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Effectiveness of Extrafine Single Inhaler Triple Therapy in Chronic Obstructive Pulmonary Disease (COPD) in Germany – The TriOptimize Study

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Purpose: Real-word evidence on the effectiveness of switching from dual therapies or triple therapies (multiple inhalers) to extrafine single-inhaler triple therapy (efSITT), which consists of the inhaled corticosteroid (ICS) beclomethasone, the long-acting β_2-agonist (LABA) formoterol and the long-acting muscarinic antagonist (LAMA) glycopyrronium, in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) is limited. The impact of switching to efSITT on health-related quality of life (HRQoL), COPD specific symptoms, lung function and treatment adherence were assessed in routine clinical care.

Patients and Methods: Patients were recruited at 148 sites in Germany between 2017 and 2020 in this multicenter, non-interventional observational study. Demographics, clinical data and treatment history were collected at baseline. HRQoL (measured by COPD Assessment Test [CAT]), lung function and adherence (measured by Test of Adherence to Inhalers [TAI]) were assessed at baseline and after six months. Descriptive analyses were conducted by prior treatment and GOLD groups as well as for the overall population.

Results: 55.1% of the 2623 included patients were male. Mean age was 65.8 years. 57.5% of the patients were previously treated with ICS+LABA+LAMA (multiple inhalers), 23.9% with ICS/LABA (single or two inhalers) and 18.6% with LAMA/LABA (single or two inhalers). After six months, largest mean improvements in the total CAT score were observed in the ICS/LABA (−3.9) and LAMA/LABA (−3.9) prior treatment groups as well as in patients in GOLD group B (−2.9). In the overall population, the CAT items for cough, phlegm, and dyspnea decreased on average by −0.4 points each. After six months, FEV_1 increased by 2.0 percentage points in relation to predicted values. The percentages of measured sRtot and RV of predicted values decreased by 24.5 and 4.4 percentage points, respectively. The percentage of patients with good adherence increased from 67.8% to 76.5%.

Conclusion: Treatment switch to efSITT resulted in an improvement of HRQoL, COPD specific symptoms, lung function parameters and adherence under real-world conditions.

Keywords: COPD, extrafine single inhaler triple therapy, treatment adherence, CAT score

Introduction

Due to the progressive nature of chronic obstructive pulmonary disease (COPD), an escalation from LABA/LAMA or LABA/ICS (single or two inhalers) to an intensified treatment regimen consisting of ICS+LABA+LAMA is required for many patients.[1] Apart from achieving better symptom control and lowering the risk of exacerbations, a reduction of mortality using inhaled triple therapy is currently discussed.[2–4] To achieve an optimal clinical outcome, the correct application of devices and high treatment adherence are of particular importance.[5] Non-adherence to treatment, however,

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is very common in COPD patients especially with increasing complexity of medication regimens and has been linked to higher healthcare resource utilization (HCRU) and costs, a reduction in health-related quality of life (HRQoL)[6] and higher mortality.[7] The use of multiple inhalers and mixed inhalation techniques are associated with an increased risk of exacerbations compared to single inhalers or multiple inhalers requiring one inhalation technique.[8–11] Hence, an extrafine single-inhaler triple therapy (efSITT), a combination containing the ICS beclomethasone, the LABA formoterol and the LAMA glycopyrronium was developed and has been approved for treatment of COPD in the EU in 2017. This extrafine formulation with Mass Median Aerodynamic Diameter (MMAD) of <2 µm can reach good deposition in small airways.[12,13] The efficacy and safety of this efSITT was assessed in several clinical studies showing better exacerbation prevention and lung function compared to an ICS/LABA combined therapy as well as LAMA-monotherapy.[14–17] EfSITT also reduced more effectively the exacerbation rate compared to LABA/LAMA combination therapy.[14–16,18]

As COPD patients are a highly heterogeneous population, which may not be adequately represented in randomized controlled trials, studies reflecting real-world situation are necessary.[19–21] Important aspects of everyday care such as treatment adherence are not representatively captured in clinical trials as adherence is usually ensured by default.[19]

The aim of this prospective non-interventional study was to assess changes in HRQoL, COPD specific symptoms, lung function and treatment adherence after six months of treatment with efSITT in patients with moderate-to-severe COPD under conditions of routine clinical practice in Germany. Moreover, we aimed to identify subgroups with special benefits of efSITT treatment.

Materials and Methods

Study Design and Study Population

The TriOptimize study was a multicenter, non-interventional, prospective study (NIS). Patients were recruited at 148 sites (specialist outpatient pulmonologists and centers with a focus on the treatment of airways diseases, 6 clinics and 142 private practices) in Germany between November 2017 and April 2020. Physicians prescribed efSITT regardless of patient's participation status in the study but according to its German licensed indication. The study was conducted in accordance with the latest version (2013) of the Declaration of Helsinki and was approved by the local ethics committees. The study was registered with German Clinical Trials Register (DRKS00013938). All patients gave written improved consent.

The inclusion criteria were: 1) moderate-to-severe COPD (with and without asthma), 2) physician's decision to initiate efSITT therapy within the scope of its German licensed indication, 3) at least one COPD exacerbation during the previous 12 months before starting efSITT treatment and 3) willing and able to give written consent. Patients were excluded if 1) they had been admitted to hospital for a COPD exacerbation within the last four weeks prior to study enrolment or 2) participated in another clinical trial within the last 30 days prior to enrolment in the present NIS.

Patients started with efSITT at or at most eight weeks before the baseline examination. Two follow-up visits (3 and 6 months after baseline) were anticipated.

Study Assessments

Only data available as part of routine clinical care were included. Demographic data, medical and COPD treatment history were collected at baseline. Laboratory data, COPD stage and group according to the criteria of the 2017 GOLD Report,[22] HRQoL, spirometry, and adherence were assessed at baseline and the follow-up examinations as part of routine care. HRQoL was recorded using the CAT.[23,24] Spirometry included the assessment of parameters of airflow obstruction (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV_1], inspiratory capacity [IC]). Body plethysmography was used to assess total specific airway resistance [sRtot] and static hyperinflation (residual volume [RV], total lung capacity [TLC]). The Test of Adherence to Inhalers (TAI) questionnaire is a validated questionnaire developed to identify aspects of inhaler use during daily application.[25] The questionnaire comprises ten items answered by the patient and two items answered by the physician. The patient domain summary score, analyzed in this manuscript, ranges between 10 (= worst possible score) and 50 (= best possible score).

Statistical Analysis

Patients were excluded from the statistical analysis if they violated at least one inclusion or fulfilled at least one exclusion criterion, no prior treatment group could be determined, and in case of missing baseline characteristics or off-label use of medication. Based on COPD treatment history, prior treatment was classified in three groups: ICS+LABA+LAMA (multiple inhalers), ICS/LABA or LAMA/LABA (single or two inhalers). CAT scores were grouped in four categories: low (<10), moderate (10–20), high (21–30), and very high (>30). CAT responders were defined as patients with a ≤ 2-point decrease in total CAT score.[26,27] Treatment adherence was evaluated based on the TAI score according to Plaza et al[25] poor (≤45), moderate (46–49) or good adherence (=50). Changes in type of adherence between baseline and month 6 were evaluated. In general, descriptive analyses were conducted for quantitative and qualitative variables. CAT scores (Total score, Item 1 – Cough, Item 2 – Phlegm, Item 4 – Dyspnea), CAT response, lung function parameters, and TAI scores were analyzed for the overall population as well as stratified by COPD prior treatment and GOLD group at baseline. Continuous changes between baseline and month 6 were evaluated for CAT scores, lung function parameters and TAI scores. *T*-tests were calculated to assess statistical significance of these changes. We used GLI 2012 reference equations[26] to calculated predicted values for FEV_1 and RV. Predicted values for sRtot were calculated using references values based on prediction equations introduced by Koch et al.[27] The percentages of the measured values of the predicted values were calculated (% pred). All analyses were performed using SAS (version 9.4).

Results

Demographic Data and Baseline Characteristics

In total 2763 patients were consecutively enrolled. 140 patients (5.1%) were excluded resulting in a total of 2623 patients used for the analyses. Reasons for exclusion were off-label medication (n=107), not definable prior treatment (n=31), missing baseline characteristics (n=17), no baseline visit (n=1), and/or violation of at least one inclusion criterion (n=7) or fulfillment of at least one exclusion criterion (n=7). Table 1 describes demographic and baseline characteristics. 55.1% of the patients were male. Patients' age ranged between 33 and 94 years and the mean age was 65.8 years. 35.2% of the patients were current smokers and 51.3% were former smokers. Most patients (76.9%) had at least one comorbidity. 14.0% and 8.1% of the patients reportedly suffered from non-allergic and allergic asthma, respectively. A more detailed description of the most frequent comorbidities is given in Supplemental Table 1. The average illness time for COPD was 7.2 years. Most patients suffered from moderate-to-severe COPD (GOLD stages 2 and 3, 83.4%). According to GOLD groups, the majority of the patients showed a high symptom severity (GOLD group B, 45.6% and GOLD D, 32.0%). The severity of the last exacerbation was moderate in 59.5% and severe in 7.5% of the patients. 1508 (57.5%) of the patients had received prior treatment with ICS+LABA+LAMA, 627 (23.9%) with ICS/LABA and 488 (18.6%) with LAMA/LABA, respectively. Details on concomitant medication are given in Supplemental Table 2. On average, the CAT score was 21.5 (n=2535) at baseline. At baseline, mean FEV_1 was 48.1% ± standard deviation 17.6% of predicted (1.37 L ± 0.60 L; n=1797), RV was 174.2% ± 52.7% of predicted (3.49 L ± 0.92 L; n=1693), and sRtot was 356.7% ± 248.5% of predicted (3.21 kPa*s ± 2.22 kPa*s; n=1420). Mean baseline FEV_1/FVC was 57.0% ± 20.7% (n=1693). After excluding 7 patients with implausible blood eosinophil blood counts (≥10,000/µL), the average blood eosinophil count was 219 cells/µL ± 233 cells/µL (n=569), the median value was 170 cells/µL and 94.5% of the values were within the normal range (0–550 cells/µL).

Total CAT Score

Figure 1 shows patients' quality of life based on the total CAT score. The mean total CAT score improved after 6 months of treatment with efSITT (baseline: 21.5, month 6: 18.6, mean change: −2.7). At month 6, more patients showed a low CAT score (<10: 13.9%) in comparison to baseline (5.6%). After 6 months, the proportion of patients with a high (21–30) or very high CAT score (>30) decreased in comparison to baseline. 56.0% of the patients were CAT responders. The largest improvement was observed in patients previously treated with ICS/LABA (mean change: −3.9, CAT responders: 63.0%) or LAMA/LABA (mean change: −3.9, CAT responders: 62.8%). On average, the total CAT score changed by −2.9 in patients in GOLD group B (CAT responders: 58.6%). Patients previously treated with ICS+LABA+LAMA as well as patients in GOLD group D showed lowest mean improvements (ICS+LABA+LAMA: −1.8, GOLD D: −1.9) and the lowest percentages

Table 1 Demographic and Baseline Characteristics

		Overall (n=2623)
Sex	Male, n (%)	1444 (55.1)
	Female, n (%)	1179 (44.9)
Age (year), mean ± SD		65.8 ± 9.7
BMI (kg/m^2), mean ± SD		27.4 ± 6.1
Smoking status	Current smoker, n (%)	922 (35.2)
	Ex-smoker, n (%)	1343 (51.3)
	Never, n (%)	351 (13.4)
Pack years[a], mean ± SD		39.2 ± 33.6
Comorbidities[b]	At least one, n (%)	1963 (76.9)
Average illness time (year), mean ± SD		7.2 ± 6.1
GOLD stage[c,d]	GOLD 1, n (%)	87 (3.4)
	GOLD 2, n (%)	1018 (39.6)
	GOLD 3, n (%)	1125 (43.8)
	GOLD 4, n (%)	341 (13.3)
GOLD group[d]	GOLD A, n (%)	129 (5.1)
	GOLD B, n (%)	1152 (45.6)
	GOLD C, n (%)	438 (17.3)
	GOLD D, n (%)	809 (32.0)
Severity of last exacerbation[e]	Mild, n (%)	842 (33.0)
	Moderate, n (%)	1518 (59.5)
	Severe, n (%)	190 (7.5)
Prior Treatment	ICS+LABA+LAMA, n (%)	1508 (57.5)
	ICS/LABA, n (%)	627 (23.9)
	LAMA/LABA, n (%)	488 (18.6)
Total CAT score, mean ± SD		21.5 ± 7.4
Lung function parameters[f]	FEV_1 (L), mean ± SD	1.37 ± 0.60
	FEV_1 (% pred), mean ± SD	48.1 ± 17.6
	FEV_1/FVC (%), mean ± SD	57.0 ± 20.7
	RV (L), mean ± SD	3.49 ± 0.92
	RV (% pred), mean ± SD	174.2 ± 52.7
	sRtot (kPa*s), mean ± SD	3.21 ± 2.22
	sRtot (% pred), mean ± SD	356.7 ± 248.5
Blood eosinophiles (cells/μL)[g], mean [median] ± SD		219 [170] ± 233

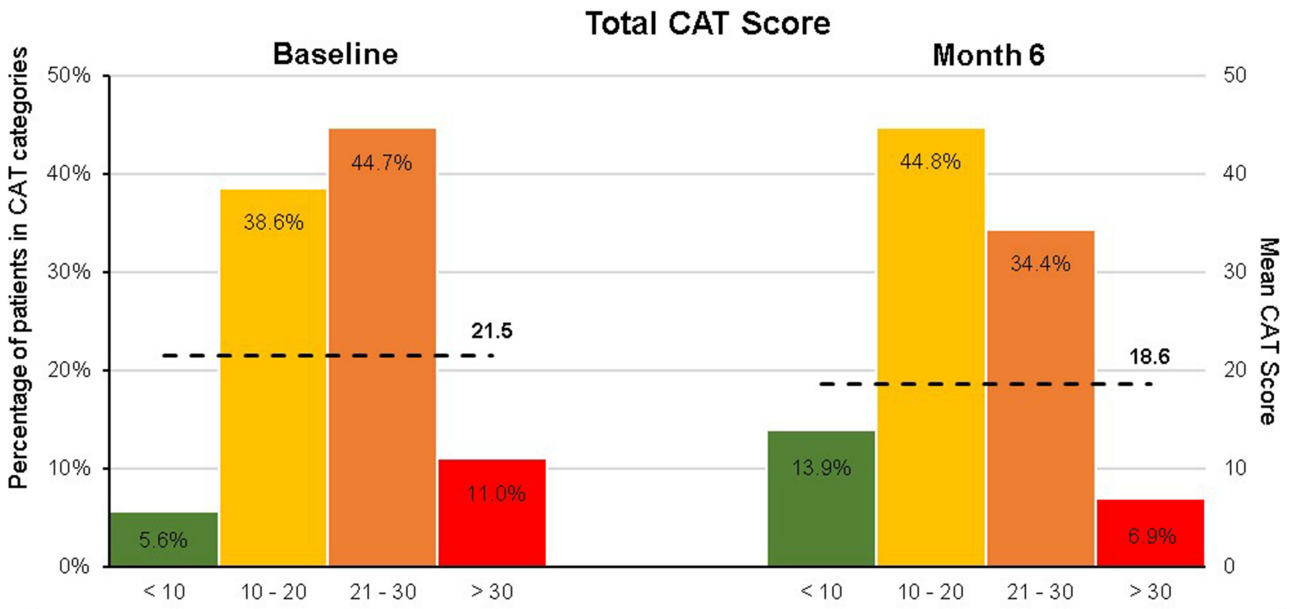
Notes: The number of missing values varied between the described demographics and baseline characteristics. [a]Limited to current smokers and ex-smokers. [b]A more detailed description of comorbidities is given in Supplemental Table 1. [c]GOLD 1 (FEV_1 ≥ 80%), GOLD 2 (FEV_1 ≥50-<80%), GOLD 3 (FEV_1 ≥30-<50%), GOLD 4 (FEV_1 <30%). [d]According to criteria of GOLD Report 2017.[22] eLimited to patients with at least one exacerbation. f Without prior bronchodilation. [g]Values ≥ 10,000/μL (n=7) were treated as missing values due to implausibility. All other eosinophil counts were ≤2100/μL.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV_1, forced expiratory volume (in 1 second), FVC, forced vital capacity, ICS, inhaled corticosteroid; kPa, kilopascal; L, liter; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; RV, residual volume; SD, standard deviation; s, second; sRtot, specific breathing resistance; % pred, percentage of predicted.

of CAT responders (ICS+LABA+LAMA: 50.7%, GOLD D: 47.8%). All mean changes were statistically significant (p-value < 0.05). Descriptions for patients in GOLD groups A and C are given in Supplemental Tables 3–5.

CAT Subitems

CAT item 1 (cough), item 2 (phlegm) and item 4 (dyspnea) are described in Figures 2–4. All three CAT items decreased on average by 0.4 in the overall population. Similar to the total CAT score, stronger mean decreases in the single CAT items were observed in patients previously treated with ICS/LABA or LAMA/LABA as well in patients in GOLD group B in comparison to patients previously treated with ICS+LABA+LAMA or patients in GOLD group D. All changes were statistically significant (p-value <0.05).



	Baseline		6 months after switch to efSITT		Change		CAT responder
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	n (%)
Overall	2535	21.5 ± 7.4	1886	18.6 ± 7.9	1864	-2.7 ± 6.4#	1043 (56.0)
ICS+LABA+LAMA	1477	21.7 ± 7.5	1074	19.7 ± 7.7	1060	-1.8 ± 6.3#	537 (50.7)
ICS/LABA	605	21.3 ± 7.4	466	17.3 ± 7.7	460	-3.9 ± 6.3#	290 (63.0)
LAMA/LABA	453	21.0 ± 7.1	346	16.9 ± 8.0	344	-3.9 ± 6.4#	216 (62.8)
GOLD B	1134	21.0 ± 7.0	860	17.9 ± 7.8	851	-2.9 ± 6.5#	499 (58.6)
GOLD D	798	23.0 ± 7.4	553	20.9 ± 7.9	550	-1.9 ± 6.5#	263 (47.8)

CAT responder: Patient with improvement in CAT Score of at least -2 points at month 6 in comparison to baseline
* p-value (t-test) < 0.05, # < 0.0001

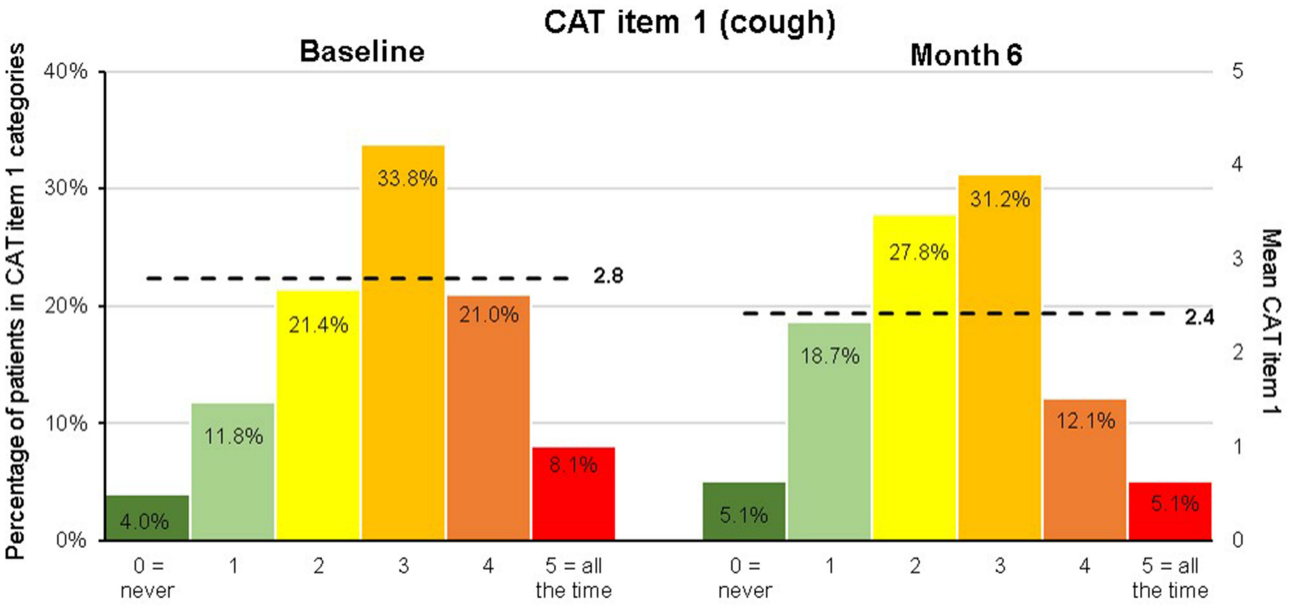
Figure 1 Health related quality of life according to the total CAT score at baseline and 6 months after switch to efSITT.

Lung Function

At baseline and month 6, spirometry without bronchodilation was performed in 69.7% and 61.1% of the patients, respectively. After 6 months of treatment with efSITT, significant mean changes of 2.0 percentage points (≙ 54.4 mL) in $FEV_{1\%pred}$, 1.21% in FEV_1/FVC, −24.5 percentage points (≙ −0.23kPa*s) in $sRtot_{\%pred}$, and −4.4 percentage points (≙ −0.1 L) in $RV_{\%pred}$ were observed in the overall population (Table 2, Supplemental Table 6). Patients previously treated with ICS/LABA showed the largest mean changes in $FEV_{1\%pred}$ (5.1 percentage points ≙ 134mL), $sRtot_{\%pred}$ (−58.4 percentage points ≙ −0.53 kPa*s), and $RV_{\%pred}$ (−16.0 percentage points ≙ −0.35 L) in comparison to other prior treatment groups. $sRtot_{\%pred}$ decreased significantly in all subgroups except for patients previously treated with LAMA/LABA. Significant decreases in $RV_{\%pred}$ were only observed in patients previously treated with ICS/LABA but in no other subgroups. The description of changes in other lung function parameters as well as for the description for patients by prior treatment and GOLD groups are given in Supplemental Tables 6 and 7.

Treatment Adherence

At baseline, 12.8% of the patients showed a poor, 19.3% a moderate, and 67.8% a good treatment adherence (Figure 5, Supplemental Table 8). 43.9% of the patients with poor baseline adherence and 64.8% of the patients with moderate baseline adherence showed a good adherence after 6 months. In total, after 6 months of treatment with efSITT, the vast majority of patients (76.5%) showed a good and only 8.2% a poor adherence. Accordingly, 13.6% of the patients with premature study discontinuation (ie TAI was not available after 6 months) dropped out because of a poor treatment adherence.



	Baseline		6 months after switch to efSITT		Change	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Overall	2551	2.8 ± 1.2	1895	2.4 ± 1.2	1880	-0.4 ± 1.3#
ICS+LABA+LAMA	1487	2.8 ± 1.3	1080	2.5 ± 1.3	1071	-0.3 ± 1.2#
ICS/LABA	610	2.9 ± 1.2	467	2.4 ± 1.2	462	-0.5 ± 1.3#
LAMA/LABA	454	2.8 ± 1.2	348	2.3 ± 1.2	347	-0.5 ± 1.3#
GOLD B	1142	2.9 ± 1.2	864	2.4 ± 1.2	858	-0.4 ± 1.3#
GOLD D	800	2.8 ± 1.3	554	2.6 ± 1.2	552	-0.2 ± 1.3#

* p-value (t-test) < 0.05, # < 0.0001

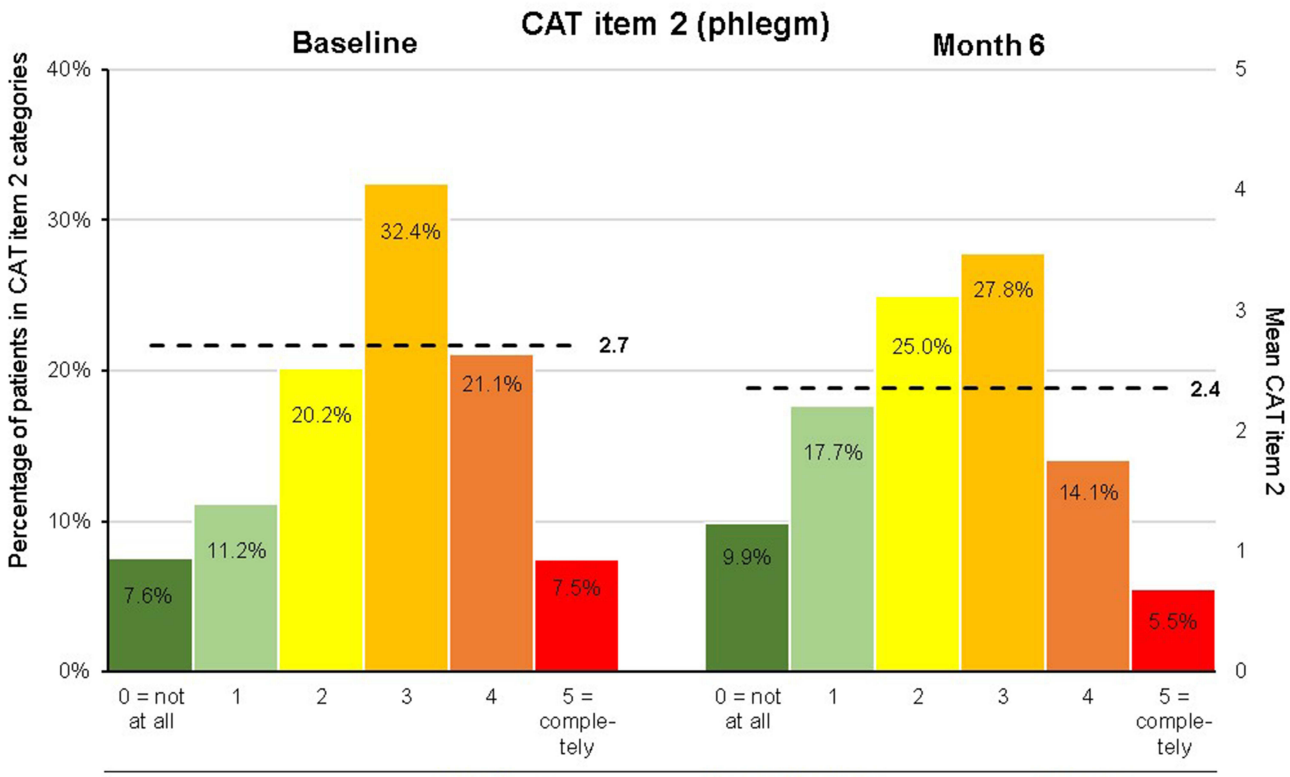
Figure 2 CAT item 1 (cough) at baseline and 6 months after switch to efSITT.

Discussion

This prospective non-interventional study provided real-world evidence on the effect of efSITT treatment on HRQoL and clinical symptoms (as measured by CAT), lung function and treatment adherence in patients with moderate-to-severe COPD in Germany. Although the efficacy and safety of a single-inhaler ICS/LABA/LAMA triple therapy was demonstrated in several randomized controlled trials,[2,3,14–16,28,29] important issues of every day care such as patient adherence to therapy were rarely addressed.[30–35] Hence, our results contribute to address the gap between evidence from controlled trials and routine clinical care.

The overall patient population in this study was characterized by poorly controlled COPD and persistent dyspnea while on their current COPD treatments at baseline. The majority of patients were in GOLD group B or with a high CAT score (>20) at baseline indicating a significant impact of COPD. Almost all patients had at least one exacerbation within the last 12 months prior to baseline. Overall, baseline demographic characteristics as well as lung function impairment status (measured by FEV_1) and the distribution of GOLD stages and groups of the study population were largely comparable to other German COPD cohorts.[36–38] The total CAT at baseline was higher compared to other German cohorts,[36,37] indicating the need for additional pharmacological intervention.

The study demonstrated that a switch from prior therapy with ICS/LABA, LAMA/LABA or prior multiple inhaler triple therapy with ICS+LABA+LAMA to efSITT was associated with an improvement in the total CAT score as well as COPD specific symptoms (cough, phlegm, dyspnea), several lung function parameters, and treatment adherence.

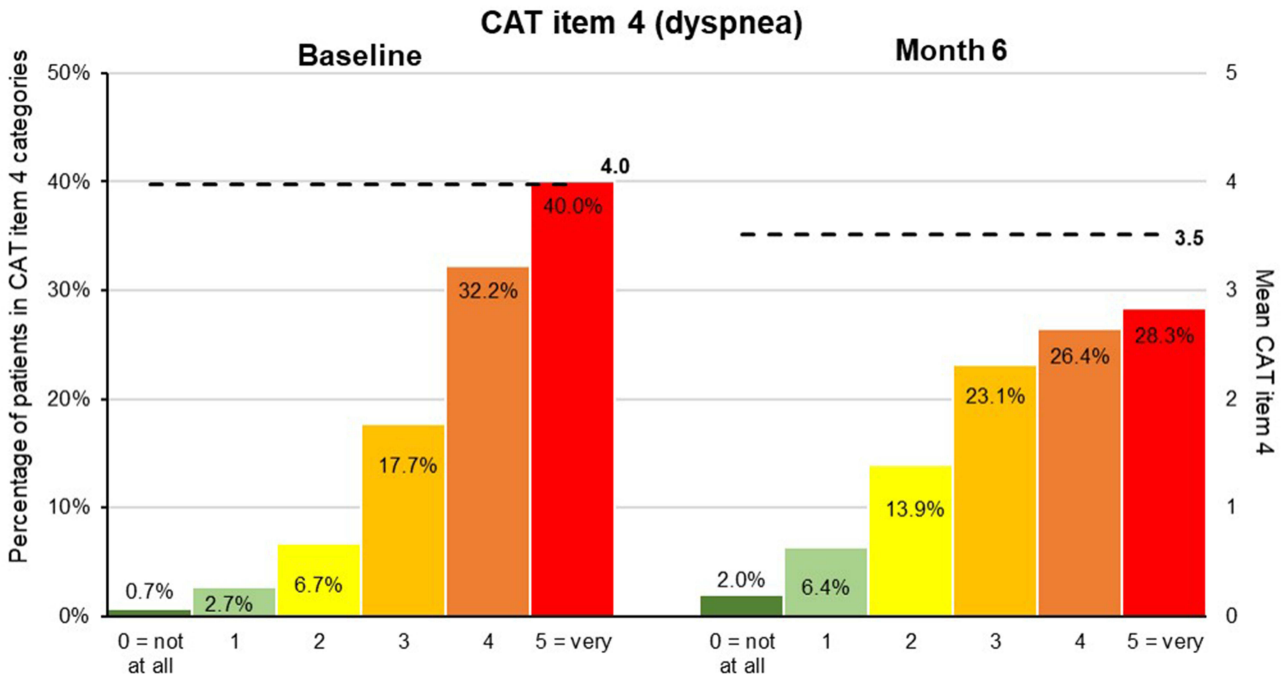


	Baseline		6 months after switch to efSITT		Change	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Overall	2550	2.7 ± 1.3	1895	2.4 ± 1.3	1880	-0.4 ± 1.3#
ICS+LABA+LAMA	1487	2.7 ± 1.3	1080	2.5 ± 1.4	1071	-0.2 ± 1.3#
ICS/LABA	609	2.8 ± 1.3	467	2.3 ± 1.3	462	-0.5 ± 1.3#
LAMA/LABA	454	2.6 ± 1.3	348	2.1 ± 1.3	347	-0.5 ± 1.4#
GOLD B	1142	2.7 ± 1.3	864	2.3 ± 1.3	858	-0.4 ± 1.4#
GOLD D	799	2.8 ± 1.3	554	2.6 ± 1.4	552	-0.2 ± 1.3*

* p-value (t-test) < 0.05, # < 0.0001

Figure 3 CAT item 2 (phlegm) at baseline and 6 months after switch to efSITT.

The total CAT score declined significantly after six months of treatment with efSITT with an average decrease of −2.7 points meeting the minimal clinically important difference (MCID) of −2.0 points.[39] A total of 56% were CAT responders (defined by a change of ≥2.0 points). Interestingly, a similar responder rate of 49% was observed in a Chinese cohort, mainly including patients without prior inhalation treatment, who received either LAMA-monotherapy, dual-therapy consisting of LABA/LAMA, ICS/LABA or multiple inhaler therapy with ICS+LABA +LAMA over a period of 6 months.[33] Our results were also comparable to the mean change of −2.8 points and a CAT responder rate of 47% in previously treated COPD patients who were escalated to a single-inhaler triple therapy containing a ICS/LABA/LAMA composition different from efSITT for 24 weeks in a previous observational study.[30] In an Austrian cohort, a mean decrease in the CAT total score by −7.2 points was observed with efSITT after 12 months.[31] Larger improvements in that study were likely due to the longer treatment period and/or specific patient characteristics. When differentiating between GOLD groups, a considerable reduction of CAT score was mainly observed for GOLD B patients (−2.9 points), whereas the mean decrease in GOLD D patients was smaller (−1.9 points). The smaller magnitude of improvement might be due to high disease burden of patients classified as GOLD group D. As anticipated, patients previously treated with LAMA/LABA and ICS/LABA benefited most from therapy escalation to efSITT. In both



	Baseline		6 months after switch to efSITT		Change	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Overall	2550	4.0 ± 1.1	1895	3.5 ± 1.3	1879	-0.4 ± 1.2#
ICS+LABA+LAMA	1486	4.0 ± 1.1	1080	3.7 ± 1.2	1070	-0.3 ± 1.1#
ICS/LABA	610	3.9 ± 1.2	467	3.2 ± 1.4	462	-0.7 ± 1.2#
LAMA/LABA	454	4.0 ± 1.1	348	3.3 ± 1.4	347	-0.6 ± 1.3#
GOLD B	1142	3.9 ± 1.1	864	3.4 ± 1.4	858	-0.5 ± 1.2#
GOLD D	800	4.3 ± 0.9	554	3.9 ± 1.1	552	-0.3 ± 1.1#

* p-value (t-test) < 0.05, # < 0.0001

Figure 4 CAT item 4 (dyspnea) at baseline and 6 months after switch to efSITT.

groups, a mean change of the total CAT score by −3.9 points and high responder rates (>60%) were observed. The mean decrease in the total CAT score (−1.8 points) and the percentage of CAT responders (50.7%) was smaller in the group previously treated with ICS+LABA+LAMA. However, these results are remarkable and indicate that efSITT offered a benefit also to patients already receiving the most intensified combination therapy prior to study start.

On subitem level, the CAT scores for cough, phlegm and dyspnea, representing predominant COPD symptoms, improved in the overall population and across all prior treatment groups and GOLD groups B and D. The greatest improvements were observed for the subitem dyspnea, followed by cough and phlegm in patients previously treated with ICS/LABA and LAMA/LABA, indicating that an anticholinergic component as well as ICS are beneficial for symptom control. As observed for the total CAT score, the magnitude of improvement in single symptom scores was smaller in patients previously treated with ICS+LABA+LAMA compared to the other prior treatment groups as well as in patients classified as GOLD group D compared to patients in GOLD group B.

Several lung function parameters improved under efSITT. Especially patients previously treated with ICS/LABA displayed an improvement of airflow obstruction (FEV_1), specific airway resistance (sRtot) and hyperinflation (RV) parameters after 6 months of efSITT treatment. The reduction of RV and sRtot, a parameter that is independent from shutter maneuver,[40] is consistent with the observed decrease of the CAT score for dyspnea. Statistically significant improvements in the percentages of predicted values of FEV_1 and sRtot were observed in GOLD groups B and D as well

Table 2 Percentage Change of Lung Function Parameters (% Pred) from Baseline to 6 Months of Treatment with efSITT Stratified by Prior Treatment and GOLD Groups B and D

	$FEV_{1\%pred}$ (%)$^{\Delta}$		$sRtot_{\%pred}$ (%)$^{\Delta}$		$RV_{\%pred}$ (%)$^{\Delta}$	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Overall	1152	2.0 ± 11.7$^{\#}$	860	−24.5 ± 158.6$^{\#}$	576	−4.4 ± 43.6*
ICS+LABA+LAMA	620	1.3 ± 10.4*	494	−17.7 ± 154.1*	335	−0.5 ± 43.8
ICS/LABA	256	5.1 ± 13.8$^{\#}$	184	−58.4 ± 140.3$^{\#}$	118	−16.0 ± 41.8$^{\#}$
LAMA/LABA	276	0.6 ± 11.7	182	−8.7 ± 182.5	123	−3.9 ± 44.1
GOLD B	536	1.8 ± 13.0*	373	−18.2 ± 146.2*	269	−3.6 ± 44.2
GOLD D	329	1.9 ± 9.2*	278	−28.0 ± 184.3*	151	−6.0 ± 44.2

Notes: *p-value (*t*-test) < 0.05, $^{\#}$< 0.0001. $^{\Delta}$Change from baseline to 6 months. % pred, percentage of measured values of predicted values; Predicted values were calculated based on prediction equations[26,27,47].

Abbreviations: FEV_1, forced expiratory volume (in 1 second); GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; sRtot, total specific breathing resistance; RV, residual volume.

as in patients previously treated with ICS+LABA+LAMA and ICS/LABA. In the latter group, sRtot was reduced most by −58.4 percentage points in relation to predicted values. Similarly, the mean change of FEV_1 by 134 mL was highest in the ICS/LABA group, which represents an increase by 5.1 percentage points and can be regarded as clinically meaningful improvement.[41,42] In the overall study population, an increase of 2.0 percentage points, ie an improvement by 54 mL, was observed, which is comparable with a change of 77 mL reported in a previous study.[30] The improvements of lung function parameters in patients previously treated with ICS/LABA underline the importance of the anticholinergic component for controlling relevant lung function parameters in moderate-to-severe COPD patients. Additionally, this is the first real-life study using data of body plethysmography to show improvement in functional parameters.

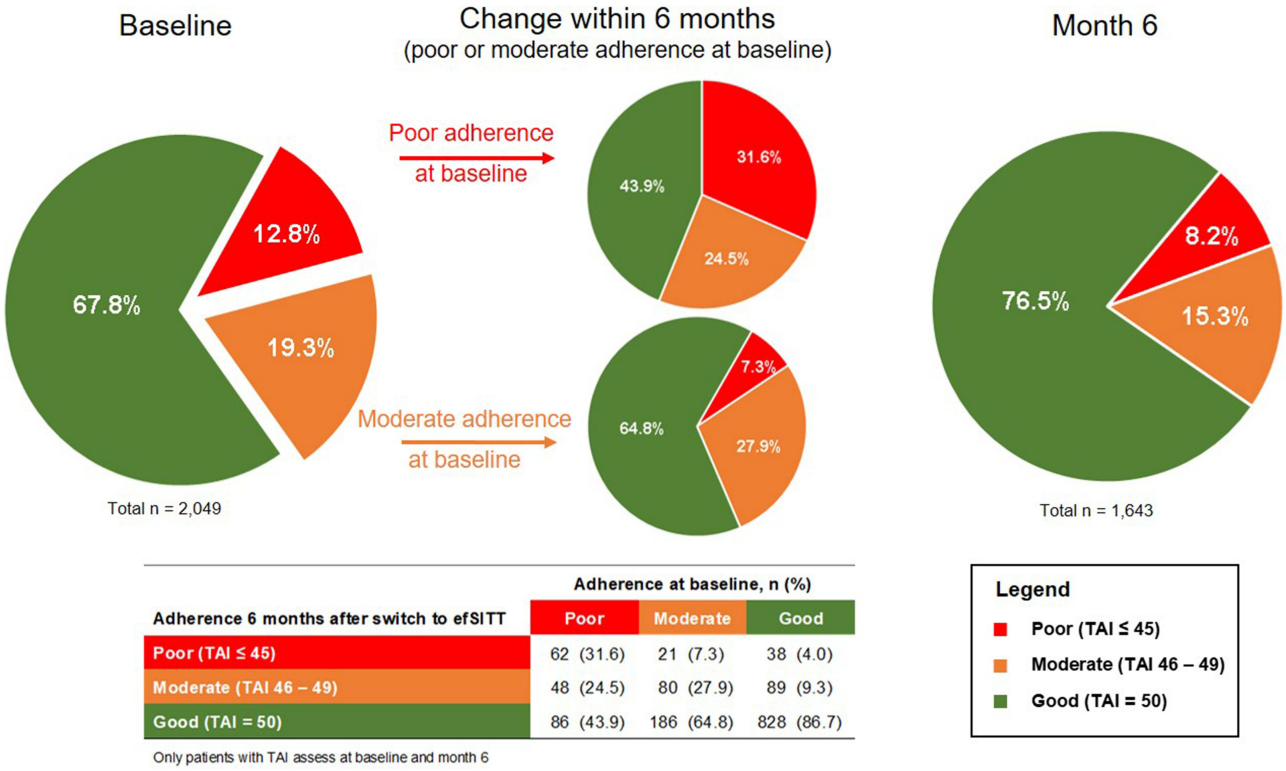


Figure 5 Change of adherence according to TAI from baseline to 6 months after switch to efSITT.

Switching treatment to efSITT also resulted in an improvement of treatment adherence. After six months, two thirds of patients with poor adherence at baseline improved to either good (44%) or intermediate adherence (25%), respectively. Among patients with intermediate adherence at baseline, almost two thirds improved to good adherence after six months. Of note, approximately two thirds of all patients already displayed good adherence at baseline. More than half of the patients (55.7%) showed a high to very high disease burden (CAT score ≥ 21) at baseline. It is reasonable to consider that these patients exhibited a high level of adherence to their medication as they perceived a high need to treat their symptoms. COPD patients with greater symptom frequency, disease severity and a history of severe exacerbations have been associated with higher adherence to inhaled medications.[7,43–45] As discussed above, the number of used inhalation devices is another important factor influencing treatment adherence. It has been shown that the use of multiple inhalers and inhalation techniques was associated with poor treatment adherence[8,9,45] and consequently had a negative impact on clinical outcomes.[10,11] Accordingly, switching to efSITT offers a benefit to patients previously using multiple inhalers. After switching to efSITT, treatment adherence continued at a high level and was even further increased in the overall population over a period of six months. Our result demonstrate that efSITT has the potential to enhance treatment adherence in the real-world practice, a dimension which has not been evaluated in controlled settings so far.[15] Good treatment adherence is associated with improved symptom control, lung function and a reduction of exacerbation risk and therefore is essential for long-term treatment success.[6,10] In addition to optimization of clinical outcomes, treatment adherence has also the potential to reduce health care costs.[6,46]

The non-interventional design of the study allowed gaining insight in the treatment adherence of patients in routine clinical practice. However, the observational nature of this study is associated with certain limitations. As data were collected during routine practice and according to physicians' discretion, data robustness might be limited due to variable quality and missing data especially for lung function parameters. Certain characteristics of the overall patient population were imbalanced such as prior treatment: Almost 60% of the patients were using free triple therapy before enrollment. Therefore, these patients benefited less from a switch to efSITT resulting in weaker improvements in HRQoL and lung function in comparison to the other prior treatment groups. The duration of our study was shorter (6 months) compared to other studies with an observational period of 12 months or more.[31,35] For a more precise evaluation of the impact of efSITT, especially for the evaluation of long-term symptom control as assessed by CAT subitems and an effect on exacerbation risk, data collection over a longer period might be necessary. Because of the absence of a simultaneous comparator treatment arm in this study, the interpretation of a cause–effect relationship between efSITT treatment and outcomes in our study is limited.

Despite these limitations, the real-world setting of our study gave an important insight in the current clinical practice. In detail, we observed improvements in HRQoL, lung function parameters, and treatment adherence after six months of efSITT treatment. Hence, even stronger improvements might be expected after a longer observational period. In addition, a significant number of COPD patients with a history of asthma were enrolled, who were excluded in a number of prior controlled trials.[15,16]

Conclusion

In conclusion, the results of this non-interventional study indicate that efSITT is a valuable treatment option in moderate-to-severe COPD patients with poor symptom control and who are at risk of exacerbations despite current treatment. EfSITT treatment was associated with an improvement in HRQoL, COPD specific symptoms, and lung function parameters after six months of treatment. Especially, patients with prior LAMA/LABA or ICS/LABA treatment benefited most from therapy escalation. Moreover, patient adherence to treatment improved with efSITT, which is particularly important for long-term disease control in COPD.

Abbreviations

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; efSITT, extrafine single-inhaler triple therapy; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, The Global Initiative for Chronic Obstructive Lung Disease (GOLD); IC, inspiratory capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-

agonist; LAMA, long-acting muscarinic antagonist; RV, residual volume; SD, standard deviation; sRtot, total specific airway resistance; TAI, test of adherence to inhalers; TLC, total lung capacity.

Data Sharing Statement

The data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the latest version (2013) of the Declaration of Helsinki and was approved by the ethics committee of the State Chamber of Physicians of Saxony as the ethics committee of the national chief investigator. The study was registered with German Clinical Trials Register (DRKS00013938). All patients gave written improved consent.

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Author Contributions

All authors significantly contributed to the work reported, either in conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors were involved in drafting, revising or critically reviewing the article and gave final approval of the version to be published. They have agreed on the journal to which the article has been submitted and to be accountable for all aspects of the work.

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