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Factors influencing treatment escalation from long-acting muscarinic antagonist monotherapy to triple therapy in patients with COPD: a retrospective THIN-database analysis

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

4

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11

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24 **ABSTRACT (293 of 300 max)**

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

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

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

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

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

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

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54 **Plain language summary**

55 In patients with chronic obstructive pulmonary disease (COPD) initiated on long-acting
56 muscarinic antagonist (LAMA) monotherapy, this study identified that COPD
57 exacerbations, lower FEV₁, “asthma,” and health care contact were associated with
58 escalation to triple therapy (LAMA + long-acting beta- agonist/inhaled corticosteroid
59 [ICS]). When treatment practices were analyzed according to the 2017 Global Initiative
60 for Chronic Obstructive Lung Disease (GOLD) strategy, many patients appear to be
61 over-treated, particularly with respect to prescription of triple therapy comprising
62 inhaled corticosteroids steroids (ICSs). Understanding factors associated with the
63 escalation of treatment to include ICSs may improve treatment practices in patients
64 with COPD, and bring them in line with the 2017 GOLD strategy, and moreover, reduce
65 the inappropriate, expensive, and potentially harmful overprescribing of ICSs for
66 COPD.

67

68 **INTRODUCTION**

69 Chronic obstructive pulmonary disease (COPD) is a complex respiratory disorder that
70 is characterized by persistent airflow limitation that is usually progressive in nature⁴ and
71 is a major cause of morbidity and mortality.¹⁻³² The World Health Organization
72 estimates that approximately 3 million people died of COPD worldwide in 2015 (5% of
73 all deaths), and predicts that due to higher smoking prevalence and aging populations
74 in many countries, the prevalence of COPD is likely to increase in the future.³⁴

75 The updated 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD)
76 strategy categorizes patients into four grades of airflow obstruction (1 through 4) based
77 on percentage of predicted forced expiratory volume in 1 second (FEV₁), and into four
78 risk groups (A through D) based on symptoms and exacerbation history.^{2-2,3} The
79 previous 2011 GOLD strategy (which was slightly adapted in 2013) used the degree of
80 airflow obstruction to contribute to A–D grouping, such that those individuals with FEV₁
81 <50% were considered as group C and D.¹ In 2013, GOLD made a minor update and
82 treated patients with one hospitalised exacerbation the same as patients with two or
83 more non-hospitalised exacerbations.¹

84 Long-term treatment with an inhaled corticosteroid (ICS) in combination with a
85 long-acting beta agonist (LABA) is recommended therapy for certain patients in GOLD
86 2011/2013 groups C and D, but now there are more preferred pathways that
87 recommend optimal bronchodilation using a long-acting muscarinic antagonist (LAMA)
88 or LAMA + LABA, before the addition of ICS therapy (as triple therapy) in patients
89 whose symptoms are not adequately controlled.²³ In some patients, such as those with
90 a history and/or findings suggestive of an asthma/COPD overlap, LABA/ICS therapy
91 may be first choice therapy, but other options should also be considered.²³ Despite
92 these treatment pathways indicating appropriate prescription of ICSs, real-world data
93 suggest that ICS may be inappropriately prescribed in some patients. For example, in a
94 study of more than 24,000 electronic patient records and patient-completed

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95 questionnaires from a large UK primary care database, ~50% of patients in both the
96 overall cohort (n=24,957) and the cohort with moderate airflow limitation (n=13,557)
97 were receiving ICS, either in combination with a LABA (26.7% for both cohorts) or in
98 combination with a LABA and a LAMA (23.2% and 19.9%, respectively).⁴⁵ These
99 findings revealed that ICSs in combination with LABA or LABA + LAMA was the most
100 frequently used treatment in patients in GOLD group A or B, and that ICSs had been
101 prescribed in 49% of patients with moderate airflow obstruction and no exacerbations
102 in the previous year.⁴⁵ In light of this, the authors concluded that ICSs were prescribed
103 irrespective of the severity of airflow limitation, asthma diagnosis, and exacerbation
104 history,^{4, 5} which is not in accordance with the 2017 GOLD strategy.²³ Studies of ICS
105 withdrawal, even in COPD patients with a history of exacerbations, have shown
106 strategies can be safely undertaken that enable patients to change to a more
107 appropriate therapy according to up-to-date guidances.^{6,7}

108 The potentially inappropriate use of ICSs in patients with COPD has economic
109 and clinical implications,^{6-10,8-12} being associated with an increased risk of adverse
110 events, including pneumonia, osteoporosis, diabetes, and cataracts.^{6,8} The increased
111 risk of pneumonia, for example, is particularly well-documented.^{7-9,9-12} The economic
112 impact of COPD and its treatment costs are considerable. For example, the UK
113 National Institute for Health and Clinical Excellence (NICE) estimated that COPD costs
114 the National Health Service (NHS) over £268 million in prescriptions alone (based on
115 2011 data).⁴⁺¹³ Furthermore, the Net Ingredient Cost of preparations containing ICSs
116 for respiratory disease (asthma and COPD) in England alone has been estimated to be
117 in excess of £700 million, based on 2014 data.⁴⁺¹³ If ICS are inappropriately prescribed
118 to certain patients, it is one more factor adding to the already high economic and social
119 burden associated with COPD.

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

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

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

135

136 **METHODS**

137 **Study design**

138 This was a retrospective analysis of anonymized electronic medical records (EMR) in
139 the UK Health Improvement Network (THIN) database, a primary care EMR data
140 resource with 3 million active patients and 385 active general practitioner (GP)
141 practices. Patients were representative of the UK population by age, gender, medical
142 conditions, and death rates adjusted for demographics and social deprivation. The
143 EMRs were consistently updated and could be followed over time. The GPs
144 contributing data to THIN provided health services under the terms of the UK's
145 NHS.⁴²¹⁴

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

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149 2016). The study was conducted in accordance with legal and regulatory requirements
150 and followed research practices described in the Guidelines for Good
151 Pharmacoepidemiology Practices issued by the International Society for
152 Pharmacoepidemiology, International Society for Pharmacoeconomics and Outcomes
153 Research guidance, and Pharmaceutical Research and Manufacturers Association
154 guidelines.

155

156 **Study periods**

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

163

164 **Participants**

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

173

174 **Statistical analysis**

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

180 Patient characteristics and comorbidities recorded at any time were descriptively
181 summarized ([Table S1](#)). Time to treatment escalation (step-up) was assessed using
182 univariate and multivariable Cox regression incorporating time-varying covariates.⁴³
183 ~~The univariate analysis included 14,866 patients, and any missing data due to missing~~
184 ~~covariates were censored for that observation.~~¹⁵ The univariate analysis included
185 14,866 patients, and any missing data due to missing covariates were censored for that
186 observation. For the multivariate Cox regression, to ensure inclusion of patients who
187 had FEV₁ and MRC recorded, the final data set reduced to 10,492. Statistically
188 significant time-varying covariates were included in the final model using a stepwise
189 model selection procedure. Factors significantly associated with treatment escalation
190 ($p < 0.05$) were retained in the model.

191 In the prespecified analysis plan, the following initial terms were included in the
192 multivariate analysis selection: age, gender, FEV₁, physician-coded asthma, chronic
193 kidney disease, mental health disorders, depression, anxiety, osteoporosis, rheumatoid
194 arthritis, lung cancer, obesity, epilepsy, diabetes, pneumonia, MRC grade, smoking
195 status, cough symptoms (number of consultations with code for cough), sputum
196 symptoms (number of consultations with code for sputum), short-acting bronchodilator
197 use, proactive COPD primary care (defined as COPD disease monitoring [including by
198 doctor or nurse], shared care disease monitoring, COPD 3-, 6-, or 12-month review
199 follow-up, COPD health education, COPD disease medication optimization, issue of
200 COPD rescue pack or advance supply of steroid medication or antibiotic medication [or
201 deferred antibiotic therapy], COPD disease leaflet given, has COPD care plan or care

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202 pathway, has COPD clinical management plan, on COPD supportive care pathway,
203 seen in COPD clinic), reactive COPD primary care (defined as nighttime or out-of-hour
204 visit; follow-up or acute visit; home-, hotel-, or nursing/residential home visit; twilight
205 visit by the practice, their cooperative, deputizing service, or local rota service; reactive
206 or cooperative surgery consultation; minor injury service; medicines management or
207 telephone consultation related to COPD), elective secondary care contact (defined as
208 COPD secondary care consultation or respiratory hospital referral), COPD
209 exacerbations (composite endpoint defined as COPD emergency admission or acute
210 exacerbation of COPD, lower respiratory tract infection, oral corticosteroids and
211 antibiotic prescription on same day, according to the definition used previously⁴⁴¹⁶), and
212 cardiovascular risk (composite endpoint defined as combined comorbidity for
213 cardiovascular risk). Cough symptoms, sputum symptoms, proactive and reactive
214 COPD primary care, and elective secondary care contact were based on Read code
215 data only.

216 A stepwise procedure was followed, which is useful where there is a large
217 number of potential explanatory variables and no underlying theory for the order on
218 which to base the model selection. The order of importance of variables automatically
219 selected in the stepwise process was: COPD exacerbations (composite), FEV₁,
220 "asthma," proactive COPD primary care, use of short-acting bronchodilators, reactive
221 COPD primary care, MRC grade, smoking status, cough symptoms, elective secondary
222 care contact, sputum symptoms, and age. Terms were retained in the model if $p < 0.05$.

223 GOLD grouping was analyzed according to GOLD 2011/2013 criteria for patients
224 with any FEV₁, and MRC available during the last 360 days of study period (and
225 exacerbations / hospitalizations as previously described),¹ and GOLD 2017
226 classification criteria for patients with any MRC available during the last 360 days of
227 study period (and exacerbations / hospitalizations as previously described).³

228

229 **RESULTS**

230 **Patient baseline characteristics**

231 In total, data from 14,866 patients were included in this analysis (Figure 1):
232 6,482/14,866 (43.6%) received treatment escalation, and 8,384/14,866 (56.4%)
233 remained on LAMA monotherapy. Overall, 1,875/14,866 patients (12.6%) were lost to
234 follow-up due to death.

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

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

244

245 **Comorbidities**

246 The most prevalent comorbidities were hypertension (44%), chronic heart disease
247 (20%), anxiety (20%), and diabetes (15%) (Table 2). Comparison of comorbidities in
248 the population studied here with those in the general population of England⁴⁵¹⁷
249 suggests that the prevalence of heart failure (6.7% vs 0.7%, respectively) and
250 osteoporosis (7.9% vs 0.1%, respectively) is greater in this COPD population, as might
251 be expected.

252

253 **Time to treatment escalation**

254 In total, 44% of the cohort received treatment escalation (Figure 2). Of these patients,
255 85% did so within 2 years of initiating LAMA monotherapy. The median time to

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256 treatment escalation from the first LAMA prescription was 155 days (interquartile range,
257 422-464 days). In the treatment escalation group, 33% of patients who had a FEV₁
258 recording had a FEV₁ <50%, and 67% had a FEV₁ ≥50%, prior to treatment escalation.

259

260 **Factors associated with treatment escalation**

261 *Univariate analysis*

262 The factors associated with treatment escalation are reported in Table 3, of which
263 COPD exacerbation was associated with the highest hazard ratio (HR, 2.68). Other
264 factors positively associated ($p<0.05$) with treatment escalation included, in decreasing
265 order of HR, MRC grade, “asthma,” elective secondary care contact, proactive COPD
266 primary care, pneumonia, cough symptoms, reactive COPD primary care, mental
267 health disorders, depression, sputum symptoms, anxiety, number of short-acting
268 bronchodilator prescriptions, and number of steroid prescriptions. Statistically
269 significant factors that were negatively associated with treatment escalation were older
270 age, higher FEV₁, and current or ex-smoker status (Table 3). A small number of COPD
271 patients in this study were recorded as never having smoked. However, the risk of
272 treatment escalation for the two larger, more clinically relevant patient groups of current
273 smokers and ex-smokers was similar (Table 3).

274

275 *Multivariate analysis*

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

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282 higher FEV₁, sputum symptoms, and being a current or ex-smoker were negatively
283 associated with treatment escalation (Table 4).

284

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

286 GOLD 2011/2013 group was determined in a subgroup of 1,064 patients with FEV₁
287 exacerbations and MRC score available during the last 12 months of the study period
288 and who received treatment escalation (Table 5); 60% were classified as being in
289 group C or D compared with 40% in A or B.

290 GOLD 2017 group was determined in a subgroup of 5,090 patients who had
291 received treatment escalation and had an MRC score during the last 12 months of the
292 study period (Table 5). In total, 35% of patients were classified as being in GOLD group
293 C or D, compared with 65% in group A or B. Similarly, GOLD 2017 grade was
294 determined in a subgroup of 1,703 patients who had received treatment escalation and
295 had an FEV₁ score during the last 12 months of the study period (Table 5). In total,
296 67% of patients were classified as being grade 1 or 2, compared with 33% grade 3 or
297 4.

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

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

303

304 **DISCUSSION**

305 This retrospective analysis of the UK THIN database was conducted to determine the
306 factors influencing treatment escalation to a LAMA + LABA/ICS (triple therapy) in
307 patients with COPD who were initiated on LAMA monotherapy. To assess prescribing
308 practices at the time of the study, we analyzed patients categorized by the then current
309 GOLD 2011/2013 groupings. In addition, as GOLD updated their guidance in 2017, we
310 also analyzed patients according to the GOLD 2017 strategy. The multivariate analysis
311 demonstrates that COPD exacerbations were the most significant factor (ie, had the
312 highest HR) associated with treatment escalation, but physician-coded asthma, MRC
313 grade, proactive COPD primary care, reactive COPD primary care, elective secondary
314 care contact, cough symptoms, and number of short-acting bronchodilator prescriptions
315 were also clinically and statistically significantly associated with treatment escalation in
316 these patients. The majority of patients had their treatment escalated within 2 years. As
317 treatment escalation (or step-down) is likely to be initiated during a point of contact with
318 a primary care provider, it would be expected that patients with treatment-defined
319 exacerbations and other consultations are more likely to receive treatment escalation.
320 Indeed, similar findings have been reported by others.^{16,17,18,19} Both lower age and
321 greater use of short-acting bronchodilators were statistically significant predictors of
322 treatment escalation in both our univariate and multivariate analyses. Although the HRs
323 are relatively small, it is of note that they represent the impact of one unit of the
324 covariate. For age, the unit is 1 year, and for short-acting bronchodilator use, the unit is
325 one extra prescription over the follow-up period. Age was negatively associated with
326 treatment escalation; therefore, if age increased by 1 year, the hazard is multiplied by
327 0.994. Given the poor recording of FEV₁ in this patient cohort, short-acting
328 bronchodilator use could be an important marker to consider in the identification of
329 patients who are more likely to require treatment optimization.

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330 Our study focused on treatment escalation in patients receiving LAMA
331 monotherapy only, and in the majority of cases we found that treatment escalation
332 occurred within 2 years of treatment initiation. A smaller retrospective cohort study of
333 3,268 patients from the US Truven Marketscan[®] Commercial Database likewise
334 demonstrated dynamic changes to COPD prescriptions within 2 years of treatment
335 initiation with a LABA.⁴⁶¹⁸ More specifically, within 24 months of follow-up, 16% of
336 patients received treatment escalation, the majority of whom had added therapy (84%)
337 progressed to triple therapy.⁴⁶¹⁸ This escalation may be a result of poor control of
338 symptoms,⁴⁶¹⁸ in line with the present study, which suggests that treatment escalation
339 is a direct result of COPD exacerbations or other symptoms that lead patients to
340 contact their primary care provider.²⁰

341 A secondary objective of this study was to analyze how GOLD strategies guide
342 treatment practices. Although UK treatment practices may be guided by NICE,¹³
343 guidelines from COPD-specific organizations, such as GOLD, are routinely updated to
344 provide care paradigms reflective of recent clinical evidence.³ We analyzed treatment
345 patterns according to GOLD grouping prior to treatment escalation by applying the
346 GOLD 2017 strategy document, in addition to the GOLD 2011/2013 strategies that
347 were contemporary to the study window. When data were analyzed using the
348 2011/2013 GOLD strategy, 60% of the 1,064 patients who received treatment
349 escalation were classified as group C or D. When data were grouped according to the
350 GOLD 2017 strategy, only 35% of the 5,090 patients who received treatment escalation
351 were classified as group C or D. Although a larger sample was available for the 2017
352 analysis, this observation indicates that fewer patients are recommended for ICS
353 treatment than under the GOLD 2011/2013 strategy, providing that they do not have
354 co-morbid asthma. Our findings reflect the impact of previous iterations of GOLD
355 strategies or other national guidances, such as NICE in the UK, but may also be a
356 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).

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357 therapy.²¹ According to the GOLD 2011/2013 strategy, which was in place during the
358 study window, patients in group D (35.6% of the population) would have been
359 recommended to receive LABA/ICS therapy.¹ In fact at the time of the study, use of
360 triple therapy was common practice and NICE 2011 guidelines recommended that
361 some patients with advanced COPD may require maintenance with oral corticosteroids,
362 when these cannot be withdrawn following an exacerbation,¹³ and many UK GPs would
363 follow this practice above all other strategies. It was not until after the period covered in
364 this study, with publication of studies such as WISDOM and FLAME,^{7,22} that many
365 doctors became aware that dual bronchodilation with LABA and LAMA is preferable to
366 use of ICS-containing regimens as first line therapy for the majority of patients with
367 COPD, particularly if the aim of treatment is to reduce the frequency of
368 exacerbations.^{21,23} The WISDOM study published in 2014 demonstrated that
369 exacerbating patients with severe COPD run in on triple therapy (according to GOLD
370 2011/2013) were *not* at a higher risk of severe exacerbations following withdrawal of
371 ICSs compared with patients who continued on triple therapy.⁷ The GOLD 2017
372 strategy now recommends that alternative treatment strategies should be considered
373 before the use of ICSs, including pulmonary rehabilitation, smoking cessation, and the
374 addition of LABA without ICSs. The present observations suggest that if the GOLD
375 2017 strategy recommendations were adopted by clinicians, there would be a reduction
376 in over-prescription of ICSs. Future studies may highlight changes in treatment practice
377 with the uptake and application of the GOLD 2017 strategy and other updates in
378 national treatment guidances since the study was sampled.

379 This retrospective analysis has several strengths, but also some limitations. The
380 THIN database is a very large data set that is representative of the UK population.⁴⁸²⁴
381 Data are collected in a non-interventional way, therefore reflecting “real-life” clinical
382 practice. Information is continually updated, permitting investigation of the effects of
383 new interventions/treatments. A literature search of the terms “THIN” and “validation”

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384 revealed that the THIN database has been validated for the Read codes for some but
385 not all of the covariates used in this study.^{14,19-23,16,25-29} It is important to note that the
386 GOLD guidelines were updated while the manuscript was in progress. Although *earlier*
387 GOLD *guidelines/guidances, such as GOLD 2011/2013*, may have been contemporary
388 to treatment practices during the study period, we *additionally* assessed patients
389 according to GOLD 2017 grouping, in order to demonstrate how physicians may need
390 to adapt their treatment practices in light of new evidence. *As we discuss above*, it is
391 likely that physicians were treating according to older GOLD strategy, or other
392 guidance *contemporary to the study window such as NICE 2011*, and this is a possible
393 explanation for the high proportion of patients in the treatment escalation group.
394 Although only a minority of the study population had FEV₁ measurements recorded in
395 the database (17.7% [n=2635/14,866]), FEV₁ measurements were not required for
396 COPD diagnosis. Furthermore, GOLD 2017 guidelines do not use FEV₁ for determining
397 categories (and hence treatment), which is a welcome change in policy, as FEV₁ has
398 been reported to be a poor predictor of exacerbation risk.^{24,30}

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

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411 **CONCLUSIONS**

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

423

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430

431 **Disclosure**

432 MD, SH, and BE are employees of Pfizer and have company stock/shares. KM was an
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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 ^p 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)

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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
<p>Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.</p> <p>^aNote: Not licensed for COPD.</p> <p>^bFor 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).</p> <p>^cIt may be inappropriate to compare across groups owing to different lengths of follow-up.</p>			

Table 2 Comorbidities recorded at any time during the study period

Comorbidity	n (%) (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

Variable (electronically coded)	Univariate analysis (N = 14,866)		
	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

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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; FEV₁, 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.

^aComposite 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.¹⁴¹⁶

^bCOPD 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.

^cNumber 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.

^dNight 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.

^eNumber of consultations with code for sputum. C/O – sputum – symptom, sputum sample obtained, sputum examination, sputum sent for examination, sputum examination: abnormal, sputum: excessive

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– 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.
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.

^aComposite 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.⁴⁴¹⁶

^bCOPD 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.

^cNight 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.

^dNumber 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.

^eHR relative to change to every 1 year difference in age.

^fNumber 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

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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.

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Table 5 Treatment escalation per GOLD 2011/2013 and 2017 classification ^{1,3}

Characteristic, n (%)	<u>GOLD 2011/2013: patients</u> <u>with any FEV₁ and MRC</u> <u>score during the last 12</u> <u>months of study period</u>	GOLD 2017: patients with any MRC score during the last 12 months of study period
	<u>Treatment escalation group</u> N=1,064	<u>Treatment escalation group</u> N=5,090
GOLD group		
A	<u>217 (20.4)</u>	1,393 (27.4)
B	<u>204 (19.2)</u>	1,900 (37.3)
C	<u>264 (24.8)</u>	777 (15.3)
D	<u>379 (35.6)</u>	1,020 (20.0)
% predicted FEV ₁		
<50%	<u>388 (36.5)</u>	=
≤50%	<u>676 (63.5)</u>	=
MRC score		
1 or 2	<u>481 (45.2)</u>	2,170 (42.6)
≥3	<u>583 (54.8)</u>	2,920 (57.4)
Primary care exacerbations		
≤1	<u>762 (71.6)</u>	3,505 (68.9)
≥2	<u>302 (28.4)</u>	1,585 (31.1)
COPD emergency admissions		
0	<u>953 (89.6)</u>	4,758 (93.5)
≥1	<u>111 (10.4)</u>	332 (6.5)
		Patients with any FEV₁ 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)

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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.		

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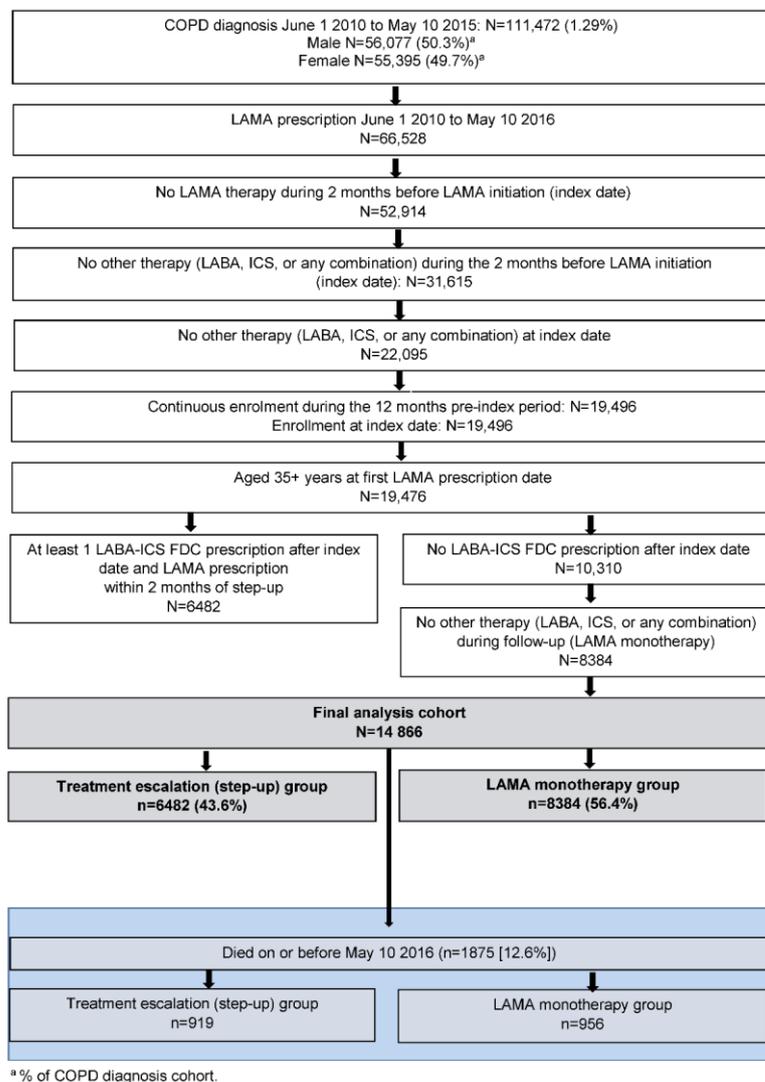


Figure 1. Cohort selection from THIN database of 8,676,730 patient records.

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

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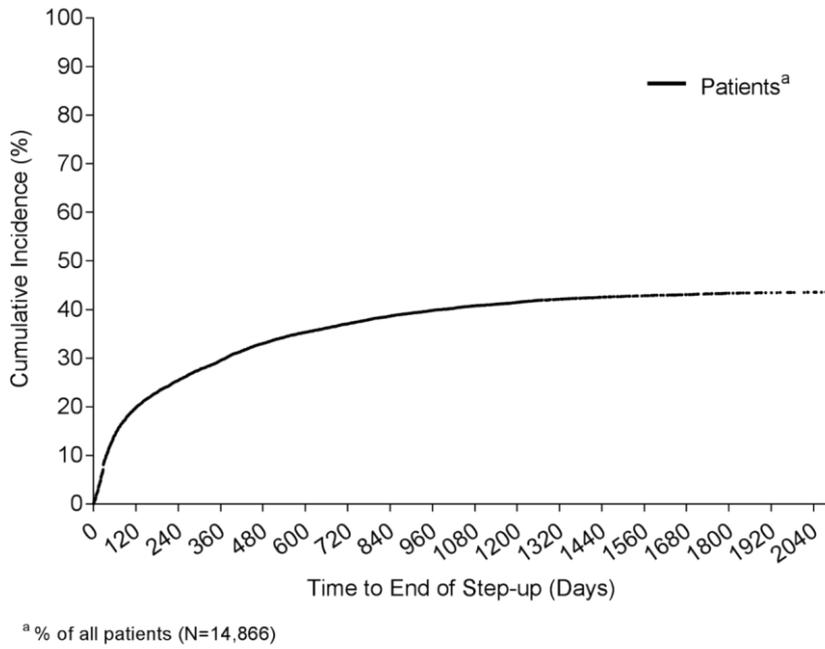


Figure 2 Cumulative time to treatment escalation.

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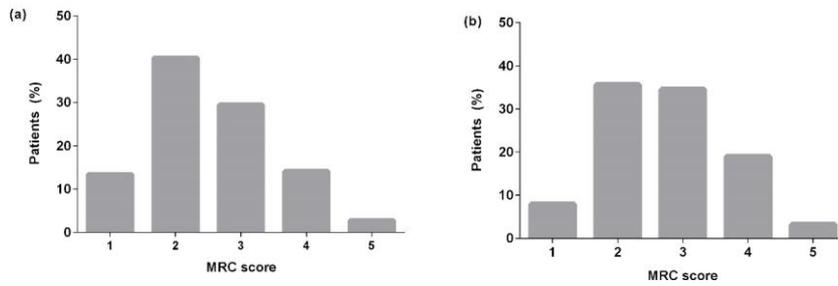


Figure 3 Medical Research Council (MRC) breathlessness score in the treatment escalation group (a) 12 months from baseline (n=2,659) and (b) during the study and follow-up period (n=5,611). Median MRC score at baseline was 2.0, and 3.0 during the study period.

[[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)
FEV₁, %	
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)

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

Abbreviations: AECOPD, acute exacerbation of COPD; FEV₁, forced expiratory volume in 1 second; LRTI, lower respiratory tract infection; MRC, Medical Research Council; OCS, oral corticosteroid; SD, standard deviation.