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ORIGINAL RESEARCH

Comparative Effectiveness and Safety of Fluticasone-Umeclidinium-Vilanterol and Beclomethasone-Glycopyrronium-Formoterol Single-Inhaler Triple Therapies for COPD: Real-World Observational Study

Mathew Cherian[1,2], Sophie Dell'Aniello[2], Samy Suissa[2,3]

[1]Department of Medicine, Respiratory Division, McGill University, Montreal, Quebec, Canada; [2]Centre for Clinical Epidemiology, Lady Davis Institute-Jewish General Hospital, Montreal, Quebec, Canada; [3]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Correspondence: Samy Suissa, Centre for Clinical Epidemiology, Lady Davis Institute-Jewish General Hospital, 3755 Cote Ste-Catherine, H-461, Montreal, Québec, H3T 1E2, Canada, Email samy.suissa@mcgill.ca

Purpose: Multiple guidelines recommend single-inhaler triple therapy (SITT) for some patients with COPD. The first two SITTs approved for COPD were beclomethasone-glycopyrronium-formoterol (BEGF, twice daily) and fluticasone-umeclidinium-vilanterol (FUV, once daily). No study has compared the effectiveness and safety of these SITTs on major outcomes.

Patients and Methods: We identified a cohort of patients with COPD, 40 years of age or older, from the United Kingdom's Clinical Practice Research Datalink. The patients who initiated treatment with FUV or BEGF were compared on the incidence of moderate or severe COPD exacerbations, and of pneumonia, over one year, after balancing baseline characteristics by propensity score weighting.

Results: The study cohort included 34,825 initiators of FUV and 39,288 initiators of BEGF, well balanced after weighing. The adjusted hazard ratio (HR) of a first moderate or severe exacerbation with FUV compared with BEGF was 0.91 (95% CI: 0.89–0.93), while for severe exacerbation it was 0.92 (95% CI: 0.86–0.97), corresponding to 27.9 fewer subjects with a moderate or severe exacerbation and 1.0 fewer with a severe exacerbation per 100 treated with FUV for one year. The HR of pneumonia requiring hospitalisation, comparing FUV with BEGF, was 1.06 (95% CI 0.99–1.13), over all patients. It was 1.14 (95% CI 1.06–1.24) among those classified as GOLD Group E, and 1.10 (95% CI 1.02–1.19) among those with a blood eosinophil count $\leq$ 300 cells/μL, corresponding to increases of 1.7 and 1.0 more subjects with a severe pneumonia per 100 treated with FUV for one year, respectively.

Conclusion: In a real-world clinical practice setting of COPD treatment, initiating triple therapy with FUV was associated with a lower incidence of moderate and severe exacerbations than with BEGF. On the other hand, the incidence of a severe pneumonia requiring hospitalisation was higher with FUV among GOLD Group E subjects or those whose blood eosinophil count is not elevated.

Keywords: cohort studies, COPD exacerbations, new-user design, observational study, pneumonia

Introduction

Multiple international thoracic societies and respiratory bodies have issued guidelines or reports that recommend some patients with COPD be treated with triple inhaler therapy, which consist of a long-acting muscarinic antagonist (LAMA), a long-acting beta agonist (LABA), and an inhaled corticosteroid (ICS).[1,2] Three different single-inhaler triple therapy (SITT) agents are approved for use in COPD in several countries. The first is beclomethasone-glycopyrronium-formoterol (BEGF, Trimbow©), a twice daily therapy available as a metered dose inhaler (MDI) or a dry power inhaler (DPI). The others are fluticasone-umeclidinium-vilanterol (FUV, Trelegy©), a once daily DPI, and budesonide-glycopyrronium-formoterol (BUGF, Trixeo©), available as a twice daily MDI. Triple therapy is recommended for

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patients with a history of multiple exacerbation and as initial therapy for those who also have a blood eosinophil count >300 cells/μL.[1]

All three inhalers were shown in randomized trials to be effective at reducing the frequency of exacerbations compared with dual bronchodilator therapy (LAMA-LABA) among patients with COPD who have frequent exacerbations.[3–5] Higher risks of pneumonia with the triple inhaler were observed in two of the trials,[3,5] but not in the other.[4] However, data on whether the three SITT options differ in their effectiveness and safety are ambiguous. Two meta-analyses of the randomized trials, using indirect comparisons across trials, did not find differences in exacerbation reduction among the varying combinations of triple therapy inhalers.[6,7] Three recent observational studies, based on US commercial claims databases, conducted direct comparisons between FUV and BUGF.[8–10] All three studies reported that FUV was associated a lower incidence of moderate or severe exacerbation, compared with BUGF. Yet, only one of the three evaluated pneumonia safety, finding no difference in hospital admissions for pneumonia.[8] However, none of these studies could investigate BEGF as it is not currently available in the US.

In view of the signals that triple inhalers may vary in their effects, we assessed the comparative effectiveness of FUV and BEGF, both available and prescribed in the United Kingdom for years, at reducing COPD exacerbations. We also assessed their comparative safety on the incidence of pneumonia, all in the context of real-world clinical practice.

Methods

Data Source

We used the Clinical Practice Research Datalink (CPRD), a primary care database from the United Kingdom (UK) that contains primary care medical records for over 50 million people enrolled from over 1800 practices. The CPRD includes demographic data, lifestyle factors and medical diagnoses, using the Systematized Medical Nomenclature for Medicine–Clinical Terminology (SNOMED CT) and Read classifications. Prescriptions are transcribed using the UK Prescription Pricing Authority Dictionary, as well as laboratory results and lung function measurements for many patients with COPD. The CPRD can be linked to the Hospital Episodes Statistics (HES) database for over 85% of the practices, which uses ICD-10 coding for diagnoses. The recorded information on medications and diagnoses has been validated and shown to be of high quality.[11–14]

Study Design

The target trial for this observational study was patients diagnosed with COPD who were deemed to need to increase their treatment to triple therapy, given as a single-inhaler triple agent available in the UK as of the end of 2017. Thus, we first formed a base cohort of all patients from the CPRD with a clinical diagnosis of COPD, who subsequently received a prescription for a single-inhaler triple agent from September 2014 to March 2021. The database of patients with COPD from which this study is based was used for several studies of COPD therapy, with no overlap with the present study which addresses an entirely novel question.[15–19] To increase the likelihood of a valid COPD diagnosis, patients had to be 40 years of age or older at their first COPD diagnosis. The two single-inhaler triple agents available in the UK during the study period were beclomethasone-glycopyrronium-formoterol (BEGF), first used in September 2017, and fluticasone-umeclidinium-vilanterol (FUV), first used in January 2018. We did not study BUGF as it was first used in the UK in March 2021. The cohort was limited to those practices linkable to the HES hospitalization database.

The study cohort employed an incident new-user design, a design that emulates a trial, with cohort entry taken as the date of the first prescription for each of the two triple agents.[20,21] A one-year baseline period prior to the study cohort entry date was required to measure covariates and define treatment initiation. Subjects could have received a LABA, LAMA or ICS, or any combination, but not a triple combination in multiple inhalers during the baseline year. Subjects were followed for up to one year from the date of study cohort entry, until death, 31 March 2021, or the end of coverage in the practice, whichever occurred first.

Outcome Events

The primary effectiveness outcome was the first moderate or severe COPD exacerbation to occur after cohort entry. A severe exacerbation was defined as a hospitalization for COPD, as per GOLD 2025 recommendations, and a moderate exacerbation by a new prescription for prednisolone. The primary safety outcome was severe pneumonia, defined as the occurrence of the first hospitalization for community-acquired pneumonia. The diagnostic and medication codes employed to measure these outcomes have been validated and used in several studies using the CPRD.[15,16,22–24]

Covariates

Several covariates were used to balance the two treatment arms, including lifestyle factors, clinical diagnoses, and prescriptions, identified from CPRD and HES data. Age, sex, body mass index (BMI), smoking status and alcohol abuse were measured at or prior to cohort entry. The severity of COPD at treatment initiation was assessed by the number of prior exacerbations (measured during the one-year baseline period) as well as most recent measures of dyspnea, FEV_1, and blood eosinophil count prior to cohort entry. Dyspnea was measured using the mMRC, CAT score or as clinically noted dyspnea symptoms, stratified as none-mild or moderate-severe.[25] The percent predicted FEV_1 measurement, generally post-bronchodiltor,[26] was calculated from the absolute FEV_1 value using age, sex and height, in race-neutral equations.[27] Baseline co-morbidity, including asthma, pneumonia requiring hospitalisation, cardiovascular and renal disease, cancer, diabetes, as well as the use of antihypertensives, oral anticoagulants, antiarrhythmic, aspirin, statin, antidiabetics, proton-pump inhibitors, NSAIDs, and opioids in the year prior to cohort entry, was measured using clinical diagnoses, hospitalizations and prescriptions.

Data Analysis

The propensity score of treatment initiation with FUV versus BEGF was estimated by logistic regression using all covariates. To balance the treatment arms, fine stratification weights were computed by dividing the propensity score into its 100 percentile strata and calculating separate weights for the FUV and BEGF arms.[28] The standardized mean difference for each covariate was computed to assess the comparability of the two treatment arms.

A weighted Cox proportional hazard regression model with a robust variance estimator was used in an as-treated analysis to estimate the hazard ratio (HR) of COPD exacerbation and pneumonia, comparing initiators of FUV with initiators of BEGF inhalers, during the first year after initiation. The as-treated analysis was based on continuous treatment, defined by the durations of successive prescriptions of the initial inhaler, with a maximal 30-day grace period between the end and start of successive prescription dates. The end of continuous treatment was defined as the end of the 30-day grace period if no prescription was written or by a switch to the other inhaler.

The data analysis for the effectiveness and safety outcomes was stratified by the GOLD group E classification (two or more moderate or one severe exacerbation) or not (one or less moderate exacerbation) during the baseline year. The analysis was also stratified by an asthma diagnosis, FEV_1 at 50% predicted, and blood eosinophil count at >300 cells/μL, all prior to cohort entry. All stratified analyses were performed using an interaction term between these factors and the treatment.

Sensitivity analyses included an intention-to-treat analysis, irrespective of the treatment duration, over the one-year follow-up. Second, the grace period between prescriptions to define continuous use for the as-treated analyses was set at 15 and 45 days. Third, we used an alternative definition for a moderate or severe exacerbation, validated in the CPRD.[22] It is defined by an outpatient or inpatient diagnosis of lower respiratory tract infection or acute exacerbation of COPD, or a prescription of COPD-specific antibiotics combined with an oral corticosteroid, or a record of two or more respiratory symptoms of acute exacerbation of COPD along with a prescription of COPD-specific antibiotics and/or an oral corticosteroid on the same day. All analyses were conducted using SAS version 9.4. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 23-002846) and the Research Ethics Committee of the Jewish General Hospital (JGH Protocol # 2024-3847), Montreal, Canada.

Results

The study cohort included 39,288 initiators of BEGF and 34,825 initiators of FUV (Figure 1). After weighing on the propensity score, the two groups were similar on all baseline characteristics (Table 1). The mean age at initiation was 71 years, and 49% were female, for both arms. Medication use patterns prior to cohort entry and baseline comorbidities were similar in both arms, with 25% also having an asthma diagnosis. There were 46% who had had two or more moderate or severe exacerbations, with 49% classified as GOLD Group E (two or more moderate or one severe exacerbation), in the year prior to cohort entry. Spirometry was available for 89% of subjects, with FEV_1% predicted similar in both groups (58%), and blood eosinophils counts, available for 88% of subjects, similar for both groups (20% had >300 cells/μL). The mean FEV_1 in liters, before weighing, was 1.41 (standard deviation (sd) 0.56) and 1.33 (sd 0.56) for FUV and BEGF respectively, while the mean FEV_1/FVC ratio was 58.6 (sd 15.3) and 57.8 (sd 15.7) for FUV and BEGF respectively. Mean duration of continuous as-treated use was equal in the two arms at 6.7 months.

The one-year cumulative incidence of a first moderate or severe exacerbation was 60.54% on FUV and 64.12% on BEGF (Figure 2). The corresponding HR of a moderate or severe exacerbation with FUV compared with BEGF was 0.91 (95% CI: 0.89–0.93) (Table 2). The reduction in moderate or severe exacerbation in patients treated with FUV compared

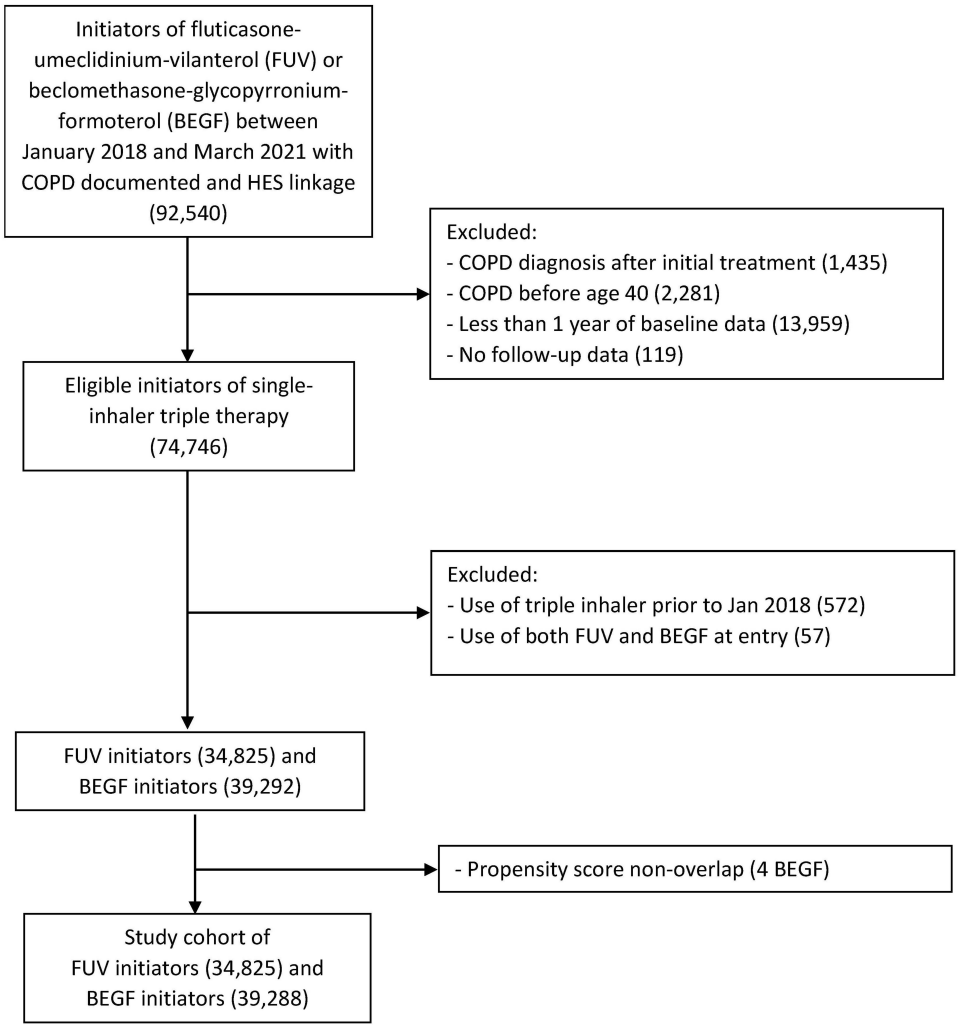

Figure 1 Flowchart of study cohort selection.

Table 1 Baseline Characteristics of the Study Cohort of 39,288 Initiators of Beclomethasone-Glycopyrronium-Formoterol (BEGF) and 34,825 Initiators Fluticasone-Umeclidinium-Vilanterol (FUV) Single-Inhalers for COPD, Weighted by Fine Stratification from Probability of Treatment Propensity Scores, with Corresponding Standardized Mean Differences

	BEGF	FUV	Standardized Mean Difference
Number of patients	39,288	34,825	
Age at cohort entry, mean(sd)	71.1 (10.2)	71.0 (10.2)	0.003
Female sex, n (%)	19,422 (49.4)	17,238 (49.5)	−0.001
Current smoker, n (%)	18,250 (46.5)	16,188 (46.5)	−0.001
Obesity Status, n (%)			
Obese	12,427 (31.6)	10,995 (31.6)	0.001
Non-Obese	25,881 (65.9)	22,962 (65.9)	−0.001
Missing	980 (2.5)	869 (2.5)	0.000
Alcohol Abuse, n (%)	932 (2.4)	828 (2.4)	0.000
FEV_1 (% predicted)*, mean (sd)	55.8 (19.6)	56.0 (19.6)	−0.009
Blood eosinophils cells/μL**, mean (sd)	247.8 (217.6)	248.4 (216.3)	−0.003
Severity of dyspnea			
None-Mild	10,427 (26.5)	9220 (26.5)	0.001
Moderate-Severe	27,673 (70.4)	24,547 (70.5)	−0.001
Missing	1188 (3.0)	1058 (3.0)	−0.001
Respiratory events and medications in year prior to cohort entry, n (%)			
Hospitalization for COPD	4777 (12.2)	4247 (12.2)	−0.001
Moderate or severe COPD exacerbation			
None	13,108 (33.4)	11,579 (33.3)	0.002
One	8132 (20.7)	7192 (20.7)	0.001
Two or More	18,048 (45.9)	16,053 (46.1)	−0.003
Pneumonia hospitalization	2661 (6.8)	2361 (6.8)	0.000
Asthma	9976 (25.4)	8850 (25.4)	0.000
LABA-ICS	30,380 (77.3)	26,905 (77.3)	0.002
LABA-LAMA	7374 (18.8)	6576 (18.9)	−0.003
LABA	979 (2.5)	860 (2.5)	0.001
LAMA	27,333 (69.6)	24,240 (69.6)	−0.001
ICS	2310 (5.9)	2044 (5.9)	0.000
Short-acting beta-agonist	37,013 (94.2)	32,781 (94.1)	0.003
Short-acting anti-muscarinic	1784 (4.5)	1557 (4.5)	0.003
Prednisolone	26,007 (66.2)	23,055 (66.2)	0.000
Methylxanthines	2292 (5.8)	2043 (5.9)	−0.001
Respiratory antibiotics	31,382 (79.9)	27,836 (79.9)	−0.001
Comorbidity in year prior to cohort entry, n (%)			
Cancer	2346 (6.0)	2087 (6.0)	−0.001
Diabetes	8459 (21.5)	7452 (21.4)	0.003
Heart failure	3177 (8.1)	2817 (8.1)	0.000
Myocardial Infarction	332 (0.8)	296 (0.9)	−0.001
Stroke	844 (2.1)	740 (2.1)	0.002
Renal disease	3050 (7.8)	2702 (7.8)	0.000
Other medications in year prior to cohort entry, n (%)			
ACE-inhibitors	10,335 (26.3)	9168 (26.3)	0.000
ARBs	4788 (12.2)	4247 (12.2)	0.000
Beta-blockers	8692 (22.1)	7697 (22.1)	0.001
Calcium-channel blockers	11,179 (28.5)	9904 (28.4)	0.000
Thiazides diuretics	3565 (9.1)	3159 (9.1)	0.000

(*Continued*)

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Table 1 (Continued).

	BEGF	FUV	Standardized Mean Difference
Antiarrhythmics	962 (2.4)	855 (2.5)	0.000
Aspirin	8376 (21.3)	7424 (21.3)	0.000
Oral anticoagulants	5528 (14.1)	4897 (14.1)	0.000
Statins	20,455 (52.1)	18,129 (52.1)	0.000
PPIs	21,364 (54.4)	18,944 (54.4)	0.000
NSAIDs	3698 (9.4)	3279 (9.4)	0.000
Opioids	17,454 (44.4)	15,504 (44.5)	−0.002

Notes: *Based on available data from 89% of subjects. **Based on available data from 88% of subjects.

BEGF was practically unchanged regardless of exacerbation history, the presence of a previous asthma diagnosis, FEV_1 % predicted (<50% vs >=50%), or blood eosinophil count (<=300 vs >300 cells/μL) (Table 2).

For severe exacerbations, the cumulative incidence at one year was 9.16% on FUV and 10.04% on BEGF (Figure 3), with a corresponding HR of 0.92 (95% CI: 0.86–0.97) (Table 3). The HRs were not affected by exacerbation history, the presence of a previous asthma diagnosis, FEV_1% predicted (<50% vs >=50%), or blood eosinophil count (<=300 vs >300 cells/μL) (Table 3).

With respect to severe pneumonia requiring hospitalisation (Figure 4), the HR comparing FUV with BEGF was 1.06 (95% CI 0.99–1.13) (Table 4). The HR was particularly increased among patients in GOLD Group E (1.14; 95% CI 1.06–1.24) and those with a blood eosinophil count ≤ 300 cells/μL (1.10; 95% CI 1.02–1.19) (Table 4).

Sensitivity analyses with varying grace periods that define continuous treatment or using an intent-to-treat approach did not alter the findings. The HR of a moderate or severe exacerbation, defined using the alternative validated definition, with FUV compared with BEGF was also of similar magnitude at 0.93 (95% CI: 0.91–0.95).

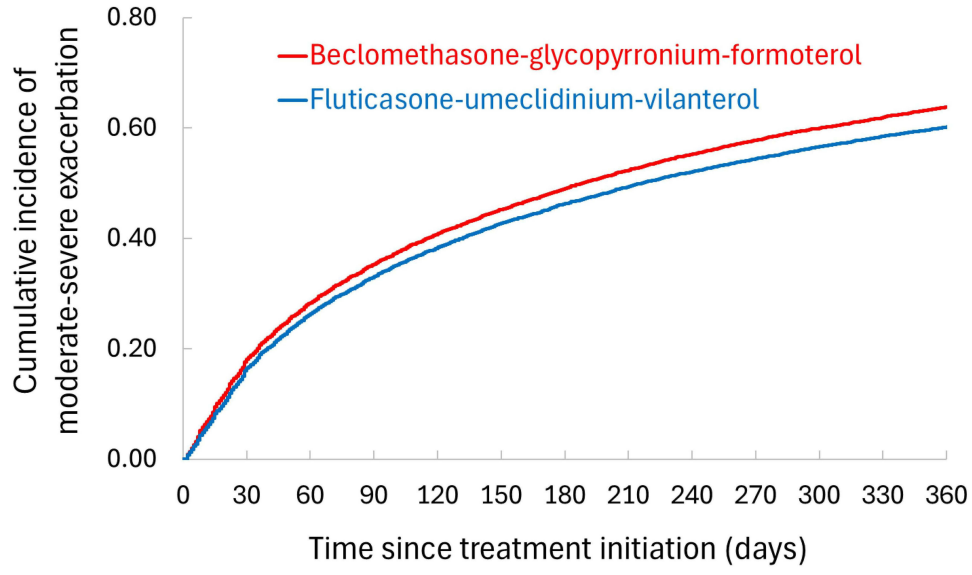

Figure 2 One-year cumulative incidence of the first moderate or severe COPD exacerbation comparing treatment initiation with beclomethasone-glycopyrronium-formoterol (BEGF) or fluticasone-umeclidinium-vilanterol (FUV), estimated using the Kaplan-Meier method, adjustment by fine stratification of the propensity score of treatment weights.

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Table 2 Adjusted Hazard Ratios of Moderate or Severe COPD Exacerbation Comparing Initial Single-Inhaler Triple Therapies with Fluticasone-Umeclidinium-Vilanterol (FUV) versus Beclomethasone-Glycopyrronium-Formoterol (BEGF) in Patients with COPD in the First Year After Treatment Initiation, from the as-Treated Analyses, Stratified by GOLD Group E Classification of Prior Exacerbations, FEV_1, Peripheral Blood Eosinophil Count and Cardiovascular Disease, Estimated from the Cox Proportional Hazards Model

	Number of Patients	Number with Events	Person-Years	Rate* per 100 per Year	Adjusted* Hazard Ratio (95% CI)
Overall					
FUV	34,825	14,960	13,176	122.3	0.91 (0.89–0.93)
BEGF	39,288	19,304	13,390	135.6	1.00 (Reference)
Group E (≥2 moderate or 1 severe exacerbation)					
FUV	15,753	10,028	4357	239.0	0.93 (0.91–0.96)
BEGF	20,314	13,728	5164	258.0	1.00 (Reference)
Not Group E (≤1 moderate exacerbation)					
FUV	19,072	4932	8819	57.3	0.87 (0.84–0.90)
BEGF	18,974	5576	8227	66.4	1.00 (Reference)
Prior asthma diagnosis					
FUV	8447	3617	3166	124.0	0.92 (0.88–0.96)
BEGF	10,333	5037	3481	136.5	1.00 (Reference)
No prior asthma diagnosis					
FUV	26,378	11,343	10,010	121.7	0.91 (0.89–0.93)
BEGF	28,955	14,267	9909	135.3	1.00 (Reference)
Baseline FEV_1 (< 50% predicted) **					
FUV	12,176	6074	4313	151.3	0.90 (0.87–0.93)
BEGF	15,051	8683	4889	168.2	1.00 (Reference)
Baseline FEV_1 (≥50% predicted) **					
FUV	19,254	7510	7764	102.4	0.93 (0.90–0.96)
BEGF	19,195	8288	7030	112.1	1.00 (Reference)
Baseline blood eosinophils (≤300 cells/μL)†					
FUV	23,580	10,227	8830	124.7	0.92 (0.90–0.94)
BEGF	27,174	13,419	9214	137.0	1.00 (Reference)
Baseline blood eosinophils (>300 cells/μL)†					
FUV	6996	3044	2662	123.0	0.89 (0.85–0.94)
BEGF	7709	3864	2604	139.2	1.00 (Reference)

Notes: *Adjusted by fine stratification weights from the probability of treatment propensity scores. **Based on available data from 89% of subjects. †Based on available data from 88% of subjects.

Discussion

Using real-world clinical practice data of patients with COPD newly initiated on single inhaler triple therapy, we found that FUV was associated with a lower incidence of moderate or severe exacerbation regardless of exacerbation history, comorbid asthma, blood eosinophil count, or level of airflow obstruction. On the other hand, the incidence of a severe pneumonia requiring hospitalisation was elevated with FUV among patients with GOLD Group E or subjects whose blood eosinophil count is ≤300 cells/μL.

To our knowledge, this is the first reported analysis directly comparing FUV with BEGF, a triple inhaler available in Europe but not in the US where all other such studies compared FUV with another triple inhaler. Nonetheless, our results are somewhat comparable to the three previous US-based studies comparing FUV with BUGF, a similar single-inhaler triple therapy but with a distinct inhaled corticosteroid, namely budesonide.[8–10] Indeed, all three studies found a lower rate or risk of moderate to severe exacerbation with initiation of FUV compared with BUGF, while using similar propensity score-matched designs from real-world administrative database settings. The first such study by Feldman

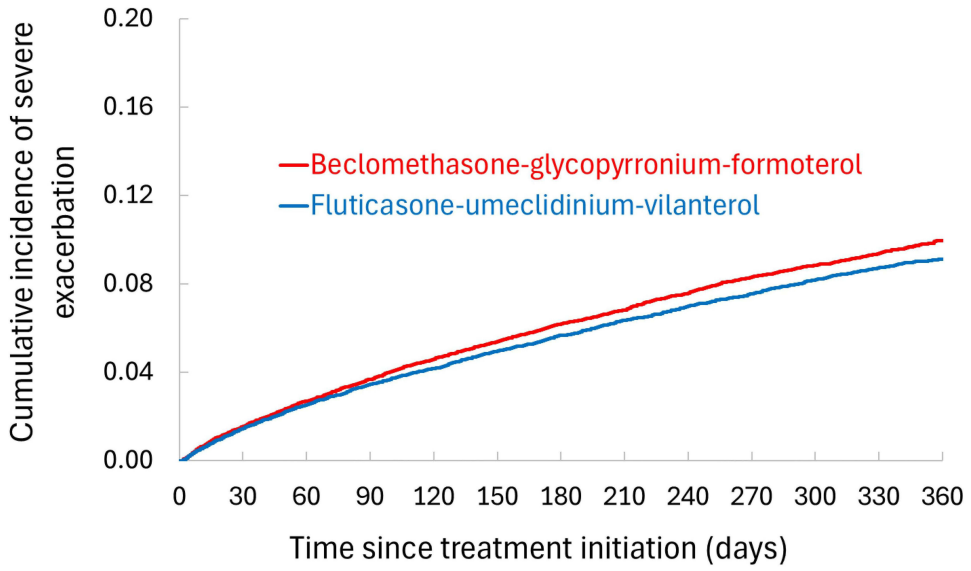

Figure 3 One-year cumulative incidence of the first severe COPD exacerbation comparing treatment initiation with beclomethasone-glycopyrronium-formoterol (BEGF) or fluticasone-umeclidinium-vilanterol (FUV), estimated using the Kaplan-Meier method, adjustment by fine stratification of the propensity score of treatment weights.

showed a 8% decrease in the incidence of moderate or severe COPD exacerbation and a 22% decrease (calculated by reversing the reported hazard ratios) for severe exacerbations with FUV compared to BUGF.[8] This latter relative decrease of 22% for severe exacerbation was somewhat larger than the 8% decrease found in our analysis based on BEGF as the comparator, although the absolute decrease was similar in both studies at around 1 less severe exacerbation per

Table 3 Adjusted Hazard Ratios of Severe COPD Exacerbation Comparing Initial Single-Inhaler Triple Therapies with Fluticasone-Umeclidinium-Vilanterol (FUV) versus Beclomethasone-Glycopyrronium-Formoterol (BEGF) in Patients with COPD in the First Year After Treatment Initiation, from the as-Treated Analyses, Stratified by GOLD Group E Classification of Prior Exacerbations, FEV_1, Peripheral Blood Eosinophil Count and Cardiovascular Disease, Estimated from the Cox Proportional Hazards Model

	Number of Patients	Number with Events	Person-Years	Rate* per 100 per Year	Adjusted* Hazard Ratio (95% CI)
Overall					
FUV	34,825	1813	19,380	10.8	0.92 (0.86–0.97)
BEGF	39,288	2824	21,497	11.8	1.00 (Reference)
Group E (≥2 moderate or 1 severe exacerbation)					
FUV	15,753	1323	8644	17.3	0.93 (0.87–1.00)
BEGF	20,314	2233	11,073	18.5	1.00 (Reference)
Not Group E (≤1 moderate exacerbation)					
FUV	19,072	490	10,736	4.8	0.90 (0.79–1.01)
BEGF	18,974	591	10,423	5.4	1.00 (Reference)
Prior asthma diagnosis					
FUV	8447	385	4688	9.7	0.95 (0.83–1.08)
BEGF	10,333	638	5602	10.3	1.00 (Reference)
No prior asthma diagnosis					
FUV	26,378	1428	14,692	11.2	0.91 (0.85–0.97)
BEGF	28,955	2186	15,895	12.3	1.00 (Reference)
Baseline FEV_1 (< 50% predicted) **					
FUV	12,176	981	6802	16.2	0.95 (0.88–1.03)
BEGF	15,051	1582	8606	16.9	1.00 (Reference)

(*Continued*)

Table 3 (Continued).

	Number of Patients	Number with Events	Person-Years	Rate* per 100 per Year	Adjusted* Hazard Ratio (95% CI)
Baseline FEV_1 (≥50% predicted) **					
FUV	19,254	586	10,981	5.9	0.87 (0.78–0.97)
BEGF	19,195	781	10,602	6.8	1.00 (Reference)
Baseline blood eosinophils (≤300 cells/μL)†					
FUV	23,580	1257	13,033	11.1	0.91 (0.85–0.98)
BEGF	27,174	2006	14,837	12.2	1.00 (Reference)
Baseline blood eosinophils (>300 cells/μL)†					
FUV	6996	386	3941	11.2	0.95 (0.83–1.08)
BEGF	7709	559	4214	11.9	1.00 (Reference)

Notes: *Adjusted by fine stratification weights from the probability of treatment propensity scores. **Based on available data from 89% of subjects. †Based on available data from 88% of subjects.

100 per year. Of note, the mean continuous treatment duration was around 200 days for both groups in our study compared with medians of 88 and 113 days for BUGF and FUV respectively in that study. Finally, unlike our study that found an increase in the risk of severe pneumonia with FUV compared with BEGF, mainly among GOLD Group E subjects or those with blood eosinophil count ≤300 cells/μL, the Feldman study found no difference in the risk of pneumonia with FUV compared to BUGF.[8] With respect to the other two studies, they also showed reductions in moderate-severe exacerbations with FUV compared to BUGF, with one conducted among participants who "stepped-up" from LABA-ICS or LABA-LAMA, but no reduction was observed in the incidence of severe exacerbations.[9,10] Furthermore, these two studies did not report on pneumonia safety.[8]

There are several potential reasons behind the reduced incidence of exacerbations with FUV compared to BEGF. First, FUV is a once-a-day inhaled medication, while BEGF is taken twice daily. Once-daily medication in COPD has been associated with higher adherence than twice-daily dosing in a large observational study, with respective median

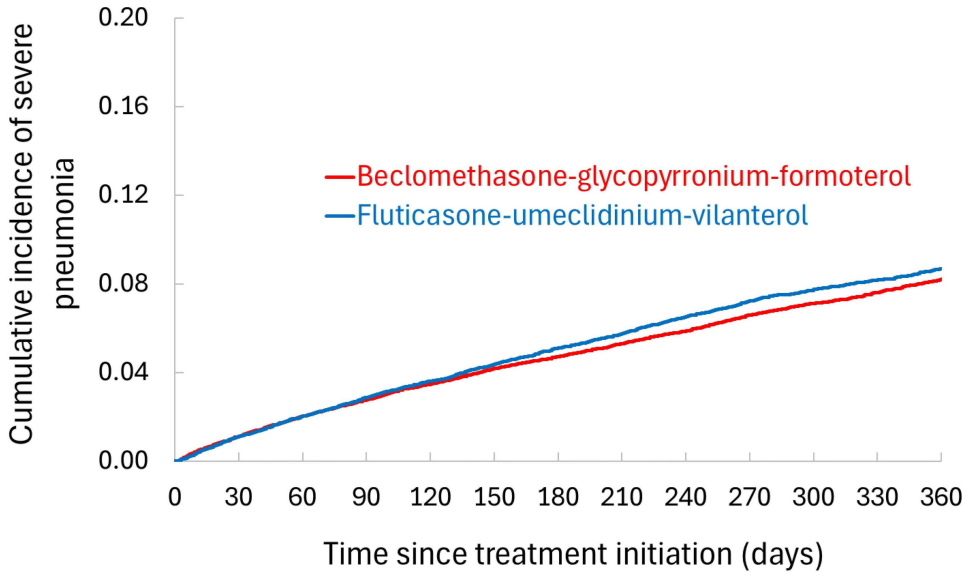

Figure 4 One-year cumulative incidence of the first pneumonia requiring hospitalisation comparing treatment initiation with beclomethasone-glycopyrronium-formoterol (BEGF) or fluticasone-umeclidinium-vilanterol (FUV), estimated using the Kaplan-Meier method, adjustment by fine stratification of the propensity score of treatment weights.

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Table 4 Adjusted Hazard Ratios of Severe Pneumonia Comparing Initial Single-Inhaler Triple Therapies with Fluticasone-Umeclidinium -Vilanterol (FUV) versus Beclomethasone-Glycopyrronium-Formoterol (BEGF) in Patients with COPD in the First Year After Treatment Initiation, from the as-Treated Analyses, Stratified by GOLD Group E Classification of Prior Exacerbations, FEV_1, Peripheral Blood Eosinophil Count and Cardiovascular Disease, Estimated from the Cox Proportional Hazards Model

	Number of Patients	Number with Events	Person-Years	Rate* per 100 per Year	Adjusted* Hazard Ratio (95% CI)
Overall					
FUV	34,825	1730	19,529	9.9	1.06 (0.99–1.13)
BEGF	39,288	2212	21,873	9.3	1.00 (Reference)
Group E (≥2 moderate or 1 severe exacerbation)					
FUV	15,753	1108	8779	13.9	1.14 (1.06–1.24)
BEGF	20,314	1490	11,443	12.2	1.00 (Reference)
Not Group E (≤1 moderate exacerbation)					
FUV	19,072	622	10,750	6.1	0.93 (0.84–1.04)
BEGF	18,974	722	10,430	6.5	1.00 (Reference)
Prior asthma diagnosis					
FUV	8447	365	4724	8.8	1.05 (0.91–1.20)
BEGF	10,333	524	5679	8.5	1.00 (Reference)
No prior asthma diagnosis					
FUV	26,378	1365	14,805	10.2	1.06 (0.99–1.14)
BEGF	28,955	1688	16,194	9.6	1.00 (Reference)
Baseline FEV_1 (< 50% predicted) **					
FUV	12,176	709	6945	11.2	1.04 (0.94–1.15)
BEGF	15,051	1015	8891	10.7	1.00 (Reference)
Baseline FEV_1 (≥50% predicted) **					
FUV	19,254	758	10,981	7.4	1.09 (0.99–1.21)
BEGF	19,195	776	10,663	6.8	1.00 (Reference)
Baseline blood eosinophils (≤300 cells/μL)†					
FUV	23,580	1253	13,127	10.6	1.10 (1.02–1.19)
BEGF	27,174	1560	15,113	9.6	1.00 (Reference)
Baseline blood eosinophils (>300 cells/μL)†					
FUV	6996	339	3974	9.6	0.99 (0.86–1.14)
BEGF	7709	459	4285	9.7	1.00 (Reference)

Notes: *Adjusted by fine stratification weights from the probability of treatment propensity scores. **Based on available data from 89% of subjects. †Based on available data from 88% of subjects.

daily adherence of 83.3% and 64.7%.[29] Achieving 80% adherence was also increased with once daily medication compared to twice daily formulations (54.8% vs 38.6%).[29] Another observational study showed an increase in the proportion of days covered with once-daily medications, corresponding to reduced hospitalizations, emergency department visits, and outpatient visits, compared to other dosing frequencies in COPD.[30]

Second, the results could be explained by differences in the delivery device. FUV is delivered in a dry powder inhaler (Ellipta) and BEGF is available in both a metered dose inhaler as well as a dry powder inhaler (NEXThaler). However, our study ended in March 2021 prior to the introduction of BEGF in the NEXThaler device. Consequently, our analysis uniquely compares FUV delivered in a dry power inhaler (Ellipta) with BEGF delivered as an MDI. MDIs require coordination of inhalation and actuation while DPIs are breathe actuated and only require a deep inspiration. Error rates in inhaler technique are higher with MDIs (up to 86.8%) compared to DPIs (60.9%).[31]

Finally, the observed differences could be due to the different molecules in the two inhalers. In comparing FUV with BEGF we are comparing two different LAMAs, two different LABAs, and two different inhaled corticosteroids. For example, fluticasone furoate has been shown to be more potent at preventing airway hyperresponsiveness compared to

budesonide.[32] On the other hand, a systematic review and network analysis found no significant difference in trough FEV_1 at 12 weeks, dyspnea, health status, or rescue medication use when comparing monotherapy umeclidinium with glycopyrronium.[33] Data on the direct comparison between vilanterol and formoterol are, however, scant.

The incidence of severe pneumonias with FUV was higher than with BEGF, especially so among patients in GOLD Group E and those with lower blood eosinophil count. Previous observational studies suggest a somewhat larger increase in the risk of pneumonia with all fluticasone-based inhalers compared with beclomethasone-based inhalers.[34–36] These studies were based on multiple different formulations, including as monotherapy and dual combinations, as well as different inhaler devices, and used different criteria to define pneumonia. Our analysis, however, was based specifically on FUV delivered via dry powder inhaler and BEGF delivered via MDI, and considered the outcome of severe pneumonia requiring hospitalization, a more homogenous contrast. Nonetheless, the potential that the elevated comparative risk of pneumonia observed with fluticasone-based inhalers could vary with the formulation, device and pneumonia definition merits further investigations.

The rates of severe pneumonia in our study were nearly 10-fold less than the moderate-to-severe exacerbation rate, but equivalent to the rates of severe exacerbation. This suggests a clinically relevant trade-off between severe exacerbations and severe pneumonia, underscoring the need to consider individual risk profiles when selecting SITT. Notably, we did not observe an increased risk of severe pneumonia with FUV compared to BEGF in certain subgroups, including non-GOLD E patients, and patients with peripheral eosinophils (>300 cells/μL). Taken together, these findings reinforce that clinicians should weigh both pneumonia and exacerbation risk profiles, alongside individual patient characteristics, when selecting optimal therapy.

This study's most important strength is that it is the first head-to-head comparison of FUV and BEGF in COPD. Furthermore, by using a new-user cohort design with propensity matching, a design that emulates a randomized trial, we were able to reduce baseline differences and confounding by indication. This is particularly important considering the absence of randomized controlled trials comparing FUV and BEGF. Third, we compared clinically relevant outcomes (exacerbation and pneumonia hospitalizations) between two widely used single inhaler therapies, in the context of actual prescribing patterns and patients. Finally, using a large real-world cohort allows our findings to enhance generalizability beyond the more selected populations included in randomized controlled trials.

The study also has limitations. Despite using propensity score-based methods to balance the two groups on many characteristics, residual confounding remains plausible in this study design. For example, physicians may prefer to prescribe a metered-dose inhaler to more frail patients who are known to exacerbate more frequently,[37] and are more likely to have a peak inspiratory flow inadequate for dry powder inhalers.[38] A covariate used in the propensity score in this study, BMI, is only an imperfect proxy for frailty. However, additional covariates used to propensity match in this study are also associated with lower peak inspiratory flow, namely sex and FEV_1.[39] Second, despite the high quality of recorded data on medication prescriptions in the CPRD, we cannot eliminate exposure misclassification as we are missing data on whether the drugs were dispensed, as well as daily inhaler adherence and appropriateness of inhaler technique. We tried to mitigate this limitation with sensitivity analyses that varied the grace period that defined continuous use. Third, despite using validated definitions for our key outcomes of exacerbations and pneumonia hospitalizations using administrative codes, these codes may not always reflect true clinical events as they can be influenced by coding practices, healthcare utilization patterns, or incomplete documentation. This could lead to some outcome misclassification and attenuate the hazard ratios. Both these misclassifications are however inherent limitations in observational studies of real-world data. Fourth, we included patients with comorbid asthma, which could introduce bias if these two inhalers are used differentially when comorbid asthma is present. However, this potential bias was ruled out as the stratified analyses by asthma co-diagnosis showed consistent findings on all outcomes in these two strata. This inclusive approach is important as it reflects the real-world clinical experience of COPD patient heterogeneity. Finally, we used a one-year follow-up after triple therapy initiation, which may have been short for the severe exacerbation outcome, though has been commonly used in trials of triple therapy.

Conclusions

In a large cohort of individuals taken from real world clinical practice, those newly initiated on single-inhaler triple therapy with FUV had a lower incidence of a moderate-severe exacerbation in the first year of treatment compared with BEGF. This held true regardless of exacerbation history, the presence of a previous asthma diagnosis, FEV_1% predicted, or blood eosinophil count. The incidence of severe pneumonia in the first year of treatment with FUV was elevated among GOLD Group E subjects or those whose blood eosinophil count is not elevated (≤300 cells/μL). Our analysis did not include the more recent formulation of BEGF in a dry powder inhaler. Further research investigating the potential effects of different agents, formulations and devices used in these triple inhalers could help to optimize the pharmacological treatment of patients with COPD.

Data Sharing Statement

Data accessed complied with relevant data protection and privacy regulations. This study is based in part on data from the Clinical Practice Research Datalink obtained under license from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the UK National Health Service as part of their care and support. Because electronic health records are classified as "sensitive data" by the UK Data Protection Act, information governance restrictions (to protect patient confidentiality) prevent data sharing via public deposition. Data are available with approval through the individual constituent entities controlling access to the data. Specifically, the primary care data can be requested via application to the Clinical Practice Research Datalink (https://www.cprd.com).

Ethics Approval

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 23-002846) and the Research Ethics Committee of the Jewish General Hospital (JGH Protocol # 2024-3847), Montreal, Quebec, Canada.

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Disclosure

Samy Suissa attended advisory committee meetings for Atara, Novartis and Panalgo, and received speaking fees from Covis Pharma and Novartis. Mathew Cherian attended advisory board meetings for AstraZeneca, GlaxoSmithKline, and Sanofi and received speaking fees from AstraZeneca and Sanofi. Sophie Dell'Aniello has no conflicts. The authors report no other conflicts of interest in this work.

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