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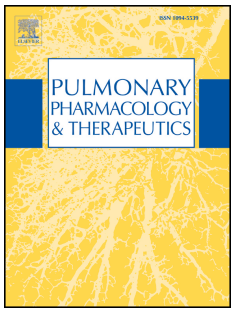

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Pharmacological approach and adherence to treatment recommendations in frequently and non-frequently exacerbating COPD patients from Italy: MISTRAL - the prospective cohort, observational study

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Abstract

Background: Several documents and guidelines provide recommendations for effective management of COPD patients. However, there is often a significant imbalance between recommended treatment of COPD patients and the actual care provided both in primary care and specialty setting. This imbalance could result in a significant negative impact on patients' health status and quality of life, leading to increased hospitalisations and health resource utilisation in COPD patients

Methods: MISTRAL was an observational, longitudinal, prospective cohort study, designed to assess the overall pharmacological approach of COPD in routine clinical practice in Italy. Eligible patients were divided into two cohorts based on their exacerbation history in the year prior to the enrolment, frequent exacerbators (FEs; ≥2 exacerbations), and non-frequent exacerbators (NFEs; ≤1 exacerbation). The primary objective was to assess adherence to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 treatment recommendations in FEs and NFEs at baseline and follow-up visits

Results: Of the 1489 enrolled patients, 1468 (98.6%; FEs, 526; NFEs, 942) were considered evaluable for analyses. At baseline, 57.8% of patients were treated according to GOLD 2011 recommendations; a greater proportion of FEs were treated according to GOLD recommendations, compared with NFEs patients at baseline (77.1% versus 46.7%; $P < 0.0001$), and all study visits. At baseline, GOLD group D patients were the most adherent (81.2%) to treatment recommendations, while group A patients were the least adherent (30.3%) at baseline, attributed mainly to overuse of inhaled corticosteroids in less severe GOLD groups. Triple therapy with long-acting muscarinic antagonist (LAMA) + long-acting β_2-agonist/inhaled corticosteroid (LABA/ICS) was the most frequent prescribed treatment at all study visits, irrespective of patient's exacerbation history. Changes in treatment were more frequent in FEs versus NFEs

Conclusions: The Mistral study reports a scarce adherence to the GOLD 2011 treatment recommendations in routine clinical practice in Italy. The adherence was particularly low in less severe, non-frequent exacerbating patients mostly for ICS overuse, and was higher in high-risk, frequent exacerbating COPD patients

Keywords: COPD, frequent exacerbators, non-frequent exacerbators, GOLD, MISTRAL, prospective cohort, real world

Abbreviations

CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eCRF, electronic case report form; FDC, fixed-dose combination; FEs, frequent exacerbators; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA/LAMA, long-acting β_2-agonist/long-acting muscarinic antagonist; NFEs, non-frequent exacerbators; LABA/ICS, long-acting β_2-agonist/inhaled corticosteroid; LAMA, long-acting muscarinic-antagonist; PDE4-I, phosphodiesterase 4-inhibitor; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterised by persistent airflow limitation and respiratory symptoms, resulting in breathlessness and poor quality of life [1]. It is ranked as the fourth leading cause of death worldwide, and is projected to become the third by 2020 [2-4]. In Europe, ~12% of population is affected by COPD [5]. Few epidemiological studies have been carried out to estimate the prevalence of COPD in Italy. In a multicenter study it was found that the prevalence of COPD ranged from 3.3% in 20–44 years age group to 5.7% in 45–64, and 13.3% in 65–84 age groups [6]. Results from a large-scale international survey, 'Confronting COPD in North America and Europe', showed that COPD was prevalent in 15% of Italian patients, aged 45–97 years [7].

Though several guidelines provide recommendations for diagnosis and effective management of COPD patients [1, 8, 9], the disease continues to remain underdiagnosed globally, and patients with COPD are often under- or inappropriately treated [10-12].

Global initiative for chronic obstructive lung disease (GOLD) strategy provides a non-biased review of the current evidence for the assessment, diagnosis and treatment of patients with COPD, which can aid the clinicians all over the world for managing patients across COPD severities. GOLD strategy, up to 2016, recommended treatment with bronchodilators (as mono or combination therapy) as first-line therapy for patients at low risk - GOLD groups A and B who are non-frequent exacerbators, while the use of inhaled corticosteroid (ICS) in combination with a bronchodilator is reserved for high risk patients - GOLD groups C and D. The GOLD 2017 document, which provided major

updates in treatment strategy, recommends dual bronchodilation (long-acting β_2-agonist/long-acting muscarinic antagonist [LABA/LAMA]) as preferred therapy for the majority of symptomatic COPD patients, including those at high risk of exacerbations (GOLD C and D). The use of ICS is limited only to the GROUP D patients who remain inadequately controlled on a LABA/LAMA therapy [1, 13].

According to GOLD recommendations, a key treatment goal for COPD is the reduction of exacerbations as these are the main contributors to clinical disease progression [1], leading to a significant impact on patients' quality of life and activities of daily living, with increased risk of hospitalisation and mortality, contributing to an enormous financial burden [14-16]. Frequent COPD exacerbators need careful attention in chronic management as this condition poses the patient at high risk of further exacerbation potentially leading to hospitalisation, rapid lung function decline, deterioration of health status, respiratory complications and death.

Over the last decades, consistent efforts have been made to standardise the diagnostic and treatment approaches for COPD. However, various studies have suggested that there is a poor adherence to these recommendations both in primary care and in specialty setting in Italy [17-19] that lead to a significant imbalance between guideline-defined treatment and actual care provided. Patients also sometimes underestimate the severity of disease, contributing further to non-adherence to guideline recommendations and adequate treatment [20].

To the best of our knowledge, there have been no studies reported so far with a particular focus on frequent and non-frequent exacerbating (FEs and NFEs) COPD patients in Italy that would help the understanding of local treatment approaches in

these groups of patients. The MISTRAL study was designed to assess, for the first time, adherence to treatment recommendations for COPD in routine clinical practice in Italy, with a particular focus on adherence to GOLD 2011 treatment recommendations in FEs and NFEs. The investigation was designed to assess the long-term prescription pattern for the management of Italian COPD patients.

2. Materials and methods

2.1 Study design

MISTRAL was a prospective cohort, non-interventional, observational, longitudinal study in COPD patients, performed at 63 pulmonologist and internal medicine outpatient clinics in Italy. The patient enrollment started in May 2013. The study was planned to evaluate, during a 3-year period, the clinical course, prescription trends and adherence to GOLD 2011 recommendations in COPD diagnosed patients, which were effective when the protocol was developed and are in line with the revisions up to GOLD 2016. However, with the recent revisions of GOLD recommendations in 2017, leading to inapplicability of GOLD 2011, and given that the analysis after 3 years would not have been scientifically relevant in light of appropriateness, the study was terminated prematurely after 24 months from the first patient enrolment, when all patients had at least one year of observation, and the results have to be interpreted in the light of original recommendations.

As per the protocol, the study was planned to include an enrolment period of at least 18 months and a prospective observation period of 36 months. The evaluations were performed during the observation period comprising six clinic visits, after the enrollment, and scheduled as per the local routine clinical practice (i.e. one visit every 6 months).

Eligible patients were divided into two cohorts based on their exacerbation history in the year prior to enrollment; patients with a history of 2 or more exacerbations, according to GOLD 2011, in the year prior to inclusion visit were categorised as FEs, and those with a history of 0 or 1 exacerbations in the year prior to inclusion visit were categorised as NFEs. According to GOLD 2011, an exacerbation was defined as an acute event characterised by a worsening of the patient's respiratory symptoms that is beyond day-to-day variations and leads to a change in medication [21]. The treating physician performed assessment as per the local medical practice. Data were recorded in the electronic case report form (eCRF). COPD assessment test (CAT) questionnaire was administered to all patients to assess COPD symptoms.

2.2 Patients

Outpatients of either gender, aged ≥40 years, with a clinical diagnosis of COPD (per GOLD 2011), current or ex-smokers with a smoking history of at least 10 pack-years were enrolled in the study. Non-smokers, patients with history of asthma, inability to self-complete questionnaires, comorbidities reducing life expectancy (<3 years) were excluded from the trial. The study was designed, implemented and reported in accordance with the guidelines for Good Pharmacoepidemiology Practices, Declaration of Helsinki, the STROBE guidelines [22], and the AIFA guideline for the classification and management of observational studies on drugs (AIFA 2008). All patients were informed about the study procedures and signed a written informed consent.

2.3 Endpoints

The primary objective of the study was to describe therapeutic approach as per GOLD 2011 recommendations in Italian COPD patients. Patients were distributed in FE and NFE cohorts at baseline based on their exacerbation history, and their persistence in

these cohorts was re-evaluated at 12- and 24-month follow-up visits. Patients were classified in GOLD groups A–D as per GOLD 2011 recommendations. Stratification of patients in FE and NFE cohorts, and GOLD groups A–D was done as per physicians' classification and eCRF calculation.

Therapeutic management of COPD in FEs and NFEs was assessed by observing ongoing therapies at study visits, including the use of ICS, and changes to prescribed treatments at 12 and 24 months. The primary outcome was to evaluate adherence to GOLD 2011 treatment recommendations in FEs and NFEs at baseline, 12- and 24-month follow-up visits. Adherence to GOLD 2011 treatment recommendations was also assessed at baseline in patients stratified in GOLD groups A–D. Proportion of patients who started a new therapy or changed an ongoing therapy or stopped an ongoing COPD therapy between follow-up visits were also described.

2.4 Statistical analysis

The sample size was not determined in order to test any priori hypothesis, as the study aim was descriptive. In order to provide an overview of the achievable precision of the estimates in different conditions some scenarios were defined, based on following: i) considering that pharmacologic treatment approach might not be the same for FEs and NFEs, it was reasonable to observe a percentage of patients treated according to GOLD 2011 recommendations ranging from 40% to 80%; ii) negligible number of patients who changed cohort (from NFEs to FEs and vice versa) during observation; iii) a 3 year drop-out rate (including not evaluable patients) of about 20%. Therefore, 600 patients were expected to be evaluable for the primary end-point in each cohort. As per the initial plan, patients were to be enrolled in 1:1 ratio based on the exacerbation

status; however, the observed ratio was 1.8 NFE per FE. The final sample size was 1468 patients at baseline (FEs, 526; NFEs, 942), 1183 at 12-month (FEs, 184; NFEs, 999 according to the reported number of exacerbation during the first year of follow-up), and 470 patients at 24-month (FEs, 72; NFEs, 398 according to the reported number of exacerbation during the second year of follow-up). Although the observed sample size distribution was different from planned, and changes from FE to NFE status were somewhat frequent, the precision of estimates was acceptable for the descriptive statistical analyses, in fact considering the FEs at 12-months the 95% CI width do not exceed 15%. Considering the number of patients arrived at 24-months (i.e. FEs = 72) the precision decrease (i.e. 95% CI width is 21%).

The analysis of the primary objective was performed on the evaluable patients (FEs vs NFEs) at baseline and follow-ups (12- and 24-months). Patients with missing values were included in the analysis. Missing values were not replaced and did not contribute to the analysis of that variable. The proportions of patients treated according to the GOLD 2011 recommendations were calculated at baseline, 12- and 24-months, along with the corresponding 95% confidence intervals.

The proportion of patients treated according to GOLD 2011 guidelines for each study cohort was calculated as $\sum_i$=A, B, C, D (m_i)/($\sum_i$=A, B, C, D n_i), where m_i is the number of patients treated according to GOLD 2011 recommendations in the i-th GOLD 2011 group, n_i is the size of the i-th group.

Usual descriptive statistics were used to describe the main socio-demographic and clinical variables

Difference in proportion of patients between cohorts was assessed by means of a chi-square test, while for continuous variable a t-test or a Wilcoxon test was applied based on data distribution. A *P* value less than 0.05 was considered as statistically significant.

All the analyses were performed with SAS 9.4 and Enterprise Guide 7.1.

3. Results

3.1 Patient disposition and baseline characteristics

Of 1489 patients enrolled, 1468 (98.6%; FE, 526; NFE, 942) were included in the evaluable set. In total, 1185 (79.6%) patients performed the 12-month follow-up, and 471 (31.6%) patients performed the 24-month follow-up (**Figure 1**). Overall, 217 (14.6 %) patients discontinued the study, with a similar rate between FEs (14.5%) and NFEs (14.6%); in particular 98 (6.6%) patients discontinued the study after 12 months. 49 (3.3%) deaths were reported during the observation period, with respiratory failure being the most common reason for death (n = 8).

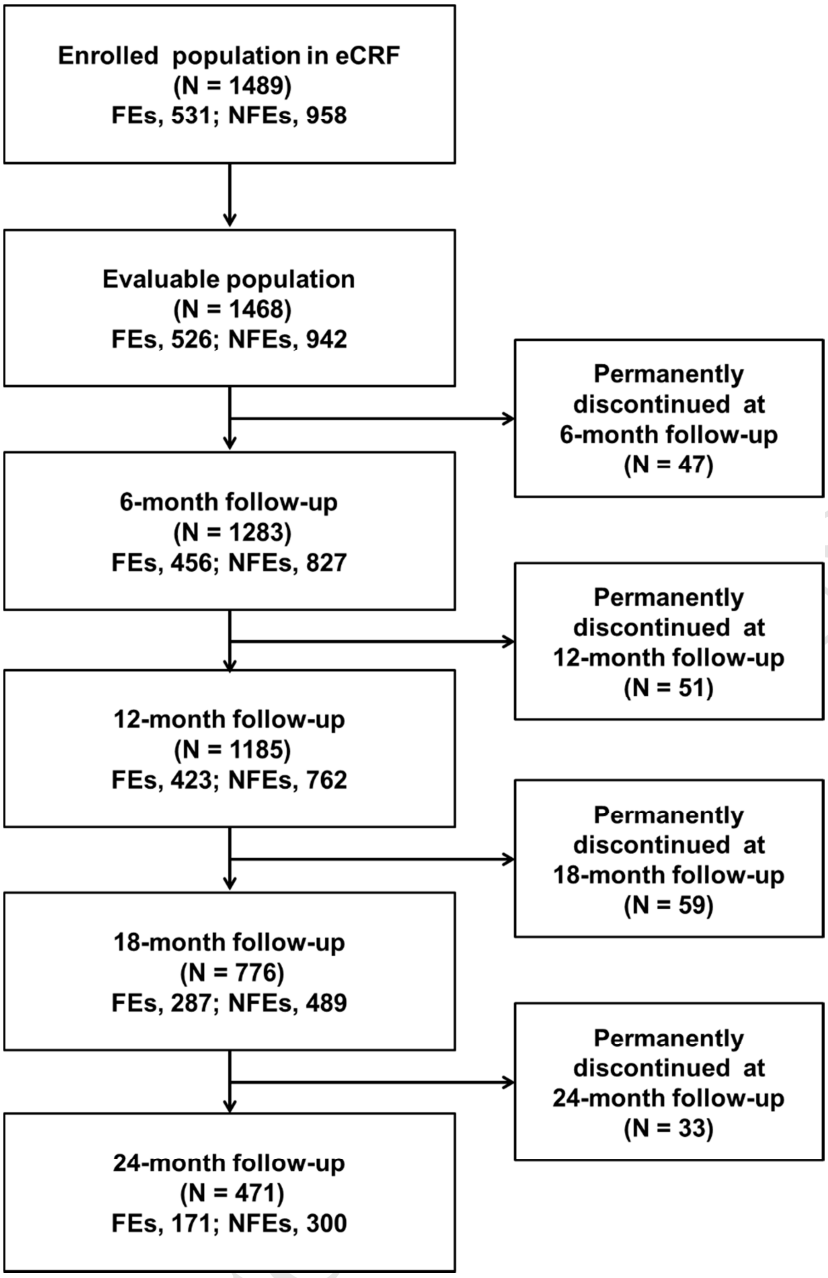

Figure 1. Patient disposition

eCRF, electronic case report forms; FEs, frequent exacerbators; NFEs, non-frequent exacerbators

The majority of patients were men (78.1%); the mean age was 69.9 ± 8.4 years with mean disease duration of approximately 7 years, and a CAT score ≥10 (n = 1155; 78.8%) in most cases. FEs had significantly longer disease duration compared with

NFEs (mean ± standard deviation duration, 8.9 ± 8.3 versus 6.4 ± 7.7 years; *P* < 0.0001). Approximately 40% of FEs had ≥3 exacerbations and 38% had ≥1 hospitalisations for COPD exacerbations in the year before the enrolment (**Table 1**). FEs had a greater risk of comorbidities than NFEs (odds ratio [95%CI], 1.74 [1.30 to 2.32]), mainly cardiovascular complications.

Characteristics	**Evaluable patients (N = 1468)**	**Frequent exacerbators (n = 526)**	**Non-frequent exacerbators (n = 942)**	***P* value**
Gender, n (%)				
Men	1146 (78.1)	408 (77.6)	738 (78.3)	0.7300*
Women	322 (21.9)	118 (22.4)	204 (21.7)	
Age, years	69.9 ± 8.4	70.7 ± 8.0	69.5 ± 8.6	0.0082#
Age groups, n (%)				
<50 years	34 (2.3)	8 (1.5)	26 (2.8)	NR
50 – 59 years	130 (8.9)	38 (7.2)	92 (9.8)	
60 – 69 years	481 (32.8)	166 (31.6)	315 (33.4)	
70 – 79 years	656 (44.7)	253 (48.1)	403 (42.8)	
≥80 years	167 (11.4)	61 (11.6)	106 (11.3)	
Occupational status, n (%)				
Unemployed	84 (5.7)	30 (5.7)	54 (5.8)	NR
Employed	230 (15.7)	65 (12.5)	165 (17.6)	
Retired	1147 (78.5)	427 (81.8)	720 (76.7)	
Smokers, n (%)				
Current	452 (30.8)	138 (26.2)	314 (33.3)	0.0047*
Former	1016 (69.2)	388 (73.8)	628 (66.7)	
Duration of COPD, years	7.3 ± 8.0	8.9 ± 8.3	6.4 ± 7.7	<0.0001#
Age at COPD diagnosis, years	62.6 ± 10.3	61.8 ± 10.3	63.1 ± 10.2	0.0249#
Number of COPD exacerbations in the 12 months prior to entering the study	1.2 ± 1.2	2.6 ± 0.9	0.5 ± 0.5	<0.0001#

Number of patients with COPD exacerbations in the 12 months prior to entering the study, n (%)				
0	484 (33.0)	0	484 (51.4)	NR
1	458 (31.2)	0	458 (48.6)	
2	314 (21.4)	314 (59.7)	0	
3	151 (10.3)	151 (28.7)	0	
>3	61 (4.2)	61 (11.6)	0	
Number of patients who had at least one COPD exacerbations in the 12 months prior study entry that required n (%)				
Systemic corticosteroid	648 (44.2)	399 (75.9)	249 (26.5)	<0.0001*
Systemic antibiotics	805 (54.9)	467 (88.8)	338 (35.9)	<0.0001*
One or more hospitalisation	313 (21.3)	200 (38.0)	113 (12.0)	<0.0001*

Table 1. Baseline demographics and clinical characteristics (evaluable population)

Data presented as mean ± standard deviation, unless otherwise specified
COPD, chronic obstructive pulmonary disease; NR, not reported
[*] *P* value are calculated with Chi-square test for comparison between cohort
[#] *P* value are calculated with t-test for comparison between cohort

3.2 Persistence of patients in the FE and NFE cohorts

The persistence of patients in each of the cohort was assessed at the12- and 24-month follow-up visits (**Figure 1**). Interestingly more than 70% of FEs at baseline shifted to NFEs at 12 and 24 months, showing an improvement in their exacerbation status; on the contrary less than 10% of NFEs at baseline worsened their exacerbation status becoming FEs at 12 and 24 months visits (**Figure 2**). The mean number of exacerbations, in the 12 months prior to entering the study, in FEs with 2-years of follow-up (n = 165) was 2.5 (range, 2 to 8), but this decreased to 1.0 (range, 0 to 6) at both 12 and 24 months follow-up. No relevant changes were observed in the mean number of exacerbations in NFEs with 2-years of follow-up (n = 282); the mean number

of exacerbation was 0.4 (range, 0 to 1) in the 12 months prior to entering to study, which changed to 0.3 (range, 0 to 3) and 0.4 (range, 0 to 7) at 12- and 24-months, respectively.

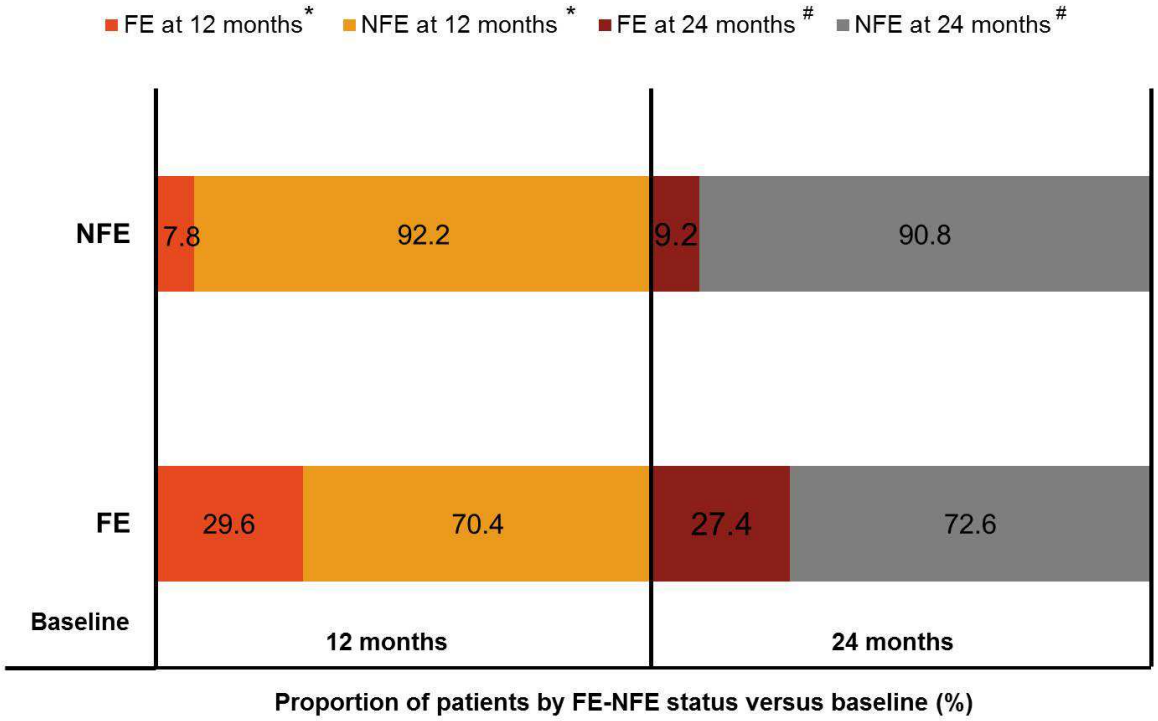

Figure 2. Persistence of patients in FE and NFE cohort

*Evaluable patients who performed 12-month follow up visit were considered
#Evaluable patients who performed 12-month and 24-follow up visit were considered
FE, frequent exacerbators; NFE, non-frequent exacerbators

3.3 COPD severity classification

Based on the physicians' classification, 20% patients were classified in GOLD group A, 36% in group B, 11% in group C and 33% in group D. This patient distribution differed from that derived from eCRF calculated data (GOLD group A, 15%; group B, 34%; group C, 6 % and group D, 45%). Accordance between physician's and eCRF calculated combined COPD assessment was found in 74.6% of patients. In the majority

of patients were classified into the more symptomatic COPD group, irrespective of classification type (**Figure 3**).

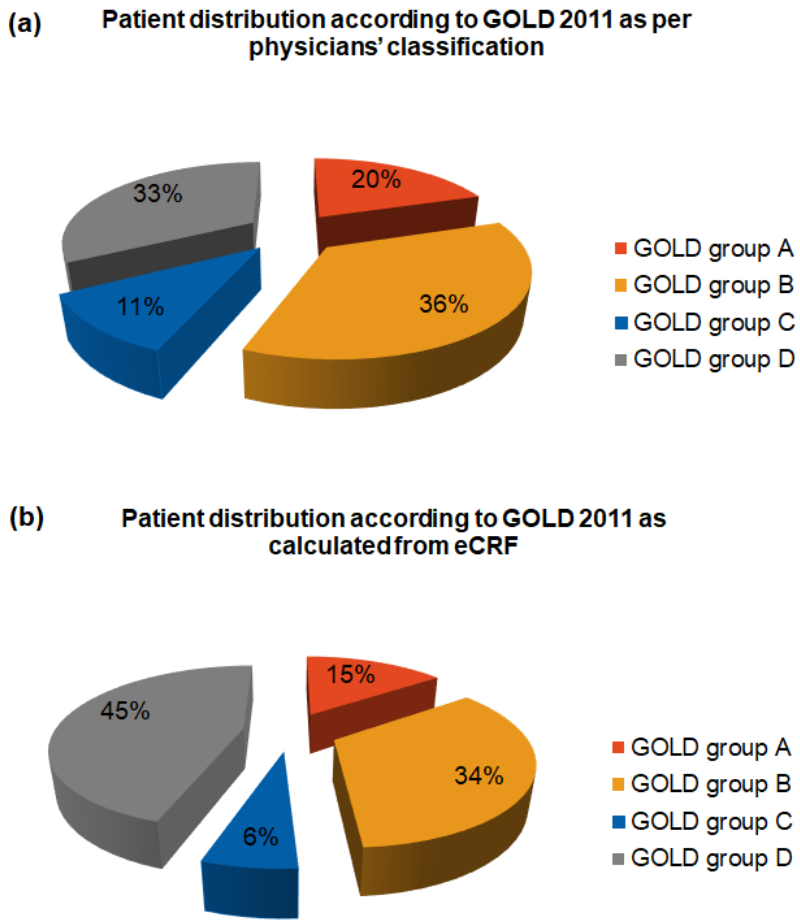

Figure 3. Patient distribution according to GOLD 2011 as per (a) physicians' classification, and (b) calculated from eCRF

eCRF, electronic case report form; GOLD, Global Initiative for Chronic Obstructive Lung Disease

3.4 Change of GOLD status during study

Nearly 60% of patients in GOLD groups A, B and D at baseline remained in the same group at 12 months; approximately 36% of group A patients at baseline shifted to more severe groups, 23% of group B shifted to group A and ~18% shifted to more severe

groups, 47% of group D patients shifted to less severe GOLD groups. On the contrary, only 24% of group C patients remained in the same class, 24% changed to a more severe group, and 52% to less severe GOLD groups (**Figure 4**). At 24 months these percentages were quite similar (**Figure S1**).

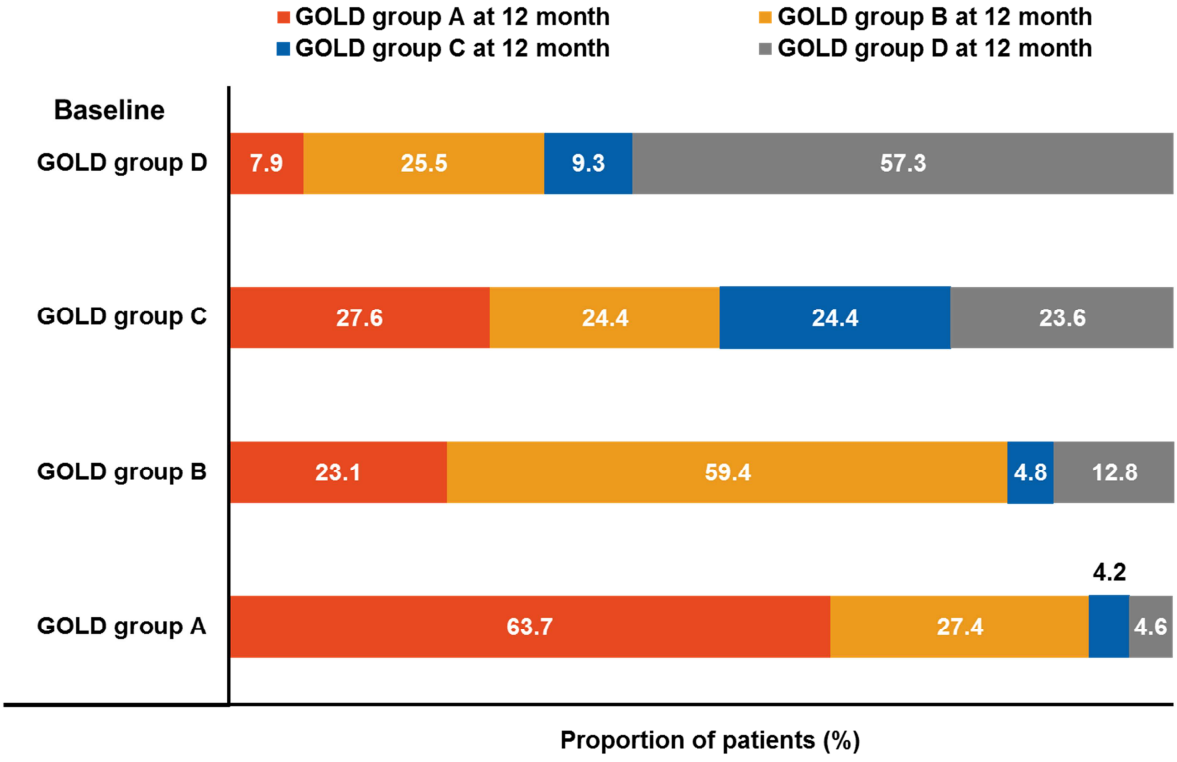

Figure 4. Persistence of patients in GOLD groups A–D at 12 months (physicians' classification)

Evaluable patients who performed 12-month follow up visit were considered
GOLD, Global Initiative for Chronic Obstructive Lung Disease

3.5 COPD management

3.5.1 Ongoing COPD therapies at baseline and follow-up visits

Of 1468 evaluable patients at baseline, 1281 (87.3%) patients had at least one ongoing COPD therapy (FEs, 478 [90.9%]; NFEs, 803 [85.2%]; **Figure 5**). At 12- and 24-month follow-up, 1152 (97.4%) and 462 (98.3%) patients had at least one ongoing therapy for

COPD respectively. Most of the patients were treated with LAMA+LABA/ICS (FDC), followed by LABA+LAMA, LAMA, and LABA/ICS at baseline. A similar treatment pattern was observed at the follow up visits (**Figure 5**). At baseline, 75.7% (n = 362) of FEs and 53.7% (n = 431) of NFEs were treated with ICS (Chi-square test $P < 0.0001$). At 12- and 24-months follow up, 74.0% and 80.3% of FEs, and 54.9% and 58.3% of NFEs were treated with ICS (Chi-square test $P < 0.0001$ and $P = 0.0005$) respectively.

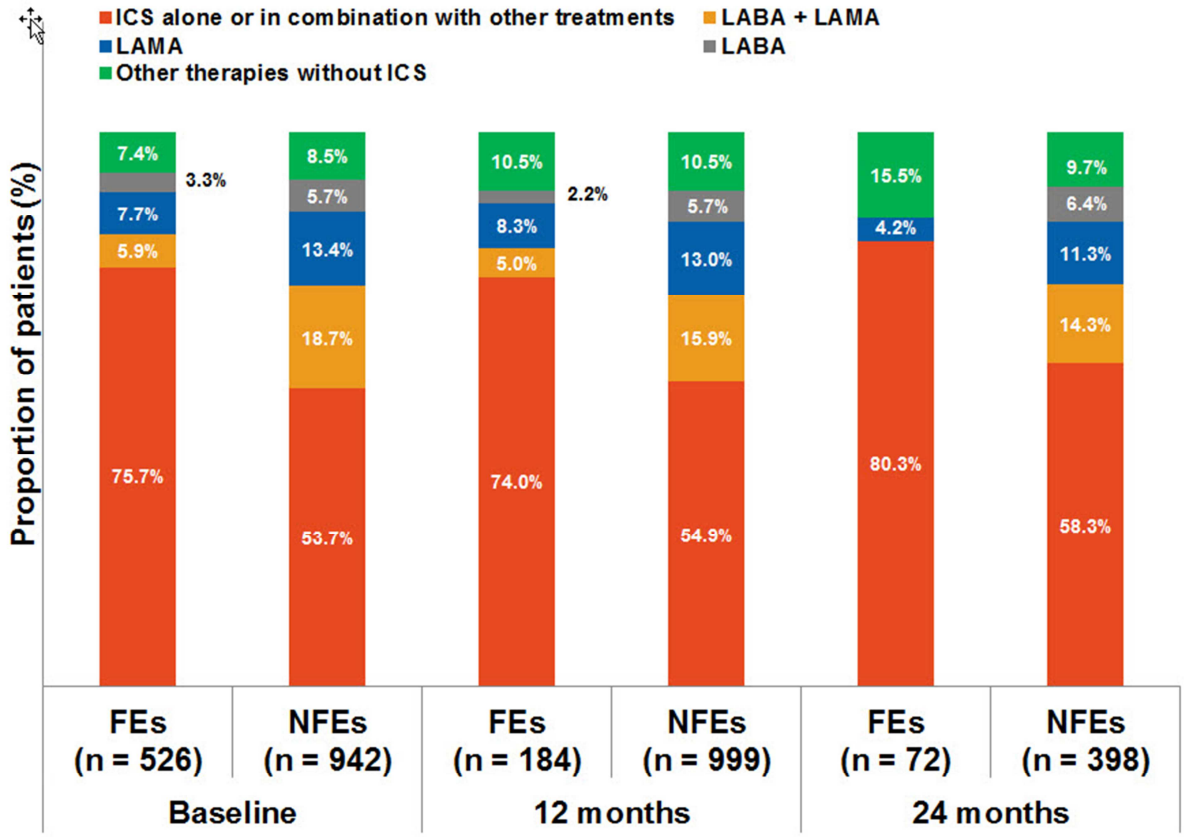

Figure 5. Ongoing COPD therapies at baseline and follow-up visits by class

Data presented as percentage of patients who took at least one therapy

COPD, chronic obstructive pulmonary disease FEs, frequent exacerbators; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; NFEs, non-frequent exacerbators

3.6 Adherence to GOLD 2011 recommendations in FEs and NFEs

At baseline, 57.8% (n = 807/1395) of patients were treated according to GOLD 2011 recommendations (GOLD classification based on eCRF data). The proportion decreased to 49.9% (n = 586/1175) at 12-month, and to 49.1% (n = 229/466) at 24-month follow-up.

FEs were more frequently treated according to GOLD recommendations than NFEs at all visits ($P < 0.0001$). At baseline, 77.1% of FEs vs 46.7% of NFEs received treatment in accordance with GOLD 2011 recommendations as per COPD classification based on eCRF. Based on physicians' evaluation, 65.4% of FEs and 43.7% of NFEs were treated as per GOLD 2011 recommendations at baseline (**Figure 6A**).

Notably, 78.4% of stable FEs and 80.7% of worsened exacerbators at 12-month were treated according to GOLD 2011 recommendations. However, only 48.4% of the stable NFEs were treated according to GOLD 2011 recommendations (**Figure 6B**).

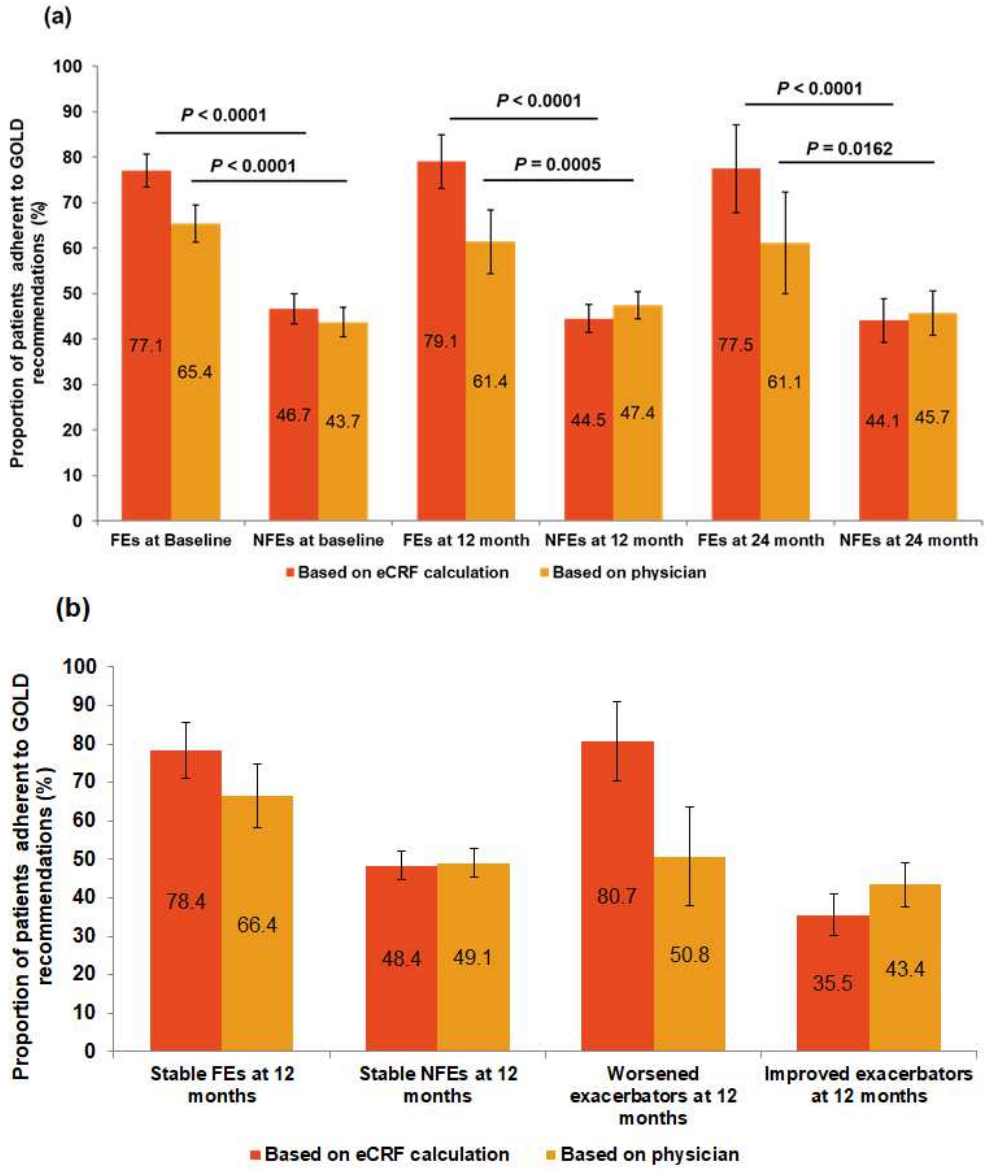

Figure 6. Adherence to GOLD recommendations in FEs and NFEs at baseline and follow-up visits

(a) Error bars represent 95% CI values. *P* values are calculated by means of chi-square test

(b) Error bars represent 95% CI values.

eCRF, electronic case report form; FEs, frequent exacerbators; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NFEs, non-frequent exacerbators

3.7 Adherence to GOLD 2011 recommendations *in GOLD groups A–D*

At baseline, treatments prescribed to GOLD group D patients were most adherent (81.2%) to GOLD recommendations, while those prescribed to GOLD group A patients were the least adherent (30.3%). The degree of adherence in GOLD groups A–D was quite similar for classifications based on eCRF calculation and physicians' classification (**Figure 7**). The non-adherence to GOLD recommendations in group A and B patients was partly due to the absence of prescribed therapies (8.2% and 10.6% respectively), but mainly due to ICS treatment that was prescribed in approximately 44% of group A and B patients. Few patients in group C (7.1%) and D (6.6%) also showed absence of any prescribed therapy. In group C, the prescription of triple therapy (LABA+LAMA+ICS) was considerably high, wherein a therapy with LAMA or LABA/ICS was recommended by GOLD 2011 report. Treatment pattern in patients classified in GOLD groups A–D based on eCRF calculation and physicians' classification was quite similar (**Figure S2**).

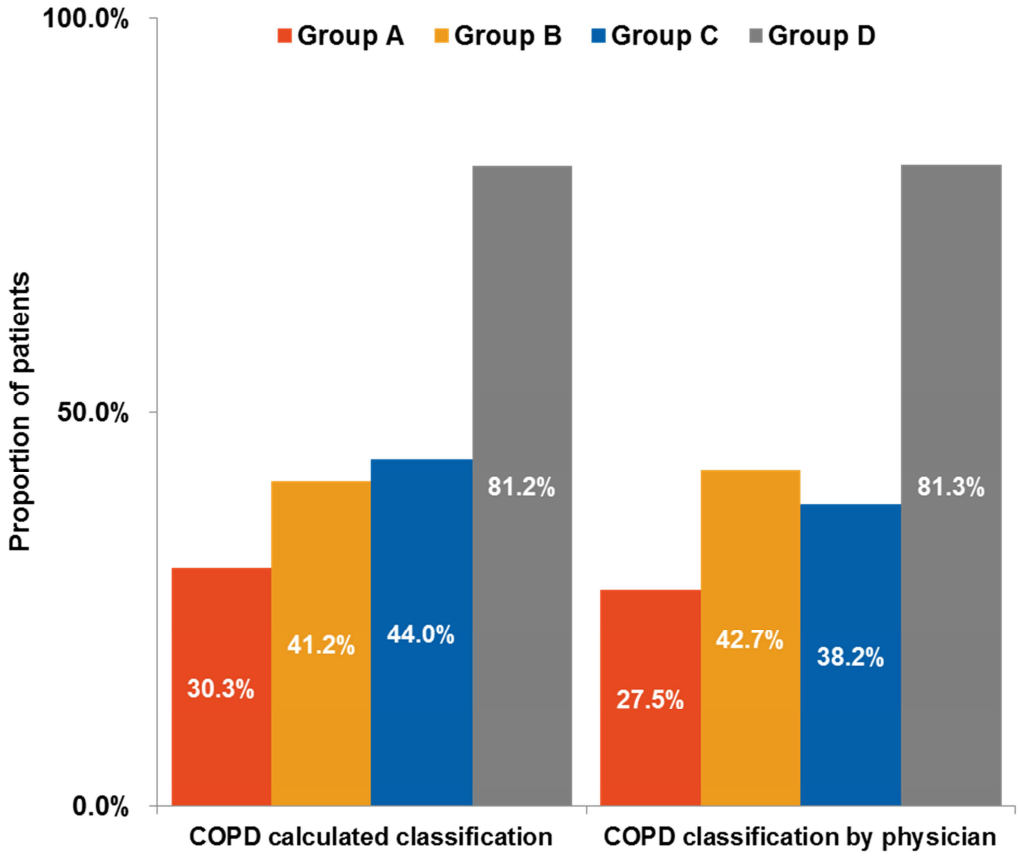

Figure 7. Adherence to GOLD 2011 recommendations in GOLD group A–D

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease

3.7.1 Proportion of patients with change in COPD therapy

Of the patients who performed 12-month follow up (n = 1185), 30.3% patients had at least one change of therapy between baseline and 12-month follow-up visit. Between 12- and 24-month follow-up, 21.0% of the evaluable patients with both 12- and 24-month follow-up visit performed (n = 446) had at least one change of therapy. Approximately 11% patients stopped at least one ongoing class of therapy (for e.g. LABA, LAMA, etc.) during the first 12 months, and between 12- and 24-month follow-up, while 27.0% and 16.8% patients started at least one new class of therapy in the first 12 month, and between 12- and 24-month follow-up respectively. Changes in COPD

therapy were more frequent in FEs versus NFEs (**Figure 8**).

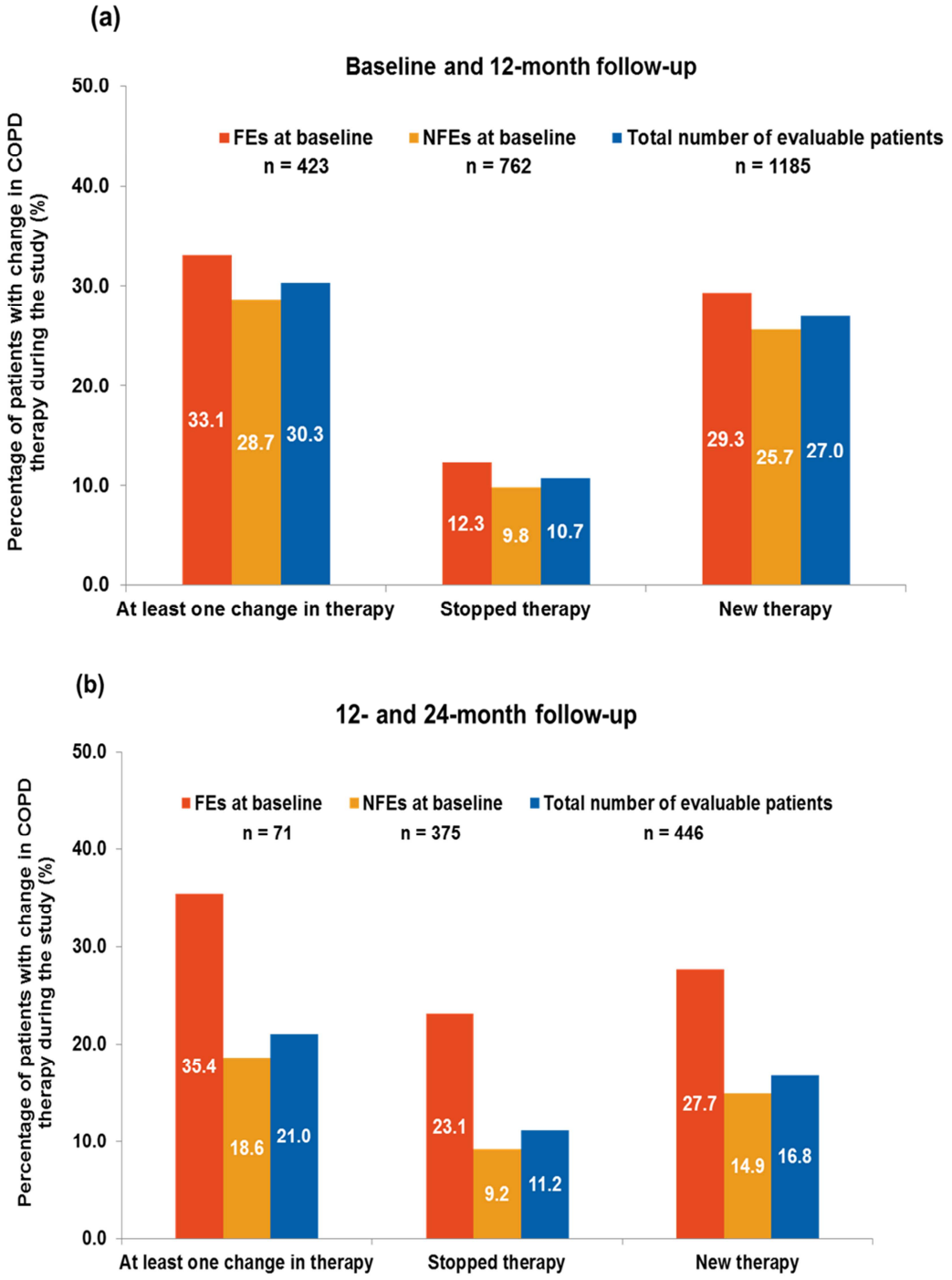

Figure 8. Patients with change in COPD medication between (a) baseline and 12-month follow-up and (b) 12- and 24-month follow-up

Percentages between baseline and 12-month follow up were calculated over total number of evaluable patients who performed 12- month follow up; percentages between 12- and 24-month follow up were calculated over total number of evaluable patients who performed 12- and 24-month follow up
COPD, chronic obstructive pulmonary disease; FEs, frequent exacerbators; NFEs, non-frequent exacerbators

4. Discussion

The MISTRAL study assessed the overall therapeutic approach for COPD patients in Italy under real-world clinical setting, with particular focus on adherence to GOLD 2011 treatment recommendations in frequently and non-frequently exacerbating patients. Patients were divided into two cohorts based on their exacerbation history in the year prior to enrollment, FEs (≥2 exacerbations) and NFEs (0 or 1 exacerbation). The COPD management approach used in Italy was found to be quite discordant with GOLD recommendations, with only 57.8% of patients treated as per GOLD 2011 recommendations at baseline and a degree of GOLD adherence that progressively worsened at 12- and 24-month follow-up.

Patients were stratified in GOLD groups A–D as per GOLD 2011 recommendations at baseline based on physicians' classification and eCRF calculation. The distribution of patients across GOLD groups based on the physicians' classification wasn't the same as calculated from eCRF data, specifically when considering severe patients. In particular 12% fewer patients were classified as GOLD D following the physician classification, compared with the eCRF data. Considering that the 'ABCD' assessment tool was introduced for first time in the GOLD 2011 update, and was a major change from the simple spirometric grading system in earlier GOLD versions [21], misalignment

in the attribution of defined disease severity could be possibly due to difficulty in the interpretation and application of this relatively new assessment tool. Other factors could be low quality of spirometry testing or physicians' lack of confidence in the interpretation of spirometry results, which are likely to contribute to incorrect severity classification of COPD patients. The GOLD 2017 report separates spirometric grading from the 'ABCD' groups; patient classification in these GOLD groups and associated pharmacotherapy recommendations are now based exclusively on patient's symptoms and exacerbation history [13]. This refinement of the ABCD assessment tool in GOLD 2017 could be seen as an opportunity to increase the degree of accordance between the calculated and physicians' attributed class of risk for COPD patients, and potentially also the degree of treatment adherence to GOLD recommendations for COPD patients.

The adherence to GOLD recommendations at baseline was higher in FEs (77.1%) versus NFEs (46.7%) when calculated from eCRF data. Of note, the adherence was 65.4% in FEs and 43.7% in NFEs as per physicians' calculation, highlighting a degree of discordance between the calculated versus physician attributed FE-NFE classification. At all follow-up visits, FEs were more frequently treated as per GOLD 2011 recommendations compared with NFEs.

Persistence of patients in FE-NFE cohorts was evaluated during the study period, and showed that many FEs at baseline improved their exacerbation status and shifted to NFEs at follow-up visits. Adherence to recommendations was high in stable FEs, and worsened exacerbators, compared with patients who were stable NFEs. This may be due to closer attention to GOLD recommendations in the more severe patients, but also potentially due to a trend towards ICS use that becomes by chance appropriate when

coming to more severe patients. This inappropriateness of treatment could potentially lead to an increase in incidence of adverse events both in FEs and in NFEs.

LAMA+LABA/ICS (FDC), LAMA monotherapy, LABA+LAMA, and LABA/ICS (FDC) were the most common ongoing medications at baseline, and during the 24-month study period. At each study visit, FEs appeared to have been treated more commonly with ICS than NFEs. In NFEs, use of ICS regimen (alone or in combination) was however high at baseline, with a progressive increase in ICS prescription over the study course. This finding is in disagreement with GOLD 2011 recommendations, as ICS long-term treatment was recommended only for patients with severe or very severe airflow limitation, and in patients with ≥ 2 exacerbations in the previous year.

In this study, there was a quite linear increase in adherence to GOLD recommended treatment with increasing severity of COPD (from 30.3% in GOLD group A to 81.2% in GOLD group D). The non-adherence in GOLD groups A and B was mainly due to inappropriate ICS prescription in almost half of the patients (44.2% in each group) in these groups, wherein bronchodilators (short- and long-acting) were recommended as per GOLD 2011 strategy. In group C patients there was a high use of triple therapy (LAMA+LABA+ICS), where a LAMA or a dual therapy with ICS and LABA was recommended

The overall impact of treatment on COPD symptoms over 24 months was apparently low during the study, with many patients shifting to a more severe GOLD group after 12 and 24 months (up to approximately 36% in group A, and approximately 24% in group C). The impact on exacerbations however was much more beneficial, given that 72.6% of FEs at baseline became NFEs during the study period, while only 9.2% (n = 26) of

NFEs became FEs. The number of COPD exacerbations in FEs decreased over study course, from 2.5 at baseline visit to 1 at 24 month. It should be further investigated if it is the COPD treatment or improved disease management due to study participation or both that is the true cause of this improvement. Another possible reason for this reduction in the number of exacerbation can be regression to mean.

The low degree of prescription in accordance with GOLD recommendations is particularly striking in light of the high degree of change of prescribed therapy during follow up, in fact more than 30% of patients modified the therapy (changed, stopped or added at least one COPD drug) during the first 12 months of follow up and 21% did so between 12 and 24 months, so the opportunity to reassess the prescribed therapy in line with GOLD recommendations has been present for most of the participant physicians. Treatment changes were more frequent among FEs than NFEs, with a marked difference observed between 12 and 24 months, especially in terms of increase of ICS use. Over 10% of evaluated population interrupted at least one therapy from 12 to 24 months, and this percentage was particularly high for FEs (23%). The high degree of modification of therapy for FEs patients could be interpreted as unsatisfactory results from the current prescribed COPD therapy in terms of symptoms, exacerbations, adverse events or other reasons.

The overall treatment rate was quite high but 12.7% of patients reported no ongoing treatment at baseline; this percentage decreased to 1.7% after 24 months, which could be due to many reasons including worsening of symptoms and airflow measures over the study course that could have driven clinician's attention to their patients, but could also be related to loss-to-follow-up of healthier patients. Approximately 11% of

symptomatic (GOLD group B) patients and 7% of symptomatic high risk patients (GOLD group D) didn't report any COPD treatment at baseline, these aren't signs of appropriateness independently of the GOLD recommendations and reasons for no treatment of COPD should be further investigated.

These results are consistent with studies in Italian patients, highlighting the wide gap that exists between the worldwide recognized recommendations and its applicability in real-life setting [23-25]. One of the reasons that may explain the non-adherence to recommendations is that it is not always clear how these recommendations can be applied in day-to-day general practitioner setting. Awareness of guideline recommendations and adapting these in routine clinical practice can optimize treatment outcomes for COPD patients [26]. The non-adherence to treatment recommendations in group A and B was mainly due to inappropriate ICS prescription, while it is proved that in low-risk COPD patients (GOLD groups A and B) use of a steroidal component neither improves symptoms, nor complications [27, 28]. On the contrary, long term use of ICS has been associated with an increased risk of pneumonia and adrenal insufficiency [29]. Aligned with these findings, studies such as ILLUMINATE, LANTERN, and FLAME demonstrated that use of LABA/ LAMA combination (indacaterol/glycopyrronium) is highly effective and superior to LABA/ICS therapy in patients with moderate-to-very severe COPD [30-32].

Consistent with our data, a recent Italian observational study showed a low level of compliance with GOLD recommendations, especially in terms of ICS over prescription [25]. Again, a similar trend of non-adherence to GOLD recommendations was reported in studies assessing clinical practice patterns in Italy [24] and Turkey [33]; which

perhaps may have negative impact on patient outcomes, health resource utilisation, and cost of care for COPD patients. Non-adherence to treatment guidelines was also observed in the multi-national, cross-sectional PUMA study in primary care centers in Latin America, which reported underuse of long-acting bronchodilators as regular maintenance therapy in COPD management [34]. A real-life study in the UK demonstrated over prescription of triple therapy (ICS+LABA+LAMA) also in patients without severe COPD symptoms and frequent exacerbations, which was mainly driven by inappropriate initiation of first COPD treatment with ICS+LABA [35].

The study presents some limitations. The planned 1:1 ratio between NFEs and FEs was not achieved; however, the actual ratio of 1.8 to 1 was sufficient for statistical purpose. Second, as the study aimed to evaluate treatment adherence to GOLD recommendations, a selection bias for enrolling those who were more probably treated according to GOLD 2011 strategy may exist. Third, due to study design, follow-up visit could be performed intermittently, which did not allow for continuous monitoring of patients during the study period. This, however, provides the true evidence of clinical practice as outpatients cannot be monitored continuously. Finally, due to update in the GOLD strategy (GOLD 2017 release), the study was terminated prematurely, and the results has to be interpreted in the light of original recommendations (GOLD 2011). One of the main results of this study is ICS overtreatment in low risk COPD patients, and considering the updated GOLD strategy document is even more restrictive in the recommendation of ICS use, MISTRAL results could potentially be also interpreted in light of recent recommendations, and considered clinically relevant to modify the

prescription pattern and the degree of adherence to international recommendations among Italian pulmonologists.

5. Conclusion

Overall, data from the MISTRAL study showed a great degree of nonadherence with GOLD recommendations in the routine clinical practice in Italy. This was particularly evident in patients at low risk and with non-frequent COPD exacerbations compared with patients at high risk with frequent COPD exacerbations. Overuse of ICS was evident during the early stages of disease.

More studies should be conducted with an aim to explore the reasons for this non-adherence to GOLD recommendations in the Italian population, and possibly to drive physicians toward a more guideline-compliant prescription trend, to standardise and improve the COPD management strategies in this population. At the same time more efforts should be done in order to increase the awareness and value of GOLD strategy and to increase the adoption of GOLD recommendations for the COPD treatment by Italian pulmonologists.

DECLARATIONS

Ethical compliance and consent to participate

The study was conducted according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all the study participants prior to initiation

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. All data generated or analysed during this study are not included in this published article

COMPETING INTERESTS

The authors received no compensation related to the development of the manuscript. Gino Scalone (GS) has received speaking fees from Astra Zeneca, and travel/accommodation expenses from Novartis, Chiesi, Guidotti, Menarini and Lofarma. Stefano Nava (SN) has received speaking fees from Chiesi, Novartis, GlaxoSmithKline, Menarini and Astra Zeneca, advisory board fees from Novartis and Astra Zeneca, and research grant from Chiesi, Guidotti and Menarini. Francesco Ventrella (FV), Guglielmo Bussoli (GB), Giosuè Angelo Catapano (GC), Alfio Pennisi (AP), Dadduzio Francesco (DF) and Riccardo Pela (RP) have no conflict of interest to declare. Pietro Schino (PS) has received speaking fees from Novartis, Chiesi, Alfasigma and Guidotti. Marta Bartezaghi (MB), Paolo Morini (PM), Alberto Porpiglia (AP) and Elisa Muscianisi (EM) are employees of Novartis. The authors reported no conflict of interest relevant to the work presented here

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AUTHORS' CONTRIBUTION

All authors have contributed substantially in data interpretation, development and revision of manuscript draft, and provided their consent and approval for publishing this manuscript

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Supplementary file

Pharmacological approach and adherence to treatment recommendations in frequently and non-frequently exacerbating COPD patients from Italy: MISTRAL - the prospective cohort, observational study

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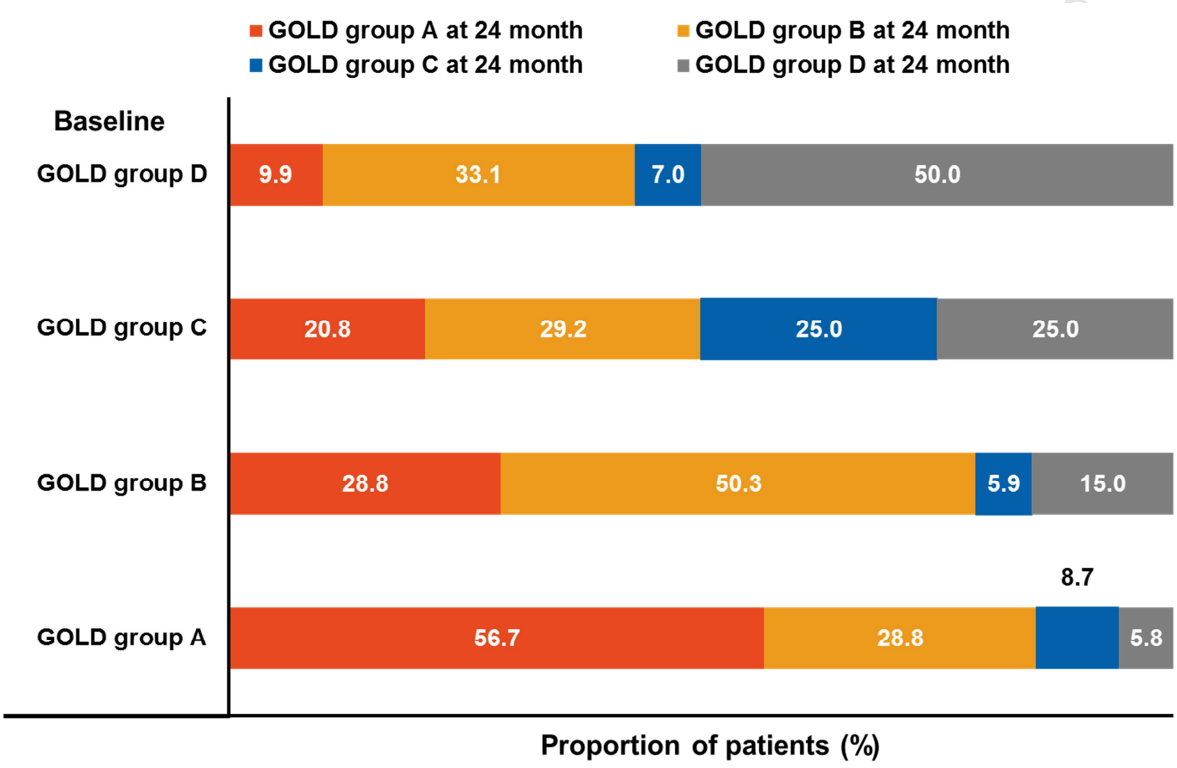

Figure S1. Persistence of patients in GOLD groups A–D at 24 months (physicians' classification)

GOLD, Global Initiative for Chronic Obstructive Lung Disease

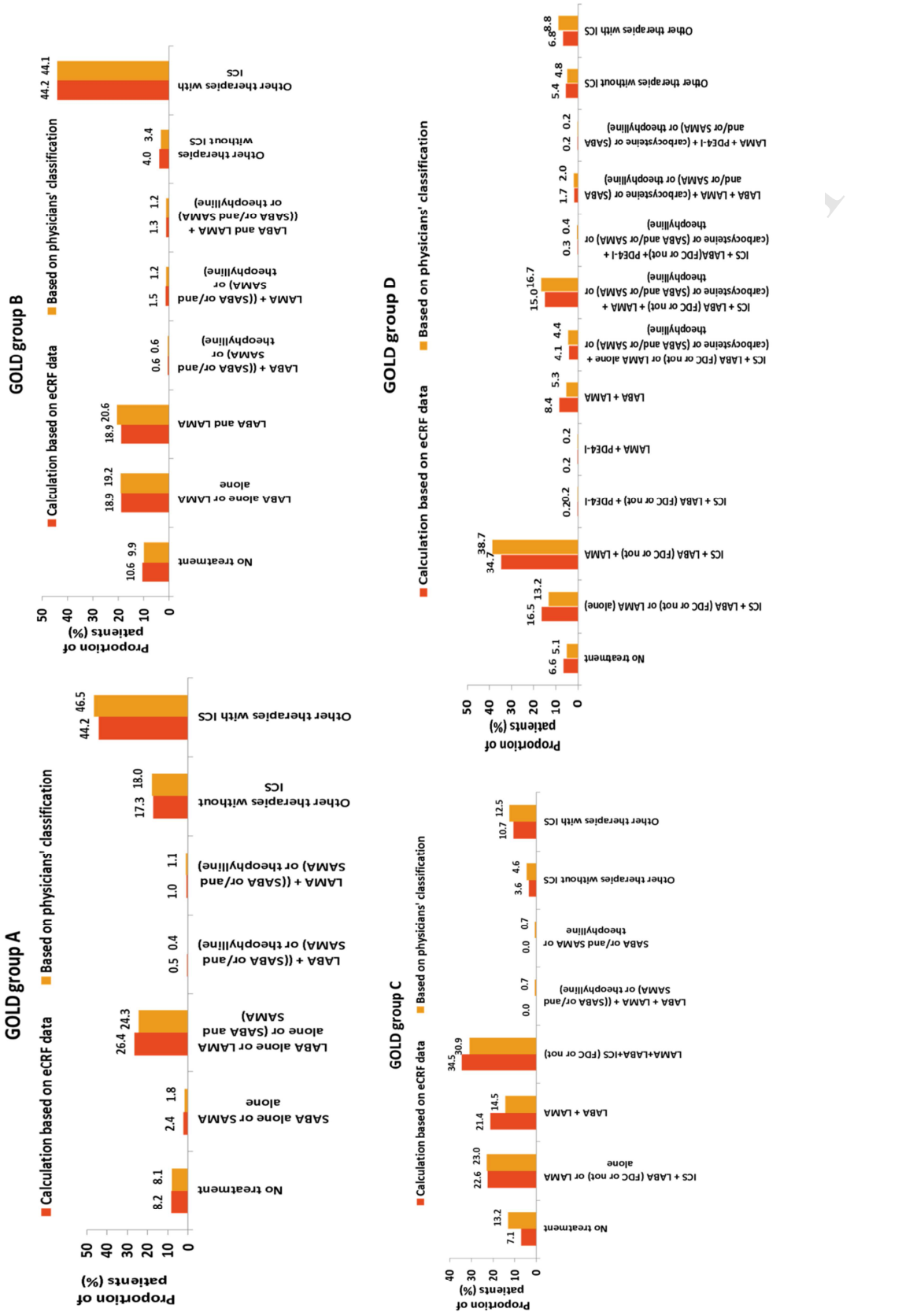
GOLD group A
Calculation based on eCRF data
Based on physicians' classification
Proportion of patients (%)
No treatment
SABA alone or SAMA alone
LABA alone or LAMA alone or (SABA and SAMA)
LABA + ((SABA or/and SAMA) or theophylline)
LAMA + ((SABA or/and SAMA) or theophylline)
Other therapies without ICS
Other therapies with ICS
GOLD group B
Calculation based on eCRF data
Based on physicians' classification
Proportion of patients (%)
No treatment
LABA alone or LAMA alone
LABA and LAMA
LABA + ((SABA or/and SAMA) or theophylline)
LAMA + ((SABA or/and SAMA) or theophylline)
LABA and LAMA + ((SABA or/and SAMA) or theophylline)
Other therapies without ICS
Other therapies with ICS
GOLD group C
Calculation based on eCRF data
Based on physicians' classification
Proportion of patients (%)
No treatment
ICS + LABA (FDC or not) or LAMA alone
LABA + LAMA
LAMA+LABA+ICS (FDC or not)
LABA + LAMA + ((SABA or/and SAMA) or theophylline)
SABA or/and SAMA or theophylline
Other therapies without ICS
Other therapies with ICS
GOLD group D
Calculation based on eCRF data
Based on physicians' classification
Proportion of patients (%)
No treatment
ICS + LABA (FDC or not) or LAMA (alone)
ICS + LABA (FDC or not) + LAMA
ICS + LABA (FDC or not) + PDE4-I
LAMA + PDE4-I
LABA + LAMA
ICS + LABA (FDC or not) or LAMA alone + (carbocysteine or (SABA and/or SAMA) or theophylline)
ICS + LABA (FDC or not) + LAMA + (carbocysteine or (SABA and/or SAMA) or theophylline)
ICS + LABA(FDC or not)+ PDE4-I + (carbocysteine or (SABA and/or SAMA) or theophylline)
LABA + LAMA + (carbocysteine or (SABA and/or SAMA) or theophylline)
LAMA + PDE4-I + (carbocysteine or (SABA and/or SAMA) or theophylline)
Other therapies without ICS
Other therapies with ICS

Figure S2. Treatment pattern at baseline in patients classified in GOLD groups A–D based on eCRF data and physicians' classification

COPD, chronic obstructive pulmonary disease; eCRF, electronic case report form; FDC, fixed-dose combination; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; PDE4-I, phosphodiesterase 4-inhibitor; SABA, short-acting β2-agonist; SAMA, short-acting muscarinic antagonist

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