ORIGINAL RESEARCH

Effects of baseline symptom burden on treatment response in COPD

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Rationale: In symptomatic patients with COPD, the decision whether to initiate maintenance treatment with a single agent or a combination of long-acting bronchodilators remains unclear.
Objective: To investigate whether baseline symptomatic status influences response to tiotropium/olodaterol treatment.
Materials and methods: Post hoc analysis of the randomized OTEMTO® studies (NCT01964352; NCT02006732), in which patients with moderate-to-severe COPD received placebo, tiotropium 5 µg, tiotropium/olodaterol 2.5/5 µg, or tiotropium/olodaterol 5/5 µg once daily for 12 weeks via the Respimat® inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany). Impact of baseline symptomatic status (modified Medical Research Council [mMRC] score) on response to treatment with tiotropium/olodaterol 5/5 µg, tiotropium 5 µg, or placebo at Week 12 was assessed by St George's Respiratory Questionnaire (SGRQ) total score and response rate, transition dyspnea index (TDI) focal score and response rate, and trough forced expiratory volume in 1 second response.
Results: Tiotropium/olodaterol improved SGRQ total scores and response rates compared with placebo and tiotropium for patients with baseline mMRC scores 0–1 and ≥2. For tiotropium/olodaterol vs tiotropium, greater improvements were observed for patients with mMRC ≥2 (SGRQ score adjusted mean treatment difference −3.44 [95% CI: −5.43, −1.46]; $P=0.0007$; SGRQ response rate ORs 2.09 [95% CI: 1.41, 3.10]; $P=0.0002$). Dyspnea, measured by TDI score, was consistently improved with tiotropium/olodaterol vs placebo for patients with mMRC scores 0–1 and ≥2 (adjusted mean treatment difference 1.63 [95% CI: 1.06, 2.20]; $P<0.0001$ and 1.60 [95% CI: 1.09, 2.10]; $P<0.0001$, respectively). In patients with mMRC scores 0–1 and ≥2, tiotropium/olodaterol consistently improved TDI response rate and lung function vs placebo and tiotropium.
Conclusions: Patients with COPD with more severe baseline dyspnea appear to derive greater health status benefit with tiotropium/olodaterol compared with tiotropium alone.
Keywords: tiotropium, olodaterol, COPD

Plain language summary

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therapeutic strategy suggests differential pharmacotherapeutic approaches for COPD as a function of symptom burden, using the modified Medical Research Council (mMRC) dyspnea scale or the COPD Assessment Test to differentiate between patients with a low or a high level of symptoms. When to initiate maintenance therapy with a single or combination of long-acting bronchodilators remains unclear. In this post hoc analysis, we show that those with more severe baseline dyspnea (mMRC score ≥2) derive greater health status benefit with combination bronchodilator treatment (tiotropium/olodaterol) compared with monotherapy (tiotropium). Our data support the GOLD suggestion that combination of long-acting bronchodilators is a preferable option for those with severe breathlessness.

Introduction

A multidimensional approach to evaluating and characterizing patients with COPD has been recommended by numerous groups.[1–3] Spirometric results, symptom severity, exacerbation risk, and comorbidity assessment are key to appropriate diagnosis and optimizing therapeutic management.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) therapeutic strategy suggests the modified Medical Research Council (mMRC) dyspnea scale or the COPD Assessment Test to differentiate between low-risk (GOLD A and B) patients requiring as-needed treatment and those patients requiring regular maintenance treatment with a long-acting muscarinic antagonist (LAMA) or long-acting β_2-agonist (LABA).[1] However, when to initiate maintenance therapy with a single agent or a combination of long-acting bronchodilators remains unclear.

Tiotropium is an established once-daily LAMA that improves lung function and reduces exacerbations in patients with COPD, as well as improving patient-reported outcomes, including dyspnea and health status.[4–10] Olodaterol is a LABA with a rapid onset of action that provides 24-hour bronchodilation and symptomatic benefits in patients with COPD.[11–14] Tiotropium/olodaterol combination therapy has demonstrated consistent benefits vs tiotropium monotherapy in patients with moderate-to-very-severe COPD in Phase III studies, with no additional safety concerns.[15–17] OTEMTO® 1 and 2 were replicate, randomized controlled trials which demonstrated that as well as improving lung function compared with placebo and tiotropium 5 μg, tiotropium/olodaterol improved health status.[17] We hypothesized that patients with greater baseline dyspnea burden would experience greater improvements in clinically relevant measures with tiotropium/olodaterol vs placebo or the individual monocomponents. Using data from the OTEMTO® studies, we investigated whether symptomatic status at baseline by mMRC score (0–1 vs ≥2) influences the effect of tiotropium/olodaterol treatment on health-related health status, dyspnea, and lung function responses. An additional objective was to understand the relationship between baseline symptom severity and baseline lung function in predicting St George's Respiratory Questionnaire (SGRQ) response. Some of the results of these studies have been previously reported in the form of an abstract.[18]

Materials and methods
Study design and treatment
The OTEMTO® studies (NCT01964352; NCT02006732) were replicate, multinational, randomized, double-blind, parallel-group, placebo-controlled trials (see Figure S1).[17] Patients received one of four treatments for 12 weeks: tiotropium/olodaterol 2.5/5 μg, tiotropium/olodaterol 5/5 μg, tiotropium 5 μg, or placebo, all given once daily using a Respimat® inhaler.

Study patients
Study patients were eligible for inclusion if they were aged ≥40 years and had moderate-to-severe COPD (GOLD II–III, post-bronchodilator forced expiratory volume in 1 second [FEV_1] ≥30% and <80% of predicted normal), FEV_1/forced vital capacity <70% predicted, and a smoking history of >10 pack-years. Key exclusion criteria included a history of asthma, a COPD exacerbation, or symptoms of lower respiratory tract infection within the previous 3 months. Patients were allowed to continue inhaled corticosteroid therapy if they were on a stable dose for 6 weeks prior to screening. Open-label salbutamol was provided as rescue medication. mMRC dyspnea scale, baseline dyspnea index (BDI), and SGRQ were measured in all patients entering the study at baseline. There were no inclusion/exclusion criteria at study entry related to mMRC, BDI, or SGRQ scores at baseline.

Assessments
Baseline symptomatic status was classified according to mMRC score 0–1 and ≥2, following the suggestion of the GOLD therapeutic strategy.[1] For the current work, analyses examining the impact of baseline dyspnea status on response to tiotropium/olodaterol 5/5 μg vs tiotropium 5 μg or placebo included: SGRQ total score (change at Week 12) and response rate (defined as the proportion of patients experiencing an SGRQ total score change ≥4.0 points lower than the baseline total score); symptoms (transition dyspnea index [TDI] focal score [at Week 12] and response rate [defined as the proportion of patients experiencing a TDI focal score ≥1 point greater than BDI]); and trough FEV_1 response (change at Week 12). While all study drug doses were included in the analysis models, we report results for the globally approved tiotropium/olodaterol 5/5 μg dose vs tiotropium 5 μg and placebo only.

Statistical analysis
SGRQ and TDI responders were compared using logistic regression. The adjusted mean treatment effect (tiotropium/olodaterol 5/5 μg minus tiotropium 5 μg or placebo) for the SGRQ total score, TDI focal score, and trough FEV_1 response was obtained by fitting a mixed-effect model for

repeated measurements. Additional analyses were conducted to evaluate the robustness of the main analysis using different baseline symptom burden cutoffs (mMRC scores 0–2 and ≥3). As some correlation has been shown between baseline mMRC and BDI scores,[19–21] sensitivity analyses using BDI score (cutoff scores of 0–4 and ≥5, and 0–5 and ≥6) were performed to examine whether treatment effect patterns observed for mMRC cutoffs could be confirmed using a different baseline symptom measure.

The effects of baseline mMRC score and baseline lung function (via GOLD stage) on SGRQ response rate after 12 weeks were assessed using multiple logistic regression analysis. This analysis included treatment, baseline GOLD stage (II or III), and baseline mMRC score (0–1 and ≥2) in the model. The analysis was conducted for the full study analysis population and for the tiotropium/olodaterol 5/5 μg treatment group.

Ethics

The trial was carried out in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation-Good Clinical Practice. Each patient signed an informed consent form according to the local regulatory and legal requirements.

Results

Patients

Overall, 1,621 patients were treated in the two OTEMTO® studies, and 1,619 had data available for mMRC and BDI. Table 1 enumerates baseline characteristics: mMRC dyspnea scale scores were 0–1 in 736 patients (45%), 0–2 in 1,275 patients (79%), ≥2 in 883 patients (55%), and ≥3 in 344 patients (21%); BDI scores were 0–4 in 265 patients (16%), 0–5 in 418 patients (26%), ≥5 in 1,354 patients (84%), and ≥6 in 1,201 patients (74%). Generally, patients with mMRC scores ≥2 had slightly lower pre-bronchodilator FEV_1 values compared with patients with mMRC 0–1 (Table 1). As expected, SGRQ total scores were higher in the patients with mMRC scores ≥2. The percentages of patients in GOLD categories II, III, and IV differed between the patient subgroups defined by baseline mMRC scores ≥2 (59.1%, 40.1%, and 0.8%, respectively) or 0–1 (70.4%, 29.3%, and 0.1%, respectively).

Health status

Tiotropium/olodaterol 5/5 μg significantly improved SGRQ scores compared with placebo for patients with mMRC scores 0–1 and ≥2 (Figures 1 and 2), with adjusted mean treatment differences of −4.20 (95% CI: −6.11, −2.29) and −5.11 (95% CI: −7.10, −3.11), respectively ($P<0.0001$ for the treatment comparison in each mMRC subgroup). When tiotropium/olodaterol was compared with tiotropium, there was a greater improvement in SGRQ score for patients with an mMRC score ≥2 (adjusted mean treatment difference −3.44 [95% CI: −5.43, −1.46]; $P=0.0007$) than for patients with an mMRC score 0–1 (adjusted mean treatment difference −0.71 [95% CI: −2.57, 1.16]; $P=0.4584$) (Figure 2). Although similar trends in treatment differences were observed for change in SGRQ total score using a higher mMRC cutoff (0–2 and ≥3), the data for the mMRC ≥3 subgroup exhibited wider CIs due to the smaller patient numbers in this subgroup compared with the mMRC 0–1, ≥2, and 0–2 subgroups (Figure 2). When BDI was used as an alternative symptom measure, the change in SGRQ total score was greater with tiotropium/olodaterol vs tiotropium or placebo in all subgroups (Figure 2). Sample sizes for the lower BDI score subgroups (0–5 and 0–4) were small, and the treatment difference data were associated with wide CIs.

The SGRQ response rates were greater for tiotropium/olodaterol vs tiotropium or placebo for patients with mMRC scores 0–1 and ≥2 (Figure 3). Again, for tiotropium/olodaterol vs tiotropium, the treatment differences in SGRQ response were more apparent in patients with more severe baseline dyspnea (mMRC ≥2 OR 2.09 [95% CI: 1.41, 3.10]; $P=0.0002$) than those with less severe baseline dyspnea (mMRC 0–1 OR 1.13 [95% CI: 0.75, 1.71]; $P=0.5654$). Similar trends were observed for the ORs for SGRQ response rate for tiotropium/olodaterol vs tiotropium for the higher mMRC cutoff (0–2 and ≥3) and for the subgroups defined by BDI (Figure 3). Again, CIs were wide for those subgroups with smaller patient numbers.

Dyspnea

Dyspnea, measured by TDI score, was consistently improved with tiotropium/olodaterol vs placebo for patients with mMRC scores 0–1 and ≥2 (adjusted mean treatment difference 1.63 [95% CI: 1.06, 2.20]; $P<0.0001$ and 1.60 [95% CI: 1.09, 2.10]; $P<0.0001$, respectively) (Figure 4). Tiotropium/olodaterol also consistently improved TDI score vs tiotropium for patients with mMRC scores 0–1 and ≥2 (adjusted mean treatment difference 0.51 [95% CI: −0.05, 1.07]; $P=0.0746$ and 0.65 [95% CI: 0.15, 1.15]; $P=0.0115$, respectively). Similar results were obtained using a higher mMRC score cutoff (0–2 and ≥3), as well as in the BDI subgroups (both cutoff values) (Figure 4). The ORs for TDI response rate were greater for tiotropium/olodaterol vs

Table I Baseline demographics and characteristics for patients with a baseline mMRC score of 0–1 and ≥2

	mMRC 0–1 (n=736)	mMRC ≥2 (n=883)
Male, n (%)	465 (63.2)	521 (59.0)
Mean (SD) age, years	64.6 (8.2)	64.9 (8.5)
Race, n (%)		
White	711 (96.6)	831 (94.1)
American Indian/Alaskan native	1 (0.1)	4 (0.5)
Asian	3 (0.4)	1 (0.1)
Black/African American	21 (2.9)	46 (5.2)
Native Hawaiian/Pacific Islander	0 (0.0)	1 (0.1)
Mean (SD) body mass index, kg/m^2	27.2 (5.3)	28.5 (6.2)
Smoking status, n (%)		
Ex-smoker	395 (53.7)	462 (52.3)
Current smoker	341 (46.3)	421 (47.7)
mMRC, n (%)		
0	117 (15.9)	–
1	619 (84.1)	–
2	–	539 (61.0)
3	–	298 (33.7)
4	–	46 (5.2)
Mean (SD) BDI	7.3 (1.9)	5.8 (2.0)
Mean (SD) pre-bronchodilator screening		
FEV$_1$, L	1.439 (0.499)	1.268 (0.470)
Mean (SD) post-bronchodilator screening		
FEV$_1$, L	1.633 (0.512)	1.453 (0.482)
% of predicted normal FEV$_1$	57.274 (12.452)	53.252 (12.814)
FEV$_1$ change from pre- to post-bronchodilator, L	0.194 (0.149)	0.185 (0.151)
FVC, L	3.227 (0.884)	2.967 (0.864)
FEV$_1$/FVC, %	51.083 (10.171)	49.670 (10.596)
GOLD, n (%)		
1 (≥80%)	1 (0.1)	0 (0.0)
2 (50–<80%)	518 (70.4)	522 (59.1)
3 (30–<50%)	216 (29.3)	354 (40.1)
4 (<30%)	1 (0.1)	7 (0.8)
Baseline pulmonary medication, n (%)	562 (76.4)	677 (76.7)
SAMA	45 (6.1)	79 (8.9)
LAMA	262 (35.6)	298 (33.7)
SABA	370 (50.3)	447 (50.6)
LABA	266 (36.1)	363 (41.1)
ICS	256 (34.8)	352 (39.9)
Xanthines	5 (0.7)	30 (3.4)
Mean (SE) SGRQ total score	35.2 (0.6)	48.9 (0.6)
GOLD, n (%)		
A	486 (66.0)	0 (0.0)
B	0 (0.0)	483 (54.7)
C	250 (34.0)	0 (0.0)
D	0 (0.0)	400 (45.3)

Abbreviations: BDI, baseline dyspnea index; 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; mMRC, modified Medical Research Council dyspnea scale; SABA, short-acting β$_2$-agonist; SAMA, short-acting muscarinic antagonist; SE, standard error; SGRQ, St George's Respiratory Questionnaire.
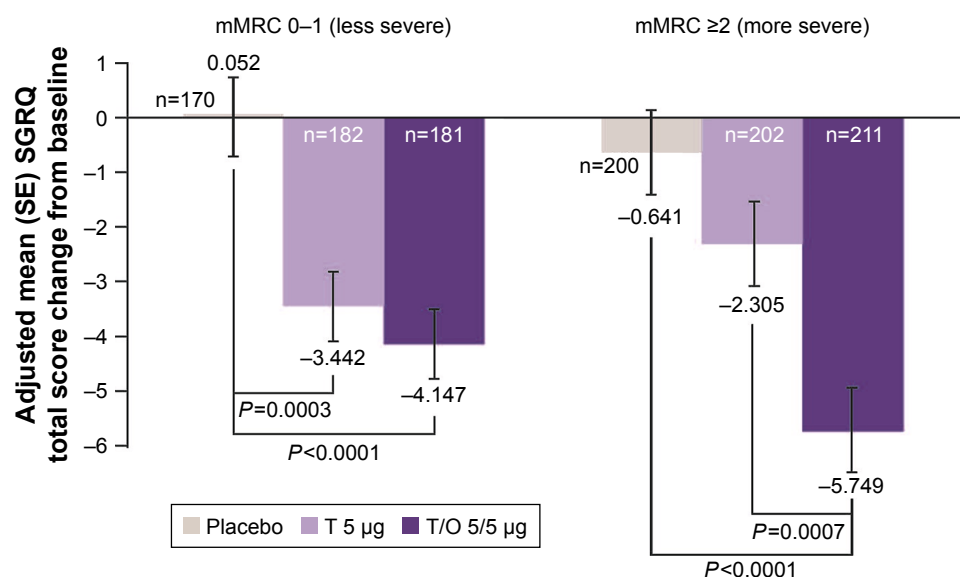
Figure 1 Adjusted mean change from baseline in SGRQ total score after 12 weeks for T/O 5/5 µg, T 5 µg, and placebo according to baseline dyspnea severity.
Note: *P*-values shown for comparisons where the treatment difference reached significance.
Abbreviations: mMRC, modified Medical Research Council dyspnea score; O, olodaterol; SE, standard error; SGRQ, St George's Respiratory Questionnaire; T, tiotropium.

tiotropium or placebo for patients with mMRC score 0–1 or ≥2, as well as with a higher mMRC cutoff and all BDI subgroups (Figure 4).

Lung function

There were improvements in lung function (trough FEV_1) with tiotropium/olodaterol vs tiotropium or placebo in patients with mMRC scores 0–1 and ≥2 (Figure 5). Lung function also improved with tiotropium/olodaterol vs tiotropium or placebo in groups stratified by the higher mMRC cutoff, except for the tiotropium/olodaterol vs tiotropium comparison for patients with mMRC ≥3 (Figure 5). Lung function improvements with tiotropium/olodaterol compared with placebo were larger in less symptomatic patients assessed by BDI (data not shown), but not as measured by baseline mMRC. For tiotropium/olodaterol compared with tiotropium, this pattern was observed both for mMRC and BDI subgroups.

Relationship between baseline lung function and symptoms as a predictor of SGRQ response

Multiple logistic regression analysis of data for the full analysis population was performed to explore the combined effect of baseline lung function and baseline symptom severity on SGRQ response after 12 weeks of treatment, using a logistic regression model that included the covariates of GOLD stage (III vs II) and mMRC (≥2 vs 0–1), as well as

treatment to adjust for known treatment differences and differences in baseline lung function. Baseline lung function (via GOLD stage) and baseline symptom severity had no effect on SGRQ response rate in the full analysis population (see Figure S2A). Multiple logistic regression analysis of data for the tiotropium/olodaterol 5/5 µg treatment group only did not indicate that baseline lung function had an effect on SGRQ response rate after 12 weeks (GOLD III vs GOLD II OR 0.88 [95% CI: 0.58, 1.34]; *P*=0.5637). However, baseline mMRC score was significantly associated with SGRQ response rate, with patients with greater baseline symptom burden exhibiting higher SGRQ response rates (mMRC ≥2 vs 0–1 OR 1.61 [95% CI: 1.07, 2.41]; *P*=0.0211) (see Figure S2B).

Discussion

The approach to COPD therapy has been suggested to be optimized by a multidimensional approach to characterize disease severity and impact. The GOLD therapeutic strategy suggests differential pharmacotherapeutic approaches as a function of symptom burden.[1] This and other therapeutic strategies[3] recommend regular maintenance treatment with a LAMA or LABA (Group B).[1] Numerous studies have shown that the combination of LAMA and LABA provides a greater improvement in lung function, as well as a greater decrease in symptoms vs placebo and the individual bronchodilators.[22,23] Whether single or dual bronchodilation should be used as first-line therapy for symptomatic patients remains unclear.
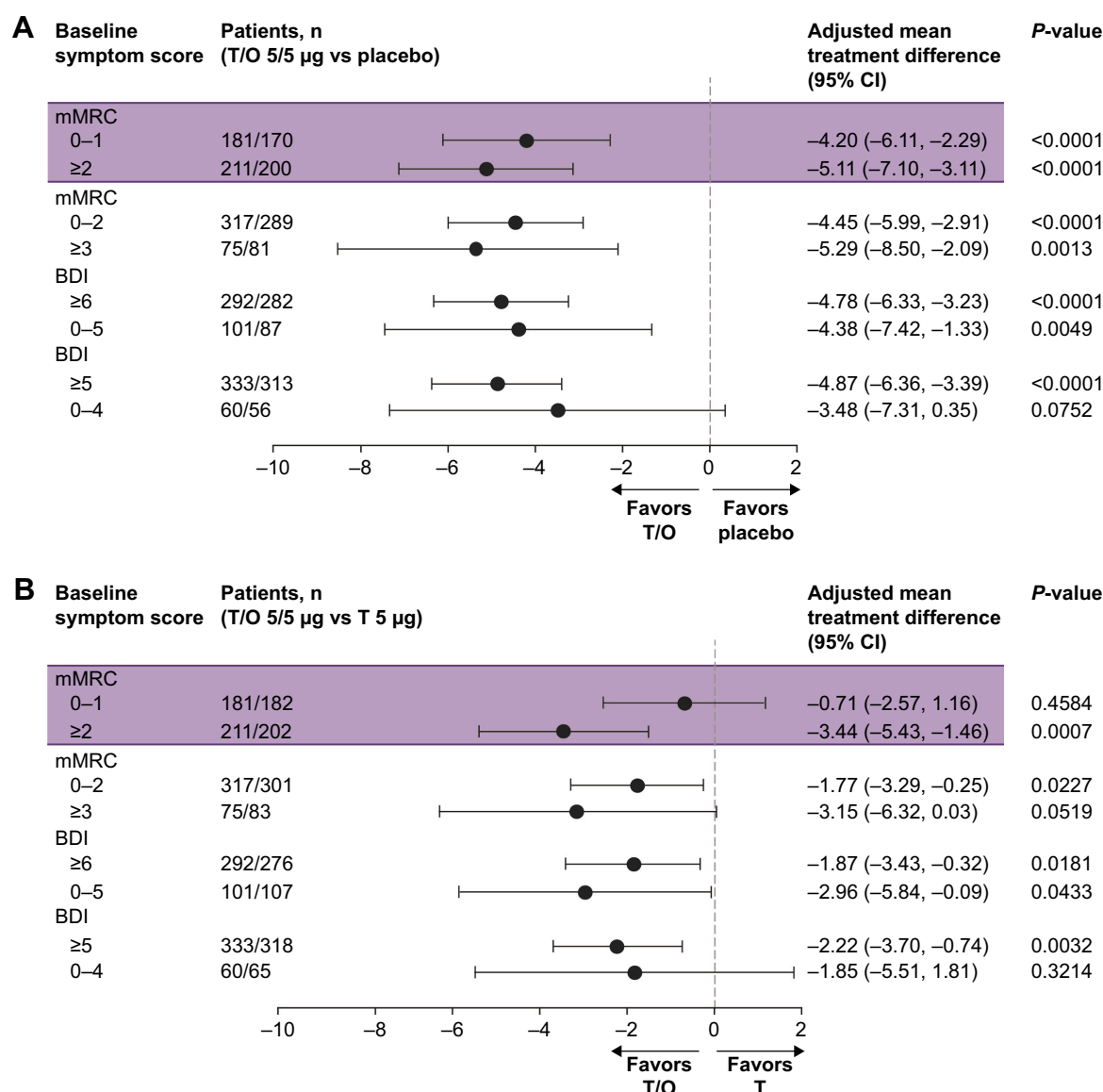
A

Baseline symptom score	Patients, n (T/O 5/5 µg vs placebo)		Adjusted mean treatment difference (95% CI)	P-value
mMRC				
0–1	181/170		−4.20 (−6.11, −2.29)	<0.0001
≥2	211/200		−5.11 (−7.10, −3.11)	<0.0001
mMRC				
0–2	317/289		−4.45 (−5.99, −2.91)	<0.0001
≥3	75/81		−5.29 (−8.50, −2.09)	0.0013
BDI				
≥6	292/282		−4.78 (−6.33, −3.23)	<0.0001
0–5	101/87		−4.38 (−7.42, −1.33)	0.0049
BDI				
≥5	333/313		−4.87 (−6.36, −3.39)	<0.0001
0–4	60/56		−3.48 (−7.31, 0.35)	0.0752

Favors T/O ← → Favors placebo

B

Baseline symptom score	Patients, n (T/O 5/5 µg vs T 5 µg)		Adjusted mean treatment difference (95% CI)	P-value
mMRC				
0–1	181/182		−0.71 (−2.57, 1.16)	0.4584
≥2	211/202		−3.44 (−5.43, −1.46)	0.0007
mMRC				
0–2	317/301		−1.77 (−3.29, −0.25)	0.0227
≥3	75/83		−3.15 (−6.32, 0.03)	0.0519
BDI				
≥6	292/276		−1.87 (−3.43, −0.32)	0.0181
0–5	101/107		−2.96 (−5.84, −0.09)	0.0433
BDI				
≥5	333/318		−2.22 (−3.70, −0.74)	0.0032
0–4	60/65		−1.85 (−5.51, 1.81)	0.3214

Favors T/O ← → Favors T

Figure 2 Forest plot of mean treatment difference in change in SGRQ total score according to baseline dyspnea severity following treatment with (**A**) T/O 5/5 µg vs placebo and (**B**) T/O 5/5 µg vs T 5 µg.
Abbreviations: BDI, baseline dyspnea index; mMRC, modified Medical Research Council dyspnea score; O, olodaterol; SGRQ, St George's Respiratory Questionnaire; T, tiotropium.
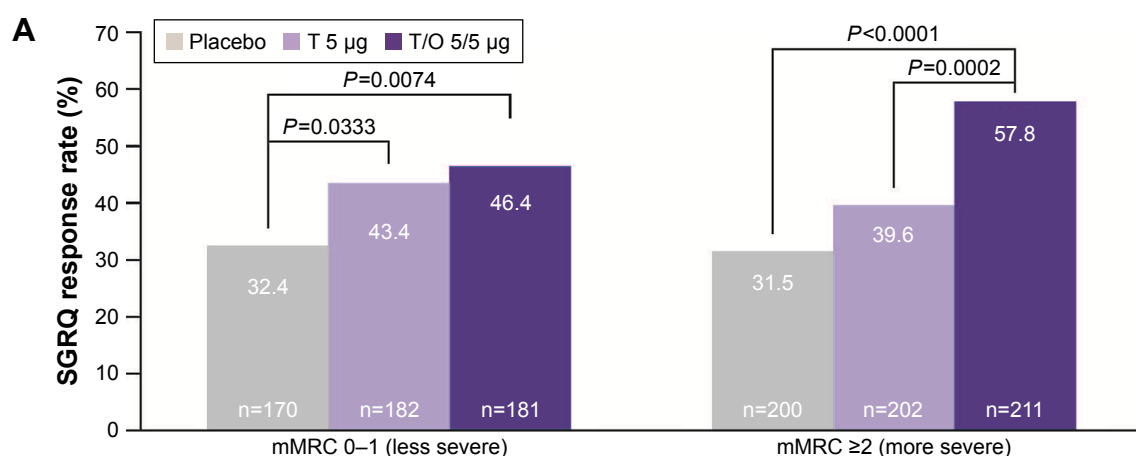
A

Figure 3 (Continued)

B

Baseline symptom score	Patients, n (T/O 5/5 µg vs placebo)		Odds ratio (95% CI)	P-value
mMRC				
0–1	181/170		1.81 (1.17, 2.80)	0.0074
≥2	211/200		2.98 (1.99, 4.47)	<0.0001
mMRC				
0–2	317/289		2.13 (1.53, 2.96)	<0.0001
≥3	75/81		3.76 (1.94, 7.30)	<0.0001
BDI				
≥6	292/282		2.19 (1.55, 3.08)	<0.0001
0–5	101/87		2.85 (1.57, 5.16)	0.0005
BDI				
≥5	333/313		2.25 (1.64, 3.11)	<0.0001
0–4	60/56		2.92 (1.37, 6.23)	0.0055

0.5 1 2 4 8

← **Favors placebo**   **Favors T/O** →

C

Baseline symptom score	Patients, n (T/O 5/5 µg vs T 5 µg)		Odds ratio (95% CI)	P-value
mMRC				
0–1	181/182		1.13 (0.75, 1.71)	0.5654
≥2	211/202		2.09 (1.41, 3.10)	0.0002
mMRC				
0–2	317/301		1.34 (0.98, 1.84)	0.0685
≥2	75/83		2.98 (1.56, 5.70)	0.0010
BDI				
≥6	292/276		1.41 (1.01, 1.96)	0.0447
0–5	101/107		2.20 (1.26, 3.83)	0.0054
BDI				
≥5	333/318		1.51 (1.11, 2.06)	0.0094
0–4	60/65		1.98 (0.97, 4.04)	0.0599

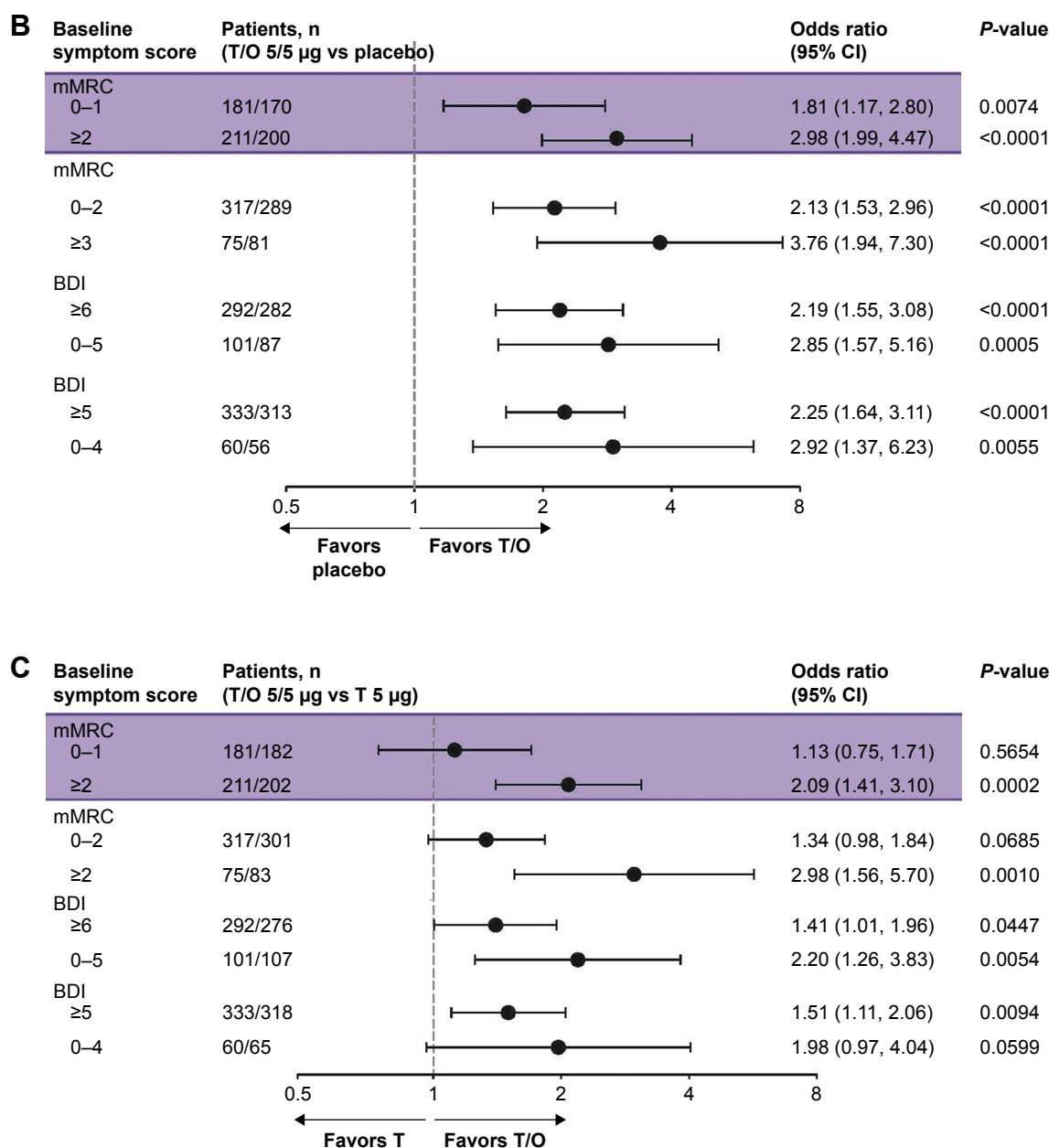0.5 1 2 4 8

← **Favors T**   **Favors T/O** →

Figure 3 (**A**) SGRQ response rate for T/O 5/5 µg, T 5 µg, and placebo according to baseline dyspnea severity (P-values shown for comparisons where the treatment difference reached significance), and (**B**) forest plot of ORs for SGRQ response rate according to baseline dyspnea severity following treatment with T/O 5/5 µg vs placebo and (**C**) T/O 5/5 µg vs T 5 µg.
Abbreviations: BDI, baseline dyspnea index; mMRC, modified Medical Research Council dyspnea score; O, olodaterol; SGRQ, St George's Respiratory Questionnaire; T, tiotropium.

Our analyses confirmed that patients with COPD with more severe dyspnea at baseline, measured using the mMRC scale, had a greater response to tiotropium/olodaterol relative to tiotropium alone in both SGRQ total score and SGRQ responder rate. Importantly, this difference between tiotropium/olodaterol and tiotropium in SGRQ responder rate was apparent for two mMRC cutoffs (0–1 versus ≥2, and 0–2 versus ≥3) and was qualitatively similar in patients stratified by BDI. Interestingly, tiotropium/olodaterol improved dyspnea compared with tiotropium alone or placebo using both TDI score and TDI

responder rate, regardless of baseline symptom status. Overall, these results suggest that patients with higher degrees of baseline symptoms, measured using mMRC, gain added clinical benefit with tiotropium/olodaterol compared with tiotropium alone for improvements in health-related health status, assessed by SGRQ; this additional benefit was less robust in patients with lesser degrees of baseline symptoms. However, in the case of symptoms measured by TDI, tiotropium/olodaterol consistently provided better improvement than tiotropium alone regardless of the degree of baseline symptoms.

The relative lung function (trough FEV_1) response with tiotropium/olodaterol vs tiotropium was greater in patients with less severe symptoms at baseline. However, patients with less severe symptoms had less severe airflow obstruction at baseline. The differential lung function response may therefore reflect the different proportions of patients with GOLD II vs III/IV impairment at baseline, and is consistent with previous findings from the trial program of improved lung function response in patients with less severe lung function impairment at baseline.[24–26] The greater FEV_1 response in patients with less severe dyspnea also reflects the larger improvement in FEV_1 that is expected in patients with less severe airflow obstruction, rather than a unique inverse relationship between change in FEV_1 and baseline dyspnea.

A multiple logistic regression analysis, including baseline lung function and symptom severity together as predictors of SGRQ response, provided additional insights. Overall, averaged across all treatment groups, baseline lung function and symptom severity did not appear to predict SGRQ response. On the other hand, for those treated with tiotropium/olodaterol, more severe symptoms at baseline related to a greater likelihood of identifying SGRQ responders. Baseline lung function did not appear to predict SGRQ response. This analysis provides reassurance that the differences in SGRQ response observed between the groups with less and more severe symptoms at baseline are not a result of the observed differential baseline lung function between these groups. Despite numerous groups suggesting the benefit of
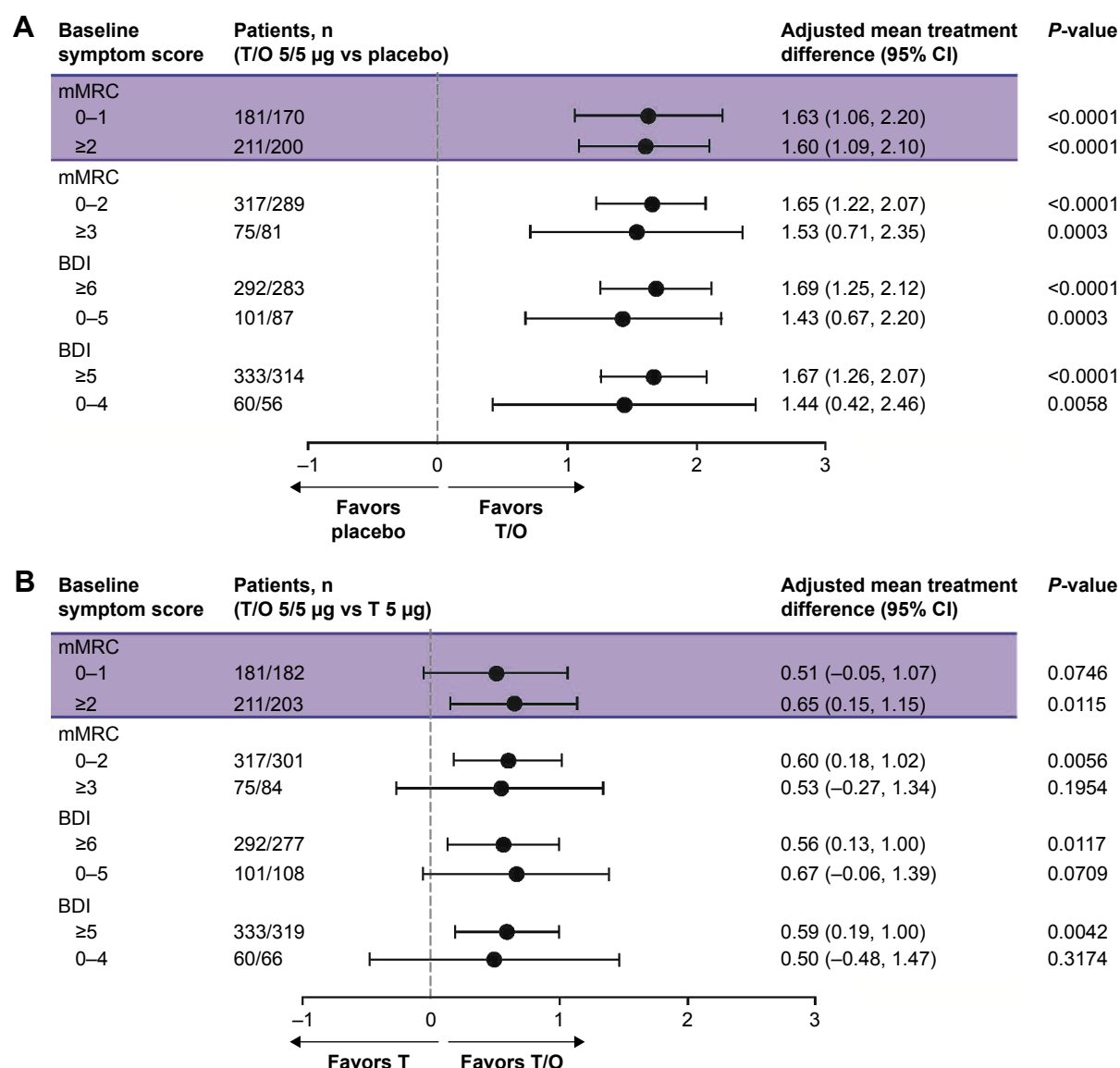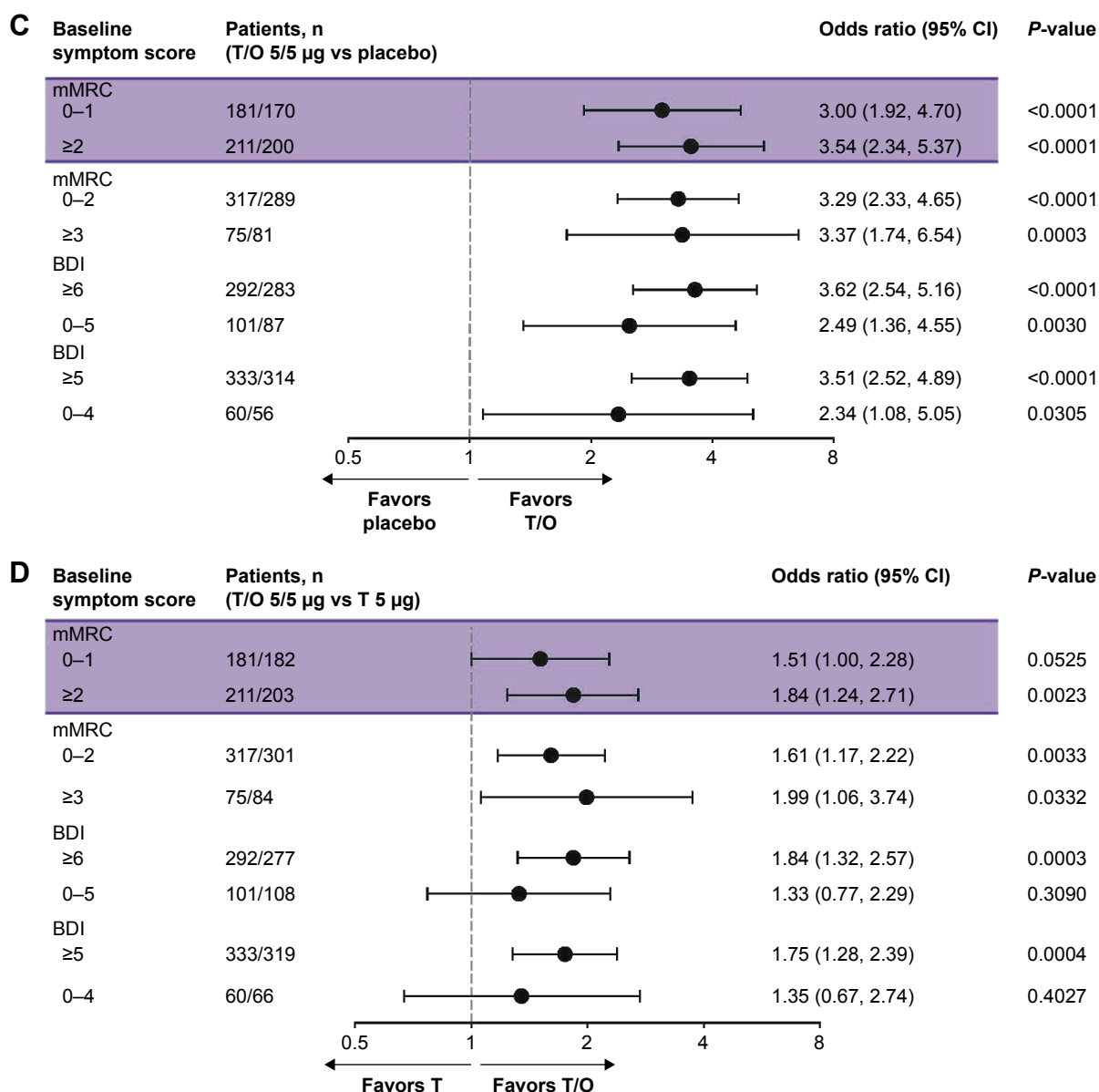

Figure 4 (*Continued*)

C

Baseline symptom score	Patients, n (T/O 5/5 µg vs placebo)		Odds ratio (95% CI)	P-value
mMRC				
0–1	181/170		3.00 (1.92, 4.70)	<0.0001
≥2	211/200		3.54 (2.34, 5.37)	<0.0001
mMRC				
0–2	317/289		3.29 (2.33, 4.65)	<0.0001
≥3	75/81		3.37 (1.74, 6.54)	0.0003
BDI				
≥6	292/283		3.62 (2.54, 5.16)	<0.0001
0–5	101/87		2.49 (1.36, 4.55)	0.0030
BDI				
≥5	333/314		3.51 (2.52, 4.89)	<0.0001
0–4	60/56		2.34 (1.08, 5.05)	0.0305

0.5   1   2   4   8

← Favors placebo | Favors T/O →

D

Baseline symptom score	Patients, n (T/O 5/5 µg vs T 5 µg)		Odds ratio (95% CI)	P-value
mMRC				
0–1	181/182		1.51 (1.00, 2.28)	0.0525
≥2	211/203		1.84 (1.24, 2.71)	0.0023
mMRC				
0–2	317/301		1.61 (1.17, 2.22)	0.0033
≥3	75/84		1.99 (1.06, 3.74)	0.0332
BDI				
≥6	292/277		1.84 (1.32, 2.57)	0.0003
0–5	101/108		1.33 (0.77, 2.29)	0.3090
BDI				
≥5	333/319		1.75 (1.28, 2.39)	0.0004
0–4	60/66		1.35 (0.67, 2.74)	0.4027

0.5   1   2   4   8

← Favors T | Favors T/O →

Figure 4 Forest plots of mean treatment difference in change in TDI focal score according to baseline dyspnea severity following treatment with (**A**) T/O 5/5 µg vs placebo and (**B**) T/O 5/5 µg vs T 5 µg, and forest plots of OR for TDI response rate according to baseline dyspnea severity following treatment with (**C**) T/O 5/5 µg vs placebo and (**D**) T/O 5/5 µg vs T 5 µg. TDI responder is defined as TDI focal score ≥1 better than baseline TDI focal score.
Abbreviations: BDI, baseline dyspnea index; mMRC, modified Medical Research Council dyspnea score; O, olodaterol; T, tiotropium; TDI, transition dyspnea index.

combining LAMA and LABA compared with the individual monocomponents, the observed absolute improvements in dyspnea and health status have often not consistently exceeded the minimum clinically important difference for the instruments used to measure these outcomes.[22,23,27] Our data suggest that baseline symptom burden may have a strong influence on these results. Previous studies have varied in the inclusion of study patients with a broad range of baseline symptoms.[28–37]

These data provide clinically relevant information for future therapeutic strategy recommendations and, more importantly, for clinicians aiding patients with COPD. For example, the GOLD document suggests baseline symptoms as a guide for the use of long-acting bronchodilators; a LAMA or LABA is suggested as a first option for patients with higher mMRC or COPD Assessment Test scores.[1] The combination of a LAMA and LABA is suggested as a potential option for those with severe breathlessness. Our data provide support for this statement and offer additional insights. Tiotropium/olodaterol provides overall lung function and health status benefits regardless of greater baseline dyspnea burden (measured by mMRC or BDI) when compared with
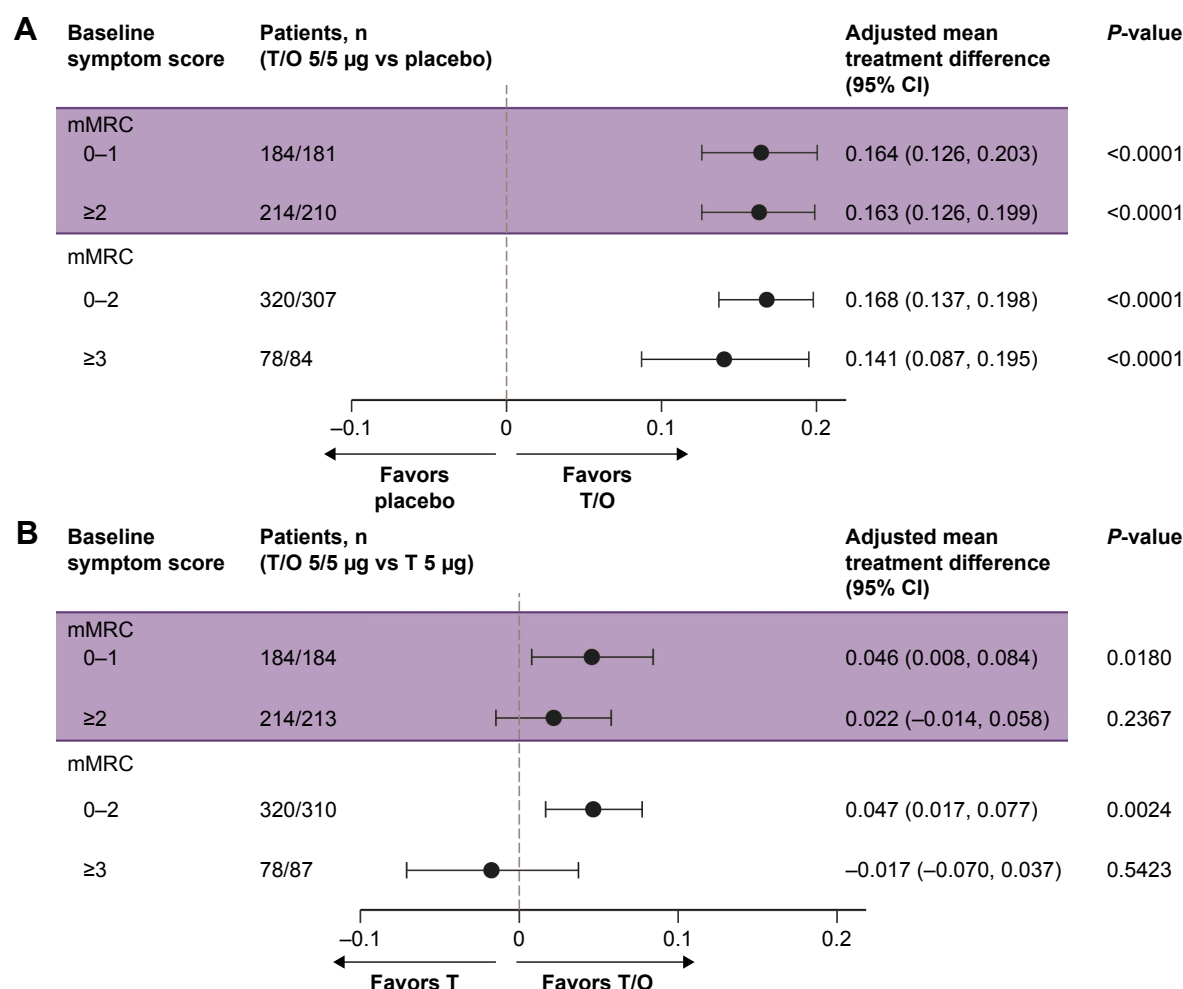
A

Baseline symptom score	Patients, n (T/O 5/5 µg vs placebo)		Adjusted mean treatment difference (95% CI)	P-value
mMRC				
0–1	184/181		0.164 (0.126, 0.203)	<0.0001
≥2	214/210		0.163 (0.126, 0.199)	<0.0001
mMRC				
0–2	320/307		0.168 (0.137, 0.198)	<0.0001
≥3	78/84		0.141 (0.087, 0.195)	<0.0001

−0.1　0　0.1　0.2

← Favors placebo　Favors T/O →

B

Baseline symptom score	Patients, n (T/O 5/5 µg vs T 5 µg)		Adjusted mean treatment difference (95% CI)	P-value
mMRC				
0–1	184/184		0.046 (0.008, 0.084)	0.0180
≥2	214/213		0.022 (−0.014, 0.058)	0.2367
mMRC				
0–2	320/310		0.047 (0.017, 0.077)	0.0024
≥3	78/87		−0.017 (−0.070, 0.037)	0.5423

−0.1　0　0.1　0.2

← Favors T　Favors T/O →

Figure 5 Forest plots of adjusted mean treatment difference in change in trough FEV_1 (L) according to baseline dyspnea severity following treatment with (**A**) T/O 5/5 µg vs placebo and (**B**) T/O 5/5 µg vs T 5 µg.
Abbreviations: FEV_1, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnea score; O, olodaterol; T, tiotropium.

tiotropium alone. Future studies of treatment-naïve patients, or those receiving only monotherapy, are needed to test escalation to LABA/LAMA, and this may be best tested in a real-world setting.

There are limitations to our work. This was a post hoc analysis with its attendant difficulties in interpretation. Our results should be considered hypothesis-generating and should be confirmed with well-designed prospective studies. The OTEMTO® studies used the GOLD I–IV categorization of COPD severity, as the A–D classification[1] had not been published when the studies were designed and initiated. Importantly, these studies included GOLD II–III patients only, so whether these results apply to patients with COPD with more severe airflow obstruction is unclear. These were short-term studies that were not designed to examine exacerbations. As such, we are unable to examine the impact of baseline symptom burden on other clinically relevant end points.

Conclusions

Based on our post hoc analyses, improvements in health status (measured using SGRQ), symptoms (measured using TDI), and lung function were observed in both symptomatic and non-symptomatic patients following treatment with tiotropium/olodaterol. More severe dyspnea, assessed by mMRC, was associated with a larger SGRQ improvement for LAMA/LABA combination compared with a LAMA alone or placebo, but did not affect lung function improvement. These results suggest that patients with COPD with greater baseline dyspnea appear to derive greater health status benefit with a dual bronchodilator combination compared with a LAMA alone.

Data sharing statement

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all

relevant material, including participant-level clinical study data, and relevant material as needed by them to fulfill their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (eg, study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html.

Prior to providing access, documents will be examined, and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link: https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html. All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analyzable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Acknowledgments

Author contributions

FJM contributed to the design and conduct of the study, and wrote the first draft of the manuscript. RA, GTF, LB, and DS contributed to the design and conduct of the study. LG was involved in all aspects of the design, conduct, and data analysis of the study. FV provided statistical support and was involved in the data analysis of this post hoc study. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Supplementary materials
Supplementary S1
Details of ethics committees for participating centres

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Health Research Ethics Board of Alberta Clinical Trials Committee, 1500, 10104 – 103 Avenue NW, Edmonton, Alberta, T5J 4A7, Canada

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Varsinais-Suomen sairaanhoitopiirin kuntayhtymän eettinen toimikunta, Kiinamyllynkatu 4-8, 20521 Turku, Finland

Ethikkommission der Ärztekammer Schleswig-Holstein, Bismarckallee 8-12, 23795 Bad Segeberg, Germany

NRES Committee North West – Greater Manchester Central, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK

Comité Ético de Investigación Clínica del Hospital Universitario Puerta de Hierro Majadahonda, C/Joaquín Rodrigo, 2, 28222-Majadahonda, (Madrid) Spain

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Sir Charles Gairdner, Human Research Ethics Committee, A Block, Hospital Avenue, Nedlands, Perth, Australia

Southern Adelaide Clinical Human Research Ethics Committee, Bedford Park 5042, Adelaide, Australia

Bellberry Human Research Ethics Committee, 129 Glen Osmond Road, Eastwood, Adelaide, Australia

Sydney Local Health District Human Research Ethics Committee – Concord Repatriation General Hospital, Sydney, Australia

CEC Ethikkommission des Landes Oberösterreich Wagner-Jauregg-Weg 15, 4020 Linz, Austria

LEC 43004, Ethikkommission des Landes Steiermark, Abt 8, FAGPSanitätsdirektion Amt der Steiermärkischen, Landesregierung, Friedrichgasse 9/E/28, 8010 Graz, Austria

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CEC (LEC 42104 site): Eticka komisia Presovskeho, samospravneho kraja, Urad Presovskeho, samospravneho kraja, Namestie mieru 208001 Presov, Slovakia

LEC: Eticka komisia Narodny ustav tuberkulozy, plucnych, chorob a hrudnikovej chirurgie 059 84 Vysne Hagy, Slovakia

LEC: Eticka komisia Urad Kosickeho, samospravneho kraja, Namestie Maratonu, Mieru 1, 042 66 Kosice, Slovakia

LEC: Eticka komisia, Nemocnica s, poliklinikou sv. Jakuba, Bardejov, ul. Sv. Jakuba 21, 085 01 01 Bardejov, Slovakia

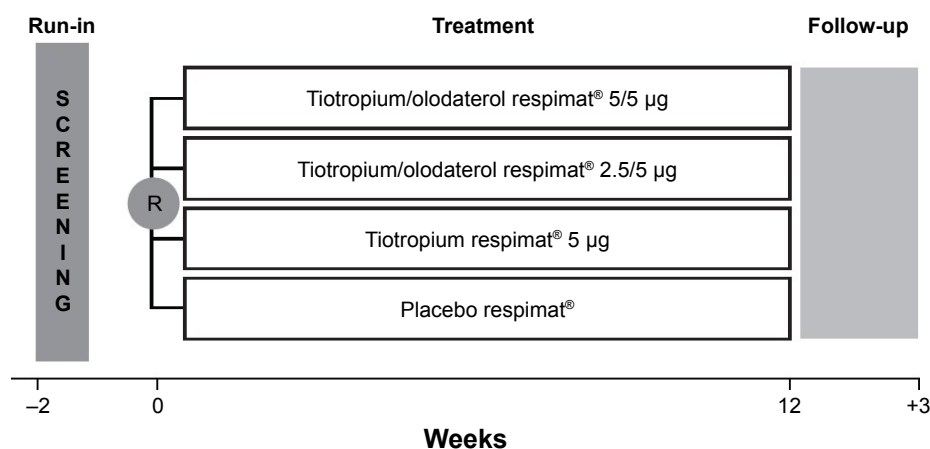Regionala Etikprövningsnämnden, i Lund, Box 133, 221 00 Lund, Sweden.

Figure S1 Study design of OTEMTO® 1 and 2.
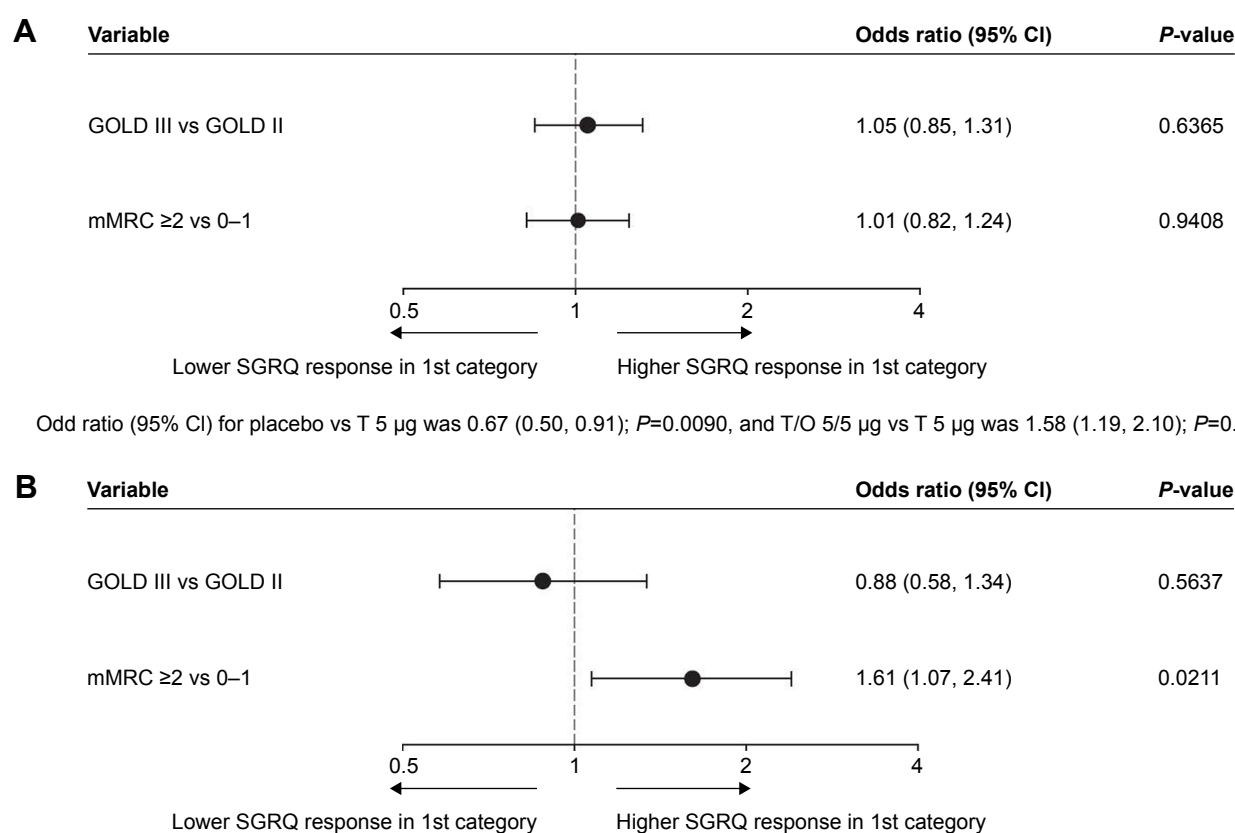**Abbreviation:** R, randomization.

Odd ratio (95% CI) for placebo vs T 5 µg was 0.67 (0.50, 0.91); *P*=0.0090, and T/O 5/5 µg vs T 5 µg was 1.58 (1.19, 2.10); *P*=0.0017

Figure S2 Forest plot of SGRQ response after 12 weeks versus baseline variables for (**A**) all treatment groups and (**B**) T/O 5/5 µg treatment group.
Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; O, olodaterol; SGRQ, St George's Respiratory Questionnaire; T, tiotropium.