Original Research

Prospective Randomized Study on Switching Triple Inhaler Therapy in COPD from Multiple Inhaler Devices to a Single Inhaler Device in a Chinese Population

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Running Head: **Triple Inhaler Therapy in COPD**

Keywords**:** COPD; triple therapy; single inhaler triple therapy; multiple inhaler triple therapy

Abbreviations**: CAT**=COPD Assessment Test; **COPD**=chronic obstructive pulmonary disease; **DPI**=dry powder inhaler; **FEV_1**=forced expiratory volume in one second; **FVC**=forced vital capacity; **GOLD**=Global Initiative for Chronic Obstructive Lung Disease; **ICS**=inhaled corticosteroids; **IQR**=inter-quartile range; **LABA**=long-acting β2-agonists; **LAMA**=long-acting muscarinic antagonists; **MARS-A**=Medication Adherence Report Scale for Asthma; **MDI**=metered dose inhaler; **MITT**=multiple inhaler triple therapy; **mMRC**=modified Medical Research Council; **QMH**=Queen Mary Hospital; **SITT**=single inhaler triple therapy

Funding Support: None

Date of Acceptance**:** December 9, 2024 | ***Publication Online Date*****:** December 13, 2024

Citation: Kwok WC, Ma TF, Tsui CK, Ho JCM, Tam TCC. Prospective randomized study on switching triple inhaler therapy in COPD from multiple inhaler devices to a single inhaler device in a Chinese population. *Chronic Obstr Pulm Dis.* 2024; Published online December 13, 2024. https://doi.org/10.15326/jcopdf.2024.0519

This article has an online supplement.

Abstract

BACKGROUND:

Triple therapy with inhaled corticosteroids and dual bronchodilator was recommended in chronic obstructive pulmonary disease (COPD) patients who had exacerbations and eosinophilia. It can be administered by single inhaler (SITT) or multiple inhaler (MITT). There was lack of evidence of the benefits of SITT over MITT in Chinese population, especially on switching from existing MITT to SITT.

METHODS:

70 Chinese patients with COPD was recruited in this open-label double-arm clinical trial to investigate the number of critical errors, mMRC dyspnoea scale, MARS-A score and satisfaction score upon switching from MITT to SITT.

RESULTS:

The mean number of critical errors were 0.4 ± 1.0 in SITT group and 1.1 ± 1.8 in MITT group, p = 0.038 at first visit; 0.2 ± 0.6 in SITT group and 0.8 ± 1.1 in MITT group, p = 0.007 at second visit. The mean change in MARS-A from baseline to first visit was +3.76 ± 7.48 in SITT group and -1.27 ± 7.76 in MITT group, p-value 0.008. 22 (59.5%) and 8 (24.2%) of the patients in SITT and MITT group had an increase in MARS-A score from baseline to first visit respectively, with adjusted OR (aOR) of 6.23 (95% CI = 1.63 – 23.77, p = 0.007), favoring SITT. There was no significant difference in the change in mMRC dyspnea scale and satisfaction score in the two groups.

CONCLUSION:

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Switching from MITT to SITT in Chinese COPD patients may have the benefits of having fewer critical error numbers and higher MARS-A score.

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Background

Among patients with chronic obstructive pulmonary disease (COPD) who had exacerbations with high blood eosinophil count, triple therapy consisting of inhaled corticosteroids (ICS) /long-acting β2-agonists (LABA) /long-acting muscarinic antagonists (LAMA) was recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD) with benefits in terms of mortality and moderate-to-severe exacerbation.(1, 2, 3, 4, 5, 6, 7, 8, 9, 10) Triple therapy can be administered by single inhaler triple therapy (SITT) or multiple inhaler triple therapy (MITT). In a recently published Delphi consensus, there was agreement among experts regarding the appropriate clinical use and benefits of triple therapy in COPD, including its mortality benefits, comparable pneumonia risk between SITT and MITT, preference of SITT for patients with high eosinophil count and exacerbation risk reduction and healthcare cost benefits with early initiation of SITT post exacerbation-related hospitalization (<30 days).(11) When compared with MITT, SITT was shown to be associated with improved treatment persistence and adherence, as well as a reduction in the risk of moderate-to-severe exacerbation, severe exacerbation, and mortality.(12, 13, 14) A real-world observational study in the United Kingdom showed that patients with SITT had improved lung function and a higher proportion of CAT improvement at 24 weeks compared with the MITT group.(15)

There has been lack of research on the benefits of SITT over MITT in the Chinese population, with the recently published study focused on the benefits of SITT in newly diagnosed cases with COPD.(12) Whether the same benefits persist in patients who are already on MITT has not been studied in Chinese population. As such, we conducted this prospective study on the treatment adherence, patients' satisfaction, critical inhaler errors and symptom control for Chinese patients with COPD who were already on MITT.

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Methods

An open-label double-arm clinical trial was conducted in Queen Mary Hospital (QMH), Hong Kong. All Chinese patients with COPD who were already on triple therapy (LABA/LAMA/ICS) via MITT who were followed up in QMH from 25/1/2022 to 14/3/2023 were included. The diagnosis of COPD was confirmed by spirometry demonstrating post-bronchodilator airflow limitation with forced expiratory volume in one second/forced vital capacity [FEV_1/FVC] ratio < 0.7. Exclusion criteria included co-existing asthma, bronchiectasis, and asthma/COPD overlap. Written informed consent was obtained. The recruited patients had history taking, physical examination, spirometry and blood taking at the time of recruitment. At the screening visit, detailed history taking, physical examination, as well as baseline assessments [body-mass indexes, complete blood count, liver & renal function test, chest X-ray, spirometry, modified Medical Research Council (mMRC) Dyspnea Scale, Medication Adherence Report Scale for Asthma (MARS-A)] were collected. Randomization was performed by REDCap software, stratified by age, gender and smoking status. While Medication Adherence Report Scale for Asthma (MARS-A) was initially developed for asthma, it is also validated in Patients with COPD.(16) The number of inhaler critical errors were checked by asking the patient to demonstrate the inhaler techniques. Inhaler technique checked at baseline at the time of recruitment. Patients were randomized to continue triple therapy with the MITT that they were using (MITT group) or switched to triple therapy with SITT via Ellipta® device (SITT group). For patients who were prescribed with MDI, spacer was also given to them for free from pharmacy and they were taught to use MDI with spacer. They were taught by pharmacists on the inhaler technique again after randomization and followed up 4 and 12 weeks afterwards. At the face-to-face inhaler teaching session, the patients were taught by the pharmacists on the proper inhaler technique including demonstration with placebo device.

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The patients were also asked to demonstrate to the pharmacist on how to use the inhaler afterwards. The patients would only be prescribed with the inhaler if the inhaler technique assessment by pharmacist deemed to be satisfactory. Patients will be assessed on mMRC dyspnoea scale, MARS-A score, inhaler satisfaction by ease-of-use questionnaire (17) and number of critical errors on follow up visits. (17, 18, 19)

Critical errors were defined as errors that seriously compromising drug delivery to the lung, which included dose preparation and dose delivery errors. The summary of the criticial errors for each type of inhaler device, which was adopted by prior studies, were included in Supplementary Table 1.

The hypothesis to be tested include whether the switch from MITT to SITT in these Patients with COPD who were on MITT before study recruitment would lead to changes in mMRC dyspnoea scale, MARS-A score, satisfaction score as in ease-of-use questionnaire and number of critical errors. The outcomes were assessed as continuous variables by the absolute changes in these scores and scales. The outcomes were also assessed as the percentage of patients who had improvement in these parameters. The assessments were done at 4 and 12 weeks after the recruitment.

The primary outcome is the number of critical errors between the two groups – SITT and MITT group. The secondary outcomes include mMRC dyspnoea scale, MARS-A score, and satisfaction score as in ease-of-use questionnaire between the two groups.

A sample size of 70, with 35 in each group, was estimated to be needed based on the primary outcome. The calculation of sample size was included in Appendix 1.

Statistical analysis

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

The demographic and clinical data were described in actual frequency, mean ± SD or median [Inter-quartile range (IQR)]. Baseline demographic and clinical data were compared between the two groups (SITT or MITT) with independent t-tests or non-parametric tests where appropriate. For the primary endpoint of interest (treatment compliance, satisfaction of the inhaler, mMRC dysnpoea scale and number of inhaler errors), the baseline and measurement at 4- and 12-week for paired samples will be tested using a non-parametric Wilcoxon signed-rank test. To identify the percentage of patients in the SITT and MITT groups with improvement of the study parameters, univariate logistic regression model was performed. Multiple logistic regression model was used to assess potential confounders that included the age, baseline mMRC dyspnea scale and baseline FEV_1. The factors above were identified as potential founders based on literatures (20, 21) for potential impact on the effect due to inhaler technique and mMRC dyspnoea scale on follow-up visits. The effect due to inhaler and mMRC dyspnoea scale and confounding variables (Age and FEV_1). were illustrated as a hypothetical directed acyclic graph in the supplementary Figure 1. The difference in causal effect in odds ratio was also estimated. Linear regression was used to estimate the association, the mean number of the study parameters and the treatment groups. Bonferroni correction was employed for multiple comparisons. The statistical significance was determined at the level of p=0.05 at two-sided test. All the statistical analyses were done using the 28th version of SPSS statistical package and R version 4.2.2 (2022-10-31).

Results

A total of 73 Chinese patients with COPD managed in Queen Mary Hospital were included. 3 were excluded as they dropped out in the study, with 33 in MITT group and 37 in SITT group.

Baseline characteristics

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

The mean age was 72.3 ± 8.4 years. There were more male patients (92.9%). The mean FEV_1 was 1.43 ± 0.61 L (64.4 ± 22.5%). The mean mMRC score was 1.94 ± 0.81. The mean MARS-A score was 45.7 ± 6.6. The results are summarized in Table 1.

Number of critical errors

The mean number of critical errors per inhaler at baseline assessment was 1.5 ± 1.6 in SITT group and 2.2 ± 2.0 in MITT group, p = 0.10. The mean number of critical errors per inhaler was significantly lower in the SITT group at first and second visit. The mean number of critical errors was 0.4 ± 1.0 in SITT group and 1.1 ± 1.8 in MITT group, p = 0.038 at first visit. The mean number of critical errors was 0.2 ± 0.6 in SITT group and 0.8 ± 1.1 in MITT group, p = 0.007 at second visit. The result was statistically significantly different for the mean number of critical error per inhaler at second visit adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnea scale, with p-value of 0.029 (Figure 1, Table 2).

mMRC dyspnoea scale

The mean baseline mMRC dyspnoea scale were 1.86 ± 0.82 and 2.03 ± 0.81 in the SITT and MITT group respectively, p 0.40. The mean mMRC dyspnoea scale were 1.84 ± 0.87 and 1.79 ± 0.89 in the SITT and MITT group at the first visit, p = 81 and 1.92 ± 0.92 and 1.94 ± 1.06 in the SITT and MITT group at the second visit, p = 0.93. There were no statistically significant difference in the mean mMRC dyspnoea in the first visit at 4 weeks and second visit at 12 weeks. (Table 2) The mean change in mMRC dyspnoea from baseline to first visit was -0.03 ± 0.65 in SITT group and -0.24 ± 1.00 in MITT group, p-value 0.28 in univariate analysis and 0.35 in multi-variate analysis adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnoa score. The mean change in mMRC dyspnea from baseline to second visit was +0.05 ± 0.71 in SITT group and -0.09

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

± 1.21 in MITT group, p-value 0.28 in univariate analysis and 0.71 in multi-variate analysis adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnoea score.

MARS-A score

The mean baseline MARS-A were 43.8 ± 6.9 and 47.9 ± 5.6 in the SITT and MITT group respectively, which is significantly higher in the MITT group, p = 0.008. There was no statistically significant difference in the mean MARS-A in the first visit and second visit, with mean MARS-A being 47.6 ± 6.6 and 46.6 ± 7.2 in the SITT and MITT group at the first visit, p = 0.58; and 46.7 ± 7.0 and 49.2 ± 2.2 in the SITT and MITT group at the second visit, p = 0.054. The mean change in MARS-A from baseline to first visit was +3.76 ± 7.48 in SITT group and -1.27 ± 7.76 in MITT group, p-value 0.008. The result was statistically significantly different after adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnoea score, with p-value of 0.008. 22 (59.5%) and 8 (24.2%) of the patients in SITT and MITT group had an increase in MARS-A score from baseline to first visit respectively, p = 0.003 (Figure 2). The odds ratio (OR) for increase of MARS-A score was 4.58 (95% confidence interval [CI] = 1.63 – 12.86, p = 0.004). The adjusted OR (aOR) was 6.23 (95% CI = 1.63 – 23.77, p = 0.007) suggesting that SITT group had higher odds to have increase in MARS-A score from baseline to first visit. The risk difference was risk difference is 35.22% (95% CI = 13.68% - 56.76%), p = 0.004. The mean change in MARS-A from baseline to second visit was +2.89 ± 9.66 in SITT group and +1.30 ±6.68 in MITT group, p-value 0.42 (Table 2). By, DAG, the estimated direct effect due to inhaler device (MITT or SITT) dominates the total effect to the response, which is similar to the finding in univariate and multivariate analysis (Supplementary Table 2).

Satisfaction score as in ease-of-use questionnaire

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The mean satisfaction score was 23.1 ± 2.1 in SITT group and 23.5 ± 4.5 in MITT group, p = 0.34. The mean change in satisfaction score from baseline to first visit was +0.38 ± 2.43 in SITT group and +0.42 ± 1.48 in MITT group, p-value 0.92 in univariate analysis and 0.66 in multi-variate analysis adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnoa score. The mean change in satisfaction score from baseline to second visit was +0.27 ± 2.59 in SITT group and +0.42 ± 1.46 in MITT group, p-value 0.76 in univariate analysis and 0.63 in multi-variate analysis adjusted for age, gender, FEV_1, FEV_1/FVC ratio and baseline mMRC dyspnoa score. (Table 2)

Discussion

In this study, we demonstrated that switching from MITT to SITT may have the benefits of having lower critical error numbers and higher MARS-A score, as early as in four weeks' time. The potential benefits could persist till 12 weeks after the switch. The results of our study are consistent with prior studies that suggest the potential benefits of SITT. Switching triple therapy from MITT to SITT might have the benefit in improving the adherence to triple therapy with lower critical errors.

While both SITT and MITT are available for COPD, whether switching from MITT to SITT is beneficial remains a question that is frequently asked by clinicians. Both clinicians and patients may be hesitant to change the current inhaler therapy if it is effective and well tolerated. In our study, the possible benefits in switch of triple therapy from MITT to SITT in patients with COPD, by improving adherence and reducing the number of critical errors were suggested. The observation may provide evidence to support this change in inhaler therapy and clinicians may

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consider the switch from MITT to SITT for patients with Group E COPD, especially if there are concerns on medication adherence and critical errors from existing inhalers.

The development and introduction of SITT is a breakthrough in COPD inhaler pharmacotherapy. Once daily SITT would bring about convenience to the patients. Yet, SITT is currently available as dry powder inhaler (DPI) (Ellipta® and Breezhaler®) and metered dose inhaler (MDI) only. This has both pros and cons from patients' and clinicians' perspective. The concern about the inspiratory flow and suitability of DPI is always a concern.(22) The main drawback of MDI is the need of hand-mouth coordination.(23) These concerns are particularly relevant in places where soft mist inhalers are the most commonly used inhaler device for LABA/LAMA, as the way of using is completely different for DPI and soft mist inhalers. It is important to assess if the switch from MITT to SITT is beneficial among patients who have been on MITT, especially preparations consisting of soft mist inhalers, which do not have SITT.

Our study suggested that switching from MITT to SITT may lead to improvement of critical error numbers and higher MARS-A score. The results would bring about reassurance to clinicians when they can have a choice to switch to SITT from MITT for their patients with COPD. The patients may benefit from the switch in inhaler device with better inhaler adherence and fewer critical errors. A higher medication adherence is also important as medication compliance and adherence is the cornerstone to chronic disease management. However, we did not observe any significant difference regarding the change in mMRC dyspnea scale in the two groups despite better adherence as measured by MARS-A score and fewer critical errors in the SITT group. This could be due to the fact that all the patients recruited had Group E COPD that required LABA/LAMA/ICS before the recruitment. The change from MITT to SITT without other major changes in pharmacotherapy

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

may not be able to bring about significant changes in mMRC dyspnea scale as the patients were receiving LABA/LAMA/ICS in both treatment groups, which has similar clinical benefits after all.

We also did not observe any significant difference in the satisfaction score in this study. While SITT was associated with better adherence and fewer critical errors, satisfaction with the inhaler device, which is a more subjective measure, may not be better when MITT was replaced by SITT. Whether patients are more satisfied with a particular inhaler device will depend on both patients' factors as well as device factors. As DPI was the SITT in this study, some patients may not be more satisfied when switched from MITT to SITT as they were started on a new inhaler device, in which DPI may not be the most preferred one for them.

Another point to note in this study is that patients who switched from MITT to SITT actually have worse lung function by FEV_1. Despite having more severe COPD, they can still use SITT well with benefits seen as early as in 4 weeks. This suggests that having more severe COPD should not be considered as an absolute contraindication to SITT with Ellipta® as long as they have adequate inspiratory flow rate and proper inhaler technique.

In our study, despite the patients were all taught by pharmacists on inhaler techniques, the patients still had criterial errors upon follow-up. Adopting standardized training model involving verbal instructions and device demonstrations by pharmacists may improve the patients' ability to use the inhalers. Furthermore, assessing patients' level of understanding of the disease is also important as it has been reported that patients' acceptance of the disease process and recommended treatment, knowledge about and faith in the treatment were factors affecting medication adherence in COPD.

We also noted that all the patients in this study had fewer critical errors in the first and second visits when compared to baseline, while the changes were more prominent in the SITT group than

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

MITT group. In our study, all patients had the inhaler technique education and checking by pharmacist after recruitment. This could help to improve the inhaler techniques of the patients in both groups with subsequent improvement in the number of critical errors. This finding illustrated the importance of the inhaler technique education and checking, which is the cornerstone to successful inhaler therapy, by reducing the number of critical errors.

In our study, MARS-A scale was used to measure treatment adherence, which was also used in other studies and has been validated in COPD. But in the current era, a probably better way to measure patients' compliance to medication including inhaler would include integrating electronic monitoring devices into the treatment regimen. While MARS-A scale was shown to have good internal validity when measured among patients with COPD or asthma, it was weakly correlated with objectively measured medication adherence, with low levels of sensitivity and specificity. Using electronic monitors, when available, shall be a better approach to monitor treatment adherence.

Our study has several limitations to address. First, the study was conducted in one tertiary centre. The relatively small sample size with a short duration of follow-up may not allow the detection of small differences among the two groups, especially the longer-term outcome. A larger scale study among Chinese population will allow a better assessment of the outcomes. Despite this, the results from our study are consistent with previous reports in the literature. Peak inspiratory flow rate was not measured in this study, as the main outcomes of interest are treatment adherence, satisfaction and critical error rates. Yet, peak inspiratory flow rate is considered to be one of the key factors in selecting an inhaled medication delivery system for the patients, in particular dry powder inhaler. A separate study focusing on peak inspiratory flow rate, in particular among patients with severe COPD is worth conducting. Furthermore, all the patients recruited including the MITT and SITT

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

group, have been on triple therapy for COPD. Whether the same benefits are seen among patients on other regimes such as single or dual bronchodilator without ICS is not confirmed in this study. A separate study is needed to assess the benefits in these patients not indicated for triple therapy. Also, different MITT were used as baseline for the included patients. Given the small scale of this study, we are not able to precisely assess the clinical benefits for each individual combination with MITT.

Conclusion

Switching from MITT to SITT in Chinese COPD patients may have the benefits of having less critical error numbers and higher MARS-A score. Clinicians may consider switching from MITT to SITT in appropriate settings.

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Acknowledgement

- Ethics approval and consent to participate

  The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (Approval number UW19-712). All the patients consented to join the study. The study was conducted in accordance with the declaration of Helsinki.

- Author Participation or Contributions

  Dr. Wang Chun Kwok was involved with study concept and design, analysis and interpretation of data, acquisition of data, drafting of manuscript, and approval of the final version of the manuscript. Dr. James Chung Man Ho, Ting Fung Ma and Ms. Chung Ki Tsui were involved with critical revision of the manuscript for important intellectual content and approval of the final version of the manuscript. Dr. Terence Chi Chun Tam was involved with the study concept and design, drafting of manuscript, critical revision of the manuscript for important intellectual content, study supervision, and approval of the final version of the manuscript.

- Data Availability Statement

  All available data is presented in the manuscript and no additional data will be provided. Data is not available to be shared.

Declaration of interest

The authors declare no conflict of interests.

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

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Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Table 1 Baseline demographic and clinical characteristics

	Whole cohort (n = 70)	Single inhaler triple therapy - SITT (n = 37)	Multiple inhaler triple therapy - MITT (n = 33)	P-values
Age (years), mean ± SD	72.3 ± 8.4	71.7 ± 8.3	72.9 ± 8.5	0.56
Male	65 (92.9%)	30 (90.9%)	35 (94.6%)	0.55
Smoking status				0.98
Current smoker	19 (27.1%)	9 (27.3%)	10 (27.0%)	
Ex-smoker	51 (72.9%)	24 (72.7%)	27 (73.0%)	
Body weight (kg), mean ± SD	63.6 ± 14.2	63.2 ± 13.3	64.0 ± 15.3	0.82
Body mass index, kg/m^2, mean ± SD	23.6 ± 4.8	22.7 ± 4.14	24.6 ± 5.35	0.10
FEV_1 (L), mean ± SD	1.43 ± 0.61	1.63 ± 0.67	1.18 ± 0.42	0.003*
FEV1 (% predicted), mean ± SD	64.4 ± 22.5	67.6 ± 22.3	60.2 ± 22.3	0.19
FVC (L), mean ± SD	3.05 ± 0.77	3.24 ± 0.83	2.80 ± 0.60	0.022
FVC (% predicted), mean ± SD	100.8 ± 21.4	100.8 ± 21.3	100.9 ± 21.9	0.99
FEV1/FVC Ratio (%), mean ± SD	46.9 ± 14.5	50.6 ± 15.2	42.4 ± 12.3	0.020*

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Bronchodilator reversibility in FEV_1 (mL), mean ± SD	73 ± 99	71 ± 105	77 ± 93	0.85
Bronchodilator reversibility in FEV_1 (%), mean ± SD	5.6 ± 8.0	4.7 ± 7.0	7.1 ± 9.5	0.42
Bronchodilator reversibility in FVC (mL), mean ± SD	51 ± 194	69 ± 211	23 ± 164	0.49
Bronchodilator reversibility in FVC (%), mean ± SD	0.14 ± 0.61	0.20 ± 0.62	0.05 ± 0.59	0.47
Blood eosinophil count at bassline (10^9/L), mean ± SD	0.29 ± 0.25	0.29 ± 0.29	0.28 ± 0.21	0.86
Baseline creatinine, (µmol/L), mean ± SD	98.2 ± 29.7	91.9 ± 19.9	105.0 ± 36.7	0.08
Baseline mMRC dyspnea scale, mean ± SD	1.94 ± 0.81	1.86 ± 0.82	2.03 ± 0.81	0.40

SD = standard deviation; mL = milliliter; * = statistically significant; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity, CAT = COPD Assessment Test, mMRC = Modified Medical Research Council

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Table 2 Clinical parameters at different visits

	Whole cohort (n = 70)	Single inhaler triple therapy - SITT (n = 37)	Multiple inhaler triple therapy - MITT (n = 33)	P-values
Number of critical errors per inhaler, mean ± SD				
Baseline	1.8 ± 1.8	1.5 ± 1.6	2.2 ± 2.0	0.10
First visit	0.7 ± 1.5	0.4 ± 1.0	1.1 ± 1.8	0.038*
Second visit	0.5 ± 0.9	0.2 ± 0.6	0.8 ± 1.1	0.007*
mMRC dyspnea scale, mean ± SD				
Baseline	1.94 ± 0.81	1.86 ± 0.82	2.03 ± 0.81	0.40
First visit	1.81 ± 0.87	1.84 ± 0.87	1.79 ± 0.89	0.81
Second visit	1.93 ± 0.98	1.92 ± 0.92	1.94 ± 1.06	0.93
MARS-A score, mean ± SD				
Baseline	45.7 ± 6.6	43.8 ± 6.9	47.9 ± 5.6	0.008*

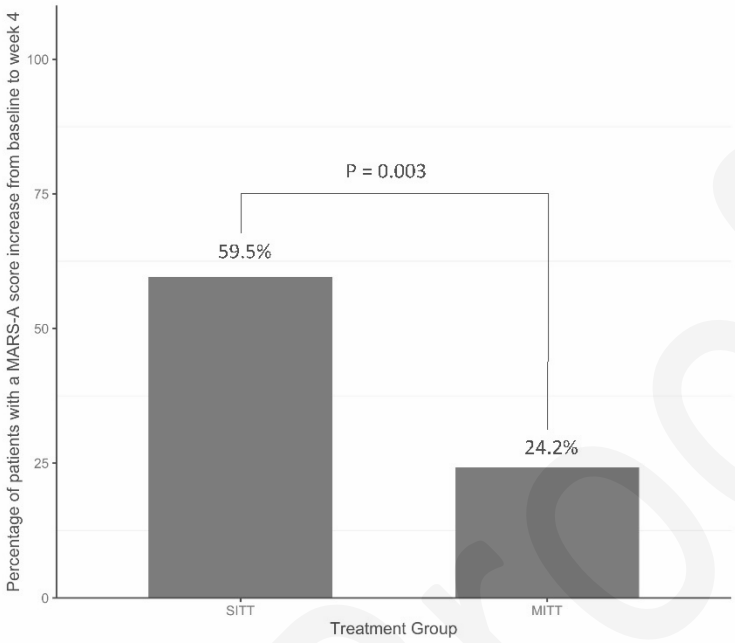
Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

First visit	47.1 ± 6.8	47.6 ± 6.6	46.6 ± 7.2	0.58
Second visit	47.9 ± 5.5	46.7 ± 7.0	49.2 ± 2.2	0.054
Satisfaction score, mean ± SD				
Baseline	23.3 ± 1.8	23.1 ± 2.1	23.5 ± 4.5	0.35
First visit	23.7 ± 0.9	23.5 ± 1.2	23.9 ± 0.2	0.039*
Second visit	23.6 ± 1.3	23.4 ± 1.7	23.9 ± 0.3	0.066

mMRC = Modified Medical Research Council, SD = standard deviation; * = statistically significant

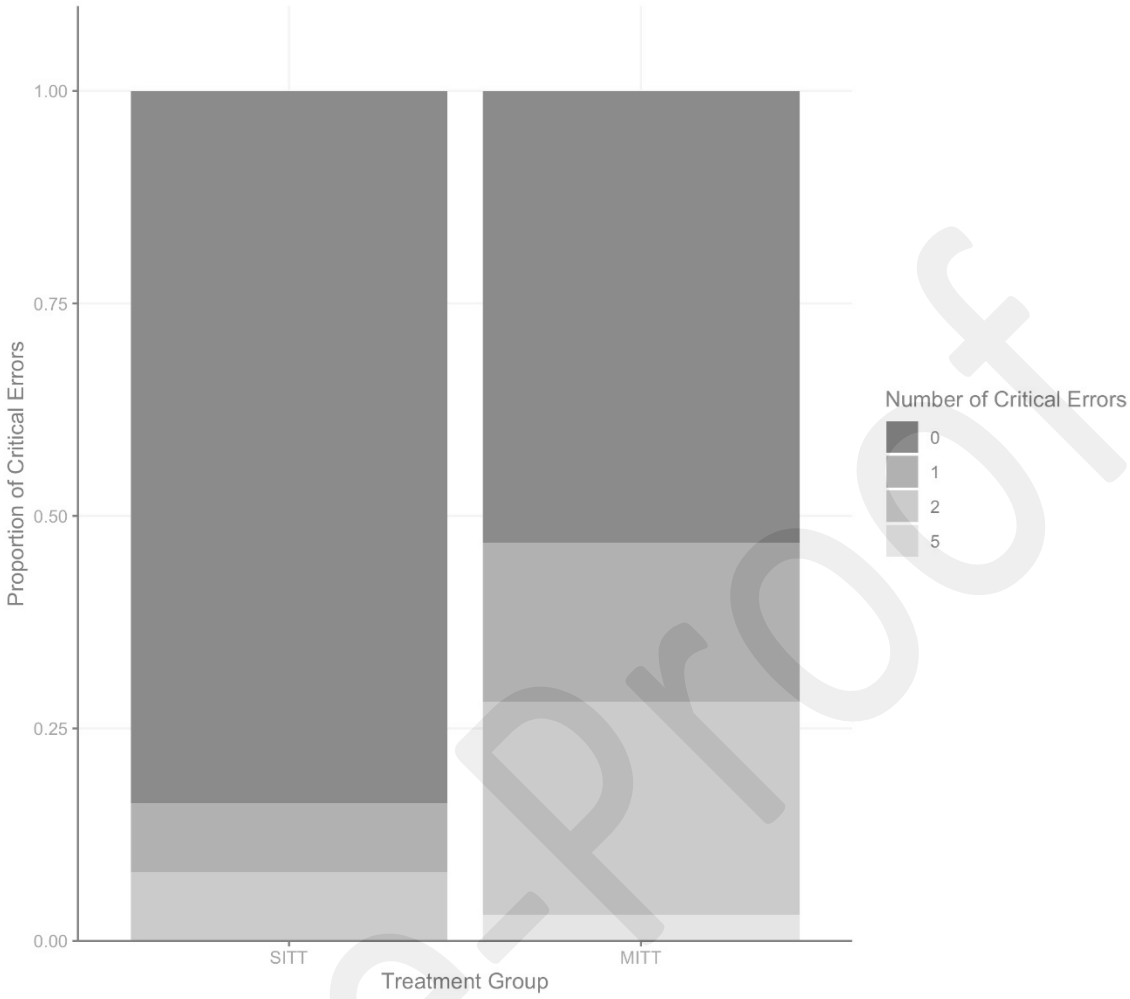
Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Figure 1 Number of critical errors at end of study visit



Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Figure 2 Percentage of patients with MARS-A score increase from baseline to week 4



Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Online Supplement

Supplementary table 1 Critical errors of the inhalers

Device	Critical error
Dry powder inhaler	
Turbuhaler	1. Did not correctly open the device
	2. Did not prime with device upright
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Breezhaler	1. Did not correctly open the device
	2. Did not place capsule in the chamber
	3. Did not close the mouthpiece
	4. Did not press button to pierce the capsule
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
	3. Did not remove capsule and check for any residual powder
Ellipta	1. Did not open the device correctly

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	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Acuhaler	1. Did not correctly open the device
	2. Did not pull the lever fully back
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Genuair	1. Did not correctly open the device
	2. Did not hold the inhaler horizontally (with the green button facing upwards) for priming
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not inhale deeply or forcefully
Soft mist device/Respimat	1. Did not twist the base one half-turn
	2. Did not correctly open the device
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not synchronize actuation and inhalation
	3. Did not inhale deeply or forcefully
Metered dose inhaler	1. Did not correctly open the device

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

	2. Did not shake the inhaler well (For suspension formulations)
	3. Did not keep inhaler upright
	1. Did not seal lips around mouthpiece during inhalation
	2. Did not synchronize actuation and inhalation
	3. Did not inhale slowly and deeply

Adopted and modified from Jang, J.G., et al., *Comparative Study of Inhaler Device Handling Technique and Risk Factors for Critical Inhaler Errors in Korean COPD Patients.* Int J Chron Obstruct Pulmon Dis, 2021. **16**: p. 1051-1059.

Supplementary table 2 Analysis results based on the hypothetical directed acyclic graph

	Odds ratio	95% CI, p-value
Average Indirect Effect	0.988	0.923 - 1.020, p= 0.462
Total Effect	0.702	0.557 - 0.878, p = 0.004
Average Direct Effect	0.711	0.564 - 0.896, p = 0.006

CI = Confidence interval

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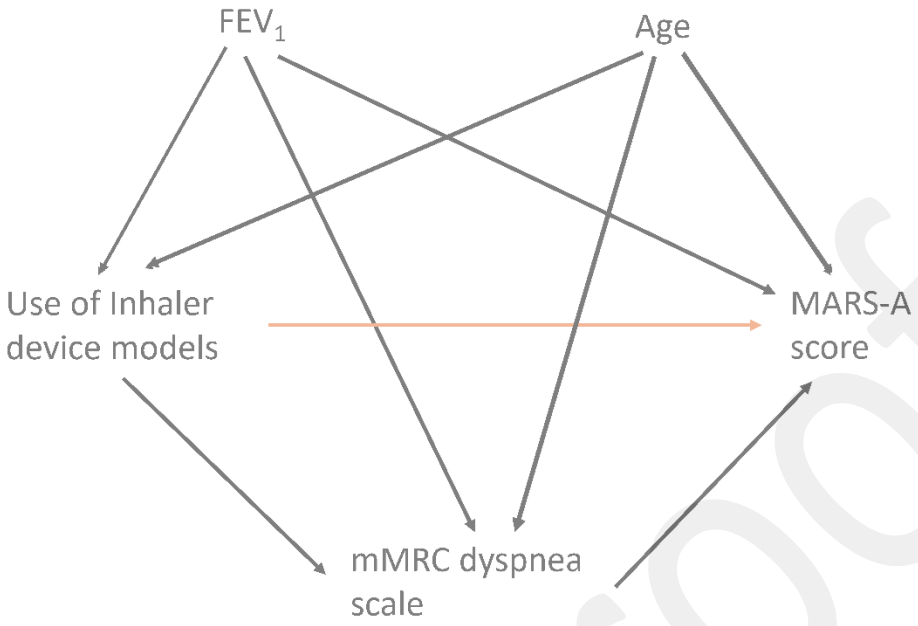
Supplementary Figure 1 Directed acyclic graph to illustrate potential confounders to be adjusted for despite randomization



Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519

Appendix 1 – Sample size calculation

Sample size can be determined by the effect size of relative hypotheses such as patient satisfaction and error rate. On the other hand, van der Palen et al. (24) considered open-label, cross-over design for comparing Ellipta® and a combination of multiple devices for Patients with COPD. van der Palen et al.(25) compared Ellipta® with other devices by interviewing both COPD and asthma patients about their error rate and other attributes of the inhaler and their preference for the Ellipta® relative to their currently-prescribed inhalers, while Svedsater et al. (26) focused in the qualitative assessment of inhalers.

The sample size can be calculated based on the results about error rate of patients from (25) for Ellipta against other devices. In particular, (24) shows that the proportions of Patients with COPD who made any error are about 20% and 50% for using Ellipta® and other device after reading the patient information leaflet respectively. The Fisher's Exact test can be used to compare the proportion in the two treatment groups (27). Assuming balanced design, the required sample size is given by 28 for each group to achieve the descried statistical power at least 80% under 95% significance level.

For other key responses, such as symptom control, the effective sizes of related statistical hypothesis would be smaller and hence lead to a larger required sample size. Moreover, some key responses, such as satisfaction and compliance in patients, would only be in ordinal scale and subject to the questionnaire design. From (26), about 75% of Patients with COPD would prefer Ellipta®. Using the approximated sample size of Wilcoxon signed-rank test (28), we have the required sample size is given by

$$n \approx \frac{(1.645 + 0.841)^2}{3\left(\frac{3}{4} - \frac{1}{2}\right)^2} \approx 33$$

Nevertheless, other non-parametric methods, such as Wilcoxon rank sum test, would be implemented in this study, which typically require a larger sample size. Overall, we suggest a sample size of 35 in each group for potential remedy such as randomization test and dropout.

Published online December 13, 2024 https://doi.org/10.15326/jcopdf.2024.0519