Online supplementary material

Add-on long-acting β2-agonist (LABA) in a separate inhaler as asthma step-up therapy versus increased dose of inhaled corticosteroid (ICS) or ICS/LABA combination inhaler

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Supplementary methods

Data source

This study was based on two large UK primary care databases: the General Practice Research Database (GPRD) and the Optimum Patient Care Research Database (OPCRD) [1]. The GPRD, which is now part of the Clinical Practice Research Datalink, contained anonymised medical record data and included 3.6 million active records from approximately 450 UK primary care practices [2–4]. The OPCRD is a quality controlled clinical research database that collects anonymous data from 300 primary care practices across the UK via the OPC clinical advisory service. The OPCRD contains medical records and patient questionnaires from a large patient population, including approximately 350,000 patients with asthma or chronic obstructive pulmonary disease (COPD) [2, 5].

Descriptive summary for the unmatched patient population

For unmatched patient data, see Table S1. Patients in the separate inhaled corticosteroids (ICS) + long-acting β2-agonist (LABA) cohort were generally older than patients in the ICS step-up and the ICS/LABA combination cohorts, and they also had earlier index dates and earlier recordings of asthma. Patients in the ICS step-up cohort had less severe asthma with fewer recorded exacerbations during the baseline period, as well as lower oral steroid, antibiotics and short-acting β2-agonist (SABA) use, compared with the add-on LABA cohorts. Patients prescribed ICS step-up therapy also had fewer hospitalisations, and a higher proportion experienced risk-domain asthma control during the baseline period. Patients prescribed separate ICS+LABA had the most severe asthma, judged by each of these characteristics. These patients also recorded higher rates of gastroesophageal reflux disease (GORD), cardiac disease, asthma and rhinitis diagnoses.

Prescribed medication

Inhaled corticosteroids can be prescribed as either fine-particle ICS (mass median aerodynamic diameter [MMAD] = 2–5 μm) or extrafine-particle ICS (MMAD ~1 μm).

During the outcome period, patients in the ICS step-up cohort were prescribed extrafine-particle beclomethasone of which the majority was Qvar (Teva). Of these patients, 54% were also prescribed extrafine-particle ICS during the baseline period.

For the FDC ICS/LABA cohort, 14% of patients were prescribed extrafine-particle ICS during the baseline period, while virtually all were prescribed fine-particle formulations during the outcome period (fluticasone/salmeterol, budenoside/formoterol or beclomethasone/formoterol).

Patients in the separate ICS+LABA cohorts were prescribed either fine-particle or extrafine-particle ICS during the baseline and outcome period (10–12% were prescribed an extrafine-particle formulation during the baseline period and 11–12% during the outcome period).

Further data on medication during the baseline and outcome periods are shown in Table S2.

Study oversight

Teva Pharmaceuticals Limited funded the data acquisition and analysis, and data access to the OPCRD was co-funded by Research in Real-Life Ltd (RiRL). Teva Pharmaceuticals Ltd did not influence the conduct of the study, the final interpretation of the findings, or the decision to submit the manuscript for publication. The authors in the RiRL research team collected and analysed data, and one of the authors wrote the first draft of the manuscript. All authors contributed to the study design, the selection of outcome measures, the writing of the manuscript, and the decision to submit for publication.

Statistical analysis

Baseline characterisation of patients indicated that there were statistically and clinically significant differences between cohorts, and we therefore carried out a matched cohort analysis. Before matching, patients in the ICS step-up cohort had, on average, markers of less severe asthma, for example lower prescribed ICS doses and fewer recorded exacerbations. Patients in the separate ICS+LABA cohort had markers of more severe asthma, whereas a higher proportion of patients in the ICS/LABA combination cohort were male.

For the purposes of matching, doses of budesonide and large-particle beclomethasone (Clenil Modulite, Chiesi) were halved, and 250 and 500 μg of fluticasone were set to be equivalent to 200 and 400 μg of extrafine beclomethasone, respectively. At the index date, ICS doses are reported as half budesonide doses, while extrafine beclomethasone and fluticasone doses are reported without modification (Table S1).

Potential confounders examined

To reduce the possibility of selection bias, numerous potential confounding variables were assessed.

Potential confounders examined at, (or closest to), the relevant index date

- Age
- Sex
- Height
- Weight
- Lung function, in terms of peak flow readings
- Smoking status

Potential confounders examined regardless of when they occurred relative to the index date

- Date of first asthma, other respiratory and allergy-related diagnosis (where known)
- Other respiratory or other confounding diagnoses, including: rhinitis, smoking history, COPD, GORD and cardiac disease. Comorbidities were expressed using the Charlson comorbidity index (CCI).

Potential confounders examined in the year before the index date

- All asthma, allergy, and other respiratory treatments
- Where ICS have been prescribed, the total dose prescribed as actual dose for extrafine beclomethasone (Qvar) and fluticasone and half of prescribed dose of budesonide and large-particle beclomethasone (Clenil) for equivalence with extrafine beclomethasone
- Number of GP consultations for asthma or other respiratory illness
- SABA dose (as defined in Secondary outcomes above)
- Proxy composite measure for asthma control
- Number of hospital outpatient department (OPD) attendances where asthma was recorded as the reason for referral
- Number of asthma or possibly respiratory-related hospitalisations (a non-specific hospitalisation code and an asthma / respiratory code within a 1-week window)
- Number of prescriptions for any antibiotic where the reason for the prescription is either a lower or upper respiratory tract infection (LRTI or URTI)
- Other medications that might interfere with asthma control, eg, β-blockers, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol

References

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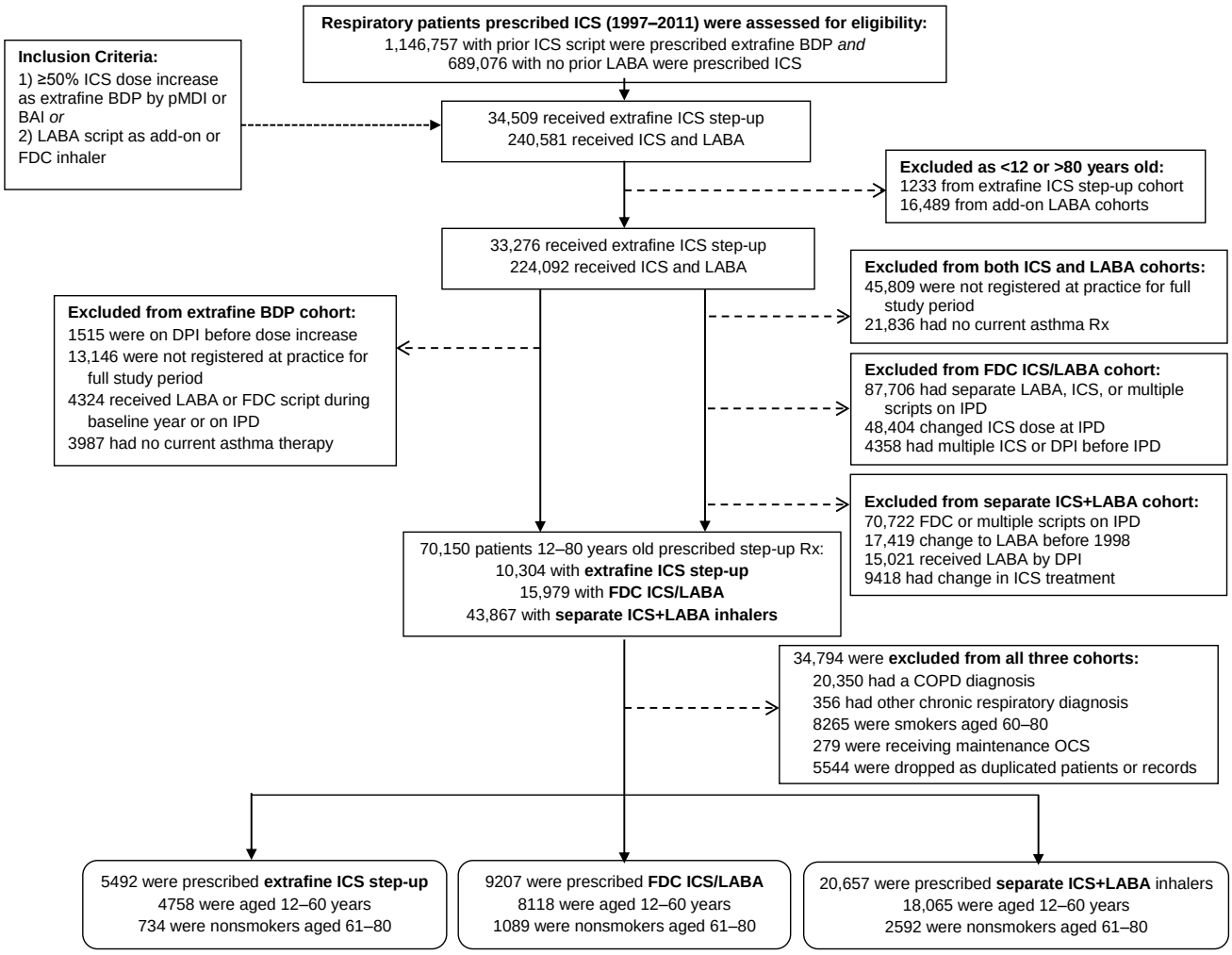
5. Jones RCM, Price D, Ryan D, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. *Lancet Respir Med* 2014: **4**: 267–276.

Supplementary figure

Figure S1 Patient selection in the datasets for extrafine particle BDP or add-on LABA via separate or fixed dose combination inhalers. Abbreviations: BDP = beclomethasone dipropionate; COPD = chronic obstructive pulmonary disease; DPI = dry powder inhaler; FDC = fixed-dose combination, GPRD = General Practice Research Database; ICS = inhaled corticosteroid; LABA = long-acting β2-agonist; OCS = oral corticosteroid, OPCRD = Optimum Patient Care Research Database; pMDI = pressurised metered-dose inhaler; Rx = therapy; Script = prescription.



Supplementary tables

Table S1 Baseline data for unmatched patient populations for patients prescribed an increased dose of inhaled corticosteroids (ICS), or a fixed dose combination (FDC) inhaler containing ICS / long-acting β2-agonist (LABA), compared with ICS and LABA in separate inhalers.

Characteristic	**ICS step-up (n = 5492)**	**Separate ICS + LABA (n = 20,657)**	**FDC ICS/LABA (n = 9207)**	**p-value***
Female sex, n (%)	3282 (59.8)	12,964 (62.8)	5498 (59.7)	<0.001
Age in years at index date, mean (SD)	41.5 (17.3)	43.0 (16.1)	41.0 (16.7)	<0.001
Risk-domain asthma control, n (%)	3750 (68.3)	11,426 (55.3)	5656 (61.4)	<0.001
Severe exacerbations, n (%)				<0.001
0	4289 (78.1)	13,437 (65.0)	6637 (72.1)	
1	848 (15.4)	4642 (22.5)	1761 (19.1)	
2	247 (4.5)	1588 (7.7)	545 (5.9)	
≥3	108 (2.0)	990 (4.8)	264 (2.9)	
Acute respiratory events, n (%)				<0.001
0	3796 (69.1)	11,593 (56.1)	5794 (62.9)	
1	1099 (20.0)	5357 (25.9)	2144 (23.3)	
2	399 (7.3)	2189 (10.6)	812 (8.8)	
≥3	198 (3.6)	1518 (7.3)	457 (5.0)	
SABA dose (μg/day), median (IQR)[§]	219.2 (109.6−438.4)	274.0 (109.6−602.7)	219.2 (109.6−548.0)	<0.001
Last ICS dose before index date	313.0 (123.4)	632.1 (394.6)	567.2 (358.4)	<0.001

(μg), mean (SD)[f]				
ICS dose at index date (μg), mean (SD)[f]	663.5 (246.3)	631.1 (393.9)	564.8 (356.5)	<0.001
Asthma consultation in primary care, mean (SD)	1.2 (1.2)	1.6 (1.6)	1.5 (1.4)	<0.001
Year of index prescription, median (IQR)	2006 (2003−2007)	2003 (2001−2005)	2005 (2003−2007)	<0.001
Year of asthma diagnosis, median (IQR)[+]	1997 (1990−2002)	1995 (1988−2000)	1997 (1990−2002)	<0.001
Body mass index (kg/m^2), mean (SD)[+]	27.3 (6.3)	27.9 (6.5)	27.6 (6.4)	<0.001
Charlson Comorbidity Index, n (%)				<0.001
0	4829 (87.9)	17,513 (84.8)	8052 (87.5)	
1	339 (6.2)	1725 (8.4)	643 (7.0)	
≥2	324 (5.9)	1419 (6.9)	512 (5.6)	
Cardiac disease, n (%)[†]	258 (4.7)	1376 (6.7)	401 (4.4)	<0.001
≥1 prescription during prior 12 months, n (%)				
Nonsteroidal anti-inflammatory drug	1209 (22.0)	4791 (23.2)	2043 (22.2)	0.059
β2-blocker	161 (2.9)	516 (2.5)	244 (2.7)	0.191
Paracetamol	1139 (20.7)	4994 (24.2)	2018 (21.9)	<0.001
Database code for asthma,	5208 (94.8)	20,174 (97.7)	8921 (96.9)	<0.001

n (%)				
Asthma prescriptions, median (IQR)	5 (3−8)	6 (3−10)	5 (3−9)	<0.001
Spacer device used, n (%)	684 (12.5)	3738 (18.1)	1349 (14.7)	<0.001
All primary care consultations, median (IQR)	7 (4−11)	7 (4−12)	7 (4−12)	<0.001
Oropharyngeal candidiasis, n (%)	203 (3.7)	901 (4.4)	328 (3.6)	0.002
Rhinitis, n (%)[†]	1315 (23.9)	5490 (26.6)	2309 (25.1)	<0.001
Gastroesophageal reflux, n (%)[†]	590 (10.7)	2774 (13.4)	1020 (11.1)	<0.001
Antibiotic prescription, n (%)				<0.001
0	4633 (84.4)	16,682 (80.8)	7541 (81.9)	
1	649 (11.8)	2765 (13.4)	1211 (13.2)	
≥2	210 (3.8)	1210 (5.9)	455 (4.9)	

[*]Kruskal-Wallis test. [¶]Closest to index date, either prior to or at first diagnosis after the index date. [+]Non-missing values. [§]Salbutamol equivalent. [ƒ]Beclomethasone dipropionate equivalents. [†]Recorded at any time.

Abbreviations: FDC = fixed-dose combination; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β2-agonist; SABA: short-acting β2-agonist SD = standard deviation.

Table S2 Additional baseline demographic and clinical characteristics for two 2-way comparisons of a step-up in asthma therapy using either an increased dose of inhaled corticosteroids (ICS), or a fixed dose combination (FDC) inhaler containing ICS / long-acting β2-agonist (LABA), compared with ICS and LABA in separate inhalers.

	ICS step-up vs separate ICS+LABA		**FDC ICS/LABA vs separate ICS+LABA**	
Characteristic	**ICS step-up (n = 3232)**	**Separate ICS + LABA (n = 6464)**	**FDC ICS/LABA[◊] (n = 7529)**	**Separate ICS + LABA (n = 15,058)**
Medication during baseline, n (%)				
Extrafine-particle ICS (Qvar)[#]	1598 (49.4)	675 (10.4)	931 (12.4)	1354 (9.0)
Extrafine-particle ICS (generic)[¶]	161 (5.0)	91 (1.4)	113 (1.5)	192 (1.3)
Other drugs	1473 (45.6)	5698 (88.2)	6485 (86.1)	13,512 (89.7)
Medication during outcome, n (%)				
Extrafine-particle ICS (Qvar)[#]	2905 (89.9)	710 (11.0)	0 (0.0)	1422 (9.4)
Extrafine-particle ICS (generic)[+]	327 (10.1)	101 (1.6)	4 (0.0)	205 (1.4)
Other drugs	0 (0.0)	5653 (87.5)	7525 (100)	13,431 (89.2)
Year of index prescription, mean ± SD	2005 ± 2.6	2004 ± 2.7***	2005 ± 2.2	2003 ± 2.8***
Years since first asthma code, median (IQR)	8.3 (2.6–15.7)	7.3 (2.2–14.8)*	8.3 (2.1–15.7)	8 (2–16)
Body mass index	27.6±6.3	27.7±6.3	27.8±6.5	27.8±6.4

(kg/m^2), mean ± SD[§]				
Charlson Comorbidity Index, n (%)				
0	2817 (87.2)	5526 (85.5)	6546 (86.9)	12,852 (85.3)***
1	214 (6.6)	527 (8.2)	552 (7.3)	1210 (8.0)
≥2	201 (6.2)	411 (6.4)	431 (5.7)	996 (6.6)
Peak expiratory flow (% predicted), mean ± SD[f]	85.1 ± 19.8	85.2 ± 20.0	83.1 ± 19.3	84.1 ± 20.1*
Cardiac disease, n (%)[†]	170 (5.3)	427 (6.6)**	361 (4.8)	932 (6.2)***
≥1 prescription during prior 12 months, n (%)				
Nonsteroidal anti-inflammatory drug	726 (22.5)	1454 (22.5)	1734 (23.0)	3417 (22.7)
β2-blocker	96 (3.0)	183 (2.8)	204 (2.7)	365 (2.4)
Paracetamol	700 (21.7)	1451 (22.4)	1725 (22.9)	3547 (23.6)
Database code for asthma, n (%)	3110 (96.2)	6263 (96.9)	7285 (96.8)	14,711 (97.7)***
Asthma prescriptions, median (IQR)	5 (3–9)	5 (3–9)	6 (3–9)	6 (3–9)**
Spacer device used, n (%)	456 (14.1)	988 (15.3)	1117 (14.8)	2661 (17.7)***
All primary care consultations, median (IQR)	7 (4–12)	7 (4–12)	7 (4–12)	7 (4–12)***
Oropharyngeal	125 (3.9)	225 (3.5)	288 (3.8)	615 (4.1)

candidiasis, n (%)				
Rhinitis, n (%)[‡]	815 (25.2)	1660 (25.7)	1898 (25.2)	3931 (26.1)
Gastroesophageal reflux, n (%)[‡]	373 (11.5)	836 (12.9)*	862 (11.4)	1956 (13.0)***
Antibiotic prescription for LRTI, n (%)				
0	2698 (83.5)	5406 (83.6)	6065 (80.6)	12,322 (81.8)*
1	397 (12.3)	757 (11.7)	1055 (14.0)	1919 (12.7)
≥2	137 (4.2)	301 (4.7)	409 (5.4)	817 (5.4)

*p≤0.05, **p<0.01, ***p<0.001, conditional logistic regression for two-way comparison between cohorts.

[◊]Fluticasone/salmeterol, budenoside/formoterol or beclomethasone/formoterol.

[#]Beclomethasone dipropionate (Qvar Autohaler®; Qvar Easi-Breathe® or Qvar cfc free inhaler®). [¶]Extrafine-particle Beclomethasone inhaler or extrafine-particle Beclomethasone breath-actuated inhaler. [+]Extrafine-particle Beclomethasone inhaler, extrafine-particle Beclomethasone breath-actuated inhaler or extrafine-particle Beclomethasone/formoterol combination inhaler. [§]Recorded data for body mass index were available for 2973 (92.0%) and 5917 (91.5%) in the ICS step-up and separate ICS+LABA cohorts, respectively, and for 6914 (91.8%) and 13,874 (92.1%) in the FDC ICS/LABA and separate ICS+LABA cohorts, respectively. [ƒ]Recorded peak expiratory flow data were available for 2267 (70.1%) and 4193 (64.9%) in ICS and separate ICS+LABA cohorts, respectively, and for 5254 (69.8%) and 10,015 (66.5%) in ICS/LABA combination and separate ICS+LABA cohorts, respectively. [†]Comorbid cardiac disease was captured through coded diagnosis in the databases. [‡]Rhinitis and gastroesophageal reflux disease diagnoses were captured through database coding.

Abbreviations: FDC = fixed-dose combination; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β2-agonist; LRTI = lower respiratory tract infection; SD = standard deviation.