Characterisation of patients with chronic obstructive pulmonary disease initiating single-device inhaled corticosteroids/long-acting β₂-agonist dual therapy in a primary care setting in England

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ABSTRACT
Introduction  Treatment pathways of patients with chronic obstructive pulmonary disease (COPD) receiving single-device dual therapies in England remain unclear. This study describes the characteristics of patients with COPD before initiating treatment with a single-device inhaled corticosteroid/long-acting β₂-agonist (ICS/LABA) in primary care in England.

Methods  This is a retrospective, descriptive study of linked primary and secondary healthcare data (Clinical Practice Research Datalink Aurum, Hospital Episode Statistics). Patients with COPD were indexed on first prescription of fixed-dose, single-device ICS/LABA (June 2015–December 2018). Demographics, clinical characteristics, prescribed treatments, healthcare resource use (HCRU) and direct healthcare costs were assessed over 12 months pre-index. Incident users (indexed on first ever prescription) could be non-triple users (no concomitant long-acting muscarinic antagonist at index); a subset were initial maintenance therapy (IMT) users (no history of pre-index maintenance therapy).

Results  Overall, 13 451 incident users (non-triple users: 7448, 55.4%; IMT users: 5162, 38.4%) were indexed on beclomethasone dipropionate/formoterol (6122, 45.5%), budesonide/formoterol (2703, 20.1%) or Other ICS/LABA combinations (4626, 34.4%). Overall, 20.8% of incident users had comorbid asthma and 42.6% had ≥1 moderate-to-severe acute exacerbation of COPD pre-index. Baseline characteristics were similar across indexed therapies. At 3 months pre-index, 45.3% and 35.4% of non-triple and IMT users were receiving maintenance treatment. HCRU and direct healthcare costs were similar across indexed treatments. Prescribing patterns varied regionally.

Conclusion  Patient characteristics, prior treatments, prior COPD-related HCRU and direct healthcare costs were similar across single-device ICS/LABAs in primary care in England. A high proportion of patients were not receiving any respiratory medication pre-index, indicating that prescribing in primary care in England is more closely aligned with national guidelines than global treatment strategies. Comorbid asthma may have influenced prescribing decisions. Less than half of users had preindex exacerbations, suggesting that ICS/LABA is not being prescribed principally based on exacerbation history.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is currently the third global leading cause of mortality, responsible for approximately 6% of the total deaths globally.1 In the UK, COPD is the second most common lung disease after asthma, affecting...
around 2% of the total population. COPD is associated with a substantial clinical and economic burden worldwide, with exacerbations contributing significantly to disease burden.

Long-acting bronchodilators (including long-acting muscarinic antagonists (LAMA)) and long-acting β₂-agonists (LABA) either as monotherapy or in combination, are the mainstay of maintenance treatment for patients with COPD. Inhaled corticosteroids (ICS) are also indicated for some patients as maintenance therapy in combination with long-acting bronchodilators. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report recommends a stepwise approach to treatment, with ICS/LABA dual therapy as a maintenance therapy option for patients at increased risk of exacerbations. The UK National Institute for Health and Care Excellence (NICE) guidelines also recommend ICS/LABA therapy for patients with COPD and features such as a history of asthma, an elevated blood eosinophil count or substantial variation in spirometry assessments over time. ICS/LABA therapy has been shown to improve lung function and health status and to reduce rates of moderate or severe exacerbations compared with either ICS or LABA alone.

In the UK, five fixed-dose single-inhaler ICS/LABA therapies are licensed for treatment of COPD or asthma in adults: beclometasone dipropionate/formoterol fumarate (BDP/FOR), budesonide/formoterol (BUD/FOR), fluticasone propionate/salmeterol (FP/SAL), fluticasone propionate/formoterol (FP/FOR) and fluticasone furoate/vilanterol (FF/VI). Of these, four combinations (BDP/FOR, BUD/FOR, FP/SAL and FF/VI) are licensed for treatment of COPD, although FF/VI is only indicated for patients with an exacerbation history and is not indicated as a general maintenance therapy for all patients with COPD.

In England, it is unclear how different single-device ICS/LABA therapies are used in routine clinical practice. As such, there is a need to describe the treatment pathways and characteristics of patients receiving different treatments prior to ICS/LABA initiation to inform the design of future studies comparing the effectiveness of different single-device dual-inhaler therapies. The aim of this study was to provide a clear picture of the characteristics of a cohort of patients in England with COPD before initiation of dual therapy. This in turn can inform the design of future studies comparing the effectiveness of different single-device dual-inhaler therapies, as the characteristics of any baseline population will already have been clearly established by this study. The focus of the study was therefore to describe the characteristics of patients with COPD prior to initiation of treatment with a single-device ICS/LABA dual therapy, including baseline demographic and clinical characteristics, prior treatments prescribed, prior healthcare resource use (HCRU) and direct healthcare costs, in a general practice (GP) cohort in England.

METHODS

Study design

This study was a retrospective, longitudinal cohort study using linked primary care electronic medical record data and secondary care administrative data from the Clinical Practice Research Datalink (CPRD-Aurum) and Hospital Episode Statistics (HES) databases, respectively. CPRD-Aurum contains longitudinal, representative anonymised electronic health records of primary care interactions in England. It provides data on demographics, diagnosis, symptoms, prescriptions, referrals, immunisations, lifestyle factors, tests and results and represents approximately 13% of the living population as of September 2018. The HES data sets that were linked to CPRD-Aurum in this study were admitted patient care (including data on basic patient demographics, date and method of hospital admission and discharge, diagnoses, specialists seen and procedures undertaken), outpatient (including outpatient appointment dates, specialty, clinical diagnosis and procedures), and accident and emergency (A&E; including diagnoses, investigations and attendance outcomes).

The indexing period spanned from 1 June 2015 to 31 December 2018 (figure 1A). The index date was defined as the earliest prescription of a single-device ICS/LABA therapy within the indexing period. The baseline period comprised the 12 months prior to index.

Study population

Eligible patients had ≥1 COPD diagnosis in the primary care setting at ≥35 years of age, had ≥1 prescription for a single-device ICS/LABA within the indexing period, a forced expiratory volume in 1 s to forced vital capacity (FEV₁:FVC) ratio <0.7 at any time prior to and including the index date, ≥12 months of pre-index continuous registration with a GP, had data eligible for linkage to HES and had no diagnosis of medical conditions incompatible with a COPD diagnosis at any time (including conditions related to lung or bronchial developmental anomalies, degenerative processes, pulmonary resection or other respiratory disorders that could interfere with COPD diagnosis).

ICS/LABA users were classified into two mutually exclusive cohorts, prevalent users and incident users. Prevalent users had ≥1 prescription of a single-device or an open combination ICS/LABA prior to the index date; incident users were those with no prior single-device or open combination ICS/LABA on the index date. Within the incident user cohort, non-triple users were those with no concomitant LAMA use on the index date; initial maintenance therapy (IMT) users were a subset of non-triple users who had no history of maintenance therapy. All cohorts were further stratified by indexed therapy (BDP/FOR, BUD/FOR or Other
ICS/LABA combinations (included FP/SAL, FP/FOR and FF/VI; figure 1B).

Outcomes

Study outcomes assessed during the baseline period included the demographic and clinical characteristics of prevalent and incident users, COPD-related treatment use, all-cause and COPD-related HCRU, and all-cause and COPD-related direct healthcare costs in incident users at various time points.

Age was assessed as of the index date, sex and region were included as the last recorded at the time of data cut-off. Acute exacerbations of COPD (AECOPD; moderate-to-severe, moderate and severe), GOLD 2019 classification and blood eosinophil count were assessed in the 12 months prior to and including the index date.

FEV1/FVC ratio, FEV1 % predicted, Medical Research Council (MRC) Dyspnoea Scale score and current asthma diagnosis were assessed in the 24 months prior to and including the index date (historical asthma was defined as an asthma diagnosis >24 months prior to the index date; the CPRD-Aurum database has a long median duration of follow-up, as such the number of patients with <24 months of prior data is expected to be low). Both current and historical were defined according to an algorithm using a set of validated specific diagnosis codes, a commonly used method for classification in COPD studies. Body mass index, smoking status and comorbidities (reported based on the presence of diagnosis codes) were assessed at any time prior to and including the index date (not restrained by the study period). Where more than one value was available in the patient’s record, the most recent measurement prior to or on the index date was reported.

Moderate AECOPD was defined as any of the following (derived from primary care records): a prescription for antibiotics and oral corticosteroids for 5–14 days each, respiratory symptoms and a prescription of antibiotics or oral corticosteroids on the same day, a lower respiratory tract infection medical code or an AECOPD-specific medical code, as described previously. Severe exacerbations were those requiring hospital admission (derived from HES).

To evaluate treatment pathways in the baseline period, COPD-related inhaled therapy use was assessed in incident users only at 3, 6, 9 and 12 months prior to and including the index date. COPD-related and all-cause HCRU (medication use, GP consultations, outpatient visits, inpatient stays (hospitalisations) and A&E visits) and direct healthcare costs were assessed in incident users in the 12-month baseline period (0–3, >3–6, >6–12 and 0–12 months). The cumulative length of stay (days) across all hospitalisations per patient with ≥1 hospitalisation was also reported.
HCRU and direct healthcare costs were classified as COPD-related if a COPD-related event (prescription medication, diagnosis or service provider) was recorded on the same day. Costs were derived from data reported by the Personal Social Service Resource Unit (PSSRU),16 the National Health Service (NHS) Drug Tariff compiled and provided by NHS Prescription Services17 and NHS England.18 For all sources of unit cost data, the most recent version available at the time of analysis was used (PSSRU 2019; Drug Tariff 2019; National Tariff 2019/2020).16–18

Statistical analysis
All patients who met the inclusion criteria were included in the study and no formal sample size calculations were performed. Outcomes were analysed descriptively. Medication use was reported as the number and percentage of prescriptions for each class of COPD medication; all other resources were reported as counts. All-cause and COPD-related direct healthcare costs were reported as total values and by HCRU type. Resource users were defined as those who had at least one unit of use for the respective healthcare service.

Patient and public involvement
Patients and the public were not involved in the design, or conduct, or reporting or dissemination plans of the research.

RESULTS

Demographic and clinical characteristics
In total, 78 245 patients were prescribed single-device ICS/LABA during indexing and met the eligibility criteria. Of these, 64 794 (82.8%) were prevalent users and 13 451 (17.2%) were incident users. Among incident users, 7448 (55.4%) were non-triple users (BDP/FOR: n=3601; BUD/FOR: n=1432; Other ICS/LABA combinations: n=2415) and 5162 (38.4%) patients were IMT users (BDP/FOR: n=2427; BUD/FOR: n=1056; Other ICS/LABA combinations: n=1679) (table 1 and online supplemental figure S1).

Baseline demographic and clinical characteristics were generally similar across prevalent and incident users, with the exception of the proportion of patients with current or historical asthma diagnosis (current: 37.3% prevalent vs 20.8% incident; historical: 62.1% prevalent vs 26.4% incident) (table 1 and online supplemental table S1). Baseline characteristics were similar across indexed therapies.

The majority of incident users were in the western regions. Numerically greater proportions of patients indexed on BDP/FOR were seen in the North West, Yorkshire and The Humber, East and West Midlands, East of England, and South Central regions relative to the overall proportion of users in those regions, while greater proportions of patients indexed on BUD/FOR were seen in the North East, and greater proportions of patients indexed on Other ICS/LABA combinations were found in London, South West and South East Coast (table 1 and online supplemental figure S2). Just under half of patients were in the two most deprived quintiles based on the 2015 Index of Multiple Deprivation (IMD) score (table 1 and online supplemental figure S2). Among incident users with available MRC dyspnoea scores (non-triple: 73.9%; IMT: 60.6%), the majority had scores of 1–3 (non-triple users: 67.6%; IMT users: 56.3%) and approximately 31% of patients had GOLD grade ≥ 3 (severe to very severe airflow limitation). Eosinophil counts were equivalent among both non-triple and IMT users; 32.6% of patients had <150 cells/µL and 67.4% had ≥150 cells/µL. However, 44.9% and 44.2%, respectively, did not have eosinophil data available. Depression and rheumatoid/osteoarthritis were the most common comorbidities among non-triple and IMT user cohorts and these comorbidities were similar across indexed therapies.

In the incident user cohort, slightly more patients receiving Other ICS/LABA combinations experienced ≥1 moderate-to-severe AECOPD (45.2%) or had GOLD 2019 category C–D (47.7%) than those receiving BDP/FOR (41.5% and 43.1%) or BUD/FOR (40.1% and 42.5%). In both cohorts, slightly more patients receiving BDP/FOR had a current asthma diagnosis (IMT users: 31.6%; non-triple users: 27.8%) than those indexed on BUD/FOR (IMT users: 23.1%; non-triple users: 22.1%) or Other ICS/LABA combinations (IMT users: 25.3%; non-triple users: 23.4%).

Treatment pathways
Overall, 55.5% of incident patients were not receiving an inhaled COPD therapy at 12 months prior to index, decreasing to 43.1% at 3 months. Short-acting bronchodilators and ICS monotherapy were the most frequently prescribed treatments among patients receiving inhaled therapy (figure 2A,B). Treatment patterns were similar across indexed therapies, with patients indexed on BDP/FOR comprising the greatest proportion of those prescribed ICS monotherapy at 3 months pre-index. Treatment patterns were generally similar at all other time points between non-triple and IMT users and across indexed therapies (online supplemental figure S3).

Of the incident patients who experienced ≥1 AECOPD during the 12-month baseline period, the majority were not receiving an inhaled COPD therapy at 3 months prior to index (figure 2C). In general, treatment patterns were similar across patients with and without an AECOPD in the year prior to index.

HCRU and direct healthcare costs

Over the 12 months pre-index, the mean total COPD-related direct healthcare costs for incident users were higher for non-triple users than IMT users (figure 3A). Minimal differences in direct COPD-related healthcare costs were observed between indexed therapies
### Table 1: Demographic and clinical characteristics of incident users

| Characteristics                  | Overall incident users | Non-triple users | IMT users |
|----------------------------------|------------------------|------------------|-----------|
|                                  | n=13,451               | n=6,122          | n=4,626   |
|                                  | BDP/FOR n=2,703        | BUD/FOR n=4,626  | BUD/FOR n=1,432 |
|                                  | BDP/FOR n=3,301        | BUD/FOR n=1,432  | Other ICS/ LABA n=2,415 |
|                                  | Overall n=7,448         | Overall n=1,432  | Other ICS/ LABA n=2,415 |
|                                  | BDP/FOR n=2,427        | BUD/FOR n=1,056  | Other ICS/ LABA n=1,679 |

#### Demographic characteristics

- **Age at index, years, mean (SD)**
  - Overall: 68.7 (10.8)
  - Non-triple: 68.7 (10.8)
  - Other: 68.8 (10.8)
  - BDP/FOR: 68.5 (11.1)
  - BUD/FOR: 68.3 (11.2)
  - Other ICS/LABA: 68.6 (10.9)
- **Female, n (%)**
  - Overall: 6046 (45.0)
  - Non-triple: 2818 (46.0)
  - Other: 926 (20.4)
  - BDP/FOR: 564 (7.6)
  - BUD/FOR: 1432 (21.0)
  - Other ICS/LABA: 2415 (46.1)
- **Patient region, n (%)**
  - North East: 1262 (9.4)
  - North West: 2649 (19.7)
  - Yorkshire and The Humber: 530 (3.9)
  - East Midlands: 412 (3.1)
  - West Midlands: 2397 (17.8)
  - East of England: 663 (4.9)
  - South West: 1567 (11.7)
  - South Central: 1623 (12.1)
  - London: 1435 (10.7)
  - South East Coast: 909 (6.8)
  - Socioeconomic status, IMD, n (%)
    - Quintile 1: 2110 (15.7)
    - Quintile 2: 2325 (17.3)
    - Quintile 3: 2587 (19.2)
    - Quintile 4: 2939 (21.9)
    - Quintile 5: 3483 (25.9)
- **BMI at index, kg/m², mean (SD)**
  - Overall: 27.8 (6.9)
  - Non-triple: 27.8 (6.8)
  - Other ICS/LABA: 27.8 (6.8)
  - BDP/FOR: 27.7 (6.8)
  - BUD/FOR: 27.9 (6.8)
  - Other ICS/LABA: 27.7 (6.7)
- **Smoking status at index, n (%)**
  - Current smoker: 7149 (53.2)
  - Former smoker: 5951 (44.2)
  - Non-smoker: NR
  - Unknown: NR

Continued
| Characteristics | Overall incident users | Non-triple users | IMT users |
|-----------------|-----------------------|-----------------|-----------|
|                 | Overall n=13 451      | BDP/FA n=6122   | BUD/FA n=2703 | Other ICS/ LABA* n=4626 |
| Mean (SD)       | 58.6 (13.4)           | 58.5 (13.4)     | 59.3 (13.8) | 58.3 (13.3) |
| % predicted FEV1, mean (SD)§ | 9979 (46.19) | 2009 (33.51) | 5468 (2710) | 1037 (1037) |
| Overall n=7448  | BDP/FA n=3601         | BUD/FA n=1432   | Other ICS/ LABA* n=2415 |
| Mean (SD)       | 58.9 (13.4)           | 59.8 (13.8)     | 59.0 (12.7) | 59.2 (12.8) |
| % predicted FEV1, mean (SD)§ | 7448 (3712) | 1721 (3766) | 682 (1829) | 765 (1172) |
| Category, n (%) |                       |                 |           |            |
| GOLD 1: FEV1 % predicted ≥80% | 1410 (14.1) | 674 (14.6) | 269 (13.4) | 467 (13.9) |
| GOLD 2: FEV1 % predicted ≥50%–<80% | 5359 (53.7) | 2480 (53.7) | 1072 (53.4) | 1807 (53.9) |
| GOLD 3: FEV1 % predicted ≥30%–<50% | 2749 (27.6) | 1248 (27.0) | 566 (28.2) | 933 (27.9) |
| GOLD 4: FEV1 % predicted <30% | 461 (4.6) | 217 (4.7) | 102 (5.1) | 142 (4.2) |
| MRC Dyspnoea Scale score, n (%) | 1† 1748 (13.0) | 817 (13.4) | 345 (12.8) | 586 (12.7) |
| 2               | 4803 (35.7)           | 2200 (35.9)     | 969 (35.9) | 1634 (35.3) |
| 3               | 2927 (21.8)           | 1306 (21.3)     | 586 (21.7) | 1035 (22.4) |
| 4               | 1028 (7.6)            | 454 (7.4)       | 203 (7.5) | 371 (8.0) |
| 5¶             | 157 (1.2)             | 84 (1.4)        | 22 (0.8) | 51 (1.1) |
| Unknown         | 2788 (20.7)           | 1261 (20.6)     | 578 (21.4) | 949 (20.5) |
| Number of comorbidities, mean (SD) | 1.9 (1.5) | 1.8 (1.5) | 1.8 (1.5) | 1.9 (1.5) |
| Comorbidities, n (%) |                         |                 |           |            |
| Depression      | 5647 (42.0)           | 2509 (41.0)     | 1170 (43.3) | 1968 (42.5) |
| Anxiety         | 3648 (27.1)           | 1681 (27.5)     | 725 (26.8) | 1242 (26.6) |
| Gastro-oesophageal reflux disease | 3119 (23.2) | 1445 (23.6) | 603 (22.3) | 1071 (23.2) |
| Acute myocardial infarction | 1565 (11.6) | 705 (11.5) | 294 (10.9) | 566 (12.2) |
| Congestive heart failure | 1788 (13.3) | 785 (12.8) | 350 (13.0) | 653 (14.1) |
| Stroke          | 1655 (12.3)           | 743 (12.1)      | 335 (12.4) | 577 (12.5) |
| Bronchiectasis  | 483 (3.6)             | 221 (3.6)       | 91 (3.4) | 171 (3.7) |
| Dementia/cognitive impairment | 1481 (11.0) | 686 (11.2) | 255 (9.4) | 540 (11.7) |
| Rheumatoid/osteoarthritis | 5498 (40.9) | 2490 (40.7) | 1108 (41.0) | 1900 (41.1) |

Continued
Table 1 Continued

| Characteristics | Overall incident users | Non-triple users | IMT users |
|-----------------|------------------------|-----------------|----------|
|                 | Overall n=13 451       | BDP/FOR n=6122  | BUD/FOR n=7703 |
| Current asthma diagnosis, n (%)§ | 2797 (20.8) | 1429 (23.3) | 509 (18.8) | 859 (18.6) | 1884 (25.3) | 1002 (27.8) | 316 (22.1) | 566 (23.4) | 1436 (27.8) | 768 (31.6) | 244 (23.1) | 424 (25.3) |
| Historical asthma diagnosis, n (%)§ | 3545 (26.4) | 1701 (27.8) | 684 (25.3) | 1160 (25.1) | 2168 (29.1) | 1085 (30.1) | 403 (28.1) | 680 (28.2) | 1466 (28.4) | 741 (30.5) | 270 (25.6) | 455 (27.1) |
| AECOPD in the 12 months prior to index | | | | | | | | | | | | |
| Moderate-to-severe | | | | | | | | | | | | |
| Patients with ≥1 AECOPD, n (%) | 5717 (42.5) | 2543 (41.5) | 1085 (40.1) | 2089 (45.2) | 2886 (38.8) | 1379 (38.3) | 517 (36.1) | 990 (41.0) | 1920 (37.2) | 892 (36.8) | 367 (34.8) | 661 (39.4) |
| Mean AECOPD per patient‡ (SD) | 0.7 (1.0) | 0.7 (1.0) | 0.6 (0.9) | 0.6 (0.9) | 0.5 (0.9) | 0.6 (0.9) | 0.5 (0.8) | 0.6 (0.9) | 0.5 (0.8) | 0.5 (0.9) | 0.5 (0.8) | 0.6 (0.9) |
| Moderate | | | | | | | | | | | | |
| Patients with ≥1 AECOPD, n (%) | 4686 (34.8) | 2079 (34.0) | 888 (32.9) | 1719 (37.2) | 2424 (32.6) | 1140 (31.7) | 444 (31.0) | 840 (34.8) | 1576 (30.5) | 730 (30.1) | 294 (27.8) | 552 (32.9) |
| Mean AECOPD per patient‡ (SD) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) | 0.5 (0.9) |
| Severe | | | | | | | | | | | | |
| Patients with ≥1 AECOPD, n (%) | 1596 (11.9) | 711 (11.6) | 307 (11.4) | 578 (12.5) | 680 (9.1) | 353 (9.8) | 107 (7.5) | 220 (9.1) | 472 (9.1) | 224 (9.2) | 96 (9.1) | 152 (9.1) |
| Mean AECOPD per patient‡ (SD) | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.4) | 0.1 (0.3) | 0.1 (0.4) | 0.1 (0.3) | 0.1 (0.3) | 0.1 (0.3) | 0.1 (0.3) |
| GOLD 2019 group, n (%) | | | | | | | | | | | | |
| A | 3832 (34.7) | 1830 (36.3) | 799 (36.4) | 1203 (31.7) | 2327 (40.6) | 1168 (41.7) | 469 (43.0) | 690 (37.5) | 1449 (43.2) | 720 (44.5) | 310 (45.3) | 419 (39.9) |
| B | 2283 (20.7) | 1041 (20.6) | 463 (21.1) | 779 (20.5) | 1038 (18.1) | 511 (18.3) | 190 (17.4) | 337 (18.3) | 525 (15.7) | 262 (16.2) | 102 (14.9) | 161 (15.3) |
| C | 1763 (16.0) | 754 (15.0) | 355 (16.2) | 654 (17.3) | 930 (16.2) | 403 (14.4) | 189 (17.3) | 338 (18.4) | 552 (16.5) | 237 (14.7) | 123 (18.0) | 192 (18.3) |
| D | 3155 (28.6) | 1419 (28.1) | 580 (26.4) | 1156 (30.5) | 1436 (25.1) | 717 (25.6) | 242 (22.2) | 477 (25.9) | 827 (24.7) | 398 (24.6) | 150 (21.9) | 279 (26.6) |
| Eosinophil count, 10⁹ cells/L, mean (SD) | | | | | | | | | | | | |
| n | 7200 | 3261 | 1474 | 2465 | 4101 | 1975 | 799 | 1327 | 2879 | 1349 | 601 | 929 |
| Mean (SD) | 0.24 (0.16) | 0.24 (0.16) | 0.23 (0.16) | 0.24 (0.16) | 0.24 (0.16) | 0.24 (0.16) | 0.23 (0.16) | 0.24 (0.16) | 0.24 (0.16) | 0.23 (0.16) | 0.23 (0.16) | 0.24 (0.16) |

Values of 'n' are indicated in italics to differentiate from the Mean (SD).
*Includes fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumurate and fluticasone furoate/vilanterol.
†Not troubled by breathlessness except on strenuous exercise.
‡Included all patients with or without ≥1 AECOPD; results based on small numbers of patients (n<5) were suppressed, as well as related values to protect primary suppression.
§Current and historical asthma were not mutually exclusive.
¶Too breathless to leave the house or breathe when dressing or undressing.
AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BDP, beclomethasone dipropionate; BMI, body mass index; BUD, budesonide; FEV₁, forced expiratory volume in 1 s; FOR, formoterol; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IMD, Index of Multiple Deprivation; IMT, initial maintenance therapy; LABA, long-acting β₂-agonist; MRC, Medical Research Council; NR, not reported; SD, standard deviation.
During the baseline period, COPD-related HCRU was similar across indexed therapies (table 2). All-cause HCRU was also similar across treatment cohorts (table 2 and online supplemental table S2). In the 12 months prior to index, non-triple users had a COPD-related cumulative mean (standard deviation) length of stay per patient of 7.0 days (16.0); the corresponding value for IMT users was 6.2 days (13.3). Patients indexed on Other ICS/LABA combinations had slightly longer COPD-related inpatient stays than those indexed on BDP/FOR (non-triple users: 7.0 days (16.1); IMT users: 6.0 days (11.6)) or BUD/FOR (non-triple users: 6.0 days (15.6); IMT users: 5.2 days (16.5)) in the same time period. Similar results were generally observed across indexed therapies and for all-cause inpatient stays.

(figure 3 and online supplemental table S2). Inpatient stays were consistently the greatest contributor to mean COPD-related direct healthcare costs among resource users across all indexed therapies and time periods.
### Table 2: COPD-related HCRU for incident users over 12 months and at 0–3 months prior to index in incident users

|                          | Total incident users | Non-triple users | IMT users |
|--------------------------|----------------------|------------------|-----------|
|                          | Overall n=13 451     | BDP/FOR n=6122   | BUD/FOR n=2703 | Other ICS/LABA* n=6122 | Overall n=7448 | BDP/FOR n=3601 | BUD/FOR n=1432 | Other ICS/LABA* n=2515 | Overall n=5162 | BDP/FOR n=2427 | BUD/FOR n=1056 | Other ICS/LABA* n=1679 |
| **12 months prior to index** |                      |                  |            |
| GP consultations, n (%)† | 9850 (73.2)          | 4493 (73.4)      | 1961 (72.5) | 3396 (73.4) | 5081 (68.2) | 2496 (69.3) | 959 (67.0) | 1626 (67.3) | 3196 (61.9) | 1544 (63.6) | 626 (59.3) | 1026 (61.1) |
| Events, mean (SD)‡       | 2.4 (1.8)            | 2.4 (1.8)        | 2.4 (1.7) | 2.4 (1.7) | 2.2 (1.6) | 2.2 (1.7) | 2.2 (1.5) | 2.1 (1.6) | 1.9 (1.4) | 1.9 (1.4) | 2.0 (1.5) | 1.8 (1.2) |
| Outpatient visits, n (%)† | 2180 (16.2)          | 1039 (17.0)      | 426 (15.8) | 715 (15.5) | 1074 (14.4) | 560 (15.6) | 201 (14.0) | 313 (13.0) | 747 (14.5) | 383 (15.8) | 149 (14.1) | 215 (12.8) |
| Events, mean (SD)‡       | 2.4 (2.4)            | 2.4 (2.5)        | 2.2 (2.0) | 2.5 (2.5) | 2.2 (2.1) | 2.2 (2.1) | 2.0 (1.4) | 2.3 (2.5) | 2.1 (1.9) | 2.1 (2.0) | 2.1 (1.4) | 2.1 (2.0) |
| Inpatient stays, n (%)†   | 3146 (23.4)          | 1395 (22.8)      | 613 (22.7) | 1138 (24.6) | 1444 (19.4) | 709 (19.7) | 258 (18.0) | 477 (19.8) | 869 (16.8) | 410 (16.9) | 172 (16.3) | 287 (17.1) |
| Events, mean (SD)‡       | 1.8 (2.0)            | 1.8 (2.1)        | 1.8 (2.5) | 1.8 (1.6) | 1.8 (1.8) | 1.8 (2.0) | 1.6 (1.4) | 1.8 (1.8) | 1.5 (1.3) | 1.5 (1.4) | 1.3 (0.8) | 1.6 (1.6) |
| A&E visits, n (%)†        | 334 (2.5)            | 150 (2.5)        | 52 (1.9)  | 132 (2.9) | 147 (2.0) | 85 (2.4)  | 18 (1.3)  | 44 (1.8)  | 88 (1.7)  | 41 (1.7)  | 12 (1.1)  | 35 (2.1)  |
| Events, mean (SD)‡       | 1.2 (0.6)            | 1.3 (0.6)        | 1.2 (0.4) | 1.3 (0.7) | 1.2 (0.5) | 1.2 (0.6) | 1.0 (0)  | 1.2 (0.5) | 1.1 (0.3) | 1.1 (0.3) | 1.0 (0)  | 1.1 (0.4) |

| 0–3 months prior to index |                      |                  |            |
| GP consultations, n (%)† | 5769 (42.9)          | 2635 (43.0)      | 1169 (43.3) | 1965 (42.5) | 2847 (38.2) | 1409 (39.1) | 538 (37.6) | 900 (37.3) | 1897 (36.8) | 911 (37.5) | 377 (35.7) | 609 (36.3) |
| Events, mean (SD)‡       | 1.5 (0.8)            | 1.5 (0.8)        | 1.4 (0.8) | 1.4 (0.7) | 1.3 (0.7) | 1.4 (0.7) | 1.4 (0.7) | 1.3 (0.6) | 1.3 (0.6) | 1.3 (0.6) | 1.4 (0.7) | 1.3 (0.6) |
| Outpatient visits, n (%)† | 1473 (11.0)          | 725 (11.8)       | 295 (10.9) | 453 (8.8) | 710 (9.5) | 382 (10.6) | 143 (10.0) | 185 (7.7) | 534 (10.3) | 270 (11.1) | 115 (10.9) | 149 (8.9) |
| Events, mean (SD)‡       | 1.6 (1.4)            | 1.6 (1.4)        | 1.5 (0.8) | 1.7 (1.7) | 1.5 (1.4) | 1.5 (1.4) | 1.4 (0.8) | 1.6 (1.7) | 1.5 (1.1) | 1.5 (1.2) | 1.4 (0.7) | 1.5 (1.0) |
| Inpatient stays, n (%)†   | 1738 (12.9)          | 769 (12.6)       | 334 (12.4) | 635 (13.7) | 768 (10.3) | 388 (10.8) | 130 (9.1) | 250 (10.4) | 519 (10.1) | 238 (9.8) | 103 (9.8) | 178 (10.6) |
| Events, mean (SD)‡       | 1.4 (1.2)            | 1.4 (1.5)        | 1.3 (0.9) | 1.3 (0.8) | 1.3 (0.7) | 1.3 (0.7) | 1.3 (0.7) | 1.2 (0.6) | 1.2 (0.6) | 1.1 (0.4) | 1.2 (0.7) |
| A&E visits, n (%)†        | 190 (1.4)            | 89 (1.5)         | 28 (1.0)  | 73 (1.6)  | 84 (1.1)  | 52 (1.4)  | 9 (0.6)   | 23 (1.0)  | 56 (1.1)  | 25 (1.0)  | 7 (0.7)   | 24 (1.4)  |
| Events, mean (SD)‡       | 1.2 (0.5)            | 1.2 (0.5)        | 1.2 (0.5) | 1.2 (0.6) | 1.1 (0.4) | 1.2 (0.4) | 1.0 (0)   | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1.0 (0)   | 1.1 (0.3) |

*Included fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate and fluticasone furoate/vilanterol.
†Defined as patients who had at least one unit of use for respective healthcare service.
‡Calculated only for patients with >1 use during the time period.
A&E, accident and emergency; BDP, beclomethasone dipropionate; BUD, budesonide; COPD, chronic obstructive pulmonary disease; FOR, formoterol; GP, general practice; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; LABA, long-acting β2-agonist.
DISCUSSION

This study retrospectively assessed the characteristics of patients with COPD receiving ICS/LABA therapy in a primary care setting in England. Overall, in the 12 months prior to index, demographics and clinical characteristics in this patient population were generally similar across indexed therapies. Compared with those receiving BDP/FOR or BUD/FOR, incident users indexed on Other ICS/LABA combinations appeared to have more severe disease based on their history of moderate/severe AECOPD and GOLD 2019 categorisation. Patients who had received ICS/LABA therapy prior to index (prevalent users) also showed evidence of more severe disease and had a higher prevalence of comorbidities (including asthma) than those who had not received ICS/LABA therapy prior to index (incident users).

The GOLD strategy report and the UK NICE guidelines suggest that ICS/LABA may be prescribed as IMT for patients with COPD and a history of asthma. Our finding that over 60% of prevalent users in England had a history of asthma suggests that these patients may frequently be prescribed ICS/LABA. Moreover, approximately 20% of incident users had a current asthma diagnosis, further suggesting that ICS/LABA may have been prescribed for that reason and as per UK NICE guidelines.

The GOLD strategy report recommends consideration of ICS/LABA as IMT for patients with a history of asthma or patients with a significant exacerbation history and a blood eosinophil count >300 cells/µL and a stepwise escalation from a LAMA or a LABA to ICS/LABA (guided by blood eosinophil count) for patients who continue to experience exacerbations. In this study, fewer than 20% of incident users were receiving an LAMA prior to an ICS/LABA therapy prior to index (prevalent users) also showed evidence of more severe disease and had a higher prevalence of comorbidities (including asthma) than those who had not received ICS/LABA therapy prior to index (incident users).

In support of this, we observed geographical variation in prescribing patterns, with most prevalent and incident users located in western regions, likely due to differing practices across local clinical commissioning groups and the greater representation of patients in these regions in the CPRD-Aurum database. In England, it has been identified that referrals, diagnosis and treatments differ significantly across practices; aspects include quality of spirometry undertaken and interpretation of results, support for self-care and treatment optimisation. Furthermore, clinical commissioning groups may lead to different regional pricing and prescription switching, further influencing prescribing patterns in primary care. These patterns represent substantial variation in care given to patients with COPD within England; almost half of non-triple and IMT patients were in the two IMD quintiles indicative of greater deprivation. A recent post-hoc analysis of the Salford Lung Studies in COPD has also shown that 52% of participants included were in the most deprived quintile. While the level of deprivation did not influence treatment outcomes in the Salford Lung Studies, it was found to be associated with greater HCRU and costs. The geographical variation in prescribing patterns and its effects should be taken into close consideration in future observational studies as a potential confounding factor. This variation in care, along with the specifics of patients’ primary and secondary care, could affect outcomes and subsequently the generalisability of any findings from specific regions of England. Furthermore, this variation highlights how diagnostic and treatment decisions by primary care physicians also drive prescribing patterns in conjunction with patients’ characteristics. Further studies exploring the drivers behind inconsistent implementation and variation in treatment of patients diagnosed with COPD by GPs in primary care will be of interest, as the discrepancies in diagnosis and management suggest that prescribing patterns may be affected.

Prior COPD-related and all-cause HCRU were similar between non-triple and IMT users and across indexed therapies, even though non-triple users experienced numerically more moderate-to-severe and moderate AECOPDs in the year prior to index and had clinical characteristics potentially indicative of more advanced disease than IMT users. The lack of numerical differences in total healthcare costs may also be related to variation in familiarity and implementation across different international, national and local guidelines. In support of this, we observed geographical variation in prescribing patterns, with most prevalent and incident users located in western regions, likely due to differing practices across local clinical commissioning groups and the greater representation of patients in these regions in the CPRD-Aurum database. In England, it has been identified that referrals, diagnosis and treatments differ significantly across practices; aspects include quality of spirometry undertaken and interpretation of results, support for self-care and treatment optimisation. Furthermore, clinical commissioning groups may lead to different regional pricing and prescription switching, further influencing prescribing patterns in primary care. These patterns represent substantial variation in care given to patients with COPD within England; almost half of non-triple and IMT patients were in the two IMD quintiles indicative of greater deprivation. A recent post-hoc analysis of the Salford Lung Studies in COPD has also shown that 52% of participants included were in the most deprived quintile. While the level of deprivation did not influence treatment outcomes in the Salford Lung Studies, it was found to be associated with greater HCRU and costs. The geographical variation in prescribing patterns and its effects should be taken into close consideration in future observational studies as a potential confounding factor. This variation in care, along with the specifics of patients’ primary and secondary care, could affect outcomes and subsequently the generalisability of any findings from specific regions of England. Furthermore, this variation highlights how diagnostic and treatment decisions by primary care physicians also drive prescribing patterns in conjunction with patients’ characteristics. Further studies exploring the drivers behind inconsistent implementation and variation in treatment of patients diagnosed with COPD by GPs in primary care will be of interest, as the discrepancies in diagnosis and management suggest that prescribing patterns may be affected.
be due to similar inpatient stay costs, which seemed to be the
greatest contributor to COPD-related and all-cause health-
care costs among patients who used healthcare services.
Inpatient stays seemed to be the main driver of costs even
though only approximately one-third of patients had expe-
rienced an inpatient visit over the 12-month period prior
to index; this is in line with several studies that have shown
hospitalisations are the main drivers of direct healthcare
costs in patients with COPD. Costs for GP visits were
numerically lower than for inpatient stays, even though
nearly all patients (>99%) had GP consultations. In
contrast, a previous UK retrospective study showed that GP
interactions contributed more to costs than moderate-to-
severe exacerbations and non-COPD hospitalisations.
This disparity may have arisen because a smaller propor-
tion of patients with severe (FEV1 ≥30%–50% predicted)
or very severe COPD (FEV1 <30% predicted) were
included in that study (27%) compared with the present
study (approximately 32%–36%), as these patients would
be expected to experience more frequent and severe
exacerbations than populations with milder disease.

This study has several strengths, including the
real-world insight into prescribing patterns in England
and the large cohort which is representative of the UK
population. Patients with COPD are largely managed
in the primary care setting in the UK and thus
CPRD-Aurum adequately captures the majority of a patient’s
COPD healthcare journey, even though it does not cover
privately insured patients. This study is not without its limi-
tations. First, only medications prescribed in the primary care
setting were recorded, so patients may have initiated ICS/
LABA therapy earlier than the index date if they received an
earlier prescription through secondary care. Second, in this
study, over 20% of patients had a current asthma diagnosis.
In England, it has been shown that clinicians have difficulties
diagnosing up to 19.8% of patients based on clinical presenta-
tion and spirometry results, which can lead to inappropriate
diagnoses and treatment initiation. The approach used
in this study does not allow for potential misdiagnosis of
asthma as COPD and vice versa to be identified; as such,
the potential inclusion of patients with asthma–COPD
overlap syndrome cannot be ruled out. Similarly, COPD
and COPD-related chronic airflow limitations were not differen-
tiated; however, patients were required to have
received a diagnosis of COPD, be at least 35 years of
age and have an FEV1/FVC ratio of <0.7, in line with a
definition of COPD which was validated against patient
notes. Third, approximately 25% of patients were
missing MRC score and 25% of patients were missing
GOLD status data; however, these were not necessary
for inclusion in the study and as such did not impact the
representativeness of the study sample. In addition, approx-
imately 50% of patients were missing eosinophil count data,
which precluded further analysis on whether this treatable
trait is taken into account in ICS prescribing in a real-world
setting in England. Patients with asthma and COPD may also
require a different treatment from those with COPD only
and could arguably be classified as having asthma–COPD
overlap syndrome rather than asthma and COPD. However,
suggested treatment generally involves both ICS and LABA
therapy and they were considered appropriate to include
in this cohort. Additionally, a small percentage of patients
in the cohort are neither current nor historical smokers.
However, the proportions of smokers in this study are in
line with what would be expected in a population of patients
with COPD in the UK. Finally, direct costs may have been
underestimated as some tariffs are negotiated locally and
not nationally.

CONCLUSIONS
This real-world study showed that patients with COPD
initiating single-device ICS/LABA therapy in England
had similar clinical characteristics, HCRU and direct
healthcare costs across indexed therapies. Real-world
prescribing in England appears to be more closely aligned
with national guidelines than GOLD treatment strategy,
although asthma may have influenced prescribing
decisions. Less than half of incident users had an
exacerbation during the baseline period, suggesting that
ICS/LABA is not being prescribed principally based on
exacerbation history, even though the primary role of ICS
treatment in patients with COPD is to reduce the risk of
exacerbations. These findings can help inform the design
of future studies comparing the effectiveness of different
single-device dual-inhaler therapies.

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Characterisation of patients with chronic obstructive pulmonary disease initiating single-device inhaled corticosteroids/long-acting β₂-agonist dual therapy in a primary care setting in England

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## SUPPLEMENTARY MATERIAL

### Supplementary Table S1. Demographic and clinical characteristics of prevalent users

| Characteristic                           | Overall N=64,794 | BDP/FOR N=8,163 | BUD/FOR N=17,027 | Other ICS/LABA N=39,604 |
|-----------------------------------------|-----------------|-----------------|------------------|------------------------|
| **Demographic characteristics**         |                 |                 |                  |                        |
| Age at index, years, mean (SD)          | 70.9 (10.6)     | 70.4 (11.0)     | 70.4 (10.6)      | 71.3 (10.5)            |
| Female, n (%)                           | 30,838 (47.6)   | 4084 (50.0)     | 7927 (46.6)      | 18,827 (47.5)          |
| **Patient region, n (%)**               |                 |                 |                  |                        |
| North East                              | 4853 (7.5)      | 254 (3.1)       | 1340 (7.9)       | 3259 (8.2)             |
| North West                              | 14,129 (21.8)   | 1912 (23.4)     | 3461 (20.3)      | 8756 (22.1)            |
| Yorkshire & The Humber                  | 2708 (4.2)      | 445 (5.5)       | 822 (4.8)        | 1441 (3.6)             |
| East Midlands                           | 1481 (2.3)      | 311 (3.8)       | 559 (3.3)        | 611 (1.5)              |
| West Midlands                           | 11,964 (18.5)   | 1847 (22.6)     | 2757 (16.2)      | 7360 (18.6)            |
| East of England                         | 3002 (4.6)      | 439 (5.4)       | 650 (3.8)        | 1913 (4.8)             |
| South West                              | 8690 (13.4)     | 682 (8.4)       | 2776 (16.3)      | 5232 (13.2)            |
| South Central                           | 6593 (10.2)     | 1337 (16.4)     | 1460 (8.6)       | 3796 (9.6)             |
| London                                  | 6595 (10.2)     | 663 (8.1)       | 2039 (12.0)      | 3893 (9.8)             |
| South East Coast                        | 4777 (7.4)      | 273 (3.3)       | 1162 (6.8)       | 3342 (8.4)             |
| **Socioeconomic status – IMD, n (%)**   |                 |                 |                  |                        |
| Quintile 1                              | 9927 (15.3)     | 1278 (15.7)     | 2718 (16.0)      | 5931 (15.0)            |
| Quintile 2                              | 11,426 (17.7)   | 1478 (18.1)     | 3030 (17.8)      | 6918 (17.5)            |
| Quintile 3                              | 12,322 (19.0)   | 1570 (19.2)     | 3407 (20.0)      | 7345 (18.6)            |
| Quintile 4                              | 13,973 (21.6)   | 1668 (20.4)     | 3723 (21.9)      | 8582 (21.7)            |
### Clinical characteristics

| Quintile 5 | 17 090 (26.4) | 2165 (26.5) | 4134 (24.3) | 10 791 (27.3) |
|------------|----------------|-------------|-------------|---------------|

#### BMI at index, kg/m²

| n | 50 769 | 6654 | 13 438 | 30 677 |
| Mean (SD) | 28.9 (8.0) | 28.4 (7.4) | 28.8 (7.9) | 29.0 (8.2) |

#### Smoking status at index, n (%)

| Current smoker | 28 251 (43.6) | 3727 (45.7) | 7443 (43.7) | 17 081 (43.1) |
| Former smoker | 34 363 (53.0) | 4124 (50.5) | 8968 (52.7) | 21 271 (53.7) |
| Non-smoker | 2180 (3.4) | 312 (3.8) | 616 (3.6) | 1252 (3.2) |

#### FEV₁/FVC ratio

| n | 46 174 | 5808 | 12 403 | 27 963 |
| Mean (SD) | 57.5 (14.9) | 58.4 (14.5) | 57.4 (14.9) | 57.4 (14.9) |

#### % predicted FEV₁

| n | 39 901 | 5448 | 10 717 | 23 736 |
| Mean (SD) | 56.8 (19.1) | 57.9 (19.0) | 56.9 (19.0) | 56.5 (19.1) |

#### Category, n (%)

| GOLD 1: FEV₁ % predicted ≥80% | 4951 (12.4) | 740 (13.6) | 1332 (12.4) | 2879 (12.1) |
| GOLD 2: FEV₁ % predicted ≥50–<80% | 20 609 (51.7) | 2827 (51.9) | 5592 (52.2) | 12 190 (51.4) |
| GOLD 3: FEV₁ % predicted ≥30–<50% | 11 457 (28.7) | 1546 (28.4) | 3037 (28.3) | 6874 (29.0) |
| GOLD 4: FEV₁ % predicted <30% | 2884 (7.2) | 335 (6.2) | 756 (7.1) | 1793 (7.6) |

#### MRC Dyspnoea Scale score, n (%)

| 1<sup>b</sup> | 6532 (10.1) | 954 (11.7) | 1771 (10.4) | 3807 (9.6) |
| 2 | 21 270 (32.8) | 2617 (32.1) | 5897 (34.6) | 12 756 (32.2) |
| 3 | 19 281 (29.8) | 2400 (29.4) | 5034 (29.6) | 11 847 (29.9) |
| Comorbidities, n (%) | 11 343 (17.5) | 1326 (16.2) | 2803 (16.5) | 7214 (18.2) |
|---------------------|----------------|-------------|-------------|-------------|
| Depression           | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Anxiety              | 3752 (5.8)     | 562 (6.9)   | 896 (5.3)   | 2294 (5.8)  |
| Gastroesophageal reflux disease | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Acute myocardial infarction | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Congestive heart failure | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Stroke               | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Bronchiectasis       | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Dementia/cognitive impairment | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Rheumatoid/osteoarthritis | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Current asthma diagnosis, n (%)<sup>a</sup> | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Historical asthma diagnosis, n (%)<sup>b</sup> | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| AECOPD in the 12 months prior to index | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Moderate-to-severe   | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Patients with ≥1 AECOPD, n (%) | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Mean number of AECOPD per patient<sup>c</sup> (SD) | 0.8 (1.2)     | 0.8 (1.2)   | 0.7 (1.1)   | 0.8 (1.2)   |
| Moderate             | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Patients with ≥1 AECOPD, n (%) | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Mean number of AECOPD per patient<sup>c</sup> (SD) | 0.6 (1.0)     | 0.6 (1.0)   | 0.5 (1.0)   | 0.6 (1.0)   |
| Severe               | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Patients with ≥1 AECOPD, n (%) | 2616 (4.0)     | 304 (3.7)   | 626 (3.7)   | 1686 (4.3)  |
| Mean number of AECOPD per patient<sup>c</sup> (SD) | 0.6 (1.0)     | 0.6 (1.0)   | 0.5 (1.0)   | 0.6 (1.0)   |
| Patients with ≥1 AECOPD, n (%)               | 8522 (13.2) | 1193 (14.6) | 2037 (12.0) | 5292 (13.4) |
|--------------------------------------------|-------------|-------------|-------------|-------------|
| Mean number of AECOPD per patient* (SD)    | 0.2 (0.5)   | 0.2 (0.6)   | 0.2 (0.5)   | 0.2 (0.6)   |
| GOLD 2019 group, n (%)                     |             |             |             |             |
| A                                          | 18 366 (29.7) | 2252 (29.2) | 5281 (32.4) | 10 833 (28.7) |
| B                                          | 17 376 (28.1) | 1996 (25.9) | 4584 (28.2) | 10 796 (28.6) |
| C                                          | 6005 (9.7)   | 845 (11.0)  | 1551 (9.5)  | 3609 (9.6)   |
| D                                          | 20 029 (32.4) | 2621 (34.0) | 4862 (29.9) | 12 546 (33.2) |
| Eosinophil count, 10^9 cells/μL            |             |             |             |             |
| n                                          | 31 848       | 4069        | 8599        | 19 180       |
| Mean (SD)                                  | 0.24 (0.2)   | 0.24 (0.2)  | 0.24 (0.2)  | 0.24 (0.2)   |

*Included fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate, and fluticasone furoate/vilanterol; **Not troubled by breathlessness except on strenuous exercise; †Too breathless to leave the house, or breathless when dressing/undressing; ‡Current and historical asthma were not mutually exclusive; §Included all patients with or without ≥1 AECOPD.

AECOPD, acute exacerbation of COPD; BDP, beclomethasone dipropionate; BMI, body mass index; BUD, budesonide; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FOR, formoterol; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IMD, index of multiple deprivation; IMT, initial maintenance therapy; LABA, long-acting β₂-agonist; MRC, Medical Research Council; SD, standard deviation.
**Supplementary Table S2.** COPD-related HCRU and direct healthcare costs for incident users

|                     | Incident users | Non-triple users | IMT users |
|---------------------|----------------|-----------------|-----------|
|                     | Overall        | BDP/FOR n=13451 | BDP/FOR n=6122 | BUD/FOR n=2703 | Other ICS/LABA n=6122 | Overall | BDP/FOR n=7448 | BUD/FOR n=3601 | BUD/FOR n=1432 | Other ICS/LABA n=2515 | Overall | BDP/FOR n=5162 | BUD/FOR n=2427 | BUD/FOR n=1056 | Other ICS/LABA n=1679 |
| 12 months prior to index |                |                 |                  |                   |                        |         |                 |                   |                   |                        |         |                 |                   |                   |                        |
| **GP consultations, n (%)** | 9850 (73.2)    | 4493 (73.4)     | 1961 (72.5)      | 3396 (73.4)       | 5081 (68.2)            | 2496 (69.3) | 959 (67.0)      | 1626 (67.3)       | 3196 (61.9)       | 1544 (63.6)            | 626 (59.3) | 1026 (61.1)       |
| **Events, mean (SD)** | 2.4 (1.8)       | 2.4 (1.8)       | 2.4 (1.7)        | 2.4 (1.7)         | 2.2 (1.6)              | 2.2 (1.7)  | 2.2 (1.5)       | 2.1 (1.6)         | 1.9 (1.4)         | 1.9 (1.4)              | 2.0 (1.5) | 1.8 (1.2)         |
| **Total costs, £, mean (SD)** | 89 (66.7)       | 90 (68.6)       | 89 (64.5)        | 89 (65.3)         | 81 (62.2)              | 82 (65.0)  | 81 (58.1)       | 80 (60.07)        | 71 (51.4)         | 71 (51.6)              | 76 (57.5) | 68 (46.9)         |
| **Outpatient visits, n (%)** | 2180 (16.2)     | 1039 (17.0)     | 426 (15.8)       | 715 (15.5)        | 1074 (14.4)            | 560 (15.6) | 201 (14.0)      | 313 (13.0)        | 747 (14.5)        | 383 (15.8)             | 149 (14.1) | 215 (12.8)        |
| **Events, mean (SD)** | 2.4 (2.4)       | 2.4 (2.5)       | 2.2 (2.0)        | 2.5 (2.5)         | 2.2 (2.1)              | 2.2 (2.1)  | 2.0 (1.4)       | 2.3 (2.5)         | 2.1 (1.9)         | 2.1 (2.0)              | 2.1 (1.4) | 2.1 (2.0)         |
| **Total costs, £, mean (SD)** | 367 (290.0)     | 371 (287.3)     | 341 (247.5)      | 378 (315.7)       | 344 (258.6)            | 346 (251.0) | 316 (207.9)     | 359 (297.8)       | 337 (233.9)       | 339 (225.4)             | 325 (193.4) | 340 (272.0)       |
| **Inpatient stays, n (%)** | 3146 (23.4)     | 1395 (22.8)     | 613 (22.7)       | 1138 (24.6)       | 1444 (19.4)            | 709 (19.7) | 258 (18.0)      | 477 (19.8)        | 869 (16.8)        | 410 (16.9)              | 172 (16.3) | 287 (17.1)        |
| **Events, mean (SD)** | 1.8 (2.0)       | 1.8 (2.1)       | 1.8 (2.5)        | 1.8 (1.6)         | 1.8 (1.8)              | 1.8 (2.0)  | 1.6 (1.4)       | 1.8 (1.8)         | 1.5 (1.3)         | 1.5 (1.4)              | 1.3 (0.8) | 1.6 (1.6)         |
| **Total costs, £, mean (SD)** | 3533 (4527.2)   | 3448 (4359.7)   | 3469 (4853.1)    | 3671 (4547.5)     | 3469 (4441.4)          | 3318 (4181.5) | 3243 (4166.8) | 3816 (4923.0)    | 3104 (3735.9)   | 3082 (3588.0)          | 2761 (3808.7) | 3340 (3892.0)     |
| **A&E visits, n (%)** | 334 (2.5)       | 150 (2.5)       | 52 (1.9)         | 132 (2.9)         | 147 (2.0)              | 85 (2.4)   | 18 (1.3)        | 44 (1.8)         | 88 (1.7)         | 41 (1.7)               | 12 (1.1)  | 35 (2.1)         |
| **Events, mean (SD)** | 1.2 (0.6)       | 1.3 (0.6)       | 1.2 (0.4)        | 1.3 (0.7)         | 1.2 (0.5)              | 1.2 (0.6)  | 1.0 (0)        | 1.2 (0.5)         | 1.1 (0.3)        | 1.1 (0.3)              | 1.0 (0)   | 1.1 (0.4)         |
| **Total costs, £, mean (SD)** | 218 (131.1)     | 222 (133.3)     | 179 (95.1)       | 229 (138.7)       | 205 (115.1)            | 210 (125.3) | 160 (67.7)      | 215 (107.4)       | 192 (86.7)        | 185 (71.2)              | 160 (62.3) | 212 (105.8)       |
| Event Type                        | >6–12 months prior to index | >3–6 months prior to index |
|----------------------------------|----------------------------|---------------------------|
| **GP consultations, n (%)**      | 5742 (42.7)                | 4007 (29.8)               |
| **Events, mean (SD)**            | 1.7 (1.1)                  | 1.1 (0.4)                 |
| **Total costs, £, mean (SD)**    | 63 (41.2)                  | 187 (107.0)               |
| **Outpatient visits, n (%)**     | 859 (6.4)                  | 1331 (9.9)                |
| **Events, mean (SD)**            | 2.0 (1.9)                  | 1.5 (1.9)                 |
| **Total costs, £, mean (SD)**    | 296 (228.1)                | 2831 (3710.3)             |
| **Inpatient stays, n (%)**       | 1331 (9.9)                 | 2831 (3710.3)             |
| **Events, mean (SD)**            | 1.5 (1.9)                  | 1.5 (0.4)                 |
| **Total costs, £, mean (SD)**    | 296 (228.1)                | 2831 (3710.3)             |
| **A&E visits, n (%)**            | 98.0 (7.9)                 | 1.0 (0.4)                 |
| **Events, mean (SD)**            | 1.1 (0.4)                  | 1.1 (0.4)                 |
| **Total costs, £, mean (SD)**    | 187 (107.0)                | 1.7 (1.1)                 |

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|                      | 0–3 months prior to index | 1–2 years prior to index |
|----------------------|--------------------------|-------------------------|
|                      | Events, mean (SD)        | Total costs, £, mean (SD) |
|                      | 1.4 (0.7)                | 1.4 (0.7)                |
|                      | 1.4 (0.7)                | 1.4 (0.7)                |
|                      | 1.4 (0.7)                | 1.4 (0.7)                |
|                      | 1.4 (0.7)                | 1.3 (0.6)                |
|                      | 1.4 (0.7)                | 1.3 (0.6)                |
|                      | 1.4 (0.7)                | 1.3 (0.5)                |
|                      | 1.4 (0.7)                | 1.3 (0.6)                |
|                      | 1.4 (0.7)                | 1.3 (0.6)                |
|                      | 1.4 (0.7)                | 1.3 (0.6)                |
| Outpatient visits, n (%)* | 726 (5.4)              | 726 (5.4)                |
|                      | 346 (5.7)                | 346 (5.7)                |
|                      | 236 (5.1)                | 236 (5.1)                |
|                      | 345 (4.6)                | 345 (4.6)                |
|                      | 178 (4.9)                | 178 (4.9)                |
|                      | 64 (4.5)                 | 64 (4.5)                 |
|                      | 103 (4.3)                | 103 (4.3)                |
|                      | 227 (4.4)                | 227 (4.4)                |
|                      | 118 (4.9)                | 118 (4.9)                |
|                      | 50 (4.7)                 | 50 (4.7)                 |
|                      | 59 (3.5)                 | 59 (3.5)                 |
| A&E visits, n (%)*    | 74 (0.6)                 | 33 (0.5)                 |
|                      | 31 (0.7)                 | 31 (0.7)                 |
|                      | 16 (0.4)                 | 16 (0.4)                 |
|                      | NR*                      | NR*                     |
|                      | 11 (0.2)                 | 11 (0.2)                 |
|                      | 6 (0.3)                  | 6 (0.3)                  |
|                      | 184 (39.4)               | 184 (39.4)               |
| GP consultations, n (%)* | 5769 (42.9)             | 2635 (43.0)              |
|                      | 1169 (43.3)              | 1965 (42.5)              |
|                      | 2847 (38.2)              | 1409 (39.1)              |
|                      | 538 (37.6)               | 900 (37.3)               |
|                      | 1897 (36.8)              | 1897 (36.8)              |
|                      | 911 (37.5)               | 911 (37.5)               |
|                      | 377 (35.7)               | 377 (35.7)               |
|                      | 609 (36.3)               | 609 (36.3)               |
| Total costs, £, mean (SD) | 2805 (3152.9)          | 2819 (3327.6)             |
|                      | 2478 (2995.7)            | 2969 (3012.4)            |
|                      | 2777 (3064.6)            | 2717 (3178.4)            |
|                      | 1960 (1762.9)            | 3342 (3374.5)            |
|                      | 2478 (2538.6)            | 2414 (2678.9)            |
|                      | 2240 (2158.7)            | 2694 (2509.2)            |
| Inpatient stays, n (%)* | 943 (7.0)               | 413 (6.8)                |
|                      | 189 (7.0)                | 341 (7.4)                |
|                      | 428 (5.8)                | 208 (5.8)                |
|                      | 81 (5.7)                 | 139 (5.8)                |
|                      | 207 (4.0)                | 105 (4.3)                |
|                      | 34 (3.2)                 | 68 (4.1)                 |
|                      | 1.3 (0.8)                | 1.4 (0.9)                |
|                      | 1.3 (0.9)                | 1.4 (0.8)                |
|                      | 1.4 (0.9)                | 1.4 (1.0)                |
|                      | 1.2 (0.4)                | 1.2 (0.4)                |
|                      | 1.4 (0.9)                | 1.2 (0.6)                |
|                      | 1.3 (0.7)                | 1.1 (0.2)                |
|                      | 1.3 (0.5)                | 1.3 (0.5)                |
|                      | 1.0 (0.1)                | 1.0 (0.2)                |
|                      | 1 (0)                    | 1 (0)                    |
|                      | 1 (0)                    | 1 (0)                    |
|                      | 1 (0)                    | 1 (0)                    |
|                      | 1 (0)                    | 1 (0)                    |
|                      | 1 (N/A)                  | 1 (N/A)                  |
|                      | 1 (0)                    | 1 (N/A)                  |
|                      | 184 (39.4)               | 184 (39.4)               |
| Outpatient visits, n (%)* | 1473 (11.0)             | 725 (11.8)               |
|                      | 295 (10.9)               | 453 (9.8)                |
|                      | 710 (9.5)                | 382 (10.6)               |
|                      | 185 (7.7)                | 143 (10.0)               |
|                      | 534 (10.3)               | 270 (11.1)               |
|                      | 115 (10.9)               | 149 (8.9)                |
| Events, mean (SD) | 1.6 (1.4) | 1.6 (1.4) | 1.5 (0.8) | 1.7 (1.7) | 1.5 (1.4) | 1.5 (1.4) | 1.4 (0.8) | 1.6 (1.7) | 1.5 (1.1) | 1.5 (1.2) | 1.4 (0.7) | 1.5 (1.0) |
|------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Total costs, £, mean (SD) | 253 (188.9) | 252 (181.3) | 229 (136.8) | 272 (225.0) | 241 (178.3) | 241 (168.2) | 225 (138.9) | 254 (220.6) | 252 (167.5) | 256 (163.5) | 221 (135.7) | 267 (193.1) |
| Inpatient stays, n (%) | 1738 (12.9) | 769 (12.6) | 334 (12.4) | 635 (13.7) | 768 (10.3) | 388 (10.8) | 130 (9.1) | 250 (10.4) | 519 (10.1) | 238 (9.8) | 103 (9.8) | 178 (10.6) |
| Events, mean (SD) | 1.4 (1.2) | 1.4 (1.5) | 1.3 (0.9) | 1.3 (0.8) | 1.3 (0.7) | 1.3 (0.8) | 1.3 (0.7) | 1.3 (0.7) | 1.2 (0.6) | 1.2 (0.6) | 1.1 (0.4) | 1.2 (0.7) |
| Total costs, £, mean (SD) | 2705 (2804.3) | 2728 (2689.4) | 2479 (2586) | 2797 (3039.1) | 2648 (2760.2) | 2598 (2597.1) | 2366 (2761.1) | 2871 (2990.0) | 2467 (2460.7) | 2518 (2350.5) | 2082 (2246.0) | 2622 (2702.2) |
| A&E visits, n (%) | 190 (1.4) | 89 (1.5) | 28 (1.0) | 73 (1.6) | 84 (1.1) | 52 (1.4) | 9 (0.6) | 23 (1.0) | 56 (1.1) | 25 (1.0) | 7 (0.7) | 24 (1.4) |
| Events, mean (SD) | 1.2 (0.5) | 1.2 (0.5) | 1.2 (0.5) | 1.2 (0.6) | 1.1 (0.4) | 1.2 (0.4) | 1 (0) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1 (0) | 1.1 (0.3) |
| Total costs, £, mean (SD) | 216 (108.7) | 218 (93.0) | 196 (103.2) | 221 (127.7) | 207 (84.3) | 211 (87.7) | 196 (37.0) | 200 (91.4) | 200 (76.9) | 194 (56.5) | 188 (36.5) | 211 (101.4) |

a Defined as patients who had at least one unit of use for respective healthcare service; b Calculated for patients with ≥1 use during the time period; c Included fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate, and fluticasone furoate/vilanterol. d Results based on small numbers of patients (n<5) were suppressed, as well as related values to protect primary suppression.

A&E, Accident & Emergency; BDP, beclomethasone dipropionate; BUD, budesonide; COPD, chronic obstructive pulmonary disease; FOR, formoterol; GP, general practice; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; LABA, long-acting β<sub>2</sub>-agonist, N/A, not applicable; NR, not reported; SD, standard deviation.
### Supplementary Table S3. All-cause HCRU and direct healthcare costs for incident users

|                      | Incident users | Non-triple users | IMT users |
|----------------------|----------------|-----------------|-----------|
|                      | Overall n=13   | BDP/FOR n=6122  | BUD/FOR n=2703 | Overall n=7448 | BDP/FOR n=3601 | BUD/FOR n=1432 | Overall n=5162 | BDP/FOR n=2427 | BUD/FOR n=1056 | Other ICS/LABA n=1679 |
| 12 months prior to index |                |                 |             |                |                 |                 |                |                 |                 |                      |
| **GP consultations, n (%)** | 13.384 (99.5) | 6097 (99.6)     | 2690 (99.5) | 4597 (99.4)    | 7406 (99.4)     | 3588 (99.6)     | 1425 (99.5)    | 2393 (99.1)     | 5124 (99.3)     | 2414 (99.5)     | 1050 (99.4)     | 1660 (98.9)     |
| **Events, mean (SD)** | 13.0 (9.6)     | 12.8 (9.2)      | 12.8 (9.6)  | 13.5 (10.3)    | 12.9 (9.8)      | 12.6 (9.4)      | 12.7 (9.8)     | 13.4 (10.4)     | 12.1 (9.1)      | 12.0 (9.1)      | 11.8 (9.6)      | 12.4 (8.7)     |
| **Total costs, £, mean (SD)** | 459 (343.2)    | 449 (320.4)     | 456 (343.4) | 474 (370.6)    | 455 (347.4)     | 443 (325.5)     | 453 (352.3)    | 474 (374.6)     | 427 (321.0)     | 420 (310.8)     | 422 (346.5)     | 441 (318.6)    |
| **Outpatient visits, n (%)** | 9103 (67.7)    | 4086 (66.7)     | 1844 (68.2) | 3173 (68.6)    | 4999 (67.1)     | 2374 (65.9)     | 975 (68.1)     | 1650 (68.3)     | 3389 (65.7)     | 1578 (65.0)     | 700 (66.3)      | 1111 (66.2)    |
| **Events, mean (SD)** | 6.3 (8.0)      | 6.3 (9.1)       | 6.3 (7.3)   | 6.2 (6.8)      | 6.3 (8.5)       | 6.3 (7.9)       | 6.3 (7.2)      | 6.2 (6.8)       | 6.0 (8.2)       | 6.1 (9.6)       | 5.9 (6.8)       | 5.9 (6.7)      |
| **Total costs, £, mean (SD)** | 3301 (4480.4)  | 3250 (4424.2)   | 3163 (4578.0) | 3450 (4492.3) | 3224 (4395.9)   | 3217 (4455.6)   | 2993 (3861.6)  | 3367 (4591.8)   | 3096 (4114.0)   | 3181 (4432.7)   | 2769 (3630.0)   | 3184 (3908.6)  |
| **Inpatient stays, n (%)** | 4969 (36.9)    | 2218 (36.2)     | 1021 (37.8) | 1730 (37.4)    | 2642 (35.5)     | 1281 (35.6)     | 499 (34.9)     | 862 (35.7)      | 1805 (35.0)     | 855 (35.2)      | 373 (35.3)      | 577 (34.4)     |
| **Events, mean (SD)** | 2.1 (4.6)      | 2.1 (4.0)       | 2.2 (5.7)   | 2.2 (4.6)      | 2.1 (4.7)       | 2.0 (2.1)       | 2.4 (7.3)      | 2.2 (5.5)       | 2.1 (4.6)       | 2.0 (2.1)       | 1.8 (2.2)       | 2.4 (7.4)      |
| **Total costs, £, mean (SD)** | 3301 (4480.4)  | 3250 (4424.2)   | 3163 (4578.0) | 3450 (4492.3) | 3224 (4395.9)   | 3217 (4455.6)   | 2993 (3861.6)  | 3367 (4591.8)   | 3096 (4114.0)   | 3181 (4432.7)   | 2769 (3630.0)   | 3184 (3908.6)  |
| **A&E visits n (%)** | 4553 (33.9)    | 2019 (33.0)     | 934 (34.6)  | 1600 (34.6)    | 2393 (32.1)     | 1148 (31.9)     | 462 (32.3)     | 783 (32.4)      | 1670 (32.4)     | 781 (32.2)      | 339 (32.1)      | 550 (32.8)     |
| **Events, mean (SD)** | 1.8 (2.0)      | 1.8 (1.4)       | 1.7 (1.3)   | 1.8 (2.9)      | 1.8 (1.9)       | 1.8 (1.5)       | 1.6 (1.2)      | 1.8 (2.7)       | 1.7 (2.3)       | 1.7 (1.3)       | 1.6 (1.0)       | 1.8 (3.5)      |
| Event | Inpatient stays, n (%)<sup>a</sup> | Outpatient visits, n (%)<sup>b</sup> | GP consultations, n (%)<sup>c</sup> | Total costs, £, mean (SD) | Total costs, £, mean (SD) | Total costs, £, mean (SD) | Total costs, £, mean (SD) |
|-------|----------------------------------|----------------------------------|----------------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Total costs, £, mean (SD) | 270 (336.0) | 268 (250.3) | 250 (220.3) | 286 (462.0) | 263 (309.3) | 264 (254.2) | 241 (213.0) | 275 (413.2) | 252 (376.6) | 247 (230.8) | 228 (173.2) | 274 (579.7) |
| >6–12 months prior to index | | | | | | | | | | | | |
| Events, mean (SD)<sup>b</sup> | 6.6 (5.5) | 6.4 (5.2) | 6.5 (5.5) | 6.7 (5.7) | 6.6 (5.5) | 6.5 (5.4) | 6.5 (5.5) | 6.7 (5.8) | 6.1 (5.3) | 6.1 (5.4) | 6.1 (5.3) | 6.2 (5.2) |
| Total costs, £, mean (SD) | 231 (194.5) | 226 (183.5) | 231 (197.9) | 239 (206.1) | 232 (197.0) | 227 (188.2) | 233 (197.2) | 240 (209.1) | 218 (186.2) | 215 (183.3) | 219 (192.6) | 221 (186.5) |
| Inpatient stays, n (%)<sup>b</sup> | 6930 (51.5) | 3094 (50.5) | 1400 (51.8) | 2436 (52.7) | 3846 (51.6) | 1817 (50.5) | 745 (52.0) | 1284 (53.2) | 2506 (48.6) | 1190 (49.0) | 499 (47.3) | 817 (48.7) |
| Events, mean (SD)<sup>b</sup> | 3.9 (4.9) | 3.9 (5.7) | 3.9 (4.3) | 3.8 (4.0) | 3.9 (5.2) | 3.9 (6.3) | 4.0 (4.3) | 3.8 (3.9) | 3.8 (5.2) | 3.8 (6.1) | 3.9 (4.3) | 3.8 (3.9) |
| Total costs, £, mean (SD) | 366 (505.4) | 358 (499.7) | 375 (527.5) | 372 (499.5) | 365 (511.8) | 348 (468.6) | 390 (500.5) | 374 (520.7) | 355 (511.4) | 339 (462.1) | 374 (552.8) | 367 (551.7) |
| Inpatient stays, n (%)<sup>b</sup> | 2693 (20.0) | 1170 (19.1) | 564 (20.9) | 959 (20.7) | 1493 (20.1) | 712 (19.8) | 285 (19.9) | 496 (20.5) | 986 (19.1) | 474 (19.5) | 196 (18.6) | 316 (18.8) |
| Events, mean (SD)<sup>b</sup> | 1.7 (3.4) | 1.7 (2.9) | 1.8 (4.0) | 1.8 (3.6) | 1.7 (3.2) | 1.6 (1.5) | 2.0 (4.9) | 1.8 (3.6) | 1.8 (3.7) | 1.6 (1.3) | 1.7 (2.1) | 2.1 (6.0) |
| Total costs, £, mean (SD) | 2492 (3337.9) | 2458 (3499.1) | 2555 (3342.6) | 2496 (3103.3) | 2490 (2812.7) | 2469 (3210.1) | 2624 (3320.1) | 2443 (3022.7) | 2529 (3129.6) | 2571 (3382.7) | 2504 (2988.6) | 2480 (2812.7) |
| A&E visits, n (%)<sup>c</sup> | 2224 (16.5) | 974 (15.9) | 462 (17.1) | 788 (17.0) | 1218 (16.4) | 575 (16.0) | 229 (16.0) | 414 (17.1) | 849 (16.5) | 407 (16.8) | 169 (16.0) | 273 (16.3) |
| Events, mean (SD)<sup>c</sup> | 1.4 (1.3) | 1.4 (1.0) | 1.4 (0.8) | 1.5 (1.8) | 1.5 (1.4) | 1.5 (1.0) | 1.4 (0.9) | 1.6 (2.0) | 1.4 (1.2) | 1.4 (0.9) | 1.3 (0.7) | 1.5 (1.7) |
| Total costs, £, mean (SD) | 209 (221.7) | 203 (177.7) | 195 (149.2) | 224 (293.8) | 213 (230.6) | 208 (180.7) | 199 (158.8) | 229 (311.4) | 205 (212.8) | 202 (160.7) | 179 (123.2) | 227 (303.8) |
| Event                  | >3–6 months prior to index | 0–3 months prior to index |
|------------------------|-----------------------------|---------------------------|
| GP consultations, n (%) | 10 876 (80.9) | 198 (183.4) |
| Events, mean (SD)      | 3.8 (3.1)       | 1.3 (1.1)       |
| Total costs, £, mean (SD) | 133 (111.9) | 198 (183.4) |
| Outpatient visits, n (%) | 5 415 (40.3) | 1465 (10.9)    |
| Events, mean (SD)      | 2.6 (2.7)       | 1.5 (1.9)       |
| Total costs, £, mean (SD) | 248 (344.9) | 2335 (3035.5) |
| Inpatient stays, n (%) | 1 708 (12.7) | 1465 (10.9) |
| Events, mean (SD)      | 1.5 (1.9)       | 1.3 (1.1)       |
| Total costs, £, mean (SD) | 2353 (3035.5) | 198 (183.4) |
| A&E visits, n (%)      | 1 465 (10.9) | 198 (183.4) |
| Events, mean (SD)      | 1.5 (1.9)       | 1.3 (1.1)       |
| Total costs, £, mean (SD) | 2353 (3035.5) | 198 (183.4) |
| GP consultations, n (%)<sup>a</sup> | 12 250 (91.1) | 5569 (91.0) | 2469 (91.3) | 4212 (91.1) | 6753 (90.7) | 3265 (90.9) | 1302 (91.1) | 2186 (90.5) | 2214 (91.2) | 961 (91.0) | 1530 (91.1) |
| Events, mean (SD)<sup>b</sup> | 4.3 (3.2) | 4.2 (3.1) | 4.2 (3.2) | 4.3 (3.3) | 4.2 (3.2) | 4.1 (3.1) | 4.3 (3.4) | 4.1 (3.1) | 4.1 (3.0) | 4.1 (3.2) | 4.3 (3.1) |
| Total costs, £, mean (SD) | 149 (112.7) | 147 (108.1) | 150 (117.7) | 151 (117.9) | 148 (112.4) | 145 (106.3) | 148 (113.0) | 152 (102.7) | 146 (108.3) | 143 (103.9) | 151 (107.9) |
| Outpatient visits, n (%)<sup>a</sup> | 6031 (44.8) | 2744 (44.8) | 1223 (45.3) | 2064 (44.6) | 3279 (44.0) | 1575 (43.7) | 2469 (45.0) | 1060 (43.9) | 2261 (43.8) | 1058 (45.8) | 719 (42.8) |
| Events, mean (SD)<sup>b</sup> | 2.7 (2.8) | 2.7 (2.9) | 2.7 (2.7) | 2.7 (2.8) | 2.7 (2.9) | 2.7 (3.0) | 2.7 (2.6) | 2.7 (2.9) | 2.6 (2.7) | 2.6 (2.8) | 2.6 (2.6) | 2.6 (2.7) |
| Total costs, £, mean (SD) | 271 (334.7) | 263 (307.0) | 276 (345.2) | 279 (362.6) | 260 (333.8) | 252 (287.4) | 269 (320.3) | 267 (399.6) | 262 (336.2) | 252 (281.9) | 269 (404.7) |
| Inpatient stays, n (%)<sup>a</sup> | 2345 (17.4) | 1036 (16.9) | 468 (17.3) | 841 (18.2) | 1166 (15.7) | 568 (15.8) | 210 (14.7) | 388 (16.1) | 837 (16.2) | 378 (16.2) | 288 (17.2) |
| Events, mean (SD)<sup>b</sup> | 1.5 (1.8) | 1.5 (1.9) | 1.5 (2.0) | 1.4 (1.6) | 1.5 (1.8) | 1.4 (1.0) | 1.6 (2.7) | 1.5 (2.1) | 1.4 (1.5) | 1.4 (1.0) | 1.2 (0.6) | 1.5 (2.3) |
| Total costs, £, mean (SD) | 2433 (2736.3) | 2473 (2628.3) | 2212 (2523.8) | 2507 (2963.1) | 2321 (2637.5) | 2364 (2581.2) | 2038 (2430.6) | 2410 (2861.8) | 2182 (2465.1) | 2252 (2440.2) | 1887 (2117.6) | 2266 (2675.1) |
| A&E visits n (%)<sup>a</sup> | 2164 (16.1) | 957 (15.6) | 425 (15.7) | 782 (16.9) | 1055 (14.2) | 512 (14.2) | 191 (13.3) | 352 (14.6) | 751 (14.6) | 340 (14.0) | 145 (13.7) | 266 (15.8) |
| Events, mean (SD)<sup>b</sup> | 1.4 (1.0) | 1.4 (0.8) | 1.3 (0.7) | 1.4 (1.3) | 1.3 (0.8) | 1.4 (0.8) | 1.3 (0.7) | 1.4 (0.9) | 1.3 (1.2) | 1.3 (0.7) | 1.2 (0.6) | 1.4 (1.9) |
| Total costs, £, mean (SD) | 220 (172.8) | 222 (151.7) | 204 (141.1) | 226 (208.6) | 213 (153.1) | 218 (157.3) | 199 (146.6) | 212 (150.3) | 207 (207.2) | 204 (147.9) | 194 (141.3) | 218 (287.0) |

<sup>a</sup>Defined as patients who had at least one unit of use for respective healthcare service; <sup>b</sup>Calculated for patients with ≥1 use during the time period; <sup>c</sup> Included fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate, and fluticasone furoate/vilanterol.

A&E, Accident & Emergency; BDP, beclomethasone dipropionate; BUD, budesonide; FOR, formoterol; GP, general practice; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; LABA, long-acting β<sub>2</sub>-agonist; SD, standard deviation.
**Supplementary Figure S1.** Participant screening and categorisation process

- 143,689 patients without a single-device ICS/LABA inhaler prescription within the indexing period with a prior COPD diagnosis
- 38,602 patients without a COPD diagnostic code at 35 years of age or above
- 42,776 patients without FEV1/FVC <0.7 prior to index
- 14,483 patients not continuously registered with a GP for ≥12 months prior to index
- 47,275 patients without a record linked to HES
- 3,086 patients with a medical condition incompatible with a COPD diagnosis

COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GP, general practice; HES, Hospital Episode Statistics; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; LABA, long-acting β2-agonist.
Supplementary Figure S2. Regional distribution of incident patients

Indexed therapies are shown as percentages of the total patients of the given region.

*Includes fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate, and fluticasone furoate/vilanterol.

BDP, beclometasone dipropionate; BUD, budesonide; FOR, formoterol; ICS, inhaled corticosteroids; LABA, long-acting β₂-agonist.
Supplementary Figure S3. Treatment classes prescribed for A) non-triple users or B) IMT users prior to index

A) Non-triple users

- Included fluticasone propionate/salmeterol, fluticasone propionate/formoterol fumarate, and fluticasone furoate/vilanterol;
- Included treatment with SABA, SAMA or SABA/SAMA fixed and open combinations;
- Included phosphodiesterase-4 inhibitors, methylxanthines, and treatment combinations not reflected elsewhere.

B) IMT users

- Results based on small numbers of patients (n<5) were suppressed, as well as related values to protect primary suppression

BDP, beclomethasone dipropionate; BUD, budesonide; FOR, formoterol; ICS, inhaled corticosteroids; IMT, initial maintenance therapy; LABA, long-acting β<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; SABA, short-acting β<sub>2</sub>-agonist; SABD, short-acting bronchodilator; SAMA, short-acting muscarinic antagonist.