International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Paradigm Shift in the Treatment of Chronic Obstructive Pulmonary Disease Improves Patient Outcomes

Yi-Jen Huang[1], Kwua-Yun Wang[2–5], Wu-Chien Chien[6], Chi-Hsiang Chung[6,7], Li-Ting Kao[8–10], Senyeong Kao[7], Chih-Feng Chian[11]

[1]Department of Nursing, University of Kang Ning, Taipei, Taiwan; [2]School of Nursing, National Defense Medical Center, Taipei, Taiwan; [3]Nursing Department, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Rui Guang Healthcare Group, Taipei, Taiwan; [5]College of Nursing, National Yang Ming Chiao Tung University, Taipei, Taiwan; [6]Department of Medical Research, Tri-Service General Hospital, Taipei, Taiwan; [7]School of Public Health, National Defense Medical Center, Taipei, Taiwan; [8]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan; [9]School of Pharmacy, National Defense Medical Center, Taipei, Taiwan; [10]Department of Pharmacy Practice, Tri-Service General Hospital, Taipei, Taiwan; [11]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Correspondence: Chih-Feng Chian, Email sonice3982@gmail.com



**Purpose:** This study evaluates the real-world impact of LAMA+LABA combination therapy on COPD outcomes, bridging the gap between experimental data and clinical practice. It aims to assess whether the paradigm shift in the treatment of chronic obstructive pulmonary disease has improved patient outcomes, particularly in terms of acute exacerbations, hospitalizations, and mortality, while providing insights to guide clinical and policy decisions.

**Patients and Methods:** This retrospective study analyzes cohorts derived from outpatient and inpatient medical records from Taiwan's National Health Insurance Research Database. It includes individuals diagnosed with COPD in two periods: 2012–2014 and 2016–2018.

**Results:** The paradigm shift in COPD treatment has led to a significant transition in medication selection, moving away from single-agent or supplementary inhaled corticosteroid (ICS) regimens (from 99.61% to 20.99%) towards the use of dual bronchodilators or triple therapy (from 0.38% to 79.02%). The analysis between long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs) revealed no statistically significant differences in emergency department visits and hospitalizations. However, LABAs were associated with a notable reduction in all-cause mortality compared to LAMAs (aHR 0.674–0.765). Additionally, the widespread adoption of dual bronchodilator therapy and the implementation of precise guidelines for ICS use have led to significant reductions in emergency department visits (aHR 0.557–0.735), decreased hospitalizations (aHR 0.610–0.725), and improved mortality outcomes (aHR 0.226–0.294) among COPD patients.

**Conclusion:** The paradigm shift in treatment approaches has led to substantial improvements in patient outcomes for COPD, regardless of the treatment regimen employed. This development marks a significant advancement in enhancing both the efficacy and precision of COPD management.

**Plain Language Summary:**

**Why was this study done?**

Chronic obstructive pulmonary disease (COPD) is a lung condition that makes breathing difficult. A treatment combining two inhaled medications, long-acting muscarinic antagonists (LAMA) and long-acting beta-agonists (LABA), was approved in 2013 and shown to help in clinical trials. We wanted to see if it works as well in everyday healthcare settings.

**What did the researchers do and find?**

Using a health database in Taiwan, we studied COPD patients treated with LAMA+LABA. The results showed fewer hospital visits and better symptom control, confirming the benefits seen in clinical trials.

**What do these results mean?**

LAMA+LABA helps people with COPD in real-world settings, improving their quality of life. This supports its wider use as an effective treatment.

Received: 13 December 2024
Accepted: 3 June 2025
Published: 17 June 2025

**Keywords:** COPD, acute exacerbation, mortality

# Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, significantly impacting patient quality of life and healthcare systems. Effective management of COPD relies on pharmacological treatments to reduce symptoms, prevent exacerbations, and improve long-term outcomes. In recent years, there has been a paradigm shift in COPD management, particularly with the introduction of dual bronchodilator therapy, combining long-acting muscarinic antagonists (LAMAs) and long-acting beta-agonists (LABAs).

Since the approval of the first LAMA+LABA combination therapy in 2013, clinical trials have demonstrated its benefits, establishing these combinations as a key treatment option for COPD. In the single-agent regimen, there was a prevailing inclination towards the preference for LAMAs over LABAs.[1–4] Dual bronchodilators (LABA + LAMA) are recommended for individuals who are exhibiting severe symptoms or are at higher risk for exacerbation, rather than using a single agent or in combination with an inhaled corticosteroid (ICS).[5–13] An escalating body of research has underscored that a rise in eosinophil count could serve as a pivotal factor in determining the appropriateness of incorporating ICS into the treatment regimen.[14–17] This evolution and modification decrease the cohort of COPD patients prescribed singular therapeutic agents or supplementary ICS. Simultaneously, the demographics receiving dual bronchodilator therapies or triple therapy (ICS+LABA+LAMA) regimens is anticipated to expand.

COPD causes persistent symptoms of varying severity, including breathlessness, chronic cough, and fatigue, which can limit daily activities and independence. In addition to reducing the above symptoms as much as possible, the goal of treatment is to prevent acute exacerbation. According to statistics, each acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD) leads to a decline in lung function by approximately 34.7 mL per year.[18] Additionally, COPD exacerbations increase mortality by 10–30%.[19] Furthermore, exacerbations decrease the quality of life and raise the risk of future exacerbations.

This study investigates the impact of the shift in COPD treatment guidelines on patient outcomes, focusing on Taiwan's National Health Insurance Research Database (NHIRD). It analyzes how the use of single, dual, and triple therapies evolved over two time periods (2012–2014 and 2016–2018) and examines key outcomes, such as emergency department (ED) visits, hospitalizations, and mortality rates. By comparing these outcomes across different treatment regimens, the study aims to provide insights into the effectiveness of current COPD management strategies and identify opportunities for improvement in clinical practice.

# Patients and Methods

## Study Design and Data Source

This was a retrospective study in a cohort extracted from the records of the outpatients and inpatients in NHIRD. This database covers over 99% of Taiwan's 23 million residents, providing comprehensive medical records for the entire population. To protect privacy, all data were anonymized through scrambling and translation processes, ensuring that individuals could not be identified at any stage of analysis.[20] The data source was provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare. This research received approval and exemption from review by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No.: E202316040), as it exclusively utilized anonymized databases, thereby mitigating ethical review requirements.

## Cohort Identification

Initially, individuals diagnosed with COPD were identified through the occurrence of medical codes (ICD-9-CM 491–492, 496; ICD-10-CM J40-J44, J98.2-J98.3) on three or more occasions. The selected cohort included individuals over 40 years of age, aligning with the age range most commonly used to distinguish COPD from asthma. The data were divided into two time periods, 2012–2014 and 2016–2018, to allow for a comparative analysis of changes in COPD medication guidelines and real-world medication use.

Medication use was assessed by reviewing the administrative claims database, with usage defined as periods extending beyond 60 days. This threshold was chosen based on the policy for "refillable prescriptions for chronic illness patients", which requires patients to make more than three medical visits per year and maintain consistent adherence to their prescribed medications. Six medication groups were defined for the analysis: 1) LAMAs only, 2) LABAs only, 3) LAMA+ICS, 4) LABA+ICS, 5) LAMA+LABA, and 6) LAMA+LABA+ICS (Figure 1).

## Outcomes Definition

COPD exacerbation was defined as any admission to the ED or hospitalization due to COPD. Mortality included all causes of death, with additional subgroup analyses conducted for deaths related to stroke or myocardial infarction (MI). Stroke was identified using the codes ICD-9-CM 430–431, 433–435, 436, 362.3; and ICD-10-CM I60-I61, I63-I64, H34.1, G45, while MI was identified using ICD-9-CM 410–412, 429.79; and ICD-10-CM I21-I23, I24.1, I25.2. A reevaluation of the patient's medication regimen was undertaken at the point of outcome assessment, considering the potential for adjustments in medication prescriptions as the trajectory of COPD progressed. Consequently, patients failing to meet the predefined inclusion criteria were excluded from the analysis. This precautionary measure was implemented to mitigate the risk of potential inaccuracies in the outcome results attributable to patients who deviated from the original cohort grouping. As explained earlier, outcomes occurring within a period of less than 60 days were excluded from the analyses.

## Statistical Analysis

The data were analyzed using SPSS statistical software (version 22) (IBM Corp., Armonk, NY, USA). Cox regression models were applied to determine hazard ratios, adjusting for relevant factors and comorbidities. Statistical significance was defined as a two-sided p-value of less than 0.05.

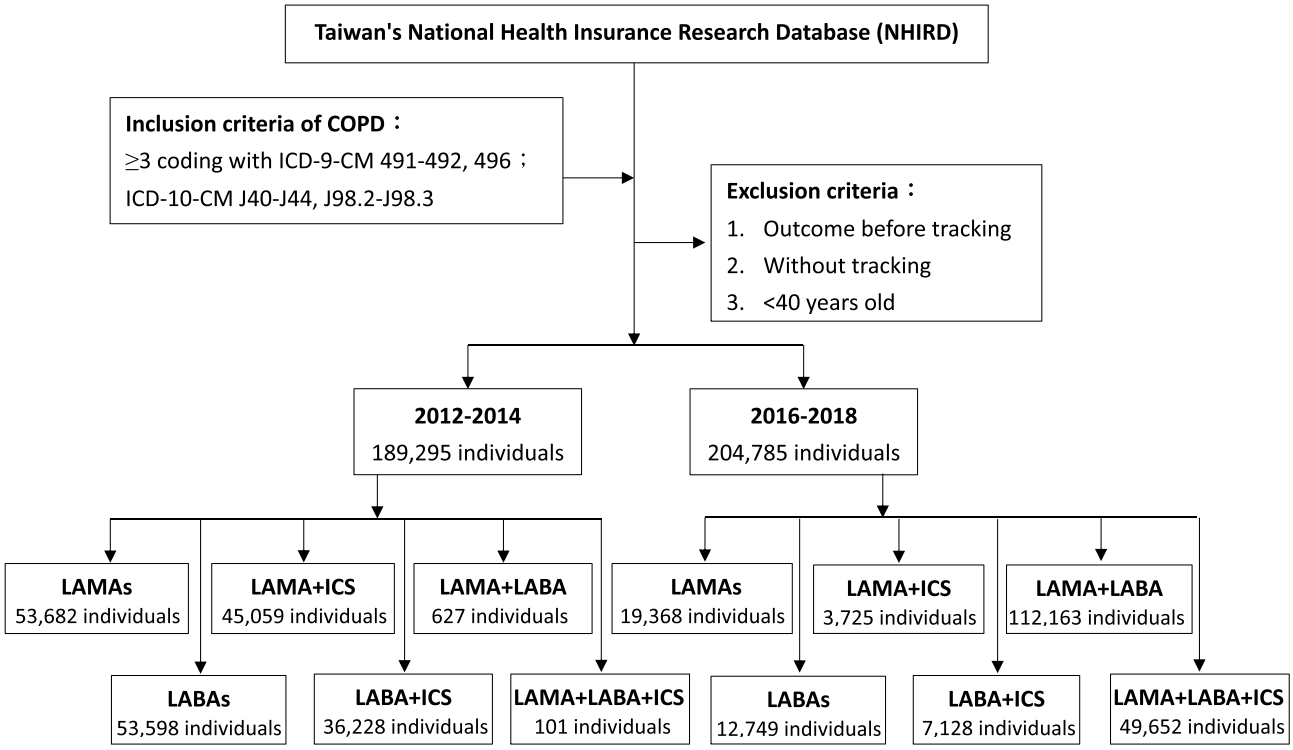


**Figure 1** Flowchart of study cohort selection.


https://doi.org/10.2147/COPD.S511593

## Results

The study design flowchart is depicted in Figure 1. The NHIRD comprises a collective total of 394,080 records spanning the duration between January 1, 2012, to December 31, 2014, as well as January 1, 2016, to December 31, 2018. First, attributable to alterations in medication guidelines, the proportion of COPD patients utilizing singular therapeutic agents or augmenting treatment with additional ICS (LAMA+ICS or LABA+ICS) declined markedly, decreasing from 99.61% during the period spanning 2012–2014 to 20.99% between 2016 and 2018. Conversely, the cohort of patients prescribed dual bronchodilators or triple therapy exhibited a substantial escalation, rising from 0.38% in 2012–2014 to 79.02% in 2016–2018. Furthermore, there was a discernible reduction in the overall utilization of ICS among COPD patients, decreasing from 42.99% to 29.55%, as detailed in Table 1.

Second, upon the adoption of novel treatment guidelines for medication selection among patients with COPD, discernible enhancements were observed across all outcomes, irrespective of the chosen treatment regimen. Notably, individuals receiving treatment with dual bronchodilators and triple therapy exhibited the most substantial improvements in their clinical outcomes. The treatment cohort that exhibited the most pronounced benefit encompassed individuals administered dual bronchodilators, demonstrating noteworthy reductions in ED visits [adjusted hazard ratios (aHR) 0.557, 95% confidence interval (CI) 0.372–0.701, $p < 0.001$], hospitalizations (aHR 0.725, 95% CI 0.562–0.911, $p < 0.001$), all-cause mortality (aHR 0.211, 95% CI 0.137–0.378, $p < 0.001$), MI mortality (aHR 0.226, 95% CI 0.175–0.384, $p < 0.001$), and stroke mortality (aHR 0.203, 95% CI 0.154–0.360, $p < 0.001$).

Furthermore, individuals diagnosed with COPD who were prescribed triple therapy demonstrated notable improvements in various outcomes, including reductions in ED visits (aHR 0.753, 95% CI 0.583–0.920, $p = 0.010$), hospitalizations (aHR 0.610, 95% CI 0.431–0.862, $p < 0.001$), all-cause mortality (aHR 0.375, 95% CI 0.189–0.489, $p < 0.001$), MI mortality (aHR 0.294, 95% CI 0.201–0.408, $p < 0.001$), and stroke mortality (aHR 0.291, 95% CI 0.198–0.372, $p < 0.001$), as depicted in Figure 2 and Table 1.

Third, sustained lower rates of all-cause mortality were noted in patients treated with LABAs compared to those receiving LAMAs, irrespective of revisions in medication guidelines (aHR 0.765, 95% CI 0.689–0.875, $p > 0.001$ in 2012–2014 and aHR 0.674, 95% CI 0.578–0.789, $p < 0.001$ in 2016–2018). Nevertheless, rates of ED visits and hospitalizations did not demonstrate statistically significant differences between these two groups.

Lastly, subsequent to the adoption of new medication guidelines during the period of 2016–2018, patients treated with triple therapy and dual bronchodilators began to exhibit comparatively favorable prognoses. Specifically, the dual bronchodilator group exhibited the most favorable outcomes, particularly in terms of all-cause mortality. Notably, the dual bronchodilator group demonstrated superior outcomes across various parameters, encompassing all-cause mortality (aHR 0.482, 95% CI 0.284–0.592, $p < 0.001$), stroke mortality (aHR 0.448, 95% CI 0.333–0.574, $p < 0.001$), MI mortality (aHR 0.567, 95% CI 0.373–0.734, $p < 0.001$), ED visits (aHR 0.572, 95% CI 0.341–0.782, $p < 0.001$) or hospitalizations (aHR 0.564, 95% CI 0.198–0.372, $p < 0.001$) (Figure 2 and Table 1). Similarly, the triple therapy group exhibited improvements in all-cause mortality (aHR 0.859, 95% CI 0.591–1.083, $p < 0.433$), stroke mortality (aHR 0.765, 95% CI 0.652–0.802, $p < 0.001$), ED visits (aHR 0.873, 95% CI 0.725–0.980, $p = 0.045$), and hospitalizations (aHR 0.592, 95% CI 0.326–0.789, $p < 0.001$).

## Discussion

Our study showed a significant improvement in patient outcomes for those diagnosed with COPD after modifications to medication guidelines. Notably, numerous studies consistently demonstrated that LAMAs are more effective than LABAs in managing and controlling COPD.[1–4] However, contrary to expectations, our findings revealed no statistically significant differences between LAMAs and LABAs in terms of ED visits or hospitalization rates, regardless of the updated guidelines. Interestingly, LABAs were more effective than LAMAs in reducing all-cause mortality (aHR 0.674–0.765).

Furthermore, our findings indicate that as medication guidelines evolve, COPD patients treated with dual bronchodilators experience better outcomes compared to other therapeutic approaches. This observation aligns with most previous studies, which consistently highlight the advantages of dual bronchodilators over single agents[8–13] or the addition of ICS.[9–13] However, according to a systematic review and meta-analysis, dual bronchodilator therapy showed

**Table 1** Comparing Results from 2012–2014 and 2016–2018 Using Cox Regression

| Outcomes | Year | 2012–2014 | | | | | | | 2016–2018 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Groups | n | events | PYs | Rate | aHR | 95% CI | *p* | n | events | PYs | Rate | aHR | 95% CI | *p* |
| All-cause mortality | LAMA | 53,682 | 1592 | 106,141.53 | 1499.88 | *Reference* | | | 19,368 | 315 | 38,582.34 | 816.44 | *Reference* | | |
| | LABA | 53,598 | 1227 | 105,435.98 | 1163.74 | 0.765 | 0.689–0.875 | < 0.001 | 12,749 | 140 | 25,441.49 | 550.28 | 0.674 | 0.578–0.789 | < 0.001 |
| | LAMA + ICS | 45,059 | 1068 | 90,788.18 | 1176.36 | 0.786 | 0.625–0.894 | < 0.001 | 3725 | 71 | 7361.08 | 964.53 | 1.098 | 0.765–1.746 | 0.388 |
| | LABA + ICS | 36,228 | 753 | 73,258.98 | 1027.86 | 0.685 | 0.531–0.786 | < 0.001 | 7128 | 105 | 14,233.39 | 737.70 | 0.904 | 0.569–1.724 | 0.481 |
| | LAMA + LABA + ICS | 101 | 5 | 175.22 | 2853.56 | 1.872 | 0.894–2.188 | 0.286 | 49,652 | 701 | 99,968.47 | 701.22 | 0.859 | 0.591–1.083 | 0.433 |
| | LAMA + LABA | 627 | 31 | 984.07 | 3150.18 | 1.912 | 0.943–2.372 | 0.198 | 112,163 | 568 | 212,830.25 | 266.88 | 0.482 | 0.284–0.592 | < 0.001 |
| Stroke mortality | LAMA | 53,682 | 545 | 108,731.25 | 501.24 | *Reference* | | | 19,368 | 105 | 39,169.62 | 268.06 | *Reference* | | |
| | LABA | 53,598 | 490 | 108,613.42 | 451.14 | 0.891 | 0.792–0.978 | 0.037 | 12,749 | 34 | 25,749.36 | 132.04 | 0.593 | 0.304–0.786 | < 0.001 |
| | LAMA + ICS | 45,059 | 336 | 91,345.87 | 367.83 | 0.735 | 0.622–0.826 | < 0.001 | 3725 | 22 | 7,201.30 | 305.50 | 1.086 | 0.586–1.376 | 0.489 |
| | LABA + ICS | 36,228 | 247 | 73,452.29 | 336.27 | 0.672 | 0.533–0.733 | < 0.001 | 7128 | 34 | 14,368.31 | 236.63 | 0.812 | 0.627–0.960 | 0.035 |
| | LAMA + LABA + ICS | 101 | 2 | 183.31 | 1091.05 | 1.973 | 0.531–2.782 | 0.498 | 49,652 | 210 | 100,289.22 | 209.39 | 0.765 | 0.625–0.802 | < 0.001 |
| | LAMA + LABA | 627 | 10 | 997.85 | 1002.15 | 1.820 | 0.452–2.601 | 0.535 | 112,163 | 229 | 227,257.93 | 100.77 | 0.448 | 0.333–0.571 | < 0.001 |
| MI mortality | LAMA | 53,682 | 158 | 108,953.25 | 145.02 | *Reference* | | | 19,368 | 53 | 39,255.56 | 135.01 | *Reference* | | |
| | LABA | 53,598 | 160 | 108,731.84 | 147.15 | 1.015 | 0.724–1.302 | 0.235 | 12,749 | 36 | 25,860.29 | 139.21 | 1.031 | 0.561–1.682 | 0.448 |
| | LAMA + ICS | 45,059 | 211 | 91,404.92 | 230.84 | 1.592 | 1.028–1.943 | 0.036 | 3725 | 17 | 7551.94 | 225.11 | 1.665 | 0.802–1.805 | 0.245 |
| | LABA + ICS | 36,228 | 157 | 73,483.06 | 213.65 | 1.473 | 0.892–1.862 | 0.171 | 7128 | 30 | 14,449.23 | 207.62 | 1.428 | 0.903–1.734 | 0.096 |
| | LAMA + LABA + ICS | 101 | 1 | 189.26 | 528.37 | 1.986 | 0.975–2.817 | 0.092 | 49,652 | 149 | 100,539.65 | 148.20 | 1.091 | 0.825–1.271 | 0.138 |
| | LAMA + LABA | 627 | 6 | 1013.08 | 592.25 | 2.065 | 1.003–2.986 | 0.048 | 112,163 | 161 | 227,556.81 | 70.75 | 0.567 | 0.373–0.734 | < 0.001 |
| ED visits | LAMA | 53,682 | 52,045 | 108,903.74 | 47,789.91 | *Reference* | | | 19,368 | 17,804 | 39,181.62 | 45,439.67 | *Reference* | | |
| | LABA | 53,598 | 51,389 | 107,629.36 | 47,746.27 | 0.998 | 0.672–1.447 | 0.435 | 12,749 | 11,053 | 25,782.02 | 42,870.96 | 0.943 | 0.881–1.073 | 0.109 |
| | LAMA + ICS | 45,059 | 43,803 | 91,319.78 | 47,966.61 | 1.005 | 0.735–1.593 | 0.384 | 3725 | 3425 | 7539.97 | 45,424.58 | 0.998 | 0.840–1.184 | 0.182 |
| | LABA + ICS | 36,228 | 35,732 | 73,242.25 | 48,786.05 | 1.023 | 0.741–1.606 | 0.372 | 7128 | 6481 | 14,474.86 | 44,774.18 | 0.982 | 0.845–1.099 | 0.155 |
| | LAMA + LABA + ICS | 101 | 59 | 126.45 | 46,658.76 | 0.976 | 0.606–1.392 | 0.498 | 49,652 | 40,297 | 100,261.83 | 40,191.77 | 0.873 | 0.725–0.980 | 0.045 |
| | LAMA + LABA | 627 | 473 | 1009.24 | 46,866.95 | 0.981 | 0.635–1.425 | 0.411 | 112,163 | 99,786 | 392,570.42 | 25,418.62 | 0.572 | 0.314–0.782 | < 0.001 |
| Hospitalization | LAMA | 53,682 | 43,785 | 108,315.73 | 40,423.49 | *Reference* | | | 19,368 | 15,642 | 39,206.13 | 39,896.82 | *Reference* | | |
| | LABA | 53,598 | 43,558 | 107,751.24 | 40,424.59 | 0.996 | 0.842–1.101 | 0.268 | 12,749 | 10,019 | 25,775.68 | 38,869.97 | 0.974 | 0.825–1.098 | 0.176 |
| | LAMA + ICS | 45,059 | 34,755 | 91,330.58 | 38,054.07 | 0.941 | 0.765–1.052 | 0.355 | 3725 | 2730 | 7562.53 | 36,099.03 | 0.906 | 0.783–1.243 | 0.267 |
| | LABA + ICS | 36,228 | 30,170 | 73,261.52 | 41,181.24 | 1.019 | 0.903–1.276 | 0.097 | 7128 | 5398 | 14,379.25 | 37,540.21 | 0.948 | 0.801–1.082 | 0.201 |
| | LAMA + LABA + ICS | 101 | 42 | 108.26 | 38,795.49 | 0.958 | 0.827–1.035 | 0.273 | 49,652 | 23,710 | 100,276.31 | 23,644.67 | 0.592 | 0.326–0.789 | < 0.001 |
| | LAMA + LABA | 627 | 315 | 1,010.11 | 31,184.72 | 0.894 | 0.765–0.980 | 0.040 | 112,163 | 51,246 | 225,701.42 | 22,705.22 | 0.564 | 0.311–0.748 | < 0.001 |

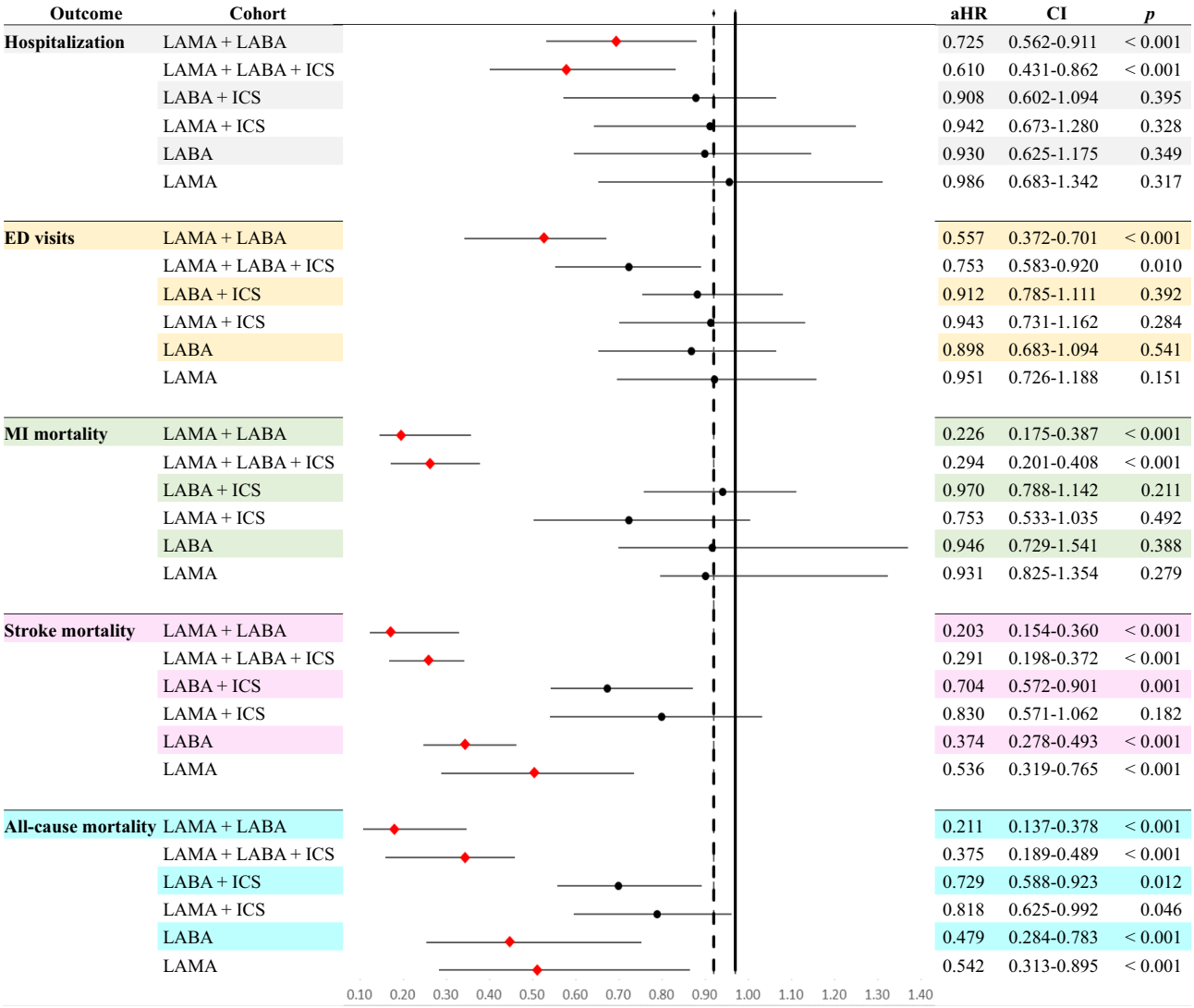


**Figure 2** Forest plot of 2016–2018 versus 2012–2014 (Reference).
**Notes**: ◆ and boldface of the word mean statistically significant ($p$ values < 0.05); ● means not statistically significant.
**Abbreviations**: ED visits, emergency department visits; aHR, adjusted hazard ratio; CI, confidence interval.

similar exacerbation rates and serious adverse events compared to LABA+ICS, though it was associated with a slight increase in all-cause mortality from 1% to 1.4%.[13]

Our data analysis indicates that before the paradigm shift, combining a single agent with ICS therapy was more effective than dual bronchodilator treatment. However, following the paradigm shift, this trend reversed, with the dual bronchodilator group showing better outcomes, regardless of ED visits, hospitalizations, or mortality rates. This improvement may be linked to clearer medication guidelines and more defined use of ICS. These findings further support the validity and accuracy of the current COPD treatment guideline.

In the early stages, medication guidelines seemed to take a cautious approach to incorporating ICS use, likely due to conflicting study results and concerns about its link to increased pneumonia risk.[21,22] The use of single-agent therapy combined with ICS in COPD has significantly decreased, as evidence shows a loss of therapeutic benefit with this regimen findings consistent with our research.[23,24] Moreover, an increasing number of studies confirm that ICS offers the greatest benefit for individuals with elevated eosinophil levels, reinforcing its role as the standard for ICS use. Additionally, dual bronchodilator therapy has consistently shown superior efficacy compared to single-agent treatments.

The strength of our study lies in leveraging health insurance databases, which offer real-world data that accurately reflect clinical practices. Furthermore, using existing health insurance data presents a cost-effective alternative to large-scale prospective studies, saving both time and resources. By analyzing the entire database rather than a sampling database, we eliminate concerns about selection bias or sample representativeness, ensuring the validity and reliability of our results.

To accurately identify COPD patients, we validated the diagnosis using three or more medical codes for COPD in the Taiwan NHIRD, excluding any patients diagnosed before the index date.[25] Outcomes occurring within 60 days were excluded, and we carefully reviewed each patient's medication status for every reported outcome to ensure its relevance to the group. This approach helped minimize the risk of immortal time bias. These rigorous criteria were implemented to increase the reliability and validity of our results, making the study more dependable.

This study also has certain limitations that should be taken into consideration. First, the omission of key clinical characteristics and their correlations with laboratory data, including inflammatory markers or pulmonary function test results, is a notable constraint. This gap limited our ability to establish causal relationships and provide detailed explanations for both the direct and indirect outcomes observed. Nonetheless, the database used for this study is a comprehensive national health insurance repository, containing the complete medical records of more than 23 million residents. These records reflect real-world clinical outcomes across a broad range of disease-related issues. While a definitive causal link remains unclear, the findings nonetheless reveal an undeniable truth.

Second, we did not conduct a detailed analysis of the specific effects of individual medications, pharmaceutical manufacturers, dosages, or various drug combinations. However, our sensitivity analysis highlighted the robustness of our findings, supporting the validity of our conclusions. Finally, while our study did not allow for a precise assessment of patient adherence rates to medications, our insurance policy criteria required individuals to visit medical institutions more than three times per year for inclusion. In addition, the progressive nature of COPD generally promotes consistent medication adherence, as patients seek to manage distressing symptoms effectively.

This study confirmed substantial improvements in ED visits, hospitalizations, and mortality outcomes among COPD patients as medication guidelines were updated. These findings mark significant progress toward achieving greater efficacy and precision in COPD management. Future research should prioritize subgroup analyses to further refine treatment strategies.

## Conclusion

The widespread adoption of dual bronchodilators and clear guidelines for ICS use have led to significant improvements in ED visits, hospitalizations, and mortality outcomes among COPD patients. Additionally, while no significant differences were observed in ED visits and hospitalizations between LAMAs and LABAs, LABAs significantly reduced all-cause mortality.

## Acknowledgments

We appreciate the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW), Taiwan, for providing the National Health Insurance Research Database (NHIRD) and supported in part by the Tri-Service General Hospital (TSGHIRB No.: E202316040).

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011;364(12):1093–1103. PMID: 21428765. doi:10.1056/NEJMoa1008378
2. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;2012(9):CD009157. PMID: 22972134; PMCID: PMC8935978. doi:10.1002/14651858.CD009157.pub2
3. Decramer ML, Chapman KR, Dahl R, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. *Lancet Respir Med*. 2013;1(7):524–533. PMID: 24461613. doi:10.1016/S2213-2600(13)70158-9

4. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. *Cochrane Database Syst Rev*. 2018;12(12):CD012620. PMID: 30521694; PMCID: PMC6517098. doi:10.1002/14651858.CD012620.pub2
5. van Noord JA, Aumann JL, Janssens E, et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur Respir J*. 2005;26(2):214–222. PMID: 16055868. doi:10.1183/09031936.05.00140404
6. Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J*. 2015;45(4):969–979. Erratum in: Eur Respir J. 2015;45(6):1763. DOI: 10.1183/09031936.50136014. PMID: 25573406; PMCID: PMC4391658. doi:10.1183/09031936.00136014
7. Rodrigo GJ, Plaza V. Efficacy and safety of a fixed-dose combination of indacaterol and Glycopyrronium for the treatment of COPD: a systematic review. *Chest*. 2014;146(2):309–317. PMID: 24556877. doi:10.1378/chest.13-2807
8. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res*. 2015;16(1):92. PMID: 26233481; PMCID: PMC4531806. doi:10.1186/s12931-015-0250-2
9. Rodrigo GJ, Neffen H. A systematic review of the efficacy and safety of a fixed-dose combination of umeclidinium and vilanterol for the treatment of COPD. *Chest*. 2015;148(2):397–407. PMID: 25798635. doi:10.1378/chest.15-0084
10. Horita N, Nagashima A, Kaneko T. Long-acting β-agonists (LABA) combined with long-acting muscarinic antagonists or LABA combined with inhaled corticosteroids for patients with stable COPD. *JAMA*. 2017;318(13):1274–1275. PMID: 28973232. doi:10.1001/jama.2017.11903
11. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med*. 2016;374 (23):2222–2234. PMID: 27181606. doi:10.1056/NEJMoa1516385
12. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest*. 2008;134(2):255. doi:10.1378/chest.07-2138
13. Fukuda N, Horita N, Kaneko A, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2023;6(6). doi:10.1002/14651858.CD012066.pub3
14. Pascoe S, Locantore N, Dransfield MT, et al. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med*. 2015;3(6):435–442. Epub 2015 Apr 12. Erratum in: Lancet Respir Med. 2015 Jun;3(6):e19. PMID: 25878028. doi:10.1016/S2213-2600(15)00106-X
15. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med*. 2016;4(9):731–741. PMID: 27460163. doi:10.1016/S2213-2600(16)30148-5
16. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2015;192(4):523–525. PMID: 26051430; PMCID: PMC4595668. doi:10.1164/rccm.201502-0235LE
17. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med*. 2018;6(2):117. doi:10.1016/S2213-2600(18)30006-7
18. Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85–91. PMID: 28610675. doi:10.1016/j.rmed.2017.04.013
19. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. *Ann Am Thorac Soc*. 2013;10(2):81–89. PMID: 23607835. doi:10.1513/AnnalsATS.201208-043OC
20. Hsieh CY, Su CC, Shao SC, et al. Taiwan's national health insurance research database: past and future. *Clin Epidemiol*. 2019;11:349–358. PMID: 31118821; PMCID: PMC6509937. doi:10.2147/CLEP.S196293
21. Festic E, Bansal V, Gupta E, Scanlon PD. Association of inhaled corticosteroids with incident pneumonia and mortality in COPD patients; systematic review and meta-analysis. *COPD*. 2016;13(3):312–326. PMID: 26645797; PMCID: PMC4951104. doi:10.3109/15412555.2015.1081162
22. Aggarwal B, Jones P, Casas A, et al. Association between increased risk of pneumonia with ICS in COPD: a continuous variable analysis of patient factors from the IMPACT study. *Pulm Ther*. 2024;10(2):183–192. PMID: 38446336; PMCID: PMC11282004. doi:10.1007/s41030-024-00255-1
23. Matera MG, Calzetta L, Puxeddu E, Rogliani P, Cazzola M. A safety comparison of LABA+LAMA vs LABA+ICS combination therapy for COPD. *Expert Opin Drug Saf*. 2018;17(5):509–517. PMID: 29505318. doi:10.1080/14740338.2018.1448786
24. Tariq SM, Thomas EC. Maintenance therapy in COPD: time to phase out ICS and switch to the new LAMA/LABA inhalers? *Int J Chron Obstruct Pulmon Dis*. 2017;12:1877–1882. PMID: 28694698; PMCID: PMC5491575. doi:10.2147/COPD.S138006
25. Ho TW, Ruan SY, Huang CT, Tsai YJ, Lai F, Yu CJ. Validity of ICD9-CM codes to diagnose chronic obstructive pulmonary disease from National Health Insurance claim data in Taiwan. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3055–3063. PMID: 30323577; PMCID: PMC6174682. doi:10.2147/COPD.S174265