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Effect of carbocysteine on exacerbations and lung function in patients with mild-to-moderate chronic obstructive pulmonary disease: a multicentre, double-blind, randomised, placebo-controlled trial

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Effect of carbocysteine on exacerbations and lung function in patients with mild-to-moderate chronic obstructive pulmonary disease: a multicentre, double-blind, randomised, placebo-controlled trial

Running title: Carbocysteine in mild-to-moderate COPD.

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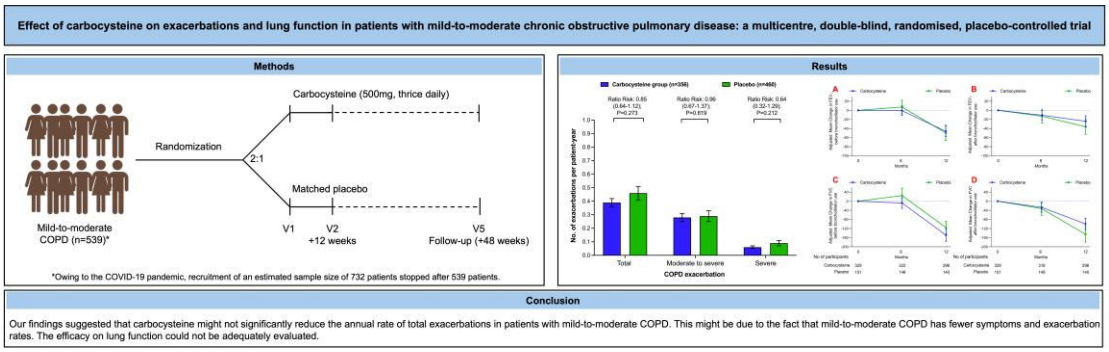
Data Sharing Statement

All the individual participant data collected during the trial (including the data dictionary) will be available, after deidentification, immediately after publication with no end date. Applications for access to data should be made in writing to Prof. Pixin Ran (pxran@gzhmu.edu.cn) who will arrange for request be reviewed, data will be provided after approved by investigators and data transfer agreement has been signed.

Graphical Abstract



Abstract

Objectives: Carbocysteine can reduce the frequency of acute exacerbations and improve symptoms to a certain extent in severe to very severe chronic obstructive pulmonary disease (COPD) patients. The objective of the study was to evaluate the efficacy of carbocysteine on the rate of exacerbations and pulmonary function for mild-to-moderate COPD patients.

Methods: In this phase 4, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial, we randomly assigned mild-to-moderate COPD patients in a 2:1 ratio to treatment with carbocysteine (500mg, thrice daily) or matched placebo for 48 weeks. Eligible participants were 40-80 years of age. The coprimary outcomes were the annual rate of exacerbations of COPD (mild, moderate or severe) during the 48-week trial period or the difference in the FEV_1 before bronchodilator use at 48-week from baseline.

Results: Owing to slower-than-anticipated recruitment caused by the COVID-19 pandemic, recruitment of an estimated sample size of 732 patients stopped after 539 patients. The sample size was indeed reached for the annual rate of exacerbations but not for pulmonary function. Among 539 patients, 362 were randomized to receive carbocysteine and 177 to receive matched placebo. There was no significant difference in the annual rate of exacerbations of COPD between carbocysteine group and placebo group (0.39 vs. 0.46 per patient year; relative risk [RR], 0.85; 95% confidence interval [CI], 0.64–1.13; P = 0.273). Based on the available sample size, the difference in the change of FEV_1 before bronchodilator use at

48 weeks between carbocysteine group and placebo group has not been observed (46±10 vs. 49±14 ml; mean difference, 4; 95% CI, -29–36; adjusted P = 0.827).

Conclusions: Our findings suggested that carbocysteine might not significantly reduce the annual rate of total exacerbations in patients with mild-to-moderate COPD. The findings may have been compromised by an overestimation of the efficacy of carbocysteine on reducing exacerbations in mild-to-moderate COPD and potential confounding by baseline imbalances. The efficacy on lung function could not be adequately evaluated.

Clinical trial registered with Chictr.org.cn (ChiCTR1800016712).

Keywords: carbocysteine; exacerbations; lung function; mild-to-moderate COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death worldwide(1). Exacerbations of COPD are the main cause of COPD disease progression, so reducing the frequency of exacerbation in COPD patients is the main treatment goal of COPD. Accumulating evidence indicates that early intervention for COPD can bring more benefit(2-5). Mild-to-moderate COPD accounts for 92.7% of COPD patients in China(6), and exacerbations causes worse damage to their lung function than severe to very severe COPD(7).

Although mild-to-moderate COPD patients have mild symptoms, they often present with cough, sputum and dyspnea. These symptoms are often caused by increased airway secretions and increased viscosity(8). Carbocysteine is a mucolytic agent that can help relieve mucus obstruction in the respiratory tract by breaking down the mucin structure in sputum and improving sputum clearance. In addition, carbocysteine has free radical scavenging and anti-inflammatory properties(9). The PEACE study showed that carbocysteine can reduce the frequency of acute exacerbations and improve symptoms to a certain extent in patients with severe to very severe COPD(10). For patients with mild-to-moderate COPD, the effect of carbocysteine remains unclear. We conducted a prospective trial to investigate the effect of carbocysteine on the annual rate of exacerbations and the lung function in patients with mild-to-moderate COPD.

Methods

TRIAL DESIGN AND OVERSIGHT

We conducted this phase 4, multicenter, double-blind, randomized, placebo-controlled,

parallel-group trial at 14 centers in mainland China. The recruitment was conducted in tertiary care hospitals with specialized respiratory departments. Patients who met the eligibility criteria during a 2-week screening period were randomly assigned in a 2:1 ratio to receive 1500 mg (500mg, thrice daily) carbocysteine or matching placebo taken orally daily for 48 weeks. Randomization was centralized and conducted with the use of block sizes of four, stratified according to trial site. Salbutamol (100 μg) was provided as rescue medication. Long-term use (regular and continuous use of drugs for more than one month is considered long-term use) of other COPD medications (i.e., inhaled glucocorticoid, LAMA or LABA) should be avoided during the trial. Participants who were taking COPD medications at enrollment were allowed to continue to use them during the trial. This study was registered on the Chinese Clinical Trial Registry, number ChiCTR1800016712.

The trial protocol was approved by the local institutional review board or independent ethics committee at each site, according to the requirement of the Chinese guidelines for Good Clinical Practice, and all the patients provided written informed consent. The trial protocol, including the statistical analysis plan, is available in the Supplementary Appendix. The National Key Technology Research and Development Program of the 13th National 5-year Development Plan funded the trial but had no role in the design, acquiral or analysis of the data, or interpretation of the results in this trial. The BaiYunShan Pharmaceutical General Factory donated masked trial medication and placebo. The first and last authors designed the trial and analyzed the data. All the authors had access to and participated in the interpretation of the data presented herein and provided input into the drafting and final approval of the manuscript for submission. The authors vouch for the accuracy and completeness of the data

and for the fidelity of the trial to the protocol.

PATIENTS

Eligible patients were 40 to 80 years of age and had had physician-diagnosed COPD at the time of screening, and had no COPD exacerbation occurring in the 4 weeks before randomization. Patients were required to have a postbronchodilator ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC) of less than 0.70 and a postbronchodilator FEV_1 of 50% or more of the predicted normal value, had chronic respiratory symptoms and/or risk factors for COPD (e.g., smoking, biofuel exposure, air pollution). The key exclusion criteria were asthma, bronchiectasis, active pulmonary tuberculosis, diffuse panbronchiolitis, interstitial lung disease, major systemic disease, and patients receiving mucolytic agents for more than 3 months since before the screening period. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

END POINTS

The coprimary end points were the annual rate of exacerbations of COPD (mild, moderate or severe) during the 48-week trial period and the difference in the FEV_1 before bronchodilator use at 48-week from baseline. A COPD exacerbation was defined as worsening of at least two major symptoms (cough, sputum volume, sputum purulence, wheezing, or dyspnea) that persisted for at least 48 hours, after the presence of cardiac insufficiency, pulmonary embolism, pneumothorax, pleural effusion, or cardiac arrhythmia had been ruled out(11). The primary end point was not adjusted for multiplicity.

Secondary end points included: the difference in the FEV_1 after bronchodilator use at 48-week from baseline, the difference in the FVC before and after bronchodilator use at 48-week from baseline, the time until the first COPD exacerbation of any severity during the treatment period; the change from baseline to week 48 in the COPD Assessment Test (CAT) score (scores range from 0 to 40, with higher scores indicating more severe disease). The key safety end points were adverse events and serious adverse events that occurred after initiation of carbocysteine or placebo.

Subgroup analyses of the primary end point were also performed. A subgroup analyses were performed post hoc for subgroups defined according to CAT score (≥10). All the secondary and subgroup analyses are exploratory in nature and were not adjusted for multiplicity.

STATISTICAL ANALYSIS

Efficacy was evaluated in full analysis set (FAS), which included all patients who underwent randomization, were treated with at least one dose of study medication, and had available post-baseline data on exacerbation (FAS for exacerbation) or available spirometry data (FAS for lung function) within 12 months. Safety was evaluated in the safety population, which included all patients who received at least one dose of study medication.

Sample size was calculated based on the coprimary outcomes. First, referring to the Tie-COPD study(3), we estimated that a sample of 433 patients (288 in carbocysteine group and 145 in placebo group) would provide the trial with 90% power to detect a between-group difference in the annualized rate of mild, moderate or severe exacerbations of 0.23 (0.27 per

patient-year for the carbocysteine group and 0.50 per patient-year for the placebo group) at week 48 at a two-sided alpha level of 0.05 based on an anticipated withdrawal rate of 15%. Second, we estimated that a sample of 732 patients (488 in carbocysteine group and 245 in placebo group) would provide the trial with 90% power to detect a between-group difference in the FEV_1 before and after bronchodilator use at 48-week from baseline of 105 mL at week 48 at a two-sided alpha level of 0.05 based on an anticipated withdrawal rate of 15%. We estimated that a total of 732 patients (488 in carbocysteine group and 245 in placebo group) would be required for the primary analysis.

The exacerbation rate was analyzed with the use of a poisson regression, with correction for exposure to the trial regimen and overdispersion. The total number of events occurring during the 48-week trial period as the response variable, and the natural log of the duration of receipt of medication was used as an offset variable. The difference in the FEV_1 before and after bronchodilator use at 48-week from baseline was assessed with the use of a random coefficient regression model that time as the random effect, group, age, gender, baseline smoking status, GOLD grading, body mass index and baseline FEV_1 as the fixed effect. The change from baseline to week 48 in the CAT total score was assessed with the use of a Repeated-measures ANOVA. The time until the first COPD exacerbation of any severity was evaluated using the Kaplan-Meier survival curve and log-rank test to determine the difference between the two groups. Additional details regarding the statistical methods are provided in the Supplementary Appendix. Statistical analyses were performed using SAS 9.4 (SAS Institute, USA), and all reported P values are two-sided.

Results

PATIENTS

From March 8, 2018 through January 15, 2022, a total of 539 patients underwent randomization: 362 to the carbocysteine group and 177 to the placebo group (Figure 1). The sample size was indeed reached for the annual rate of exacerbations but not for pulmonary function. In total, 83.4% of the patients in the carbocysteine group and 81.4% of those in the placebo group completed the 48-week trial period. The demographic and disease characteristics of the two groups were well balanced at baseline (Table 1). The mean age of the patients was 64±7 years. Patients were predominantly male. Overall, 51.6% of the patients were current smokers, and 14.9% were receiving therapy. At baseline, 6.0%, 0.0%, 3.8%, 0.4 and 4.7% of patients were using LAMA, LAMA+LABA, LABA+ICS, LAMA+LAMA+ICS, or other medications, respectively. Changes in concomitant medications during the trial were shown in Figure S3. The mean percentage of predicted FEV_1 value after bronchodilator use is 75.9±15.8. The mean number of moderate or severe exacerbations of COPD in the previous year, the mean CAT score, the mean mMRC dyspnea scale score, and the mean CCQ score were similar in the two groups (Table 1).

PRIMARY END POINT

At week 48, the annual rate of total COPD exacerbations was no different in the carbocysteine group compared with the placebo group. The annualized rate of total exacerbations of COPD was 0.39±0.03 per patient-year in the carbocysteine group and 0.46±0.05 per patient-year in the placebo group (relative risk, 0.85; 95% CI, 0.64 to 1.13; P=0.273) (Table 3). The annualized

rate of moderate or severe exacerbations of COPD was 0.28±0.03 per patient-year in the carbocysteine group and 0.29±0.04 per patient-year in the placebo group (relative risk, 0.96; 95% CI, 0.67 to 1.37; P=0.819). Results were similar in exploratory subgroups analysis.

The efficacy on lung function could not be adequately evaluated. Based on the available sample size, carbocysteine resulted in a no difference FEV_1 before bronchodilator use than placebo at week 48. Changes from baseline in the before bronchodilator use FEV_1 during the 48-week trial period are shown in Table 2 and Figure 2. At week 48, the least-squares mean change from baseline in the before bronchodilator use FEV_1 was 46±10 ml in the carbocysteine group and 49±14 ml in the placebo group; the least-squares mean difference was 4 ml (95% CI, -29 to 36; adjusted P=0.827). Changes in other lung-function variables are shown in Table 2.

SECONDARY AND OTHER END POINTS

Exacerbations

The time until the first exacerbation event of any severity for carbocysteine as compared with placebo is shown in FigureS2 (hazard ratio, 0.96; 95% CI, 0.66 to 1.39). The time until the first exacerbation event of moderate or severe severity for carbocysteine as compared with placebo (hazard ratio, 1.01; 95% CI, 0.66 to 1.56).

Quality of life

At week 48, the decrease from baseline in CAT total score was –1.3 points (95% CI, –1.8 to -0.8) in the carbocysteine group and –1.2 points (95% CI, –1.9 to –0.5) in the placebo group

(least-squares mean difference, –0.2 points; 95% CI, –0.8 to 0.5) (Table S3). There were no significant differences in mMRC scores and CCQ scores between the two groups at different time points (Table S4 and S5).

Subgroup analyses of primary end points

Similar to the results of the primary analysis, the CAT score (≥10) subgroup analysis suggested that the annualized rate of total COPD exacerbations were no difference among patients in the carbocysteine group than among those in the placebo group (Table 3). However, the carbocysteine group showed a lower exacerbation risk after adjustment (Table S8).

SAFETY

The incidence of adverse events was similar in the two groups (18.0% in the carbocysteine group and 15.8% in the placebo group, P = 0.538) (TableS6). 5.5% serious adverse events were reported in patients treated with carbocysteine, and 6.2% serious adverse events were reported in patients treated with placebo (P = 0.747). Adverse events that resulted in death occurred in 0.0% of the patients in the carbocysteine group and in 0.0% of those in the placebo group.

Discussion

This trial demonstrated that carbocysteine might not reduce the annual rate of exacerbations in mild-to-moderate COPD. The efficacy on lung function could not be adequately evaluated. Based on the available sample size, the difference in the change of FEV_1 before bronchodilator

use at 48 weeks between carbocysteine group and placebo group has not been observed. Previous studies have shown that mucolytics can reduce exacerbations, but in a meta-analysis that included only studies conducted after 2000, when the authors considered that inhaled COPD treatments had improved significantly, they did not find any effect of N-acetylcysteine on reducing COPD exacerbations(12). The study from Poole et al. also showed that the effect of mucolytics in reducing exacerbations decreased significantly over time, especially after 2000(13). Therefore, the results of this study cannot be directly compared with those evaluating mucolytics when COPD treatment was less developed.

In a network meta-analysis, the authors compared the efficacy of erdosteine 600 mg/day, carbocysteine 1500 mg/day, and N-acetylcysteine 1200 mg/day in COPD, and found that carbocysteine and N-acetylcysteine could not reduce exacerbation rates (14). A trial using another mucolytics, N-acetylcysteine, 1200 mg/day to treat mild-to-moderate COPD for 2 years also found no benefit in reducing exacerbation rates(15). A meta-analysis including 28 studies involving 6723 participants demonstrated that mucolytics appear to be useful for reducing flare-ups in people with COPD or chronic bronchitis(13). In this meta-analysis, the populations were dominated by moderate to severe COPD, and the annual exacerbation rate in the placebo group was 2.51, while the annual exacerbation rate in mild-to-moderate COPD in this study was only 0.46. The effect of carbocysteine may vary among COPD patients of different severity. Previous studies have found that carbocysteine can reduce the risk of acute exacerbations in people with moderate to severe COPD and more respiratory symptoms(10, 16). Our exploratory subgroup analysis (CAT ≥10) also suggested that the carbocysteine group had a lower exacerbation risk after adjustment (Table S8). Compared with previous studies,

the study population in this study was mild-to-moderate COPD, 76.8% of them had no history of acute exacerbations in the previous year, and 74.4% of them had a CAT score of less than 10. In patients with mild-to-moderate COPD, the underlying lesions are mild, and sputum problems may not be the main cause of acute exacerbations(17). On the contrary, in patients with severe COPD, the viscosity and amount of sputum may be more significant problems, so carbocysteine may show more obvious efficacy in these patients(18). Cazzola et al. showed that specific differences in patient-related characteristics were potential effect modifiers for statistical models, the effectiveness of mucolytics was more effective in patients with frequent exacerbations(19). Our results showed that carbocysteine was ineffective due to the milder stage of disease, yet previous studies and our exploratory subgroup analysis suggest that carbocysteine may be beneficial in COPD patients with frequent exacerbations and more symptoms.

The main mechanism of action of carbocysteine is to reduce the viscosity of sputum by breaking down glycoproteins in sputum(9). However, the pathophysiological mechanism of acute exacerbation of COPD is complex, involving multiple factors such as airway inflammation, infection, and airway smooth muscle spasm(20). Treating sputum problems with mucolytics alone may not be enough to significantly improve the overall symptoms and course of acute exacerbation. This suggests that in the treatment of acute exacerbation, a single pharmacological action may not cover all pathophysiological mechanisms, and a comprehensive treatment strategy may be more effective.

Randomized controlled trials performed in different countries(10, 16, 21) used different dosages of carbocysteine (1500 to 2700 mg/d). Different dosages may produce different

efficacy and safety. This variation limits the applicability of the findings of this study in clinical contexts where higher dosages are standard. Higher dosages may provide better benefits, yet the GOLD guidelines do not make recommendations on dosage. In China, the recommended dosage of carbocysteine is 1500mg/day(22). The dosage in this study is consistent with the PEACE Study which has been previously proven to reduce the rate of exacerbations in moderate to severe COPD in the Chinese population(10). For dosage selection, a balance should be achieved between efficacy and safety.

Several studies have documented that both inhaled corticosteroids and long-acting bronchodilators can reduce exacerbation rate(23), so concomitant COPD medications during the trial are potential confounding factors. To minimize the potential impact, we reanalyzed the primary end point by adding previous medication for COPD at baseline as a covariate, and the results remained after adjustment (Table S7 and S8). In addition, the trial protocol required that participants were not allowed to add new COPD medications during the trial. Therefore, concomitant COPD medications during the trial are unlikely to affect the results.

Part of this trial was conducted during the COVID-19 pandemic, previous studies found that the strict lockdown was associated with the reductions in acute exacerbations of COPD, likely due to reduced transmission of respiratory virus infections in the COVID-19 pandemic(24-26). Nevertheless, COVID-19 is unlikely to have affected the results of this study for the following reasons. Firstly, a lower baseline exacerbation rate may have an impact on the exacerbation rate in this trial, however, 95% participants were enrolled in this study before the presence of COVID-19 (January 30, 2020). Therefore, the influence of COVID-19 on patient screening and enrollment in this study was minimal. Secondly, we observed an exacerbation

rate of 0.46 per patient-year in the placebo group, which is comparable to the annual exacerbation rate of mild-to-moderate COPD reported previously(3, 27). Therefore, we believe that the strict lockdown policy during the trial have a little effect on reducing the exacerbation rate in this study. Since this study is a double-blind clinical trial, the impact of COVID-19 on follow-up and the rates of exacerbations for both the carbocysteine group and the placebo group should be consistent. It is unlikely that COVID-19 would significantly affect the study conclusions.

This study had some limitations. Firstly, the coronavirus 2019 (Covid-19) pandemic led to slow recruitment and termination of the trial before full recruitment, with 10 sites ultimately participating and recruitment stopped after 539 patients were enrolled (362 in carbocysteine group and 177 in placebo group). A post-hoc power analysis showed that this sample size could provide 98% power for annualized rate of exacerbations and 81% power for the FEV_1 before and after bronchodilator use. The sample size was indeed reached for the annual rate of exacerbations but not for pulmonary function. Secondly, because the difference in the annual rate of COPD exacerbation of any severity and lung function between the two groups was overestimated when calculating the sample size, this trial may not have been sufficiently powered to detect the effect of carbocysteine on primary end point. Thirdly, the study population were mainly Chinese male, which may limit the inference of the results to other demographics, particularly females or populations from different regions. Future studies in more diverse study populations are needed to improve the applicability of the findings across various patient groups.

In conclusion, our findings suggested that carbocysteine might not significantly reduce

the annual rate of total exacerbations in patients with mild-to-moderate COPD. Our findings may have been compromised by an overestimation of the efficacy of carbocysteine on reducing exacerbations in mild-to-moderate COPD and potential confounding by baseline imbalances. In addition, carbocysteine was very well tolerated.

Ethical approval

This trial was approved by the ethics committee at each hospital according to the requirements of Chinese clinical trial guidelines. All patients provided written informed consent before enrolment.

Funding

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Author contributions

YZ, LL, FW, ZD, HL, HH, HZ, YW, LW, QC and SC contributed equally to this work. PR and QW had the idea for and designed the study. PR and QW supervised the study. FW and YZ did the statistical analysis. All authors contributed to the acquisition, analysis, or interpretation of data. FW, HL, YZ, and PR wrote the draft manuscript. All authors revised the manuscript and approved the final version before submission. FW, PR, and YZ affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Artificial intelligence involvement

None of the material has been partially or totally produced with the help of any artificial intelligence software or tool.

Acknowledgements

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Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

Yes

If yes; please provide name of the ethical committee approving these experiments and the registration number. :

The Ethics Committee of The First Hospital of China Medical University（2017-128-3）

If yes; please confirm authors compliance with all relevant ethical regulations. :

Yes

If yes; please confirm that written consent has been obtained from all patients. :

Yes

3. Does your study include a clinical trial?:

Yes

If yes; please confirm that experiments have been conducted according to the CONSORT guidelines. :

Yes

Please provide name of the ethical committee approving these experiments and the registration

number:

The Ethics Committee of The First Hospital of China Medical University (2017-128-3). Clinical trial registered with Chictr.org.cn (ChiCTR1800016712).

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

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Table 1. Characteristics of the Patients at Baseline (Full Analysis Set) *

Variable	Carbocysteine Group (N=356)	Placebo Group (N=175)	P Value†
Age-yr	64±7	65±7	0.063
Male sex-no. (%)	318 (89.3)	159 (90.9)	0.583
Body-mass index‡	22.8±3.5	22.5±3.1	0.357
Smoking status			0.252
Never smoked	60 (16.9)	20 (11.4)	
Current smoking	115 (32.3)	62 (35.4)	
Former smoking	181 (50.8)	93 (53.1)	
Smoking index-pack-yr§	46.4±29.8	41.0±23.3	0.051
Previous medication for COPD-no. (%)	51 (14.3)	28 (16.0)	0.610
LAMA	21 (41.2)	11 (39.3)	
LAMA+LABA	0	0	
LABA+ICS	15 (29.4)	5 (17.9)	
LAMA+LAMA+ICS	1 (2.0)	1 (3.6)	
Other medications※	14 (27.5)	11 (39.3)	
Acute exacerbation in the previous year-no. (%)	88 (24.7)	35 (20.0)	0.226
No. of Acute exacerbation in the previous year	0.40±0.83	0.37±0.91	0.728
Spirometric values at baseline			

Before bronchodilator use			
FEV_1-liters	1.90±0.54	1.83±0.54	0.201
FEV_1-% of predicted value	72.2±16.0	69.5±17.6	0.070
FVC-liters	3.31±0.75	3.22±0.80	0.226
FEV_1:FVC ratio	57.3±8.8	56.9±8.6	0.622
After bronchodilator use			
FEV_1-liters	2.01±0.54	1.95±0.53	0.258
FEV_1-% of predicted value	76.5±15.6	74.6±16.2	0.178
FVC-liters	3.42±0.74	3.36±0.79	0.483
FEV_1:FVC ratio	58.9±8.2	58.2±7.9	0.377
Airflow reversibility-no. (%)[¶]	60 (16.9)	33 (18.9)	0.568
GOLD stage, n (%)			0.710
1	177 (49.7)	84 (48.0)	
2	179 (50.3)	91 (52.0)	
CAT score[‖]			
Mean score	6.7±5.6	6.7±5.8	0.990
Distribution-no. (%)			0.501
<10	268 (75.3)	127 (72.6)	
≥10	88 (24.7)	48 (27.4)	
mMRC dyspnea scale score[**]			
Mean score	0.7±0.7	0.7±0.7	0.932
Distribution-no. (%)			0.283

<2	308 (87.0)	157 (90.2)	
≥2	46 (13.0)	17 (9.8)	
CCQ score[††]	0.96±0.78	1.00±0.74	0.594

* Data are mean ± standard deviation or n (%).

[†] The P value of continuous variable is calculated by student t test or Wilcoxon rank sum test, and the P value of classified variable is calculated by chi square test.

[‡] Body mass index is the weight in kilograms divided by the height in meters squared.

[※] Other medications include methoxyphenamine, theophylline and traditional Chinese medicine.

[§]The smoking index is defined as the number of cigarettes smoked per day multiplied by the number of years of smoking. The smoking index was 296 current or former smokers in the Carbocysteine group and 155 in the placebo group.

[¶]Airflow reversibility is defined as an increase of 200ml or more in FEV_1 after the use of bronchodilators, which is 12% or more higher than that measured before the use of bronchodilators.

[‖]The score of the chronic obstructive Pulmonary Disease Assessment Test (CAT) ranges from 0 to 40, and a higher score indicates that the disease is more serious.

[**] The modified Medical Research Council (mMRC) dyspnea scale scores between 0 and 4, and the higher the score, the more severe the dyspnea.

[††] The score of the Clinical COPD questionnaire (CCQ) is between 0 and 6. The higher the score, the worse the clinical control.

Table 2. Annual Declines in Lung Function before and after Bronchodilator Use. *

Variable	Decline per Year			P Value	
	Carbocysteine Group (N=329)	**Placebo Group (N=151)**	**Mean Difference (95% CI)**	Unadjusted	Adjusted[†]
FEV_1 (ml)					
Before bronchodilator use	46±10	49±14	4 (-29 to 36)	0.832	0.827
After bronchodilator use	24±9	36±13	12 (-19 to 43)	0.444	0.443
FVC (ml)					
Before bronchodilator use	148±21	115±30	-33 (-106 to 39)	0.365	0.390
After bronchodilator use	99±19	144±27	45 (-21 to 111)	0.178	0.179
FEV_1 (% of predicted value)					
Before bronchodilator use	1.9±0.4	2.4±0.6	0.5 (-0.8 to 1.9)	0.433	0.434
After bronchodilator use	1.1±0.4	1.7±0.5	0.7 (-0.6 to 1.9)	0.290	0.295
FVC (% of predicted value)					
Before bronchodilator use	4.6±0.6	4.6±0.9	0.0 (-1.3 to 1.3)	0.987	0.985
After bronchodilator use	3.2±0.6	4.9±0.8	1.7 (-0.2 to 3.6)	0.082	0.082

Plus–minus values are means ± standard error per year.

Abbreviations: CI= confidence interval; FEV_1=forced expiratory volume in one second; FVC= forced vital capacity.

* Analysis was in the full analysis set for lung function.

† P values were adjusted by the fixed-effect covariates, including age, sex, body-mass index, baseline smoking status, GOLD stage, center, and individual spirometric values at baseline (FEV_1, FVC, percent of predicted FEV_1, and percent of predicted FVC before and after bronchodilator use).

Table 3. Acute Exacerbations of Chronic Obstructive Pulmonary Disease*.

Variable	Carbocysteine Group	Placebo Group	Relative Risk† (95% CI)	P Value
Total population	N=356	N=175		
No. of exacerbations per patient-year				
Total	0.39±0.03	0.46±0.05	0.85 (0.64-1.13)	0.273
Of moderate or severe	0.28±0.03	0.29±0.04	0.96 (0.67-1.37)	0.819
Of severe	0.06±0.01	0.09±0.02	0.64 (0.32-1.29)	0.212
CAT < 10	N=268	N=127		
No. of exacerbations per patient-year				
Total	0.39±0.04	0.41±0.06	0.94 (0.67-1.33)	0.740
Of moderate or severe	0.28±0.03	0.24±0.05	1.14 (0.74-1.76)	0.543
Of severe	0.04±0.01	0.05±0.02	0.86 (0.32-2.32)	0.760
CAT ≥ 10	N=88	N=48		
No. of exacerbations per patient-year				
Total	0.42±0.07	0.62±0.12	0.68 (0.40-1.13)	0.140
Of moderate or severe	0.27±0.06	0.42±0.10	0.65 (0.34-1.22)	0.175
Of severe	0.10±0.04	0.20±0.07	0.50 (0.19-1.33)	0.164

Plus–minus values are means ±SE. The number of exacerbations or hospitalizations per patient-year was the number of times of exacerbation for a single patient per year.

Abbreviations: RR=relative risk; CI= confidence interval; CAT= COPD Assessment Test.

* Analysis was in the full analysis set for Exacerbation.

† The relative risk was calculated with the use of Poisson regression, with correction for exposure to the trial regimen and overdispersion.

Figure Legends

Figure 1. Randomization and Follow-up of Patients with Chronic Obstructive Pulmonary Disease of GOLD Stage 1 or 2.

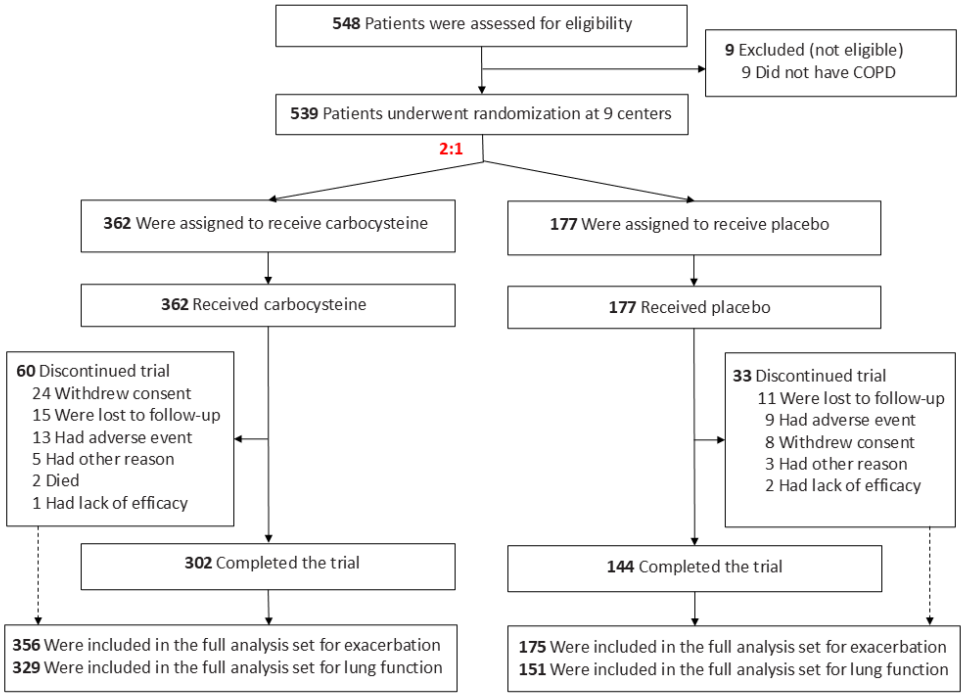

Figure 2. Adjusted Mean Change from Baseline in Forced Expiratory Volume in 1 Second and Forced Vital Capacity before and after Bronchodilator Use. *

Error bars are 95% confidence intervals.

***** Analysis was in the full analysis set for lung function.