ORIGINAL RESEARCH

Differential Outcomes Following 4 Weeks of Aclidinium/Formoterol in Patients with COPD: A Reanalysis of the ACTIVATE Study

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Rationale: It is difficult to predict the effects of long-acting bronchodilators (LABD) on lung function, exercise capacity and physical activity in patients with chronic obstructive pulmonary disease (COPD). Therefore, the multidimensional response to LABD was profiled in COPD patients participating in the ACTIVATE study and randomized to LABD.

Methods: In the ACTIVATE study, patients were randomized to aclidinium bromide/formoterol fumarate (AB/FF) or placebo for four weeks. The primary outcomes included (1) lung function as measured by functional residual capacity (FRC), residual volume (RV), and spirometric outcomes; (2) exercise performance as measured by a constant work rate cycle ergometry test (CWRT); and (3) physical activity (PA) using an activity monitor. Self-organizing maps (SOMs) were used to create an ordered representation of the patients who were randomly assigned to four weeks of AB/FF and cluster them into different outcome groups.

Results: A total of 250 patients were randomized to AB/FF (n = 126) or placebo (n = 124). Patients in the AB/FF group (39.6% women) had moderate-to-severe COPD, static hyperinflation (FRC: 151.4 (27.7)% predicted) and preserved exercise capacity. Six clusters with differential outcomes were identified. Patients in clusters 1 and 2 had significant improvements in lung function compared to the remaining AB/FF-treated patients. Patients in clusters 1 and 3 had significant improvements in CWRT time, and patients in clusters 2, 3 and 6 had significant improvements in PA compared to the remaining AB/FF-treated patients.

Conclusion: Individual responses to 4 weeks of AB/FF-treatment in COPD are differential and the degree of change differs across domains of lung function, exercise capacity and PA. These results indicate that clinical response to LABD therapy is difficult to predict and is non-linear, and show doctors that it is important to look at multiple outcomes simultaneously when evaluating the clinical response to LABD therapy.

Clinical Trial Registration: The original ACTIVATE study was registered on ClinicalTrials.gov, registration number NCT02424344.

Keywords: COPD, hyperinflation, physical activity

Introduction

Long-acting bronchodilators (LABDs) are the cornerstone of pharmacological therapy in patients with mild to very severe chronic obstructive pulmonary disease (COPD),[1] as they generally increase the forced expiratory volume in the first second (FEV1),[2,3] lower the degree of breathlessness,[4,5] improve exercise performance[6–9] and health status,[3,5] and reduce exacerbation rates.[3,10] The effects of LABDs on lung hyperinflation and objectively measured physical activity (PA) remain indecisive.[2–4,9,11–14]

The benefits of LABD therapy can vary to a great extent between patients with COPD.[5] To date, it is difficult to truly understand which patients *do* or *do not* benefit from LABDs, as studies only show aggregated data from individuals. Individual patients may respond differentially regarding a variety of clinically relevant outcomes, with variable degree and direction of outcome effect, suggesting non-linearity. Statistical methods, such as self-organizing maps (SOMs), can be used to create an ordered representation of multi-dimensional data, to simplify complexity and to reveal meaningful associations.[15–17] The use of composite endpoints (eg, change in lung function (≥100 mL in FEV1), Health status (≥4-units in St George's Respiratory Questionnaire [SGRQ]), and the incidence of moderate/severe exacerbations) for the assessment of clinically important deterioration in COPD was recently proposed.[18] However, the response to LABD therapy on multiple outcomes simultaneously has scarcely been investigated in COPD.[19] This, however, will provide a greater insight in the response to LABDs in COPD, and will advance the field by identifying the appropriate subgroup of patients for the appropriate treatment. In turn, this might help clinicians provide their patients with the right treatment, by evaluating the treatment response through various outcomes. Using the data from the ACTIVATE study,[9] where the effect of LABD therapy on lung hyperinflation, exercise endurance and PA was studied, we aimed to identify multidimensional outcome patterns for LABD therapy in patients with COPD, including static and dynamic lung function measures, exercise performance and PA by performing a cluster analysis. Moreover, we aimed to determine the initial characteristics associated with these patterns. Based on the multiple pulmonary (ie airflow limitation, lung hyperinflation, and impaired diffusion capacity) and extra-pulmonary components (ie lower-limb muscle weakness, fatigue, depression, and anxiety) that contribute to the pathophysiology of the disease and the clinical presentation of patients with COPD, a priori, we expected a heterogenous and non-linear response to LABDs.

Methods

Study Design

The ACTIVATE study was an 8-week randomized, double-blind, placebo-controlled study investigating the effects of aclidinium bromide/formoterol fumarate (AB/FF) 400/12 µg twice daily on lung hyperinflation, exercise endurance time (EET) and PA in patients with moderate-to-severe COPD.[9] The study objectives of the original manuscript were to study the effect of AB/FF versus placebo on lung hyperinflation, exercise endurance time, and physical activity in patients with moderate-to-severe COPD.

Patients who fulfilled the inclusion/exclusion criteria were randomized according to a 1:1 randomization ratio to one of the two treatment arms to randomly receive either AB/FF 400/12 µg twice daily or placebo BID for 8 weeks double-blind treatment phase. The block size of the randomization scheme was not communicated to the investigators. The length of this block was 4 to make it impossible to guess for any allocation. Randomization data were kept strictly confidential, and randomization codes were only available for data analysis just after the unblinding of the allocated treatment, ie after locking the database upon termination of the trial.

Patients received either AB/FF 400/12 µg or placebo twice daily via a multidose dry powder inhaler (Genuair™/ Pressair®) (ClinicalTrials.gov number: NCT02424344). During the first four weeks of the study, patients received pharmacotherapy alone (AB/FF or placebo) and, during the second four weeks, behavioral intervention was added to both treatment arms. AB/FF demonstrated improvements in static and dynamic hyperinflation, exercise capacity and physical activity versus placebo after four weeks of treatment. We only analyzed the outcomes after the first four weeks to solely focus on the pharmacotherapy effects of AB/FF.

The original ACTIVATE trial was approved by local ethics committees (Table S1) and performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.[9] All patients provided written informed consent prior to conducting any study-specific procedures.

Patients

The key inclusion criteria for the ACTIVATE study were COPD patients aged ≥40 years with a functional residual capacity (FRC) ≥120%, post-bronchodilator FEV_1 ≥40% and <80% of the predicted value, FEV_1/FVC <70%, and a modified Medical Research Council (mMRC) dyspnea grade ≥2. Detailed inclusion and exclusion criteria are available in the primary publication.[9] Two hundred and fifty patients who completed the study were randomized to AB/FF (n = 126) or placebo (n = 124), based on the actual treatment assignment. Patients who completed week four entered the analyses.

Measurements

Lung function was assessed using whole-body plethysmography (FRC, residual volume[20] and specific airway conductance [sG_{AW}]) and spirometry (forced vital capacity [FVC] and FEV_1) before exercise, at baseline (pre-dose at day one on treatment), and at week four, as described previously[4] in accordance with current recommendations.[21–23] EET was measured using a constant work rate cycle ergometry test (CWRT) to symptom limitation at 75% of the pre-determined peak work rate (W_{max}) at baseline and at 3 h post-dose at week four.[4] Inspiratory capacity (IC) was measured using a spirometer at rest, during, and at the end of the CWRT. PA levels were measured at baseline and at week four using an activity monitor (DynaPort MoveMonitor, McRoberts B.V., the Hague, the Netherlands) for a period of one week, worn by patients 24 hours per day.[24,25] The average number of steps taken per day, the time in moderate-intensity activities per day (>3 metabolic equivalents [MET] as estimated by the accelerometer), and the activity-related energy expenditure were recorded.[4] PA experience was assessed using the Daily PROactive Physical Activity in COPD (D-PPAC) instrument, a daily recall, electronic, hybrid (patient-reported outcome (PRO) and activity monitor) tool developed by the Innovative Medicines Initiative PROactive project.[24] The seven-item D-PPAC PRO was filled out by patients every evening for a week, over baseline week and over week four. The D-PPAC consists of three scores: amount domain (combining two PRO items plus two activity monitor outputs (steps per day and vector magnitude units [VMU] per minute)); the difficulty domain (five PRO items) and a total score (calculated as the average of both domain scores). Each score ranges from 0 to 100 points, where higher numbers indicate a better physical activity experience.[9]

Statistics

Comparison of outcomes at week four within the AB/FF treated group and between this and the placebo group included assessment of change from baseline in lung hyperinflation (FRC and RV), airflow limitation (FEV_1, FVC and sG_{AW}), EET and IC during CWRT, D-PPAC scores (total, amount and difficulty), percentage of inactive patients (<6000 steps per day) and PA time spent at different intensities (<1.5, 1.5–3.0 and >3.0 METS).[9]

Statistical analyses were performed using Viscovery SOMine 7.2 build 6719 by Viscovery Software GmbH (www. viscovery.net). Self-organizing maps (SOMs, also referred to as Kohonen maps)[26,27] were used to create an ordered representation of the patients, who were randomly assigned to four weeks of AB/FF and cluster them into outcome groups. The SOM method can be viewed as a non-parametric regression technique that converts multi-dimensional data spaces into lower dimensional abstractions. SOM generates a non-linear representation of the data distribution and allows the user to identify homogenous data groups visually. The attributes that drive the ordering process of the patients in the map were the differences in the outcome indicators: change in pre-dose FRC (expressed in % of baseline), change in pre-dose FEV1 (expressed in % of baseline), change in isotime IC (expressed in % of baseline), change in CWRT endurance time in seconds (expressed as change from baseline), change in D-PPAC amount in arbitrary units (expressed as change from baseline), the change in number of steps/day (expressed as change from baseline) and the change in PA time spent >3 METS (expressed as change from baseline). Patients with similar outcome profiles were placed close to each other on the map. Based on the ordering in the map, the hierarchical SOM-Ward Cluster algorithm was applied, to group the patients into outcome clusters. Data records were ordered by Viscovery based on the similarity of the existing attributes. If attribute values were missing for a specific patient, this patient was matched to the SOM based on all other attributes whose values were known. Indeed, data records with missing values or invalid entries are recognized by Viscovery and treated appropriately in the analysis. No imputation of missing values is necessary when creating of an SOM model. The basic operation with an SOM is to look up the best-matching node. If an

input data record is not complete (has missing values), then the look-up is limited to the available values. That is, the SOM is treated as if the nodes were shorter vectors (in math speak: the SOM is projected into the data space that consists of the available values), and then the lookup is conducted on this reduced map. This happens for each individual record. In this way, missing values are so to speak "substituted" with the lookup values of the matching nodes.

The ordering of our model was based on 7 attributes of which 1 up to 20 of 126 values were missing, ie the percentual changes in FEV1 (1 missing), FRC (5 missing), and IC isotime (12 missing), as well as the absolute changes in CWRT times (1 missing), D-PPAC amount (20 missing), Steps/day (12 missing), and Time >3 METS, [%of day] (12 missing). The SOM-Ward Cluster algorithm of Viscovery is a hybrid algorithm that applies the classical hierarchical method of Ward on top of the SOM topology. Summary variables in clinical characteristics for the study sample and for each cluster were presented as mean (standard deviation[28]) for quantitative variables, and percentage for discrete variables. Data of the lung function attributes, exercise and PA assessments were sigma-transformed to mitigate the effects of extreme values. The mean change per cluster from the intervention group was compared with the mean change from the whole placebo group using an unpaired t-test. Viscovery identified for each cluster the clinical characteristics and demographical factors that differ significantly from the average of the whole AB/FF-treated sample or the placebo-treated sample using the integrated two-sided t-test with a confidence of 95%.

Results
Baseline Characteristics
Two hundred and fifty patients who completed the study were randomized to AB/FF (n = 126) or placebo (n = 124), based on the actual treatment assignment. At baseline, the 126 patients in the AB/FF group (38% women) had moderate-to-severe COPD (mean (SD) post-bronchodilator FEV1: 60.3 (10.7)% predicted), severe static hyperinflation (mean (SD) FRC: 151.4 (27.7)% predicted) and were using multiple pulmonary medications before the study. Fifty-five percent of the patients were physically inactive (<6000 steps per day); and patients generally had a rather preserved exercise capacity (mean (SD) CWRT time: 452 (184) seconds). There were no differences at baseline as compared to the placebo group (Table 1).

Mean Improvements Following 4 Weeks AB/FF
Compared to placebo, significant improvements in AB/FF were found for FEV_1, FVC and sG_{aw}, with a significant reduction in RV (Table 2). With AB/FF, EET improved significantly, as well as percentage of IC during exercise at isotime and at the end of exercise, indicating improvement in dynamic hyperinflation (Table 3). Moreover, significant improvements were found for D-PPAC questionnaire scores, VMU, steps per day and time spent >3 METs (Table 3). These results have been reported in more detail in the original ACTIVATE study.[9]

Multidimensional Profiling of AB/FF Group
The 126 patients in the AB/FF group were clustered into six groups with distinct multidimensional outcome profiles (Figure 1).

- Patients in *Cluster 1* (n = 19) had significantly larger mean improvements in FEV_1, FVC, FRC, RV, sG_{AW} (Table 2), CWRT time, resting IC, IC isotime, post-exercise IC, resting SpO_2, resting dyspnea (Table 3), and D-PPAC difficulty (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvement in D-PPAC amount was significantly smaller (Table 4). Overall, this cluster improved the most after treatment with AB/FF compared to the remaining AB/FF-treated patients (Figure 2).
- Patients in *Cluster 2* (n = 17) had significantly larger mean improvements in FEV_1, FRC, RV (Table 2), and D-PPAC amount (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvement in CWRT time was significantly smaller (Table 3).

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Table 1 Baseline Characteristics

	AB/FF (n = 126)	Placebo (n = 124)
General characteristics		
% women	38	42
Age, years	63 (8)	62 (8)
BMI, kg/m^2	26.3 (3.4)	26.1 (3.6)
mMRC dyspnea grade	2.1 (0.3)	2.1 (0.3)
Current smokers, % patients	64	62
Number of medications	5.4 (3.0)	5.1 (3.0)
Number of exacerbations	0.3 (0.5)	0.4 (1.1)
Pulmonary function		
FEV$_1$, liters	1.5 (0.5)	1.6 (0.5)
FVC, liters	3.3 (0.9)	3.3 (1.0)
FRC, liters	5.0 (1.2)	4.8 (1.1)
RV, liters	4.2 (1.1)	4.0 (1.0)
sG$_{aw}$, sec^{-1} kPa^{-1}	0.5 (0.3)	0.5 (0.3)
Exercise-related attributes		
CWRT time, seconds	452 (184)	460 (184)
Resting IC, L	2.4 (0.6)	2.3 (0.6)
Isotime IC, L	2.4 (0.6)	2.3 (0.6)
Post-exercise IC, L	2.4 (0.6)	2.3 (0.6)
Resting SpO$_2$, %	96.5 (1.7)	96.0 (2.4)
Post-exercise SpO$_2$, %	95.1 (2.8)	95.5 (2.4)
Resting dyspnea, points	0.7 (1.4)	0.5 (1.1)
Post-exercise dyspnea, points	6.6 (2.7)	5.9 (2.4)
Resting fatigue, points	0.2 (0.7)	0.2 (0.5)
Post-exercise fatigue, points	5.5 (3.0)	5.8 (2.3)
Physical activity-related attributes		
D-PPAC amount, points	54 (13)	53 (14)
D-PPAC difficulty, points	69 (14)	71 (14)
VMU, /min	3.2 (1.0)	3.2 (1.1)
Steps per day	6170 (2897)	6184 (3063)
% patients <6000 steps per day	55	49
Time <1.5 METs, min/day	1244 (71)	1241 (75)
Time <1.5 METs, % of day	86 (5)	86 (5)
Time 1.5–3.0 METs, min/day	94 (41)	96 (40)
Time 1.5–3.0 METs, % of day	6.5 (2.9)	6.6 (2.8)
Time >3 METs, min/day	102 (39)	103 (48)
Time >3 METs, % of day	7.1 (2.7)	7.2 (3.3)

Abbreviations: AB/FF, aclidinium bromide/formoterol fumarate; BMI, body mass index; mMRC, modified Medical Research Council; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; FRC, functional residual volume; RV, residual volume; sG$_{AW}$, specific airway conductance; sec, seconds; kPa, kilopascal; CWRT, constant work rate test; IC, inspiratory capacity; SpO$_2$, oxygen saturation; HR, heart rate; bpm, beats per minute; D-PPAC, Daily PROactive Physical Activity in COPD; VMU, vector magnitude units; MET, metabolic equivalents; min, minute.

- Patients in *Cluster 3* (n = 25) had significantly larger mean improvements in CWRT time (Table 3), D-PPAC amount, VMU, steps per day, and time spent >3 METs (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvement in time spent <1.5 METs were significantly smaller (Table 4).
- Patients in *Cluster 4* (n = 21) had significantly smaller mean improvements in FEV$_1$ (Table 2), resting IC, IC isotime, post-exercise IC (Table 3), D-PPAC amount, VMU, steps per day, time spent 1.5–3 METs, and time spent >3 METs (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvements in FRC (Table 2) and time spent <1.5 METs (Table 4) were larger.

Table 2 Change from Baseline (L) and % of Improvement in Pre-Dose Spirometry and Whole Body Plethysmography After 4 Weeks of Treatment

	AB/FF (n = 126)	AB/FF						Placebo (n = 124)
		Cluster 1 (n = 19)	Cluster 2 (n = 17)	Cluster 3 (n = 25)	Cluster 4 (n = 21)	Cluster 5 (n = 24)	Cluster 6 (n = 20)	
FEV$_1$								
• Liters	0.19 (0.26) ++	0.42 (0.27) + ++	0.28 (0.18) ++	0.19 (0.20) ++	0.10 (0.22) ++	0.06 (0.30) •	0.14 (0.18) ++	−0.03 (0.17)
• % improvement	14 (20) ++	34 (20) + ++	24 (17) + ++	13 (19) ++	6 (13) • ++	4 (22) •	9 (12) ++	−1.0 (12)
FVC								
• Liters	0.24 (0.40) ++	0.60 (0.43) + ++	0.29 (0.30) ++	0.31 (0.38) ++	0.07 (0.33) •	0.05 (0.37) •	0.15 (0.35) ++	−0.02 (0.30)
• % improvement	8 (16) ++	20 (12) + ++	11 (11) ++	12 (24) ++	2 (11)	1 (13) •	4 (11) ++	−0.4 (9)
FRC								
• Liters	−0.15 (0.60)	−0.82 (0.29) • ••	−0.65 (0.29) • ••	−0.18 (0.30)	−0.34 (0.26) ••	0.45 (0.53) + ++	0.31 (0.59) + ++	−0.02 (0.50)
• % improvement	3 (11)	13 (4) + ++	12 (4) + ++	4 (6)	7 (6) + ++	−9 (9) • ••	−6 (11) • ••	0.2 (11)
RV								
• Liters	−0.21 (0.63) ••	−0.83 (0.30) • ••	−0.49 (0.45) • ••	−0.28 (0.43)	−0.25 (0.22)	0.24 (0.76) +	0.14 (0.72) +	−0.04 (0.59)
• % improvement	4 (16) ++	17 (7) + ++	11 (11) + ++	6 (10)	7 (6) ++	−5 (20) •	−6 (21) •	−0.3 (16)
sG$_{AW}$								
• sec^{-1} kPa^{-1}	0.13 (0.22) ++	0.20 (0.23) ++	0.19 (0.19) ++	0.13 (0.14) ++	0.14 (0.24) ++	0.07 (0.24) ++	0.11 (0.28) ++	−0.02 (0.21)
• % improvement	37 (54) ++	62 (48) + ++	60 (61) ++	35 (40) ++	30 (44) ++	22 (66) ++	24 (54) ++	0.0 (31)

Notes: • mean change is smaller compared to the mean change of the remaining active-treated patients (P<0.05); •• mean change is smaller compared to the mean change of all placebo-treated patients (P<0.05); + mean change is larger compared to the mean change of the remaining active-treated patients (P<0.05); ++ mean change is larger compared to the mean change of all placebo-treated patients (P<0.05). Clusters 1 to 6 only contain active treated patients. Attributes used for clustering are presented in bold.

Abbreviations: AB/FF, aclidinium bromide/formoterol fumarate; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; FRC, functional residual volume; RV, residual volume; sG$_{AW}$= specific airway conductance; sec, seconds; kPa, kilopascal.

Table 3 Change from Baseline in Exercise-Related Attributes After Four Weeks of Treatment

	AB/FF (n = 126)	AB/FF						Placebo (n = 124)
		Cluster 1 (n = 19)	Cluster 2 (n = 17)	Cluster 3 (n = 25)	Cluster 4 (n = 21)	Cluster 5 (n = 24)	Cluster 6 (n = 20)	
CWRT time								
• Seconds	43 (197) ++	257 (224) + ++	−79 (68) • ••	160 (121) + ++	27 (224)	−81 (136) • ••	−38 (81) •	−8 (136)
• % improvement	15 (52) ++	79 (66) + ++	−18 (15) • ••	38 (28) + ++	5 (31)	−7 (54) • ••	−7 (22) •	2 (35)
Resting IC								
• Liters	0.2 (0.4)	0.6 (0.4) + ++	0.3 (0.4) ++	0.4 (0.3) ++	0.0 (0.5) •	0.2 (0.3) ++	0.1 (0.3) ++	0.0 (0.3)
• % improvement	10 (18) ++	26 (16) + ++	13 (21) ++	15 (17) ++	1 (20) •	7 (13) ++	3 (12)	−2 (15)
IC isotime								
• Liters	0.2 (0.4)	0.5 (0.3) + ++	0.3 (0.3) ++	0.3 (0.3) + ++	0.0 (0.4) •	0.2 (0.3) ++	0.0 (0.3) •	0.0 (0.3)
• % improvement	10 (17) ++	28 (22) + ++	13 (13) ++	14 (11) ++	2 (15) •	10 (15) ++	−1 (12) •	−0.3 (14)
Post-exercise IC								
• Liters	0.2 (0.4)	0.5 (0.3) + ++	0.2 (0.3) ++	0.3 (0.3) ++	0.0 (0.4) •	0.2 (0.4) ++	0.0 (0.2) •	0.0 (0.3)
• % improvement	10 (17) ++	25 (21) + ++	10 (14) ++	12 (11) ++	3 (15) •	10 (18) ++	−2 (11) •	0.0 (15)
Resting SpO$_2$								
• %	0.1 (2.1)	1.7 (2.4) + ++	0.3 (1.9)	−0.2 (1.6)	−0.3 (2.3)	−0.5 (1.8)	0.3 (1.9)	0.4 (2.3)
SpO$_2$ isotime								
• %	0.1 (2.5)	0.8 (2.0)	−0.4 (2.0)	−0.6 (2.0)	0.2 (2.8)	0.1 (2.8)	0.5 (3.0)	−0.3 (2.4)
Post-exercise SpO$_2$								
• %	−0.1 (2.6)	0.3 (1.9)	−0.5 (2.1)	−0.6 (2.1)	0.0 (2.9)	−0.1 (3.3)	0.6 (3.0)	−0.4 (2.5)
Resting dyspnea								
• Points	−0.1 (1.1)	−0.6 (1.4) • ••	−0.1 (0.7)	−0.2 (0.9)	0.1 (0.9)	−0.1 (1.3)	0.3 (1.2)	−0.0 (0.8)
Dyspnea isotime								
• Points	−0.5 (2.5)	−1.4 (3.1) ••	−0.3 (2.3)	−1.1 (2.4) ••	−0.1 (2.2)	0.2 (2.8)	−0.6 (1.8)	−0.1 (1.9)
Post-exerc. dyspnea								
• Points	−0.3 (2.3)	0.2 (2.8)	−0.7 (1.8)	−0.2 (2.7)	−0.5 (2.4)	−0.1 (2.2)	−0.8 (1.8)	−0.0 (1.8)
Resting fatigue								
• Points	−0.0 (0.8)	−0.0 (0.2)	−0.1 (0.3)	0.2 (0.6)	−0.1 (0.3)	−0.1 (1.5)	0.3 (0.6)	−0.0 (0.7)
Fatigue isotime								
• Points	0.2 (2.1)	−0.2 (2.5)	0.4 (1.9)	−0.2 (2.9)	0.6 (1.5)	0.5 (1.6)	0.3 (1.9)	−0.1 (1.7)
Post-exerc. fatigue								
• Points	0.4 (2.2)	0.9 (2.2)	−0.2 (2.2)	0.8 (2.9)	0.2 (2.2)	−0.0 (1.8)	0.5 (1.6)	−0.0 (1.8)

Notes: • mean change is smaller compared to the mean change of the remaining active-treated patients (P<0.05); •• mean change is smaller compared to the mean change of all placebo-treated patients (P<0.05); + mean change is larger compared to the mean change of the remaining active-treated patients (P<0.05); ++ mean change is larger compared to the mean change of all placebo-treated patients (P<0.05). Clusters 1 to 6 only contain active treated patients. Attributes used for clustering are presented in bold.
Abbreviations: AB/FF, aclidinium bromide/formoterol fumarate; CWRT, constant work rate test; IC, inspiratory capacity; SpO$_2$, oxygen saturation; HR, heart rate; bpm, beats per minute.
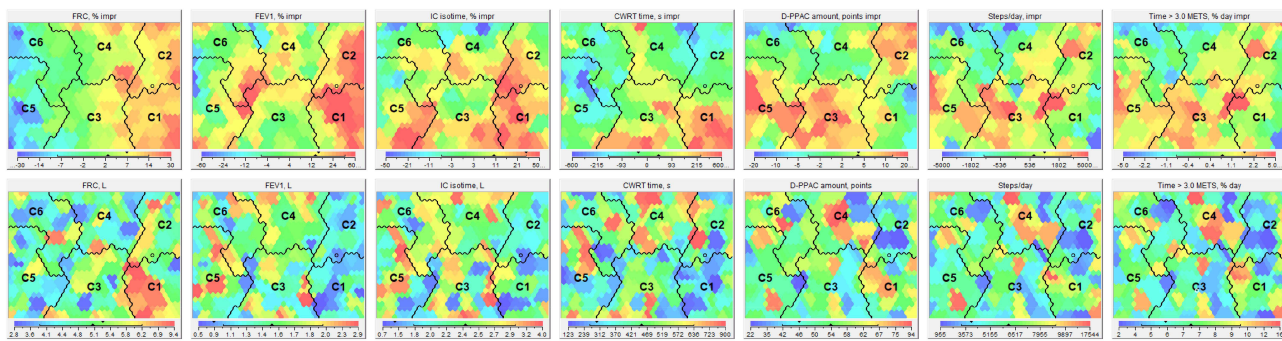
Figure 1 Weighted attributes (improvements) and their baseline values in the AB/FF group. Panels generated using Viscovery (Viscovery Software GmbH, Vienna, Austria). The Viscovery program placed all patients on a specific position in the map based on their multidimensional outcome profile. The more subjects resemble in terms of their response to AB/FF after four weeks, the closer they are on the map, and the more they differ, the further they are away from each other. When looking at an outcome measure, an area is coloured red when the outcome was very good, yellow when the outcome was good, green when there was no major change, and blue when the outcome was negative/towards the worse. The panels in the first row illustrate the percentage of improvement after four weeks of treatment with AB/FF in pre-dose functional respiratory capacity (FRC), pre-dose forced expiratory volume in the first second (FEV$_1$), inspiratory capacity (IC) at isotime during constant work rate cycle ergometry (CWRT), cycle endurance time (CWRT), the amount of self-reported activity by Daily PROactive Physical Activity in COPD (D-PPAC), the number of steps per day, and the percentage of the day patients were very physically active (>3 metabolic equivalents [METs]). The second row shows the same outcomes at baseline of the AB/FF-treated patients.

- Patients in *Cluster 5* (n = 24) had significantly smaller mean improvements in FEV$_1$, FVC, FRC, RV (Table 2), CWRT time (Table 3), and time spent <1.5 METs (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvements in D-PPAC amount, VMU, steps per day, time spent 1.5–3 METs, and time spent >3 METs (Table 4) were significantly larger.
- Patients in *Cluster 6* (n = 20) had significantly smaller mean improvements in FRC, RV (Table 2), CWRT time, IC isotime, post-exercise IC (Table 3), D-PPAC amount, VMU, steps per day, time spent 1.5–3 METs, and time spent >3 METs (Table 4) compared to the remaining AB/FF-treated patients; while the mean improvement in time spent <1.5 METs were significantly larger (Table 4). Overall, this cluster improved the least after treatment with AB/FF compared to the remaining AB/FF-treated patients (Figure 1).

Individual AB/FF Clusters versus Placebo

- Patients in *Cluster 1* had significantly larger mean improvements in FEV$_1$, FVC, FRC, RV, sG$_{AW}$ (Table 2), CWRT time, resting IC, IC isotime, post-exercise IC, resting SpO$_2$, resting dyspnea, dyspnea isotime (Table 3), and D-PPAC difficulty (Table 4) compared to placebo.
- Patients in *Cluster 2* had significantly larger mean improvements in FEV$_1$, FVC, FRC, RV, sG$_{AW}$ (Table 2), resting IC, IC isotime, post-exercise IC (Table 3), D-PPAC amount, VMU, steps per day, and time spent >3 METs (Table 4) compared to placebo; while the mean improvements in CWRT time (Table 3) and time spent <1.5 METs (Table 4) were significantly smaller.
- Patients in *Cluster 3* had significantly larger mean improvements in FEV$_1$, FVC, sG$_{AW}$ (Table 2), CWRT time, resting IC, IC isotime, post-exercise IC, dyspnea isotime (Table 3), D-PPAC amount, VMU, steps per day, and time spent >3 METs (Table 4) compared to placebo; while the mean improvement in time spent <1.5 METs was significantly smaller (Table 4).
- Patients in *Cluster 4* had significantly larger mean improvements in FEV$_1$, FRC, RV, and sG$_{AW}$ compared to placebo (Table 2).
- Patients in *Cluster 5* had significantly smaller mean improvements in FRC (Table 2), CWRT time (Table 3), and time spent <1.5 METs (Table 4) compared to placebo; while the mean improvements in sG$_{AW}$ (Table 2), resting IC, IC isotime, post-exercise IC (Table 3), D-PPAC amount, VMU, steps per day, time spent 1.5–3 METs, and time spent >3 METs (Table 4) were significantly larger.

Table 4 Changes in Physical Activity-Related Attributes

	AB/FF (n =126)	AB/FF						Placebo (n = 124)
		Cluster 1 (n = 19)	Cluster 2 (n = 17)	Cluster 3 (n = 25)	Cluster 4 (n = 21)	Cluster 5 (n = 24)	Cluster 6 (n = 20)	
D-PPAC amount								
• Points	4.0 (7.4) ++	0.4 (5.2) •	9.4 (5.8) + ++	8.3 (3.8) + ++	−1.9 (4.9) •	8.4 (8.0) + ++	−2.3 (5.2) •	0.5 (8.0)
D-PPAC difficulty								
• Points	3.8 (8.1) ++	8.1 (9.2) + ++	4.9 (8.0)	2.1 (6.2)	3.1 (5.3)	2.5 (6.0)	2.6 (11.6)	0.9 (7.6)
D-PPAC total								
• Points	3.9 (5.6) ++	4.3 (5.4) ++	7.1 (5.8) + ++	5.2 (3.4) ++	0.6 (3.7) •	5.4 (4.6) ++	0.1 (7.2) •	0.7 (5.4)
VMU								
• Per min	0.3 (0.6) ++	0.0 (0.4)	0.5 (0.6) ++	0.5 (0.4) + ++	−0.1 (0.6) •	0.6 (0.7) + ++	−0.1 (0.5) •	0.0 (0.5)
Steps per day								
• N	687 (1899) ++	630 (2163)	1206 (1238) ++	1619 (1515) + ++	−354 (1775) •	1524 (1893) + ++	−844 (1294) •	−148 (1731)
<6000 steps per day								
• % patients	−16 ••	0	−31 ••	−17 ••	−6	−52 • ••	17 +	6
Time <1.5 METS								
• min/day	−15 (38) ••	−13 (37)	−24 (29) ••	−32 (21) • ••	8 (29) +	−38 (43) • ••	18 (29) + ++	−1 (35)
• % of day	−1.0 (2.6) ••	−0.9 (2.6)	−1.7 (2.0) ••	−2.3 (1.5) • ••	0.6 (2.0) +	−2.7 (3.0) • ••	1.2 (2.0) + ++	−0.1 (2.5)
Time 1.5–3.0 METs								
• min/day	4 (23)	2 (19)	9 (19)	9 (18)	−7 (22) •	14 (28) + ++	−7 (25) •	2 (25)
• % of day	0.3 (1.6)	0.1 (1.3)	0.6 (1.4)	0.6 (1.3)	−0.5 (1.5) •	1.0 (2.0) + ++	−0.5 (1.7) •	0.1 (1.8)
Time >3 METs								
• min/day	11 (22) ++	11 (28) +	15 (17) ++	23 (15) + ++	−1 (16) •	24 (20) + ++	−11 (15) •	−1 (25)
• % of day	0.8 (1.6) ++	0.8 (1.9)	1.1 (1.2) ++	1.6 (1.0) + ++	−0.1 (1.1) •	1.6 (1.4) + ++	−0.8 (1.0) •	0.0 (1.7)

Notes: • mean change is smaller compared to the mean change of the remaining active-treated patients (P<0.05); •• mean change is smaller compared to the mean change of all placebo-treated patients (P<0.05); + mean change is larger compared to the mean change of the remaining active-treated patients (P<0.05); ++ mean change is larger compared to the mean change of all placebo-treated patients (P<0.05). Clusters 1 to 6 only contain active treated patients. Attributes used for clustering are presented in bold.

Abbreviations: AB/FF, aclidinium bromide/formoterol fumarate; D-PPAC, Daily PROactive Physical Activity in COPD; VMU, vector magnitude units; MET, metabolic equivalents; min, minute.
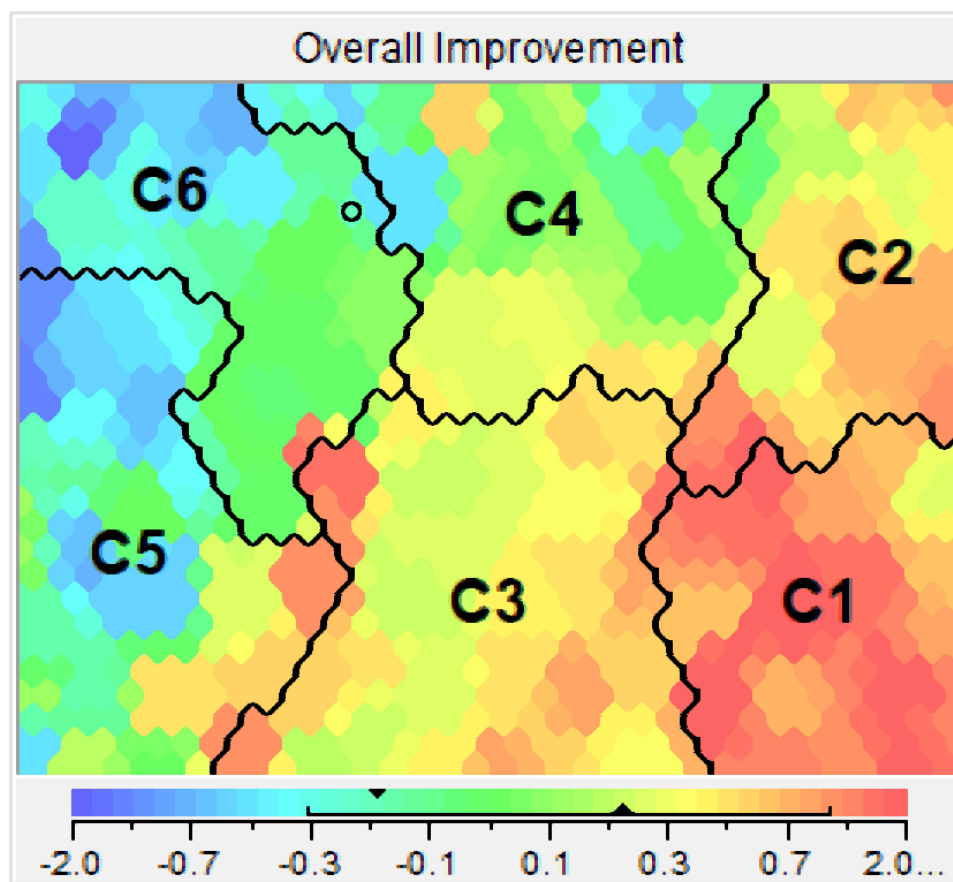
Figure 2 Overall improvement following 4 weeks of AB/FF. The overall improvement of the AB/FF-treated patients. The overall improvement is based on the weighted standardized improvements between initial and 4-week assessment of the seven outcome indicators, as shown in Figure 1. Using the colour scale shown below the overall improvement picture, colours can be matched to the corresponding values. Values below 0 (green towards blue) indicate a deterioration, whereas values above 0 (green towards red) indicate an overall improvement in the outcomes.

- Patients in *Cluster 6* had significantly larger mean improvements in FEV_1, FVC, sG_{AW} (Table 2), and time spent <1.5 METs (Table 4) compared to placebo; while the mean improvement in FRC was significantly smaller (Table 2).

Cluster Characteristics

Baseline characteristics of the six AB/FF-treated clusters are outlined in Table 5. There were differences in baseline characteristics between the clusters. Patients in *Cluster 5* were somewhat older, had the highest proportion of physically inactive patients (<6000 steps per day), and used more medication during or 15 days prior to the study. Patients in *Clusters 1* and *2* had the worst baseline degree of airflow limitation. Patients in *Cluster 1* also had more static hyperinflation and the lowest CWRT time compared to the remaining AB/FF-treated patients. Patients in *Cluster 4* had the highest CWRT time and spent most time of the day in 1.5–3.0 METs. There were no clinically relevant differences between the patients in *Cluster 3* or *6* versus the patients in the remaining clusters.

Discussion

This is the first study to cluster patients with COPD based on multiple outcomes following four weeks of dual-bronchodilation therapy. It shows that there are differential outcomes across the domains of lung function, exercise capacity and PA following 4 weeks of AB/FF-treatment (summarizing in Table 6). Current baseline characteristics cannot confidently explain these responses to AB/FF-treatment. These results indicate that response to dual-bronchodilation therapy is difficult to predict and outcomes are differential in COPD patients with static lung hyperinflation at the start of

Table 5 Baseline Characteristics by Cluster

	AB/FF (n = 126)	AB/FF						Placebo (n = 124)
		Cluster 1 (n = 19)	Cluster 2 (n = 17)	Cluster 3 (n = 25)	Cluster 4 (n = 21)	Cluster 5 (n = 24)	Cluster 6 (n = 20)	
General characteristics								
% women	38	37	53	24	48	29	45	42
Age, years	63 (8)	61 (8)	64 (8)	62 (9)	62 (6)	66 (9) + ++	62 (8)	62 (8)
BMI, kg/m^2	26.3 (3.4)	26.2 (3.3)	25.8 (3.8)	27.6 (3.0) +	25.2 (3.2)	26.2 (3.9)	26.2 (3.4)	26.1 (3.6)
mMRC dyspnea grade	2.1 (0.3)	2.1 (0.2)	2.1 (0.2)	2.1 (0.3)	2.1 (0.4)	2.1 (0.3)	2.2 (0.4)	2.1 (0.3)
Current smokers, % patients	64	63	59	56	81	58	70	62
Medication used during or pre-treatment, number	5.4 (3.1)	4.8 (2.5)	5.7 (2.4)	5.4 (3.4)	4.6 (2.5)	6.6 (3.9) + ++	4.9 (3.1)	5.1 (3.0)
Types of medication during the study (next to the experimental/placebo)								
Respiratory, % patients	95.2	94.7	94.1	92.0	95.2	100.0	95.0	95.2
Cardiovascular, % patients	59.5	52.6	64.7	52.0	61.9	75.0	50.0	57.3
Anti-depression/anti-anxiety, % patients	9.5	0	11.8	4.0	19.0	16.7	5.0	16.1
Pain/anti-inflammatory, % patients	37.3	26.3	47.1	40.0	28.6	41.7	40.0	38.7
Osteoporosis, % patients	4.8	5.3	5.9	4.0	4.8	4.2	5.0	7.3
Diabetes, % patients	11.9	5.3	5.9	16.0	4.8	20.8	15.0	12.9
Antibiotics, % patients	5.6	5.3	11.8	0.0	4.8	4.2	10.0	2.4
Anti-allergic, % patients	7.9	5.3	5.9	12.0	4.8	8.3	10.0	4
Antacids, % patients	20.6	21.1	11.8	24.0	14.3	25.0	25.0	18.5
Other, % patients	41.3	31.6	58.8	36.0	42.9	37.5	45.0	41.1
Number of exacerbations	0.3 (0.5)	0.4 (0.6)	0.2 (0.4)	0.1 (0.3)	0.5 (0.7) +	0.5 (0.7)	0.2 (0.4)	0.4 (1.1)
Pre-dose spirometry and whole-body plethysmography								
FEV$_1$, liters	1.5 (0.5)	1.2 (0.3) • ••	1.2 (0.3) • ••	1.7 (0.5)	1.7 (0.4) +	1.6 (0.5)	1.6 (0.4)	1.6 (0.5)
FVC, liters	3.3 (0.9)	3.1 (0.9)	2.8 (0.9) • ••	3.5 (1.1)	3.3 (0.8)	3.3 (0.9)	3.5 (0.8)	3.3 (1.0)
FRC, liters	5.0 (1.2)	6.2 (1.7) + ++	5.3 (1.2)	5.1 (0.9)	4.6 (0.9)	4.6 (1.0) •	4.9 (1.0)	4.8 (1.1)
RV, liters	4.2 (1.1)	5.3 (1.5) + ++	4.5 (1.0) ++	4.3 (0.9)	3.6 (0.7) •	3.8 (0.9) •	4.2 (1.0)	4.0 (1.0)
sG$_{aw}$, sec^{-1} kPa^{-1}	0.5 (0.3)	0.4 (0.6)	0.4 (0.2)	0.4 (0.2)	0.6 (0.2)	0.5 (0.2)	0.5 (0.3)	0.5 (0.3)
Exercise-related attributes								
CWRT time, seconds	452 (184)	353 (125) • ••	445 (190)	457 (180)	561 (188) + ++	472 (196)	416 (169)	460 (184)
Resting IC, L	2.4 (0.6)	2.2 (0.6)	2.0 (0.4) •	2.6 (0.7)	2.4 (0.5)	2.5 (0.7)	2.5 (0.5)	2.3 (0.6)
Isotime IC, L	2.4 (0.6)	2.1 (0.6) •	2.0 (0.3) •	2.6 (0.7)	2.6 (0.5)	2.4 (0.7)	2.5 (0.6)	2.3 (0.6)
Post-exercise IC, L	2.4 (0.6)	2.1 (0.6)	2.0 (0.5) •	2.6 (0.7) ++	2.5 (0.5)	2.3 (0.7)	2.4 (0.6)	2.3 (0.6)
Resting SpO$_2$, %	96.5 (1.7)	95.4 (2.2) •	96.3 (1.7)	97.0 (1.3) ++	97.0 (1.6)	96.8 (1.2)	96.2 (1.8)	96.0 (2.4)
Post-exercise SpO$_2$, %	95.1 (2.8)	94.4 (2.2)	95.6 (2.5)	96.2 (2.1) +	95.3 (2.5)	94.5 (2.8)	94.3 (3.8)	95.5 (2.4)

(Continued)

Table 5 (Continued).

	AB/FF (n = 126)	AB/FF						Placebo (n = 124)
		Cluster 1 (n = 19)	Cluster 2 (n = 17)	Cluster 3 (n = 25)	Cluster 4 (n = 21)	Cluster 5 (n = 24)	Cluster 6 (n = 20)	
Resting dyspnea, points	0.7 (1.4)	1.0 (2.0)	0.9 (1.7)	0.6 (1.2)	0.4 (0.9)	0.8 (1.6)	0.6 (1.2)	0.5 (1.1)
Post-exercise dyspnea, points	6.6 (2.7)	6.7 (2.8)	6.9 (2.7)	7.0 (2.6)	6.4 (2.6)	6.5 (2.8)	5.8 (2.9)	5.9 (2.4)
Resting fatigue, points	0.2 (0.7)	0.0 (0.1)	0.2 (0.4)	0.2 (0.6)	0.1 (0.3)	0.4 (1.3)	0.3 (0.8)	0.2 (0.5)
Post-exercise fatigue, points	5.5 (3.0)	5.2 (2.8)	6.1 (3.2)	6.2 (3.3)	5.3 (2.8)	5.7 (2.8)	4.4 (3.0) ••	5.8 (2.3)
Physical activity-related attributes								
D-PPAC amount, points	54 (13)	57 (12)	49 (13)	52 (9)	59 (17)	51 (13)	57 (13)	53 (14)
D-PPAC difficulty, points	69 (14)	68 (13)	66 (16)	71 (16)	73 (14)	65 (13)	73 (12)	71 (14)
VMU, /min	3.2 (1.0)	3.3 (0.9)	3.0 (1.1)	3.0 (0.9)	3.6 (1.2)	3.0 (1.0)	3.4 (1.0)	3.2 (1.1)
Steps per day	6170 (2897)	6631 (3367)	5567 (2551)	5713 (2394)	7136 (3896)	5617 (2616)	6507 (2390)	6184 (3063)
% patients <6000 steps per day	55	39	69	57	56	76 + ++	33 •	49
Time <1.5 METs, min/day	1244 (71)	1245 (60)	1267 (61)	1263 (51)	1203 (107) •	1254 (55)	1231 (74)	1241 (75)
Time <1.5 METs, % of day	86 (5)	86 (4)	88 (4)	88 (4)	84 (7) •	87 (4)	85 (5)	86 (5)
Time 1.5–3.0 METs, min/day	94 (41)	86 (27)	83 (32)	83 (28)	124 (62) + ++	90 (33)	100 (48)	96 (40)
Time 1.5–3.0 METs, % of day	6.5 (2.9)	6.0 (1.9)	5.8 (2.2)	5.8 (1.9)	8.6 (4.3) + ++	6.2 (2.3)	6.9 (3.3)	6.6 (2.8)
Time >3 METs, min/day	102 (39)	109 (45)	91 (35)	95 (34)	113 (52)	96 (32)	109 (34)	103 (48)
Time >3 METs, % of day	7.1 (2.7)	7.6 (3.1)	6.3 (2.4)	6.6 (2.4)	7.8 (3.6)	6.7 (2.2)	7.6 (2.4)	7.2 (3.3)

Notes: • mean baseline value is smaller compared to the mean baseline value of the remaining active-treated patients (P<0.05); •• mean baseline value is smaller compared to the mean baseline value of all placebo-treated patients (P<0.05); + mean baseline value is larger compared to the mean baseline value of the remaining active-treated patients (P<0.05); ++ mean baseline value is larger compared to the mean baseline value of all placebo-treated patients (P<0.05). Clusters 1 to 6 only contain active treated patients.

Abbreviations: AB/FF, aclidinium bromide/formoterol fumarate; BMI, body mass index; mMRC, modified Medical Research Council; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FRC, functional residual volume; RV, residual volume; sG_{AW}, specific airway conductance; sec, seconds; kPa, kilopascal; CWRT, constant work rate test; IC, inspiratory capacity; SpO_2, oxygen saturation; HR, heart rate; bpm, beats per minute; D-PPAC, Daily PROactive Physical Activity in COPD; VMU, vector magnitude units; MET, metabolic equivalents; min, minute.

Table 6 Summarizing Changes in Outcome Indicators per Cluster

Compared to Change in Remaining Experimental Clusters						
	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**
FRC, % baseline improvement	☺	☺	-	☺	☹	☺
FEV1, % baseline improvement	☺	☺	-	☹	☹	-
IC isotime, % baseline improvement	☺	-	-	☹	-	☹
CWRT, s improvement	☺	☹	☺	-	☹	☹
D-PPAC amount, points improvement	☹	☺	☺	☹	☺	☹
Steps per day improvement	-	-	☺	☹	☺	☹
Time >3 METS, % day improvement	-	-	☺	☹	☺	☹
Compared to Change in Placebo Group						
	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**	**Cluster 5**	**Cluster 6**
FRC, % baseline improvement	☺	☺	-	☺	☹	☹
FEV1, % baseline improvement	☺	☺	☺	☺	-	☺
IC isotime, % baseline improvement	☺	☺	☺	-	☺	-
CWRT, s improvement	☺	☹	☺	-	☹	-
D-PPAC amount, points improvement	-	☺	☺	-	☺	-
Steps per day improvement	-	☺	☺	-	☺	-
Time >3 METS, % day improvement	-	☺	☺	-	☺	-

Notes: ☺, significantly better response; ☹, significantly better response; -, comparable response.

the study. Based on the current findings, clinicians do need to consider multiple outcomes simultaneously when evaluating LABD therapy in patients with COPD.

Generally, LABD leads to an improved lung function and exercise capacity in patients with COPD,[6,7,29] although the outcome can vary considerably between patients.[30–32] The current results corroborate these findings (Figure 1; Table 6).

The current analyses show that specific subgroups of patients (eg, *Clusters 1, 2* and *4*) have a significant reduction in FRC after 4 weeks of treatment, which was greater compared to placebo. Clinicians should be aware of this important finding, as in the original ACTIVATE study, there was no significant effect of AB/FF-treatment on FRC compared to placebo.[9] In contrast, patients in Clusters 5 and 6 had a worse change in FRC after four weeks of treatment compared to placebo. In a large observational study, Bhatt et al found that 9% of the COPD patients had a paradoxical lung function (decrease in FEV_1 and/or FVC) response to β2-agonists.[33] This was associated with respiratory morbidity, current smoking and was more common in African-Americans.[33] The mechanisms underlying a paradoxical outcome remain currently unknown.

Patients in *Cluster 4* showed significant improvement in static hyperinflation, but smaller mean improvements in IC at rest, isotime and post-exercise. The IC is the difference between TLC and FRC. Since it is assumed that TLC does not change in reaction to bronchodilator therapy,[34] it is remarkable that IC at rest did not change particularly in these patients. The IC maneuver during exercise might be challenging for COPD patients; however, patients in *Clusters 1, 2* and *3 did* show significant improvements in IC at isotime. It is unclear why this was not shown in patients in *Cluster 4*.

Patients in almost all clusters, except for *Cluster 5*, showed improvement of FEV_1; however, this does not always seem to correlate with reduction of lung volume at rest (Table 2; *Cluster 3, 6*). It has been described that the volume response of short-acting bronchodilators is reduced in patients with mild/moderate COPD, compared to patients with more severe airflow limitation,[35,36] while absolute FEV1 outcome is larger in those with mild/moderate disease.[36] However, baseline FEV_1 in *Clusters 3* and *6* was comparable to other clusters (Table 5), and thus difference in the degree of airflow limitation cannot explain the differential lung volume outcome. Moreover, the differential outcome between flow and volume also cannot be explained by a history of asthma since this was an exclusion criterion of the original study, or differences in medication since subjects in this study all used the same LABD. All studies that investigated these differential outcomes in the lung function domain used short-acting bronchodilation, while long-acting bronchodilation was used in the ACTIVATE study.

Increasing PA in patients with COPD has been challenging,[20] as multiple factors influence PA, including but not limited to fatigue, mobility problems, fear, lack of drive, weather and the impact on breathing, and underestimation of the importance of physical activity.[37] Interestingly, PA did not change in Cluster 1, even though these patients generally had the greatest improvements in lung function and exercise capacity. These patients did report less difficulty, which also seems to be a clinically relevant finding for patients with COPD. It provides further validation of the use of both amount and difficulty when addressing PA experience in patients with COPD. Finally, these data also show that providing optimal pharmacotherapy to patients with COPD will in most cases not be sufficient to also improve exercise capacity and/or physical activity. This is most likely due to extra-pulmonary and behavioral traits that partially determine PA and exercise capacity, which are not treated by respiratory pharmacotherapy.

Patients in *Clusters 2* and *4* showed significant improvements in dynamic and static lung function, which did not transfer to a greater EET. Then again, patients in *Cluster 2* were able to increase their amount of PA. This was also true for patients in *Cluster 5*, who also increased the amount of PA, while the change in lung function, and EET was worse compared to placebo. Patients in *Cluster 3* had significant improvements in the dynamic lung function, but not in FRC, which did result in an increased EET and amount of PA. A non-linear outcome has been reported previously in patients with COPD following pulmonary rehabilitation.[17]

This is the first study to report a detailed non-linear outcome following LABD in patients with COPD. The non-linear outcome of LABD seems unpredictable, as the currently available clinical characteristics shown at baseline overlap between the six Clusters to a great extent. These findings emphasize the clinical complexity of the usual care for patients with COPD.[38] This study shows a differential multidimensional response to LABD in a well-characterized, homogeneous subgroup of patients with COPD and hyperinflation. This study also has limitations. First, because this is a well-characterized subgroup of patients and a specific bronchodilator is used, the generalizability of the results in the general COPD population and other bronchodilators is limited. There was also a lower limit to the FEV_1 in the inclusion, which left out more severe COPD patients, since the researchers did not want to give subjects with very severe COPD a placebo inhaler. However, other inclusion criteria were a notable level of dyspnea (mMRC 2) and hyperinflation (FRC > 120% of predicted), which have been shown to be important factors limiting exercise capacity and PA in patients with COPD. Second, this study showed short-term effects only, and thus exacerbations, possibly the most important outcome, are not assessed, along with other clinically relevant outcomes including levels of dyspnea and quality of life. Third, the sample size is limited, and larger studies assessing multiple outcomes regarding this topic are needed to further establish the variable response of COPD patients to LABDs. Also, the limited sample size withheld us from comparing the clusters head to head. Fourth, these exploratory analyses are hypothesis-generating only, as they were not formulated a priori as an aim of the ACTIVATE study. Lastly, inhaler use errors were not assessed, which obviously do occur in patients with COPD and may, at least partially, explain the current between-group differences.[39] However, the differential outcomes within clusters cannot be explained by this.

In conclusion, the current study profiled the multidimensional outcomes (including lung function, exercise capacity and physical activity) for four weeks of LABD. Patients, healthcare professionals and payers need to start realising that individual patients with COPD respond differently to LABD. To truly understand the impact of LABD in patients with COPD, multiple outcomes have to be considered simultaneously. By assessing just one or two outcomes, clinicians might miss critical information about the LABD therapy response and withhold patients from optimal therapy. Indeed, outcomes may even differ between dynamic and static lung function attributes. Moreover, a significant improvement in lung function attributes does not automatically transfer to an increased exercise capacity and/or physical activity in patients with COPD.

Abbreviation

AB/FF, aclidinium bromide/formoterol fumarate; Bpm, beats per minute; CWRT, Constant Work Rate cycle ergometry Test; COPD, chronic obstructive pulmonary disease; D-PPAC, Daily PROactive Physical Activity in COPD; EET, exercise endurance time; FEV1, forced expiratory volume in the first second; FRC, functional residual capacity; FVC, forced vital capacity; HR, heart rate; IC, inspiratory capacity; kPa, kilopascal; LABDs, long-acting bronchodilators; MET, metabolic equivalents; Min, minute; mMRC, modified Medical Research Council; PA, physical activity; PRO, patient-reported outcome; RV, residual volume; sG_{aw}, specific airway conductance; SOMs, self-organizing maps; SpO_2, peripheral capillary oxygen saturation; VMU, vector magnitude units; W_{max}, peak work rate.

Data Sharing Statement

Scientists who are interested in doing analyses on the ACTIVATE database should go to https://www.mystudywindow.com/completed.

Author Contributions

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

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