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Indacaterol vs tiotropium in COPD patients classified as GOLD A and B

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Summary
Introduction: According to current GOLD strategy, patients with COPD classified as groups A and B may be treated with inhaled bronchodilators, either long-acting β_2-agonist (LABA) or long-acting muscarinic antagonist (LAMA). However, there is little guidance on which class of agent is preferred and a lack of prospective data to differentiate the two.
Methods: In this study, we performed post-hoc analyses of pooled data from two prospective, controlled clinical trials comparing the LABA indacaterol and LAMA tiotropium in 1422 patients with moderate airflow limitation and no history of exacerbations in the previous year. This population fits the definitions of GOLD A and B groups and could be further stratified by symptom severity using Baseline Dyspnea Index (i.e. modeling GOLD A or B) and inhaled corticosteroid (ICS) use at baseline. Outcomes measured after 12 weeks of treatment were lung function (forced expiratory volume in 1 s; FEV_1), health status (St George's Respiratory Questionnaire; SGRQ), symptoms (Transition Dyspnea Index; TDI) and rescue medication use.
Results: In 'GOLD A' patients not receiving ICS, differences favored indacaterol versus

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tiotropium (trough FEV_1 0.05 L; rescue medication use −0.41 puffs/day; TDI total score 0.94 points; SGRQ total score −3.13 units, all $p < 0.01$). In 'GOLD B, no ICS' patients, compared with tiotropium, indacaterol treatment increased trough FEV_1 (0.055 L, $p < 0.05$) and permitted a larger reduction in rescue medication use (−0.81 puffs/day, $p = 0.004$). In all patients, and in patients not using ICS, differences favored indacaterol for all variables.

Conclusions: Our findings suggest that patients in GOLD groups A and B may experience greater benefits with indacaterol than with tiotropium.

1. Introduction

Patients with mild or moderate airflow limitation (forced expiratory volume in 1 s [FEV_1] ≥50% predicted), with fewer than two exacerbations in the past year (not requiring hospitalization), are classified as Global initiative for chronic Obstructive Lung Disease (GOLD) groups A (fewer symptoms) or B (more symptoms) [1]. The current recommended drug treatment for such patients is bronchodilators, ranging from short-acting agents given as needed to long-acting agents given alone or in combination, the intensity of treatment depending on the patient's level of symptoms [1]. There is a paucity of prospective studies evaluating different bronchodilator treatments in these groups; the available data are usually sub-analyses of larger studies or pooled data [2–4].

We were interested to explore the comparative efficacy and safety of the long-acting muscarinic antagonist (LAMA) tiotropium and the long-acting β_2-agonist (LABA) indacaterol, by means of a post-hoc analysis using data from two randomized controlled trials that compared these agents in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) [5,6]. While entry criteria for those trials were set before the new COPD GOLD assessment scheme was published in 2011, it was possible to identify a subgroup of patients who were within the GOLD groups A and B, by virtue of FEV_1 ≥50% predicted (mild or moderate airflow limitation) and a history of no exacerbations in the previous year. This subgroup could be differentiated according to baseline symptom severity to provide a close match with the separate groups A (fewer symptoms) and B (more symptoms). Although in the GOLD scheme inhaled corticosteroids (ICS) should not be administered to patients in GOLD groups A and B [1], many of these patients do receive ICS in practice, which led us to analyze patients receiving ICS separately. Our objective was to evaluate the comparative efficacy and safety of indacaterol and tiotropium in patient groups that closely modeled GOLD groups A and B.

2. Methods

2.1. Study design

Data were pooled from two randomized, parallel-group trials. One trial compared indacaterol 150 μg, indacaterol 300 μg and placebo, double blinded, with open-label tiotropium 18 μg, all taken once daily for 6 months (INHANCE; NCT00463567) [5]. The second, fully blinded trial (INTENSITY; NCT00900731) compared treatment with indacaterol 150 μg or tiotropium 18 μg, both taken once daily for 12 weeks [6]. The latter trial did not include a placebo treatment arm, and the placebo data from the other trial were not included in the present analysis. Data for the indacaterol 300 μg treatment group (in the INHANCE trial only) were not included in the present analysis since 150 μg is the starting dose, which is therefore relevant to the subgroups evaluated here.

2.2. Patients

The entry criteria for the two source trials were almost identical and have been fully described previously [5,6]. Briefly, the trials enrolled patients aged ≥40 years with moderate-to-severe COPD (FEV_1 <80% and ≥30% predicted; FEV_1/forced vital capacity 0.7), with a smoking history of ≥10 or ≥20 pack-years. Patients with a history of asthma or a recent COPD exacerbation were not allowed into the trial. A threshold level of symptoms was not required at trial entry, but symptom severity was recorded at baseline, together with information on whether patients had an exacerbation in the previous year (the number of exacerbations was not captured). Patients receiving ICS continued this treatment at an unchanged and stable dose during the trial. Use of salbutamol as rescue medication was allowed as needed, and recorded during the trial. Patients gave their written informed consent, and the trials were approved by the ethics committees or review boards at the investigating centers.

For the present analysis, we identified a subgroup of patients who were defined at the time of trial entry as having mild or moderate COPD (now classified as airflow limitation of GOLD grade 1 or 2; post-bronchodilator FEV_1 ≥50% predicted) and no exacerbations in the year prior to trial entry. This subgroup could be further divided according to ICS use at baseline (yes or no) and the severity of dyspnea, according to the Baseline Dyspnea Index (BDI) score (≥7 or <7). The modified Medical Research Council (mMRC) scale, which measures breathlessness and is included in the GOLD assessment, was measured in only one of the two trials and was therefore not considered for the present analysis. BDI cut-off values of ≥7 and <7 were chosen because 7 was the median score both in the pooled population and in the trial in which mMRC was recorded (in that trial, 48% of patients had mMRC scores of 0 or 1 and 52% had mMRC scores of 2 or more). Additionally, 7 is the mid-point of the 13-point BDI scale. We believe therefore that the BDI provides a comparable split to mMRC.

2.3. Assessments and variables

Spirometry was performed at clinic visits using standard techniques. Trough FEV_1 was the mean of measurements at 23 h 10 min and 23 h 45 min post dose. For both trials from which the data were derived, trough FEV_1 at 12 weeks was the primary efficacy variable. A difference versus placebo of 100 mL has been reported as the minimum clinically important difference (MCID) [7].

Dyspnea was assessed by BDI at baseline and Transition Dyspnea Index (TDI) total score at 12 weeks [8,9]. The TDI score measures the change from baseline state (BDI), and the MCID is 1 point [10]. Health status was assessed by St George's Respiratory Questionnaire (SGRQ) total score at 12 weeks. The MCID of the SGRQ total score is −4 units, compared with either baseline or placebo [11,12]. The use of salbutamol as rescue medication was recorded by patients in daily diaries and analyzed as the mean change from baseline over 12 weeks. Reported adverse events (AEs) during the entire study periods (6 months for INHANCE and 12 weeks for INTENSITY) were summarized and adjusted for length of exposure to treatment.

2.4. Statistical analysis

Trough FEV_1 after 12 weeks of treatment was analyzed using a mixed-effect model analysis of covariance with treatment, smoking status, country, and study as fixed effects and baseline FEV_1 and FEV_1 reversibility as covariates. Center nested within country was also included as a random effect except where this resulted in non-convergence of the model. In these cases (this applied to the responder analysis for FEV_1 for all subgroups apart from the 'All patients' group), center within country was not included. The same model (with appropriate covariates) was used to analyze mean TDI and SGRQ scores and rescue medication use. For trough FEV_1, TDI and SGRQ scores, missing values were imputed by carrying forward the last observation as long as it occurred at least 28 days after randomization. Data are presented as least squares means with standard errors or associated 95% confidence intervals for differences between treatments.

The proportions of patients who achieved the MCID improvement in trough FEV_1 (0.100 L), TDI or SGRQ (changes of at least +1 unit and −4 units, respectively) were analyzed using logistic regression. The model included the same covariates as for trough FEV_1 with the inclusion of the appropriate baseline value. The estimated adjusted odds ratios (OR) were calculated along with the associated 95% confidence intervals.

No powering or sample size calculations were performed for this post-hoc analysis, and no adjustment was made for multiplicity.

3. Results

3.1. Defined subgroups

The patient subgroups were labeled as follows. The whole group of 'All patients' (n = 1422) comprised patients with FEV_1 ≥50% predicted and no exacerbations in the previous year. The 'All patients' subgroup was further divided according to baseline ICS use as 'All patients, no ICS' (n = 806) and 'All patients, with ICS' (n = 616). BDI data were available for 1393 patients, who were described as 'GOLD A' (having a BDI score of ≥7, i.e. fewer symptoms) (n = 822) or 'GOLD B' (having a BDI score of <7, i.e. more symptoms) (n = 571). Patients in the two latter groups not receiving ICS at baseline were described, respectively, as 'GOLD A, no ICS' (n = 505) and 'GOLD B, no ICS' (n = 287).

3.2. Patient disposition and baseline characteristics

In the 'All patients' group, nearly all the patients (n = 1376, 97%) had moderate airflow limitation and 43% were receiving ICS. The 'All patients' group represented 59% of the patients in the two source trials combined. Of the 700 patients in the tiotropium group, 467 (67%) were from INTENSITY and had received treatment in a blinded fashion. Among the patients with BDI data, 41% had BDI scores <7 points (more severe symptoms).

Table 1 shows the baseline characteristics of all patients and the no-ICS subgroups. The two treatment groups matched closely for each subgroup. Compared with 'GOLD A, no ICS', the 'GOLD B, no ICS' patients tended to have a longer duration of COPD (by ∼2 years), a longer smoking history (by ∼3–4 years) and a slightly lower post-bronchodilator FEV_1 (by 70–110 mL). Their rescue use was higher (∼1.5 puffs/day) and, most notably, the SGRQ score was ∼20 units worse.

Baseline data for the remaining subgroups are shown in Supplementary Table S1. Compared with the 'GOLD A' subgroup, the 'GOLD B' subgroup had a longer duration of COPD (1–2 years), higher frequency of ICS use, longer smoking history, used more rescue medication (by about 1.5 puffs/day), and had a worse SGRQ score by about 20 units. Similarly, the 'All patients with ICS' (compared with 'All patients, no ICS') (Tables 1 and S1) had a longer duration of COPD (∼2 years), used more rescue medication (about 1 puff/day) and had a lower (worse) dyspnea score (∼0.5 point). SGRQ scores were similar.

3.3. Efficacy

In the 'All patients' group, indacaterol was more efficacious than tiotropium, with statistically significant differences for trough FEV_1 (30 mL), rescue use, TDI and SGRQ. Indacaterol-treated patients were significantly and 36–50% more likely to achieve the MCID in FEV_1, TDI and SGRQ (Table 2).

In the 'All patients, no ICS' subgroup, and in the 'GOLD A, no ICS' subgroup, indacaterol had improved efficacy over tiotropium, with significant differences in all variables apart from the percentage of FEV_1 responders (Tables 3 and 4).

In the smaller 'GOLD B, no ICS' subgroup, statistically significantly greater improvements were observed in trough FEV_1 and rescue medication use with indacaterol compared with tiotropium (Table 5).

The changes from baseline in trough FEV_1 and SGRQ and the TDI scores in each of the subgroups are depicted in Fig. 1.

Table 1 Baseline characteristics of patients in the 'All patients' group and the no-ICS subgroups.

	'All patients'		'All patients, no ICS'		'GOLD A, no ICS'		'GOLD B, no ICS'	
	IND150	TIO	IND150	TIO	IND150	TIO	IND150	TIO
N	722	700	407	399	256	249	143	144
Age, years	64 (8.9)	64 (8.6)	63 (8.9)	63 (8.8)	63 (8.5)	62 (8.5)	63 (9.5)	64 (9.2)
Male, %	64	63	63	63	64	64	63	61
Duration of COPD, years	6.5 (6.16)	6.8 (6.60)	5.4 (5.34)	6.0 (6.28)	4.5 (4.23)	5.2 (5.25)	6.8 (6.68)	7.0 (7.29)
Mild/moderate airflow limitation, %	3/97	3/97	5/95	4/96	5/95	3/97	4/96	4/96
ICS use, %	44	43	0	0	0	0	0	0
Smoking history, years	44 (20.5)	44 (22.3)	44 (21.1)	44 (21.1)	43 (19.6)	43 (20.1)	46 (23.7)	47 (22.6)
FEV_1 post-SABA at screening, L	1.75 (0.432)	1.73 (0.433)	1.79 (0.446)	1.79 (0.452)	1.82 (0.439)	1.83 (0.454)	1.75 (0.463)	1.72 (0.438)
Rescue use, puffs/day	3.1 (3.57)	3.2 (3.19)	2.6 (3.20)	2.8 (3.13)	2.2 (2.51)	2.3 (3.04)	3.5 (3.93)	3.7 (3.05)
SGRQ total score, units	40 (18.0)	41 (17.8)	38 (17.8)	41 (17.3)	31 (14.9)	34 (14.4)	49 (16.4)	53 (15.1)
BDI total score, points	7.1 (2.26)	7.0 (2.18)	7.4 (2.34)	7.2 (2.08)	8.7 (1.50)	8.5 (1.36)	5.0 (1.44)	5.1 (1.19)

Data are mean (SD) unless otherwise stated. BDI, Baseline Dyspnea Index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IND150, indacaterol 150 μg; SABA, short-acting β_2-agonist; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium 18 μg.

Efficacy comparisons in the other subgroups are shown in the Supplementary Tables S2–S6. For all comparisons, indacaterol was either significantly better than or not significantly different from tiotropium. In the 'with ICS' subgroups, the effects of indacaterol and tiotropium were largely similar, although indacaterol was generally more effective in improving health status (Tables S2, S5 and S6).

3.4. Safety

Table 6 shows the overall incidence of and the most frequently occurring AEs and serious adverse events (SAEs). Although there was a numerically larger rate of AEs with indacaterol, the reverse was true for the rate of SAEs. Two patients died: one was a sudden death at home (a 52-year-old man receiving indacaterol in the INHANCE study) and the other was a result of cardiac arrest (a 62-year-old man receiving tiotropium in the INTENSITY study). Neither death was suspected by the investigator of being related to the study drug. AE data were comparable between treatments in the various subgroups (not shown).

4. Discussion

The major findings of these post-hoc pooled analyses were that indacaterol provided greater improvements in trough FEV_1, dyspnea and health status compared with tiotropium after 12 weeks in subgroups of patients with mild or moderate COPD and no history of exacerbations, irrespective of symptom severity. In the 'All patients, no ICS' subgroup, indacaterol performed better than tiotropium for the outcomes measured. In 'GOLD A, no ICS' patients, indacaterol performed better than tiotropium for all outcomes, while in 'GOLD B, no ICS' patients the two treatments were generally similarly efficacious, although indacaterol treatment permitted a larger increase in trough FEV_1 and reduction in rescue medication use.

Table 2 Efficacy in the 'All patients' group after 12 weeks of treatment.

Variable	No. of patients (IND150)	No. of patients (TIO)	Difference, IND150−TIO, LSM or OR	SE	95% CI	p-Value
Trough FEV_1, L	663	648	0.03	0.011	0.01, 0.05	0.002
Patients with ≥0.10 L improvement in FEV_1	383/663	340/648	OR = 1.36		1.06, 1.75	0.017
Change in rescue use, puffs/day	680	654	−0.45	0.104	−0.65, −0.24	<0.0001
TDI total score, points	662	639	0.59	0.158	0.28, 0.90	0.0002
Patients with ≥1-point improvement in TDI	413/662	339/639	OR = 1.50		1.20, 1.89	0.0005
SGRQ total score, units	664	647	−2.48	0.605	−3.66, −1.29	<0.0001
Patients with ≥4-unit improvement in SGRQ	337/664	275/647	OR = 1.49		1.18, 1.87	0.0008

CI, confidence interval; IND150, indacaterol 150 μg; FEV_1, forced expiratory volume in 1 s; LSM, least squares mean; OR, odds ratio; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium 18 μg.

Table 3 Efficacy in the 'All patients, no ICS' subgroup after 12 weeks of treatment.

Variable	No. of patients (IND150)	No. of patients (TIO)	Difference, IND150−TIO, LSM or OR	SE	95% CI	p-Value
Trough FEV_1, L	375	367	0.05	0.015	0.02, 0.08	0.0008
Patients with ≥0.10 L improvement in FEV_1	207/375	187/367	OR = 1.36		0.98, 1.88	0.068
Change in rescue use, puffs/day	382	375	−0.54	0.128	−0.79, −0.29	<0.0001
TDI total score, points	375	359	0.77	0.204	0.37, 1.17	0.0002
Patients with ≥1-point improvement in TDI	242/375	196/359	OR = 1.66		1.21, 2.29	0.0018
SGRQ total score, units	373	363	−2.08	0.833	−3.71, −0.44	0.013
Patients with ≥4-unit improvement in SGRQ	192/373	159/363	OR = 1.47		1.08, 2.01	0.015

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; IND150, indacaterol 150 μg; LSM, least squares mean; OR, odds ratio; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium 18 μg.

Baseline data suggested a higher use of rescue medication and worse symptom scores in the 'with ICS' subgroups, and a higher level of ICS use among patients with the worse BDI scores. ICS treatment is not recommended for patients in GOLD A and B groups [1]. When the present trials were being performed, the GOLD recommendations were to reserve ICS for patients with stage 3 or 4 (severe or very severe) airflow limitation and repeated exacerbations [13]. In our population, it is conceivable that ICS were being inappropriately prescribed for patients with more severe symptoms rather than for patients at high risk of exacerbations [1], although it is also possible that ICS were being used for patients with exacerbations, lowering the frequency to below one a year. Inappropriate use of ICS in patients with moderate COPD has been reported elsewhere [14–16], despite the risk of side effects associated with this form of treatment [17]. When patients were stratified on the basis of symptoms, the resulting groups with more symptoms were similar in terms of airflow limitation compared with those with fewer symptoms, but there were large differences in health status. While symptoms are one of the domains in SGRQ, the data illustrate the importance of symptoms, specifically dyspnea, to the broader aspects of a patient's life. SGRQ scores in the present analysis ('Group A', 33–34; 'Group B', 50–52 units) were similar to those of group A and B patients in the ECLIPSE cohort (32 and 55 units, respectively). In that study, the risk of exacerbation and mortality in 'Group B' was similar to that in 'Group C' despite their moderate airflow limitation, indicating that the importance of symptoms for risk and poor outcomes should not be overlooked [18].

Current GOLD recommendations provide a multi-modal patient assessment model including airflow limitation, exacerbation history and symptom severity. The model allows for the use of a simple measure of symptoms such as the modified Medical Research Council (mMRC) scale, but recommends a more comprehensive assessment of symptoms and their impact on health status using the COPD Assessment Test (CAT) or COPD Control Questionnaire. The SGRQ, commonly used to assess the effects of drug treatment on health status in clinical trials, is regarded as too complex for routine use [1]. The BDI/TDI requires some

Table 4 Efficacy in the 'GOLD A, no ICS' subgroup after 12 weeks of treatment.

Variable	No. of patients (IND150)	No. of patients (TIO)	Difference, IND150−TIO, LSM or OR	SE	95% CI	p-Value
Trough FEV_1, L	239	232	0.05	0.018	0.01, 0.08	0.008
Patients with ≥0.10 L improvement in FEV_1	128/239	118/232	OR = 1.26		0.82, 1.92	0.287
Change in rescue use, puffs/day	243	235	−0.41	0.132	−0.67, −0.15	0.002
TDI total score, points	241	231	0.94	0.254	0.44, 1.44	0.0002
Patients with ≥1-point improvement in TDI	159/241	126/231	OR = 1.93		1.27, 2.93	0.002
SGRQ total score, units	238	232	−3.13	0.950	−5.00, −1.26	0.001
Patients with ≥4-unit improvement in SGRQ	125/238	96/232	OR = 1.77		1.18, 2.66	0.006

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IND150, indacaterol 150 μg; LSM, least squares mean; OR, odds ratio; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium 18 μg.

Table 5 Efficacy in the 'GOLD B, no ICS' subgroup after 12 weeks of treatment.

Variable	No. of patients (IND150)	No. of patients (TIO)	Difference, IND150–TIO, LSM or OR	SE	95% CI	p-Value
Trough FEV_1, L	129	129	0.055	0.028	0.00, 0.110	0.049
Patients with $\geq$0.10 L improvement in FEV_1	76/129	67/129	OR = 1.52		0.85, 2.73	0.154
Change in rescue use, puffs/day	132	134	−0.81	0.277	−1.36, −0.27	0.004
TDI total score, points	134	128	0.65	0.372	−0.09, 1.38	0.083
Patients with $\geq$1-point improvement in TDI	83/134	70/128	OR = 1.64		0.94, 2.86	0.082
SGRQ total score, units	129	125	−0.79	1.674	−4.09, 2.51	0.636
Patients with $\geq$4-unit improvement in SGRQ	64/129	59/125	OR = 1.19		0.67, 2.09	0.554

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; IND150, indacaterol 150 μg; LSM, least squares mean; OR, odds ratio; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium 18 μg.

judgment from the interviewer in questioning the patient and selecting a score, meaning that the measure is better suited for use in clinical trials rather than everyday practice [10]. A computerized version completed by the patient is also available [19]. However, because mMRC was used only in one of the source trials [5], BDI was chosen to define the subgroups in the present analysis and provided a split of similar proportions to those defined by mMRC (0–1 or $\geq$2). A previous report using factor analysis showed that mMRC and BDI were almost identical in their correlations with physiologic data and performed almost the same in assessing dyspnea in COPD patients, with similar (normal) distributions [20]. Therefore, the BDI is considered a suitable surrogate for defining the patients based on symptoms, given that dyspnea is the major symptom of patients with COPD.

The patient groups in the present analysis are also indirectly comparable to GOLD A and B in terms of baseline SGRQ scores, which have been shown to correlate with CAT scores, one of the GOLD-recommended assessments, with CAT scores of <10 and $\geq$10 used to discriminate GOLD A and B. In the 'no-ICS, BDI $\geq$7' patients in the present analysis ('GOLD A'), their mean baseline SGRQ scores of 31–34 units would approximate to a CAT score of 12, while SGRQ scores of 49–53 units in the 'no-ICS, BDI <7' patients ('GOLD B') translate to a CAT score of about 20 [21]. Nevertheless, the subgroup analysis does not fully model GOLD groups A and B. Because the original trials only recorded whether an exacerbation had occurred in the last year rather than the number of events, the resulting patient subgroups (no exacerbations in past year) are probably lower risk than the GOLD groups A and B, which allow for an exacerbation (provided not resulting in hospitalization) in the previous year.

The present data set was pooled from two randomized, prospective trials with closely similar designs and patient inclusion criteria. Other prospective comparisons between indacaterol and tiotropium conducted by the same sponsor were not appropriate for inclusion in the present data set owing to differences in study design and patient populations. A third-party blinded crossover comparison in patients with moderate-to-severe COPD had a treatment duration of only 14 days [22] and reported a 40 mL advantage in trough FEV_1 for indacaterol 150 μg. A 52-week comparison was conducted in patients with severe and very severe COPD and at least one exacerbation in the previous year (GOLD groups C + D, although defined by airflow limitation rather than exacerbation history) [2].

Three potential limitations to this analysis are acknowledged. First, there is potential bias due to open-label administration in one-third of the patients receiving tiotropium, since patients' subjective assessments may be affected by previous experience with the drug. In the blinded comparison, from which 66% of the present patients were drawn, indacaterol and tiotropium were not significantly different in their effect on trough FEV_1 at 12 weeks, but significant differences in favor of indacaterol were observed for TDI (0.58 points, OR 1.49) and SGRQ (−2.1 units, OR 1.43) as well as rescue medication use (−0.54 puffs/day) [6]. These data were very similar to the differences in the whole subgroup of 'All patients' in the present analysis (TDI, 0.59 points, OR 1.50; SGRQ −2.5 units, OR 1.49; rescue use −0.45 puffs/day; see Table 2). Furthermore, smaller differences between indacaterol and tiotropium in many subjective variables in the open-label study [5] than in the fully blinded study [6] argue against a major confounding effect of open-label tiotropium.

Second, the 12-week duration may not have been long enough for treatment-associated improvements in patients' health status to evolve fully [23]. However, 12 weeks is a realistic timeframe in terms of any improvements that might be expected to occur when treatments are initiated in primary care, and would be more acceptable to both patients and physicians than would changes that require a longer period to become manifest. In analysis of data from the 26-week INHANCE study, there was a significant −2.3 unit treatment difference ($p \leq 0.01$) between indacaterol 150 μg and tiotropium 18 μg in SGRQ total score [5]. Additionally, a recent post-hoc analysis of indacaterol trials compared the efficacy of indacaterol with placebo and tiotropium in GOLD A and B patients over 6 months [24]. In this analysis, although not significant, the difference in SGRQ score was larger between indacaterol and placebo

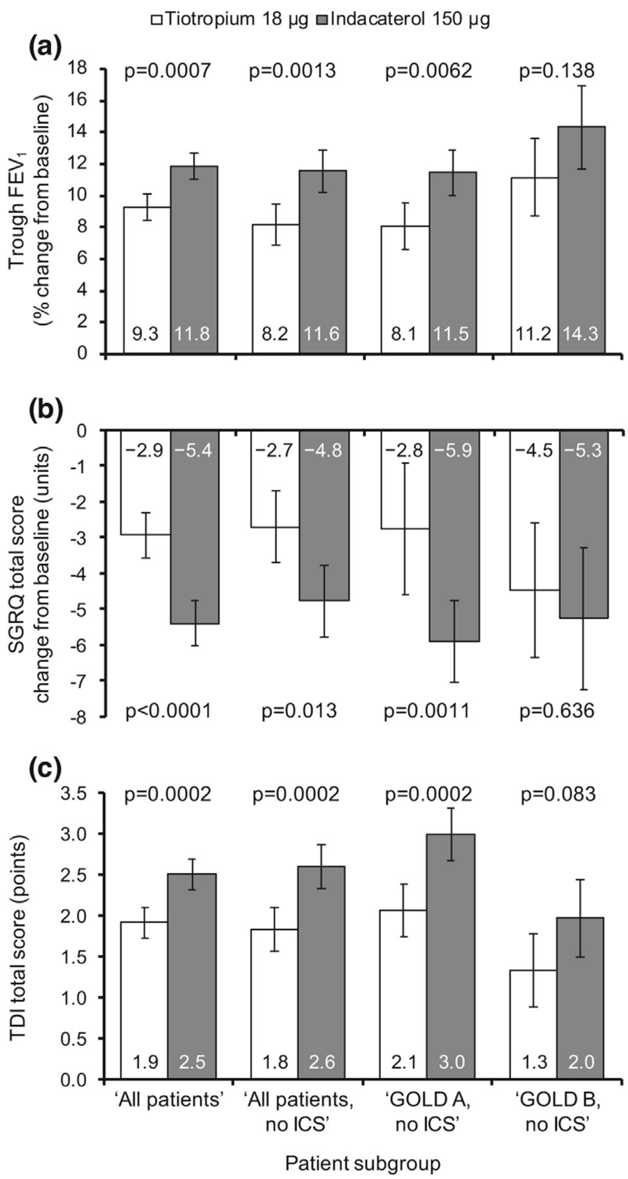

Figure 1 Changes from baseline to week 12 in (a) trough FEV_1 (%) and (b) SGRQ total score, and (c) TDI total score. Data are LSM ± standard errors. Absolute values (LSM) for changes from baseline in trough FEV_1 with indacaterol and tiotropium were, respectively, in the 'All patients' group: 0.152 and 0.119 L; 'All patients, no ICS': 0.151 and 0.102 L; 'GOLD A, no ICS': 0.154 and 0.106 L; 'GOLD B, no ICS': 0.199 and 0.143 L. FEV_1, forced expiratory volume in 1 s; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LSM, least squares mean; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

compared with tiotropium and placebo in GOLD A and B patients. Indacaterol 150 μg was the only treatment that significantly improved SGRQ total score compared with placebo in GOLD A patients [24].

Third, increasing levels of stratification resulted in small numbers of patients and may have contributed to the lack of statistically significant treatment differences in some of the subgroups, especially in the 'GOLD B, no ICS' subgroup. Nevertheless, overall, significant differences were observed and allow some conclusions to be drawn in terms of appropriate treatment and the effects of long-acting bronchodilators in these groups.

The results confirm the value of long-acting bronchodilator treatment in patients with COPD in GOLD group A and B patients. They also show that many such patients are treated with ICS, contrary to the previous or currently

Table 6 AEs overall and most frequently occurring (incidence in either treatment group ≥0.05 per patient-year for AEs and ≥0.01 per patient-year for SAEs) adjusted for exposure in the 'All patients' group.

	Indacaterol 150 μg	Tiotropium 18 μg
Patients (n)	722	700
Patients with ≥1 AE	411	359
Total patient-years	249.9	202.5
Number of AEs (AEs per patient-year)	1346 (5.39)	1036 (5.12)
COPD worsening	104 (0.42)	80 (0.40)
Headache	67 (0.27)	48 (0.24)
Nasopharyngitis	62 (0.25)	54 (0.27)
Cough	53 (0.21)	38 (0.19)
Upper respiratory tract infection	36 (0.14)	21 (0.10)
Muscle spasms	35 (0.14)	4 (0.02)
Influenza	24 (0.10)	10 (0.05)
Sinusitis	23 (0.09)	10 (0.05)
Back pain	19 (0.08)	14 (0.07)
Arthralgia	18 (0.07)	5 (0.02)
Oropharyngeal pain	17 (0.07)	15 (0.07)
Dyspnea	16 (0.06)	17 (0.08)
Bronchitis	16 (0.06)	11 (0.05)
Lower respiratory tract infection	16 (0.06)	10 (0.05)
Viral upper respiratory tract infection	15 (0.06)	8 (0.04)
Hypertension	15 (0.06)	7 (0.03)
Nausea	15 (0.06)	6 (0.03)
Diarrhea	14 (0.06)	7 (0.03)
Urinary tract infection	13 (0.05)	15 (0.07)
Dry mouth	5 (0.02)	25 (0.12)
SAEs (per patient-year)		
Patients with ≥1 SAE	33	36
Total patient-years	249.9	202.5
Number of SAEs (AEs per patient-year)	49 (0.20)	56 (0.28)
COPD	7 (0.03)	5 (0.02)
Angina pectoris	3 (0.01)	0
Coronary artery disease	3 (0.01)	1 (0.01)
Atrial fibrillation	2 (0.01)	3 (0.02)
Pneumonia	2 (0.01)	2 (0.01)
Syncope	2 (0.01)	2 (0.01)
Arrhythmia	0	2 (0.01)
Coronary artery occlusion	0	2 (0.01)
Peripheral arterial occlusive disease	0	2 (0.01)

AEs, adverse events; COPD, chronic obstructive pulmonary disease; SAEs, serious adverse events.

recommended GOLD treatment strategy, and suggest that patients may have been given ICS on the basis of symptoms alone rather than recommended predictors of risk (i.e. airflow limitation and history of frequent exacerbations), although it acknowledged that theoretically a very good response to ICS may also have accounted for the lack of exacerbations. Compared with tiotropium, indacaterol improved lung function and provided a greater benefit in terms of dyspnea and health status in the population of patients with largely moderate airflow limitation and no exacerbations in the previous year. Indacaterol was more efficacious than tiotropium in the subgroup with fewer symptoms, classed as GOLD A in the present analysis, with significant improvements in lung function, less dyspnea and rescue use, and better health status. Our findings suggest that patients in GOLD groups A and B may experience greater benefits with indacaterol than with tiotropium.

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Conflict of interest statements

DAM has received consulting fees for advisory boards from Boehringer Ingelheim, GSK, Novartis, Sunovion and Theravance. He receives royalties from CRC Press (Dyspnea 3rd Edition) and from MAPI (use of BDI/TDI). He is on Speaker's Bureau of Boehringer Ingelheim, GlaxoSmithKline, and Sunovion. His website (http://www.donaldmahler.com) is an educational website for those with COPD and their families. His current position is Director of Respiratory Services at Valley Regional Hospital in Claremont, NH.

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PA is a full-time employee of Novartis. At the time of writing, DL was a full-time employee of Novartis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2015.05.012.

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