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GOLD 2017 treatment pathways in 'real life': An analysis of the DACCORD observational study

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ABSTRACT

Introduction: The 2017 update to the Global Initiative for Obstructive Lung Disease (GOLD) strategy document includes recommendations for treatment intensification or step-down in chronic obstructive pulmonary disease (COPD), although recognises that limited supporting information is available.
DACCORD is an ongoing observational, non-interventional study, recruiting patients following COPD maintenance treatment change or initiation, a subset of whom were receiving a long-acting β_2-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) fixed-dose combination (FDC) on entry. Since there were no requirements in terms of prior medication (and no washout before commencing LABA/LAMA FDC), this provides an opportunity to generate 'real world' data to test the GOLD 2017 recommendations.
Methods: To reduce heterogeneity, the current analyses include patients receiving indacaterol/glycopyrronium at baseline, and who, prior to the study, were receiving no COPD maintenance medication ('none'), LABA or LAMA monotherapy ('mono'), LABA plus inhaled corticosteroid (ICS; 'LABA/ICS'), or triple therapy ('triple'). At the baseline visit, data collected included: demographic and disease characteristics; COPD Assessment Test (CAT); and exacerbations in the 6 months prior to entry. At 3, 6, 9 and 12 months data on exacerbations were collected, with CAT recorded at 3 and 12 months.
Results: A total of 2724 patients were included in the baseline analyses: 795, 954, 598 and 377 in the 'none', 'mono', 'LABA/ICS' and 'triple' subgroups, respectively. There were no clinically relevant differences in baseline demographics between the four groups. In terms of disease characteristics, the 'triple' group had the highest proportion of patients with a disease duration of more than 1 year since diagnosis and with severe/very severe airflow limitation, but a similar percentage of non-exacerbators compared to the 'none' group.
Over the 1-year follow-up, the majority of patients in all four subgroups did not exacerbate (exacerbation rates 0.16, 0.19, 0.21, and 0.26 in the 'none', 'mono', 'LABA/ICS' and 'triple' groups, respectively). At 12 months, 61.4%, 65.0%, 71.0% and 52.4% of patients had a clinically relevant improvement in CAT score.
Conclusions: Overall, the results support the GOLD recommendations in suggesting that a switch from a mono-bronchodilator or LABA plus ICS to LABA/LAMA FDC is a valid treatment option for patients with COPD. The results also validate the use of a LABA/LAMA FDC as initial maintenance treatment for COPD, and provide first 'real world' evidence to support the newly added 'step down' recommendation (from triple to LABA/LAMA FDC).

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1. Introduction

COPD is typically a progressive disease, and as a consequence patients are likely to require treatment intensification over time [1]. The 2017 update to the Global Initiative for Obstructive Lung Disease (GOLD) strategy document includes a number of recommendations for treatment intensification – either due to exacerbations or symptoms [1]. The document also includes a suggestion that patients should be 'stepped down' from triple therapy with a long-acting β_2-agonist (LABA), a long-acting muscarinic antagonist (LAMA) and an inhaled corticosteroid (ICS) to dual bronchodilation with a LABA plus a LAMA in the event of lack of efficacy or the presence of adverse events. However, GOLD recognise that relatively limited information is available to support these recommendations, with few interventional randomised clinical trials having examined such treatment changes.

DACCORD is an ongoing observational, non-interventional study being conducted in primary and secondary care throughout Germany [2]. We have previously reported data from the first cohort of patients, who entered DACCORD following COPD maintenance treatment change or initiation, approximately two thirds of whom started or switched to a treatment regimen including glycopyrronium prior to entry [3–6]. In one of the publications, we described 2-year follow-up data from a subgroup of patients from whom ICS was withdrawn prior to entry [4]. In the current manuscript, we describe data from the second cohort of patients, approximately two thirds of whom either started or switched to a regimen containing a LABA/LAMA fixed-dose combination (FDC) prior to entry. Since there were no requirements in terms of prior medication to be eligible for the study, the population recruited was previously receiving a range of COPD maintenance medication, with some receiving no maintenance medication prior to entry, some receiving LABA or LAMA monotherapy, some receiving LABA plus ICS, and some receiving triple therapy. Since there was no washout before commencing LABA/LAMA FDC, this provides an opportunity to generate 'real world' data in support of the GOLD 2017 recommendations.

The two aims of this analysis were: to describe the baseline demographics and disease characteristics of patients initiating LABA/LAMA FDC in clinical practice from these four treatment pathways; and to determine the clinical course of patients following this treatment change (therefore providing data to test the new GOLD recommendations).

2. Methods

2.1. Trial design

DACCORD is an ongoing, longitudinal, prospective non-interventional study. The cohort analysed for this manuscript includes approximately 4000 patients who had either newly initiated LABA/LAMA FDC, or who had switched to a regimen including a LABA/LAMA FDC. This cohort also included a control group of approximately 2000 patients receiving any other COPD maintenance therapy.

Specific visits are not mandated by the protocol, but, consistent with usual care in Germany, it was anticipated that data would be recorded approximately every three months. At the baseline visit, data collected in Internet-based electronic case report forms included: demographic and disease characteristics; prescribed prior COPD medication; COPD Assessment Test (CAT); exacerbations in the 6 months prior to entry (defined based on prescription of oral steroids and/or antibiotics or hospitalization); and forced expiratory volume in 1 s (FEV_1). At 3, 6, 9 and 12 months data on exacerbations and prescribed COPD medication were collected, with CAT recorded at 3 and 12 months.

2.2. Participants

The main inclusion criteria were a diagnosis of COPD fulfilling the German COPD Disease Management Program (DMP) criteria (one of which is that COPD is confirmed by spirometry testing), age ≥40 years, and initiating or changing COPD maintenance medication. Given the non-interventional nature of the study, the decision to initiate or change medication was made by the patients' physicians prior to inclusion in DACCORD. In order to recruit as broad a population as possible, patients were excluded only if they were in the asthma DMP, or if they were participating in a randomised clinical trial. In particular, use of oxygen and participation in a pulmonary rehabilitation programme did not impact eligibility. The study is registered in the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (http://www.encepp.eu/encepp/viewResource.htm?id=6316), and was approved by the ethics committee of the University of Erlangen-Nuremberg. All patients provided written informed consent prior to inclusion.

2.3. Statistical methods

The subgroup analyses reported in this manuscript were not formally powered. To reduce heterogeneity of the results, patients were included if they were receiving only LABA/LAMA FDC on entry (so, for example, patients also receiving theophylline or PDE4-inhibitors were excluded). In addition, although any LABA/LAMA FDC was permitted in DACCORD, almost all patients were receiving indacaterol/glycopyrronium (perhaps because recruitment into this cohort commenced shortly after commercial availability of this FDC, and before other combinations were launched). It was therefore decided that, in order to further reduce heterogeneity, data would be analysed only from patients receiving indacaterol/glycopyrronium at baseline. Baseline data are therefore reported for all patients receiving only indacaterol/glycopyrronium on entry, and who, prior to the study, were receiving no COPD maintenance medication, LABA or LAMA monotherapy, LABA plus ICS, or triple therapy. Post-baseline analyses were performed on all patients in the baseline population who received only indacaterol/glycopyrronium throughout Year 1, and who attended Visit 4 (the 1-year visit) and at least two of the three intermediate visits.

Exacerbation rates were estimated using a negative binomial regression model with annualised numbers of exacerbation as dependent variable and no independent variable. For CAT total score, mean values are presented, together with the proportion of patients with clinically relevant (i.e., ≥2 unit) changes from baseline – either improvement or worsening.

3. Results

3.1. Participants

As shown in Fig. 1, of the 4056 patients recruited into the LABA/LAMA arm of DACCORD, 3351 were receiving only indacaterol/glycopyrronium (and no other COPD maintenance medication) on entry. Of the 2724 patients in the four groups analysed, 1724 (64.0%) completed a full year of follow-up whilst still receiving only indacaterol/glycopyrronium. Most of the exclusions from the 1-year analysis were due to missing visits; 327 patients (12.0%) completed the follow-up period but had some change in COPD maintenance medication (switch, add-on or discontinuation).

There were no clinically relevant differences in baseline demographics between the four groups, although there was a higher proportion of patients <65 years of age in the 'no maintenance'

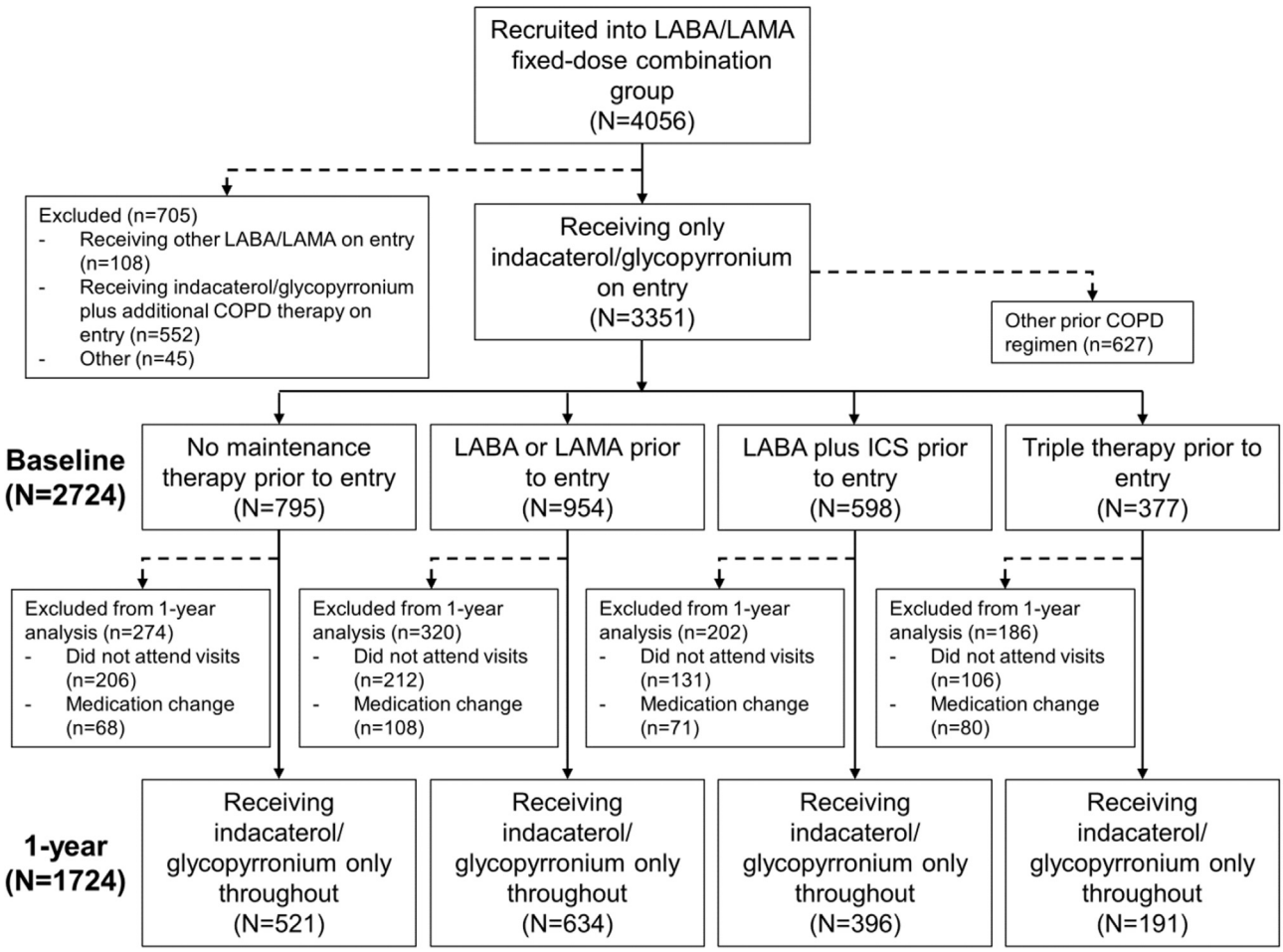

Fig. 1. Patient disposition, according to maintenance medication prior to entry.

group than the other three groups, and this group also contained a higher proportion of current smokers (Table 1). There were more marked differences between the groups in terms of disease characteristics. Patients newly initiating treatment tended to be more recently diagnosed, and to be exacerbation free. In contrast, the group previously on triple therapy had the highest proportion of patients with disease duration of more than 1 year since diagnosis, and the highest proportion of patients with severe and very severe airflow limitation – although a similar proportion of non-exacerbators to the 'no prior medication' group. Of note, the mean modified Medical Research Council (mMRC) dyspnoea and CAT scores indicated a moderately high impact of the disease on patients in all four groups, with more than 60% of patients previously receiving ICS-containing therapy reporting an mMRC dyspnoea score >1.

3.2. Outcomes over 1 year

3.2.1. No prior maintenance treatment

Of the 589 patients who commenced therapy with indacaterol/glycopyrronium and had full 1-year follow-up data, 521 (88%) continued to receive indacaterol/glycopyrronium alone over the 1-year follow-up period.

The majority of patients in this subgroup did not exacerbate, either during the 6 months before recruitment ('baseline') or during the 1-year follow-up (Fig. 2a). The annualised exacerbation rate during the 1-year follow-up period was 0.16 (95% confidence limit 0.12, 0.21). Even in the subgroup of patients who exacerbated in the 6 months before recruitment, the 1-year exacerbation rate was relatively low (0.35 [0.23, 0.53]), although higher than in patients who did not exacerbate prior to recruitment (0.12 [0.09, 0.17]).

There was an improvement in mean CAT total score over the follow-up period, from 18.4 (SD 8.0) at baseline to 15.6 (7.6) at 3 months and 15.0 (7.5) at 12 months, with the difference from baseline at both 3 and 12 months exceeding the clinically relevant difference (2 units). This improvement was reflected in the proportion of patients with a clinically relevant improvement, with more than half of the patients reporting an improvement by 3 months, and over 60% by 12 months (Table 2).

3.2.2. Switch from LABA or LAMA

Of the 742 patients who switched from LABA or LAMA monotherapy to indacaterol/glycopyrronium prior to entering DACCORD who had full 1-year follow-up data, 634 (85.4%) continued to receive indacaterol/glycopyrronium alone over the 1-year follow-up period.

The proportion of patients in this subgroup reporting an exacerbation during the 1-year follow-up period was approximately half that reporting exacerbations during the 6 months prior to recruitment (Fig. 2b). The annualised exacerbation rate during the 1-year follow-up period was 0.19 (95% confidence limit 0.15, 0.24). In the subgroup of patients who did not exacerbate during the 6 months before recruitment the 1-year exacerbation rate was 0.11 (0.08, 0.15), lower than in patients who exacerbated before

Table 1
Baseline demographics and disease characteristics.

	Prior COPD maintenance medication			
	None (N = 795)	LABA or LAMA (N = 954)	LABA + ICS (N = 598)	Triple therapy (N = 377)
Sex, male, n (%)	459 (57.7)	586 (61.4)	338 (56.5)	214 (56.8)
Age (years), mean (SD)	64.8 (10.4)	66.6 (10.4)	67.1 (10.3)	68.2 (9.4)
Age groups, n (%)				
<65	393 (49.4)	403 (42.2)	241 (40.3)	130 (34.5)
65–75	267 (33.6)	330 (34.6)	219 (36.6)	156 (41.4)
>75	135 (17.0)	221 (23.2)	138 (23.1)	91 (24.1)
BMI (kg/m^2), mean (SD)	27.6 (5.8)	27.5 (5.4)	27.7 (5.6)	27.7 (6.4)
Smoking status, n (%)				
Ex-smoker	228 (28.7)	380 (39.8)	237 (39.6)	182 (48.3)
Current smoker	365 (45.9)	380 (39.8)	212 (35.5)	140 (37.1)
Never smoker	201 (25.3)	193 (20.2)	149 (24.9)	55 (14.6)
Missing	1 (0.1)	1 (0.1)	0	0
Duration since primary diagnosis, n (%)				
≤1 year	438 (55.1)	245 (25.7)	128 (21.4)	59 (15.6)
>1 year	357 (44.9)	709 (74.3)	470 (78.6)	318 (84.4)
FEV_1% predicted, mean (SD)[a]	65.9 (21.4)	65.7 (20.3)	66.2 (23.3)	57.1 (19.5)
FEV_1% predicted, n (%)[a]				
≥80%	184 (23.1)	216 (22.6)	146 (24.4)	47 (12.5)
50 to <80%	422 (53.1)	533 (55.9)	299 (50.0)	182 (48.3)
30 to <50%	167 (21.0)	179 (18.8)	133 (22.2)	124 (32.9)
<30%	22 (2.8)	26 (2.7)	20 (3.3)	24 (6.4)
mMRC dyspnoea score, mean (SD)	1.5 (1.0)	1.5 (1.0)	1.8 (1.0)	1.9 (1.1)
mMRC dyspnoea score, n (%)				
0–1	435 (54.7)	500 (52.4)	234 (39.1)	149 (39.5)
≥2	360 (45.3)	454 (47.6)	364 (60.9)	228 (60.5)
CAT, mean (SD)	18.1 (8.1)	18.2 (7.6)	20.8 (7.7)	18.3 (7.8)
CAT score, n (%)				
0–<10	133 (16.7)	126 (13.2)	52 (8.7)	53 (14.1)
10–20	341 (42.9)	459 (48.1)	220 (36.8)	181 (48.0)
>20–30	263 (33.1)	316 (33.1)	270 (45.2)	114 (30.2)
>30	58 (7.3)	53 (5.6)	56 (9.4)	29 (7.7)
Number of exacerbations in the 6 months prior to entry, n (%)				
0	659 (82.9)	734 (76.9)	413 (69.1)	301 (79.8)
1	106 (13.3)	146 (15.3)	114 (19.1)	56 (14.9)
≥2	28 (3.5)	63 (6.6)	60 (10.0)	16 (4.2)
Missing	2 (0.3)	11 (1.2)	11 (1.8)	4 (1.1)
Comorbidities, n (%)				
Alpha-1 antitrypsin deficiency	0	0	2 (0.3)	0
Bronchiectasis	6 (0.8)	11 (1.2)	5 (0.8)	6 (1.6)
Bronchial carcinoma	13 (1.6)	13 (1.4)	10 (1.7)	8 (2.1)
Sleep apnoea	63 (7.9)	80 (8.4)	41 (6.9)	42 (11.1)
Cardiovascular disease	397 (49.9)	554 (58.1)	333 (55.7)	242 (64.2)
Diabetes mellitus type 2	144 (18.1)	192 (20.1)	120 (20.1)	60 (15.9)
Osteoporosis	35 (4.4)	47 (4.9)	42 (7.0)	32 (8.5)
Psychiatric disorders	86 (10.8)	92 (9.6)	44 (7.4)	39 (10.3)

COPD = chronic obstructive pulmonary disease; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; BMI = body-mass index; FEV_1 = forced expiratory volume in 1 s; SD = standard deviation; mMRC = modified Medical Research Council; CAT = COPD Assessment Test.
[a] Random spirometry, assessed without requirement for washout of COPD medication or additional inhalation of short-acting β_2-agonist.

recruitment (0.39 [0.28, 0.55]).

Mean CAT total score improved by a clinically relevant amount over the follow-up period, from 18.0 (SD 7.6) at baseline to 15.6 (6.9) at 3 months and 14.9 (7.0) at 12 months. More than half of the patients reported a clinically relevant improvement by 3 months, and nearly two-thirds by 12 months (Table 2).

3.2.3. Switch from LABA plus ICS

Of the 467 patients who switched from LABA plus ICS to indacaterol/glycopyrronium prior to entering DACCORD and who had full 1-year follow-up data, 396 (84.8%) continued to receive indacaterol/glycopyrronium alone over the 1-year follow-up period. An ICS-containing regimen was reinitiated by 48 patients, only 7 of whom reinitiated the ICS following a documented exacerbation.

Although approximately one third of the patients in this subgroup reported at least one exacerbation during the 6 months before recruitment, fewer than 15% reported an exacerbation during the 1-year follow-up period (Fig. 2c). The annualised exacerbation rate during the 1-year follow-up period was 0.21 (95% confidence limit 0.15, 0.28). In the subgroup of patients who exacerbated in the 6 months before recruitment, the 1-year exacerbation rate was 0.28 (0.17, 0.48), similar to the rate in patients who did not exacerbate prior to recruitment (0.17 [0.12, 0.23]).

Mean CAT total score improved over the follow-up period by a clinically relevant amount, from 21.2 (SD 7.1) at baseline to 17.9 (6.4) at 3 months and 17.4 (6.4) at 12 months. More than half of the patients reported a clinically relevant improvement by 3 months, and over two-thirds by 12 months (Table 2).

3.2.4. Switch from triple therapy

Of the 271 patients who switched from triple therapy to indacaterol/glycopyrronium prior to entering DACCORD, 191 (70.5%) continued to receive indacaterol/glycopyrronium alone over the 1-year follow-up period. An ICS-containing regimen was reinitiated

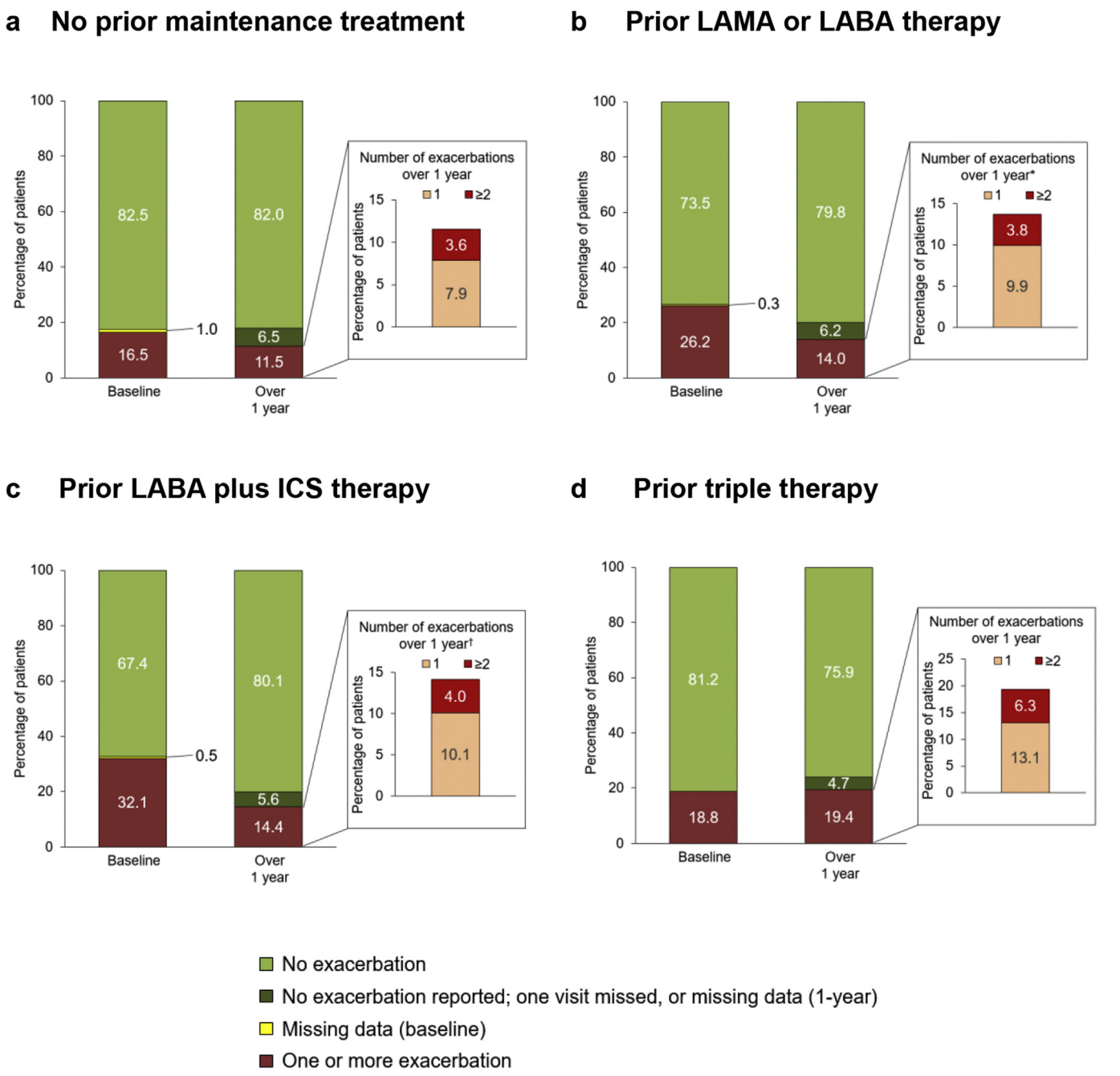

Fig. 2. Percentage of patients reporting exacerbations at baseline and over one year in those previously receiving a) no maintenance treatment (N = 521); b) LABA or LAMA therapy (N = 634); c) LABA plus ICS (N = 396); d) triple therapy (N = 191).
Data missing from *2 patients, and †1 patient, who reported at least one exacerbation, but not the number. LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

by 61 patients, but only 18 following a documented exacerbation.

Despite the withdrawal of ICS, a similar proportion of patients exacerbated during the 6 months before recruitment and over the 1-year follow-up (Fig. 2d). The annualised exacerbation rate during the 1-year follow-up period was 0.26 (95% confidence limit 0.19, 0.37). In the subgroup of patients who did not exacerbate in the 6 months before recruitment, the 1-year exacerbation rate was 0.20 (0.14, 0.30), numerically lower than the rate in patients who exacerbated during the 6 months before recruitment (0.50 [0.27, 0.92]).

Mean CAT total score improved over the follow-up period, from 18.0 (SD 7.7) at baseline to 17.1 (7.3) at 3 months and 16.2 (7.4) at 12 months. Approximately half of the patients reported a clinically relevant improvement by 3 and 12 months (Table 2).

4. Discussion

Over the 1-year follow-up of DACCORD, the use of LABA/LAMA FDC was associated with a generally reduced risk of exacerbations (with a very low percentage of patients with ≥2 exacerbations), and an improvement in health status compared with the previous treatment regimen. These improvements were observed in all four

Table 2
Number and percentage of patients with a clinically relevant worsening, no change, or improvement in CAT total score.

	Worsening ≥2 units	No change	Improvement ≥2 units
Patients previously receiving no maintenance treatment (N = 521)			
At 3 months[a]	74 (14.2)	157 (30.1)	285 (54.7)
At 12 months	85 (16.3)	116 (22.3)	320 (61.4)
Patients previously receiving LABA or LAMA therapy (N = 634)			
At 3 months[b]	75 (11.8)	189 (29.8)	363 (57.3)
At 12 months	86 (13.6)	136 (21.5)	412 (65.0)
Patients previously receiving LABA plus ICS (N = 396)			
At 3 months[c]	39 (9.8)	78 (19.7)	276 (69.7)
At 12 months	54 (13.6)	61 (15.4)	281 (71.0)
Patients previously receiving triple therapy (N = 191)			
At 3 months[a]	42 (22.0)	53 (27.7)	91 (47.6)
At 12 months	39 (20.4)	52 (27.2)	100 (52.4)

Data missing for: a) 5 patients, b) 7 patients, c) 3 patients. CAT = COPD Assessment Test; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid.

subgroups, supporting the role of LABA/LAMA FDCs in the management of COPD.

It is perhaps not surprising that the group initiating maintenance treatment would benefit from a LABA/LAMA FDC, given the wealth of clinical trial data that demonstrate the benefit of bronchodilator treatment in this population [7–11]. The results from the subgroup previously receiving monotherapy with a LABA or a LAMA are more informative, given that data on the relative efficacy of mono- and dual-bronchodilators have predominantly been provided by parallel group interventional studies [12–15]. There has been considerable debate to what extent LABA/LAMA combinations show more pronounced effects on patient reported outcomes such as health-related quality of life compared to single bronchodilators. This analysis demonstrates that 65% of patients switched from single to dual bronchodilation improve beyond the MCID.

Of more interest, perhaps, are the groups switching from LABA plus ICS or triple therapy. The LABA plus ICS group included the highest proportion of patients with a history of exacerbations, yet following the switch the rate of exacerbations was only 0.2 per patient per year. Furthermore, almost three quarters of patients reported an improvement in health status. These findings are consistent with the results of the interventional FLAME study, in which patients randomised to receive a LABA/LAMA FDC experienced fewer exacerbations and an improvement in health status compared with those receiving a LABA plus an ICS – although the differences between the groups in mean SGRQ-C total score in FLAME were below the MCID, with fewer than 50% of patients reporting a clinically relevant improvement [16]. The group switching from triple therapy to LABA/LAMA FDC add to the body of evidence on the withdrawal of ICS in the management of COPD, including interventional studies [17,18], observational studies [19], and data from the first cohort of DACCORD [4]. In particular, when comparing the 6 months prior to entry with the 1-year follow-up data there was no increase in the percentage of patients exacerbating.

Persistence to medication was notably high in all four analysed subgroups, suggesting that LABA/LAMA FDC therapy was both effective and accepted by patients. Persistence was lowest in the group switched from triple therapy, although even in this group more than 70% of patients were still receiving LABA/LAMA FDC alone at the end of the 1-year follow-up, compared with 88, 85 and 85% in the other three subgroups. In the LABA plus ICS and triple therapy groups, more than half of the treatment change involved reinitiation of ICS; the reason for this reinitiation is unclear, since most of these patients had not experienced an exacerbation.

Previous versions of the GOLD strategy document provided guidance only on initial maintenance treatment. The 2017 revision includes for the first time a series of treatment algorithms for the management of COPD, as yet based mostly on expert opinion [1]. For patients who experience persistent symptoms or further exacerbations despite monotherapy with a long-acting bronchodilator, the recommended next step in treatment is the use of a LABA plus a LAMA; for those patients who experience symptoms or exacerbate despite a LABA plus an ICS, switching to a LABA plus a LAMA is one of two options. Moreover, in patients who have a lack of efficacy despite receiving triple therapy, removal of the ICS component of therapy (i.e., to LABA plus LAMA) is a recognised treatment option. The baseline disease characteristics of the recruited patients in DACCORD largely support these recommendations, in that although the majority of patients in all groups had not experienced any exacerbations during the 6 month baseline period, almost all of the patients were symptomatic at baseline. This suggests that (in this population at least) initiation or switching was more likely to be driven by symptoms than exacerbations, especially in the LABA plus ICS and triple therapy groups, in which nearly two thirds of patients had an mMRC dyspnoea score >1, and over 85% had a CAT score >10. The low exacerbation history could limit the generalisability of these findings. However, this was a population that was being managed in standard primary and secondary care practices across Germany, and is similar to populations recruited into other observational studies [20–22], so we believe that it is representative of the general 'real life' COPD population, in contrast to the typical interventional clinical trial, which has little to do with clinical practice.

As might be anticipated, patients who had previously been on triple therapy were more likely to have been diagnosed more than 1 year prior to entry, and had the highest degree of airflow limitation. Of note, this subgroup was less likely to have a history of exacerbations than the subgroup switched from LABA plus ICS. Unfortunately, since the reason for switching was not recorded, we do not know whether ICS was indicated for these patients at the time of initiation, but the low proportion of exacerbating patients in this group does provide additional support to the suggestion from database studies that the gradual drift to triple therapy is driven more by symptoms than exacerbations [23]. It is important to note that although they were the two smallest subgroups, the numbers of patients in the triple therapy and LABA plus ICS subgroups suggest that physicians are becoming comfortable with the concept of withdrawing ICS in patients with COPD – at least in appropriately selected patients.

The high proportion of the 'no maintenance' patients initiating treatment with a LABA plus LAMA in DACCORD is somewhat surprising, given documents such as GOLD generally recommend a mono-bronchodilator as initial treatment, except for patients who are highly symptomatic and at high risk of exacerbations [1]. However, although few of these patients had a history of exacerbations, they had a high symptom load on entry to DACCORD, suggesting that the initial diagnosis was driven by the presence of symptoms and not by an exacerbation. GOLD says of patients in Group B, 'for patients with severe breathlessness initial therapy with two bronchodilators may be considered', and in observational studies patients receiving a mono-bronchodilator often report a high degree of symptoms [24].

The main strength of this study is that a representative 'real world' population was recruited, with patients continuing to be managed in primary or secondary care (rather than in specialist research centres). In particular, the decision to initiate or switch to a LABA/LAMA was taken prior to the decision to include a patient, rather than being mandated by the protocol (as would be the case in an interventional study). The main weakness (typical of

observational studies) is that only data collected as a result of standard care are available, and so, for example, we do not know the reasons behind the treatment initiation or change and so have attempted to use clinical data to interpret these reasons. In addition, since we sought to describe the clinical course of COPD within the four groups of patients following treatment initiation or change, we did not adjust the 1 year data to take account of differences between groups in baseline characteristics, such as smoking history, number of exacerbations or CAT total score. We also did not collect data on the use of non-COPD medication during the study (such as participation in pulmonary rehabilitation); however, the large numbers of patients in each subgroup, and the relatively limited availability of pulmonary rehabilitation in Germany makes us confident that the results we observed are due to treatment change or initiation.

5. Conclusion

Overall, the results obtained in this cohort support the GOLD recommendations in suggesting that in patients who are symptomatic while receiving a mono-bronchodilator or LABA plus ICS, the switch to LABA/LAMA FDC is a valid treatment option. The results also validate the use of a LABA/LAMA FDC as first maintenance treatment for symptomatic COPD patients. Furthermore, the analyses provide first real world evidence on the 'step down' from triple to LABA/LAMA FDC.

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Conflict of interest

Dr Worth reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Klosterfrau, Menarini, Novartis and Takeda.

Dr Buhl reports personal fees from AstraZeneca, Chiesi, GlaxoSmithKline and Teva, and grants and personal fees from Boehringer Ingelheim, Novartis and Roche.

Dr Criée reports personal fees from Boehringer Ingelheim, Chiesi, GSK, Novartis, Takeda and Berlin-Chemie.

Dr Kardos reports personal fees from Novartis, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Menarini and Takeda.

Dr Lossi is employed at Novartis Pharma GmbH, Nürnberg, the sponsor of the study.

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