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ORIGINAL RESEARCH

Treatment Patterns, Healthcare Utilization and Clinical Outcomes of Patients with Chronic Obstructive Pulmonary Disease Initiating Single-Inhaler Long-Acting β_2-Agonist/Long-Acting Muscarinic Antagonist Dual Therapy in Primary Care in England

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Purpose: Selection of treatments for patients with chronic obstructive pulmonary disease (COPD) may impact clinical outcomes, healthcare resource use (HCRU) and direct healthcare costs. We aimed to characterize these outcomes along with treatment patterns, for patients with COPD following initiation of single-inhaler long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) dual therapy in the primary care setting in England.

Patients and Methods: This retrospective cohort study used linked primary care electronic medical record data (Clinical Practice Research Datalink-Aurum) and secondary care administrative data (Hospital Episode Statistics) in England to assess outcomes for patients with COPD who had a prescription for one of four single-inhaler LAMA/LABA dual therapies between 1st June 2015–31st December 2018 (indexing period). Outcomes were assessed during a 12-month follow-up period from the index date (date of earliest prescription of a single-inhaler LAMA/LABA within the indexing period). Incident users were those without previous LAMA/LABA dual therapy prescriptions prior to index; this manuscript focuses on a subset of incident users: non-triple therapy users (patients without concomitant inhaled corticosteroid use at index).

Results: Of 10,991 incident users included, 9888 (90.0%) were non-triple therapy users, indexed on umeclidinium/vilanterol (n=4805), aclidinium/formoterol (n=2109), indacaterol/glycopyrronium (n=1785) and tiotropium/olodaterol (n=1189). At 3 months post-index, 63.3% of non-triple therapy users remained on a single-inhaler LAMA/LABA, and 22.1% had discontinued inhaled therapy. Most patients (86.9%) required general practitioner consultations in the first 3 months post-index. Inpatient stays were the biggest contributor to healthcare costs. Acute exacerbations of COPD (AECOPDs), adherence, time-to-triple therapy, time-to-first on-treatment moderate-to-severe AECOPD, time-to-index treatment discontinuation, HCRU and healthcare costs were similar across indexed therapies.

Conclusion: Patients initiating treatment with single-inhaler LAMA/LABA in primary care in England were unlikely to switch treatments in the first three months following initiation, but some may discontinue respiratory medication. Outcomes were similar across indexed treatments.

Keywords: COPD, single-inhaler LAMA/LABA dual therapy, primary care setting, treatment patterns, clinical outcomes

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Plain Language Summary

Some patients with chronic obstructive pulmonary disease (COPD) in England are prescribed long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) dual bronchodilator therapy. Four single-inhaler LAMA/LABA medications are available in England: aclidinium bromide/formoterol fumarate, indacaterol/glycopyrronium, tiotropium bromide/olodaterol, or umeclidinium/vilanterol. Here, we describe how use of these treatments changed, and effects of treatment on COPD burden and healthcare service use during the 12 months following the first recorded prescription between 1st June 2015 and 31st December 2018 for patients not using inhaled corticosteroids. We collected data from two large databases containing records from general practitioners (GPs) and hospitals, including information on prescriptions, health service use, healthcare-related costs, and clinical outcomes including COPD exacerbations and patients' adherence to their prescriptions in this period.

We found that most patients were still using their dual therapy inhaler 3 months after prescription. Of those who were not, more than half stopped taking any form of inhaled COPD medication. Patients using each medicine were similar in terms of exacerbations, adherence, and use of healthcare services. Hospital stays accounted for most of the healthcare costs. While 86.9% of patients had GP consultations within 3 months of their first prescription, only 27.5% needed to visit their GP between 3 and 6 months after prescription.

This study shows that patients receiving a single-inhaler dual therapy are unlikely to switch to a different treatment in the first few months after initiation, but some may stop taking LAMA/LABA therapy. The four dual therapies were similar in measures of burden on healthcare resources and clinical outcomes.

Introduction

Reducing the incidence of acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) is considered a key aspect of improving patient quality of life and reducing direct healthcare costs,[1] and along with reducing associated hospitalizations was rated the most important outcome by patients with COPD.[2] Higher adherence to medication is also associated with a reduction in healthcare resource utilization (HCRU) and costs. These factors can contribute to the already high clinical and economic burden of COPD, which is around £1.9 million each year in the UK.[3] By 2030, annual direct healthcare costs of COPD are estimated to increase to £2.32 billion and £159 million in England and Scotland, respectively.[4]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report recommends a stepwise approach for pharmacological treatment of COPD.[5] Long-acting β_2-agonist (LABA) or long-acting muscarinic antagonist (LAMA) monotherapy is recommended as initial maintenance treatment for symptomatic patients with COPD (patients with COPD Assessment Test [CAT] score ≥10) who are not at risk of exacerbations leading to hospitalization; and escalation to LAMA/LABA dual therapy is recommended for symptomatic patients who are at risk of exacerbations or continue to suffer from dyspnea. LAMA/LABA dual therapy can also be considered as initial maintenance therapy (IMT) for patients with a modified British Medical Research Council (mMRC) Questionnaire score ≥2 or a CAT score ≥10 without a history of severe exacerbations with severe breathlessness.[6] Similarly, the National Institute for Health Care and Excellence (NICE) guidelines in the UK indicate that LAMA/LABA dual therapy should be offered as IMT to patients with COPD who are breathless or have exacerbations and do not have asthmatic features or features suggesting responsiveness to inhaled corticosteroids (ICS).[7] For patients who develop further exacerbations on LAMA/LABA dual therapy and who have a blood eosinophil count ≥100 cells/μL, the GOLD strategy report recommends stepping up to ICS/LAMA/LABA triple therapy.[6] The NICE guidelines recommend patients on LAMA/LABA should step up to triple therapy if they have a severe exacerbation or two moderate exacerbations within a year; triple therapy can be considered if their day-to-day symptoms adversely impact their quality of life.[7]

In the UK, approximately 4.5% of the population over 40 years of age live with diagnosed COPD.[8] Four single-inhaler LAMA/LABA dual therapies are approved for treatment of COPD: aclidinium/formoterol (ACL/FOR), indacaterol/glycopyrronium (IND/GLY), tiotropium/olodaterol (TIO/OLO), and umeclidinium/vilanterol (UMEC/VI). All of these therapies improve lung function, reduce COPD symptoms, and reduce the risk of exacerbations compared with LAMA or LABA monotherapy.[3,9–11]

The characteristics, treatments prescribed, HCRU, and costs in the year prior to initiation of single-inhaler dual LAMA/LABA therapy in a primary care setting in England have been recently described.[12] This study subsequently aimed to identify treatment patterns, HCRU, direct healthcare costs, and clinical outcomes of patients with COPD

following initiation of single-inhaler LAMA/LABA dual therapy in the primary care setting in England to understand the impact on the economic and clinical burden of COPD following initiation of single-inhaler LAMA/LABA dual therapies.

Methods

Study Design

This retrospective longitudinal cohort study used linked primary care electronic medical record data and secondary care administrative data in England to assess multiple outcomes for patients with COPD following initiation of single-inhaler LAMA/LABA dual therapies. Primary care data were collected from Clinical Practice Research Datalink (CPRD-Aurum) which, as of September 2018, captured data for over 19 million patients; of note, 7 million of these patients were alive and currently contributing at that time.[13] Secondary care data including details on patient demographics and diagnoses, inpatient admissions, outpatient appointments, and accident and emergency (A&E) attendances were collected from Hospital Episode Statistics (HES). The indexing period began on 1st June 2015 (to ensure that all included patients had access to all four available dual therapies at the time of prescription) until 31st December 2018. The index date was defined as the date of the earliest prescription of a single-inhaler LAMA/LABA dual therapy within the indexing period. The baseline period was the 12-months prior to the index date and the follow-up period spanned from the index date until the study period end date (31st December 2019), the end of data availability, or patient death, whichever happened first. The study design schematic is shown in Figure 1.

Study Population

Inclusion criteria required patients to have at least one diagnostic code of COPD at ≥35 years of age in a primary care setting and a forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio of <0.7 at any time prior to and including index date. Patients also needed at least one prescription of a single-inhaler LAMA/LABA within the index period, a primary care record linked to HES, and continuous registration with a general practitioner (GP) practice for a minimum of 12 months prior to the index date. Patients were excluded if they had one or more diagnostic codes for non-COPD respiratory conditions that could interfere with COPD diagnosis (eg, cystic or pulmonary fibrosis, pulmonary resection).

Incident users were those with no previous LAMA/LABA dual therapy prescriptions prior to the index date and included non-triple therapy users (no concomitant ICS use at index date) and IMT users (no prescription of COPD maintenance therapy prior to the index date). Patients were further categorized by indexed therapy (ACL/FOR, IND/GLY, TIO/OLO, and UMEC/VI).

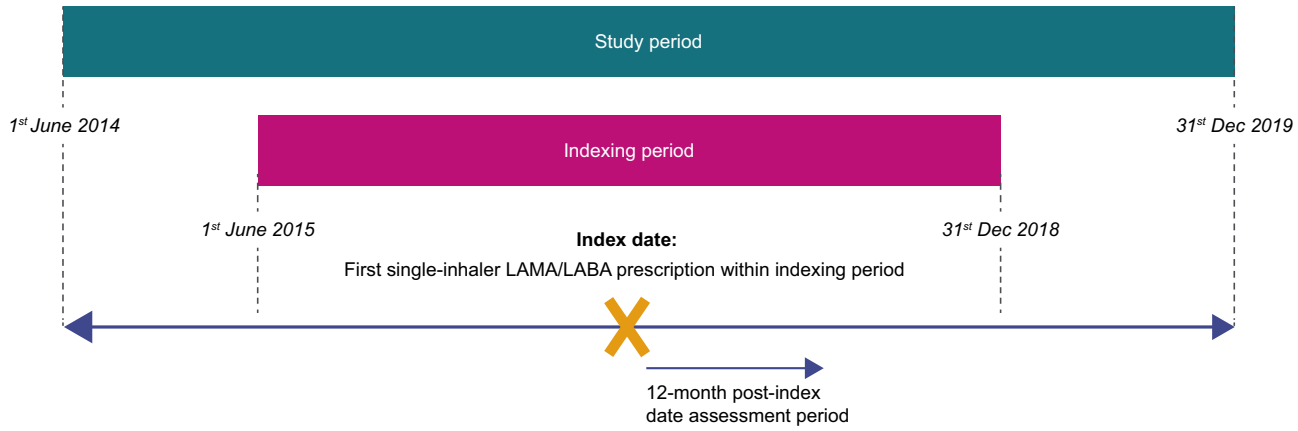


Figure 1 Study design schematic.
Abbreviations: LABA, long-actingβ_2-agonist; LAMA, long-acting muscarinic antagonist.

Outcomes

Outcome measures were assessed in the 12 months post-index. Treatment patterns and clinical outcomes were assessed at 3, 6, 9 and 12-months post-index. Treatments were categorized as ICS only, LABA only, LAMA only, ICS/LABA, LAMA/LABA, ICS/LAMA/LABA, any short-acting bronchodilator, other treatment, or no respiratory treatment. COPD-related and all-cause HCRU, and COPD-related and all-cause direct healthcare costs were measured in the following intervals: index date to ≤3 months, >3 to ≤6 months, >6 to ≤12 months, and index date to ≤12 months post-index. HCRU categories included prescriptions prescribed in a primary care setting, primary care consultations, outpatient visits, inpatient visits, and A&E visits. Clinical outcomes were assessed for non-triple therapy users and the subset of IMT users within the non-triple therapy user group. Clinical outcomes included the proportion of patients experiencing moderate or severe AECOPDs at 3, 6, 9 and 12 months post-index date, AECOPD exacerbation rate (number of moderate-to-severe AECOPDs per time on treatment), time to initiation of triple therapy, time to first on-treatment moderate-to-severe AECOPD, time to index treatment discontinuation (a gap of >30 days between the end of a dual therapy prescription's days of supply and the following fill), and index treatment adherence (proportion of days covered [PDC] ≥80%, calculated by dividing the days covered by a fixed time interval [ie, 6, 12, 18 and/or 24 months]). Treatment adherence was recorded at 6, 12, 18 and 24 months post-index.

Statistical Analysis

All patients who met the inclusion criteria were included. All analyses are descriptive, and treatments were not compared statistically. Counts, means and standard deviations (SD) were reported for continuous variables, and frequencies and proportions were reported for categorical variables. HCRU and direct healthcare costs were reported by HCRU category for patients who had at least one use in that category (resource users). Kaplan–Meier survival analyses were performed to assess cumulative hazard rates for time to initiation of triple therapy, time to first on-treatment COPD-related moderate-to-severe AECOPD, and time to discontinuation. Results were not reported for values corresponding to less than five patients in order to comply with the CPRD's standard reporting policy on small cell counts (ie, no cell counts or estimates based on them should be reported).

Results

Study Population

In total, 19,141 patients had a prescription of a single-inhaler LAMA/LABA therapy and were eligible for inclusion, 10,991 (57.4%) of whom were incident users. Of the incident users, 2963 (27.0%) were IMT users and 9888 (90.0%) were non-triple therapy users. Among non-triple therapy users, indexed therapy was UMEC/VI for 4805 patients (48.6%), ACL/FOR for 2109 (21.3%), IND/GLY for 1785 (18.1%), and TIO/OLO for 1189 (12.0%).

Treatment Pathways

Overall, 63.3% of non-triple therapy users remained on a single-inhaler LAMA/LABA at 3 months post-index date (Figure 2). UMEC/VI was the most frequently prescribed respiratory medication among non-triple therapy users, and UMEC/VI and IND/GLY had the most users remaining on a single-inhaler LAMA/LABA at 3 months (UMEC/VI: 65.2%, IND/GLY: 64.8%) (Figure 2). Overall, the proportion of non-triple therapy users who remained on a single-inhaler LAMA/LABA decreased to 55.5% at 6 months after index date (Supplementary Figure 1A) and remained relatively stable during the rest of the follow-up period (55.2% at 9 months and 53.4% at 12 months) (Supplementary Figure 1B and C).

Overall, ICS/LAMA/LABA triple therapy uptake was initially low, with only 2.3% of non-triple therapy users escalating from LAMA/LABA dual therapy to ICS/LAMA/LABA triple therapy 3 months post-index (Figure 2); escalations to triple therapy increased over the follow-up period, reaching 7.1% after 12 months (Supplementary Figure 1). Overall, 22.1% of non-triple therapy users had stopped taking respiratory therapies at 3 months after index

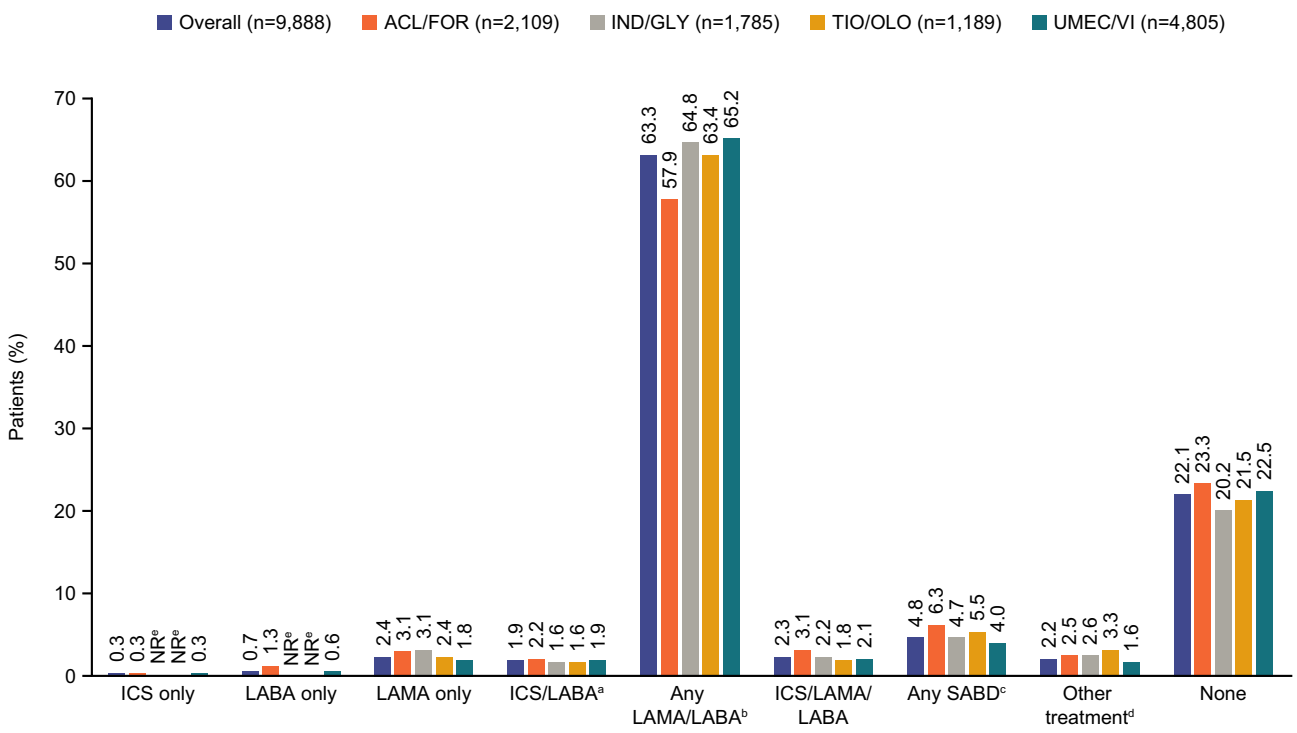


Figure 2 Respiratory therapies prescribed at 3 months after index date (non-triple therapy users). [a]Included BDP/FOR, BUD/FOR, FP/SAL, FP/FOR and FP/VI; [b]Included treatment with UMEC/VI, IND/GLY, TIO/OLO, or ACL/FOR; [c]Included treatment with SABA, SAMA or SABA/SAMA fixed and open combinations; [d]Included phosphodiesterase-4 inhibitors, methylxanthines, and treatment combinations not reflected elsewhere; [e]Results based on small numbers of patients (n<5) were suppressed, as well as the next-smallest value to protect primary suppression.

Abbreviations: ACL, aclidinium; BDP, beclomethasone; BUD, budesonide; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-actingβ_2-agonist; LAMA, long-acting muscarinic antagonist; NR, not reported; OLO, olodaterol; SABA, short-actingβ_2-agonist; SABD, short-acting bronchodilator; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

date (Figure 2), and this number did not increase notably at 12 months (Supplementary Figure 1). At 3 months post-index, a small proportion of patients had stepped down to LAMA only (2.4%) or LABA only (0.7%) (Figure 2).

HCRU and Direct Healthcare Costs

In the 3 months following the index date, 86.9% of non-triple users had a COPD-related GP consultation, decreasing to 27.5% between >3 and ≤6 months post-index. The proportion of patients with COPD-related inpatient stays remained more constant, at 9.7% of patients in both the first 3 months and between >3 and ≤6 months following index (Table 1; Supplementary Table 1). COPD-related and all-cause HCRU were similar among non-triple therapy users and across indexed therapies between index and ≤3 months and between >3 and ≤6 months.

Total COPD-related (Table 2) and all-cause (Supplementary Table 2) direct healthcare costs in the 3 months following the index date and from >3 and ≤6 months were similar across indexed therapies. Among the health resource used during the first 3 and 6 months of the follow-up period, inpatient stays were the greatest contributor to the COPD-related costs. TIO/OLO had particularly high costs due to inpatient stays >3 to ≤6 months following index (Figure 3). COPD-related and all-cause direct healthcare costs were similar for all indexed therapies during all time periods (Table 2; Supplementary Table 2). The mean (SD) cumulative length of COPD-related inpatient stays in the 3 months following the index date was 5.2 (12.9) days and was similar across indexed therapies and at all time periods (Supplementary Table 3).

When all elements of HCRU are considered, the overall mean (SD) total COPD-related cost was £1058 (2828.5) and the all-cause cost was £2177 (4135.4); costs were similar across indexed treatments (Table 2; Supplementary Table 2).

Table 1 COPD-Related HCRU Following Index Date (Non-Triple Therapy Users)

	Overall (n=9888)	ACL/FOR (n=2109)	IND/GLY (n=1785)	TIO/OLO (n=1189)	UMEC/VI (n=4805)
Index date to ≤3 months following index					
Prescriptions, n (%)	4772 (49.2)	1124 (54.2)	955 (54.9)	619 (53.0)	2074 (44.0)
GP consultations, n (%)	8427 (86.9)	1870 (90.2)	1452 (83.5)	984 (84.3)	4121 (87.4)
Mean (SD) per resource user	1.61 (0.81)	1.63 (0.86)	1.61 (0.80)	1.59 (0.83)	1.61 (0.80)
Outpatient visits, n (%)	776 (8.0)	126 (6.1)	185 (10.6)	114 (9.8)	351 (7.4)
Mean (SD) per resource user	1.88 (2.13)	1.80 (1.92)	2.09 (2.56)	1.84 (2.07)	1.81 (1.98)
Inpatient stays, n (%)	944 (9.7)	210 (10.1)	188 (10.8)	122 (10.5)	424 (9.0)
Mean (SD) per resource user	1.42 (1.18)	1.38 (1.03)	1.51 (1.46)	1.49 (1.69)	1.37 (0.89)
A&E visits, n (%)	43 (0.4)	13 (0.6)	NR[b]	NR[b]	24 (0.5)
Mean (SD) per resource user	1.16 (0.53)	1.31 (0.85)	NR[b]	NR[b]	1.13 (0.34)
>3 to ≤6 months following index					
Prescriptions, n (%)	4091 (43.1)	932 (45.8)	822 (48.6)	540 (47.5)	1797 (38.7)
GP consultations, n (%)	2613 (27.5)	587 (28.9)	510 (30.2)	299 (26.3)	1217 (26.2)
Mean (SD) per resource user	1.32 (0.66)	1.39 (0.73)	1.32 (0.63)	1.32 (0.68)	1.29 (0.63)
Outpatient visits, n (%)	720 (7.6)	137 (6.7)	174 (10.3)	100 (8.8)	309 (6.7)
Mean (SD) per resource user	1.80 (2.09)	1.57 (1.47)	1.63 (1.77)	2.04 (2.33)	1.93 (2.38)
Inpatient stays, n (%)	922 (9.7)	196 (9.6)	186 (11.0)	129 (11.4)	411 (8.9)
Mean (SD) per resource user	1.40 (1.40)	1.35 (1.46)	1.37 (0.87)	1.57 (1.96)	1.39 (1.37)
A&E visits, n (%)	29 (0.3)	8 (0.4)	NR[b]	NR[b]	18 (0.4)
Mean (SD) per resource user	1.14 (0.44)	1.13 (0.35)	NR[b]	NR[b]	1.17 (0.51)
>6 to ≤12 months following index					
Prescriptions, n (%)	4567 (50.2)	1039 (53.2)	930 (57.9)	592 (54.2)	2006 (45.2)
GP consultations, n (%)	3897 (42.9)	867 (44.4)	745 (46.4)	448 (41.0)	1837 (41.4)
Mean (SD) per resource user	1.59 (1.02)	1.68 (1.12)	1.62 (1.00)	1.60 (1.20)	1.53 (0.93)
Outpatient visits, n (%)	863 (9.5)	177 (9.1)	188 (11.7)	114 (10.4)	384 (8.7)
Mean (SD) per resource user	1.97 (1.92)	2.47 (2.74)	1.85 (1.64)	1.89 (1.47)	1.81 (1.67)
Inpatient stays, n (%)	1406 (15.5)	315 (16.1)	252 (15.7)	174 (15.9)	665 (15.0)
Mean (SD) per resource user	1.55 (1.32)	1.57 (1.45)	1.69 (1.50)	1.54 (0.96)	1.50 (1.27)
A&E visits, n (%)	33 (0.4)	10 (0.5)	NR[b]	NR[b]	19 (0.4)
Mean (SD) per resource user	1.24 (0.56)	1.00 (0)	NR[b]	NR[b]	1.32 (0.67)
12 months following and including index[a]					
Prescriptions, n (%)	5556 (61.1)	1268 (64.9)	1077 (67.1)	705 (64.6)	2506 (56.4)
GP consultations, n (%)	8468 (93.2)	1840 (94.3)	1490 (92.8)	992 (90.8)	4146 (93.4)
Mean (SD) per resource user	2.62 (1.77)	2.77 (1.93)	2.69 (1.79)	2.57 (1.87)	2.54 (1.65)
Outpatient visits, n (%)	1455 (16.0)	278 (14.2)	323 (20.1)	203 (18.6)	651 (14.7)
Mean (SD) per resource user	2.91 (3.29)	3.00 (3.46)	2.94 (3.25)	2.97 (3.12)	2.83 (3.29)
Inpatient stays, n (%)	2391 (26.3)	536 (27.5)	430 (26.8)	305 (27.9)	1120 (25.2)
Mean (SD) per resource user	1.82 (1.90)	1.75 (1.67)	1.95 (2.06)	2.00 (2.69)	1.75 (1.66)
A&E visits, n (%)	84 (0.9)	24 (1.2)	NR[b]	NR[b]	49 (1.1)
Mean (SD) per resource user	1.26 (0.66)	1.21 (0.51)	NR[b]	NR[b]	1.27 (0.73)

Notes: [a]Included index date; [b]Results based on small numbers of patients (n<5) were suppressed, as well as the next-smallest value to protect primary suppression.
Abbreviations: A&E, accident and emergency; ACL, aclidinium; COPD, chronic obstructive pulmonary disorder; FOR, formoterol fumarate; GP, general practitioner; GLY, glycopyrronium; HCRU, healthcare resource use; IND, indacaterol; NR, not reported; OLO, olodaterol; SD, standard deviation; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

Table 2 COPD-Related Direct Healthcare Costs During the Follow-Up Period (Non-Triple Therapy Users)

COPD-Related Healthcare Direct Costs Per Resource User, Mean (SD), GBP	Overall (n=9888)	ACL/FOR (n=2109)	IND/GLY (n=1785)	TIO/OLO (n=1189)	UMEC/VI (n=4805)
Index date to ≤3 months following index					
Prescriptions	n=4772 30 (46.3)	n=1124 35 (48.9)	n=955 29 (43.5)	n=619 31 (47.7)	n=2074 28 (45.5)
GP consultations	n=8427 60 (30.7)	n=1870 61 (32.8)	n=1452 60 (30.2)	n=984 60 (31.1)	n=4121 60 (29.8)
Outpatient visits	n=776 262 (253.7)	n=126 259 (227.3)	n=185 271 (301.7)	n=114 260 (235.3)	n=351 259 (241.5)
Inpatient stays	n=944 2971 (3675.4)	n=210 2859 (3528.9)	n=188 2927 (3666.0)	n=122 2927 (3177.5)	n=424 3059 (3888.1)
A&E visits	n=43 211 (120.4)	n=13 248 (192.8)	NR[b] NR[b]	NR[b] NR[b]	n=24 192 (69.4)
Total costs	371 (1448.7)	375 (1419.7)	401 (1511.4)	391 (1371.2)	354 (1456.4)
>3 to ≤6 months following index					
Prescriptions	n=4091 26 (41.4)	n=932 31 (46.7)	n=822 26 (40.9)	n=540 24 (39.5)	n=1797 23 (39.0)
GP consultations	n=2613 48 (25.8)	n=587 51 (28.6)	n=510 48 (28.6)	n=299 48 (26.3)	n=1217 47 (24.7)
Outpatient visits	n=720 238 (228.9)	n=137 234 (197.7)	n=174 215 (197.4)	n=100 272 (244.7)	n=309 242 (251.5)
Inpatient stays	n=922 2754 (3310.7)	n=196 2351 (3233.0)	n=186 2760 (3237.0)	n=129 3234 (2910.1)	n=411 2792 (3482.3)
A&E visits	n=29 215 (83.0)	n=8 241 (65.9)	NR[b] NR[b]	NR[b] NR[b]	n=18 215 (89.2)
Total costs	298 (1302.6)	263 (1208.4)	334 (1353.3)	397 (1406.1)	276 (1295.6)
>6 to ≤12 months following index					
Prescriptions	n=4567 40 (70.1)	n=1039 49 (77.6)	n=930 40 (65.9)	n=592 38 (71.5)	n=2006 36 (67.1)
GP consultations	n=3897 58 (38.3)	n=867 62 (41.8)	n=745 60 (38.1)	n=448 59 (45.3)	n=1837 56 (24.6)
Outpatient visits	n=863 265 (233.6)	n=177 331 (309.4)	n=188 243 (219.8)	n=114 248 (191.5)	n=384 250 (204.7)
Inpatient stays	n=1406 3196 (3960.7)	n=315 3079 (3834.8)	n=252 3168 (4065.3)	n=174 3593 (5003.5)	n=665 3159 (33,663.2)
A&E visits	n=33 212 (105.7)	n=10 162 (56.4)	NR[b] NR[b]	NR[b] NR[b]	n=19 226 (119.3)
Total costs	520 (1886.7)	538 (1863.5)	519 (1916.1)	591 (2310.6)	494 (1765.4)
12 months following index[a]					
Prescriptions	n=5556 75 (132.2)	n=1268 91 (146.1)	n=1077 76 (127.0)	n=705 74 (134.2)	n=2506 67 (125.5)
GP consultations	n=8468 97 (65.8)	n=1840 103 (72.1)	n=1490 100 (67.1)	n=992 95 (70.0)	n=4146 94 (61.0)

(*Continued*)

Table 2 (Continued).

COPD-Related Healthcare Direct Costs Per Resource User, Mean (SD), GBP	Overall (n=9888)	ACL/FOR (n=2109)	IND/GLY (n=1785)	TIO/OLO (n=1189)	UMEC/VI (n=4805)
Outpatient visits	n=1455	n=278	n=323	n=203	n=651
	392 (376.5)	423 (391.3)	381 (387.4)	394 (351.8)	385 (372.2)
Inpatient stays	n=2391	n=536	n=430	n=305	n=1120
	3610 (4691.7)	3285 (4177.6)	3704 (4937.4)	4160 (5450.6)	3579 (4595.2)
A&E visits	n=84	n=24	NR[b]	NR[b]	n=49
	225 (121.9)	222 (105.2)	NR[b]	NR[b]	220 (130.6)
Total costs	1058 (2828.5)	1038 (2596.1)	1091 (2965.3)	1259 (3354.5)	1005 (2728.8)

Notes: [a]Included index date; [b]Results based on small numbers of patients (n<5) were suppressed, as well as the next-smallest value to protect primary suppression.

Abbreviations: A&E, accident and emergency; ACL, aclidinium; COPD, chronic obstructive pulmonary disease; FOR, formoterol fumarate; GBP, British pound sterling; GLY, glycopyrronium; GP, general practitioner; IND, indacaterol; NR, not reported; OLO, olodaterol; SD, standard deviation; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

Clinical Endpoints

The proportion of patients who experienced ≥1 moderate-to-severe AECOPD during follow-up decreased slightly over time. The proportion of patients indexed on IND/GLY who experienced ≥1 moderate-to-severe AECOPD was numerically higher compared with all other indexed treatments across all time periods (Table 3). The mean exacerbation rate remained in the range of 0.01–0.03 rate per month across indexed therapies and throughout all time points from 3 to 12 months post-index.

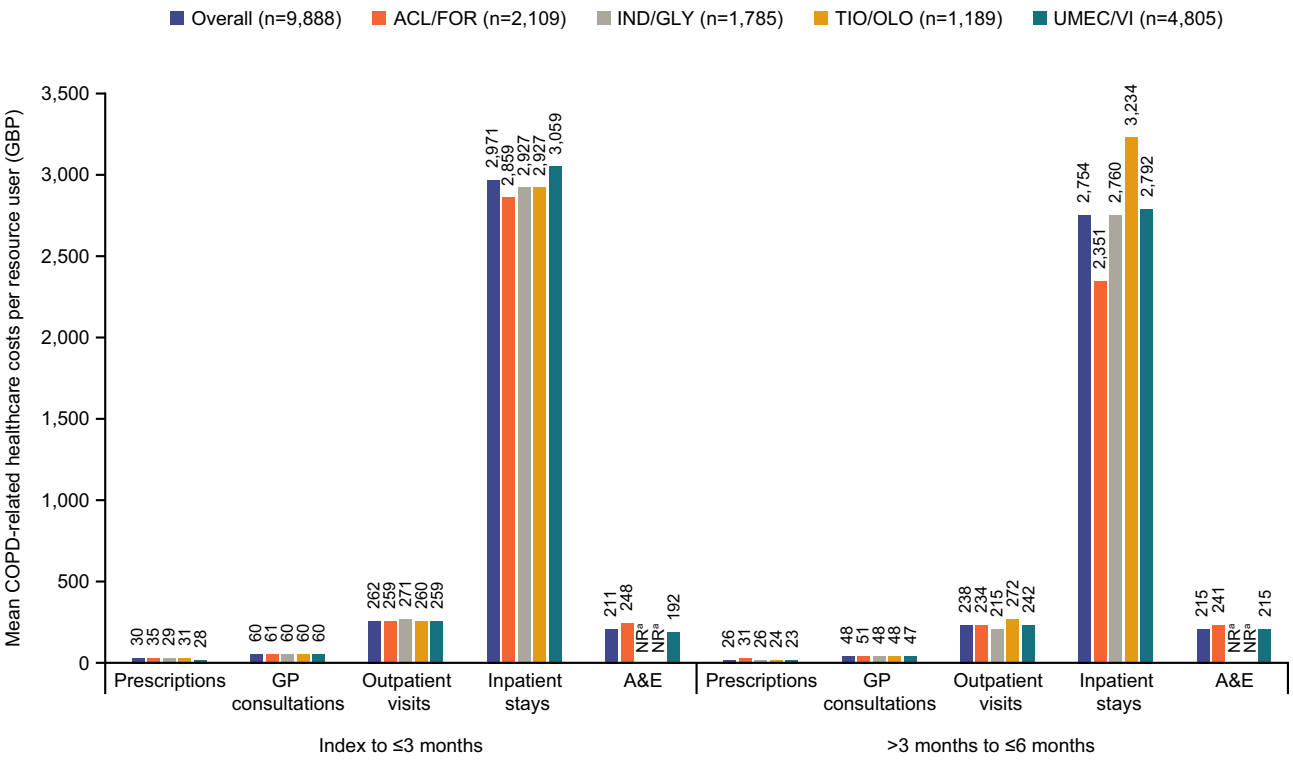


Figure 3 COPD-related costs over the index to ≤3 months and >3 to ≤6 months post-index time periods (non-triple therapy users). [a]Results based on small numbers of patients (n<5) were suppressed, as well as the next-smallest value to protect primary suppression.

Abbreviations: A&E, accident and emergency; ACL, aclidinium; COPD, chronic obstructive pulmonary disease; FOR, formoterol fumarate; GBP, British pound sterling; GP, general practitioner; GLY, glycopyrronium; IND, indacaterol; NR, not reported; OLO, olodaterol; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

Table 3 Moderate-to-Severe AECOPDs During the Follow-Up Period (Non-Triple Therapy Users)

	Overall (n=9888)	ACL/FOR (n=2109)	IND/GLY (n=1785)	TIO/OLO (n=1189)	UMEC/VI (n=4805)
3 months post-index date					
Patients with ≥1 moderate-to-severe AECOPD, n (%)	491 (5.0)	117 (5.5)	119 (6.7)	45 (3.8)	210 (4.4)
Per patient, mean (SD)	0.05 (0.25)	0.06 (0.27)	0.07 (0.29)	0.04 (0.22)	0.05 (0.23)
Exacerbation rate, mean (SD)	0.02 (0.11)	0.02 (0.12)	0.03 (0.13)	0.02 (0.12)	0.02 (0.10)
6 months post-index date					
Patients with ≥1 moderate-to-severe AECOPD, n (%)	845 (8.5)	185 (8.8)	195 (10.9)	89 (7.5)	376 (7.8)
Per patient, mean (SD)	0.11 (0.39)	0.12 (0.41)	0.14 (0.45)	0.09 (0.36)	0.10 (0.37)
Exacerbation rate, mean (SD)	0.02 (0.11)	0.02 (0.11)	0.03 (0.12)	0.02 (0.12)	0.02 (0.10)
9 months post-index date					
Patients with ≥1 moderate-to-severe AECOPD, n (%)	1089 (11.0)	240 (11.4)	241 (13.5)	122 (10.3)	486 (10.2)
Per patient, mean (SD)	0.16 (0.51)	0.17 (0.55)	0.20 (0.58)	0.14 (0.47)	0.14 (0.47)
Exacerbation rate, mean (SD)	0.02 (0.11)	0.02 (0.11)	0.03 (0.12)	0.02 (0.12)	0.02 (0.10)
12 months post-index date					
Patients with ≥1 moderate-to-severe AECOPD, n (%)	1304 (13.2)	287 (13.6)	287 (16.1)	146 (12.3)	584 (12.2)
Per patient, mean (SD)	0.21 (0.63)	0.22 (0.67)	0.25 (0.71)	0.18 (0.57)	0.19 (0.59)
Exacerbation rate, mean (SD)	0.02 (0.11)	0.02 (0.11)	0.03 (0.11)	0.02 (0.12)	0.02 (0.10)

Abbreviations: ACL, aclidinium; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; FOR, formoterol fumarate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; SD, standard deviation; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

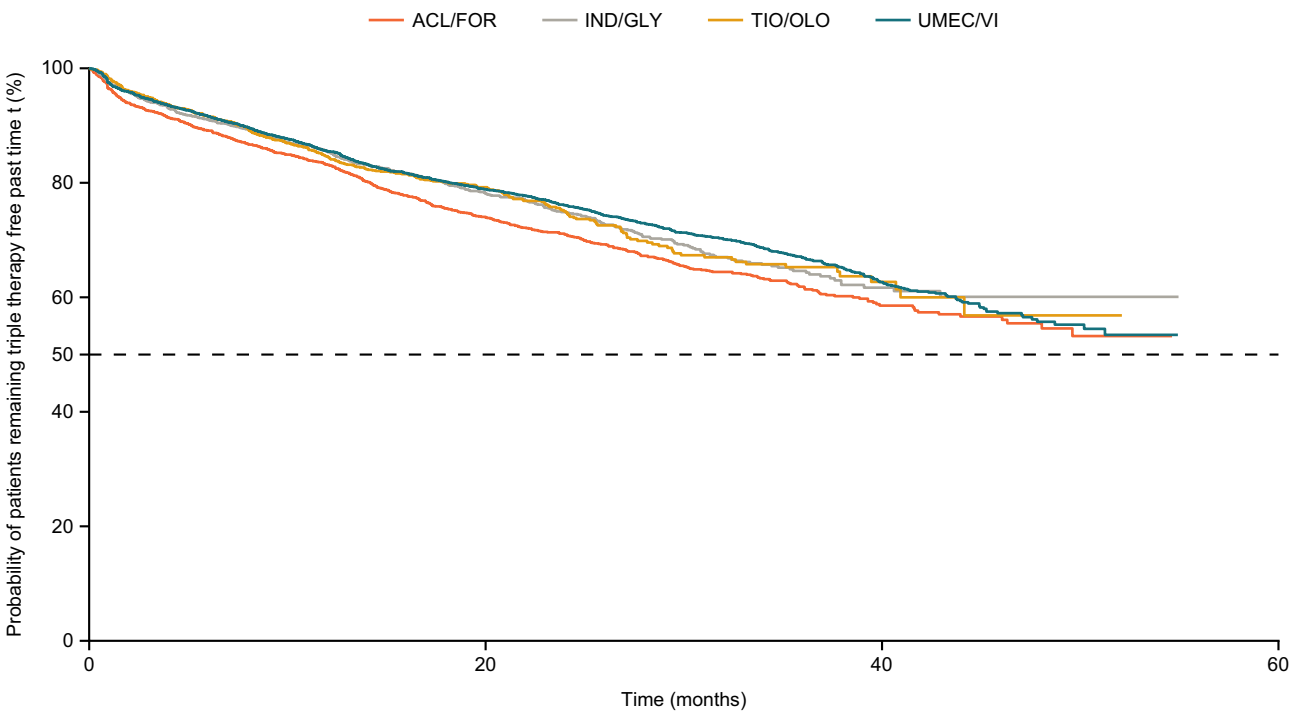
Kaplan–Meier analyses showed that the cumulative hazard rates for time-to-triple therapy increased steadily during the 12-month follow-up period across all indexed therapies, ranging from 0.156 for patients indexed on UMEC/VI to 0.184 for those indexed on ACL/FOR at 12 months after index (Figure 4). The cumulative hazard of a first on-treatment COPD-related moderate-to-severe AECOPD also increased gradually over the 12-month follow-up period across all indexed therapies (Figure 5). IND/GLY had the highest cumulative hazard rate of a first on-treatment COPD-related moderate-to-severe AECOPD among non-triple therapy users, at all time-points.

Across all indexed therapies, the overall median time to discontinuation of index treatment was 4.6 months. Patients indexed on ACL/FOR had the shortest median time to discontinuation among non-triple therapy users (3.5 months) (Figure 6). Overall, adherence (the proportion of patients with PDC ≥80%) declined from 43.6% at 6 months post-index to 35.4% at 24 months post-index; a similar trend was observed for all indexed therapies. Across all time points, the proportion of patients with PDC ≥80% was the smallest for patients indexed on ACL/FOR, decreasing from 36.5% at 6 months post-index to 30.1% at 24 months post-index (Supplementary Table 4).

Discussion

This retrospective, longitudinal study described treatments, HCRU, direct healthcare costs and clinical outcomes of patients with COPD following initiation of single-inhaler LAMA/LABA therapy in the primary care setting in England, following previous description of characteristics, treatments prescribed, HCRU, and costs prior to initiation in the same cohort.[12] We found that 63.3% of patients continued taking LAMA/LABA in the 3 months following index, with more than half remaining on the treatment after 6 months. Of the 44% of patients who discontinued dual therapy by 3 months post-index, most (one quarter of total patients) discontinued respiratory medication use, with relatively few patients stepping up to triple therapy or stepping down to LAMA or LABA monotherapy (<2.5% each). This suggests that patients receiving a single-inhaler LAMA/LABA are unlikely to switch treatments in the first few months after initiation, but some may discontinue respiratory medication over time.

The burden of COPD on the healthcare system, as measured by HCRU and direct healthcare costs was similar across the four single-inhaler LAMA/LABA dual therapies available in England. While around 10% of patients were hospitalized in the first 3 months post-index, inpatient stays still accounted for the largest portion of direct healthcare costs for



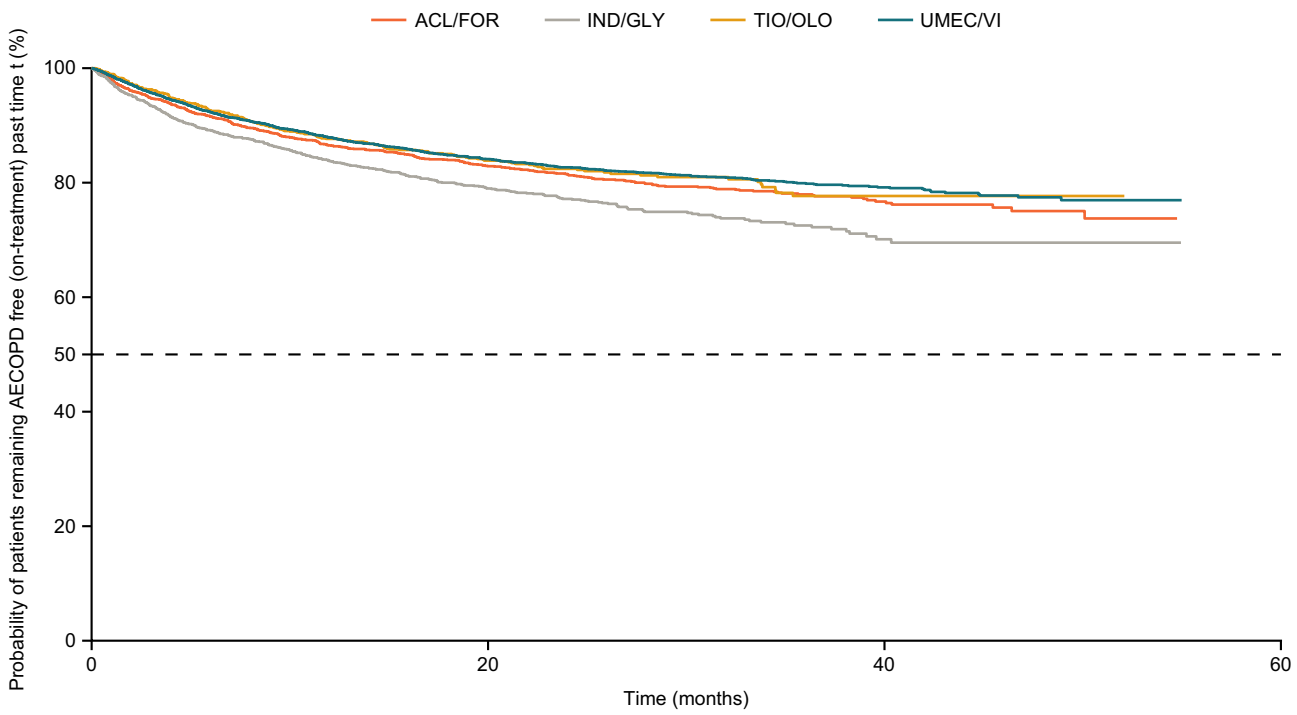
Cumulative hazard rate	ACL/FOR (n=2,109)	IND/GLY (n=1,785)	TIO/OLO (n=1,189)	UMEC/VI (n=4,805)
3 months	0.077	0.060	0.052	0.055
6 months	0.115	0.093	0.089	0.087
9 months	0.152	0.125	0.129	0.122
12 months	0.184	0.157	0.167	0.156

Figure 4 Kaplan–Meier plots of time-to-triple therapy (non-triple therapy users) Median time to triple therapy was not calculated as the 50% cumulative probability was not reached.
Abbreviations: ACL, aclidinium; FOR, formoterol fumarate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

all indexed therapies. These results indicate that, aside from numerically higher inpatient costs for the TIO/OLO treatment in the >3 to ≤6 months period, there is minimal notable variation between the four dual therapies on overall burden on healthcare resources in England and emphasize the importance of limiting hospitalizations from a healthcare cost perspective. In this study, total COPD-related direct healthcare costs per resource user 12 months post-index were £1058, while all-cause direct healthcare costs were £2177. A previous study of patients in the UK estimated the mean total annual COPD management cost per patient as £2108, due to exacerbations, non-COPD hospitalizations, and GP interactions, and did not specify patients prescribed a specific treatment.[14]

The cumulative probability of escalation to triple therapy increased steadily over time, as did the cumulative risk of experiencing a first on-treatment moderate-to-severe AECOPD, which is consistent with the exacerbation rate remaining constant throughout the 12-month follow-up period. Clinical outcomes and treatment adherence were generally similar across indexed therapies, except for IND/GLY consistently having the numerically highest cumulative hazard rate of a first on-treatment COPD-related moderate-to-severe AECOPD among non-triple therapy users.

Less than 50% of non-triple therapy users were classified as adherent (PDC ≥80%) to indexed therapy 6 months following index date, consistent with the median time to discontinuation, which ranged from 3.5 to 5.4 months. However, the rate of discontinuation decreased over time, suggesting that while most patients discontinued treatment within the first 6 months after a first prescription of LAMA/LABA dual therapy, those that were still taking a LAMA/LABA were likely to remain on treatment in the longer term. In general, patients taking ACL/FOR pre-index appeared to have poorer

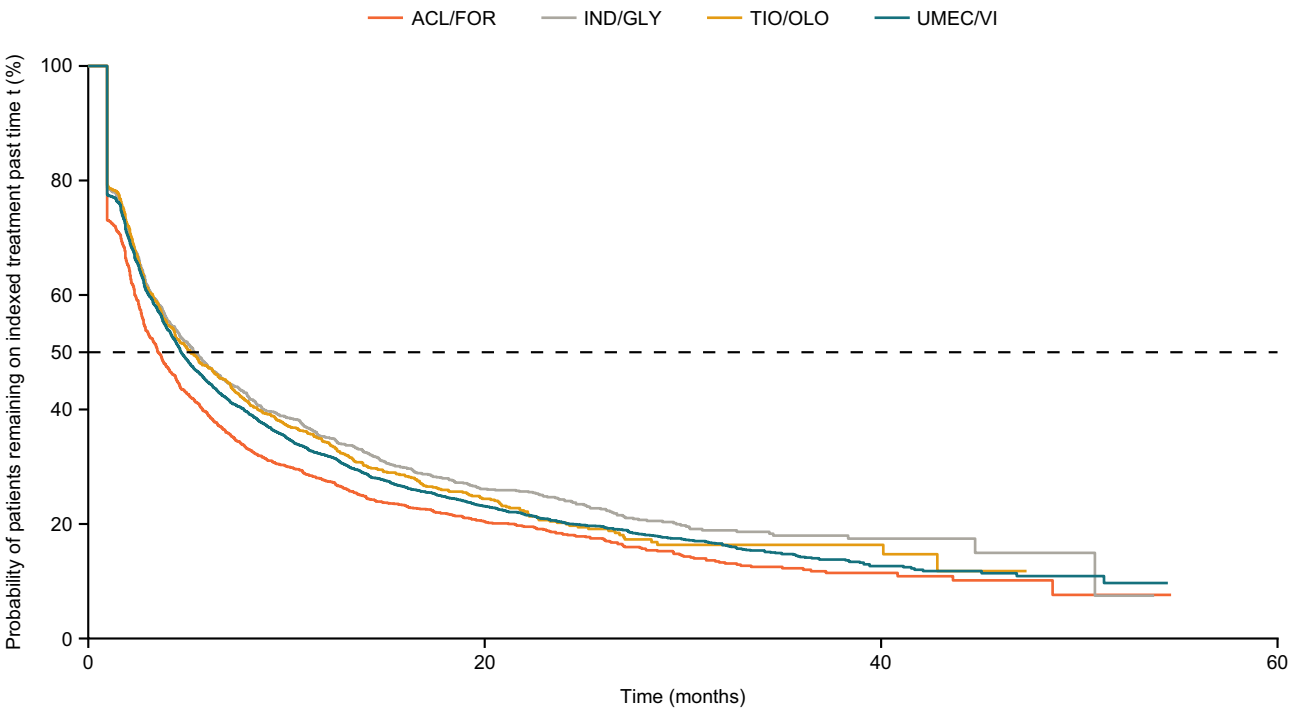


Cumulative hazard rate	ACL/FOR (n=2,109)	IND/GLY (n=1,785)	TIO/OLO (n=1,189)	UMEC/VI (n=4,805)
3 months	0.054	0.068	0.038	0.044
6 months	0.088	0.114	0.077	0.080
9 months	0.118	0.144	0.108	0.105
12 months	0.145	0.177	0.132	0.129

Figure 5 Kaplan–Meier plots of time-to-first on-treatment moderate-to-severe AECOPD (non-triple therapy users) Median time to first AECOPD was not calculated as the 50% cumulative probability was not reached.
Abbreviations: ACL, aclidinium; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FOR, formoterol fumarate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

adherence from 6 months and had a shorter median time to discontinuation than those indexed on alternative LAMA/LABAs. Although the reasons for this and its clinical importance cannot be determined here, this finding is consistent with previous studies suggesting that ACL/FOR has the lowest adherence of the four treatments in real-world studies, including patients from the UK, which may be related to differences in the devices used to deliver treatment.[15,16] Factors influencing adherence to ACL/FOR may include a lack of confidence in correctly administering the full dose with this inhaler, which may result in overdosing,[16] and the requirement for two doses per day.[15] Long-term adherence to treatment has important implications for healthcare usage and associated costs,[17–19] so while our findings show that almost half of the patients in this study are able to comply with maintenance therapy, there is scope for improved patient management to optimize lung function and quality of life, and reduce the burden to the healthcare system. Increased personalization of treatment to ensure patients are receiving optimal treatment for symptom alleviation and minimal adverse effects could be one example of this.[20,21] Close follow-up and assessment of COPD progression, as well as development of a self-management plan and ongoing continuous education are important measures that could be implemented to help improve patient adherence in primary care settings.

Limitations of this study include the use of medical records, which may not represent reliable assessments of prescription medication use. Prescription medications may not have been dispensed or consumed as prescribed, so patient adherence rates may have been overestimated. Prescription medications were recorded only in the primary care setting and thereby exclude COPD medications administered in hospital or other secondary care setting. However, as treatment would typically be continued



	ACL/FOR (n=2,109)	IND/GLY (n=1,785)	TIO/OLO (n=1,189)	UMEC/VI (n=4,805)
Median time to discontinuation, months	3.5	5.4	5.2	4.7
Cumulative hazard rate				
3 months	0.580	0.458	0.464	0.475
6 months	0.884	0.711	0.717	0.770
9 months	1.113	0.894	0.908	0.958
12 months	1.244	1.019	1.043	1.110
18 months	1.473	1.245	1.321	1.363

Figure 6 Kaplan–Meier plots of time-to-discontinuation of index treatment (non-triple therapy users).
Abbreviations: ACL, aclidinium; FOR, formoterol fumarate; GLY, glycopyrronium; IND, indacaterol; OLO, olodaterol; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

in primary care, misclassification of dual therapy use is unlikely. We also cannot be sure that medications were prescribed specifically for the treatment of COPD rather than comorbid asthma, although the requirement of a COPD diagnosis for study inclusion is an accepted approach to identify patients with COPD[22] and ensured this study focused on medications for treating COPD. Finally, direct healthcare costs are likely to have been underestimated because of local differences in prices.

Despite these limitations, this study based on medical records has several strengths and prescription records from medical databases are widely recognized as a useful source of data on medication use.[23] In particular, use of the CPRD-Aurum database was a major strength of this study, as this database covered 10% of GP practices in England in September 2018,[13] and is widely considered to be a large, highly representative cross-section of the whole population of England. Our sample can therefore be considered an accurate representation of the nationwide situation at the time the data were collected (between 1st June 2015 and 31st December 2019) and the findings may be generalizable. The follow-up period did not extend beyond the 31st December 2019 to exclude the COVID-19 pandemic and avoid any changes to the data expected due to that period. Some caveats should be noted; for example, privately insured patients were not included in this study as they are not covered by the CPRD-Aurum database; however, the data from the database include patients registered with a primary GP and under the NHS, which is 98% of

the UK population.[24] Exclusion of patients with other respiratory conditions also affected generalizability, as many patients with COPD suffer from comorbid respiratory conditions[25] that may affect prognosis. For example, previous research has shown a 6.1% prevalence of pulmonary fibrosis in patients with COPD, which is significantly associated with increased mortality risk.[26] Despite the acknowledged limitations, electronic medical records have several advantages over other adherence measures, which often rely on patient recall; in particular, they are less prone to error without any patient-related biases,[27] and represent an observation of effects in the real-world rather than under optimal conditions.[28]

Conclusion

This study found that patients initiating a single-inhaler LAMA/LABA in primary care in England are unlikely to switch treatments in the first few months, but some may discontinue respiratory medication over time. Aside from numerically higher inpatient costs for the TIO/OLO treatment at >3 to ≤6 months, minimal differences were observed between the four dual therapies on measures of burden on healthcare resources in the year after initiation. Clinical outcomes and treatment patterns were broadly similar across treatments, with the only notable exception being IND/GLY's consistently numerically higher cumulative hazard rate of a first on-treatment COPD-related moderate-to-severe AECOPD.

Abbreviations

A&E, accident and emergency; ACL, aclidinium; AECOPD, acute exacerbation of COPD; BDP, beclomethasone; BUD, budesonide; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CPRD-Aurum, Clinical Practice Research Datalink; FEV_1, forced expiratory volume in 1 second; FOR, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; HCRU, healthcare resource utilization; HES, Hospital Episode Statistics; ICS, inhaled corticosteroid; IMT, initial maintenance therapy; IND, indacaterol; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified British Medical Research Council; NICE, National Institute for Health Care and Excellence; OLO, olodaterol; PDC, proportion of days covered; SABA, short-acting β_2-agonist; SABD, short-acting bronchodilator; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; TIO, tiotropium bromide; UMEC, umeclidinium; VI, vilanterol.

Data Sharing Statement

This study is based in part on data from the CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the NHS as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone.

Data from HES Copyright © (2022), re-used with the permission of The Health & Social Care Information Centre. All rights reserved. Authors had access to the study data for the purposes of this work only. Data were accessed through an existing GSK license to address pre-specified research questions only. Therefore, the data cannot be broadly disclosed or made publicly available at this time. Access to each database can be requested via the respective websites.

Ethics Approval and Informed Consent

Approval of this study was provided by the GSK Protocol Review Committee and by the Independent Scientific Advisory Committee (ISAC), which reviewed the protocol and approved access to CPRD data (ISAC study no. 20_000145). No personal subject contact or primary collection of individual human data occurred, and anonymized patient-level data were used in this analysis; patient consent was therefore not required.

This study complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred. Personal identifiers, and personal identifiable information was removed by the database provider prior to receipt by the study team. Study results are in tabular form and aggregate analyses that omits subject identification, therefore informed consent, ethics committee or institutional review board (IRB) approval were not required. This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

AC, GR, CC, and ASI are employees of GSK and hold stock and shares at GSK. ASI is also a part-time member of the McMaster university faculty. TT, RWo and RWi are employees of Adelphi Real World, which received funding from GSK to conduct the study, but not for manuscript development. VB was an employee of Adelphi Real World at the time of the study, and is currently an employee of Bayer AG UK, and holds stock and shares in Bayer AG UK. Adelphi Real World is a business that provides consulting and other research services to pharmaceutical, device, government, and non-government organizations. Adelphi Real World employees work with a variety of companies and organizations and are expressly prohibited from receiving any payment or honoraria directly from these organizations for services rendered. The authors report no other conflicts of interest in this work.

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