Modifications in COPD Treatment According to GOLD Guideline Recommendations

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Abstract

INTRODUCTION Polypharmacy of respiratory medications is commonly seen in COPD patients. Reduction of COPD therapy in patients with overtreatment may have benefits by providing adherence to the guideline recommendations. We aimed to investigate effects of treatment de-escalation in COPD.

METHODS This multi-center, prospective study was carried out in four pulmonary outpatient clinics. Overtreated patients (according to GOLD 2017) were recommended to undergo de-escalation of treatment (reduction group I), and those who were under appropriate treatment were recommended a stepwise de-escalation (reduction group II). Patients who declined de-escalation were in non-reduction group I. Non-reduction group II consisted of patients under appropriate treatment. Inhalation device skill, symptom control and quality of life (QOL) were assessed at baseline and 6-month follow-up.

RESULTS At baseline visit, 55.9% of participants (76/136) were overtreated. There were de-escalation in 54 patients (35: reduction group I, 19: reduction group II). Non- reduction groups I and II included 37 and 45 patients, respectively. FEV 1 of patients with appropriate treatment improved significantly (p=0.033). There was a significant improvement in QOL in reduction group I (p=0.005) and II (p=0.011). Patients who reduced/quitted smoking during follow-up recorded significant improvements in FEV 1 and drug inhalation skills score (p=0.034 and p=0.023, respectively). Overtreatment had an estimated additional cost of 119.57$/year for each patient.

CONCLUSION Overtreatment is a common problem in COPD. De-escalation of inhaler medications can improve QOL. Appropriate treatment according to guidelines positively affects respiratory parameters. Reduction/discontinuation of smoking improves both inhaler adherence and spirometric measurements. De-escalation of inhaler treatment should be considered in overtreated patients.

Background

The treatment algorithms based on chronic obstructive pulmonary disease (COPD) stages were updated and revised in the new guidelines (GOLD 2017) to assess the patients with COPD in a better way and to manage COPD treatment (1). The appropriate treatment based on the guidelines is important for disease control, improvement in spirometric measurements and reduction on treatment costs, which also may be associated with reduced mortality (2,3,4).

Adherence to the current guidelines in the treatment of stable COPD is poor in many countries (5). Previous studies have indicated that 45–62% of COPD patients are not being treated appropriately according to their GOLD stages (5,6). More than half of COPD patients were found to be overtreated in several studies (6, 7), mostly because of using inhaled corticosteroids (ICSs) in treatment protocol. The inappropriate use of ICS according to the GOLD guidelines was 8% in mild COPD and 31% in moderate COPD (8). A study in Turkey revealed that the most common inappropriate treatment was ICS, and a high proportion of COPD patients were undergoing triple inhaler treatment (long-acting beta-2 agonist [LABA] + long-acting antimuscarinic [LAMA] + ICS) (9).

The medications used in COPD attenuate disease symptoms by inducing bronchodilation, reducing inflammation and promoting secretion clearance, although these may be associated with many adverse events. ICSs in particular are commonly used inappropriately and are associated with a wide range of adverse events, from hoarseness to pneumonia (10).

As polypharmacy adversely affects adherence to treatment, inhalation device skill is an important parameter in disease control (11). Combined multiple inhaler treatments may also have an adverse impact on treatment adherence (12).

The present study investigates the effects of treatment de-escalation on inhaler treatment adherence, quality of life and symptom control in COPD patients according to the current GOLD 2017 guidelines (13).

Methods

The present study included stable COPD patients under inhaler treatment who were admitted to the pulmonary diseases outpatient clinic of one of four study centers between April 2017 and July 2017. Ethical approval was received from the Ethics Committee of Çanakkale 18 Mart University.

The COPD diagnosis was verified using spirometric measurements. Airway obstruction was defined as the ratio of forced expiratory volume in the first second (FEV_1) to forced vital capacity (FVC) of less than 70% (13).

The staging of COPD was performed according to the GOLD 2017 guidelines using a COPD assessment test (CAT), as well as the modified British Medical Research Council (mMRC) dyspnea scale, which assesses the symptoms, number of disease exacerbations and risk status. Patients were classified into groups A, B, C and D based on this combined grading system, and evaluated if they had undergone the appropriate treatment according to the GOLD 2017 guidelines or not. The patients were recommended with a de-escalation of treatment according guidelines if they were overtreated (reduction group I), or a stepwise de-escalation if they were appropriately treated (reduction in number of medications, reduction group II). The suitability of de-escalation in reduction group II was evaluated and decided by the participator pulmonologists of the study. The overtreated patients who did not accept treatment de-escalation were assigned to the non- reduction group I. The patients undergoing appropriate treatment according to the guidelines were assigned to non- reduction group II.

The patients who did not fill in the scales, those who were illiterate, those who could not perform pulmonary function tests and those with acute exacerbations of COPD were excluded.

Demographic, diagnostic and therapeutic data (inhaled and nebulized medications, smoking status, number of COPD exacerbations and hospitalizations in the preceding year), and comorbidities of the patients were recorded. A 10-item assessment tool **(Appendix 1)** was designed based on the literature for the assessment of inhalation technique of the patients (14, 15) .

The *primary endpoint* of the study was to evaluate quality of life at sixth month. Secondary endpoints included the evaluation of spirometric parameters, symptom control and inhalation device skill score after six months.

The patients were invited for a follow up assessment 6^{th} months after their enrollment in the study, during which their adherence, quality of life and symptom status (using mMRC or CAT) were re-evaluated and compared with the baseline visit.

The Turkish version of Saint George's respiratory questionnaire (SGRQ) was used to assess QOL, which has already been formally *validated* in *Turkish* population (16).

The monthly and yearly cost of medications used for COPD was calculated at the baseline visit. The sum of costs were converted from Turkish Liras (TL) to US Dollars ($) at the current exchange rate.

The statistical analyses were performed using Statistical Package for Social Science (SPSS) for Windows (version 15.0SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means and standard deviation and categorical variables were expressed as numbers and percentages. The mean values of the groups were compared using the Student's t-test and the median values were compared using the Mann-Whitney U-test. Categorical variables were compared using Fisher's exact and Chi-square tests. A confidence level of 95% and a p value of less than 0.05 indicated statistical significance.

Results

A total of 150 patients who met the inclusion criteria, underwent the baseline study visit. Among these patients, 14 could not be reached during the study period or did not attend the 6-month visit, and these patients were subsequently excluded from the study. Of the 136 patients who completed the study, 120 (88.2%) were male and 16 (11.8%) were female. The mean age of the study population was 64.77±10.29.

Of the total, 80 (58.8%) of the patients had at least one comorbidity other than COPD, with the most common comorbidity being hypertension (46%). The mean number of drugs (used for comorbidities) was 3.36±2.25.

The number of active smokers, ex-smokers and never smokers were 54 (39.7%), 62 (45.6%), and 20 (14.7%), respectively. The mean pack/years of smoking was 51.45±28.88. Of the patients, 66.2% reported passive smoke exposure, and all of the never smokers had a history of passive smoke exposure.

The mean reported duration of COPD was 4.9±1.1 years. The mean number of inhaled medications was 1.98±0.76. The mean number of COPD exacerbations during the preceding year was 1.1±0.14 and the mean FEV_1 value was 1.64±0.61 L (56.1±16.9%). According to their FEV_1 values, 9.6% had mild, 54.4% had moderate, 26.5% had severe and 9.5% had very severe COPD. According to the combined (ABCD) staging, 47.1% had stage A, 15.4% had stage B, 8.1% had stage C and 29.4% had stage D COPD. All demographics according to GOLD groups are in **Table 1.**

Among the patients 77.2% had dyspnea, 35.2% had cough and 24.3% had sputum production at the baseline visit. The physical examination findings included rhonchi in 19.8% and rales in 15.4%. The physical examination was normal in 64.8%.

The results of the baseline treatment of the patients are presented in **Figure 1**. At the baseline visit, 44.1% of the patients were under appropriate treatment according to the guidelines, while 55.9% were being overtreated. The treatment protocol of 98.6% of the overtreated patients included ICS.

Treatment was de-escalated in 54 patients (39.7%) in the baseline visit, and among these, 35 were being overtreated (reduction group I). On the other hand, 19 were receiving appropriate treatment according to the guidelines and underwent a stepwise de-escalation under the advice of their clinicians (reduction group II). The non-reduction group (patients who declined to undergo treatment de-escalation) included 37 overtreated patients (non- reduction group I). Forty-five patients who were receiving appropriate treatment according to the guidelines were in non- reduction group II. The consort diagram is in **Figure 2.**

Among the patients who underwent a treatment de-escalation, ICS+LABA was discontinued in 28, ICS was discontinued in 11, theophylline was discontinued in nine, LAMA was discontinued in six and nebulized treatment was discontinued in four. During the six month study period, 39 of participants experienced COPD exacerbations, and the mean number of exacerbations was 0.45 ±0.11.

The mean mMRC and SGRQ had decreased while the FEV1 value and inhalation device skill scores had increased at the 6-month visit when compared to the baseline visit. The mean inhalation device skill score increased from 7.96±2.14 points at the baseline visit to 8.24±2.3 points at the 6-month visit. The inhalation device skill score increased in 44.2%, decreased in 15.4% and did not change in 40.4% of the patients.

The mean FEV_1 value and mMRC, adherence and SGRQ scores improved in patients whose COPD medications were de-escalated, however the differences were not statistically significant (p=0.471, p=0.675, p=0.23 and p=0.093, respectively. **Table 2**).

The patients in whom treatment was de-escalated were similar to those who continued their treatment regimens in terms of the presence of COPD exacerbations and improvements in FEV1, mMRC and inhaler device use performance (p=0.137, p=0.213, p=0.326 and p=0.272, respectively). QOL improved significantly in the COPD patients whose treatment was de-escalated (p=0.005, **Table 3**).

The patients under appropriate treatment according to the guidelines were more likely to experience COPD exacerbations and had better improvement in FEV_1 than those who had non-adherent treatment to GOLD 2017 (p<0.001 and p=0.032, respectively). However, there were no statistically significant improvements in mMRC, adherence or SGRQ scores between two groups (p=0.296, p=0.179 and p=0.097, respectively. **Table 4**).

Non- reduction group I had less improvement in their FEV1 and SGRQ scores (p=0.045 and p=0.043, respectively) than non- reduction group II, while the patients with improvement in their pulmonary function parameters were statistically higher than in non- reduction group II at the second visit (p=0.033).

Improvement in quality of life at the sixth-month follow up was better in the reduction group II (stepwise de-escalation group) when compared to non- reduction group II (p=0.011). On the other hand, the FEV_1 value, inhalation device skill score and frequency of COPD exacerbations were similar in reduction group II and non- reduction group II (p=0.588, p=0.317 and p=0.328, respectively).

At the second visit, 31 of the 54 (57.4%) active smokers had reduced their habit and four (7.4%) had quitted. The improvements in FEV_1 values and inhalation device skill were better in the patients who had reduced or discontinued smoking (p=0.034 and p=0.023, respectively).

The estimated additional cost of overtreatment was 119.57$/year for each patient. If all of the patients were under appropriate treatment according to the guidelines, the total monthly cost would be 538.07$ less, corresponding to a total yearly saving of 6,456.85$.

Discussion

In the present study, 44% of the patients were under appropriate treatment according to the guidelines, which was similar to the findings of previous literature. Studies from foreign countries reported that one-third to two-thirds of COPD patients were under appropriate treatment according to the guidelines (5, 6), while studies in Turkey reported that nearly half of all COPD patients are under appropriate treatment (7, 17).

Several studies have reported that adherence to the current guidelines in stable COPD is poor (1). Appropriate treatment may lead to symptom control and improvement in general health. One surrogate marker of general health is quality of life. Poor adherence to inhalation treatment leads to an aggravation of symptoms and a worsening quality of life (18). In the present study, the de-escalation of inhaled treatment was significantly associated with improvement in quality of life. The use of multiple inhalers for different medications more than doubles the risk of treatment errors (19). It can be suggested that the increase in quality of life in our study was attributable to the improvement in inhaled treatment adherence as a result of the reduction of the number of inhaler devices in use.

Most of the earlier studies assessing the reduction of inhaled treatment in COPD involved a discontinuation of ICS, and in most of these studies, COPD exacerbation was similar in the patients who stopped and those who continued ICS (20, 21). However, FEV_1 was found to decrease significantly in patients who discontinued ICS. Contrary to these reports, a de-escalation of treatment (according to the guidelines) resulted in a significant increase in FEV_1 at the 6-month follow up in the present study. We think that this increase may be due to the improvement in inhaler device adherence and the high rate of reduction/cessation of smoking in this group.

The use of appropriate treatment according to the guidelines not only improves spirometric measurements, but also reduces treatment costs and even mortality (2). Overtreatment in COPD is reported to cause a huge cost burden (17, 22). Both appropriate treatment according to the guidelines and a de-escalation of overtreatment led to significant cost savings in the present study, however a long-term follow up is needed to identify the effects of this intervention on mortality.

Active smoking is a typical characteristic of a COPD patient with poor adherence. In one study, the lack of adherence to the treatment was three times more common in active smokers when compared with former smokers (23). In the present study, the patients who quitted smoking showed improvements in both pulmonary function tests and in inhalation device skill. From this it can be understood that counselling encouraging smoking cessation can play a key role in improving treatment adherence in patients with COPD.

In the present study, COPD exacerbations were more common in patients undergoing appropriate treatment according to the guidelines. The high-risk patients were generally found to be under multiple inhaled treatments, while non-adherent treatment procedures were generally seen in the low-risk COPD patient group. COPD exacerbations are thus most commonly seen in patients under appropriate treatment according to the guidelines, and so this finding in the present study was anticipated.

Our findings further indicate that a de-escalation of treatment can lead to an improvement in quality of life. The individualized approach to de-escalation was recommended for the first time in GOLD 2017 guideline (1). Provided that optimal bronchodilator treatment is administered, treatment may be de-escalated in suitable patients. However, there are only a few studies supporting this, and studies involving large samples will be needed if more solid conclusions are to be drawn.

One of the main limitations of the present study is the small sample size, in particular, the low number of patients in the subgroups. The lack of randomization and inadequate homogeneity of the groups and treatment options were the other limitations, also including the lack of standardized approaches (other than the guidelines) in selection which medications had been discontinued. Besides, having the participating pulmonologists decide on appropriateness of treatment de-escalation of some patients may be a bias.

The present study supports the treatment recommendations laid out in the guidelines, and to the best of our knowledge, is the first prospective study in Turkey to investigate the effects of a de-escalation of inhaled treatments. Previous studies have tended to focus on the discontinuation of ICSs, while the present study also provides information about the effects of discontinuing medications other than ICSs. The present study can thus be considered as pioneering in stepwise de-escalation of COPD treatment in literature.

Conclusions

Overtreatment is commonly seen in COPD treatment. A de-escalation of inhaled treatment (including a stepwise de-escalation) improves quality of life. An appropriate treatment that follows the guidelines can have a positive effect on respiratory parameters. The cessation or reduction of smoking in patients with COPD improves both adherence to inhaled treatment and spirometric measurements. De-escalation of treatment should be considered in overtreated COPD patients, especially if they are not in the high-risk groups.

Abbreviations

COPD: Chronic obstructive pulmonary disease

QOL: quality of life

MRC: Medical Research Council

SGRQ: Saint George's respiratory questionnaire

ICS: inhaled corticosteroid

LABA: long-acting beta-2 agonist

LAMA: long-acting antimuscarinic antagonist

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants. Canakkale 18 Mart University institutional review board approved this study.

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.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

OT, SS, SAA, NO, NTH and AM collected patient data. OT analyzed the data and was major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: Demographics of the patients (according to GOLD groups)

Demographics and characteristics	COPD Group A	COPD Group B	COPD Group C	COPD Group D
Age ± SD (mean)	63.88 ± 8.95	66.47 ± 13.59	66.65 ± 9.68	64.62 ± 11.16
Male/female (n)	55/11	15/4	17/0	33/1
FEV1 - % ± SD	66.53 ± 14.63	48.42 ± 13.49	54.35 ± 16.13	41.06 ± 17.64
Presence of comorbidities (n)	41/66	13/19	10/17	16/34
Smoking ± SD (mean) (package.year)	46.66 ± 26.28	56.26 ± 28.48	54.12 ± 25.33	59.16 ± 34.72
Presence of COPD exacerbations (last year) (n)	5/66	4/19	15/17	31/34

Table 2: Comparison of study parameters in first and second visits among patients in whom inhaled treatment was de-escalated

Parameters	1st Visit	2nd Visit	p value
FEV_1 (%)	50.48	59.43	0.471
Inhalation device skill score	8.6	8.91	0.23
mMRC score	1.62	1.57	0.675
SGRQ score	48.46	45.24	0.093

FEV_1: forced expiratory volume in the first second,

mMRC: modified British Medical Research Council dyspnea scale,

SGRQ: Saint George's respiratory questionnaire

Significant p values are represented in bold text.

Table 3: Comparison of the changes in the patients who underwent de-escalation and those who continued their inhaled treatment regimen

The changes in patient characteristics in the 2nd visit		Patients who underwent de-escalation (n = 54)	Patients who continued their treatment regimen (n = 82)	p value
COPD exacerbation	Present	20	34	0.137
	Absent	34	48	
Improvement in mMRC score	Present	11	17	0.326
	Absent	43	65	
Improvement in FEV1	Present	29	41	0.213
	Absent	25	41	
Improvement in inhalation device skill score	Present	41	48	0.272
	Absent	13	34	
Improvement in quality of life	Present	37	44	**0.005**
	Absent	17	38	

COPD: Chronic obstructive pulmonary disease

Significant p values are represented in bold text.

Table 4: Comparison of the changes in patients who were under appropriate treatment according to the guidelines and those under inappropriate treatment

The changes in study variables in the 2nd visit		Patients under appropriate treatment according to the guidelines (n = 64)	Patients under inappropriate treatment according to the guidelines (n = 72)	p value
COPD exacerbation	Present	44	11	**<0.001**
	Absent	20	61	
Improvement in mMRC score	Present	16	14	0.296
	Absent	48	58	
Improvement in FEV1	Present	37	35	**0.033**
	Absent	27	37	
Improvement in inhalation device skill score	Present	42	47	0.179
	Absent	22	25	
Improvement in quality of life	Present	36	37	0.097
	Absent	28	35	

COPD: Chronic obstructive pulmonary disease

Significant p values are represented in bold text.

Figures

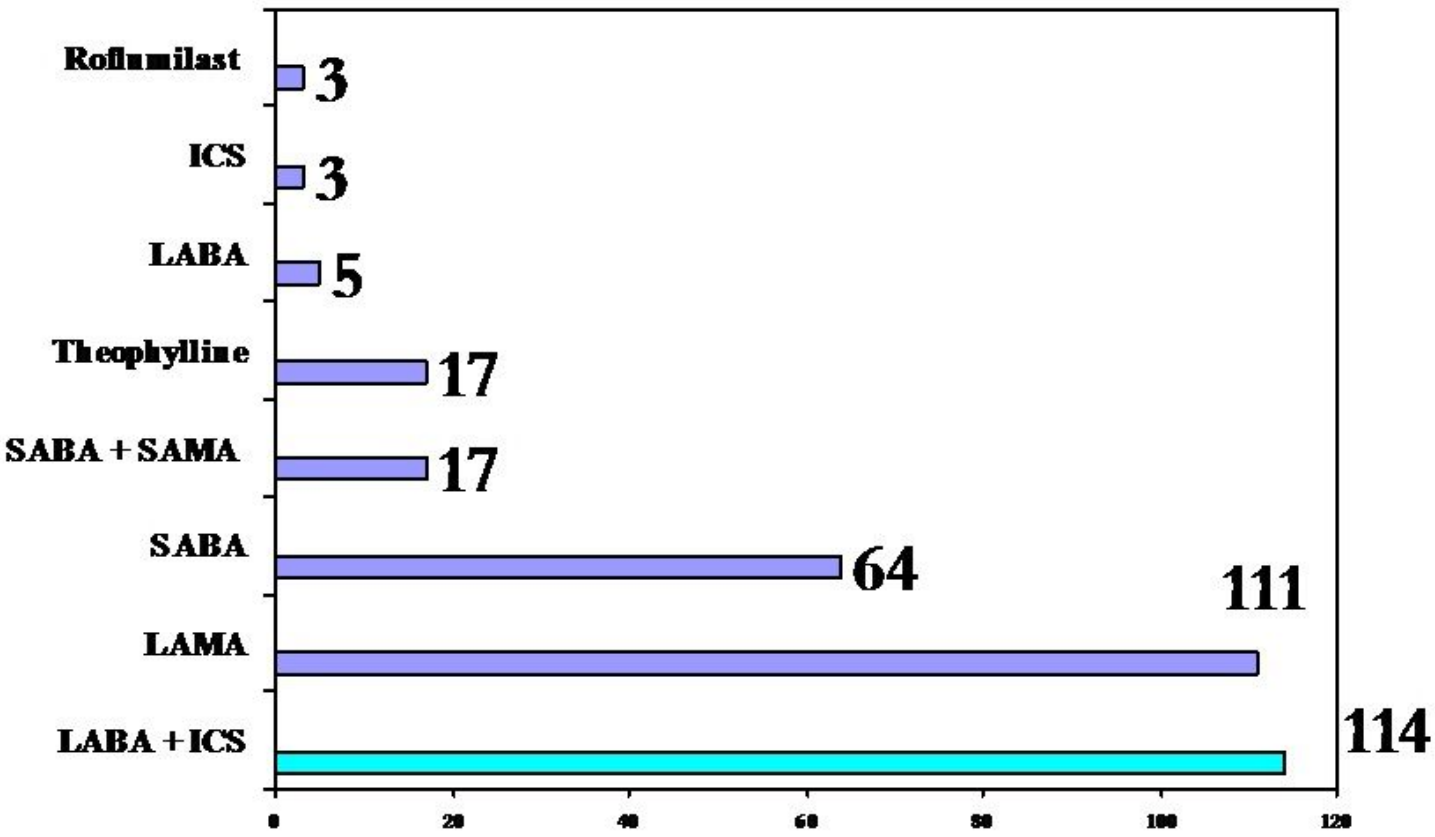

Figure 1

Baseline treatment of participants

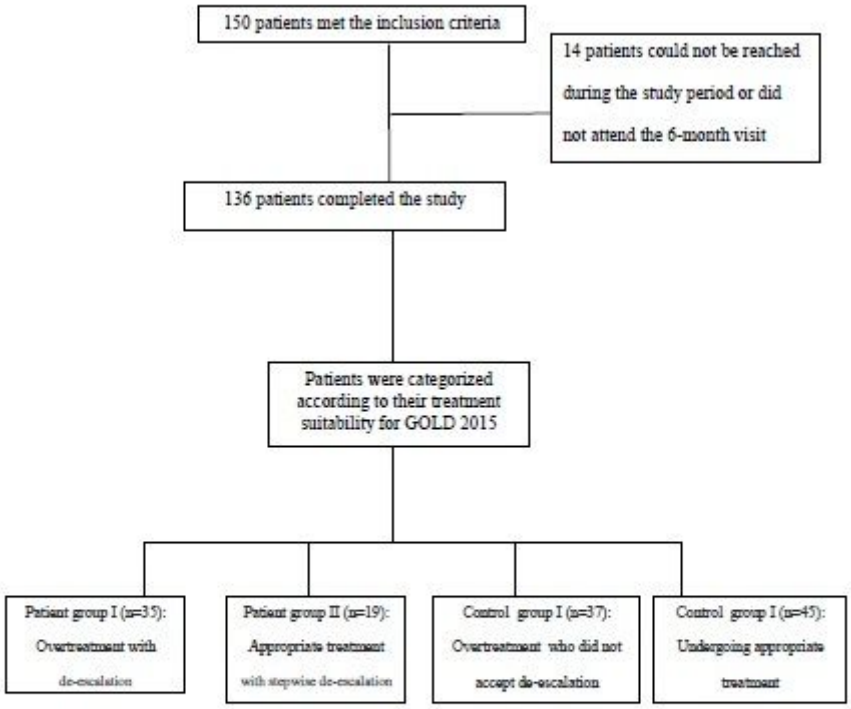

Figure-2: Consort diagram of patient enrollment.

COPD: Chronic obstructive pulmonary disease.

GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Figure 2

The consort diagram