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# Factors influencing treatment escalation from LAMA monotherapy to triple therapy in patients with COPD: a retrospective THIN database analysis

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## ABSTRACT (293 of 300 max)

**Purpose:** Inappropriate use of an inhaled corticosteroid (ICS) for chronic obstructive pulmonary disease (COPD) has clinical and economic disadvantages. This retrospective analysis of the UK Health Improvement Network (THIN) database identified factors influencing treatment escalation (step-up) from long-acting muscarinic antagonist (LAMA) to triple therapy (LAMA + long-acting beta agonist/ICS). Secondary objectives included time to step-up from first LAMA prescription, Global Initiative for Chronic Obstructive Lung Disease (GOLD) grouping (2011/2013, 2017), and Medical Research Council (MRC) grade prior to treatment escalation.

**Methods:** Data were included from 14,866 people ≥35 years old, with a COPD diagnosis (01 June 2010–10 May 2015), and initiated on LAMA monotherapy. The most commonly used LAMA at baseline was tiotropium (92%).

**Results:** Multivariate analysis (n=10,492 patients) revealed that COPD exacerbations, lower $FEV_1$, "asthma," MRC grade, proactive and reactive COPD primary care, elective secondary care contact, cough, and number of short-acting bronchodilator prescriptions were positively associated with treatment escalation ($p<0.05$). Being older, being a current/ex-smoker, or having increased sputum symptom codes were negatively associated with treatment escalation ($p<0.05$). Median MRC score was 2 at baseline and 3 prior to treatment escalation. Using the last MRC reading and exacerbation history in the year prior to escalation, GOLD 2017 groupings were as follows: A, 27.4%; B, 37.3%; C, 15.3%; D, 20.0%. In patients with available FEV1 measures, exacerbations and MRC code (n=1,064), GOLD 2011/2013 groupings were: A (20.4%), B (19.2%), C: (24.8%), D: 35.6%).

**Conclusions:** While the presence of COPD exacerbations seems to be the main driver for treatment escalation, according to the 2017 GOLD strategy many patients appear to be over-treated as they would not be recommended for treatment escalation.

Reviewing patients' treatment in the light of the new GOLD strategy has the potential to reduce inappropriate use of triple therapy.

**Keywords:** inhaled corticosteroid; treatment step-up; GOLD 2017 grouping; patient over-treatment

**Plain language summary**

In patients with chronic obstructive pulmonary disease (COPD) initiated on long-acting muscarinic antagonist (LAMA) monotherapy, this study identified that COPD exacerbations, lower $FEV_1$, "asthma," and health care contact were associated with escalation to triple therapy (LAMA + long-acting beta- agonist/inhaled corticosteroid [ICS]). When treatment practices were analyzed according to the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, many patients appear to be over-treated, particularly with respect to prescription of triple therapy comprising inhaled corticosteroids steroids (ICSs). Understanding factors associated with the escalation of treatment to include ICSs may improve treatment practices in patients with COPD, and bring them in line with the 2017 GOLD strategy, and moreover, reduce the inappropriate, expensive, and potentially harmful overprescribing of ICSs for COPD.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder that is characterized by persistent airflow limitation that is usually progressive in nature[1] and is a major cause of morbidity and mortality.[1-3,2] The World Health Organization estimates that approximately 3 million people died of COPD worldwide in 2015 (5% of all deaths), and predicts that due to higher smoking prevalence and aging populations in many countries, the prevalence of COPD is likely to increase in the future.[3,4]

The updated 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy categorizes patients into four grades of airflow obstruction (1 through 4) based on percentage of predicted forced expiratory volume in 1 second ($FEV_1$), and into four risk groups (A through D) based on symptoms and exacerbation history.[2]–.[2,3] The previous 2011 GOLD strategy (which was slightly adapted in 2013) used the degree of airflow obstruction to contribute to A–D grouping, such that those individuals with $FEV_1$ <50% were considered as group C and D.[1] In 2013, GOLD made a minor update and treated patients with one hospitalised exacerbation the same as patients with two or more non-hospitalised exacerbations.[1]

Long-term treatment with an inhaled corticosteroid (ICS) in combination with a long-acting beta agonist (LABA) is recommended therapy for certain patients in GOLD 2011/2013 groups C and D, but now there are more preferred pathways that recommend optimal bronchodilation using a long-acting muscarinic antagonist (LAMA) or LAMA + LABA, before the addition of ICS therapy (as triple therapy) in patients whose symptoms are not adequately controlled.[2,3] In some patients, such as those with a history and/or findings suggestive of an asthma/COPD overlap, LABA/ICS therapy may be first choice therapy, but other options should also be considered.[2,3] Despite these treatment pathways indicating appropriate prescription of ICSs, real-world data suggest that ICS may be inappropriately prescribed in some patients. For example, in a study of more than 24,000 electronic patient records and patient-completed

questionnaires from a large UK primary care database, ~50% of patients in both the overall cohort (n=24,957) and the cohort with moderate airflow limitation (n=13,557) were receiving ICS, either in combination with a LABA (26.7% for both cohorts) or in combination with a LABA and a LAMA (23.2% and 19.9%, respectively).[4,5] These findings revealed that ICSs in combination with LABA or LABA + LAMA was the most frequently used treatment in patients in GOLD group A or B, and that ICSs had been prescribed in 49% of patients with moderate airflow obstruction and no exacerbations in the previous year.[4,5] In light of this, the authors concluded that ICSs were prescribed irrespective of the severity of airflow limitation, asthma diagnosis, and exacerbation history,[4,5] which is not in accordance with the 2017 GOLD strategy.[2,3] Studies of ICS withdrawal, even in COPD patients with a history of exacerbations, have shown strategies can be safely undertaken that enable patients to change to a more appropriate therapy according to up-to-date guidances.[6,7]

The potentially inappropriate use of ICSs in patients with COPD has economic and clinical implications,[6,10,8,12] being associated with an increased risk of adverse events, including pneumonia, osteoporosis, diabetes, and cataracts.[6,8] The increased risk of pneumonia, for example, is particularly well-documented.[7,10,9,12] The economic impact of COPD and its treatment costs are considerable. For example, the UK National Institute for Health and Clinical Excellence (NICE) estimated that COPD costs the National Health Service (NHS) over £268 million in prescriptions alone (based on 2011 data).[11,13] Furthermore, the Net Ingredient Cost of preparations containing ICSs for respiratory disease (asthma and COPD) in England alone has been estimated to be in excess of £700 million, based on 2014 data.[11,13] If ICS are inappropriately prescribed to certain patients, it is one more factor adding to the already high economic and social burden associated with COPD.

Guidelines from expert panels such as GOLD are developed and routinely updated to aid most appropriate treatment practices, supported by clinical

observations. Therefore, understanding the pathway and predictors for treatment escalation in COPD may help identify patients for whom alternative treatment strategies or treatment escalation without ICSs may be more appropriate.

This study was conducted to determine the factors influencing treatment escalation (step-up) to a LAMA + LABA/ICS fixed-dose combination (FDC) inhaler (triple therapy) in patients with COPD who were initiated on LAMA monotherapy, and included assessment of patients and their treatment using ~~the updated GOLD 2017 classification criteria.~~both the GOLD 2011/2013 and the more up-to-date GOLD 2017 classification criteria.[1,3] The primary objective was to identify factors significantly associated with time to step-up from LAMA monotherapy to LAMA + LABA/ICS (triple therapy). Secondary objectives included assessing time to step-up from first LAMA prescription, GOLD category according to 2017 criteria, and change in breathlessness (MRC [Medical Research Council]) score prior to treatment escalation.

## METHODS

### Study design

This was a retrospective analysis of anonymized electronic medical records (EMR) in the UK Health Improvement Network (THIN) database, a primary care EMR data resource with 3 million active patients and 385 active general practitioner (GP) practices. Patients were representative of the UK population by age, gender, medical conditions, and death rates adjusted for demographics and social deprivation. The EMRs were consistently updated and could be followed over time. The GPs contributing data to THIN provided health services under the terms of the UK's NHS.[~~12~~14]

The THIN Data Collection Scheme is approved by the UK South-East Multicentre Research Ethics Committee (SRC). Approval for this study was gained from the IMS Health Independent Scientific Board (SRC Reference: 16THIN; approval: 29 March

2016). The study was conducted in accordance with legal and regulatory requirements and followed research practices described in the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, International Society for Pharmacoeconomics and Outcomes Research guidance, and Pharmaceutical Research and Manufacturers Association guidelines.

**Study periods**

The study period included data up until 10 May 2016 and was the time from the index event (date of first LAMA prescription) until the time at which the patient received LAMA + LABA/ICS (triple therapy, defined as any LABA/ICS FDC prescription after initiation of LAMA monotherapy; patients must have also received a LAMA within 2 months of treatment escalation). Patients were included if they had a COPD diagnosis between 01 June 2010 and 10 May 2015, allowing for at least 1 year of follow-up.

**Participants**

Data were extracted for patients who had a diagnosis of COPD (but excluding an asthma diagnosis), who were ≥35 years old, and who received LAMA monotherapy only (aclidinium, glycopyrronium, tiotropium, or umeclidinium) as initial COPD treatment prior to treatment escalation. Data from patients who started therapy comprising a LAMA in combination with any other COPD maintenance therapy (LABA, ICS, or LABA/ICS FDC), or who had a history of LAMA, LABA, LABA/LAMA FDC, ICS, or LABA/ICS use in the 2-month (60-day) pre-index period, were excluded. Use of reliever medications, mucolytics, and xanthines was accepted.

**Statistical analysis**

As the study was a retrospective non-interventional database analysis of anonymized patient records, a formal sample size was not calculated. A feasibility calculation was carried out to assess the potential size of the population to be studied. SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA) was used for all analyses. No missing data imputations and no multiplicity adjustments were performed.

Patient characteristics and comorbidities recorded at any time were descriptively summarized (Table S1). Time to treatment escalation (step-up) was assessed using univariate and multivariable Cox regression incorporating time-varying covariates.[13] ~~The univariate analysis included 14,866 patients, and any missing data due to missing covariates were censored for that observation.~~[15] The univariate analysis included 14,866 patients, and any missing data due to missing covariates were censored for that observation. For the multivariate Cox regression, to ensure inclusion of patients who had $FEV_1$ and MRC recorded, the final data set reduced to 10,492. Statistically significant time-varying covariates were included in the final model using a stepwise model selection procedure. Factors significantly associated with treatment escalation ($p<0.05$) were retained in the model.

In the prespecified analysis plan, the following initial terms were included in the multivariate analysis selection: age, gender, $FEV_1$, physician-coded asthma, chronic kidney disease, mental health disorders, depression, anxiety, osteoporosis, rheumatoid arthritis, lung cancer, obesity, epilepsy, diabetes, pneumonia, MRC grade, smoking status, cough symptoms (number of consultations with code for cough), sputum symptoms (number of consultations with code for sputum), short-acting bronchodilator use, proactive COPD primary care (defined as COPD disease monitoring [including by doctor or nurse], shared care disease monitoring, COPD 3-, 6-, or 12-month review follow-up, COPD health education, COPD disease medication optimization, issue of COPD rescue pack or advance supply of steroid medication or antibiotic medication [or deferred antibiotic therapy], COPD disease leaflet given, has COPD care plan or care

pathway, has COPD clinical management plan, on COPD supportive care pathway, seen in COPD clinic), reactive COPD primary care (defined as nighttime or out-of-hour visit; follow-up or acute visit; home-, hotel-, or nursing/residential home visit; twilight visit by the practice, their cooperative, deputizing service, or local rota service; reactive or cooperative surgery consultation; minor injury service; medicines management or telephone consultation related to COPD), elective secondary care contact (defined as COPD secondary care consultation or respiratory hospital referral), COPD exacerbations (composite endpoint defined as COPD emergency admission or acute exacerbation of COPD, lower respiratory tract infection, oral corticosteroids and antibiotic prescription on same day, according to the definition used previously~~14~~16), and cardiovascular risk (composite endpoint defined as combined comorbidity for cardiovascular risk). Cough symptoms, sputum symptoms, proactive and reactive COPD primary care, and elective secondary care contact were based on Read code data only.

A stepwise procedure was followed, which is useful where there is a large number of potential explanatory variables and no underlying theory for the order on which to base the model selection. The order of importance of variables automatically selected in the stepwise process was: COPD exacerbations (composite), $FEV_{1,}$ "asthma," proactive COPD primary care, use of short-acting bronchodilators, reactive COPD primary care, MRC grade, smoking status, cough symptoms, elective secondary care contact, sputum symptoms, and age. Terms were retained in the model if $p<0.05$.

GOLD grouping was analyzed according to GOLD 2011/2013 criteria for patients with any $FEV_{1,}$ and MRC available during the last 360 days of study period (and exacerbations / hospitalizations as previously described),[1] and GOLD 2017 classification criteria for patients with any MRC available during the last 360 days of study period (and exacerbations / hospitalizations as previously described).[3]

## RESULTS

### Patient baseline characteristics

In total, data from 14,866 patients were included in this analysis (Figure 1): 6,482/14,866 (43.6%) received treatment escalation, and 8,384/14,866 (56.4%) remained on LAMA monotherapy. Overall, 1,875/14,866 patients (12.6%) were lost to follow-up due to death.

Patient baseline characteristics are given in Table 1. The mean age of the overall population was 68 years, and 54% were male. In the treatment escalation group, the mean age was 68 years, and 55% were male. The most commonly used LAMA at baseline was tiotropium (92%).

Of patients who received treatment escalation, the majority were prescribed fluticasone propionate 500 µg/salmeterol 50 µg (as Seretide® 500 Accuhaler; 29%), followed by salmeterol 25 µg/fluticasone 250 µg (as Seretide® 250 Evohaler, 16%). The Seretide® 250 Evohaler inhaler device does not have a license for the treatment of COPD.

### Comorbidities

The most prevalent comorbidities were hypertension (44%), chronic heart disease (20%), anxiety (20%), and diabetes (15%) (Table 2). Comparison of comorbidities in the population studied here with those in the general population of England[~~15~~17] suggests that the prevalence of heart failure (6.7% vs 0.7%, respectively) and osteoporosis (7.9% vs 0.1%, respectively) is greater in this COPD population, as might be expected.

### Time to treatment escalation

In total, 44% of the cohort received treatment escalation (Figure 2). Of these patients, 85% did so within 2 years of initiating LAMA monotherapy. The median time to

treatment escalation from the first LAMA prescription was 155 days (interquartile range, 422-464 days). In the treatment escalation group, 33% of patients who had a $FEV_1$ recording had a $FEV_1$ <50%, and 67% had a $FEV_1$ ≥50%, prior to treatment escalation.

**Factors associated with treatment escalation**

*Univariate analysis*

The factors associated with treatment escalation are reported in Table 3, of which COPD exacerbation was associated with the highest hazard ratio (HR, 2.68). Other factors positively associated ($p$<0.05) with treatment escalation included, in decreasing order of HR, MRC grade, "asthma," elective secondary care contact, proactive COPD primary care, pneumonia, cough symptoms, reactive COPD primary care, mental health disorders, depression, sputum symptoms, anxiety, number of short-acting bronchodilator prescriptions, and number of steroid prescriptions. Statistically significant factors that were negatively associated with treatment escalation were older age, higher $FEV_1$, and current or ex-smoker status (Table 3). A small number of COPD patients in this study were recorded as never having smoked. However, the risk of treatment escalation for the two larger, more clinically relevant patient groups of current smokers and ex-smokers was similar (Table 3).

*Multivariate analysis*

The multivariate analysis included 10,492 patients, 4,591 of whom received treatment escalation. Observations confirmed that COPD exacerbations remained the factor most closely associated with treatment escalation (Table 4). Other factors, in decreasing order of hazard ratio, were "asthma," MRC grade, proactive COPD primary care, reactive COPD primary care, elective secondary care contact, cough symptoms, and number of short-acting bronchodilator prescriptions (all $p$<0.05). Age at index date,

higher $FEV_1$, sputum symptoms, and being a current or ex-smoker were negatively associated with treatment escalation (Table 4).

**GOLD grade and group classification of patients prior to treatment escalation**

GOLD 2011/2013 group was determined in a subgroup of 1,064 patients with $FEV_1$ exacerbations and MRC score available during the last 12 months of the study period and who received treatment escalation (Table 5); 60% were classified as being in group C or D compared with 40% in A or B.

GOLD 2017 group was determined in a subgroup of 5,090 patients who had received treatment escalation and had an MRC score during the last 12 months of the study period (Table 5). In total, 35% of patients were classified as being in GOLD group C or D, compared with 65% in group A or B. Similarly, GOLD 2017 grade was determined in a subgroup of 1,703 patients who had received treatment escalation and had an $FEV_1$ score during the last 12 months of the study period (Table 5). In total, 67% of patients were classified as being grade 1 or 2, compared with 33% grade 3 or 4.

**Assessment of treatment escalation per Medical Research Council (MRC) group**

Median (lower, upper quartiles) Medical Research Council (MRC) score in the treatment escalation group was 2.00 (interquartile range: 2.00-3.00) at baseline (n=3,823) and 3.00 (2.00, 3.00) during the study period (n=5,611; Figure 3), suggesting that patients became more breathless prior to treatment escalation.

## DISCUSSION

This retrospective analysis of the UK THIN database was conducted to determine the factors influencing treatment escalation to a LAMA + LABA/ICS (triple therapy) in patients with COPD who were initiated on LAMA monotherapy. To assess prescribing practices at the time of the study, we analyzed patients categorized by the then current GOLD 2011/2013 groupings. In addition, as GOLD updated their guidance in 2017, we also analyzed patients according to the GOLD 2017 strategy. The multivariate analysis demonstrates that COPD exacerbations were the most significant factor (ie, had the highest HR) associated with treatment escalation, but physician-coded asthma, MRC grade, proactive COPD primary care, reactive COPD primary care, elective secondary care contact, cough symptoms, and number of short-acting bronchodilator prescriptions were also clinically and statistically significantly associated with treatment escalation in these patients. The majority of patients had their treatment escalated within 2 years. As treatment escalation (or step-down) is likely to be initiated during a point of contact with a primary care provider, it would be expected that patients with treatment-defined exacerbations and other consultations are more likely to receive treatment escalation. Indeed, similar findings have been reported by others.[~~16,17~~18,19] Both lower age and greater use of short-acting bronchodilators were statistically significant predictors of treatment escalation in both our univariate and multivariate analyses. Although the HRs are relatively small, it is of note that they represent the impact of one unit of the covariate. For age, the unit is 1 year, and for short-acting bronchodilator use, the unit is one extra prescription over the follow-up period. Age was negatively associated with treatment escalation; therefore, if age increased by 1 year, the hazard is multiplied by 0.994. Given the poor recording of $FEV_1$ in this patient cohort, short-acting bronchodilator use could be an important marker to consider in the identification of patients who are more likely to require treatment optimization.

Our study focused on treatment escalation in patients receiving LAMA monotherapy only, and in the majority of cases we found that treatment escalation occurred within 2 years of treatment initiation. A smaller retrospective cohort study of 3,268 patients from the US Truven Marketscan® Commercial Database likewise demonstrated dynamic changes to COPD prescriptions within 2 years of treatment initiation with a LABA.[~~16~~18] More specifically, within 24 months of follow-up, 16% of patients received treatment escalation, the majority of whom had added therapy (84%) progressed to triple therapy.[~~16~~18] This escalation may be a result of poor control of symptoms,[~~16~~18] in line with the present study, which suggests that treatment escalation is a direct result of COPD exacerbations or other symptoms that lead patients to contact their primary care provider.[20]

A secondary objective of this study was to analyze how GOLD strategies guide treatment practices. Although UK treatment practices may be guided by NICE,[13] guidelines from COPD-specific organizations, such as GOLD, are routinely updated to provide care paradigms reflective of recent clinical evidence.[3] We analyzed treatment patterns according to GOLD grouping prior to treatment escalation by applying the GOLD 2017 strategy document, in addition to the GOLD 2011/2013 strategies that were contemporary to the study window. When data were analyzed using the 2011/2013 GOLD strategy, 60% of the 1,064 patients who received treatment escalation were classified as group C or D. When data were grouped according to the GOLD 2017 strategy, only 35% of the 5,090 patients who received treatment escalation were classified as group C or D. Although a larger sample was available for the 2017 analysis, this observation indicates that fewer patients are recommended for ICS treatment than under the GOLD 2011/2013 strategy, providing that they do not have co-morbid asthma. Our findings reflect the impact of previous iterations of GOLD strategies or other national guidances, such as NICE in the UK, but may also be a result of an increase over time in the proportion of patients who are receiving triple

**Commented [DM1]:** Note that the denominators in each of the GOLD11 and GOLD17 analyses are different (n=1064 vs n=5090) (may want to refer to Table 5 in brackets so that this is clear).

therapy.[21] According to the GOLD 2011/2013 strategy, which was in place during the study window, patients in group D (35.6% of the population) would have been recommended to receive LABA/ICS therapy.[1] In fact at the time of the study, use of triple therapy was common practice and NICE 2011 guidelines recommended that some patients with advanced COPD may require maintenance with oral corticosteroids, when these cannot be withdrawn following an exacerbation,[13] and many UK GPs would follow this practice above all other strategies. It was not until after the period covered in this study, with publication of studies such as WISDOM and FLAME,[7,22] that many doctors became aware that dual bronchodilation with LABA and LAMA is preferable to use of ICS-containing regimens as first line therapy for the majority of patients with COPD, particularly if the aim of treatment is to reduce the frequency of exacerbations.[21,23] The WISDOM study published in 2014 demonstrated that exacerbating patients with severe COPD run in on triple therapy (according to GOLD 2011/2013) were *not* at a higher risk of severe exacerbations following withdrawal of ICSs compared with patients who continued on triple therapy.[7] The GOLD 2017 strategy now recommends that alternative treatment strategies should be considered before the use of ICSs, including pulmonary rehabilitation, smoking cessation, and the addition of LABA without ICSs. The present observations suggest that if the GOLD 2017 strategy recommendations were adopted by clinicians, there would be a reduction in over-prescription of ICSs. Future studies may highlight changes in treatment practice with the uptake and application of the GOLD 2017 strategy and other updates in national treatment guidances since the study was sampled.

This retrospective analysis has several strengths, but also some limitations. The THIN database is a very large data set that is representative of the UK population.[~~18~~24] Data are collected in a non-interventional way, therefore reflecting “real-life” clinical practice. Information is continually updated, permitting investigation of the effects of new interventions/treatments. A literature search of the terms “THIN” and “validation”

revealed that the THIN database has been validated for the Read codes for some but not all of the covariates used in this study.[~~14,19-23~~16,25-29] It is important to note that the GOLD guidelines were updated while the manuscript was in progress. Although ~~earlier~~ GOLD ~~guidelines~~guidances, such as GOLD 2011/2013, may have been contemporary to treatment practices during the study period, we additionally assessed patients according to GOLD 2017 grouping, in order to demonstrate how physicians may need to adapt their treatment practices in light of new evidence. As we discuss above, it is likely that physicians were treating according to older GOLD strategy, or other guidance contemporary to the study window such as NICE 2011, and this is a possible explanation for the high proportion of patients in the treatment escalation group. Although only a minority of the study population had $FEV_1$ measurements recorded in the database (17.7% [n=2635/14,866]), $FEV_1$ measurements were not required for COPD diagnosis. Furthermore, GOLD 2017 guidelines do not use $FEV_1$ for determining categories (and hence treatment), which is a welcome change in policy, as $FEV_1$ has been reported to be a poor predictor of exacerbation risk.[~~24~~30]

Other limitations of this study include noncompliance to medication prescriptions, which results in inaccurate assumptions of drug-related exposure; validation gaps and the fact that some covariates, even though validated (eg, COPD exacerbations and emergency admissions), may be poorly reported. A Hospital Episode Statistics-linked subset of the THIN database could have been employed for secondary care COPD exacerbations, but it would have significantly reduced the number of eligible patients. However, comorbidities were chosen using Read codes used in the Quality and Outcomes Framework where relevant, which are well recorded. As with any database study, the quality of spirometry is not always assured. Finally, whether the current observations on treatment escalation can be generalized to the wider, non-UK COPD population is unknown and would require further study.

## CONCLUSIONS

Overall, 44% of COPD patients in UK primary care received treatment escalation from LAMA monotherapy to triple therapy (LAMA + ICS/LABA). While the presence of COPD exacerbations appears to be the main driver for treatment escalation in this cohort, according to the 2017 GOLD strategy, 65% of the cohort who had their treatment escalated were classified as GOLD group A or B and would therefore not now be recommended for treatment escalation. Reviewing patients' treatment in light of updated GOLD strategy has the potential to reduce inappropriate prescription of triple therapy. If treatment escalation is needed in these patients, the GOLD strategy suggests the use of alternative strategies without ICSs.[23] Given the gaps identified in EMR data recording, education around appropriate assessment and recording of data is required to guide rational treatment decisions and review.

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## Disclosure

MD, SH, and BE are employees of Pfizer and have company stock/shares. KM was an employee of Pfizer at the time of study conduct. RJ reports no conflicts of interest in relation to this study, but reports personal fees from Astra Zeneca, Boehringher Ingelheim, Chiesi, Cipla, GSK, Novartis, and Pfizer. JRH reports personal fees for advisory boards and educational activities and support to attend meetings from pharmaceutical companies that make medicines to treat COPD.

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**Table 1** Patient characteristics at baseline

| Characteristic | All N=14,866 | Monotherapy[a] n=8,384 | Treatment escalation[b] n=6,482 |
|---|---|---|---|
| Age, years | | | |
| Mean±SD | 68.4±10.7 | 68.8±10.9 | 67.8±10.5 |
| Range | 35–101 | 35–99 | 36–101 |
| Sex, n (%) | | | |
| Female | 6,781 (45.6) | 3,843 (45.8) | 2,938 (45.3) |
| Male | 8,085 (54.4) | 4,541 (54.2) | 3,544 (54.7) |
| LAMA therapy initiated, n (%) | | | |
| Tiotropium Handihaler | 12,501 (84.1) | 6,858 (81.8) | 5,643 (87.1) |
| Tiotropium Respimat | 1,183 (8.0) | 611 (7.3) | 572 (8.8) |
| Aclidinium | 623 (4.2) | 471 (5.6) | 152 (2.3) |
| Glycopyrronium | 487 (3.3) | 376 (4.5) | 111 (1.7) |
| Umeclidinium | 87 (0.6) | 79 (0.9) | 8 (0.1) |
| ICS/LABA[b] stepped up to, n (%) | | | |
| Fostair NEXThaler 200/6[a] | – | – | 1 (0.02) |
| Flutiform 50/5[a] | – | – | 1 (0.02) |
| Fostair NEXThaler 100/6 | – | – | 16 (0.25) |
| DuoResp Spiromax 320/9 | – | – | 19 (0.29) |
| Flutiform 250/5[a] | – | – | 24 (0.37) |
| Relvar Ellipta 184 µg[a] | – | – | 34 (0.52) |
| Flutiform 125/5[a] | – | – | 41 (0.63) |
| Seretide 50 Evohaler[a] | – | – | 64 (0.99) |
| Relvar Ellipta 92 µg | – | – | 139 (2.1) |
| Symbicort 100/6 Turbohaler[a] | – | – | 154 (2.4) |

| | | | |
|---|---|---|---|
| Seretide 100 Accuhaler[a] | – | – | 178 (2.8) |
| Seretide 250 Accuhaler[a] | – | – | 399 (6.2) |
| Fostair 100/6 | – | – | 462 (7.1) |
| Seretide 125 Evohaler[a] | – | – | 508 (7.8) |
| Symbicort 200/6 Turbohaler | – | – | 667 (10.3) |
| Symbicort 400/12 Turbohaler | – | – | 915 (14.1) |
| Seretide 250 Evohaler[a] | – | – | 1,022 (15.8) |
| Seretide 500 Accuhaler | | | 1,849 (28.5) |
| Time to treatment escalation, days | | | |
| Mean±SD | – | – | 324.6±392.1 |
| Range | – | – | 1–2,080 |
| Time to end of follow-up[c], days | | | |
| Mean±SD | 535.1±437.7 | 697.8± 400.0 | 324.6±392.1 |
| Range | 0–2,080 | 0–1,193 | 1–2,080 |

**Abbreviations:** ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

[a]Note: Not licensed for COPD.

[b]For the monotherapy group, follow-up was measured up to 1,193 days to reflect a similar period to that of follow-up in the treatment escalation group (calculated as the 95th percentile of distribution of the time to escalation).

[c]It may be inappropriate to compare across groups owing to different lengths of follow-up.

**Table 2** Comorbidities recorded at any time during the study period

| **Comorbidity** | **n (%)**<br><br>**(N=14,866)** |
|---|---|
| Hypertension | 6,603 (44.4) |
| Chronic heart disease | 3,036 (20.4) |
| Anxiety | 2,969 (20.0) |
| Diabetes | 2,174 (14.6) |
| Depression | 1,967 (13.2) |
| Asthma | 1,965 (13.2) |
| Cerebrovascular disease | 1,695 (11.4) |
| Atrial fibrillation | 1,464 (9.9) |
| Osteoporosis | 1,174 (7.9) |
| Heart failure | 990 (6.7) |
| Mental health disorders (QOF) | 882 (5.9) |
| Obesity | 826 (5.6) |
| Lung cancer | 416 (2.8) |
| Rheumatoid arthritis | 380 (2.6) |
| Epilepsy | 337 (2.3) |
| Chronic kidney disease | 247 (1.7) |
| **Abbreviation:** QOF = Quality and Outcomes Framework. | |

**Table 3** Univariate Cox regression analysis with significant ($p$<0.05) unadjusted predictors of treatment escalation

| | **Univariate analysis (N = 14,866)** | | |
|---|---|---|---|
| **Variable (electronically coded)** | **HR** | 95% CI | ***P*-value** |
| Composite: COPD exacerbations[a] | 2.675 | 2.534–2.823 | <0.0001 |
| MRC grade (vs 1) | | | <0.0001 |
| Grade 5 | 2.489 | 2.009–3.083 | <0.0001 |
| Grade 4 | 1.988 | 1.781–2.219 | <0.0001 |
| Grade 3 | 1.571 | 1.434–1.721 | <0.0001 |
| Grade 2 | 1.183 | 1.086–1.288 | 0.0001 |
| Asthma | 2.210 | 2.079–2.350 | <0.0001 |
| Elective secondary care contact | 1.466 | 1.371–1.569 | <0.0001 |
| Proactive COPD primary care[b] | 1.303 | 1.275–1.332 | <0.0001 |
| Pneumonia | 1.246 | 1.147–1.354 | <0.0001 |
| Number of cough symptoms[c] | 1.209 | 1.183–1.236 | <0.0001 |
| Reactive COPD primary care[d] | 1.191 | 1.100–1.290 | <0.0001 |
| Mental health disorders | 1.187 | 1.075–1.311 | 0.0007 |
| Depression | 1.160 | 1.082–1.243 | <0.0001 |
| Number of sputum symptoms[e] | 1.149 | 1.108–1.193 | <0.0001 |
| Anxiety | 1.125 | 1.060–1.194 | 0.0001 |
| Number of short-acting bronchodilator prescriptions | 1.041 | 1.038–1.045 | <0.0001 |
| Number of steroid prescriptions | 1.026 | 1.023–1.028 | <0.0001 |
| Age[f] | 0.997 | 0.995–1.00 | 0.0251 |
| $FEV_1$ | 0.979 | 0.976–0.982 | <0.0001 |

| | | | |
|---|---|---|---|
| Smoking status (vs never smoked) | | | |
| Current | 0.716 | 0.649–0.791 | <0.0001 |
| Ex | 0.769 | 0.697–0.848 | <0.0001 |

**Abbreviations:** AECOPD, acute exacerbation of COPD; CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; HR, hazard ratio; LRTI, lower respiratory tract infection; MRC, Medical Research Council; OCS, oral corticosteroid.

**Note:** Data ordered by HR.

[a]Composite endpoint: If COPD emergency admission or AECOPD or LRTI or OCS + antibiotic occurred on the same day, 1 was assigned (otherwise 0). We used time-varying covariates (so patient has 0 assigned until the first occurrence of any of those). This has been validated in a previous paper.[14,16]

[b]COPD disease monitoring; disease monitoring by doctor; disease monitoring by nurse; shared care disease monitoring; COPD 3-monthly, 6-monthly, and annual reviews; COPD follow-up; COPD health education; COPD disease medication optimization; issue of COPD rescue pack or advance supply of steroid medication or antibiotic medication or deferred antibiotic therapy; COPD disease leaflet given, has COPD care plan; has COPD care pathway; has COPD clinical management plan; on COPD supportive care pathway; seen in COPD clinic.

[c]Number of consultations with code for cough: C/O – cough, dry cough, productive cough-clear sputum, productive cough-green sputum, productive cough-yellow sputum, productive cough not otherwise specified (NOS), coughing up phlegm, night cough present, chesty cough, bronchial cough, morning cough, evening cough, cough with fever, difficulty in coughing up sputum, cough symptom NOS, nocturnal cough/wheeze, cough aggravates symptom, cough swab, [D]cough, [D]cough with hemorrhage.

[d]Night visits; after-hours visits; follow-up visits; acute visits; home visits; hotel visits; nursing home visits; residential home visits; twilight visits; visits by the practice, their cooperative, deputizing service, or local rota service; reactive surgery consultations; co-op surgery consultations; minor injury service; medicines management; or telephone consultation related to COPD.

[e]Number of consultations with code for sputum. C/O – sputum – symptom, sputum sample obtained, sputum examination, sputum sent for examination, sputum examination: abnormal, sputum: excessive

– mucoid, sputum: mucopurulent, sputum: fetid/offensive, yellow sputum, green sputum, dark green sputum, pale green sputum, sputum appearance, brown sputum, white sputum, volume of sputum, copious sputum, profuse sputum moderate sputum, grey sputum, sputum microscopy, sputum: pus cells present, sputum: organism on gram stain, sputum microscopy NOS, sputum evidence of infection, sputum appears infected, sputum culture, sputum examination NOS, sputum sent for C/S, [D]abnormal sputum, [D]sputum abnormal – amount, [D]sputum abnormal – color, [D]sputum abnormal – odor, [D]abnormal sputum – tenacious, [D]abnormal sputum NOS, [D]positive culture findings in sputum, sputum clearance, difficulty in coughing up sputum, acute purulent bronchitis, chesty cough, bronchial cough, productive cough NOS, coughing up phlegm.

[f]HR relative to change to every 1 year difference in age.

**Table 4** Multivariate analysis outcomes: predictors of treatment escalation

| | **Multivariate Cox regression analysis (N = 10,492)** | | |
|---|---|---|---|
| | **HR** | **95% CI** | ***P*-value** |
| COPD exacerbations: composite[a] | 2.114 | 1.870–2.389 | <0.0001 |
| Asthma | 1.948 | 1.695–2.238 | <0.0001 |
| MRC grade (vs 1) | | | <0.0001 |
| 2 | 1.167 | 1.005–1.355 | 0.0430 |
| 3 | 1.403 | 1.189–1.656 | <0.0001 |
| 4 | 1.757 | 1.420–2.174 | <0.0001 |
| 5 | 1.923 | 1.135–3.258 | 0.0151 |
| Proactive COPD primary care[b] | 1.273 | 1.213–1.337 | <0.0001 |
| Reactive COPD primary care[c] | 1.246 | 1.173–1.324 | <0.0001 |
| Elective secondary care contact | 1.186 | 1.031–1.364 | 0.0171 |
| Cough symptoms[d] | 1.101 | 1.055–1.149 | <0.0001 |
| Number of short-acting bronchodilator prescriptions | 1.030 | 1.023–1.037 | <0.0001 |
| Age at index date[e] | 0.994 | 0.989–0.999 | 0.0324 |
| $FEV_1$ | 0.980 | 0.977–0.983 | <0.0001 |
| Number of sputum symptoms[f] | 0.907 | 0.833–0.988 | 0.0249 |
| Smoking status (vs never smoked) | | | |
| Current | 0.544 | 0.424–0.700 | <0.0001 |
| Ex | 0.702 | 0.552–0.892 | 0.0038 |

**Abbreviations:** AECOPD, acute exacerbation of COPD; CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; HR, hazard ratio; LRTI, lower respiratory tract infection; MRC, Medical Research Council; OCS, oral corticosteroid.

**Note:** Multivariate analysis included 10,492 patients, of whom 4591 received treatment escalation. Data are ordered by HR.

[a]Composite endpoint: If COPD emergency admission or AE COPD or LRTI or OCS + antibiotic occurred on the same day, 1 was assigned (otherwise 0). We used time-varying covariates (so patient has 0 assigned until the first occurrence of any of those). This has been validated in a previous paper.[~~14~~16]

[b]COPD disease monitoring; disease monitoring by doctor; disease monitoring by nurse; shared care disease monitoring; COPD 3-monthly, 6-monthly, and annual reviews; COPD follow-up; COPD health education; COPD disease medication optimization; issue of COPD rescue pack or advance supply of steroid medication or antibiotic medication or deferred antibiotic therapy; COPD disease leaflet given; has COPD care plan; has COPD care pathway; has COPD clinical management plan; on COPD supportive care pathway; seen in COPD clinic.

[c]Night visits; after-hours visits; follow-up visits; acute visits; home visits; hotel visits; nursing home visits; residential home visits; twilight visits; visits by the practice, their cooperative, deputizing service, or local rota service; reactive surgery consultations; co-op surgery consultations; minor injury service; medicines management; or telephone consultation related to COPD.

[d]Number of consultations with code for cough: C/O – cough, dry cough, productive cough-clear sputum, productive cough-green sputum productive cough-yellow sputum, productive cough not otherwise specified (NOS), coughing up phlegm, night cough present, chesty cough, bronchial cough, morning cough, evening cough, cough with fever, difficulty in coughing up sputum, cough symptom NOS, nocturnal cough/wheeze, cough aggravates symptom, cough swab, [D]cough, [D]cough with hemorrhage.

[e]HR relative to change to every 1 year difference in age.

[f]Number of consultations with code for sputum. C/O – sputum – symptom, sputum sample obtained, sputum examination, sputum sent for examination, sputum examination: abnormal, sputum: excessive – mucoid, sputum: mucopurulent, sputum: fetid/offensive, yellow sputum, green sputum, dark green sputum, pale green sputum, sputum appearance, brown sputum, white sputum, volume of sputum, copious sputum, profuse sputum moderate sputum, grey sputum, sputum microscopy, sputum: pus cells present, sputum: organism on gram stain, sputum microscopy NOS, sputum evidence of infection, sputum appears infected, sputum culture, sputum

| |
|---|
| examination NOS, sputum sent for C/S, [D]abnormal sputum, [D]sputum abnormal – amount, [D]sputum abnormal – color, [D]sputum abnormal – odor, [D]abnormal sputum – tenacious, [D]abnormal sputum NOS, [D]positive culture findings in sputum, sputum clearance, difficulty in coughing up sputum, acute purulent bronchitis, chesty cough, bronchial cough, productive cough NOS, coughing up phlegm. |

**Table 5** Treatment escalation per GOLD 2011/2013 and 2017 classification [1,3]

| Characteristic, n (%) | GOLD 2011/2013: patients with any $FEV_1$ and MRC score during the last 12 months of study period | GOLD 2017: patients with any MRC score during the last 12 months of study period |
|---|---|---|
| | Treatment escalation group N=1,064 | Treatment escalation group N=5,090 |
| GOLD group | | |
| A | 217 (20.4) | 1,393 (27.4) |
| B | 204 (19.2) | 1,900 (37.3) |
| C | 264 (24.8) | 777 (15.3) |
| D | 379 (35.6) | 1,020 (20.0) |
| % predicted $FEV_1$ | | |
| <50% | 388 (36.5) | – |
| ≤50% | 676 (63.5) | – |
| MRC score | | |
| 1 or 2 | 481 (45.2) | 2,170 (42.6) |
| ≥3 | 583 (54.8) | 2,920 (57.4) |
| Primary care exacerbations | | |
| ≤1 | 762 (71.6) | 3,505 (68.9) |
| ≥2 | 302 (28.4) | 1,585 (31.1) |
| COPD emergency admissions | | |
| 0 | 953 (89.6) | 4,758 (93.5) |
| ≥1 | 111 (10.4) | 332 (6.5) |
| | | **Patients with any $FEV_1$ measurement at any time during study period** |
| | | **Treatment escalation group N=1,703** |
| GOLD grade | – | |
| 1: $FEV_1$ ≥80% | | 241 (14.2) |
| 2: $FEV_1$ 50–79% | | 907 (53.3) |
| 3: $FEV_1$ 30–49% | | 480 (28.2) |
| 4: $FEV_1$ <30% | | 75 (4.4) |

| | | |
|---|---|---|
| Predicted $FEV_1$ | = | |
| <50% | | 555 (32.6) |
| ≥50% | | 1,148 (67.4) |

**Abbreviations:** COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council.

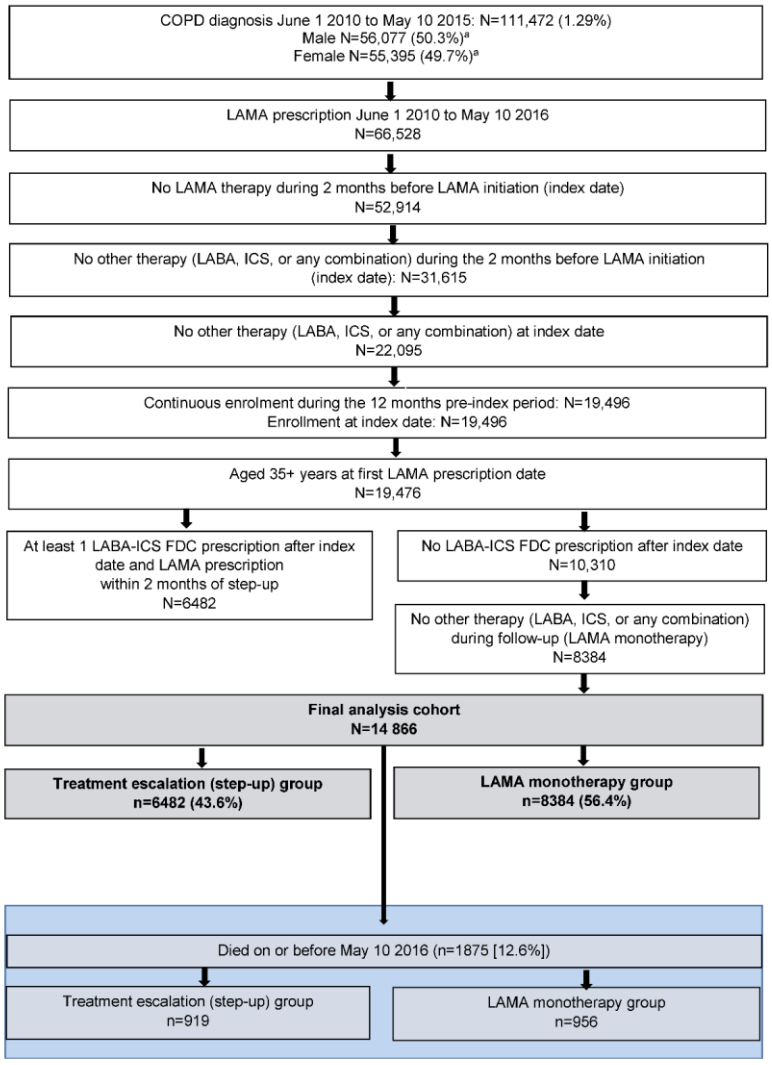


**Figure 1.** Cohort selection from THIN database of 8,676,730 patient records.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

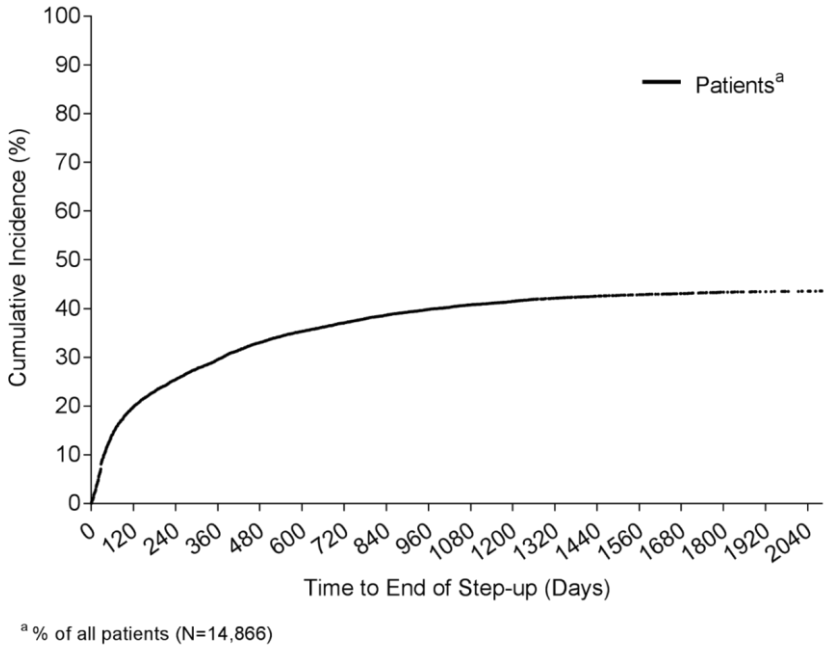


**Figure 2** Cumulative time to treatment escalation.

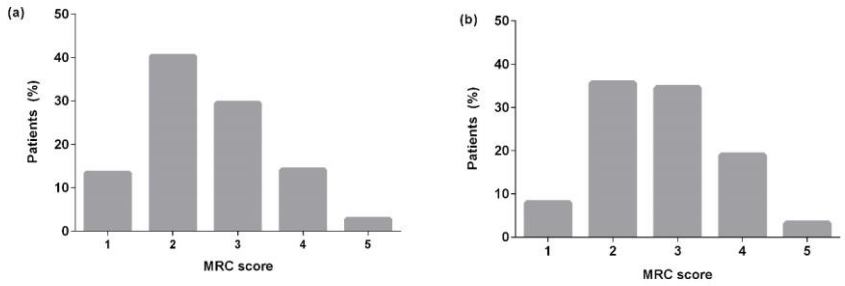


**Figure 3** Medical Research Council (MRC) breathlessness score in the treatment escalation group (a) 12 months from baseline (n=2,659) and (b) during the study and follow-up period (n=5,611). Median MRC score at baseline was 2.0, and 3.0 during the study period.

**[[Supplement]]**

**Supplemental Table 1** Covariates (during the analyzed baseline period)

| Covariate | Overall population N=14,866 |
|---|---|
| Smoking status, n (%) | |
| Unknown | 7 (0.1) |
| Current smoker | 7,049 (47.4) |
| Ex-smoker | 6,697 (45.1) |
| Never smoked | 1,113 (7.5) |
| MRC score (as categorical), n (%) | |
| Unknown | 6,466 (43.5) |
| Grade 1 | 1,437 (9.7) |
| Grade 2 | 3,730 (25.1) |
| Grade 3 | 2,134 (14.4) |
| Grade 4 | 925 (6.2) |
| Grade 5 | 174 (1.2) |
| MRC score (as numeric) | |
| Mean (SD) | 2.4 (1.0) |
| $FEV_1$, % | |
| Mean (SD) | 64.0 (17.9) |
| COPD disease severity, n (%) | |
| Unknown | 10,96 (68.6) |
| Mild | 2,217 (14.9) |
| Moderate | 1,993 (13.4) |
| Severe | 444 (3.0) |
| Very severe | 16 (0.1) |

| | |
|---|---|
| Respiratory hospital referral recorded, n (%) | 997 (6.7) |
| Elective secondary care contact (COPD secondary care consultation or respiratory hospital referral), n (%) | 2,911 (19.6) |
| Acute exacerbations of COPD, Mean (SD) | 0.3 (1.1) |
| COPD emergency admissions, Mean (SD) | 0.04 (0.3) |
| LRTI events, Mean (SD) | 2.8 (5.2) |
| Cough-related events, Mean (SD) | 1.9 (3.3) |
| Sputum-related events, Mean (SD) | 0.5 (1.6) |
| Oral corticosteroid prescriptions, Mean (SD) | 3.7 (14.7) |
| Oral antibiotics prescriptions, Mean (SD) | 9.0 (11.3) |
| Short-acting bronchodilator prescriptions, Mean (SD) | 14.7 (34.2) |
| COPD proactive primary care consultations, Mean (SD) | 1.5 (2.2) |
| COPD reactive primary care consultations, Mean (SD) | 1.0 (2.6) |
| Elective secondary care consultation, n (%) | 2,068 (13.9) |
| Composite endpoint: Exacerbations (COPD emergency admission or AECOPD or LRTI or OCS + antibiotic), n (%) | 10,805 (72.7) |

**Abbreviations:** AECOPD, acute exacerbation of COPD; $FEV_1$, forced expiratory volume in 1 second; LRTI, lower respiratory tract infection; MRC, Medical Research Council; OCS, oral corticosteroid; SD, standard deviation.