e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2024; 16(10); 130-136

Original Research Article

Comparative Study between the Effects of Triple Therapy (LAMA –LABA – ICS) and Lama- LABA in COPD Patients

Swapnamoy Ghosh[1], Animesh Mandal[2], Ranjit Kumar Haldar[3], Saibal Mandal[4]

[1]MD Resident, Respiratory Medicine resident, FEAACI, CCEBDM, EPGCD, Department of Respiratory Medicine, IPGMER and SSKM Hospital, Bhowanipore, Kolkata, West Bengal 700020

[2]Assosciate Professor, MD Respiratory Medicine, Department of Respiratory Medicine, IPGMER and SSKM Hospital, Bhowanipore, Kolkata, West Bengal 700020

[3]Assistant Professor, MD Respiratory Medicine, Department of Respiratory Medicine, IPGMER and SSKM Hospital, Bhowanipore, Kolkata, West Bengal 700020

[4]RMO, MD Respiratory Medicine, Department of Respiratory Medicine, IPGMER and SSKM Hospital, Bhowanipore, Kolkata, West Bengal 700020

Received: 01-07-2024 Revised: 15-08-2024 / Accepted: 21-09-2024

Corresponding author: Dr. Swapnamoy Ghosh

Conflict of interest: Nil

Abstract

Introduction: The progressive respiratory ailment known as chronic obstructive pulmonary disease (COPD) is linked to a high rate of morbidity and death. Inhaled corticosteroids (ICS) and bronchodilators are commonly used in combination treatment for pharmacological management. The purpose of this research is to examine the effects of dual therapy (LAMA-LABA) and triple therapy (LAMA-LABA-ICS) on individuals with COPD.

Aims: To compare the effects of LABA-LAMA and LABA-LAMA-ICS combination in the two treatment groups; to comprehend the effects of individual LABA + LAMA and LABA+LAMA+ICS in COPD patients; and to investigate various COPD variables such as FEV1/FVC ratio, FEV1, DLCO, 6-minute walk test, and frequency of exacerbations in COPD at one-, three-, and six-month intervals.

Materials and Methods: The present study was a comparative clinical trial. The study Period will be July 2023 to August 2024 And Data Collection from July 2023 to July 2024 Analysis August 2024 at department of the department of respiratory medicine, IPGME & R and SSKMH, Kolkata. Total 100 patients were included in this study.

Result: We found that, FEV1 Change after 12 weeks was less in LABA LAMA [.0336± .0165] compared to LABA LAMA ICS [.0600 ±.0326] but this was statistically significant ($p<0.0001$). Our study showed that, FEV1 Change after 24 weeks was more in LABA LAMA [.1008 ± .0314] compared to LABA LAMA ICS [.0878±.0383] but this was statistically significant ($p<0.0001$). We observed that, FEV1 Change after 52 weeks was lower in LABA LAMA [.0500± .0182] compared to LABA LAMA ICS [.1508±.0397] but this was statistically significant ($p<0.0001$). We found that, 6 MWD Change after 52 weeks (Meteres) was lower in LABA LAMA [153.0204 ± 48.7239] compared to LABA LAMA ICS [229.2553 ±54.3985] but this was statistically significant ($p<0.0001$). In our study, Improvement in Dyspneoa SGRQ Scoring was more in LABA LAMA ICS [22.0040 ±7.2832] compared to LABA LAMA [16.6800 ± 4.8379] but this was statistically significant ($p<0.0001$).

Conclusion: We came to the conclusion that a comparative research offers strong evidence for triple therapy's (LAMA-LABA-ICS) advantage over dual therapy (LAMA-LABA) in the treatment of COPD. Triple therapy is superior to dual therapy in terms of improving lung function, symptom management, and quality of life outcomes. It also reduces the incidence of flare-ups. These results emphasize the need of maximizing COPD therapy through individualized therapeutic strategies catered to the requirements of each patient.

Keywords: COPD (Chronic Obstructive Pulmonary Disease), Triple therapy and LAMA (Long-acting Muscarinic Antagonist).

Introduction

It has been suggested recently that patients with COPD who have significant symptoms and a history of exacerbations add inhaled corticosteroid to their long-acting muscarinic antagonist and long-acting beta agonist combination medication, since this lowers the frequency of exacerbations. Furthermore, this medication has been demonstrated to have a decreasing influence on

mortality. But because the majority of the data comes from the IMPACT research, a sizable randomized controlled trial, it's still uncertain whether or not the ICS add-on medication is helpful. A sizable new ETHOS study was conducted recently to elucidate the impacts of the ICS add-on.

Worldwide, chronic obstructive pulmonary disease, or COPD, is the third most common cause of mortality [1]. Dyspnea, coughing, and sputum production are among the symptoms that intensify during COPD exacerbations, which are linked to an increased risk of death. Depending on the severity, either single or dual inhaled bronchodilators are advised for therapy to lessen the symptoms and the exacerbation. The addition of inhaled corticosteroid (ICS) to combination therapy involving long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA) has been suggested if patients have a history of exacerbations and severe symptoms. This is because ICS reduces the incidence of exacerbations [2]. Recently, it has also been demonstrated that this medication lowers mortality. Nevertheless, administering extra ICS medication may raise the risk of pneumonia in individuals with severe COPD. As such, the overall benefit for these patients should be considered when making a choice about the long-term usage of ICS.

Too far, five systematic studies have been conducted to assess the safety and effectiveness of adding ICS to LAMA/LABA therapy. But there are a number of biases in the studies that are included, such the use of several breathing devices [3] employing distinct LABA for the comparative groups or a 24-week evaluation period.

It is therefore unclear whether or not the ICS add-on therapy is effective because the majority of the data from these systematic reviews comes from a single big randomized controlled trial (RCT), the IMPACT research, which was conducted over a 52-week period using a single inhaler device. In an effort to shed light on the ICS add-on effects, a sizable new ETHOS study was conducted recently [4].

In order to assess the effectiveness and safety, including the ETHOS experiment, we thus carried out a systematic review and meta-analysis. In order to compare the effectiveness and safety of ICS/LAMA/LABA (triple) vs LAMA/LABA treatment, we looked for pertinent randomized control clinical studies. We then measured exacerbations, quality of life (QOL), dyspnea score, lung function, and adverse events including pneumonia and death. Additionally, we contrasted the outcomes of a meta-analysis of ICS add-on to LAMA/LABA with those of ICS removal from triple treatment.

Material and Methods

Study design: comparative clinical trial.

Place of study: outdoor and indoor patient department of the department of respiratory medicine, IPGME & R AND SSKMH, Kolkata.

Period of study: The study Period will be July 2023 to August 2024.

Study population: patients in indoor patient department of the department of respiratory medicine, IPGME & R and SSKMH, Kolkata.

Sample size: 100 patients of COPD.

Inclusion Criteria:

1. Patients with equal to or more than one exacerbation in last 1 year.
2. Patients having history of at least one exacerbation needing hospital admission.
3. Age more than 40 years.
4. Patients giving consent for the study.

Exclusion Criteria:

1. Patients less than 40years of age
2. Patients with history of asthma
3. Patients of asthma COPD overlap
4. Patients with lung malignancy and COPD
5. Patients with heart failure and COPD.
6. Patients having history of tuberculosis.

Data collection and interpretation: Cases of COPD was selected, according to clinical and radiological purview and followed up at regular intervals for adherence of therapy and the improvements was tabulated by doing performance assessment in PFT and 6MWT and the number of exacerbations during the study period.

Clinical, laboratory investigations and parameters, and procedures: as per pre-defined case record format.

Statistical analysis plan: Data was analysed through proper tables and charts, appropriate statistical methods was applied thereby.

Ethical clearance: was given by ethics committee

Work plan: The study Period will be July 2023 to August 2024

Data collection: July 2023 to July 2024 Analysis August 2024

Statistical Analysis: For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples.

Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test ($\chi 2$ test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various t-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a t value is determined, a p-value can be found using a table of values from Student's t-distribution .If the calculated p-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.

P-value $\leq$ 0.05 was considered for statistically significant.

Result

Table 1: Distribution of mean FEV1 Change after 12 weeks: Therapy

		Number	Mean	SD	Minimum	Maximum	Median	p-value
FEV1 Change after 12 weeks	LABA LAMA	50	0.0336	0.0165	0.0100	0.1200	0.0300	<0.0001
	LABA LAMA ICS	50	0.0600	0.0326	0.0200	0.1800	0.0500	
FEV1 Change after 24 weeks	LABA LAMA	50	0.0500	0.0182	0.0300	0.1400	0.0500	<0.0001
	LABA LAMA ICS	50	0.0878	0.0383	0.0400	0.2000	0.0800	
FEV1 Change after 52 weeks	LABA LAMA	50	0.1008	0.0314	0.0400	0.2000	0.0900	<0.0001
	LABA LAMA ICS	50	0.1508	0.0397	0.0800	0.2700	0.1500	

Table 2: Distribution of mean FVC Change at 12 weeks: Therapy

		Number	Mean	SD	Minimum	Maximum	Median	p-value
FVC Change at 12 weeks	LABA LAMA	50	0.0592	0.0213	0.0100	0.1200	0.0600	<0.0001
	LABA LAMA ICS	50	0.0998	0.0363	0.0200	0.2000	0.1000	
FVC Change in 24 weeks	LABA LAMA	50	0.0804	0.0247	0.0100	0.1400	0.0800	<0.0001
	LABA LAMA ICS	50	0.1328	0.0559	0.0600	0.4000	0.1200	
FVC Change after 52 weeks	LABA LAMA	50	0.1336	0.0395	0.0300	0.2800	0.1200	<0.0001
	LABA LAMA ICS	50	0.1984	0.0842	0.0600	0.6000	0.1800	

Table 3: Distribution of mean Number of exacerbations in 24 weeks: Therapy

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Number of exacerbations in 24 weeks	LABA LAMA	50	0.0020	.0040	0.0000	0.0100	0.0000	0.2799
	LABA LAMA ICS	50	0.0012	0.0033	0.0000	0.0100	0.0000	
Number Of Exacerbations In 52 Weeks	LABA LAMA	50	0.0040	0.0061	0.0000	0.0200	0.0000	0.0188
	LABA LAMA ICS	50	0.0016	0.0037	0.0000	0.0100	0.0000	

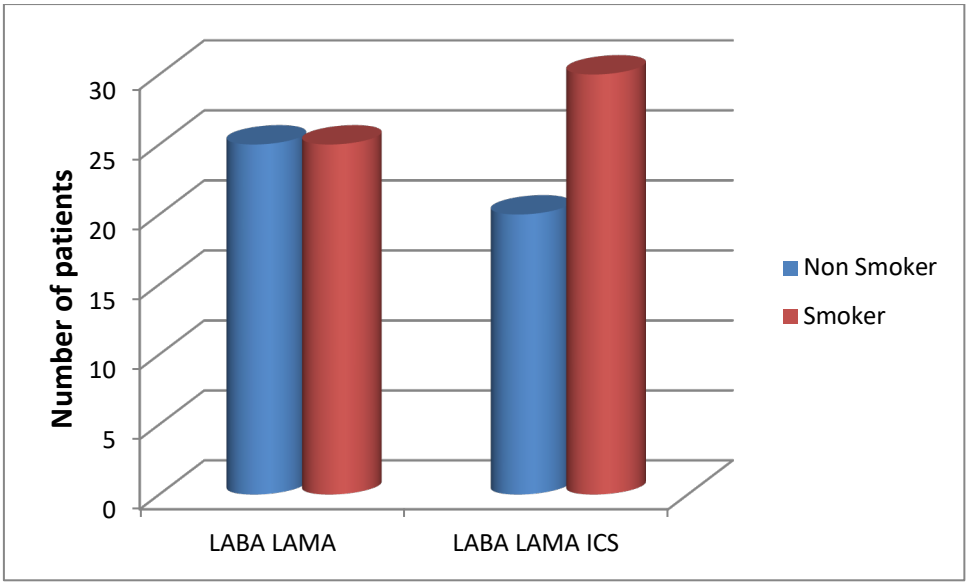

Figure 1: Association between Smoking Status: Therapy

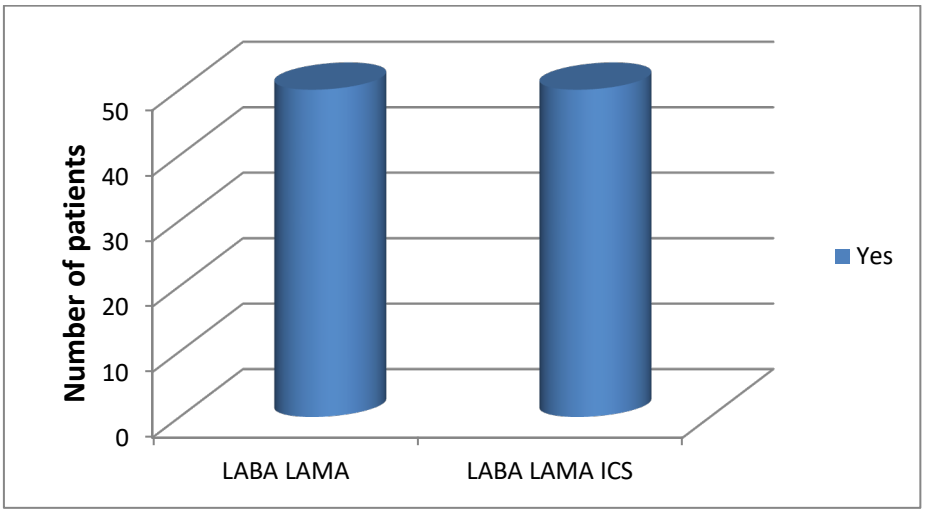

Figure 2: Association between Received Immunisation: Therapy

After 12 weeks, the mean FEV1 Change (mean± s.d.) of the patients in LABA LAMA Was.0336±.0165. After 12 weeks, the mean FEV1 Change (mean± s.d.) of patients in LABA LAMA ICS was.0600 ±.0326. After receiving therapy for 12 weeks, the mean FEV1 Change distribution was statistically significant (p=<0.0001). After 24 weeks, the mean FEV1 Change (mean ± s.d.) of the patients in LABA LAMA Was .1008 ±.0314.

The mean FEV1 Change (mean± s.d.) of patients in LABA LAMA ICS was.0878±.0383 after 24 weeks. After receiving therapy for 24 weeks, the mean FEV1 Change distribution was statistically significant (p=<0.0001). After 52 weeks (mean± s.d.), the mean FEV1 Change for patients in LABA LAMA Was.0500±.0182. After 52 weeks, the mean FEV1 Change (mean± s.d.) of patients in LABA LAMA ICS was.1508±.0397. After 52 weeks of therapy, the mean FEV1 Change distribution was statistically significant (p<0.0001). The mean FVC Change (mean± standard deviation) of the patients in LABA LAMA was .0592±.0213 at 12 weeks. The mean FVC Change (mean± standard deviation) of the patients in LABA LAMA ICS was.0998±.0363 at 12 weeks. At 12 weeks with therapy, the mean FVC Change distribution was statistically significant (p=<0.0001). The mean FVC Change (mean ± standard deviation) of the patients in LABA LAMA was .0804 ±.0247 at 24 weeks.

The mean FVC Change (mean± standard deviation) of the patients in LABA LAMA ICS was.1328±.0559 at 24 weeks. At 24 weeks with therapy, the mean FVC Change distribution was statistically significant (p=<0.0001). The mean FVC Change (mean± standard deviation) of the patients in LABA LAMA was .1336±.0395 at 52 weeks. The mean FVC Change (mean± standard deviation) of the patients in LABA LAMA ICS was.1984±.0842 at 52 weeks. At 52 weeks with

therapy, the mean FVC Change distribution was statistically significant (p=<0.0001). The mean number of exacerbations per patient in 24 weeks (mean ± s.d.) in LABA LAMA was .0020 ±.0040. The mean number of exacerbations per patient in 24 weeks (mean ± s.d.) with LABA LAMA ICS was.0012 ±.0033. The mean number of exacerbations throughout a 24-week period of therapy did not exhibit a statistically significant distribution (p=0.2799). The mean number of exacerbations per patient in 52 weeks (mean ± s.d.) in LABA LAMA was .0040 ±.0061. The mean number of exacerbations per patient in 52 weeks (mean ± s.d.) with LABA LAMA ICS was.0016 ±.0037. The mean number of exacerbations over the 52-week therapy period showed a statistically significant distribution (p=0.0188). 25 (50.0%) of the patients in LABA LAMA were non-smokers, and 25 (50.0%) were smokers. Thirty patients (60.0%) and twenty (40.0%) did not smoke in LABA LAMA ICS. The relationship between therapy and smoking status was not statistically significant (p= 0.3148). Of the patients in LABA LAMA, 50 (100.0%) had received an immunization. 50 individuals (100.0%) in LABA LAMA ICS had received vaccinations.

Discussion

This study is a comparative clinical trial conducted at the outdoor and indoor patient departments of the Department of Respiratory Medicine, IPGME&R and SSKMH, Kolkata, from July 2023 to August 2024. The study focuses on 100 patients diagnosed with COPD (Chronic Obstructive Pulmonary Disease). Participants are required to meet inclusion criteria, such as having had at least one exacerbation in the past year and being over 40 years of age. Exclusion criteria include conditions like asthma, lung malignancy, and heart failure. Data is collected through clinical and radiological assessments, with regular follow-up to monitor adherence to therapy and improvements in pulmonary function tests (PFT), 6-minute walk tests (6MWT), and the number of exacerbations during the study period. The data is analyzed using appropriate statistical methods and represented through tables and charts. Ethical approval was obtained from the ethics committee, and data collection is scheduled from July 2023 to July 2024, with analysis planned for August 2024. Tashkin DP et al [5](2017) found that Data on various free or fixed-dose combinations of inhaled medications, such as long-acting β2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and/or inhaled corticosteroids (ICS), for the treatment of chronic obstructive pulmonary disease (COPD), have been gathered in recent years from randomized clinical trials. Out of the 100 patients in our research, the majority were between the ages of 40 and 50 [42 (42.0%)] but this was not statistically significant (p=0.8604). Fens T et al [6](2019) examined that using The Netherlands as a reference case, to evaluate the financial impact of limiting the use of inhaled corticosteroids (ICS) inappropriately in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines indication for ICS use in the chronic obstructive pulmonary disease (COPD) population. The model calculates how pharmacologic COPD maintenance therapies affect clinical events (such as pneumonias and exacerbations), as well as the expenditures and use of related healthcare services. Cheng WC et al [7](2020) observed that for chronic pulmonary obstructive disease (COPD), triple therapy is superior than dual therapy in that it can lessen symptoms, lower the likelihood of acute exacerbations (AEs), and enhance lung function.

According to our research, a greater percentage of patients in LABA LAMA experienced one exacerbation in a 24-week period [10 (20.0%)] compared to LABA LAMA ICS [6 (12.0%).] but this was statistically significant (p=0.0275). We found that fewer patients in LABA LAMA experienced the number of exacerbations in 52 weeks [14 (28.0%)] compared to LABA LAMA ICS [8 (16.0%)] but this was statistically significant (p=0.0474).

In our study, higher number of [30 (60.0%)] patients were Smoker in LABA LAMA ICS compared to LABA LAMA [25 (50.0%)] but this was not statistically significant (p= 0.3148). We discovered that the proportion of each group that received vaccinations was equal [50 (100.0%)] LABA LAMA and LABA LAMA ICS.

Lozano R et al [8] (2012) found that debates on health policy require accurate and timely information on the main causes of mortality in populations as well as how they are changing. We attempted to estimate yearly mortality for the globe and 21 regions between 1980 and 2010 for 235 causes, with uncertainty intervals (UIs), individually by age and sex in the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010).

Suissa S et al [9](2020) found that variable outcomes were observed in randomized trials and observational studies examining triple treatment combinations of long-acting muscarinic antagonist (LAMA), long-acting beta2-agonist (LABA), and inhaled corticosteroid (ICS) for COPD. Using 2002 to 2015, we were able to identify a cohort of > 55-year-old patients with COPD using the UK's Clinical Practice Research Datalink. In our study, Age was higher in LABA LAMA ICS [54.5800 ±10.0389] compared to LABA LAMA [54.0600 ± 8.6742] but this was not statistically significant (p=0.7823). Cheng WC et al [10](2020) observed

that for chronic pulmonary obstructive disease (COPD), triple therapy is superior than dual therapy in that it can lessen symptoms, lower the likelihood of acute exacerbations (AEs), and enhance lung function. Right now.

The most frequent symptoms of COPD are an increase in COPD Assessment Test (CAT) scores of ≥ 2 (13/49, 26.5%) and a fall in forced expiratory volume in 1 second (FEV1) of ≥ 100 mL from baseline (25/49, 51%); many of these individuals react to the addition of a long-acting muscarinic antagonist (LAMA).

We found that, FEV1 Change after 12 weeks was less in LABA LAMA [.0336± .0165] compared to LABA LAMA ICS [.0600 ±.0326] but this was statistically significant (p<0.0001).

Our study showed that, FEV1 Change after 24 weeks was more in LABA LAMA [.1008 ± .0314] compared to LABA LAMA ICS [.0878±.0383] but this was statistically significant (p<0.0001). We observed that, FEV1 Change after 52 weeks was lower in LABA LAMA [.0500± .0182] compared to LABA LAMA ICS [.1508±.0397] but this was statistically significant (p<0.0001). It was found that, FVC Change at 12 weeks was most in LABA LAMA ICS [.0998± .0363] compared to LABA LAMA [.0592± .0213] but this was statistically significant (p<0.0001). We examined that, FVC Change in 24 weeks was higher in LABA LAMA ICS [.1328± .0559] compared to LABA LAMA [.0804± .0247] but this was statistically significant (p<0.0001).

In our study, FVC Change after 52 weeks was less in LABA LAMA [.1336± .0395] compared to LABA LAMA ICS [.1984± .0842] but this was statistically significant (p<0.0001). We found that, 6 MWD Change after 52 weeks (Meteres) was lower in LABA LAMA [153.0204 ± 48.7239] compared to LABA LAMA ICS [229.2553 ±54.3985] but this was statistically significant (p<0.0001).

Our study showed that, Number of exacerbations in 24 weeks was lower in LABA LAMA ICS [.0012 ±.0033] compared to LABA LAMA [.0020 ± .0040] but this was not statistically significant (p=0.2799). We observed that, Blood Sugar was more in LABA LAMA [.0040 ± .0061] compared LABA LAMA ICS [.0016 ±.0037] but this was statistically significant (p=0.0188).

In our study, Improvement in Dyspneoa SGRQ Scoring was more in LABA LAMA ICS [22.0040 ±7.2832] compared to LABA LAMA [16.6800 ± 4.8379] but this was statistically significant (p<0.0001).

Conclusion

Overall, even though both triple treatment and LAMA-LABA show promise in managing COPD symptoms and reducing the incidence of exacerbations, our data suggest that triple therapy may offer further benefits in these areas. Treatment choices, however, have to be determined by the particular characteristics and preferences of the patient, taking into consideration factors including the severity of the illness, a history of exacerbations, and the potential for negative consequences. To confirm these findings and improve the treatment strategies for COPD patients, more research involving longer-term trials and empirical data is required.

Reference

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2095–128
2. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J. 2019; 53:1900164.
3. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2007; 146:545–55.
4. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med. 2020; 383:35–48.
5. Tashkin DP, Taube C. Triple therapy for chronic obstructive pulmonary disease management. Are our expectations fulfilled? American Journal of Respiratory and Critical Care Medicine. 2017 Aug 15; 196(4):402-4.
6. Fens T, van der Pol S, Kocks JW, Postma MJ, van Boven JF. Economic impact of reducing inappropriate inhaled corticosteroids use in patients with chronic obstructive pulmonary disease: ISPOR's guidance on budget impact in practice. Value in Health. 2019 Oct 1; 22(10):1092-101.
7. Cheng WC, Wu BR, Liao WC, Chen CY, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. When to use initial triple therapy in COPD: adding a LAMA to ICS/LABA by clinically important deterioration assessment. International Journal of Chronic Obstructive Pulmonary Disease. 2020 Dec 22:3375-84.

8. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, AlMazroa MA. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The lancet. 2012 Dec 15; 380(9859):2095-128.
9. Suissa S, Dell'Aniello S, Ernst P. Comparative effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: cohort study in real-world clinical practice. Chest. 2020 Apr 1; 157(4):846-55.
10. Cheng WC, Wu BR, Liao WC, Chen CY, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. When to use initial triple therapy in COPD: adding a LAMA to ICS/LABA by clinically important deterioration assessment. International Journal of Chronic Obstructive Pulmonary Disease. 2020 Dec 22:3375-84.