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ORIGINAL RESEARCH

Real-World Effectiveness and Safety of Extrafine Triple Therapy in COPD Patients with Comorbid and Cardiovascular Conditions

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Purpose: This study evaluated the real-world effectiveness and safety of extrafine single-inhaler triple therapy (SITT) with beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide (BDP/FF/GB) in chronic obstructive pulmonary disease (COPD) patients with diverse comorbidity burdens, cardiovascular (CV) history, or CV risk.

Patients and Methods: A pooled analysis of six observational studies assessed outcomes in subgroups with 1–2 or ≥3 comorbidities, CV history, or CV risk. Endpoints included COPD Assessment Test (CAT) scores, exacerbation, lung function (FEV_1), adherence (TAI-10), and cardiopulmonary events, evaluated at 3, 6, and 12 months. Comparisons were made with reference populations (0 comorbidities, no CV history, and no CV risk).

Results: Among 5356 patients, 2431 had 1–2 comorbidities, 1087 had ≥3, 312 had a CV history, and 117 met CV-risk criteria. CAT scores decreased significantly in all subgroups following SITT initiation. Patients with comorbidities showed smaller CAT improvements vs those without, while CV history/risk groups showed greater CAT improvements than their reference groups up to month 6. Regardless of comorbidity burden or CV history, most patients remained exacerbation-free and FEV_1 improved, with no long-term differences between groups. Adherence improved as well, with patients with ≥3 comorbidities potentially showing higher adherence over the long term. Cardiopulmonary events were more frequent in higher-comorbidity groups early on but became similar over time. Patients with a CV history consistently reported more cardiopulmonary events than those without, while those with CV risk achieved similar results compared to no-risk group at any time point.

Conclusion: This analysis provides real-world evidence supporting extrafine BDP/FF/GB SITT as an effective and safe option for COPD patients with comorbidities, including CV history or risk. These findings help address an evidence gap in vulnerable populations and support timely initiation of SITT in high-risk patients in clinical practice.

Keywords: comorbidity burden, cardiovascular risk, cardiovascular events, beclometasone dipropionate, formoterol fumarate, glycopyrronium bromide

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and progressive respiratory condition characterized by persistent airflow limitation and chronic airway inflammation, and is a major contributor to morbidity and mortality worldwide.[1–3] Recent estimates place the global prevalence of COPD at 10.3%,[1] with the disease ranking as the fourth leading cause of death globally, accounting for approximately 5% of all deaths.[4] Notably, the burden of COPD is further compounded by the presence of multiple comorbidities commonly associated with the disease, which can accelerate disease progression and worsen overall patient outcomes.[5]

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Cardiovascular disease (CVD) is among the most prevalent and clinically significant comorbidities in patients with COPD,[6–8] reflecting a close pathophysiological interplay rather than a mere coincidence of shared risk factors such as smoking or aging.[9,10] Systemic inflammation is thought to be a central mechanism linking the two conditions, exacerbated by factors such as hypoxia, oxidative stress, and reduced physical activity.[11,12] Moreover, CVD and COPD appear to have a bidirectional relationship: the presence of CVD increases the risk and severity of COPD exacerbations,[13] while exacerbations can themselves precipitate acute cardiovascular events, including myocardial infarction and stroke.[14,15]

Triple therapy combining inhaled corticosteroid (ICS), long-acting beta-agonist (LABA), and long-acting muscarinic antagonist (LAMA) is increasingly recommended for patients with moderate-to-severe COPD and frequent exacerbations,[16] based on evidence of improved lung function, reduced exacerbation rates, and better quality of life compared to dual therapy.[17–23] Recent RCTs have also suggested a potential reduction in all-cause mortality with single-inhaler triple therapy (SITT), possibly driven by decreased cardiovascular (CV) mortality.[18,23–26] However, the CV benefits of ICS-containing regimens remain uncertain, as observational studies suggest possible protective effects, while RCTs have not consistently confirmed these findings.[10,27,28] Furthermore, the exclusion of high-risk CV patients and methodological limitations in prior studies highlight the need for further research to clarify the CV safety and potential benefits of triple therapy in real-world COPD populations.[29]

To help address this evidence gap and inform treatment selection and risk-benefit assessment of triple therapy in routine clinical practice, this article presents a pooled analysis of six real-world studies evaluating the effectiveness and safety of extrafine SITT (beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide [BDP/FF/GB]) in patients with COPD.[30–36] While follow-up extended to 12 months in two studies, the present report focuses primarily on 6-month outcomes, as this time point captures the largest number of patients in the pooled dataset. The analysis places particular emphasis on subgroup evaluations, including patients with comorbidities, those with CV comorbidities, and patients at CV risk. By assessing outcomes such as health-related quality of life (HRQoL), exacerbation rates, lung function, treatment adherence, and occurrence of cardiopulmonary events, this study aims to provide valuable insights into the therapeutic profile of SITT in these vulnerable populations.

Materials and Methods

Study Design

This pooled analysis was based on anonymized patient-level data from six independent, prospective, multicenter observational cohort studies conducted across Europe.[30–36] All studies were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice, received approval from the respective ethics committees, and included patients who had provided informed consent.

Each study evaluated the real-world effectiveness and safety of extrafine SITT (BDP/FF/GB, 87/5/9 µg; Trimbow®, Chiesi Farmaceutici S.p.A., Parma, Italy) in patients with COPD, in whom the decision to initiate BDP/FF/GB SITT had been made independently by the treating physician as part of routine clinical care.

Before conducting the post hoc pooled analysis, a gap analysis was performed to verify whether the included studies had a sufficiently comparable design and whether their data could be meaningfully integrated. This evaluation covered the available study materials, including protocols and clinical study reports; database format and structure; differences in patient populations; limitations to parameter integration; endpoint availability, completeness, method, and timing of collection; variables requiring coding; and potential language-related issues due to the multinational nature of the studies. Based on these findings, data were harmonized where necessary, including standardization of follow-up visits as baseline, defined as the initial study visit (Month 0), first follow-up between Days 60 and 120 (Month 3), second follow-up between Days 150 and 210 (Month 6), and third follow-up between Days 300 and 390 (Month 12), as well as harmonization of selected categorical variables and outcomes definitions. These steps enabled a post hoc pooled analysis of COPD Assessment Test (CAT) scores, exacerbation frequency, forced expiratory volume in one second (FEV_1) values, 10-item Test of Adherence to Inhalers (TAI-10) scores, and adverse events.

Detailed information on participating countries and centers, recruitment periods, data collection methods and harmonization, participant selection, and follow-up structure for each individual study can be found in the original

publications of the studies included in the pooled analysis,[30–35] as well as in a previous publication based on the pooled dataset, which reports results for the overall population and other relevant subgroup analyses.[36]

Subgroup Analysis

For the purposes of this publication, the analyses focused on the following patient subgroups: (i) COPD patients stratified by comorbidity burden, defined as having 0, 1–2, or ≥3 comorbidities; (ii) COPD patients classified according to the presence of CV comorbidities and/or ≥1 CV event occurring in the previous year (CV history group) versus those with neither (No CV history group); and (iii) COPD patients classified as at CV risk at baseline - defined as having ≥1 CV event in the previous year or ≥3 CV risk factors recorded in the medical history - versus those not meeting these criteria (CV risk group vs No CV risk group).

Patients were categorized based on the number of comorbidities to reflect increasing levels of clinical burden, a stratification that has been used in previous studies as a proxy for frailty or clinical complexity. However, it should be noted that no universally accepted or standardized definition of clinical complexity based on the number of comorbidities exists. Therefore, the chosen categorization (0, 1–2, ≥3 comorbidities) was based on available literature and pragmatic considerations. Specifically, 0 comorbidities indicate a "robust" patient profile, 1–2 comorbidities reflect a moderate burden, and ≥3 comorbidities represent a high burden, often associated with frailty or clinical complexity.[37–41]

Based on patients' medical histories, CV events and comorbidities were identified using codes from the International Classification of Diseases (ICD)[42] as reported in Table S1, while CV risk factors included hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia (abnormal lipid or cholesterol levels), and obesity.

Efficacy and safety endpoints relevant to the subgroup analyses were evaluated at 3, 6, and 12 months relative to baseline within each subgroup. Additionally, comparisons were made between each subgroup and its corresponding reference population - patients without comorbidities, those without a CV history, and those not meeting the criteria for CV risk - to identify potential intergroup differences. The 12-month data were included for completeness but should be interpreted with caution, as patient numerosity at this time point was substantially lower than at earlier assessments.

Objectives and Endpoints

This publication presents a selection of the original study endpoints, limited to those pertinent to the predefined subgroup analyses and supported by adequate sample size to ensure reliable evaluation.

The primary objective was to assess the effect of BDP/FF/GB SITT on HRQoL, measured by: (i) the mean change in CAT scores[43] from baseline to 3, 6, and 12 months; (ii) the classification of CAT score absolute changes into three categories - Decrease, No Change, or Increase - with the corresponding proportion of patients reported at each time point; and (iii) the proportion of patients achieving a clinically meaningful treatment response, defined as a reduction of at least two points in the CAT score.[44]

Secondary objectives included evaluating the impact of BDP/FF/GB SITT on: (i) exacerbation frequency, based on the mean number of events and the distribution of patients experiencing 0, 1, 2, or >2 exacerbations at each follow-up visit, as well as comparisons with the incidence during the one-year pre-treatment period; (ii) lung function, assessed through mean changes in FEV_1 from baseline to 3, 6, and 12 months; and (iii) treatment adherence, measured by mean changes in TAI-10 scores[45] over the same intervals.

Safety was evaluated by reporting the proportion of patients who experienced at least one cardiopulmonary event during the 12-month follow-up period. Cardiopulmonary events were defined as the time to the first occurrence of a severe cardiac or COPD-related event, including acute heart failure (first acute healthcare visit or hospitalization due to heart failure), myocardial infarction (hospitalization resulting from a heart attack), severe COPD exacerbation (requiring hospitalization or major medical intervention), or cardiopulmonary death (attributed to either a cardiac or respiratory cause).

Statistical Analysis

A formal sample size calculation was not applicable, as this pooled analysis was based on pre-existing data. However, the overall sample size was sufficient to ensure adequate statistical power to detect clinically meaningful differences in the primary endpoint (change in CAT score) and key secondary endpoints.

Three analysis populations were defined for statistical analysis: the enrolled population, which included all patients who provided informed consent; the safety analysis set (SAF), comprising all patients who received at least one dose of SITT; and the full analysis set (FAS), which included all patients from the SAF who had at least one post-baseline follow-up visit. Missing data were not imputed in order to avoid introducing assumptions that could potentially bias the results.

Safety evaluations were conducted using the SAF population, while all efficacy analyses were based on the FAS. Baseline characteristics were described for both the SAF and FAS populations.

Continuous variables were summarized as means and standard deviations (SD), median, interquartile range (IQR), minimum, and maximum values, while categorical variables were reported as count and percentages. Where applicable, 95% confidence intervals (CIs) were calculated to support key estimates.

To assess changes from baseline to 3, 6, and 12 months, paired *t*-tests were used for normally distributed data. In cases where normality assumptions were not satisfied, the Wilcoxon signed-rank test was applied. Two-sided 95% CIs were reported to describe the direction and extent of observed changes over time.

Comparisons between subgroups at each follow-up point (3, 6, and 12 months) were performed using independent samples t-tests for normally distributed variables, or the Mann–Whitney *U*-test for non-normally distributed data.

Statistical significance was determined using a two-sided alpha level of 0.05. All analyses were performed using SAS® software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline Characteristics

Overall, the pooled analysis included 5523 enrolled patients with COPD, of whom 4541 were included in the full analysis set (FAS). Among the safety analysis set (SAF; N=5356), 2431 (45.4%) patients had 1–2 comorbidities (moderate comorbidity burden), 1087 (20.3%) had ≥3 comorbidities (high comorbidity burden), and 1838 (34.3%) had no comorbidities. A total of 312 (5.8%) patients had CV comorbidities and/or a history of CV events in the previous year (CV history group), whereas 5044 (94.2%) COPD patients had no such history (No CV history group). Additionally, 117 (2.2%) patients were classified as being at CV risk at baseline (CV risk group), while 5239 (97.8%) were not (No CV risk group). Subgroup numerosity for each assessed variable at each time point is reported in the Supplementary Materials.

Patients without comorbidities were primarily male (60.6%), aged ≥56 years (84.9%), and either current or former smokers (93.8%). The average (SD) time since COPD diagnosis in this group was 7.0 (5.7) years, and 79.8% had moderate or severe COPD. The most common prior treatments were LABA/LAMA (37.2%) and ICS/LABA (43.8%) combinations. This general profile was consistent across groups with comorbidities, with trends in certain demographic and disease characteristics becoming progressively more pronounced as the number of comorbidities increased (eg, older age, longer time since COPD diagnosis, a higher proportion of GOLD stage 4 disease, and greater use of prior triple therapy).

Patients without a history of CV disease were predominantly male (59.9%), aged ≥56 years (88.1%), and either current or former smokers (90.4%). These characteristics were more pronounced in those with a CV history. The average duration since COPD diagnosis was longer in the CV history group compared to those without, while the prevalence of moderate or severe COPD was high in both groups. Regarding prior treatment, patients without CV history most commonly received either a LABA/LAMA combination (33.1%) or an ICS/LABA combination (45.9%). In contrast, those with a CV history were more often treated with a triple therapy (28.2%) or a LABA/LAMA combination (25.3%).

A comparable trend was observed when stratifying patients by CV risk. Those without CV risk were mostly male (60.6%), aged ≥56 years (88.6%), and current or former smokers (90.5%), while higher proportions were again seen in the CV risk group. The mean time since COPD diagnosis was longer among patients with CV risk than those without and the proportion of patients with moderate or severe COPD was high in both groups. Prior treatment patterns also showed parallels: while those without CV risk were mainly treated with either a LABA/LAMA (32.9%) or ICS/LABA combination (45.2%), patients with CV risk more frequently received a LABA/LAMA combination (26.5%), an ICS/LABA combination (20.5%), or a triple therapy (8.6%).

Detailed baseline characteristics of patients in all subgroups are presented in Tables S2–S6.

CAT Scores

Treatment with BDP/FF/GB SITT was associated with a marked improvement in COPD impact among patients with moderate and high comorbidity burden, as evidenced by significant reductions in CAT scores at 3 and 6 months compared to baseline ($p < 0.0001$; Figure 1A).

At month 6, mean CAT scores decreased by 3.8 points (95% CI: −4.2; −3.5) in patients with moderate comorbidity burden and by 3.0 points (95% CI: −3.5; −2.4) in those with high comorbidity burden, indicating a similar magnitude of improvement across subgroups. Overall, patients without comorbidities demonstrated significantly greater improvements in CAT scores when compared with those having moderate or high comorbidity burden ($p < 0.001$; Figure 1B).

In patients at CV risk and those with a CV history, CAT scores decreased significantly from baseline at both 3 and 6 months ($p < 0.0001$; Figure 2A), underscoring the effectiveness of BDP/FF/GB SITT in alleviating COPD burden in these subpopulations as well.

Mean CAT scores decreased after 6 months by 6.2 points (95% CI: −7.4; −4.9) in patients with a CV history and by 7.0 points (95% CI: −8.7; −5.3) in those with CV risk. By month 6, most patients in both the CV history and CV risk groups showed either a reduction or stabilization in their CAT scores, with no increase observed in 84.0% and 90.7% of patients, respectively. Furthermore, a clinically meaningful treatment response - defined as a decrease of at least two points in the CAT score - was achieved by 73.3% of patients in the CV history group and 81.5% in the CV risk group (Table S7). Compared with patients without CV history or risk (Figure 2B and C), those in the CV history and CV risk groups showed significantly greater improvements in CAT scores up to month 6 of treatment ($p < 0.05$), with scores becoming similar to those of the no CV history/risk group by month 12.

Detailed results from the subgroup analysis of CAT scores are presented in Table S8, including data through 12 months.

Number of Exacerbations

Across all comorbidity groups, including patients without comorbidities, the majority of patients remained exacerbation-free following BDP/FF/GB SITT initiation (Figure 3A–C).

In the subgroup with moderate comorbidity burden, the mean (SD) number of exacerbations increased over time, from 0.1 (0.3) at month 3 to 0.2 (0.5) at month 6. Despite the natural increase in exacerbations over time, the majority of

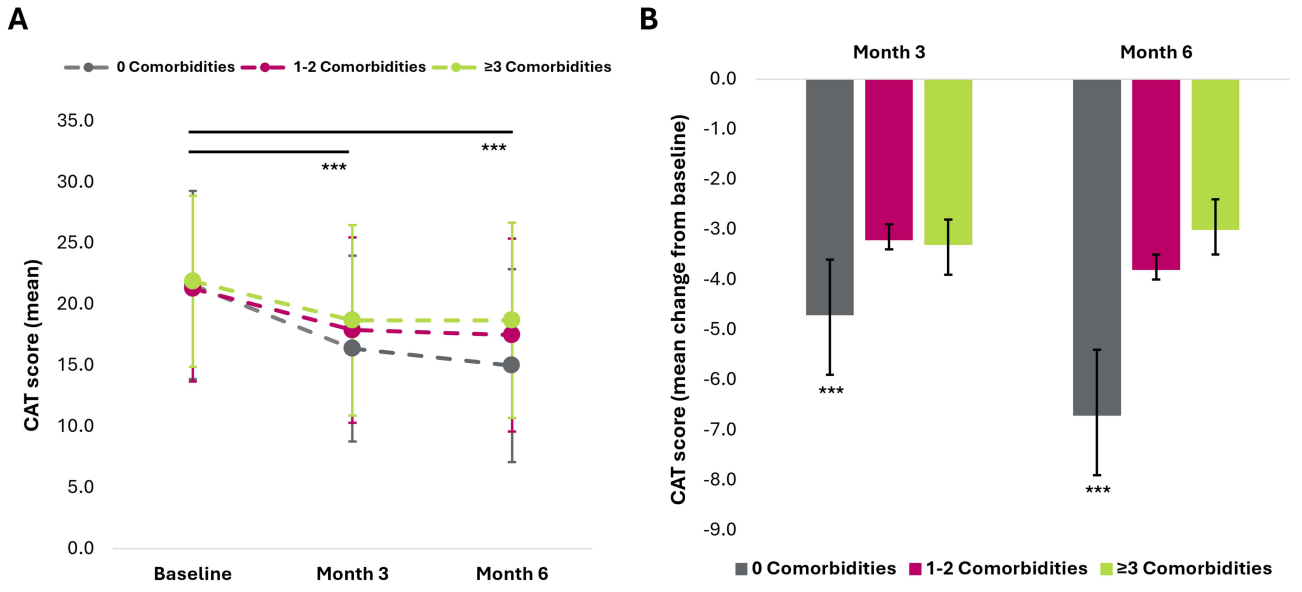

Figure 1 (**A**) Mean CAT scores over time for the 0, 1–2, and ≥3 comorbidities groups. Error bars indicate standard deviation. ***p < 0.0001; within-group comparison of baseline values versus all other timepoints, using a paired *t*-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. Sample sizes were as follows: 0 comorbidities, N = 1630, 1265, and 1197; 1–2 comorbidities, N = 1985, 1456, and 1412; ≥3 comorbidities, N = 906, 475, and 588 at baseline, month 3, and month 6, respectively. (**B**) Mean changes from baseline in CAT scores at months 3 and 6 for patients with comorbidities compared to those without comorbidities. Error bars indicate 95% confidence intervals. ***p < 0.0001; comparison of the 0 comorbidity group versus all other groups at each timepoint, using an independent samples *t*-test for normally distributed data or the Mann–Whitney *U*-test otherwise.

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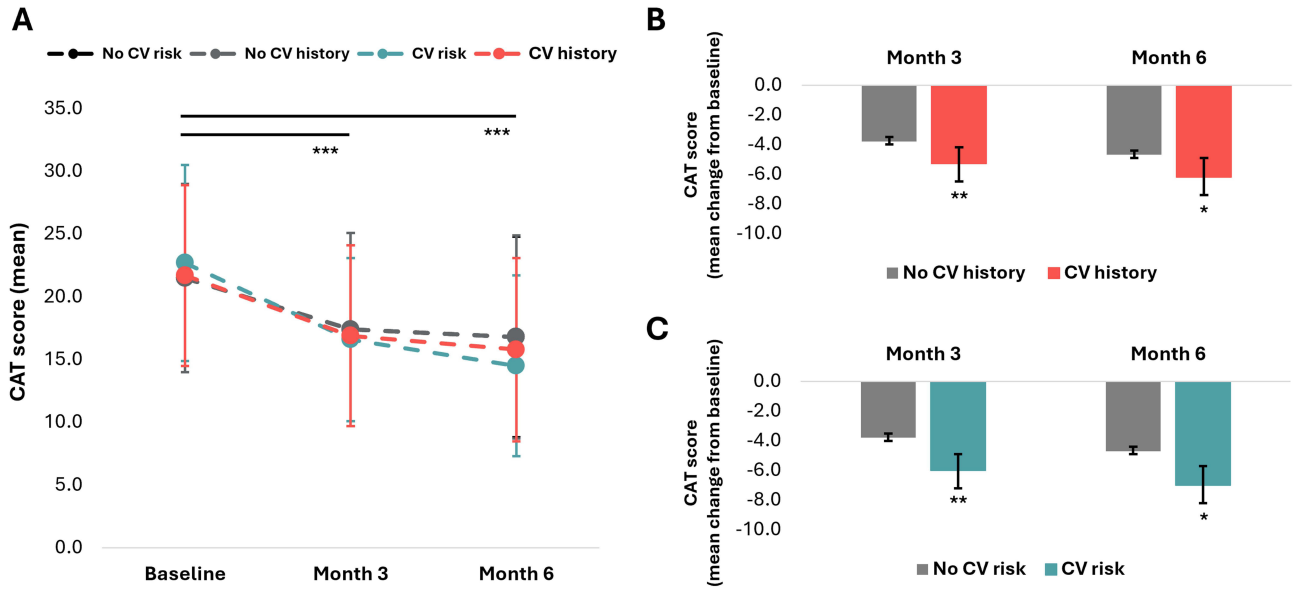

Figure 2 (**A**) Mean CAT scores over time for the CV history group, the CV risk group, and those without. Data from the No CV risk group are not visually distinguishable, as they completely overlap with those from the No CV history group. Error bars represent standard deviation. ***p < 0.0001; within-group comparison of baseline values versus all other timepoints, using a paired *t*-test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. Sample sizes were as follows: CV history, N = 279, 126, and 150; No CV history, N = 4242, 3070, and 3047; CV risk, N = 111, 67, and 54; No CV risk, N = 4410, 3129, and 3143 at baseline, month 3, and month 6, respectively. (**B** and **C**) Mean changes from baseline in CAT scores at months 3 and 6 for the CV history group versus the group without CV history (**B**), and for the CV risk group versus the group without CV risk (**C**). Error bars represent 95% confidence intervals. *p < 0.05, **p < 0.01; within timepoints across groups comparison using independent samples *t*-test for normally distributed data or Mann–Whitney *U*-test otherwise.

patients had no exacerbations at 3 and 6 months (Figure 3B). Compared to the year prior to switching to BDP/FF/GB SITT, the proportion of patients with any exacerbations declined significantly (Figure 3D; $p < 0.0001$), with a sharp drop from 94.2% at baseline to 16.0% at month 6.

A similar trend was observed in the subgroup with high comorbidity burden. The mean (SD) number of exacerbations rose from 0.1 (0.4) at month 3 to 0.3 (0.6) at month 6. Nonetheless, the majority of patients continued to report no exacerbations (Figure 3C) and the proportion of patients experiencing any exacerbations decreased significantly from 90.0% at baseline to 19.6% at month 6 (Figure 3D; $p < 0.0001$). Patients with high comorbidity burden experienced a significantly higher mean number of exacerbations than those without comorbidities at months 3 and 6 ($p < 0.05$); however, this difference was no longer observed by month 12 (Table S9).

In the CV history group, the mean (SD) number of exacerbations increased from 0.2 (0.5) at month 3 to 0.4 (0.7) at month 6. Despite this progression, most patients reported no more than one exacerbation at both time points (Figure 4A and B). Compared to the year before BDP/FF/GB SITT initiation, the proportion of patients with any exacerbations significantly decreased (Figure 4C; $p < 0.0001$) from 86.2% at baseline to 32.9% at month 6. Throughout the 12-month period, patients without a CV history experienced significantly fewer exacerbations than those with a CV history ($p < 0.01$, Table S9).

Due to the limited sample size, exacerbation rates were not analyzed in the CV risk group.

FEV_1 Values

Treatment with BDP/FF/GB SITT led to significant improvements in lung function among patients with moderate comorbidity burden, with FEV_1 values showing consistent increases from baseline at months 3 and 6 ($p \leq 0.0001$). Specifically, the mean (95% CI) changes from baseline in FEV_1 were 0.10 L (0.08; 0.12) at month 3 and 0.08 L (0.06; 0.10) at month 6. A comparable trajectory was observed in the high-burden subgroup, where lung function improved significantly at months 3 and 6 ($p < 0.0001$), with mean (95% CI) increases of 0.10 L (0.07; 0.13) and 0.10 L (0.07; 0.14), respectively. When comparing these subgroups to patients without comorbidities, no statistically significant differences in FEV_1 values were observed at any timepoint up to 12 months (Table S10).

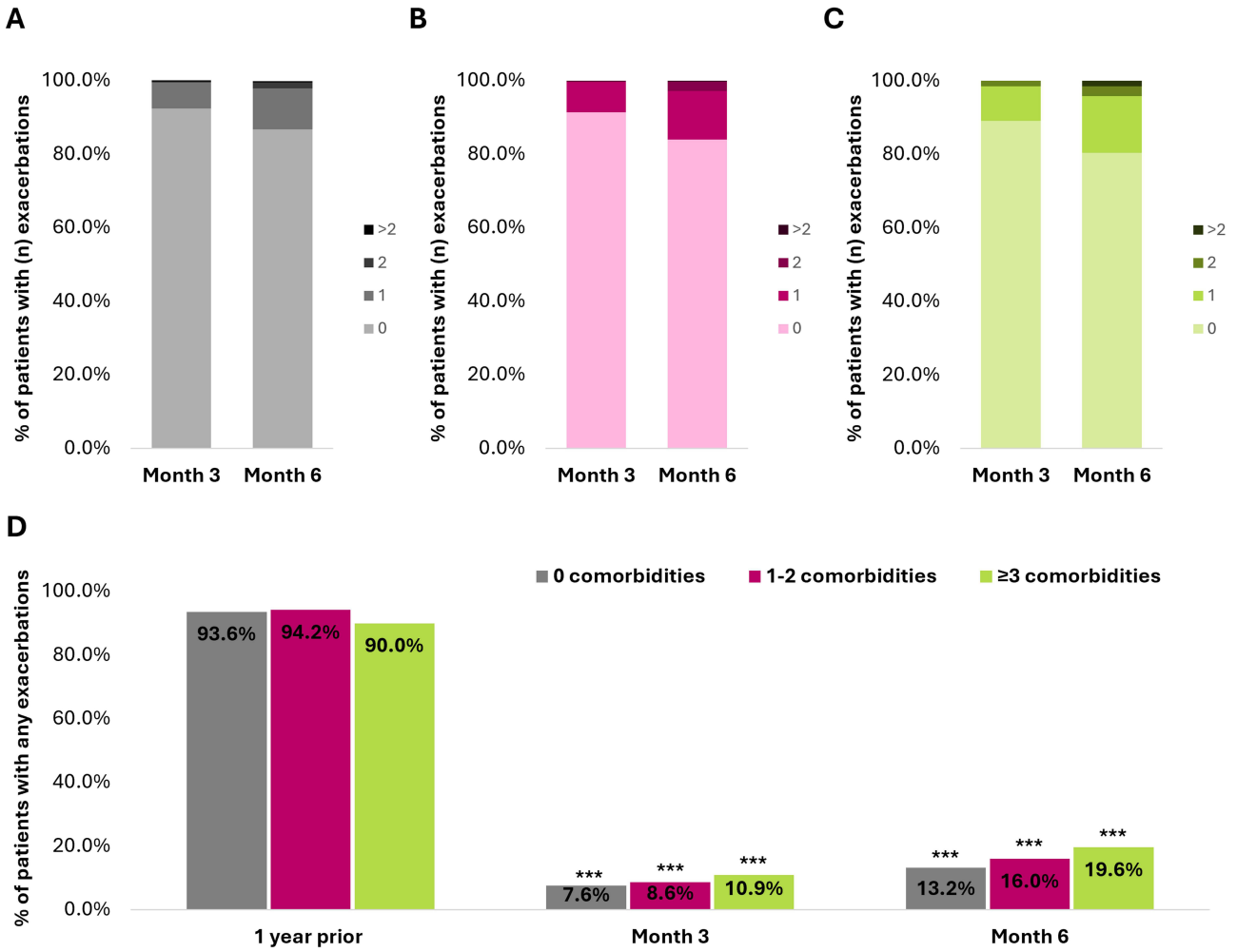

Figure 3 (**A**–**C**) Proportion of patients in the 0 (**A**), 1–2 (**B**), and ≥3 (**C**) comorbidities group experiencing 0, 1, 2, or more than 2 exacerbations at months 3 and 6. At Month 3, the proportions of patients with 0, 1, 2, and >2 exacerbations were 92.4%, 7.1%, 0.3%, and 0.3% in those with 0 comorbidities; 91.4%, 8.2%, 0.3%, and 0.1% in those with 1–2 comorbidities; and 89.1%, 9.4%, 1.5%, and 0.0% in those with ≥3 comorbidities. At Month 6, the corresponding proportions were 86.8%, 11.1%, 1.6%, and 0.4%; 84.0%, 13.2%, 2.5%, and 0.3%; and 80.4%, 15.4%, 2.7%, and 1.6%, respectively. Sample sizes were as follows: 0 comorbidities, N = 708 and 675; 1–2 comorbidities, N = 1377 and 1339; ≥3 comorbidities, N = 588 and 565 at month 3 and month 6, respectively. (**D**) Comparison of the percentage of patients reporting any exacerbations at each timepoint relative to the year prior to switching to SITT in the 0, 1–2, and ≥3 comorbidities group. ***p < 0.0001; within-group comparison of 1 year prior values versus all other timepoints, using two-sample paired *t*-test for normally distributed data or Wilcoxon signed-rank test otherwise.

Similarly, patients with a CV history demonstrated significant lung function gains at month 3 and 6 ($p < 0.05$). In this group, the mean (95% CI) FEV_1 increases from baseline were 0.10 L (0.04; 0.16) at month 3 and 0.11 L (0.02; 0.20) at month 6. Although patients without a CV history initially showed significantly higher FEV_1 values than those with CV history at month 3 ($p < 0.0001$), this difference was no longer evident by month 6 and remained absent at month 12 (Table S10).

Given the limited sample size, lung function analysis was not conducted for the CV risk group.

TAI-10 Scores

Treatment with BDP/FF/GB SITT was linked to improvements in treatment adherence across subgroups with moderate and high comorbidities burdens, as reflected by statistically significant increases in TAI-10 scores from baseline at months 3 and 6 ($p < 0.05$). In the subgroup with moderate comorbidity burden, the mean (SD) TAI-10 scores were 47.9 (4.1) at baseline, 48.6 (3.4) at month 3, and 48.5 (4.0) at month 6. Corresponding mean (95% CI) increases were 0.5 (0.3; 0.7) at month 3 and 0.6 (0.4; 0.8) at month 6. Among patients with high comorbidity burden, adherence also improved, with mean (SD) TAI-10 scores increasing from 47.4 (4.9) at baseline to 48.7 (2.9) at month 3 and 48.2 (3.6) at month 6. The corresponding mean (95% CI) changes were 0.4 (0.0; 0.7) and 1.1 (0.7; 1.5), respectively. By month 12, patients

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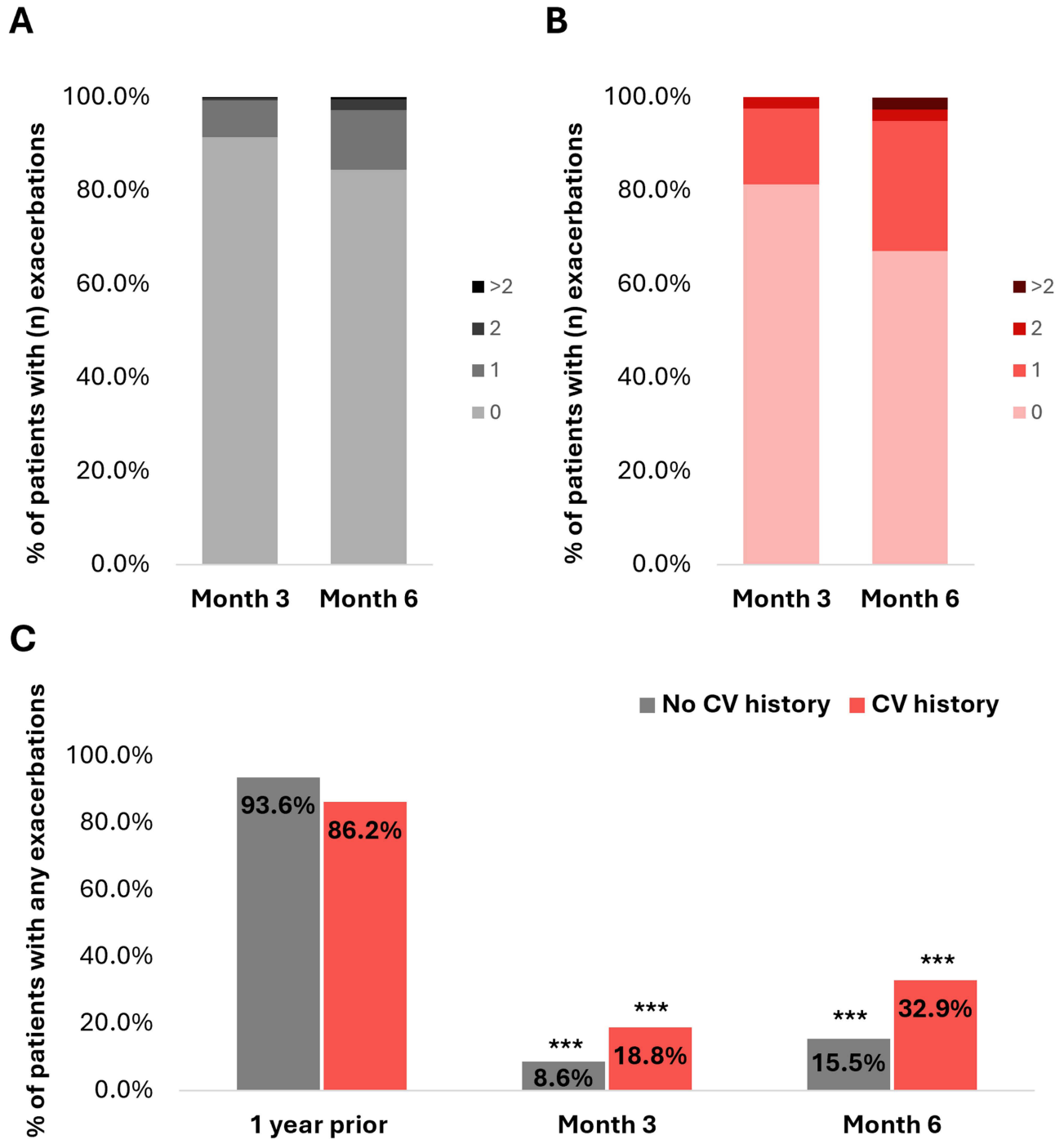

Figure 4 (**A** and **B**) Proportion of patients without a CV history (**A**) and those in the CV history group (**B**) experiencing 0, 1, 2, or more than 2 exacerbations at months 3 and 6. At Month 3, the proportions of patients with 0, 1, 2, and >2 exacerbations were 91.4%, 7.9%, 0.5%, and 0.2% in those without CV history, and 81.3%, 16.3%, 2.5%, and 0.0% in those with CV history. At Month 6, the corresponding proportions were 84.5%, 12.7%, 2.3%, and 0.6% in patients without CV history, and 67.1%, 27.8%, 2.5%, and 2.5% in those with CV history. Sample sizes were as follows: CV history, N = 80 and 79; No CV history, N = 2593 and 2500 at month 3 and month 6, respectively. (**C**) Comparison of the percentage of patients reporting any exacerbations at each timepoint relative to the year prior to switching to SITT in the CV history group. ***$p < 0.0001$; within-group comparison of 1 year prior values versus all other timepoints, using two-sample paired *t*-test for normally distributed data or Wilcoxon signed-rank test otherwise.

with a high comorbidity burden showed significantly higher adherence than those without comorbidities ($p < 0.05$) and than the moderate-burden group ($p < 0.05$); at month 6, adherence in the high-burden group was also higher than in the moderate-burden group ($p < 0.05$, Table S11).

In the CV history subgroup, adherence improvements reached statistical significance at certain time points but not at all assessments; however, TAI-10 scores consistently remained within the intermediate-to-high adherence range (TAI-10 > 45). Mean (SD) TAI-10 scores were 47.5 (4.6) at baseline, 47.3 (6.3) at month 3, and 46.9 (6.7) at month 6. The corresponding mean (95% CI) changes from baseline were 1.1 (0.3; 2.0) at month 3 ($p < 0.01$) and 1.0 (0.0; 2.0) at month 6 (not significant). Furthermore, adherence did not differ significantly from that of patients without a CV history at any time point up to 12 months (Table S11).

Due to the limited sample size, adherence data for the CV risk group were not analyzed.

Cardiopulmonary Events

In the moderate-burden group, the proportion of patients experiencing at least one cardiopulmonary event were 0.5% (N=12) at baseline, 1.2% (N=30) at month 3, 0.5% (N=13) at month 6, and 0.4% (N=10) at month 12. In the high-burden group, corresponding values were: 0.6% (N=6) at baseline, 2.8% (N=30) at month 3, 1.2% (N=13) at month 6, and 0.6% (N=6) at month 12. Among patients without comorbidities, proportions remained consistently low: 0.2% (N=2) at baseline, 0.7% (N=13) at month 3, 0.6% (N=11) at month 6, and 0.2% (N=2) at month 12. A statistically significant difference was observed at month 3, with a higher proportion of patients in the high-burden group experiencing at least one event compared to those with fewer or no comorbidities ($p < 0.01$). This difference remained significant at month 6 when comparing the moderate- and high-burden groups. No significant differences were found at baseline or month 12 across subgroups.

In the CV history group, the proportion of patients with at least one event was 2.2% (N=7) at baseline, 4.2% (N=13) at month 3, 2.6% (N=8) at month 6, and 1.3% (N=4) at month 12. In contrast, patients without a CV history showed significantly lower proportions at each time point ($p < 0.01$): 0.3%, 1.2%, 0.6%, and 0.3%, respectively. For patients classified as in CV risk group, proportions with at least one event were 0.0% at baseline, 3.4% (N=4) at month 3, 0.0% at month 6, and 1.7% (N=2) at month 12. These values were not significantly different from those observed in patients without CV risk at any time point: 0.4% (N=21), 1.3% (N=69), 0.7% (N=37), and 0.3% (N=18), respectively.

Discussion

Although COPD has traditionally been characterized by progressive deterioration of lung function, it is now widely recognized as a complex, multi-systemic chronic inflammatory condition with a significant burden of extrapulmonary manifestations.[46,47] Comorbidities - particularly those of CV origin - are highly prevalent in this population and are known to hinder the achievement of key therapeutic goals in COPD management, including the improvement of HRQoL, reduction in exacerbation frequency, and preservation of pulmonary function.[48,49]

Building upon a pooled analysis of six real-world studies conducted across Europe,[30–36] this subgroup evaluation sought to generate evidence on the role of extrafine BDP/FF/GB SITT in the management of COPD patients with comorbid conditions, including CV comorbidities and patients at CV risk. This real-world analysis likely encompassed more severe and comorbid patients than those typically included in randomized controlled trials. By focusing on key clinical outcomes such as CAT scores, exacerbation rates, and lung function, the analysis underscored the ability of SITT to positively impact several disease dimensions in these vulnerable populations. Importantly, these findings extend previous evidence in the overall COPD population treated with extrafine BDP/FF/GB, including a systematic review and meta-analysis that incorporated some of the studies contributing to the present pooled analysis,[50] as well as a dedicated report from the overall population of this pooled dataset,[36] both of which had already demonstrated consistent improvements in clinical outcomes.

In line with existing literature,[5,51,52] patients without comorbidities consistently experienced greater improvements in CAT scores throughout the treatment period. However, meaningful reductions were already evident by month 6 in the comorbidity subgroups, with mean decreases of almost 4 points in patients with a moderate burden and approximately 3 points in those with a high burden. By month 6, patients with a CV history and those at CV risk achieved even greater mean reductions of approximately 6 and 7 points, respectively. Although 12-month data were available for fewer patients, CAT scores appeared to continue to decline, approaching mean values of ~16 across subgroups. Notably, patients with a CV history and those at CV risk showed greater improvements in CAT scores compared to their respective reference groups (ie, those without a CV history and those not meeting CV risk criteria) up to the 6-month timepoint.

These findings are particularly noteworthy given the evolving understanding of a clinically meaningful CAT score. While GOLD guidelines use a threshold of ≥10 to define symptomatic patients,[16] growing evidence suggests that this cut-off may not be entirely realistic.[53,54] Studies indicate that the commonly used mMRC dyspnea scale cut-off of ≥2 aligns more closely with a CAT score of ≥17, while an mMRC score ≤1 corresponds better to CAT scores ≤10.[55,56] This discrepancy has led to more nuanced proposals for defining clinical control and stability in COPD.[57,58] One such practical definition of clinical control identifies patients as stable if their CAT score is ≤16 and no exacerbations occurred in the prior three months.[5,59–61] Thus, the improvements observed in this study, with the majority of patients across comorbidity burdens and CV subgroups approaching the CAT 16 threshold, support the potential of BDP/FF/GB SITT to contribute meaningfully to the clinical stability and control of COPD patients with complex comorbidity profiles.

Indeed, in line with this definition of clinical control, the majority of patients remained free from exacerbations through the first 6 months of follow-up, irrespective of comorbidity burden or CV history. Given the expected reduction in subgroups numbers over time and the accumulation of exacerbations with longer observation, a decline in the proportion of exacerbation-free patients was anticipated and was indeed observed; however, it is noteworthy that the percentage of patients experiencing any exacerbation at all assessed time points, including 12 months, remained significantly lower than the proportion who had reported at least one exacerbation in the year preceding SITT initiation. Furthermore, the observation that exacerbations increased with comorbidity burden in the short term but not in the long term is of particular interest - not merely because the initial association is consistent with established evidence,[13,62] but because it may suggest that BDP/FF/GB SITT mitigates this effect over time.

These improvements in exacerbations were accompanied by significant gains in lung function, as increases in FEV_1 from baseline were observed across all analyzed subgroups throughout the treatment period. Notably, patients with moderate and high comorbidity burden maintained lung function values comparable to those without comorbidities while receiving BDP/FF/GB SITT. Although a short-term difference favoring patients without a CV history over those with such a history was evident at month 3, this difference was no longer present by month 6. This convergence in outcomes may further support the notion that BDP/FF/GB SITT can reach sustained clinical control in real-world COPD management, including in patients with comorbidities, who are traditionally considered more difficult to stabilize.[5]

Beyond these favorable efficacy outcomes, treatment adherence also improved, as reflected by significant increases in TAI-10 scores across all comorbidity- and CV-related subgroups at month 3 and across all comorbidity groups at month 6, with no significant between-group differences. As discussed above, interpretation of longer-term results, is tempered by decreasing numbers of patients over time; nevertheless, it is noteworthy that after one year of BDP/FF/GB SITT treatment, patients with a high comorbidity burden were significantly more adherent than those with moderate burden and those without comorbidities. If this finding reflects a genuine trend, it may be of particular interest for two reasons. First, it contrasts with existing literature, which typically reports lower adherence among patients with multiple comorbidities - likely due to the complexity of managing several medications simultaneously.[63,64] Second, this observation is especially relevant in light of the well-established association between higher adherence and improved clinical outcomes in COPD.[65–67] It is plausible that patients with a higher comorbidity burden were more adherent because they experienced tangible clinical benefits from treatment, potentially reinforcing adherence through a positive feedback loop. Enhanced adherence in this cohort is also likely attributable to the use of a single inhaler device, which simplifies treatment administration and reduces the inhaler technique errors commonly observed with multiple-device regimens.[68,69] The use of SITT may thus support long-term disease management not only through its pharmacologic effects but also by facilitating better patient adherence with treatment.

In addition, the analysis yielded reassuring safety results. A statistically higher number of cardiopulmonary events was observed during the first 3 to 6 months in patients with a higher comorbidity burden (≥3 comorbidities vs 1–2 and no comorbidities), reflecting their increased baseline vulnerability. By month 12, this difference was no longer observed, which - although potentially influenced by reduced numbers - may also suggest a stabilizing effect of treatment over time. When considering CV-related subgroups, patients without a CV history consistently had significantly fewer events, whereas event rates did not differ significantly between CV risk and no-risk groups at any assessed time point. These findings indicate that while pre-existing cardiovascular disease may continue to influence safety outcomes, the presence of cardiovascular risk factors alone did not confer a significantly elevated risk under BDP/FF/GB SITT. These findings align with the rationale of the ongoing THARROS trial (ID: NCT06283966 on ClinicalTrials.gov), which aims to

demonstrate that initiating SITT in patients with cardiopulmonary risk - rather than waiting for events to occur - may offer a proactive strategy to prevent severe outcomes and optimize COPD management.

Supporting this perspective, it is worth noting that the systemic inflammation characteristic of COPD may contribute not only to the progression but also to the development of comorbid conditions.[70,71] Therefore, the timely initiation of SITT - rather than postponing treatment escalation despite evident clinical need - may offer benefits that extend beyond the control of respiratory symptoms. By stabilizing COPD-related inflammation and reducing exacerbation frequency early in the disease course, SITT could potentially help prevent the emergence or worsening of inflammation-driven comorbidities. These insights support a proactive approach to SITT implementation as part of a broader, long-term strategy to preserve clinical stability and improve overall health outcomes in patients with COPD.

The findings of this subgroup analysis should be interpreted in light of its inherent limitations. As an observational study, it is subject to potential sources of bias, including confounding and selection bias. While the included studies were generally comparable in terms of methodology and patient characteristics, differences existed in aspects such as inclusion criteria, timing of assessments, and sample sizes across subgroups and follow-up periods. To mitigate the impact of these discrepancies, data were carefully harmonized, and all methodological procedures were transparently reported. Moreover, selection bias is expected to be mitigated by the large and representative real-world populations included, further strengthened by the pooled design reflecting routine clinical practice with minimal restrictive eligibility criteria. Since analyses were conducted on available data without imputation, missing data and loss to follow-up may have influenced results, although transparency was ensured through reporting of subgroup numerosity at each time point. Finally, although the multicenter European real-world setting supports external validity, differences in healthcare systems, treatment practices, and patient characteristics may limit the direct generalizability of these findings to non-European populations or other clinical contexts.

Conclusions

This subgroup analysis offers valuable real-world evidence supporting the effectiveness of extrafine BDP/FF/GB SITT in managing COPD patients with varying comorbidity burdens. By stratifying outcomes based on the number of comorbidities as well as the presence of cardiovascular history or risk, the study shows consistent improvements in symptoms, lung function, exacerbations, treatment adherence, and cardiopulmonary safety across all subgroups, typically considered more difficult to treat. This suggests that the effectiveness of single-inhaler triple therapy is maintained irrespective of comorbidity burden, supporting its use in multimorbid COPD patients encountered in routine clinical practice. These findings address a key gap in the literature, where data on triple therapy in comorbid COPD populations remain scarce, and align with emerging strategies that support timely initiation of SITT in high-risk patients. Overall, the results reinforce the clinical value of SITT in delivering stable and comprehensive disease control in a real-world COPD population.

Abbreviations

SITT, single-inhaler triple therapy; BDP/FF/GB, beclometasone dipropionate/formoterol fumarate/glycopyrronium bromide; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CAT, COPD Assessment Test; CVD, Cardiovascular disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; HRQoL, health-related quality of life; ICD, International Classification of Diseases; SAF, safety analysis set; FAS, full analysis set; SD, standard deviations; IQR, interquartile range; CIs, confidence intervals.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This pooled analysis was based on anonymized patient-level data from six independent, prospective, multicenter observational cohort studies conducted across Europe.[30–35] All studies were conducted in accordance with the principles

of the Declaration of Helsinki and Good Clinical Practice, received approval from the respective ethics committees, and included patients who had provided informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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