

Comparative analysis of budesonide/formoterol and fluticasone/salmeterol combinations in COPD patients: findings from a real-world analysis in an Italian setting

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Aim: The objective of this study was to evaluate the different outcomes associated with the use of budesonide/formoterol compared to fluticasone/salmeterol in fixed combinations in patients with COPD in a “real-world” setting. The outcomes included exacerbation rates and health care costs.

Patients and methods: An observational retrospective cohort analysis, based on administrative databases of three local health units, was conducted. Patients with at least one prescription of fixed-dose combination of inhaled corticosteroids and long-acting β_2 -agonists (budesonide/formoterol or fluticasone/salmeterol), at dosages and formulations approved for COPD in Italy, between January 1, 2009 and December 31, 2011 (inclusion period), were included. Patients were followed until December 2012, death or end of treatment (follow-up period), whichever occurred first. Patients were included if they were aged ≥ 40 years and had at least 6 months of follow-up. Propensity score matching was performed to check for confounding effects. Number of hospitalizations for COPD and number of oral corticosteroid and antibiotic prescriptions during follow-up were analyzed using Poisson regression models. The cost analysis was conducted from the perspective of the National Health System.

Results: After matching, 4,680 patients were analyzed, of which 50% were males with a mean age of 64 ± 13 years. In the Poisson regression models, the incidence rate ratio for budesonide/formoterol as compared to fluticasone/salmeterol was 0.84 (95% confidence interval [CI]: 0.74–0.96, $P=0.010$) for number of hospitalizations, 0.89 (95% CI: 0.87–0.92, $P<0.001$) for number of oral corticosteroid prescriptions and 0.88 (95% CI: 0.86–0.89, $P<0.001$) for number of antibiotic prescriptions. The mean annual expenditure for COPD management was €2,436 for patients treated with budesonide/formoterol and €2,784 for patients treated with fluticasone/salmeterol.

Conclusion: Among patients with COPD, treatment with a fixed combination of budesonide/formoterol was associated with fewer exacerbations and a lower, but not significant, cost of illness than the treatment with fluticasone/salmeterol. Real-world analyses are requested to ameliorate interventions to address unmet needs, optimizing treatment pathways to improve COPD-related burden and outcomes.

Keywords: COPD, exacerbations, inhaled corticosteroids, long-acting β_2 -agonist, budesonide/formoterol, fluticasone/salmeterol

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Introduction

COPD is a complex and progressive disease characterized by persistent airflow obstruction and is often complicated by exacerbations.¹ According to the latest World

Health Organization estimates, COPD has affected 65 million people worldwide and is predicted to become the third leading cause of death by 2030.²

A COPD exacerbation is generally defined as “an acute event characterized by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication”.¹ Exacerbations are classified as mild, moderate, or severe, based on the intensity of the medical intervention required to control symptoms. Recurrent exacerbations are associated with a rapid decline in lung function (a low forced expiratory volume in 1 second [FEV₁]), an impairment of health-related quality of life in a patient, an increase in hospitalization rates and an enhancement in the risk of death.^{3–5} Owing to its chronic and progressive nature, COPD represents a substantial economic burden in direct and indirect health care costs.¹

COPD treatments aim to improve quality of life and control symptoms while reducing exacerbation risk.¹ Pharmacological therapy is used to reduce symptoms and frequency and severity of exacerbations and improve health status and exercise tolerance.⁶

Recent guidelines,¹ issued by the Global Initiative for Chronic Obstructive Lung Disease, suggest that a fixed combination of inhaled corticosteroids (ICSs) and long-acting β_2 -agonists (LABAs) offers a better convenience than ICSs and LABAs administered separately, improving in lung function and health status and reducing exacerbations in patients with moderate to very severe COPD.^{1,7} These recommendations are based on the best evidence available from published literature.^{7–11}

Scientific evidence from published studies^{12–14} suggests that ICS/LABA combination therapies might not have the same exacerbation rates, in terms of health care utilization, on COPD management in a health care setting. Several ICS/LABA combination products are available that differ in pharmacokinetic profile and dose of both active substances.¹⁴ Currently, there are five ICS/LABA combinations available in the market of Italy: the older fluticasone propionate/salmeterol and budesonide/formoterol combinations and the more recent beclomethasone/formoterol and fluticasone propionate/formoterol combinations. While the first three combinations are indicated for treatment of both COPD and asthma, the last is recommended only for treating asthma.¹ Moreover, also fluticasone furoate/vilanterol combination has been introduced in the market, with the indication for COPD treatment, but very limited data are available for this combination.¹

The purpose of this study was to assess the different outcomes associated with the use of the two more frequently

used ICS/LABA fixed-dose combinations,¹⁴ budesonide/formoterol compared to fluticasone/salmeterol, for the management of COPD in a real-world setting. The outcomes included exacerbation rates and COPD health care costs for COPD management.

Patients and methods

This retrospective cohort study was conducted using administrative databases of three Italian local health units (LHUs) geographically distributed throughout the national territory. In particular, the following databases were used: Demographic Database, containing demographic information; Medications Prescription Database, providing information for each medication prescription; Hospital Discharge Database, containing information on hospitalization, according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Outpatient Specialist Services Database, collecting information on visits or outpatient services provided to the patient. To guarantee patient privacy, each subject was assigned an anonymous univocal numeric code. No identifiers related to patients were provided to the researchers. The patient code in each database permitted electronic linkage between all databases. Informed consent is not required by the LHU ethics committee for the use of encrypted retrospective information. This study was notified to the local ethics committee in each participating LHU according to the Italian law regarding the conduct of observational analysis and the LHU Ethics Committees approved the study.¹⁵

Cohort definition

Patients with at least one prescription of a fixed-dose combination of ICSs and LABAs (budesonide/formoterol or fluticasone/salmeterol), at dosages and formulations approved for COPD in Italy, between January 1, 2011 and December 31, 2011 (inclusion period), were included.

The index date was identified according to the first prescriptions of ICS/LABA during the inclusion period. Patients were followed until December 2012, death or end of treatment (follow-up period), whichever occurred first. Patients were included if they were aged ≥ 40 years and if they had at least 6 months follow-up between the first and the last prescription of ICS/LABA. Patients who were transferred to another LHU during the follow-up period were excluded from the analysis.

Definition and study period

Data on baseline characteristics, including demographics, and clinical characteristics of patients were also investigated

within 1 year before the index date (characterization period). In particular, all patients were characterized according to the following parameters: number of previous visits or hospitalizations related to COPD (ICD-9-CM codes of primary or accessory discharge reasons: 490–496 excluding 493) and number of previous use of antibiotics (ATC code: J01), oral corticosteroids (ATC code: H02), tiotropium (ATC code: R03BB04), ICSs (ATC code: R03BA), short-acting β -agonists (ATC code: R03AC), LABAs (ATC codes: R03AC12, R03AC13), angiotensin receptor blockers (ATC codes: C09C, C09D), β -adrenergic blocking agents (ATC code: C07), statins (ATC code: C10AA), calcium channel blockers drugs (ATC code: C08) and thiazide (ATC code: C03A). The presence of comorbidity, such as diabetes, asthma, cancer, rheumatoid arthritis, heart failure, hypertension and stroke, was assessed by Charlson Comorbidity Index (CCI).¹⁶ The CCI is an indicator that uses the ICD-9-CM codes of hospitalizations or the ATC code on drugs prescribed as a proxy of pathology; for example, if a diagnosis of diabetes cannot be identified through the hospital admission code, the CCI considers as a proxy the use of antidiabetic agents. Because the CCI assigns points to various conditions, the sum of the scores defines the severity of the patient in terms of comorbidity. All comorbidities were evaluated in the 1-year period before the index data; the CCI score reflects a patient's overall health status. The number of COPD hospitalizations, oral corticosteroids and antibiotics prescriptions, during the follow-up period, was also evaluated.

The rate of COPD-related exacerbations was calculated as the number of exacerbations during the follow-up period. A COPD-related exacerbation was defined as a COPD-related hospitalization or visit with a diagnosis of COPD and a prescription of oral corticosteroids or antibiotics.

Statistical analysis

Continuous variables were reported as mean and standard deviation (median and range if appropriate), whereas categorical variables were expressed as numbers and percentages.

The propensity score matching technique was used to reduce potential patient selection bias derived from the observational nature of the study and to create more comparable cohorts through a 1:1 paring.

The propensity score was calculated using a logistic regression model, and for each individual, the probability of receiving budesonide/formoterol or fluticasone/salmeterol was estimated, based on baseline characteristics. Hosmer–Lemeshow and C-statistic tests were used to assess model

calibration and model discrimination. All patients were then matched 1:1 within each quintile of propensity score.

Hospitalizations for COPD and prescriptions of oral corticosteroids and antibiotics during the follow-up period were analyzed using Poisson regression models. The two groups were compared in relation to the incidence of hospitalizations for COPD, number of prescriptions for oral corticosteroids and number of antibiotic prescriptions. Since the groups concerned were matched for all baseline characteristics, the three outcomes considered were compared by univariate Poisson models, which took into consideration not only the dependent variable expressed by a count but also the exposure time of patients.

The *P*-values <0.05 were considered to be statistically significant, and all statistical analyses were conducted using SPSS statistical software for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Cost analysis

The cost analysis was conducted with the perspective of the National Health System. Costs were reported in euros. Drug costs were evaluated using the Italian National Health Service purchase at the time of analysis. We repeated the same analysis using the actual price of drug (reference years: 2015–2016). Hospitalization costs were calculated using the diagnosis-related group tariff. Costs of instrumental and laboratory tests were defined according to the tariffs applied by regions.

Results

The characteristics of patients treated with budesonide/formoterol or fluticasone/salmeterol, prior and after propensity matching – comparison, are shown in Table 1. After propensity score matching, a total of 4,680 patients met inclusion criteria and were analyzed. The patients had a mean age of 64 years with an equal gender distribution. In the Poisson regression models, the incidence rate ratio for patients treated with budesonide/formoterol, compared to patients treated with fluticasone/salmeterol, was 0.84 (95% confidence interval [CI]: 0.74–0.96, $P=0.010$) for number of hospitalizations, 0.89 (95% CI: 0.87–0.92, $P<0.001$) for number of oral corticosteroid prescriptions and 0.88 (95% CI: 0.86–0.89, $P<0.001$) for number of antibiotic prescriptions (Figure 1). The COPD-related health care costs (in term of drugs, hospitalizations, visits, diagnostic tests) are shown in Figure 2A.

During the follow-up period, the mean annual cost for COPD management was €2,436 for patients treated with

Table I Characteristics of patients initiating treatment with budesonide/formoterol or fluticasone/salmeterol prior and after propensity matching – comparison

Characteristics	Prior to matching		After matching
	Fluticasone/salmeterol	Budesonide/formoterol	Fluticasone/salmeterol
n	11,474	4,680	4,680
Age, years (mean $\pm$ SD)	67.4 $\pm$ 12.7	63.7 $\pm$ 13.0	63.7 $\pm$ 13.2
Male (%)	53	50	50
CCI (mean $\pm$ SD)	2.02 $\pm$ 1.27	1.79 $\pm$ 1.10	1.76 $\pm$ 1.21
Pre-index utilization			
COPD-related hospitalization (n, %)	626 (5.5)	220 (4.7)	240 (5.1)
Tiotropium (n, %)	2,830 (24.7)	945 (20.2)	847 (18.1)
ICSs (n, %)	3,645 (31.8)	1,295 (27.7)	1,258 (26.9)
SABAs (n, %)	2,571 (22.4)	1,006 (21.5)	996 (21.3)
LABAs (n, %)	592 (5.2)	224 (4.8)	238 (5.1)
Antibiotics (n, %)	8,574 (74.7)	3,226 (68.9)	3,179 (67.9)
Oral corticosteroids (n, %)	4,097 (35.7)	1,424 (30.4)	1,432 (30.6)
Angiotensin receptor blockers (n, %)	3,436 (29.9)	1,172 (25.0)	1,163 (24.9)
β -adrenergic blocking agents (n, %)	1,910 (16.6)	633 (13.5)	608 (13.0)
Statins (n, %)	2,540 (22.1)	818 (17.5)	798 (17.1)
Calcium channel blockers drugs (n, %)	2,734 (23.8)	903 (19.3)	887 (19.0)
Thiazides (n, %)	31 (0.3)	18 (0.4)	10 (0.2)

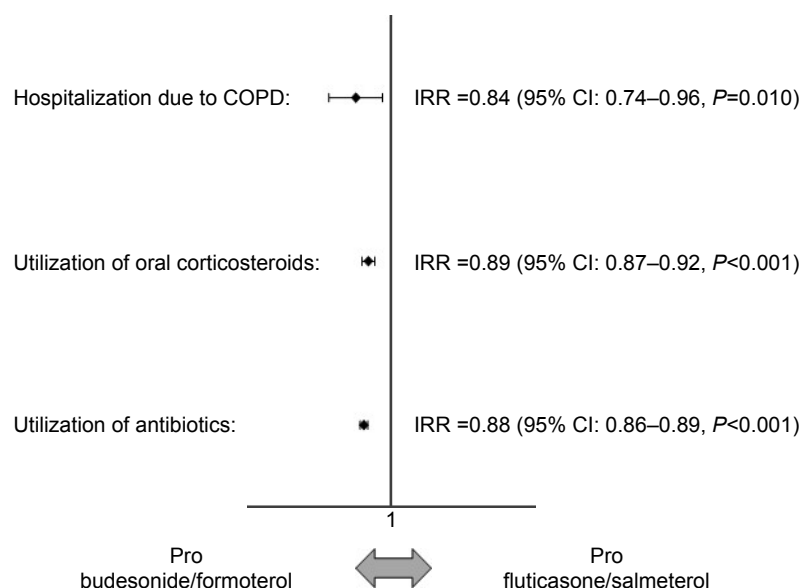
Abbreviations: SD, standard deviation; CCI, Charlson Comorbidity Index; ICS, inhaled corticosteroid; SABA, short-acting β -agonist; LABA, long-acting β 2-agonist.

budesonide/formoterol and €2,784 for patients who used fluticasone/salmeterol (P -value = 0.181). The average health care cost related to COPD management, using the actualized drug (adrenergics in combination with corticosteroids or other drugs, ATC code: R03AK) costs, is shown in Figure 2B. Among patients with COPD, treatment with a fixed-dose combination of budesonide/formoterol was associated with fewer exacerbations and a lower cost of illness than the treatment with fluticasone/salmeterol.

Discussion

In this retrospective analysis in a “real-world” setting, we demonstrated that patients treated with a fixed-dose combination of budesonide/formoterol show a lower COPD-related exacerbation than those treated with fluticasone/salmeterol combination.

The current COPD guideline recommends that a combined use of ICS/LABA should be prescribed only if the patient has persistent breathlessness or repeated exacerbations

**Figure I** Propensity score-matched populations of COPD patients treated with budesonide/formoterol and fluticasone/salmeterol fixed combinations.

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

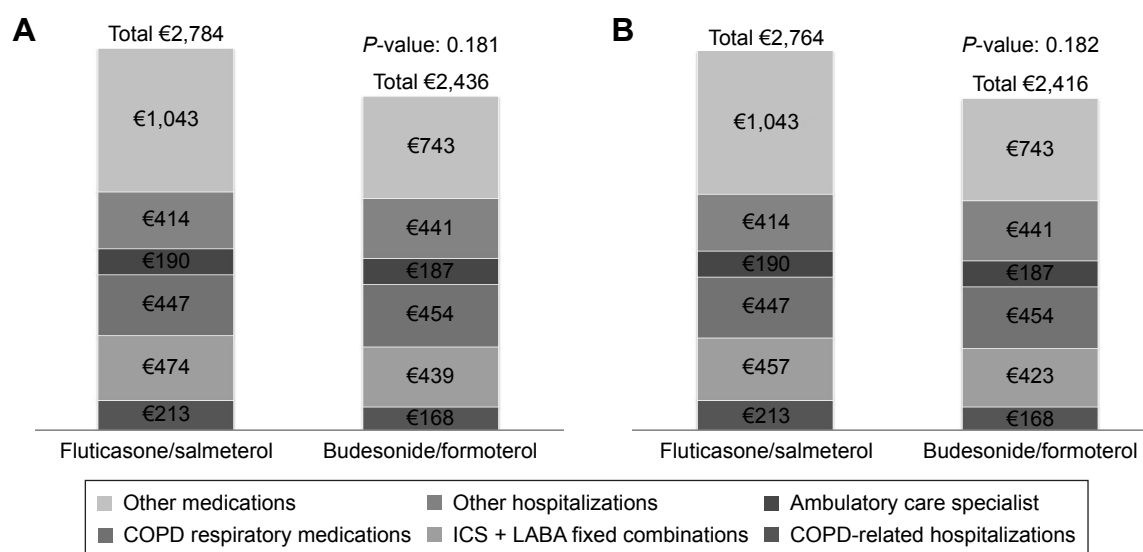


Figure 2 (A) The mean health care cost during the follow-up period. **(B)** The mean health care cost during the follow-up period (actualized ATC R03 costs). **Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist.

despite optimal bronchodilator therapy and should be discontinued if there is no benefit after 4 weeks.^{1,8} In Italy, both budesonide/formoterol¹⁷ and fluticasone/salmeterol¹⁸ fixed-dose combinations are indicated for symptomatic treatment of patients with severe COPD ($FEV_1 < 50\%$ predicted normal for budesonide/formoterol and $FEV_1 < 60\%$ predicted normal for fluticasone/salmeterol) and a history of frequent exacerbations, who have significant symptoms despite regular therapy with long-acting bronchodilators.

Our findings are not dissimilar from those of other reports in the literature so far.^{13,14,19} Both budesonide/formoterol and fluticasone/salmeterol demonstrated reduction in the overall rate of exacerbations, although published studies^{13,20} suggest differences in the exacerbation rates between the two ICS/LABA combinations (budesonide/formoterol and fluticasone/salmeterol). A matched-cohort, register-linkage study¹³ in Sweden reported that long-term treatment with a fixed combination of budesonide/formoterol was associated with a significant lower health care consumption-defined exacerbations than fluticasone/salmeterol in patients with COPD (difference of 26.6%; $P < 0.0001$). A Canadian study¹⁹ also found that the risk of exacerbations requiring emergency department visits (adjusted relative risk [RR] = 0.75; 95% CI: 0.58–0.97), hospitalizations (adjusted RR = 0.61; 95% CI: 0.47–0.81) for COPD and anticholinergic medication use (adjusted RR = 0.71; 95% CI: 0.57–0.89) was lower with fixed-dose budesonide/formoterol than with fixed-dose fluticasone/salmeterol during 1 year of analysis. In contrast to our study, the administrative claims database study conducted

by Kern et al²⁰ in the US found similar rates of utilization of health care resources and rates of exacerbations (rate ratio = 1.02; 95% CI: [0.96–1.09], $P = 0.56$) between patients initiating budesonide/formoterol or fluticasone/salmeterol during the first year of starting therapy. Since, there is no generally agreed definition for an exacerbation of COPD, because exacerbations have a variety of causes and severities, the direct comparison between studies is difficult.²¹ Also, variability in disease severity among patients included might play an important role in the interpretation of data.

Another aspect of this study is the evaluation of the COPD-related consumption of health care resources. COPD is one of the most worldwide burdensome diseases;¹² according to the latest European estimates, the direct annual health costs of COPD are ~€23.3 million.²²

Our findings suggest that, in an Italian health care setting, better outcomes can be achieved at a lower, but not significant, overall cost if patients are treated with budesonide/formoterol instead of fluticasone/salmeterol. Our results are similar to some published studies that have assessed the health care resource utilization in patients initiating budesonide/formoterol or fluticasone/salmeterol in a real-world setting.^{23,24} Economic analysis in Germany has shown that combining budesonide and formoterol in one device is less costly (in terms of medication, visits, referrals, and hospitalization) compared to combining fluticasone/salmeterol in a real clinical setting.²³ In contrast, other studies^{20,25} have reported no significant differences in total COPD-related medical costs after initiation of combination therapy; however, costs for

controller medications for the budesonide/formoterol group were slightly lower during the observation period.

Increasing evidence suggests that COPD exacerbations and the comorbid nature of the disease pose a significant and increasing economic and social burden.^{22,26–28} The majority of COPD expenditures are due to complications and hospitalizations, many of which are preventable. As with other chronic diseases, improved health care management can reduce poor outcomes and decrease costs related to COPD.²² Likewise, the best choice among available ICS/LABA fixed-dose combinations should be considered as one of the primary goals of COPD management.

This was a retrospective study using administrative data, and neither accuracy of COPD diagnoses could be verified nor was information available on the severity of disease. Despite this, we used a validated study design in which patients were propensity score matched with respect to a number of confounders. Considering the observational nature of the present study, we cannot surely conclude that medication was the only factor responsible for the observed outcome differences. The results and conclusions of this study are limited to the population analyzed.

Conclusion

Our findings show that treatment with a fixed combination of budesonide/formoterol was associated with fewer exacerbations and lower, but not significant, cost of illness than that with fluticasone/salmeterol in patients with COPD. Real-world analyses are requested to ameliorate interventions to address unmet needs and optimize treatment pathways to improve COPD-related burden and outcomes.

Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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