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Clinical Trial Paper

A two-year evaluation of the 'real life' impact of COPD on patients in Germany: The DACCORD observational study

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ABSTRACT

Introduction: DACCORD is an observational, non-interventional study being conducted in German primary and secondary care centres. The study aims to describe the impact of disease (including exacerbations) and treatments over 2 years on 'real-life' patients with chronic obstructive pulmonary disease (COPD).

Materials and methods: Patients had a clinical and spirometry diagnosis of COPD, were aged ≥40 years and, on recruitment, were initiating or changing COPD maintenance medication. The only exclusion criteria were asthma and randomised clinical trial participation. Exacerbations data were collected every 3 months. COPD medication, COPD Assessment Test (CAT) and forced expiratory volume in 1 s (FEV_1) were recorded at baseline and after 1 and 2 years.

Results: A total of 6122 patients were recruited, 3137 (51.2%) of whom completed the 2-year visit. The mean age of these patients was 65.6 years, 59% were male, 69% had mild or moderate airflow limitation, and their mean COPD Assessment Test (CAT) total score was 20.3. Overall, there was a trend towards decreasing COPD exacerbation rates over the 2-year follow-up period, with rates of 0.390 during Year 1 and 0.347 during Year 2. Rates were lower in patients with no exacerbation during the 6 months prior to entry (0.263 and 0.251 during Years 1 and 2, respectively), with 51.6% of patients having no exacerbation during the 6 months prior to entry and over the 2-year follow-up. Approximately 50% of the overall population experienced a clinically relevant improvement from baseline in CAT total score at Year 1 and 2. When assessed by treatment class (or classes), persistence to medication was high (77.8% in Year 1 and 71.4% in Year 2).

Conclusions: Overall, the 2-year follow-up data from DACCORD suggest that for most patients with COPD exacerbations are a rare event. For the majority of patients, the focus should be on managing symptoms, and the impact that these symptoms have on their daily lives. Even for those patients who do exacerbate, although prevention of exacerbations is an important factor, management of symptoms should be a key consideration. DACCORD also suggests that COPD disease progression is not inevitable – providing patients are receiving pharmacological treatment.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is generally considered to be a progressive disease, with patients experiencing a gradual loss in lung function together with increasing symptoms [1]. The evaluation of the severity of COPD should take both current

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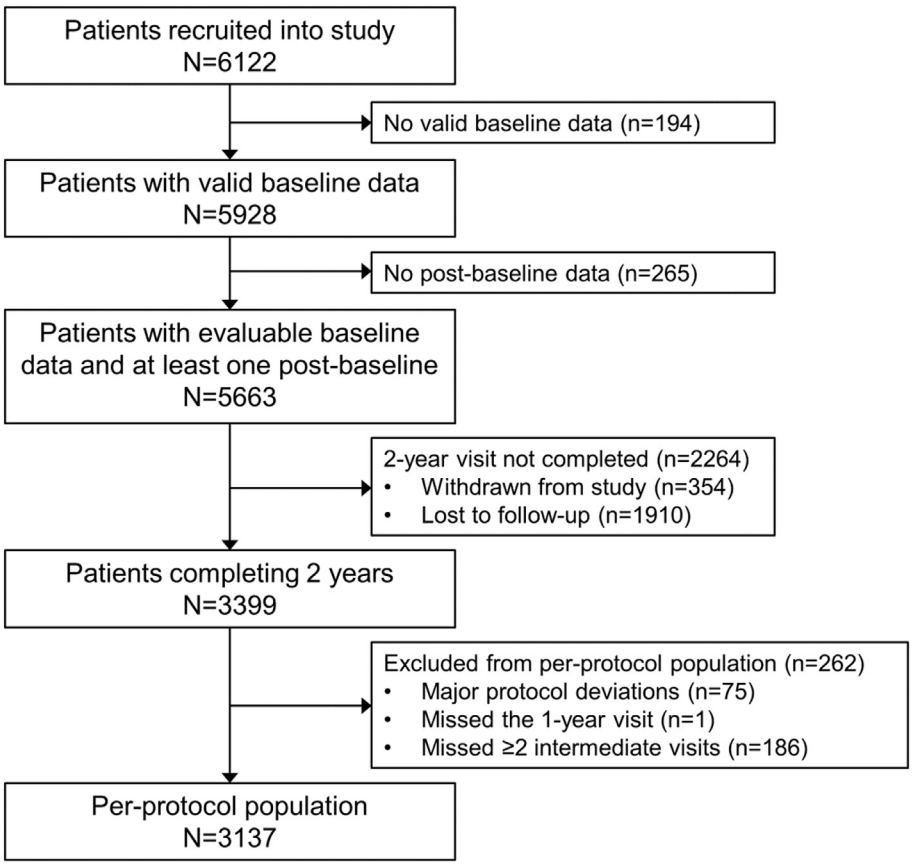

Fig. 1. Patient flow through DACCORD.

symptoms and future risk of exacerbations into account, with the Global Initiative for Chronic Obstructive Lung Disease suggesting a combined assessment [1]. A key driver of the costs [2,3] and healthcare resource utilisation [4,5] of COPD is exacerbations (in addition to comorbidities [6]). Clinical trials for new treatments (especially those conducted to support regulatory approval) are often designed around exacerbation prevention – and perhaps as a consequence exacerbation reduction has become considered the main focus of treatment. However, the main day-to-day impact of the disease on patients is associated with symptoms (or coping strategies to avoid symptoms) – and symptoms are the main driver for patients to visit their physician [7].

The majority of data on the progression of COPD come from randomised, interventional clinical trials, such as TORCH and UPLIFT [8,9]. Such studies tend to recruit relatively narrow, selected populations, and so may not be generalizable. Furthermore, the specialised nature of the investigators may mean that the care that these patients receive may not be representative of standard care. Observational studies conducted in broader populations therefore have an important role in examining COPD disease progression, such as the Copenhagen City Heart Study [10]. Although these studies support the theory that COPD is a progressive disease, this was most marked in specific subgroups of patients, for example those with moderate airflow limitation [11], suggesting that progression is not inevitable.

DACCORD, or Die ambulante Versorgung mit langwirksamen Bronchodilatatoren: COPD-Register in Deutschland (English translation: Outpatient Care With Long-Acting Bronchodilators: COPD Registry in Germany) is a non-interventional study, being conducted in primary and secondary care in Germany, that seeks to measure the impact of COPD (including exacerbations) on patients over a 2-year follow-up period. It is, to our knowledge, the largest such study in COPD to date.

2. Materials and methods

2.1. Trial design

As this is a non-interventional study, specific visits are not mandated by the protocol. However, 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 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-monthly visits exacerbations data were collected. At the 1-year and 2-year visits, data collected included prescribed COPD medication, CAT, exacerbations, and lung function. Full details of the methods have been previously published [12], together with the detailed baseline characteristics of the patients recruited [13], and the first year follow-up [14].

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

Table 1
Baseline demographics and disease characteristics.

	Per-protocol population (N = 3137)	Patients excluded from per-protocol population (N = 2791)
Sex, n (%)		
Male	1854 (59.1)	1683 (60.3)
Female	1283 (40.9)	1108 (39.7)
Age (years), mean (SD)	65.6 (10.1)	65.8 (10.5)
Age groups, n (%)		
<65 years	1445 (46.1)	1270 (45.5)
65–75 years	1174 (37.4)	986 (35.3)
>75 years	518 (16.5)	535 (19.2)
BMI (kg/m^2), mean (SD)	27.3 (5.6)	27.3 (5.5)
Duration since primary diagnosis on entry to the study, n (%)		
≤1 year	729 (23.2)	853 (30.6)
>1 year	2408 (76.8)	1938 (69.4)
FEV_1 (L)[a], mean (SD)	1.7 (0.7)	1.7 (0.8)
FEV_1 (percent predicted)[a], mean (SD)	62.9 (24.4)	62.7 (28.0)
FEV_1 (percent predicted)[a], n (%)		
≥80%	622 (19.8)	523 (18.7)
50 to <80%	1542 (49.2)	1345 (48.2)
30 to <50%	820 (26.1)	755 (27.1)
<30%	153 (4.9)	166 (5.9)
Smoking status at baseline, n (%)		
Ex-smoker	1369 (43.6)	1041 (37.3)
Current smoker	1152 (36.7)	1122 (40.2)
Never-smoker	603 (19.2)	534 (19.1)
Missing	13 (0.4)	94 (3.4)
Symptoms at baseline, n (%)		
Yes	3048 (97.2)	2655 (95.1)
No	86 (2.7)	111 (4.0)
Missing	3 (0.1)	25 (0.9)
mMRC, mean (SD)	1.9 (1.0)	1.8 (1.1)
CAT, mean (SD)	20.3 (7.6)	19.7 (7.7)
COPD maintenance medication, n (%)		
LAMA	1120 (35.7)	1113 (39.9)
LABA/LAMA/ICS	934 (29.8)	725 (26.0)
LABA/LAMA	497 (15.8)	404 (14.5)
Regimen containing a theophylline or PDE-4 inhibitor	270 (8.6)	193 (6.9)
LABA/ICS	120 (3.8)	111 (4.0)
LABA	87 (2.8)	87 (3.1)
LAMA/ICS	52 (1.7)	33 (1.2)
Missing	57 (1.8)	125 (4.5)
Comorbidities, n (%)		
Alpha-1 antitrypsin deficiency	7 (0.2)	7 (0.3)
Bronchiectasis	31 (1.0)	45 (1.6)
Bronchial carcinoma	42 (1.3)	51 (1.8)
Cardiovascular disease	1697 (54.1)	1391 (49.8)
Diabetes mellitus type 2	462 (14.7)	396 (14.2)
Osteoporosis	203 (6.5)	205 (7.3)
Psychiatric disorders	363 (11.6)	289 (10.4)
Sleep apnoea	243 (7.7)	232 (8.3)

[a] Random spirometry, assessed without requirement for washout of COPD medication or additional inhalation of short-acting β_2-agonist. BMI = body-mass index; FEV_1 = forced expiratory volume in 1 s; SD = standard deviation; mMRC = modified Medical Research Council dyspnoea scale; CAT = COPD Assessment Test; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta$_2$-agonist; ICS = inhaled corticosteroid; PDE = phosphodiesterase.

medication. Given the non-interventional nature of the study, the decision to initiate or change medication had to be 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. 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.

3. Objectives

The main objective of the study is to collect data on the typical care of patients with COPD in Germany. In particular, we seek:

1. To document exacerbations.
2. To measure patient-reported outcomes (PROs) in terms of CAT.
3. To assess patient persistence to COPD maintenance treatment.

3.1. Sample size and statistical methods

There was no specific sample size calculation for DACCORD – the size of the study was determined by a need to collect data that are representative of COPD management throughout Germany. As there are approximately 900 respiratory specialists in Germany, we considered that inviting 300 of these, distributed throughout the country, would be representative. We also invited 100 primary care physicians who specialise in pulmonology. We then asked each centre to recruit 15 patients (ideally consecutive), giving a total of 6000 patients.

Exacerbation rates were estimated using a negative binomial

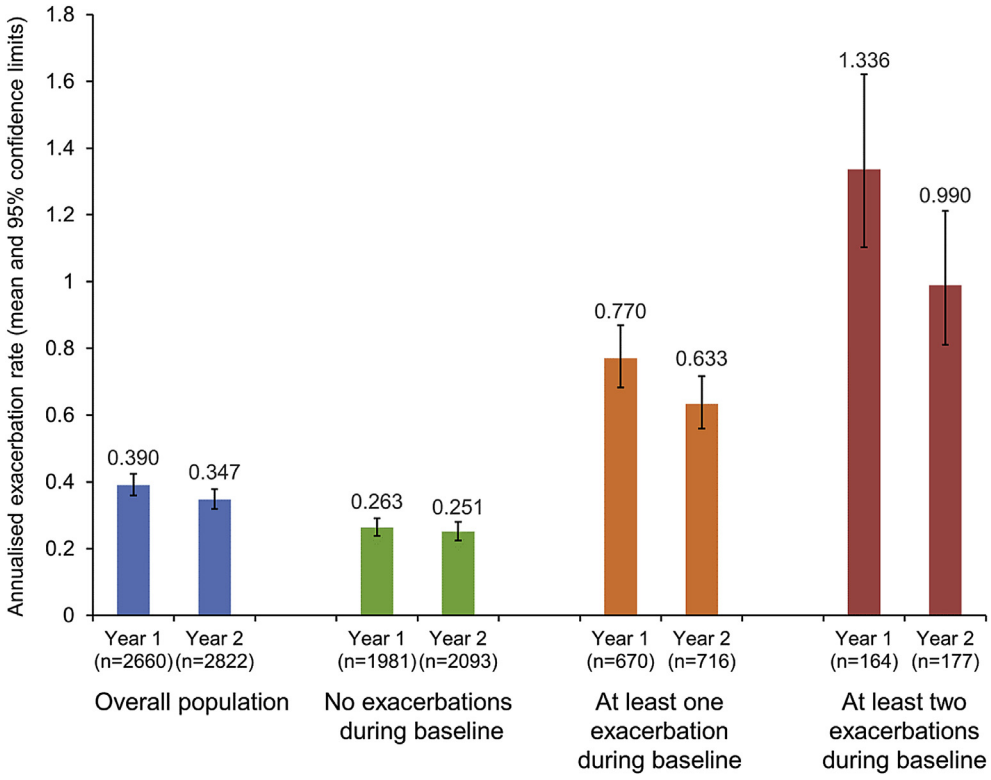

Fig. 2. Annualised moderate and severe exacerbation rate, overall, and for patients with no exacerbations during the baseline period, at least 1 exacerbation during the baseline period, and at least 2 exacerbations during the baseline period.

regression model with annualised numbers of exacerbation as dependent variable and no independent variable. This analysis included only patients with a complete set of exacerbation data. For CAT total score, absolute changes from baseline are presented, together with the proportion of patients with clinically relevant (i.e., ≥2 unit) changes from baseline – either improvement or worsening. Medication persistence was analysed at treatment class level, with patients considered 'persistent' if they were receiving the same class of COPD maintenance treatment at the annual visits as at baseline; 'switch' indicates that patients were receiving medication from a different class, whereas 'add-on' is used for the patients who were receiving an additional class on top of the baseline class(es). The GOLD 2011 group was calculated on the basis of CAT total score.

The main analyses were performed on the per protocol population, which includes all patients in the recruited population who attended both the 1- and 2-year visits and at least two of the three intermediate visits per year with no relevant deviations from the observational plan.

4. Results

4.1. Participants

A total of 6122 patients were recruited from 349 primary and secondary care sites across Germany, with the first patient entering the study in October 2012 and the last completing in January 2016. Of these, 3137 (51.2%) completed the 2-year visit, had no major protocol deviations, had evaluable baseline data, and had data recorded for the 1-year visit and at least two of the three intermediate visits each year (Fig. 1). This per-protocol population is the focus of the results reported here. Their baseline demographics and disease characteristics are reported in Table 1, together with the characteristics of the patients excluded from these analyses.

4.2. Outcomes

4.2.1. Exacerbations

Overall, there was a trend towards decreasing exacerbation rates over the 2-year follow-up period. Excluding patients with missing values, the annualised exacerbation rate was 0.390 during Year 1 and 0.347 during Year 2 (Fig. 2). The rates were lower in patients who had no exacerbations during the baseline period than in the patients who had one or more exacerbations during the 6 months prior to entry, and was highest in the patients with two or more exacerbations during the 6 months prior to entry (annualised rates in Year 1 of 0.263, 0.770 and 1.336, for no exacerbations, ≥1 exacerbation and ≥2 exacerbations during baseline, respectively) (Fig. 2).

At a population level, 25.7% of patients had ≥1 exacerbation during the baseline period, with 26.2% and 23.2% reporting ≥1 exacerbation during Year 1 and Year 2, respectively. When patients were subgrouped according to exacerbations during the baseline period (yes vs no), the majority of patients with no exacerbation prior to baseline also experienced no exacerbation in Year 1 or in Year 2 (51.6% of the overall population; Fig. 3). However, a large proportion of patients who exacerbated during the 6-month baseline period also did not exacerbate during Year 1 or Year 2 (327 patients, or 10.4% of the overall population). Importantly, the 132 patients who experienced ≥2 exacerbations in Year 1 appeared to be equally likely to experience 0, 1 or ≥2 exacerbations in Year 2, with the 'frequent exacerbator' phenotype comprising a very small subset of the DACCORD population (50 patients, or 1.6% of the overall population). A total of 127 patients (4.0%) were hospitalised

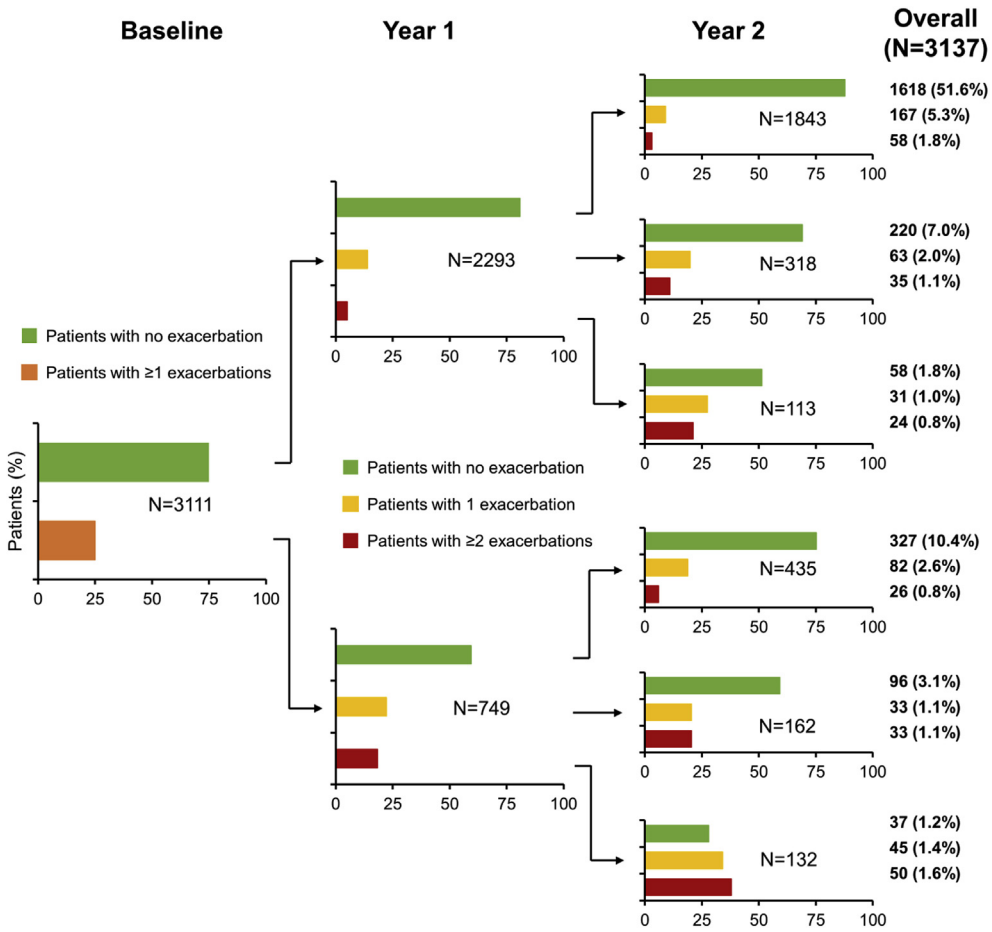

Fig. 3. Progression of COPD exacerbations, from baseline through Years 1 and 2.

Table 2
CAT total score, absolute, change from baseline and percentage of patients with clinically relevant changes at Years 1 and 2.

	Baseline	Year 1	Year 2
Absolute score			
Mean (SD)	20.3 (7.6)	18.5 (7.5)	18.0 (7.6)
1st quartile, 3rd quartile	15.0, 26.0	13.0, 24.0	12.0, 23.0
Change from baseline			
Mean (SD)		−1.8 (5.8)	−2.3 (6.5)
1st quartile, 3rd quartile		−4.0, 1.0	−6.0, 1.0
Number (%) of patients with:			
Improvement by ≥ MCID[a]		1554 (49.5)	1701 (54.2)
No clinically relevant change		665 (21.2)	726 (23.1)
Worsening by ≥ MCID[a]		918 (29.3)	710 (22.6)

[a] MCID = minimum clinically important difference (change from baseline of 2 units). CAT = COPD Assessment Test; SD = standard deviation.

for an exacerbation during the 6-month baseline period, compared with 111 (3.5%) in Year 1 and 108 (3.4%) in Year 2.

4.2.2. CAT progression

The mean CAT total score at baseline was above 20, with an interquartile range varying between 15 and 26, as would be expected for a symptomatic population (Table 2). There was a slight reduction from baseline in total score at the end of Year 1, with a further slight reduction at the end of Year 2. Approximately 50% of patients experienced a clinically relevant improvement from baseline in CAT total score at Year 1 and 2, with between 22 and 29% reporting a clinically relevant worsening.

We also analysed the proportion of patients with a clinically relevant improvement from baseline in CAT at both visits ('sustained improvement'), or a clinically relevant worsening from baseline at both visits ('sustained worsening'). A total of 1215 patients (38.7%) had a sustained improvement and 402 (12.8%) had a sustained worsening. The annualised exacerbation rate was lower in patients with a sustained improvement (0.324 [95% CL 0.284, 0.370] over the 2-year follow up) than in those with a sustained worsening (0.529 [0.440, 0.636]).

4.2.3. Change in GOLD 2011

The percentage of patients in each of the four GOLD 2011 categories was similar at the end of Year 2 compared with Year 1, with more than 50% of patients at both visits classified as GOLD B (Fig. 4). Compared with baseline, fewer patients were in the high risk Group D at the end of either Year 1 or Year 2, largely due to a reduction in the number of patients in the subgroups that assign risk due to exacerbation history.

We also calculated the proportion of patients who stayed in the same GOLD category throughout the study (i.e., at baseline, Year 1 and Year 2). Overall, just under 50% of patients (1373 patients; 43.8%) were in the same category throughout the study. Of the patients classified as GOLD A at baseline, 44.5% continued to be classified as GOLD A at Year 1 and Year 2. Values for GOLD B, C and D were 64.2, 12.1 and 24.8%, respectively – suggesting that patients in

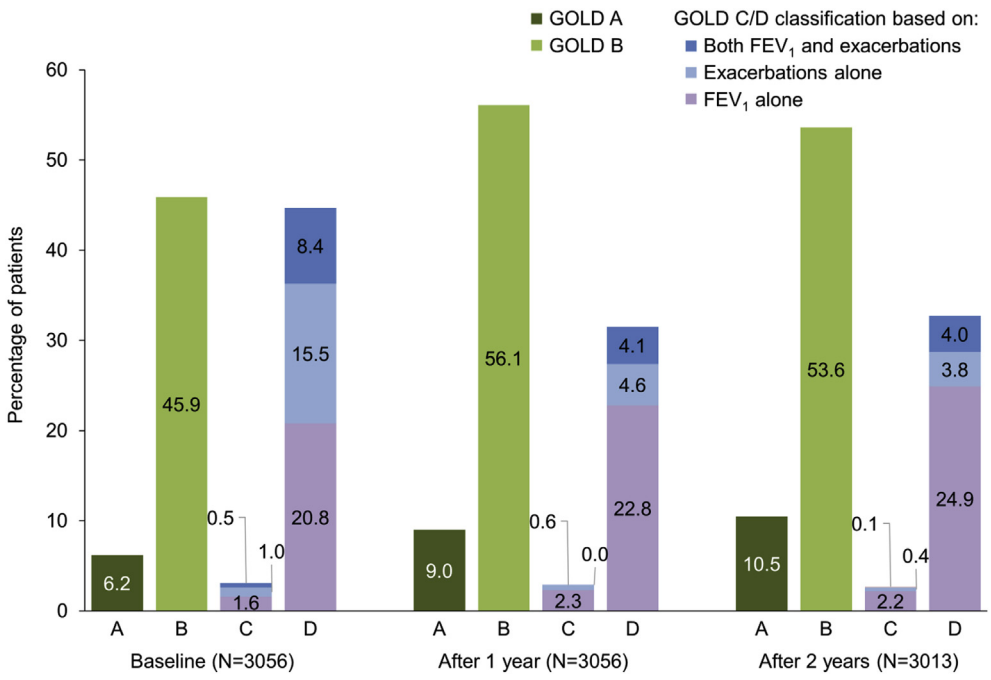

Fig. 4. Percentages of patients in GOLD 2011 categories at baseline and Years 1 and 2.
GOLD = Global Initiative for Obstructive Lung Disease; FEV_1 = forced expiratory volume in 1 second.
2 patients in Category C and 11 in Category D at the 1-year visit, and 13 in Category D at the 2-year visit had insufficient data to be assigned to a sub-category, and so are not included.

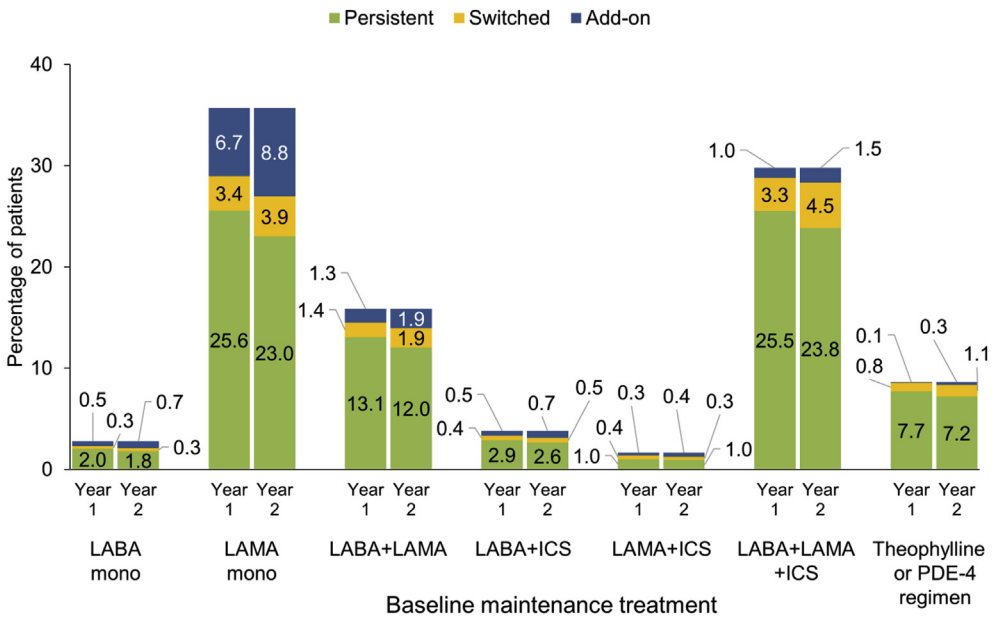

Fig. 5. Persistence with COPD maintenance medication at 1- and 2-years (N = 3137).
LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; PDE = phosphodiesterase.

GOLD Group B had the least change in disease severity over the 2 years.

4.2.4. Change in COPD maintenance medication use

As shown in Fig. 5, when assessed by treatment class (or classes) persistence to COPD maintenance medication was high in all groups. The largest change was in patients receiving LAMA monotherapy on entry to DACCORD, approximately 20% of whom were receiving add-on therapy by the end of Year 1, with a further increase in add-on use by the end of Year 2.

5. Discussion

Our main finding was the low overall rate of exacerbations

during the 2-year follow-up, especially in the subset of patients with no exacerbations during the 6-month baseline. Indeed, the majority of patients did not exacerbate, either during baseline period, or over the 2 years of follow-up. This was despite the recruitment of a broad, representative and symptomatic population seeking medical attention due to COPD. This population had a high symptom load on entry to the study (with 97.2% of patients reporting at least one symptom, and a mean mMRC score of 1.9), and a mean CAT total score above 20 on entry. Despite a quarter of the population having a worsening in CAT over the 2 years, the persistence to medication (at a class level at least) was high.

In DACCORD, the 'non-exacerbator' phenotype appeared to be stable; nearly three quarters of the patients with no exacerbations during the baseline period experienced no exacerbations in either Year 1 or Year 2. This is consistent with an analysis of ECLIPSE, in which patients with no exacerbations during the first year of follow-up tended not to exacerbate during Years 2 or 3 [15]. However, in contrast to the ECLIPSE analysis, in which the 'frequent exacerbator' phenotype was also reasonably stable (12% of the overall population in that study experienced ≥2 exacerbations in Year 1, Year 2 and Year 3), we found that very few patients in DACCORD met this definition. It is possible that this discrepancy was a result of the study design of DACCORD, in that patients were recruited after a decision had been made to initiate or change medication, with the baseline exacerbation history only collected over 6 months. However, patients who experienced ≥2 exacerbations in Year 1 seemed to be as likely to experience 0 and ≥2 exacerbations in Year 2 – and given the overall high persistence to medication, a change was unlikely over this period. Taken together, these data suggest that (at least in this real life population), exacerbations are rare events. This is consistent with the findings of the PATHOS retrospective study, in which the annual rate of COPD exacerbations has been decreasing over time, from 3.0 in 1999 to 1.3 in 2009 [16], coinciding with the introduction of new, effective bronchodilators.

The CAT data are some of the most intriguing from DACCORD. Given we recruited a population following medication initiation or change, it is not surprising that the majority of patients (97.2%) had symptoms at baseline, and in turn that the mean CAT score indicated a moderately high impact on health-related quality of life. However, it is much harder to explain why a significant proportion of this symptomatic population had a CAT score <10 (9.3% of the population being in GOLD 2011 Groups A or C at baseline), and so were considered to have no (or few) symptoms according to this questionnaire. It is possible, therefore, that the CAT questionnaire is not fully capturing all of the symptoms that determine the impact of the disease. However, it should be highlighted that CAT was a relatively new questionnaire at the time that DACCORD recruitment began. Indeed, we believe that DACCORD is one of the first 2-year follow-up studies to include CAT.

A high attrition rate is a particular challenge with multi-year studies. This applies not just to observational studies such as DACCORD, but also to randomised controlled trials. For example, only 60% of patients completed the 3-year follow-up period in TORCH [8] and 59% completed the 4-year follow-up in UPLIFT [9]. The high proportion of patients excluded from the analysis (close to 50% of the recruited population) means that we need to be cautious in extrapolating these data. However, the baseline characteristics of the per-protocol population were very consistent with the population that were not included in the analysis, which provides some reassurance that disease severity or baseline characteristics did not result in any differential drop-out. Further, although an intention-to-treat analysis (typically used in interventional trials) may have meant that we could have included data from more patients, we believe that our analysis, by including only the patients with complete (or nearly complete) datasets, is the most appropriate when analysing disease management.

6. Conclusions

Overall, the 2-year data presented here suggest that in real life for most patients with COPD who are receiving pharmacological treatment, exacerbations are rare events. For the majority of patients, the focus should be on managing symptoms and the impact that these symptoms have on their daily lives. Even for those patients who do exacerbate, although prevention of exacerbations is an important factor, management of symptoms should be a key consideration. Another important aspect of the study is that it suggests that decline is not an inevitable component of COPD (with many of the patients in DACCORD improving, as measured by CAT) – providing patients receive pharmacological treatment.

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Declaration of interest

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

Dr Vogelmeier reports personal fees from Almirall, AstraZeneca, Berlin Chemie – Menarini, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, and Takeda, and grants and personal fees from Grifols.

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 Takeda, and grants and personal fees from Boehringer Ingelheim, Novartis and Roche.

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

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

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

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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.2017.02.007.

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