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ORIGINAL RESEARCH

Real-World Effectiveness of Single-Inhaler Triple Treatment Through Assorted Respiratory Outcomes When Switched From Multiple-Inhaler Triple Therapies (RESTART): A Prospective Cohort Study of Korean Patients With COPD

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Purpose: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition characterized by persistent airflow limitation, leading to significant morbidity and mortality. Despite the effectiveness of multiple inhaler triple therapy (MITT), its complexity often results in poor adherence and suboptimal outcomes. Transitioning to single inhaler triple therapy (SITT) may enhance adherence, leading to improved clinical outcomes and quality of life of patients. The Real-World Effectiveness of Single Inhaler Triple Treatment through Assorted Respiratory Outcomes when Switched from Multiple Inhaler Triple Therapies (RESTART) study aimed to evaluate the clinical benefits of switching from MITT to SITT using fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in a real-world Korean setting.

Patients and Methods: This prospective, multicenter, observational study enrolled 107 patients, aged 40 and older, with diagnosed COPD, all previously on MITT. The patients were transitioned to once-daily FF/UMEC/VI administered via the ELLIPTA inhaler. The primary outcome was a change in the COPD Assessment Test (CAT) score after 24 weeks. The secondary outcomes included changes in lung function, exacerbation rates, Modified Medical Research Council Dyspnea Scale scores, and Treatment Satisfaction–Visual Analysis Scale (TS-VAS) scores.

Results: A total of 91 patients completed the 24-week observation. CAT scores significantly improved (mean change = 1.40 points, $P = 0.007$). Lung function also improved, with a mean increase in the FEV1/FVC ratio (mean change = 4.31%, $P = 0.005$). Exacerbation rates decreased significantly (incidence rate ratio = 0.45, $P = 0.016$). Treatment satisfaction increased, with a mean TS-VAS score rise of 1.71 points ($P < 0.001$).

Conclusion: The transition from MITT to SITT significantly improved COPD symptom management, pulmonary function, exacerbation rate, and treatment satisfaction in Korean cohort. Using a single inhaler to simplify therapy might increase patient compliance and improve clinical outcomes of COPD management.

Keywords: real-world evidence, single-inhaler triple treatment, chronic obstructive pulmonary disease, adherence, chronic obstructive pulmonary disease assessment test score

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive condition that severely affects the respiratory system, causing persistent symptoms such as breathlessness, chronic cough, and sputum production.[1,2] The primary characteristic of COPD is airflow limitation, which is not completely reversible and tends to deteriorate with time,[3] making it the fourth leading cause of death and sixth highest burden of disability worldwide.[4,5] In South Korea, the prevalence of COPD is high, varying from 12.9 to 16.7% among those aged 40 years and older,[6,7] which is the 11th leading cause of death, with a 5-year mortality rate of 25.4%.[6–9]

The primary goals of COPD management are to alleviate symptoms; increase exercise tolerance; avoid disease progression; and minimize the frequency and severity of exacerbations. Inhaled therapies are critical for treating COPD and include inhaled corticosteroids (ICS), long-acting beta2-agonists (LABA), and long-acting muscarinic antagonists (LAMA). These drugs can be used alone or in combination, depending on disease severity and patient's individual needs,[10–13] and are adopted in Korean clinical settings.[14,15]

However, the complexity of these regimens often contributes to poor adherence, leading to suboptimal outcomes such as uncontrolled symptoms, increased exacerbations, and a decline in overall lung function, which is a major impediment to COPD management.[16] Increased hospitalizations, higher healthcare costs, and even mortality can compound these outcomes, underscoring the need for a simpler medication regimen.[17,18]

Patients receiving multiple agents experience the burden of managing multiple inhalers, dosing schedules, and inhaler techniques, which can be another major factor for non-compliance, particularly in older adults or those with cognitive and physical limitations.[19] Several real-world studies have demonstrated decreased adherence and symptom persistence in patients administered multiple inhalers.[20–22]

Single-inhaler triple therapy (SITT) was introduced by combining ICS, LABA, and LAMA into a single device, with proven efficacy and safety in patients with COPD.[23,24] There is consensus on utilizing a single inhaler instead of several to reduce treatment complexity, minimize dosing errors, and improve patient compliance.[25] This simplification is particularly beneficial for older patients with multiple health issues. Well-controlled clinical trials have shown that SITT is as effective as multiple inhaler triple therapy (MITT) in managing COPD symptoms and preventing exacerbations,[26,27] whereas in real-world investigations, SITT provides more benefits with adherence, persistence, and even clinical outcomes such as exacerbations and healthcare resource utilization costs.[27–31] The patterns of inhaler prescription in Korea between 2015 and 2018 revealed that combinations involving two or more inhalers had the highest proportion of triple therapy usage.[32] MITT is also referred to as open triple treatment, while SITT is referred to as closed triple treatment.[33] Despite these favorable findings, there has only been a retrospective approach in the real world, without prospective studies to assess the therapeutic value of SITT over MITT. Moreover, although studies have been conducted in Western countries, research in Asian countries, particularly South Korea, remains limited due to its distinct healthcare delivery structure. This prospective cohort study, Real-World Effectiveness of Single Inhaler Triple Treatment through Assorted Respiratory Outcomes when Switched from Multiple Inhaler Triple Therapies (RESTART), aimed to investigate the clinical benefit of switching from MITT to Ellipta SITT in patients with COPD in Korean clinical setting.

Materials and Methods

Study Objective and Design

The RESTART study is an observational, multicenter, prospective cohort study designed to elucidate the effectiveness of SITT in patients who were previously prescribed MITT for COPD in real-world clinical practice in Korea. Specifically, the study investigates the clinical benefits of switching from MITT to Ellipta SITT for the management of COPD within the Korean clinical setting. To assess the clinical outcomes, symptom control, pulmonary function, exacerbation rates, the Modified Medical Research Council (mMRC) score, and patient-reported outcomes such as treatment satisfaction were evaluated. Furthermore, the exposure of once-daily SITT was FF/UMEC/VI (fluticasone furoate [100 μg]/umeclidinium [62.5 μg]/vilanterol [25 μg]) delivered by the ELLIPTA inhaler which was the only available SITT in Korea. The primary objective was to evaluate the effectiveness of 24-week once-daily regimen of FF/UMEC/VI in the change from the baseline COPD Assessment Test (CAT) score.

Patients ≥40 years of age were enrolled and treated with SITT. The inclusion and exclusion criteria were designed to include a diverse patient group reflective of standard prescription practices, in alignment with the SITT combination of FF/UMEC/VI approval and reimbursement criteria on the Health Insurance Review and Assessment.

All patients provided written informed consent. In addition, the study was approved by the Gyeongsang National University Hospital local institutional review and Ethics Committee Boards (No. GNUH 2022–06-002), also registered under CRIS (No. PRE20220903-001) with describing study design comprising patients and treatments. This study was conducted according to the Declaration of Helsinki.

Patient Selection and Collection Items

This study was conducted at three university-affiliated hospitals in Korea from June 2022 to May 2024. Patients enrolled were aged 40 years or older and treated with SITT. Details on the inclusion and exclusion criteria for this study are provided in Supplementary Table 1. Patients aged ≥40 years, with a confirmed diagnosis of COPD, who had been receiving MITT for >90 days prior to enrollment, and who agreed to participate were enrolled in this study. Patients who had previously undergone SITT were excluded. Patients with unstable COPD due to exacerbation within 4 weeks after the first visit were also excluded. If patient failed to attend follow-up appointments or disregarded medical directives, which might have affected the research outcomes, we opted to discontinue therapy. Furthermore, we excluded patients who had unstable COPD resolution of an exacerbation within 4 weeks after the first visit. The number of exacerbations was assessed at each clinical visit after SITT initiation; the level of exacerbation was confirmed by specialists using the standard Global Initiative for Obstructive Lung Disease (GOLD) guideline classification.

The collected Patient-Reported Outcomes included the CAT, mMRC, and Treatment Satisfaction–Visual Analysis Scale (TS-VAS) scores, which were assessed during patient visits at baseline (time of initial drug change) and at week 24. The incidence of adverse events was documented at each clinic visit.

Outcomes

The prespecified primary endpoint was the change from the baseline CAT score into that at 24 weeks after drug switching. Secondary endpoints included change from baseline in the mMRC score, forced expiratory volume in 1 s (FEV1), TS-VAS score, and exacerbation rate within 1 year. The predicted values of FEV1 and forced vital capacity of lungs (FVC) were calculated using Korean applicable referenced equations.[34] To conduct additional analyses on the dissimilarity between the devices, the types of inhaler devices used at baseline were identified and classified into non-Ellipta and Ellipta groups.

Statistical Analyses

A sample size of 107 patients was computed to have 80% power for detecting a 2-point change in the CAT score from the baseline. The null hypothesis of this study was that there would be no difference in CAT scores at week 24. Regarding the analysis of primary and secondary outcomes at week 24, a paired *t*-test was performed. Additionally, the proportion of CAT responders was analyzed using logistic regression, considering the baseline CAT score and exacerbation history as covariates. All statistical analyses were carried out using the SAS® package (version 9.4).

Results

Patient Cohort

A total of 107 patients were enrolled during the pre-single-inhaler triple treatment period. Of these, 91 patients met the eligibility criteria for analysis based on the CAT and mMRC assessments. Subsequently, two patients were lost to follow-up, reducing the TS-VAS population to 89 participants. Further follow-up resulted in the loss of four additional participants, leaving a final sample size of 85 patients for the lung function analysis. Overall, four participants discontinued due to non-serious adverse events (e.g. dry mouth), one due to a serious non-drug-related adverse event (death), and 11 were lost to follow-up. The inclusion and exclusion of participants are depicted in the flowchart (Supplementary Figure 1). The baseline characteristics of the participants are summarized in Table 1.

Table 1 Demographics and Clinical Characteristics During the Pre-Single Inhaler Triple Treatment Period (N = 107)

Characteristics		
Age, years, mean ± SD	74.13	± 8.23
Sex, n (%)		
Male	94	(88)
Female	13	(12)
Height, cm, mean ± SD*	163.88	± 8.1
Weight, kg, mean ± SD*	61.48	± 10.54
Smoking history, n(%)		
Never smoker	23	(21)
Ever smoker	84	(79)
Smoking history, mean, ± SD**	42.19	± 25.28
Patients Experienced exacerbations, n (%)	58	(54)
Number of exacerbations, n (%)		
0	69	(64)
1	26	(24)
≥2	12	(11)
Rate of exacerbations per person per year, mean ± SD	1.00	± 1.08
CAT score in baseline, mean ±SD***	17.66	± 8.19
Lung Function in baseline,		
FEV1 in baseline period, L, mean± SD	1.44	± 0.57
FVC in baseline period, L, mean± SD	2.59	± 0.84
FVC/FEV1 in baseline period, %, mean± SD	52.78	± 15.38
Treatment Group as GOLD criteria, n (%)*		
GOLD A	13	(12)
GOLD B	75	(71)
GOLD C	2	(2)
GOLD D	16	(15)
Inhaler Device Type in baseline, n (%)		
Ellipta MITT	44	(42)
Non-Ellipta MITT	62	(58)
Respiratory disease history and Comorbid diseases, n (%)****		
Bronchiectasis	18	(17)
Chronic bronchitis	31	(29)
Emphysema	39	(37)
Pulmonary fibrosis	17	(16)
Previous history of TB	14	(13)
Measles	2	(2)
Whooping cough	1	(1)
Pneumonia	5	(5)
Bronchial asthma	16	(15)
Allergic rhinitis	1	(1)
Atopic dermatitis	1	(1)
Drug allergy	0	(0)

Notes: GOLD criteria based on Global initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report. *Data captured from 106 subjects, **Data captured from 77 subjects, ***Data captured from 105 subjects, ****Some subjects recorded more than one disease.

Abbreviations: SD, standard deviation; CAT, COPD assessment test; FEV1, forced expiratory volume in 1 second ;FVC, forced vital capacity; MITT, multiple-inhaler triple therapy; TB, Tuberculosis.

The mean age of the participants was 74 years, with male preponderance (88%, n = 94). Of the total 107 participants, 21% (n = 23) were classified as never smokers, whereas the majority, 79% (n = 84), were categorized as ever smokers. Among them, 29 participants are current smokers. Exacerbation history revealed that 54% (n = 58) of the participants experienced at least one exacerbation per year.

Clinical assessments included the CAT score, with a mean score of 17.66 (standard deviation [SD] = 8.19) among the 105 participants, indicating a moderate impact on health status. Lung function tests were conducted in 106 participants, according to the GOLD criteria; 11% (n = 12) of the participants were in GOLD stage 1, 44% (n = 47) in GOLD stage 2, 30% (n = 32) in GOLD stage 3, and 15% (n = 16) in GOLD stage 4. The mean mMRC score was 1.84 [SD] = 0.74). The distribution of mMRC scores showed that 1% (n=1) of the participants had a score of 0, 33% (n = 35) had a score of 1, 47% (n = 50) had a score of 2, and 19% (n=20) had a score of 3 (Table 1, Supplementary Table 2).

Regarding the types of inhaler devices used at baseline, 42% (n=44) of the participants used the Ellipta MITT, whereas 58% (n=62) used non-Ellipta.

Comorbidities were reported in 49% (n=52) of the patients, with the most frequent being hypertension (20%), followed by peripheral vascular disease (12%), diabetes mellitus (10%), congestive heart failure (9%), and cardiovascular issues with a history of myocardial infarction (4%). Respiratory comorbidities or histories were prevalent, with emphysema (37%), chronic bronchitis (29%), and bronchiectasis (17%) being the most common; no participants reported drug allergies (Table 1, Supplementary Table 2).

Efficacy Results at Week 24

This study assessed changes in the CAT scores from baseline to week 24 across different patient characteristics. The analysis included 91 patients at baseline and at 24 weeks. Overall, there was a significant reduction in the mean CAT score from 17.37 to 15.98, with a mean change of 1.40 points (P = 0.007). This indicated an improvement in the patients' health status over the 24-week period. Patients aged ≥70 years (n = 67) had a mean reduction in CAT score of 1.40 points (P = 0.033); in those ≤70 years (n = 24), the mean reduction was 1.38 points (P = 0.052) (Table 2).

Table 2 Efficacy Results at Week 24 (N=107)

Characteristics	Baseline			Week 24		Change from Baseline			*P*-value[a]
	Mean	n	(%)	Mean	n	(%)	Mean	SE	
CAT Score, mean, n	17.37	91		15.98	91		**−1.40**	**0.50**	0.007
Inhaler type									
Ellipta MITT	16.57	37	(41)	15.24	37	(41)	−1.32	0.85	0.126
Non-Ellipta MITT	17.93	54	(59)	16.48	54	(59)	−1.44	0.63	0.026
Exacerbation									
No exacerbation	16.21	57	(63)	14.96	57	(63)	−1.25	0.59	0.040
≥1 exacerbation	19.32	34	(37)	17.68	34	(37)	−1.65	0.93	0.084
Age									
≥70	16.93	67	(74)	15.52	67	(74)	−1.40	0.64	0.033
<70	18.63	24	(26)	17.25	24	(26)	−1.38	0.67	0.052
Sex									
Male	17.60	80	(88)	16.15	80	(88)	−1.45	0.55	0.009
Female	15.73	11	(12)	14.73	11	(12)	−1.00	1.28	0.453
Smoking history									
Never smoker	19.90	20	(22)	19.25	20	(22)	−0.65	0.52	0.116
Ever smoker	16.66	71	(78)	15.06	71	(78)	−1.61	0.87	0.008

(*Continued*)

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Table 2 (Continued).

Characteristics	Baseline			Week 24			Change from Baseline		*P*-value[a]
	Mean	n	(%)	Mean	n	(%)	Mean	SE	
Lung function (GOLD)									
GOLD 1	14.25	12	(13)	13.50	12	(13)	−0.75	0.83	0.384
GOLD 2	14.40	40	(44)	13.40	40	(44)	−1.00	0.77	0.2
GOLD 3	20.41	29	(32)	18.48	29	(32)	−1.93	1.11	0.092
GOLD 4	24.20	10	(11)	22.00	10	(11)	−2.20	0.81	0.024
Adherence									
PDC≥0.9	17.02	52	(57)	15.38	52	(57)	−1.63	0.63	0.012
PDC<0.9	17.85	39	(43)	16.77	39	(43)	−1.08	0.83	0.204
mMRC, mean, n	1.81	91		1.76	91		−0.19	0.10	0.070
TS-VAS, mean, n	5.76	89		7.47	89		1.71	0.20	<0.001
Previous Inhaler type									
Ellipta MITT	5.68	37	(42)	7.73	37	(42)	2.05	0.33	<0.001
Non-Ellipta MITT	5.83	52	(58)	7.29	52	(58)	1.46	0.24	<0.001
Exacerbation									
No exacerbation	5.93	56	(63)	7.68	56	(63)	1.75	0.25	<0.001
Any exacerbation	5.48	33	(37)	7.12	33	(37)	1.64	0.33	<0.001
Age									
≥ 70	5.96	24	(27)	7.17	24	(27)	1.21	0.34	0.002
<70	5.69	65	(73)	7.58	65	(73)	1.89	0.24	<0.001
Sex									
Male	5.79	78	(88)	7.40	78	(88)	1.60	0.21	<0.001
Female	5.55	11	(12)	8.00	11	(12)	2.45	0.56	0.001
Smoking history									
Never smoker	6.05	20	(22)	7.10	20	(22)	1.05	0.47	0.039
Ever smoker	5.68	69	(78)	7.58	69	(78)	1.90	0.21	<0.001
Lung function (GOLD)									
GOLD 1	5.25	12	(13)	7.75	12	(13)	2.50	0.47	<0.001
GOLD 2	5.64	39	(44)	7.69	39	(44)	2.05	0.31	<0.001
GOLD 3	5.96	28	(31)	7.18	28	(31)	1.21	0.34	0.002
GOLD 4	6.30	10	(11)	7.10	10	(11)	0.80	0.47	0.120
Adherence									
PDC ≥ 0.9	5.90	51	(57)	7.67	51	(57)	1.63	0.35	<0.001
PDC < 0.9	5.58	38	(43)	7.21	38	(43)	1.76	0.23	<0.001
Lung function									
FEV1 L, mean, n	1.48	85		1.52	85		0.04	0.04	0.404
FVC L, mean, n	2.62	85		2.60	85		−0.02	0.05	0.733
FEV1 pred (%), mean, n	55.86	85		57.02	85		1.16	1.46	0.427
FVC pred (%), mean, n	66.19	85		65.73	85		−0.46	1.22	0.706
FEV1/FVC, mean, n	53.22	85		57.54	85		4.31	1.50	0.005

Notes: GOLD criteria based on Global initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report.; [a]The p-value for the mean change from baseline in each subgroup.

Abbreviations: SE, standard Error; CAT, COPD assesment test; MITT, multiple-inhaler triple therapy; mMRC, modified medical research council dyspnea scale; TS-VAS, treatment satisfaction visual analog scale; PDC, Proportion of Days Covered; FEV1, forced expiratory volume in 1; FVC, forced vital capacity.

We also assessed the proportion of CAT responders at week 24 among the participants using different inhaler types. A total of 91 participants were evaluated, of whom 48 (52.7%) were classified as CAT responders, indicating a clinically meaningful improvement (≥2 point) in their CAT scores at week 24. In contrast, 43 (47.3%) patients were classified as non-responders. Among CAT responders, 29 (53.7%) used non-Ellipta inhalers and 19 (51.4%) used Ellipta MITT inhalers. In the non-responder group, 25 (46.3%) patients used non-Ellipta and 18 (48.6%) used Ellipta MITT (Figure 1, Supplementary Table 3).

The study evaluated the change in mMRC score; overall, there was a small, non-significant reduction in the mean mMRC score from 1.81 at baseline to 1.76 at week 24 (mean = 0.19, P = 0.070), indicating slight improvement in dyspnea symptoms (Table 2).

Eighty-five participants with normal lung function population were included in the study. The mean FEV1 demonstrated a marginal increase from baseline to week 24 (mean = 0.04, P = 0.404), whereas FVC decreased slightly (mean = −0.02, P = 0.733). The percentage of predicted FEV1 increased from the baseline (mean = 1.16%, P = 0.427), which was not statistically significant. In addition, the FEV1/FVC ratio significantly improved (mean = 4.31%, P = 0.005) (Table 2).

There was a significant improvement in the TS-VAS scores, with the mean score increasing from baseline. A total of 89 people were evaluated in the TS-VAS scores population, yielding a mean change of 1.71 points (P < 0.001). Participants who used the Ellipta MITT before study participation (n = 37) showed a significant increase in the TS-VAS score from 5.68 to 7.73, (mean = 2.05, P < 0.001). Similarly, those who used non-Ellipta before study participation (n =52) also experienced significant improvement, with their mean TS-VAS scores increasing from 5.83 to 7.29, (mean = 1.46, P < 0.001) (Table 2).

The results indicated a substantial decrease in the overall number of COPD exacerbations among individuals from baseline to week 24. COPD exacerbations among participants decreased significantly from baseline to week 24. At baseline, 34 participants experienced 53 exacerbation events, whereas at week 24, only 10 participants experienced 11 events (incidence rate ratio [IRR] of 0.45 (95% confidence interval [CI]: 0.24–0.86), P = 0.016). The combined category of moderate/severe COPD exacerbations showed a reduction from 30 participants (45 events) to 9 participants (10 events), with an IRR of 0.51 (95% CI: 0.25–1.01, P = 0.052) (Table 3).

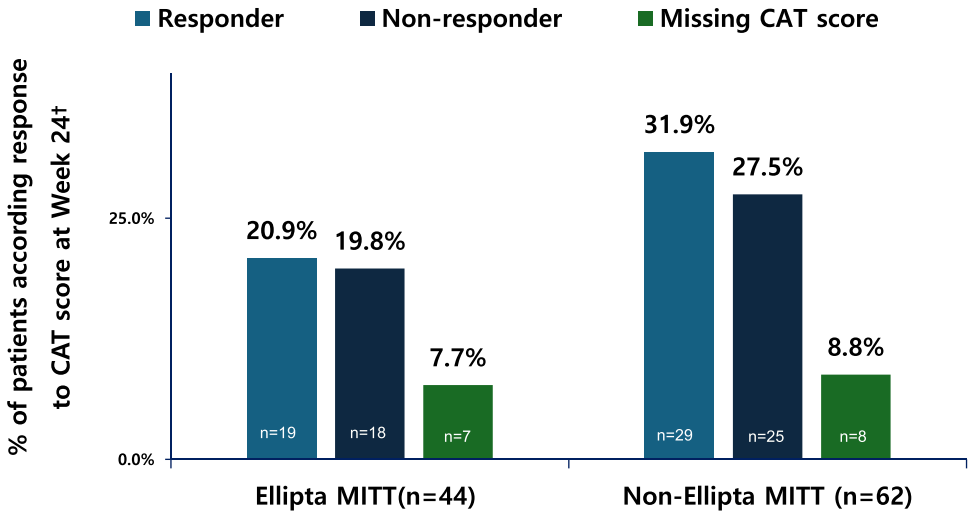

Figure 1 CAT responder of Ellipta MITT vs non-Ellipta MITT, †Response defined as a CAT score of 2 units below baseline or lower.
Abbreviation: mFAS population, modified Full analysis Set population (n=91).

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Table 3 Summary of COPD Exacerbations (N=91)

Characteristics	Baseline[a]		Week 24		IRR (95% CI)[b]	*P*-value
Number of any exacerbations	**Subject**	**Event**	**Subject**	**Event**		
Total No.	34	53	10	11	0.45 (0.24–0.86)	0.016
Total duration at risk						
Participants with a mild COPD exacerbation	5	8	1	1	0.27 (0.03–2.17)	0.219
Participants with a moderate COPD exacerbation	26	41	8	9	0.50 (0.24–1.03)	0.062
Participants with a severe COPD exacerbation	4	4	1	1	0.54 (0.06–4.86)	0.585
Participants with a moderate/severe COPD exacerbation	30	45	9	10	0.51 (0.25–1.01)	0.052
Total number of COPD exacerbations per participant, n (%)						
0	57	(63)	81	(89)		
1	23	(25)	9	(10)		
≥2	11	(12)	1	(1)		

Note: [a]Exacerbation number in previous 1 year, [b]Exacerbation number per person year
Abbreviations: IRR, Incidence Rate Ratio; CI, confidence interval.

Discussion

In this real-world prospective observational study, patients with COPD previously treated with MITT who transitioned to Ellipta SITT (FF/UMEC/VI) experienced improvements in clinical outcomes and treatment satisfaction. The CAT score, TS-VAS score, FEV1/FVC ratio, and IRR of exacerbation showed significant improvement compared with baseline; mMRC score and FEV1 showed a favorable trend, but did not show statistical significance. Furthermore, among the subgroups of previous treatment, the non-Ellipta group showed a significant improvement in CAT score.

A recently emerging treatment goal for COPD is achieving disease stability, which encompasses maintaining lung function, reducing exacerbations, and improving overall health status.[35] Triple therapy, combining ICS, LABA, and LAMA in a single regimen, has demonstrated significant clinical benefits in patients with COPD by improving symptoms, enhancing lung function, and reducing the frequency of exacerbations, ultimately enhancing patients' quality of life.[2,23,27,28,36] Studies have demonstrated that triple therapy yields greater improvements in FEV1 compared with dual therapies.[23,37,38] Furthermore, patients receiving triple therapy experience fewer COPD exacerbations, which are crucial for preventing disease progression, reducing hospitalization rates, and lowering mortality as evidenced by various studies. Overall, the evidence strongly supports the use of triple therapy for managing moderate-to-severe COPD, particularly in patients with a history of frequent exacerbations.[2,23,38,39]

Our study, while limited in scale and duration, focused on evaluating the real-world effectiveness of simplifying triple therapy through a single-inhaler device, aiming to improve adherence and optimize clinical outcomes.

Previous studies reported that patients receiving SITT have higher adherence rates than do those receiving MITT. A retrospective analysis from USA found that Ellipta SITT (FF/UMEC/VI) users showed adherence rate with proportion of days covered (PDC) as 0.67 at 6 months and 0.61 at 12 months, while that for the MITT users were 0.43 and 0.39, respectively, and also the favored with adherent (PDC ≥ 0.8) patients' ratio (33.6% vs 14.9% at 12-month). SITT users were nearly twice as likely as MITT users to persist at 12 months (34.4vs. 14.9%; $P < 0.001$). Another retrospective study from an English real-world primary care setting found comparable outcomes with longer observations of up to 18 months; however, the disparity remained between groups.[30] These studies demonstrated that the multi-step process required with MITT contributes to higher rates of missed doses and discontinuation, particularly in older adults or those with cognitive or physical impairments.

Furthermore, efforts have been made to investigate the improvements in clinical outcomes with SITT in well-controlled trials and real-world settings. Phase IV studies, which compared Ellipta SITT (FF/UMEC/VI) with twice-daily MITT (budesonide/formoterol [BUD/FOR]+ tiotropium [TIO]), observed significant improvement in FEV1, but not for SGRQ and CAT scores between the groups.[27] One of the key findings from the INTREPID study,[28] a randomized Phase IV effectiveness trial, investigated the impact of switching from MITT to SITT using the ELLIPTA device in

patients with COPD, was that users of ELLIPTA SITT demonstrated a higher ratio of CAT responders compared with those who continued using non-ELLIPTA MITT (47 vs 40%, odds ratio [OR] 1.31, $P < 0.001$). The sub-group of prior medication with non-Ellipta MITT also showed similar results in both groups (47 vs 41%, OR 1.28, $P = 0.004$).[28] CAT score change from baseline at week 24 in Ellipta SITT and non-Ellipta MITT groups was −2.8 ± 6.3 (mean ± SD) and −1.3 ± 6.0, respectively. Our study showed similar results: 52.7% of patients who switched to SITT achieved a CAT response, and each previous medication subgroup with non-Ellipta-MITT and Ellipta-MITT showed similar results, achieving 53.7 and 51.4%, respectively. CAT score improvement was also observed −1.40 ± 0.50 (mean ± SE, $P = 0.007$) change during 24-week period. This difference was not enough to show the minimum clinically important difference (MCID) for CAT as 2-point decrease.[39] However, since the participants have already received active control with triple treatment before being enrolled to our study, this result is expectable and showed similar with previous study. Of note, the sub-group of previous medication with non-Ellipta MITT group also showed significant change (−1.44 ± 0.63, $P = 0.026$), whereas the change in the Ellipta MITT group was not significant (−1.32 ± 0.85, $P = 0.126$). It may be assumed that Ellipta MITT users have already accustomed with the same inhaler type; hence, improving adherence to the same extent as non-Ellipta MITT users was insufficient. Pulmonary function changes in FEV1 from our study showed a 40 mL numerical improvement, despite showing no enough significance ($P = 0.404$), with a similar trend to that in the INTREPID study, which showed a 50 mL difference ($P < 0.001$) of Ellipta SITT compared with non-Ellipta MITT.[28]

Exacerbations, which are among the most clinically relevant outcomes in COPD management, have been shown in several studies to be affected by adherence. A retrospective study from England found that switching from non-Ellipta MITT to Ellipta SITT resulted in a significant reduction in moderate (RR 0.78, $P < 0.0001$), severe (RR 0.81, $P = 0.002$), and moderate-to-severe (RR 0.79, $P < 0.0001$) exacerbations during 6 months.[40] Another retrospective study in the United States found that switching from MITT to Ellipta SITT resulted in a decrease in the mean number of exacerbations by patients over a 12-month period for moderate-to-severe (from 1.4 to 1.2, $P = 0.001$) and moderate (from 1.1 to 0.9, $P < 0.001$) exacerbations, but not for severe (from 0.3 to 0.3, $P = 0.415$) exacerbations.[31] Our study also found a significant decrease in overall exacerbation with an IRR of 0.45 ($P = 0.017$), and comparable results were seen in the sub-groups with moderate (IRR 0.50, $P = 0.062$), severe (IRR 0.54, $P = 0.585$), and moderate-to-severe (IRR 0.51, $P = 0.0518$) exacerbations. Since our study was conducted including a prospective cohort with a limited sample size, it was not sufficient to test each subgroup (91 participants from our study, compared with 2533 (from England) and 912 (from the United States. However, the aligned trends could still be found.

We further explored the Quality of Life measured with TS-VAS scaling from 0 to 10, starting from baseline (5.76) to week 24 (7.47), showing a significant improvement ($p < 0.001$). This significance was found in most subgroups of patient characteristics, with the exception of pulmonary function using GOLD 4, which was significant in some subgroups when compared with the CAT score. This suggests that even if there are some patients whose clinical outcomes do not improve sufficiently, achieving treatment satisfaction, providing that the primary cause is the use of a simplified therapy with a single device, is still feasible. This may help support decisions made not just based on adherence and clinical outcomes, but also on a patient-centered approach with simple treatment.

This study has several limitations. First, our study employed a single-arm design to assess clinical outcomes in a pre-post cohort. The lack of a comparison group may have caused extrinsic factors throughout the study period, influencing the outcome. In addition, we were unable to obtain the baseline adherence characteristics. Therefore, we were unable to define improvement and instead examined adherence during SITT treatment. Second, our sample size was insufficient to evaluate additional endpoints and perform stratified analyses, such as severity of exacerbations, differences between devices and bronchodilators, or subgroups. Consequently, we focused on exploring potential trends rather than drawing definitive conclusions. Third, beyond reducing the number of inhalers, 58% (62/102) of participants also experienced a change in inhaler device type, which could have influenced the results. However, subgroup analysis based on MITT device type (Ellipta and non-Ellipta) showed significant improvements in CAT and VAS scores even when transitioning from non-Ellipta MITT to Ellipta SITT. Finally, since this study was conducted at three healthcare centers in South Korea's southeastern region, the findings may not fully represent the national population.

According to a recent study,[41] smoking cessation in patients with COPD leads to improvements in various COPD outcomes even one month after quitting, highlighting the importance for smoking cessation. However, since smoking

cessation was not an intervention in our study, its direct impact could not be evaluated. Future research should further explore the role of smoking cessation strategies in COPD management to provide comprehensive insights into optimizing patient care.

One of the studies on SITT[42] conducted in Germany is similar to our research. Notably, a German study on SITT reported differences in FEV1 over a 12-month period, which aligns with our findings despite differences in study design. Our study, like this research, used the change in CAT score as the primary endpoint. However, due to differing considered references, the sample size was calculated to be smaller. Additionally, We focused on observing the transition from multiple devices to a single device and our results showed similar outcomes to those observed in the INTREPID study.[28]

This study represents the first prospective cohort investigation of clinical outcomes associated with switching to Ellipta SITT in MITT users, contributing valuable evidence from the South Korean population. Additionally, we analyzed outcomes based on patient characteristics such as inhaler type, exacerbation history, age, sex, and adherence, underscoring the potential benefits of simplifying therapy with a single device.

Conclusion

We investigated whether switching from MITT to a SITT with FF/UMEC/VI resulted in improved clinical outcomes such as symptom score, pulmonary function, exacerbation, and treatment satisfaction. The findings indicated that a simplified approach with a single device could be beneficial not only for adherence, but also for clinical outcomes in the management of COPD.

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Disclosure

Hana Lim is an employee of GSK. However, this study was conducted independenlty without any support (financial or material) from the company. Dong Han Kim was employee of GSK at the time of study start and now is an employee of Sanofi. The authors report no other conflicts of interest in this work.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med*. 2017;195(5):557–582. doi:10.1164/rccm.201701-0218PP
2. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Am J Respir Crit Care Med*. 2023;207(7):819–837. doi:10.1164/rccm.202301-0106PP
3. Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med*. 2022;206(11):1317–1325. doi:10.1164/rccm.202204-0671PP
4. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403(10440):2100–2132. doi:10.1016/S0140-6736(24)00367-2
5. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403(10440):2133–2161. doi:10.1016/S0140-6736(24)00757-8
6. Kim SH, Lee H, Kim Y, et al. Recent prevalence of and factors associated with chronic obstructive pulmonary disease in a rapidly aging society: Korea national health and nutrition examination survey 2015–2019. *J Korean Med Sci*. 2023;38(14):e108. doi:10.3346/jkms.2023.38.e108
7. Kim SH, Park JE, Yang B, et al. National trend in the prevalence and mortality of COPD in South Korea from 2008 to 2017. *BMJ Open Respir Res*. 2024;11(1):e002391. doi:10.1136/bmjresp-2024-002391
8. Park S, Kim MS, Yon DK; GBD 2019 South Korea BoD Collaborators. Population health outcomes in South Korea 1990–2019, and projections up to 2040: a systematic analysis for the global burden of disease study 2019. *Lancet Public Health*. 2023;8(8):e639–e650. doi:10.1016/S2468-2667(23)00122-6
9. Park SC, Kim DW, Park EC, et al. Mortality of patients with chronic obstructive pulmonary disease: a nationwide population-based cohort study. *Korean J Intern Med*. 2019;34:1272–1278. doi:10.3904/kjim.2017.428
10. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775–789. doi:10.1056/NEJMoa063070
11. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–1554. doi:10.1056/NEJMoa0805800

12. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. *N Engl J Med*. 2016;374 (23):2222–2234. doi:10.1056/NEJMoa1516385
13. Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196(4):438–446. doi:10.1164/rccm.201703-0449OC
14. Jung KS, Park HY, Park SY, et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med*. 2023;106(3):382–389. doi:10.1016/j.rmed.2011.09.004
15. Park YB, Rhee CK, Yoon HK, et al. Revised (2018) COPD clinical practice guideline of the Korean academy of tuberculosis and respiratory disease: a summary. *Tuberc Respir Dis*. 2018;81(4):261–273. doi:10.4046/trd.2018.0029
16. Sanduzzi A, Balbo P, Candoli P, et al. COPD: adherence to therapy. *Multidiscip Respir Med*. 2014;9:60. doi:10.1186/2049-6958-9-60
17. Vestbo J, Anderson JA, Calverley PMA, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*. 2009;64 (11):939–943. doi:10.1136/thx.2009.113662
18. Mäkelä MJ, Backer V, Larsson K, et al. Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD. *Respir Med*. 2013;107(10):1481–1490. doi:10.1016/j.rmed.2013.04.005
19. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. *Int J Chron Obstruct Pulmon Dis*. 2010;5:401–406. doi:10.2147/COPD.S14715
20. Yu AP, Guérin A, Ponce de Leon P, et al. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. *J Med Econ*. 2011;14(4):486–496. doi:10.3111/13696998.2011.594123
21. Bogard M, Stanford RH, Laliberté F, et al. Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *Int J Chron Obstruct Pulmon Dis*. 2019;14:343–352. doi:10.2147/COPD.S184653
22. Ismaila A, Corriveau D, Vaillancourt J, et al. Impact of adherence to treatment with tiotropium and fluticasone propionate/salmeterol in chronic obstructive pulmonary diseases patients. *Curr Med Res Opin*. 2014;30(7):1427–1436. doi:10.1185/03007995.2014.908828
23. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378 (18):1671–1680. doi:10.1056/NEJMoa1713901
24. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
25. Miravitlls M, Acharya S, Aggarwal B, et al. Clinical concepts for triple therapy use in patients with COPD: a delphi consensus. *Int J Chron Obstruct Pulmon Dis*. 2023;18:1853–1866. doi:10.2147/COPD.S424128
26. Bremner PR, Birk R, Brealey N, et al. Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: a randomized non-inferiority study. *Respir Res*. 2018;19(1):19. doi:10.1186/s12931-018-0724-0
27. Ferguson GT, Brown N, Compton C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. *Respir Res*. 2020;21:131. doi:10.1186/s12931-020-01360-w
28. Halpin DMG, Worsley S, Ismaila AS, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Res*. 2021;7(2):00950–2020. doi:10.1183/23120541.00950-2020
29. Mannino D, Bogart N, Benjamin W, et al. Adherence and persistence to once-daily single-inhaler versus multiple-inhaler triple therapy among patients with chronic obstructive pulmonary disease in the USA: a real-world study. *Respir Med*. 2022;197:106807. doi:10.1016/j.rmed.2022.106807
30. Halpin DMG, Rothnie KJ, Banks V, et al. Comparative adherence and persistence of single- and multiple-inhaler triple therapies among patients with chronic obstructive pulmonary disease in an English real-world primary care setting. *Int J Chron Obstruct Pulmon Dis*. 2022;17:2417–2429. doi:10.2147/COPD.S370540
31. Hanania NA, Bunner SH, Bengton LGS, et al. COPD exacerbations, costs, and health care resource utilization before and after initiation of fluticasone furoate/umeclidinium/vilanterol in routine care in the USA. *Int J Chron Obstruct Pulmon Dis*. 2023;18:407–418. doi:10.2147/COPD.S378867
32. Lim H, Park M. Analysis of treatment patterns in COPD patients using health insurance claims data: focusing on inhaled medications. *Korean J Clin Pharm*. 2022;32(3):155–165. doi:10.24304/kjcp.2022.32.3.155
33. Liao KM, Wang JJ, Ho CH. Real-world experience of treating chronic obstructive pulmonary disease with triple therapy. *Int J Chronic Obstr*. 2023;18:1057–1066. doi:10.2147/COPD.S404039
34. Choi JK, Paek D, Lee JO. Normal predictive values of spirometry in Korean population. *Tuberc Respir Dis*. 2005;58(3):230–242. doi:10.4046/trd.2005.58.3.230
35. Han MK, Vanfeteren LEGW, Kolterer S, et al. Striving for stability in patients with COPD: a new way forward? *Adv Ther*. 2024;41:3977–3981. doi:10.1007/s12325-024-02982-y
36. Rothnie KJ, Wood RP, Czira A, et al. Outcomes of patients with COPD switching from multiple-inhaler to once-daily single-inhaler triple therapy in a real-world primary care setting in England: a retrospective pre-post cohort study. *BMJ Open Respir Res*. 2024;11:e001890. doi:10.1136/bmjresp-2023-001890
37. Papi A, Vestbo J, Fabbri L, et al. Outcomes of patients with COPD switching from multiple-inhaler to once-daily single-inhaler triple therapy in a real-world primary care setting in England: a retrospective pre-post cohort study.
38. Gaduzo S, McGovern V, Roberts J, et al. When to use single-inhaler triple therapy in COPD: a practical approach for primary care health care professionals. *Int J Chron Obstruct Pulmon Dis*. 2019;14:391–401. doi:10.2147/COPD.S173901
39. Kon SSC, Canavan JL, Jones SE, et al. Minimum clinically important difference for the COPD assessment test: a prospective analysis. *Lancet Respir Med*. 2014;2(3):195–203. doi:10.1016/S2213-2600(14)70001-3
40. Bogart M, Bengtson LG, Johnson MG, et al. Outcomes following initiation of triple therapy with fluticasone furoate/umeclidinium/vilanterol versus multiple-inhaler triple therapy among medicare advantage with part D beneficiaries and those commercially enrolled for health care insurance in the United States. *Int J Chron Obstruct Pulmon Dis*. 2024;19:97–110. doi:10.2147/COPD.S424497
41. Pezzuto A, Ricci A, D'Ascanio M, et al. Short-term benefits of smoking cessation improve respiratory function and metabolism in smokers. *Int J Chron Obstruct Pulmon Dis*. 2024;19:1. doi:10.2147/COPD.S439064

42. Beeh KM, Scheithe K, Schmutzler H, et al. Real-world effectiveness of fluticasone furoate/umeclidinium/vilanterol once-daily single-inhaler triple therapy for symptomatic COPD: the ELLITHE non-interventional trial. *Int J Chron Obstruct Pulmon Dis*. 2024;19:205–216. doi:10.2147/COPD.S427770
43. Agustí A, Richard B, Celli BR, et al. Global initiative for chronic obstructive lung disease 2022 report: GOLD executive summary.