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ORIGINAL RESEARCH

Inhaled Triple Therapy with Extrafine Single Inhaler Versus Multiple Devices in Chronic Obstructive Pulmonary Disease (TRIPOLI): A Post-Authorization Retrospective Study

Eva Cabrera César[1], Javier López García[1], Daniel Enrique Vega Lizarazo[1], Miguel Benítez-Cano Gamonoso[1], Mercedes Segura Romero[1], Sara Sanchez Martín[1], Mónica I León Nieto[2], Diego González-Segura Alsina[2], José Luis Velasco Garrido[1]

[1]Pulmonology Department, Virgen de la Victoria University Hospital, Málaga, Spain; [2]Chiesi España, Barcelona, Spain

Correspondence: José Luis Velasco Garrido, Pulmonology Department, Virgen de la Victoria University Hospital, Campus de Teatinos s/N, Puerto de la Torre, Málaga, 29010, Spain, Email jlvelascogarrido@hotmail.com

Background: Triple therapy significantly enhances both clinical and functional outcomes in patients with uncontrolled chronic obstructive pulmonary disease (COPD), even when they are already receiving treatment. However, it is often prescribed with multiple inhalers, which can affect adherence to treatment. The evidence on the effectiveness of extrafine single inhaler triple therapy (efSITT) compared to multiple inhalers triple therapy (MITT) in patients with moderate-to-severe COPD in the real-world setting is limited.

Methods: TRIPOLI was a unicentric retrospective observational study that compared one year of efSITT with beclomethasone dipropionate, formoterol fumarate dihydrate, and glycopyrronium with one year of MITT in terms of exacerbations, use of rescue medication, adherence, and lung function in patients with COPD.

Results: A total of 71 patients were analyzed. The mean number of total and moderate exacerbations showed a significant reduction of 27.56% ($p = 0.0043$) and 29.56% ($p = 0.0008$), respectively, after efSITT. The percentage of patients with poor adherence decreased from 30.2% to 9.9% with efSITT and the proportion of patients with complete adherence increased from 55.8% to 81.7%. An improvement of 2.29% was described in mean forced expiratory volume in the first second (% pred). No differences were observed in the rate of pneumonia between the treatment with efSITT and MITT.

Conclusion: The TRIPOLI study suggests that switching from MITT to efSITT might reduce exacerbations in patients with moderate-to-severe COPD, likely attributable to improved adherence in real-world settings.

Keywords: chronic obstructive pulmonary disease, triple inhalation therapy, *extrafine particl*es, medication adherence, respiratory function tests, real-world

Introduction

Current guidelines recommend the administration of triple therapy with inhaled corticosteroid (ICS), long-acting β2-agonist (LABA), and long-acting muscarinic antagonist (LAMA) for patients with Chronic Obstructive Pulmonary Disease (COPD) who continue to experience exacerbations despite being on dual therapy with LABA/LAMA and having an eosinophil blood count of ≥100 cells/μL, or those on LAMA with an eosinophil count of ≥300 cells/μL. Additionally, it could be considered in treatment-naïve patients with an eosinophil count of ≥300 cells/μL.[1] Several clinical trials have demonstrated that triple therapy significantly enhances clinical and functional outcomes in these groups of patients.[2–4] Furthermore, a recent meta-analysis has confirmed that triple therapy reduces the frequency of moderate or severe exacerbations more effectively than either monotherapy or dual therapy.[5]

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In patients with COPD, the inhalation technique is frequently suboptimal,[6,7] and persistence and compliance to treatment are often inadequate.[8] Poor adherence can lead to severe consequences, including increased mortality, morbidity, and hospitalizations.[9]

Given that triple therapy is typically prescribed using two different inhalers, patients may struggle with the proper use of one or more inhalers, thereby further complicating adherence to treatment.[10]

Simplifying treatment regimens by reducing the number of inhalers and/or using devices that require a consistent inhalation technique can be advantageous for COPD patients. Implementing single-inhaler triple therapy (SITT) represents a potential strategy for improving adherence, providing an alternative to multiple-inhaler triple therapy (MITT).

Trimbow® (Chiesi España S.A.U). is an extrafine single-inhaler triple therapy (efSITT) combination available in the European market. It is approved for the maintenance treatment of adult patients with moderate-to-severe COPD who are not adequately controlled by the combination of LABA/ICS or LABA/LAMA. The active ingredients in this formulation are beclomethasone dipropionate, formoterol fumarate dihydrate, and glycopyrronium (BDP/FF/G). The product is available in two fixed-dose inhalers, a pressurized metered-dose inhaler (pMDI) and the innovative multi-dose dry-powder inhaler NEXThaler, delivering an extra fine formulation.

The evidence regarding the effectiveness of transitioning from MITT to efSITT in patients with moderate-to-severe COPD in a real-world setting is limited. Furthermore, no studies specifically examined the effectiveness of efSITT and adherence to this treatment within the Spanish context.

In this regard, the TRIPOLI study was designed to evaluate the impact of switching from MITT to efSITT with BDP/FF/G. The study focuses on assessing changes in the rate of moderate-to-severe exacerbations, the use of rescue medication, treatment adherence, and lung function.

Materials and Methods

The TRIPOLI study was a single-center retrospective observational study conducted within the pulmonology department of the Hospital Virgen De La Victoria in Málaga, Spain. The study aimed to evaluate the impact of one-year treatment with efSITT with BDP/FF/G 87/5/9 µg pressurized metered dose inhaler (pMDI) on the exacerbation rate, the use of rescue medication, adherence, and lung function in COPD patients who had previously been treated with MITT for one year.

To maintain the observational nature of the study, all data on the variables of interest were extracted from clinical records, and no additional diagnostic or therapeutic interventions were conducted beyond routine clinical practice.

The study adhered to the fundamental ethical principles outlined in the Declaration of Helsinki, Good Pharmacoepidemiology Practices, and the current Spanish regulation governing observational studies. The study protocol (CHI-BEC-2020-02) received approval from the accredited regional Independent Ethics Committee (IEC) of Hospital Virgen de la Victoria of Málaga. Researchers received explicit approval from the IEC for the waiver of informed consent, based on the criteria collected in the International Ethical Guidelines for Health-related Research Involving Humans (Council for International Organizations of Medical Sciences —CIOMS— and World Health Organization —WHO—, Geneva 2016).

Patients eligible for inclusion were required to meet the following criteria: (1) confirmed diagnosis of COPD; (2) treatment with efSITT for a minimum duration of one year; (3) a history of at least one year on MITT prior to transitioning to efSITT; and (4) one or more exacerbations during the year of treatment with MITT.

Exclusion criteria included: (1) lack of access to complete medical histories and/or pharmaceutical records detailing prescription dispensation; and (2) participation in a clinical trial that interfered with standard clinical practice during the follow-up period.

The efSITT regimen comprised 87 µg of beclomethasone dipropionate, 5 µg of formoterol fumarate dihydrate, and 9 µg of glycopyrronium pMDI. The prior MITT regime could involve any combination of active ingredients administered via various inhalers. According to the Summary of Product Characteristics (SmPC) for Trimbow®, the recommended dosage is two inhalations twice daily, with a maximum daily dose of four inhalations. All treatment decisions were made at the discretion of the treating physician and were not dictated by the study protocol.

The primary endpoint was the number of moderate and severe exacerbations observed over a one-year period of efSITT compared to a preceding year with MITT. Secondary endpoints included the number of moderate exacerbations, the number of severe exacerbations, the use of rescue therapy, adherence to treatment, and lung function, all assessed over one year of efSITT compared to one year of MITT.

Exacerbations were classified according to the 2019 GOLD guidelines (7). Moderate exacerbations were defined as a worsening of respiratory symptoms requiring treatment with SABA or SAMA, along with antibiotics and/or oral corticosteroids. Severe exacerbations were characterized by the need for hospitalization, a visit to the hospital emergency department, or association with acute respiratory failure.

Adherence was defined by the percentage of prescribed inhalers dispensed by the pharmacy. Complete adherence was considered to be a collection rate of 80% or more; partial adherence was defined as a collection rate between 50% and 79%; and poor adherence was defined as a collection rate below 50%.

Lung function was assessed by calculating the percentage of the predicted values for forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. Safety was evaluated based on the number of pneumonia episodes reported.

The sample size calculation was determined to ensure that the primary objective of the study could be achieved. In the TRINITY study,[2] the rate of severe exacerbations was reported as 0.07 [95% CI 0.05–0.09; standard deviation (SD) = 0.335]. Assuming an alpha risk of 0.05 for a precision of 0.07 units in a two-sided test, a standard deviation of 0.335, and an anticipated loss rate of no more than 10% due to missing data or other factors inherent in a retrospective study, the required random sample size was calculated to be 98 patients.

Descriptive statistical analysis was conducted for all variables. Continuous variables were summarized using the number of valid cases, mean, and SD. Categorical variables were described using absolute and relative frequencies of each category over the total number of valid values (N). Comparisons of categorical variables were performed using analysis of variance (ANOVA), the chi-square test, or Fisher's exact test, as appropriate. For continuous variables, the Student's *t*-test was employed for independent samples, while longitudinal comparisons were made using the paired Student's *t*-test, with the baseline value serving as a control. A statistical significance level of 0.05 (two-tailed) was applied to all comparisons. P-values were calculated only for descriptive purposes.

Results

A total of 93 subjects were examined for eligibility. Of these, 22 subjects (23.7%) were excluded from the analysis due to the absence of exacerbations during the year they were treated with MITT, leaving 71 subjects (76.3%) who were included in the final analysis. Most of the subjects were male (78.9%), with a mean age of 72.71 years (SD = 9.03). Most of the patients were ex-smokers (97.2%), with an average history of COPD spanning 9.17 (4.35) years. The most prevalent comorbidities were arterial hypertension, obesity, cardiac disorders, and dyslipidemia (Table 1).

The mean duration of triple therapy prior to the transition to efSITT was 3.24 (1.30) years. Only 22.5% of subjects had previously received extrafine particle triple therapy. Within the MITT regimen, the most prescribed LAMA were tiotropium (50.7%) and glycopyrronium (35.2%); the most prescribed LABA were formoterol (49.3%) and indacaterol (26.8%); and the most prescribed ICS were budesonide (62.0%) and beclomethasone (21.1%) (Table 2). The most common MITT combinations were glycopyrronium/indacaterol/budesonide (21,1%) and tiotropium/formoterol/budesonide (18,3%) (Figure 1).

There was a significant reduction in the mean number of total exacerbations, decreasing from 3.52 (2.37) during the year on MITT to 2.55 (2.69) during the year of treatment with efSITT, representing a 27.56% reduction (p = 0.0043). Additionally, the mean number of moderate exacerbations was reduced by 29.56% (p = 0.0008). The 8.8% reduction in the mean incidence of severe exacerbations was not statistically significant (p = 0.7795). A 39.55% reduction in the mean number of exacerbations requiring urgent primary care visits was observed after one year of treatment with efSITT compared to the preceding year on MITT (p = 0.002). Differences in the incidence of exacerbations requiring visits to the hospital, and exacerbations requiring hospitalization were not significant (Figure 2).

Table 1 Demographic and Clinical Characteristics

Variable	N	Value
Age (years), *mean (SD)*	69	72.71 (9.03)
Gender, n *(%)*		
Men	71	56 (78.9%)
Women	71	15 (21.1%)
BMI, *mean (SD)*	16	29.04 (6.96)
Comorbidities, n *(%)*		
Arterial hypertension	71	46 (64.8%)
Obesity	29	14 (48.3%)
Cardiac disorders	71	32 (45.1%)
Dyslipidaemia	71	31 (43.7%)
Oxigenotherapy	71	19 (26.8%)
Allergy	71	13 (18.3%)
Sleep apnoea–hypopnea syndrome	71	11 (15.5%)
Diabetes	71	11 (15.5%)
Diabetes	71	11 (15.5%)
Depression	71	11 (15.5%)
Pulmonary hypertension	71	7 (9.9%)
GERD	71	5 (7.0%)
Neurological disorder	71	4 (5.6%)
Other	71	32 (45.1%)
Smoking habit, n *(%)*		
Ex-smoker	71	69 (97.2%)
Smoker	71	1 (1.4%)
No smoker	71	1 (1.4%)
Packs per year for ex-smokers (pack year^2), *mean (SD)*	58	55.22 (29.92)
Time since COPD diagnosis (years), *mean (SD)*	71	9.17 (4.35)

Abbreviations: BMI, Body mass index; COPD, Chronic obstructive pulmonary disease, GERD, Gastroesophageal reflux disease, SD, Standard deviation.

The mean number of times requiring the administration of antibiotics was significantly smaller during the efSITT period than during the MITT period (35.10% reduction, p = 0,0012). No differences were observed in the need for rescue medication or corticosteroids (Figure 3).

Adherence data during the year of MITT was available for 43 patients. Among these, 13 patients (30.2%) exhibited poor adherence, 6 patients (14%) showed partial adherence, and 24 (55.8%) achieved complete adherence. Following the transition to efSITT, all patients who had previously demonstrated poor adherence, as well as 66.7% of those with partial adherence to MITT, achieved complete adherence. After one year of efSITT treatment, only 7 out of 71 patients (9.9%) exhibited poor adherence, 6 patients (8.5%) had partial adherence, and 58 patients (81.7%) achieved complete adherence (Figure 4).

Table 2 Triple Therapy Before Extrafine Single Inhaler Triple Therapy

Variable	N	Value
Previous triple therapy with extrafine particle, n *(%)*	71	16 (22.5%)
Time in triple therapy (years), *mean (SD)*	71	3.24 (1.30)
LAMA		
Tiotropium	71	36 (50.7%)
Glycopyrronium	71	25 (35.2%)
Aclidinium	71	9 (12.7%)
Umeclidinium	71	1 (1.4%)
LABA		
Formoterol	71	35 (49.3%)
Indacaterol	71	19 (26.8%)
Olodaterol	71	7 (9.9%)
Salmeterol	71	5 (7.0%)
Vilanterol	71	5 (7.0%)
ICS		
Budesonide	71	44 (62.0%)
Beclomethasone	71	15 (21.1%)
Fluticasone	71	10 (14.1%)
Ciclesonide	71	2 (2.8%)

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; SD, standard deviation.

An improvement in the percentage of FEV_1 predicted (FEV_1% pred) was observed after one year of efSITT treatment, with a mean value increasing from 46.09% (16.34) before efSITT to 51.47% (16.83) after efSITT, representing a mean increase of 2.29% (13.90). Conversely, no improvement was observed after one year of MITT treatment, with

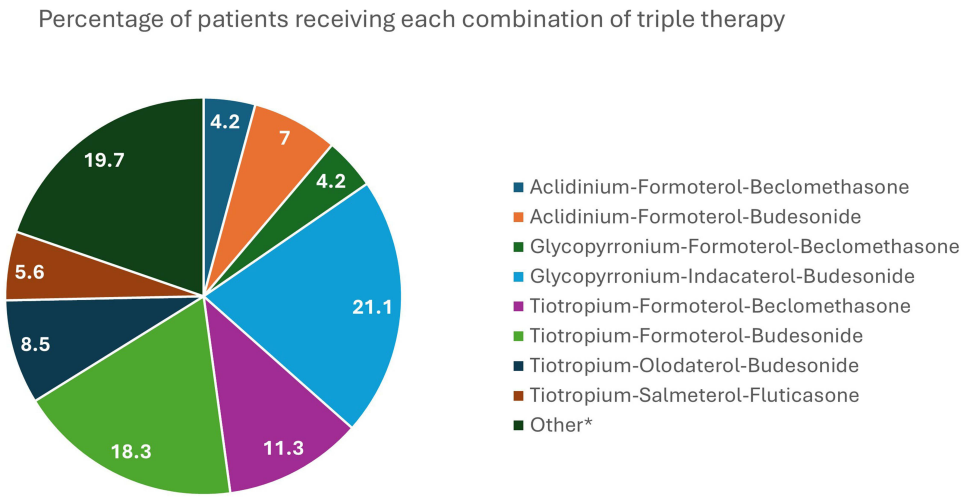

Figure 1 Combinations of triple therapy used before the switch to extrafine single inhaler triple therapy. *Other combinations prescribed to less than 3% of patients.

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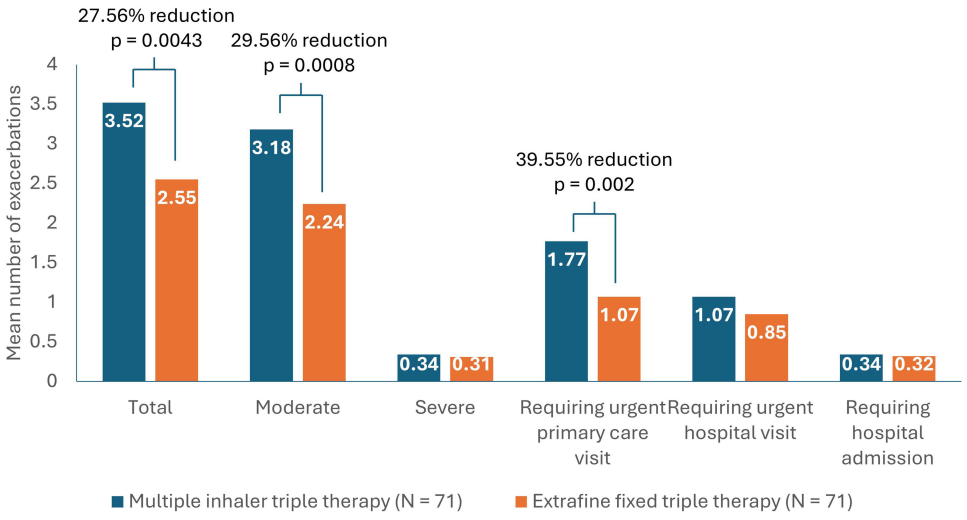

Figure 2 Incidence of exacerbations.

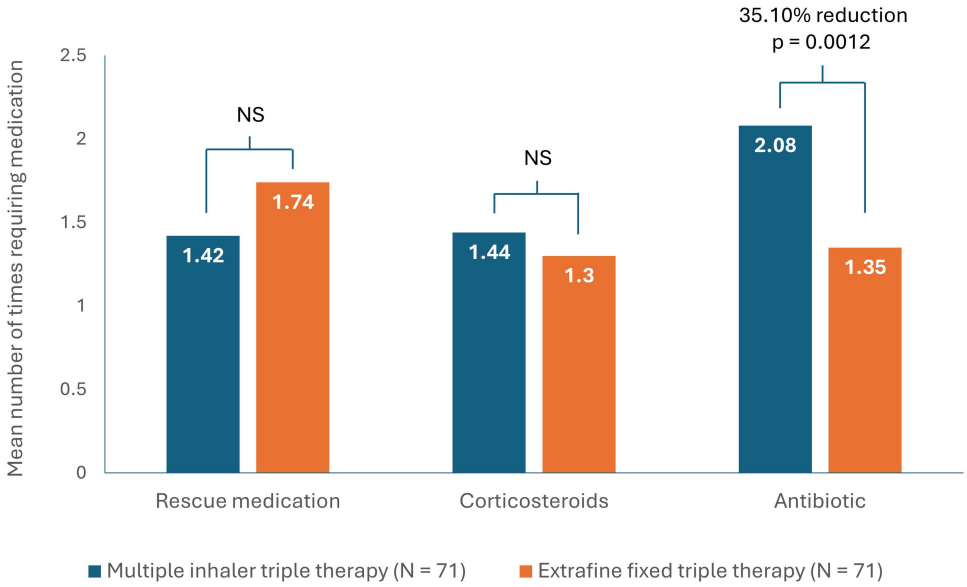

Figure 3 Requirements of rescue medication, corticosteroids, and antibiotics.
Abbreviation: NS, Non-significant.

FEV_1% pred decreasing from 50.75% (14.20) before MITT to 46.88% (16.46) after MITT, reflecting a mean reduction of 4.68% (11.78). The difference in the mean change between efSITT and MITT was statistically significant (p = 0.0333). The differences in the changes in FVC % pred and the FEV_1/FVC ratio with MITT and efSITT were not statistically significant (Table 3).

No differences were observed in the rate of pneumonia between the treatment with efSITT and MITT.

Discussion

This retrospective non-interventional study provides real-world evidence about the effectiveness of efSITT in reducing exacerbations, enhancing lung function, and improving treatment adherence among patients with moderate-to-severe COPD in Spain. The study population consisted of individuals diagnosed with COPD who were treated with efSITT with BDP/FF/G for one year and had experienced at least one exacerbation during the previous year of treatment with MITT. Our findings indicate that transitioning from MITT to efSITT is associated with a reduction in the frequency of both total

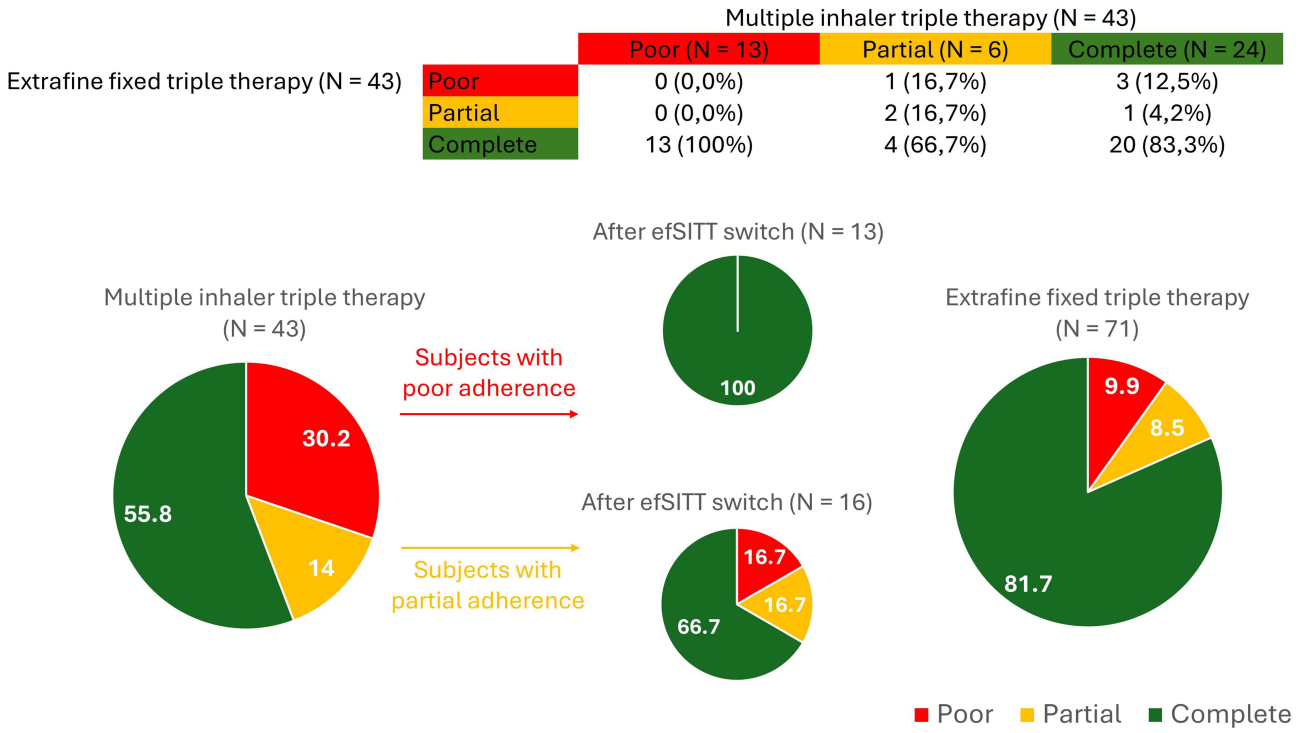

Figure 4 Change of adherence from multiple inhaler triple therapy to extrafine single inhaler triple therapy.
Abbreviations: efSITT, extrafine single inhaler triple therapy; N, Number of patients analyzed.

and moderate exacerbations, as well as improvements in FEV_1% pred, treatment adherence, and the need for antibiotic administration.

Evaluating the exacerbation rate is crucial, as their occurrence not only increases the risk of subsequent exacerbations but also significantly raises both short-term in-hospital and long-term mortality.[11–13] Three major trials explored the efficacy of efSITT with BDP/FF/G in reducing the rate of exacerbations over a 52-week treatment, among other variables. In the TRILOGY trial, efSITT demonstrated a 23% reduction in COPD exacerbations compared to BDP/FF.[4] The TRIBUTE trial showed a 15% decrease versus indacaterol/glycopyrronium,[3] while the TRINITY trial recorded a 20% reduction compared to tiotropium.[2] Additionally, the TRINITY trial indicated that efSITT was as effective as MITT for most outcomes, and it notably reduced the rate of moderate-to-severe exacerbations in patients with a history of multiple exacerbations in the preceding year. However, these trials were conducted under rigorously controlled conditions that could have amplified the results, including expert monitoring of exacerbations and high adherence rates typical of clinical trials. In fact, adherence rates for COPD patients in clinical trials are notably high, ranging from 70% to 90%,[14–16] while in everyday clinical settings, adherence tends to be significantly lower, falling between 10% and 40%.[17,18]

Table 3 Changes in Lung Function After One Year of Each Treatment

	Multiple Inhaler Triple Therapy				Extrafine Single Inhaler Triple Therapy				p value
	N	Mean Value Before	Mean Value After	Mean Change (SD)	N	Mean Value Before	Mean Value After	Mean Change (SD)	
FEV_1% pred	41	50.75 (14.20)	46.88 (16.46)	−4.68 (11.78)	47	46.09 (16.34)	51.47 (16.83)	2.29 (13.90)	0.0333
FVC % pred	38	64.99 (17.04)	62.50 (17.96)	−3.36 (16.82)	42	61.56 (17.84)	65.83 (18.65)	1.98 (17.22)	0.4745
FEV_1/FVC (%)	40	77.40 (16.17)	75.15 (18.36)	−1.72 (17.03)	57	74.56 (18.36)	78.17 (20.08)	0.48 (2.60)	0.3891

Abbreviations: FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; SD, standard deviation.

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In our study, although conducted in a real-world setting, the switch from MITT to efSITT resulted in a comparable reduction of 27.56% in the rate of moderate and severe exacerbations and a 29.56% reduction in the incidence of moderate exacerbations. Conversely, the reduction observed in severe exacerbations did not reach statistical significance. This indicates that the overall reduction in exacerbations observed was predominantly due to a decrease in moderate exacerbations that did not necessitate hospitalization.

Few real-world studies have assessed the effectiveness of efSITT in patients with COPD.[19–24] Some studies were not specifically designed to compare efSITT with MITT but included a subset of patients who had been previously treated with MITT before commencing efSITT. In the TRIVOLVE study, 76% of the participants had previously used MITT, and 65% of these individuals switched to efSITT for its ease of use. This study reported improvements in inhalation technique, adherence, symptoms, patient satisfaction, and lung function, but the authors did not examine the rate of exacerbations.[19] Similarly, the TriOptimize study involved 57% of patients who had been previously on treatment with MITT, in whom improvements in health-related quality of life, symptom management, and adherence were observed.[20] In the TRICOP study, nearly half of the patients had previously received MITT, and improvements in lung function, symptom control, and exacerbations were noted.[21] The TRITRIAL study enrolled 34% of subjects treated with MITT and found that efSITT improved patients' health-related quality of life, sleep quality, adherence, and reduced symptoms and exacerbation risk.[22] Lastly, the RATIONALE trial concluded that early introduction of fixed triple combination results in improvements in adherence, symptom scores, exacerbation frequency and quality of life, and 27.4% of the patients included had previously been treated with MITT.[24]

To our knowledge, there are limited studies specifically evaluating the impact of switching from MITT to single-inhaler triple therapy (SITT) within the same patient cohort. Therefore, our findings contribute valuable evidence regarding efSITT in routine clinical practice. One such study, the TRIWIN study, was a multicenter, non-interventional, prospective investigation conducted in Greece. It focused on patients with moderate to severe COPD who remained symptomatic despite receiving MITT at the time of inclusion. Over a 24-week period of treatment with efSITT, the proportion of participants using rescue medication decreased from 16.2% to 7.4%. Additionally, there were improvements in FEV_1%pred, FVC %pred, and adherence during the study period.[25]

In our study, we observed a substantial reduction in antibiotic use with efSITT. This may be attributed to the lower risk of developing lower-respiratory tract infections after initiating extrafine beclomethasone, compared to other non-extrafine inhaled corticosteroids.[26] However, this finding in routine clinical practice needs further confirmation through additional studies.

The success of long-term treatment largely depends on patient adherence, which is critical for enhancing symptom control and lung function and for reducing the risk of exacerbation.[27,28] In addition to optimizing clinical outcomes, good adherence is also associated with reduced healthcare costs.[27,29] Prior to the advent of SITT, patients undergoing triple therapy often needed to use multiple inhalers daily.[30,31] The complexity associated with managing multiple inhalers has been linked to inadequate inhalation technique,[32,33] leading to suboptimal symptom control.[34] Consequently, fixed-dose combinations of two bronchodilators and an ICS were developed to streamline therapy. Unlike multiple inhalers, the utilization of a single inhaler can simplify dosing, potentially improving adherence to the regimen, and thereby enhancing the overall effectiveness of the treatment.

Our study indicates that transitioning to efSITT confers notable advantages for patients who previously used multiple inhalers. Following the switch to efSITT, adherence to treatment was significantly improved in our cohort over the course of one year. These findings suggest that efSITT may offer substantial benefits in terms of enhancing adherence in real-world settings, an aspect not thoroughly assessed in controlled clinical environments.

Consistent with our findings, the TriOptimize study reported that transitioning from MITT to efSITT positively impacts patient adherence.[20] Furthermore, the OPTI retrospective analysis indicated that adherence is notably higher among patients receiving SITT compared to those on MITT, based on a cohort of over 3000 patients in France.[35] Additionally, research by Miravitlles et al demonstrated that enhanced adherence resulting from a switch from MITT to SITT in COPD patients led to a substantial reduction in exacerbations and associated healthcare costs.[36]

In our study, safety was assessed by evaluating the incidence of pneumonia, which did not show a significant difference between the periods of MITT and efSITT.

The non-interventional design of this study provided valuable insights into patient adherence to treatment in routine clinical practice, addressing some of the limitations inherent in controlled trials. Nevertheless, the observational and retrospective nature of this study introduces certain limitations. To address this limitation, the number of patients evaluated for each variable is provided to account for missing values. Our study was based on retrospective real-world data, so some missing information was expected. However, any missing data would affect both the pre- and post-device switch periods equally. Second, the sample size is relatively modest, and the study was conducted at a single site within a specific healthcare area in Spain. Given the variations of clinical practices in different healthcare systems and environments, further research involving multiple centers across different regions of Spain would be beneficial and could validate the applicability of our findings and extend the results to broader populations and settings. Lastly, the method used to evaluate adherence in this study has inherent limitations, as it does not necessarily reflect the accuracy of the inhalation technique or whether the patient is taking the medication at the proper dose.

Conclusions

In conclusion, our results suggest that efSITT might reduce the rate of exacerbations in patients with moderate-to-severe COPD previously treated with MITT in the real-world setting, probably by improving treatment adherence. Similar studies in other regions of the country and further large-scale studies are needed to validate and expand upon these results.

Abbreviations

BDP, Beclomethasone dipropionate; COPD, Chronic obstructive pulmonary disease; efSITT, Extrafine single-inhaler triple therapy; FEV_1, Forced expiratory volume in the first second; FF, Formoterol fumarate dihydrate; FVC, Forced vital capacity; G, Glycopyrronium; GOLD, Global initiative for chronic obstructive lung disease; ICS, Inhaled corticosteroid; LABA, Long-acting β2-agonist; LAMA, Long-acting muscarinic antagonist; MITT, Multiple-inhaler triple therapy; pMDI, pressurized metered dose inhaler; SABA, Short-acting β2-agonist; SAMA, Short-acting muscarinic antagonist; SD, Standard deviation; SmPC, Summary of product characteristics; SITT, Single-inhaler triple therapy.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

The study protocol (CHI-BEC-2020-02) was approved by the accredited regional Independent Ethics Committee (IEC) of Hospital Virgen de la Victoria of Málaga.

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Disclosure

The authors report there are no competing interests to declare for this work.

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