Chintal H. Shah

chintalhshah@gmail.com | chintalshah@umaryland.edu

www.linkedin.com/in/chintalshah | Google scholar

EDUCATION

University of Maryland, Baltimore, USA
PhD in Pharmaceutical Health Services Research 2018-2023
Dissertation: The Economic Burden of Chronic Obstructive Pulmonary Disease and Comparative Effectiveness of Maintenance Inhaler Medications in the United States

University of Florida, Gainesville, Florida, USA
MS in Pharmaceutical Outcomes and Policy 2016-2018
Thesis: Factors Affecting Adherence to Hormonal Therapy in Breast Cancer Patients

Prin. K. M. Kundnani College of Pharmacy, University of Mumbai, India
Bachelor of Pharmacy 2012-2016

EXPERIENCE

Graduate Research Assistant
University of Maryland, Baltimore 2019-2023
Led several projects focused on the delivery of patient care in the US Healthcare system. Tasks included, but were not limited to: Idea development, study conceptualization, design and direction of experiments, study execution and data analysis, administrative tasks (Institutional Review Board compliance, Data Use Agreements, etc.), manuscript writing and submission, problem solving, mentoring rotation students, poster presentations, and grant writing. *Mentor: Dr. Zafari.*

Value and evidence generation predoctoral fellow- Rare disease
Takeda Pharmaceuticals 2022-2023
Worked on projects in the HAE, hematology, and rare disease space. Tasks included, but were not limited to: Developing Requests For Proposals for distribution and reviewing submitted vendor proposals, working with and managing multiple projects with various vendors (10+), providing scientific leadership and strategy inputs, conceptualizing and executing studies to support product development and life cycle management, identifying projects that align with strategic imperatives and marquee programs, data interpretation, and disseminating findings through internal presentations as well as conference abstracts, posters and manuscripts. *Mentor: Dr. Schultz.*

Health Economic and Outcomes Research (HEOR) Intern
Takeda Pharmaceuticals 2021
Worked on projects in the rare disease space. Tasks included, but not limited to: Developing a feasible research question, analyzing, and interpreting results from internal databases, and presentation of findings to larger internal HEOR group. *Mentor: Dr. Schultz.*

Graduate Teaching Assistant
University of Maryland, Baltimore 2018-2019
In this role my tasks were: coordinating classes, developing assignments and exam questions, uploading lectures, leading discussions, holding office hours, grading assignments and exams, and proctoring exams.
Courses:
Pharamcoeconomics and pharmacoepidemiology course (Fall 2018), level: PharmD, Instructors: Dr. Mullins & Dr. Zafari
Medical evidence course (spring 2019), level: PharmD, Instructors: Dr. Cooke & Dr. Doshi

Quality control Intern
Raptakos Brett and Co. 2015
In this role, I helped test and document the quality of the pharmaceutical products produced on site.

INTERESTS

Health economics, Outcomes research, Pharmacoepidemiology, COPD, Hematology, Rare diseases, Neurological disorders, Endocrine disorders, Psychiatric disorders, Oncology, Real-world data analysis, Economic modelling, Big data, Machine learning, Quality of Life research, Cost-effectiveness research, Burden of Illness research

ANALYSIS SKILLS

Programming

- SAS, R, Stata

Datasets analyzed

- Medicare Fee-for service data (Chronic conditions warehouse), Medical expenditure panel survey (MEPS), IQVIA Pharmetrics plus commercial claims dataset, TrinetX dataset, National Ambulatory Medical Care Survey (NAMCS), Medicare and Medicaid spending dashboard, National Health and Nutrition Examination Survey (NHANES), Census Bureau's American Community Survey, Health and Retirement Survey, Korea Health Panel Study Database, Truven MarketScan claims data

PUBLICATIONS

Peer-reviewed research articles

- Zafari Z, Park JE, **Shah CH**, DosReis S, Gorman EF, Hua W, Ma Y, Tian F. The state of use and utility of negative controls in pharmacoepidemiologic studies (in press, American Journal of Epidemiology)
- **Shah CH**, Princic N, Evans KA, Schultz BG. Real-world changes in costs over time among patients in the United States with hereditary angioedema on long-term prophylaxis with lanadelumab. *J Med Econ*. 2023;26(1):871-877. doi:10.1080/13696998.2023.2232260
- **Shah CH**, Reed RM, Wastila L, Onukwugha E, Gopalakrishnan M, Zafari Z. Direct Medical Costs of COPD in the USA: An Analysis of the Medical Expenditure Panel Survey 2017–2018. *Appl Health Econ Health Policy*. Published online June 3, 2023. doi:10.1007/s40258-023-00814-8
- **Shah CH**, Dave CV. Healthcare costs associated with comorbid cardiovascular and renal conditions among persons with diabetes, 2008–2019. *Diabetol Metab Syndr*. 2022;14(1):179. doi:10.1186/s13098-022-00957-z
- **Shah CH**, Onukwugha E. Direct medical and indirect absenteeism costs among working adult ADHD patients in the United States. *Expert Rev Pharmacoecon Outcomes Res*. Published online May 11, 2022:1-8. doi:10.1080/14737167.2022.2073223
- Sistani F, Reed RM, **Shah CH**, Zafari Z. Trends in Medicaid spending on inhalers in the United States, 2012-2018. *JMCP*. 2021;27(12):1744-1749. doi:10.18553/jmcp.2021.27.12.1744
- **Shah CH**, Onukwugha E, Zafari Z, Villalonga-Olives E, Park JE, Slejko JF. Economic burden of comorbidities among COPD Patients hospitalized for acute exacerbations: an analysis of a commercially insured population. *Expert Rev Pharmacoecon Outcomes Res*. 2022;22(4):683-690. doi:10.1080/14737167.2021.1981291

- **Shah CH**, Reed RM, Liang Y, Zafari Z. Association between lung function and future risks of diabetes, asthma, myocardial infarction, hypertension and all-cause mortality. *ERJ Open Res*. 2021;7(3):00178-02021. doi:10.1183/23120541.00178-2021
- **Shah CH**, Reed RM, Villalonga-Olives E, et al. Quantifying heterogeneity of physical and mental health-related quality of life in chronic obstructive pulmonary disease patients in the United States. *Expert Review of Respiratory Medicine*. 2020;14(9):937-947. doi:10.1080/17476348.2020.1776612
- **Shah CH**, Brown JD. Reliability and Validity of the Short-Form 12 Item Version 2 (SF−12v2) Health-Related Quality of Life Survey and Disutilities Associated with Relevant Conditions in the U.S. Older Adult Population. *Journal of Clinical Medicine*. 2020;9(3):661. doi:10.3390/jcm9030661
- **Shah CH**, Balkrishnan R, Diaby V, Xiao H. Examining factors associated with adherence to hormonal therapy in breast cancer patients. *Research in Social and Administrative Pharmacy*. 2020;16(4):574-582. doi:10.1016/j.sapharm.2019.08.005
- **Shah CH**, Xiao H. Disparities in prescription of opioids among prostate cancer patients of various racial groups. *Pain Management*. 2019;9(3):273-281. doi:10.2217/pmt-2018-0076

Other publications

- Cox IA, Pontinha VM, Wagner T, **Shah CH**, Vu M, Tran J, Dulie J, Kom T. By the Numbers: Aging as a Contributor to Healthcare Costs. ISPOR Value and Outcomes Spotlight. July/August 2021, Vol 7, No. 4, Page 21 (All authors had equal contribution)
- Gandhi AB, **Shah CH**, Shaikh N, Nili M, Williams K, Pontinha V. By the Numbers: Behavioral Economics. ISPOR Value and Outcomes Spotlight. July/August 2020, Vol 6, No. 4, Page 24 (All authors had equal contribution)
- Gandhi AB, **Shah CH**, Shaikh N, Nili M, Williams K, Pontinha V. By the Numbers: Innovative Pricing Models. ISPOR Value and Outcomes Spotlight. May/June 2020, Vol 6, No. 3, Page 18 (All authors had equal contribution)
- Gandhi AB, **Shah CH**, Shaikh N, Nili M, Williams K. By the Numbers: The State of Health Technology Assessment (HTA). ISPOR Value and Outcomes Spotlight. March/April 2020, Vol 6, No. 2, Page 25 (All authors had equal contribution)
- Nili M, **Shah CH**, Williams K, Gandhi AB. By the Numbers: The New Digital Healthcare Ecosystem. ISPOR Value and Outcomes Spotlight. March/April 2020, Vol 6, No. 1, Page 20 (All authors had equal contribution)

CONFERENCE ABSTRACTS

AMCP Nexus 2023 conference

- Zhang K, **Shah CH**, Graham CN, McBayne T, Schultz RG. A Cost Model Comparing Long-term Prophylaxis Options for Hereditary Angioedema: Lanadelumab and Berotralstat
- Princic N, Evans KA, **Shah CH**, Sing K, Juethner S, Schultz RG. Characteristics of patients with hereditary angioedema on long-term prophylaxis with lanadelumab who did and did not down-titrate lanadelumab during 18 months of treatment persistence

AMCP 2023 Annual conference

- **Shah CH**, Princic N, Evans KA, Schultz RG. Changes in costs over time in patients with hereditary angioedema on long-term prophylaxis with lanadelumab

APHA 2022 Annual conference

- **Shah CH**, Qato D, Saini J, Zafari Z. Trends in Medicaid spending on buprenorphine for treatment of opioid use disorder in Maryland, 2002-2020

ISPOR 2022 Europe Conference

- Agh T, Hiligsmann M, Jakab I, Beaudart C, Manias E, Borah B, Pednekar P, Zeber J, Turcu-Stiolica A, Daly C, **Shah C**, Atal S, Sharma M, Zhao Y, Dimitrova M, Kamat S, Milky G, Hutchinson D, Gangan N, Unni E, Brzozowska M, Hajimiri SH, Janodia M, Peterson A. Criteria for Value Assessment of Medication Adherence-Enhancing Interventions: Preliminary Results of a Systematic Review

ICPE 2022 Annual International Conference

- Park JE, Zafari Z, **Shah CH**, DosReis S, Gorman EF, Hua W, Ma Y, Tian F. The state of use and utility of negative controls in Pharmacoepidemiologic studies

ISPOR 2022 Annual International Conference

- **Shah C**, Onukwugha E. Direct Medical and Indirect Absenteeism Costs among Working Adult ADHD Patients in the United States

ISPOR 2021 Annual International Conference

- **Shah C**, Onukwugha E, Zafari Z, Olives EV, Park JE, Slejko JF- Economic Burden of Comorbidities Among COPD Patients Experiencing Acute Exacerbations: an Analysis of a Commercially Insured Population
- **Shah C**, Zafari Z. Direct Medical and Mortality Related Costs Among COPD Patients in the United States, 2017-2018

ASHP Midyear 2020 Virtual Conference

- Sistani F, **Shah C**, Reed R, Zafari Z. Medicare part D expenditures on asthma and COPD inhalers

ISPOR 2020 Asia-Pacific Conference

- **Shah C**, Liang Y, Zafari Z. Prospective Association between Lung Function and the Incidence of Diabetes, Asthma, Myocardial Infarction, Hypertension and All-Cause Mortality: Competing Risks Model
- Hong K, Park JE, **Shah C**. Health Service Utilization of Adults with Supplemental Private Health Insurance in South Korea: 2014-2016
- **Shah C**, Brown JD. Reliability and Validity of the SF-12V2 Health-Related Quality of Life Survey and Disutilities Associated with Relevant Conditions in the U.S. Older Adult Population

ISPOR 2020 Annual International Conference

- Park JE, **Shah CH**. Direct Medical Costs of Chronic Obstructive Pulmonary Disease in the United States, 2011-2015

American Thoracic Society 2020 International Conference

- Zafari Z, **Shah C**, Reed RM, Eakin M. Predicting Physical and Mental Health-Related Quality of Life in Patients with Chronic Obstructive Pulmonary Disease in the United States

ISPOR 2019 Annual International Conference

- **Shah C**, Balkrishnan R, Diaby V, Xiao H. Examining Factors Affecting Adherence to Hormonal Therapy in Breast Cancer Patients, Using Data from the Medical Expenditure Panel Survey (2011-2015)
- **Shah C**, Desai R, Park J. Trends in The Burden Of Out Of Pocket Payments In Diabetes Care: An Analysis Of The Medical Expenditure Panel Survey

ISPOR 2018 Asia-Pacific Conference

- Huo J, Xiao H, Garg M, **Shah C**, Wilkie DJ, Mainous AG. The Economic Burden of Sickle Cell Disease in the United States

ISPOR 2018 Annual International Conference

- **Shah C**, Xiao H. Prescription Pattern of Opioids Among Prostate Cancer Patients of Various Racial Groups
- Desai R, **Shah C**. Cost Effectiveness and Budget Impact of Introducing Long-Acting Atypical Antipsychotics in the United States Healthcare System

CURRENT PROJECTS

Trends in Medicaid spending on buprenorphine for treatment of opioid use disorder in Maryland

TEACHING

Guest lecturer in the Comparative Effectiveness Research & Pharmacoeconomics I course 2023
Topic: Quality Adjusted Life Years (QALY): An overview of the history and practical consideration in the use of Health-related Quality-of-Life metrics, level: PhD, PharmD & MS, Instructor: Dr. Zafari

Guest lecturer in the Research Methods 2 course 2022
Topic: Introduction to Machine learning: An overview, level: PhD, Instructors: Dr. Onukwugha & Dr. Slejko

Guest lecturer in the Comparative Effectiveness Research & Pharmacoeconomics I course 2022
Topic: Quality Adjusted Life Years (QALY): An overview of the history and practical consideration in the use of Health-related Quality-of-Life metrics, level: PhD, PharmD & MS, Instructor: Dr. Zafari

Presenter and moderator at the ISMPP Annual Meeting Checklist Roundtable 2022
Topic: CHEERS checklist, level: medical publications professionals, References: Dr. Husereau & Dr. Mullins

Guest lecturer in the Comparative Effectiveness Research & Pharmacoeconomics I course 2021
Topic: Practical Considerations in the Application of Patient Reported Outcomes: An overview using the example of Health-related Quality-of-Life metrics, level: PhD, PharmD & MS, Instructor: Dr. Zafari

HONORS AND AWARDS

PHSR Department Travel scholarship 2023

ICPE 2022 Conference scholarship 2022

ISPOR Student Leader Distinguished Service award 2022

The Donald O. Fedder Memorial Fellowship 2022

UMB Graduate Student Association Travel award 2022

ISPOR Student Leader Distinguished Service award 2021

UMB Graduate Student Association Professional Development award 2021

UMB Graduate Student Association COVID-19 WFH support award 2020

Rho Chi Honor Society 2020

Dean’s list 2019

Nominated to Golden Key International Honor Society 2016, 2017

JRD Tata scholarship for pharmacy 2015, 2016

3rd place for poster on 'Industrial and community pharmacy' at INFRA 2014

CERTIFICATIONS

Duke University- Introduction to Machine Learning (Coursera)

Learn Python - Full course for Beginners By Mike Dane (freeCodeCamp.org)

Learn R Course (Codecademy)

Introduction to Budget Impact Analysis (ISPOR Distance learning program)

Calibration and Validation of dissolution testers (Electrolab India Pvt. Ltd.)

PROFESSIONAL MEMBERSHIPS & VOLUNTEER WORK

Graduate student representative for the Department of Pharmaceutical Health Services Research Department to the Graduate Student Association 2020-2023

Graduate student representative for the Department of Pharmaceutical Health Services Research Department Admission's Committee 2021-2022

The Professional Society for Health Economics and Outcomes Research (ISPOR)
- Student member 2015-2023
- Chair of the education committee of the ISPOR student network 2021-2022
- Co-chair of the meeting planning committee of the ISPOR student network 2019-2021
- Chapter President for University of Maryland, Baltimore chapter 2019-2020
- Secretary for the University of Florida chapter 2017-2018

International Society for Pharmacoepidemiology (ISPE)
- Student member 2016-2023
- Treasurer for the University of Florida chapter 2017-2018

Rotaract Club of Prin. K.M. Kundnani College of Pharmacy (University of Mumbai)
- Student member 2012-2016
- Finance Director (Board of Directors) 2015-2016
- Web communications director (Board of Directors) 2013-2015

Student Council at Prin. K.M. Kundnani College of Pharmacy (University of Mumbai)
- Alumni in Charge 2015-2016

Clinical and Community Pharmacy Club at Prin. K.M. Kundnani College of Pharmacy (University of Mumbai)
- Student member 2012-2016

PEER-REVIEW ACTIVITY

Journals/Conferences peer-reviewed for:

- BMC Public Health
- CHEST
- JMIR Public Health and Surveillance
- BMC Health Services Research
- International Journal of Chronic Obstructive Pulmonary Disease
- Scientific Reports
- Journal of General Internal Medicine
- JMIR Biomedical Engineering
- JMIR Research Protocols
- Exploratory Research in Clinical and Social Pharmacy
- Medicine
- Open Journal of Obstetrics and Gynecology
- Breast Cancer Research and Treatment
- JMIR Cancer
- JMIRx | Med
- Advances in Breast Cancer Research
- Global Research in Gynecology and Obstetrics
- Journal of Biomedical Research & Environmental Sciences
- Journal of women's Health and Gynecology (jwhg)
- JMIR Perioperative Medicine
- JMIR Dermatology
- JMIR Formative Research
- Interactive Journal of Medical Research
- ISPOR (Conference)
- ICPE (Conference)

ABSTRACT

Title of dissertation: The Economic Burden of Chronic Obstructive Pulmonary Disease and Comparative Effectiveness of Maintenance Inhaler Medications in the United States

Chintal H. Shah, Doctor of Philosophy, 2023

Dissertation directed by: Zafar Zafari, MSc, PhD, Assistant Professor, Department of Practice, Sciences, and Health Outcomes Research

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent condition in the United States (US). Among individuals with moderate to very severe COPD, inhalation therapy is the mainstay of disease management, with the goal to reduce COPD exacerbations. Maintenance medications, especially combinations of long-acting $beta_2$ agonist (LABA)/long-acting muscarinic antagonist (LAMA) or LABA/inhaled corticosteroids (ICS), are commonly used. This dissertation aimed to examine the (i) economic burden of COPD, (ii) comparative effectiveness of LABA/LAMA and LABA/ICS fixed dose combination (FDC) single inhaler therapy across various subgroups, and (iii) comparative effectiveness of LABA/LAMA combinations with different ingredients and inhaler types, vilanterol/umeclidinium (VI/UMEC) and olodaterol/tiotropium (OLO/TIO).

Methods

Medical Expenditure Panel Survey data was used to estimate the economic burden of COPD (Aim 1). COPD-specific (adjusted) costs were determined for various service categories using a regression-based weighted two-part model among patients aged 45 years and older. Medicare Chronic Conditions Warehouse data was used for the comparative effectiveness studies (Aim 2, Aim 3). A new user active comparator retrospective cohort study design was utilized, and the outcome of interest was time to first COPD exacerbation. To ensure comparability between groups, they were matched based on their high-dimensional propensity scores.

Results

The total COPD-specific direct medical cost was 2018 US $4,322 (Standard Error (SE): US $577) per patient per year with prescription drugs contributing US $1,887 (SE: US $216). The resultant overall annual total COPD-specific cost was US $24.0 billion, with prescription drugs contributing US $10.5 billion. For the interclass comparative effectiveness analysis, the hazard ratio (HR) of time to COPD exacerbation was 0.846 (95% Confidence interval (CI): 0.776-0.923) for LABA/ICS compared to LABA/LAMA initiators. Among LABA/LAMA FDCs, the HR of time to first COPD exacerbation was 0.948 (95% CI: 0.813-1.105) for individuals initiating OLO/TIO versus VI/UMEC.

Conclusion

This dissertation found that COPD poses a significant economic burden on the US healthcare system, with prescription drugs being a major contributor. Optimizing therapy can help reduce this burden. While a statistically significant interclass difference was

observed between LABA/LAMA and LABA/ICS initiators, no statistically significant intraclass difference was observed between initiators of LABA/LAMA FDCs: VI/UMEC and OLO/TIO.

The Economic Burden of Chronic Obstructive Pulmonary Disease and Comparative Effectiveness of Maintenance Inhaler Medications in the United States

by

Chintal H. Shah

Dissertation submitted to the Faculty of the Graduate School of the

University of Maryland, Baltimore in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

2023

To my family

ACKNOWLEDGEMENTS

Thank you to my advisor, Dr. Zafar Zafari, for your guidance, training, and continued support. Also, thank you for giving me the opportunity to work on very interesting projects, and learn from you and the teams.

Thank you Dr. Eberechukwu Onukwugha, Dr. Linda Wastila, Dr. Robert Reed, and Dr. Mathangi Gopalakrishnan for all your feedback and help with the dissertation.

Thank you, Bob Schultz, for your guidance over the duration of the internship and fellowship with Takeda. I learnt a lot from you, professionally and personally.

Dr. C. Daniel Mullins and Dr. Danya Qato were mentors throughout the PhD, and I thank you for your constant guidance and support.

The PhD journey requires complete dedication over an extended period of time, and I thank my family for their love, patience, support and understanding. I am especially grateful for the support of my parents, siblings, and grandparents.

I would like to thank my friends, cohort, and classmates for all your support and love. I learnt a lot from you all. In particular, I would like to thank Jeong-eun, Piran, Sachet, Chintan, Kayleigh, Haeyoung, Tsung-Ying, Jannat, Kareshma, Uzma, Aakash, Savyasachi, Colleen, Jeremy, Raj, Katiyar, Sarthak, and Bharadwaj. They are my family away from home.

I thank the PHSR faculty, staff, and students for their support and encouragement during my graduate training.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACh	Acetylcholine (ACh)
AHRQ	Agency for Healthcare Research and Quality
BETOS	Berenson-Eggers Type of Service
cAMP	Cyclic adenosine monophosphate
CCW	Chronic Conditions Data Warehouse
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPT	Current Procedural Terminology
DME	Durable medical equipment
DPI	Dry powder inhaler
DX	Diagnosis
FDC	Fixed dose combination
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCR	Glucocorticoid receptors
GERD	Gastroesophageal reflux disease
GLM	Generalized linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCPCS	Healthcare Common Procedure Coding System
HCUP	Healthcare Cost and Utilization Project
HDAC2	Histone deacetylase 2

hdPS	High-dimensional Propensity Score
HHA	Home health agency
HOP	Hospital outpatient
HR	Hazard ratio
HRRP	Hospital Readmissions Reduction Program
ICD-10 CM	International Classification of Diseases (Tenth Revision)-Clinical Modification codes
ICD-9 CM	International Classification of Diseases (Ninth Revision)-Clinical Modification codes
ICS	Inhaled corticosteroids
IMPACT	Informing the Pathway of COPD Treatment
LABA	Long-acting beta$_2$ agonist
LAMA	Long-acting muscarinic antagonist
MDI	Metered dose inhaler
MedPAR	Medicare Provider Analysis and Review
MEPS	Medical Expenditure Panel Survey
MTM	Medication therapy management
NAMCS	National Ambulatory Medical Care Survey
NAMCS-ED	National Ambulatory Medical Care Survey: Emergency Department
Nf-kB	Nuclear factor kappa B
NHAMCS-OP	National Hospital Ambulatory Medical Care Survey: Outpatient Department
NHDS	National Hospital Discharge Survey

NHHCS	National Home and Hospice Care Survey
NHIS	National Health Interview Survey
OLO/TIO	Olodaterol/tiotropium
PCS	Procedure Coding System
PDE4	Phosphodiesterase-4
PHCE	Personal Health Care Expenditure
RCT	Randomized clinical trial
RWD	Real-world data
RWE	Real-world evidence
SABA	Short-acting beta$_2$ agonist
SAMA	Short-acting muscarinic antagonist
SE	Standard Error
SMD	Standardized mean difference
SMI	Soft mist inhaler
SNF	Skilled nursing facility
TIOSPIR	Tiotropium Respimat Inhaler and the Risk of Death in COPD
US	United States
US FDA	United States Food & Drug Administration
VI/UMEC	Vilanterol/umeclidinium

1. CHAPTER 1: Introduction

Rationale and statement of problem

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease in the United States (US) [1]. It has been estimated that 4.6% of adults have ever been diagnosed with COPD in the US [2]. This is an underestimation, as greater than 50% of adults with low pulmonary function are not diagnosed [3,4]. COPD is a major source of mortality and morbidity, and was the fourth leading cause of death in the US [5,6].

COPD poses a significant financial burden on affected individuals and the healthcare system as a whole. Previous studies have estimated the economic burden of COPD mostly from a single payer perspective [7–9]. Further, since the publication of previous nationally representative work, significant changes have taken place in the US healthcare system [10–12]. Some of these changes include passing of the Patient Protection and Affordable Care Act, consolidation of Medicare part D for prescription drugs, as well as introduction of new therapies for the management and treatment of COPD. Additionally, in the last decade, as a response to high drug prices, generic medications have gained widespread acceptance and availability, including COPD medications [13]. This dissertation aims to provide an updated, nationally representative estimate of the economic burden of COPD. The direct medical costs for the management of COPD will be examined (for different categories of prescription drugs, emergency room visits, inpatient visits, office-based visits, outpatient visits, home health visits) from different payers' perspectives using 2017-2018 data.

The key goal in the management of COPD is the reduction of exacerbations as they have a detrimental impact on the clinical progression of disease and patients' health status. In patients with moderate to very severe COPD, inhalation therapy using long-acting $beta_2$ agonists (LABAs), long-acting muscarinic antagonists (LAMAs), or inhaled corticosteroids (ICSs) is the primary approach for managing the disease. These inhalers, and their combinations, are considered more convenient and effective compared to short-acting inhalers in preventing exacerbations and maintaining control of COPD symptoms [14–17]. Previous clinical trials and observational studies that evaluated the comparative effectiveness of LABA/LAMA and LABA/ICS combination maintenance medications for COPD found different results and were carried out across a variety of settings [18–23]. The findings from these studies highlight the need for population and setting specific studies based on the available medication options in the US. Prior work also found discrepancies in the rates of exacerbations based on the drug combination used as well as other factors such as the number of prior exacerbations [20,24]. These discrepancies highlight the potential for optimizing maintenance medication therapy in COPD [25]. The goal of this dissertation is to examine the comparative effectiveness of combination maintenance therapy single inhalers LABA/LAMA versus LABA/ICS in the management of COPD among Medicare beneficiaries in the US, using an incident, new user, retrospective matched cohort observational study design. Further, these results will be evaluated in various subgroups that could potentially help optimize therapy.

Among a certain class of COPD inhaler medications, there is limited guidance on the specific combinations to utilize. As a result, considerable uncertainty persists regarding the selection of medications, particularly between the two most used

LABA/LAMA combinations in the US: vilanterol/umeclidinium (VI/UMEC) and olodaterol/tiotropium (OLO/TIO). The main contributing factor to this lack of direction is the scarcity of evidence available to inform the guidelines [26,27]. Since each of these options offers a distinct efficacy and safety profile, personalized COPD management has the potential to be a viable approach [27]. This drug class was chosen to examine intraclass class differences due to the existing knowledge gap as well as the recent approval of newer therapies in this drug class. These specific drug combinations, that also have different mechanisms of drug delivery, in the LABA/LAMA drug class will be compared in terms of preventing future COPD exacerbation among Medicare beneficiaries with COPD, using an incident, new user, retrospective matched cohort observational study design.

Significance

This research will contribute to the literature in the following ways:

- Provide an updated, and nationally representative estimate of the economic burden of COPD in the US.
- Estimate the out-of-pocket cost burden of COPD on patients.
- Understand the distribution of direct medical costs across service categories, among COPD patients.
- Evaluate the comparative effectiveness of combination maintenance therapy single inhalers LABA/LAMA versus LABA/ICS in the management of COPD among Medicare beneficiaries in the US.

- Among LABA/LAMA single inhalers, the comparative effectiveness of VI/UMEC versus OLO/TIO will be evaluated among Medicare beneficiaries in the US. These are the most commonly used LABA/LAMA combinations.
- Use of recent data also will help better capture the newer combinations available in the US healthcare system.
- The long follow-up time will help better characterize the long-term impacts of using these medications designated for long-term use. Previous research has suggested that patients who remain on treatment for longer periods of time might experience different outcomes based on the length of the follow-up [28]. While clinical trials can capture the short-term impact of these maintenance medication choices, studies with a longer follow-up using real-world data (RWD) are needed.
- Studying these medications in the Medicare populations will help observe the comparative effectiveness of the therapies in an older comparatively sicker population. Previous research has suggested that the drug utilization behaviors of this older population may differ from younger groups [22].
- Less than 10% of COPD patients in the community would be eligible for participation in the major COPD trials that inform clinical guidelines [29]. This proportion is most likely even lower among the older Medicare beneficiaries and limits the generalizability of the findings. Use of RWD from observational studies can help generate evidence that is more generalizable to the patients that consume the medications.
- Identification of various subgroups that may benefit from a medication could help optimize therapy.

- Besides containing different pharmacological entities, VI/UMEC and OLO/TIO are dispensed through different types of inhalers, and their comparative effectiveness may help guide choice of therapy.

Specific aims

Aim 1: To estimate the updated, nationally representative COPD-specific and all-cause economic burden of COPD management in the US and quantify the overall cost, out-of-pocket cost, and cost by service type, including prescription drugs, emergency room visits, inpatient visits, office-based visits, outpatient visits, and home health visits among COPD patients in the US.

Aim 2: To examine the comparative effectiveness of combination maintenance therapy single inhalers LABA/LAMA and LABA/ICS in the management of COPD in the US using high-dimensional propensity score techniques and Medicare data, across various subgroups.

Aim 3: To examine the comparative effectiveness of combination maintenance therapy single LABA/LAMA inhalers VI/UMEC and OLO/TIO in the management of COPD in the US using high-dimensional propensity score techniques and Medicare data.

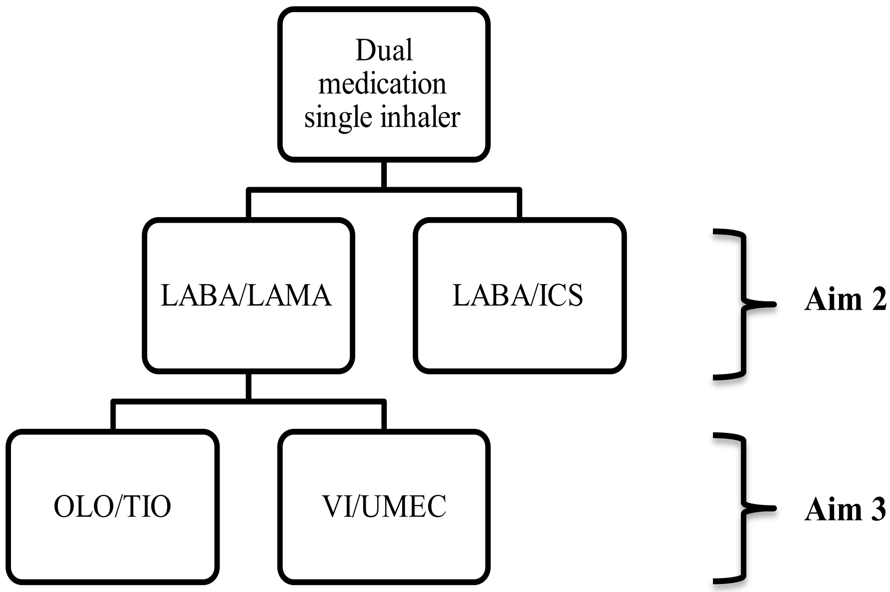


Figure 1. Overview of aim 2 and aim 3 comparisons

2. CHAPTER 2: Background

Definition and Epidemiology of COPD

COPD is a progressive respiratory disorder. The defining characteristics of COPD are obstructive ventilatory pattern, cough symptoms, production of sputum, dyspnea, and an insidious lung function decline [30–32]. It is an irreversible condition and most often associated with tobacco smoking, which may result in chronic respiratory failure [30]. Raherison et al. include the following components in their definition of COPD: presence of chronic bronchitis with permanent airway obstruction (forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio less than 0.70), presence of chronic obstructive bronchitis with hypoxemia (chronic respiratory failure), and destruction of the walls of the alveolar ducts past the terminal bronchiole accompanied by unusually large distil airways (emphysema) [30,33,34]. A key characterization of COPD is periods of acute worsening of respiratory symptoms (exacerbations) [32]. Besides the symptoms and exacerbations, increased morbidity and mortality are associated with COPD. Some important comorbidities of COPD include congestive heart failure, hypertension, type 2 diabetes mellitus, depressive disorder, and obesity [35].

As per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [32], some of the known risk factors for COPD are: tobacco smoke [36], indoor and outdoor air pollution [37], occupational exposures, genetic factors [38], age and sex, socioeconomic status [39], and infections [40].

One of the mainstays in the diagnosis of COPD, in addition to the presence of the symptoms characteristic of COPD, is the use of spirometry to detect the presence of persistent airflow restrictions [32]. A FEV_1/FVC value less than 0.70 is a confirmation of these restrictions [32].

Prevalence of COPD

COPD is a highly prevalent disease that, according to According to the Centers for Disease Control and Prevention and the National Center for Health Statistics, 4.6% of adults have ever been diagnosed with US [2]. The prevalence of COPD is, however, underreported, as greater than 50% of adults with low pulmonary function are not aware of their COPD unless tested by a clinician [3,4]. In addition COPD is a major source of mortality and morbidity, and was the fourth leading cause of death in the US in 2017 [5,6]. COPD is more common in older adults than younger adults, with a higher COPD prevalence among adults aged 65 years and older [41].

Burden of COPD

The projected future 20-year (2019 to 2038) direct medical costs attributable to COPD were estimated at US $801 billion, and an additional US $101 billion in indirect costs, in the US [42]. Total Medicare spending was higher for beneficiaries with COPD compared to persons without COPD of the same age [43]. Among Medicare beneficiaries, the COPD-related pharmacy costs were found to account for 40% of the healthcare spending, with the remaining 60% accounting towards medical costs [44]. The mean COPD-related costs among Commercially Insured and Medicare Advantage-insured patients were 2008 U.S. $ 1,875 and $ 2,784 for pharmacy and medical costs respectively in 2009 [44].

Though studies have examined the economic burden of COPD using single payer data sources, there is a lack of recent data that examines the economic burden of COPD in a nationally representative US sample. The few studies that have done so are presented in ***Table 1*** below.

In addition to the financial burden on affected individuals and the healthcare system as a whole, COPD also has a negative impact on both mental and physical health [5,44].

Table 1. Review of studies that examined the economic burden of COPD in a nationally representative all-payer sample

First author (publication year)	**Data**	**Key Results**	**Takeaways**
Strassels (2001) [10]	1987 National Medical Expenditure Survey	• 25% of total medical expenditure was COPD-related. The total medical expenditure was 1987 US $6,469. • 68% and 8% of total direct medical expenditures in persons with COPD were for inpatient hospitalizations and prescription medications, respectively.	• Majority of COPD patients were publicly insured. • Substantial burden of COPD, especially inpatient hospitalizations, on healthcare cost. • In 1987, ipratropium bromide metered dose inhaler was the only drug specifically indicated for the treatment of COPD-associated bronchospasm.
Miller (2005) [11]	2000 Medical Expenditure Panel Survey (MEPS)	• The mean attributable cost per patient was estimated at 2000 US $2,507. Greater than half of these costs ($1,365) were associated with hospitalization. • The mean excess cost of COPD, adjusted for sociodemographic factors and smoking status, was estimated at $4,932 per patient.	• COPD-associated healthcare costs and usage were considerably high. • The annual per patient costs were similar to the costs for other chronic conditions frequently observed in middle aged and elderly individuals.

Table 1. Continued

First author (publication year)	**Data**	**Key Results**	**Takeaways**
Wilson (2000) [45]	Multiple sources (1985 to 1994 National Health Interview Survey (NHIS), U.S. census reports, Center for Disease Control death certificates, 1993 National Hospital Discharge Survey (NHDS), Healthcare Cost and Utilization Project (HCUP-3), 1993 National Ambulatory Medical Care Survey (NAMCS), National Hospital Ambulatory Medical Care Survey: Outpatient Department (NHAMCS-OP), National Home and Hospice Care Survey (NHHCS), National Ambulatory Medical Care Survey: Emergency Department (NAMCS-ED) 1993)	• Chronic bronchitis and emphysema contributed to a total of 1996 US $14.5 billion in annual direct costs. • Emphysema had an annual cost of $1,341 per prevalent case while chronic bronchitis had an annual cost of $816 per prevalent case. • Hospital stays were responsible for the highest proportion of costs followed by medication costs.	• Chronic bronchitis and emphysema had a large burden on the US healthcare system. • This burden was amplified due to, in addition to the high cost per prevalent case, the high prevalence of chronic bronchitis and emphysema in the population.

Table 1. Continued

First author (publication year)	**Data**	**Key Results**	**Takeaways**
Foster (2006) [46]	Systematic review	• Range for COPD-attributable costs (2005 US $): 2,700-5,900. • Range for COPD costs using the excess cost estimates (2005 US $): 6,100-6,600.	• There was a wide range of cost estimates, especially using the COPD-attributable cost approach. • Discrepancies between older and newer data underline the short shelf life of results from cost-of-illness studies and highlight the need for frequent updates.

Management of COPD and medications

Patients' symptoms are significantly increased beyond baseline during exacerbations and are characteristic of COPD [15]. These COPD exacerbations often result in hospitalization or emergency department visits and have various important clinical and societal implications [47]. The consequent structural changes in the lung that irreversibly deteriorate the airflow have adverse effects on health status thereby affecting the course of COPD [15]. Thus, prevention of COPD exacerbations and their prompt and appropriate treatment are a major goal in the management of COPD [15].

Pharmacological therapy is used to manage and reduce symptoms of COPD, lessen the frequency and severity of exacerbations, enhance exercise tolerance, and improve health status [32]. Given that COPD is an irreversible condition, pharmacological therapy, at best, helps maintain status and does not improve the progressive decline in lung function, which is the hallmark of COPD [48]. As per the

GOLD guidelines, the pharmacological classes of medications for the management of COPD are: bronchodilators, antimuscarinic drugs, methylxanthines, combination bronchodilator therapy, anti-inflammatory agents, ICS, triple inhaled therapy, oral glucocorticoids, phosphodiesterase-4 (PDE4) inhibitors, antibiotics, and mucolytic and antioxidant agents [32]. These options have been presented in ***Appendix A***.

Bronchodilators are a drug class that make breathing easier by relaxing the muscles in the walls of the lungs and widening the airways [49]. These medications are used to treat conditions such as COPD where the airways get blocked and asthma where the airways get inflamed. Bronchodilators may be short-acting or long-acting. While short-acting bronchodilators serve to provide short-term relief from sudden bouts of breathlessness, long-acting bronchodilators aim to help control breathlessness and are used regularly. There are two major types of bronchodilators: $beta_2$ agonists and anticholinergics. Both these types are available as short-acting and long-acting formulations.

$Beta_2$ agonists work by acting on the $beta_2$ adrenergic receptors. These receptors are densely present on the smooth muscle cells of the airways and $beta_2$ agonists bind to them. The binding leads to interaction with intracellular G proteins which in turn stimulates the production of intracellular cyclic adenosine monophosphate (cAMP) [50]. The resultant activation of protein kinase A leads to phosphorylation and consequent smooth muscle relaxation.

The lungs contain the M1, M2, and M3 muscarinic receptors [51]. Activation of these receptors results in bronchoconstriction and mucus secretion in the airways [52].

Blocking these receptors, particularly the M3 receptor, is therapeutically very useful for reducing symptoms and improving lung function in COPD patients [51]. Muscarinic antagonists work by competitively blocking the binding of acetylcholine (ACh) to muscarinic receptors, leading to an anticholinergic response [53]. This in turn leads to an increase in airflow due to blocking of the cholinergic tone at the smooth muscles of airways [51].

ICSs help reduce inflammation and prevent flare-ups [49]. They have potent glucocorticoid activity, and activate specific glucocorticoid receptors (GCR) that are found in the cytoplasm of most mammalian cell types [50,54]. Additionally, they suppress inflammation predominantly through the switching off of multiple activated inflammatory genes by reversing histone acetylation using histone deacetylase 2 (HDAC2) [55]. HDAC2 mediated deacetylation of the GCR enables it to bind to nuclear factor kappa B (Nf-kB) [50]. During inflammation, Nf-kB is often increased in various types of cells and tends to promote the activation of genes that produce pro-inflammatory proteins [50]. The binding to Nf-kB helps nullify its effects as a pro-inflammatory molecule [56]. These medications have negligible systemic side effects at doses most often used, but may increase the risk of developing pneumonia at very high doses [55].

Combination inhaler maintenance medications

Several medications are available to manage COPD. Inhalation therapy is the preferred therapeutic option among patients with moderate to very severe COPD. Long-acting inhalers containing LABA, LAMA, or ICS are preferred over short-acting inhalers due to their added convenience and effectiveness [14–17]. Studies have shown that combining LABA/ICS, LABA/LAMA, or LABA/LAMA/ICS can potentially enhance treatment outcomes and be more effective than using either agent alone [57–62].

The US Food & Drug Administration (FDA) has approved a number of new single inhaler combination drugs for the management of COPD [63]. These include a vilanterol/fluticasone furoate combination single inhaler (Breo Ellipta) in 2013, and generic versions of salmeterol/fluticasone propionate in 2019, among the LABA/ICS single inhaler combinations. Among the single inhaler LABA/LAMA combinations, VI/UMEC (Anoro Ellipta) in 2013, OLO/TIO (Stiolto Respimat) in 2015, formoterol/glycopyrrolate (Bevespi Aerosphere) in 2016, and formoterol/ aclidinium (Duaklir Pressair) in 2019, are recently approved medications in the US. The wider availability of these medications has led to an increased use of these single inhaler combination drugs in the past few years [64,65]. There are a number of combination medications such as formoterol/beclomethasone (Fostair), formoterol/mometasone (Zenhale), and indacaterol/glycopyrronium (QVA149) that are widely available in Europe or Canada, but not in the US [66]. Thus, there exists a need for a US-based evaluation of the comparative effectiveness of these novel single inhaler combination options based on recent data.

Types of inhalers

There are three major types of inhalers. These are metered dose inhalers (MDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs). MDIs contain the medication as well as other products such as a propellant (often hydrofluoroalkane) that helps deliver the medication to the lungs [67]. Some of the newer formulations utilize a technology wherein drug crystals are attached to porous particles of phospholipids, providing a stable, homogeneous suspension that delivers a constant drug dose for the entire duration of use of the inhaler [67]. This inhaler generally requires the user to time their breath with the spraying of the medication. DPIs contain a dose of one or more medications in a dry powder form and deliver a fine powder to the lungs when inhaled. While this type of inhaler does not require coordination of inhalation and pressing of the cannister, the patient must inhale more forcefully when using a DPI compared to inhalation when using MDI. The SMI is a novel, multidose, propellant-free, hand-held, liquid inhaler [68]. SMIs emit medications in a finely dispersed mist that is expelled at a slower pace and lingers in the air for a longer duration than the aerosol produced by MDIs. The generation of the aerosol does not depend on the patient's inspiratory effort and these inhalers, also known as Respimat inhalers, are propellant-free [67].

Prior research found that the appropriate technique of inhaler use and error rates may differ based on the type of device used [69,70]. However, it was also shown that after individual training, these difference based on the device type may be less prominent [69]. Thus, there is an increased emphasis on proper training and education in order to ensure appropriate use of inhalers [69,71]. These differing modes of delivery may also impact healthcare resource utilization, exacerbations, and readmission rates [72] Simplifying inhaler regimens may reduce device misuse, improve clinical outcomes, and reduce healthcare resource utilization [73].

Hospital Readmissions Reduction Program (HRRP) and cost of exacerbations

The Hospital Readmissions Reduction Program (HRRP) was implemented in 2012, under section 3025 of the Patient Protection and Affordable Care Act [74]. As part of the HRRP, hospitals face penalties with reduced Medicare reimbursements for an excess of 30-day readmissions related to six conditions/procedures, one of them being COPD (added in 2014 amendment) [74–76]. Consequently, there has been an increased focus on readmissions within 30 days of a COPD-related visit. Various strategies have been implemented by hospitals to reduce the rate of these readmissions, including the use of algorithms to identify 'high risk' patients, and intervene with either change in therapeutic regimen, use of services such as medication therapy management (MTM), education at discharge, and scheduling of follow-up visits to ensure a smooth transition in care [77,78]. These changes have an impact on the management of COPD.

A study by Dalal et al. utilized US hospital administrative data and found that the cost of inpatient stays for COPD exacerbations ranged from 2008 US $7,242 to US $20,757, based on the complexity of the admission [79]. Another study that utilized a commercial health plan claims database found that the mean cost for acute COPD exacerbations that lead to hospitalizations was 2015 US $19,687 [35]. This cost is consistently higher than the cost of COPD exacerbations in other countries. In their systematic review, Toy et al. found that the estimated cost of exacerbations varied widely between studies in non-US countries, and ranged from $88 to $7,757 per exacerbation (2007 US dollars) [80–90]. The vast difference between the costs in the US and non-US settings are indicative of the high healthcare costs in the US, compared to the rest of the world. As demonstrated earlier, there is a lack of recent data on the cost of COPD management in a nationally representative US sample.

Potential for optimizing therapy

The aim of personalized medicine is to shape medical decision making based on individual characteristics and non-individual-level factors of the patient to optimize care and achieve treatment goals. One of the goals of medical decision making is to balance the benefits and risks of therapy based on information available and reasonable judgment. Given the heterogeneity in the progression of COPD, varying severity, as well as the availability of a plethora of treatment options, COPD is a disease area where patients may benefit from the implementation of personalized medication. For example, the choice of treatment may be based on the perceived risk of exacerbations in the patient, and patients could be stratified based on this risk. Previous research has found that certain medications for COPD are most effective in more severe patients, but may not be the best option for patients who are less severe [91,92]. For instance, Yu et al. found that roflumilast provided a net benefit only when used by COPD patients at a high risk of severe exacerbations [91]. Researchers from the University of Zurich have shown how COPD treatments could be personalized based on their findings from a benefit-harm modeling study [93]. Suissa et al. evaluated the comparative effectiveness of specific LABA/ICS drug combinations in terms of reduction of COPD exacerbations and found that the incidence of severe exacerbation was 25% lower in individuals that initiated formoterol/

budesonide than those that initiated salmeterol/fluticasone among patients with no prior exacerbations but was no different among patients with prior exacerbations [24]. Sposato et al. asked the question ‘Which LABA/LAMA should be chosen in COPD patients in real life?’ in their similarly titled study [94]. Based on comparisons between specific combinations as well as subgroups using Italian data from the electronic prescribing/dispensing database archives of South-East Tuscany, they concluded that each LABA/LAMA combination could have a specific efficacy profile in COPD and that it might be considered for personalized medication. Calverley et al, in their 2018 double-blind, randomized, parallel-group, active-controlled trial (DYNAGITO) compared olodaterol and tiotropium against only tiotropium in terms of prevention of COPD exacerbations and found that while the reduction in exacerbations in the overall sample was smaller than they anticipated and the level of significance was not reached, there were some subgroups that showed large improvements [95]. These results highlight the potential for personalized medicine in the management of COPD. There are two major ways that COPD therapy management may be optimized:

1. Identification of subgroups, based on demographic as well as clinical characteristics, wherein the effect in a subgroup (for example, based on number of prior exacerbations) may differ from the entire population effect.
2. Comparison of the individual medications in a drug class that may have differential effects in a population of interest.

Role of Real-World Data and Medicare

The 21st Century Cures Act defined real-world evidence (RWE) as ‘data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials (RCTs)’ [96]. Further, the US FDA has embraced RWE and RWD in order to monitor post market safety and adverse events, and make regulatory decisions, including the approval of new indications for previously approved drug entities [97]. Besides the FDA, the healthcare fraternity is using RWE and RWD to support coverage decisions, inform guidelines, develop decision support tools for implementation in clinical practice, and support clinical trials designs and observational studies. RWE and RWD offer the following advantages over clinical trials: longer follow-up periods allow to observe longer-term outcomes, results are more generalizable to the population that consumes the medication and also more reflective of clinical practice, generally cheaper to conduct, and give the ability to study rare conditions and outcomes due to generally larger sample sizes. While RCTs remain the gold standard for decision making, and RWE and RWD cannot replace them, they provide valuable information and can help support and supplement RCTs so that we can practice more evidence-based and personalized medicine.

One such dataset option for RWE is the Medicare dataset provided by the Centers for Medicare & Medicaid Services (CMS). Medicare beneficiaries form a significant proportion of the US adult population, and nearly 63 million individuals were enrolled in the Medicare program in 2019 [98]. Medicare beneficiaries have a number of distinct characteristics, needs, and circumstances that differentiate them from the rest of the US working adult population, and makes providing appropriate healthcare services to them a greater challenge [99]. In general, Medicare beneficiaries have poorer health status, more comorbidities, lower literacy levels, and suffer from a greater number of chronic conditions compared to their non-Medicare counterparts [99]. These characteristics, along with their complex needs, circumstances, and decreased mobility make managing their health and navigating the complex healthcare system challenging [99]. Even in the case of COPD, it is more prevalent in older adults than younger adults, with a higher COPD prevalence among adults aged 65 years and older, which represents the population of Medicare beneficiaries [17]. The distinctiveness of older patients with chronic obstructive pulmonary disease (COPD) lies not only in the evident consequences of declining lung function but also in the consequential influence on various other organ systems and the heightened comorbidity burden they experience [100,101].

Given the unique characteristics and needs of the Medicare population, analysis of Medicare data is critical for understanding the provision of healthcare to older adults in the US and serves as an important source of RWE to patients, healthcare providers, decision makers, and other stakeholders [102].

Propensity score and high-dimensional propensity score

Propensity score adjustment is a statistical method that is utilized in pharmacoepidemiology to minimize bias when estimating the effect of a medication on an outcome of interest using observational data. It allows researchers to design and analyze observational studies such that they mimic some of the characteristics of RCTs [103]. The propensity score is a single value that represents the probability of being assigned to a treatment conditional on a number of baseline characteristics, such as age, sex, and medical history [103]. This score can be obtained by fitting a logistic regression model that predicts treatment assignment based on the baseline covariates. After obtaining the propensity score, it can be used to match comparable individuals in both groups or adjust for confounding variables between the treated and untreated groups. Matching involves selecting individuals with similar propensity scores in both groups, while adjustment involves including the propensity score as a covariate in a regression model to estimate the treatment effect. The goal of propensity score adjustment is to reduce the bias that can arise from confounding by accounting for baseline differences between the treated and untreated groups. By doing so, the method can improve the validity of treatment effect estimates in observational studies.

High-dimensional Propensity Score (hdPS) is a statistical technique proposed, developed and tested by Schneeweiss et al., that is used to control for confounding in pharmacoepidemiologic studies [104]. This method is an extension of the traditional propensity score approach and provides an empirical method to control for a large number of covariates in observational studies that utilize huge, 'high-dimensional' data such as claims data or electronic health record data. The underlying rationale behind this approach is that a large number of variables from health care data may collectively serve as proxies for unobserved factors [104]. hdPS is an automated, data-driven analytical approach that helps covariate selection by empirically identifying pre-exposure variables and proxies for inclusion in the propensity score model [105]. Prior research has demonstrated the potential benefits of using hdPS over more traditional approaches [106–

109] and there has also been an increased usage of this method since its introduction in 2009.

3. CHAPTER 3: Direct medical costs of COPD in the United States: An analysis of the Medical Expenditure Panel Survey 2017-2018

Abstract
Aim

In this study, we aimed to provide a nationally representative estimate of the economic burden of chronic obstructive pulmonary disease (COPD) by examining direct medical costs among individuals aged 45 years and older in the United States (US).

Methods

Medical Expenditure Panel Survey (2017-2018) data were used to estimate the direct medical costs associated with COPD. All-cause (unadjusted) cost and COPD-specific (adjusted) cost were determined for the various service categories using a regression-based approach among patients with COPD. We developed a weighted two-part model and adjusted for various demographic, socioeconomic, and clinical characteristics.

Results

The study sample consisted of 23,590 patients, of which 1,073 had COPD. Patients with COPD had a mean age of 67.4 years (Standard Error (SE): 0.41), and the total all-cause

---

Shah, C.H.; Reed, R.M.; Wastila, L.; Onukwugha, E.; Gopalakrishnan, M.; Zafari, Z. Direct Medical Costs of COPD in the USA: An Analysis of the Medical Expenditure Panel Survey 2017–2018. *Appl Health Econ Health Policy* **2023**, doi:10.1007/s40258-023-00814-8.

mean medical cost per patient per year (PPPY) was 2018 US $19,449 (SE: US $865); of which US $6,145 (SE: US $295) was for prescription drugs. Using the regression approach, the mean total COPD-specific cost was US $4,322 (SE: US $ 577) PPPY with prescription drugs contributing US $1,887 (SE: 216) PPPY. These results represent an annual total COPD-specific cost of US $24.0 billion, with prescription drugs contributing US $10.5 billion. The mean annual out-of-pocket spending accounted for 7.5% (mean: US $325) of the total COPD-specific cost; for COPD-specific prescription drug cost, 11.3% (mean: US $212) was out-of-pocket cost.

Conclusion

COPD poses a significant economic burden on healthcare payers and patients 45 years of age and older in the US. While prescription drugs account for almost half of the total cost, more than 10% of the prescription drug cost was out-of-pocket.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease. The defining characteristics of COPD are obstructive ventilatory patterns, cough symptoms, production of sputum, dyspnea, and a progressive lung function decline [30–32]. It is an irreversible condition and may result in chronic respiratory failure [30]. According to the Centers for Disease Control and Prevention and the National Center for Health Statistics, 4.6% of adults have ever been diagnosed with COPD in the United States (US) [2]. It is estimated that more than 50% of individuals with COPD remain undiagnosed [3,4]. COPD presents a major source of mortality and morbidity and was the fourth leading cause of death in the US in 2017 [6]. COPD has been shown to have detrimental impacts on both mental and physical health leading to a lower health-related quality-of-life among patients [5].

COPD imposes substantial economic burdens on patients, the healthcare system, and US society. A recent study projected that the annual direct medical costs attributable to COPD would increase from 46.91 billion to US $57.86 billion over a 20-year period [42]. Similarly, the study estimated that the indirect absenteeism costs, measured by days of work missed, would rise from US $6.82 billion to US $6.97 billion in 20 years [42]. Other studies have estimated the economic burden of COPD from a single payer with substantial emphasis being on the cost of exacerbations in individuals with COPD [7–9,35,110]. Moreover, prior research has found that demographic and socioeconomic characteristics of patients, healthcare utilization, and medical costs tend to vary widely between different payers [111–113].

In recent years, significant changes have taken place in the US healthcare system, including the passage of the Patient Protection and Affordable Care Act, introduction of the Hospital Readmissions Reduction Program that penalized rehospitalization for conditions including COPD [74], consolidation of Medicare part D for prescription drugs, and introduction of new therapies for the management and treatment of COPD [10–12]. In addition, lower cost generic medications have gained widespread acceptance and availability as an alternative to high price of their branded counterparts in the last decade [13]. These changes led to an increase in prescription drug access and spending, and a consequent decrease in inpatient care spending over time [64,114,115].

Given changes in the management of COPD and the US healthcare system in recent years, there exists a need for updated estimates of the direct medical costs of COPD across payers to capture the burden posed by COPD in the US. In this study we aim to provide an updated, nationally representative estimate of the COPD-specific and all-cause economic burden of COPD by analyzing the 2017-2018 Medical Expenditure Panel Survey (MEPS). We quantify the overall cost, out-of-pocket cost, and cost by service type, including prescription drugs, emergency room visits, inpatient visits, office-based visits, outpatient visits, and home health visits among COPD patients.

Methods

Data source

We utilized data from the 2017-2018 MEPS, a de-identified, publicly available database provided by the Agency for Healthcare Research and Quality (AHRQ) [116].

The survey collects data from families, medical providers, and employers across the US and is based on a nationally representative subsample of households. The subsample of households participated in the National Health Interview Survey, which is carried out by the National Center for Health Statistics. AHRQ uses an overlapping panel design to collect data on demographic and socioeconomic characteristics, healthcare utilization, and health status, among other attributes about non-institutionalized individuals from households in the US. This design involves preliminary contact followed by five rounds of interviews over a two-and-a-half-year period. The data collected covers a period of two calendar years for each household. The sampling design of the survey includes stratification, clustering, multiple stages of selection, and disproportionate sampling (complex survey design methods). Survey sample weights are based on the Current Population Survey and are computed and provided by the MEPS administrators.

The two major components of MEPS data are the household component and the insurance component. We used the full-year consolidated data file and the medical conditions file from the household component of the MEPS dataset. The full-year consolidated data file [116] contains information on demographic characteristics of the sample in addition to employment, health status, quality of care, healthcare spending, patient satisfaction, and health insurance coverage estimates. The medication conditions file [116] contains information on the reported medical conditions among the sample.

Study sample

Respondents with COPD were identified using the following International Classification of Diseases (Tenth Revision)-Clinical Modification codes (ICD-10 CM): J42 ('unspecified chronic bronchitis'), J43 ('emphysema'), J44 ('chronic obstructive pulmonary disease') [117]. As COPD diagnosis has been shown to be uncommon in individuals younger than 45 years of age, our sample was limited to adults who were at least 45 years old [41,118,119]. Non-respondents and individuals with missing information on variables of interest were excluded. The sample selection process is depicted in ***Figure 2.***

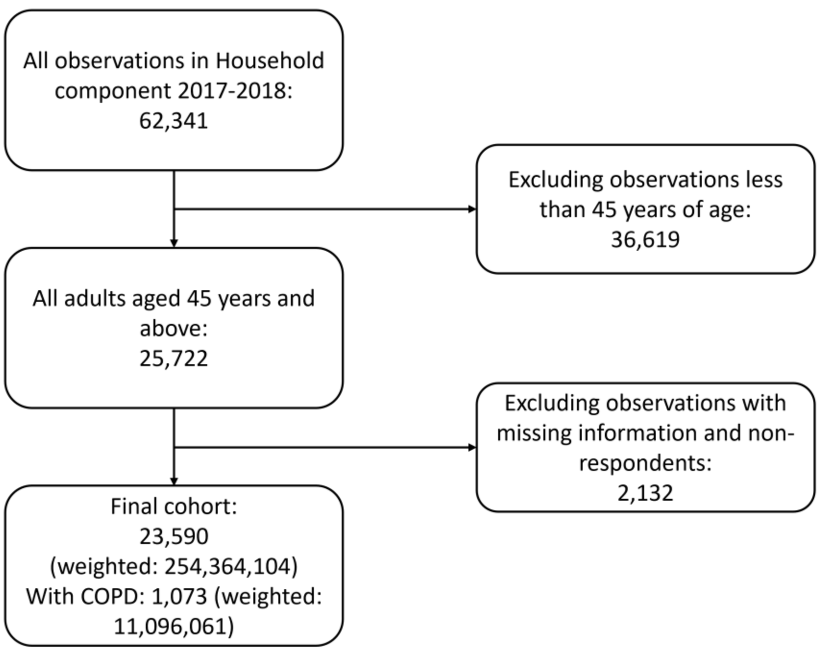


Figure 2. Flow diagram illustrating the sample selection process

Statistical analysis

Given the cross-sectional study design nature of MEPS, all demographic, socioeconomic, and clinical characteristics were measured during the observation year and reported for both individuals with and without COPD. In addition to the unadjusted all-cause healthcare cost among individuals with COPD, we calculated the COPD-specific cost for the various service categories. Therefore, we estimated cost using two approaches: 1) unadjusted cost; 2) adjusted cost using regressions. For the unadjusted all-cause estimates, only individuals with COPD were included in the analysis. For the regression-based COPD-specific estimates, the entire sample with or without COPD was included in the analysis.

Outcomes

The primary outcome of interest was the COPD-specific cost. The service categories examined included inpatient stays, outpatient visits, emergency room visits, office-based visits, home health visits, and prescribed medicines. In addition, all-cause medical cost, including both COPD-specific and non-COPD-specific cost, among COPD patients for these categories was determined. Out-of-pocket cost representing the patient economic burden was also estimated. The focus of our analysis was on direct medical cost; other societal costs, such as lost work, disability cost, and caregiver cost, were not included in our model.

Covariates

In the regression model we adjusted for the following covariates: age, insurance coverage, sex, race, marital status, family income, current smoking status, region of residence, education level, and comorbid conditions. Age was categorized into five-year interval groups “45-49”, “50-54”, “55-59”, “60-64”, “65-69”, “70-74”, “75-79”, and “80 and above”. The three types of insurance were categorized as any private, public only, and uninsured. Family income as a percentage of the poverty line was grouped as “poor” (less than 100% of the poverty line), “near poor” (100% to less than 125% of the poverty line), “low income” (125% to less than 200% of the poverty line), “middle income” (200% to less than 400% of the poverty line), and “high income” (greater than or equal to 400% of the poverty line). Specific comorbid conditions adjusted for included angina, arthritis, asthma, cancer, chronic heart disease, high cholesterol, diabetes, high blood pressure, myocardial infarction, stroke, other heart conditions, depression, and anxiety, as these conditions have been identified as priority conditions by MEPS [120].

Model

For the regression-based model, the dependent variable was all-cause medical cost. The primary independent variable of interest in the regression was COPD diagnosis in order to estimate the incremental contribution of COPD on the overall cost. To obtain estimates for the out-of-pocket cost, the regression model was implemented wherein the outcome of interest was all-cause out-of-pocket cost and presence of COPD was the primary independent variable. Out-of-pocket costs were estimated for prescription drugs, other (cost besides prescription drug cost) and total cost.

The regression approach utilized a two-part model. The first part consisted of a logistic regression wherein the outcome was a binary indicator that took a value of 1 when a respondent reported any expenditure and took on a value of 0 when individuals reported no expenditure. The outcome of the second part of the two-part model was the expenditure amount. The model parameters in the second part were estimated using a generalized linear model (GLM) with a log link function and gamma distribution [121–123]. These procedures were carried out using the 'twopm' STATA programs [124]. The marginal effect of COPD on the cost was determined to estimate the COPD-specific cost using the delta method. The aforementioned covariates and operationalizations were utilized for both analyses: COPD-specific total cost and COPD-specific out-of-pocket cost.

The complex survey design used to collect the data was accounted for by using appropriate analytical procedures such as SURVEYFREQ, SURVEYMEANS, domain statements, and svy in the analyses [125]. All the costs were adjusted to 2018 values using the Personal Health Care Expenditure (PHCE) component of the National Health Expenditure Accounts provided by the U.S. Department of Health and Human Services, as recommended by Dunn et al. [126–128]. All analyses were carried out using SAS 9.4 and STATA MP 16 [129,130].

Results

The study sample consisted of 23,590 (weighted: 254,364,104) patients, of which 1,073 (weighted: 11,096,061) had COPD during the study period. Compared with individuals without COPD, a higher proportion of COPD patients were female (59% versus 53%), 65 years and older (59% vs. 38%), white (88% versus 81%), and had only public insurance (49% versus 27%). In addition, COPD patients were 2.5 times more likely to be current smokers and had a higher prevalence of angina (12% versus 3%), arthritis (69% versus 40%), asthma (40% versus 11%), cancer (28% versus 18%), chronic heart disease (24% versus 8%), high cholesterol (63% versus 46%), diabetes (27% versus 17%), high blood pressure (68% versus 49%), myocardial infarction (18% versus 6%), stroke (15% versus 6%), other heart conditions (35% versus 15%), depression (22% versus 10%), and anxiety (22% versus 10%). The other demographic and clinical characteristics of patients with and without COPD are presented in ***Table 2***.

All-cause medical cost (unadjusted) among COPD patients

The all-cause medical cost among COPD patients represents both COPD-specific and non-COPD-specific costs. Among COPD patients, the total all-cause mean annual per patient medical cost was 2018 US $19,449 (Standard Error (SE): US $865; 95% Confidence Interval (CI): US $17,748-US $21,151); of which US $6,145 (SE: US $295; 95% CI: US $5,564-US $6,726) was for prescription drugs, US $592 (SE: US $83; 95% CI: US $429-US $754) was for emergency room visits, US $5,330 (SE: US $504; 95% CI: US $4,339-US $6,322) was for inpatient visits, US $3,323 (SE: US $183, 95% CI: US $2,962-US $3,683) was for office-based visits, US $1,399 (SE: US $198, 95% CI: US $1,010-US $1,788) was for outpatient visits, and US $1,495 (SE: US $208, 95% CI: US $1,086-US $1,904) was for home health visits. While the mean annual total cost among COPD patients was US $19,449, there was a significant amount of between-individual variation in annual costs (standard deviation: US $22,647). These results are presented in ***Table 3.***

COPD-specific medical cost

Based on the regression model, the total COPD-specific incremental expenditure per patient per year was US $4,322 (SE: US $577, 95% CI: 3,187-5,457); out of which US $1,887 (SE: US $216, 95% CI: US $1,462-US $2,312) was for prescription drugs, US $137 (SE: US $30, 95% CI: US $78-US $196) was for emergency room visits, US $1,003 (SE: US $233, 95% CI: US $544-US $1,461) was for inpatient visits, US $384 (SE: US $171, 95% CI: US $47-US $720) was for office-based visits, US $133 (SE: US $117, 95% CI: -US $98-US $364) was for outpatient visits, and US $250 (SE: US $77, 95% CI: US $98-US $401) was for home health visits. The results are presented in ***Table 3***. These results represent an annual total cost of US $24.0 billion, with prescription drugs contributing US $10.5 billion of this cost among the total sample of the weighted population with COPD in the US. The complete regression results of the two-part model for COPD-specific total cost (marginal effects) are presented in ***Table 4.*** In addition, the regression results by service categories are provided in ***Appendix B.***

COPD-specific out-of-pocket cost

The mean annual per person out-of-pocket spending for COPD was US $325, which accounted for 7.5% of the total COPD-specific cost. Of this, out-of-pocket spending for COPD prescription drugs was on average US $212 per patient per year, accounting for 11.3% of the total COPD prescription drug cost. The mean annual per person out-of-pocket spending for other COPD costs (other than prescription drug cost) was US $113, accounting for 4.6% of the total other COPD-specific spending. These results are depicted in ***Figure 3.***

Table 2. Demographic characteristics of individuals with COPD and individuals without COPD, 2017-2018

	Among individuals with COPD			**Among non-COPD individuals**			**Rao-Scott Chi-Square Test**
Covariates	**Frequency**	**Weighted Frequency**	**Percent**	**Frequency**	**Weighted Frequency**	**Percent**	**P-value**
Age= 45-49 years	44	503,468	4.54%	3,386	37,135,886	15.27%	<0.01
Age= 50-54 years	85	739,231	6.66%	3,419	38,237,946	15.72%	<0.01
Age= 55-59 years	147	1,502,817	13.54%	3,500	38,106,852	15.66%	0.14
Age= 60-64 years	177	1,837,374	16.56%	3,223	36,735,440	15.10%	0.33
Age= 65-79 years	164	1,604,982	14.46%	3,008	31,299,027	12.87%	0.23
Age= 70-74 years	184	1,933,165	17.42%	2,395	24,526,841	10.08%	<0.01
Age= 75-79 years	136	1,504,519	13.56%	1,532	15,937,489	6.55%	<0.01
Age= 80 years and above	136	1,470,505	13.25%	2,054	21,288,562	8.75%	<0.01
Region= Northeast	173	1,822,303	16.42%	3,776	43,632,653	17.94%	0.40
Region= Midwest	272	2,658,704	23.96%	4,620	52,092,364	21.41%	0.23
Region=West	177	1,757,187	15.84%	5,500	56,441,568	23.20%	<0.01
Region=South	658	4,857,867	43.78%	8,621	91,101,458	37.45%	0.01
Highest education: less than High school	226	1,845,717	16.63%	3,500	25,180,093	10.35%	<0.01
Highest education: High School/ GED	602	6,507,975	58.65%	10,322	108,802,541	44.73%	<0.01
Highest education: other degree	113	1,322,915	11.92%	2,076	26,129,043	10.74%	0.38
Highest education: Bachelors degree	83	900,357	8.11%	3,939	49,676,744	20.42%	<0.01
Highest education: Masters/PhD degree	49	519,097	4.68%	2,680	33,479,622	13.76%	<0.01
Insurance= Any private	460	5,395,585	48.63%	13,953	167,119,953	68.70%	<0.01
Insurance= Public only	589	5,434,224	48.97%	7,192	64,531,798	26.53%	<0.01
Insurance= Uninsured	24	266,252	2.40%	1,372	11,616,292	4.78%	<0.01
Sex= Female	658	6,566,796	59.18%	12,277	128,530,524	52.83%	<0.01
Race=White only	892	9,728,594	87.68%	17,019	196,494,946	80.77%	<0.01
Race=Black only	132	955,157	8.61%	3,589	27,055,754	11.12%	0.02
Race=Other/ Multiple reported	49	412,310	3.72%	1,909	19,717,343	8.11%	<0.01

Table 2. Continued

	Among individuals with COPD			Among non-COPD individuals			Rao-Scott Chi-Square Test
Covariates	**Frequency**	**Weighted Frequency**	**Percent**	**Frequency**	**Weighted Frequency**	**Percent**	**P-value**
Marital status= Currently married	425	4,665,197	42.04%	13,001	149,383,029	61.41%	<0.01
Family income= Poor	255	2,046,598	18.44%	3,004	21,510,481	8.84%	<0.01
Family income= Near poor	88	864,116	7.79%	1,022	8,704,289	3.58%	<0.01
Family income= Low	191	1,882,671	16.97%	3,038	27,790,254	11.42%	<0.01
Family income= Medium	301	3,347,452	30.17%	6,209	63,552,902	26.12%	0.03
Family income=High	238	2,955,224	26.63%	9,244	121,710,117	50.03%	<0.01
Current smoker	364	3,587,698	32.33%	3,142	31,880,363	13.11%	<0.01
Angina	129	1,360,232	12.26%	724	7,634,168	3.14%	<0.01
Arthritis	773	7,681,255	69.23%	9,195	97,301,240	40.00%	<0.01
Asthma	463	4,471,728	40.30%	2,471	26,012,876	10.69%	<0.01
Cancer	303	3,074,670	27.71%	3,728	42,945,141	17.65%	<0.01
Chronic heart disease	250	2,660,880	23.98%	1,899	19,017,297	7.82%	<0.01
High cholesterol	697	6,981,095	62.92%	10,554	112,171,359	46.11%	<0.01
Diabetes	304	2,996,928	27.01%	4,282	41,057,347	16.88%	<0.01
High blood pressure	766	7,562,243	68.15%	11,519	118,023,644	48.52%	<0.01
Myocardial infarction	192	2,050,501	18.48%	1,386	13,629,466	5.60%	<0.01
Stroke	163	1,685,397	15.19%	1,522	14,691,288	6.04%	<0.01
Other heart conditions	370	3,853,877	34.73%	3,451	37,138,898	15.27%	<0.01
Depression	249	2,489,952	22.44%	2263	23,508,682	9.66%	<0.01
Anxiety	258	2,461,395	22.18%	2195	24,011,770	9.87%	<0.01
Total	1,073	11,096,061	100.00%	22,517	243,268,043	100.00%	

Table 3. Healthcare costs (COPD-specific and All-cause medical) among COPD patients, by visit type

Service category	**All-cause (unadjusted) medical cost**	**Fully adjusted model COPD-specific (Regression approach) medical cost [a,b]**
	Mean annual per person cost (Standard Error; 95% Confidence Interval) (2018 US $)	
Prescription drugs	US $6,145 (SE: 295: 95% CI: US $5,564-US $6,726)	US $1,887 (SE:216; 95% CI: US $1,462-US $2,312)*
Emergency room	US $592 (SE: 83; 95% CI: US $429-US $754)	US $137 (SE:30; 95% CI: US $78-US $196)*
Inpatient	US $5,330 (SE: 504; 95% CI: US $4,339-US $6,322)	US $1,003 (SE:233; 95% CI: US $544-US $1,461)*
Office-based	US $3,323 (SE: 183; 95% CI: US $2,962-US $3,683)	US $384 (SE:171; 95% CI: US $47-US $720)*
Outpatient	US $1,399 (SE: 198; 95% CI: US $1,010-US $1,788)	US $133 (SE:117; 95% CI: -US $98-US $364)
Home health	US $1,495 (SE: 208; 95% CI: US $1,086-US $1,904)	US $250 (SE:77; 95% CI: US $98-US $401)*
Total	US $19,449 (SE: 865; 95% CI: US $17,748-US $21,151)	US $4,322 (SE:577; 95% CI: 3,187-5,457)*

[*]Difference is statistically significant at the 95% confidence level.

[a] Covariates adjusted for include: age (categorized into 5-year intervals), insurance status, sex, race, region, highest level of education, marital status, family income, current smoking status, and comorbid conditions (Angina, arthritis, asthma, cancer, chronic heart disease, high cholesterol, diabetes, high blood pressure, myocardial infarction, stroke, other heart conditions, depression, anxiety).

[b] For two-part regression: first part: logit; second part: generalized linear model (family=gamma, link=log).

Table 4. Results of marginal effect two-part regression to determine excess cost of COPD on total healthcare expenditure

Covariate	Reference	Marginal effect	Standard error	p-value
Race=Black only	Race=White only	-478.26	556.64	0.39
Race=Other/Multiple reported		-1931.44	673.08	<0.01
Age=50-54 years	Age=45-50 years	2273.89	807.49	<0.01
Age=55-59 years		1355.79	659.22	0.04
Age=60-64 years		2495.48	741.67	<0.01
Age=65-69 years		2377.35	641.97	<0.01
Age=70-74 years		2269.05	713.16	<0.01
Age=75-79 years		1947.01	731.38	<0.01
Age=80 years and older		3967.38	776.76	<0.01
Marital status=Currently married	Marital status=Not currently married	-562.18	348.51	0.11
Region= Northeast	Region=South	1311.32	619.43	0.04
Region= Midwest		308.93	535.12	0.56
Region=West		714.73	582.85	0.22
Sex= Female	Sex= Male	-201.61	362.89	0.58
Highest education: High School/ GED	Highest education: less than High school	885.32	597.29	0.14
Highest education: other degree		1237.20	760.21	0.11
Highest education: Bachelors degree		961.03	684.46	0.16
Highest education: Masters/PhD degree		2026.58	812.63	0.01
Current smoker	Not current smoker	604.68	543.95	0.27
Insurance= Uninsured	Insurance= Any private	-9569.09	1222.43	<0.01
Insurance= Public only		-498.97	375.76	0.19
Family income= Poor	Family income= Medium	1757.19	633.74	<0.01
Family income= Near poor		1415.56	785.53	0.07
Family income= Low		254.62	625.26	0.68
Family income=High		519.32	398.37	0.19
Angina		-381.21	727.20	0.60
Arthritis		3122.23	347.84	<0.01
Asthma		3004.80	596.20	<0.01
Cancer		4475.02	447.27	<0.01
Chronic heart disease		2513.72	510.22	<0.01
High cholesterol		30.41	374.75	0.94
Diabetes		5136.56	496.96	<0.01
High blood pressure		1724.31	361.17	<0.01
Myocardial infarction		2465.04	593.01	<0.01
Other heart conditions		3147.90	388.78	<0.01
Stroke		3551.34	632.29	<0.01
Depression		2901.41	437.12	<0.01
Anxiety		3559.01	498.11	<0.01
Chronic Obstructive Pulmonary Disease		4322.22	576.92	<0.01

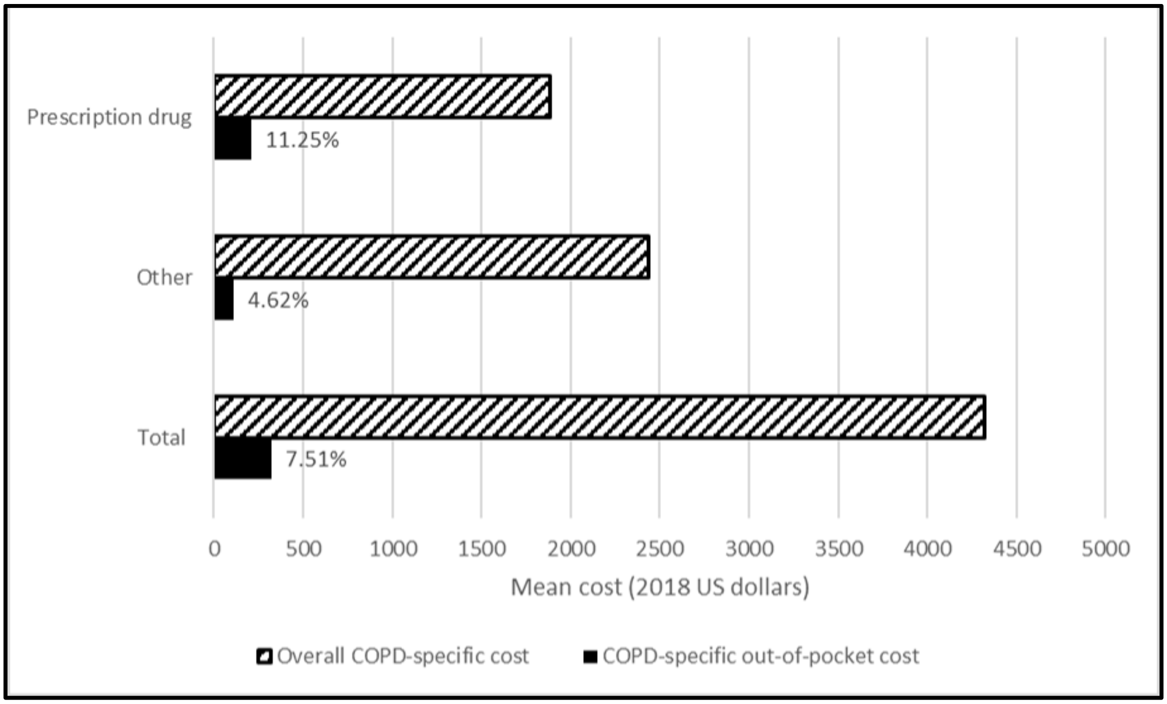


Figure 3. Mean annual out-of-pocket and overall COPD-specific cost, by service category, per person with COPD

All values are in 2018 US dollars. Prescription and total cost based on the results of a fully adjusted two-part regression (described in text). Other costs estimated by the difference in results of the regression analyses for total and prescription drug costs.

Discussion

In this study, we reported COPD-specific and all-cause direct medical costs among patients with COPD estimated using data from a nationally representative sample of non-institutionalized US adults. Our results reveal differences in sociodemographic and clinical characteristics—including differences in comorbidities— between individuals with and without COPD. We found that the mean annual per patient COPD-specific cost and all-cause medical cost was US $4,322 and US $19,449, respectively.

In comparison with previous nationally representative studies, our results demonstrate a shift in the age distribution and cost of COPD in recent years in the US. We found that 59% of COPD patients were 65 years old and above in 2017-2018, compared with 47% in 2007 [12], 63% in 2000 [11], and 74% in 1987 [10]. These aforementioned changes could be due to a complex interplay of factors such as a decrease in the age of first diagnosis of COPD [131], an increase in life expectancy, changes in the age distribution in the population [132], and a steady decrease in the rates of smoking, a major risk factor of COPD over this period [133]. With respect to sex and race distributions among COPD patients, we found no major changes since 2007 [12].

Our findings are indicative of a shift in the distribution and drivers of COPD-specific cost in recent years. While inpatient care and prescription drugs respectively accounted for 68% and 8% of the total all-cause unadjusted expenditures among COPD patients in 1987 [10], the corresponding estimates in our study were 27% and 32%. This is an interesting finding as it shows over time the proportion of all-cause expenditures due to inpatient care reduced while spendings on prescription drugs increased. Recent work by Celi et al. has demonstrated that COPD treatments, especially newer options, were able to not only improve symptoms and reduce exacerbations, but were also shown to improve patient prognosis in terms of all-cause mortality, which may partially help explain the recent shift in cost [134].

When compared to MEPS 2000 data [11], our study shows an increase of 72% in mean annual COPD-specific medical cost. The main driver for this increase is an 8-fold rise in the mean COPD-attributable prescription drug cost. Such an increase in prescription drug cost was accompanied by a 27% decrease in inpatient spending compared with data from 2000 [11]. Higher prescription drug cost and lower inpatient cost compared with earlier periods are indicative of a shift in the way COPD is managed and perhaps the introduction of novel, more effective drugs that lead to better management of COPD, but at an increased prescription drug cost [135].

The shift toward higher prescription drugs cost and lower inpatient cost suggests effectiveness of maintenance therapy in reducing costly healthcare events such as hospitalizations [136]. Therefore, efforts to increase access and adherence to medications can be pivotal in preventing future hospitalizations while saving money for patients and payers.

At the individual-level, we estimated the mean annual COPD-specific direct medical costs to be US $4,322 per patient. Our MEPS-derived estimate for cost of COPD is in line with previous costs estimates for moderate-to-severe COPD ($3,706-$5,675) [42]. Given lung function data is not available in MEPS, we could not define the distribution of our study participants across different clinical severity grades of COPD. However, given COPD is underdiagnosed in milder stages of disease, and that a good proportion of individuals included in our study had at least one healthcare resource use due to COPD, our results may be more representative of moderate-to-severe COPD [42,137,138].

Further, this study found that the patient burden in terms of out-of-pocket cost was on average US $325 per year, which was 7.5% of the total COPD-specific spending. Our out-of-pocket cost estimate is nearly 3-fold higher than the estimate reported in a previous study (US $111), mainly because the population in the previous study was restricted to working individuals with COPD [139], and that their sample was younger. In addition, it is most likely that the out-of-pocket costs vary by insurer, but we were not able to obtain such estimates due to the small sample sizes for subgroup analysis across insurers.

Appropriate use of medications is necessary for disease management, but paying high out-of-pocket cost can be expensive for some patients and can be a barrier for filling prescription drugs and maintaining adherence [140–144]. While policies to increase access to, and reduce copays for medications can save money for the healthcare system in the long run, given the heterogeneity of lung function decline and progression of COPD [145], ensuring the provision of right medication that meets the clinical needs and preferences of a given patient can be as important. Certain medications for COPD are most effective in more severe clinical stages of the disease, while providing a lesser effect for milder COPD [91,92]. For example, Yu et al. found that roflumilast provided a net benefit only when used by COPD patients at a high risk of severe exacerbations [91]. Other researchers have shown how COPD treatments could be personalized based on benefit-harm modeling frameworks [93]. In addition, clinical risk-stratification models that incorporate patients' preferences may optimize treatment benefits while increasing patients' adherence.

A major strength of our study is that it uses nationally representative data of non-institutionalized US adults and provides updated estimates of the economic burden of morbidity from both patient and payer perspectives. Nonetheless, our study is subject to some limitations and the results of this analysis should be interpreted in light of the following caveats. Since MEPS is a survey that is conducted among non-institutionalized individuals, our results do not extend to individuals who are institutionalized. Given that a single household member responds to the survey on behalf of all other household members, the data is susceptible to survey and recall biases. MEPS attempts to overcome these limitations in a number of ways, including using the medical provider component to supplement, replace, validate, and impute health care expenditures [146]. Some of the covariates adjusted for are not truly independent of COPD and are linked both through cigarette smoking as well as susceptibility and other mechanisms. A regression approach controlling for these comorbidities is really taking a very conservative approach to estimation. It also is important to note that the comorbidities included in the regression models are not necessarily mutually independent and were chosen to control for confounding. In addition, omitted variable bias due to unmeasured confounding may affect the results. Though our study utilized a regression-based incremental cost approach, other approaches may also be utilized to estimate the cost-of-illness [147,148]. Costs examined in this study were all medical in nature and did not include other societal costs such as lost work, disability, caregiver, and other intangible costs. As such, the cost estimates provided here underestimate the true societal burden.

Conclusion

This study quantifies the substantial economic burden of COPD in the US. With projected population ageing in the years to come, the national burden of COPD will remain on the rise. An interesting finding of this study is the shift in the proportion of costs toward pharmacy and away from hospitalizations in COPD patients over time, with prescription drugs accounting for almost half of the overall direct medical cost among COPD patients in more recent years.

4. CHAPTER 4: Comparative effectiveness of LABA/LAMA and LABA/ICS single inhaler fixed dose combinations among COPD patients: A high-dimensional propensity score matched new user cohort study in a US Medicare population

Abstract

Introduction

Among patients with moderate to very severe chronic obstructive pulmonary disease (COPD), inhalation therapy is the mainstay of disease management. Inhalers containing long-acting beta$_2$ agonists (LABA), long-acting muscarinic antagonists (LAMA), or inhaled corticosteroids (ICS) and their combinations are preferred options. This study aimed to examine the comparative effectiveness of single inhaler fixed dose combination classes LABA/LAMA versus LABA/ICS across the subgroups of sex, age, history of prior COPD exacerbations, prior use of supplemental oxygen, and presence of comorbid allergic rhinitis, in the United States (US).

Methods

We utilized a new user, active comparator retrospective design and a nationally representative sample of Medicare Fee-for-Service beneficiaries aged 65 years and older. The outcome of interest was time to first occurrence of a COPD exacerbation. To ensure that the groups were comparable, they were 1:1 matched based on their high-dimensional propensity scores.

Results

The study cohort included 12,912 pairs of LABA/LAMA initiators matched to LABA/ICS initiators. The relative hazard ratio of time to COPD exacerbation was 0.846 (95% Confidence interval: 0.776-0.923) for LABA/ICS compared to LABA/LAMA initiators. The results remained consistent across sex. This benefit was no longer statistically significant among individuals with prior oxygen use, comorbid allergic rhinitis, or any prior exacerbation in the past year. In all these subgroups, except among individuals aged 85 years or greater, the point estimates still favored LABA/ICS.

Conclusion

We found that LABA/ICS combinations were more effective at reducing the time to first exacerbation compared to LABA/LAMA combinations, and the results were largely consistent across most subgroups.

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent condition that is characterized by persistent respiratory symptoms and gradual worsening of airflow [149]. COPD is also a major source of morbidity and mortality, and has a detrimental impact on physical and mental wellbeing [5,35,150,151]. These in turn lead to significant socioeconomic burdens [152,153].

Exacerbations, where patients' symptoms are significantly increased beyond baseline, are characteristic of COPD [15]. Exacerbations often require hospitalization or emergency department visits and have important clinical implications [47]. Exacerbations can affect the course of COPD due to consequent structural changes in the lung that irreversibly deteriorate the airflow, which in turn adversely affect health status through various mechanisms [15]. Hence, prevention of exacerbations and their timely treatment remain a major goal in the management of COPD [15].

Pharmacological therapy is used to alleviate COPD symptoms, lessen the frequency and severity of exacerbations, enhance exercise tolerance, and improve health status [32]. Among patients with moderate to very severe COPD, inhalation therapy is the mainstay of disease management, with inhalers containing long-acting beta$_2$ agonists (LABA), long-acting muscarinic antagonists (LAMA), or inhaled corticosteroids (ICS) considered more convenient and effective than short-acting inhalers in terms of preventing exacerbations [14–17]. Prior research has demonstrated that combinations of LABA/ICS and LABA/LAMA allow for treatment optimization and are superior to either agent alone [57–62]. The US Food & Drug Administration (FDA), has approved a number of single inhaler fixed dose combination (FDC) drugs for the management of COPD [63].

Prior head-to-head clinical trials that examined the comparative effectiveness of LABA/LAMA and LABA/ICS in preventing COPD exacerbations produced mixed, inconsistent results [18]. Three trials reported that LABA/LAMA was more effective than LABA/ICS combinations in the prevention of exacerbations among patients with COPD [154–156]. Four other trials, however, reported no significant differences between LABA/LAMA and LABA/ICS combinations in terms of reducing COPD exacerbations [157–160]. The US-based Informing the Pathway of COPD Treatment (IMPACT) trial on the other hand found that the annual rate of severe exacerbations was higher in the LABA/LAMA group than the LABA/ICS group [19]. These trials differed in a number of ways including being conducted in different participating countries, various combinations of specific medications and combination types (fixed dose single inhaler versus dual inhaler), and differing lengths of follow-up. The trials also had varied inclusion and exclusion criteria, such as compulsory discontinuation of maintenance medications prior to randomization, withdrawal of ICS among patients assigned to LABA/LAMA, and inclusion of patients with an asthma component [20,21,161,162]. Moreover, the trials were not designed to examine differences in exacerbations between the groups and there is the need for studies with longer follow-up times and appropriate statistical methods and tests to enable this comparison.

In addition to clinical trials, observational studies have utilized real-world data to compare LABA/LAMA and LABA/ICS combinations in a different, more generalizable setting [20–22]. Studies by Suissa et al. and Samp et al. found that combinations of LABA/LAMA were as effective as combinations of LABA/ICS [22,163]. However, these studies were not restricted to single inhaler FDCs. In their recent study in a Taiwanese population, Wang et al. compared specific LABA/LAMA and LABA/ICS combinations and found that while some comparisons favored LABA/ICS, some comparisons favored LABA/LAMA, and other comparisons found no statistically significant difference in terms of preventing COPD exacerbations [20]. These study results highlight the need for population and setting specific studies based on available medication options.

COPD is more common in older adults than younger adults [41]. Medicare beneficiaries in this age group form a significant percentage of the US adult population [98]. They exhibit a range of distinctive characteristics, needs, and circumstances that differentiate them from the working adult population in the US, and pose a significant challenge in delivering appropriate healthcare services to Medicare beneficiaries [99]. In general, Medicare beneficiaries demonstrate poorer health status, a higher prevalence of comorbidities, lower levels of literacy, and a greater burden of chronic conditions compared to non-Medicare individuals [99]. These characteristics, coupled with their complex needs, circumstances, and reduced mobility, contribute to the difficulties involved in managing their health and navigating the complicated healthcare system [99]. The distinctiveness of older patients with COPD lies not only in the evident consequences of declining lung function but also in the consequential influence on various other organ systems and the heightened comorbidity burden they experience [100,101]. Given the unique characteristics and needs of the Medicare population, the analysis of Medicare data serves as a vital source of real-world evidence for patients, healthcare providers, decision-makers, and other stakeholders [102].

This study aimed to leverage real-world Medicare data (2013-2019) to examine the comparative effectiveness of single inhaler FDC classes LABA/LAMA versus LABA/ICS over a longer follow-up period in the management of COPD among Medicare beneficiaries aged 65 and older in the US, and to examine these results in various subgroups of interest.

Methods

Data source and study design

We used a nationally representative sample of Medicare Fee-for-Service beneficiaries in the Chronic Conditions Data Warehouse (CCW) database (2013-2019). This claims-based data source consisted of a 5% random sample of Centers for Medicare & Medicaid Services' Medicare beneficiaries for years 2013-2016 and a 20% random sample (inclusive of the 5% sample population) of Medicare beneficiaries for years 2017-2019. It contained data on Medicare beneficiaries' demographic characteristics, healthcare resource utilization, and diagnoses.

We utilized a new user, active comparator, retrospective cohort design to estimate the comparative effectiveness of single inhaler FDC maintenance medications, specifically LABA/LAMA and LABA/ICS, for mitigating the time to first exacerbation in patients with COPD.

Study cohort inclusion and exclusion criteria

This retrospective cohort study included individuals who had a diagnosis of COPD and were at least 65 years of age during the entire period of inclusion (lookback period, induction period, and follow-up period). Individuals were followed from their first prescription of a single inhaler FDC (index date) between 1st May 2014 (LABA/LAMA single inhaler FDCs first became available) and 31st December 2019. Follow-up started 30-days post index date (i.e., following a 30-day induction period). This period allowed us to observe the effect of the medication and helped avoid protopathic bias as the effect of drugs may not occur immediately following initiation [22,164–168]. Continuous enrollment in medical and pharmacy benefits in Medicare (Parts A, B, and D coverage) for at least 12 months prior to the index date (lookback period), during the 30-day induction period, and at least 1 month post the start of follow-up (after the induction period) was required. The follow-up period ended when the individual stopped being persistent on the medication class, died, lost continuous enrollment, experienced the outcome of interest, or switched to the comparator medication class or triple therapy. Persistence was defined as having a gap in days of supply less than 14 days. Individuals could change specific drug combinations as long as they were persistent in the drug class. Patients with a prior diagnosis of asthma were excluded as LABA/ICS is a preferred therapeutic option among individuals with a prior history of asthma or with asthma-COPD overlap [20–22]. Further, we also excluded individuals with lung cancer, those that used either triple therapy [20], LABA/LAMA or LABA/ICS dual inhaler therapy (defined as the prescription of both the drugs on the same day) [24,163] in the lookback period prior to the index date, had Medicare Part C coverage during the study period, experienced the outcome in the induction period or had a prescription of the medication of interest for more than 120 days of supply. The study schematic is presented in ***Figure 4***. The algorithm used to identify COPD patients is provided in ***Appendix C.***

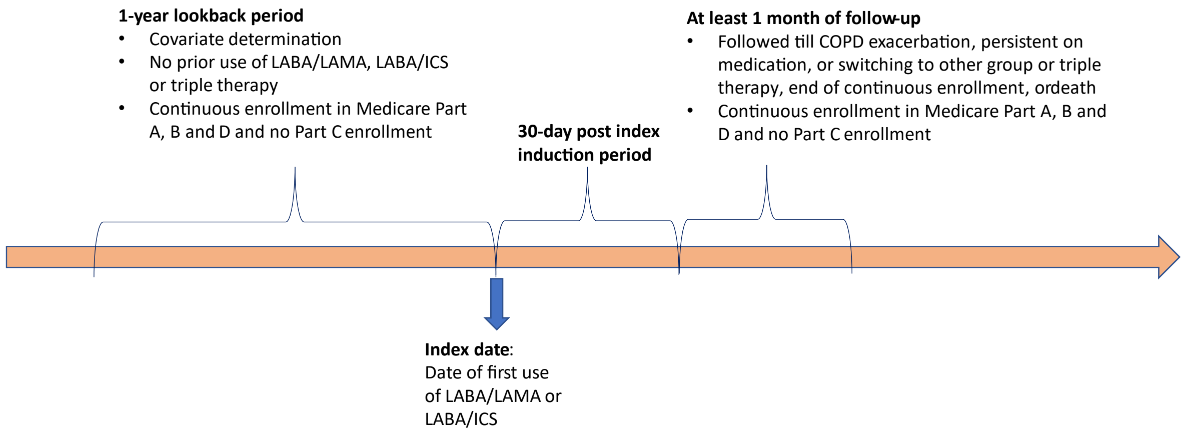


Figure 4. Study schematic

Outcomes and covariates

The outcome of interest was the time to first occurrence of a COPD exacerbation. COPD exacerbations were determined based on the presence of either an inpatient hospitalization or emergency department visit with a principal diagnosis for COPD (ICD-9 CM: 491, 492, 496; ICD-10 CM: J41-J44) [40,61].

Covariates used in the propensity score model were a combination of investigator defined covariates and empirically identified covariates determined via the high-dimensional propensity score (hdPS) algorithm developed by Schneeweiss et al. [104]. The investigator defined covariates included age, sex, race, year of index date, supplemental oxygen use in the lookback period, number of prior COPD exacerbations in the lookback period, number of prescriptions (short-acting bronchodilators, long-acting bronchodilators, and inhaled corticosteroids) in the lookback period, and prior comorbidities (breast cancer, colorectal cancer, endometrial cancer, prostate cancer, stroke/transient ischemic attack, acute myocardial infarction, chronic kidney disease, diabetes, depression, allergic rhinitis, and pneumonia). Emergency department visits for COPD exacerbations that lead to inpatient stays counted as only one exacerbation.

Statistical analysis

Descriptive statistics for the two groups were examined and reported as means for continuous variables and percentages for categorical variables. The distribution of medications used in each group and incidence rate of the first COPD exacerbation were also reported. To ensure that the groups were comparable, the two combination classes of interest were matched based on their propensity scores. The propensity scores were computed using the hdPS approach [104,169]. The hdPS approach was utilized as it makes most use of the data, and empirically identifies the covariates to adjust for in the propensity score model. The 200 most frequent codes (any position) in each of eight data dimensions of diagnosis, procedure, and prescription drug claims from various settings were identified [104,170]. The frequency of recurrence of the codes was accounted for by creating the following indicator variables: once (>=once); sporadic (>=median); and frequent (>=75th percentile). Subsequently there were a total of 4,800 empirically identified covariates (200 covariates for each dimension*8 dimensions*3 frequency codes). These covariates were prioritized using the method proposed by Bross, wherein the potential for bias is estimated based on the variable's prevalence as well as its univariate association with the treatment and outcome [104,171,172]. Based on this prioritization, the top 200 empirically identified covariates were selected to be a part of the propensity score model [104,173,174]. The propensity score was estimated using logistic multivariable regression, adjusting for the selected empirically defined as well as predefined variables and modeled for the probability of being prescribed LABA/LAMA. Based on these scores, 1:1 nearest neighbor matching was carried out with a caliper of 0.05 [169,175]. The performance of matching was evaluated using covariate balance diagnostic methods such as the standardized mean difference (SMD) for covariates between groups, and visual histogram comparisons [170,176]. An absolute SMD of 0.1 or less was used to indicate sufficient balance between the two groups [105,177]. These steps, data dimensions, and details on the implementation of hdPS have been described in more detail in ***Appendix D.***

Cox regression models were used to estimate the hazard ratio of the time to first COPD exacerbation. All analyses were performed using SAS Studio software. The level of confidence and statistical significance was determined at the 95% level.

Subgroups and sensitivity analysis

The aforementioned analysis was conducted across a number of subgroups of interest to examine potential heterogeneity of the effect in various subgroups as well as the robustness of the results. The subgroups were based on the following characteristics: (i) sex, (ii) age, (iii) history of prior COPD exacerbations, (iv) prior use of supplemental oxygen, and (v) presence of comorbid allergic rhinitis. These specific subgroups were chosen as they are basic demographic groups (sex, age), as well as important groups with regards to the management of COPD (prior exacerbation history, use of supplemental oxygen, allergic rhinitis). As a sensitivity analysis and to examine the robustness of the results, the definition of persistence was varied from a maximal permissible gap of 14 days in days of supply for the index medication class in the primary analysis to a permissible gap of (i) 0 days, (ii) 7 days, and (iii) 30 days. Additionally, we conducted a negative control analysis to evaluate the presence of unmeasured confounding. For the negative control analysis, the exact same study described above was carried out with one major change; the primary outcome event was gastroesophageal reflux disease (GERD), which is not expected to have any association with the exposure [20,178,179]. More information on the negative control analysis is provided in ***Appendix E.*** The analysis was also carried out implementing an intention-to-treat design, wherein individuals remained in the group based on the index medication regardless of discontinuation, augmentation, or switching of the index medication [180,181].

Results

The final base cohort included 49,892 individuals with COPD that were new users of either LABA/LAMA or LABA/ICS single inhaler FDCs. Of these, 13,404 were users of LABA/LAMA fixed-dose combinations. After implementing hdPS and matching the groups based on the propensity score, there were 12,912 pairs of LABA/LAMA and LABA/ICS new users. The characteristics of these groups are presented in ***Table 5.*** Prior to matching, based on the SMD, the two groups were not balanced on age (SMD: 0.105), sex (SMD: 0.107 for female), race (SMD: 0.106 for white), number long-acting bronchodilator prescriptions in the past year (SMD: 0.227), number of ICS prescriptions in the previous year (SMD: 0.115), supplemental oxygen use (SMD: 0.129), and pneumonia (SMD: 0.111). Post matching, good matching balance across all covariates was demonstrated between the groups. The propensity score overlap is presented in ***Appendix F***.

The average length of follow-up was 2.9 months, with a maximum of 67 months for the LABA/LAMA group, and 2.4 months, with a maximum of 63.9 months for the LABA/ICS group. Throughout the study period, the most frequently used LABA/LAMA combination was vilanterol/umeclidinium (80%), followed by olodaterol/tiotropium (14%), and formoterol/glycopyrrolate (6%). The corresponding most frequently used index LABA/ICS combinations were vilanterol/fluticasone (38%), followed by formoterol/budesonide (36%), and salmeterol/fluticasone (25%). The most used index LABA/LAMA combinations were vilanterol/umeclidinium (76%), olodaterol/tiotropium (15%), and formoterol/glycopyrrolate (8%), while the most frequently used index LABA/ICS drugs were formoterol/budesonide (40%), vilanterol/fluticasone (31%), and salmeterol/fluticasone (27%).

Table 5. Characteristics of study population by drug, before and after matching

	Before matching			After matching		
Variables	**LABA/LAMA (N=13,404)**	**LABA/ICS (N=36,488)**	**Standardized difference**	**LABA/LAMA (N=12,912)**	**LABA/ICS (N=12,912)**	**Standardized difference**
Age in years[1], Mean±SD	75.7±6.7	76.4±7.4	0.105	75.7±6.7	75.7±6.9	0.007
Sex: Female, n(%)	6,815 (50.8)	20,497 (56.2)	0.107	6,601 (51.1)	6,581 (51.0)	0.011
Race: Black, n(%)	608 (4.5)	2,290 (6.3)	0.077	602 (4.7)	586 (4.5)	0.004
Race: White, n(%)	11,837 (88.3)	30,900 (84.7)	0.106	11,365 (88.0)	11,398 (88.3)	0.006
Race: Other, n(%)	959 (7.2)	3,298 (9.0)	0.069	945 (7.3)	928 (7.2)	0.011
Number of COPD exacerbations[2], Mean±SD	0.4±1.1	0.3±0.9	0.094	0.4±1.1	0.4±1.0	0.023
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.6±2.0	0.2±1.1	0.227	0.5±1.7	0.4±1.7	0.024
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.5±2.9	1.4±2.8	0.031	1.4±2.9	1.4±2.9	0.005
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.115	0.2±0.9	0.2±0.8	0.001
Supplemental oxygen use[2], Mean±SD	2,489 (18.6)	5,042 (13.8)	0.129	2,322 (18.0)	2,361 (18.3)	0.001
Breast cancer[3], n(%)	686 (5.1)	1,919 (5.3)	0.006	654 (5.1)	664 (5.1)	0.005
Colorectal cancer[3], n(%)	315 (2.4)	903 (2.5)	0.008	303 (2.3)	302 (2.3)	0.001
Endometrial cancer[3], n(%)	61 (0.5)	229 (0.6)	0.024	60 (0.5)	58 (0.4)	0.005
Prostate cancer[3], n(%)	727 (5.4)	1,900 (5.2)	0.010	699 (5.4)	723 (5.6)	0.008
Stroke-Transient Ischemic attack[3], n(%)	1,331 (9.9)	4,430 (12.1)	0.071	1,285 (10.0)	1,276 (9.9)	0.006
Acute myocardial infarction[3], n(%)	526 (3.9)	1,639 (4.5)	0.028	508 (3.9)	485 (3.8)	0.000
Chronic kidney disease[3], n(%)	5,509 (41.1)	15,751 (43.2)	0.042	5,321 (41.2)	5,348 (41.4)	0.002
Diabetes[3], n(%)	4,959 (37.0)	14,847 (40.7)	0.076	4,813 (37.3)	4,803 (37.2)	0.016
Depression[3], n(%)	4,823 (36.0)	14,276 (39.1)	0.065	4,668 (36.2)	4,697 (36.4)	0.001
Allergic rhinitis[2], n(%)	1,824 (13.6)	5,824 (16.0)	0.066	1,784 (13.8)	1,759 (13.6)	0.002
Pneumonia[2], n(%)	2,554 (19.1)	8,603 (23.6)	0.111	2,489 (19.3)	2,525 (19.6)	0.007

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

The incidence rate of the first COPD exacerbation was 36.91 per 100 per year in the entire matched cohort. Individuals with LABA/LAMA had an incidence rate of 38.84 per 100 per year, while individuals with LABA/ICS had an incidence rate of 34.58 per 100 per year for a first COPD exacerbation ***(Table 6)***. This rate varied between the subgroups. The incidence rate with regards to a first COPD exacerbation was highest amongst individuals with more than one COPD exacerbation in the past year (136.36 per 100 per year among LABA/LAMA users and 134.77 per 100 per year among LABA/ICS users). Individuals with one exacerbation in the past year (54.42 per 100 per year among LABA/LAMA users and 51.12 per 100 per year among LABA/ICS user), and prior oxygen use in the preceding year (56.14 per 100 per year among LABA/LAMA users and 54.86 per 100 per year among LABA/ICS users) also had a higher incidence rate of first COPD exacerbations than the overall population. These results have been presented in ***Figure 5.***

Table 6. Hazard ratio of time to first COPD exacerbation among new users of LABA/ICS versus LABA/LAMA in patients with COPD

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	12,912	890	2,573.659	34.581	0.846 (95% Confidence interval: 0.776-0.923)
LABA/LAMA	12,912	1204	3,099.565	38.844	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.

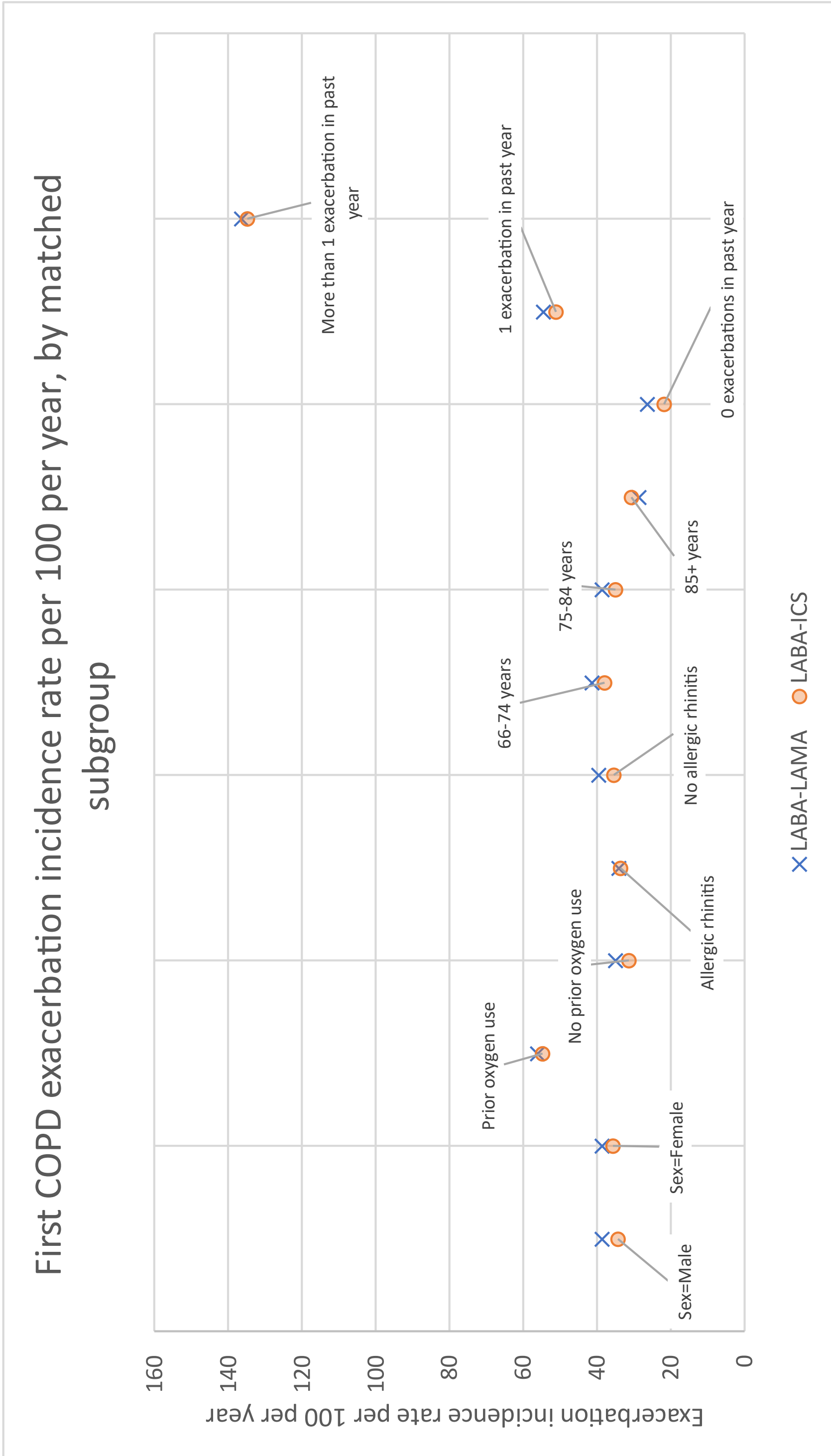


Figure 5. Exacerbation incidence rate per 100 per year, by subgroup

In the overall cohort, the hazard ratio (HR) for the first exacerbation was 0.846 (95% Confidence interval (CI): 0.776-0.923) for individuals on LABA/ICS as compared to LABA/LAMA, representing a difference of 15.4% in favor of LABA/ICS FDCs. The cumulative incidence of a first COPD exacerbation between the two groups has been depicted in ***Appendix F***. Across various subgroups this HR was statistically significantly different in the following groups: males (HR: 0.844, 95% CI: 0.745-0.957), females (HR: 0.882, 95% CI: 0.782-0.996), those with no prior oxygen use (0.855, 95% CI: 0.773-0.946), those with no allergic rhinitis (HR: 0.855, 95% CI: 0.779-0.938), individuals aged greater than 65 years and less than 75 years (0.880, 95% CI: 0.780-0.993), people aged greater than 74 years and less than 85 years (HR: 0.853, 95% CI: 0.741-0.981), and those with zero exacerbations in the past year (HR: 0.790, 95% CI: 0.698-0.895). These results are depicted in ***Figures 6 and 7.*** The complete demographic distributions, and pre- and post- matching characteristics and distribution for each of the subgroups is presented in ***Appendix F.***

The statistical significance of the overall results did not change when the persistence definition was altered to allow a maximum permissible gap of 0 days/no gap (HR: 0.900, 95% CI: 0.812-0.996), 7 days (HR: 0.861, 95% CI: 0.786-0.945), and 30 days (HR: 0.857, 95% CI: 0.791-0.928) in the days supply, demonstrating the robustness of the results to the persistence definition. The negative control analysis found that there was no statistically significant difference in the incidence of GERD between the two groups (HR: 0.955, 95% CI: 0.875-1.042) and the results are presented in ***Appendix F***. The intention-to-treat analysis cohort had an average of five times longer follow-up, but the results did not change the overall direction and statistical significance of the main analysis (HR: 0.909, 95% CI: 0.866-0.954).

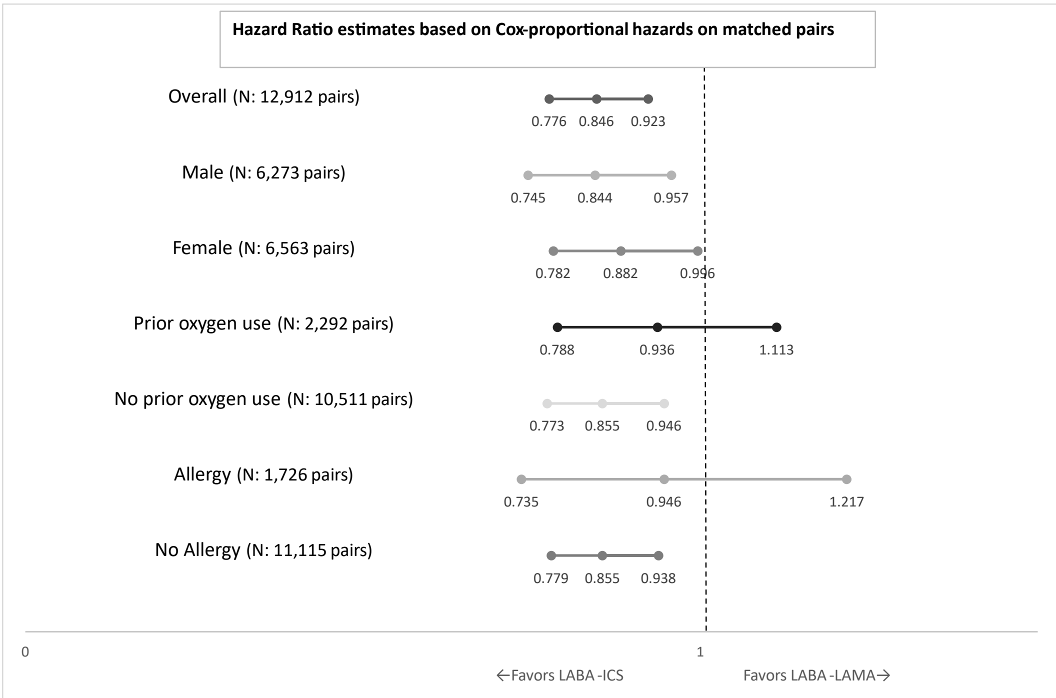


Figure 6. Hazard ratios of the time to first exacerbation between LABA/ICS and LABA/LAMA, across subgroups

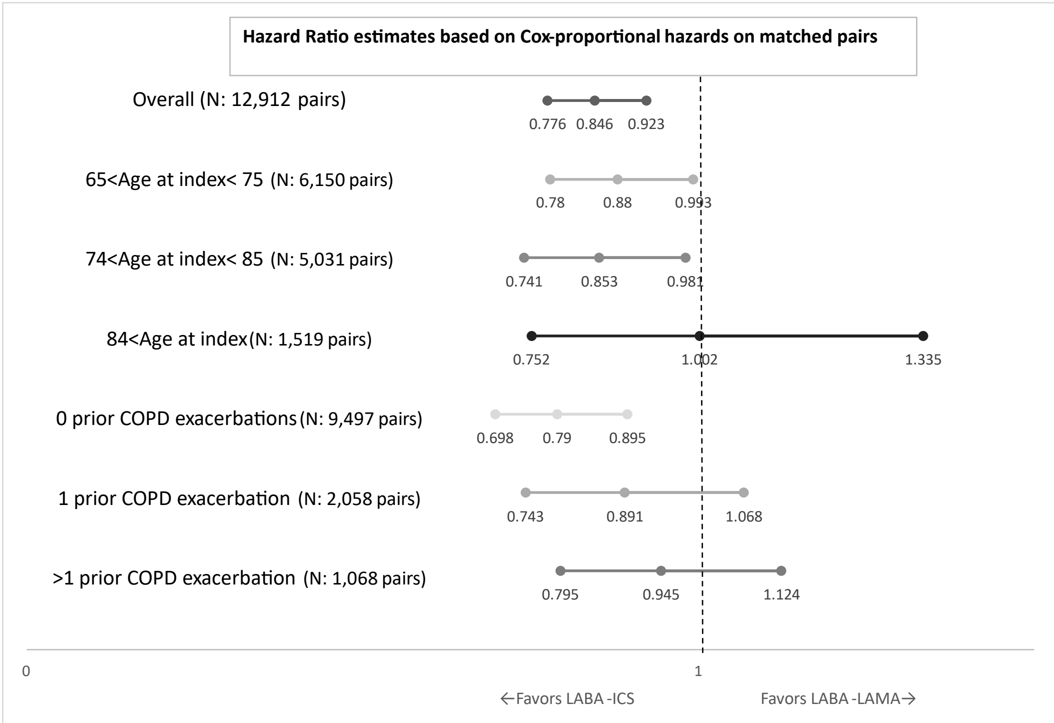


Figure 7. Hazard ratios of the time to first exacerbation between LABA/ICS and LABA/LAMA, across subgroups

Discussion

Our study found that among new users of maintenance single inhaler FDC therapies, individuals with a prior history of COPD exacerbations in the past year or supplemental oxygen use in the previous year, had the highest incidence rates of first COPD exacerbations among Medicare beneficiaries with COPD aged 65 years and older in the US. Maintenance combination therapy with LABA/ICS was more effective compared to LABA/LAMA, in terms of reducing the time to the first COPD exacerbation. These results were consistent across most subgroups.

Compared to prior clinical trials that examined the comparative effectiveness of LABA/LAMA and LABA/ICS in terms of reducing COPD exacerbations, our study results differed from the ones that found LABA/LAMA to be preferred [154–156], or there to be no differences between the drug classes [157–160]. There could be a number of potential reasons for this. All the clinical trials that found LABA/LAMA combinations to be superior to LABA/ICS combinations compared indacaterol/glycopyrronium as the LABA/LAMA combination and did not have any sites in the US [154–156]. This combination is not available in the US. The studies that found no difference between the combinations were not primarily designed to compare exacerbations between the two drug classes, had limited follow-up periods (6 to 24 weeks), only one had sites based in the US [158], and only two had drug combinations that are available in the US [158,159]. Inclusion and exclusion criteria, combinations of specific medications, combination types (fixed dose single inhaler versus dual inhaler), participating nations, and design choices also varied significantly between the studies. Our findings were in line with the findings from the IMPACT trial, but they only found LABA/ICS to be marginally better than LABA/LAMA and did not compare these combinations directly statistically [19]. The IMPACT trial was based in the US, but it also included individuals with asthma and like the aforementioned studies, had a limited follow-up period and sample size. The Cochrane airways group in their recent systematic review and meta-analysis of RCTs found that in terms of preventing exacerbations, LABA/LAMA and LABA/ICS were similar [23]. However, when subgroups were compared based on the specific drug used, the comparison between vilanterol/umeclidinium and LABA/ICS found that LABA/ICS was favorable in terms of preventing exacerbations. This is in line with the findings from this study where more than three-fourths of the sample used vilanterol/umeclidinium. The comparison between indacaterol/glycopyrronium and LABA/ICS favored the former in the aforementioned study.

A major challenge with the results from RCTs is their limited external validity. Travers et al. found that less than 10% of COPD patients in the community would be eligible to participate in the major COPD trials that inform clinical guidelines, and this number is probably even lesser in an older Medicare population [29]. Clinical trials are the gold standard of evidence, however observational studies can help complement them and provide information that is more generalizable and leverage real-world utilization data to expand our understanding of these drugs.

Observational studies have employed real-world data to assess the effectiveness of LABA/LAMA and LABA/ICS combinations in a broader and more representative setting [20–22]. Studies by Suissa et al. and Samp et al. found that combinations of LABA/LAMA were as effective as combinations of LABA/ICS [22,163]. However, the studies were not restricted to single inhaler FDCs. The study by Suissa et al. was based in the United Kingdom and examined only tiotropium-based LABA/LAMA inhalers. Tiotropium-based LABA/LAMA FDC inhalers formed a small proportion of the inhalers used in the US. Wang et al. used Taiwanese population data and found that while some comparisons favored LABA/ICS (indacaterol/glycopyrronium over formoterol fumarate/budesonide), some favored LABA/LAMA (vilanterol/umeclidinium over salmeterol/fluticasone), and others found no statistically significant difference (comparisons between indacaterol/glycopyrronium and salmeterol/fluticasone, vilanterol/umeclidinium and formoterol fumarate/budesonide, indacaterol/glycopyrronium and formoterol fumarate/beclomethasone dipropionate, vilanterol/umeclidinium and formoterol fumarate/beclomethasone dipropionate) in terms of reducing the time to the first COPD exacerbation post drug use. These findings emphasize the importance of conducting studies that are tailored to the population, combination, and setting under investigation, based on the medication alternatives that are currently accessible.

The overall result where LABA/ICS was more effective at reducing the time to first exacerbation among COPD patients, remained consistent across sex in the subgroup analyses. This benefit however was no longer statistically significant among individuals with prior oxygen use, comorbid allergic rhinitis, or any prior exacerbation in the past year. In all these subgroups the point estimates still favored LABA/ICS, but partly due to the smaller sample sizes, the confidence intervals were much larger and no longer statistically significant. One important takeaway from the subgroup analysis was that among individuals with a prior history of exacerbations, the comparative benefit of LABA/ICS over LABA/LAMA reduced as the number of prior exacerbations increased. This result highlighted that the main goal in the management of COPD should to prevent exacerbations from occurring in the first place, and the interventions to better manage COPD should target preventing the first exacerbation.

The overall results did not change upon varying the definition of persistence. The negative control analysis that found no statistically significant difference between the groups in terms of experiencing the negative control outcome of GERD, helped reduce the concerns of unmeasured confounding, though it cannot be completely ruled out.

Our study adds to the literature in several ways as it allowed us to compare these maintenance medications dispensed by single inhaler devices in a more generalizable population over a longer follow-up time, using combinations that are available in the US, and have very limited prior evidence. Further, we compared these medications in an older and growing Medicare population, which differs considerably from the populations used in previous studies. We also had a large sample size compared to prior trials. We explored the comparative effectiveness across various clinically important subgroups. This study is subject to several limitations. Given that the study was restricted to individuals that were new users and persistent, the representativeness of the population may be affected. Further, as with other claims-based data sources, it is not possible to ensure that the prescribed medications were consumed or even administered correctly. We were not able to adjust for prior smoking status and other clinical measures such as forced expiratory volume in 1 second (FEV_1) readings and eosinophil counts as this information was not available. Future research should aim to expand on this work especially by comparing these drugs in more subgroups in order to identify potential avenues in COPD management that could benefit from personalized medicine. The comparative effectiveness of the specific FDCs within a drug class should be further examined in future research.

Conclusion

Our study examined the comparative effectiveness of LABA/LAMA and LABA/ICS single inhaler FDCs in the Medicare population in the US using a new user, retrospective cohort study design. We found that LABA/ICS combinations were more effective at reducing the time to first exacerbation compared to the LABA/LAMA combinations. However, future research should aim to further expand this work by comparing individual drug combinations in these classes against one another and examine the comparisons across more subgroups and settings that may contain clinical readings and measures.

5. CHAPTER 5: Comparative effectiveness of olodaterol/tiotropium and vilanterol/umeclidinium among COPD patients: A high-dimensional propensity score matched new user cohort study in a US Medicare population

Abstract

Introduction

Two long-acting muscarinic antagonist inhaler fixed dose combinations, olodaterol/tiotropium (OLO/TIO) and vilanterol/umeclidinium (VI/ UMEC), have once-a-day dosing for managing chronic obstructive pulmonary disease (COPD). Each, however, in addition to having different ingredients, has a different drug delivery mechanism; OLO/TIO uses the newer soft mist inhaler, while VI/UMEC uses the dry powder inhaler. This study aimed to compare these inhalers in terms of ability to prevent COPD exacerbations over a longer follow-up in a United States (US) Medicare population.

Methods

We employed a new user, active comparator design using a nationally representative sample of Medicare Fee-for-Service beneficiaries aged 65 years and above with a diagnosis of COPD. The outcome of interest was duration to first occurrence of a COPD exacerbation. To ensure comparability between the groups, we performed 1:3 (VI/UMEC:OLO/TIO) nearest neighbor matching based on their high-dimensional propensity scores.

Results

The study included 2,263 initiators of OLO/TIO matched to 6,789 VI/UMEC initiators. The incidence rate of the first COPD exacerbation was 40.8 per 100 per year (39.9 per 100 per year among OLO/TIO initiators and 41.1 per 100 per year among VI/UMEC initiators). The adjusted hazard ratio of the time to first COPD exacerbation was 0.948 (95% Confidence interval: 0.813-1.105) for individuals initiating OLO/TIO versus those initiating VI/UMEC.

Conclusion

We found that there was no statistically significant difference between the two groups, OLO/TIO and VI/UMEC, in terms of reducing the time to first exacerbation among COPD patients aged 65 years and older on Medicare in the US.

Introduction

Chronic obstructive pulmonary disease is (COPD) is a chronic respiratory disorder that progresses gradually and is distinguished by its obstructive ventilatory pattern, potentially leading to chronic respiratory failure [30]. COPD is a leading cause of morbidity and mortality, with consequent detrimental impacts on physical health and mental wellbeing [5,35,150,151]. COPD is more prevalent in older adults than younger adults [41].

The major therapeutic goal in management of COPD among patients with moderate to very severe COPD is reduction of exacerbations [32]. Pharmacotherapy, especially the use of long-acting maintenance inhalation therapy, is the cornerstone of COPD disease management [182]. In recent years, a variety of long-acting fixed dose combination (FDC) options have become available for maintenance therapy. Combinations containing a long-acting $beta_2$ agonist (LABA) and a long-acting muscarinic antagonist (LAMA), due to synergistic effects have been shown to improve patient outcomes over monotherapy containing only LABA or LAMA, in addition to simplifying treatment regimens, thereby increasing patient adherence [183,184].

There are several long-acting FDC $beta_2$ agonist and muscarinic antagonist (LABA/LAMA) inhalers available in the United States (US) (***Appendix G***) [66]. Of these FDC LABA/LAMA inhalers, only two inhaler combinations, olodaterol/tiotropium (OLO/TIO) and vilanterol/umeclidinium (VI/UMEC), have once-a-day dosing. Each, however, in addition to having different ingredients, has different drug delivery mechanisms; OLO/TIO uses the newer soft mist inhaler (SMI), while VI/UMEC uses a dry powder inhaler (DPI). These different delivery mechanisms have distinct characteristics that could affect drug administration and adherence, which in turn can affect outcomes such as quality-of-life, number of healthcare visits, and exacerbations [72,185,186]. While most treatment guidelines direct healthcare providers towards a class of medication, scant guidance on specific combinations to use is available. Consequently, there remains substantial uncertainty with regards to the choice of medications, especially between the most widely used LABA/LAMA combinations in the US: OLO/TIO and VI/UMEC. A major reason for this lack of direction is the paucity of evidence to inform guidelines [26,27]. Given that each of these options has a unique efficacy and safety profile, there exists a potential for personalized COPD management [27].

Most current literature on FDC therapies, specifically OLO/TIO and VI/UMEC, is focused on comparisons with either placebo or monotherapy [95,187–189]. However, even these trials were not designed to evaluate the long-term risk of COPD exacerbations [190]. In terms of direct or indirect comparisons between VI/UMEC and OLO/TIO there have been very few studies. To compensate for the lack of trials comparing these drugs, researchers have employed systematic reviews and network meta-analyses to address this gap [191–195]. The recent systematic review by Fukuda et al., as a part of the Cochrane airways group, found that though the overall results showed that LABA/LAMA and LABA/inhaler corticosteroid (ICS) were similar in terms of preventing exacerbations, the results varied based on the specific LABA/LAMA drug compared [23]. Since systematic reviews and meta-analyses are only as reliable and informative as the information available, they too are hampered by the limitations of the contributing trials.

In addition to lack of information on comparisons between these inhalers directly from clinical trials, and indirectly through systematic reviews and network meta-analyses, there also is a lack of evidence from observational studies. Even the trials that reported COPD exacerbations either were not designed to examine them as an outcome, or had a limited duration of follow-up, most often both. Further, as Calzetta et al. pointed out, it is unlikely that these longer duration head-to-head trials will be carried out given the costs associated with them as well as the lack of interest on part of the manufacturers due to the potential that the results may be unfavorable to them [191]. Since heterogeneities of effect may exist, and the fact that the trials were restricted to short follow-up periods for medications that are intended to be used as maintenance therapy over a longer period, there is a need to examine this comparison in the population of interest.

The Medicare population, especially patients with COPD, exhibits several unique characteristics that distinguish it from other populations. Medicare beneficiaries are predominantly aged 65 years and over and the prevalence of COPD has been shown to increase with age [196]. Individuals with COPD have a substantial comorbidity burden, and this burden is even greater among older individuals on Medicare, further complicating care [35,100,197,198]. In a nutshell, Medicare beneficiaries have poorer health status, more comorbidities, lower literacy levels, reduced mobility, and suffer from more chronic conditions compared to their non-Medicare counterparts, thereby making them unique [99].

Observational studies provide a great opportunity to compare specific LABA/LAMA combinations with different ingredients and distinct mechanisms of delivery. This study aimed to compare once-a-day single inhaler LABA/LAMA FDCs delivered by a SMI (OLO/TIO) against those delivered through a DPI (VI/UMEC) in terms of ability to prevent COPD exacerbations over a longer follow-up in a US Medicare population.

Methods

Data source and study design

A nationally representative sample of Medicare Fee-for-Service beneficiaries was obtained from the Chronic Conditions Data Warehouse (CCW) database (2013-2019). This dataset was provided by the Centers for Medicare & Medicaid Services (CMS) and consists of a 5% random sample of Medicare beneficiaries for years 2013-2016 and a 20% random sample (inclusive of the 5% sample population) of Medicare beneficiaries for years 2017-2019. Information on demographic characteristics, healthcare utilization, and diagnoses related to Medicare beneficiaries was available in this dataset.

We employed a new user, active comparator retrospective cohort study design and compared two different FDC single inhaler LABA/LAMA maintenance therapies (VI/UMEC and OLO/TIO) that dispense different medications through distinct mechanisms (soft-mist inhaler and dry powder inhaler) and are comprised of different therapeutic drugs.

Study cohort inclusion and exclusion criteria

The study cohort included individuals with a diagnosis of COPD that were aged 65 years and older for the entire study duration, including the one-year lookback period. The index date was the date of first prescription of a LABA/LAMA single inhaler FDC (OLO/TIO or VI/UMEC). The study period was from 1st May 2014 to 31st December 2019, based on when the LABA/LAMA single inhaler FDCs first became available in the US. In order to avoid protopathic bias, where a drug is initiated in response to early symptoms, and allow us to observe the effect of the drugs of interest, the follow-up period started 30 days after the index date [22,164–168]. To be eligible for inclusion in the cohort, continuous enrollment in pharmacy and medical benefits in Medicare (Parts A, B, and D coverage) for at least 12 months prior to index date (lookback period), during the 30-day induction period, and at least 1 month post the start of follow-up was necessary. Follow-up ended when the patient stopped being persistent on the medication, died, lost continuous enrollment, experienced a COPD exacerbation that resulted in healthcare utilization, added ICS to their regimen, switched to a LABA/ICS FDC, switched to a LABA/LAMA FDC besides the index medication, switched to LABA/LAMA dual inhaler therapy (defined as being dispensed both a LABA and LAMA medication on the same day), or initiated triple therapy. A gap in days of supply less than 14 days was used to define medication persistence.

Patients with a prior diagnosis of asthma, or lung cancer were excluded from the study cohort. Further, individuals that used either triple therapy, LABA/LAMA dual inhaler therapy (defined as the prescription of both the drugs on the same day), or a LABA/LAMA single inhaler FDC in the lookback period were excluded [24,163].

Individuals that had Medicare Part C coverage during the study period, experienced a COPD exacerbation in the induction period, or had a prescription of the medication of interest for more than 120 days of supply were also excluded. The algorithm used to identify COPD patients is presented in ***Appendix C.*** The study design is schematically illustrated in ***Figure 8***.

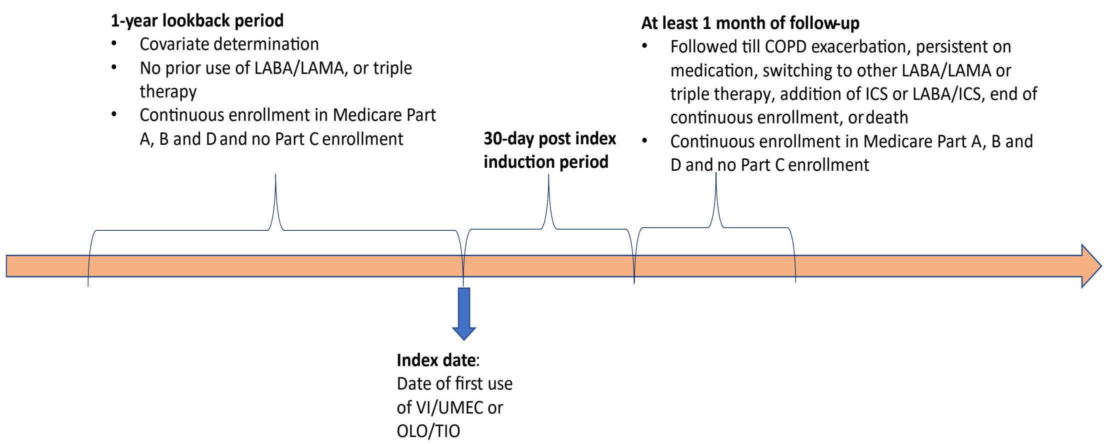


Figure 8. Study schematic

Outcomes and covariates

The outcome examined in this study was time to first COPD exacerbation following use of OLO/TIO or VI/UMEC FDCs. COPD exacerbations are defined as the presence of either an inpatient hospitalization or emergency department visit with a principal diagnosis for COPD (International Classification of Diseases (Ninth Revision)-Clinical Modification codes: 491,492, 496; International Classification of Diseases (Tenth Revision)-Clinical Modification codes: J41-J44) [40,61].

Covariates included in the propensity score model were investigator defined covariates and empirically identified covariates, with the latter being determined via the high-dimensional propensity score (hdPS) algorithm developed by Schneeweiss et al. [104]. Investigator defined covariates included age, sex, race, year of index date, supplemental oxygen use in the lookback period, number of prior COPD exacerbations in the lookback period, number of prescriptions (short-acting bronchodilators, long-acting bronchodilators, inhaled corticosteroids, and LABA/ICS maintenance medications) in the lookback period, and prior comorbidities (breast cancer, colorectal cancer, endometrial cancer, prostate cancer, stroke/transient ischemic attack, acute myocardial infarction, chronic kidney disease, diabetes, depression, allergic rhinitis, and pneumonia). To avoid double counting, if an emergency department visit for a COPD exacerbation led to an inpatient stay, it counted as only one exacerbation.

Statistical analysis

Baseline characteristics of initiators of OLO/TIO and VI/UMEC were presented as percentages for categorical variables and means for continuous variables. The relative distribution of these two medications by year, and incidence rate of the first COPD exacerbation were also reported. Propensity scores estimate the conditional probability of receiving a treatment, contingent on a number of observed covariates [199,200]. These scores have been widely used in epidemiological research to adjust for potential confounding. In this study, we matched the two groups based on the propensity scores modeled on the probability of being prescribed OLO/TIO and estimated via the hdPS approach, as this method allows researchers to combine investigator-defined covariates with empirically-identified, data-driven covariates [104,169]. Thus, this method allowed us to optimally use all the data available.

To identify the data-driven covariates, the 200 most frequent codes in each of eight data dimensions of diagnosis, procedure, and prescription claims from various settings were identified. Recurrence of the codes and their frequency was accounted for by creating the following indicator variables: once (>=once); sporadic (>=median); and frequent (>=75th percentile). This resulted in a total of 4,800 empirically identified covariates (200 covariates for each dimension*8 dimensions*3 frequency codes). The method proposed by Bross, which estimates the potential for bias based on the variable's prevalence as well as its univariate association with the treatment and outcome, was used to prioritize the covariates [104,171,172]. The top 200 covariates were empirically identified to be a part of the propensity score model [104,173,174]. The model used to estimate the propensity score was a logistic multivariable regression that adjusted for the selected empirical as well as predefined variables. Matching was implemented using the 1:3 nearest neighbor matching approach. A caliper of 0.05 was utilized to facilitate the matching [169,175]. Standardized mean differences (SMD) were reported for covariates between groups, and a histogram of the propensity score distribution was visually inspected before and after matching to evaluate the degree of balance between the groups. An absolute SMD of 0.1 or less indicated sufficient balance between the two groups [105,177]. More details on the implementation of hdPS have been outlined in ***Appendix D.***

Hazard ratios of the time to first COPD exacerbation were estimated using Cox regression models. To examine the sensitivity of the results to the definition of persistence, the definition was altered from a maximum permissible gap of 14 days in days of supply for the index medication in the main analysis to a maximal permissible gap of (i) 0 days, (ii) 7 days, and (iii) 30 days. To evaluate the presence of unmeasured confounding, we conducted a negative control analysis. For the negative control analysis, the study design criteria mentioned above were utilized with one major alteration; the outcome of interest was changed to gastroesophageal reflux disease (GERD), for which no association is expected with the exposure [20,178,179]. More information on the negative control analysis is provided in ***Appendix E.*** An intention-to-treat design, wherein individuals remained in the group based on the index medication regardless of discontinuation, augmentation, or switching of the index medication was carried out as a sensitivity analysis [180,181]. All analyses were carried out using SAS Studio software. The level of confidence and statistical significance was determined at the 95% level.

Results

The study cohort included a total of 16,072 new initiators of LABA/LAMA (OLO/TIO or VI/UMEC) with a diagnosis of COPD. 2,739 were new OLO/TIO users and 13,333 were new VI/UMEC users. Post-matching, there were 2,263 users of OLO/TIO and 6,789 users of VI/UMEC. Both groups had similar mean age (76 years) and evenly distributed sex. Initiators of VI/UMEC had a higher proportion of supplemental oxygen use and a greater number of prescriptions for long-acting bronchodilators in the one-year lookback period, pre-matching. Post-matching, the groups were balanced on all covariates. The pre- and post-matching characteristics of these individuals, stratified by the index drug, have been presented in ***Table** 7*. The graphical representation of the propensity score distribution before and after matching is provided in ***Appendix H.***

Among the initiators of OLO/TIO and VI/UMEC, the percentage of VI/UMEC initiators changed from 100% in 2014 to 85% in 2015 and 74% in 2016 following the introduction of OLO/TIO. Since 2017 there has been a steady rise in the percentage of VI/UMEC initiators from 78% in 2017 to 85% in 2019. The distribution of new drug initiation in the pre-matched cohort has been presented in ***Figure 9***. The length of follow-up in the matched groups was an average of 2.8 months (maximum: 43.6 months) for OLO/TIO initiators and 3.1 months (maximum: 67 months) for VI/UMEC initiators.

The incidence rate of the first COPD exacerbation was 40.8 per 100 per year (39.9 per 100 per year among OLO/TIO initiators and 41.1 per 100 per year among VI/UMEC initiators). The adjusted hazard ratio (HR) of the time to first COPD exacerbation was 0.948 (95% Confidence interval (CI): 0.813-1.105) for individuals initiating OLO/TIO versus those initiating VI/UMEC. The main results have been presented in ***Table 8*** and the corresponding cumulative incidence curves for the comparators have been presented in ***Appendix H***.

Table 7. Characteristics of study population by drug, before and after matching

	Before matching			After matching		
Variables	**OLO/TIO (N=2,739)**	**VI/UMEC (N=13,333)**	**Standardized difference**	**OLO/TIO (N=2,263)**	**VI/UMEC (N=6,789)**	**Standardized difference**
Age in years[1], Mean±SD	75.5±6.5	75.7±6.7	0.027	75.6±6.6	75.6±6.7	0.009
Sex: Female, n(%)	1,346 (49.1)	6,851 (51.4)	0.026	1,141 (50.4)	3,429 (50.5)	0.002
Race: Black, n(%)	93 (3.4)	638 (4.8)	0.045	86 (3.8)	269 (4.0)	0.008
Race: White, n(%)	2,474 (90.3)	11,778 (88.3)	0.070	2,028 (89.6)	6,067 (89.4)	0.008
Race: Other, n(%)	172 (6.3)	917 (6.9)	0.064	149 (6.6)	453 (6.7)	0.004
Number of COPD exacerbations[2], Mean±SD	0.6±1.3	0.5±1.2	0.045	0.5±1.2	0.5±1.2	0.006
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	1.6±3.0	1.0±2.5	0.204	1.1±2.4	1.0±2.5	0.024
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.8±3.3	1.6±3.0	0.070	1.6±3.1	1.6±3.0	0.005
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.4±1.1	0.4±1.2	0.006	0.4±1.1	0.4±1.2	0.011
Number of prescriptions for LABA/ICS[2], Mean±SD	0.8±2.1	0.9±2.2	0.026	0.8±2.2	0.8±2.1	0.019
Supplemental oxygen use[2], Mean±SD	664 (24.2)	2,692 (20.2)	0.227	479 (21.2)	1,386 (20.4)	0.019
Breast cancer[3], n(%)	132 (4.8)	656 (4.9)	0.098	112 (4.9)	330 (4.9)	0.004
Colorectal cancer[3], n(%)	56 (2.0)	318 (2.4)	0.005	51 (2.3)	154 (2.3)	0.001
Endometrial cancer[3], n(%)	7 (0.3)	68 (0.5)	0.023	7 (0.3)	20 (0.3)	0.003
Prostate cancer[3], n(%)	164 (6.0)	710 (5.3)	0.041	124 (5.5)	393 (5.8)	0.013
Stroke-Transient Ischemic attack[3], n(%)	233 (8.5)	1,328 (10.0)	0.029	211 (9.3)	624 (9.2)	0.005
Acute myocardial infarction[3], n(%)	102 (3.7)	531 (4.0)	0.050	81 (3.6)	257 (3.8)	0.011
Chronic kidney disease[3], n(%)	1,046 (38.2)	5,499 (41.2)	0.013	879 (38.8)	2,633 (38.8)	0.001
Diabetes[3], n(%)	949 (34.6)	4,900 (36.8)	0.062	793 (35.0)	2,387 (35.2)	0.002
Depression[3], n(%)	949 (34.6)	4,859 (36.4)	0.044	794 (35.1)	2,370 (34.9)	0.004
Allergic rhinitis[2], n(%)	419 (15.3)	1,812 (13.6)	0.038	325 (14.4)	951 (14.0)	0.010
Pneumonia[2], n(%)	546 (19.9)	2,658 (19.9)	0.049	431 (19.0)	1,309 (19.3)	0.006

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information; LABA/ICS: Long-acting $Beta_2$-agonist/Inhaled corticosteroid combination

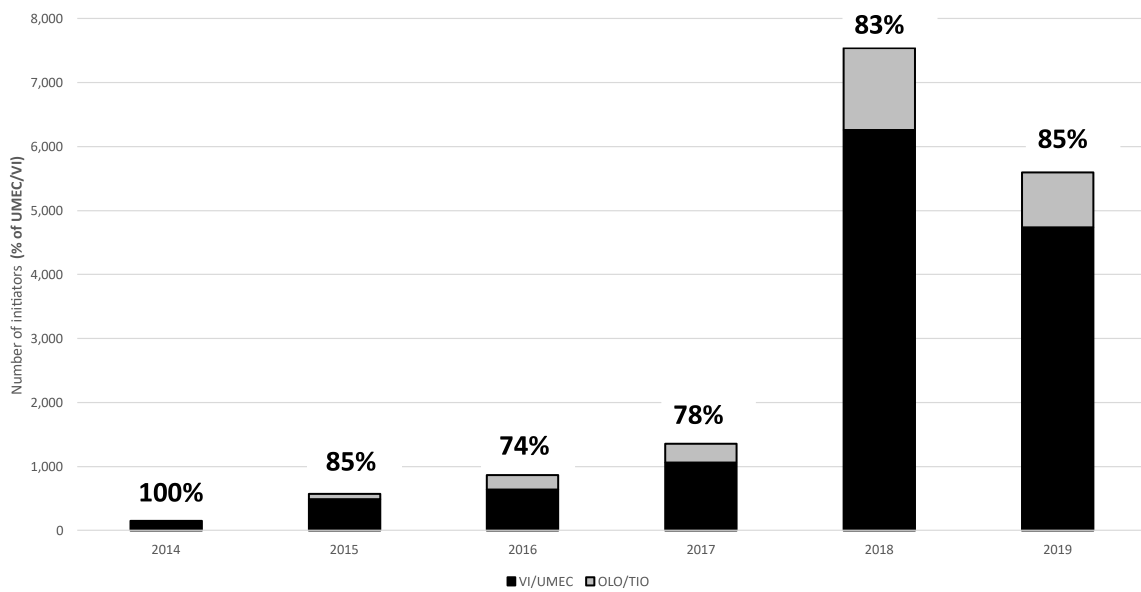


Figure 9. Proportion of OLO/TIO and VI/UMEC new initiation by year

Table 8. Hazard ratio of time to first COPD exacerbations among new users of OLO/TIO versus VI/UMEC in patients with COPD

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
OLO/TIO	2,263	211	528.6	39.916	0.948 (95% Confidence interval: 0.813-1.105)
VI/UMEC	6,789	717	1,746.1	41.063	1 (Reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.

The results were not sensitive to the definition of persistence and changing this definition did not change the statistical significance of the results. When the maximal permissible gap in days of supply was increased to 30 days, the HR of the time to first COPD exacerbation for OLO/TIO versus VI/UMEC was 0.940 (95% CI: 0.813-1.086). When the maximum permissible gap was decreased, the corresponding HRs were 0.947

(95% CI: 0.802-1.117) when decreased to a gap of 7 days and 0.964 (95% CI: 0.797-1.165) when decreased to a gap of 0 days for OLO/TIO versus VI/UMEC. The negative control analysis found no statistically significant difference between the two groups for incidence of GERD, among these patients (HR: 1.055, 95% CI: 0.903-1.233 for OLO/TIO versus VI/UMEC). The results of the intention-to-treat analysis did not differ from the overall conclusion of the main analysis (HR: 0.987, 95% CI: 0.902-1.081), but the follow-up period was four times longer compared to the main, as-treated analysis.

Discussion

Among COPD patients aged 65 and greater and on Medicare in the US, we found the percentage of VI/UMEC initiators was 85% of once-a-day FDC inhaler initiators. The OLO/TIO and VI/UMEC drug combinations belong to the same long-acting maintenance medication class of LABA/LAMA but operate through different mechanisms of delivery. VI/UMEC utilizes DPI and OLO/TIO uses SMI. Among these new initiators, there was no statistically significant difference between OLO/TIO and VI/UMEC in terms of reducing the time to first exacerbation.

Prior work has examined the effectiveness of OLO/TIO and VI/UMEC in terms of preventing COPD exacerbations. The clinical trials are mainly restricted to comparison of the FDCs against placebo or monotherapy. Buhl et al. in their 52-week two replicate, randomized, double-blind, parallel-group, multicenter, phase III trials (TOnado 1 and 2) found that there was a reduction in exacerbations with OLO/TIO versus the monotherapy components [189]. In the 2013 24-week, double-blind, placebo-controlled, parallel-group study, Donohue et al. examined the efficacy and safety of once-daily, inhaled VI/UMEC in patients with COPD [187]. They found that VI/UMEC was associated with a lower risk of COPD exacerbations than placebo. In the study by Donohue et al. in 2014, the safety and tolerability of once-daily VI/UMEC was compared against placebo in a 52-week, randomized, double-blind, placebo-controlled study [188]. Unsurprisingly, the medication was better at reducing COPD exacerbation than placebo. These previous studies were not designed to evaluate the long-term risk of COPD exacerbations, and additional studies are needed to evaluate the effectiveness in reducing exacerbations, especially against an active comparator. Calverley et al. in their 52-week double-blind, randomized, parallel-group, active-controlled trial (DYNAGITO) compared the combination OLO/TIO versus tiotropium alone [95]. Their findings suggested that the reduction in exacerbation rates was smaller than anticipated and failed to reach the planned level of significance. However, there were subgroups of patients that showed large improvements. This further highlights the need for studies in population that may be of interest and vastly different from the populations used in clinical trials, such as the population of Medicare beneficiaries in the US.

In their post hoc analysis of an eight-week, randomized, open-label, assessor-blind, two-period crossover study [190], Navarrete et al. found that the incidence of exacerbations was low and similar between VI/UMEC and OLO/TIO [201]. However, there is a need for long-term studies to assess differences between the two groups in terms of the COPD exacerbations. Schluter et al. in their systematic review and meta-analysis found that there were non-significant differences in terms of exacerbations across the LABA/LAMA combination treatment comparisons [192]. The Tiotropium

Respimat Inhaler and the Risk of Death in COPD (TIOSPIR) trial found similar safety and exacerbations efficacy profiles between DPI and SMI inhalers. These findings are in line with the results of our study. On the other hand, Lee et al. in their systematic review and Bayesian network meta-analysis found that VI/UMEC was significantly superior to OLO/TIO in terms of reducing the number of total exacerbations [195]. The studies by Schluter et al. and Lee et al. included trials that were not designed to evaluate COPD exacerbations.

Our study adds to the current knowledge base on several fronts. It compared the two most widely used LABA/LAMA maintenance medications in a US-based Medicare population using real-world data. Head-to-head trials are unlikely to be carried out comparing these drugs due to the costs associated with them and the uncertainty of results [191]. Further, this study overcomes the limitation of prior clinical studies and meta-analysis that have been hindered by limited length of follow-up as well as being based on trials not designed to compare these drugs in terms of COPD exacerbations. However, this study is an observational study based on claims data and thereby is not immune to the limitations inherent to these types of studies. While drug claims are a great source of information on medications that have been prescribed and dispensed, they are not able to provide information on whether medications were consumed correctly, if consumed at all. Further, we were not able to account for clinical information such as forced expiratory volume in 1 second (FEV_1) values and blood eosinophil counts, and also restricted our study cohort to new users of the medications while they were persistent on their medications. The latter may limit the representativeness of the results. Based on this study, it would not be possible to disentangle the effects of the different mechanisms of delivery from the different drug combinations. Future research should look to evaluate this comparison in other populations. Given that generic options are not available, and that previous research has found cost-effectiveness differences outside US [202], addition of a cost-element into this comparison in the form of a cost-effectiveness study can also potentially help with comparing these drugs on multiple criteria.

Conclusion

Our study examined the comparative effectiveness of once-daily FDC LABA/LAMA inhalers of VI/UMEC and OLO/TIO that operate through different mechanisms of action in terms of reducing the time to first COPD exacerbation. We found that there was no statistically significant difference between the two groups, OLO/TIO and VI/UMEC, in terms of reducing the time to first exacerbation among COPD patients aged 65 years and older and on Medicare in the US. Future studies should aim to expand on this work, in different populations and settings.

6. CHAPTER 6: Summary, Implications, and Future direction

Summary

We quantified the economic burden of COPD in the US using nationally representative data. We found that there was a significant increase in the cost of COPD management over the past few years, and a key driver of this increased cost was prescription drugs. A shift in the management of COPD was also demonstrated, compared to prior, comparable research. While prescription drug costs rose multifold, inpatient spending on COPD fell. This change was indicative of a change in the way COPD is managed. At the same time, there was an increase in the out-of-pocket burden on patients, especially for drugs used to manage COPD. These costs remain high and continue to be a barrier for filling prescription drugs and maintaining adherence, especially among socioeconomically deprived patients.

We also examined the comparative effectiveness of maintenance inhaler medication FDCs of LABA/ICS and LABA/LAMA in an older Medicare population. This population is unique in many ways, especially given the increased comorbidity burden among older patients with COPD. We found that prior COPD exacerbations and supplemental oxygen use were associated with increased incidence rates of COPD exacerbations. We also found that among these COPD patients, initiation of LABA/ICS led to a statistically significant reduction in the time to a COPD exacerbation. This result remained largely consistent across the various subgroups examined.

Clinical guidelines provide scant direction with regards to the choice of a combination medication within a class. We examined the comparative effectiveness of

LABA/LAMA FDC combinations of VI/UMEC and OLO/TIO single inhaler FDCs in a Medicare population with COPD. We found no statistically significant difference between the combinations in terms of preventing COPD exacerbations. In addition to having different pharmacological components, these combinations have different mechanisms of delivery; VI/UMEC uses a DPI while OLO/TIO uses a SMI mode of delivery.

Implications

The updated estimates of COPD's economic burden have critical implications for interventions aimed at better managing the disease and reducing expenses. By understanding the economic impact, policymakers and healthcare providers can allocate resources effectively and design targeted interventions to optimize COPD management practices. These findings provide a basis for evaluating the cost-effectiveness of various interventions, such as early detection programs, smoking cessation initiatives, and improved access to affordable treatments. Changes in COPD management practices and associated costs can significantly influence decision-making processes for various stakeholders, including policymakers, healthcare providers, patients, and other relevant parties. Our study results offer valuable guidance for these stakeholders, helping them make informed decisions regarding resource allocation, policy development, and identification of areas where cost reductions are feasible. Informed decision-making can lead to improved patient care, enhanced policy effectiveness, and optimized healthcare resource utilization.

There exists a lot of contrasting evidence around the choice of FDC single inhaler combination medication class. Studies differ by type (RCTs, observational studies, systematic reviews, and meta-analyses), location of conduct, medications included, inclusion and exclusion criteria, etc. These all contribute to the heterogeneity of the results. Thus, there is a need for population specific comparisons between available treatment options in the population of interest. This study was carried out in a sample of Medicare beneficiaries, and this population generally consists of vulnerable older adults with an increased burden of comorbidities. They represent a significant proportion of the aging US population, and these results can provide guidance on the choice of maintenance medications. Further we identified subgroups that experienced an increased incidence rate of exacerbations and could benefit from targeted interventions. The results from this dissertation could help guide therapy choices and optimize the management of COPD, especially among Medicare beneficiaries in the US.

The choice of a specific medication among a class of maintenance medications can help take a step closer to optimizing disease management through the implementation of personalized medicine. In this analysis, we did not find a statistically significant difference between the LABA/LAMA single inhaler FDCs (VI/UMEC and OLO/TIO) compared in terms of prevention of COPD exacerbations. However, this result can help healthcare providers, and patients choose between these two medications based on other factors such as patient preference, costs, and adherence to the medications.

Future direction

COPD is a condition that leads to not only significant direct medical costs, but also indirect medical, direct non-medical, and other societal costs. These non-direct medical costs may include caregiver costs, costs of absenteeism, transportation costs, lost productivity costs, and costs due to premature death, among others. Future research should aim to examine these costs in more detail. Although policies aimed at enhancing medication access and reducing copays can result in long-term cost savings for the healthcare system, it is equally crucial to prioritize the provision of appropriate medications tailored to the unique clinical needs and preferences of individual COPD patients. Therefore, future investigations should focus on exploring the influence of patient preferences on both treatment adherence and clinical outcomes. By doing so, a more comprehensive understanding of the interplay between patient preferences, adherence, and treatment outcomes can be gained, ultimately informing the development of personalized interventions, improving patient care and reducing the cost of COPD management.

While this dissertation aimed to examine the potential heterogeneity in terms of preference of LABA/LAMA or LABA/ICS in various subgroups based on demographic and clinical factors, we were limited to information that was available in claims data. Use of data that contains information on clinical information and laboratory values such as FEV_1 readings and eosinophil count values to define these subgroups can help expand this work further. Also, given the uniqueness of Medicare beneficiaries with COPD, expansion of this work to other patient populations, specific to the setting may be needed.

Given that the comparison between OLO/TIO and VI/UMEC yielded no statistically significant differences between the groups in terms of preventing COPD exacerbations, future research can expand on this work to include other components. One such component may be patient adherence to the medications. Another component could be the addition of costs in the comparison between medications. These additional components could be utilized to inform choice of treatment to provide optimal patient care. Future research should look to further explore the potential for personalized medication in COPD patients and how this may help reduce the high cost burden it imposes.

7. Appendix

Appendix A: COPD medication classification

Appendix table 1. Classification of medications used for COPD, based on GOLD guidelines

Drug class	**Specific medications**
Short-acting $Beta_2$-Agonists (SABA)	Fenoterol Levalbuterol Salbutamol (albuterol) Terbutaline
Long-acting $Beta_2$-Agonists (LABA)	Arformoterol Formoterol Indacaterol Olodaterol Salmeterol
Short-acting muscarinic antagonist (SAMA)	Ipratropium bromide Oxitropium bromide
Long-acting muscarinic antagonist (LAMA)	Aclidinium bromide Glycopyrronium bromide Tiotropium Umecledinium Glycopyrrolate Revefenacin
Combination of Short-acting $Beta_2$-Agonist and muscarinic antagonist in one device (SABA/SAMA)	Fenoterol/ipratropium Salbutamol/ipratropium
Combination of Long-acting $Beta_2$-Agonist and Anticholinergic in one device (LABA/LAMA)	Formoterol/aclidinium Formoterol/glycopyrronium Indacaterol/ glycopyrronium Vilanterol/umeclidinium Olodaterol/tiotropium
Combination of Long-acting $Beta_2$-Agonist and inhaled corticosteroid in one device (LABA/ICS)	Formoterol/beclomtasone Formoterol/budesonide Formoterol/mometasone Salmeterol/fluticasone Vilanterol/fluticasone furoate
Triple combination in one device	Fluticasone/umeclidinium/vilanterol Beclometasone/formoterol/glycopyrronium
Methylxanthines	Aminophylline Theophylline
Phosphodiesterase-4-inhibitors	Roflumilast
Mucolytic agents	Erdosteine Carbocysteine N-acetylcysteine

Appendix B: Aim 1 results (Regression results by service category)

Appendix table 2. Results of marginal effect two-part regression to determine excess cost of COPD on prescription drug healthcare expenditure

Covariate	Reference	Marginal effect	Standard error	p- value
Race=Black only	Race=White only	-24.69	244.24	0.92
Race=Other/Multiple reported		-113.18	346.55	0.74
Age=50-54 years	Age=45-50 years	1,121.26	509.54	0.03
Age=55-59 years		397.88	342.12	0.25
Age=60-64 years		202.38	345.29	0.56
Age=65-69 years		282.20	333.32	0.40
Age=70-74 years		173.90	356.46	0.63
Age=75-79 years		-257.61	330.85	0.44
Age=80 years and older		36.60	329.83	0.91
Marital status=Currently married	Marital status=Not currently married	103.90	171.17	0.54
Region= Northeast	Region=South	190.57	220.94	0.39
Region= Midwest		-182.07	243.71	0.46
Region=West		-1.11	302.64	1.00
Sex= Female	Sex= Male	-221.68	182.10	0.22
Highest education: High School/ GED	Highest education: less than High school	689.82	204.38	<0.01
Highest education: other degree		785.69	334.26	0.02
Highest education: Bachelors degree		578.85	260.45	0.03
Highest education: Masters/PhD degree		1,042.12	341.93	<0.01
Current smoker	Not current smoker	364.17	250.78	0.15
Insurance= Uninsured	Insurance= Any private	-2,165.19	645.76	<0.01
Insurance= Public only		162.36	151.24	0.28
Family income= Poor	Family income= Medium	759.18	219.18	<0.01
Family income= Near poor		939.48	405.57	0.02
Family income= Low		113.68	205.25	0.58
Family income=High		87.77	187.49	0.64
Angina		-190.57	240.82	0.43
Arthritis		1,099.03	161.02	<0.01
Asthma		1,201.76	236.85	<0.01
Cancer		1,091.18	224.31	<0.01
Chronic heart disease		969.52	241.65	<0.01
High cholesterol		157.59	187.07	0.40
Diabetes		2,774.39	142.79	<0.01
High blood pressure		-108.64	161.06	0.50
Myocardial infarction		27.91	211.32	0.90
Other heart conditions		851.21	175.24	<0.01
Stroke		736.45	231.02	<0.01
Depression		861.90	156.92	<0.01
Anxiety		1,374.14	201.48	<0.01
Chronic Obstructive Pulmonary Disease		1,886.97	216.07	<0.01

Appendix table 3. Results of marginal effect two-part regression to determine excess cost of COPD on emergency room healthcare expenditure

Covariate	**Reference**	**Marginal effect**	**Standard error**	**p- value**
Race=Black only	Race=White only	25.56	20.37	0.21
Race=Other/Multiple reported		-71.66	40.63	0.08
Age=50-54 years	Age=45-50 years	-3.31	31.94	0.92
Age=55-59 years		-18.70	32.42	0.56
Age=60-64 years		-37.03	31.35	0.24
Age=65-69 years		-54.55	32.93	0.10
Age=70-74 years		-136.69	35.12	0.00
Age=75-79 years		-104.77	36.64	<0.01
Age=80 years and older		-35.69	31.33	0.26
Marital status=Currently married	Marital status=Not currently married	-21.52	16.10	0.18
Region= Northeast	Region=South	20.83	24.29	0.39
Region= Midwest		-18.65	25.32	0.46
Region=West		68.65	22.33	<0.01
Sex= Female	Sex= Male	15.92	15.70	0.31
Highest education: High School/ GED	Highest education: less than High school	6.51	23.22	0.78
Highest education: other degree		0.61	28.97	0.98
Highest education: Bachelors degree		-26.65	29.26	0.36
Highest education: Masters/PhD degree		-23.74	31.07	0.45
Current smoker	Not current smoker	43.60	21.39	0.04
Insurance= Uninsured	Insurance= Any private	-242.83	42.23	<0.01
Insurance= Public only		-62.49	18.27	<0.01
Family income= Poor	Family income= Medium	28.78	27.70	0.30
Family income= Near poor		-44.40	29.90	0.14
Family income= Low		-8.01	21.20	0.71
Family income=High		7.48	20.59	0.72
Angina		82.66	36.34	0.02
Arthritis		103.25	15.82	<0.01
Asthma		39.30	20.67	0.06
Cancer		35.76	17.99	0.05
Chronic heart disease		8.52	23.75	0.72
High cholesterol		20.36	15.71	0.20
Diabetes		35.34	16.48	0.03
High blood pressure		68.62	16.33	<0.01
Myocardial infarction		60.60	27.42	0.03
Other heart conditions		95.41	15.46	<0.01
Stroke		115.08	23.10	<0.01
Depression		42.09	17.85	0.02
Anxiety		61.98	20.45	<0.01
Chronic Obstructive Pulmonary Disease		137.11	29.82	<0.01

Appendix table 4. Results of marginal effect two-part regression to determine excess cost of COPD on inpatient healthcare expenditure

Covariate	**Reference**	**Marginal effect**	**Standard error**	**p- value**
Race=Black only	Race=White only	-242.10	229.93	0.29
Race=Other/Multiple reported		-625.04	338.86	0.07
Age=50-54 years	Age=45-50 years	782.17	362.13	0.03
Age=55-59 years		657.49	354.24	0.06
Age=60-64 years		1,002.40	343.24	<0.01
Age=65-69 years		867.19	340.95	0.01
Age=70-74 years		774.37	391.89	0.05
Age=75-79 years		684.32	359.35	0.06
Age=80 years and older		1,183.91	349.16	<0.01
Marital status=Currently married	Marital status=Not currently married	-21.65	156.56	0.89
Region= Northeast	Region=South	415.79	293.20	0.16
Region= Midwest		213.74	206.85	0.30
Region=West		302.51	213.32	0.16
Sex= Female	Sex= Male	-345.80	150.63	0.02
Highest education: High School/ GED	Highest education: less than High school	-17.40	235.19	0.94
Highest education: other degree		-119.96	322.09	0.71
Highest education: Bachelors degree		-529.61	298.01	0.08
Highest education: Masters/PhD degree		-413.84	348.48	0.24
Current smoker	Not current smoker	124.41	197.76	0.53
Insurance= Uninsured	Insurance= Any private	-4,010.39	615.30	<0.01
Insurance= Public only		-449.63	185.44	0.02
Family income= Poor	Family income= Medium	99.29	233.86	0.67
Family income= Near poor		31.28	299.76	0.92
Family income= Low		128.37	237.11	0.59
Family income=High		-189.34	198.13	0.34
Angina		-84.85	317.19	0.79
Arthritis		368.82	164.28	0.03
Asthma		113.28	218.82	0.61
Cancer		792.18	189.00	<0.01
Chronic heart disease		579.28	216.26	<0.01
High cholesterol		-293.36	161.98	0.07
Diabetes		605.52	181.17	<0.01
High blood pressure		1,025.25	189.98	<0.01
Myocardial infarction		1,231.69	244.08	<0.01
Other heart conditions		802.41	161.87	<0.01
Stroke		1,063.85	226.70	<0.01
Depression		698.20	218.04	<0.01
Anxiety		378.99	216.71	0.08
Chronic Obstructive Pulmonary Disease		1,002.76	233.06	<0.01

Appendix table 5. Results of marginal effect two-part regression to determine excess cost of COPD on office-based healthcare expenditure

Covariate	Reference	Marginal effect	Standard error	p- value
Race=Black only	Race=White only	-169.36	163.62	0.30
Race=Other/Multiple reported		-665.94	165.08	<0.01
Age=50-54 years	Age=45-50 years	418.46	224.80	0.06
Age=55-59 years		287.38	203.85	0.16
Age=60-64 years		642.92	255.36	0.01
Age=65-69 years		283.29	203.83	0.17
Age=70-74 years		466.19	214.81	0.03
Age=75-79 years		423.05	220.50	0.06
Age=80 years and older		359.35	233.84	0.13
Marital status=Currently married	Marital status=Not currently married	-80.08	97.30	0.41
Region= Northeast	Region=South	-12.01	136.66	0.93
Region= Midwest		21.90	157.02	0.89
Region=West		106.33	142.88	0.46
Sex= Female	Sex= Male	202.78	96.32	0.04
Highest education: High School/ GED	Highest education: less than High school	401.53	192.77	0.04
Highest education: other degree		577.51	231.08	0.01
Highest education: Bachelors degree		678.57	203.97	<0.01
Highest education: Masters/PhD degree		972.19	213.38	<0.01
Current smoker	Not current smoker	-185.43	179.71	0.30
Insurance= Uninsured	Insurance= Any private	-2,223.57	316.24	<0.01
Insurance= Public only		-34.65	109.67	0.75
Family income= Poor	Family income= Medium	-5.84	172.05	0.97
Family income= Near poor		-92.48	219.44	0.67
Family income= Low		-218.32	169.26	0.20
Family income=High		233.75	108.90	0.03
Angina		-295.59	208.22	0.16
Arthritis		737.35	103.12	<0.01
Asthma		434.88	128.18	<0.01
Cancer		1,180.95	137.14	<0.01
Chronic heart disease		782.18	181.53	<0.01
High cholesterol		133.12	97.44	0.17
Diabetes		623.99	167.13	<0.01
High blood pressure		204.97	107.52	0.06
Myocardial infarction		122.18	199.57	0.54
Other heart conditions		752.11	118.43	<0.01
Stroke		338.94	165.79	0.04
Depression		544.03	108.88	<0.01
Anxiety		621.58	110.19	<0.01
Chronic Obstructive Pulmonary Disease		383.59	170.97	0.03

Appendix table 6. Results of marginal effect two-part regression to determine excess cost of COPD on outpatient healthcare expenditure

Covariate	**Reference**	**Marginal effect**	**Standard error**	**p- value**
Race=Black only	Race=White only	34.65	96.19	0.72
Race=Other/Multiple reported		-248.73	150.78	0.10
Age=50-54 years	Age=45-50 years	118.01	126.84	0.35
Age=55-59 years		181.19	117.94	0.13
Age=60-64 years		241.29	111.24	0.03
Age=65-69 years		225.88	115.19	0.05
Age=70-74 years		7.23	124.24	0.95
Age=75-79 years		-26.08	133.61	0.85
Age=80 years and older		-46.91	152.04	0.76
Marital status=Currently married	Marital status=Not currently married	-52.16	65.09	0.42
Region= Northeast	Region=South	407.55	81.98	<0.01
Region= Midwest		322.15	82.39	<0.01
Region=West		41.66	85.35	0.63
Sex= Female	Sex= Male	84.03	59.75	0.16
Highest education: High School/ GED	Highest education: less than High school	166.55	103.02	0.11
Highest education: other degree		294.21	132.72	0.03
Highest education: Bachelors degree		259.95	120.75	0.03
Highest education: Masters/PhD degree		382.06	130.57	<0.01
Current smoker	Not current smoker	27.91	86.81	0.75
Insurance= Uninsured	Insurance= Any private	-531.38	556.61	0.34
Insurance= Public only		-189.92	68.22	<0.01
Family income= Poor	Family income= Medium	-116.82	122.07	0.34
Family income= Near poor		20.29	145.70	0.89
Family income= Low		-104.58	103.69	0.31
Family income=High		78.81	70.70	0.27
Angina		132.58	167.06	0.43
Arthritis		203.86	66.99	<0.01
Asthma		298.06	73.90	<0.01
Cancer		515.24	76.48	<0.01
Chronic heart disease		299.36	122.07	0.02
High cholesterol		18.84	65.54	0.77
Diabetes		109.99	69.53	0.12
High blood pressure		242.47	60.99	<0.01
Myocardial infarction		-115.14	132.35	0.39
Other heart conditions		363.06	75.83	<0.01
Stroke		218.51	100.99	0.03
Depression		268.23	85.44	<0.01
Anxiety		258.53	77.14	<0.01
Chronic Obstructive Pulmonary Disease		132.91	117.26	0.26

Appendix table 7. Results of marginal effect two-part regression to determine excess cost of COPD on home health healthcare expenditure

Covariate	Reference	Marginal effect	Standard error	p- value
Race=Black only	Race=White only	257.88	75.70	<0.01
Race=Other/Multiple reported		114.23	125.34	0.36
Age=50-54 years	Age=45-50 years	69.73	161.31	0.67
Age=55-59 years		38.11	166.57	0.82
Age=60-64 years		176.49	150.30	0.24
Age=65-69 years		416.39	149.51	<0.01
Age=70-74 years		314.10	151.11	0.04
Age=75-79 years		558.13	166.38	<0.01
Age=80 years and older		1,025.83	176.58	<0.01
Marital status=Currently married	Marital status=Not currently married	-241.17	61.83	<0.01
Region= Northeast	Region=South	182.33	73.61	0.01
Region= Midwest		4.87	72.26	0.95
Region=West		1.00	93.43	0.99
Sex= Female	Sex= Male	-74.19	62.81	0.24
Highest education: High School/ GED	Highest education: less than High school	-340.58	89.75	<0.01
Highest education: other degree		-321.65	117.00	<0.01
Highest education: Bachelors degree		-306.53	126.78	0.02
Highest education: Masters/PhD degree		-444.51	147.05	<0.01
Current smoker	Not current smoker	-239.47	86.99	<0.01
Insurance= Uninsured	Insurance= Any private	-1,171.01	287.57	<0.01
Insurance= Public only		266.55	78.53	<0.01
Family income= Poor	Family income= Medium	361.72	79.51	<0.01
Family income= Near poor		328.95	134.19	0.02
Family income= Low		188.62	78.90	0.02
Family income=High		-188.18	85.49	0.03
Angina		34.95	99.01	0.72
Arthritis		96.45	68.05	0.16
Asthma		-2.14	70.09	0.98
Cancer		219.59	72.75	<0.01
Chronic heart disease		95.13	81.95	0.25
High cholesterol		1.50	68.99	0.98
Diabetes		265.77	69.15	<0.01
High blood pressure		40.81	75.40	0.59
Myocardial infarction		246.61	79.02	<0.01
Other heart conditions		39.76	58.98	0.50
Stroke		390.85	78.35	<0.01
Depression		242.86	82.01	<0.01
Anxiety		285.09	88.70	<0.01
Chronic Obstructive Pulmonary Disease		249.57	76.90	<0.01

Appendix C: Definition of COPD algorithm

Appendix table 8. Definition of COPD algorithm

Valid ICD-9/ CPT4/ HCPCS Codes	**Valid ICD-10/CPT4/HCPCS Codes**	**Number/Type of Claims to Qualify[1]**
DX 490, 491.0, 491.1, 491.8, 491.9, 492.0, 492.8, 491.20, 491.21, 491.22, 494.0, 494.1, 496 (any DX on the claim)	DX J40, J41.0, J41.1, J41.8, J42, J43.0, J43.1, J43.2, J43.8, J43.9, J44.0, J44.1, J44.9, J47.0, J47.1, J47.9 (any DX on the claim)	At least 1 inpatient, SNF, HHA *OR* 2 HOP *OR* Carrier claims with DX codes

[1] Carrier claims refer to claim types 71 and 72 (not durable medical equipment [DME] claim types 81 or 82), and excludes any claims for which line item Berenson-Eggers Type of Service (BETOS) code variable equals D1A, D1B, D1C, D1D, D1E, D1F, D1G (which is DME), or O1A (which is ambulance services). The intent of the algorithm is to exclude claims where the services do not require a licensed health care professional. When two claims are required, they must occur at least one day apart.
ICD: International Classification of Disease; CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; DX: Diagnosis; SNF: Skilled nursing facility; HHA: Home health agency; HOP: Hospital outpatient; DX: Diagnosis

Appendix D: Steps, data dimensions, and details on the implementation of hdPS

Appendix table 9. Steps in implementing hdPS

I. Identifying covariates	II. Prioritizing covariates	III. Estimating treatment effect
1. Identified covariates as (a) predefined and investigator defined covariates; (b) determined data dimensions & observation period for empirical covariate assessment.	4. Prioritized covariates by calculating the bias for each covariate using the Bross formula and ranked them based on this bias.	6. Estimated propensity score using multivariable regression, adjusting for the empirical as well as predefined variables.
2. Assessed the prevalence of codes and determined of the level of granularity.	5. Selected the top 200 covariates with the highest bias ranking.	7. Used the hdPS score in the exposure-outcome model to adjust for confounding using matching.
3. Assessed the frequency of recurring codes as: once (>=once), sporadic (>=median) and frequent (>=75th percentile).		

Sources: Schneeweiss et al.[104], Rassen et al.[105]

- The following data dimensions (level of granularity) were defined:
    i. Predefined demographic covariates: age, sex, race, calendar year of index date.
    ii. Investigator defined covariates: supplemental oxygen use in the lookback period, number of prior COPD exacerbations in the lookback period, number of prescriptions (short-acting bronchodilators, long-acting bronchodilators, and inhaled corticosteroids) in the lookback period, and prior comorbidities (breast cancer, colorectal cancer, endometrial cancer, prostate cancer, stroke/transient ischemic attack, acute myocardial infarction, chronic kidney disease, diabetes, depression, allergic rhinitis, and pneumonia).
    iii. Data dimensions for hdPS: (a) Institutional diagnosis claims via the Medicare Provider Analysis and Review (MedPAR) file (3-digit ICD-10

CM codes); (b) Institutional procedure claims via the MedPAR file (3-digit ICD-10 Procedure Coding System (PCS) codes); (c) Outpatient diagnosis claims (3-digit ICD-10 CM codes); (d) Outpatient procedure claims (5-digit Healthcare Common Procedure Coding System (HCPCS) codes); (e) Non-institutional office-based diagnosis claims via the Carrier file (3-digit ICD-10 CM codes); (f) Non-institutional office-based procedure claims via the Carrier file (5-digit HCPCS codes); (g) Prescription drug utilization using drug claims (Generic drug names); (h) Claims for durable medical equipment (5-digit HCPCS codes).

- Since the files contained a mix of ICD-9 and ICD-10 codes, all codes were be converted to ICD-10 using the General Equivalence Mappings provided by the National Bureau of Economic Research [203]. For this analysis, and based on the recommendations of previous research, up to 200 covariates were identified for each of the eight domains identified above [104,173,174].
- To account for the frequency of recurring codes, the following indicator variables were used for each of the aforementioned empirical covariates: once (>=once); sporadic (>=median); and frequent (>=75th percentile). Subsequently there were a total of 4,800 empirically identified covariates (200 covariates for each dimension*8 dimensions *3 frequency codes).
- These covariates were prioritized based on the method Schneewiess et al. recommended [104]. This is the Bross method and based on this method, the top 200 empirically identified covariates were selected to be a part of the propensity score model [104,171,204].

$$\frac{P_{C1}\left(RR_{CD}-1\right)+1}{P_{C0}\left(RR_{CD}-1\right)+1}, \text{ for all values of } RR_{CD}$$

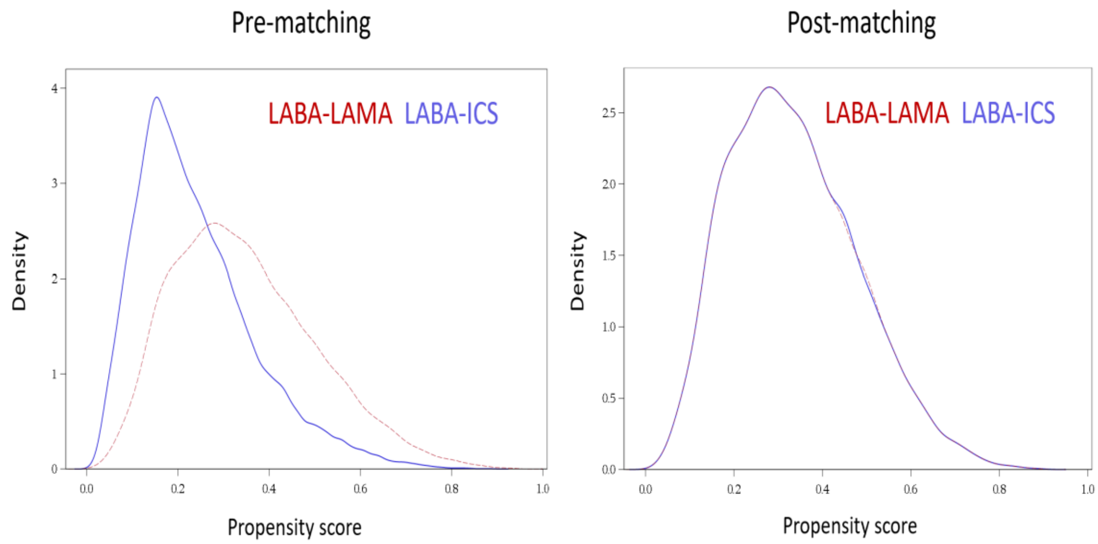
Bross' bias estimation formula
P: Prevalence, C: Confounder, D: Outcome, RR: Relative risk, P_{C1}: Prevalence of the confounder in group 1, P_{C0}: Prevalence of the confounder in group 0, RR_{CD}: Relative risk between the confounder and the outcome

- The propensity score was estimated using multivariable logistic regression, adjusting for the empirically selected as well as predefined variables. The regression was modeled for the probability of being prescribed LABA/LAMA for aim 2 and OLO/TIO for aim 3.
- Based on propensity scores, individuals from the two cohorts were matched [21].

Appendix E: Negative control analysis

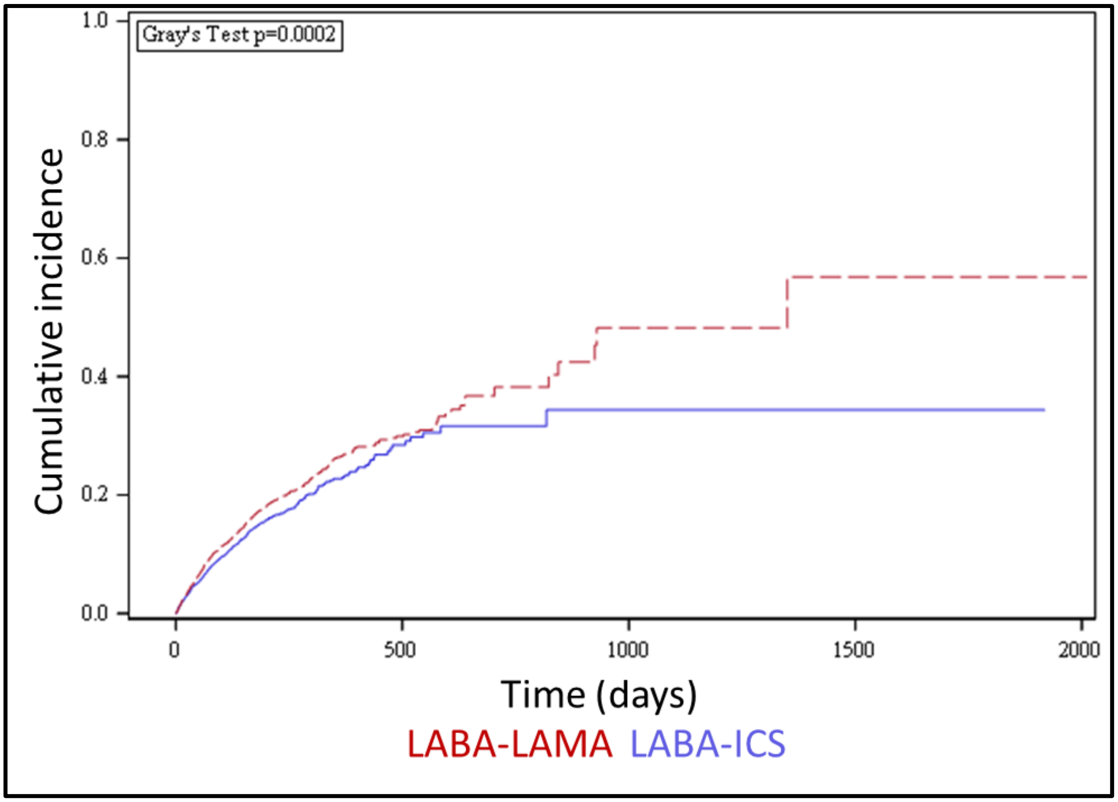
For the negative control analysis, the study described in the primary analysis was carried out with one major change; the primary endpoint was gastroesophageal reflux disease (GERD) [20]. GERD was used as a negative control outcome to evaluate the presence of unmeasured confounding, based on the assumption that (a) there was no plausible causal effect of the exposure on the negative control outcome [20], and that (b) GERD had a similar bias structure with the exposure as the outcome of interest (COPD exacerbation) [178,179].

Appendix F: Aim 2 results



Appendix figure 1. Propensity score distribution before and after matching (Overall results)

Note: Modeled around the probability of receiving LABA/LAMA



Appendix figure 2. Cumulative incidence of the first COPD exacerbation, comparing LABA/ICS and LABA/LAMA initiators with persistent use, via the Kaplan-Meier method

Appendix table 10. Characteristics of study population by drug, before and after matching (Among males)

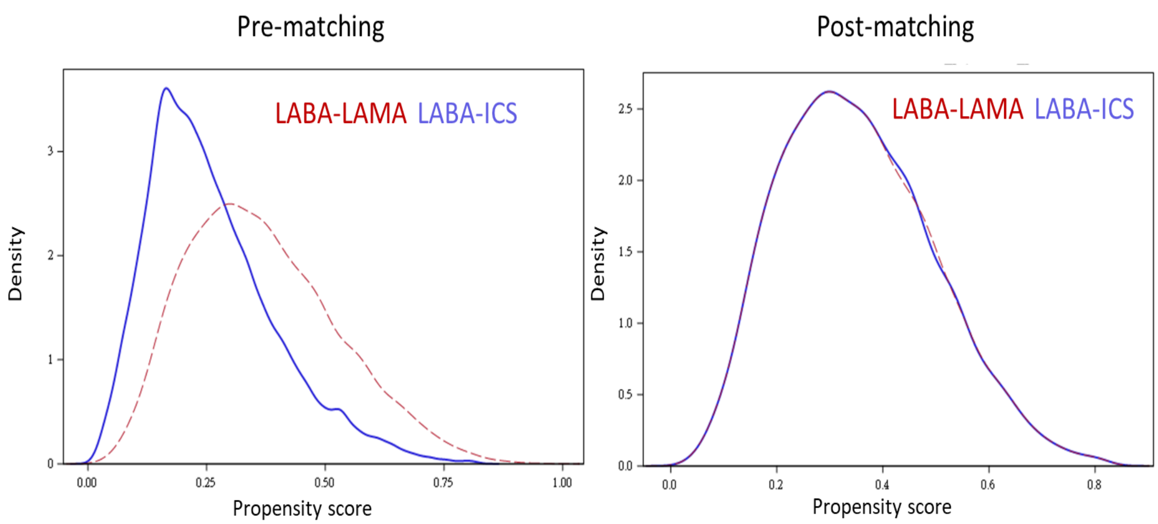
	Before matching			After matching		
Variables	**LABA/LAMA (N=13,404)**	**LABA/ICS (N=36,488)**	**Standardized difference**	**LABA/LAMA (N=6,273)**	**LABA/ICS (N=6,273)**	**Standardized difference**
Age in years[1], Mean±SD	75.3±6.5	75.9±7.0	0.082	75.4±6.5	75.4±6.7	0.003
Race: Black, n(%)	297 (4.5)	1,025 (6.4)	0.084	295 (4.7)	289 (4.6)	0.005
Race: White, n(%)	5,723 (86.9)	13,369 (83.6)	0.092	5,421 (86.4)	5,391 (85.9)	0.014
Race: Other, n(%)	569 (8.6)	1,597 (10.0)	0.047	557 (8.9)	593 (9.5)	0.020
Number of COPD exacerbations[2], Mean±SD	0.4±1.1	0.4±0.9	0.074	0.4±1.1	0.4±1.0	0.020
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±1.8	0.2±1.2	0.185	0.4±1.6	0.4±1.7	0.001
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.4±2.9	1.3±2.8	0.028	1.4±2.9	1.4±2.9	0.004
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.8	0.3±1.2	0.111	0.2±0.8	0.2±0.8	0.010
Supplemental oxygen use[2], Mean±SD	1,101 (16.7)	2,015 (12.6)	0.116	989 (15.8)	1,020 (16.3)	0.013
Breast cancer[3], n(%)	8 (0.1)	17 (0.1)	0.004	7 (0.1)	8 (0.1)	0.005
Colorectal cancer[3], n(%)	155 (2.4)	439 (2.7)	0.025	147 (2.3)	146 (2.3)	0.001
Prostate cancer[3], n(%)	726 (11.0)	1,900 (11.9)	0.027	699 (11.1)	706 (11.3)	0.004
Stroke-Transient Ischemic attack[3], n(%)	648 (9.8)	1,927 (12.1)	0.071	620 (9.9)	591 (9.4)	0.016
Acute myocaridal infarction[3], n(%)	316 (4.8)	827 (5.2)	0.017	303 (4.8)	301 (4.8)	0.001
Chronic kidney disease[3], n(%)	2,942 (44.7)	7,513 (47.0)	0.047	2,800 (44.6)	2,781 (44.3)	0.006
Diabetes[3], n(%)	2,744 (41.6)	7,096 (44.4)	0.055	2,636 (42.0)	2,604 (41.5)	0.010
Depression[3], n(%)	1,796 (27.3)	4,747 (29.7)	0.054	1,718 (27.4)	1,693 (27.0)	0.009
Allergic rhinitis[2], n(%)	850 (12.9)	2,248 (14.1)	0.034	807 (12.9)	835 (13.3)	0.013
Pneumonia[2], n(%)	1,295 (19.7)	3,823 (23.9)	0.103	1,234 (19.7)	1,231 (19.6)	0.001

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 11. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among males)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	6,273	427	1,246.23 1	34.263	0.844 (95% Confidence interval: 0.745-0.957)
LABA/LAMA	6,273	580	1,499.15 9	38.688	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 3. Propensity score distribution before and after matching (Among males)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 12. Characteristics of study population by drug, before and after matching (Among females)

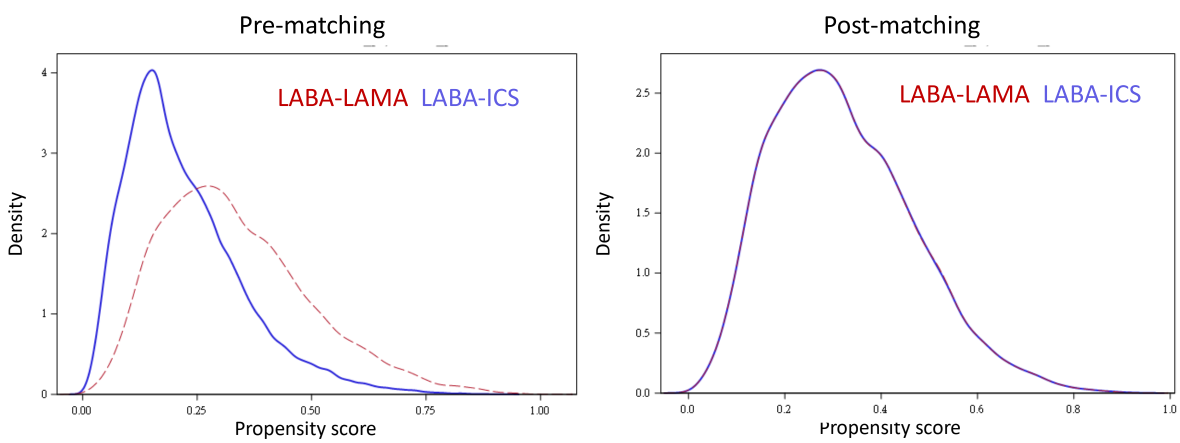
	Before matching			After matching		
Variables	**LABA/LAMA (N=6,815)**	**LABA/ICS (N=20,497)**	**Standardized difference**	**LABA/LAMA (N=6,563)**	**LABA/ICS (N=6,563)**	**Standardized difference**
Age in years[1], Mean±SD	76.0±6.9	76.8±7.7	0.112	76.0±7.0	75.9±7.2	0.017
Race: Black, n(%)	311 (4.6)	1,265 (6.2)	0.071	305 (4.6)	326 (5.0)	0.015
Race: White, n(%)	6,114 (89.7)	17,531 (85.5)	0.127	5,870 (89.4)	5,875 (89.5)	0.002
Race: Other, n(%)	390 (5.7)	1,701 (8.3)	0.101	388 (5.9)	362 (5.5)	0.017
Number of COPD exacerbations[2], Mean±SD	0.5±1.1	0.3±0.9	0.112	0.4±1.1	0.4±1.0	0.001
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.6±2.1	0.2±1.1	0.263	0.5±1.7	0.5±1.7	0.016
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.5±2.9	1.4±2.8	0.034	1.5±2.9	1.5±2.7	0.003
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.116	0.2±0.9	0.2±0.9	0.006
Supplemental oxygen use[2], Mean±SD	1,388 (20.4)	3,027 (14.8)	0.148	1,289 (19.6)	1,336 (20.4)	0.018
Breast cancer[3], n(%)	678 (9.9)	1,902 (9.3)	0.023	642 (9.8)	636 (9.7)	0.003
Colorectal cancer[3], n(%)	160 (2.3)	464 (2.3)	0.006	154 (2.3)	167 (2.5)	0.013
Endometrial cancer[3], n(%)	61 (0.9)	229 (1.1)	0.022	59 (0.9)	65 (1.0)	0.009
Stroke-Transient Ischemic attack[3], n(%)	683 (10.0)	2,503 (12.2)	0.070	669 (10.2)	701 (10.7)	0.016
Acute myocaridal infarction[3], n(%)	210 (3.1)	812 (4.0)	0.048	207 (3.2)	212 (3.2)	0.004
Chronic kidney disease[3], n(%)	2,567 (37.7)	8,238 (40.2)	0.052	2,491 (38.0)	2,491 (38.0)	0.000
Diabetes[3], n(%)	2,215 (32.5)	7,751 (37.8)	0.111	2,164 (33.0)	2,172 (33.1)	0.003
Depression[3], n(%)	3,027 (44.4)	9,529 (46.5)	0.042	2,949 (44.9)	2,986 (45.5)	0.011
Allergic rhinitis[2], n(%)	974 (14.3)	3,576 (17.4)	0.086	949 (14.5)	989 (15.1)	0.017
Pneumonia[2], n(%)	1,259 (18.5)	4,780 (23.3)	0.119	1,231 (18.8)	1,235 (18.8)	0.002

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 13. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among females)

Treatment group	**Number of patients**	**Number of events**	**Person years**	**Rate per 100 per year**	**Hazard ratio (post matching)[1]**
LABA/ICS	6,563	466	1,305.22 1	35.70276	0.882 (95% Confidence interval: 0.782-0.996)
LABA/LA MA	6,563	611	1,582.29 7	38.61475	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 4. Propensity score distribution before and after matching (Among females)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 14. Characteristics of study population by drug, before and after matching (Among oxygen users)

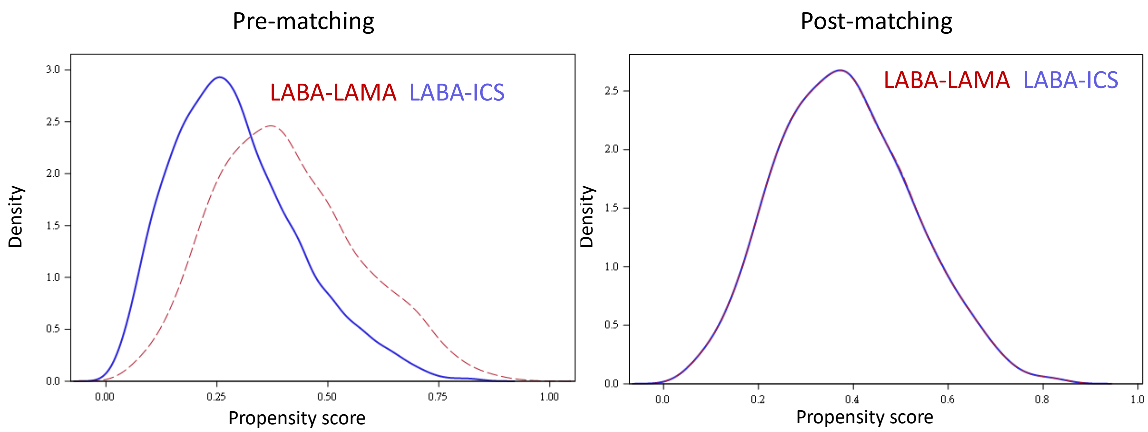
	Before matching			After matching		
Variables	**LABA/LAMA (N=13,404)**	**LABA/ICS (N=36,488)**	**Standardized difference**	**LABA/LAMA (N=2,292)**	**LABA/ICS (N=2,292)**	**Standardized difference**
Age in years[1], Mean±SD	76.4±6.7	76.8±7.4	0.067	76.5±6.7	76.6±7.2	0.019
Sex: Female, n(%)	1,388 (55.8)	3,027 (60.0)	0.087	1,290 (56.3)	1,287 (56.2)	0.003
Race: Black, n(%)	97 (3.9)	259 (5.1)	0.060	94 (4.1)	97 (4.2)	0.007
Race: White, n(%)	2,272 (91.3)	4,516 (89.6)	0.058	2,081 (90.8)	2,088 (91.1)	0.011
Race: Other, n(%)	120 (4.8)	267 (5.3)	0.022	117 (5.1)	107 (4.7)	0.020
Number of COPD exacerbations[2], Mean±SD	0.8±1.4	0.7±1.4	0.050	0.8±1.4	0.7±1.4	0.014
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.7±2.1	0.3±1.4	0.194	0.5±1.8	0.5±1.8	0.001
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.8±3.3	1.8±3.4	0.006	1.7±3.2	1.7±3.1	0.024
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.8	0.3±1.3	0.112	0.2±0.9	0.2±0.8	0.003
Breast cancer[3], n(%)	2,489 (18.6)	5,042 (13.8)	0.000	2,322 (18.0)	2,361 (18.3)	0.000
Colorectal cancer[3], n(%)	144 (5.8)	296 (5.9)	0.004	136 (5.9)	135 (5.9)	0.002
Endometrial cancer[3], n(%)	59 (2.4)	159 (3.2)	0.048	54 (2.4)	65 (2.8)	0.030
Prostate cancer[3], n(%)	11 (0.4)	45 (0.9)	0.055	10 (0.4)	8 (0.3)	0.014
Stroke-Transient Ischemic attack[3], n(%)	124 (5.0)	252 (5.0)	0.001	119 (5.2)	108 (4.7)	0.022
Acute myocaridal infarction[3], n(%)	248 (10.0)	651 (12.9)	0.093	236 (10.3)	243 (10.6)	0.010
Chronic kidney disease[3], n(%)	125 (5.0)	318 (6.3)	0.056	115 (5.0)	112 (4.9)	0.006
Diabetes[3], n(%)	1,265 (50.8)	2,692 (53.4)	0.051	1,174 (51.2)	1,168 (51.0)	0.005
Depression[3], n(%)	1,023 (41.1)	2,324 (46.1)	0.101	960 (41.9)	924 (40.3)	0.032
Allergic rhinitis[2], n(%)	993 (39.9)	2,323 (46.1)	0.125	926 (40.4)	923 (40.3)	0.003
Pneumonia[2], n(%)	320 (12.9)	692 (13.7)	0.026	302 (13.2)	299 (13.0)	0.004

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 15. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among oxygen users)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	2,292	235	428.3641	54.85987	0.936 (95% Confidence interval: 0.788-1.113)
LABA/LAMA	2,292	293	521.8645	56.14484	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 5. Propensity score distribution before and after matching (Among oxygen users)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 16. Characteristics of study population by drug, before and after matching (Among oxygen non-users)

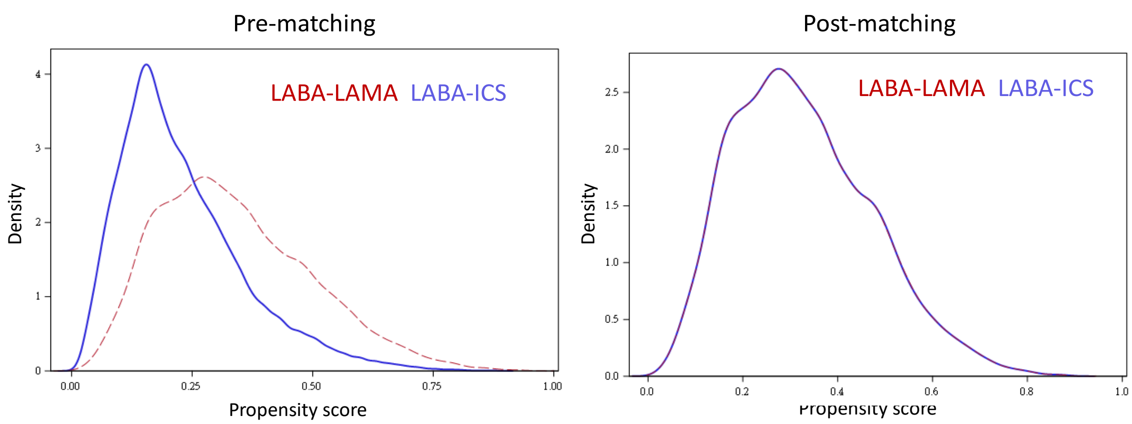
	Before matching			After matching		
Variables	**LABA/LAMA (N=10,915)**	**LABA/ICS (N=31,446)**	**Standardized difference**	**LABA/LAMA (N=10,511)**	**LABA/ICS (N=10,511)**	**Standardized difference**
Age in years[1], Mean±SD	75.5±6.7	76.3±7.4	0.117	75.5±6.7	75.4±7.0	0.014
Sex: Female, n(%)	5,427 (49.7)	17,470 (55.6)	0.117	5,259 (50.0)	5,283 (50.3)	0.005
Race: Black, n(%)	511 (4.7)	2,031 (6.5)	0.078	502 (4.8)	491 (4.7)	0.005
Race: White, n(%)	9,565 (87.6)	26,384 (83.9)	0.107	9,184 (87.4)	9,181 (87.3)	0.001
Race: Other, n(%)	839 (7.7)	3031 (9.6)	0.069	825 (7.8)	839 (8.0)	0.005
Number of COPD exacerbations[2], Mean±SD	0.4±1.0	0.3±0.8	0.085	0.4±1.0	0.4±0.9	0.004
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±1.9	0.2±1.1	0.229	0.4±1.7	0.4±1.6	0.016
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.4±2.8	1.3±2.7	0.027	1.4±2.8	1.4±2.7	0.006
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.115	0.2±0.9	0.2±0.9	0.004
Breast cancer[3], n(%)	542 (5.0)	1,623 (5.2)	0.009	519 (4.9)	524 (5.0)	0.002
Colorectal cancer[3], n(%)	256 (2.3)	744 (2.4)	0.001	245 (2.3)	239 (2.3)	0.004
Endometrial cancer[3], n(%)	50 (0.5)	184 (0.6)	0.018	47 (0.4)	48 (0.5)	0.001
Prostate cancer[3], n(%)	603 (5.5)	1,648 (5.2)	0.013	573 (5.5)	572 (5.4)	0.000
Stroke-Transient Ischemic attack[3], n(%)	1,083 (9.9)	3,779 (12.0)	0.067	1,052 (10.0)	1,007 (9.6)	0.014
Acute myocaridal infarction[3], n(%)	401 (3.7)	1,321 (4.2)	0.027	392 (3.7)	367 (3.5)	0.013
Chronic kidney disease[3], n(%)	4,244 (38.9)	13,059 (41.5)	0.054	4,098 (39.0)	4,134 (39.3)	0.007
Diabetes[3], n(%)	3,936 (36.1)	12,523 (39.8)	0.078	3,816 (36.3)	3,725 (35.4)	0.018
Depression[3], n(%)	3,830 (35.1)	11,953 (38.0)	0.061	3,708 (35.3)	3,773 (35.9)	0.013
Allergic rhinitis[2], n(%)	1,504 (13.8)	5,132 (16.3)	0.071	1,454 (13.8)	1,446 (13.8)	0.002
Pneumonia[2], n(%)	1,774 (16.3)	6,783 (21.6)	0.136	1,733 (16.5)	1,817 (17.3)	0.021

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 17. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among oxygen non-users)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	10,511	667	2,127.4908	31.351	0.855 (95% Confidence interval: 0.773-0.946)
LABA/LAMA	10,511	893	2,555.5565	34.943	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 6. Propensity score distribution before and after matching (Among oxygen non-users)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 18. Characteristics of study population by drug, before and after matching (Among those with allergic rhinitis)

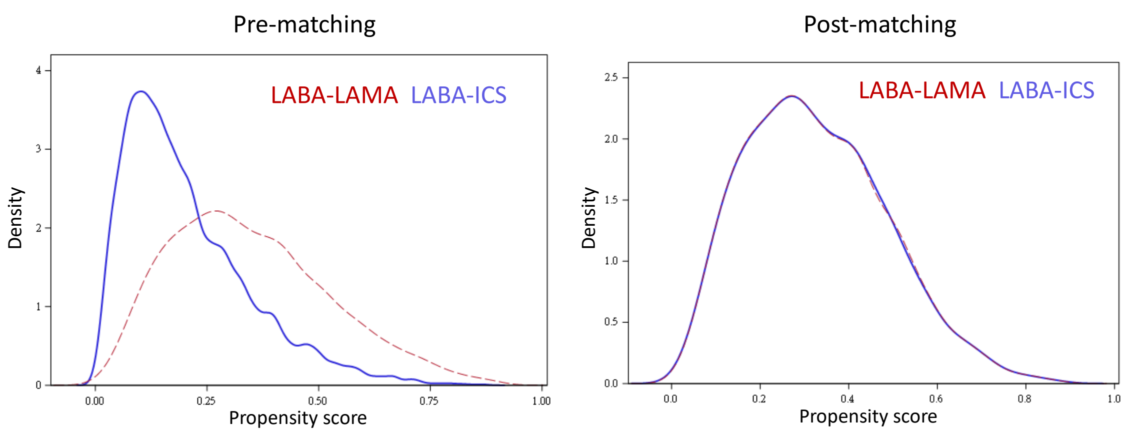
	Before matching			After matching		
Variables	**LABA/LAMA (N=1,824)**	**LABA/ICS (N=5,824)**	**Standardized difference**	**LABA/LAMA (N=1,726)**	**LABA/ICS (N=1,726)**	**Standardized difference**
Age in years[1], Mean±SD	75.7±6.8	76.4±7.3	0.094	75.8±6.8	75.9±6.9	0.012
Sex: Female, n(%)	974 (53.4)	3,576 (61.4)	0.162	932 (54.0)	929 (53.8)	0.003
Race: Black, n(%)	88 (4.8)	324 (5.6)	0.033	84 (4.9)	76 (4.4)	0.022
Race: White, n(%)	1,579 (86.6)	4,883 (83.8)	0.077	1,491 (86.4)	1,501 (87.0)	0.017
Race: Other, n(%)	959 (7.2)	3,298 (9.0)	0.069	945 (7.3)	928 (7.2)	0.011
Number of COPD exacerbations[2], Mean±SD	0.5±1.1	0.3±0.8	0.144	0.4±1.0	0.4±0.9	0.032
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±1.8	0.2±1.1	0.209	0.4±1.6	0.4±1.7	0.009
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.6±2.8	1.5±2.8	0.016	1.6±2.8	1.5±2.6	0.023
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.5±1.3	0.7±1.8	0.162	0.5±1.3	0.5±1.2	0.020
Supplemental oxygen use[2], Mean±SD	320 (17.5)	692 (11.9)	0.160	282 (16.3)	287 (16.6)	0.008
Breast cancer[3], n(%)	96 (5.3)	348 (6.0)	0.031	92 (5.3)	105 (6.1)	0.032
Colorectal cancer[3], n(%)	46 (2.5)	125 (2.1)	0.025	43 (2.5)	49 (2.8)	0.022
Endometrial cancer[3], n(%)	8 (0.4)	38 (0.7)	0.029	8 (0.5)	10 (0.6)	0.016
Prostate cancer[3], n(%)	89 (4.9)	280 (4.8)	0.003	86 (5.0)	82 (4.8)	0.011
Stroke-Transient Ischemic attack[3], n(%)	177 (9.7)	690 (11.8)	0.069	165 (9.6)	170 (9.8)	0.010
Acute myocaridal infarction[3], n(%)	59 (3.2)	205 (3.5)	0.016	56 (3.2)	58 (3.4)	0.006
Chronic kidney disease[3], n(%)	733 (40.2)	2,370 (40.7)	0.010	694 (40.2)	707 (41.0)	0.015
Diabetes[3], n(%)	700 (38.4)	2,304 (39.6)	0.024	656 (38.0)	645 (37.4)	0.013
Depression[3], n(%)	691 (37.9)	2,345 (40.3)	0.049	648 (37.5)	647 (37.5)	0.001
Pneumonia[2], n(%)	393 (21.5)	1,364 (23.4)	0.045	365 (21.1)	381 (22.1)	0.023

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 19. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among those with allergic rhinitis)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	1,726	113	337.212 9	33.50999	0.946 (95% Confidence interval: 0.735-1.217)
LABA/LA MA	1,726	131	385.629	33.97047	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 7. Propensity score distribution before and after matching (Among those with allergic rhinitis)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 20. Characteristics of study population by drug, before and after matching (Among those without allergic rhinitis)

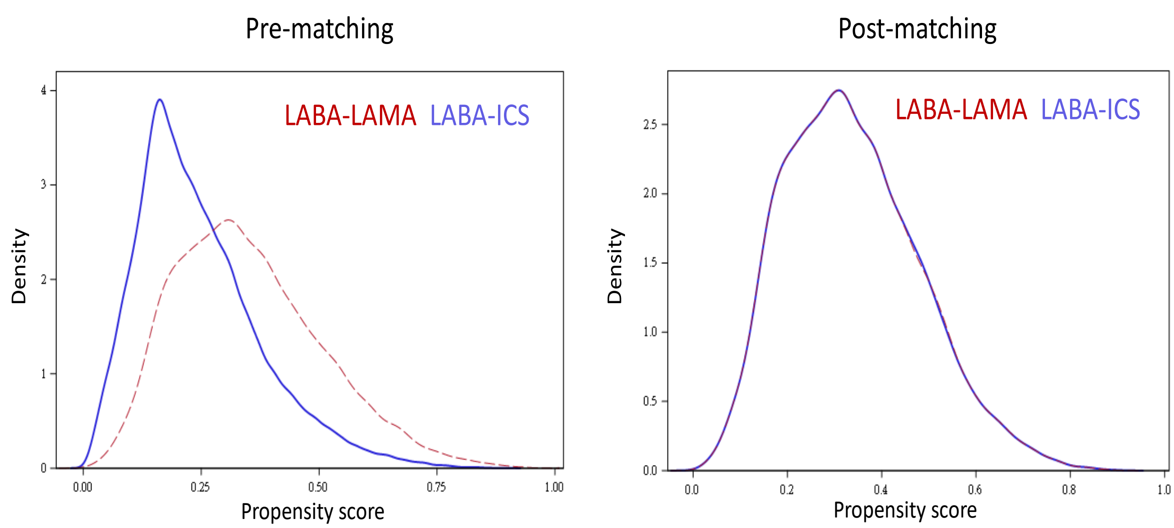
	Before matching			After matching		
Variables	**LABA/LAMA (N=11,580)**	**LABA/ICS (N=30,664)**	**Standardized difference**	**LABA/LAMA (N=11,115)**	**LABA/ICS (N=11,115)**	**Standardized difference**
Age in years[1], Mean±SD	75.7±6.7	76.4±7.4	0.106	75.7±6.7	75.7±7.0	0.004
Sex: Female, n(%)	5,841 (50.4)	16,921 (55.2)	0.095	5,638 (50.7)	5,626 (50.6)	0.002
Race: Black, n(%)	520 (4.5)	1,966 (6.4)	0.085	515 (4.6)	519 (4.7)	0.002
Race: White, n(%)	10,258 (88.6)	26,017 (84.8)	0.110	9,811 (88.3)	9,840 (88.5)	0.008
Race: Other, n(%)	802 (6.9)	2,681 (8.7)	0.068	789 (7.1)	756 (6.8)	0.012
Number of COPD exacerbations[2], Mean±SD	0.4±1.1	0.4±0.9	0.085	0.4±1.1	0.4±1.0	0.012
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.6±2.0	0.2±1.1	0.229	0.5±1.7	0.4±1.6	0.020
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.4±2.9	1.3±2.8	0.035	1.4±2.9	1.4±2.9	0.008
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.1±0.8	0.2±1.1	0.094	0.1±0.8	0.1±0.8	0.005
Supplemental oxygen use[2], Mean±SD	2,169 (18.7)	4,350 (14.2)	0.123	2,033 (18.3)	2,055 (18.5)	0.005
Breast cancer[3], n(%)	590 (5.1)	1,571 (5.1)	0.001	558 (5.0)	549 (4.9)	0.004
Colorectal cancer[3], n(%)	269 (2.3)	778 (2.5)	0.014	262 (2.4)	267 (2.4)	0.003
Endometrial cancer[3], n(%)	53 (0.5)	191 (0.6)	0.023	53 (0.5)	50 (0.4)	0.004
Prostate cancer[3], n(%)	638 (5.5)	1,620 (5.3)	0.010	619 (5.6)	630 (5.7)	0.004
Stroke-Transient Ischemic attack[3], n(%)	1,154 (10.0)	3,740 (12.2)	0.071	1,120 (10.1)	1,119 (10.1)	0.000
Acute myocaridal infarction[3], n(%)	467 (4.0)	1,434 (4.7)	0.032	448 (4.0)	440 (4.0)	0.004
Chronic kidney disease[3], n(%)	4,776 (41.2)	13,381 (43.6)	0.048	4,600 (41.4)	4,654 (41.9)	0.010
Diabetes[3], n(%)	4,259 (36.8)	12,543 (40.9)	0.085	4,138 (37.2)	4,214 (37.9)	0.014
Depression[3], n(%)	4,132 (35.7)	11,931 (38.9)	0.067	3,997 (36.0)	4,054 (36.5)	0.011
Pneumonia[2], n(%)	2,161 (18.7)	7,239 (23.6)	0.121	2,096 (18.9)	2,114 (19.0)	0.004

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 21. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among those without allergic rhinitis)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	11,115	782	2,202.95 7	35.49774	0.855 (95% Confidence interval: 0.779-0.938)
LABA/LA MA	11,115	1,066	2,697.64 3	39.51598	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 8. Propensity score distribution before and after matching (Among those without allergic rhinitis)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 22. Characteristics of study population by drug, before and after matching (Among individuals aged less than 75 years)

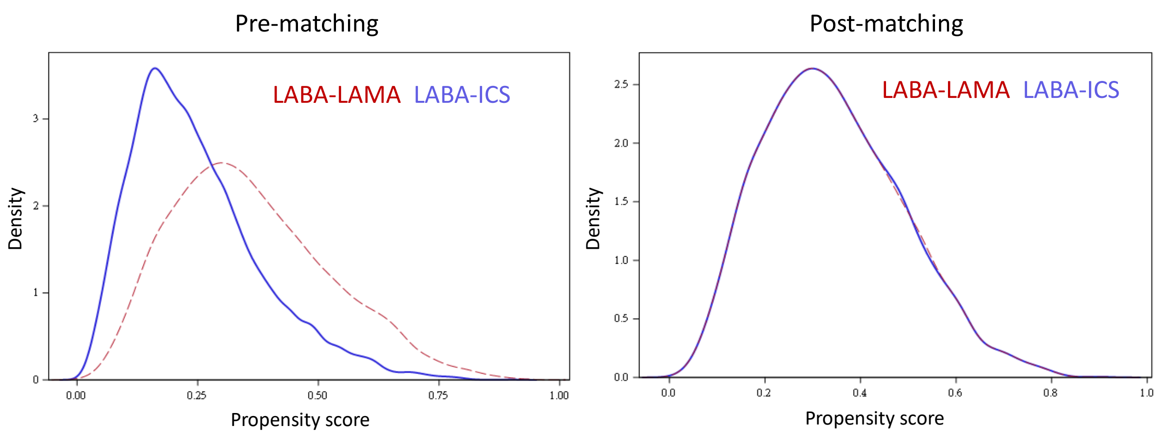
	Before matching			**After matching**		
Variables	**LABA/LAMA (N=6,501)**	**LABA/ICS (N=16,805)**	**Standardized difference**	**LABA/LAMA (N=6,150)**	**LABA/ICS (N=6,150)**	**Standardized difference**
Age in years[1], Mean±SD	70.1±2.6	69.9±2.6	0.056	70.1±2.6	70.1±2.6	0.004
Sex: Female, n(%)	3,192 (49.1)	9,141 (54.4)	0.106	3,060 (49.8)	3,036 (49.4)	0.008
Race: Black, n(%)	332 (5.1)	1,243 (7.4)	0.095	330 (5.4)	333 (5.4)	0.002
Race: White, n(%)	5,721 (88.0)	14,120 (84.0)	0.115	5,380 (87.5)	5,386 (87.6)	0.003
Race: Other, n(%)	448 (6.9)	1,442 (8.6)	0.063	440 (7.2)	431 (7.0)	0.006
Number of COPD exacerbations[2], Mean±SD	0.5±1.0	0.4±0.9	0.091	0.5±1.0	0.4±1.0	0.016
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.6±2.0	0.2±1.2	0.224	0.5±1.7	0.4±1.7	0.014
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.7±3.2	1.5±3.0	0.036	1.6±3.2	1.6±3.1	0.008
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.8	0.3±1.3	0.128	0.2±0.9	0.2±0.9	0.007
Supplemental oxygen use[2], Mean±SD	1,083 (16.7)	2,166 (12.9)	0.106	983 (16.0)	937 (15.2)	0.021
Breast cancer[3], n(%)	273 (4.2)	706 (4.2)	0.000	257 (4.2)	259 (4.2)	0.002
Colorectal cancer[3], n(%)	116 (1.8)	285 (1.7)	0.007	110 (1.8)	125 (2.0)	0.018
Endometrial cancer[3], n(%)	20 (0.3)	110 (0.7)	0.050	20 (0.3)	18 (0.3)	0.006
Prostate cancer[3], n(%)	266 (4.1)	585 (3.5)	0.032	244 (4.0)	242 (3.9)	0.002
Stroke-Transient Ischemic attack[3], n(%)	497 (7.6)	1,558 (9.3)	0.058	479 (7.8)	461 (7.5)	0.011
Acute myocaridal infarction[3], n(%)	248 (3.8)	671 (4.0)	0.009	236 (3.8)	243 (4.0)	0.006
Chronic kidney disease[3], n(%)	2,259 (34.7)	5,986 (35.6)	0.018	2,140 (34.8)	2,153 (35.0)	0.004
Diabetes[3], n(%)	2,340 (36.0)	6,611 (39.3)	0.069	2,226 (36.2)	2,250 (36.6)	0.008
Depression[3], n(%)	2,490 (38.3)	6,739 (40.1)	0.037	2,378 (38.7)	2,367 (38.5)	0.004
Allergic rhinitis[2], n(%)	874 (13.4)	2,682 (16.0)	0.071	834 (13.6)	859 (14.0)	0.012
Pneumonia[2], n(%)	1,135 (17.5)	3,462 (20.6)	0.080	1,086 (17.7)	1,059 (17.2)	0.012

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 23. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals aged less than 75 years)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	6,150	469	1,235.74	37.95297	0.880 (95% Confidence interval: 0.780-0.993)
LABA/LAMA	6,150	617	1,493.681	41.30735	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 9. Propensity score distribution before and after matching (Among individuals aged less than 75 years)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 24. Characteristics of study population by drug, before and after matching (Among individuals aged greater than 74 and less than 85 years)

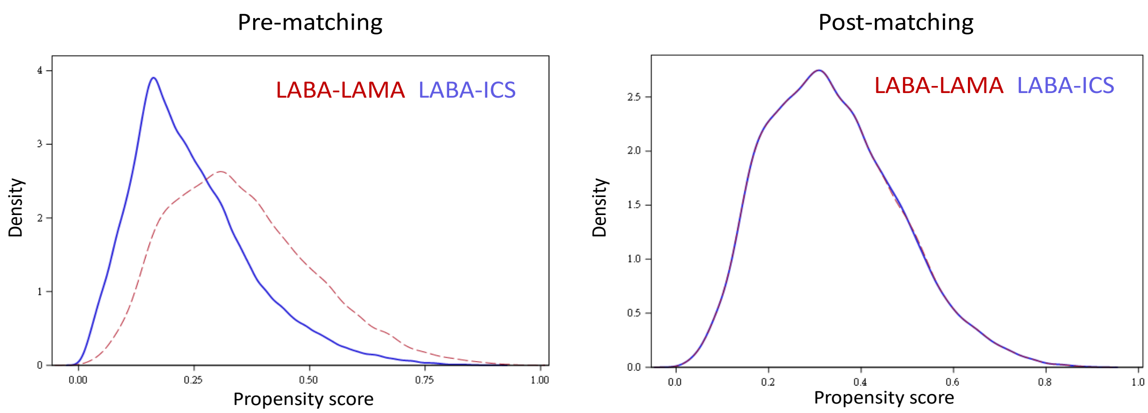
	Before matching			**After matching**		
Variables	**LABA/LAMA (N=5,325)**	**LABA/ICS (N=13,839)**	**Standardized difference**	**LABA/LAMA (N=5,031)**	**LABA/ICS (N=5,031)**	**Standardized difference**
Age in years[1], Mean±SD	78.7±2.8	79.0±2.8	0.091	78.7±2.8	78.7±2.8	0.003
Sex: Female, n(%)	2,735 (51.4)	7,642 (55.2)	0.077	2,579 (51.3)	2,606 (51.8)	0.011
Race: Black, n(%)	218 (4.1)	777 (5.6)	0.071	212 (4.2)	206 (4.1)	0.006
Race: White, n(%)	4,759 (89.4)	11,855 (85.7)	0.112	4,481 (89.1)	4,506 (89.6)	0.016
Race: Other, n(%)	348 (6.5)	1,207 (8.7)	0.082	338 (6.7)	319 (6.3)	0.015
Number of COPD exacerbations[2], Mean±SD	0.4±1.2	0.3±0.9	0.097	0.4±1.2	0.4±1.0	0.020
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±1.9	0.2±1.1	0.218	0.4±1.6	0.4±1.6	0.011
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.3±2.6	1.2±2.5	0.032	1.3±2.6	1.3±2.7	0.007
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.101	0.2±0.9	0.2±0.9	0.002
Supplemental oxygen use[2], Mean±SD	1,078 (20.2)	2,033 (14.7)	0.147	977 (19.4)	982 (19.5)	0.003
Breast cancer[3], n(%)	304 (5.7)	800 (5.8)	0.003	282 (5.6)	276 (5.5)	0.005
Colorectal cancer[3], n(%)	139 (2.6)	413 (3.0)	0.023	134 (2.7)	124 (2.5)	0.013
Endometrial cancer[3], n(%)	30 (0.6)	87 (0.6)	0.008	28 (0.6)	23 (0.5)	0.014
Prostate cancer[3], n(%)	341 (6.4)	908 (6.6)	0.006	327 (6.5)	316 (6.3)	0.009
Stroke-Transient Ischemic attack[3], n(%)	602 (11.3)	1871 (13.5)	0.067	585 (11.6)	579 (11.5)	0.004
Acute myocaridal infarction[3], n(%)	214 (4.0)	668 (4.8)	0.039	205 (4.1)	193 (3.8)	0.012
Chronic kidney disease[3], n(%)	2,414 (45.3)	6,520 (47.1)	0.036	2,292 (45.6)	2259 (44.9)	0.013
Diabetes[3], n(%)	2,030 (38.1)	5,929 (42.8)	0.096	1,930 (38.4)	1914 (38.0)	0.007
Depression[3], n(%)	1,828 (34.3)	5,217 (37.7)	0.070	1,744 (34.7)	1758 (34.9)	0.006
Allergic rhinitis[2], n(%)	747 (14.0)	2,236 (16.2)	0.060	712 (14.2)	739 (14.7)	0.015
Pneumonia[2], n(%)	1,028 (19.3)	3,341 (24.1)	0.118	995 (19.8)	1002 (19.9)	0.003

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 25. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals aged greater than 74 and less than 85 years)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	5,031	344	986.3628	34.87561	0.853 (95% Confidence interval: 0.741-0.981)
LABA/LAMA	5,031	463	1,197.656	38.65883	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 10. Propensity score distribution before and after matching (Among individuals aged greater than 74 and less than 85 years)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 26. Characteristics of study population by drug, before and after matching (Among individuals aged greater than 84 years)

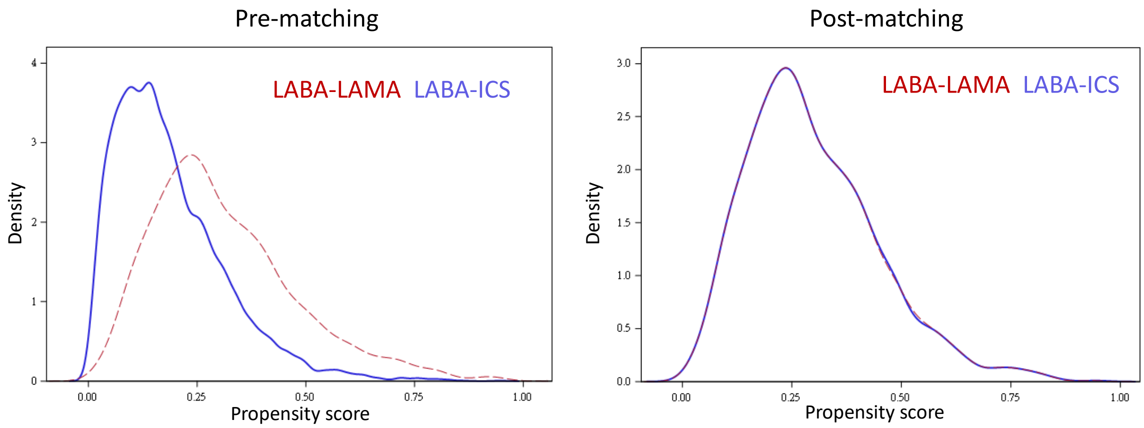
	Before matching			After matching		
Variables	**LABA/LAMA (N=1,578)**	**LABA/ICS (N=5,844)**	**Standardized difference**	**LABA/LAMA (N=1,519)**	**LABA/ICS (N=1,519)**	**Standardized difference**
Age in years[1], Mean±SD	88.4±3.1	88.9±3.4	0.170	88.4±3.1	88.4±3.2	0.005
Sex: Female, n(%)	888 (56.3)	3,714 (63.6)	0.149	861 (56.7)	859 (56.6)	0.003
Race: Black, n(%)	58 (3.7)	270 (4.6)	0.047	58 (3.8)	58 (3.8)	0.000
Race: White, n(%)	1,357 (86.0)	4,925 (84.3)	0.048	1,306 (86.0)	1,293 (85.1)	0.024
Race: Other, n(%)	163 (10.3)	649 (11.1)	0.025	155 (10.2)	168 (11.1)	0.028
Number of COPD exacerbations[2], Mean±SD	0.3±0.8	0.3±0.8	0.051	0.3±0.8	0.3±0.8	0.002
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±2.0	0.2±0.9	0.247	0.4±1.8	0.4±1.5	0.041
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.1±2.7	1.2±2.8	0.021	1.2±2.7	1.1±2.2	0.011
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.8	0.3±1.3	0.113	0.2±0.8	0.2±0.8	0.009
Supplemental oxygen use[2], Mean±SD	328 (20.8)	843 (14.4)	0.168	309 (20.3)	312 (20.5)	0.005
Breast cancer[3], n(%)	109 (6.9)	413 (7.1)	0.006	101 (6.6)	104 (6.8)	0.008
Colorectal cancer[3], n(%)	60 (3.8)	205 (3.5)	0.016	57 (3.8)	59 (3.9)	0.007
Endometrial cancer[3], n(%)	11 (0.7)	32 (0.5)	0.019	10 (0.7)	11 (0.7)	0.008
Prostate cancer[3], n(%)	120 (7.6)	407 (7.0)	0.025	115 (7.6)	106 (7.0)	0.023
Stroke-Transient Ischemic attack[3], n(%)	232 (14.7)	1,001 (17.1)	0.066	222 (14.6)	234 (15.4)	0.022
Acute myocaridal infarction[3], n(%)	64 (4.1)	300 (5.1)	0.051	61 (4.0)	57 (3.8)	0.014
Chronic kidney disease[3], n(%)	836 (53.0)	3,245 (55.5)	0.051	807 (53.1)	810 (53.3)	0.004
Diabetes[3], n(%)	589 (37.3)	2,307 (39.5)	0.044	566 (37.3)	589 (38.8)	0.031
Depression[3], n(%)	505 (32.0)	2,320 (39.7)	0.161	488 (32.1)	492 (32.4)	0.006
Allergic rhinitis[2], n(%)	203 (12.9)	906 (15.5)	0.076	197 (13.0)	178 (11.7)	0.038
Pneumonia[2], n(%)	391 (24.8)	1,800 (30.8)	0.135	377 (24.8)	369 (24.3)	0.012

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 27. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals aged greater than 84 years)

Treatment group	**Number of patients**	**Number of events**	**Person years**	**Rate per 100 per year**	**Hazard ratio (post matching)[1]**
LABA/ICS	1,519	89	291.2307	30.55997	1.002 (95% Confidence interval: 0.752-1.335)
LABA/LAMA	1,519	99	345.5222	28.65228	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 11. Propensity score distribution before and after matching (Among individuals aged greater than 84 years)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 28. Characteristics of study population by drug, before and after matching (Among individuals with zero exacerbations in the preceding year)

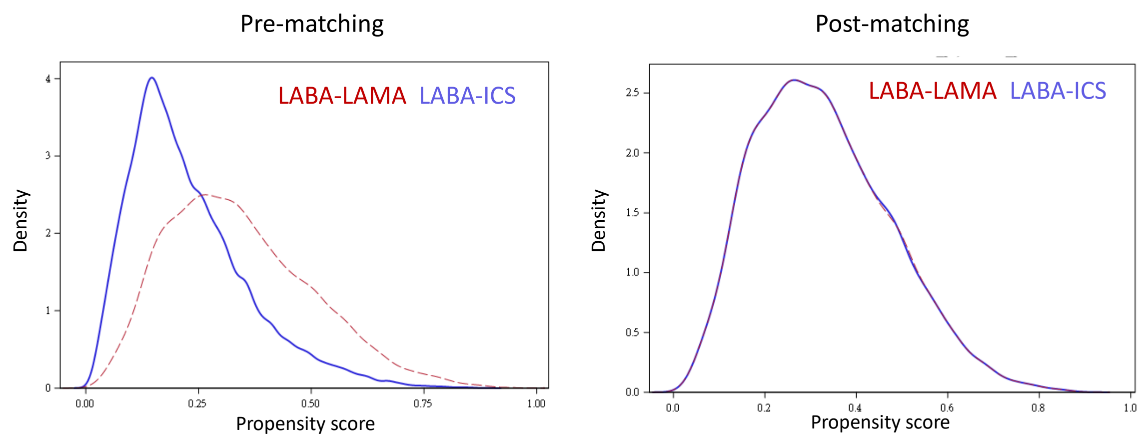
	Before matching			After matching		
Variables	**LABA/LAMA (N=9,910)**	**LABA/ICS (N=28,648)**	**Standardized difference**	**LABA/LAMA (N=9,497)**	**LABA/ICS (N=9,497)**	**Standardized difference**
Age in years[1], Mean±SD	75.9±6.8	76.7±7.5	0.105	76.0±6.8	76.0±7.1	0.000
Sex: Female, n(%)	5,026 (50.7)	16,169 (56.4)	0.115	4,846 (51.0)	4,870 (51.3)	0.005
Race: Black, n(%)	466 (4.7)	1,765 (6.2)	0.064	457 (4.8)	470 (4.9)	0.006
Race: White, n(%)	8,665 (87.4)	24,058 (84.0)	0.099	8,282 (87.2)	8,245 (86.8)	0.012
Race: Other, n(%)	779 (7.9)	2,825 (9.9)	0.070	758 (8.0)	782 (8.2)	0.009
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.5±1.9	0.2±1.0	0.229	0.4±1.6	0.4±1.6	0.033
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.3±2.7	1.2±2.6	0.021	1.3±2.6	1.2±2.6	0.004
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.8	0.3±1.2	0.125	0.2±0.8	0.2±0.8	0.010
Supplemental oxygen use[2], Mean±SD	1,514 (15.3)	3,206 (11.2)	0.121	1,413 (14.9)	1,422 (15.0)	0.003
Breast cancer[3], n(%)	503 (5.1)	1,542 (5.4)	0.014	472 (5.0)	499 (5.3)	0.013
Colorectal cancer[3], n(%)	245 (2.5)	722 (2.5)	0.003	232 (2.4)	231 (2.4)	0.001
Endometrial cancer[3], n(%)	49 (0.5)	179 (0.6)	0.017	48 (0.5)	52 (0.5)	0.006
Prostate cancer[3], n(%)	563 (5.7)	1,500 (5.2)	0.020	537 (5.7)	527 (5.5)	0.005
Stroke-Transient Ischemic attack[3], n(%)	1,014 (10.2)	3,536 (12.3)	0.067	983 (10.4)	999 (10.5)	0.006
Acute myocaridal infarction[3], n(%)	376 (3.8)	1,269 (4.4)	0.032	366 (3.9)	360 (3.8)	0.003
Chronic kidney disease[3], n(%)	4,111 (41.5)	12,430 (43.4)	0.039	3,969 (41.8)	4,030 (42.4)	0.013
Diabetes[3], n(%)	3,796 (38.3)	11,924 (41.6)	0.068	3,673 (38.7)	3,695 (38.9)	0.005
Depression[3], n(%)	3,498 (35.3)	11,097 (38.7)	0.071	3,365 (35.4)	3,373 (35.5)	0.002
Allergic rhinitis[2], n(%)	1,341 (13.5)	4,707 (16.4)	0.081	1,293 (13.6)	1,357 (14.3)	0.019
Pneumonia[2], n(%)	1,695 (17.1)	6,201 (21.6)	0.115	1,647 (17.3)	1,695 (17.8)	0.013

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 29. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals with zero exacerbations in the preceding year)

Treatment group	**Number of patients**	**Number of events**	**Person years**	**Rate per 100 per year**	**Hazard ratio (post matching)**[1]
LABA/ICS	9,497	426	1,958.89 1	21.747	0.790 (95% Confidence interval: 0.698-0.895)
LABA/LA MA	9,497	617	2,335.11 6	26.42267	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 12. Propensity score distribution before and after matching (Among individuals with zero exacerbations in the preceding year)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 30. Characteristics of study population by drug, before and after matching (Among individuals with one exacerbation in the preceding year)

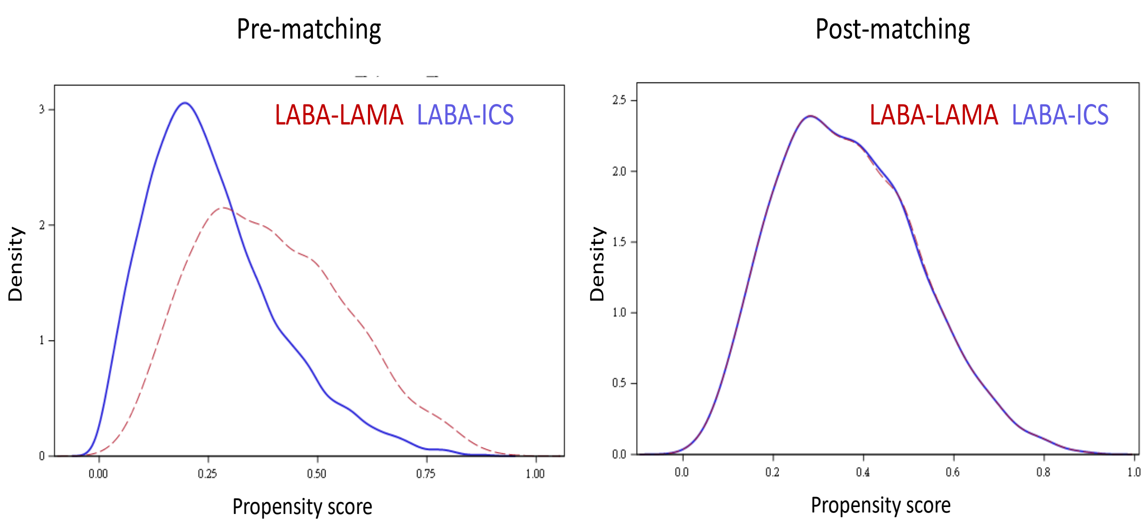
	Before matching			After matching		
Variables	**LABA/LAMA (N=2,278)**	**LABA/ICS (N=5,331)**	**Standardized difference**	**LABA/LAMA (N=2,058)**	**LABA/ICS (N=2,058)**	**Standardized difference**
Age in years[1], Mean±SD	75.1±6.5	75.7±7.1	0.089	75.2±6.6	75.2±6.8	0.008
Sex: Female, n(%)	1,137 (49.9)	2,971 (55.7)	0.117	1,050 (51.0)	1,065 (51.7)	0.015
Race: Black, n(%)	99 (4.3)	367 (6.9)	0.110	94 (4.6)	86 (4.2)	0.019
Race: White, n(%)	2,052 (90.1)	4,630 (86.9)	0.101	1,849 (89.8)	1,861 (90.4)	0.020
Race: Other, n(%)	127 (5.6)	334 (6.3)	0.029	115 (5.6)	111 (5.4)	0.009
Number of COPD exacerbations[2], Mean±SD	1.0±0.0	1.0±0.0	0.000	1.0±0.0	1.0±0.0	0.000
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.7±2.1	0.3±1.3	0.201	0.6±1.9	0.5±1.8	0.022
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.8±3.2	1.6±3.0	0.059	1.7±3.2	1.8±3.3	0.006
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.099	0.2±1.0	0.2±1.0	0.021
Supplemental oxygen use[2], Mean±SD	542 (23.8)	1,059 (19.9)	0.095	458 (22.3)	481 (23.4)	0.027
Breast cancer[3], n(%)	112 (4.9)	279 (5.2)	0.014	102 (5.0)	117 (5.7)	0.032
Colorectal cancer[3], n(%)	44 (1.9)	122 (2.3)	0.025	40 (1.9)	39 (1.9)	0.004
Endometrial cancer[3], n(%)	6 (0.3)	29 (0.5)	0.044	6 (0.3)	4 (0.2)	0.020
Prostate cancer[3], n(%)	112 (4.9)	289 (5.4)	0.023	100 (4.9)	106 (5.2)	0.013
Stroke-Transient Ischemic attack[3], n(%)	212 (9.3)	613 (11.5)	0.072	195 (9.5)	178 (8.6)	0.029
Acute myocaridal infarction[3], n(%)	97 (4.3)	236 (4.4)	0.008	88 (4.3)	97 (4.7)	0.021
Chronic kidney disease[3], n(%)	907 (39.8)	2,248 (42.2)	0.048	811 (39.4)	801 (38.9)	0.010
Diabetes[3], n(%)	765 (33.6)	1,988 (37.3)	0.078	696 (33.8)	694 (33.7)	0.002
Depression[3], n(%)	846 (37.1)	2,067 (38.8)	0.034	775 (37.7)	777 (37.8)	0.002
Allergic rhinitis[2], n(%)	312 (13.7)	752 (14.1)	0.012	280 (13.6)	291 (14.1)	0.015
Pneumonia[2], n(%)	537 (23.6)	1,584 (29.7)	0.139	501 (24.3)	480 (23.3)	0.024

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 31. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals with one exacerbation in the preceding year)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	2,058	207	404.898	51.12398	0.891 (95% Confidence interval: 0.743-1.068)
LABA/LAMA	2,058	273	501.6838	54.41675	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 13. Propensity score distribution before and after matching (Among individuals with one exacerbation in the preceding year)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 32. Characteristics of study population by drug, before and after matching (Among individuals with more than 1 exacerbation in the preceding year)

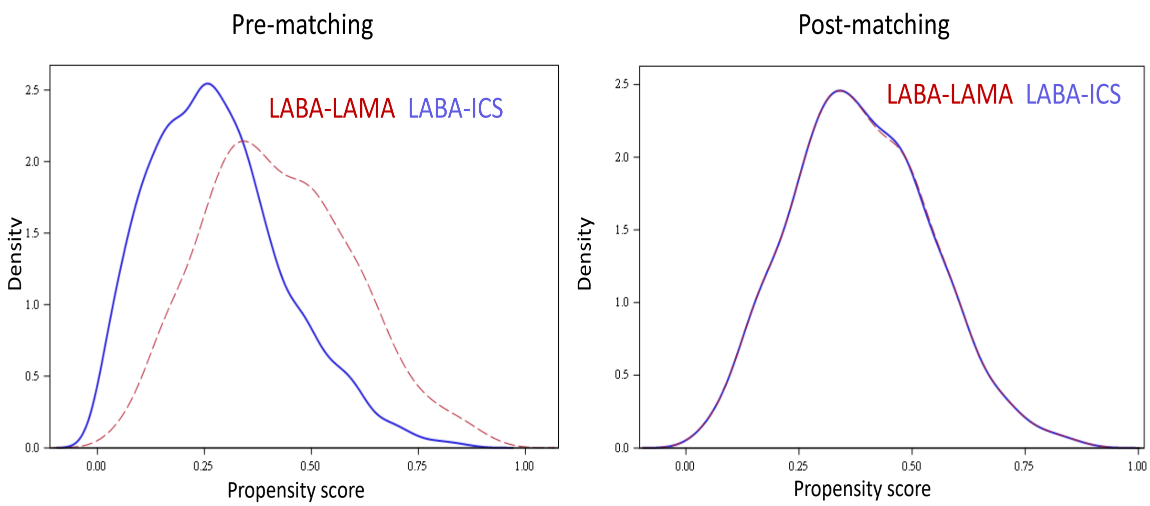
	Before matching			**After matching**		
Variables	**LABA/LAMA (N=1,216)**	**LABA/ICS (N=2,509)**	**Standardized difference**	**LABA/LAMA (N=1,068)**	**LABA/ICS (N=1,068)**	**Standardized difference**
Age in years[1], Mean±SD	74.8±6.1	75.1±6.8	0.042	74.8±6.2	74.8±6.5	0.004
Sex: Female, n(%)	652 (53.6)	1357 (54.1)	0.009	575 (53.8)	592 (55.4)	0.032
Race: Black, n(%)	43 (3.5)	158 (6.3)	0.128	41 (3.8)	41 (3.8)	0.000
Race: White, n(%)	1,120 (92.1)	2,212 (88.2)	0.133	975 (91.3)	969 (90.7)	0.020
Race: Other, n(%)	53 (4.4)	139 (5.5)	0.054	52 (4.9)	58 (5.4)	0.025
Number of COPD exacerbations[2], Mean±SD	3.0±2.0	3.0±1.6	0.028	3.0±1.9	2.9±1.5	0.055
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.8±2.2	0.4±1.5	0.209	0.6±1.8	0.6±1.9	0.020
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	2.3±3.8	2.5±4.2	0.061	2.4±3.9	2.4±4.0	0.012
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±1.0	0.3±1.4	0.079	0.2±1.0	0.2±1.0	0.014
Supplemental oxygen use[2], Mean±SD	433 (35.6)	777 (31.0)	0.099	357 (33.4)	361 (33.8)	0.008
Breast cancer[3], n(%)	71 (5.8)	98 (3.9)	0.090	49 (4.6)	59 (5.5)	0.043
Colorectal cancer[3], n(%)	26 (2.1)	59 (2.4)	0.014	23 (2.2)	27 (2.5)	0.025
Endometrial cancer[3], n(%)	6 (0.5)	21 (0.8)	0.042	5 (0.5)	3 (0.3)	0.031
Prostate cancer[3], n(%)	52 (4.3)	111 (4.4)	0.007	48 (4.5)	41 (3.8)	0.033
Stroke-Transient Ischemic attack[3], n(%)	105 (8.6)	281 (11.2)	0.086	94 (8.8)	108 (10.1)	0.045
Acute myocaridal infarction[3], n(%)	53 (4.4)	134 (5.3)	0.046	49 (4.6)	51 (4.8)	0.009
Chronic kidney disease[3], n(%)	491 (40.4)	1,073 (42.8)	0.048	424 (39.7)	413 (38.7)	0.021
Diabetes[3], n(%)	398 (32.7)	935 (37.3)	0.095	345 (32.3)	365 (34.2)	0.040
Depression[3], n(%)	479 (39.4)	1,112 (44.3)	0.100	418 (39.1)	424 (39.7)	0.012
Allergic rhinitis[2], n(%)	171 (14.1)	365 (14.5)	0.014	145 (13.6)	148 (13.9)	0.008
Pneumonia[2], n(%)	322 (26.5)	818 (32.6)	0.135	295 (27.6)	290 (27.2)	0.011

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 33. Hazard ratio of time to first COPD exacerbation among new users of LABA/LAMA versus LABA/ICS in patients with COPD (Among individuals with more than 1 exacerbation in the preceding year)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
LABA/ICS	1,068	239	177.3415	134.7682	0.945 (95% Confidence interval: 0.795-1.124)
LABA/LAMA	1,068	279	204.6023	136.3621	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 14. Propensity score distribution before and after matching (Among individuals with more than 1 exacerbation in the preceding year)

Note: Modeled around the probability of receiving LABA/LAMA

Appendix table 34. Characteristics of study population by drug, before and after matching (negative control analysis)

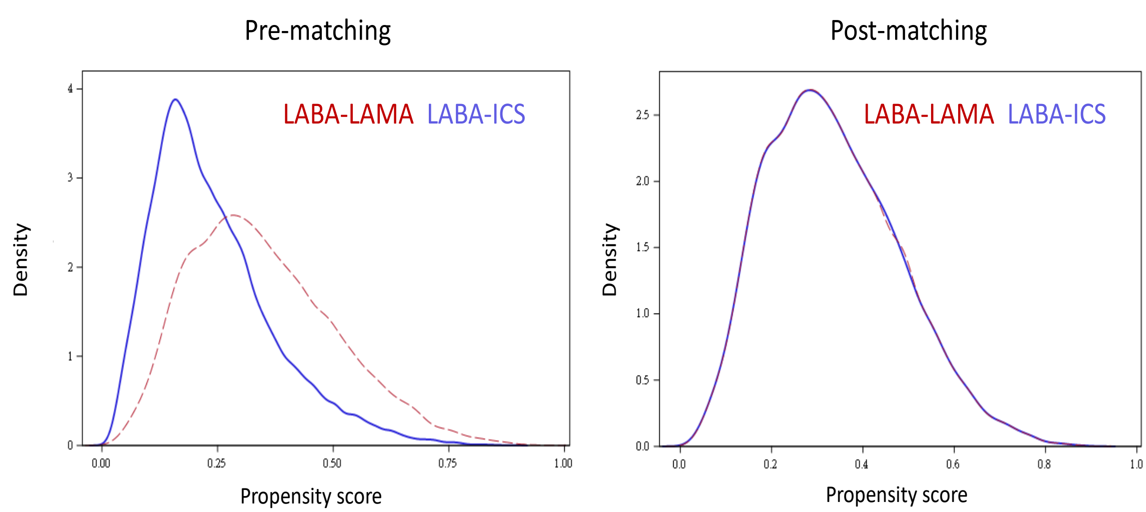
	Before matching			After matching		
Variables	**LABA/LAMA (N=13,404)**	**LABA/ICS (N=36,488)**	**Standardized difference**	**LABA/LAMA (N=12,884)**	**LABA/ICS (N=12,884)**	**Standardized difference**
Age in years[1], Mean±SD	75.7±6.7	76.4±7.4	0.105	75.7±6.8	75.7±7.0	0.006
Sex: Female, n(%)	6,815 (50.8)	20,497 (56.2)	0.107	6,583 (51.1)	6,534 (50.7)	0.008
Race: Black, n(%)	608 (4.5)	2,290 (6.3)	0.077	596 (4.6)	596 (4.6)	0.000
Race: White, n(%)	11,837 (88.3)	30,900 (84.7)	0.106	11,345 (88.1)	11,331 (87.9)	0.003
Race: Other, n(%)	959 (7.2)	3,298 (9.0)	0.069	943 (7.3)	957 (7.4)	0.004
Number of COPD exacerbations[2], Mean±SD	0.4±1.1	0.3±0.9	0.094	0.4±1.1	0.4±1.0	0.015
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	0.6±2.0	0.2±1.1	0.227	0.5±1.7	0.4±1.6	0.026
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.5±2.9	1.4±2.8	0.031	1.4±2.9	1.4±2.8	0.006
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.2±0.9	0.3±1.2	0.115	0.2±0.9	0.2±0.9	0.003
Supplemental oxygen use[2], Mean±SD	2,489 (18.6)	5,042 (13.8)	0.129	2,325 (18.0)	2,332 (18.1)	0.001
Breast cancer[3], n(%)	686 (5.1)	1,919 (5.3)	0.006	655 (5.1)	631 (4.9)	0.009
Colorectal cancer[3], n(%)	315 (2.4)	903 (2.5)	0.008	310 (2.4)	317 (2.5)	0.004
Endometrial cancer[3], n(%)	61 (0.5)	229 (0.6)	0.024	61 (0.5)	54 (0.4)	0.008
Prostate cancer[3], n(%)	727 (5.4)	1,900 (5.2)	0.010	701 (5.4)	692 (5.4)	0.003
Stroke-Transient Ischemic attack[3], n(%)	1,331 (9.9)	4,430 (12.1)	0.071	1,299 (10.1)	1,261 (9.8)	0.010
Acute myocaridal infarction[3], n(%)	526 (3.9)	1,639 (4.5)	0.028	513 (4.0)	491 (3.8)	0.009
Chronic kidney disease[3], n(%)	5,509 (41.1)	15,751 (43.2)	0.042	5,324 (41.3)	5,354 (41.6)	0.005
Diabetes[3], n(%)	4,959 (37.0)	14,847 (40.7)	0.076	4,798 (37.2)	4,833 (37.5)	0.006
Depression[3], n(%)	4,823 (36.0)	14,276 (39.1)	0.065	4,657 (36.1)	4,659 (36.2)	0.000
Allergic rhinitis[2], n(%)	1,824 (13.6)	5,824 (16.0)	0.066	1,767 (13.7)	1,789 (13.9)	0.005
Pneumonia[2], n(%)	2,554 (19.1)	8,603 (23.6)	0.111	2,483 (19.3)	2,465 (19.1)	0.004

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 35. Hazard ratio of gastroesophageal reflux disease for new users of LABA/LAMA versus LABA/ICS in patients with COPD (negative control analysis)

Treatment group	**Number of patients**	**Number of events**	**Person years**	**Rate per 100 per year**	**Hazard ratio (post matching)[1]**
LABA/ICS	12,884	252	2,939.567	8.57269	0.955 (95% Confidence interval: 0.875-1.042)
LABA/LAMA	12,884	257	3,581.262	7.176241	1 (reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 15. Propensity score distribution before and after matching (negative control analysis)

Note: Modeled around the probability of receiving LABA/LAMA

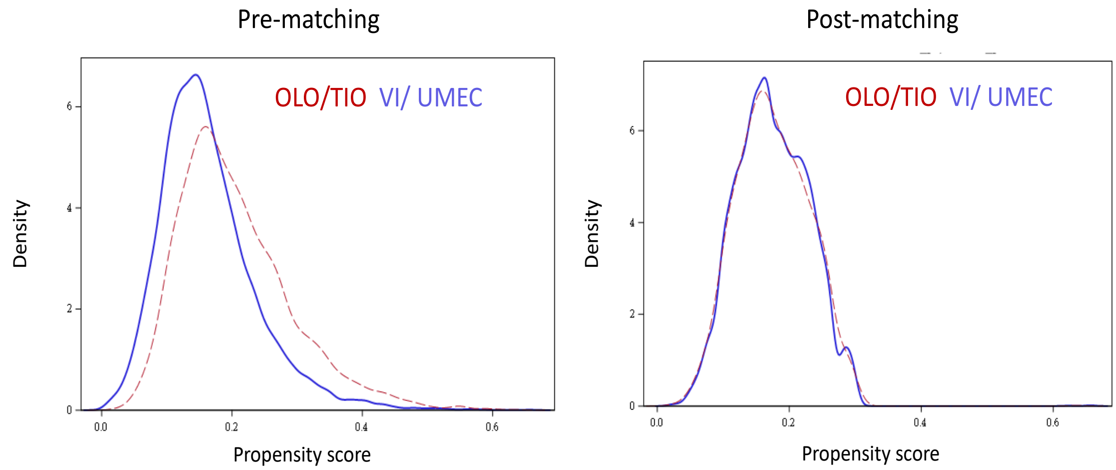
Appendix G: LABA/LAMA therapies in the US

Appendix table 36. Currently available LABA/LAMA therapies in the US

Agents	Brand names	Dosing
Combination long-acting muscarinic antagonist/long-acting beta$_2$ agonist inhalers		
Aclidinium 400 mcg/formoterol 12 mcg	Duaklir Pressair	1 inhalation twice daily; DPI
Glycopyrrolate 9 mcg/formoterol 4.8 mcg	Bevespi Aerosphere	2 inhalations twice daily; MDI
Tiotropium 2.5 mcg/olodaterol 2.5 mcg per	Stiolto Respimat	2 inhalations once daily; SMI
Umeclidinium 62.5 mcg/vilanterol 25 mcg	Anoro Ellipta	1 inhalation once daily; DPI

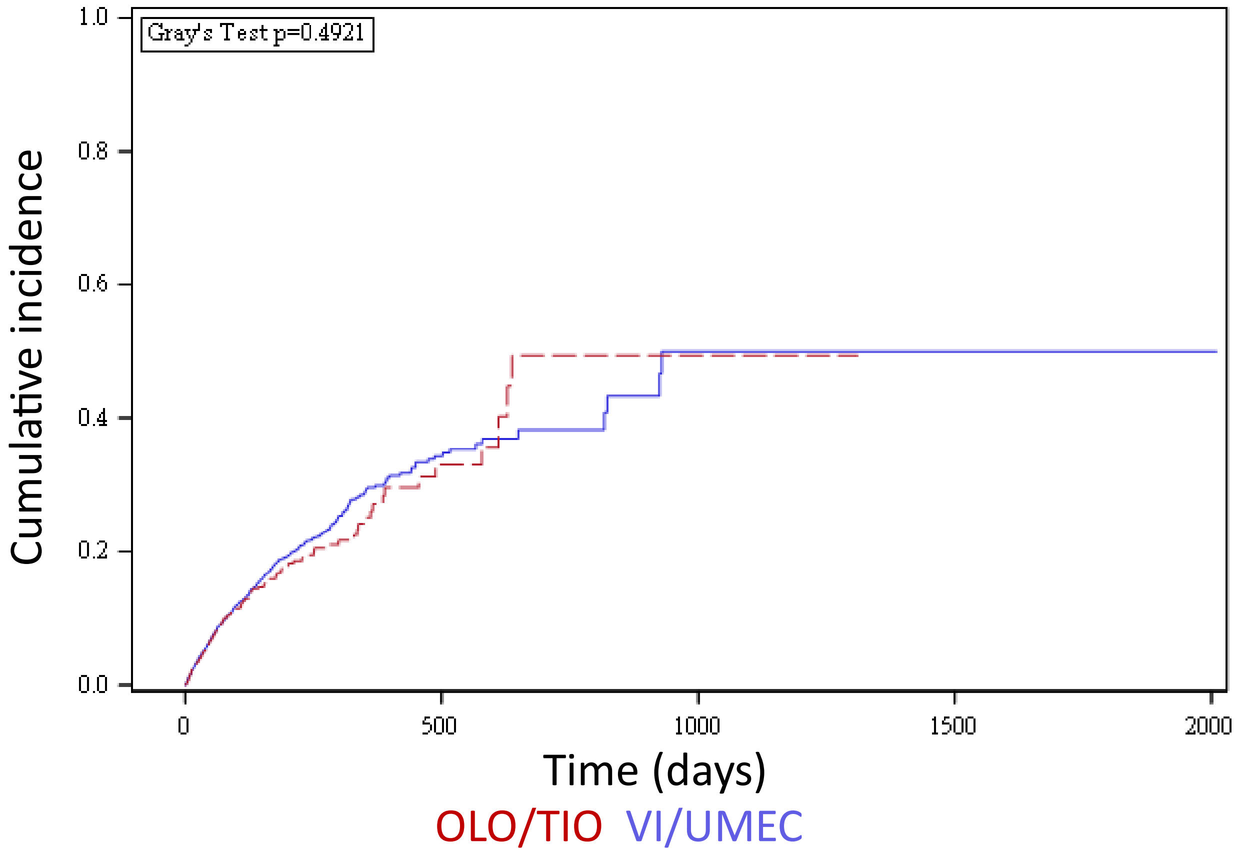
DPI: dry powder inhaler; MDI: metered dose inhaler; SMI: soft mist inhaler.

Appendix H: Aim 3 results



Appendix figure 16. Propensity score distribution before and after matching (Overall results)

Modeled around the probability of receiving OLO/TIO



Appendix figure 17. Cumulative incidence of the time to first COPD exacerbation, comparing OLO/TIO and VI/UMEC initiators with persistent use, via the Kaplan-Meier method

Appendix table 37. Characteristics of study population by drug, before and after matching (negative control analysis)

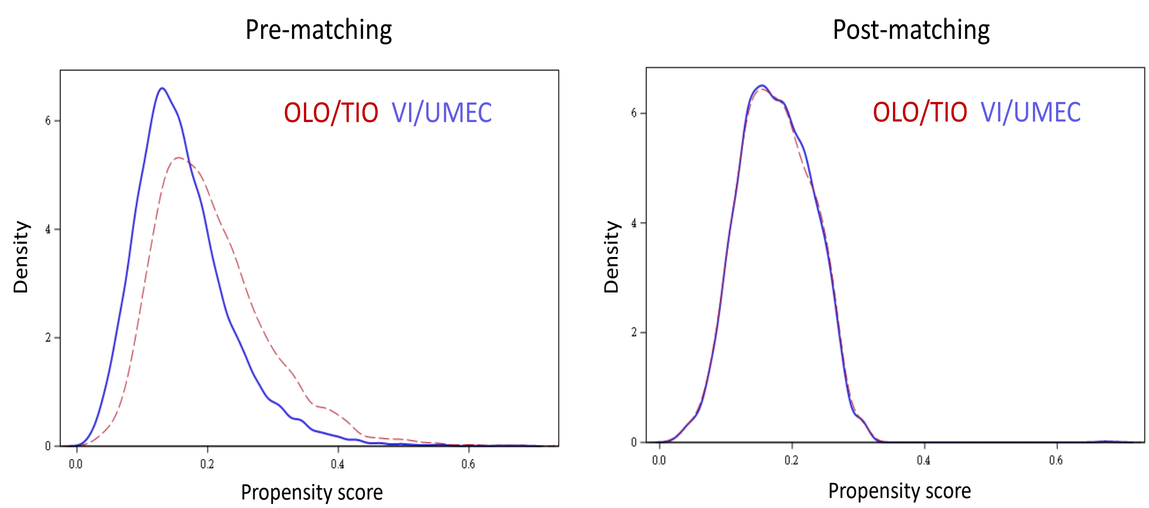
	Before matching			After matching		
Variables	**OLO/TIO (N=2,739)**	**VI/UMEC (N=13,333)**	**Standardized difference**	**OLO/TIO (N=2,267)**	**VI/UMEC (N=6,801)**	**Standardized difference**
Age in years[1], Mean±SD	75.5±6.5	75.7±6.7	0.027	75.6±6.6	75.5±6.7	0.008
Sex: Female, n(%)	1,346 (49.1)	6,851 (51.4)	0.026	1,137 (50.2)	3,375 (49.6)	0.011
Race: Black, n(%)	93 (3.4)	638 (4.8)	0.045	87 (3.8)	243 (3.6)	0.014
Race: White, n(%)	2,474 (90.3)	11,778 (88.3)	0.070	2,025 (89.3)	6,112 (89.9)	0.018
Race: Other, n(%)	172 (6.3)	917 (6.9)	0.064	155 (6.8)	446 (6.6)	0.011
Number of COPD exacerbations[2], Mean±SD	0.6±1.3	0.5±1.2	0.045	0.5±1.2	0.5±1.3	0.018
Number of prescriptions for long-acting bronchodilators[2], Mean±SD	1.6±3.0	1.0±2.5	0.204	1.1±2.4	1.1±2.5	0.013
Number of prescriptions for short-acting bronchodilators[2], Mean±SD	1.8±3.3	1.6±3.0	0.070	1.6±3.0	1.6±2.9	0.001
Number of prescriptions for inhaled corticosteroids[2], Mean±SD	0.4±1.1	0.4±1.2	0.006	0.3±1.1	0.4±1.2	0.011
Number of prescriptions for LABA/ICS[2], Mean±SD	0.8±2.1	0.9±2.2	0.026	0.8±2.2	0.8±2.1	0.012
Supplemental oxygen use[2], Mean±SD	664 (24.2)	2,692 (20.2)	0.227	490 (21.6)	1424 (20.9)	0.017
Breast cancer[3], n(%)	132 (4.8)	656 (4.9)	0.098	112 (4.9)	311 (4.6)	0.017
Colorectal cancer[3], n(%)	56 (2.0)	318 (2.4)	0.005	49 (2.2)	159 (2.3)	0.012
Endometrial cancer[3], n(%)	7 (0.3)	68 (0.5)	0.023	7 (0.3)	24 (0.4)	0.008
Prostate cancer[3], n(%)	164 (6.0)	710 (5.3)	0.041	125 (5.5)	389 (5.7)	0.009
Stroke-Transient Ischemic attack[3], n(%)	233 (8.5)	1,328 (10.0)	0.029	199 (8.8)	617 (9.1)	0.010
Acute myocardial infarction[3], n(%)	102 (3.7)	531 (4.0)	0.050	85 (3.7)	265 (3.9)	0.008
Chronic kidney disease[3], n(%)	1,046 (38.2)	5,499 (41.2)	0.013	883 (39.0)	2,642 (38.8)	0.002
Diabetes[3], n(%)	949 (34.6)	4,900 (36.8)	0.062	802 (35.4)	2,390 (35.1)	0.005
Depression[3], n(%)	949 (34.6)	4,859 (36.4)	0.044	791 (34.9)	2,331 (34.3)	0.013
Allergic rhinitis[2], n(%)	419 (15.3)	1,812 (13.6)	0.038	323 (14.2)	959 (14.1)	0.004
Pneumonia[2], n(%)	546 (19.9)	2,658 (19.9)	0.049	439 (19.4)	1,267 (18.6)	0.019

[1]On the index date, [2] In the 1-year preceding index date, [3]Based on the Medicare Chronic conditions file information

Appendix table 38. Hazard ratio of gastroesophageal reflux disease for new users of OLO/TIO versus VI/UMEC in patients with COPD (negative control analysis)

Treatment group	Number of patients	Number of events	Person years	Rate per 100 per year	Hazard ratio (post matching)[1]
OLO/TIO	2,267	48	613.098	7.830	1.055 (95% Confidence interval: 0.903-1.233)
VI/UMEC	6,801	150	2,091.37 0	7.172	1 (Reference group)

[1]Matched on high-dimensional propensity scores. Hazard ratios obtained from the Cox-proportional hazards model.



Appendix figure 18. Propensity score distribution before and after matching (negative control analysis)

Modeled around the probability of receiving OLO/TIO

Appendix I: Reprint agreement for Aim 1

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS

Jun 14, 2023

This Agreement between Mr. Chintal Shah ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	5567730716293
License date	Jun 14, 2023
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Applied Health Economics and Health Policy
Licensed Content Title	Direct Medical Costs of COPD in the USA: An Analysis of the Medical Expenditure Panel Survey 2017–2018
Licensed Content Author	Chintal H. Shah et al
Licensed Content Date	Jun 3, 2023
Type of Use	Thesis/Dissertation
Requestor type	non-commercial (non-profit)
Format	print and electronic
Portion	full article/chapter
Will you be translating?	no

Circulation/distribution	1000 - 1999
Author of this Springer Nature content	yes
Title	The Economic Burden of Chronic Obstructive Pulmonary Disease and Comparative Effectiveness of Maintenance Inhaler Medications in the United States
Institution name	University of Maryland, Baltimore
Expected presentation date	Jul 2023
Requestor Location	Mr. Chintal Shah 220 N Arch street, 12th Floor BALTIMORE, MD 21201 United States Attn: University of Maryland Baltimore
Total	0.00 USD

Terms and Conditions

Springer Nature Customer Service Centre GmbH Terms and Conditions

The following terms and conditions ("Terms and Conditions") together with the terms specified in your [RightsLink] constitute the License ("License") between you as Licensee and Springer Nature Customer Service Centre GmbH as Licensor. By clicking 'accept' and completing the transaction for your use of the material ("Licensed Material"), you confirm your acceptance of and obligation to be bound by these Terms and Conditions.

1. Grant and Scope of License

1. 1. The Licensor grants you a personal, non-exclusive, non-transferable, non-sublicensable, revocable, world-wide License to reproduce, distribute, communicate to the public, make available, broadcast, electronically transmit or create derivative works using the Licensed Material for the purpose(s) specified in your RightsLink Licence Details only. Licenses are granted for the specific use requested in the order and for no other use, subject to these Terms and Conditions. You acknowledge and agree that the rights granted to you under this License do not include the right to modify, edit, translate, include in collective works, or create derivative works of the Licensed Material in whole or in part unless expressly stated in your RightsLink

Licence Details. You may use the Licensed Material only as permitted under this Agreement and will not reproduce, distribute, display, perform, or otherwise use or exploit any Licensed Material in any way, in whole or in part, except as expressly permitted by this License.

1. 2. You may only use the Licensed Content in the manner and to the extent permitted by these Terms and Conditions, by your RightsLink Licence Details and by any applicable laws.

1. 3. A separate license may be required for any additional use of the Licensed Material, e.g. where a license has been purchased for print use only, separate permission must be obtained for electronic re-use. Similarly, a License is only valid in the language selected and does not apply for editions in other languages unless additional translation rights have been granted separately in the License.

1. 4. Any content within the Licensed Material that is owned by third parties is expressly excluded from the License.

1. 5. Rights for additional reuses such as custom editions, computer/mobile applications, film or TV reuses and/or any other derivative rights requests require additional permission and may be subject to an additional fee. Please apply to journalpermissions@springernature.com or bookpermissions@springernature.com for these rights.

2. Reservation of Rights

Licensor reserves all rights not expressly granted to you under this License. You acknowledge and agree that nothing in this License limits or restricts Licensor's rights in or use of the Licensed Material in any way. Neither this License, nor any act, omission, or statement by Licensor or you, conveys any ownership right to you in any Licensed Material, or to any element or portion thereof. As between Licensor and you, Licensor owns and retains all right, title, and interest in and to the Licensed Material subject to the license granted in Section 1.1. Your permission to use the Licensed Material is expressly conditioned on you not impairing Licensor's or the applicable copyright owner's rights in the Licensed Material in any way.

3. Restrictions on use

3. 1. Minor editing privileges are allowed for adaptations for stylistic purposes or formatting purposes provided such alterations do not alter the original meaning or intention of the Licensed Material and the new figure(s) are still accurate and representative of the Licensed Material. Any other changes including but not limited to, cropping, adapting, and/or omitting material that affect the meaning, intention or moral rights of the author(s) are strictly prohibited.

3. 2. You must not use any Licensed Material as part of any design or trademark.

3. 3. Licensed Material may be used in Open Access Publications (OAP), but any such reuse must include a clear acknowledgment of this permission visible at the same time as the figures/tables/illustration or abstract and which must indicate that the Licensed Material is not part of the governing OA license but has been reproduced with permission. This may be indicated according to any standard referencing system but must include at a minimum 'Book/Journal title, Author, Journal Name (if applicable),

Volume (if applicable), Publisher, Year, reproduced with permission from SNCSC'.

4. STM Permission Guidelines

4. 1. An alternative scope of license may apply to signatories of the STM Permissions Guidelines ("STM PG") as amended from time to time and made available at https://www.stm-assoc.org/intellectual-property/permissions/permissions-guidelines/.

4. 2. For content reuse requests that qualify for permission under the STM PG, and which may be updated from time to time, the STM PG supersede the terms and conditions contained in this License.

4. 3. If a License has been granted under the STM PG, but the STM PG no longer apply at the time of publication, further permission must be sought from the Rightsholder. Contact journalpermissions@springernature.com or bookpermissions@springernature.com for these rights.

5. Duration of License

5. 1. Unless otherwise indicated on your License, a License is valid from the date of purchase ("License Date") until the end of the relevant period in the below table:

Reuse in a medical communications project	Reuse up to distribution or time period indicated in License
Reuse in a dissertation/thesis	Lifetime of thesis
Reuse in a journal/magazine	Lifetime of journal/magazine
Reuse in a book/textbook	Lifetime of edition
Reuse on a website	1 year unless otherwise specified in the License
Reuse in a presentation/slide kit/poster	Lifetime of presentation/slide kit/poster. Note: publication whether electronic or in print of presentation/slide kit/poster may require further permission.
Reuse in conference proceedings	Lifetime of conference proceedings
Reuse in an annual report	Lifetime of annual report
Reuse in training/CME materials	Reuse up to distribution or time period indicated in License
Reuse in newsmedia	Lifetime of newsmedia
Reuse in coursepack/classroom materials	Reuse up to distribution and/or time period indicated in license

6. Acknowledgement

6. 1. The Licensor's permission must be acknowledged next to the Licensed Material in print. In electronic form, this acknowledgement must be visible at the same time as the figures/tables/illustrations or abstract and must be hyperlinked to the journal/book's homepage.

6. 2. Acknowledgement may be provided according to any standard referencing system and at a minimum should include "Author, Article/Book Title, Journal name/Book imprint, volume, page number, year, Springer Nature".

7. Reuse in a dissertation or thesis

7. 1. Where 'reuse in a dissertation/thesis' has been selected, the following terms apply: Print rights of the Version of Record are provided for; electronic rights for use only on institutional repository as defined by the Sherpa guideline (www.sherpa.ac.uk/romeo/) and only up to what is required by the awarding institution.

7. 2. For theses published under an ISBN or ISSN, separate permission is required. Please contact journalpermissions@springernature.com or bookpermissions@springernature.com for these rights.

7. 3. Authors must properly cite the published manuscript in their thesis according to current citation standards and include the following acknowledgement: '*Reproduced with permission from Springer Nature'*.

8. License Fee

You must pay the fee set forth in the License Agreement (the "License Fees"). All amounts payable by you under this License are exclusive of any sales, use, withholding, value added or similar taxes, government fees or levies or other assessments. Collection and/or remittance of such taxes to the relevant tax authority shall be the responsibility of the party who has the legal obligation to do so.

9. Warranty

9. 1. The Licensor warrants that it has, to the best of its knowledge, the rights to license reuse of the Licensed Material. **You are solely responsible for ensuring that the material you wish to license is original to the Licensor and does not carry the copyright of another entity or third party (as credited in the published version).** If the credit line on any part of the Licensed Material indicates that it was reprinted or adapted with permission from another source, then you should seek additional permission from that source to reuse the material.

9. 2. EXCEPT FOR THE EXPRESS WARRANTY STATED HEREIN AND TO THE EXTENT PERMITTED BY APPLICABLE LAW, LICENSOR PROVIDES THE LICENSED MATERIAL "AS IS" AND MAKES NO OTHER REPRESENTATION OR WARRANTY. LICENSOR EXPRESSLY DISCLAIMS ANY LIABILITY FOR ANY CLAIM ARISING FROM OR OUT OF THE CONTENT, INCLUDING BUT NOT LIMITED TO ANY ERRORS, INACCURACIES, OMISSIONS, OR DEFECTS CONTAINED THEREIN, AND ANY IMPLIED OR EXPRESS WARRANTY AS TO MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. IN NO EVENT SHALL LICENSOR BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, PUNITIVE, OR EXEMPLARY DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, VIEWING OR USE OF THE LICENSED MATERIAL REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION,

DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION APPLIES NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

10. Termination and Cancellation

10. 1. The License and all rights granted hereunder will continue until the end of the applicable period shown in Clause 5.1 above. Thereafter, this license will be terminated and all rights granted hereunder will cease.

10. 2. Licensor reserves the right to terminate the License in the event that payment is not received in full or if you breach the terms of this License.

11. General

11. 1. The License and the rights and obligations of the parties hereto shall be construed, interpreted and determined in accordance with the laws of the Federal Republic of Germany without reference to the stipulations of the CISG (United Nations Convention on Contracts for the International Sale of Goods) or to Germany´s choice-of-law principle.

11. 2. The parties acknowledge and agree that any controversies and disputes arising out of this License shall be decided exclusively by the courts of or having jurisdiction for Heidelberg, Germany, as far as legally permissible.

11. 3. This License is solely for Licensor's and Licensee's benefit. It is not for the benefit of any other person or entity.

Questions? For questions on Copyright Clearance Center accounts or website issues please contact springernaturesupport@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777. For questions on Springer Nature licensing please visit https://www.springernature.com/gp/partners/rights-permissions-third-party-distribution

Other Conditions:

Version 1.4 - Dec 2022

Questions? customercare@copyright.com.

8. References

1. American Lung Association COPD Prevalence Available online: https://www.lung.org/research/trends-in-lung-disease/copd-trends-brief/copd-prevalence (accessed on 12 January 2022).
2. National Center for Health Statistics. *Percentage of COPD, Emphysema, or Chronic Bronchitis for Adults Aged 18 and over, United States, 2019. National Health Interview Survey.*; 2022;
3. CDC - Basics About COPD - Chronic Obstructive Pulmonary Disease (COPD) Available online: https://www.cdc.gov/copd/basics-about.html (accessed on 21 August 2020).
4. Mannino, D.; Buist, A.; Petty, T.; Enright, P.; Redd, S. Lung Function and Mortality in the United States: Data from the First National Health and Nutrition Examination Survey Follow up Study. *Thorax* **2003**, *58*, 388–393, doi:10.1136/thorax.58.5.388.
5. Shah, C.H.; Reed, R.M.; Villalonga-Olives, E.; Slejko, J.F.; Eakin, M.N.; So, J.Y.; Zafari, Z. Quantifying Heterogeneity of Physical and Mental Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease Patients in the United States. *Expert Review of Respiratory Medicine* **2020**, *14*, 937–947, doi:10.1080/17476348.2020.1776612.
6. Murphy, S.L. Mortality in the United States, 2017. **2018**, 8.
7. Chapel, J.M.; Ritchey, M.D.; Zhang, D.; Wang, G. Prevalence and Medical Costs of Chronic Diseases Among Adult Medicaid Beneficiaries. *Am J Prev Med* **2017**, *53*, S143–S154, doi:10.1016/j.amepre.2017.07.019.

8. Patel, J.G.; Coutinho, A.D.; Lunacsek, O.E.; Dalal, A.A. COPD Affects Worker Productivity and Health Care Costs. *Int J Chron Obstruct Pulmon Dis* **2018**, *13*, 2301–2311, doi:10.2147/COPD.S163795.
9. Dalal, A.A.; Christensen, L.; Liu, F.; Riedel, A.A. Direct Costs of Chronic Obstructive Pulmonary Disease among Managed Care Patients. *Int J Chron Obstruct Pulmon Dis* **2010**, *5*, 341–349, doi:10.2147/COPD.S13771.
10. Strassels, S.A.; Smith, D.H.; Sullivan, S.D.; Mahajan, P.S. The Costs of Treating COPD in the United States. *Chest* **2001**, *119*, 344–352, doi:10.1378/chest.119.2.344.
11. Miller, J.D.; Foster, T.; Boulanger, L.; Chace, M.; Russell, M.W.; Marton, J.P.; Menzin, J. Direct Costs of COPD in the U.S.: An Analysis of Medical Expenditure Panel Survey (MEPS) Data. *COPD* **2005**, *2*, 311–318.
12. Blanchette, C.M.; Dalal, A.A.; Mapel, D. Changes in COPD Demographics and Costs over 20 Years. *J Med Econ* **2012**, *15*, 1176–1182, doi:10.3111/13696998.2012.713880.
13. Mann, M.; Meyer, R.J. Drug Development for Asthma and COPD: A Regulatory Perspective. *Respiratory Care* **2018**, *63*, 797–817, doi:10.4187/respcare.06009.
14. Dahl, R.; Greefhorst, L.A.; Nowak, D.; Nonikov, V.; Byrne, A.M.; Thomson, M.H.; Till, D.; Della Cioppa, G.; Formoterol in Chronic Obstructive Pulmonary Disease I Study Group Inhaled Formoterol Dry Powder versus Ipratropium Bromide in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* **2001**, *164*, 778–784, doi:10.1164/ajrccm.164.5.2007006.

15. Rennard, S.I.; Farmer, S.G. Exacerbations and Progression of Disease in Asthma and Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc* **2004**, *1*, 88–92, doi:10.1513/pats.2306026.
16. Terry, P.D.; Dhand, R. Inhalation Therapy for Stable COPD: 20 Years of GOLD Reports. *Adv Ther* **2020**, *37*, 1812–1828, doi:10.1007/s12325-020-01289-y.
17. Charlie Strange, M.D.; Valery Walker, M.S.; Junliang Tong, P.; Maureen Carlyle, M.P.H.; Jonathan Kurlander, M.S.; Lauren A. Millette, P.; Eric Wittbrodt, P. A Retrospective Claims Analysis of Dual Bronchodilator Fixed-Dose Combination Versus Bronchodilator Monotherapy in Patients with Chronic Obstructive Pulmonary Disease. *Chronic Obstructive Pulmonary Diseases:Journal of the COPD Foundation 6*, 221–232.
18. Horita, N.; Goto, A.; Shibata, Y.; Ota, E.; Nakashima, K.; Nagai, K.; Kaneko, T. Long-acting Muscarinic Antagonist (LAMA) plus Long-acting Beta-agonist (LABA) versus LABA plus Inhaled Corticosteroid (ICS) for Stable Chronic Obstructive Pulmonary Disease (COPD). *Cochrane Database of Systematic Reviews* **2017**, doi:10.1002/14651858.CD012066.pub2.
19. Lipson, D.A.; Barnhart, F.; Brealey, N.; Brooks, J.; Criner, G.J.; Day, N.C.; Dransfield, M.T.; Halpin, D.M.G.; Han, M.K.; Jones, C.E.; et al. Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD. *N Engl J Med* **2018**, *378*, 1671–1680, doi:10.1056/NEJMoa1713901.
20. Wang, M.-T.; Lai, J.-H.; Huang, Y.-L.; Liou, J.-T.; Cheng, S.-H.; Lin, C.W.; Pan, H.-Y.; Hsu, Y.-J.; Tsai, C.-L. Comparative Effectiveness and Safety of Different Types of Inhaled Long-Acting B2-Agonist Plus Inhaled Long-Acting Muscarinic

Antagonist vs Inhaled Long-Acting B2-Agonist Plus Inhaled Corticosteroid Fixed-Dose Combinations in COPD A Propensity Score-Inverse Probability of Treatment Weighting Cohort Study. *Chest* **2021**, *160*, 1255–1270, doi:10.1016/j.chest.2021.05.025.

21. Suissa, S.; Dell'Aniello, S.; Ernst, P. Comparative Effectiveness and Safety of LABA-LAMA vs LABA-ICS Treatment of COPD in Real-World Clinical Practice. *CHEST* **2019**, *155*, 1158–1165, doi:10.1016/j.chest.2019.03.005.
22. Samp, J.C.; Joo, M.J.; Schumock, G.T.; Calip, G.S.; Pickard, A.S.; Lee, T.A. Comparative Effectiveness of Long-Acting Beta2-Agonist Combined with a Long-Acting Muscarinic Antagonist or Inhaled Corticosteroid in Chronic Obstructive Pulmonary Disease. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* **2017**, *37*, 447–455, doi:10.1002/phar.1913.
23. Fukuda, N.; Horita, N.; Kaneko, A.; Goto, A.; Kaneko, T.; Ota, E.; Kew, K.M. 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 of Systematic Reviews* **2023**, doi:10.1002/14651858.CD012066.pub3.
24. Suissa, S.; Dell'Aniello, S.; Ernst, P. Comparing Initial LABA-ICS Inhalers in COPD: Real-World Effectiveness and Safety. *Respir Med* **2021**, *189*, 106645, doi:10.1016/j.rmed.2021.106645.
25. Krishnan, J.A. Con: Comparative Effectiveness Research. *Am J Respir Crit Care Med* **2011**, *183*, 975–976, doi:10.1164/rccm.201008-1300ED.

26. Cazzola, M.; Page, C.; Rogliani, P.; Calzetta, L.; Matera, M.G. Dual Bronchodilation for the Treatment of COPD: From Bench to Bedside. *British Journal of Clinical Pharmacology* **2022**, *88*, 3657–3673, doi:10.1111/bcp.15390.
27. Matera, M.G.; Rinaldi, B.; Belardo, C.; Cazzola, M. Pharmacotherapy of LAMA/LABA Inhaled Therapy Combinations for Chronic Obstructive Pulmonary Disease: A Clinical Overview. *Expert Review of Clinical Pharmacology* **2022**, *15*, 1269–1281, doi:10.1080/17512433.2022.2134113.
28. Kern, D.M.; Davis, J.; Williams, S.A.; Tunceli, O.; Wu, B.; Hollis, S.; Strange, C.; Trudo, F. Comparative Effectiveness of Budesonide/Formoterol Combination and Fluticasone/Salmeterol Combination among Chronic Obstructive Pulmonary Disease Patients New to Controller Treatment: A US Administrative Claims Database Study. *Respiratory Research* **2015**, *16*, 52, doi:10.1186/s12931-015-0210-x.
29. Travers, J.; Marsh, S.; Caldwell, B.; Williams, M.; Aldington, S.; Weatherall, M.; Shirtcliffe, P.; Beasley, R. External Validity of Randomized Controlled Trials in COPD. *Respiratory Medicine* **2007**, *101*, 1313–1320, doi:10.1016/j.rmed.2006.10.011.
30. Raherison, C.; Girodet, P.-O. Epidemiology of COPD. *European Respiratory Review* **2009**, *18*, 213–221, doi:10.1183/09059180.00003609.
31. Vestbo, J.; Hurd, S.S.; Agustí, A.G.; Jones, P.W.; Vogelmeier, C.; Anzueto, A.; Barnes, P.J.; Fabbri, L.M.; Martinez, F.J.; Nishimura, M.; et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary

Disease: GOLD Executive Summary. *Am. J. Respir. Crit. Care Med.* **2013**, *187*, 347–365, doi:10.1164/rccm.201204-0596PP.

32. Global Initiative for Chronic Obstructive Lung Disease *POCKET GUIDE TO COPD DIAGNOSIS, MANAGEMENT, AND PREVENTION: A Guide for Health Care Professionals*; Fontana, Wisconsin, 2020;
33. Snider, G.L. Distinguishing among Asthma, Chronic Bronchitis, and Emphysema. *Chest* **1985**, *87*, 35S-39S, doi:10.1378/chest.87.1.35s.
34. MacNee, W. Pathogenesis of Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc* **2005**, *2*, 258–266, doi:10.1513/pats.200504-045SR.
35. Shah, C.H.; Onukwugha, E.; Zafari, Z.; Villalonga-Olives, E.; Park, J.; Slejko, J.F. Economic Burden of Comorbidities among COPD Patients Hospitalized for Acute Exacerbations: An Analysis of a Commercially Insured Population. *Expert Review of Pharmacoeconomics & Outcomes Research* **2021**, *0*, 1–8, doi:10.1080/14737167.2021.1981291.
36. Kohansal, R.; Martinez-Camblor, P.; Agustí, A.; Buist, A.S.; Mannino, D.M.; Soriano, J.B. The Natural History of Chronic Airflow Obstruction Revisited: An Analysis of the Framingham Offspring Cohort. *Am J Respir Crit Care Med* **2009**, *180*, 3–10, doi:10.1164/rccm.200901-0047OC.
37. Eisner, M.D.; Anthonisen, N.; Coultas, D.; Kuenzli, N.; Perez-Padilla, R.; Postma, D.; Romieu, I.; Silverman, E.K.; Balmes, J.R.; Committee on Nonsmoking COPD, Environmental and Occupational Health Assembly An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of

Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* **2010**, *182*, 693–718, doi:10.1164/rccm.200811-1757ST.

38. Hunninghake, G.M.; Cho, M.H.; Tesfaigzi, Y.; Soto-Quiros, M.E.; Avila, L.; Lasky-Su, J.; Stidley, C.; Melén, E.; Söderhäll, C.; Hallberg, J.; et al. MMP12, Lung Function, and COPD in High-Risk Populations. *N Engl J Med* **2009**, *361*, 2599–2608, doi:10.1056/NEJMoa0904006.
39. Beran, D.; Zar, H.J.; Perrin, C.; Menezes, A.M.; Burney, P.; Forum of International Respiratory Societies working group collaboration Burden of Asthma and Chronic Obstructive Pulmonary Disease and Access to Essential Medicines in Low-Income and Middle-Income Countries. *Lancet Respir Med* **2015**, *3*, 159–170, doi:10.1016/S2213-2600(15)00004-1.
40. Klooster, K.; ten Hacken, N.H.T.; Hartman, J.E.; Kerstjens, H.A.M.; van Rikxoort, E.M.; Slebos, D.-J. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. *N Engl J Med* **2015**, *373*, 2325–2335, doi:10.1056/NEJMoa1507807.
41. Akinbami, L.J. Chronic Obstructive Pulmonary Disease Among Adults Aged 18 and Over in the United States, 1998–2009. **2011**, 8.
42. Zafari, Z.; Li, S.; Eakin, M.N.; Bellanger, M.; Reed, R.M. Projecting Long-Term Health and Economic Burden of Chronic Obstructive Pulmonary Disease in the United States. *CHEST* **2020**, *0*, doi:10.1016/j.chest.2020.09.255.
43. Menzin, J.; Boulanger, L.; Marton, J.; Guadagno, L.; Dastani, H.; Dirani, R.; Phillips, A.; Shah, H. The Economic Burden of Chronic Obstructive Pulmonary

Disease (COPD) in a U.S. Medicare Population. *Respiratory Medicine* **2008**, *102*, 1248–1256, doi:10.1016/j.rmed.2008.04.009.

44. Dalal, A.A.; Liu, F.; Riedel, A.A. Cost Trends among Commercially Insured and Medicare Advantage-Insured Patients with Chronic Obstructive Pulmonary Disease: 2006 through 2009. *Int J Chron Obstruct Pulmon Dis* **2011**, *6*, 533–542, doi:10.2147/COPD.S24591.
45. Wilson, L.; Devine, E.B.; So, K. Direct Medical Costs of Chronic Obstructive Pulmonary Disease: Chronic Bronchitis and Emphysema. *Respiratory Medicine* **2000**, *94*, 204–213, doi:10.1053/rmed.1999.0720.
46. Foster, T.S.; Miller, J.D.; Marton, J.P.; Caloyeras, J.P.; Russell, M.W.; Menzin, J. Assessment of the Economic Burden of COPD in the U.S.: A Review and Synthesis of the Literature. *COPD: Journal of Chronic Obstructive Pulmonary Disease* **2006**, *3*, 211–218, doi:10.1080/15412550601009396.
47. Müllerova, H.; Maselli, D.J.; Locantore, N.; Vestbo, J.; Hurst, J.R.; Wedzicha, J.A.; Bakke, P.; Agusti, A.; Anzueto, A. Hospitalized Exacerbations of COPD: Risk Factors and Outcomes in the ECLIPSE Cohort. *Chest* **2015**, *147*, 999–1007, doi:10.1378/chest.14-0655.
48. Montuschi, P. Pharmacological Treatment of Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis* **2006**, *1*, 409–423.
49. Bronchodilators Available online: https://www.nhsinform.scot/tests-and-treatments/medicines-and-medical-aids/types-of-medicine/bronchodilators (accessed on 13 May 2023).

50. Ejiofor, S.; Turner, A.M. Pharmacotherapies for COPD. *Clin Med Insights Circ Respir Pulm Med* **2013**, *7*, 17–34, doi:10.4137/CCRPM.S7211.

51. Buels, K.S.; Fryer, A.D. Muscarinic Receptor Antagonists: Effects on Pulmonary Function. *Handb Exp Pharmacol* **2012**, 317–341, doi:10.1007/978-3-642-23274-9_14.

52. Barnes, P.J. Muscarinic Receptors in Lung. *Postgrad Med J* **1987**, *63 Suppl 1*, 13–19.

53. Naji, A.; Gatling, J.W. Muscarinic Antagonists. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2023.

54. Liang, T.Z.; Chao, J.H. Inhaled Corticosteroids. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2023.

55. Barnes, P.J. Inhaled Corticosteroids. *Pharmaceuticals (Basel)* **2010**, *3*, 514–540, doi:10.3390/ph3030514.

56. Ito, K.; Yamamura, S.; Essilfie-Quaye, S.; Cosio, B.; Ito, M.; Barnes, P.J.; Adcock, I.M. Histone Deacetylase 2–Mediated Deacetylation of the Glucocorticoid Receptor Enables NF-KB Suppression. *J Exp Med* **2006**, *203*, 7–13, doi:10.1084/jem.20050466.

57. Wilt, T.J.; Niewoehner, D.; MacDonald, R.; Kane, R.L. Management of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review for a Clinical Practice Guideline. *Ann Intern Med* **2007**, *147*, 639–653, doi:10.7326/0003-4819-147-9-200711060-00009.

58. Miller-Larsson, A.; Selroos, O. Advances in Asthma and COPD Treatment: Combination Therapy with Inhaled Corticosteroids and Long-Acting Beta 2-

Agonists. *Curr Pharm Des* **2006**, *12*, 3261–3279, doi:10.2174/138161206778194187.

59. Welte, T. Optimising Treatment for COPD – New Strategies for Combination Therapy. *International Journal of Clinical Practice* **2009**, *63*, 1136–1149, doi:10.1111/j.1742-1241.2009.02139.x.

60. Mammen, M.J.; Pai, V.; Aaron, S.D.; Nici, L.; Alhazzani, W.; Alexander, P.E. Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease. A Systematic Review and Meta-Analysis in Support of the American Thoracic Society Clinical Practice Guideline. *Annals ATS* **2020**, *17*, 1133–1143, doi:10.1513/AnnalsATS.201912-915OC.

61. 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*, CD012620, doi:10.1002/14651858.CD012620.pub2.

62. Chen, C.-Y.; Chen, W.-C.; Huang, C.-H.; Hsiang, Y.-P.; Sheu, C.-C.; Chen, Y.-C.; Lin, M.-C.; Chu, K.-A.; Lee, C.-H.; Wei, Y.-F. LABA/LAMA Fixed-Dose Combinations versus LAMA Monotherapy in the Prevention of COPD Exacerbations: A Systematic Review and Meta-Analysis. *Ther Adv Respir Dis* **2020**, *14*, 1753466620937194, doi:10.1177/1753466620937194.

63. van Haarst, A.; McGarvey, L.; Paglialunga, S. Review of Drug Development Guidance to Treat Chronic Obstructive Pulmonary Disease: US and EU Perspectives. *Clinical Pharmacology & Therapeutics* **2019**, *106*, 1222–1235, doi:10.1002/cpt.1540.

64. Sistani, F.; Reed, R.M.; Shah, C.H.; Zafari, Z. Trends in Medicaid Spending on Inhalers in the United States, 2012-2018. *JMCP* **2021**, *27*, 1744–1749, doi:10.18553/jmcp.2021.27.12.1744.

65. Feldman, W.B.; Gagne, J.J.; Kesselheim, A.S. Trends in Medicare Part D Inhaler Spending: 2012–2018. *Annals ATS* **2021**, *18*, 548–550, doi:10.1513/AnnalsATS.202008-1082RL.

66. Combination LAMA-LABA Inhalers for COPD - UpToDate Available online: https://www.uptodate.com/contents/image?imageKey=PULM%2F116691#! (accessed on 29 January 2023).

67. Patient Education: Inhaler Techniques in Adults (Beyond the Basics) - UpToDate Available online: https://www.uptodate.com/contents/inhaler-techniques-in-adults-beyond-the-basics (accessed on 14 May 2023).

68. Anderson, P. Use of Respimat® Soft Mist™ Inhaler in COPD Patients. *Int J Chron Obstruct Pulmon Dis* **2006**, *1*, 251–259.

69. Lee, H.Y.; Song, J.H.; Won, H.-K.; Park, Y.; Chung, K.B.; Lim, H.-J.; Ahn, Y.M.; Lee, B.J. Comparing Inhaler Use Technique Based on Inhaler Type in Elderly Patients with Respiratory Disease. *Tuberc Respir Dis (Seoul)* **2021**, *84*, 46–54, doi:10.4046/trd.2020.0021.

70. Schreiber, J.; Sonnenburg, T.; Luecke, E. Inhaler Devices in Asthma and COPD Patients – a Prospective Cross-Sectional Study on Inhaler Preferences and Error Rates. *BMC Pulmonary Medicine* **2020**, *20*, 222, doi:10.1186/s12890-020-01246-z.

71. Usmani, O.S. Choosing the Right Inhaler for Your Asthma or COPD Patient. *Ther Clin Risk Manag* **2019**, *15*, 461–472, doi:10.2147/TCRM.S160365.

72. Singer, D.; Bengtson, L.G.; Elliott, C.; Buikema, A.R.; Franchino-Elder, J. Healthcare Resource Utilization, Exacerbations, and Readmissions Among Medicare Patients with Chronic Obstructive Pulmonary Disease After Long-Acting Muscarinic Antagonist Therapy Initiation with Soft Mist versus Dry Powder Inhalers. *COPD* **2020**, *15*, 3239–3250, doi:10.2147/COPD.S284678.
73. Usmani, O.S.; Hickey, A.J.; Guranlioglu, D.; Rawson, K.; Stjepanovic, N.; Siddiqui, S.; Dhand, R. The Impact of Inhaler Device Regimen in Patients with Asthma or COPD. *The Journal of Allergy and Clinical Immunology: In Practice* **2021**, *9*, 3033-3040.e1, doi:10.1016/j.jaip.2021.04.024.
74. Centers for Medicare and Medicaid Services Hospital Readmissions Reduction Program (HRRP) Available online: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html (accessed on 16 September 2019).
75. Feemster, L.C.; Au, D.H. Penalizing Hospitals for Chronic Obstructive Pulmonary Disease Readmissions. *Am J Respir Crit Care Med* **2014**, *189*, 634–639, doi:10.1164/rccm.201308-1541PP.
76. Centers for Medicare and Medicaid Services (CMS), HHS Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Fiscal Year 2014 Rates; Quality Reporting Requirements for Specific Providers; Hospital Conditions of Participation; Payment Policies Related to Patient Status. Final Rules. *Fed Regist* **2013**, *78*, 50495–51040.

77. Luder, H.R.; Frede, S.M.; Kirby, J.A.; Epplen, K.; Cavanaugh, T.; Martin-Boone, J.E.; Conrad, W.F.; Kuhlmann, D.; Heaton, P.C. TransitionRx: Impact of Community Pharmacy Postdischarge Medication Therapy Management on Hospital Readmission Rate. *J Am Pharm Assoc (2003)* **2015**, *55*, 246–254, doi:10.1331/JAPhA.2015.14060.

78. Portillo, E.C.; Wilcox, A.; Seckel, E.; Margolis, A.; Montgomery, J.; Balasubramanian, P.; Abshire, G.; Lewis, J.; Hildebrand, C.; Mathur, S.; et al. Reducing COPD Readmission Rates: Using a COPD Care Service During Care Transitions. *Fed Pract* **2018**, *35*, 30–36.

79. Dalal, A.A.; Shah, M.; D'Souza, A.O.; Rane, P. Costs of COPD Exacerbations in the Emergency Department and Inpatient Setting. *Respir Med* **2011**, *105*, 454–460, doi:10.1016/j.rmed.2010.09.003.

80. Toy, E.L.; Beaulieu, N.U.; McHale, J.M.; Welland, T.R.; Plauschinat, C.A.; Swensen, A.; Duh, M.S. Treatment of COPD: Relationships between Daily Dosing Frequency, Adherence, Resource Use, and Costs. *Respiratory Medicine* **2011**, *105*, 435–441, doi:10.1016/j.rmed.2010.09.006.

81. Simoens, S.; Decramer, M.; De Coster, S.; Celis, G.; Laekeman, G. Clinical and Economic Analysis of Antimicrobial Therapy of Chronic Obstructive Pulmonary Disease Exacerbations. *Int. J. Clin. Pract.* **2007**, *61*, 200–206, doi:10.1111/j.1742-1241.2006.01240.x.

82. O'Reilly, J.F.; Williams, A.E.; Rice, L. Health Status Impairment and Costs Associated with COPD Exacerbation Managed in Hospital. *Int. J. Clin. Pract.* **2007**, *61*, 1112–1120, doi:10.1111/j.1742-1241.2007.01424.x.

83. Jahnz-Różyk, K.; Targowski, T.; From, S. Comparison of Outpatient and Inpatient Costs of Moderate and Severe Exacerbations of Chronic Obstructive Pulmonary Disease in Poland. *Advances in Respiratory Medicine* **2008**, *76*, 426–430.

84. Mittmann, N.; Kuramoto, L.; Seung, S.J.; Haddon, J.M.; Bradley-Kennedy, C.; FitzGerald, J.M. The Cost of Moderate and Severe COPD Exacerbations to the Canadian Healthcare System. *Respir. Med.* **2008**, *102*, 413–421, doi:10.1016/j.rmed.2007.10.010.

85. Oostenbrink, J.B.; Molken, M. Resource Use and Risk Factors in High-Cost Exacerbations of COPD. *Respir. Med.* **2004**, *98*, 883–891, doi:10.1016/j.rmed.2004.02.013.

86. Andersson, F.; Borg, S.; Jansson, S.A.; Jonsson, A.C.; Ericsson, A.; Prutz, C.; Ronmark, E.; Lundback, B. The Costs of Exacerbations in Chronic Obstructive Pulmonary Disease (COPD). *Respir. Med.* **2002**, *96*, 700–708, doi:10.1053/rmed.2002.1334.

87. Miravitlles, M.; Murio, C.; Guerrero, T.; Gisbert, R. Pharmacoeconomic Evaluation of Acute Exacerbations of Chronic Bronchitis and COPD. *Chest* **2002**, *121*, 1449–1455, doi:10.1378/chest.121.5.1449.

88. Llor, C.; Naberan, K.; Cots, J.M.; Molina, J.; Miravitlles, M. Economic Evaluation of the Antibiotic Treatment of Exacerbations of Chronic Bronchitis and COPD in Primary Care. *Int. J. Clin. Pract.* **2004**, *58*, 937–944, doi:10.1111/j.1368-5031.2004.00293.x.

89. Schermer, T.R.J.; Saris, C.G.J.; van den Bosch, W.J.H.M.; Chavannes, N.H.; van Schayck, C.P.; Dekhuijzen, P.N.R.; van Weel, C. Exacerbations and Associated

Healthcare Cost in Patients with COPD in General Practice. *Monaldi Arch Chest Dis* **2006**, *65*, 133–140, doi:10.4081/monaldi.2006.558.

90. Masa, J.F.; Sobradillo, V.; Villasante, C.; Jiménez-Ruiz, C.A.; Fernández-Fau, L.; Viejo, J.L.; Miravitlles, M. Costs of chronic obstructive pulmonary disease in Spain. Estimation from a population-based study. *Arch. Bronconeumol.* **2004**, *40*, 72–79, doi:10.1016/s1579-2129(06)60198-5.

91. Yu, T.; Fain, K.; Boyd, C.M.; Singh, S.; Weiss, C.O.; Li, T.; Varadhan, R.; Puhan, M.A. Benefits and Harms of Roflumilast in Moderate to Severe COPD. *Thorax* **2014**, *69*, 616–622, doi:10.1136/thoraxjnl-2013-204155.

92. Guerra, B.; Gaveikaite, V.; Bianchi, C.; Puhan, M.A. Prediction Models for Exacerbations in Patients with COPD. *Eur Respir Rev* **2017**, *26*, 160061, doi:10.1183/16000617.0061-2016.

93. Yebyo, H.G.; Braun, J.; Menges, D.; Riet, G. ter; Sadatsafavi, M.; Puhan, M.A. Personalising Add-on Treatment with Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease: A Benefit–Harm Modelling Study. *The Lancet Digital Health* **2021**, *0*, doi:10.1016/S2589-7500(21)00130-8.

94. Sposato, B.; Petrucci, E.; Serafini, A.; Lena, F.; Lacerenza, L.G.; Montagnani, A.; Alessandri, M.; Cresti, A.; Scala, R.; Rogliani, P.; et al. Which LABA/LAMA Should Be Chosen in COPD Patients in Real Life? *Pulmonary Pharmacology & Therapeutics* **2021**, *71*, 102076, doi:10.1016/j.pupt.2021.102076.

95. Calverley, P.M.A.; Anzueto, A.R.; Carter, K.; Grönke, L.; Hallmann, C.; Jenkins, C.; Wedzicha, J.; Rabe, K.F. Tiotropium and Olodaterol in the Prevention of Chronic Obstructive Pulmonary Disease Exacerbations (DYNAGITO): A Double-Blind,

Randomised, Parallel-Group, Active-Controlled Trial. *The Lancet Respiratory Medicine* **2018**, *6*, 337–344, doi:10.1016/S2213-2600(18)30102-4.

96. 21st Century Cures Act (2016 - H.R. 34) Available online: https://www.govtrack.us/congress/bills/114/hr34 (accessed on 28 January 2023).
97. Commissioner, O. of the Real-World Evidence Available online: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (accessed on 28 January 2023).
98. Tarazi, W.; Welch, W.P.; Nguyen, N.; Bosworth, A.; Sheingold, S.; Lew, N.D.; Sommers, B.D. Medicare Beneficiary Enrollment Trends and Demographic Characteristics. *US Department of Health and Human Services, Assistant Secretary for Planning and Evaluation, Office of Health Policy Issue Brief* **2022**, 5.
99. The Unique Needs of Medicare Beneficiaries. *National Academy of Social Insurance*.
100. Schwab, P.; Dhamane, A.D.; Hopson, S.D.; Moretz, C.; Annavarapu, S.; Burslem, K.; Renda, A.; Kaila, S. Impact of Comorbid Conditions in COPD Patients on Health Care Resource Utilization and Costs in a Predominantly Medicare Population. *Int J Chron Obstruct Pulmon Dis* **2017**, *12*, 735–744, doi:10.2147/COPD.S112256.
101. Shah, C.H.; Reed, R.M.; Liang, Y.; Zafari, Z. Association between Lung Function and Future Risks of Diabetes, Asthma, Myocardial Infarction, Hypertension and All-Cause Mortality. *ERJ Open Res* **2021**, *7*, 00178–02021, doi:10.1183/23120541.00178-2021.

102. Mues, K.E.; Liede, A.; Liu, J.; Wetmore, J.B.; Zaha, R.; Bradbury, B.D.; Collins, A.J.; Gilbertson, D.T. Use of the Medicare Database in Epidemiologic and Health Services Research: A Valuable Source of Real-World Evidence on the Older and Disabled Populations in the US. *Clin Epidemiol* **2017**, *9*, 267–277, doi:10.2147/CLEP.S105613.

103. Austin, P.C. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* **2011**, *46*, 399–424, doi:10.1080/00273171.2011.568786.

104. Schneeweiss, S.; Rassen, J.A.; Glynn, R.J.; Avorn, J.; Mogun, H.; Brookhart, M.A. High-Dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data. *Epidemiology* **2009**, *20*, 512–522, doi:10.1097/EDE.0b013e3181a663cc.

105. Rassen, J.A.; Blin, P.; Kloss, S.; Neugebauer, R.S.; Platt, R.W.; Pottegård, A.; Schneeweiss, S.; Toh, S. High-Dimensional Propensity Scores for Empirical Covariate Selection in Secondary Database Studies: Planning, Implementation, and Reporting. *Pharmacoepidemiology and Drug Safety n/a*, doi:10.1002/pds.5566.

106. Polinski, J.M.; Schneeweiss, S.; Glynn, R.J.; Lii, J.; Rassen, J.A. Confronting “Confounding by Health System Use” in Medicare Part D: Comparative Effectiveness of Propensity Score Approaches to Confounding Adjustment. *Pharmacoepidemiol Drug Saf* **2012**, *21 Suppl 2*, 90–98, doi:10.1002/pds.3250.

107. Garbe, E.; Kloss, S.; Suling, M.; Pigeot, I.; Schneeweiss, S. High-Dimensional versus Conventional Propensity Scores in a Comparative Effectiveness Study of

Coxibs and Reduced Upper Gastrointestinal Complications. *Eur J Clin Pharmacol* **2013**, *69*, 549–557, doi:10.1007/s00228-012-1334-2.

108. Guertin, J.R.; Rahme, E.; Dormuth, C.R.; LeLorier, J. Head to Head Comparison of the Propensity Score and the High-Dimensional Propensity Score Matching Methods. *BMC Med Res Methodol* **2016**, *16*, 22, doi:10.1186/s12874-016-0119-1.
109. Payet, C.; Polazzi, S.; Obadia, J.-F.; Armoiry, X.; Labarère, J.; Rabilloud, M.; Duclos, A. High-Dimensional Propensity Scores Improved the Control of Indication Bias in Surgical Comparative Effectiveness Studies. *Journal of Clinical Epidemiology* **2021**, *130*, 78–86, doi:10.1016/j.jclinepi.2020.10.003.
110. Iheanacho, I.; Zhang, S.; King, D.; Rizzo, M.; Ismaila, A.S. Economic Burden of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Literature Review. *Int J Chron Obstruct Pulmon Dis* **2020**, *15*, 439–460, doi:10.2147/COPD.S234942.
111. Lopez, E.; Claxton, G.; Schwartz, K.; Ochieng, N.; 2020 Comparing Private Payer and Medicare Payment Rates for Select Inpatient Hospital Services. *KFF* 2020.
112. Comparing Commercial and Medicare Professional Service Prices Available online: https://healthcostinstitute.org/hcci-research/comparing-commercial-and-medicare-professional-service-prices (accessed on 23 April 2022).
113. Bureau, U.C. Health Insurance Coverage in the United States: 2020 Available online: https://www.census.gov/library/publications/2021/demo/p60-274.html (accessed on 24 April 2022).
114. What Are the Recent and Forecasted Trends in Prescription Drug Spending? *Peterson-KFF Health System Tracker*.

115. Patient Trends in Hospital Inpatient Stays in the United States, 2005-2014 #225 Available online: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb225-Inpatient-US-Stays-Trends.jsp?msclkid=429efea3c33911ec8a63ef8a50af1cd3 (accessed on 23 April 2022).
116. Medical Expenditure Panel Survey Home Available online: https://meps.ahrq.gov/mepsweb/ (accessed on 2 October 2018).
117. Gothe, H.; Rajsic, S.; Vukicevic, D.; Schoenfelder, T.; Jahn, B.; Geiger-Gritsch, S.; Brixner, D.; Popper, N.; Endel, G.; Siebert, U. Algorithms to Identify COPD in Health Systems with and without Access to ICD Coding: A Systematic Review. *BMC Health Services Research* **2019**, *19*, 737, doi:10.1186/s12913-019-4574-3.
118. Ward, M.M.; Javitz, H.S.; Smith, W.M.; Bakst, A. Direct Medical Cost of Chronic Obstructive Pulmonary Disease in the U.S.A. *Respiratory Medicine* **2000**, *94*, 1123–1129, doi:10.1053/rmed.2000.0933.
119. Anecchino, C.; Rossi, E.; Fanizza, C.; De Rosa, M.; Tognoni, G.; Romero, M. Prevalence of Chronic Obstructive Pulmonary Disease and Pattern of Comorbidities in a General Population. *Int J Chron Obstruct Pulmon Dis* **2007**, *2*, 567–574.
120. Medical Expenditure Panel Survey Topics: Priority Conditions -- General Available online: https://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=41Z-1 (accessed on 1 July 2022).
121. Park, R.E. Estimation with Heteroscedastic Error Terms. *Econometrica* **1966**, *34*, 888–888, doi:10.2307/1910108.
122. Deb, P.; Norton, E.C.; Manning, W.G. *Health Econometrics Using Stata*; Stata Press: College Station, Texas, 2017; ISBN 978-1-59718-228-7.

123. Deb, P.; Norton, E.C. Modeling Health Care Expenditures and Use. *Annu. Rev. Public Health* **2018**, *39*, 489–505, doi:10.1146/annurev-publhealth-040617-013517.

124. Belotti, F.; Deb, P.; Manning, W.G.; Norton, E.C. Twopm: Two-Part Models. *The Stata Journal* **2015**, *15*, 3–20, doi:10.1177/1536867X1501500102.

125. Tompkins, L.; Siller, A.B. Analyzing Complex Sample Survey Data: A New Beginning. 3.

126. U.S. Department of Health and Human Services National Health Expenditure Accounts: Methodology Paper, 2019. **2019**, 44.

127. Using Appropriate Price Indices for Expenditure Comparisons Available online: https://meps.ahrq.gov/about_meps/Price_Index.shtml (accessed on 23 February 2023).

128. Dunn, A.; Grosse, S.D.; Zuvekas, S.H. Adjusting Health Expenditures for Inflation: A Review of Measures for Health Services Research in the United States. *Health Serv Res* **2018**, *53*, 175–196, doi:10.1111/1475-6773.12612.

129. SAS 9.4 Software Available online: https://www.sas.com/en_us/software/sas9.html (accessed on 31 October 2019).

130. StataCorp. 2019. Stata Statistical Software: Release 16.

131. James, G.D.; Donaldson, G.C.; Wedzicha, J.A.; Nazareth, I. Trends in Management and Outcomes of COPD Patients in Primary Care, 2000–2009: A Retrospective Cohort Study. *npj Prim Care Resp Med* **2014**, *24*, 1–7, doi:10.1038/npjpcrm.2014.15.

132. US Population by Year, Race, Age, Ethnicity, & More Available online: https://usafacts.org/data/topics/people-society/population-and-demographics/our-changing-population/ (accessed on 27 April 2023).

133. American Lung Association *Tobacco Trends Brief*;

134. Celi, A.; Latorre, M.; Paggiaro, P.; Pistelli, R. Chronic Obstructive Pulmonary Disease: Moving from Symptom Relief to Mortality Reduction. *Therapeutic Advances in Chronic Disease* **2021**, *12*, 20406223211014028, doi:10.1177/20406223211014028.

135. Stuart, B.; Doshi, J.A.; Briesacher, B.; Wrobel, M.V.; Baysac, F. Impact of Prescription Coverage on Hospital and Physician Costs: A Case Study of Medicare Beneficiaries with Chronic Obstructive Pulmonary Disease. *Clin Ther* **2004**, *26*, 1688–1699, doi:10.1016/j.clinthera.2004.10.012.

136. Quint, J.K.; Montonen, J.; Esposito, D.B.; He, X.; Koerner, L.; Wallace, L.; de la Hoz, A.; Miravitlles, M. Effectiveness and Safety of COPD Maintenance Therapy with Tiotropium/Olodaterol versus LABA/ICS in a US Claims Database. *Adv Ther* **2021**, *38*, 2249–2270, doi:10.1007/s12325-021-01646-5.

137. Almagro, P.; Soriano, J.B. Underdiagnosis in COPD: A Battle Worth Fighting. *The Lancet Respiratory Medicine* **2017**, *5*, 367–368, doi:10.1016/S2213-2600(17)30133-9.

138. Lamprecht, B.; Soriano, J.B.; Studnicka, M.; Kaiser, B.; Vanfleteren, L.E.; Gnatiuc, L.; Burney, P.; Miravitlles, M.; García-Rio, F.; Akbari, K.; et al. Determinants of Underdiagnosis of COPD in National and International Surveys. *Chest* **2015**, *148*, 971–985, doi:10.1378/chest.14-2535.

139. Syamlal, G. Medical Expenditures Attributed to Asthma and Chronic Obstructive Pulmonary Disease Among Workers — United States, 2011–2015. *MMWR Morb Mortal Wkly Rep* **2020**, *69*, doi:10.15585/mmwr.mm6926a1.

140. Patel, M.R.; Press, V.G.; Gerald, L.B.; Barnes, T.; Blake, K.; Brown, L.K.; Costello, R.W.; Crim, C.; Forshag, M.; Gershon, A.S.; et al. Improving the Affordability of Prescription Medications for People with Chronic Respiratory Disease. An Official American Thoracic Society Policy Statement. *Am J Respir Crit Care Med* **2018**, *198*, 1367–1374, doi:10.1164/rccm.201810-1865ST.

141. Reynolds, E.L.; Burke, J.F.; Banerjee, M.; Kerber, K.A.; Skolarus, L.E.; Magliocco, B.; Esper, G.J.; Callaghan, B.C. Association of Out-of-Pocket Costs on Adherence to Common Neurologic Medications. *Neurology* **2020**, *94*, e1415–e1426, doi:10.1212/WNL.0000000000009039.

142. Consumer Reports Survey: One In Four People Who Regularly Take Meds Hit with Sticker Shock at the Pharmacy Available online: https://www.prweb.com/releases/2017/05/prweb14337582.htm (accessed on 2 July 2022).

143. Khot, U.N.; Vogan, E.D.; Militello, M.A. Nitroprusside and Isoproterenol Use after Major Price Increases. *New England Journal of Medicine* **2017**, *377*, 594–595, doi:10.1056/NEJMc1700244.

144. Biggers, A.; Shi, Y.; Charlson, J.; Smith, E.C.; Smallwood, A.J.; Nattinger, A.B.; Laud, P.W.; Neuner, J.M. Medicare D Subsidies and Racial Disparities in Persistence and Adherence With Hormonal Therapy. *JCO* **2016**, *34*, 4398–4404, doi:10.1200/JCO.2016.67.3350.

145. Zafari, Z.; Sin, D.D.; Postma, D.S.; Löfdahl, C.-G.; Vonk, J.; Bryan, S.; Lam, S.; Tammemagi, C.M.; Khakban, R.; Man, S.F.P.; et al. Individualized Prediction of Lung-Function Decline in Chronic Obstructive Pulmonary Disease. *CMAJ : Canadian Medical Association Journal* **2016**, *188*, 1004, doi:10.1503/cmaj.151483.

146. Stagnitti, M.N.; Machlin, S.R.; Zodet, M.W.; Saleska, E. Methodology Report #32: Design, Methods, and Field Results of the Medical Expenditure Panel Survey Medical Provider Component (MEPS MPC) Including the Medical Organizations Survey (MOS) - 2016 Data Year 2018.

147. Pagano, E.; Petrelli, A.; Picariello, R.; Merletti, F.; Gnavi, R.; Bruno, G. Is the Choice of the Statistical Model Relevant in the Cost Estimation of Patients with Chronic Diseases? An Empirical Approach by the Piedmont Diabetes Registry. *BMC Health Serv Res* **2015**, *15*, 582, doi:10.1186/s12913-015-1241-1.

148. Onukwugha, E.; McRae, J.; Kravetz, A.; Varga, S.; Khairnar, R.; Mullins, C.D. Cost-of-Illness Studies: An Updated Review of Current Methods. *PharmacoEconomics* **2016**, *34*, 43–58, doi:10.1007/s40273-015-0325-4.

149. Biener, A.I.; Decker, S.L.; Rohde, F. Prevalence and Treatment of Chronic Obstructive Pulmonary Disease (COPD) in the United States. *JAMA* **2019**, *322*, 602–602, doi:10.1001/jama.2019.10241.

150. Murphy, T.E.; McAvay, G.J.; Allore, H.G.; Stamm, J.A.; Simonelli, P.F. Contributions of COPD, Asthma, and Ten Comorbid Conditions to Health Care Utilization and Patient-Centered Outcomes among US Adults with Obstructive Airway Disease. *Int J Chron Obstruct Pulmon Dis* **2017**, *12*, 2515–2522, doi:10.2147/COPD.S139948.

151. Sin, D.D.; Anthonisen, N.R.; Soriano, J.B.; Agusti, A.G. Mortality in COPD: Role of Comorbidities. *Eur Respir J* **2006**, *28*, 1245–1257, doi:10.1183/09031936.00133805.

152. Zafari, Z.; Li, S.; Eakin, M.N.; Bellanger, M.; Reed, R.M. Projecting Long-Term Health and Economic Burden of COPD in the United States. *CHEST* **2021**, *159*, 1400–1410, doi:10.1016/j.chest.2020.09.255.

153. Shah, C.H.; Reed, R.M.; Wastila, L.; Onukwugha, E.; Gopalakrishnan, M.; Zafari, Z. Direct Medical Costs of COPD in the USA: An Analysis of the Medical Expenditure Panel Survey 2017–2018. *Appl Health Econ Health Policy* **2023**, doi:10.1007/s40258-023-00814-8.

154. Vogelmeier, C.F.; Bateman, E.D.; Pallante, J.; Alagappan, V.K.; D'Andrea, P.; Chen, H.; Banerji, D. Efficacy and Safety of Once-Daily QVA149 Compared with Twice-Daily Salmeterol–Fluticasone in Patients with Chronic Obstructive Pulmonary Disease (ILLUMINATE): A Randomised, Double-Blind, Parallel Group Study. *The Lancet Respiratory Medicine* **2013**, *1*, 51–60, doi:10.1016/S2213-2600(12)70052-8.

155. Zhong, N.; Wang, C.; Zhou, X.; Zhang, N.; Humphries, M.; Wang, L.; Thach, C.; Patalano, F.; Banerji, D. LANTERN: A Randomized Study of QVA149 versus Salmeterol/Fluticasone Combination in Patients with COPD. *Int J Chron Obstruct Pulmon Dis* **2015**, *10*, 1015–1026, doi:10.2147/COPD.S84436.

156. Wedzicha, J.A.; Banerji, D.; Chapman, K.R.; Vestbo, J.; Roche, N.; Ayers, R.T.; Thach, C.; Fogel, R.; Patalano, F.; Vogelmeier, C.F. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. *New England Journal of Medicine* **2016**, *374*, 2222–2234, doi:10.1056/NEJMoa1516385.

157. Rabe, K.F.; Timmer, W.; Sagkriotis, A.; Viel, K. Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD. *Chest* **2008**, *134*, 255–262, doi:10.1378/chest.07-2138.

158. Donohue, J.F.; Worsley, S.; Zhu, C.-Q.; Hardaker, L.; Church, A. Improvements in Lung Function with Umeclidinium/Vilanterol versus Fluticasone Propionate/Salmeterol in Patients with Moderate-to-Severe COPD and Infrequent Exacerbations. *Respiratory Medicine* **2015**, *109*, 870–881, doi:10.1016/j.rmed.2015.04.018.

159. Singh, D.; Worsley, S.; Zhu, C.-Q.; Hardaker, L.; Church, A. Umeclidinium/Vilanterol versus Fluticasone Propionate/Salmeterol in COPD: A Randomised Trial. *BMC Pulm Med* **2015**, *15*, 91, doi:10.1186/s12890-015-0092-1.

160. Vogelmeier, C.; Paggiaro, P.L.; Dorca, J.; Sliwinski, P.; Mallet, M.; Kirsten, A.-M.; Beier, J.; Seoane, B.; Segarra, R.M.; Leselbaum, A. Efficacy and Safety of Aclidinium/Formoterol versus Salmeterol/Fluticasone: A Phase 3 COPD Study. *Eur Respir J* **2016**, *48*, 1030–1039, doi:10.1183/13993003.00216-2016.

161. Suissa, S. Run-in Bias in Randomised Trials: The Case of COPD Medications. *European Respiratory Journal* **2017**, *49*, doi:10.1183/13993003.00361-2017.

162. Suissa, S.; Ariel, A. Triple Therapy Trials in COPD: A Precision Medicine Opportunity. *European Respiratory Journal* **2018**, *52*, doi:10.1183/13993003.01848-2018.

163. Suissa, S.; Dell'Aniello, S.; Ernst, P. Comparative Effectiveness of Initial LAMA versus LABA in COPD: Real-World Cohort Study. *COPD: Journal of Chronic*

Obstructive Pulmonary Disease **2021**, *18*, 1–8, doi:10.1080/15412555.2021.1877649.

164. Horwitz, R.I.; Feinstein, A.R. The Problem of "Protopathic Bias" in Case-Control Studies. *The American Journal of Medicine* **1980**, *68*, 255–258, doi:10.1016/0002-9343(80)90363-0.
165. Arfè, A.; Corrao, G. The Lag-Time Approach Improved Drug–Outcome Association Estimates in Presence of Protopathic Bias. *Journal of Clinical Epidemiology* **2016**, *78*, 101–107, doi:10.1016/j.jclinepi.2016.03.003.
166. Sharma, K.C.; Stevens, D.; Casey, L.; Kesten, S. Effects of High-Dose Inhaled Fluticasone Propionate via Spacer on Cell-Mediated Immunity in Healthy Volunteers. *Chest* **2000**, *118*, 1042–1048, doi:10.1378/chest.118.4.1042.
167. Newman, S.P. Deposition and Effects of Inhaled Corticosteroids. *Clin Pharmacokinet* **2003**, *42*, 529–544, doi:10.2165/00003088-200342060-00003.
168. Chang, T.-Y.; Chien, J.-Y.; Wu, C.-H.; Dong, Y.-H.; Lin, F.-J. Comparative Safety and Effectiveness of Inhaled Corticosteroid and Long-Acting B2-Agonist Combinations in Patients With COPD. *CHEST* **2020**, *157*, 1117–1129, doi:10.1016/j.chest.2019.12.006.
169. Pharmacoepidemiology Toolbox.
170. Rassen, J.A.; Blin, P.; Kloss, S.; Neugebauer, R.S.; Platt, R.W.; Pottegård, A.; Schneeweiss, S.; Toh, S. High-Dimensional Propensity Scores for Empirical Covariate Selection in Secondary Database Studies: Planning, Implementation, and Reporting. *Pharmacoepidemiology and Drug Safety* **2023**, *32*, 93–106, doi:10.1002/pds.5566.

171. Bross, I.D. Spurious Effects from an Extraneous Variable. *J Chronic Dis* **1966**, *19*, 637–647, doi:10.1016/0021-9681(66)90062-2.

172. Erratum: High-Dimensional Propensity Score Adjustment in Stu... : Epidemiology Available online: https://journals.lww.com/epidem/Fulltext/2018/11000/Erratum__High_dimensional_Propensity_Score.34.aspx (accessed on 26 July 2023).

173. Schuster, T.; Pang, M.; Platt, R.W. On the Role of Marginal Confounder Prevalence – Implications for the High-Dimensional Propensity Score Algorithm. *Pharmacoepidemiology and Drug Safety* **2015**, *24*, 1004–1007, doi:10.1002/pds.3773.

174. Hallas, J.; Pottegård, A. Performance of the High-Dimensional Propensity Score in a Nordic Healthcare Model. *Basic & Clinical Pharmacology & Toxicology* **2017**, *120*, 312–317, doi:10.1111/bcpt.12716.

175. Austin, P.C. Optimal Caliper Widths for Propensity-Score Matching When Estimating Differences in Means and Differences in Proportions in Observational Studies. *Pharm Stat* **2011**, *10*, 150–161, doi:10.1002/pst.433.

176. Tazare, J.; Wyss, R.; Franklin, J.M.; Smeeth, L.; Evans, S.J.W.; Wang, S.V.; Schneeweiss, S.; Douglas, I.J.; Gagne, J.J.; Williamson, E.J. Transparency of High-Dimensional Propensity Score Analyses: Guidance for Diagnostics and Reporting. *Pharmacoepidemiology and Drug Safety* **2022**, *31*, 411–423, doi:10.1002/pds.5412.

177. Austin, P.C. Balance Diagnostics for Comparing the Distribution of Baseline Covariates between Treatment Groups in Propensity-Score Matched Samples. *Statistics in Medicine* **2009**, *28*, 3083–3107, doi:10.1002/sim.3697.

178. Lipsitch, M.; Tchetgen Tchetgen, E.; Cohen, T. Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. *Epidemiology* **2010**, *21*, 383–388, doi:10.1097/EDE.0b013e3181d61eeb.

179. Park, J.; Zafari, Z.; Shah, C.H.; DosReis, S.; Gorman, E.F.; Hua, W.; Ma, Y.; Tian, F. The State of Use and Utility of Negative Controls in Pharmacoepidemiologic Studies. In Proceedings of the PHARMACOEPIDEMIOLOGY AND DRUG SAFETY; WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2022; Vol. 31, pp. 203–204.

180. Suarez, E.A.; Setoguchi, S. Chapter 6 - What Is the Research Question? In *Pragmatic Randomized Clinical Trials*; Girman, C.J., Ritchey, M.E., Eds.; Academic Press, 2021; pp. 71–83 ISBN 978-0-12-817663-4.

181. Gupta, S.K. Intention-to-Treat Concept: A Review. *Perspect Clin Res* **2011**, *2*, 109–112, doi:10.4103/2229-3485.83221.

182. December 2019, G.I. for C.O.L.D. GOLD COPD 2020 Strategy Available online: https://www.guidelines.co.uk/respiratory/gold-copd-2020-strategy/455088.article (accessed on 21 August 2020).

183. Nici, L.; Mammen, M.J.; Charbek, E.; Alexander, P.E.; Au, D.H.; Boyd, C.M.; Criner, G.J.; Donaldson, G.C.; Dreher, M.; Fan, V.S.; et al. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* **2020**, *201*, e56–e69, doi:10.1164/rccm.202003-0625ST.

184. Cazzola, M.; Matera, M.G. Bronchodilators: Current and Future. *Clin Chest Med* **2014**, *35*, 191–201, doi:10.1016/j.ccm.2013.10.005.

185. Iwanaga, T.; Tohda, Y.; Nakamura, S.; Suga, Y. The Respimat® Soft Mist Inhaler: Implications of Drug Delivery Characteristics for Patients. *Clin Drug Investig* **2019**, *39*, 1021–1030, doi:10.1007/s40261-019-00835-z.

186. Small, M.; Anderson, P.; Vickers, A.; Kay, S.; Fermer, S. Importance of Inhaler-Device Satisfaction in Asthma Treatment: Real-World Observations of Physician-Observed Compliance and Clinical/Patient-Reported Outcomes. *Adv Ther* **2011**, *28*, 202–212, doi:10.1007/s12325-010-0108-4.

187. Donohue, J.F.; Maleki-Yazdi, M.R.; Kilbride, S.; Mehta, R.; Kalberg, C.; Church, A. Efficacy and Safety of Once-Daily Umeclidinium/Vilanterol 62.5/25 Mcg in COPD. *Respir Med* **2013**, *107*, 1538–1546, doi:10.1016/j.rmed.2013.06.001.

188. Donohue, J.F.; Niewoehner, D.; Brooks, J.; O'Dell, D.; Church, A. Safety and Tolerability of Once-Daily Umeclidinium/Vilanterol 125/25 Mcg and Umeclidinium 125 Mcg in Patients with Chronic Obstructive Pulmonary Disease: Results from a 52-Week, Randomized, Double-Blind, Placebo-Controlled Study. *Respir Res* **2014**, *15*, 78, doi:10.1186/1465-9921-15-78.

189. Buhl, R.; Maltais, F.; Abrahams, R.; Bjermer, L.; Derom, E.; Ferguson, G.; Fležar, M.; Hébert, J.; McGarvey, L.; Pizzichini, E.; et al. Tiotropium and Olodaterol Fixed-Dose Combination versus Mono-Components in COPD (GOLD 2-4). *Eur Respir J* **2015**, *45*, 969–979, doi:10.1183/09031936.00136014.

190. Feldman, G.J.; Sousa, A.R.; Lipson, D.A.; Tombs, L.; Barnes, N.; Riley, J.H.; Patel, S.; Naya, I.; Compton, C.; Alcázar Navarrete, B. Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic

Chronic Obstructive Pulmonary Disease: A Randomized Study. *Adv Ther* **2017**, *34*, 2518–2533, doi:10.1007/s12325-017-0626-4.

191. Calzetta, L.; Rogliani, P.; Matera, M.G.; Cazzola, M. A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD. *Chest* **2016**, *149*, 1181–1196, doi:10.1016/j.chest.2016.02.646.
192. Schlueter, M.; Gonzalez-Rojas, N.; Baldwin, M.; Groenke, L.; Voss, F.; Reason, T. Comparative Efficacy of Fixed-Dose Combinations of Long-Acting Muscarinic Antagonists and Long-Acting B2-Agonists: A Systematic Review and Network Meta-Analysis. *Ther Adv Respir Dis* **2016**, *10*, 89–104, doi:10.1177/1753465815624612.
193. Sion, K.Y.J.; Huisman, E.L.; Punekar, Y.S.; Naya, I.; Ismaila, A.S. A Network Meta-Analysis of Long-Acting Muscarinic Antagonist (LAMA) and Long-Acting B2-Agonist (LABA) Combinations in COPD. *Pulm Ther* **2017**, *3*, 297–316, doi:10.1007/s41030-017-0048-0.
194. Aziz, M.I.A.; Tan, L.E.; Wu, D.B.-C.; Pearce, F.; Chua, G.S.W.; Lin, L.; Tan, P.-T.; Ng, K. Comparative Efficacy of Inhaled Medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD: A Systematic Review and Network Meta-Analysis. *International Journal of Chronic Obstructive Pulmonary Disease* **2018**, *13*, 3203–3231, doi:10.2147/COPD.S173472.
195. Lee, H.W.; Park, J.; Jang, E.J.; Lee, C.-H. Comparisons of Exacerbations and Mortality among LAMA/LABA Combinations in Stable Chronic Obstructive Pulmonary Disease: Systematic Review and Bayesian Network Meta-Analysis. *Respiratory Research* **2020**, *21*, 310, doi:10.1186/s12931-020-01540-8.

196. Adeloye, D.; Song, P.; Zhu, Y.; Campbell, H.; Sheikh, A.; Rudan, I. Global, Regional, and National Prevalence of, and Risk Factors for, Chronic Obstructive Pulmonary Disease (COPD) in 2019: A Systematic Review and Modelling Analysis. *The Lancet Respiratory Medicine* **2022**, *10*, 447–458, doi:10.1016/S2213-2600(21)00511-7.

197. Schnell, K.; Weiss, C.O.; Lee, T.; Krishnan, J.A.; Leff, B.; Wolff, J.L.; Boyd, C. The Prevalence of Clinically-Relevant Comorbid Conditions in Patients with Physician-Diagnosed COPD: A Cross-Sectional Study Using Data from NHANES 1999–2008. *BMC Pulmonary Medicine* **2012**, *12*, 26, doi:10.1186/1471-2466-12-26.

198. Medicare Enrollees with COPD Compared to the General Population. *Avalere Health* 2021.

199. Rosenbaum, P.R.; Rubin, D.B. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika* **1983**, *70*, 41–55, doi:10.2307/2335942.

200. Rubin, D.B. Using Propensity Scores to Help Design Observational Studies: Application to the Tobacco Litigation. *Health Services & Outcomes Research Methodology* **2001**, *2*, 169–188, doi:10.1023/A:1020363010465.

201. Alcázar Navarrete, B.; Boucot, I.; Naya, I.; Tombs, L.; Lipson, D.A.; Compton, C.; Sousa, A.R.; Feldman, G. Umeclidinium/Vilanterol Versus Tiotropium/Olodaterol in Maintenance-Naïve Patients with Moderate Symptomatic Chronic Obstructive Pulmonary Disease: A Post Hoc Analysis. *Pulm Ther* **2018**, *4*, 171–183, doi:10.1007/s41030-018-0057-7.

202. Driessen, M.T.; Whalen, J.; Seewoodharry Buguth, B.; Vallejo-Aparicio, L.A.; Naya, I.P.; Asukai, Y.; Alcázar-Navarrete, B.; Miravitlles, M.; García-Río, F.; Risebrough, N.A. Cost-Effectiveness Analysis of Umeclidinium Bromide/Vilanterol 62.5/25 Mcg versus Tiotropium/Olodaterol 5/5 Mcg in Symptomatic Patients with Chronic Obstructive Pulmonary Disease: A Spanish National Healthcare System Perspective. *Respir Res* **2018**, *19*, 224, doi:10.1186/s12931-018-0916-7.

203. ICD-9-CM to and from ICD-10-CM and ICD-10-PCS Crosswalk or General Equivalence Mappings Available online: https://www.nber.org/research/data/icd-9-cm-and-icd-10-cm-and-icd-10-pcs-crosswalk-or-general-equivalence-mappings (accessed on 16 January 2023).

204. Enders, D.; Ohlmeier, C.; Garbe, E. The Potential of High-Dimensional Propensity Scores in Health Services Research: An Exemplary Study on the Quality of Care for Elective Percutaneous Coronary Interventions. *Health Services Research* **2018**, *53*, 197–213, doi:10.1111/1475-6773.12653.