Doctor of Medicine

Comparison of the effects of dual bronchodilators with single bronchodilators in group B COPD patients according to the FEV_1 level: patient-level pooled analysis of phase-3 RCTs

Group B 만성폐쇄성폐질환 환자에서
폐기능 수치에 따른 이중기관지확장제와
단일기관지확장제의 효과 비교

The Graduate School of the University of Ulsan
Department of Medicine
Kang, Jieun

Comparison of the effects of dual bronchodilators with single bronchodilators in group B COPD patients according to the FEV_1 level: patient-level pooled analysis of phase-3 RCTs

Supervisor: Yeon-Mok Oh

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Kang Jieun

Department of Medicine
Ulsan, Korea
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This certifies that the dissertation of Kang Jieun is approved

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Committee Chairman Professor Shim Tae Sun

Committee Member Professor Oh Yeon-Mok

Committee Member Professor Lee Sei Won

Committee Member Professor Lee Jae Seung

Committee Member Professor Lee Bo Young

Department of Medicine
Ulsan, Korea
August 2020

Abstract

Rationale: Global initiative for Obstructive Pulmonary Disease (GOLD) consensus document serves as an important reference for clinicians in assessment and management of patients with chronic obstructive pulmonary disease (COPD). The 2017 revised version of the document removed forced expiratory volume at 1 s (FEV_1) from the criteria used in patient grouping, leaving only the severity of symptoms and exacerbation history. To test the hypothesis that lower FEV_1 level (<50%pred.) identifies a population more likely to benefit from dual bronchodilators than single bronchodilator treatment, this study compared the effects of dual and single bronchodilators in group B COPD patients according to the FEV_1 level.

Methods: This study was a patient-level pooled analysis of the phase-3 randomized controlled trials of dual bronchodilators. Individual patient level data were obtained from the available trials provided by sponsor companies. Glycopyrronium/indacaterol, umeclidinium/vilanterol, or tiotropium/olodaterol were the dual bronchodilators of interest. Studies with a parallel-design and duration longer than 8 weeks were included. Data were obtained from ClinicalStudyDataRequest.com. Study outcomes were changes in trough FEV_1, St. George's Respiratory Questionnaire (SGRQ) score, proportion of SGRQ responders, rate of acute exacerbation, time to first exacerbation, and a risk of adverse events.

Results: A total of 12 studies were included in this pooled analysis. Among patients in the 2017 GOLD group B, 8043 had FEV_1 less than 50% of the predicted value (%pred.) and 6406 had FEV_1 ≥50%pred. Dual bronchodilator treatment was significantly effective than long-acting beta-2 agonist (LABA) or long-acting muscarinic antagonist (LAMA) in improving trough FEV_1, regardless of the baseline FEV_1 level. In patients with FEV_1 <50%pred., dual bronchodilator treatment consistently showed a significant association with a greater reduction in SGRQ scores and proportion of SGRQ responder regardless of the comparator; however, in patients with FEV_1 ≥50%pred., dual bronchodilator treatment was only better than LAMA, not LABA. Time to first exacerbation was significantly longer with dual bronchodilators compared with LABA in patients with FEV_1 <50%pred.; but there was no difference between dual bronchodilators and single bronchodilators in patients with FEV_1 ≥50%pred. The risk of adverse events was similar between dual and single bronchodilator treatment.

Conclusions: In conclusion, the benefit of dual bronchodilators over single bronchodilators were consistently significant in improving FEV_1 and health-related quality of life without increasing the risk of adverse events in GOLD group B COPD patients with FEV_1 <50%pred. Patients with lower FEV_1 may be the population who are likely to benefit from more intensive treatment.

Keywords: bronchodilator; chronic obstructive pulmonary disease; forced expiratory volume at 1 s.

Contents

List of tables and figures

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major causes responsible for chronic morbidity and mortality worldwide.[1-3] It is characterized by irreversible airflow limitation and respiratory symptoms such as cough, sputum, and dyspnea.[4] Global initiative for Obstructive Lung Disease (GOLD) consensus document on COPD, is not a clinical guideline, but serves as an important reference for clinicians in assessment and management of patients with COPD.[5] While its update is released annually, substantial revisions are made in every few years. In the previous version of GOLD document, COPD patients were divided into stages 1–4 based on the severity of airflow limitation (forced expiratory volume at 1 second [FEV_1]).[6] Given that FEV_1 reflects only one aspect of COPD,[7] GOLD introduced a new classification system in 2011, an A-B-C-D grouping. In addition to FEV_1, it incorporated the degree of respiratory symptoms, represented by modified British Medical Research Council (mMRC) grade or COPD assessment test (CAT) score, and the number of acute exacerbations in the previous year.[5, 8, 9] Initial treatment recommendations were also provided for each A-B-C-D group.[9]

In 2017, GOLD report underwent a major revision by removing FEV_1 from the classification criteria leaving only the symptom level and exacerbation history.[10] Following the change, some patients who belonged to a high-risk group (C or D) due to FEV_1 <50% of the predicted value (%pred.) are now classified as a low-risk group (A or B). It has been shown that this change occurred in a considerable proportion of COPD patients. López et al. showed in their study that GOLD 2017 decreased the proportion of patients in group D by about one-half (24.4% to 11.7%) and increased the proportion of group B (14.0% to 26.7%).[11] In another study, Faner et al. also found that a substantial proportion of patients in group D decreased (from 40.0 to 15.0%) due to relocation to B.[12]

The change in patient disposition may lead to a different choice of initial treatment regimen. Among 2017 GOLD group B patients, those with FEV_1 less than 50%pred. would have been classified as group D and have received treatment accordingly, if the 2011 criteria were applied. However, they are now classified as group B and the first choice of treatment for them is a single bronchodilator, either long-acting beta-2 agonist (LABA) or long-acting

muscarinic antagonist (LAMA). It has not been determined whether the treatment difference between single and dual bronchodilators are considerable among patients with broad range of airflow limitation. To test the hypothesis that lower FEV_1 level (<50%pred.) identifies a population more likely to benefit from dual bronchodilators than single bronchodilator treatment, this study compared the effects of dual and single bronchodilators in group B COPD patients according to the FEV_1 level (<50%pred. vs. ≥50%pred.).

Materials and Methods

Data sources

This study was a patient-level pooled analysis of the phase-3 randomized controlled trials that evaluated the efficacy of dual bronchodilators compared with single bronchodilators. We obtained the individual patient level data from the available trials provided by sponsor companies. Glycopyrronium/indacaterol (Ultibro Breezehaler, Novartis), umeclidinium/vilanterol (Anoro Ellipta, GSK), and tiotropium/olodaterol (Spiolto Respimat, Boehringer-Ingelheim) were the dual bronchodilators of interest.

Individual patient level data of the clinical trials are open to outside researchers through ClinicalStudyDataRequest.com (CSDR). CSDR is a consortium of global pharmaceutical companies including GlaxoSmithKline, Astellas Pharma, Bayer, Novartis, Roche, and Sanofi, as well as academic research funders including The Bill & Melinda Gates Foundation, The UK Medical Research Council, and The Wellcome Trust.[13)] It was launched in 2013 to facilitate data sharing among independent investigators[13, 14)] by providing deidentified raw data of global clinical trials from multiple sponsors.[15)]

To gain access to the patient-level data from CSDR, a study proposal which include a list of the clinical trials that a researcher wishes to obtain as well as the purpose of the study should be submitted via a web-based portal. Availability of the clinical trial data that are not listed on the CSDR website can be inquired to the responsible sponsors. The study proposal is reviewed by an Independent Review Panel for scientific importance and qualification of the research team. Once accepted after the review, researchers are provided with the access to the deidentified data. Analysis of the data is only possible in a closed system provided by CSDR with in-built SAS (SAS Institute, Cary, NC) and R (R Foundation, Austria) statistical software and it is not feasible to download the raw data outside of the closed system. In addition, data outside of CSDR cannot be merged with the data provided by CSDR.

Eligibility criteria

Data of phase-3 randomized controlled trials that evaluated the efficacy of dual bronchodilators (glycopyrronium/indacaterol, umeclidinium/vilanterol, and

tiotropium/olodaterol) in COPD patients meeting the following criteria were requested to the sponsor companies: 1) comparison between dual and single bronchodilators with/without a placebo arm, 2) parallel design, 3) study duration longer than 8 weeks, and 4) study outcomes including any of the following: changes in trough FEV_1, St. George's Respiratory Questionnaire (SGRQ), risk of acute exacerbation, or adverse events. Studies were excluded if 1) the comparator was not relevant to the study purpose (e.g., comparison between dual and inhaled corticosteroid (ICS)/LABA; 2) the dual bronchodilator was not given as a fixed dose combination; 3) the study was performed on patients who were not responsive to monotherapy; and 4) data regarding baseline symptom levels (mMRC grade, CAT or SGRQ score) and previous exacerbation were not adequately addressed. We submitted the study proposal to CSDR on March 15, 2018 and gained access to the requested data on January 2, 2019.

Study outcomes

The outcomes of this pooled analysis included a change in trough FEV_1, change in SGRQ score, proportion of SGRQ responder, rate of acute exacerbation, time to first exacerbation, and the risk of adverse events. A change in trough FEV_1 was the difference between pre-dose FEV_1 values at baseline and at the end of each study. SGRQ responder was defined as a patient who achieved the minimum clinically important difference (MCID) threshold of 4 points. The incidence rate of acute exacerbation was estimated for 6 months.

Statistical analysis

For summing up individual patient level data, generalized linear mixed model using stratified study-effect or random study-effects. For continuous variable such as change in trough FEV_1, FEV_1 % of the predicted, SGRQ score from baseline, mean number of exacerbations, linear mixed model with random effect was applied with adjusted multiple treatment comparison. The least squares mean change from baseline values for each treatment group were reported with their associated standard errors and 95% confidence interval (CI). For binary data, generalized linear mixed model using Penalized Quasi-likelihood estimation. Odds ratio and 95% confidence interval were estimated for binary data. Cox's proportional hazard model with random effect was used to summarize time to first exacerbation data. the hazard ratio (HR)

and the corresponding 95% CI was estimated. All analyses were performed using the Statistical Analysis System (SAS) statistical software package, version 9.4. SAS Institute Inc., Cary, NC, USA.

Results

Characteristics of the included studies

A total of 12 randomized controlled trials were included in this study. All studies shared common inclusion criteria; patients were diagnosed with COPD by spirometry (post-bronchodilator FEV_1/forced vital capacity <0.7), aged 40 years or older, and with smoking history of more than 10 pack-years. The baseline characteristics of the patients (excluding placebo arms) included in the 12 studies and the types of study endpoints are described in Table S1 and Table S2. All studies measured trough FEV_1 and recorded the development of adverse events. SGRQ and acute exacerbation were evaluated in 8 and 10 studies, respectively.

Baseline characteristics of GOLD group B patients

From the 12 studies, 20204 patients who received either dual bronchodilator or single bronchodilator were identified. As shown in Table 1, a total of 14449 patients were classified as GOLD group B based on the 2017 revised classification criteria. Among them, 55.7% (n = 8043) had FEV_1 less than 50%pred. meeting the criteria for 2011 GOLD group D.

Baseline clinical characteristics of 2017 GOLD group B patients and those according to the FEV_1 level are shown in Table 2. The mean ages were 48.6 and 44.3 years in patients with FEV_1 ≥50%pred. and FEV_1 <50%pred., respectively. Mean FEV_1 values were 1.5 L (54.6%pred.) and 1.0 L (35.1%pred.), respectively. In both groups, tiotropium/olodaterol was the most frequently used dual bronchodilator followed by umeclidinium/vilanterol. Among single bronchodilators, tiotropium was most commonly used in both groups.

Trough FEV_1 changes

Changes in trough FEV_1 from baseline according to treatment are shown in Table 3. Regardless of the baseline FEV_1 level, dual bronchodilator treatment showed greater FEV_1 improvement compared with LABA or LAMA monotherapy.

Table 4 and Fig. 1 show the least squares mean (LSM) differences between dual and single bronchodilators in change from baseline in FEV_1. Regardless of the baseline FEV1, dual bronchodilator treatment showed significantly greater FEV_1 improvement from baseline

Table 1. Number of patients according to the 2011 and 2017 GOLD classification

	2017 GOLD A	2017 GOLD B	2017 GOLD C	2017 GOLD D	Total
2011 GOLD A	994 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	994 (4.9)
2011 GOLD B	0 (0.0)	6406 (31.7)	0 (0.0)	0 (0.0)	6406 (31.7)
2011 GOLD C	667 (3.3)	0 (0.0)	358 (1.8)	0 (0.0)	1025 (5.1)
2011 GOLD D	0 (0.0)	8043 (39.8)	0 (0.0)	3736 (18.5)	11779 (58.3)
Total	1661 (8.2)	14449 (71.5)	358 (1.8)	3736 (18.5)	20204 (100.0)

Data are presented as number (%).

GOLD, Global initiative for Obstructive Lung Disease.

Table 2. Baseline characteristics of GOLD group B patients according to the FEV_1 level

	All	FEV_1 ≥50%pred.	FEV_1 <50%pred.
Number of patients	14449	6406	8043
Age	64.7 ± 8.6	64.6 ± 8.9	64.7 ± 8.4
Male	9853 (68.2)	4139 (64.6)	5821 (70.9)
Current smoker	5305 (36.7)	2929 (45.7)	3455 (42.1)
Smoking pack-years	46.2 ± 22.2	48.6 ± 22.0	44.3 ± 22.2
Body mass index	26.8 ± 5.8	27.4 ± 5.8	26.3 ± 5.8
FEV_1, L	1.2 ± 0.5	1.5 ± 0.4	1.0 ± 0.3
FEV_1, %pred.	43.8 ± 13.5	54.6 ± 9.2	35.1 ± 9.3
No of acute exacerbation in the preceding year			
0	12331 (85.3)	5307 (82.9)	6471 (80.5)
1	2118 (14.7)	1099 (17.2)	1572 (19.5)
≥2	0 (0.0)	0 (0.0)	0 (0.0)
Treatment			
Tiotropium/olodaterol	4528 (31.3)	2018 (31.5)	2510 (31.2)
Umeclidinium/vilanterol	1487 (10.3)	691 (10.8)	796 (9.9)
Glycopyrronium/indacaterol	791 (5.5)	299 (4.7)	492 (6.1)
Tiotropium	4869 (33.7)	2218 (34.6)	2651 (33.0)
Glycopyrronium	469 (3.2)	171 (2.7)	298 (3.7)
Umeclidinium	522 (3.6)	233 (3.6)	289 (3.6)
Indacaterol	624 (4.3)	213 (3.3)	411 (5.1)
Olodaterol	658 (4.6)	327 (5.1)	331 (4.1)
Vilanterol	501 (3.5)	236 (3.7)	265 (3.3)

Data are presented as means ± SD or number (%).

GOLD, Global initiative for Obstructive Lung Disease; FEV_1, forced expiratory volume at 1 s; %pred., % of the predicted value.

Table 3. Magnitude of improvement in trough FEV_1 from baseline

	Treatment difference from baseline (mL)			
	LABA	LAMA	Single	Dual
FEV_1 ≥50%pred.	74 ± 232	88 ± 239	81 ± 234	150 ± 234
FEV_1 <50%pred.	62 ± 208	81 ± 209	71 ± 210	147 ± 209

Data are presented as means ± SD.

LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

Table 4. Treatment differences between dual and single bronchodilators in change from baseline in FEV_1 (mL)

	Dual vs. LABA		Dual vs. LAMA		Dual vs. Single	
	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p
FEV_1 ≥50%pred.	76 (49 – 102)	<0.001	61 (42 – 81)	<0.001	61 (42 – 81)	<0.001
FEV_1 <50%pred.	85 (64 – 106)	<0.001	66 (49 – 83)	<0.001	66 (49 – 83)	<0.001

LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

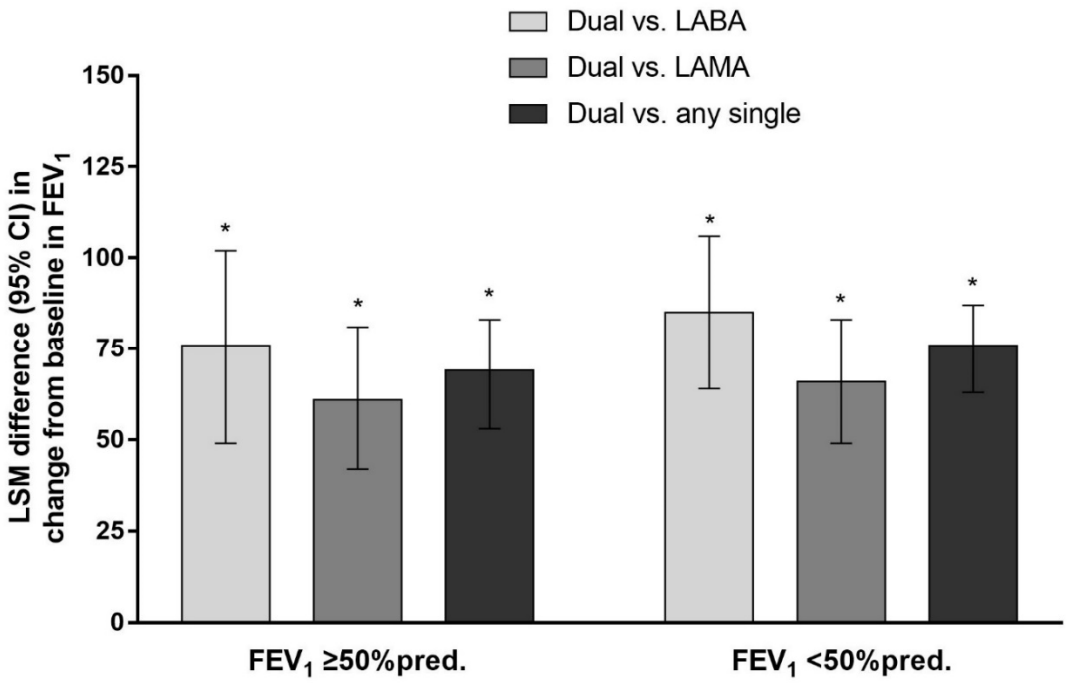

Fig 1. Treatment in change from baseline in FEV_1

FEV_1, forced expiratory volume at 1 s; LSM, least squares mean; CI, confidence interval; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

compared with LABA, LAMA, or any single bronchodilator treatment (all p<0.001).

SGRQ

All bronchodilator treatment achieved a reduction in SGRQ score greater than MCID of 4 points. (Table 5). However, greater reduction was shown with dual bronchodilator treatment than LABA or LAMA monotherapy. When analyzed according to the baseline FEV_1 level, in patients with FEV_1 ≥50%pred., the treatment difference was significant between dual bronchodilator treatment and LAMA (-1.1; 95% CI, -2.2 – 0.0; p = 0.048) but not significant between dual and LAMA (-0.3; 95% CI, -1.8 – 1.2; p = 0.868) as shown in Table 6 and Fig. 2. In patients with FEV_1 <50%pred., dual bronchodilator treatment was consistently more effective than single bronchodilator treatment regardless of the comparator; the treatment differences between dual bronchodilator and LABA (-2.1; 95% CI, -3.5 – -0.7; p<0.001) or dual bronchodilator and LAMA (-1.8; 95% CI, -2.9 – -0.7; p<0.001) were significantly larger than observed in those with FEV_1 ≥50%pred.

Fig. 3 and Fig. 4 shows the difference in the proportion of SGRQ responders according to the FEV_1 level. In patients with FEV_1 ≥50%pred., the proportion of SGRQ responders was significantly different between dual bronchodilator treatment and LAMA monotherapy but not between dual bronchodilator and LABA monotherapy. In patients with FEV_1 <50%pred., the differences in the proportion of SGRQ responders were consistently greater with dual bronchodilator treatment than LAMA or LABA monotherapy.

Acute exacerbation

Regarding exacerbation rates, there were no significant differences between LABA, LAMA, and dual bronchodilator treatment irrespective of the FEV_1 level (Table 7). In patients with FEV_1 <50%pred., time to first exacerbation was found to be significantly longer with dual bronchodilator treatment than with LABA monotherapy (HR, 1.331; 95% CI, 1.113 – 1.544; p = 0.001) whereas no significant difference was found compared with LAMA (Fig. 5). In patients with FEV_1 ≥50%pred., there was no significant difference between dual and single bronchodilator treatment, either LABA or LAMA, although there was a favorable trend for dual bronchodilator treatment over LABA monotherapy (HR, 1.236; 95% CI, 0.998 – 1.532;

Table 5. Magnitude of reduction in SGRQ scores from baseline

	Treatment difference from baseline			
	LABA	LAMA	Single	Dual
FEV_1 ≥50%pred.	-6.8 ± 12.5	-6.0± 12.9	-6.3± 12.8	-7.2 ± 12.5
FEV_1 <50%pred.	-5.5 ± 12.8	-5.9 ± 12.8	-5.7 ± 12.8	-7.6 ± 12.1

SGRQ, St. George's Respiratory Questionnaire; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

Table 6. Treatment differences between dual and single bronchodilators in change from baseline in SGRQ scores

	Dual vs. LABA		Dual vs. LAMA		Dual vs. Single	
	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p
FEV_1 ≥50%pred.	-0.3 (-1.8 – 1.2)	0.868	-1.1 (-2.2 – -0.0)	0.048	-0.9 (-1.73 – -0.07)	0.032
FEV_1 <50%pred.	-2.1 (-3.5– -0.7)	0.001	-1.8 (-2.9 – -0.7)	<0.001	-1.9 (-2.68 – -1.09)	<0.001

LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

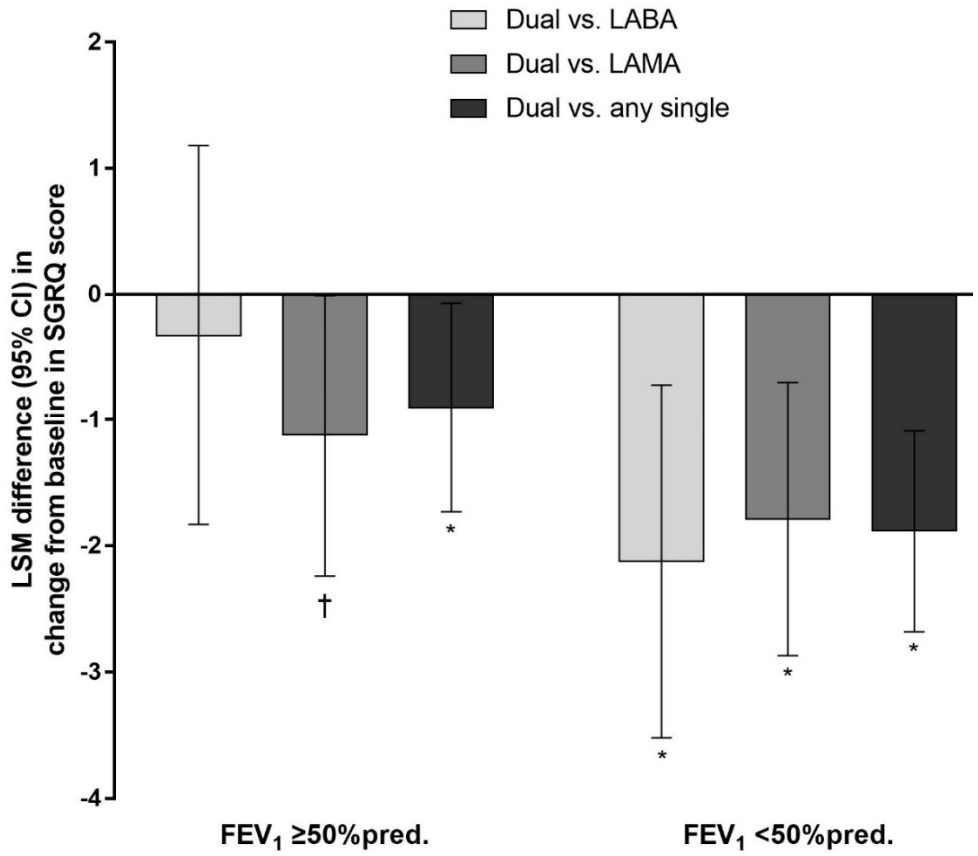

Fig. 2. Treatment difference in change from baseline in SGRQ score

SGRQ, St. George's Respiratory Questionnaire; LSM, least squares mean; CI, confidence interval; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

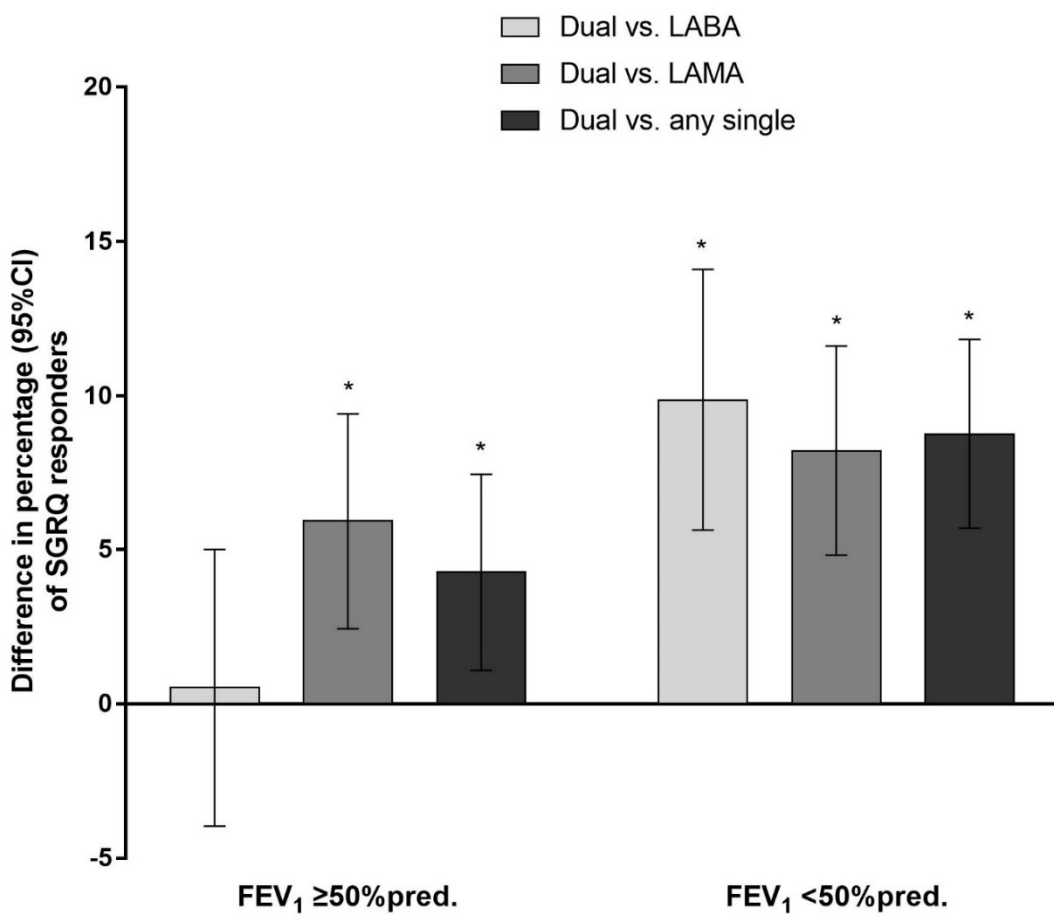

Fig. 3. Difference in percentage of SGRQ responders

SGRQ, St. George's Respiratory Questionnaire; CI, confidence interval; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

FEV_1	LABA	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	385	1080	1.479 (1.234 – 1.774)	0.013
≥50%pred.	375	992	1.082 (0.890 – 1.316)	0.544
FEV_1	LAMA	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	792	1080	1.429 (1.241 – 1.645)	0.020
≥50%pred.	763	992	1.311 (1.136 – 1.514)	0.001
FEV_1	Single	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	1177	1080	1.444 (1.269 – 1.644)	<0.001
≥50%pred.	1138	992	1.244 (1.089 – 1.421)	0.001

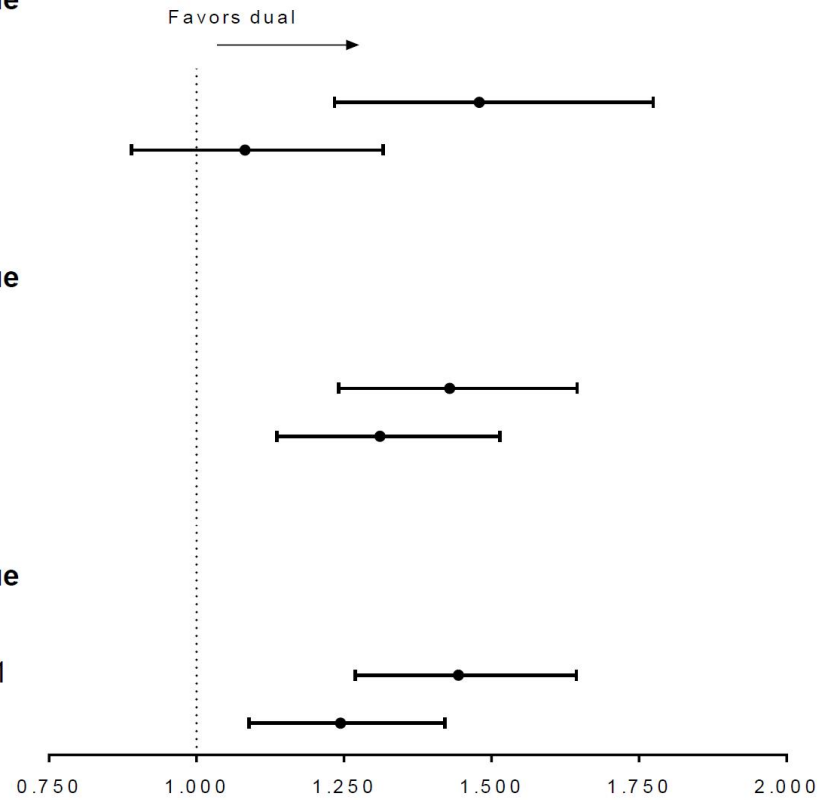

Fig. 4. Odds ratio for SGRQ responder rate according to FEV_1 level

SGRQ, St. George's Respiratory Questionnaire; FEV_1, forced expiratory volume at 1 s; LABA, long-acting beta-2 agonist; CI, confidence interval; LAMA, long-acting muscarinic antagonist.

Table 7. Treatment differences between dual and single bronchodilators in estimated exacerbation rates per 6 months

	Dual vs. LABA		Dual vs. LAMA		Dual vs. Single	
	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p	Treatment difference (95% CI)	p
FEV_1 ≥50%pred.	0.0 (-0.1 – 0.0)	0.176	0.0 (0.0 – 0.0)	0.459	0.0 (0.0 – 0.0)	0.086
FEV_1 <50%pred.	0.0 (-0.1– 0.0)	0.194	0.0 (0.0 – 0.0)	0.625	0.0 (0.0 – 0.0)	0.141

LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume at 1 s.

FEV_1	LABA	Dual	Hazard ratio (95% CI)	p-value
	n	n		
<50%pred.	1007	3798	1.311 (1.113 – 1.544)	0.001
≥50%pred.	776	2618	1.236 (0.998 – 1.532)	0.053
FEV_1	LAMA	Dual	Hazard ratio (95% CI)	p-value
	n	n		
<50%pred.	3238	3798	1.070 (0.983 – 1.164)	0.118
≥50%pred.	2418	2618	1.079 (0.963 – 1.210)	0.191
FEV_1	Single	Dual	Hazard ratio (95% CI)	p-value
	n	n		
<50%pred.	4245	3798	1.100 (1.015 – 1.193)	0.020
≥50%pred.	3194	2618	1.100 (0.986 – 1.228)	0.088

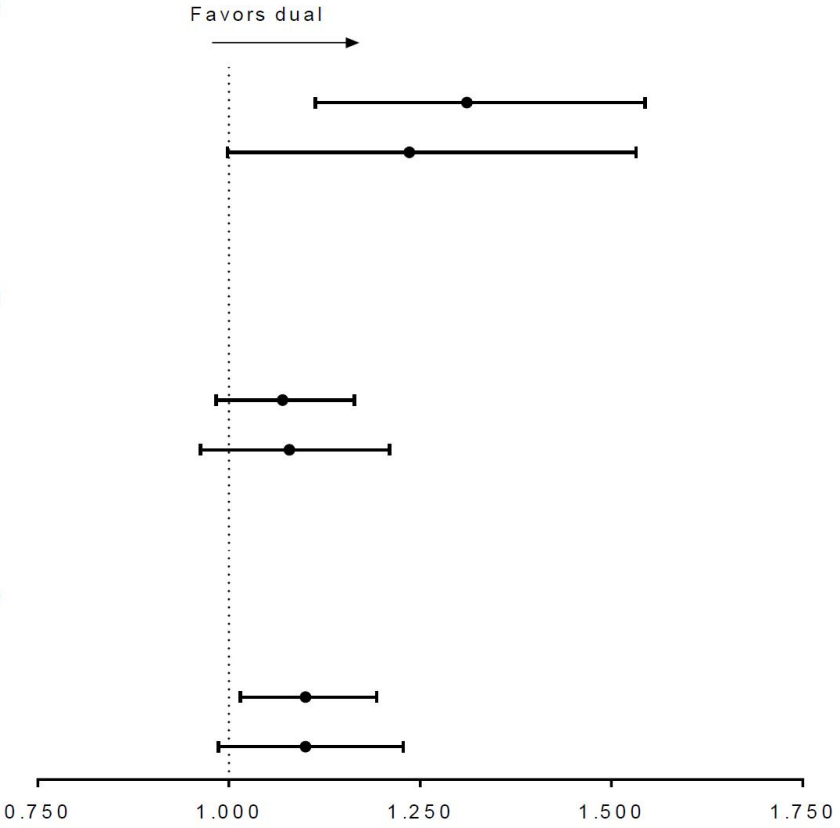

Fig. 5. Hazard ratio for time to first exacerbation according to FEV_1 level

FEV_1, forced expiratory volume at 1 s; LABA, long-acting beta-2 agonist; CI, confidence interval; LAMA, long-acting muscarinic antagonist.

p = 0.053).

Adverse events

There was no significant difference in the risk of any adverse events between dual and single bronchodilator treatment in both patients with FEV_1 <50%pred. and ≥50%pred. (Fig. 6).

FEV_1	LABA	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	1007	3798	0.932 (0.792 – 1.097)	0.466
≥50%pred.	776	3238	1.017 (0.847 – 1.221)	0.847

FEV_1	LAMA	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	3238	3798	0.977 (0.880 – 1.084)	0.843
≥50%pred.	2622	3008	1.071 (0.955 – 1.200)	0.346

FEV_1	Single	Dual	Odds ratio (95% CI)	p-value
	n	n		
<50%pred.	4245	3798	0.967 (0.876 – 1.066)	0.497
≥50%pred.	3398	3008	1.059 (0.952 – 1.179)	0.291

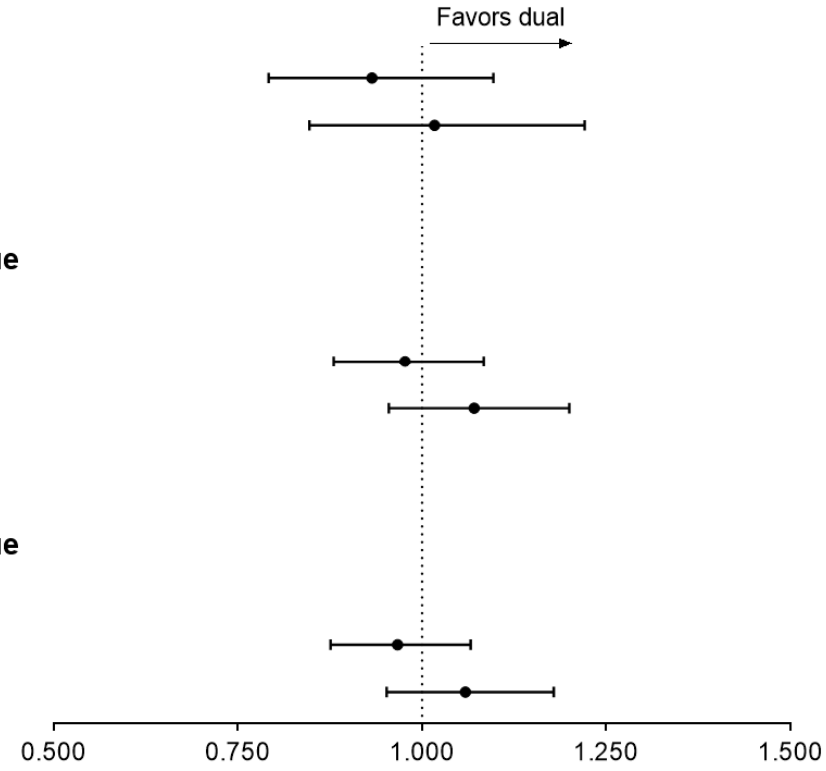

Fig. 6. Odds ratio for the development of any adverse events according to FEV_1 level

FEV_1, forced expiratory volume at 1 s; LABA, long-acting beta-2 agonist; CI, confidence interval; LAMA, long-acting muscarinic antagonist.

Discussion

This study compared the effects of dual and single bronchodilators according to the FEV_1 level in GOLD group B patients to determine whether patients with FEV_1 of less than 50%pred. are more likely to benefit from dual bronchodilators than those with FEV_1 ≥50%pred. Dual bronchodilators were significantly associated with greater FEV_1 improvement irrespective of the baseline FEV_1. Regarding health-related quality of life, dual bronchodilators were more effective than single bronchodilators; but the magnitude of treatment difference was more prominent in patients with FEV_1 <50%pred.

Patients' symptom severity represented as mMRC grade or CAT score and the number of exacerbations in the preceding year are the two criteria that classify COPD patients according to the revised GOLD report. The criteria reflect heterogeneity of COPD patients better than FEV_1 alone. However, there are also limitations of these criteria. The number of acute exacerbations in the previous year is used as one of the grouping criteria because the history of exacerbation is an important predictor for a future risk of exacerbation.[16] However, the number of exacerbations may have annual variability in frequency.[17] Donaldson et al. evaluated stability of the exacerbation frequency in 1823 COPD patients who had follow-up data of 2 years or more. They categorized patients as a frequent exacerbator (≥ 2 per year) or infrequent exacerbator (0 or 1 per year) based on the number of exacerbations in the first year. Approximately 24% of the patients moved to a different category from the initial one in the second year. In 17% of the patients categorized as infrequent exacerbators, it was changed to frequent exacerbators in the following year. Given that patients with poor lung function have an increased risk of exacerbation,[18, 19] risk stratification by exacerbation history may change year by year and is not sufficient enough to capture all patients at risk. Another limitation is that considerable number of exacerbations are unreported.[20, 21] In the study of Langsetmo et al., patients were asked to contact the study center when they have a sustained (at least 24 hours) worsening of any symptoms.[20] Patients were also asked to record symptom changes and rescue medication use in diary every day. The study found that only less than one-third of exacerbations were reported to the study center. In addition, patients with poor lung function may underestimate the severity of symptoms by reducing their activity level, as the GOLD

document acknowledged.[10] Therefore, there is a possibility that the current criteria underestimate the risk of patients by utilizing somewhat subjective criteria.

The number of patients relocated from group D to B in our study was 8043 accounting for 55.7% of the 2017 GOLD B group. Such shift of a substantial proportion of patients was consistent with several previous reports.[11, 22-26] Tudoric et al. analyzed data from a study which included 3361 COPD patients in central and eastern European countries.[22] They reported that 20.4% of the entire cohort moved from group D to group B according to the revised classification. In another study where 1053 COPD patients were retrospectively analyzed in Taiwan, the proportion of group D decreased by greater than half (from 34.2% to 11.6%) whereas group B increased from 40.6% to 63.2%.[24] These relocated patients are those who were classified as group D solely by FEV_1. It has been shown that there are more patients who are classified as group D by FEV_1 than by frequent exacerbation history in large COPD cohorts such as ECLIPSE, Copenhagen, and COPD gene cohort.[27, 28] Considering these findings together, GOLD group B now includes substantial proportion of patients with FEV_1 <50%pred. following the 2017 revision of the classification criteria, although there are differences in number depending on the cohorts or regions.

Group B patients according to the revised A-B-C-D classification was shown associated with a higher mortality risk than group C patients.[29] This may be partly due to the fact that patients with severe airflow limitation moved to group B from D. Patients relocated to group B are those with lower lung function and may benefit from a more intensive treatment. Although mortality outcome was not measured in our study, it appeared that patients with FEV_1 <50%pred. were more likely to benefit from dual bronchodilator treatment than those with higher lung function in terms of patients' health-related quality of life. The treatment difference between dual and single bronchodilators was more noticeable in patients with FEV_1 less than 50%pred. The absolute change of SGRQ score achieved with dual bronchodilators vs. LABA or LAMA was greater and the proportion of SGRQ responders was also numerically greater in patients with FEV_1 <50%pred. The findings suggest that patients with lower lung function are more likely to benefit from more intensive treatment than single bronchodilator treatment with regard to health-related quality of life; however, the 2017 GOLD revision does not take FEV_1 into account in deciding the treatment. The treatment strategy that GOLD

recommends in group B patients is basically a step-up approach from a single bronchodilator, either LABA or LAMA, to a dual bronchodilator. However, it is important to note that many patients require a subsequent step-up treatment. Wurst el al. found that nearly half of the patients who had started treatment with either a LABA or LAMA required additional bronchodilator within 24 months.[30] This finding may suggest that some patients classified as a low risk group need more intensive treatment than currently recommended from the beginning.

The difference between dual and single bronchodilator treatment regarding the exacerbation rate was not significantly different. However, time to first exacerbation appeared to be longer with dual bronchodilators than with LABA monotherapy. Particularly in patients with FEV_1 <50%pred., the time to first exacerbation was significantly longer with dual bronchodilators. Our study patients were those with a low risk of exacerbation according to the GOLD classification criteria. Therefore, it might have been difficult to demonstrate a difference in the exacerbation rate between dual and single bronchodilator treatment. However, dual bronchodilator treatment may be more effective than LABA monotherapy in preventing acute exacerbation in patients with FEV_1 <50%pred.

To understand the results of our study correctly, limitation should be addressed. First of all, this study included the phase-3 randomized controlled trials that are sponsored by pharmaceutical companies and there is an issue that pharmaceutical industry sponsored trials tend to report favorable outcomes with their products.[31] However, this may not be true in all cases; although excluded from our analysis, SPARK study, sponsored by Novartis, did not find superiority of glycopyrronium/indacaterol over tiotropium in reducing the risk of acute exacerbation.[32] Similarly, DYNAGITO study which aimed to demonstrate the efficacy of tiotropium/olodaterol versus tiotropium in reducing the risk of acute exacerbation failed to meet the predefined statistical significance.[33] Second, studies that evaluated efficacy of aclidinium/formoterol (Duaklir Genuair, AstraZeneca) and glycopyrronium/formoterol (Bevespi Aerosphere, AstraZeneca), other dual bronchodilators available in clinical practice, were not included in this study. The corresponding pharmaceutical company (AstraZeneca) was not part of CSDR and their data were not available from the system. Further, there is a concern that twice-daily medications may differ in efficacy from once-daily bronchodilators;[34]

in fact, FEV_1 improvement with aclidinium/vilanterol seemed to be far less than glycopyrronium/indacaterol and umeclidinium/vilanterol in a meta-analsysis.[35] Third, only one study (DYNAGITO) evaluated acute exacerbation risk as a primary outcome among the included studies. Although 9 of 12 studies provided data regarding the development of acute exacerbation, except for DYNAGITO, they were not powered for this outcome. Of note, DYNAGITO included the greatest number of patients among the included 12 studies and the results regarding acute exacerbation might have been derived largely from DYNAGITO. Lastly, cost-effectiveness of dual bronchodilators was not assessed in this study. However, several previous studies have found that dual bronchodilators are cost-effective in COPD patients.[36-38] Hoogendoorn et al. found that tiotropium/olodaterol resulted in an increase in quality-adjusted life-years and savings in costs compared with tiotropium alone.[38] Particularly in South Korea, the costs are almost similar between dual and single bronchodilators, further supporting the use of dual bronchodilators.

In conclusion, we found that the benefit of dual bronchodilators over single bronchodilators were consistently significant in improving FEV_1 and health-related quality of life without increasing the risk of adverse events in GOLD group B COPD patients with FEV_1 <50%pred. The magnitude of treatment difference with regards to SGRQ was also greater in those with FEV_1 <50%pred. Considering that group B patients with severe and very severe airflow limitation are subject to a single bronchodilator treatment following the 2017 GOLD revision, a better strategy is needed to recommend more intensive treatment in this group.

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Appendix

Table S1. Baseline characteristics of the patients (excluding placebo arms) included in the 12 studies

NCT numbers	Intervention	No. of patients	Age, years	Male	BMI, kg/m^2	FEV_1, L	FEV_1, %pred.	Current smoker	F/U period
NCT01727141	GLY/IND	260	64.3 ± 10.8	170 (65.4)	27.2 ± 4.9	1.3 ± 0.4	46.1 ± 13.1	126 (48.5)	12 w
	GLY	261	63.7 ± 10.3	183 (70.1)	27.7 ± 5.2	1.3 ± 0.5	44.9 ± 13.4	131 (50.2)	
	IND	260	63.9 ± 10.2	186 (71.5)	27.6 ± 5.2	1.3 ± 0.5	45.2 ± 13.3	130 (50.0)	
NCT01712516	GLY/IND	250	63.6 ± 9.2	1154 (61.6)	27.2 ± 4.9	1.3 ± 0.5	45.0 ± 12.6	132 52.8	12 w
	GLY	251	63.6 ± 8.8	144 (57.4)	27.6 ± 5.7	1.3 ± 0.5	45.7 ± 13.3	137 (54.6)	
	IND	251	63.1 ± 9.2	150 (59.8)	27.7 ± 5.2	1.3 ± 0.5	45.7 ± 13.2	136 (54.2)	
NCT01682863	GLY/IND	347	64.7 ± 8.1	220 (63.6)	–	1.2 ± 0.5	45.1 ± 12.7	167 (48.3)	56 w
	IND	172	63.1 ± 9.0	127 (73.8)	–	1.3 ± 0.5	43.8 ± 11.7	85 (49.4)	
NCT01777334	UMEC/VI	454	61.9 ± 8.5	310 (68.3)	27.9 ± 5.9	1.3 ± 0.5	41.5 ± 12.6	270(59.5)	24 w
	TIO	451	62.7 ± 8.5	303 (67.2)	26.8 ± 5.5	1.3 ± 0.5	41.5 ± 12.6	243 (53.9)	
NCT01316900	UMEC/VI	426	63.0 ± 8.8	299 (70.2)	26.9 ± 5.7	1.3 ± 0.5	43.3 ± 13.4	222 (52.1)	24 w
	TIO	208	62.6 ± 9.4	140 (67.3)	27.6 ± 5.5	1.3 ± 0.5	43.8 ± 13.6	99 (47.6)	
	VI	209	63.2 ± 9.1	143 (68.4)	27.4 ± 5.7	1.3 ± 0.5	43.7 ± 13.3	106 (50.7)	
NCT01313650	UMEC/VI	413	63.1 ± 8.7	305 (73.9)	27.3 ± 6.0	1.3 ± 0.5	42.8 ± 13.3	203 (49.2)	24 w
	UMEC	418	63.9 ± 9.1	298 (71.3)	26.5 ± 5.6	1.2 ± 0.5	41.9 ± 13.6	207 (49.5)	
	VI	421	62.7 ± 8.5	285 (67.7)	26.6 ± 5.9	1.2 ± 0.5	42.6 ± 13.4	199 (47.3)	
NCT01316913	UMEC/VI	432	64.4 ± 8.6	288 (66.7)	26.6 ± 5.9	1.2 ± 0.5	42.0 ± 13.5	188 (43.5)	24 w
	UMEC	222	64.5 ± 8.3	148 (66.7)	26.5 ± 5.7	1.1 ± 0.5	40.7 ± 12.7	98 (44.1)	
	TIO	215	65.2 ± 8.3	153 (71.2)	26.4 ± 6.1	1.2 ± 0.4	42.0 ± 13.5	102 (47.4)	
NCT02296138	TIO/OLO	3951	66.5 ± 8.4	2793 (70.7)	26.3 ± 5.9	1.2 ± 0.4	46.4 ± 17.1	1443 (36.5)	52 w
	TIO	3952	66.3 ± 8.5	2848 (72.1)	26.2 ± 5.8	1.2 ± 0.4	45.7 ± 11.9	1486 (37.6)	
NCT01964352	TIO/OLO	406	64.7 ± 8.5	230 (56.7)	27.2 ± 5.6	1.3 ± 0.5	48.4 ± 13.6	210 (51.7)	12 w
	TIO	204	64.9 ± 8.1	125 (61.3)	28.3 ± 6.0	1.3 ± 0.5	47.8 ± 13.2	98 (48.0)	
NCT02006732	TIO/OLO	404	64.7 ± 8.5	259 (64.1)	28.1 ± 5.8	1.4 ± 0.5	47.9 ± 13.6	182 (45.1)	12 w
	TIO	203	64.7 ± 8.4	130 (64.0)	28.4 ± 6.4	1.4 ± 0.5	49.4 ± 12.9	91 (44.8)	
NCT01431274	TIO/OLO	1044	64.5 ± 8.1	773 (74.0)	25.6 ± 5.4	1.2 ± 0.5	43.7 ± 14.8	385 (36.9)	52 w
	TIO	1052	64.2 ± 8.5	775 (73.7)	26.0 ± 5.5	1.2 ± 0.5	44.1 ± 15.1	403 (38.3)	

	OLO	528	63.7 ± 8.0	386 (73.1)	25.6 ± 5.7	1.2 ± 0.5	43.7 ± 15.5	196 (37.1)	
NCT01431287	TIO/OLO	1015	63.4 ± 8.0	717 (70.6)	26.0 ± 5.7	1.2 ± 0.5	43.4 ± 15.1	387 (38.1)	52 w
	TIO	1014	63.7 ± 8.6	734 (72.4)	25.8 ± 5.3	1.2 ± 0.5	43.3 ± 15.4	355 (35.0)	
	OLO	510	64.7 ± 8.3	378 (74.1)	26.1 ± 5.8	1.2 ± 0.5	44.4 ± 15.1	182 (35.7)	

Data are presented as means ± SD or number (%). Numbers of patients are presented based on the full analysis set.

BMI, body mass index; FEV_1, forced expiratory volume at 1 s; %pred., % of the predicted value; F/U, follow-up; GLY; glycopyrronium; IND, indacaterol; UMEC, umeclidinium; VI, vilanterol; TIO, tiotropium; OLO, olodaterol; SD, standard deviation.

Table S2. Types of study endpoints of the included 12 studies

	No of patients	Trough FEV_1	Change of trough FEV_1	FEV_1 AUC 0-12h	FEV_1 AUC 0-6h	FEV_1 AUC 0-3h	% of patients TDI ≥ 1	SGRQ score	% of SGRQ responder	No. of acute exacerbation	No. of adverse events
NCT01727141	781	o	o	o				o	o	o	o
NCT01712516	752	o	o	o				o	o	o	o
NCT01682863	519	o	o							o	o
NCT01777334	905	o	o		o			o	o	o	o
NCT01316900	843	o	o		o		o	o	o	o	o
NCT01313650	1252	o	o		o			o	o	o	o
NCT01316913	869	o	o		o		o	o	o	o	o
NCT02296138	7903	o	o							o	o
NCT01964352	610	o	o			o		o	o		o
NCT02006732	607	o	o			o		o	o		o
NCT01431274	2624	o	o			o		o	o	o	o
NCT01431287	2539	o	o			o		o	o	o	o

FEV_1, forced expiratory volume at 1 s; AUC, area under the curve; TDI, transition dyspnea index; SGRQ, St. George's Respiratory Questionnaire.

국문요약

만성폐쇄성폐질환 환자에서 기관지 확장제에 대한 치료 반응 예측모델

GOLD consensus document 는 만성폐쇄성폐질환 환자를 A-D 네 그룹으로 분류하고 이에 따른 치료 시작 방침을 제시하고 있다. 2017 년 개정된 환자 분류 기준은 환자의 증상 점수와 지난해 악화력을 바탕으로 하고 있고, 폐기능(forced expiratory volume at 1 s; FEV_1)은 더 이상 고려하지 않는다. 따라서 B 군에는 FEV_1 이 예측치의 50% 미만인 중증 기류제한을 보이는 환자도 포함되게 되었다. B 군에 해당하는 환자는 단일기관지확장제로 치료를 시작하도록 권고하고 있는데, 폐기능과 무관하게 단일기관지확장제로 초치료를 시작하는 것이 이중기관지확장제를 사용하는 것과 차이가 없는지에 대해서는 연구가 부족하다.

이 연구에서는 이중기관지확장제의 효과를 연구한 3 상 무작위 임상 시험의 개별환자 데이터를 취합하여 사후 분석을 진행하였다. 분석에 포함한 이중기관지확장제는 glycopyrronium/indacaterol, umeclidinium/vilanterol, or tiotropium/olodaterol 이었으며, 이 약제를 단일기관지확장제와 비교한 연구의 개별환자 데이터를 연구를 진행했던 스폰서 제약회사로부터 제공받았다. 교차 설계의 연구와 8 주 미만으로 시행된 연구는 제외하였다. 연구 결과로는 FEV_1 의 변화, 세인트 조지 호흡기 설문 점수(St. George's Respiratory Questionnaire; SGRQ)의 변화, SGRQ 4 점 이상 개선된 환자(SGRQ responder)의 비율, 악화 횟수 및 첫 악화까지 걸린 시간, 부작용의 발생 빈도를 조사하였다.

총 12 개의 연구로부터 14,449 명의 B 군 환자 데이터를 추출하였다. 이 중에서 8,043 명은 FEV_1 값이 예측치의 50% 미만이었고, 6,406 명은 예측치의 50% 이상이었다. FEV_1 향상에 있어서는 기저 FEV_1 값과 무관하게 이중기관지확장제가 단일 기관지 확장제에 비해 효과적이었다. 삶의 질의 경우, FEV_1 이 예측치의 50% 미만인 환자에서는 이중기관지확장제가 단일기관지확장제에 비해 SGRQ 점수 감소와 SGRQ responder 비율 모두에 있어 일관되게 더 효과적인 것으로 나타났다. 하지만 FEV_1 이 예측치의 50% 이상인 환자에서는 이중기관지확장제가 단일기관지확장제 중 흡입지속성항콜린제(long-acting muscarinic antagonist)에 비해서만 유의하게 더 효과적인 것으로 나타났고, 흡입지속성베타-2 작용제(long-acting beta-2 agonist)와는 차이가 없었다. FEV_1 이 예측치의 50%

미만인 환자에서는 이중기관지확장제가 흡입지속성베타-2 작용제(long-acting beta-2 agonist)에 비해 유의하게 첫 악화까지 걸리는 시간을 연장시켜주는 것으로 나타났으나, FEV_1 이 예측치의 50% 이상인 환자에서는 이중기관지확장제와 단일기관지확장제 사이에 유의한 차이가 없었다.

결론적으로 만성폐쇄성폐질환 B 군에 속하는 환자에게 이중기관지확장제를 사용하는 것이 단일기관지확장제를 사용하는 것에 비해 폐기능과 삶의 질 향상에 있어서 유리하였는데, 특히 그 효과는 FEV_1 이 예측치의 50% 미만인 환자에서 일관되게 나타났다. 따라서 폐기능이 낮은 환자에서는 초기치료로 단일기관지확장제보다 이중기관지확장제를 사용하는 것이 더 유리할 수 있겠다.