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Real-world effectiveness evaluation of budesonide/formoterol Spiromax for the management of asthma and chronic obstructive pulmonary disease in the UK

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ABSTRACT

Objectives Budesonide/formoterol (BF) Spiromax® is an inhaled corticosteroid/long-acting β₂-agonist fixed-dose combination (FDC) inhaler, designed to minimise common inhaler errors and provide reliable and consistent dose delivery in asthma and chronic obstructive pulmonary disease (COPD). We evaluated non-inferiority of BF Spiromax after changing from another FDC inhaler, compared with continuing the original inhaler.

Methods Patients with asthma and/or COPD who switched to BF Spiromax were matched (1:3) with non-switchers. Data were obtained from the Optimum Patient Care Research Database and Clinical Practice Research Datalink in the UK. The primary end point was the proportion of patients achieving disease control (using the risk domain control (RDC) algorithm); secondary end points were: exacerbation rate, short-acting β₂-agonist (SABA) use and treatment stability (achieved RDC; no maintenance treatment change). Non-inferiority was defined as having 95% CI lower bound above −10%, using conditional logistic regression and adjusted for relevant confounders.

Results Comparing 385 matched patients (asthma 253; COPD 132) who switched to BF Spiromax with 1091 (asthma 743; COPD 348) non-switchers, non-inferiority of BF Spiromax in RDC was demonstrated (adjusted difference: +6.6%; 95% CI −0.3 to 13.5). Among patients with asthma, switchers to BF Spiromax versus BF Turbuhaler® reported fewer exacerbations (adjusted rate ratio (RR) 0.76;95% CI 0.60 to 0.99; p=0.044); were less likely to use high daily doses of SABA (adjusted OR 0.71;95% CI 0.52 to 0.98; p=0.034); used fewer SABA inhalers (adjusted RR 0.92;95% CI 0.86 to 0.99; p=0.019); and were more likely to achieve treatment stability (adjusted OR 1.44;95% CI 1.02 to 2.04; p=0.037). No significant differences in these end points were seen among patients with COPD.

Conclusions Among UK patients with asthma and COPD, real-world use of BF Spiromax was non-inferior to BF Turbuhaler in terms of disease control. Among patients with asthma, switching to BF Spiromax was associated with reduced exacerbations, reduced SABA use and

Strengths and limitations of this study

► Clearly defined *a priori* hypothesis, end points and sample size.
► A non-selective patient population, obtained through the use of real-world data from validated databases of primary care patients, with sufficient follow-up period for observing relevant outcomes.
► Hospital admissions, accident and emergency (A&E) attendances and outpatient visits are not systematically recorded in primary care databases, and the applied definition to identify asthma-related hospital admissions or A&E events may have given rise to false positive events.
► Potential effects of inhaler technique on the reported outcomes could not be taken into account, as this would require close observation and communication with each patient as they demonstrated their inhaler technique.
► Observed differences in secondary outcomes could have arisen as a consequence of factors unrelated to the inhalers that might not have been captured in the data set.

improved treatment stability versus continuing on BF Turbuhaler.

INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are common respiratory conditions.[1][2] Cornerstone asthma/COPD treatment consists of inhaled therapy with proven efficacy in randomised clinical trials (RCTs).[3][4] In real life, however, incorrect inhaler use is common in patients with asthma or COPD, resulting in poor symptom control and worse outcomes.[5][6] Specifically, critical inhaler errors were reported in a review of 3660 patients;[7] insufficient respiratory effort

in dry-powder inhaler (DPI) users and actuation before inhalation in metered-dose inhaler (MDI) users were found to be associated with uncontrolled asthma.[7]

In April 2014, marketing authorisation was granted for DuoResp® Spiromax® (Teva Pharmaceutical Industries, Petach Tikva, Israel), an inhaler containing a fixed-dose combination (FDC) of the inhaled corticosteroid (ICS) budesonide and the long-acting β_2-agonist (LABA) formoterol (budesonide/formoterol (BF)). The Spiromax inhaler was designed to maximise ease of use, reliability of dosing and consistency of lung deposition[8 9] in patients with asthma or COPD. Spiromax is a breath-actuated, multidose DPI that is similar in design and appearance to MDI, but uses a different internal configuration. Drug delivery is via the X-ACT® system, consisting of active metering (on opening the cap, an air pump transfers the drug from the drug reservoir to the dose cup) and cyclone separator technology (turbulent airflow), which breaks up the dry-powder blend and separates fine drug particles from larger lactose particles.[8] Spiromax requires only one preparation step (opening the cap) and provides consistent dose delivery across a broad range of inspiratory flow rates.[8 9] Recent findings suggest that Spiromax is associated with a reduced number of errors related to dose preparation, undertaking the steps needed to correctly deliver the dose during inhalation and handling the device after inhalation, as well as being easier for patients and healthcare professionals to use compared with other DPIs.[10 11] BF Spiromax has demonstrated pharmacokinetic bioequivalence to BF Turbuhaler® (AstraZeneca UK Limited, UK) in healthy volunteers.[12 13] A recent independent study of COPD found BF Spiromax to have a faster onset of bronchodilation than BF Turbuhaler, likely due to differences in drug deposition between the two devices.[14] However, evidence for the real-world effectiveness of BF Spiromax in comparison with other inhalers in patients with asthma and/or COPD is lacking.

The current study was part of a multiphase assessment of real-world outcomes over 1 year in patients with asthma and/or COPD who switched to BF Spiromax compared with patients who remained on another device, using data from two UK primary care administrative databases. The primary objective of this phase of the study was to evaluate the non-inferiority of changing from another FDC inhaler to BF Spiromax versus continuing to use the original FDC inhaler, in terms of achieving disease control, based on the risk domain control (RDC) algorithm; secondary objectives included the effects of the switch on the occurrence of moderate/severe exacerbations and respiratory-related hospitalisations, treatment stability and short-acting β2-agonist (SABA) use.

METHODS
Patients and study design
This was a matched, historic cohort study of patients with asthma and/or COPD using two validated primary care databases of patients in the UK, the Optimum Patient Care

Research Database (OPCRD) and the Clinical Practice Research Datalink (CPRD).[15 16] OPCRD is governed by The Anonymous Data Ethics Protocols and Transparency committee, commissioned by the Respiratory Effectiveness Group.[17] CPRD is a UK government research service, jointly supported by the National Institute for Health Research and the Medicines and Healthcare Products Regulatory Agency, that provides access to anonymised National Health Service (NHS) data. It operates under a range of UK and European laws as well as NHS and other guidelines.[16] This study is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (Register number EUPAS13238).[18]

The OPCRD and CPRD databases were searched 2010 onwards to identify prescriptions of BF Spiromax, BF Turbuhaler and fluticasone propionate/salmeterol (FS) Accuhaler/Diskus (GlaxoSmithKline, Uxbridge, UK) in patients ≥18 years of age with asthma and/or COPD (figure 1). The OPCRD and CPRD data sets for this study were constructed separately and checked for overlap before pooling to exclude duplicate patients. Patients had to have at least 2 years of data, comprising a minimum of one baseline year and 1 year of outcome period. Patients were required to have at least three prescriptions for ICS/LABA FDC (BF Spiromax, BF Turbuhaler or FS Accuhaler® /Diskus®) therapy during the baseline period. Switch patients must have evidence of an initial BF Spiromax prescription in the outcome period as well as at least one supplementary prescription for BF Spiromax in the 1 year outcome period to ensure consistent usage. Likewise, patients remaining on their inhaler required at least one repeat prescription in the outcome period. We only included patients switching to BF Spiromax who were registered at practices considered to have a policy of BF Spiromax adoption or wholesale change (ie, the decision to switch inhaler was based on cost savings instead of clinical reasons). Such practices were identified as those at which at least five patients changed to BF Spiromax within a 3-month period. The current study includes only patients who stayed on BF Turbuhaler or switched from BF Turbuhaler to BF Spiromax, due to the low number of patients who switched from FS Accuhaler/Diskus to BF Spiromax. The date of the first prescription of BF Spiromax or the (matched) date of the repeat prescription for BF Turbuhaler in the control arm was the index date. The recommended dosing instructions of BF Turbuhaler and BF Spiromax in adults are the same (asthma: one to two inhalations twice daily; COPD: two inhalations twice daily), and we observed no significant differences in prescribed dose between BF Spiromax and BF Turbuhaler in the disease groups.

Patients with asthma were required to have a diagnostic code (Read code)[19] for asthma and/or at least two prescriptions for asthma therapy during the baseline year, and to have no other chronic respiratory disease diagnosis. Patients with COPD were required to be at least 40 years of age at first prescription for BF Spiromax or the matching BF Turbuhaler prescription, and to have
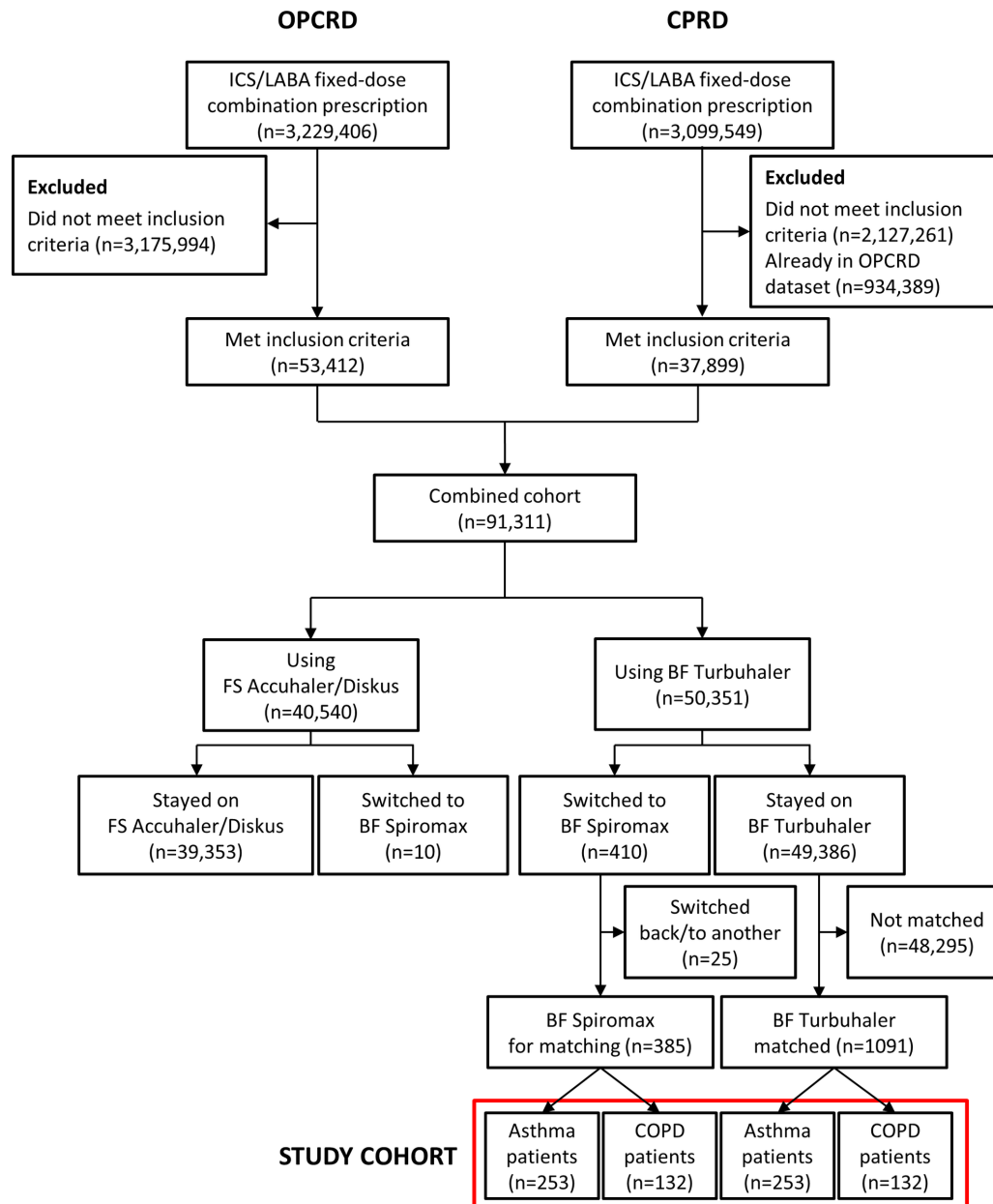
Figure 1 Patient flow diagram (prior to matching). BF, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; FS, fluticasone propionate/salmeterol; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; OPCRD, Optimum Patient Care Research Database.

a diagnostic code for COPD and a postbronchodilator $FEV_1/FVC < 0.70$ consistent with the criteria for inclusion in the UK register of patients with COPD (Quality and Outcomes Framework). The subgroup of patients with only an asthma diagnosis is referred to henceforth as the asthma group. The patients with a COPD diagnosis (with or without an asthma diagnosis) are henceforth referred to as the COPD group.

Outcome measures

The primary outcome was disease control as assessed by RDC, a composite measure that has been used in several similar matched historical cohort studies to define absence of exacerbations.[20–23] To achieve RDC in this study, patients must not have an asthma/COPD-related

hospital admission, an asthma/COPD-related accident and emergency (A&E) attendance or a course of oral corticosteroids (OCS) during the outcome period. In addition, patients in the COPD group must not have received antibiotics for a lower respiratory tract infection (LRTI).

Secondary outcomes included the number of moderate/severe exacerbations and hospitalisations, and change in treatment stability. A moderate/severe exacerbation (for COPD) or severe exacerbation (for asthma) was defined following the American Thoracic Society/European Respiratory Society Task Force position statements.[24] Lower respiratory hospitalisations were identified and classified as follows: definite hospitalisations were

those with a lower respiratory code, including asthma and LRTI codes; or a generic hospitalisation Read code that has been recorded on the same day as a lower respiratory consultation; definite+probable hospitalisations were those occurring within a 7-day window (either side of the hospitalisation date) of a lower respiratory Read code. Adequate treatment stability was defined as achieving RDC and no increase in dose, change in delivery device, and change in type of ICS and/or use of LABAs, theophylline, long-acting muscarinic antagonists, or leukotriene receptor antagonists.[22] Additional outcomes were SABA usage, which was expressed as average daily SABA dosage during the outcome year and calculated from prescriptions as ((*Count of inhalers × doses in pack × µg strength*)/365), and a pneumonia event which was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest X-ray within 1 month (definite pneumonia).

Statistical analyses

It was estimated that 349 patients would have 90% power to demonstrate non-inferiority of BF Spiromax and BF Turbuhaler for achieving RDC, at a one-sided significance level of 0.050. For the calculation, an expected difference in proportions of zero was used, assuming that the proportion of discordant pairs was 0.458. This assumption was based on previous studies showing that a weighted average of 71.6% of patients with asthma and COPD prescribed FDC therapy have no exacerbations over a 1-year period.[25 26]

Descriptive statistics of all baseline demographic characteristics, comorbidities, medication use, indicators of disease severity and other patient characteristics were computed separately for the patients in the BF Spiromax and BF Turbuhaler groups and for patients in the asthma and COPD groups. In cases where multiple observations existed for a patient, one was randomly selected. Continuous variables were summarised using the number of non-missing observations, percentage of non-missing observations, mean, SD, median and IQR (difference between the 25th and 75th centiles), and a p value for the Kruskal-Wallis equality-of-populations rank test. Binary and categorical variables were summarised using the percentage of non-missing observations, the frequency and percentages (based on the non-missing sample size) of observed levels, and a p value for the Pearson's χ^2 test of independent categories.

Patients who switched to BF Spiromax were compared with matched controls who stayed on BF Turbuhaler. Mixed matching was performed 1:3 so that each BF Spiromax patient would be matched with up to three patients who remained on BF Turbuhaler (see supplementary methods in appendix for a full description of the mixed matching process). Mixed matching was performed to increase precision of the effect estimates. Because the analyses were conducted on all of the matched patients, which could introduce residual confounding due to imbalanced matching ratios, a sensitivity analysis was performed in which the outcome analyses were also performed in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Matching was performed using the most relevant confounders which were identified based on baseline imbalance and bias potential in relation to the primary outcome. For asthma, these confounders included age, gender, number of antibiotic courses, number of OCS courses, Global Initiative for Asthma control categories, number of exacerbations and RDC; matching confounders for COPD included age, gender, drug therapy, ICS average daily dose, number of antibiotic courses, number of exacerbations and Global Initiative for Chronic Obstructive Lung Disease risk categories. Baseline imbalance was assessed using the standardised mean difference (SMD), which, unlike a p value, is not affected by the number of observations in a sample,[27 28] and provides information on the size of the difference. An SMD of ≤10% was assumed to represent sufficient balance between the arms,[29] and the formula used is presented in the supplementary methods in appendix. Bias potential is the degree to which the observed association between the exposures of interest and the outcome is affected by conditioning on another variable; the formula is presented in the supplementary methods in appendix. A sensitive bias potential cut-off of ≥2% was used for this study.

Baseline variables with highest bias potential that were also insufficiently balanced were presented to a panel of experts for final selection. Following matching, the process was repeated in the matched sample to identify any residual confounding.

After mixed matching, conditional logistic regression of the between-patient difference in the primary outcome was performed to provide a 95% CI with which to assess non-inferiority. Analyses were undertaken for the patients in the asthma and COPD groups combined, as well as by disease group. The model was adjusted for baseline variables that remained with bias potential after matching. Non-inferiority was claimed if the lower bound of the 95% CI for the primary end point (RDC) was above −10%, a difference widely regarded as clinically important for many outcomes in respiratory studies,[30 31] and used previously in similar real-life studies of patients in primary care settings.[22 23] If non-inferiority was achieved, superiority was tested.

Secondary outcomes were analysed in the matched sample and adjusted for baseline variables that remained with bias potential after matching, and reported as conditional rate ratios (RRs) or ORs with their 95% CIs. Number of exacerbations and hospitalisations were analysed in the matched sample using conditional Poisson regression to obtain estimates of relative rates. Treatment stability was analysed in the matched sample using conditional logistic regression, and SABA usage was analysed in the matched sample using conditional ordinal logistic regression, after the SABA average daily dose was categorised.

All statistical analyses were conducted using Stata MP6 V.12 and Stata SE V.14 (StataCorp, College Station, Texas, USA). A statistically significant result was defined as p<0.05.

Patient and public involvement

No patients or public were involved in the design or conduct of this retrospective database study.

RESULTS
Study population

Overall, 420 patients switched to BF Spiromax (figure 1). Of the patients who used BF Turbuhaler, 410 switched to BF Spiromax and 49 386 remained on BF Turbuhaler. Baseline characteristics of these unmatched patients are shown in supplementary table 1, where imbalanced covariates (SMD >10%) for asthma include mean age, drug therapy, ICS average daily dose and number of exacerbations in baseline years; those for COPD include smoking status, drug therapy and ICS average daily dose.

For the matched analysis, a total of 385 patients switching to BF Spiromax were analysed; a total of 1091 patients who stayed on BF Turbuhaler were matched to the switch patients (figure 1). Twenty-five patients who switched back to BF Turbuhaler or to another FDC ICS/LABA were not included in the analysis. In the baseline characteristics of the matched patients, covariates with SMD >10% in the asthma group were body mass index and ischaemic heart disease; for COPD they were smoking status, ischaemic heart disease, heart failure, number of exacerbations and number of acute OCS courses (table 1).

Outcomes analyses

Descriptive statistics of disease outcomes in the matched patients are shown in table 2. The FDC average daily dose was numerically lower among patients using BF Spiromax in the asthma group (382.1 µg vs 505.3 µg) and mean per cent RDC was higher among patients using BF Spiromax in both the asthma (73.1% vs 68.0%) and COPD (40.2% vs 37.1%) groups (table 2).

The lower bound of the 95% CI of the adjusted percentage difference in the frequency of achieving RDC in the combined population was −0.3%, meeting the criterion for non-inferiority of switching to BF Spiromax compared with continuing on BF Turbuhaler (figure 2). Although a higher proportion of patients achieved RDC in the group that switched to BF Spiromax compared with patients who stayed on BF Turbuhaler, the difference was not statistically significant, and the mean between-group difference was less than the 10% considered to be clinically relevant.[22 23 30 31] In the sensitivity analysis where only BF Spiromax switchers that had three matched controls were used, a significant difference was shown in the combined patients group (adjusted % difference 8.3; 95% CI 1.0% to 15.6%; p=0.025) (data not shown). In the sensitivity analysis, the adjusted percentage difference was nearly 10% in the COPD group but there was a wide

CI (adjusted % difference 9.9; 95% CI −2.4% to 22.2%; p=0.114). Similarly, in the asthma group, the adjusted percentage difference was 6.5% (95% CI −2.7% to 15.7%; p=0.168). The conditional logistic regression model in all matched patients showed an adjusted OR of 1.31 (95% CI 0.99 to 1.73; p=0.061) for BF Spiromax versus BF Turbuhaler for RDC, which did not achieve statistical significance. However, in the sensitivity analysis, the OR of 1.41 was statistically significant (95% CI 1.05 to 1.90; p=0.022) (data not shown).

Secondary outcomes shown are expressed as adjusted conditional RRs (figure 3a) and ORs (figure 3b) separately for patients with asthma and those with COPD. Among patients with asthma, switchers to BF Spiromax versus BF Turbuhaler reported fewer exacerbations, were less likely to use high amounts of SABA daily dose, used fewer SABA inhalers and were more likely to achieve treatment stability. Among patients with COPD, no significant differences in these end points were seen between those who switched to BF Spiromax and those staying on BF Turbuhaler. CIs for patients who switched to BF Spiromax show a trend effect for lower risk of being on high-dose SABA therapy and reduction in use of SABA inhalers in the COPD group. In the combined patients group, significance among switchers to BF Spiromax was noted in SABA average daily dose (OR 0.70; 95% CI 0.53 to 0.94; p=0.017), reduction in use of SABA inhalers (RR 0.94; 95% CI 0.89 to 0.99; p=0.012) and improved treatment stability (OR 0.74; 95% CI 0.56 to 0.99; p=0.041).

DISCUSSION

This study, the first to compare the real-world effectiveness of switching to the BF Spiromax inhaler from BF Turbuhaler, found that among 253 patients with asthma and 132 patients with COPD, BF Spiromax showed non-inferiority with respect to achievement of disease control to BF Turbuhaler in matched patients with asthma and/or COPD. In the primary analysis in the combined population, patients who switched to BF Spiromax had 31% higher odds of achieving RDC compared with those who remained on BF Turbuhaler; however, this finding did not meet the threshold for statistical significance.

Patients in the asthma group who switched to BF Spiromax had significantly reduced SABA use, fewer exacerbations and greater treatment stability compared with matched patients who remained on BF Turbuhaler. Some of the observed reductions in SABA use associated with BF Spiromax may have arisen as a result of patients using their new device as a reliever medication in addition to its use as maintenance therapy. The use of BF in a single-inhaler maintenance and quick-relief therapy regimen has been recommended as an improved method of administering ICS/LABA therapy.[32 33] However, the recommendations are not device-specific; as such, SABA use was not expected to differ between switchers to Spiromax and those who remained on Turbuhaler. The difference may be partially explained by the greater resemblance to an

Table 1 Patient characteristics in matched analysis

Variable	Patients with asthma				Patients with COPD			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P value	SMD (%)
Mean (SD) age, years	55.9 (15.3)	55.8 (15.1)	0.9101	0.7	70.5 (8.8)	70.5 (8.5)	0.9512	0.2
Men, n (%)	112 (44.3)	331 (44.5)	0.9382	0.6	66 (50.0)	184 (52.9)	0.5736	5.7
Body mass index*, n (%)			0.4038	12.1			0.6977	7.4
<18.5 kg/m²	3 (1.3)	9 (1.2)			6 (4.7)	11 (3.2)		
18.5 to <25 kg/m²	65 (27.2)	163 (22.5)			46 (35.7)	112 (32.4)		
25 to <30 kg/m²	88 (36.8)	265 (36.5)			39 (30.2)	120 (34.7)		
>30 kg/m²	83 (34.7)	289 (39.8)			38 (29.5)	103 (29.8)		
Smoking status†, n (%)			0.7393	5.2			0.5696	10.8
Non-smoker	126 (50.8)	397 (53.6)			14 (10.6)	48 (13.9)		
Current smoker	44 (17.7)	123 (16.6)			36 (27.3)	98 (28.3)		
Ex-smoker	78 (31.5)	220 (29.7)			82 (62.1)	200 (57.8)		
Cardiovascular disease, n (%)								
Ischaemic heart disease	13 (5.1)	62 (8.3)	0.0951	12.8	22 (16.7)	78 (22.4)	0.1662	14.5
Heart failure	1 (0.4)	8 (1.1)	0.3225	8.0	4 (3.0)	23 (6.6)	0.1286	16.7
Exacerbations, n (%)			0.9869	3.6			0.7809	12.9
0	199 (78.7)	593 (79.8)			54 (40.9)	156 (44.8)		
1	42 (16.6)	120 (16.2)			38 (28.8)	106 (30.5)		
2	7 (2.8)	18 (2.4)			15 (11.4)	35 (10.1)		
3	4 (1.6)	9 (1.2)			13 (9.8)	28 (8.0)		
≥4	1 (0.4)	3 (0.4)			12 (9.1)	23 (6.6)		
No. of respiratory-related hospital admissions, n (%)			1.0000	0			0.1460	2.8
0	253 (100.0)	743 (100.0)			129 (97.7)	338 (97.1)		
1	0	0			1 (0.8)	9 (2.6)		
≥2	0	0			2 (1.5)	1 (0.3)		
Uncontrolled risk domain control, n (%)	70 (27.7)	194 (26.1)	0.6278	3.5	78 (59.1)	192 (55.2)	0.4397	7.9

Continued

Table 1 Continued

Variable	Patients with asthma				Patients with COPD			
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	P value	SMD (%)	BF Spiromax (n=132)	BF Turbuhaler (n=348)	P value	SMD (%)
No. of antibiotic courses, n (%)			0.8362	5.5			0.9478	6.4
0	212 (83.8)	630 (84.8)			74 (56.1)	198 (56.9)		
1	34 (13.4)	99 (13.3)			37 (28.0)	104 (29.9)		
2	5 (2.0)	12 (1.6)			11 (8.3)	26 (7.5)		
3	1 (0.4)	1 (0.1)			4 (3.0)	8 (2.3)		
≥4	1 (0.4)	1 (0.1)			6 (4.5)	12 (3.4)		
No. of acute OCS courses, n (%)			0.9869	3.6			0.6813	14.4
0	199 (78.7)	593 (79.8)			79 (59.8)	225 (64.7)		
1	42 (16.6)	120 (16.2)			28 (21.2)	74 (21.3)		
2	7 (2.8)	18 (2.4)			9 (6.8)	20 (5.7)		
3	4 (1.6)	9 (1.2)			7 (5.3)	15 (4.3)		
≥4	1 (0.4)	3 (0.4)			9 (6.8)	14 (4.0)		
Average daily SABA dose, n (%)			0.4055	4.9			0.3524	8.4
0 µg /day	64 (25.3)	224 (30.1)			23 (17.4)	65 (18.7)		
>0 µg/day to ≤200 µg/day	70 (27.7)	196 (26.4)			22 (16.7)	66 (19.0)		
>200 µg/day to ≤400 µg/day	56 (22.1)	139 (18.7)			32 (24.2)	78 (22.4)		
>400 µg/day to ≤600 µg/day	25 (9.9)	59 (7.9)			5 (3.8)	29 (8.3)		
>600 µg/day	38 (15.0)	125 (16.8)			50 (37.9)	110 (31.6)		

*Some missing data for this parameter: n=239 for asthma on BF Spiromax, n=726 for asthma on BF Turbuhaler; n=129 for COPD on BF Spiromax, n=346 for COPD on BF Turbuhaler.
†Some missing data for this parameter: n=248 for asthma on BF Spiromax, n=740 for asthma on BF Turbuhaler; n=346 for COPD on BF Turbuhaler.
BF, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; OCS, oral corticosteroids; SABA, short-acting β₂-agonist; SMD, standardised mean difference.

Table 2 Descriptive statistics of disease outcomes in the matched cohorts of patients.

Outcomes	Patients with asthma		Patients with COPD	
	BF Spiromax (n=253)	BF Turbuhaler (n=743)	BF Spiromax (n=132)	BF Turbuhaler (n=348)
% Risk domain control	73.1	68.0	40.2	37.1
No. of exacerbations (SD)	0.3 (0.7)	0.4 (0.7)	1.1 (1.4)	1.0 (1.4)
% Treatment stability	72.7	66.9	39.4	37.1
SABA average daily dose (SD)	1.4 (1.9)	1.5 (2.9)	2.6 (2.9)	2.4 (2.3)
No. of SABA inhalers (SD)	5.1 (6.8)	5.5 (10.7)	9.5 (11.0)	8.7 (8.5)
No. of antibiotics prescriptions (SD)	0.2 (0.7)	0.4 (0.8)	0.7 (1.1)	0.8 (1.1)
No. of acute OCS courses (SD)	0.3 (0.7)	0.3 (0.7)	1.0 (1.7)	0.9 (1.3)
FDC ICS average daily dose (SD)	382.1 (351.3)	505.3 (585.0)	555.3 (427.1)	561.8 (646.1)
No. of FDC inhalers (SD)	14.0 (8.9)	10.8 (5.6)	15.0 (6.7)	11.9 (5.4)
No. of respiratory A&E attendances (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)	0.1 (0.4)
No. of probable respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.1 (0.4)	0.1 (0.5)
No. of definite respiratory inpatient hospitalisations (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.3)	0.1 (0.4)
% Probable pneumonia*	0.0	0.0	3.0	2.3
% Definite pneumonia*	0.0	0.0	2.3	0.6

A&E, accident and emergency; BF, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; ICS, inhaled corticosteroid; OCS, oral corticosteroid; SABA, short-acting β_2 agonist.
*A pneumonia event was defined as having a Read coded diagnosis (probable pneumonia), or a Read coded diagnosis with a hospital admission or chest X-ray within 1 month (definite pneumonia).

MDI device of Spiromax compared with Turbuhaler. No significant differences between patients who switched and those who did not were observed in the COPD group. This might be partly caused by lower statistical power in the COPD group, which included approximately half the number of patients as in the asthma group, and by the general notion that the reduction in exacerbation frequency with ICS is less in COPD compared with asthma.[34] Another factor that could have contributed is the much older age (~15 years) of patients in the COPD group. Age is a proxy for many health-related characteristics, and there is evidence of a negative correlation between advancing age and correct inhaler technique across MDI and the varying DPI devices.[35]

Switching asthma medications is often necessary for several reasons, including regaining or achieving asthma control or to constrain healthcare costs. Due to the retrospective design of our study, reasons for switching inhaler were not captured. However, we selected BF Spiromax patients registered at practices considered to have a policy of BF Spiromax adoption or wholesale change. While we cannot exclude some inhaler switches being induced by clinical reasons, the requirement for practices to have at least five patients switch to BF Spiromax within a 3-month
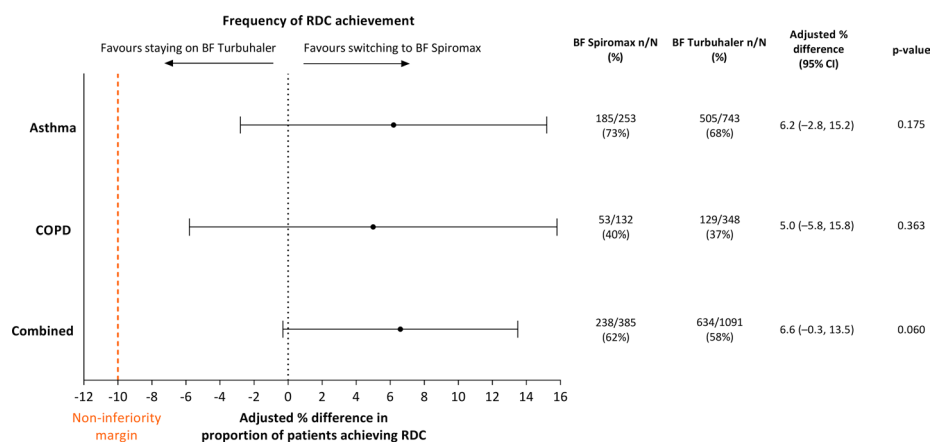
Figure 2 Frequency of achievement of RDC in patients switching to BF Spiromax and those continuing on BF Turbuhaler. BF, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; RDC, risk domain control.
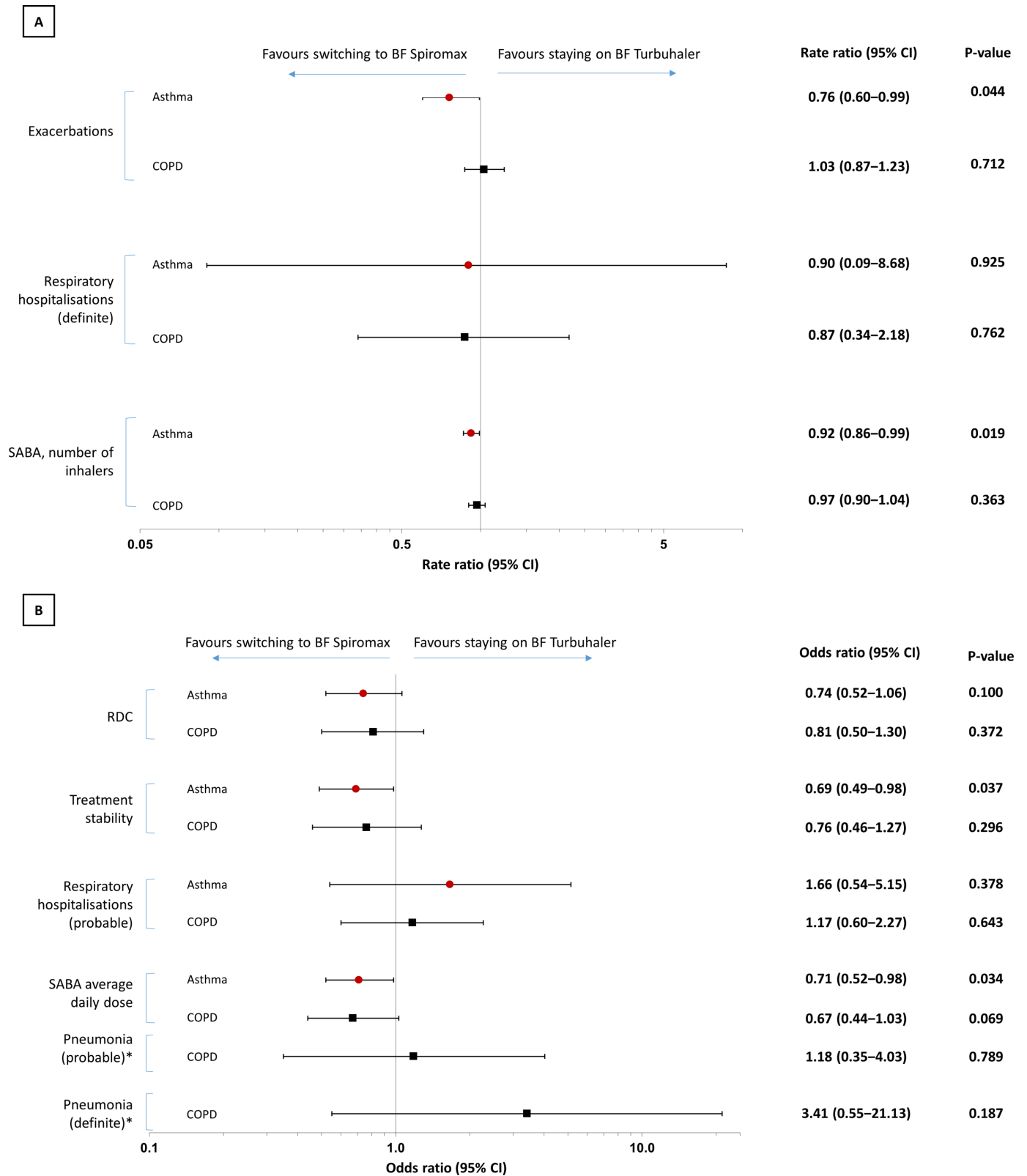
Figure 3 Clinical outcomes expressed as adjusted conditional (A) rate ratios (95% CI) and (B) ORs (95% CI), among patients switching to BF Spiromax versus continuing on BF Turbuhaler in the matched analysis. *Model did not converge in the asthma group. BF, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; RDC, risk domain control; SABA, short-acting β_2 agonist.

period means that in our view it is probable that many of the switches to BF Spiromax at these centres were driven by economic rationales. Thus, it is expected that

any differences between treatments in our study result from the switch in inhalers rather than improvement in poor disease control. A switch to a different inhaler may

potentially increase patient-practice contact, in terms of additional evaluation and teaching of inhaler technique, which may confound the results. However, in a pilot study which has been published only in abstract form,[36] 76% of 114 patients were switched to BF Spiromax without consultation, suggesting that any confounding created by additional physician teaching for those who switched versus those remaining on original therapy was limited in the overall patient population. Indeed, previous findings have shown that most patients with asthma who have had their inhaler device switched without their consent believed that cost issues were a factor.[37] As such, it is likely that many of the switches experienced by our patient cohort took place at least in part for economic reasons.

The results observed in this real-world study are consistent with previous evidence gained from RCTs where BF Spiromax was found to have similar efficacy to BF Turbuhaler.[38] The suggestion of potential superiority on secondary outcome measures in the current study, a result which was not seen in RCTs, might plausibly reflect differences in ease of use and/or adherence between the inhalers when prescribed in routine care. Patients participating in respiratory RCTs usually represent only between 1% and 5% of the true population of patients with asthma or COPD[39] and the proportion of patients with COPD in primary care who would be eligible for inclusion in recent large pharmaceutically sponsored COPD studies has ranged from 17% to 42%.[40] In addition, adherence to treatment in real-world observational studies is usually much lower than in RCTs.[41] Moreover, proper inhaler technique is often artificially high in clinical trials because of patient selection, extensive training, and close monitoring, which may explain why minimal differences in outcomes between devices have been observed in RCTs.[42] However, in daily practice, patients' differential ability to correctly use their inhaler may result in larger differences in health outcomes. Previous studies have shown that study participants and healthcare professionals find it easier to learn how to use the Spiromax inhaler correctly, compared with other DPIs.[10 11] Furthermore, patients are able to achieve slightly higher peak inspiratory flow rates with the Spiromax inhaler compared with the Turbuhaler.[43]

This study had a clearly defined *a priori* hypothesis, end points and sample size, as is recommended for this type of observational research.[44] A particular strength was the non-selective patient population obtained through the use of real-world data from validated databases of primary care patients. The size and scope of these databases allowed for the collection of important clinical variables and a sufficient follow-up period for observing relevant outcomes. In addition, the study's time horizon of 1 year has minimised the impact of potential seasonal differences in disease activity.[45] Overall, the study was well powered to investigate the primary outcome which was RDC of disease.

The inclusion of matched patients in our analysis of RDC risked introducing residual confounding due to imbalanced matching ratios. We therefore performed a sensitivity analysis in the subpopulation of patients in the BF Spiromax arm with exactly three matched patients in the BF Turbuhaler arm. Compared with patients who remained on BF Turbuhaler, patients who switched to BF Spiromax had 31% and 41% higher odds of achieving RDC in the primary analysis and sensitivity analysis, respectively, with the difference reaching statistical significance in the sensitivity analysis only. Regardless of whether significance was achieved, the difference in odds with BF Spiromax versus BF Turbuhaler is quite similar between the primary and sensitivity analyses, supporting the overall validity of our assumptions for the effect of BF Spiromax versus BF Turbuhaler on achieving disease control.

Limitations of the study are important to note. The use of databases to evaluate outcomes depends on the information registered, which is for clinical and routine use rather than research purposes. Possible issues include the fact that hospital admissions, A&E attendances and outpatient visits are not systematically recorded in primary care databases and the applied definition to identify asthma-related hospital admissions or A&E events may give false positive events. However, this limitation would apply equally to both groups. In addition, inhaler technique could not be taken into account for this study as this would require close observation and communication with each patient as they demonstrated their inhaler technique. Regarding the secondary outcomes, we cannot rule out the possibility that the observed differences were caused by factors unrelated to the inhalers, as patients who switched to BF Spiromax may have differed from non-switchers in ways not captured in our data set. Comparison with other ICS/LABA FDCs would have been useful to determine any differences attributable to pharmacological effect; however, there were insufficient patient numbers for such comparisons. An important limitation in observational studies is the potential for confounding of the associations arising from systematic differences between the patients being compared. In this study, confounding was minimised where possible using matching techniques to create cohorts that were comparable in terms of important demographic and clinical characteristics as recommended by the Respiratory Effectiveness Group.[44] Multivariate models were adjusted by those variables that continued to confound the associations of interest after matching. However, in the COPD group, due to a limited number of patients, only a restricted set of variables could be used for matching and model adjustment. Therefore, we cannot ensure confounding of the association of interest was sufficiently addressed in this group. Furthermore, as previously discussed, the selection of patients from practices which were required to have at last five switchers to BF Spiromax in a 3-month period could potentially have introduced a bias in favour of practices with greater than average asthma/COPD expertise and involvement in care of patients with asthma/COPD.

This real-world analysis showed that switching from BF Turbuhaler to BF Spiromax was associated with no loss of symptom control and may be beneficial in some patients. These data validate, in a real-world population of patients with asthma and COPD and clinical setting, similar efficacy to that previously demonstrated in an RCT.[38] Such validation is important for primary practitioners as it provides reassurance that BF Spiromax is effective in real-world primary care patients, and not just in the carefully selected and closely monitored cohorts of patients typical of RCTs. It should however be noted that periodical assessments of adherence, motivation and inhaler technique are still likely to be required to ensure that optimal inhaler use is maintained in the long term.[46–51] Further research may be needed to assess the extent to which the results of this analysis are generalisable to patients outside of the UK.

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