotics prescribed with a lower respiratory consultation; (c) coded admission to emergency department or hospital for COPD; (d) recorded hospitalisation admission on same day as a lower respiratory consultation (excluding the cases in which the only lower respiratory code recorded on that day was for a lung function test)

[#]Defined as all courses that are not maintenance therapy and/or all courses for which dosing instructions suggest exacerbation treatment (e.g. 6-1 reducing, or 30 mg as directed) and/or all courses with no dosing instructions but unlikely to be maintenance therapy owing to prescription strength or frequency of prescriptions

[**]Lower respiratory consultation refers to lower respiratory diagnostic codes (including asthma, COPD, and lower respiratory tract infection [LRTI] read codes), or asthma/COPD review codes excluding any monitoring letter codes, or lung function and/or asthma monitoring AND any additional respiratory examinations, referrals, chest x-rays, or events. When >1 oral corticosteroid courses/antibiotic prescriptions occurred within 2 weeks of each other, these events were considered to be the result of the same course

[††]GOLD grades based on 2011 GOLD guidelines[14]: **A** = Low risk, low symptom burden, mMRC = 0-1 and $FEV_1 \geq 50\%$ and/or low exacerbation rate (0-1/year); **B** = Low risk, higher symptom burden, mMRC ≥ 2 and $FEV_1 \geq 50\%$ and/or low exacerbation rate (0-1/year); **C** = High risk, low symptom burden, mMRC = 0-1 and $FEV_1 < 50\%$ and/or high exacerbation rate (≥ 2/year); **D** = High risk, higher symptom burden, mMRC ≥ 2 and $FEV_1 < 50\%$ and/or high exacerbation rate (≥ 2/year)

[§§]With a diagnostic code recorded at any time prior to or at the index date; asthma patients with asthma resolved codes were excluded

[¶¶]Calculated for the year prior to index date

Table 4: Incidence of oral thrush by ICS dose

BUD/FOR DPI + FP/SAL DPI cohort	Intended ICS daily dose* (µg)			Total
	<500	**500-999**	**≥1000**	
Oral thrush, n (%)	210 (5.6)	61 (6.8)	169 (7.4)	440 (6.3)
Total, n (%)	3,747 (100)	899 (100)	2,284 (100)	6,930 (100)
Unadjusted OR (95% CI)	1.00	1.22 (0.82, 1.83)	1.36 (1.06, 1.73)	
Adjusted OR (95% CI)†	1.00	1.33 (0.63, 2.82)	1.42 (0.70, 2.88)	
FP/SAL pMDI + FP/SAL DPI cohort	Intended ICS daily dose* (µg)			Total
	<500	**500-999**	**≥1000**	
Oral thrush, n (%)	35 (4.7)	123 (5.4)	329 (7.2)	487 (6.4)
Total, n (%)	748 (100)	2,300 (100)	4,552 (100)	7,600 (100)
Unadjusted OR (95% CI)	1.00	1.36 (0.82, 2.24)	1.91 (1.20, 3.05)	
Adjusted OR (95% CI)‡	1.00	1.47 (0.88, 2.46)	1.97 (1.22, 3.17)	

Abbreviations: BUD/FOR = budesonide/formoterol fumarate dihydrate; DPI = dry powder inhaler; FP/SAL = fluticasone propionate/salmeterol xinafoate; pMDI = pressurised metered-dose inhaler

*Expressed in FP equivalent units

†Adjusted for gastroesophageal reflux disease (GERD) in the baseline period and treatment group in the outcome period

‡Adjusted for spacer device use and treatment group in the outcome period

Figure 1

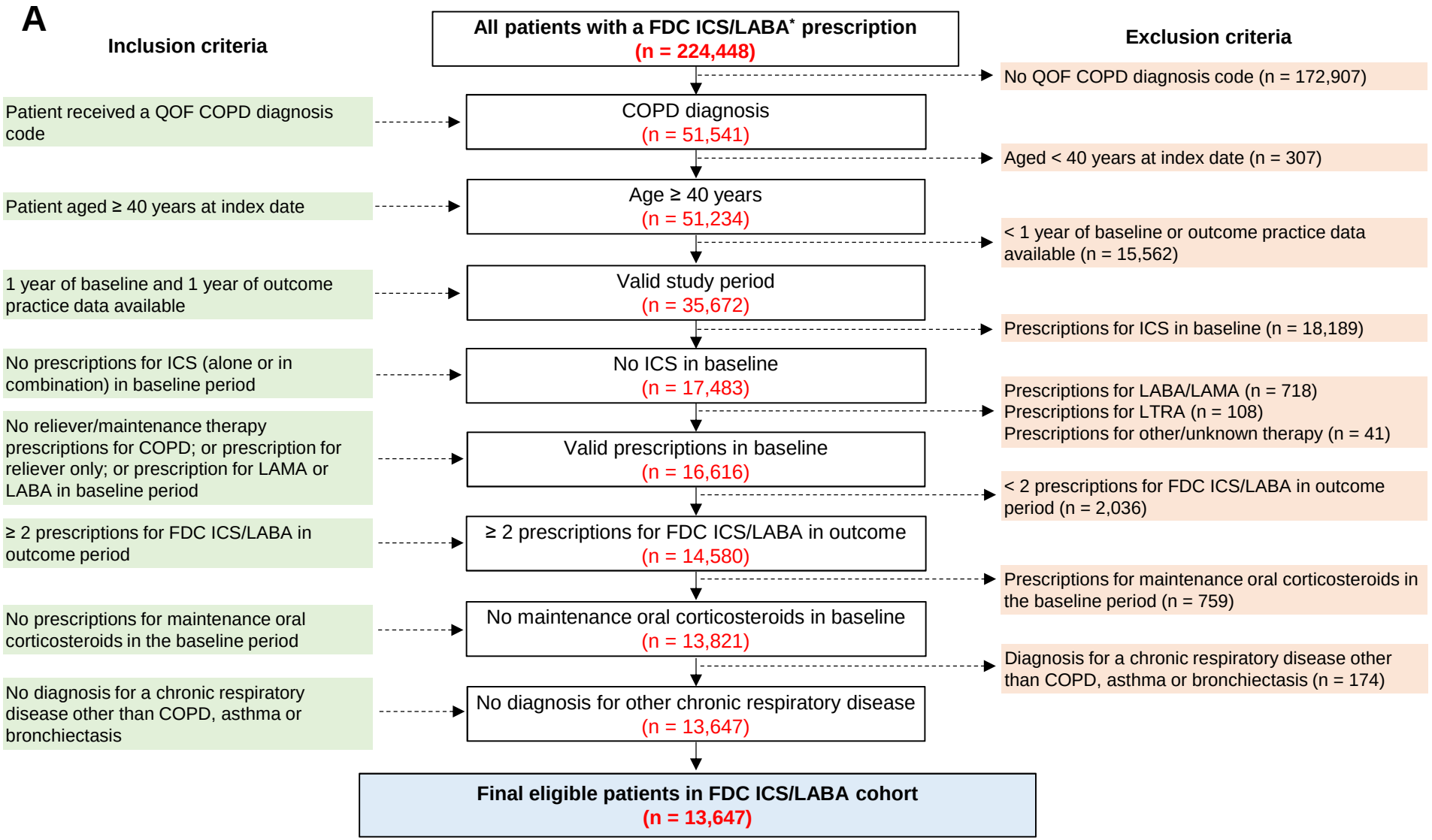
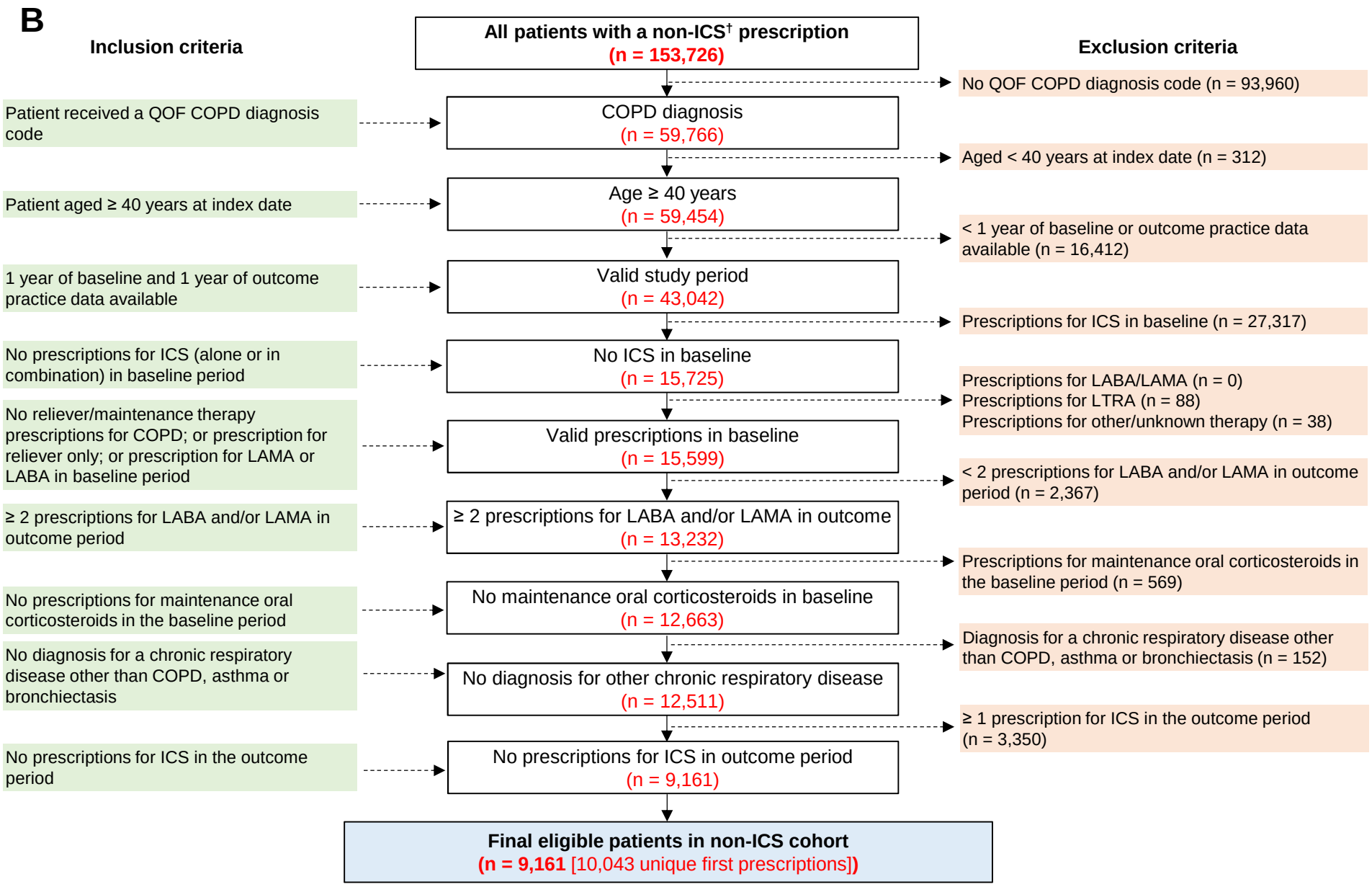
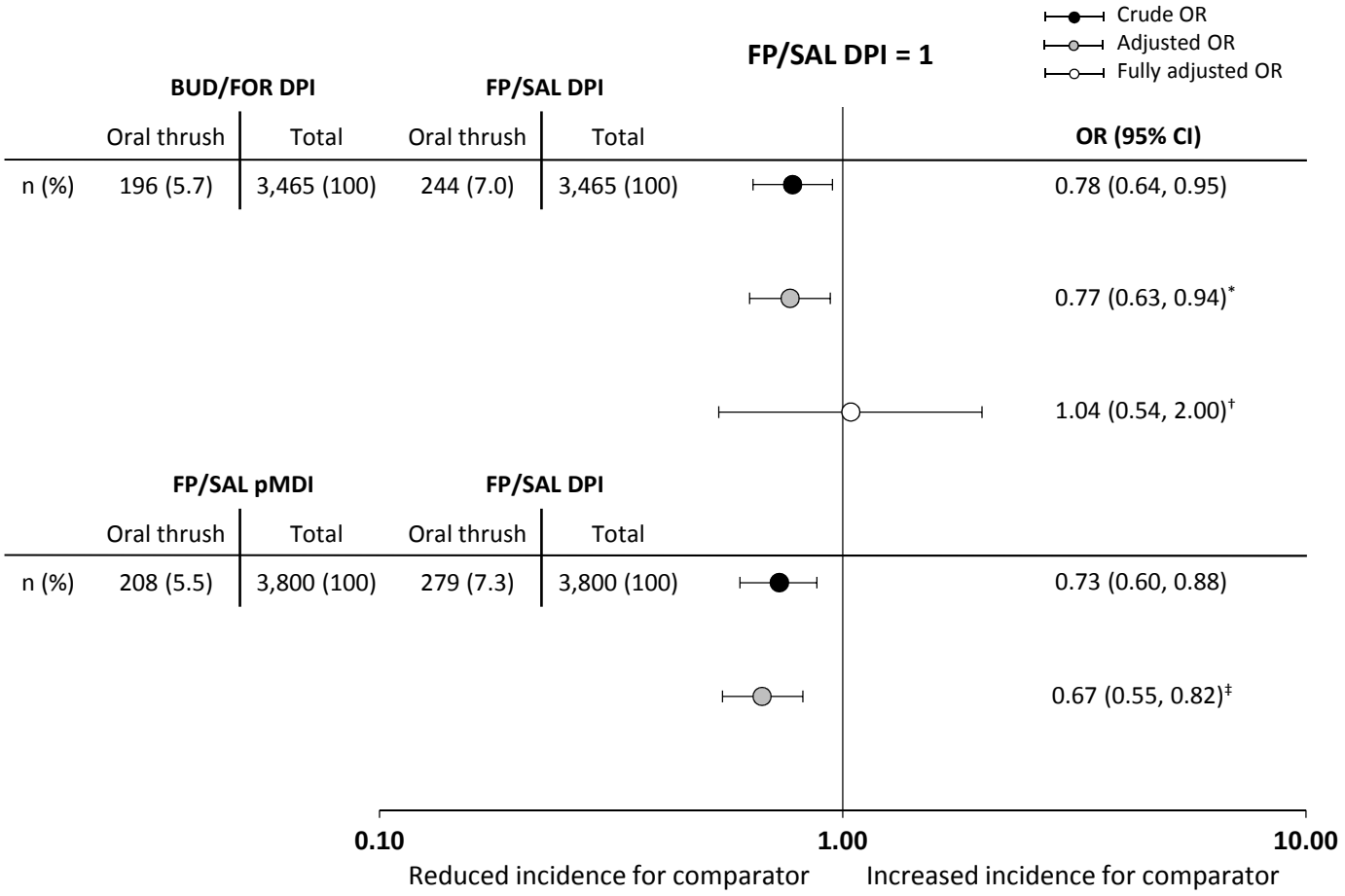


Figure 1




Crude OR
Adjusted OR
Fully adjusted OR
FP/SAL DPI = 1
BUD/FOR DPI
FP/SAL DPI
Oral thrush
Total
Oral thrush
Total
OR (95% CI)
n (%)
196 (5.7)
3,465 (100)
244 (7.0)
3,465 (100)
0.78 (0.64, 0.95)
0.77 (0.63, 0.94)*
1.04 (0.54, 2.00)†
FP/SAL pMDI
FP/SAL DPI
Oral thrush
Total
Oral thrush
Total
n (%)
208 (5.5)
3,800 (100)
279 (7.3)
3,800 (100)
0.73 (0.60, 0.88)
0.67 (0.55, 0.82)‡
0.10
1.00
10.00
Reduced incidence for comparator
Increased incidence for comparator

Highlights

- Real-life occurrence of oral thrush in patients with COPD prescribed ICS is reported
- Effect of different ICS types, doses, and delivery devices is investigated
- Some therapeutic strategies are more protective than others against oral thrush