ORIGINAL ARTICLE
COPD

Comparative effectiveness of triple therapy *versus* dual bronchodilation in COPD

Jaco Voorham[1], Massimo Corradi[2], Alberto Papi[3], Claus F. Vogelmeier[4], Dave Singh[5], Leonardo M. Fabbri[3,6], Marjan Kerkhof[1], Janwillem H. Kocks[1,7], Victoria Carter[1] and David Price[1,8]

Affiliations: [1]Observational and Pragmatic Research Institute, Singapore, Singapore. [2]Dept of Medicine and Surgery, University Hospital of Parma, Parma, Italy. [3]Dept of Medical Sciences, University of Ferrara, Ferrara, Italy. [4]Dept of Internal Medicine, Pulmonary and Critical Care Medicine, University of Marburg, Member of the German Centre for Lung Research (DZL), Marburg, Germany. [5]University of Manchester, Manchester University NHS Foundation Trust, Manchester, UK. [6]COPD Center, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden. [7]General Practitioners Research Institute, Groningen, The Netherlands. [8]Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, UK.

Correspondence: David B. Price, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen AB25 2ZD, UK. E-mail: dprice@opri.sg

ABSTRACT This real-world study compared the effectiveness of triple therapy (TT; long-acting muscarinic antagonists (LAMAs)/long-acting inhaled β-agonists (LABAs)/inhaled corticosteroids (ICSs)) *versus* dual bronchodilation (DB; LAMAs/LABAs) among patients with frequently exacerbating COPD. A matched historical cohort study was conducted using United Kingdom primary care data. Patients with COPD aged ⩾40 years with a history of smoking were included if they initiated TT or DB from no maintenance/LAMA therapy and had two or more exacerbations in the preceding year. The primary outcome was time to first COPD exacerbation. Secondary outcomes included time to treatment failure, first acute respiratory event, and first acute oral corticosteroid (OCS) course. Potential treatment effect modifiers were investigated. In 1647 matched patients, initiation of TT reduced exacerbation risk (adjusted hazard ratio (HR) 0.87, 95% CI 0.76–0.99), risk of acute respiratory event (HR 0.74, 95% CI 0.66–0.84) and treatment failure (HR 0.83, 95% CI 0.73–0.95) compared with DB. Risk reduction for acute respiratory events was greater for patients with higher rates of previous exacerbations. At baseline blood eosinophil counts (BECs) $\geqslant 0.35\times10^9$ cells·L^{-1}, TT was associated with lower risk of OCS prescriptions than DB. This study provides real-life evidence of TT being more effective in reducing exacerbation risk than DB, which became more accentuated with increasing BEC and previous exacerbation rate.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent and progressive airflow limitation with a proportion of patients suffering from exacerbations of the disease [1]. The mainstay of therapeutic management in COPD are long-acting inhaled bronchodilators, either long-acting muscarinic antagonists (LAMAs) or long-acting inhaled β-agonists (LABAs), with the primary aim of reducing symptoms and exacerbations while improving wellbeing [2]. A combination of LAMAs/LABAs is recommended in patients where disease control is not satisfactory using long-acting bronchodilator monotherapy, and inhaled corticosteroids (ICSs) can be added for triple therapy (TT; ICS plus LAMA plus LABA) for those with persisting exacerbations [2]. However, ICS use has been associated with an increased risk of adverse events, including pneumonia [3], bone fracture, and skin thinning/easy bruising [4]. ICS therapy is widely prescribed in clinical practice in patients with COPD [5, 6].

TT has been shown to be more effective than an ICS/LABA combination for the treatment of COPD [7, 8]. Recent randomised controlled clinical trials (RCTs) support the efficacy of TT compared with dual bronchodilation (DB) with LAMAs/LABAs in selected populations [9, 10]. In addition, a higher blood eosinophil count (BEC) in patients with COPD has been associated with an increased benefit from ICSs in terms of exacerbation reduction [11]. There has been a call for representative, longer-term studies to determine the potential benefits of TT *versus* DB therapy, to improve the evidence which informs real-life prescribing decisions [12, 13]. This study aims to compare the real-world effectiveness of TT *versus* DB in the treatment of patients with frequently exacerbating COPD and to explore the potential heterogeneity of the effectiveness driven by patient and therapy characteristics.

Methods

Study design and data sources

A matched historical cohort study was conducted on patients with COPD in the United Kingdom (UK). Data were extracted from two databases: the Optimum Patient Care Research Database (OPCRD; https://opcrd.co.uk/) and the Clinical Practice Research Datalink (CPRD; www.cprd.com/). The OPCRD contains anonymised, longitudinal medical record data for over 5 million patients from 650 primary care practices. It is a high-quality data source used regularly in clinical, epidemiological, and pharmaceutical research [14, 15]. The CPRD contains anonymised primary care data for 5 million patients from >600 general practices in the UK. The overlap in practices covered by these two databases is <5%. To maximise the sample size, data were extracted from both the OPCRD and CPRD for patients who stepped-up between 2003 and 2017 from no prior maintenance therapy or LAMA monotherapy for COPD, to either DB or TT. Data were combined, and duplicates were removed. The data extracted included demographic and clinical characteristics, prescriptions, and data on comorbidities.

The quality of some data is driven by the Quality and Outcomes Framework (QOF) in the UK including diagnostic and annual spirometry and mMRC recording [16]. The clinical data are mostly recorded using read codes, and the QOF requires spirometry to confirm the COPD diagnostic read codes in the UK. The diagnosis of COPD in CPRD has been validated [17].

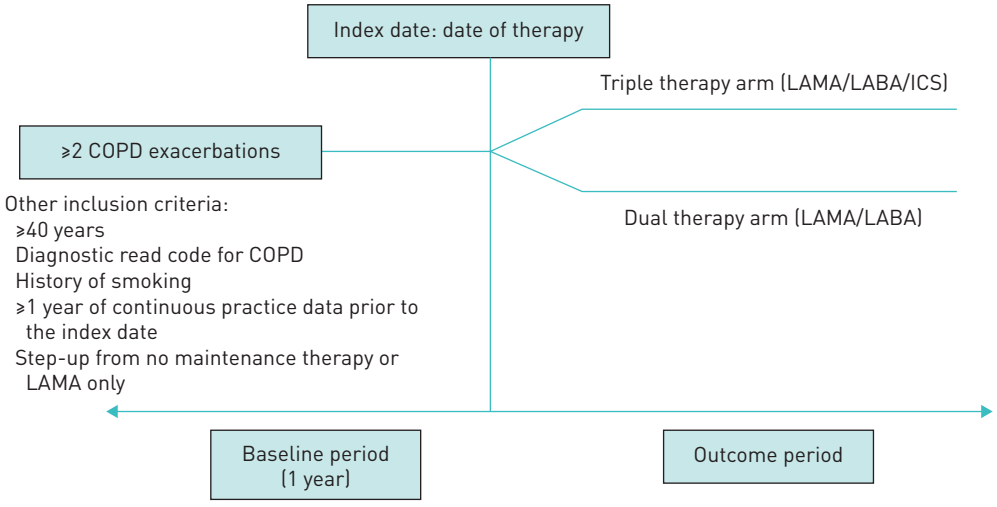

FIGURE 1 Study design. ICS: inhaled corticosteroid; LABA: long-acting inhaled ß-agonist; LAMA: long-acting muscarinic antagonist.

This study included a 1-year baseline period preceding the index date, and an outcome period after the index date, ending at the last date of data extraction or patient deregistration (figure 1). The index date was defined as the date of therapy step-up. Patients were divided into the following two cohorts (exposure groups): patients initiating TT (LAMAs/LABAs/ICSs) and patients initiating DB therapy (LAMAs/LABAs) without ICSs, both from prior no maintenance therapy or LAMA monotherapy. Patients on all inhaler combinations of the treatments under study were included. To avoid the inclusion of patients under DB treatment who recently stopped ICSs, patients were excluded if they had been treated with ICSs in the 12 months prior to the index date. This exclusion was conducted because stepping down ICSs could potentially bias the results in favour of TT.

Study population

Patients who met the following criteria were eligible for inclusion: a diagnostic read code for COPD, aged ⩾40 years, history of smoking, had ⩾1 year of continuous data prior to the index date (baseline year), and ⩾2 moderate/severe exacerbations in the baseline year. The exclusion criteria included active asthma at or after the index date (defined as ⩾1 diagnostic read code for asthma or ⩾1 asthma monitoring or review read code recorded on or after the index date), a diagnostic code for asthma–COPD overlap syndrome, and a diagnostic code ever for other chronic lower respiratory conditions. All code lists are available from the study authors.

Study outcomes

The primary outcome was the time to first COPD exacerbation to avoid the exclusion of patients who were lost to follow-up from the analyses. Secondary outcomes included time to first acute respiratory event, time to treatment failure, time to first acute oral corticosteroid (OCS) course, time to first antibiotic prescription with evidence of a lower respiratory primary care consultation, modified Medical Research Council (mMRC) dyspnoea score within 18 months after the index date, time to first pneumonia diagnosis, and the number of occurrences in the first year of the outcome period of the following: exacerbations, acute OCS courses, antibiotic prescriptions with evidence of a lower respiratory primary care consultation and acute respiratory events. Definition of study outcomes are listed in table 1.

TABLE 1 Study outcomes and definitions

Primary

1) Time to first exacerbation
   Respiratory-related hospital attendance/admission AND/OR
   Respiratory-related emergency room attendance AND/OR
   Prescription of acute OCS course AND/OR
   Antibiotics prescribed with evidence of lower respiratory consultation on the same day

Secondary

2) Time to first acute respiratory event
   Respiratory-related consultation, not for annual monitoring review
3) Time to treatment failure
   Prescription of additional chronic therapy (theophylline or other methylxanthines); maintenance OCS; PDE4 inhibitor; macrolides (*e.g.* azithromycin, erythromycin); mucolytics (*e.g.* carbocysteine, *N*-acetylcysteine); LTRA (nedocromil) AND/OR
   An exacerbation (as defined above)
4) Time to first acute OCS course
5) Time to first antibiotics prescription with evidence of lower respiratory consultation, to avoid misclassification of antibiotics being prescribed for another reason [18]

Number of occurrences in the first 1-year outcome period of:

6) Exacerbations
7) Acute OCS courses
8) Antibiotic prescriptions with evidence of lower respiratory consultation
9) Acute respiratory events

10) mMRC score within 18 months after index date; ⩾2 *versus* <2
11) Time to first pneumonia diagnosis
    Chest radiography AND/OR
    Diagnostic code

OCS: oral corticosteroid; PDE: phosphodiesterase; LTRA: leukotriene receptor antagonist; mMRC: modified Medical Research Council dyspnoea scale.

Data analysis

All data were analysed using Stata MP/6 version 15.1 (StataCorp, College Station, TX, USA). The number of clinical events or measurements occurring at the index date were included in the baseline characterisation, however, prescriptions of drugs at the index date were not included. Standardised mean difference (SMD) was used to quantify differences in both continuous and categorical variables between the treatment cohorts at baseline. An SMD ⩽10% indicated sufficient balance between treatment cohorts. The p-values were also reported for differences at baseline using Pearson's Chi-squared test for categorical variables and the Kruskal–Wallis equality-of-populations rank test for variables on a continuous or ordinal scale. Binary and categorical variables were summarised with frequencies and percentages, whereas distributions and descriptive statistics of central tendency (medians and means) and dispersion (SD and interquartile range) were produced for quantitative variables.

Patients in the DB and TT cohorts were propensity score matched to account for potential biases, such as indication bias, where different treatment combinations could be selected for patients with different disease severity. A propensity score was created using a logistic regression model including all baseline variables [19, 20]. The cohorts were matched 1 to 3 without replacement using nearest neighbour calliper matching. After matching, the SMD was recalculated to verify the accuracy of the propensity score model. To assess the robustness of findings with regards to potential restriction of the study population due to the matching, the inverse probability of treatment weighting (IPTW) approach, which uses all available patients, was used for sensitivity analyses.

The follow-up duration was summarised and the unadjusted incidence rate for each outcome per patient-year of follow-up time was calculated for the treatment cohorts. To compare the incidence rate per outcome between the treatment cohorts, unadjusted incidence rate ratios (IRRs) with 95% confidence intervals (CI) were calculated.

The proportion of patients improving, remaining unchanged, and worsening from the 1-year baseline to the first year of the outcome period in terms of the number of outcome events of interest was calculated, and a number needed to benefit (NNB) was derived from these values. NNB provides a measure for the benefit of a treatment while also taking account of the patients who remained unchanged and worsened due to the treatment [21]. For this specific analysis, only patients with ⩾1 year of follow-up were included.

The start of follow-up for each patient was their index date. The end of follow-up was defined as the earliest date at which the patient developed the outcome of interest, transferred out of the practice, died, or the date of the practice's last data collection. A time-to-event analysis was performed to estimate the association between treatment and time to first outcome event with right censoring at loss to follow-up. Stratified Cox regression was used to estimate hazard ratios (HRs) of the treatment effect for each outcome, adjusted for any residual confounders following matching. Holm's method was used to indicate which of the 10 secondary outcomes were significant after adjustment for multiple testing [22]. The proportional hazard assumption was evaluated visually by means of a log–log plot of survival. Conditional negative binomial regression was used to compare count outcomes, and conditional logistic regression was used to compare binary outcomes. Residual confounders were selected by assessing their bias potential, the relative change in the coefficient resulting from their addition to the model predicting the outcome of interest. A coefficient change of ⩾2% designated the variable as a confounder. See supplementary table 1 for the covariates identified as showing residual confounding and used to adjust for in the multivariable models in the matched cohort. A p-value <0.05 was considered statistically significant. An intention-to-treat design was used, thus allowing patients in the two treatment cohorts to change their therapy during follow-up, without being censored or otherwise removed from the analyses. A sensitivity analysis excluding patients with a history of asthma prior to the index date was carried out *post hoc* to confirm that any effect seen was not due to asthma.

To assess the effect modification, an interaction term between treatment and candidate modifiers (number of exacerbations, most recent BEC, level of airflow limitation, GOLD risk group, and number of nonrespiratory drugs prescribed in baseline year) was added to the models adjusted for confounders. For the time to pneumonia diagnosis, the effect modification could not be assessed due to a small number of events. Results were presented for the other 10 outcomes. Holm's method was used to indicate which outcomes were significant after adjustment for multiple testing for each candidate modifier separately (10 tests). Patients were categorised into a GOLD risk group based on their mMRC score. We selected the mMRC score instead of the COPD Assessment Test score as we previously observed mMRC to be more conservative in classifying patients into GOLD risk groups [23].

Results

There were 1181 patients with 2864 patient-years of follow-up in the TT arm and 466 patients with 1090 patient-years of follow-up in the DB arm. For a flow diagram of patient selection see figure 2. The

demographic and clinical characteristics of matched patients are presented in table 2 and supplementary table 2. Over 90% (72/77) characteristics were well balanced between the matched cohorts, indicated by SMD <10%. The mean age of patients in both treatment cohorts was 69 years and about half were male. Nearly half of the patients had an mMRC score between 2–4, corresponding to GOLD group D. The number of nonreliever drugs taken by patients at baseline is presented in supplementary table 3. Following matching, the number of nonreliever drugs were balanced between the TT arm and the DB arm. Almost half of the DB-initiating patients did not change their therapy for the duration of their follow-up; this was the case for 58% of TT initiators (Supplementary Table 4). See Supplementary Table 5 for baseline characteristics of the unmatched cohorts.

Patients in both arms showed great improvement in the number of exacerbations, acute respiratory events, acute OCS courses, and antibiotics courses from the baseline 1-year period to the first year of follow-up period. The proportion of patients who showed an improvement in the number of exacerbations, acute respiratory events, and acute OCS courses were higher for those initiating TT compared with patients initiating DB (table 3). The proportion of patients worsening was mostly lower for TT. This resulted in the number of patients needed to benefit from TT ranging 10–21 for these outcomes, and higher for the number of antibiotics courses (134). These statistics were similar to the unmatched cohort (data not shown).

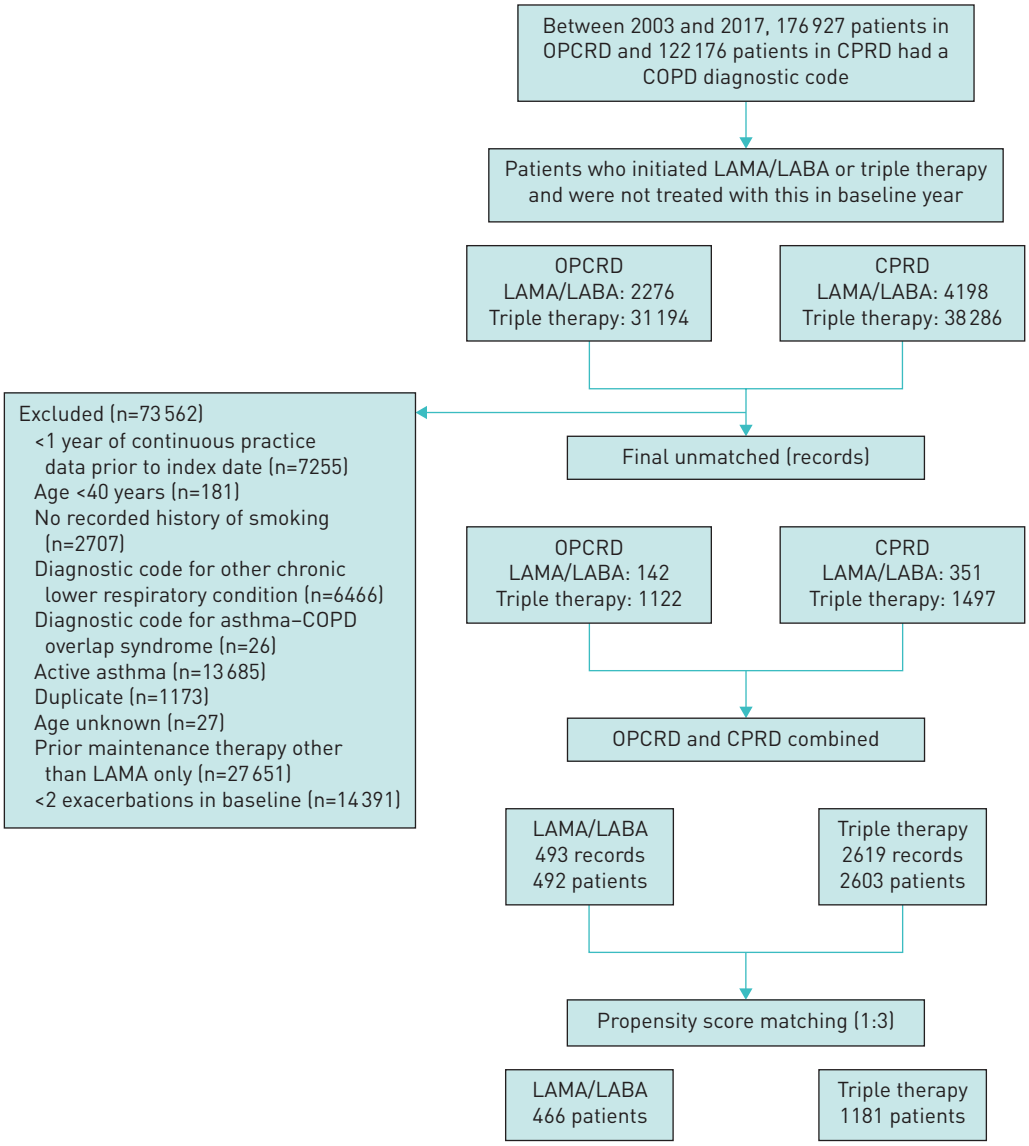

FIGURE 2 Flow diagram of patient selection. CPRD: Clinical Practice Research Datalink; LABA: long-acting inhaled ß-agonist; LAMA: long-acting muscarinic antagonist; OPCRD: Optimum Patient Care Research Database.

TABLE 2 Patient baseline characterisation, matched

	LAMA/LABA (n=466)	Triple therapy (n=1181)	p-value	SMD
Age years	69.2±10.7/70.0 (15.0)	69.4±10.2/69.0 (14.0)	0.672	2.0
⩾40– <60 years	92 (19.7%)	194 (16.4%)	0.278	6.8
⩾60– <80 years	295 (63.3%)	778 (65.9%)		
⩾80 years	79 (17.0%)	209 (17.7%)		
Males	233 (50.0%)	603 (51.1%)	0.699	2.1
Index year	2013.2±3.4/2014.0 (5.0)	2012.5±2.9/2013.0 (4.0)	<0.001	21.8
BMI n (% nonmissing)	463 (99.4%)	1167 (98.8%)	0.506	7.5
<18.5 kg·m^{-2}	22 (4.8%)	69 (5.9%)		
⩾18.5– <25 kg·m^{-2}	145 (31.3%)	397 (34.0%)		
⩾25– <30 kg·m^{-2}	159 (34.3%)	376 (32.2%)		
⩾30 kg·m^{-2}	137 (29.6%)	325 (27.8%)		
Current smoker				
No	256 (54.9%)	653 (55.3%)	0.896	0.7
Yes	210 (45.1%)	528 (44.7%)		
Asthma diagnosis, ever	38 (8.2%)	153 (13.0%)	0.006	15.7
Charlson Comorbidity Index				
⩽1	333 (71.5%)	845 (71.5%)	0.999	0.1
2–4	76 (16.3%)	190 (16.1%)		
5–9	26 (5.6%)	67 (5.7%)		
⩾10	31 (6.7%)	79 (6.7%)		
Blood eosinophil count n (% nonmissing)	391 (83.9%)	983 (83.2%)	0.808	2.2
<0.05×10^9 cells per L	8 (2.0%)	31 (3.2%)		
0.05–0.14×10^9 cells per L	110 (28.1%)	267 (27.2%)		
0.15–0.24×10^9 cells per L	110 (28.1%)	281 (28.6%)		
0.25–0.34×10^9 cells per L	80 (20.5%)	187 (19.0%)		
0.3–0.44×10^9 cells per L	27 (6.9%)	86 (8.7%)		
0.4–0.54×10^9 cells per L	23 (5.9%)	54 (5.5%)		
0.5–0.64×10^9 cells per L	10 (2.6%)	30 (3.1%)		
⩾0.65×10^9 cells per L	23 (5.9%)	47 (4.8%)		
SABA prescriptions				
0	63 (13.5%)	237 (20.1%)	0.021	8.1
1–2	103 (22.1%)	235 (19.9%)		
3–5	100 (21.5%)	220 (18.6%)		
6–9	108 (23.2%)	241 (20.4%)		
⩾10	92 (19.7%)	248 (21.0%)		
Salbutamol-equivalent average daily SABA dose				
0 µg	63 (13.5%)	237 (20.1%)	0.033	8.9
1–100 µg	48 (10.3%)	110 (9.3%)		
101–200 µg	83 (17.8%)	189 (16.0%)		
201–300 µg	58 (12.4%)	110 (9.3%)		
301–400 µg	41 (8.8%)	102 (8.6%)		
>400 µg	173 (37.1%)	433 (36.7%)		
SAMA prescriptions				
0	415 (89.1%)	1044 (88.4%)	0.982	1.6
1	11 (2.4%)	31 (2.6%)		
2	7 (1.5%)	19 (1.6%)		
⩾3	33 (7.1%)	87 (7.4%)		
LAMA prescriptions				
0	139 (29.8%)	343 (29.0%)	0.001	13.9
1–3	89 (19.1%)	213 (18.0%)		
4–6	81 (17.4%)	135 (11.4%)		
7–9	56 (12.0%)	124 (10.5%)		
10–12	63 (13.5%)	216 (18.3%)		
⩾13	38 (8.2%)	150 (12.7%)		
Average daily OCS dose				
<2.5 mg	379 (81.3%)	983 (83.2%)	0.433	1.2
⩾2.5– <5 mg	52 (11.2%)	112 (9.5%)		

Continued

TABLE 2 Continued

	LAMA/LABA (n=466)	Triple therapy (n=1181)	p-value	SMD
⩾5– <7.5 mg	18 (3.9%)	31 (2.6%)		
⩾7.5 mg	16 (3.4%)	49 (4.1%)		
5 mg	0 (0.0%)	4 (0.3%)		
6 mg	1 (0.2%)	2 (0.2%)		
Acute respiratory events in baseline year[#]				
0	22 (4.7%)	53 (4.5%)	0.797	5.0
1	48 (10.3%)	116 (9.8%)		
2	90 (19.3%)	200 (16.9%)		
3	96 (20.6%)	256 (21.7%)		
⩾4	210 (45.1%)	556 (47.1%)		
Exacerbations in baseline year[#]				
2	287 (61.6%)	698 (59.1%)	0.718	3.4
3	105 (22.5%)	284 (24.0%)		
4	34 (7.3%)	101 (8.6%)		
⩾5	40 (8.6%)	98 (8.3%)		
Acute OCS courses in baseline year[#]				
0	95 (20.4%)	234 (19.8%)	0.700	1.7
1	117 (25.1%)	328 (27.8%)		
⩾2	254 (54.5%)	619 (52.4%)		
Antibiotic courses in baseline year[#]				
0	80 (17.2%)	202 (17.1%)	0.627	2.9
1	115 (24.7%)	296 (25.1%)		
2	183 (39.3%)	435 (36.8%)		
3	63 (13.5%)	165 (14.0%)		
4	13 (2.8%)	55 (4.7%)		
⩾5	12 (2.6%)	28 (2.4%)		
GOLD severity (% nonmissing)	373 (80.0%)	957 (81.0%)	0.394	8.0
Mild, FEV_1 >80% predicted	44 (11.8%)	105 (11.0%)		
Moderate, FEV_1 50–80% predicted	190 (50.9%)	447 (46.7%)		
Severe, FEV_1 30–50% predicted	94 (25.2%)	281 (29.4%)		
Very severe, FEV_1 <30% predicted	45 (12.1%)	124 (13.0%)		
GOLD risk group[¶] n (% nonmissing)	389 (83.5%)	976 (82.6%)	0.187	7.9
C	236 (60.7%)	554 (56.8%)		
D	153 (39.3%)	422 (43.2%)		
mMRC score n (% nonmissing)	389 (83.5%)	976 (82.6%)	0.671	5.7
0, not troubled by breathlessness	37 (9.5%)	98 (10.0%)		
1, short of breath	199 (51.2%)	456 (46.7%)		
2, slower in walking	96 (24.7%)	266 (27.3%)		
3, stopping for breath	49 (12.6%)	131 (13.4%)		
4, too breathless to leave the house	8 (2.1%)	25 (2.6%)		

Data are presented as mean±SD/median (interquartile range) unless otherwise stated. LAMA: long-acting muscarinic antagonist; LABA: long-acting inhaled ß-agonist; SMD: standardised mean difference; IQR: interquartile range; BMI: body mass index; SABA: short-acting inhaled ß-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroid; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; mMRC: modified Medical Research Council dyspnoea scale. [#]includes the index date; [¶]: symptom and risk based. p-values are for the Kruskal–Wallis equality-of-populations rank test or Pearson's Chi-squared test of independent categories, where appropriate.

Unadjusted IRRs

For the primary outcome (time to first exacerbation), the average duration of follow-up per patient was 0.74 and 0.87 years in the TT and DB arms, respectively. The incidence rate of a first exacerbation in the outcome period was lower in the TT arm (0.79/patient-year) compared with the DB arm (0.91), equating to an unadjusted IRR of 0.87 (95% CI 0.76–0.99; table 4). The IRRs for time to an acute respiratory event and treatment failure were also in favour of TT, as were those for time until first acute OCS course and first antibiotics course, although the differences for the latter two outcomes were not statistically significant (table 4).

TABLE 3 Number of patients improving or worsening from baseline to the first outcome year, matched

	Improved		Unchanged		Worsened		NNB
	LAMA/LABA	Triple therapy	LAMA/LABA	Triple therapy	LAMA/LABA	Triple therapy	
Exacerbations	225 (73.5%)	651 (78.2%)	41 (13.4%)	96 (11.5%)	40 (13.1%)	85 (10.2%)	21
Acute respiratory events	173 (56.5%)	550 (66.1%)	51 (16.7%)	123 (14.8%)	82 (26.8%)	159 (19.1%)	10
Acute OCS courses	158 (51.6%)	494 (59.4%)	98 (32.0%)	213 (25.6%)	50 (16.3%)	125 (15.0%)	15
Antibiotics courses	193 (63.1%)	523 (62.9%)	72 (23.5%)	218 (26.2%)	41 (13.4%)	91 (10.9%)	134
mMRC score	32 (16.7%)	32 (6.1%)	101 (52.6%)	264 (50.2%)	59 (30.7%)	163 (31.0%)	

LAMA: long-acting muscarinic antagonist; LABA: long-acting inhaled ß-agonist; NNB: number needed for one patient to benefit from triple therapy [21]; OCS: oral corticosteroid; mMRC: modified Medical Research Council dyspnoea scale.

Multivariable outcome models

The effect sizes of TT *versus* DB for the outcomes of interest are presented in table 5. All time-to-event adjusted analyses results were in favour of TT. A significantly reduced risk in favour of TT was seen for the primary outcome of first exacerbation (HR 0.87, 95% CI 0.76–0.99). Among the secondary outcomes, first acute respiratory event (HR 0.74, 95% CI 0.66–0.84) and treatment failure (HR 0.83, 95% CI 0.73–0.95) were significantly in favour of TT after statistical adjustment and correction for multiple testing. A reduced risk in favour of TT was also seen for first acute OCS course and first antibiotics course, but these did not reach significance. Results of the conditional negative binomial regression showed significantly lower acute OCS courses rate (rate ratio (RR) 0.80, 95% CI 0.66–0.98) and acute respiratory events rate (RR 0.79, 95% CI 0.70–0.90) in the TT group. The effect sizes in the sensitivity analyses using IPTW were similar to the time-to-event models (data not shown) as were the results after excluding patients with a history of asthma (for some outcomes a slightly stronger effect was seen; supplementary table 6).

Effect modification

The results presented below are based on the investigation of the effect of the number of previous exacerbations and baseline BEC as continuous variables. On visual inspection, the results using the categorical representation of these potential effect modifiers did not show a meaningful difference with the

TABLE 4 Unadjusted incidence rate (IR) ratios for time-to-event outcomes, by matched treatment cohort

	Patients and follow-up years per cohort				Events per cohort		Comparison	
	Cohort	Patients	Total years	Mean±SD years[#]	Events	IR per patient-year	IR difference (95% CI)	IR ratio (95% CI)
Exacerbation (primary outcome)	TT	1181	1022	0.74±0.88	812	0.794	−0.119 (−0.233– −0.004)	0.870 (0.763–0.994)
	DB	466	346	0.87±1.04	316	0.913		
Acute respiratory event (secondary outcome)	TT	1181	592	0.37±0.53	957	1.618	−0.560 (−0.803– −0.316)	0.743 (0.659–0.840)
	DB	466	172	0.50±0.73	374	2.178		
Treatment failure (secondary outcome)	TT	1181	867	0.60±0.77	874	1.008	−0.227 (−0.374– −0.080)	0.816 (0.720–0.927)
	DB	466	278	0.73±0.92	343	1.236		
Acute OCS course (secondary outcome)	TT	1181	1367	1.02±1.21	683	0.499	−0.058 (−0.134–0.019)	0.896 (0.777–1.037)
	DB	466	477	1.16±1.28	266	0.557		
Antibiotics course (secondary outcome)	TT	1181	1341	1.00±1.17	659	0.491	−0.052 (−0.129–0.025)	0.904 (0.781–1.049)
	DB	466	465	1.14±1.27	253	0.544		
Pneumonia diagnosis (secondary outcome)	TT	1181	2772	2.24±2.16	62	0.022	−0.003 (−0.014–0.009)	0.899 (0.560–1.480)
	DB	466	1044	2.35±2.00	26	0.025		

OCS: oral corticosteroid; TT: triple therapy; DB: dual bronchodilation with long-acting muscarinic antagonist/long-acting inhaled ß-agonist. [#]: mean follow-up time in years available.

TABLE 5 Unadjusted and adjusted effects of triple therapy compared with dual bronchodilation (baseline) on outcomes of interest during the outcome period

Outcome	Patients	Unadjusted		Adjusted	
		HR (95% CI)	p-value	HR (95% CI)	p-value
First exacerbation	1647	0.90 (0.79–1.02)	0.111	0.87 (0.76–0.99)	0.040
First acute respiratory event	1647	0.79 (0.70–0.88)	<0.001*	0.74 (0.66–0.84)	<0.001*
Treatment failure	1647	0.86 (0.76–0.98)	0.020	0.83 (0.73–0.95)	0.005*
First acute OCS course	1647	0.95 (0.82–1.09)	0.437	0.93 (0.80–1.07)	0.298
First antibiotics course	1647	0.91 (0.79–1.04)	0.171	0.89 (0.77–1.04)	0.138
Pneumonia diagnosis	1647	1.26 (0.80–1.98)	0.325	0.71 (0.21–2.38)	0.573
		RR (95% CI)	**p-value**	**RR (95% CI)**	**p-value**
Exacerbation rate	1138	0.85 (0.73–1.00)	0.056	0.86 (0.73–1.01)	0.068
Acute OCS courses rate	1138	0.83 (0.68–1.01)	0.067	0.80 (0.66–0.98)	0.030
Antibiotics courses rate	1138	0.88 (0.72–1.06)	0.183	0.91 (0.75–1.10)	0.332
Acute respiratory events rate	1138	0.80 (0.70–0.90)	<0.001	0.79 (0.70–0.90)	<0.001*
		OR (95% CI)	**p-value**	**RR (95% CI)**	**p-value**
mMRC ⩾2	885	1.20 (0.86–1.68)	0.293	1.12 (0.76–1.66)	0.566

HR: hazard ratio; OCS: oral corticosteroid; mMRC: modified Medical Research Council dyspnoea scale; RR: rate ratio. *: p<0.05 after controlling for 10 statistical tests for secondary outcomes performed following Holm's method [22].

results using the continuous modifiers. This was confirmed by the model fit statistics. The differences in Akaike's information criterion (AIC) and Bayesian information criterion (BIC), which take the number of parameters introduced by categorical variables into account, show no evidence of better fit (lower AIC or BIC) with the use of categorical variables (supplementary table 7).

The number of exacerbations in the baseline year showed significant effect modification with the primary outcome (time to the first exacerbation) and with the secondary outcomes of time to the first acute respiratory event and OCS course (figure 3a and supplementary table 8). The higher the exacerbation rate in the baseline year, the greater the risk reduction for a future outcome in the TT initiators compared with the DB initiators. After controlling for multiple testing, significant effect modification was found for the time to the first acute respiratory event. The HR was 0.79 (95% CI 0.66–0.95) for patients with two exacerbations compared with 0.19 (95% CI 0.04–0.87) for patients with five exacerbations in the baseline year.

The baseline BEC modified the effect of the comparison significantly for all time to the first event outcomes, except time to the first antibiotics course (figure 3b and supplementary table 9). After controlling for multiple testing, significant effect modification was found for the time to the first acute OCS course prescribed. At a count $<0.05\times10^9$ cells·L^{-1} the effect was in favour of DB (HR 1.24, 95% CI 1.01–1.53), and from a count of 0.35×10^9 cells·L^{-1} onwards TT showed a significantly greater risk-reducing effect than DB.

The level of airflow limitation, GOLD risk group, and the number of nonrespiratory drugs prescribed did not show significant effect modification with any of the study outcomes (supplementary figure 3).

Discussion

Our study shows that stepping-up from no prior maintenance therapy or LAMA monotherapy for COPD to TT was associated with a greater reduction in the risk of exacerbation, acute respiratory event and treatment failure than to a DB therapy in the study population. This association in favour of TT was significantly greater for patients with higher rates of exacerbations in the year prior to step-up. TT was also associated with a lower risk of outcome events than DB in patients with a higher BEC. However, we did not find a significant difference in benefit from TT by GOLD severity and risk group. If this observation is true, and not caused by limited power, this could be likely due to the existence of COPD phenotypes with lower responsiveness within the higher risk GOLD group D. In both unadjusted IRR analysis and multivariate outcome model analysis, rates of pneumonia in both treatment groups were similar and not significantly different.

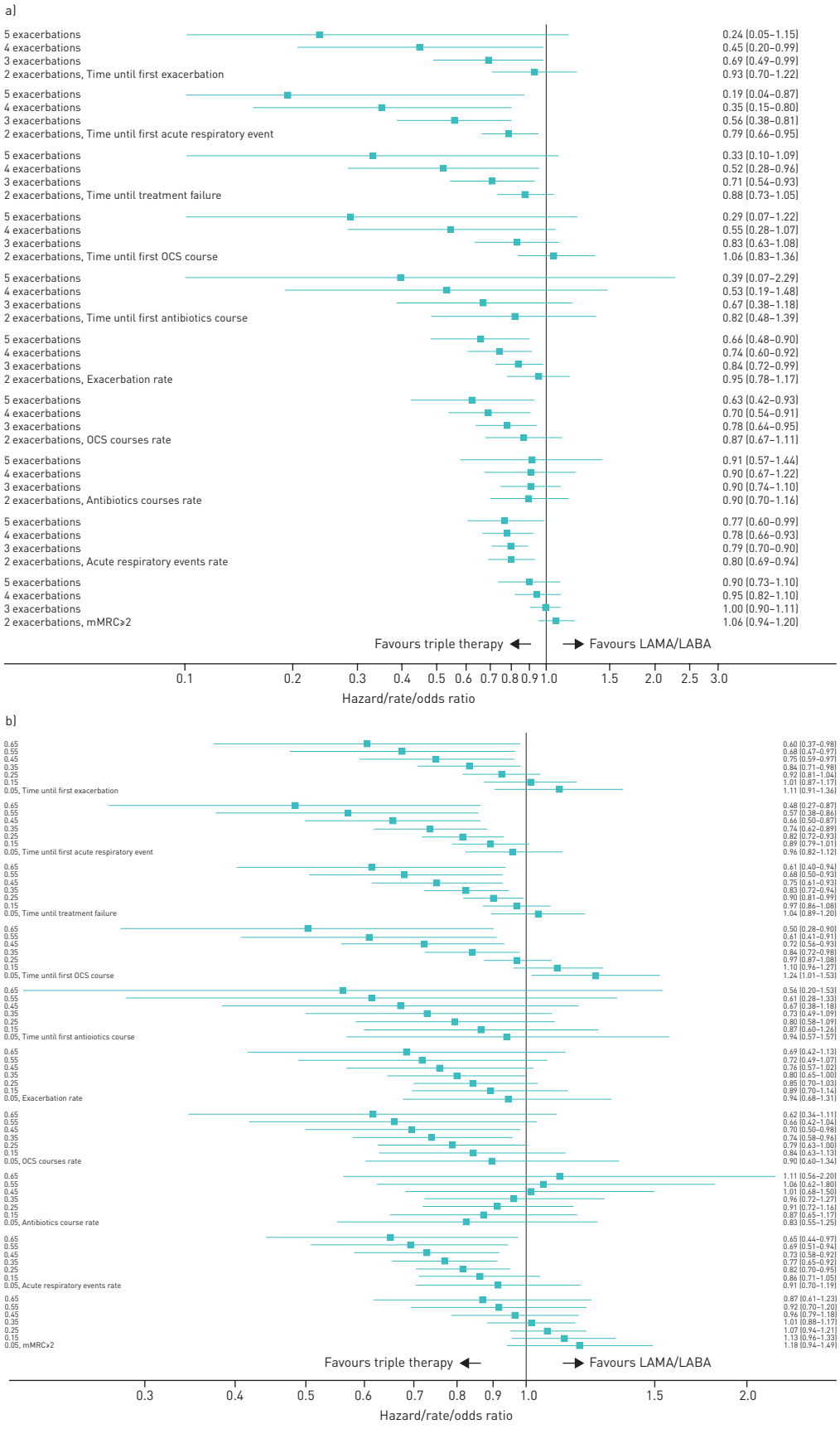

FIGURE 3 a) Effect modification by number of exacerbations in the baseline year. b) Effect modification by baseline blood eosinophil count. LAMA: long-acting muscarinic antagonist; LABA: long-acting inhaled ß-agonist.

Real-world evidence has been scarce on the comparative effectiveness of TT *versus* DB for COPD. Results from two recently published RCTs showed significantly larger reduction in rate of exacerbations with TT compared with DB therapy in selected COPD populations [9, 10]. There are however limitations inherent to clinical trials. Participants are usually younger and not as severely ill as might be expected. Thus, they are not fully representative of the real-world population the therapy would target. Also, different inclusion and exclusion criteria are used for various clinical trials which complicates interpretation of data. Therefore, it is important to supplement the findings of trials with evidence from observational studies. Our timely real-world study complements and adds to the growing body of evidence in favour of TT for some COPD patient populations.

A recent real-life study compared the treatment effectiveness of TT to DB using patients in the DACCORD cohort [24]. In contrast to our study, they reported fewer exacerbations among patients who received DB than TT. This might be due to the difference in patient population between both studies. Our study includes patients with at least two exacerbations in the baseline year while >70% patients in DACCORD had no exacerbation 6 months prior to study entry. As shown in the current study, patients with higher baseline exacerbation have a greater benefit from TT. In addition, the previous study also included patients who remained with their therapy, while we included patients who had no maintenance therapy or only LAMA monotherapy at baseline.

Our study has many strengths. Firstly, we included only a population of patients who stepped-up to either DB or TT and excluded patients with evidence of active asthma, asthma–COPD overlap syndrome, and those prescribed the therapy under study at any point during the baseline year. Some RCTs have also included patients in the DB group stepping down in their treatment from TT. The abrupt withdrawal of ICSs during randomisation in these patients could have led to COPD exacerbations and thus exaggerated the benefit of TT evident in the trial [10, 25, 26]. Secondly, we selected a homogeneous population of patients who would be eligible for TT treatment according to GOLD recommendations, *i.e.* those who had two or more exacerbations in the baseline year. Thirdly, we have examined effect modifiers to help identify possible subgroups of patients that might benefit more from a treatment. In this study, patients with a higher number of exacerbations in the baseline year and patients with a higher BEC had more benefit from TT. Fourthly, the treatment groups we compared had well-balanced baseline characteristics after matching and any residual measured confounding was accounted for in the analyses. Although we cannot fully exclude residual bias by indication due to unmeasured characteristics, the risk of residual bias from differences in COPD severity is likely to be small due to the availability of detailed information. Finally, sensitivity analyses showed that restriction of the patient population during matching did not affect results of time-to-event models. The exclusion of patients with a prior history of asthma gave similar results (or a slightly stronger effect) meaning that the observed effects were not attributable to asthma.

Some limitations however also need consideration. We may have underestimated the relative effectiveness of TT as we performed an intention-to-treat analysis without considering a step-up to TT in the DB group during follow-up, which occurred in a third of patients. Also, our study was based only on multi-inhaler TT whereas today, two fixed-dose single-inhaler TTs are available on the market [27], with a possible benefit on adherence. On the other hand, 38.4% patients on DB were initiated on a single inhaler. Another limitation of our study is that despite the large numbers of patients with COPD in the databases, we did not achieve sufficient statistical power for analysing outcomes with low incident rates, such as pneumonia. This is partly due to fact that DB has only recently been introduced as an alternative treatment option in guidelines.

In conclusion, this real-world observational study found that TT was associated with a significantly greater reduction in exacerbation risk and risk of other outcomes compared with DB in patients with a history of at least two exacerbations in the previous year. The risk reduction effect for secondary outcomes, including acute respiratory events and prescription of an acute OCS course, increased with prior exacerbation rate and baseline BEC. Our results add to the emerging body of evidence in favour of TT over DB in patients with frequent exacerbations in the management of COPD.

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References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2018. www.goldcopd.org.
2 Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Eur Respir J* 2017; 49: 1700214.
3 Suissa S. Number needed to treat in COPD: exacerbations *versus* pneumonias. *Thorax* 2013; 68: 540–543.
4 Price D, Yawn B, Brusselle G, *et al.* Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013; 22: 92–100.
5 Vestbo J, Vogelmeier C, Small M, *et al.* Understanding the GOLD 2011 strategy as applied to a real-world COPD population. *Respir Med* 2014; 108: 729–736.
6 Price D, West D, Brusselle G, *et al.* Management of COPD in the UK primary-care setting: an analysis of real-life prescribing patterns. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 889–904.
7 Singh D, Papi A, Corradi M, *et al.* Single inhaler triple therapy *versus* inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963–973.
8 Lipson DA, Barnacle H, Birk R, *et al.* FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017; 196: 438–446.
9 Papi A, Vestbo J, Fabbri L, *et al.* Extrafine inhaled triple therapy *versus* dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076–1084.
10 Lipson DA, Barnhart F, Brealey N, *et al.* Once-daily single-inhaler triple *versus* dual therapy in patients with COPD. *N Eng J Med* 2018; 378: 1671–1680.
11 Siddiqui SH, Pavord ID, Barnes NC, *et al.* Blood eosinophils: a biomarker of COPD exacerbation reduction with inhaled corticosteroids. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 3669–3676.
12 Gaebel K, McIvor RA, Xie F, *et al.* Triple therapy for the management of COPD: a review. *COPD* 2011; 8: 206–243.
13 Short PM, Williamson PA, Elder DHJ, *et al.* The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting beta-agonist therapy in COPD. *Chest* 2012; 141: 81–86.
14 Belhassen M, Nibber A, Van Ganse E, *et al.* Inappropriate asthma therapy-a tale of two countries: a parallel population-based cohort study. *NPJ Prim Care Respir Med* 2016; 26: 16076.
15 Halpin DM, Kerkhof M, Soriano JB, *et al.* Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. *Respir Res* 2016; 17: 120.
16 Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; 44: 827–836.
17 Quint JK, Müllerova H, DiSantostefano RL, *et al.* Validation of chronic obstructive pulmonary disease recording in the clinical practice research datalink (CPRD-GOLD). *BMJ Open* 2014; 4: e005540.
18 Rothnie KJ, Mullerova H, Hurst JR, *et al.* Validation of the recording of acute exacerbations of COPD in UK primary care electronic healthcare records. *PLoS One* 2016; 11: e0151357.
19 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46: 399–424.
20 Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat* 1985; 39: 33–38.
21 Guyatt GH, Juniper EF, Walter SD, *et al.* Interpreting treatment effects in randomised trials. *BMJ* 1998; 316: 690–693.
22 Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979; 6: 65–70.
23 Price DB, Baker CL, Zou KH, *et al.* Real-world characterization and differentiation of the Global Initiative for Chronic Obstructive Lung Disease strategy classification. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 551–561.
24 Buhl R, Criee CP, Kardos P, *et al.* Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 2557–2568.
25 Wedzicha JA, Banerji D, Chapman KR, *et al.* Indacaterol-glycopyrronium *versus* salmeterol-fluticasone for COPD. *N Engl J Med* 2016; 374: 2222–2234.
26 Wedzicha JA, Decramer M, Ficker JH, *et al.* Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; 1: 199–209.
27 Ga duzo S, McGovern V, Roberts J, *et al.* When to use single-inhaler triple therapy in COPD: a practical approach for primary care health care professionals. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 391–401.