International Journal of COPD

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ORIGINAL RESEARCH

Severe exacerbation and pneumonia in COPD patients treated with fixed combinations of inhaled corticosteroid and long-acting beta2 agonist

This article was published in the following Dove Press journal:
International Journal of COPD
21 August 2017
Number of times this article has been viewed

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Background: It remains unclear whether severe exacerbation and pneumonia of COPD differs between patients treated with budesonide/formoterol and those treated with fluticasone/salmeterol. Therefore, we conducted a comparative study of those who used budesonide/formoterol and those treated with fluticasone/salmeterol for COPD.

Methods: Subjects in this population-based cohort study comprised patients with COPD who were treated with a fixed combination of budesonide/formoterol or fluticasone/salmeterol. All patients were recruited from the Taiwan National Health Insurance database. The outcomes including severe exacerbations, pneumonia, and pneumonia requiring mechanical ventilation (MV) were measured.

Results: During the study period, 11,519 COPD patients receiving fluticasone/salmeterol and 7,437 patients receiving budesonide/formoterol were enrolled in the study. Pairwise matching (1:1) of fluticasone/salmeterol and budesonide/formoterol populations resulted in to two similar subgroups comprising each 7,295 patients. Patients receiving fluticasone/salmeterol had higher annual rate and higher risk of severe exacerbation than patients receiving budesonide/formoterol (1.2219/year vs 1.1237/year, adjusted rate ratio, 1.08; 95% CI, 1.07–1.10). In addition, patients receiving fluticasone/salmeterol had higher incidence rate and higher risk of pneumonia than patients receiving budesonide/formoterol (12.11 per 100 person-years vs 10.65 per 100 person-years, adjusted hazard ratio [aHR], 1.13; 95% CI, 1.08–1.20). Finally, patients receiving fluticasone/salmeterol had higher incidence rate and higher risk of pneumonia requiring MV than patients receiving budesonide/formoterol (3.94 per 100 person-years vs 3.47 per 100 person-years, aHR, 1.14; 95% CI, 1.05–1.24). A similar trend was seen before and after propensity score matching analysis, intention-to-treat, and as-treated analysis with and without competing risk.

Conclusions: Based on this retrospective observational study, long-term treatment with fixed combination budesonide/formoterol was associated with fewer severe exacerbations, pneumonia, and pneumonia requiring MV than fluticasone/salmeterol in COPD patients.

Keywords: COPD, ICS/LABA, exacerbation, pneumonia

Introduction

COPD is characterized by progressive and persistent airflow limitation.[1] The disease is a major cause of chronic morbidity and is estimated to be the third leading cause of death worldwide by 2020.[2–4] Exacerbation of COPD is a significant contributor to mortality, especially in patients who require hospitalization.[5–8] Several studies[9–13] have demonstrated that a fixed-dose combination of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) can effectively reduce the risk of COPD exacerbation.

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http://dx.doi.org/10.2147/COPD.S139035

In Taiwan, there are two fixed-dose combinations of inhaled LABA and ICS available as treatment for COPD, namely budesonide/formoterol (Symbicort Turbuhaler, AztraZeneca) and fluticasone/salmeterol (Seretide Accuhaler and Seretide Evohaler, GlaxoSmithKline). Both combinations have been shown to result in fewer exacerbation episodes and to improve quality of life.[9–13] However, it remains unclear whether the two combinations are equally effective at reducing the frequency of exacerbations.

Previously, our study and other studies all showed that ICSs are significantly associated with an increased risk of pneumonia in COPD patients.[13,14] Findings from the PATHOS study revealed that budesonide/formoterol is more effective than fluticasone/salmeterol in preventing exacerbations and pneumonia in patients with moderate and severe COPD.[13,15] However, most of the patients in that study were of Scandinavian origin, making it difficult to generalize their findings to Asian populations, such as Taiwanese.

The Taiwan National Health Insurance Research Database (NHIRD) consists of standard computerized claims documents submitted by medical institutions seeking reimbursement through the National Health Insurance (NHI) program. The NHI program provides the medical needs for more than 23 million people, representing >98% of the population in Taiwan, and records clinical diagnoses according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. In this population-based study, we compared the effects of budesonide/formoterol and fluticasone/salmeterol on the occurrence of severe exacerbation and pneumonia in propensity score-matched COPD patients with long-term follow-up sourced from the Taiwan NHIRD.

Methods

Data source

This study used a subset of the NHIRD comprising information on 2,200,000 individuals with COPD, representing 60.5% of all patients with heart or lung disease in the NHI database (n=3,635,539). This cohort was followed longitudinally from 1997 to 2010. The records of patients retrieved from the NHIRD were anonymized and de-identified prior to analysis. Therefore, no informed consent was required and it was specifically waived by the Institutional Review Board. Ethics approval was obtained from the Institutional Review Board of NHRI.

Selection of patients with COPD

Adult patients with COPD ≥40 and ≤100 years were identified using ICD-9-CM codes 491, 492, and 496. Inclusion criteria included a record of at least three outpatient or one inpatient visits for COPD and ever undergone a lung function test within 1 year before and after the diagnosis of COPD had been established. Thus, a total of 141,855 patients were identified as having COPD. Of those patients, only 18,956 patients received a fixed ICS and LABA combination (budesonide/formoterol Turbuhaler or fluticasone/salmeterol Accuhaler or Metered Dose Inhaler) (Figure 1). The index date was defined as the date of the first fixed ICS/LABA combination prescription after COPD had been diagnosed. Patients were followed until 31 December 2010, or the end of treatment with a fixed combination, emigration or death.

Outcome measurements

Severe exacerbation was defined as COPD-related hospitalizations or emergency department visits. Pneumonia was defined as COPD patients who developed pneumonia requiring emergency department or hospital admission. Pneumonia requiring mechanical ventilation (MV) was defined as COPD patients with pneumonia and using MV for respiratory failure.

Exposure measures and potential confounders

Fixed ICS/LABA combinations were defined as Anatomical Therapeutic Chemical (ATC) codes R03AK06 or R03AK07 as previous report.[14] COPD exacerbation events were calculated only during the same fixed ICS/LABA combination usage period. If the patient changed to the other fixed ICS/LABA combination, the patient was censored. In order to control for potential confounding factors, data regarding the use of ICSs (ATC code R03BA), LABAs (ATC codes R03AC12 and R03AC13), short-acting β2-agonists (SABAs; ATC code R03AC), and other related drugs were assessed.

Statistical analysis

We used pairwise 1:1 propensity score matching (greedy 5-to-1 digit matching without replacement) and logistic regression to reduce concerns related to nonrandom assignment of patients to treatments.[16] The propensity score method is used to reduce potential confounding caused by unbalanced covariates. The matching starts with the smallest population (7,437 patients in the budesonide/formoterol group) and matches them 1:1 to the larger treatment group. Patients treated with either treatment combination were matched on the following criteria: age, sex, number of prescriptions for antibiotics, oral steroids, ICS, long-acting and short-acting bronchodilators, diagnosis of diabetes, cancer, heart failure, hypertension, stroke, and the number of previous severe

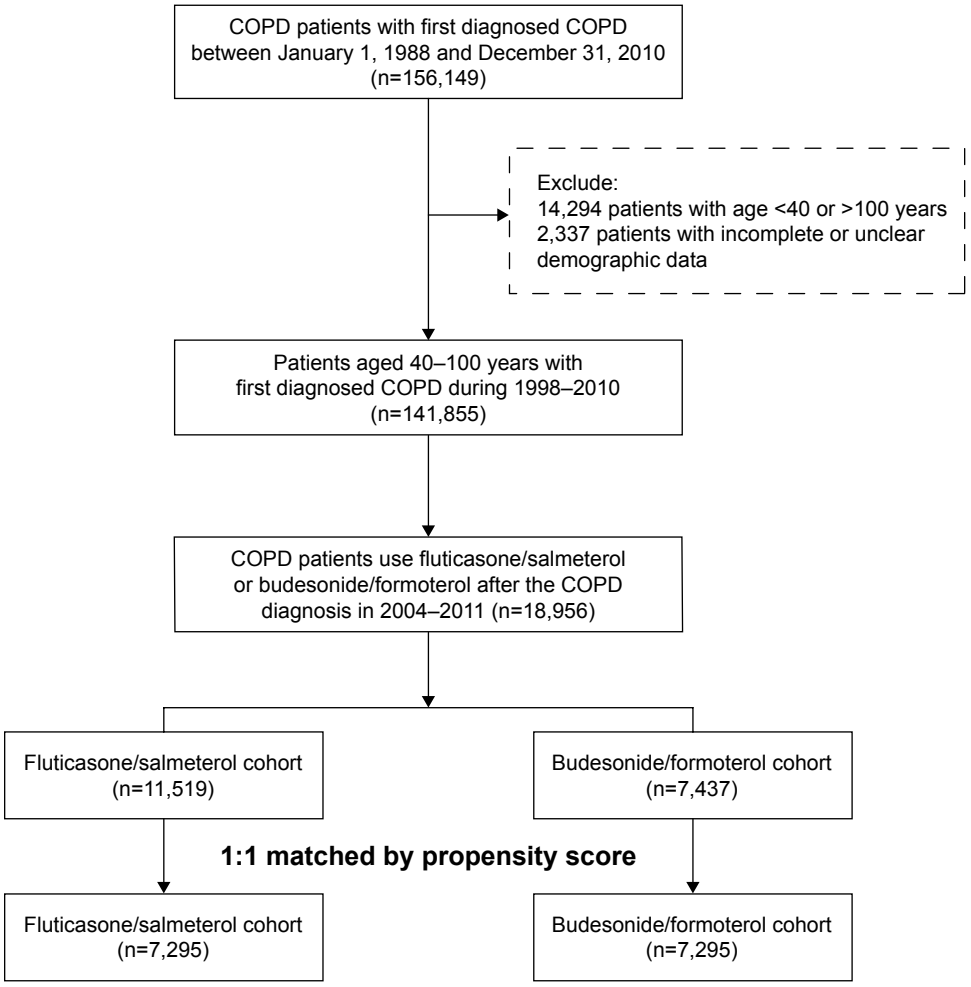

Figure 1 Flow chart of study cohort selection.

COPD exacerbations – COPD-related hospitalizations or emergency department visits.

Intention-to-treat analyses were used as the primary analyses for this study because of more reliable estimates of comparative treatment effectiveness in real-world applications. Both cohorts were followed, until the study outcome, according to original treatment allocation, regardless of adherence to or subsequent withdrawal or deviation from the inclusion criteria. In the as-treated analyses, the person-time in the as-treated population, a subset of all person-time in the intention-to-treat analyses, was censored on the day of medication add-on, switching, or discontinuation. Cox regression models were used to calculate the crude and adjusted hazard ratios (aHRs) of different outcomes including mortality, pneumonia, and pneumonia requiring MV between the two study cohorts. Adjusted HRs and 95% CIs were calculated by using Cox regression models adjusted for propensity scores (continuous).

The annual severe exacerbation event rate (emergency department visits or admissions to hospital) observed with each ICS/LABA regimen was compared between the groups using Poisson regression, with events as the dependent variable and time on specific fixed combination treatment as an offset variable. A P-value of <0.05 was considered to indicate statistical significance in all analyses. The software packages used for data analysis included SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Overall, 18,956 patients received a fixed ICS/LABA combination (11,519 patients receiving fluticasone/salmeterol and 7,437 patients receiving budesonide/formoterol). Table 1 summarizes the demographic characteristics of these two groups. Before propensity score matching, patients receiving fluticasone/salmeterol were older and more male patients received budesonide/formoterol. Patients receiving fluticasone/salmeterol had more frequent severe acute exacerbations, and less use of COPD inhaled and oral drugs except long-acting muscarinic antagonist

Table 1 Baseline characteristics of COPD patients prescribed fluticasone/salmeterol and budesonide/formoterol before and after matching by propensity score matching

Variables	Before propensity score matching					After propensity score matching				
	Fluticasone/ salmeterol		Budesonide/ formoterol		*P*-value	Fluticasone/ salmeterol		Budesonide/ formoterol		*P*-value
Patient (n)	11,519		7,437			7,295		7,295		
Age (year)	65.95±10.26		63.28±10.40		<0.0001	63.66±10.33		63.53±10.30		0.4334
Male gender	8,801	76.40%	5,434	76.14%	<0.0001	5,386	73.83%	5,360	73.47%	0.6251
Index year										
2004	1,963	17.04%	1,430	20.04%	<0.0001	1,439	19.73%	1,408	19.30%	0.9301
2005	1,261	10.95%	1,231	17.25%		1,102	15.11%	1,146	15.71%	
2006	1,326	11.51%	990	13.87%		987	13.53%	972	13.32%	
2007	1,486	12.90%	973	13.63%		991	13.58%	967	13.26%	
2008	1,375	11.94%	843	11.81%		841	11.53%	833	11.42%	
2009	1,543	13.40%	762	10.68%		746	10.23%	762	10.45%	
2010	1,571	13.64%	815	11.42%		818	11.21%	814	11.16%	
2011	994	8.63%	393	5.51%		371	5.09%	393	5.39%	
Monthly income, n (%)										
<19,100	4,040	35.07%	2,481	34.76%	0.0006	2,429	33.30%	2,455	33.65%	0.8927
19,100–41,999	6,012	52.19%	3,874	54.28%		3,831	52.52%	3,805	52.16%	
≥42,000	1,467	12.74%	1,082	15.16%		1,035	14.19%	1,035	14.19%	
Hospital level, n (%)										
Level 1	4,651	40.38%	3,077	43.11%	<0.0001	2,944	40.36%	3,004	41.18%	0.7384
Level 2	4,887	42.43%	2,907	40.73%		2,920	40.03%	2,880	39.48%	
Level 3	1,477	12.82%	1,016	14.24%		1,016	13.93%	990	13.57%	
Level 4 (rural area)	504	4.38%	437	6.12%		415	5.69%	421	5.77%	
COPD severe AE										
0	6,340	55.04%	4,580	64.17%	<0.0001	4,443	60.90%	4,457	61.10%	0.7490
1	1,915	16.62%	1,102	15.44%		1,122	15.38%	1,090	14.94%	
≥2	3,264	28.34%	1,755	24.59%		1,730	23.71%	1,748	23.96%	
Medication for COPD										
LABA	412	3.58%	366	5.13%	<0.0001	338	4.63%	347	4.76%	0.7247
SABA	3,400	29.52%	2,514	35.22%	<0.0001	2,396	32.84%	2,426	33.26%	0.5975
LAMA	1,488	12.92%	711	9.96%	<0.0001	694	9.51%	708	9.71%	0.6941
ICS	3,155	27.39%	2,591	36.30%	<0.0001	2,459	33.71%	2,478	33.97%	0.7396
Medication for hypertension										
Alpha-blocker	1,258	10.92%	782	10.96%	0.3784	802	10.99%	774	10.61%	0.4552
Beta-blocker	3,159	27.42%	1,910	26.76%	0.0082	1,902	26.07%	1,889	25.89%	0.8061
Calcium-channel Blocker	5,579	48.43%	3,358	47.05%	<0.0001	3,306	45.32%	3,315	45.44%	0.8810
Diuretic	4,359	37.84%	2,450	34.33%	<0.0001	2,413	33.08%	2,432	33.34%	0.7384
ACEI or ARB	4,139	35.93%	2,492	34.92%	0.0006	2,494	34.19%	2,456	33.67%	0.5064
Other medication										
Aspirin	1,542	13.39%	813	11.39%	<0.0001	782	10.72%	807	11.06%	0.5064
Clopidogrel	633	5.50%	335	4.69%	0.0025	321	4.40%	331	4.54%	0.6887
Ticlopidine	221	1.92%	117	1.64%	0.0794	120	1.64%	116	1.59%	0.7929
Dipyridamole	1,558	13.53%	886	12.41%	0.0012	889	12.19%	881	12.08%	0.8392
Nitrate	153	1.33%	77	1.08%	0.0721	74	1.01%	76	1.04%	0.8696
Statin	1,429	12.41%	896	12.55%	0.4635	867	11.88%	883	12.10%	0.6835
NSAID	8,791	76.32%	5,748	80.54%	0.1222	5,676	77.81%	5,636	77.26%	0.4275
Anti-hyperglycemic drugs	1,857	16.12%	1,019	14.28%	<0.0001	1,015	13.91%	1,011	13.86%	0.9237
Proton-pump inhibitor	1,371	11.90%	804	11.27%	0.0213	781	10.71%	793	10.87%	0.7488
Baseline comorbidities										
Charlson score (mean ± SD)	1.64±1.00		1.55±0.90		<0.0001	1.55±0.90		1.55±0.90		0.5337
Myocardial infarction	190	1.65%	95	1.33%	0.0398	86	1.18%	94	1.29%	0.5485
Congestive heart failure	1,030	8.94%	584	8.18%	0.0087	567	7.77%	584	8.01%	0.6016
Peripheral vascular disease	92	0.80%	52	0.73%	0.4412	53	0.73%	52	0.71%	0.9220
Cerebrovascular disease	578	5.02%	279	3.91%	<0.0001	255	3.50%	276	3.78%	0.3532
Dementia	194	1.68%	67	0.94%	<0.0001	65	0.89%	67	0.92%	0.8612

(*Continued*)

Table 1 (*Continued*)

Variables	Before propensity score matching					After propensity score matching				
	Fluticasone/ salmeterol		Budesonide/ formoterol		*P*-value	Fluticasone/ salmeterol		Budesonide/ formoterol		*P*-value
Rheumatologic disease	114	0.99%	74	1.04%	0.9710	71	0.97%	70	0.96%	0.9326
Peptic ulcer disease	1,703	14.78%	1,052	14.74%	0.2231	1,018	13.95%	1,032	14.15%	0.7387
Hemiplegia or paraplegia	7	0.06%	2	0.03%	0.2958	2	0.03%	2	0.03%	1.0000
Renal disease	271	2.35%	153	2.14%	0.1794	148	2.03%	152	2.08%	0.8155
Moderate/severe liver disease	1,255	10.90%	706	9.89%	0.0020	675	9.25%	701	9.61%	0.4614
Cancer	375	3.26%	239	3.35%	0.8738	241	3.30%	234	3.21%	0.7440
Diabetes mellitus	372	3.23%	202	2.83%	0.0440	205	2.81%	199	2.73%	0.7621

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; AE, acute exacerbation; ARB, angiotensin II receptor blocker; ICS, inhaled corticosteroid; LABA, long acting beta agonists; LAMA, long acting antimuscarinics; NSAID, nonsteroidal anti-inflammatory drugs; SABA, short acting beta agonists.

than patients receiving budesonide/formoterol. Pairwise matching (1:1) of fluticasone/salmeterol and budesonide/formoterol populations resulted in two similar subgroups each comprising 7,295 patients.

Effect on severe exacerbation

Following matching, the post-index all severe exacerbation rates were 1.2219 and 1.1237 per patient-year in the fluticasone/salmeterol and budesonide/formoterol groups, respectively (adjusted rate ratio 1.08, 95% CI, 1.07–1.10) (Table 2). Patients treated with fluticasone/salmeterol had significantly higher rates of hospitalization (rate ratio 1.11, 95% CI, 1.08–1.13) or emergency department visits (rate ratio 1.09, 95% CI, 1.07–1.11) for COPD (Table 2). The results before matching were the same as following matching.

Effect on pneumonia and pneumonia requiring MV

Patients receiving fluticasone/salmeterol had higher incidence rate and higher risk of pneumonia than patients receiving budesonide/formoterol (12.11 per 100 person-years vs 10.65 per 100 person-years, aHR, 1.13; 95% CI, 1.08–1.20) (Table 3). In addition, patients receiving fluticasone/salmeterol had higher incidence rate and higher risk of pneumonia requiring MV than patients receiving budesonide/formoterol (3.94 per 100 person-years vs 3.47 per 100 person-years, aHR, 1.14; 95% CI, 1.05–1.24; Table 3). Finally, patients receiving fluticasone/salmeterol had higher incidence rate and higher risk of mortality than patients receiving budesonide/formoterol (4.89 vs 4.50, aHR, 1.09; 95% CI, 1.01–1.17; Table 3). Similar results were obtained for both cohorts before propensity score matching.

We obtained similar results in the sensitivity analyses (Table 4). In the as-treated analyses, we found the group of fluticasone/salmeterol had higher risk of pneumonia and pneumonia requiring MV. When death was treated as a competing risk, the risks of pneumonia and pneumonia requiring MV still remained lower in budesonide/formoterol group.

Discussion

This national population-based study compromising two matched cohorts each comprising 7,295 COPD patients

Table 2 Yearly rates and rate ratios of severe exacerbation, hospitalization for COPD, and emergency department visits for COPD exacerbation in a matched cohort of COPD patients prescribed fluticasone/salmeterol and budesonide/formoterol

	Fluticasone/ salmeterol cohort	Budesonide/ formoterol cohort	Crude RR	(95% CI)	Adjusted RR*	(95% CI)
	Yearly rate	Yearly rate				
Before propensity score matching						
Severe exacerbation	1.3368	1.1096	1.05	(1.04–1.07)	1.06	(1.04–1.07)
Hospitalization for COPD	0.6271	0.4827	1.14	(1.11–1.16)	1.10	(1.07–1.12)
Emergency department visits for COPD	1.0380	0.8601	1.06	(1.04–1.07)	1.07	(1.05–1.08)
After propensity score matching						
Severe exacerbation	1.2219	1.1237	1.08	(1.07–1.10)	1.08	(1.07–1.10)
Hospitalization for COPD	0.5455	0.4915	1.11	(1.08–1.13)	1.11	(1.08–1.13)
Emergency department visits for COPD	0.9528	0.8688	1.09	(1.07–1.11)	1.09	(1.07–1.11)

Note: *Adjusted for propensity score.
Abbreviation: RR, rate ratio.

Table 3 Event rates and risks of pneumonia, pneumonia requiring MV in a matched cohort of COPD patients prescribed fluticasone/salmeterol and budesonide/formoterol

	Fluticasone/salmeterol cohort			Budesonide/formoterol cohort			Crude HR (95% CI)	Adjusted HR* (95% CI)
	Event	Person-year	Incidence rate (per 100 person-years)	Event	Person-year	Incidence rate (per 100 person-years)		
Before propensity score matching								
Mortality	2,438	41,741.61	5.84	1,359	30,807.16	4.41	1.32 (1.24–1.41)	1.09 (1.01–1.17)
Pneumonia	4,610	32,150.0	14.34	2,610	24,829.2	10.51	1.31 (1.25–1.38)	1.13 (1.08–1.20)
Pneumonia requiring MV	1,895	39,367.10	4.81	1,004	29,496.66	3.40	1.39 (1.28–1.50)	1.13 (1.04–1.24)
After propensity score matching								
Mortality	1,461	29,857.98	4.89	1,349	29,955.79	4.50	1.09 (1.02–1.17)	1.09 (1.01–1.17)
Pneumonia	2,839	23,448.09	12.11	2,569	24,124.61	10.65	1.12 (1.06–1.17)	1.13 (1.08–1.20)
Pneumonia requiring MV	1,118	28,373.96	3.94	996	28,671.31	3.47	1.16 (1.07–1.25)	1.14 (1.05–1.24)

Note: *Adjusted for propensity score.
Abbreviations: HR, hazard ratio; MV, mechanical ventilation.

treated with either fluticasone/salmeterol or budesonide/formoterol has several significant findings. Most important of all, we found that the budesonide/formoterol group had fewer episodes of severe exacerbations than the fluticasone/salmeterol group. Moreover, patients treated with budesonide/formoterol had a significantly lower rate of hospitalization or emergency department visit for COPD exacerbation. In addition, the episodes of pneumonia and pneumonia requiring MV were significantly higher in the fluticasone/salmeterol group than in the budesonide/formoterol group. Our findings indicate that fixed combination budesonide/formoterol is more effective in preventing severe exacerbation of COPD and pneumonia than fluticasone/salmeterol.

One of the strengths of the present study is that it is a nationwide population-based cross-sectional study that includes almost all patients with COPD in Taiwan. In fact, the NHI program covers 99.0% of Taiwan's population and the NHRID contains near complete follow-up information for the whole study population. In addition, the database is routinely monitored for diagnostic accuracy by the National Health Insurance Bureau. The diagnosis of COPD in most patients was made by physicians based on clinical findings without pulmonary function test results. To improve the accuracy of the COPD diagnosis, only patients who had received pulmonary function tests within 1 year of receiving a diagnosis of COPD were enrolled. In this study, we also used propensity score matching to minimize the effects of possible confounding variables. Therefore, our study should be representative of the status of patients with COPD in Taiwan who are treated with fixed ICS/LABA combinations. Besides we also performed sensitivity analyses and calculated competing risk with mortality.

Blais et al conducted a 1-year, population-based, matched cohort study of 2,262 patients using data sourced from administrative health care databases from the Canadian province of Quebec and found no significant differences in frequency of COPD exacerbations between patients treated with fluticasone/salmeterol and those who received budesonide/formoterol (0.71 vs 0.63 exacerbation/patient-year).[17] Although the rate of COPD exacerbations in the year after the index date was lower in the budesonide/formoterol group than in the fluticasone/salmeterol group after adjustment for confounding factors (adjusted risk ratio. 0.88, 95% CI, 0.76–1.00), the difference did not reach statistical significance.[17] In contrast, the PATHOS study in Sweden, which enrolled two cohorts of 2,738 patients each, comprising more than 19,000 patient-years, who were followed for up to 11 years, found that budesonide/

Table 4 Sensitivity analyses for risk of pneumonia and pneumonia requiring MV among COPD patients using fluticasone/salmeterol and budesonide/formoterol

	Before propensity score matching		After propensity score matching	
	Crude	Adjusted*	Crude	Adjusted*
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary analysis				
Mortality	1.32 (1.24–1.41)	1.09 (1.01–1.17)	1.09 (1.02–1.17)	1.09 (1.01–1.17)
Pneumonia	1.31 (1.25–1.38)	1.13 (1.08–1.20)	1.12 (1.06–1.17)	1.13 (1.08–1.20)
Pneumonia requiring MV	1.39 (1.28–1.50)	1.13 (1.04–1.24)	1.16 (1.07–1.25)	1.14 (1.05–1.24)
ITT analysis + competing risk				
Mortality	–	–	–	–
Pneumonia	1.24 (1.17–1.30)	1.08 (1.03–1.14)	1.11 (1.05–1.18)	1.11 (1.05–1.18)
Pneumonia requiring MV	1.27 (1.17–1.38)	1.09 (1.01–1.18)	1.09 (1.00–1.19)	1.09 (1.00–1.19)
As-treated analysis				
Mortality	1.54 (1.39–1.70)	1.23 (1.09–1.37)	1.25 (1.12–1.38)	1.21 (1.08–1.35)
Pneumonia	1.44 (1.34–1.54)	1.17 (1.08–1.26)	1.17 (1.09–1.25)	1.17 (1.08–1.26)
Pneumonia requiring MV	1.70 (1.51–1.91)	1.32 (1.16–1.51)	1.34 (1.19–1.52)	1.32 (1.15–1.51)
As-treated analysis + competing risk				
Mortality	–	–	–	–
Pneumonia	1.32 (1.22–1.42)	1.11 (1.03–1.20)	1.12 (1.03–1.22)	1.12 (1.03–1.22)
Pneumonia requiring MV	1.48 (1.30–1.68)	1.20 (1.06–1.37)	1.21 (1.05–1.40)	1.21 (1.05–1.39)

Note: *Adjusted for propensity score.
Abbreviations: HR, hazard ratio; MV, mechanical ventilation; ITT, intention-to-treat.

formoterol was significantly associated with fewer exacerbations than fluticasone/salmeterol in the first year and that the difference between the two combinations increased with study duration.[15] The discrepancy in findings between the population-based study performed in Canada and that in Sweden may be due to differences in sample size or study duration. In our study, which included more than 30,000 patients and a longer follow-up period than in the PATHOS study or the study by Blais et al, the findings were similar to those reported in the PATHOS study.[15] Finally, consistent with previous studies in western countries,[15,17] we found budesonide/formoterol was associated with significantly lower rates of emergency department visits and hospitalization due to COPD than fluticasone/salmeterol. The above-mentioned findings suggest that fixed combination budesonide/formoterol more effectively prevents exacerbation of COPD than fluticasone/salmeterol in Caucasian as well as Asian populations.

Several factors may help to explain the differences in effectiveness between budesonide/formoterol and fluticasone/salmeterol. For example, studies have shown that budesonide/formoterol results in a more rapid onset of bronchodilation and offers faster symptom control than fluticasone/salmeterol.[18,19] Better symptom control may contribute to the lower rate of emergency department visits or hospitalizations in the long term.[17] The pharmacokinetic and pharmacodynamic characteristics of the two combinations may also explain, at least in part, the differences in effectiveness between fluticasone and budesonide. Several studies have demonstrated that fluticasone is a more lipophilic corticosteroid than budesonide, allowing for its longer retention in the airway, and that it is a more potent immunosuppressant, thereby facilitating bacterial colonization and infection-associated exacerbations.[19–23]

There are several limitations in this study. First, we did not have detailed data on pulmonary function test results or quality of life assessment. Therefore, we could not evaluate the severity of COPD or determine whether every patient received an ICS/LABA combination according to the recommended guidelines.[1] Second, despite our use of propensity score matching, it is still possible that residual confounding factors, such as duration of COPD, smoking habit, the result of pulmonary function test or prior number of COPD exacerbation without hospitalizations were not taken into account in the analysis. Third, this study was not a randomized controlled study. Nonetheless, our findings are derived from the real world's situation, and are more likely to be reflective of common clinical practice.

Conclusion

In our retrospective comparative study of ICS/LABA medication utilization for COPD, long-term treatment with the fixed combination of budesonide/formoterol was associated with fewer health care utilization-defined exacerbations than fluticasone/salmeterol in patients with moderate and severe COPD.

Acknowledgments

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Disclosure

The authors report no conflicts of interest in this work.

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