OPEN ACCESS

Check for updates

Comparative effectiveness and safety of single inhaler triple therapies for chronic obstructive pulmonary disease: new user cohort study

William B Feldman,[1,2,3] Samy Suissa,[4] Aaron S Kesselheim,[1,3] Jerry Avorn,[1,3] Massimiliano Russo,[5] Sebastian Schneeweiss,[1,3] Shirley V Wang[1,3]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA 02120, USA

[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

[3]Harvard Medical School, Boston, MA, USA

[4]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montréal, McGill University, Montreal, QC, Canada

[5]Department of Statistics, Ohio State University, Columbus, OH, USA

Correspondence to: W B Feldman wbfeldman@bwh.harvard.edu or (@wbfeldman on X; ORCID 0000-0003-3467-5869)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2024;387:e080409
http://dx.doi.org/10.1136/bmj-2024-080409

Accepted: 06 November 2024

ABSTRACT

OBJECTIVE
To compare the effectiveness and safety of budesonide-glycopyrrolate-formoterol, a twice daily metered dose inhaler, and fluticasone-umeclidinium-vilanterol, a once daily dry powder inhaler, in patients with chronic obstructive pulmonary disease (COPD) treated in routine clinical practice.

DESIGN
New user cohort study.

SETTING
Longitudinal commercial US claims data.

PARTICIPANTS
New initiators of budesonide-glycopyrrolate-formoterol or fluticasone-umeclidinium-vilanterol between 1 January 2021 and 30 September 2023 who had a diagnosis of COPD and were aged 40 years or older.

MAIN OUTCOME MEASURES
In this 1:1 propensity score matched study, the main outcome measures were first moderate or severe COPD exacerbation (effectiveness) and first admission to hospital with pneumonia (safety) while on treatment. Potential confounders were measured in the 365 days before cohort entry and included in propensity scores. Hazard ratios and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards regression model.

RESULTS
The study cohort included 20 388 propensity score matched pairs of new users initiating single inhaler triple therapy. Patients who received budesonide-glycopyrrolate-formoterol had a 9% higher incidence of first moderate or severe COPD exacerbation (hazard ratio 1.09 (95% CI 1.04 to 1.14); number needed to harm 38) compared with patients receiving fluticasone-umeclidinium-vilanterol and an identical incidence of first admission to hospital with pneumonia (1.00 (0.91 to 1.10)). The hazard of first moderate COPD exacerbation was 7% higher (1.07 (1.02 to 1.12); number needed to harm 54) and the hazard of first severe COPD exacerbation 29% higher (1.29 (1.12 to 1.48); number needed to harm 97) among those receiving budesonide-glycopyrrolate-formoterol compared to fluticasone-umeclidinium-vilanterol. Prespecified sensitivity analyses yielded similar findings to the primary analysis.

CONCLUSIONS
Budesonide-glycopyrrolate-formoterol was not associated with improved clinical outcomes compared with fluticasone-umeclidinium-vilanterol. Given the added climate impact of metered dose inhalers, health systems seeking to decrease use of these products may consider steps to promote further prescribing of fluticasone-umeclidinium-vilanterol compared with budesonide-glycopyrrolate-formoterol in people with COPD.

STUDY REGISTRATION
Center for Open Science Real World Evidence Registry (https://osf.io/6gdyp/).

WHAT IS ALREADY KNOWN ON THIS TOPIC
Triple inhaler therapy is recommended for some patients with chronic obstructive pulmonary disease (COPD) and is available in the United States as budesonide-glycopyrrolate-formoterol and fluticasone-umeclidinium-vilanterol

However, the comparative effectiveness and safety of budesonide-glycopyrrolate-formoterol, a twice daily metered dose inhaler, and fluticasone-umeclidinium-vilanterol, a once daily dry powder inhaler, is unknown

WHAT THIS STUDY ADDS
In a cohort of patients with COPD treated in clinical practice, budesonide-glycopyrrolate-formoterol was not associated with improved clinical outcomes compared to fluticasone-umeclidinium-vilanterol

People receiving budesonide-glycopyrrolate-formoterol had a 9% higher hazard of moderate or severe COPD exacerbation and an identical hazard of first admission to hospital with pneumonia compared with people receiving fluticasone-umeclidinium-vilanterol

Introduction
International guidelines recommend triple inhaler treatment for some patients with chronic obstructive pulmonary disease (COPD), consisting of an inhaled corticosteroid, a long acting muscarinic antagonist, and a long acting β-agonist.[1] Two single inhalers with these triple therapies are marketed in the US: budesonide-glycopyrrolate-formoterol (Breztri Aerosphere), a twice daily metered dose inhaler, and fluticasone-umeclidinium-vilanterol (Trelegy Ellipta), a once daily dry powder inhaler. Both combinations have shown superiority over long acting muscarinic antagonist-long acting β-agonists and inhaled corticosteroid-long acting β-agonists in pivotal randomized controlled trials in select patients with COPD,[2 3] and may be prescribed according to clinical guidelines when inhaled corticosteroid-long acting muscarinic antagonist-long acting β-agonists are indicated.[1]

Many health systems worldwide have sought to reduce reliance on metered dose inhalers like budesonide-glycopyrrolate-formoterol since they contain propellants (hydrofluoroalkanes) that contribute to greenhouse gas emissions that are not

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

found in dry powder inhalers; for example, emissions associated with metered dose inhalers represent 3% of the entire carbon footprint of the National Health Service in the UK.[4 5] Yet, metered dose and dry powder formulations of single inhaler triple therapy have not been compared head-to-head in randomized controlled trials.

Research into the comparative effectiveness and safety of triple therapy in people with COPD has generated mixed findings. The adverse effect of pneumonia has been consistently shown in clinical trials and observational research of inhaled corticosteroids.[2 3 6-8] But one recent study using data from the UK found that budesonide-based triple therapy was associated with fewer admissions to hospital with pneumonia and reduced all cause mortality compared with fluticasone-based triple therapy.[9] This finding was consistent with earlier observational studies and a systematic review showing decreased pneumonia risk for patients with COPD who received budesonide-based rather than fluticasone-based regimens.[10-13] Some researchers have hypothesized that fluticasone could increase pneumonia risk due to slower airway absorption, higher lipophilicity, and more potent immunosuppressive effects.[13]

These studies, however, have not analyzed potential intraclass differences among patients receiving single inhaler triple therapy. The recent UK study included patients receiving triple therapy via separate inhalers and using a variety of inhaler types (single inhaler triple therapy was not yet available during the study period); other studies focused on dual combination rather than triple combination regimens, which may limit generalizability to patients with more severe disease. In addition, prior observational studies comparing budesonide and fluticasone analyzed short acting fluticasone propionate rather than the longer acting fluticasone furoate, which is found in fluticasone-umeclidinium-vilanterol.

In contrast to studies suggesting a potential safety advantage for budesonide-based triple therapy, other recent research has suggested reduced effectiveness. A network meta-analysis of randomized controlled trials found that budesonide-glycopyrrolate-formoterol was associated with more annual moderate or severe COPD exacerbations than fluticasone-umeclidinium-vilanterol.[14] However, this study aggregated data from trials with different inclusion criteria, with some systematically enrolling patients with more severe COPD, and thus comparisons across trials may be subject to bias. In addition, the authors did not analyze pneumonia risk in the two treatment groups because of inconsistencies in how different trials defined the outcome.

Given ongoing clinical uncertainty, we sought to compare the effectiveness and safety of budesonide-glycopyrrolate-formoterol and fluticasone-umeclidinium-vilanterol in patients with COPD who are treated in routine clinical practice. Rigorous studies of longitudinal health care data offer an important tool to help inform treatment guidelines and shape prescribing practices when randomized controlled trials have not been performed.[15] Such research may be especially valuable for developing a generalizable evidence-base in COPD because patients treated in routine clinical practice tend to be older, have more comorbidities, and include more women than patients who are generally enrolled in randomized controlled trials.[16-23]

Methods

Study cohort

The study was completed using Optum's de-identified Clinformatics Data Mart, a database of administrative health claims for members of large commercial and Medicare Advantage health plans (appendix methods). We included patients who initiated budesonide-glycopyrrolate-formoterol (exposure) or fluticasone-umeclidinium-vilanterol (referent) between 1 January 2021 and 30 September 2023 in the analysis. The study began in 2021, the first full year after budesonide-glycopyrrolate-formoterol was approved in the US; both the exposure and referent were marketed in the US throughout the study period.

All patients were required to have a diagnosis of COPD based on International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) codes (J41.x, J42.x, J43.x, J44.x). We included patients with three outpatient claims or one inpatient claim in the prior three years (positive predictive value 0.82 (95% confidence interval (CI) 0.72 to 0.89)) to capture patients with active COPD.[24] We excluded people younger than 40 years to increase the specificity of the COPD diagnosis, and we required that all patients have at least 365 days of continuous enrollment in the dataset before cohort entry. Patients with COPD who also had prior asthma diagnoses were included in the analysis. Patients were excluded if they had received either budesonide-glycopyrrolate-formoterol, fluticasone-umeclidinium-vilanterol, or an inhaled corticosteroid-long acting muscarinic antagonist-long acting β-agonist combination via separate inhalers (defined as dispensing of inhalers with ingredients from all three classes via any combination within 30 days of each other) during the 365 days before cohort entry. We also excluded patients who received both budesonide-glycopyrrolate-formoterol and fluticasone-umeclidinium-vilanterol or who received triple therapy plus another maintenance inhaler on the cohort entry date. By contrast, patients who received monotherapy (long acting muscarinic antagonist, long acting β-agonist, or inhaled corticosteroid) or dual therapy (long acting muscarinic antagonist-long acting β-agonist or inhaled corticosteroid-long acting β-agonist) during the baseline assessment period were included in the analysis.

Assessment of covariates

Potential confounders, including baseline lung disease, comorbidities, healthcare use, and medication use, were measured leading up to and including the 365 days before cohort entry and were included

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

in propensity scores (see appendix methods for a complete list of covariates included in the propensity score model). We assessed socioeconomic covariates (mean copayments, total copayments, and unique brand-to-generic prescription fills) until the day before cohort entry. Any prior history of asthma was assessed using all available data. Eosinophil levels can fluctuate over time, therefore, we used the most recent measured value in the 180 days before cohort entry. We measured demographic covariates (age, gender, race, and region), calendar year and season of index prescription, and whether the index prescription was written by a pulmonologist on the day of cohort entry (see appendix figure 1 for a timeline of covariate assessment).

Primary outcomes and follow-up

The primary outcomes were the first moderate or severe COPD exacerbation (effectiveness) and the first admission to hospital with pneumonia (safety). Moderate exacerbations were defined by fills of prednisone prescribed for 5-14 days (positive predictive value 0.73),[25] and severe COPD exacerbations by admission to hospital with a COPD diagnosis code (specified above) in the primary position (positive predictive value 0.86 based on ICD-9-CM codes; conversion to ICD-10-CM codes was performed based on clinical review).[26] If a patient met criteria for both a moderate and severe COPD exacerbation within 14 days of each other, the exacerbation was considered to be a severe exacerbation starting on the day when criteria for the exacerbation were first met. This categorization of COPD exacerbations requiring systemic steroids (moderate) versus those requiring admission to hospital (severe) is used in the Global Initiative for Chronic Obstructive Lung Disease guidelines and has been widely used in randomized controlled trials and other observational studies.[1-3 6-8 27-29] Admission to hospital with pneumonia was defined based on ICD-10-CM codes (J.09.X1, J10.xx-J18.x, A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, A54.84, B01.2, B05.2, B06.81, B77.81, J85.1, J22) in any position(positive predictive value 0.88 based on ICD-9-CM codes; conversion to ICD-10-CM codes was performed based on clinical review).[30] Patients were followed up for up to one year, the end of data, or until they had an outcome of interest, discontinued treatment (with a grace period of 60 days permitted between inhaler fills), added or switched maintenance inhalers, died, or were disenrolled from insurance.

Prespecified secondary, subgroup, and sensitivity analysis

Secondary outcomes included all cause mortality, first moderate exacerbation, first severe exacerbation, annual rate of moderate or severe exacerbations (analyzed separately and as a composite), and annual rate of admission to hospital with pneumonia. Unadjusted and adjusted results are reported for primary and secondary outcomes.

Subgroups of interest included patients who: (1) had Global Initiative for Chronic Obstructive Lung Diseasegroup E disease; (2) had at least one moderate or severe COPD exacerbation during the baseline assessment period; (3) had at least one severe COPD exacerbation during the baseline assessment period; (4) received any baseline maintenance inhaler before cohort entry; (5) had a prior diagnosis code for asthma; (6) had a diagnosis of asthma in the prior three years; (7) had eosinophil levels above 300 µL; (8) underwent spirometry during the baseline assessment period; and (9) received the initial budesonide-glycopyrrolate-formoterol or fluticasone-umeclidinium-vilanterol prescription from a pulmonologist (appendix table 1). All subgroup analyses were done for patients meeting the relevant subgroup criterion and for the remainder of patients not meeting the subgroup criterion.

To check the robustness of our findings, we conducted several prespecified sensitivity analyses. We varied the grace period permitted between prescription fills (from 60 days to 30 days and 90 days), performed an as-started analysis (with no censoring for treatment discontinuation or switching in the matched population), and excluded early events (in the first 30 days and first 60 days after cohort entry) (appendix table 2). We also varied the definitions of outcomes in our analysis (appendix methods), and we did a post-hoc sensitivity analysis limiting follow-up to 180 days.

Statistical analysis

Our primary analysis was a 1:1 propensity score matched analysis. We used nearest neighbor matching and a caliper of 0.01 on the propensity score scale. We estimated propensity scores using logistic regression, including all covariates previously mentioned without further variable selection. The targeted estimand was the average treatment effect among patients with COPD receiving budesonide-glycoypyrrolate-formoterol. In the case of missing data for covariates in our model, we used a missing indicator. For our time-to-event analyses, we estimated hazard ratios (HRs) and 95% CIs using a Cox proportional hazards regression model. We estimated absolute risk differences at 365 days, and we calculated the number needed to harm as 1/absolute risk difference when the 95% confidence interval for the risk difference excluded the null.[31] When analyzing annual rates of COPD exacerbations and admission to hospital with pneumonia in secondary analyses, we performed negative binomial regression. In prespecified sensitivity analysis, we conducted 1:1 high dimensional propensity score matching to adjust for hundreds of covariates generated through automated selection based on outpatient and inpatient diagnosis codes, procedures, and pharmacy claims.[32-34]

All analyses were completed using the Aetion Evidence Platform v4.73 (Aetion, Inc), which carries out some statistical computations using R v3.4.2, and Stata, v16.1 (StataCorp). The Aetion Evidence Platform has been used extensively in the academic literature, including in studies showing the reproducibility of real world evidence and successfully emulating

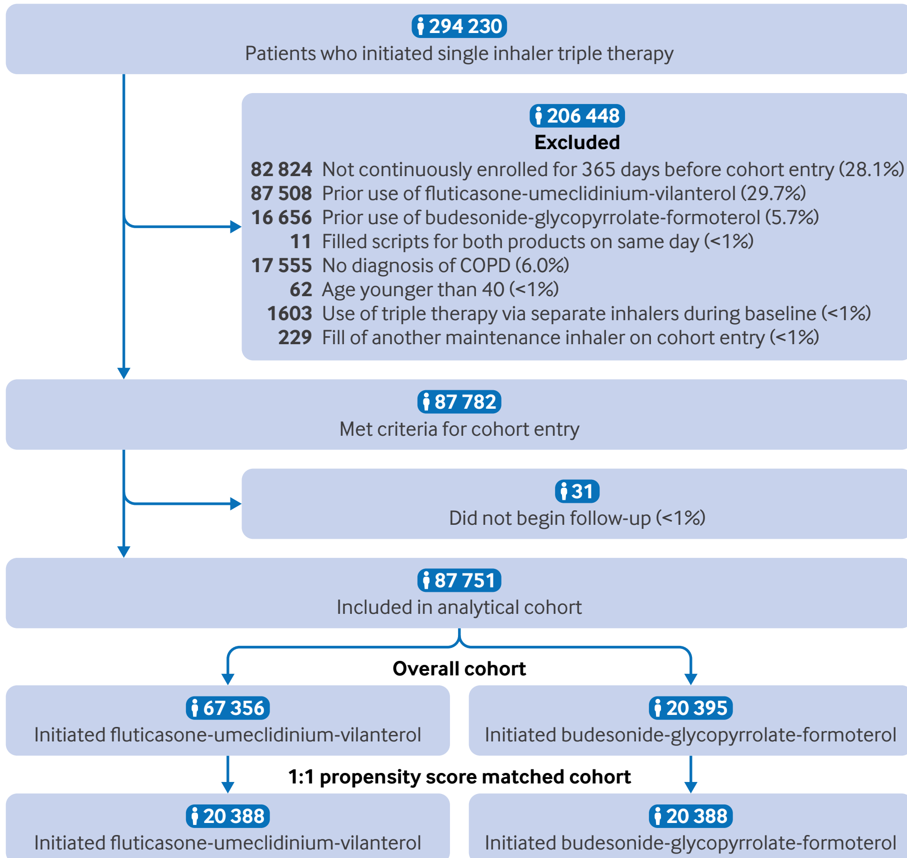

Fig 1 | Study cohort, including the number of patients excluded and the rationales for exclusion. COPD=chronic obstructive pulmonary disease

randomized controlled trials.[35 36] The platform has been through comprehensive internal quality checks and validation processes and has been directly tested against both de novo programming and other quality checked analytical workflows used by the US Food and Drug Administration Sentinel Initiative.[37] The study was approved by the Mass General Brigham Institutional Review Board (2023P000164) and the protocol was preregistered at the Center for Open Science Real World Evidence Registry (https://osf.io/6gdyp/) before the study began.

Patient and public involvement
Our dataset included only de-identified patients, and data use agreements precluded us from contacting these patients. In addition, our funding did not support patient or public involvement.

Results
The cohort included 87 751 patients (67 356 new users of fluticasone-umeclidinium-vilanterol and 20 395 new users of budesonide-glycopyrrolate-formoterol) (fig 1), from which 20 388 matched pairs were identified for the primary analysis (see table 1 for select baseline characteristics of the two treatment groups and appendix table 3 for the full set of baseline characteristics). The populations were highly overlapping in the unadjusted cohort and further aligned after matching (appendix figure 2), with mean absolute standardized differences of 0.028 before matching and 0.004 after matching.

Primary effectiveness and safety outcomes
Patients in the matched cohort had 7729 moderate or severe exacerbations during 15 229 person years of follow-up, giving a crude incidence of 507.5 events per thousand person years. Those receiving budesonide-glycopyrrolate-formoterol had a 9% increased hazard of first moderate or severe COPD exacerbation compared with patients receiving fluticasone-umeclidinium-vilanterol (HR 1.09 (95% CI 1.04 to 1.14)) (table 2). The absolute risk difference at 365 days was 2.6% (95% CI 0.8% to 4.4%) and the number needed to harm 38. Median follow-up time was 88 days (interquartile range 65 to 164 days) among patients receiving budesonide-glycopyrrolate-formoterol and 113 days (74 to 206 days) among patients receiving fluticasone-umeclidinium-vilanterol (reasons for censoring are given in appendix table 4).

A total of 1812 people had their first admission to hospital with pneumonia in the matched cohort during 17 281 person years of follow-up (crude incidence of 104.9 per 1000 person years). The hazard of first admission to hospital with pneumonia was identical between the two treatment groups (HR 1.00 (95% CI 0.91 to 1.10); absolute risk difference 0.4% (95% CI

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

Table 1 | Select baseline characteristics of patients initiating single-inhaler triple therapy in the matched cohort

Outcome	Fluticasone-umeclidinium-vilanterol (n=20 388)	Budesonide-glycopyrrolate-formoterol (n=20 388)	Absolute standardize difference
Age, mean (SD)	70.8 (9.0)	70.8 (8.9)	0.006
Female gender, no. (%)	11 354 (55.7)	11 318 (55.5)	0.004
Race/ethnic group*, no. (%):			
White	14 862 (72.9)	14 878 (73.0)	0.002
Asian	257 (1.3)	271 (1.3)	<0.001
Black	2621 (12.9)	2586 (12.7)	0.006
Hispanic	1290 (6.3)	1300 (6.4)	0.004
Region† no. (%):			
Northeast	1853 (9.1)	1874 (9.2)	0.003
Midwest	3962 (19.4)	3882 (19.0)	0.010
South	11 427 (56.0)	11 500 (56.4)	0.008
West	3142 (15.4)	3127 (15.3)	0.003
Year of cohort entry:			
2021	5665 (27.8)	5731 (28.1)	0.007
2022	7481 (36.7)	7464 (36.6)	0.002
2023	7242 (35.5)	7193 (35.3)	0.004
Season of cohort entry:			
Winter	4083 (20.0)	4081 (20.0)	<0.001
Spring	6432 (31.5)	6432 (31.5)	<0.001
Summer	5824 (28.6)	5830 (28.6)	<0.001
Fall	4049 (19.9)	4045 (19.8)	0.003
Baseline lung disease:			
Baseline GOLD group E‡ no. (%)	9919 (48.7)	9946 (48.8)	0.003
Moderate COPD exacerbations, mean (SD)	0.71 (1.15)	0.72 (1.15)	0.006
Severe COPD exacerbations, mean (SD)	0.06 (0.28)	0.06 (0.28)	0.003
SABA fills, mean (SD)	3.11 (4.19)	3.09 (4.10)	0.006
SAMA fills, mean (SD)	0.11 (0.84)	0.11 (0.79)	<0.001
SAMA-SABA fills, mean (SD)	0.75 (2.24)	0.76 (2.28)	0.006
Admission to hospital with pneumonia, mean (SD)	0.10 (0.38)	0.10 (0.39)	0.009
Respiratory antibiotic fills, mean (SD)	1.80 (2.18)	1.81 (2.20)	0.008
Any prior claim for asthma§, no. (%)	8195 (40.2)	8229 (40.4)	0.003
Home oxygen or equipment claim, no. (%)	6156 (30.2)	6213 (30.5)	0.006
CPAP or BiPAP, no. (%)	2313 (11.3)	2316 (11.4)	<0.001
Spirometry, no. (%)	8443 (41.4)	8456 (41.5)	0.001
Index prescription by pulmonologist, no. (%)	2316 (11.4)	2364 (11.6)	0.007
Smoking, no. (%)	13 780 (67.6)	13 763 (67.5)	0.002
Pulmonary rehabilitation, no. (%)	164 (0.8)	176 (0.9)	0.006
Long acting muscarinic antagonist, no. (%)	2441 (12.0)	2452 (12.0)	0.002
Long acting β-agonist, no. (%)	176 (0.9)	169 (0.8)	0.004
Inhaled corticosteroid, no. (%)	1321 (6.5)	1300 (6.4)	0.004
Long acting muscarinic antagonist-long acting β-agonist, no. (%)	2978 (14.6)	2965 (14.5)	0.002
Inhaled corticosteroid-long acting β-agonist, no. (%)	7534 (37.0)	7647 (37.5)	0.011
Chronic azithromycin, no. (%)	310 (1.5)	346 (1.7)	0.014
Roflumilast, no. (%)	251 (1.2)	250 (1.2)	<0.001
Chronic prednisone, no. (%)	1672 (8.2)	1673 (8.2)	<0.001
Events within 30 days of cohort entry, no. (%):			
Moderate or severe COPD exacerbation	3142 (15.4)	3169 (15.5)	0.004
Respiratory antibiotic fill	4647 (22.8)	4646 (22.8)	<0.001
Baseline eosinophils, no. (%):			
CBC with differential performed	13 480 (66.1)	13 480 (66.1)	<0.001
Eosinophil categories¶:			
>300/μL	1168 (5.7)	1171 (5.7)	<0.001
>100 to ≤300/μL	2840 (13.9)	2789 (13.7)	0.006
≤100/μL	1862 (9.1)	1884 (9.2)	0.003
Other co-morbidities:			
Combined comorbidity index, mean (SD)	3.87 (3.11)	3.87 (3.15)	0.001
Frailty score, mean (SD)	0.20 (0.07)	0.21 (0.07)	0.006
Obstructive sleep apnea, no. (%)	4897 (24.0)	4874 (23.9)	0.003
Hypertension, no. (%)	16 606 (81.4)	16 590 (81.4)	0.002
Diabetes, no. (%)	6297 (34.0)	7008 (34.4)	0.008
Obesity, no. (%)	5571 (27.3)	5567 (27.3)	<0.001
Coronary artery disease, no. (%)	7989 (39.2)	7934 (38.9)	0.006
Peripheral vascular disease, no. (%)	6508 (31.9)	6517 (32.0)	0.001
Venous thromboembolic disease, no. (%)	784 (3.8)	809 (4.0)	0.006
Congestive heart failure, no. (%)	5417 (26.6)	5386 (26.4)	0.003
Gastroesophageal reflux disease, no. (%)	7390 (36.2)	7359 (36.1)	0.003

(Continued)

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

Table 1 | Continued

Outcome	Fluticasone-umeclidinium-vilanterol (n=20 388)	Budesonide-glycopyrrolate-formoterol (n=20 388)	Absolute standardize difference
Renal failure, no. (%)	3246(15.9)	3244 (15.9)	<0.001
Osteoporosis, no. (%)	2218 (10.9)	2280 (11.2)	0.010
Dementia/other neurological disease, no. (%)	1584 (7.8)	1593 (7.8)	0.002
Malignancy, non-metastatic, no. (%)	3094 (15.2)	3082 (15.1)	0.002
Metastatic solid organ malignancy, no. (%)	600 (2.9)	612 (3.0)	0.003
Anxiety disorder, no. (%)	6234 (30.6)	6193 (30.4)	0.004
Depression, no. (%)	5120 (25.1)	5057 (24.8)	0.007

BiPAP=Bi-level positive airway pressure; COPD=chronic obstructive pulmonary disease; CPAP=Continuous pressure airway pressure; GOLD=Global Initiative for Chronic Obstructive Lung Disease; SABA=short acting β agonist; SAMA=short acting muscarinic antagonist; SD=standard deviation.
*Race/ethnic group was unknown or missing for 2711 patients (6.6%) in the matched cohort (1358 (6.7%) patients receiving fluticasone-umeclidinium-vilanterol and 1353 patients (6.6%) receiving budesonide-glycopyrrolate-formoterol).
†Region was unknown or missing for nine patients (<0.1%) in the matched cohort (four patients (<0.1%) receiving fluticasone-umeclidinium-vilanterol and five patients (<0.1%) receiving budesonide-glycopyrrolate-formoterol).
‡A patient has GOLD group E disease, according to recent guidelines, if they have had one COPD exacerbation requiring admission to the hospital in the prior year and/or two exacerbations requiring a course of oral steroids.
§This covariate was measured using all available data for each patient (appendix figure 1).
¶Data for eosinophils were only available for 11 714 patients (28.7%) in the matched cohort (5870 patients (28.8%) receiving fluticasone-umeclidinium-vilanterol and 5844 patients (28.7%) receiving budesonide-glycopyrrolate-formoterol).

−0.6% to 1.3%)). Median follow-up time was 105 days (interquartile range 88 to 197 days) among people receiving budesonide-glycopyrrolate-formoterol and 135 days (88 to 243 days) among those receiving fluticasone-umeclidinium-vilanterol (reasons for censoring are given in appendix table 5).

Kaplan-Meier curves for the primary effectiveness and safety analyses showed consistent effects over the 365 days of follow-up (appendix figures 3 and 4). Sensitivity analyses yielded similar findings to the primary analysis when examining the outcomes of first moderate or severe COPD exacerbation (fig 2) and first admission to hospital with pneumonia (appendix figure 5).

Moderate versus severe COPD exacerbations and all cause mortality

When separately analyzing moderate and severe COPD exacerbations, patients in the matched cohort receiving budesonide-glycopyrrolate-formoterol had a 7% increased relative hazard (HR 1.07 (95% CI 1.02 to 1.12)) and a 1.9% increase in absolute risk ((95% CI 0.1% to 3.6%); number needed to harm 54) of first moderate COPD exacerbation compared with patients receiving fluticasone-umeclidinium-vilanterol. People receiving budesonide-glycopyrrolate-formoterol had a 29% increased relative hazard (1.29 (1.12 to 1.48)) and a 1.0% increased absolute risk ((0.1% to 1.9%); number needed to harm 97) of first severe COPD exacerbation. All cause mortality was similar between the two groups (HR 1.04 (95% CI 0.93 to 1.16); absolute risk difference 0.4% (95% CI −0.6% to 1.3%)). Sensitivity analyses of these secondary endpoints are given in appendix figure 6 (moderate exacerbation), appendix figure 7 (severe exacerbation), and appendix figure 8 (all cause mortality).

Cumulative events

Patients in the matched cohort who received budesonide-glycopyrrolate-formoterol had 8% more cumulative moderate or severe COPD exacerbations (incident rate ratio 1.08 (95% CI 1.04 to 1.13)), 7% more cumulative moderate exacerbations (1.07 (1.02 to 1.12)), and 26% more cumulative severe

Table 2 | COPD exacerbations, admission to hospital with pneumonia, and all cause mortality in patients receiving single inhaler triple therapy

	Unmatched cohort			Matched cohort				
Outcomes	Fluticasone-umeclidinium-vilanterol events/1000 person years	Budesonide-glycopyrro-late-formoterol events/1000 person years	HR (95% CI)	Fluticasone-umeclidinium-vilanterol events/1000 person years	Budesonide-glycopyrrolate-formoterol events/1000 person years	HR (95% CI)	Risk difference at 365 days, % (95% CI)	Number needed to harm (95% CI)*
Moderate or severe COPD exacerbation	460.7	535.9	1.14 (1.10 to 1.18)	482.8	535.7	1.09 (1.04 to 1.14)	2.6 (0.8 to 4.4)	38
Moderate COPD exacerbation	425.6	489.8	1.13 (1.09 to 1.17)	451.1	489.6	1.07 (1.02 to 1.12)	1.9 (0.1 to 3.6)	54
Severe COPD exacerbation	45.1	54.4	1.19 (1.07 to 1.32)	41.9	54.4	1.29 (1.12 to 1.48)	1.0 (0.1 to 1.9)	97
Admission to hospital with pneumonia	106.7	106.0	0.97 (0.90 to 1.04)	103.9	106.0	1.00 (0.91 to 1.10)	0.4 (−0.6 to 1.3)	N/A
All cause mortality	79.5	71.3	0.90 (0.82 to 0.98)	68.6	71.2	1.04 (0.93 to 1.16)	0.4 (−0.5 to 1.3)	N/A

CI=confidence interval; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; N/A=not available; NNH=number needed to harm.
*NNH was calculated as 1/risk difference at 365 days of follow-up. NNH was calculated only when the 95% confidence intervals for the risk difference excluded the null.

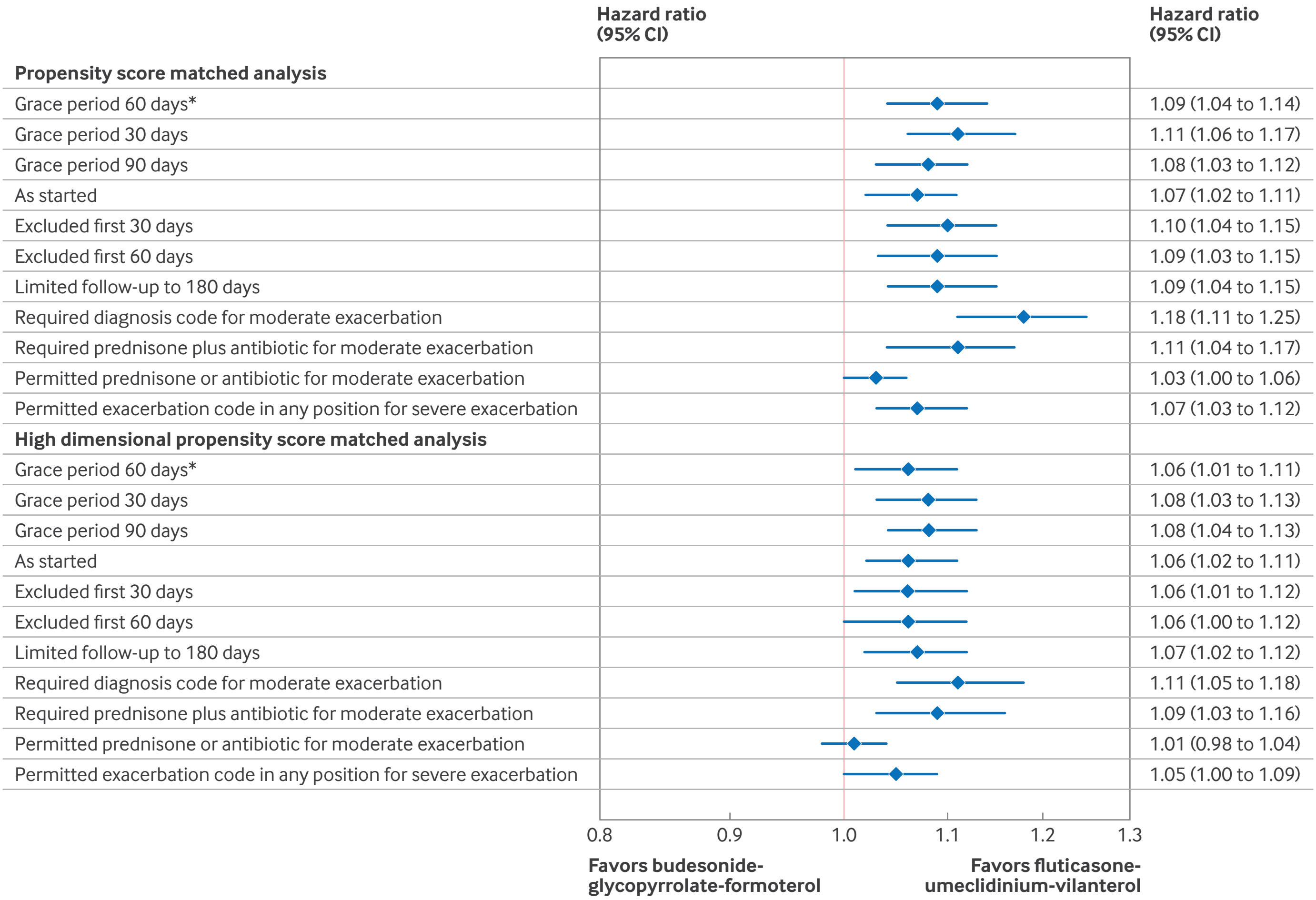

Fig 2 | Hazard ratios and 95% confidence intervals of first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in new users of budesonide-glycopyrrolate-formoterol versus fluticasone-umeclidinium-vilanterol across a range of prespecified sensitivity analyses. Patients receiving budesonide-glycopyrrolate-formoterol had a slightly higher hazard of first moderate or severe COPD exacerbation in most sensitivity analyses

exacerbations (1.26 (1.09 to 1.45)) during a maximum of one year of follow-up. Rates of cumulative admission to hospital with pneumonia were similar between the two treatment groups (1.03 (0.93 to 1.14)).

Subgroup analysis

Higher hazards of first moderate or severe COPD exacerbation in the matched cohort were observed in patients more prone to exacerbations, including people with at least one baseline moderate or severe exacerbation (HR 1.12 (95% CI 1.07 to 1.17)), at least one baseline severe exacerbation (1.15 (1.04 to 1.28)), prior baseline maintenance inhaler therapy (1.14 (1.08 to 1.20)), and eosinophil concentrations of more than 300 cells/μL (1.20 (1.02 to 1.41)) (fig 3). Such differences were not observed in patients who did not have some of the key indications for initiating triple therapy, including people with no baseline exacerbations (1.02 (0.92 to 1.14)), no baseline maintenance therapy (1.01 (0.94 to 1.10)), eosinophil counts of 100 cells/μL or lower (1.07 (0.94 to 1.22)); or eosinophil counts of between 101-300 cells/μL 1.03 (0.93 to 1.14). The risks of first admission to hospital with pneumonia among patients receiving budesonide-glycopyrrolate-formoterol versus fluticasone-umeclidinium-vilanterol were similar for all subgroups analyzed (appendix figure 9).

Discussion

Budesonide-glycopyrrolate-formoterol was associated with a slightly higher incidence of first moderate or severe COPD exacerbation and an identical incidence of first admission to hospital with pneumonia, compared with fluticasone-umeclidinium-vilanterol in patients with COPD treated in routine clinical practice. Similar findings were observed when analyzing cumulative annual exacerbations, which more fully reflect the burden of disease experienced by patients. The risks associated with use of budesonide-glycopyrrolate-formoterol were more pronounced when separately analyzing severe COPD exacerbations in a subgroup analysis—with patients receiving budesonide-glycopyrrolate-formoterol having a 29% higher hazard of first severe COPD exacerbation compared with people receiving fluticasone-umeclidinium-vilanterol. Given these outcomes and the differential climate impact

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

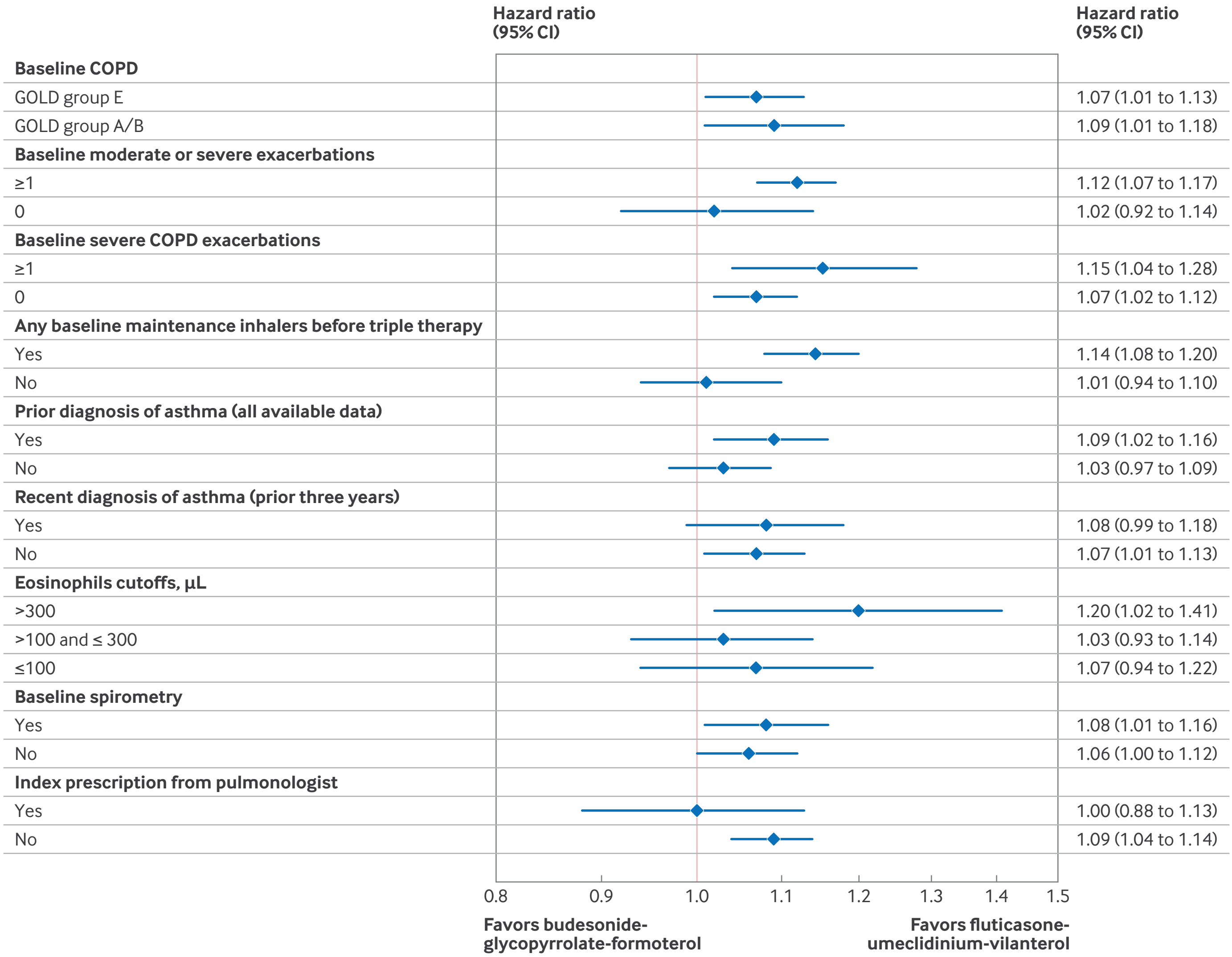

Fig 3 | Hazard ratios and 95% confidence intervals of first moderate or severe chronic obstructive pulmonary disease (COPD) exacerbation in new users of budesonide-glycopyrrolate-formoterol versus fluticasone-umeclidinium-vilanterol across a range of prespecified subgroup analyses. Patients receiving budesonide-glycopyrrolate-formoterol had a slightly higher hazard of first moderate or severe COPD exacerbation across most subgroup analyses; differences were not observed for those with milder forms of disease, including people who, during the baseline assessment period, had no COPD exacerbations, filled no scripts for maintenance inhalers, received no spirometry, and had a low eosinophil count. GOLD=Global Initiative for Chronic Obstructive Lung Disease

of single-inhaler triple therapies, health systems designing formularies and setting treatment guidelines may consider steps to increase use of fluticasone-umeclidinium-vilanterol relative to budesonide-glycopyrrolate-formoterol for patients with COPD.

Mechanistic hypotheses

Several potential reasons could explain why patients receiving fluticasone-umeclidinium-vilanterol seemed to have slightly fewer COPD exacerbations in our study. Fluticasone-umeclidinium-vilanterol is a once daily medication while budesonide-glycopyrrolate-formoterol requires twice daily dosing, and prior studies have found better adherence to inhalers with less frequent dosing.[38-41] Although we censored patients at treatment discontinuation, people receiving budesonide-glycopyrrolate-formoterol could have skipped doses at higher rates while on treatment, meaning less consistent therapeutic drug levels before censoring. Another potential explanation concerns the different techniques needed to operate the two inhalers; whereas metered dose inhalers require patients to time their breaths with actuation, dry powder inhalers only require deep inspiration. Research has suggested lower error rates with dry powder inhalers containing fluticasone-umeclidinium-vilanterol than metered dose inhalers.[42] Finally, apart from any differences in dosing or delivery devices of the two treatments, the active moieties in fluticasone-umeclidinium-vilanterol could be more effective in preventing COPD exacerbations than the active moieties in budesonide-glycopyrrolate-formoterol. Further research is needed to understand what may be driving the observed differences in our study.

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

Comparison with previous studies

The similar rates of admission to hospital with pneumonia that we observed between people receiving budesonide-glycopyrrolate-formoterol and fluticasone-umeclidinium-vilanterol stand in contrast to earlier observational studies analyzing budesonide- versus fluticasone-based therapies.[9-12] One possible explanation for our findings is that the longer acting version of fluticasone (fluticasone furoate) in single inhaler triple therapy may lead to a lower pneumonia risk than the shorter acting version (fluticasone propionate) analyzed in prior studies. Further research is needed to directly compare inhalers containing fluticasone furoate versus fluticasone propionate in patients with COPD. However, because these prior studies did not control for inhaler device type, another possibility is that the devices themselves mediated the risk of pneumonia. Although budesonide-containing dry powder inhalers for COPD are not available in the US, they are available elsewhere, which would enable comparisons of dry powder inhalers containing budesonide versus fluticasone furoate.

Implications for clinical practice

Our study may provide reassurance to health systems seeking to decrease greenhouse gas emissions by reducing use of metered dose inhalers, because the single inhaler triple therapy with the lower carbon footprint (the dry powder inhaler, fluticasone-umeclidinium-vilanterol) was also associated with slightly improved clinical outcomes. Hydrofluroalkane-134a, the propellant in budesonide-glycopyrrolate-formoterol, has 1430 times the global warming potential as carbon dioxide and contributes to greenhouse gas emissions from metered dose inhalers that are 20 times greater than the emissions from dry powder inhalers during the lifecycles of these products.[4 43] Pharmacies dispense more than 100 million metered dose inhalers in the US each year, representing nearly 90% of all inhalers prescribed, with emissions equivalent to approximately 550 000 gas fueled cars driven annually.[4 43-45] Although dry powder inhalers are associated with other environmental impacts (eg, fossil depletion and marine ecotoxic effects),[46] the global warming potential of metered dose inhalers has prompted efforts by many health systems worldwide to increase use of dry powder inhalers, with some countries, including Sweden, Denmark, and Japan, reaching rates of dry powder inhaler prescribing exceeding 50%.[4 5] As health care systems move toward lower carbon inhalers, data for the comparative effectiveness and safety of these products are important to help ensure that patients with chronic lung disease receive optimal, evidence based care.

Limitations

This study has several important limitations. Firstly, while the distributions of characteristics among people receiving the two single inhaler triple therapies were highly overlapping even before matching, the possibility of some residual confounding cannot be ruled out. Metered dose inhalers may be preferred in patients with frailty and poor inspiratory force, and such patients could have been more likely to have exacerbations in follow-up. However, under reasonable assumptions for the prevalence of suboptimal peak inspiratory force, patients receiving budesonide-glycopyrrolate-formoterol would need to be approximately 1.8 times as likely to have suboptimal peak inspiratory force. In addition, patients with suboptimal inspiratory force would need to have approximately 1.8 times the risk of experiencing a moderate or severe COPD exacerbation (appendix figure 10).[47] Yet, studies suggest that patients receiving metered dose inhalers in clinical practice are only slightly more likely to have suboptimal peak inspiratory force and only slightly more likely to experience exacerbations.[48] We adjusted for numerous covariates associated with frailty and predisposition for exacerbations, including a validated frailty index.[49] We also observed similar results when using high dimensional propensity scoring matching, which adjusts for hundreds of empirically selected covariates that may serve as proxies for confounders that are not directly measured. Because some insurance formularies in the US cover only one triple inhaler, the therapy prescribed may be dictated more by formulary design than clinical preference. Still, we cannot exclude the possibility of residual confounding as an explanation for our observation that patients receiving budesonide-glycopyrrolate-formoterol had a 9% higher hazard of moderate or severe COPD exacerbation compared with patients receiving fluticasone-umeclidinium-vilanterol.

Secondly, although we analyzed perhaps the most important safety signal related to inhaled corticosteroids (admission to hospital with pneumonia), we did not analyze other known risks such as oral thrush, osteoporosis, and adrenal insufficiency. Thirdly, rates of non-persistence were high and follow-up time was short, reflecting the reality of routine clinical practice in which patients with COPD often choose to stop taking recommended treatments.[50-53] Fourthly, because the study was completed using healthcare claims, we did not have data for daily inhaler use and technique and thus we were unable to draw further conclusions about the source of observed differences in outcomes between patients receiving budesonide-glycopyrrolate-formoterol and fluticasone-umeclidinium-vilanterol. Fifthly, data for eosinophil concentrations were only available for a subset of patients. Sixthly, the study included a broad range of patients with commercial insurance and Medicare Advantage but may not generalize to other groups in the US, particularly the uninsured. Seventhly, we included patients with COPD in our study who also had prior asthma diagnosis codes. Subgroup analyses showed similar findings to the primary analysis when analyzing patients with COPD with no asthma diagnoses in the three years before cohort entry. However, inclusion of these patients, while perhaps increasing the generalizability of our study, could have led to possible treatment heterogeneity among patients with COPD. Eighthly, while we observed that the effect size for severe exacerbations in the matched cohort (HR 1.29 (95% CI 1.12 to 1.48)) became larger after confounding adjustment, this finding occurred in the context of our exploration of multiple subgroups. Therefore, further research is needed to clarify whether this is a chance finding or whether there may be a stronger effect for more severe outcomes. Finally, our study analyzed the only two single agent triple inhalers on the US market; additional studies are needed of other triple therapies available in different parts of the world and of metered dose versus dry powder inhalers across other therapeutic classes, both for the treatment of asthma and COPD.

Conclusions

In a cohort of patients with COPD treated in routine practice, people receiving fluticasone-umeclidinium-vilanterol did not have improved clinical outcomes compared with people receiving budesonide-glycopyrrolate-formoterol. Dry powder inhalers may not be suitable for all patients with COPD. However, fluticasone-umeclidinium-vilanterol represents a safe and effective alternative to budesonide-glycopyrrolate-formoterol for health systems seeking to decrease use of metered dose inhalers.

Contributors: All authors contributed to the conception and design of the manuscript; WBF, MR, and SVW contributed to the statistical analysis; all authors contributed to the interpretation of the data; WBF drafted the manuscript; all authors contributed to critical revision of the manuscript; SSu, ASK, JA, SSc, and SVW supervised the research; WBF obtained the funding. WBF had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This work was funded by a grant (National Heart, Lung, and Blood Institute K08HL163246) to WBF. The funders had no role in the design and conduct of the study; collection, management, analysis, interpretation, of the data; review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests:All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: funding from the National Heart, Lung, and Blood Institute; outside the submitted work, WBF serves as a consultant for Alosa Health and as an expert witness in litigation against inhaler manufacturers. He previously served as a consultant for Aetion. SS attended advisory committee meetings for Atara, Novartis and Panalgo, and received speaking fees from Covis Pharma and Novartis. SS is participating in investigator-initiated grants to the Brigham and Women's Hospital from Boehringer Ingelheim, Takeda, and UCB unrelated to the topic of this study. He owns equity in Aetion Inc, a software manufacturer. He is an advisor to Temedica GmbH, a patient-oriented data generation company. His interests were declared, reviewed, and approved by the Brigham and Women's Hospital in accordance with their institutional compliance policies. SVW has been a consultant for Veracity Healthcare Analytics, Exponent Inc, and MITRE a federally funded research and development center for the Centers for Medicare and Medicaid for unrelated work.

Ethical approval: The study was approved by the Mass General Brigham Institutional Review Board (2023P000164).

Data sharing: No additional data available. Data use agreements do not permit sharing of source data or derivative analytic cohorts.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The work will be disseminated to policymakers, professional societies, and lay audiences via press releases, social media engagement, and a companion blog post.

Provenance and peer review: Not commissioned; externally peer reviewed.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

1 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD: 2024 Report. Available from: https://goldcopd.org/2024-gold-report/. Accessed February 15, 2024.
2 Rabe KF, Martinez FJ, Ferguson GT, et al, ETHOS Investigators. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020;383:35-48. doi:10.1056/NEJMoa1916046
3 Lipson DA, Barnhart F, Brealey N, et al, IMPACT Investigators. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671-80. doi:10.1056/NEJMoa1713901
4 Rabin AS, Harlan EA, Ambinder AJ. Small devices, big problems: addressing the global warming potential of metered-dose inhalers. *Ann Am Thorac Soc* 2022;19:1090-2. doi:10.1513/AnnalsATS.202202-131VP
5 Bell JPRA, Khezrian M, Kocks JW, Usamani OS. An assessment of pressurized metered-dose inhaler use in countries in europe and the rest of the world. *Am J Respir Crit Care Med* 2023;207:A6315.
6 Wedzicha JA, Banerji D, Chapman KR, et al, FLAME Investigators. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016;374:2222-34. doi:10.1056/NEJMoa1516385
7 Feldman WB, Avorn J, Kesselheim AS, Gagne JJ. Chronic obstructive pulmonary disease exacerbations and pneumonia hospitalizations among new users of combination maintenance inhalers. *JAMA Intern Med* 2023;183:685-95. doi:10.1001/jamainternmed.2023.1245
8 Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. *Chest* 2019;155:1158-65. doi:10.1016/j.chest.2019.03.005
9 Suissa S, Dell'Aniello S, Ernst P. Fluticasone-based versus budesonide-based triple therapies in copd: real-world comparative effectiveness and safety. *COPD* 2022;19:109-17. doi:10.1080/15412555.2022.2035705
10 Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax* 2013;68:1029-36. doi:10.1136/thoraxjnl-2012-202872
11 Suissa S, Dell'Aniello S, Ernst P. Comparing initial LABA-ICS inhalers in COPD: Real-world effectiveness and safety. *Respir Med* 2021;189:106645. doi:10.1016/j.rmed.2021.106645
12 Wang MT, Lai JH, Huang YL, et al. Comparative effectiveness and safety of different types of inhaled long-acting β_2-agonist plus inhaled long-acting muscarinic antagonist vs inhaled long-acting β_2-agonist plus inhaled corticosteroid fixed-dose combinations in COPD a propensity score-inverse probability of treatment weighting cohort study. *Chest* 2021;160:1255-70. doi:10.1016/j.chest.2021.05.025
13 Lodise TP, Li J, Gandhi HN, O'Brien G, Sethi S. Intraclass difference in pneumonia risk with fluticasone and budesonide in COPD: a systematic review of evidence from direct-comparison studies. *Int J Chron Obstruct Pulmon Dis* 2020;15:2889-900. doi:10.2147/COPD.S269637
14 Ismaila AS, Haeussler K, Czira A, et al. Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) triple therapy compared with other therapies for the treatment of COPD: a network meta-analysis. *Adv Ther* 2022;39:3957-78. doi:10.1007/s12325-022-02231-0
15 Gershon AS, Lindenauer PK, Wilson KC, et al. Informing healthcare decisions with observational research assessing causal effect. an official american thoracic society research statement. *Am J Respir Crit Care Med* 2021;203:14-23. doi:10.1164/rccm.202010-3943ST
16 Herland K, Akselsen JP, Skjønsberg OH, Bjermer L. How representative are clinical study patients with asthma or COPD for a larger "real life" population of patients with obstructive lung disease? *Respir Med* 2005;99:11-9. doi:10.1016/j.rmed.2004.03.026
17 Travers J, Marsh S, Caldwell B, et al. External validity of randomized controlled trials in COPD. *Respir Med* 2007;101:1313-20. doi:10.1016/j.rmed.2006.10.011
18 Walker S, Fingleton J, Weatherall M, Beasley R. Limited generalisability of UPLIFT findings to clinical practice. *Thorax* 2013;68:1066-7. doi:10.1136/thoraxjnl-2013-203724

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.

19 Scichilone N, Basile M, Battaglia S, Bellia V. What proportion of chronic obstructive pulmonary disease outpatients is eligible for inclusion in randomized clinical trials?*Respiration* 2014;87:11-7. doi:10.1159/000355082
20 Halpin DM, Kerkhof M, Soriano JB, Mikkelsen H, Price DB. Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. *Respir Res* 2016;17:120. doi:10.1186/s12931-016-0433-5
21 Woodcock A, Boucot I, Leather DA, et al. Effectiveness *versus* efficacy trials in COPD: how study design influences outcomes and applicability. *Eur Respir J* 2018;51:1701531. doi:10.1183/13993003.01531-2017
22 Çolak Y, Nordestgaard BG, Lange P, Vestbo J, Afzal S. Prognosis of patients with chronic obstructive pulmonary disease not eligible for major clinical trials. *Am J Respir Crit Care Med* 2022;206:271-80. doi:10.1164/rccm.202110-2441OC
23 Krishnan JK, Calverley PMA. Understanding the people excluded from chronic obstructive pulmonary disease clinical trials. *Am J Respir Crit Care Med* 2022;206:235-6. doi:10.1164/rccm.202204-0688ED
24 Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. *COPD* 2009;6:388-94. doi:10.1080/15412550903140865
25 Rothnie KJ, Müllerová 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. doi:10.1371/journal.pone.0151357
26 Stein BD, Bautista A, Schumock GT, et al. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations. *Chest* 2012;141:87-93. doi:10.1378/chest.11-0024
27 Feldman WB, Kesselheim AS, Avorn J, Russo M, Wang SV. Comparative effectiveness and safety of generic versus brand-name fluticasone-salmeterol to treat chronic obstructive pulmonary disease. *Ann Intern Med* 2023;176:1047-56. doi:10.7326/M23-0615
28 Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. *Lancet Respir Med* 2018;6:855-62. doi:10.1016/S2213-2600(18)30368-0
29 Suissa S, Dell'Aniello S, Ernst P. Comparative effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: cohort study in real-world clinical practice. *Chest* 2020;157:846-55. doi:10.1016/j.chest.2019.11.007
30 Kern DM, Davis J, Williams SA, et al. Validation of an administrative claims-based diagnostic code for pneumonia in a US-based commercially insured COPD population. *Int J Chron Obstruct Pulmon Dis* 2015;10:1417-25. doi:10.2147/COPD.S83135
31 Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319:1492-5. doi:10.1136/bmj.319.7223.1492
32 Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009;20:512-22. doi:10.1097/EDE.0b013e3181a663cc
33 Rassen JA, Schneeweiss S. Using high-dimensional propensity scores to automate confounding control in a distributed medical product safety surveillance system. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):41-9. doi:10.1002/pds.2328
34 Schneeweiss S. Automated data-adaptive analytics for electronic healthcare data to study causal treatment effects. *Clin Epidemiol* 2018;10:771-88. doi:10.2147/CLEP.S166545
35 Wang SV, Sreedhara SK, Schneeweiss S, Initiative R, REPEAT Initiative. Reproducibility of real-world evidence studies using clinical practice data to inform regulatory and coverage decisions. *Nat Commun* 2022;13:5126. doi:10.1038/s41467-022-32310-3
36 Wang SV, Schneeweiss S, Franklin JM, et al, RCT-DUPLICATE Initiative. Emulation of Randomized Clinical Trials With Nonrandomized Database Analyses: Results of 32 Clinical Trials. *JAMA* 2023;329:1376-85. doi:10.1001/jama.2023.4221
37 Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and Reproducibility of Observational Cohort Studies Using Large Healthcare Databases. *Clin Pharmacol Ther* 2016;99:325-32. doi:10.1002/cpt.329
38 De Keyser H, Vuong V, Kaye L, Anderson WC3rd, Szefler S, Stempel DA. Is once versus twice daily dosing better for adherence in asthma and chronic obstructive pulmonary disease? *J Allergy Clin Immunol Pract* 2023;11:2087-2093.e3. doi:10.1016/j.jaip.2023.03.053
39 Averell CM, Stanford RH, Laliberté F, Wu JW, Germain G, Duh MS. Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs. *J Asthma* 2021;58:102-11. doi:10.1080/02770903.2019.1663429
40 Mannino D, Bogart M, Wu B, et al. Adherence and persistence to once-daily single-inhaler versus multiple-inhaler triple therapy among patients with chronic obstructive pulmonary disease in the USA: A real-world study. *Respir Med* 2022;197:106807. doi:10.1016/j.rmed.2022.106807
41 Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respir Med* 2011;105:435-41. doi:10.1016/j.rmed.2010.09.006
42 Kerwin EM, Preece A, Brintziki D, Collison KA, Sharma R. ELLIPTA Dry Powder Versus Metered-Dose Inhalers in an Optimized Clinical Trial Setting. *J Allergy Clin Immunol Pract* 2019;7:1843-9. doi:10.1016/j.jaip.2019.02.023
43 Huffman P, Hough E. A Hidden Contributor to Climate Change — Asthma Inhalers. Available from: https://www.commonwealthfund.org/blog/2023/hidden-contributor-climate-change-asthma-inhalers. Accessed February 15, 2024.
44 Environmental Protection Agency. Market Characterization of the U.S. Metered Dose Inhaler Industry. Available from: https://www.epa.gov/sites/default/files/2021-03/documents/epa-hq-oar-2021-0044-0002_attachment_1-mdis.pdf. Accessed February 15, 2024.
45 Environmental Protection Agency. Greenhouse Gas Equivalencies Calculator. Available from: https://www.epa.gov/energy/greenhouse-gas-equivalencies-calculator. Accessed February 15, 2024.
46 Jeswani HK, Azapagic A. Life cycle environmental impacts of inhalers. *J Clean Prod* 2019;237:117733. doi:10.1016/j.jclepro.2019.117733.
47 Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;15:291-303. doi:10.1002/pds.1200
48 Mahler DA, Niu X, Deering KL, Dembek C. Prospective evaluation of exacerbations associated with suboptimal peak inspiratory flow among stable outpatients with COPD. *Int J Chron Obstruct Pulmon Dis* 2022;17:559-68. doi:10.2147/COPD.S353441
49 Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in medicare data: development and validation of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci* 2018;73:980-7. doi:10.1093/gerona/glx229
50 Blackstock FC, ZuWallack R, Nici L, Lareau SC. Why don't our patients with chronic obstructive pulmonary disease listen to us? the enigma of nonadherence. *Ann Am Thorac Soc* 2016;13:317-23. doi:10.1513/AnnalsATS.201509-600PS
51 Sulaiman I, Cushen B, Greene G, et al. Objective assessment of adherence to inhalers by patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;195:1333-43. doi:10.1164/rccm.201604-0733OC
52 Janjua S, Pike KC, Carr R, Coles A, Fortescue R, Batavia M. Interventions to improve adherence to pharmacological therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev* 2021;9:CD013381.
53 Bhattarai B, Walpola R, Mey A, Anoopkumar-Dukie S, Khan S. Barriers and Strategies for improving medication adherence among people living with COPD: a systematic review. *Respir Care* 2020;65:1738-50. doi:10.4187/respcare.07355

Web appendix: Supplemental appendix

BMJ: first published as 10.1136/bmj-2024-080409 on 30 December 2024. Downloaded from https://www.bmj.com/ on 13 January 2025 at INSERM Consortia. Protected by copyright.