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ORIGINAL RESEARCH

Real-World Effectiveness of Triple Extrafine Fixed-Dose Combination with Beclomethasone/Formoterol/Glycopyrronium on Symptoms and Lung Function in COPD: A Systematic Review and Meta-Analysis

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Introduction: Chronic obstructive pulmonary disease (COPD) is a significant global health issue characterized by persistent airflow limitation and inflammation. Triple fixed-dose combinations (FDCs) of inhaled corticosteroids (ICS), long-acting β2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) show promise by potentially enhancing bronchodilation and anti-inflammatory effects. Although randomized controlled trials (RCTs) provide efficacy data, they may not fully represent real-world clinical practice, highlighting the value of real-world evidence (RWE).

Methods: This study conducted a systematic review and meta-analysis of prospective observational multicenter studies to evaluate the real-world effectiveness of a triple extrafine FDC containing beclomethasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium (G) in moderate-to-severe COPD patients. Databases MEDLINE and SCOPUS were searched for relevant studies reporting on the COPD Assessment Test (CAT) score and forced expiratory volume in one second (FEV_1).

Results: The meta-analysis included seven studies with 5952 patients, indicating high methodological quality with Newcastle–Ottawa Scale scores ≥7. Results showed significant improvement in CAT scores (−5.82 95% CI −7.61 - −4.03; $P < 0.001$) and FEV_1 (127 mL 95% CI 42–212; $P < 0.001$) for extrafine BDP/FF/G FDC compared to any prior treatments (ICS/LABA, ICS+LABA, LABA/LAMA, LABA+LAMA, multiple-inhaler triple therapy, single-inhaler triple therapy), exceeding minimal clinically important differences. Heterogeneity was significant, but Egger's test suggested no significant publication bias.

Conclusion: The triple extrafine BDP/FF/G FDC effectively improves health status and lung function in real-world COPD patients, supporting its use as a viable therapeutic strategy. Further research should explore long-term outcomes and investigate specific patient subgroups to optimize individualized treatment approaches.

Keywords: COPD, symptoms, lung function, real-world evidence, meta-analysis

Introduction

Current strategies for the treatment of chronic obstructive pulmonary disease (COPD) focus on symptom alleviation and exacerbation reduction through various inhaled medication combinations.[1] Triple fixed-dose combinations (FDC) incorporating inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), and long-acting muscarinic antagonists (LAMA) offer effective therapeutic strategies, potentially providing synergistic bronchodilation and anti-inflammatory effects.[2–6]

While randomized controlled trials (RCTs) provide valuable insights into treatment efficacy and safety under controlled conditions, their findings may not fully reflect real-world clinical practice.[7,8] This is particularly relevant with evolving drug development, which now includes biologics and potentially stem cell.[9–12] Current combination

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therapies often target more specific patient populations, making traditional RCTs less practical for evaluating treatment effects in these contexts.[13–16] Therefore, real-world evidence (RWE), derived from observational studies, plays an increasingly critical role in complementing RCT data, providing insights into effectiveness and safety across diverse patient populations.[17,18] However, it is crucial to acknowledge biases in observational studies and the potential for misleading conclusions, especially for moderate treatment effects.[19]

In the first large real-world, retrospective, observational study of triple FDC in COPD, it was highlighted that in ICS-naïve COPD patients, the triple FDC was not more effective than dual bronchodilators in reducing exacerbation incidence, except in those with multiple exacerbations.[20] However, a subsequent re-analysis, aligned with GOLD recommendations for COPD with a predominant exacerbation profile, suggested prioritizing triple FDC for patients in Group E and other exacerbating patients with an eosinophil count of ≥300 cells/μL.[21]

This systematic review and meta-analysis evaluates multicenter observational studies on the real-world effectiveness of a triple extrafine FDC containing beclomethasone dipropionate (BDP), formoterol fumarate (FF), and glycopyrronium (G) on symptoms, measured by the COPD Assessment Test (CAT) score, and lung function, measured by forced expiratory volume in the 1st second (FEV_1). The CAT score contributes to the comprehensive assessment of COPD and guides clinicians in decision-making and patient management. It may improve communication between physicians and COPD patients, establishing it as a robust outcome measure in real-world studies.[22–24] Additionally, a relationship exists between CAT and small airway dysfunction (SAD).[25] FEV_1 is crucial due to its strong association with health-related quality of life in COPD patients, as demonstrated by the COSYCONET cohort,[26] along with well-established correlations between FEV_1 and patient-reported outcomes.[27]

Preclinical studies demonstrated the synergistic bronchorelaxant effects of the BDP/FF/G triple combination in human airway smooth muscle, extending to both medium and small airways.[2] This synergy suggests benefits beyond improved FEV_1, potentially reducing SAD that is significantly associated with disease severity and symptoms.[28–30] This triple FDC has demonstrated improvement in peak and trough FEV_1 as well as consistent reduction in airway resistance in patients with SAD.[3]

Effects of extrafine BDP/FF/G FDC in COPD have been evaluated in a high-quality systematic review and meta-analysis of RCTs registered in PROSPERO.[31] This review reported a favorable efficacy and safety profile, ranking it similarly or superior to other triple FDCs according to the Implemented Bidimensional Surface under the cumulative ranking curve analysis (IBiS) score. However, integrating RCT findings with quantitative RWE synthesis is essential for a comprehensive understanding of effectiveness.[19] Thus, the aim of this study was to perform a systematic review and meta-analysis to evaluate extrafine BDP/FF/G FDC effectiveness in COPD patients, focusing on its impact on symptoms and lung function in real-world clinical settings.

Methods

Search Strategy and Study Eligibility

The protocol of this systematic review and meta-analysis was submitted in the international prospective register of systematic reviews (PROSPERO registration ID: CRD42024614977) and performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[32,33] The relative flow diagram is shown in Figure 1. This study satisfied all the recommended items reported by the MOOSE checklist (Table S1).[33]

A comprehensive literature search was performed for prospective observational multicenter studies written in English and reporting data on CAT and FEV_1 in COPD patients.

In this regard, the PICO (Population, Intervention, Comparator, and Outcomes) framework was applied to develop the literature search strategy, as previously reported.[34] Namely, the "Population" included moderate-to-severe COPD in real-world patients; the "Intervention" regarded triple extrafine FDC with BDP/FF/G; the "Comparator" was any prior treatment for COPD not including triple extrafine FDC with BDP/FF/G; the "Outcomes" were CAT score and FEV_1.

The search was performed in MEDLINE and SCOPUS to provide for relevant studies published with no time limit up to September 24th, 2024. The research string was as follows: "COPD AND beclomethasone AND formoterol AND

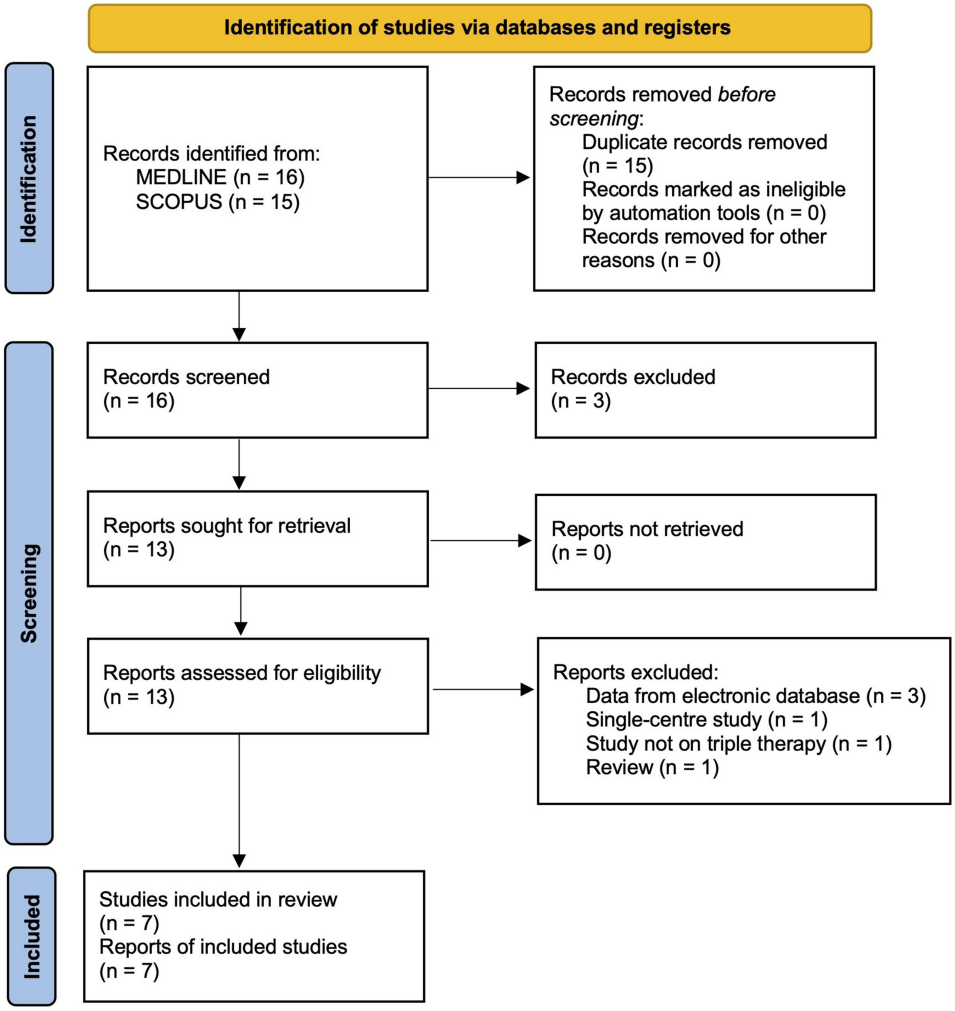

Figure 1 PRISMA 2020 flow diagram for the identification of the studies included in the systematic review and meta-analysis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

glycopyrronium AND (observational OR real-world OR real-life)". Table S2 reports the specific literature search used in MEDLINE and SCOPUS.

Study Selection

Prospective observational multicenter studies comparing triple extrafine FDC with BDP/FF/G with any prior treatment for COPD not including triple extrafine FDC with BDP/FF/G were included in the systematic review and meta-analysis. Either retrospective, cross-sectional, single center studies were excluded from the systematic review and meta-analysis. Studies not investigating triple extrafine FDC with BDP/FF/G, or retrospective, or single-center studies were excluded. Two reviewers independently examined the relevant studies identified from the literature search. The studies were selected in agreement with above mentioned criteria, and any difference in opinion concerning the eligibility was resolved by discussion leading to consensus.

Data Extraction

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations[35] from published papers and/or Supplementary Data Files. The extraction process included checks for study characteristics, treatment duration, number of analyzed patients, drugs, doses and regimen of administration, inhaler device, main inclusion criteria, age, sex, smoking history, exacerbations in the previous year, CAT score, FEV_1, and study quality

assessment via the Newcastle-Ottawa Scale (NOS). Efficacy data were extracted at the specified time-points of the studies.

The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described.[36] Cohen's Kappa ≥0.80 indicated excellent agreement, coefficients between 0.61 and 0.80 represented substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and <0.41 fair to poor agreement.[36]

Endpoints

The primary endpoint of this systematic review and meta-analysis was the CAT score, while FEV_1 was selected as the secondary endpoint.

Data Synthesis and Analysis

A pairwise meta-analysis was performed, and data were expressed as mean difference (MD) and 95% confidence interval (95% CI). Since data were selected from a series of observational studies performed by researchers operating independently and a common effect size cannot be assumed, binary random-effects model was used in order to balance the study weights and adequately estimate the 95% CI of the mean distribution of the MD for the investigated variables.[37–39]

A meta-regression using the random-effects method was also performed to investigate whether studies and patients' characteristics may represent potential effect modifiers modulating the effectiveness of BDP/FF/G FDC in COPD patients. The meta-regression was carried out by plotting the outcome variables obtained from the pairwise meta-analysis with the co-variates extracted from the included studies.[40,41] The following co-variates were included in the meta-regression analysis: study duration, prior treatment, age, sex, smoking habit, exacerbation history, blood eosinophils, FEV_1 at baseline, CAT at baseline, NOS. The resulting regression coefficient indicates how strongly the co-variates may modify the effect induced by BDP/FF/G FDC.[41]

Quality of the Studies, Risk of Bias, and Evidence Profile

The NOS was used to assess the quality of the studies.[42] A study can be awarded with a maximum of one star for each item within the "Selection" and "Outcome" categories and a maximum of two stars can be given for "Comparability". In the present systematic review, the NOS quality assessment score was established to be in the range between zero and a maximum of nine stars. Detailed information on the NOS scale is available at https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf. Studies reporting a total NOS score ≥7 were considered of high quality, whereas those reporting a total NOS score <7 were considered of low quality.[43]

The test for heterogeneity (I^2) was performed to quantify the between-study dissimilarity[44] and sensitivity analyses were carried out according to study design to identify the studies that introduced significant ($P < 0.05$) and/or substantial levels of heterogeneity ($I^2 > 50\%$).[45]

The risk of publication bias was assessed by applying the funnel plot and Egger's test as previously described.[46,47] The equation of Egger's test was as follows: $SND = a + b \times precision$, where SND represents the standard normal deviation (log of the odds ratio divided by its standard error (SE)), and precision represents the reciprocal of the SE. Evidence of asymmetry from Egger's test was considered to be significant at $P < 0.1$, and the graphical representation of 90% confidence bands is presented.[46,47]

The quality of the evidence was assessed for the primary endpoint according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, indicating ⊕⊕⊕⊕ for high-quality of evidence, ⊕⊕⊕ for moderate-quality of evidence, ⊕⊕ for low-quality of evidence, and ⊕ for very low-quality of evidence.[48]

Two reviewers independently assessed the quality of studies, risk bias, and evidence profile, and any difference in opinion was resolved by consensus.

Software and Statistical Significance

Open-MetaAnalyst and metaHUN software were used to perform the pairwise meta-analysis, funnel plot, and Egger's test (http://softmed.hacettepe.edu.tr/metaHUN/);[49,50] the visual analysis of symmetry/asymmetry of funnel plots was performed by using ChatGPT (GPT4o), an advanced Artificial Intelligence used as a model for quantitative questions;[51] the quality of evidence assessed using the GRADEpro GDT software.[48] The level of statistical significance was set at $P<0.05$.

Results

Study Characteristics

The meta-analysis included 7 multicenter, observational, prospective, real-world studies[52–58] examining the effectiveness of a triple extrafine FDC with BDP/FF/G in patients with moderate-to-severe COPD. A total of 5952 patients were analyzed across these studies. Importantly, all seven studies achieved a total NOS score of ≥7, indicating high methodological quality. The studies varied in duration (24 to 52 weeks), sample size, and specific inclusion criteria; however, all focused on patients with moderate-to-severe COPD. The studies encompassed diverse prior treatment regimens. The history of exacerbation and blood eosinophils were available only in two studies ([55,58] and,[52,53] respectively), therefore, the meta-regression analysis was not performed on these co-variates. Not all the studies reported FEV_1 with the same metrics (% predicted or mL). Detailed information on the characteristics of the studies is reported in Table 1, while Figure 2 illustrates the prevalence of prior treatments among the analyzed COPD population.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen's Kappa 0.95 and 1.00, respectively). The intra-rater reliability produced a Cohen's Kappa of 1.00 after the learning process.

Primary Endpoint – CAT Score

The overall meta-analysis showed a statistically significant ($P < 0.001$) MD in CAT score between the BDP/FF/G FDC group and the prior treatments groups (MD −5.82 95% CI −7.61 – −4.03; ⊕⊕⊕⊕; Figure 3A). Substantial and statistically significant ($P < 0.001$) heterogeneity was observed across the studies ($I^2 = 97.52\%$).

There was a clear asymmetry in the funnel plot, with more studies clustered to the left (showing a larger negative MD) and a relative lack of studies on the right (indicating a less negative MD) (Figure S1). There were also some outliers with larger SE. However, the Egger's test for publication bias was not statistically significant ($P = 0.548$).

The meta-regression analysis revealed that no factors, including study duration, significantly ($P > 0.05$) modified the effectiveness of BDP/FF/G FDC on CAT scores; only the use of multiple-inhaler triple therapy (MITT) at baseline showed a trend towards significance (coefficient 0.034, $P = 0.091$; Figure 3B).

Secondary Endpoint – FEV_1

The overall meta-analysis revealed a statistically significant ($P < 0.001$) improvement in FEV_1 with the BDP/FF/G FDC compared to prior treatments (% predicted MD 4.21 95% CI 2.29–6.12; mL MD 127 95% CI 42–212; Figure 4A and B, respectively). Substantial and statistically significant ($P < 0.001$) heterogeneity was present across the studies for FEV_1 reported as % predicted and mL ($I^2 = 78.10\%$ and 73.12%, respectively).

Funnel plots (Figure S2) suggested potential publication bias for FEV_1, with an asymmetry indicating an over-representation of studies showing larger positive effects and few studies reporting smaller MD. For FEV_1 expressed as % predicted, Egger's test confirmed this bias ($P < 0.01$). However, excluding the TRIWIN study[56] in a sensitivity analysis fully resolved this bias, resulting in a not significant Egger's test ($P = 0.124$). Concerning FEV_1 expressed as mL, Egger's test showed no statistically significant publication bias ($P = 0.229$), and a sensitivity analysis was not necessary.

Meta-regression analysis on the effect of BDP/FF/G FDC on FEV_1 expressed as % predicted identified smoking habit as a significant effect modifier (coefficient 0.160, $P < 0.05$), with current smokers showing a greater treatment effect than non-smokers and reported a trend toward significance for male sex (coefficient 0.172, $P = 0.067$). Concerning the effect of BDP/FF/G FDC on FEV_1 expressed as mL, male sex was associated with a significantly larger treatment effect (coefficient 8.182, $P < 0.01$), current smokers experienced a significantly greater improvement than non-smokers

Table 1 Study Characteristics, Patients' Demographics, Baselines, and NOS Score of the Included Studies

Study, year, PMID, Name of the Study, Reference	Study Characteristics	Treatment Duration (Weeks)	Number of Analyzed Patients	Drugs, Doses and Regimen of Administration	Inhaler device	Prior Treatment	Main Inclusion Criteria	Age (Years)	Male (%)	Current Smokers (%)	Smoking history (Pack-Years)	Exacerbations in the Previous Year (Rate)	Blood Eosinophils (cells/μL)	Baseline FEV_1 (% Predicted)	Baseline CAT SCORE	NOS Selection	NOS Comparability	NOS Outcome	Total NOS Score
Südi et al 2024, RATIONALE, 39219564[7]	Multicenter, prospective, real-life study in Hungary	52	613	BDP/FF/G, 87/5/9 μg 2 inhalations BID	NA	ICS/LABA, LABA/LAMA, MITT	Age ≥35 years, ≥1 severe or ≥2 moderate exacerbation in the 12 months before study inclusion or treatment switched due to high risk of exacerbation, previously treated with ICS/LABA, LABA/LAMA or MITT,80%> FEV_1≥ 50%, CAT score ≥10 and/or mMRC ≥2	64.5	49.4	54.2	NA	NA	NA	59.6	20.8	****	**	**	8
Richeldi et al 2024, TRITRIAL, 38435125[5]	Multicenter, prospective, real-life study in Italy	52	655	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	SITT, MITT, LABA +LAMA, LABA/LAMA, ICS +LABA, ICS/LABA, others	Age ≥40 years, moderate-to-severe COPD, start of treatment with BDP/FOR/GLY within the previous 14 days, CAT ≥10, at least one moderate or severe exacerbation in the 12 months before	71.2	68.2	25.6	NA	1.90	NA	50.2	22.5	****	**	**	8
Steiropoulos et al 2024, TRIWIN, 39049587[6]	Multicenter, prospective, real-life study in Greece	24	475	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	MITT	Age 40 to 75 years, moderate-to-severe COPD with a CAT score ≥10 despite receiving MITT	64.9	63.8	51.6	NA	NA	NA	55.4	21.4	****	**	***	9
Brusselle et al 2023, TRIVOLVE, 37562659[4]	Multicenter, prospective, real-life study in Belgium	52	126	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	ICS/LABA, LABA/LAMA, MITT	Age ≥40 years, moderate-to-severe COPD, previously treated with ICS/LABA, LABA/LAMA or MITT	66.2	67.5	NA	NA	1.95	NA	NA	21.0	****	**	**	8

Porpodis et al 2023, TRIBUNE, 36965590[3]	Multicenter, prospective, real-life study in Greece	24	1195	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	LABA +LAMA, LABA/LAMA, ICS +LABA, ICS/LABA	Age 35 to 75 years, moderate-to-severe COPD, current or former smokers (>20 pack-years), physician's decision to initiate efSITT, at least one exacerbation requiring oral steroids and/or antibiotics in the 12 months before starting efSITT, previously treated with ICS/LABA or LABA/LAMA ≥2 months prior to enrolment	NA	70.5	48.2	NA	NA	NA	52.2	20.9	***	**	***	8
Gessner et al 2022, TriOptimize, 36483674[2]	Multicenter, prospective, real-life study in Germany	24	2623	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	ICS/LABA, LABA/LAMA, MITT	Moderate-to-severe COPD, physician's decision to initiate efSITT, at least one exacerbation in the 12 months before starting efSITT	65.8	55.10	35.2	39.2	NA	219	48.1	21.50	****	**	**	8
Marth et al 2021, TRICOP, 33901786[1]	Multicenter, prospective, real-life study in Austria	52	265	BDP/FF/G, 87/5/9 μg 2 inhalations BID	pMDI	LABA +LAMA, LABA/LAMA, ICS +LABA, ICS/LABA	Moderate-to-severe COPD, not adequately treated by ICS/LABA or LABA/LAMA, or MITT	67.0	66.0	31.0	43.8	NA	NA	43.4	22.7	****	**	***	9

Notes: Asterisk indicators (*) represent the number of stars assigned by NOS to rank the quality of non-randomized studies in meta-analyses.

Abbreviations: BDP, beclomethasone dipropionate; BID, bis in die, twice daily; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; efSITT, extrafine-single inhaler triple therapy; FDC, fixed-dose combination; FEV_1, forced expiratory volume in the first second; FF, formoterol fumarate; G, glycopyrronium bromide or glycopyrrolate; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; mMRC, modified medical research council dyspnea scale; NA, not available; NOS, Newcastle-Ottawa Scale; PMID, PubMed IDentifier; pMDI, pressurized metered-dose inhaler; SITT, single-inhaler triple therapy.

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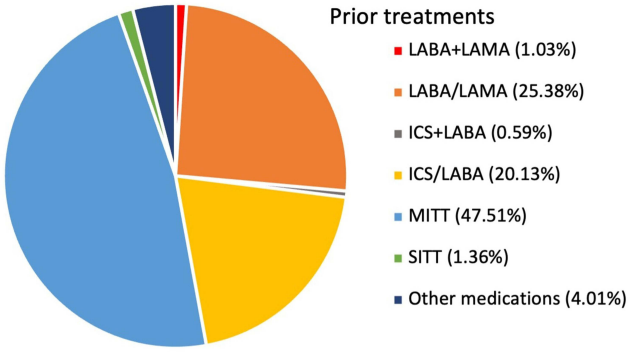

Figure 2 Pie chart reporting the percentage of prior therapies among the analyzed COPD population.
Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; MITT, multiple-inhaler triple therapy; SITT, single-inhaler triple therapy.

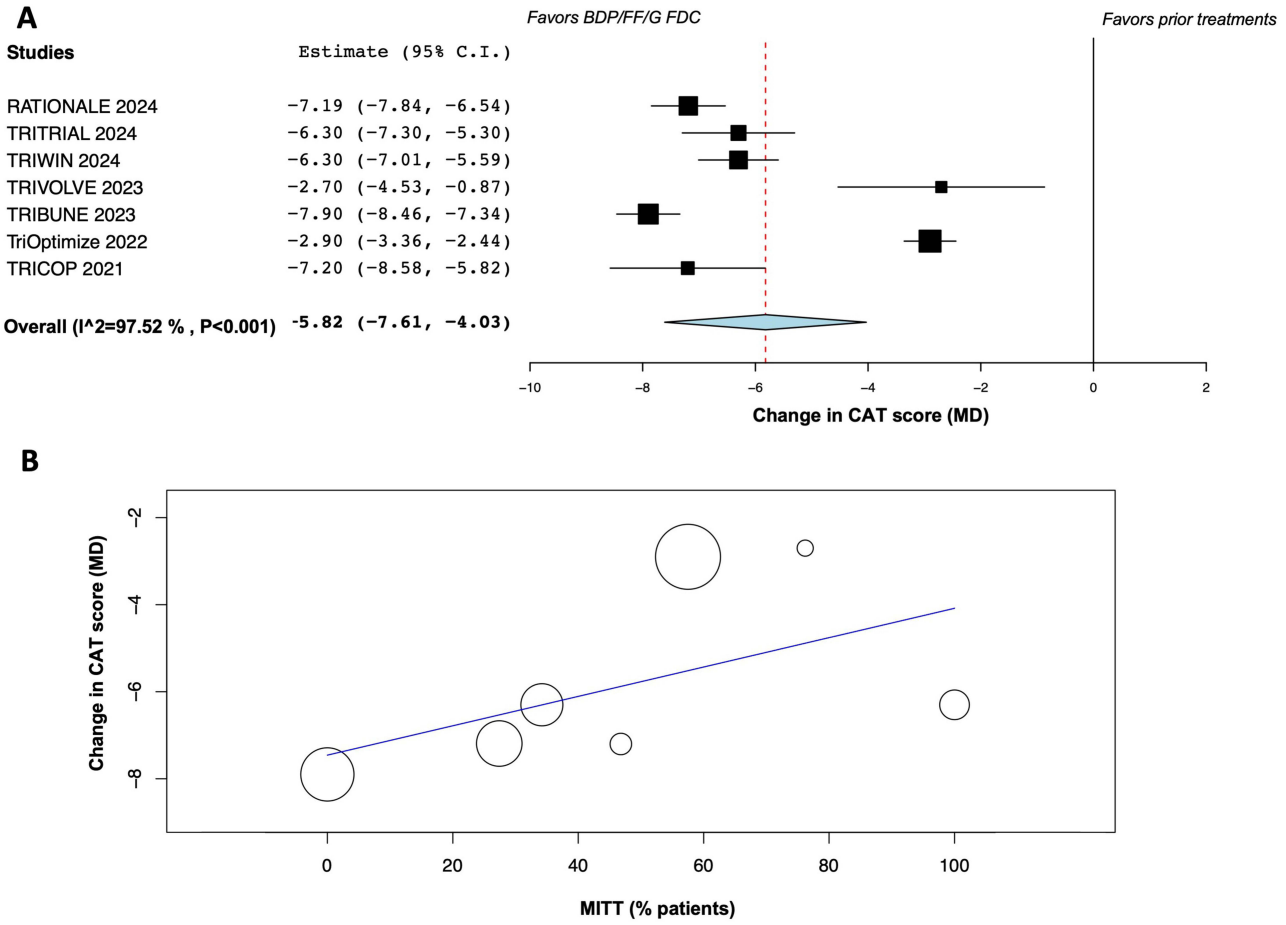

Figure 3 Forest plot showing the effectiveness of BDP/FF/G FDC on CAT score compared to prior treatments (**A**) and meta-regression analysis of the potential modification induced by MITT (**B**) in moderate-to-severe COPD patients.
Abbreviations: BDP, beclomethasone dipropionate; CAT, COPD Assessment Test, COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FF, formoterol fumarate; G, glycopyrronium; MD, mean difference; MITT, multiple-inhaler triple therapy.

(coefficient 10.496, $P < 0.001$), and greater baseline FEV_1 values were associated with a significantly larger treatment effect (coefficient 17.047, $P < 0.05$).

In the meta-regression analysis, when the co-variate "smoking habit" was analyzed together with the co-variate "use of ICS", the coefficient changed by only ±1.10% compared to the value obtained for "smoking habit" alone. This indicates that

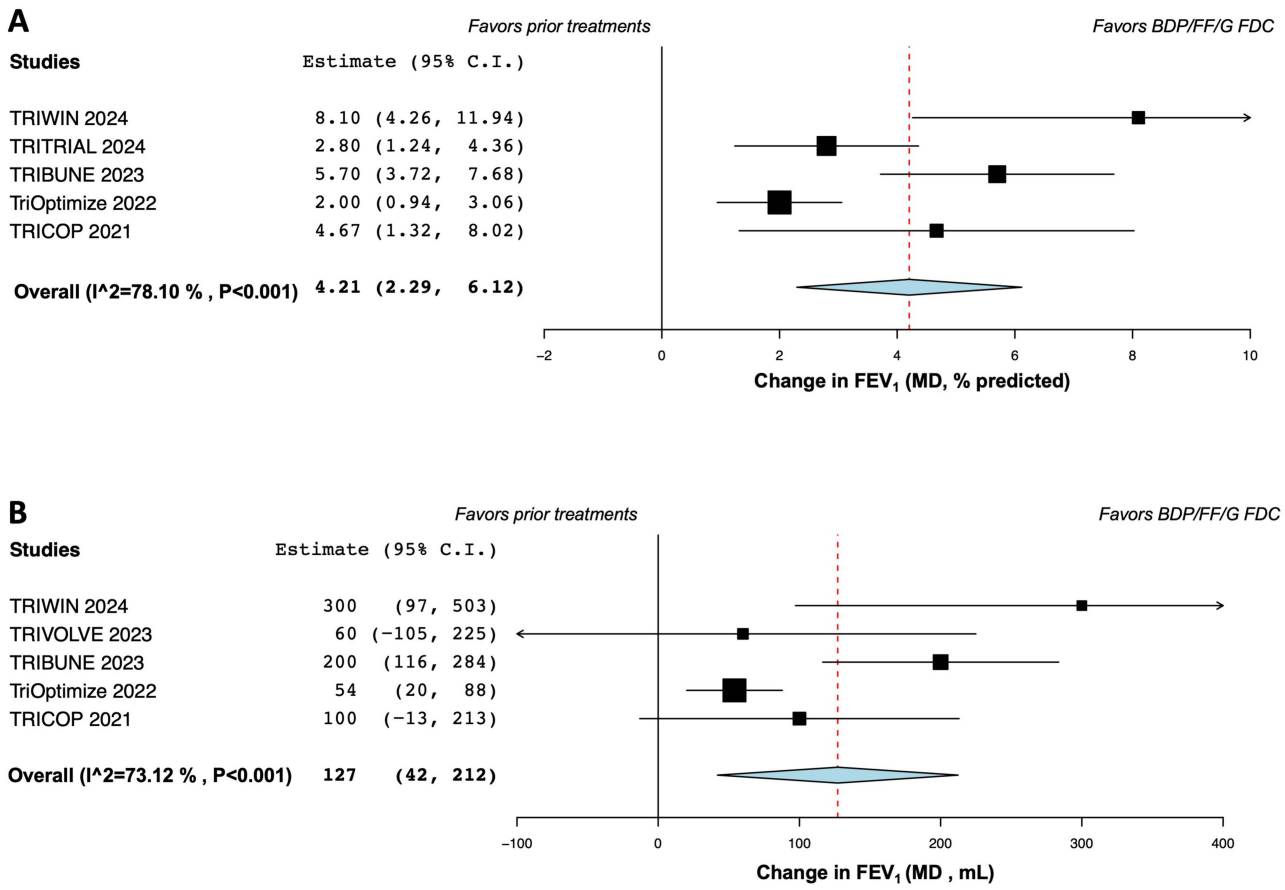

Figure 4 Forest plot showing the effectiveness of BDP/FF/G FDC on FEV_1 expressed as % predicted (**A**) and mL (**B**) compared to prior treatments in moderate-to-severe COPD patients.

Abbreviations: BDP, beclomethasone dipropionate; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FEV_1, forced expiratory volume in the 1st second; FF, formoterol fumarate; G, glycopyrronium; MD, mean difference.

the improvement in FEV_1 observed with BDP/FF/G FDC among current smokers was not significantly ($P > 0.05$) modulated by previous ICS treatment.

No other co-variates, including study duration, were identified as potential effect modifiers of BDP/FF/G FDC on FEV_1 expressed as % predicted and mL. Detailed information on meta-regression analysis of secondary endpoint is shown in Figure S3.

Discussion

COPD has emerged as a major global health challenge, characterized by persistent airflow limitation that is progressive in nature and linked to significant symptoms, morbidity, and mortality.[1] The management of COPD has evolved considerably, with recommendations emphasizing the importance of integrated and individualized treatment strategies to alleviate symptoms and minimize the risk of exacerbation.[1] In recent years, RWE has gained traction as it provides insights into treatment effectiveness beyond the controlled environments of RCTs, particularly for complex and multifactorial conditions such as COPD.[59–61] Within this context, the results of this systematic review and meta-analysis demonstrate with high-quality of evidence that triple extrafine FDC with BDP/FF/G is statistically effective in enhancing both health status, as measured by the CAT score, and lung function assessed through FEV_1 in moderate-to-severe COPD patients in a real-world setting. Notably, the significant improvements observed were clinically meaningful, with the CAT score showing a MD of ≃-6 and a corresponding minimal clinically important difference (MCID) threshold of ≥2, while FEV_1 revealed an MD of ≃130 mL, exceeding the MCID of ≥60 mL vs active comparator.[62,63] These findings underline the

therapeutic potential of the triple therapy, reflecting significant progress in managing COPD symptoms and lung function when compared to prior treatments, regardless of what they may be.

Like for previous well-performed meta-analyses of observational studies,[43,64,65] a critical aspect of the present study is the detection of significant heterogeneity across studies. The I^2 values resulting for CAT and FEV_1 indicate variability in participant response, study design, or treatment effect analysis.[45] However, despite this heterogeneity, the Egger's test did not suggest significant bias affecting the outcome estimates. This finding is important because it indicates that, while study characteristics may vary, the overall effectiveness of the triple FDC therapy has clinically relevant implications, showing consistent positive outcomes across diverse populations and prior treatments.[66,67] In other words, the direction of the effect estimates in this meta-analysis is correct, and adding data from future investigations may a yield narrower 95% CI range.[43] Furthermore, the meta-regression approach for studying the potential effect modifiers aids in interpreting individual studies, providing a lens through which different studies can contribute to a solid evidence pyramid.[68,69] Thus, this meta-analysis strongly supports the adoption of the BDP/FF/G FDC in clinical practice.

In assessing factors that may influence the effectiveness of the triple therapy, the analysis revealed that neither demographic nor baseline characteristic significantly modulated the effectiveness of the BDP/FF/G FDC combination on CAT scores. This is another important point, as it implies a generally uniform response to the therapy irrespective of patient demographics or prior treatment status; however, as expected, a trend towards significance in baseline use of MITT indicates the potential for further exploration of treatment pathways for these patients.[70,71] In contrast, the meta-regression analysis indicated multiple factors that did affect the effectiveness of the triple therapy on FEV_1. Notably, male patients exhibited greater treatment benefits relative to female patients, aligning with known biological differences in pathophysiology of COPD.[72–75] Additionally, the influence of smoking status was profound as current smokers showed better treatment outcomes than non-smokers, suggesting that habit patterns play a pivotal role in treatment response. Unexpectedly, we found that the beneficial impact of BDP/FF/G FDC on the lung function of current smokers was not related to the use or non-use of ICS in prior treatments. This finding contrasts with previous studies suggesting that COPD patients who smoke may exhibit partial resistance to ICS, as cigarette smoke significantly reduces the activity and expression of histone deacetylase 2 (HDAC2), an enzyme crucial for suppressing inflammatory gene expression.[76,77] We cannot rule out that HDAC2 inhibition in smokers may influence the risk of exacerbation, an outcome not reported in the studies included in this meta-analysis. However, while it has been demonstrated that heavier or current smokers do not gain the same benefit from ICS use on lung function and exacerbation rates as lighter or ex-smokers, these effects do not appear to reach the MCID.[78] Furthermore, patients with less severely affected lung function at baseline benefited more from the therapy, reinforcing the importance of early intervention in the COPD treatment landscape.[79,80]

This investigation emerges as the first of its kind meta-analysis and meta-regression focused specifically on the effectiveness of triple ICS/LABA/LAMA therapy within real-world COPD populations derived from prospective studies. The findings articulate a strong case for the integration of this therapeutic strategy into clinical practice, underscoring the clinical importance of individualized treatment approaches, whereby patient characteristics can significantly dictate outcomes, thereby necessitating specific patient selection for maximized therapeutic benefits.[81,82]

In terms of practical implications for clinicians, the positive outcomes reflected by both the CAT and FEV_1 metrics confirm the incorporation of the extrafine BDP/FF/G FDC into therapeutic regimens for COPD management. Given the nature of COPD as a chronic disease with multifaceted symptoms, the efficacy of this therapy is likely to enhance patient quality of life while simultaneously addressing lung function decline, integral to disease management.[83] Moreover, by capturing real-world effectiveness, these data directly contribute to evidence-based practice, encouraging physicians to align with treatment options that yield significant real-world benefits for their patients.[60]

Overall, this meta-analysis affirms the effectiveness of the triple extrafine FDC with BDP/FF/G in real-world settings, addressing a critical gap between controlled clinical trial outcomes and everyday clinical treatment experiences. With continued emphasis on personalized medicine,[81,84] future studies should endeavor to delineate distinct patient subgroups for which this therapy demonstrates optimal effectiveness. Additionally, further investigation is warranted to explore the long-term outcomes associated with the use of the triple ICS/LABA/LAMA FDC in varied populations, including those with different comorbidities and treatment histories.[85,86] Understanding the factors that maximize treatment effectiveness will enable clinicians to tailor therapy more effectively to individual patients. Future studies should also consider

conducting head-to-head trials between triple therapy and dual therapy regimens to directly compare their effects in real-world scenarios.

In conclusion, this meta-analysis highlights the significant role of the triple extrafine BDP/FF/G FDC in improving health status and lung function in patients with moderate-to-severe COPD in a real-world context. The findings support the continued use and investigation of this combination therapy as a critical strategy in COPD management.

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Disclosure

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