PHARMACO-EPIDEMIOLOGICAL STUDY OF CARDIO-RESPIRATORY SAFETY OF β2-AGONISTS FOR THE TREATMENT AND MANAGEMENT OF ASTHMA, CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND ASTHMA-COPD OVERLAP

BY

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ABSTRACT

Despite ample evidence underpinning the efficacy of β2-agonists in asthma and Chronic Obstructive Pulmonary Disease (COPD), the occurrence of β1-and β2-adrenoceptors in the heart suggests that β2-agonists may have deleterious cardiac effects. Therefore, patients who have asthma, COPD or both may be at increased risk of cardio-respiratory (CR) events because these diseases magnify the impact of these agents on the heart.

In this thesis, I performed a systematic review and meta-analyses of the literature to provide a general overview of the comparative effectiveness and safety of inhaled medications. I conducted a retrospective cohort study to investigate gender differences in new-users of inhaled corticosteroids (ICS), short-or long-acting β2-agonist (SABA or LABA), ICS/LABA, short-or long-acting muscarinic antagonist (SAMA or LAMA) and a nested case-control study to test the association between β2-agonist-based medications and safety events for cardio-respiratory outcomes of major adverse cardiovascular events (MACE), all-cause mortality, and hospitalization for pneumonia using the United Kingdom Clinical Practice Research Datalink of patients with asthma, COPD or asthma-COPD overlap between 01-January-1998 and 31-July-2018.

Results from the meta-analysis suggests that for patients with asthma–COPD overlap, LABA are associated with decreased risk of myocardial infarction in comparisons to non-LABA; and the combination therapy of ICS/LABA appears to reduce the risk of death or hospitalization in comparisons to placebo. Also, results from the gender-based analysis of pharmacotherapy use showed significant gender differences in

new-users of inhaled pharmacotherapies among obstructive airways disease patients. In regards to the cardio-respiratory outcomes, new initiation of LABA, SABA or ICS/LABA compared to SAMA in COPD or SABA compared to ICS in asthma-COPD overlap was associated with an increased risk of MACE. However, among asthmatics, β_2-agonists compared to ICS were not associated with risk of MACE. Consequently, starting LABA monotherapy or SABA monotherapy treatment was associated with an increased risk of all-cause mortality in patients with COPD. On the other hand, I observed no association with SABA, LABA or LABA/ICS in comparison with ICS or SAMA and the risk of pneumonia in patients with asthma, COPD or asthma-COPD overlap.

LAY SUMMARY

Reviewing and combining evidence from the literature, I identified that patients with both asthma and COPD who were treated with LABA alone were at increased risk of myocardial infarction in comparison to non-LABA and patients who were on combination therapy of LABA and ICS seemed to have reduced risk of death or hospitalization in comparison to placebo. Our study revealed gender differences in inhaled medication prescription among patients with asthma, COPD or asthma-COPD overlap. Furthermore, our study also showed that medications such as LABA, SABA or ICS/LABA in COPD and SABA in asthma-COPD that were used to treat these lung diseases also amplified the risk of major adverse cardiovascular events. Nevertheless, patients with COPD that were either on LABA or SABA were likely to die as these medications offered no protection in comparison to ICS. However, asthmatics who used these drugs were at no increased risk of heart diseases or death in comparison to ICS. Additionally, all patients with asthma, COPD or asthma-COPD overlap suffered no risk of being hospitalized for pneumonia in comparison to ICS or SAMA.

STATEMENT OF CO-AUTHORSHIP

I hereby declare that in all cases, the key ideas, primary contributions, study designs, execution, data analysis, interpretation and writing of manuscripts were performed by J.E.A, under the supervision of Z.G, supported by J-M.G and JF. The contribution of co-authors was generally through the provision of new ideas, suggestions, revisions and corrections. Acquisition of data for the papers presented in Chapters Three, Four and Five were acquired from Clinical Practice Research Datalink (CPRD), United Kingdom through a research grant from Canada Respiratory Research Network (CRRN), Ottawa, Canada via the Young Investigator Award, 2017.

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From a "Grateful Heart".

TABLE OF CONTENTS

ABSTRACT ii
LAY SUMMARY iv
STATEMENT OF CO-AUTHORSHIP v
ACKNOWLEDGEMENTS vi
LIST OF TABLES xi
LIST OF FIGURES xiii
LIST OF ABBREVIATIONS xv
LIST OF APPENDICES xvii
PUBLICATIONS xviii
PRESENTATIONS xx
CHAPTER 1 1
OVERVIEW 1
1.1 DESCRIPTION, PATHOPHYSIOLOGY AND DIAGNOSIS OF ASTHMA, COPD AND ASTHMA-COPD OVERLAP 1
1.1.1 DEFINITION AND EPIDEMIOLOGY OF ASTHMA 2
1.1.2 DEFINITION AND EPIDEMIOLOGY OF COPD 3
1.1.3 DEFINITION AND EPIDEMIOLOGY ASTHMA-COPD OVERLAP 6
1.1.4 DIAGNOSIS OF ASTHMA 8
1.1.5 DIAGNOSIS OF COPD 9
1.1.6 DIAGNOSIS OF ASTHMA-COPD OVERLAP 10
1.2 MANAGEMENT AND TREATMENT OF ASTHMA, COPD AND ASTHMA-COPD OVERLAP 11
1.2.1 ASTHMA 11
1.2.2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE 14
1.2.3 ASTHMA-COPD OVERLAP 15
1.3 CARDIOVASCULAR SAFETY OF INHALED β2-AGONISTS 17
1.3.1 MECHANISM AND EVIDENCE FROM THE LITERATURE 17
1.5 RESEARCH STUDY SIGNIFICANCE 21
1.6 RESEARCH OBJECTIVES, SPECIFIC AIMS 22
1.7 THESIS TEXT OUTLINE 24
1.7.1 CHAPTER 2 24
1.7.2 CHAPTER 3 24
1.7.3 CHAPTER 4 25
1.7.4 CHAPTER 5 26
1.7.5 CHAPTER 6 26
1.7.6 CHAPTER 7 26
1.7.7 CHAPTER 8 27
CHAPTER 2 28

COMPARATIVE SAFETY AND EFFECTIVENESS OF INHALED BRONCHODILATORS AND CORTICOSTEROIDS FOR TREATING ASTHMA–COPD OVERLAP: A SYSTEMATIC REVIEW AND META-ANALYSIS 28

2.1 INTRODUCTION 29

2.2 METHODS 32
2.2.1 STUDY DESIGN AND PROTOCOL REGISTRATION 32
2.2.2 ELIGIBILITY CRITERIA 32
2.2.3 OUTCOMES OF INTEREST 33
2.2.4 DATA SOURCES AND SEARCHES 33
2.2.5 DATA ITEMS AND DATA ABSTRACTION PROCESS 34
2.2.6 RISK OF BIAS ASSESSMENT 35
2.2.7 STATISTICAL ANALYSIS 36
2.2.8 SUBGROUP ANALYSIS 37

2.3 RESULTS 37
2.3.1 LITERATURE SEARCH AND STUDY SELECTION 37
2.3.2 STUDY CHARACTERISTICS 39
2.3.4 QUANTITATIVE ANALYSIS 49

2.4 DISCUSSION 55
2.4.1 MYOCARDIAL INFARCTION 55
2.4.2 PULMONARY FUNCTION TESTING (FEV_1) 56
2.4.3 DEATH OR HOSPITALIZATION FOR ASTHMA-COPD OVERLAP 57
2.4.4 ASTHMA-COPD OVERLAP EXACERBATION 58
2.4.5 NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE 59
2.4.6 FRACTURE RATES 60

2.5 CONCLUSION 61

CHAPTER 3 63

GENDER DIFFERENCES IN INHALED PHARMACOTHERAPY UTILIZATION IN PATIENTS WITH OBSTRUCTIVE AIRWAY DISEASES (OADS): A POPULATION-BASED STUDY 63

3.1 INTRODUCTION 64

3.2 METHOD 66
3.2.1 DATA SOURCES 66
3.2.2 STUDY POPULATION AND IDENTIFICATION OF INHALED PHARMACOTHERAPIES 67
3.2.2 EXPOSURE AND OUTCOMES 69
3.2.3 STATISTICAL ANALYSIS 70

3.3 RESULTS 71

3.4 DISCUSSION 82

3.5 CONCLUSION 85

CHAPTER 4 87

RISKS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS ASSOCIATED WITH B2-AGONISTS FOR THE TREATMENT OF ASTHMA, COPD, AND ASTHMA-COPD OVERLAP 87

4.1 INTRODUCTION 88

4.2 METHODS 89
4.2.1 SOURCE POPULATION 89
4.2.2 COHORT DEFINITION 90
4.2.3 NESTED CASE-CONTROL 91
4.2.4 EXPOSURE ASSESSMENT 92
4.2.5 POTENTIAL CONFOUNDERS 93
4.2.6 STATISTICAL ANALYSIS 93
4.2.7 SECONDARY ANALYSIS 94
4.2.8 SENSITIVITY ANALYSIS 94

4.3 RESULTS 95
4.4.1 SECONDARY ANALYSIS 102
4.4.2 SENSITIVITY ANALYSIS 104

4.5 DISCUSSION 106

4.6 CONCLUSION 109

CHAPTER 5 111

ASSOCIATION OF B2-AGONISTS-BASED DRUGS WITH ALL-CAUSE MORTALITY OR PNEUMONIA IN PATIENTS WITH ASTHMA, COPD OR ASTHMA-COPD OVERLAP 111

5.1 INTRODUCTION 112

5.2 METHODS 114
5.2.1 SOURCE POPULATION 114
5.2.2 STUDY COHORT 115
5.2.3 CASE-CONTROL SELECTION 116
5.2.4 EXPOSURE ASSESSMENT 117
5.2.5 COVARIATES 118
5.2.6 STATISTICAL ANALYSIS 119
5.2.7 SENSITIVITY ANALYSES 119

5.3 RESULTS 120
5.3.1 β2-AGONIST-BASED DRUGS AND THE RISK FOR ALL-CAUSE-MORTALITY 129
5.3.2 β2-AGONIST-BASED DRUGS AND HOSPITALIZATION FOR PNEUMONIA 130
5.3.3 SENSITIVITY ANALYSES 131

5.4 DISCUSSION 134

5.5 CONCLUSION 137

CHAPTER 6 139

PLANNING FOR FUTURE STUDY 139

VALIDATION OF ASTHMA-COPD OVERLAP RECORDING IN HEALTHCARE RECORDS: PROTOCOL FOR A SYSTEMATIC REVIEW 139

6.1 INTRODUCTION 140
6.1.2 RESEARCH QUESTION 144
6.2.2 LITERATURE SEARCH 144
6.2.3 INCLUSION CRITERIA 146
6.2.4 EXCLUSION CRITERIA 147
6.2.5 SELECTION PROCESSES 147
6.2.6 DATA EXTRACTION 148
6.2.7 RISK OF BIAS ASSESSMENT 148
6.2.8 DATA SYNTHESIS 149
6.3 CONCLUSION 149
CHAPTER 7 150
VALIDATION OF ASTHMA-COPD OVERLAP SYNDROME IN THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD) 150
CHAPTER 8 151
GENERAL DISCUSSION AND CONCLUSION 151
8.1. SUMMARY OF RESEARCH 151
8.2 SUMMARY OF RESULTS 153
8.3 STRENGTHS OF THE RESEARCH 155
8.4 LIMITATION 156
8.5 IMPLICATION FOR FUTURE RESEARCH 159
8.6 CONCLUSION 160
REFERENCES 161
APPENDICES 179

LIST OF TABLES

Table 2.1	Criteria used to describe and diagnose individuals with asthma-COPD overlap in publications	30
Table 2.2	Characteristics of included studies	41
Table 2.3	Quality Assessment of cohort and nested case-control studies using Newcastle-Ottawa Quality Assessment Scale (NOS)	48
Table 3.1	Baseline characteristics among patients diagnosed with asthma, COPD and asthma-COPD overlap	72
Table 3.2	Univariate (unadjusted) analyses of factors associated with different inhaled pharmacotherapies	76
Table 3.3	Multivariable analyses of gender differences in inhaled pharmacotherapies by three obstructive airway diseases	81
Table 4.1	Baseline characteristics of Primary Case Patients (major adverse cardiovascular events) and Matched Controls, stratified by patients diagnosed with Asthma, COPD and Asthma-COP Overlap respectively	97
Table 4.2	Association Between Use of inhaled β2-agonists-based Drugs and the Incidence of Major Adverse Cardiovascular Events	101
Table 4.3	Secondary Outcomes of Individual Components of Major Adverse Cardiovascular Events	103
Table 5.1	Baseline characteristics of All-Cause Mortality Case Patients and Matched Controls	123
Table 5.2	Baseline characteristics of Pneumonia Cases and Matched Controls categorized according to OAD diagnoses	125

Table 5.3 Association Between Use of inhaled β_2-agonists-based Drugs with All-Cause-Mortality and Incidence of Pneumonia**.** 130

LIST OF FIGURES

Figure 1.1	Diagnostic spirometric measures in asthma, COPD and asthma-COPD overlap	11
Figure 1.2	Stepwise treatment of asthma in adults	13
Figure 2.1	A PRISMA flow diagram details the flow of information through the different phases of the review; maps out the number of records identified, included, excluded and the reasons for their exclusion	39
Figure 2.2	Risk of bias summery for RCT studies	46
Figure 2.3	Risk for Myocardial Infarction (MI); Forest plot describing the association between long-acting β2-agonists (LABA) monotherapy vs a non-LABA (SABA and/or LAMA and/or SAMA monotherapies) and risk for MI	50
Figure 2.4	Risk for forced expiratory volume in 1 s; Forest plot describing the association between inhaled corticosteroid (ICS) alone or its combination with long-acting beta2 agonist (LABA) vs control and risk for decline in forced expiratory volume in 1s (FEV1)	51
Figure 2.5	Risk for death or hospitalization; Forest plot describing the association between inhaled combination therapy of corticosteroid and long-acting beta2-agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap	52
Figure 2.6	Risk for death or hospitalization; Forest plot subgroup analysis describing the association between inhaled combination therapy of corticosteroid and long-acting beta2-agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap	54
Figure 3.1	Flowchart of study cohort formation	68

Figure 4.1	Flowchart of Number of Patients in the Base and Study Cohort	96
Figure 4.2	Sensitivity Analyses for the Association Between the Use of SABA compared to ICS and the risk for Major Adverse Cardiovascular Event	105
Figure 5.1	Flowchart of Number of Patients in the Base and Study Cohort	121
Figure 5.2	Sensitivity Analyses for the Association Between the Use of SABA compared to SAMA or ICS and the risk for All-Cause-Mortality in COPD and Asthma patients respectively	133
Figure 6.1	Study Screening Process: PRISMA flow diagram from Moher et al	146

LIST OF ABBREVIATIONS

ACO	Asthma-COPD Overlap
AECOPD	Acute Exacerbation Chronic Obstructive Pulmonary Disease
AHR	Airway Hyperresponsiveness
AMI	Acute Myocardial Infarction
BDR	Bronchodilator Response
BDT	Bronchodilator Treatment
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
FENO	Fractional Exhaled Nitric Oxide
FVC	Forced Vital Capacity
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice
GEMA	Spanish Guideline on the Management of Asthma
GesEPOC	Spanish COPD guideline
GINA	Global Initiative for Asthma
GOLD	Global Initiative for chronic Obstructive Lung Disease
HES	Hospital Episode Stats
HRA	Health Research Authority

ICD	International Statistical Classification of Diseases and Related Health Problems
ICS	Inhaled Corticosteroid
IgE	Immunoglobulin E
ISAC	Independent Scientific Advisory Committee
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MI	Myocardial Infarction
NTM-PD	Nontuberculosis Mycobacterial-Pulmonary Disease
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
OAD	Obstructive Airway Disease
ONS	Office of National Statistics
RCT	Randomized Controlled Trial
Rx	Prescription
SABA	Short-Acting $Beta_2$-Agonist
SAMA	Short-Acting Muscarinic Antagonist
SEPAR	Spanish Society of Pulmonology and Thoracic Surgery
STD	Standard Deviation

LIST OF APPENDICES

Appendix I	Research Study Ethics Approval	179
Appendix II	Study Protocol: Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of β_2-agonists for the Treatment and Management of Asthma, COPD and Asthma-COPD Overlap	181
Appendix III	Validation of asthma-COPD overlap in the Clinical Practice Research Datalink	287
Appendix IV	PRISMA 2009 Checklist	311
Appendix V	MOOSE Checklist	314
Appendix VI	Deatailed Search Strategy for Systematic Review	316
Appendix VII	Risk of bias assessment in individual observational studies	319

PUBLICATIONS

To date, the following manuscripts have arisen from the research work presented in this thesis.

i. Amegadzie JE, Gamble JM, Farrell J, Gao Z.
Association of β2-agonists-based Drugs with All-cause Mortality or Pneumonia in patients with Asthma, COPD or Asthma-COPD Overlap (Manuscript ready to be submitted)

ii. Amegadzie JE, Gamble JM, Farrell J, Gao Z.
Risks of Major Adverse Cardiovascular Events associated with β2-agonists for the Treatment of Asthma, COPD, and Asthma-COPD Overlap: A Nested Case-Control study (Manuscript submitted and under review)

iii. Amegadzie JE, Gamble JM, Farrell J, Gao Z.
Gender Differences in Inhaled Pharmacotherapy Utilization in Patients with Obstructive Airway Diseases (OADs): A Population-Based Study. *Int J Chron Obstruct Pulmon Dis.* 2020 Sep 30;15:2355-2366. doi: 10.2147/COPD.S264580. eCollection 2020.

iv. Amegadzie JE, Gorgui J, Acheampong L, Gamble JM, Farrell J, Gao Z.

Comparative safety and effectiveness of inhaled bronchodilators and corticosteroids for treating asthma-COPD overlap: a systematic review and meta-analysis. *J Asthma* 2019 Nov 12:1-16. doi: 10.1080/02770903.2019.1687716. PMID: 31668101

v. Amegadzie JE, Badejo O, Gamble JM, Wright M, Farrell J, Jackson B, Sultana K, Hashmi M, Gao Z.
Validated methods to identify patients with asthma-COPD overlap in healthcare databases: a systematic review protocol. *BMJ Open.* 2019 Mar 13;9(3):e024306 doi: 10.1136/bmjopen-2018-024306. PMID: 30872543

PRESENTATIONS

Below is the list of presentations that have arisen from the research work outlined in this thesis.

Gender Differences in Inhaled Pharmacotherapy Utilization in Patients with Obstructive Airway Diseases (OADs): A Population-Based Study

Canadian Student Health Research Forum (CSHRF), June. 2020: Manitoba

Canadian Respiratory Research Network; January 2020: Ottawa

$Beta_2$-Agonist Initiation in Asthma-COPD Overlap(ACO) and the Risk of Adverse Cardio-Respiratory Events; A Population-Based Comparative Safety Study. Awarded Best Presenter and cash present.

Canadian Respiratory Research Network; January 2019: Ottawa

Comparative Safety and Effectiveness of Bronchodilators and Inhaled Corticosteroid for treating Asthma-COPD Overlap: Systematic Review and Meta-Analysis. Awarded Best Presenter and cash present.

Canadian Respiratory Research Network; January 2018: Ottawa

Validation of asthma-COPD overlap (ACO) in Clinical Practice Research Datalink, CPRD, UK

Faculty of Medicine Seminar Presentation; February 2018

Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of B2-Agonists for the Treatment and Management of Asthma-COPD Overlap Syndrome

Faculty of Medicine Seminar Presentation; March 2017.

CHAPTER 1

OVERVIEW

1.1 DESCRIPTION, PATHOPHYSIOLOGY AND DIAGNOSIS OF ASTHMA, COPD AND ASTHMA-COPD OVERLAP

In 1961, Orie and coworkers proposed the Dutch hypothesis, which stipulates that asthma and COPD are different expressions of a single disease entity which have genetic and environmental risk factors.[1-3] They proposed the hypothesis that various forms of airway obstruction such as asthma, chronic bronchitis, and emphysema should not be considered as separate diseases but rather as different expressions of one disease entity, a Chronic Non-specific Lung Disease (CNSLD). They further suggested that genetic factors (airway hyperresponsiveness [AHR] and atopy), endogenous factors (sex and age), and exogenous factors (allergens, infections, and smoking) all play a role in the pathogenesis of CNSLD which then ultimately lead to clinical disease depending on the timing and type of environmental exposure.[1-3] This proposal over the years became integral part of both asthma and COPD research as wide variety of research investigating differences and similarities between asthma and COPD in subsequent studies have shown that current treatment of these two diseases are different, particularly with references to ICS therapy and use of LABA and long-acting anti-muscarinic (LAMA) inhaled pharmacotherapies. For instance, whilst LABA is recommended for use in patients with COPD, it is however admonished for use in asthmatics. Also, ICS use is clinically

recommended in asthma but not recommended in COPD due to increased mortality and risk of pneumonia.[4] The Dutch hypothesis although it remains disputed has generated much research and better insight into the underlying mechanisms of asthma and COPD.[2, 3, 5]

Below in this overview, the focus is on the description and epidemiology of these two common lung diseases (asthma and COPD) and the asthma-COPD overlap, formally known as asthma-COPD overlap syndrome (ACOS).

1.1.1 DEFINITION AND EPIDEMIOLOGY OF ASTHMA

The word "asthma" originated from the Greek verb aazein, meaning 'panting' or 'short of breath'.[6] This accurate description of asthma has been credited to a Greek physician known as Aretaeus the Cappadocian and practiced in Rome in the second century. Although the description and definition of asthma is still debatable, Aretaeus the Cappadocian defined the disease, highlighting the association with exercise: "If from running, gymnastic exercises or from any other work, the breathing becomes difficult, it is called asthma".[6, 7] Asthma affects approximately 339 million people worldwide.[8] According to Statistics Canada survey data, around 2.4 million (8.1%) Canadians aged 12 years and older reported having asthma diagnosed by a health professional by a survey study conducted in 2014.[9] In the United States, approximately 7.5% of adults have asthma with about 10.5 million physician visits per year.[10]

The Global Initiative for Asthma (GINA),[11] a multi international group of health professionals and researchers striving to harmonize the description, diagnosis, and management of asthma have defined asthma based on consensus as;

> *"... a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation."*
>
> *[GINA, 2020]*

This consensus-based definition by GINA was established on consideration of the characteristics that are atypical of asthma before controller treatment is commenced, and that distinguish it from other respiratory conditions. However, airflow limitation may become persistent later in the course of the disease.[11]

1.1.2 DEFINITION AND EPIDEMIOLOGY OF COPD

Clinical understanding of chronic bronchitis component of COPD can be attributed to Badham in 1814 who used the term 'catarrh' which refers to the chronic cough and mucus accumulation associated with COPD symptoms.[12] He further described bronchiolitis and chronic bronchitis as disabling disorders.[12] Laënnec in 1821 in his Treatise of disease of the chest gave the description of the emphysema component of COPD.[13] Laënnec, a clinician and pathologist by profession, also an inventor of the stethoscope, did careful dissections of patients that he had studied during life.[14] He recognized that emphysema lungs were hyperinflated and did not empty well.[13]

Thereafter, and after several centuries, the term ‘Chronic Obstructive Pulmonary Disease’ became publicized by Briscoe and Nash in 1965.[15]

COPD is become the third leading cause of death in the world.[16] In Canada, it is estimated that 17% of the adult population have COPD, a country with a population of 36.7 million [17]. Whereas, in the US an estimated 24 million adults have COPD and it is the 3rd leading cause of death in that country.[18] Charles Fletcher, [19] chronicled the natural history of COPD and acknowledged that the risks of smoking and the resulting decline in the rate of FEV1 in smokers and ex-smokers usually leads to accelerated pathway to disabling symptoms in this patients.[20] Fletcher and his colleagues recognized that stopping smoking would slow the rate of FEV1 decline similar to the rates of reduction in age-related non-smokers.[21] This scientific evidence has led to smoking cessation in every stage of disease.

Despite smoking being the most well studied risk factor for COPD, there is substantial evidence from epidemiological studies that non-smokers may also develop airflow obstruction consistent with COPD diagnosis.[22] However, most of the evidence relating to risk factors associated with COPD are from cross-sectional studies that evaluate associations rather than causal relationships. It is noteworthy that smoking is the leading risk factor for COPD. However, less than 50% of people who smoke including heavy smokers, develop COPD.[22] It is therefore suspected that COPD is as result of complex interactions between genetic factors and environmental exposures such as smoking, occupational or socioeconomic factors.[23] Studies have reported that the prevalence of COPD is greater in men but with changes in tobacco smoking patterns the prevalence of COPD in women has almost reached that of men.[22]

The Global initiative for chronic Obstructive Lung Disease (GOLD), a similar multi international body as with GINA have defined COPD as;

> *"Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases and influenced by host factors including abnormal lung development. Significant comorbidities may have an impact on morbidity and mortality."*
>
> *[GOLD, 2020]*

Previous GOLD reports have encompassed the definition of COPD to emphasize the terms "emphysema" and "chronic bronchitis", which are not included in the definition used in recent GOLD reports.[22] Emphysema which is defined as destruction of the gas-exchange surfaces of the lungs (alveoli) thereby creating larger air spaces instead of many small ones, only describes one of several structural abnormalities present in patients with COPD. On the other hand, chronic bronchitis is related to long term inflammation of the bronchi or the presence of cough and sputum production, however, remains a useful clinical feature in COPD but is present in only a minority of subjects when this definition is used.[22] Unlike asthma, patients with COPD exhibit symptoms and airflow obstruction that is not fully reversible with medication and the disease course is progressive.[22]

1.1.3 DEFINITION AND EPIDEMIOLOGY ASTHMA-COPD OVERLAP

The notion that asthma and COPD share a common etiology has been discussed and debated since 1961 when Orie and Sluiter proposed the "Dutch hypothesis" at a bronchitis symposium in Groeningen.[1] The controversy continues today as clinicians assess and treat patients with symptoms of both asthma and COPD. This led to the birth of asthma-COPD overlap formally known as asthma-COPD overlap syndrome (ACOS).[24] The term "asthma-COPD overlap" is now being applied to the condition in which a patient has both features of asthma and COPD.[24-26] Airway inflammation in COPD differs from that of asthma.[22] COPD is characterized by neutrophilic inflammation whilst asthma is characterized predominantly by eosinophilic inflammation.[2] In obstructive airways disease patients who are 40 years and above, the clinical representation of both asthma and COPD may resemble each other. For instance, in asthma, some patients develop irreversible airway obstruction overtime as a result of airway remodelling. Concurrently, some COPD patients may develop reversible airway similar to asthmatics. In 2015, both GINA and GOLD issued a joint statement to describe this subset of patients showing features of both asthma and COPD.[24] The consensus guideline also reported that ACO includes different clinical phenotypes with several underlying mechanisms.[27] According to a case definition of asthma-COPD, it is believed that asthma-COPD overlap affects up to a quarter of patients previously thought to have COPD and up to a third of patients previously thought to have asthma.[26]

Both the GINA and GOLD guidelines declined to put forward a concise definition, citing the overarching need for better understanding involving phenotyping and underlying mechanisms pertaining to asthma-COPD overlap. Both guidelines therefore describe asthma-COPD overlap as;

> *" 'Asthma-COPD overlap' and 'asthma + COPD' are terms used to collectively describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD. "*
>
> *[GINA & GOLD]*

The GINA and GOLD consensus statements clearly acknowledged that this is a "description for clinical use," not a definition per se.[11] This group of patients are commonly known as 'overlap' due to their overlapping nature of their clinical presentation of both asthma and COPD characteristics. Without a standard definition epidemiological studies have reported varied prevalence rates ranging between 9% and 50%.[11, 26] Also, there has been consensus that patients with features of asthma-COPD overlap experience frequent exacerbations, poorer quality life, consume disproportionate amount of inhaled medications, have higher mortality rates, greater use of health-care resources and more rapid decline in lung function compared with patients to either asthma or COPD alone.[24]

1.1.4 DIAGNOSIS OF ASTHMA

In clinical diagnosis of a patient, physicians acquire information about the patient's medical history to determine symptoms, potential risk factors, family and past coupled with lung function test and examination. Symptoms of asthma include shortness of breath, wheezing and cough.[11] Past and family history of other respiratory diseases may be linked to occurrence of respiratory symptoms in childhood, a history of allergy rhinitis, a family history of asthma or allergy likely increases the diagnosis of asthma.[11] Physical examination may elicit increased difficulty in breathing, wheezing (which may sometime be absent in severe asthma exacerbation). Further examination of the nose may reveal signs of allergic rhinitis or nasal polyposis.[11] With pulmonary function test, adults with a significant response to BD (>12% and 200 ml), from baseline or (if spirometry is not available) a change in peak in expiratory flow (PEF) of at least 20% is considered to be consistent with asthma diagnosis.[11] Airway or bronchial measurement, or hyperresponsiveness can also support asthma diagnosis. Classically, methacholine challenge can be used. A fall in FEV1 from baseline of 20% with standard doses of methacholine or histamine signifies asthma.[11] Methacholine directly triggers the constriction of airway smooth muscle resulting in direct change in spirometry.[28] Gradually increasing concentrations of methacholine are inhaled and FEV1 is successively measured.[28] Other tests indicative of asthma diagnosis in adults include a positive exercise challenge test, which is measured by a fall in FEV1 from baseline of ≥10% and >200mL from baseline.[11, 28] Similarly, exhaled nitric oxide, a less invasive method of quantifying airway eosinophil level can be used for asthma diagnosis to

measure eosinophilic airway inflammation. Elevated FeNO levels >50 parts per billion may predict an improved clinical response to ICS therapy.[29]

1.1.5 DIAGNOSIS OF COPD

COPD is usually diagnosed in people above the age of 40 years, basically with majority of COPD patients developing symptoms in later life.[22, 30] Common symptoms of COPD include dyspnea that is persistent and progressive over time and characteristically worse with exercise.[22] Also, chronic cough that may be intermittent and nonproductive with recurrent wheeze, any pattern of chronic sputum production in the context of history of significant tobacco smoke, occupational or biomass exposure.[22] Family history of COPD and/or childhood factors such low birthweight and childhood respiratory infections are risk factors considered for COPD diagnosis.[22] COPD is diagnosed on the basis of persistent medical history, clinical examination, diagnostic test using spirometry which is defined as the ratio of forced expiratory volume at 1 second (FEV1) to forced vital capacity (FVC) being less than 70% or, alternatively less than the lower limit of normal (LLN).[22] Spirometry measurements are evaluated with comparison with a standard value based on age, sex, height and race.[31] It is believed that the use of FEV1/FVC ratio to define airflow obstruction may lead to over-diagnosis among the elderly and less frequent diagnosis among patients less than 45 years.[22] This means the prevalence of COPD estimates depend on the cut-off value chosen and this may vary depending on the population assessed.[22] COPD diagnosis is also characterized by inflammation in the airway in response to tobacco smoke and

environmental factors. Consequently, sputum and blood eosinophils levels in some patients are now being recognized or used to predict possible treatment with the use of steroids.[32]

1.1.6 DIAGNOSIS OF ASTHMA-COPD OVERLAP

Despite the debates surrounding the definition and description of asthma-COPD overlap, GINA and GOLD proposed diagnostic criteria of asthma-COPD overlap that includes persistent yet reversible airflow limitation (post-bronchodilator FEV1/FVC <70% and FEV1 improvement of >12% and >400 mL from baseline after bronchodilator therapy); a history of asthma diagnosed by a doctor, atopy, allergies, or exposure to noxious agents; either sputum neutrophilia or eosinophilia; and age 40 years or older.[24, 26, 33-35] The general criteria to describe and diagnose individuals with asthma-COPD overlap are described in more details in Chapter 2.

Spirometry is essential in confirming the diagnosis of asthma-COPD overlap and this should be preferably performed at the stage of the initial diagnoses.[24] Since it is practically difficult to distinguish the diagnoses of asthma-COPD overlap from other cardinal OADs, **Figure 1.1** provides spirometry definitions to distinguish these patients from asthmatics or COPD patients. Some experts have also proposed that smoking or exposure to biomass fuel should be an integral component of the definition of asthma-COPD overlap, to avoid including patients with asthma who have developed airway remodelling and fixed airflow limitation.[26]

Spirometric variable	Asthma	COPD	Asthma+COPD
Normal FEV_1/FVC pre- or post BD	Compatible with asthma	Not compatible with COPD	Not compatible
Reduced post-BD FEV_1/FVC (< lower limit of normal, or <0.7 (GOLD))	Indicates airflow limitation but may improve spontaneously or on treatment	Required for diagnosis of COPD	Required for diagnosis of asthma+COPD
Post-BD FEV_1 ≥80% predicted	Compatible with diagnosis of asthma (good asthma control or interval between symptoms)	Compatible with mild persistent airflow limitation if post-BD FEV_1/FVC is reduced	Compatible with mild persistent airflow limitation if post-BD FEV_1/FVC is reduced
Post-BD FEV_1 <80% predicted	Compatible with diagnosis of asthma. Risk factor for asthma exacerbations	An indicator of severity of airflow limitation and risk of future events (e.g. mortality and COPD exacerbations)	As for COPD and asthma
Post-BD increase in FEV_1 ≥12% and 200 mL from baseline (reversible airflow limitation).	Usual at some time in course of asthma, but may not be present when well-controlled or on controller therapy	Common and more likely when FEV_1 is low	Common and more likely when FEV_1 is low
Post-BD increase in FEV_1 >12% and 400 mL from baseline (marked reversibility)	High probability of asthma	Unusual in COPD	Compatible with asthma+COPD

BD: bronchodilator; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease.

Figure 1.1: Diagnostic spirometric measures in asthma, COPD and asthma-COPD overlap

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1.2 MANAGEMENT AND TREATMENT OF ASTHMA, COPD AND ASTHMA-COPD OVERLAP

1.2.1 ASTHMA

The treatment goal is to achieve good symptom control, maintain normal activity levels by suppressing the asthmatic inflammation to minimize the risk of asthma-related death, exacerbations, persistent airflow limitation and treatment side effects.[36] The

principles of treatment are based on both pharmacological and non-pharmacological means. However, the main aim of this thesis is to focus on pharmacological treatment, better still the safety and effectiveness of inhaled pharmacotherapies. The pharmacological options for asthma treatment fall into 3 main categories namely; controller medications, reliever (rescue) medications and add-on therapies mostly for patients with severe asthma.[11] Controller medications are used to reduce airway inflammation, control symptoms, and reduce future risks such as decline in lung function and exacerbations. Reliever/rescue medications are provided to all patients with asthma for as-needed relief of breakthrough symptoms including worsening asthma or exacerbations and for short term prevention of exercise-induced bronchoconstriction.[29] Finally, add-on therapies are considered for patients with severe asthma who have persistent symptoms with or without exacerbations despite optimized treatment with high dose controller medications and treatment of modifiable risk factors. The updated GINA guideline recommends a 5-step treatment approach for patients diagnosed with asthma as depicted in **Figure 1.2** below.[36]

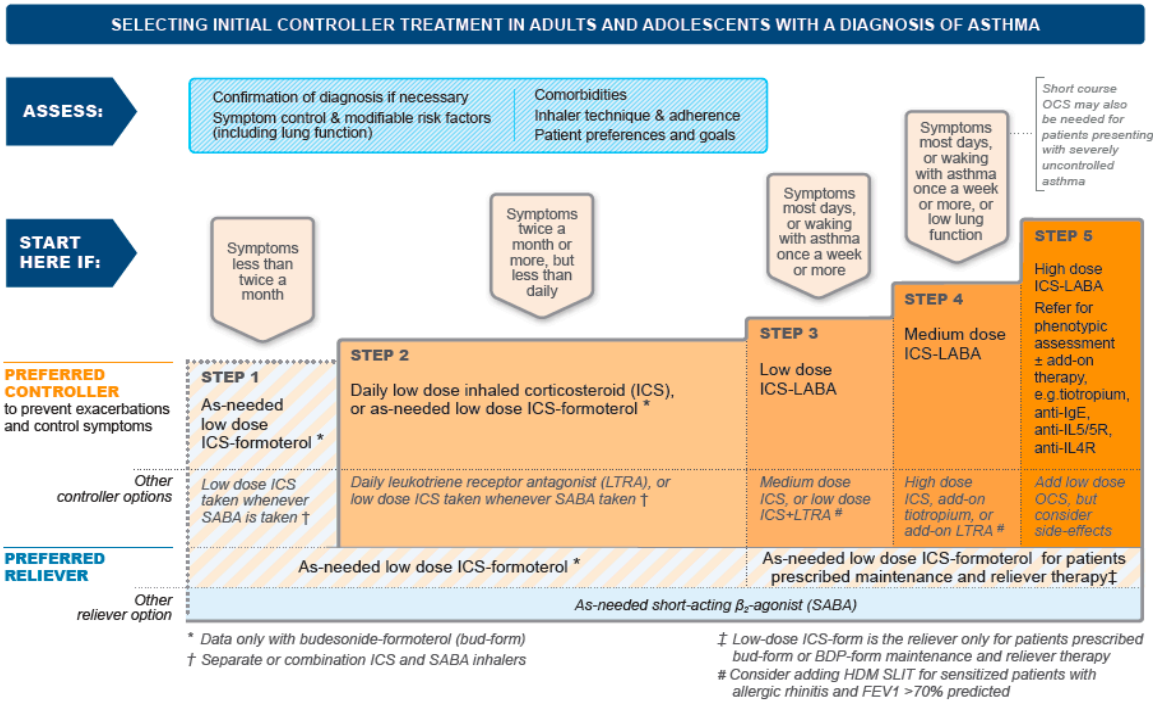

Figure 1.2: Stepwise treatment of asthma in adults.

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The choice of medication, device and dose should be based on each patient's assessment of symptoms, asthma control, risk factors and patient's preferences.[11] It is advised that patients whose asthma is partially controlled should start at step 2 and those whose asthma remains uncontrolled should start at step 3. At step 1 and 2, low dose ICS-formoterol (as needed) is recommended or separate/combination of ICS and SABA inhalers as other controller options in patients with symptoms less than twice a month. For those with step 2 disease, the recommended therapy is ICS or as-needed low dose

ICS-formoterol and this is recommended for patients with symptoms twice a month or more but less than daily. An ICS is recommended as this medication reduces inflammation and hyperresponsiveness of the airways, leading to improve asthma control, reduce risk of exacerbation and asthma attacks.[11] In patients who are unable to tolerate ICS treatment, a leukotriene receptor antagonist (LTRA) montelukast is recommended.[11, 37] At step 3 regular long-term maintenance treatment is recommended in patients with symptoms most days or waking with asthma once a week or more. A fixed dose combination of low dose ICS/LABA with additional use of as needed SABA as a relief therapy is suggested. In patients who suffer adverse effects to LABA or LABA use is contraindicated, a medium dose ICS or low dose ICS+LTRA can be used. At step 4 and 5, the recommended option is fixed-dose combination therapy ICS/LABA with the ICS at low dose or high dose respectively.[11] The risk-benefit ratio of ICS dosage (high or low) should be taking into account in respect to adverse side effect as long term use of systemic glucocorticoids should be given only in carefully selected individuals.[38]

1.2.2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

This section similar to asthma treatment and management summarizes steps and options in the context of the updated 2020 GOLD strategy report on the effectiveness and safety of inhaled pharmacotherapies used to lessen common respiratory symptoms associated with COPD such as dyspnea, cough and sputum production. Currently, there is no conclusive clinical evidence that any existing drugs for COPD modify the long-term

decline in lung function.[22] Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and general health status.[23] Initial treatment mostly commenced with rescue medication with short-acting bronchodilators for rapid symptom relief but this is not generally recommended on a regular basis.[23] Long-acting bronchodilator is normally preferred and, in some patients, a combination therapy of LAMA/LABA is prescribed for patients with acute breathlessness or LABA/ICS for patients with high blood eosinophil counts and high risk of COPD exacerbations.[32] Initial therapy with bronchodilators medication is basically to increase FEV1 and/or change spirometric variables. Bronchodilators act by altering airway smooth muscle tone and the improvement in expiratory flow to widen the airways thereby reducing hyperinflation at rest and during exercise.[32]

1.2.3 ASTHMA-COPD OVERLAP

Given the lack of randomized controlled studies of asthma-COPD overlap due to the fact that COPD patients are excluded from asthma trials and vice versa, it is difficult to provide firm treatment recommendations for these groups of patients. The asthma-COPD overlap guideline advocates treatment with asthma medication and to continue steadily with COPD medications as the disease progresses to lessen the risk of exacerbations.[11] The GINA GOLD consensus recommendation is to start treatment for asthma until further investigations have been performed.[11] Low to moderate doses of ICS, usually in combination with a long-acting bronchodilator are suggested to reduce

inflammation and control symptoms. In patients with features of asthma, LABA monotherapy should be avoided due black box warning of increased mortality in asthma patients taking LABA monotherapy.[26] For the patient with COPD features, a stepwise treatment approach is recommended, with a focus on reduction of symptoms and exacerbations. The main emphasis should be on the use of LABAs and LAMAs alone or in combination.[25, 26, 39, 40]

In a nutshell, there are inadequate clinical trial data to make evidence-based recommendations for the treatment and management of asthma-COPD overlap. This is mainly due to the fact that patients with asthma-COPD overlap are excluded from clinical trials, with most COPD trials exclude patients with a history of asthma, and most asthma trials exclude patients with subsequent diagnosis of COPD. This phenomenon results in understudy of asthma-COPD overlap patients and thus most of the treatments in this population are extrapolated from trials that enrol asthma and/or COPD patients.[39]

1.3 CARDIOVASCULAR SAFETY OF INHALED β2-AGONISTS

1.3.1 MECHANISM AND EVIDENCE FROM THE LITERATURE

β2-adrenergic agonists are class of drugs that are used as first line treatments for obstructive airways diseases including asthma, COPD and asthma-COPD overlap. These drugs mimic the functions of epinephrine by producing autonomic responses within the airway smooth muscle (ASM).[29] The onset of action and duration dictates the classification of β2-agonists. These classes divide into short-acting β2-agonists (SABAs) and long-acting beta-agonists (LABAs). β2-agonists such as SABAs and LABAs are available in inhaler form, either via metered-dose inhalers (MDIs), which aerosolize the drug, or dry powder inhalers (DPIs), with dispense powder which can be inhaled.[41] Inhalation as a route of administration is mostly preferred as it restricts the drug to the lung tissue, thereby strengthening the therapeutic effect on the airway smooth muscles resulting in dilation of the bronchial passages and relaxation of the muscle.[29]

SABAs, as they are popularly known have the shortest half-life and are for rescue or instant relief from symptoms.[11] Their onset of therapeutic action is under 5 minutes and their effect can last between 3 to 6 hours. SABAs in general, are considered as first-line drugs for acute treatment of dyspnea, symptom relief and exacerbation in patients with obstructive airways diseases.[11, 22] Typical examples of SABAs are salbutamol, and terbutaline sulfate. In contrast, LABAs, bestow prolonged and sustained treatment than SABAs due to their increased half-life and are mostly considered as maintenance treatment.[22] Most SABAs are fast acting. In the same vein, most LABAs are slow acting and the longer acting LABAs are slow onset. Only formoterol has been approved

for rescue. Some common examples of LABAs are salmeterol xinafoate, indacaterol maleate, olodaterol, vilanterol and formoterol fumarate.

β2-agonists are effective bronchodilators primarily due to their ability to relax airway smooth and are very important drugs that have been used for many years in the management of various bronchoconstrictive diseases in children and adults.[42, 43] Therefore, the activation of β2 adrenergic receptors leads to relaxation of smooth muscles in the lung, dilation and opening of the airways.[43] Stimulation of Cardiac β-adrenoceptors, an essential regulators of cardiac function leads to results in positive cardiotonic and chronotropic responses, cardiac myocyte and cardiotoxicity.[44, 45] β-adrenoceptors are linked through the stimulatory G protein (Gs) to the effector enzyme adenylyl cyclase, which is responsible for converting the substrate magnesium adenosine triphosphate to cyclic adenosine monophosphate (cAMP), with resultant activation of protein kinase A (PKA).[41, 44] cAMP is a considered positive cardiotonic and chronotropic second messenger and is a strong protagonist of cellular buildup.[44] Although, β1-adrenoceptors are classically described as the crucial proponent in activating and regulating contraction, activation of both β1-and of β2-adrenoceptors results to positive inotropy through coupling to adenylyl cyclase and production of cAMP.[44, 46] In direct opposite of the β1-adrenoceptors, studies in rats and murine, have revealed that β2-adrenoceptor, can also couple to the inhibitory G-protein (Gi).[47] This evidence in rats and murine are yet to be proven in human.

As a result of similar characteristics between the classes of adrenergic receptors in humans, β2-agonists can create an "off-target" effect in stimulating either alpha-1, alpha-2, or beta-1 receptors [41, 48] with most common side effects involving cardiovascular,

metabolic, or musculoskeletal system.[41] β2-agonists may also increase heart rate and impact blood pressure through β2-adrenoceptors in the atria, ventricles and peripheral vasculature, the latter via the baroreflex mechanism potentially inducing major adverse cardiovascular events.[49] Studies on cardiovascular safety of inhaled β2-agonists have accumulated over the years.[50-52] For instance, a study on short-term cardiovascular and autonomic effects of inhaled salbutamol in asthma found an association between acute salbutamol use and risk of sympathetic stimulation including tachycardia and muscle sympathetic nervous activity (MSNA) suggesting that salbutamol could contribute to cardiovascular morbidity and mortality in individuals using inhaled β2-agonists.[53] In a case control study conducted in the US, an adjusted odds ratio (aOR) of 3.2 (95% CI [confidence interval] 1.61 – 6.35) for AMI was found in patients receiving SABA in the 3 months prior to the AMI compared to non-users which was more pronounced in new users (aOR 7.32, 95% CI 2.34 – 22.8).[54] Heavy long-term users of SABA (at least 13 prescription in the year before) living in the UK had an increased AMI risk compared to users receiving less than 3 prescriptions (relative rate 1.6).[55]

Also, a recent open label trial on treatment responsiveness of phenotypes of symptomatic airways obstruction in adults revealed that asthma-COPD overlap patients who use LABA/ICS or LABA alone during 12 months had the highest incidence of cardiovascular disease (CVD) morbidities.[56] In recent past, there have also been calls for the withdrawal of single therapy of LABA in asthma.[57] Prior to this, safety warnings about the use of salmeterol were issued in North America as a result of serious adverse events.[58-60] In a recent network-meta-analysis for pneumonia including 54 RCTs and 21 treatments, salmeterol and fluticasone combination had the greatest risk of

pneumonia compared to placebo (surface under the cumulative ranking curve [SUCRA] = 89%).[51] In a meta-analysis of 13 single-dose randomized placebo control trials in patients with asthma and COPD, a single dose of β2-agonists (such as formoterol, salmeterol, terbutaline and salbutamol) increased the heart rate by 9.12 beats/ min (95% CI 5.32 to 12.92).[36] For trials lasting from 3 days to 1 year, β2-agonists treatment significantly increased the risk for cardiovascular event (RR [relative risk], 2.54; 95% CI 1.59 to 4.05) compared to placebo.[36] This is also due to the fact that OAD patients share other risk factors with cardiovascular disease (CVD) patients due to advanced age and decrease in physical activities caused by lung disease.[61]

1.5 RESEARCH STUDY SIGNIFICANCE

To date, there are currently no previous observational studies which examined the impact of β2-agonists medications on the risk of cardio-respiratory (CR) events including major adverse cardiovascular events, all-cause-mortality and hospitalization for pneumonia in patients with obstructive airways diseases most especially asthma-COPD overlap. My thesis project addressed this knowledge gap, by using a Clinical Practice Research Datalink (CPRD) database, composed of detailed healthcare records of patients with history of physician diagnosed asthma, COPD and asthma-COPD overlap.

The goal of my thesis was to estimate the risk of cardio-respiratory safety associated with exposure to β2-agonists among cohorts of new users of bronchodilator medications diagnosed with OADs – mainly asthma, COPD and asthma-COPD overlap. My thesis study thus provided important and novel insight for clinicians, policy-makers and patients to fully examine the safety of β2-agonists-based medications.

The research study conducted in this thesis received approval from Health Research Ethics Board at Memorial University and the study protocol was approved by the CPRD Independent Scientific Advisory Committee - ISAC 18_005RA (please see **Appendix I** for ethics approval).

1.6 RESEARCH OBJECTIVES, SPECIFIC AIMS

To investigate gender differences in new users of inhaled bronchodilators and ICS and to estimate the risk of all-cause mortality and CR safety outcomes associated with exposure to β2-agonists among cohorts of new users of bronchodilator medications diagnosed with asthma, COPD and asthma-COPD overlap. The CR safety events include pneumonia and major adverse cardiovascular events (including non-fatal myocardial infarction (MI), non-fatal stroke, heart failure (HF), arrhythmia or cardiovascular mortality. Furthermore, among patients with asthma-COPD overlap, the aim is to determine the positive predictive value (PPV) of four algorithms among patients assumed to have been diagnosed with asthma-COPD overlap syndrome within CPRD GOLD. The full protocols for the study can be found in **Appendix II** and **III**.

1.6.1 Primary Research Questions

- What are the comparative safety and effectiveness of current pharmacotherapies consisting of long-acting β2-agonists (LABA) and/or inhaled corticosteroids (ICS) in patients with asthma–COPD overlap?
- What are the prescribing patterns among genders (male vs females) in new-users of inhaled pharmacotherapies in patients with asthma, COPD or asthma-COPD overlap?
- Does exposure to short-and or-long acting β2-agonists increase or decrease the risk of major adverse cardiovascular events compared to no exposure to β2-agonists based medications?

- Does exposure to short-and or-long acting β2-agonists increase or decrease the risk of all-cause mortality or hospitalization for pneumonia compared to no exposure to β2-agonists based medications?

1.7 THESIS TEXT OUTLINE

The research study in the thesis text is presented in Eight (8) Chapters, in addition to references and appendices. The spine of each chapter is composed of Introduction, Methodology, Discussion and Conclusion sections as stipulated by the research and graduate studies (RGS).

1.7.1 CHAPTER 2

In Chapter 2, whose manuscript is published in Journal of Asthma, November 2019, I undertook a systematic review of the comparative effectiveness and safety of inhaled medications (corticosteroids and bronchodilators) in combination or alone in patients with asthma-COPD overlap for outcomes relating to both the heart and the lung. Furthermore, I performed a meta-analysis to quantify the association between inhaled corticosteroid and long-acting bronchodilator medications and the risk of cardiorespiratory outcomes and other important clinical outcomes in patients with asthma-COPD overlap.

1.7.2 CHAPTER 3

In Chapter 3, the focus was on a research study which was published in International Journal of COPD which garnered over 137 manuscript downloads and 386

views within two weeks of being published. In this original research titled "Gender Differences in Inhaled Pharmacotherapy Utilization in Patients with Obstructive Airway Diseases: A Population-Based Study", I investigated gender differences in new-users of ICS monotherapy, ICS/LABA combination therapy, LABA monotherapy, LAMA monotherapy, SABA monotherapy and SAMA monotherapy in patients with asthma, COPD or asthma-COPD overlap.

1.7.3 CHAPTER 4

Chapter 4, outlines an original research titled "Risks of Major Adverse Cardiovascular Events associated with β2-agonists for the Treatment and Management of Asthma, COPD, and Asthma-COPD Overlap: A Nested Case-Control study". In this study, I advanced the understanding of the cardio-respiratory safety of β2-agonists, by conducting a nested case-control study among new users of β2-agonists-based medications on the risk of major adverse cardiovascular event among patients with asthma, COPD and asthma-COPD overlap, controlling for time-varying nature of exposure by study design and also controlling for confounding by indication by performing a number of additional sensitivity analyses. I also conducted 5 secondary analyses based on individual components of the major adverse cardiovascular events including HF, MI, stroke, arrhythmia and cardiovascular death.

1.7.4 CHAPTER 5

In Chapter 5, I examined the Association of β2-agonists-based Drugs with All-cause Mortality or Pneumonia in patients with Asthma, COPD or Asthma-COPD Overlap.

1.7.5 CHAPTER 6

In Chaper 6, I explored the possibility of future or further research studies. In this chapter, a systematic review protocol titled "Validation of Asthma-COPD overlap Recording in Healthcare Records: Protocol for a Systematic Review" was published in the BMJ-Open Journal. The primary objectives of this future study is to explore validated methods (or algorithms) that identify patients with asthma-COPD overlap from healthcare databases and summarise the reported validity measures of these methods.

1.7.6 CHAPTER 7

In Chapter 7, an ongoing project to assess the utility of various search algorithms to best locate General Practitioner (GP) confirmed asthma-COPD overlap cases in United Kingdom electronic primary care records and to validate these algorithms has been stalled due to COVID-19 pandemic. Data collections which started very well eventually broke down as GPs are not allowed to see patients in person in the United Kingdom.

1.7.7 CHAPTER 8

Finally, in Chapter 8 all key findings are summarised and conclusions drawn with any implications for further research in the future.

CHAPTER 2

COMPARATIVE SAFETY AND EFFECTIVENESS OF INHALED BRONCHODILATORS AND CORTICOSTEROIDS FOR TREATING ASTHMA–COPD OVERLAP: A SYSTEMATIC REVIEW AND META-ANALYSIS

A VERSION OF THIS MANUSCRIPT HAS BEEN PUBLISHED IN THE JOURNAL OF ASTHMA, 2019

J. Amegadzie, J. Gorgui, L. Acheampong, JM Gamble, J. Farrell, Z. Gao (2019). Comparative Safety and Effectiveness of Inhaled Bronchodilators and Corticosteroids for treating Asthma-COPD Overlap: A Systematic Review and Meta-Analysis. *Journal of Asthma. 2019 Oct 31:1-18. doi: 10.1080/02770903.2019.1687716.*

2.1 INTRODUCTION

The notion that asthma and COPD share a common etiology has been discussed and debated since 1961 when Orie and Sluiter proposed the "Dutch hypothesis".[1] The controversy continues today as clinicians assess and treat patients with symptoms of both asthma and COPD. This phenotype of obstructive airway diseases (OADs) is known as asthma-COPD Overlap (ACO). Asthma-COPD Overlap was recently described in 2015 by both The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD". The GINA guideline also reported that asthma-COPD overlap includes different clinical phenotypes with several underlying mechanisms. [2, 3]

Just as the classification of asthma and COPD as completely separate disease is still debatable, [4, 5] the primary definition of asthma-COPD overlap is not yet clear. Various criteria which have been used over the years to describe and diagnose individuals with asthma-COPD overlap in publications are detailed in **Table 2.1**. The updated 2018 GINA clinical guideline for asthma-COPD overlap recommendations for initial treatment for clinical efficacy and safety proposes the use of corticosteroid at a low or moderate dose depending on level of symptoms; and add-on treatment with long-acting beta2-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) if necessary, or continue these together with inhaled corticosteroid (ICS) if already prescribed.[6] This consensus based treatment for patients with asthma-COPD overlap is intended to provide interim advice to clinicians in managing the disease.

Table 2.1: Criteria used to describe and diagnose individuals with asthma-COPD overlap in publications

Studies	Major Criteria	Minor criteria
GesEPOC/SEPAR Consensus Guideline, 2012 [41]	COPD per GOLD and either 2 major criteria or 1 major and 2 minor criteria are met Major Criteria: 1. Very positive BDT (increase in FEV_1> 15% and >400mL) 2. Eosinophilia in sputum 3. Personal history of asthma	Minor criteria: 1. High total IgE 2. Personal history of atopy 3. Positive BDT (increase in FEV_1>12% and >200mL) on two or more occasions
Louie et al., 2013 [42]	Major criteria: (2 major) 1. Physician diagnosis of asthma and COPD in the same patient 2. Post-Bronchodilator FEV_1 < 80 % predicted and COPD per GOLD 3. >40 years old 4. Smoking >10 pack years	Minor criteria: (2 minor and 1 major) 1. ≥15 % increase in post-bronchodilator FEV_1 or 2. ≥12 % and ≥200 ml in post-bronchodilator FEV_1
Menezes et al., 2014 [43]	Post-Bronchodilator FEV_1/FVC<0.7 and asthma (wheezing in the last 12 months plus bronchodilator response of FEV_1/FVC 200mL and 12% or medical diagnosis of asthma)	
Kiljander et al., 2015 [42]	Adults with a diagnosis of asthma and smoking (≥10 p-y) with PBD FEV_1/FVC≤0.70	
Sin et al., 2016 [44]	Major Criteria: (2 major) COPD plus; 1. Persistent airflow limitation (post-bronchodilator FEV_1/FVC <0.7 or LLN in patients ≥40 years of age) 2. 2 Methacholine challenge test positivity 3. FENO ≥ 45-50 ppb and/or sputum eosinophils > 3% 4. History of asthma	Minor Criteria: (2 minor and 1 major) COPD plus: 1. Documented history of atopy or allergic rhinitis 2. Bronchodilator reversibility of FEV_1≥200mL and 12% from baseline on ≥2 visits 3. Peripheral blood eosinophil count of ≥300 cells/mL
Van Boven et al., 2016 [45]	Primary care diagnosis of both asthma and COPD	
GesEPOC/GEMA Consensus Clinical Practice Guideline, 2017 [46]	≥35 years of age, smoker (ex-smoker) ≥10 p-y; FEV_1/FVC<0.7 post PBD<70% that persists after treatment with ICS/LABA; and Current diagnosis of asthma(GEMA criteria)	If a diagnosis of asthma cannot be established, PBD≥15% and 400 ml, and/or Eosinophilia in blood ≥300c/μL
Koblizek et al. 2017 [47]	Patients with COPD and asthma diagnosed before the age of 40 years; or with a positive bronchodilator response plus atopy	
GINA/GOLD Consensus Statement 2018 [6]	Characterize by persistent airflow limitation with several features associated with asthma and several features associated with COPD	Asthma-COPD overlap is therefore identified in clinical practice by the features it shares with both asthma and COPD

Abbreviations: COPD, chronic obstructive pulmonary disease; BDT, bronchodilator treatment; GINA, global initiative for asthma; GOLD global initiative for chronic obstructive lung disease; FEV_1, forced expiratory volume in 1s; IgE, Immunoglobulin E; FVC, forced vital capacity; FENO, fractional exhaled nitric oxide; GEMA, Spanish Guideline on the Management of Asthma;

GesEPOC, Spanish COPD guideline; SEPAR, Spanish Society of Pulmonology and Thoracic Surgery

The safety and effectiveness of pharmacotherapy treatment for this overlap population is poorly recognized and given less attention in part because clinical trials have consistently ignored this condition, as evidenced by strict inclusion and exclusion criteria that either exclude asthma patients from COPD studies or COPD patients from asthma studies plus uncertainty around disease definition precludes RCT evidence generation.[7, 8] Despite these shortcomings, the effect and impact of bronchodilators on the cardiorespiratory outcomes has been documented for patients with COPD.[9-11] However, the incidence and severity of cardiorespiratory events associated with the use of inhaled bronchodilators have not been documented in the context of asthma-COPD overlap. This is of particular concern because this population with features of both asthma and COPD experience frequent exacerbations, has poor quality of life, a more rapid decline in lung function and high mortality, and consumes a disproportionate amount of medications than asthma or COPD alone.[12] The clinical practice guideline on asthma-COPD overlap also reported that patients with asthma-COPD overlap experience worst quality of life than patients with asthma or COPD alone, yet there is limited evidence concerning the effectiveness and safety of inhaled bronchodilators and corticosteroids for patients with asthma-COPD overlap.[6]

This study aims to address the literature gap surrounding the safety and effectiveness of ICS, LABA, and LAMA medications in asthma-COPD overlap patients. We performed a systematic review of the literature to provide a general overview of what

the comparative effectiveness and safety of inhaled medications (corticosteroids and bronchodilators) is in combination or alone in patients with asthma-COPD overlap. Furthermore, when possible, we meta-analyzed included studies to quantify the association between inhaled corticosteroid and long-acting bronchodilator medications and the risk of cardiorespiratory outcomes and other important clinical outcomes in patients with asthma-COPD overlap.

2.2 METHODS

2.2.1 STUDY DESIGN AND PROTOCOL REGISTRATION

This systematic review and meta-analysis was conducted following a pre-specified protocol and guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) as reported in **Appendix VI** and **Appendix V** respectively in Appendix. [13, 14] The predefined protocol is registered in PROSPERO (CRD42018090863).

2.2.2 ELIGIBILITY CRITERIA

In order to identify the totality of evidence for both the effectiveness and safety of inhaled corticosteroids and long-acting bronchodilators within the context of asthma-COPD overlap, we included both RCTs and non-randomized designs. The later may be particularly useful for quantifying the association between drug therapies and uncommon

safety events as well as studying patient populations not represented in clinical trials.[15] Therefore, we included the following type of study designs to evaluate the effectiveness or safety of inhaled corticosteroids and bronchodilators medications in the context of cardio-respiratory outcomes: RCTs, cohort studies or nested case control studies. we excluded study designs such as meta-analyses, systematic reviews, classic case-control studies, case series, case reports or cross-sectional. Studies that did not report at least one of the following were also excluded; a) total number patients and number of patients with an event in treatment and control groups of interest, b) measure of association (risk ratio, odds ratio or mean difference) along with either confidence intervals (CI's) or p-values.

2.2.3 OUTCOMES OF INTEREST

The primary outcome of interest was the incidence of cardiorespiratory disease, defined as outcomes relating to both heart and lungs. This included myocardial infarction, pulmonary function testing (FEV_1), exacerbation and nontuberculous mycobacterial pulmonary disease (NTM-PD). Secondary outcomes considered were fracture rates, death or asthma-COPD overlap hospitalization.

2.2.4 DATA SOURCES AND SEARCHES

A comprehensive literature search was conducted in EMBASE, MEDLINE and Web of Science databases. Microsoft Excel (Microsoft Office Professional Plus 2013, Version 15.0.5007.1000) and EndNote (Version X7, Thomson Reuters) software were used to manage the study articles, references, and study data. Records were screened and

selected based on a search strategy that combined free-text, Medical Subject Headings (MeSH), EMTREE, and title/abstract (tiab or ab,ti) to identify all records examining the association between inhaled LABA or LAMA or ICS monotherapies or combination therapies of ICS/LABA, and asthma-COPD overlap primarily based on our eligibility criteria. EMTREE, title/abstract (ab,ti) and free-text terms were used to search EMBASE. This was done and led by an experienced librarian, AF, from the Health Science Library (HSL) of Memorial University together with MS, SMA and JEA. The MeSH, title/abstract and free-text terms were used to search MEDLINE. The initial search was performed on all available studies on March 6, 2018 and was subsequently updated weekly until June 1, 2018.

We also reviewed reference lists of all primary studies for additional references. We contacted authors of those identified articles with missing figures and values. Among three authors contacted, two responded and one author did not; however, this did not lead to exclusion of any of our articles identified. The search was restricted to English language. In order to identify the asthma-COPD overlap description, we created a search strategy likely to contain studies on the combination of terms based on criteria expounded in **Table 2.1** used to describe and diagnose individuals with asthma-COPD overlap in publications. The detailed search strategy is reported in **Appendix VI**.

2.2.5 DATA ITEMS AND DATA ABSTRACTION PROCESS

A data extraction form was developed and piloted on three of the included studies. An experienced respiratory specialist, JF, independently reviewed all selected studies to

ascertain that each included study clearly described patients with asthma-COPD overlap. Data extraction was performed by two independent reviewers, JEA and LA. This was to ensure accuracy in data encoding. Discrepancies in determining whether the study met our inclusion criteria during the full text review were resolved by consensus between reviewers. If consensus could not be reached, discrepancies were resolved through a third reviewer, JG. The following information was abstracted independently by JEA and LA from each included study: (1) Study characteristics (study design, sample size, source population, country, type of database used to ascertain information about exposure and outcome); (2) Patient characteristics (mean age, sex); (3) Exposure and control/comparator definitions (duration of use, dose, current/new vs. never, use of time-dependent or time-window approach or time-dependent approach); (4) Incidence of cardiorespiratory outcomes; (5) Hazard ratios, risk ratios, rate ratios, odds ratio, mean difference with corresponding 95% confidence interval (CIs); (6) Methods of adjustment for confounders (matching, newer design, risk-set sampling, regression-based adjustments, propensity scores, disease risk scores) and list of potential confounders.

2.2.6 RISK OF BIAS ASSESSMENT

The quality of each study was independently assessed by two authors (JG and LA) based on the Cochrane Risk-of-Bias assessment tool for randomized controlled trials.[16, 17] In the case of any disagreement, a third author (JEA) also assessed the study. Studies score were rated as having a high, low or unclear level of bias across seven domains. The risk of bias for the observational studies was appraised through the Newcastle-Ottawa

Quality Assessment Scale (NOS) [18] according to the procedures recommended in the Cochrane Handbook of Systematic Reviews. JEA and JG assessed the methodological quality of all the selected studies. Three parameters were evaluated: (1) population selection, (2) comparability of results, and (3) ascertainment of exposure (nested case–control) or outcome (cohort studies). Studies score one star for each area addressed, with scores between 0 and 9 (the highest level of quality). We categorize study quality according to the study score into poor (score 0–3), moderate (score 4–6) and high quality (score 7–9). The procedure in the NOS was used in conjunction with key pharmacoepidemiological (PE) study biases including but not limited to time-related biases, confounding, residual confounding, channeling bias, depletion of susceptible, lack of statistical power and switchers bias. We believe that PE studies may differ with regard to database characteristics (e.g., claims or electronic health records, EHRs database), inclusion criteria, exposure, follow-up period, definition of outcome, and the confounders adjusted for in multivariate models as done elsewhere. [19] This additional in-depth bias analysis was independently assessed by JEA and JG.

2.2.7 STATISTICAL ANALYSIS

Review Manager (RevMan version 5.3.5, Cochrane Collaboration, Oxford, UK) was used to perform data analysis at the quantitative synthesis stage. We employed the inverse variance method to quantify the association between inhaled medications of interest (ICS and/or LABA) and the risk of cardiorespiratory outcomes. A quantitative statistical analysis for dichotomous variables was carried out using the risk ratio (RR) as

the summary statistic. Mean difference (MD) was used as the summary statistic for quantitative analysis of continuous variables. Both the RR and MD values were reported as 95% CI. The level of heterogeneity between studies was evaluated by I2 statistics. I2 < 30% was considered to be low heterogeneity and I2 > 50% represented high heterogeneity. A random effects model was applied for all comparisons. Statistical significance across the studies was defined as $p < 0.05$. Weights from each study were provided by the Inverse Variance method available in RevMan. There was an inadequate number of included studies (<10) in each of the individual meta-analysis conducted for either outcome to adequately assess publication bias through a funnel plot.

2.2.8 SUBGROUP ANALYSIS

In the quantitative analysis of inhaled combination therapy of ICS/LABA versus an active comparator and risk for death or hospitalization of asthma-COPD overlap, heterogeneity was explored through subgroup analysis whereby results were stratified by use of LAMA or LABA monotherapy.

2.3 RESULTS

2.3.1 LITERATURE SEARCH AND STUDY SELECTION

A detailed flow diagram of the review selection process is shown in **Figure 2.1.** During the search process, English language, human and full-text articles filters were applied to both PubMed and EMBASE database searches, whereas English language and

full-text articles filters were applied to Web of Science reference search. A total number of 3382 references were identified via EMBASE, Medline and Web of Science out of which 2343 original articles and abstracts were independently identified and evaluated by two reviewers JEA and LA after removing 1039 duplicates. After title and abstract review, 2286 studies were excluded due to specific reasons as outlined in **Figure 2.1.** Of 57 studies meeting our initial criteria, 10 publications were retained for data extraction. However, five were not included in the meta-analysis (one RCT, one nested case-control and three cohort studies) because there were less than two studies with either a common exposure or an outcome. This was done to ensure that we were analyzing the same class of medication based on their therapeutic activity and duration of action.

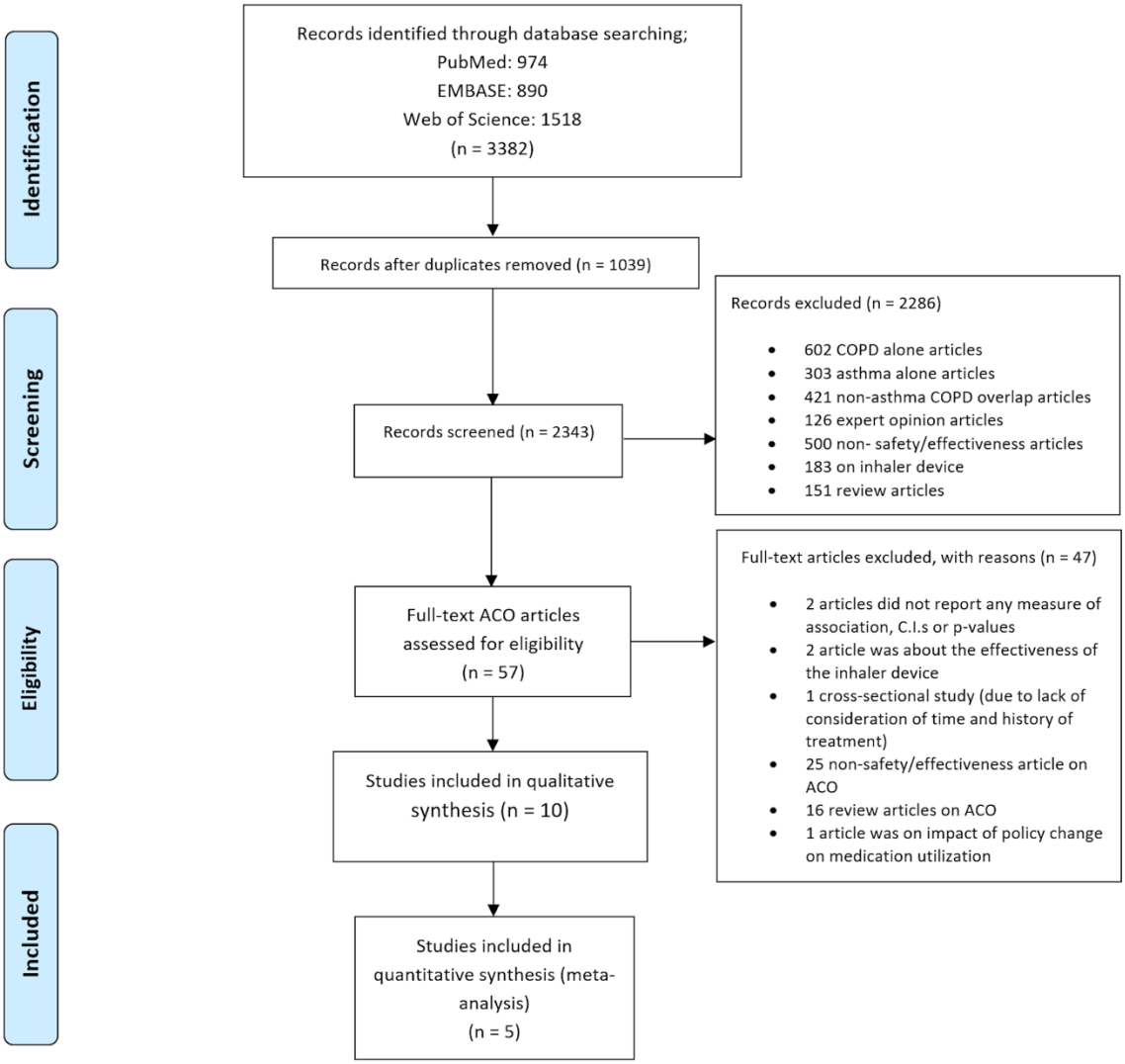

Figure 2.1: A PRISMA flow diagram details the flow of information through the different phases of the review; maps out the number of records identified, included, excluded and the reasons for their exclusion.

2.3.2 STUDY CHARACTERISTICS

A detailed overview of the characteristics of all selected studies is reported in **Table 2.2.** Of the 10 included studies, three were RCTs, six were cohort studies and one

was a nested case-control study. Study interventions included combination therapy of LABA/ICS, ICS alone, and LABA or LAMA alone. These interventions were either compared with a placebo [20, 21] or active comparators of ICS, [22] SABA or LAMA or short-acting muscarinic antagonist (SAMA).[23-25] The average follow-up time ranges between 30 days and 5.7 years for the observational studies whilst all the included RCTs have the same follow-up time of approximately 12 weeks. All the observational studies either used administrative (n=4) or electronic health record (n=3) databases.

These studies were carried out in Japan, South Korea, New Zealand, United Kingdom, Canada, Netherlands, United States and a multi-center trial conducted in Belgium, Canada, Germany, Denmark, France and Italy.

Table 2.2: Characteristics of included studies

Author and publication year	Study design	Sample size (n)	Age (years)	ACO Description and/or Diagnosis Method	Exposure / Intervention	Comparator / Control	Follow-up period	Outcome Assessed
Afonso et al. 2016[29]	Cohort	51,308 4,940	65.7 53.8	Patients with both features of "asthma AND COPD" as described by GINA/GOLD guideline (based on Read codes and ICD-9-CM documented diagnosis of both asthma and COPD).	LABA monotherapy	SABA and/or LAMA and/or SAMA monotherapies	90 days	AMI
Brode et al. 2017[23]	Nested Case Control	Cases: 2966 Controls: 11851	76.6	Patients who meet criteria for ACO as defined by the clinical guideline and documented in the database.	ICS monotherapy	SABA, LABA, SAMA or LAMA monotherapies	≤30 days	NTM-PD
Fingleton et al. 2015[26]	RCT	389	53.4	Physician diagnosis of patients with features of atopic asthma, with marked variability in airflow obstruction, emphysema, and chronic bronchitis in current smokers or ex-smokers	ICS monotherapy	SABA or SAMA monotherapies	12 weeks	FEV_1
Gershon et al. 2014[24]	Cohort	11,967	76.8	COPD patients with a codiagnosis of asthma (based on documented diagnosis of asthma and COPD);	ICS/LABA combination	LABA monotherapy or LAMA monotherapy	2.7 yrs	Composite outcome of death and hospitalization

				which the authors described as patients with asthma-COPD overlap syndrome				
Hubbard et al. 2006[25]	Cohort	407	81.0	Patients with diagnosis of airflow obstruction of both asthma and COPD described as asthma-COPD overlap syndrome based on documented Read codes in the database.	ICS monotherapy	SABA or LABA monotherapies	4.7 yrs	Fracture
Ishiura et al. 2015[20]	RCT	16		Subjects with episodic respiratory symptoms, increased airflow variability (asthma; i.e., AHR or BDR) as well as incompletely reversible airway obstruction (COPD; FEV_1/ FVC < 70% and post-bronchodilator FEV_1 <80% of predicted). AHR was defined if a ≥20% FEV_1 fall from baseline occurred after inhalation of methacholine. BDR was also defined as an increase in post-bronchodilator FEV_1 ≥200 ml and 12% compared with pre-bronchodilator FEV_1.	ICS/LABA combination therapy	Placebo	12 weeks	FEV_1

Lim et al. 2014[27]	Cohort	125	65.2	ACO was defined based on physician diagnosis of a post bronchodilator $FEV_1/FVC < 0.70$ and a positive BDR (increase in FEV1 by at least 200mL and 12% after inhalation of 200 mg of salbutamol) or AHR (a provocation concentration that caused a decrease in FEV_1 of 20% no higher than 16 mg/mL) decrease in FEV_1 of 20% no higher than 16 mg/mL. A smoking history of at least 10 pack-years and had undergone at least 2 spirometry assessments with bronchodilator reversibility testing at an interval of at least 1 0.25 year.	ICS monotherapy or in combination with LABA (defined as ICS/LABA combination)	SABA, LABA or SAMA monotherapies	5.7 yrs	Severe exacerbations
Magnussen et al. 2008[21]	RCT	472	60.2	Physician diagnosis of asthma (before the age 30), a diagnosis of COPD, post-bronchodilator FEV1 <80% predicted normal and a postbronchodilator ratio of FEV_1/FVC (forced vital capacity) <70%. Other inclusion criteria were: smoking history >10 pack-years, age ≥40 years, treatment with ICS for ≥1 year prior to study entry, and an acute bronchodilator response ≥200 ml and ≥12% of prebronchodilator FEV_1.	LAMA monotherapy	Placebo	12 weeks	FEV_1

Su et al. 2018[22]	Cohort	251,398	64.5	Patients with ACO identified by using diagnostic coding system of International Classification of Diseases (ICD), 9th Revision, Clinical Modification	ICS/LABA combination; LAMA monotherapy	LABA monotherapy or ICS monotherapy; LABA monotherapy or ICS monotherapy	1 year	Acute exacerbations
Uddin et al. 2016[28]	Cohort	64,607	66.0	Patients with both features of "asthma AND COPD" as described by GINA/GOLD guideline (based on Read codes and ICD-9-CM documented diagnosis of both asthma and COPD).	LABA monotherapy	SABA, SAMA or LAMA monotherapies	5.61 yrs	MI

Abbreviations: RCT, randomized control trial; LABA, long-acting beta-agonist; AMI, acute myocardial infarction; ICS, inhaled corticosteroid; COPD, chronic obstructive pulmonary disease; AHR, airway hyperresponsiveness; BDR, bronchodilator response; GINA, global initiative for asthma; GOLD global initiative for chronic obstructive lung disease; CPRD, clinical practice research datalink; ACO, asthma-COPD overlap; FEV_1, forced expiratory volume in 1s; SAMA, short-acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; MI, myocardial infarction; NTM-PD, nontuberculosis mycobacterial-pulmonary disease; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification.

2.3.3 RISK OF BIAS

A summary of study quality of the RCT studies is presented in **Figure 2.2**. In brief, all three RCTs were at low risk of selection bias (random sequence generation), attrition bias and reporting bias; two studies were at low risk of selection bias (allocation concealment)[20, 26] and detection bias[21, 26]; two studies were at high risk of performance bias[20, 21], one study was at high risk of selection bias and another study was at high risk of detection bias.[20, 21] Expatiating more on the risk of bias in each RCT study; in one of these studies reviewed, allocation concealment (selection bias) was not described in the article.[21] In another RCT of 168 steroid naïve participants, subjects were selected based on their self-report of symptomatology.[26] Thus, the method they used to identify subjects to be included in their dataset had a low specificity. They aimed to minimize this effect by using validated questionnaires. In another RCT study which was an open-label trial, the authors provided detailed information on the process of randomization by the opaque-sealed envelope method.[20] However, performance bias (study participants were not blinded to the intervention) was detected in this study [20] and also in another study.[21] All studies reported random sequence generation; two studies reported allocation concealment and also blinding of outcome.[21, 26]

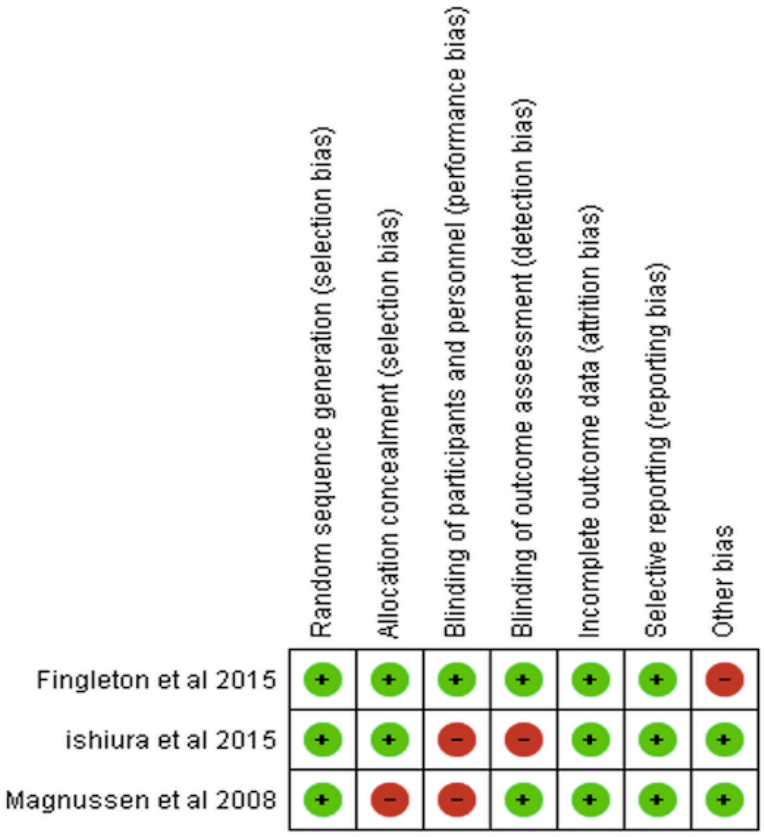

Figure 2.2: Risk of bias summary for RCT studies.

The Newcastle-Ottawa Quality Assessment Scale, NOS, was used for the quality assessment of the observational studies. In **Table 2.3**, the quality score for each study is reported. However, no studies were excluded based on the quality score grading. A summary of the in-depth key PE study quality is presented in **Appendix VII**. All the observational studies were evaluated by using an active comparator against an active treatment or exposure group. One study was susceptible to channeling bias, and depletion of susceptibles.[25] Three studies may have had time-related bias (i.e. immortal time bias).[23, 25, 27] Nevertheless, these three time-related biased studies were not in any of

meta-analysis based on our study exclusion and inclusion criteria. In addition, residual confounding may have occurred in all observational studies.

Table 2.3: Quality Assessment of cohort and nested case-control studies using Newcastle-Ottawa Quality Assessment Scale (NOS)

Nested Case Control Studies										
Study	SELECTION				COMPARABILITY	EXPOSURE			Total stars	Quality level
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Control	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Brode et al. 2017 [23]	*	*	*	*	*	*	*	*	8	High quality
Cohort studies										
Study	SELECTION				COMPARABILITY	OUTCOME			Total stars	Quality level
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts		
Su et al. 2018 [22]	*	*	*	*	**	*	*	*	9	High quality
Afonso et al. 2016 [29]	*	*	*	*	**	*	*	*	9	High quality
Gershon et al. 2014 [24]	*	*	*	*	**	*	*	*	9	High quality
Hubbard et al. 2006[25]	*		*	*		*	*	*	6	Moderate
Lim et al. 2014 [27]	*		*	*		*	*	*	6	Moderate
Uddin et al. 2016 [28]	*	*	*	*	**	*	*	*	9	High quality

2.3.4 QUANTITATIVE ANALYSIS

Eight results from five different studies that included a total of 181 603 patients with data for at least one common exposure and same outcome were included in the meta-analysis. Two studies with three different results used LABA as the primary exposure of interest and were compared to a non-LABA active ingredient of SABA, LAMA or SAMA.[28, 29] Two other studies used ICS and/or LABA as the intervention drug which were compared to a placebo or any non-ICS treatment group.[20, 26] However, the study by Magnussen et al [21] was excluded from the quantitative analysis because the intervention/exposure drug, a tiotropium (LAMA) was different from any group of intervention synthesized. Finally, one (1) of the included study had three separate results for same exposure of ICS/LABA combination therapy but three different comparators/controls. This singular study assessed ICS/LABA combination therapy and the risk of death or hospitalization for asthma-COPD overlap which was compared to either LABA monotherapy or long-acting anticholinergic (a LAMA).[24]

2.3.4.1 MYOCARDIAL INFARCTION

Two studies, all cohort studies,[28, 29] reported on the incidence of myocardial infarctions among new users of LABA vs non-LABA group comprising of SABA, LAMA or SAMA in patients with asthma-COPD overlap. Results from the study by Afonso et al. [29] were included as two separate estimators because risk ratios (RR) were provided for each database (Clinformatics and CPRD GOLD). The risk ratio was 0.80

(95% CI 0.74 to 0.87, P < 0.0001), calculated with Inverse Variance random-effects model with an I-squared of 28%, **Figure 2.3**.

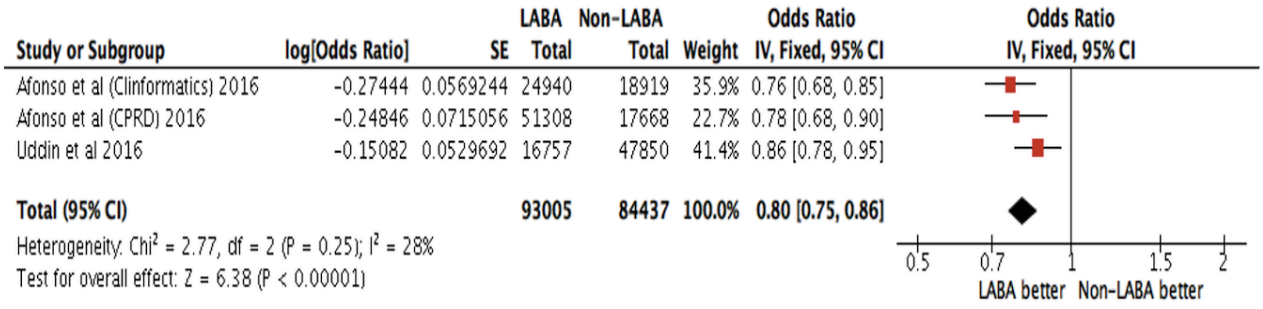

Figure 2.3: Risk for Myocardial Infarction (MI); Forest plot describing the association between long-acting β2-agonists (LABA) monotherapy vs a non-LABA (SABA and/or LAMA and/or SAMA monotherapies) and risk for MI.

2.3.4.2 PULMONARY FUNCTION TESTING (FEV_1)

Post bronchodilator (BD) spirometry test of forced expiratory volume in 1 second (FEV_1) with pre- and post-bronchodilator results was provided in three RCT studies. In the meta-analysis performed, post-bronchodilator FEV_1 (in litre, L) was defined as the period during which the patient received the study drug of ICS and/or LABA spanning the 12-weeks' trial compared to placebo. However, in the forest plot shown, all RCTs and as depicted in **Figure 2.4**, we found no clear difference in lung function decline in FEV1; mean difference (MD): 0.08 (95% CI: -0.15 to 0.32, P = 0.49, I2 = 0%).

In a different trial, Magnussen et al. [21] reported that improvements at 12 weeks with tiotropium (a LAMA) were observed for their primary endpoint of FEV1 area under the curve (AUC), from 0 to 6 hours (difference = 186 ± 24 mL, P < 0.001); and for morning pre-dose FEV_1 (difference = 98 ± 23 mL, P > 0.00). It was reported that patients with asthma-COPD overlap achieved spirometry improvements along with symptomatic benefits resulting in reduced need for rescue inhaler medication.

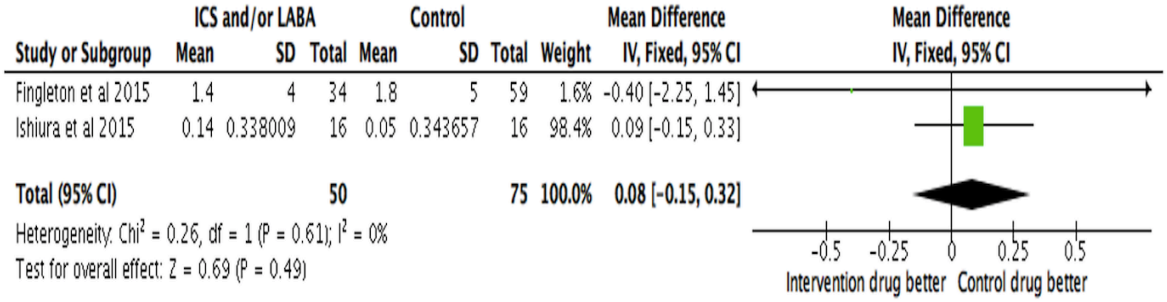

Figure 2.4: Risk for forced expiratory volume in 1 s; Forest plot describing the association between inhaled corticosteroid (ICS) alone or its combination with long-acting beta2 agonist (LABA) vs control and risk for decline in forced expiratory volume in 1s (FEV1).

2.3.4.3 DEATH OR HOSPITALIZATION FOR ASTHMA-COPD OVERLAP

A composite endpoint of death or hospitalization occurring during the period at risk (defined as when the combination therapy of ICS/LABA vs non-LABA/ICS was prescribed during the study period up to 30 days) was the study outcome by Gershon et al.[24] This singular study, had three separate results for same exposure of

ICS/LABA combination therapy but three different comparators/controls. The primary exposure of interest was LABA/ICS combination therapy and the comparators were defined as the use of LAMA or LABA monotherapy. Thus, three separate results were reported by the authors. Our meta-analysis of pooled data showed that there was a lower risk of death or hospitalization due to asthma-COPD overlap in the ICS/LABA group versus the comparator group of either LAMA or LABA monotherapy (RR = 0.82, 95% CI: 0.75– 0.90, P < 0.0001, I2 = 55%) (**Figure 2.5**).

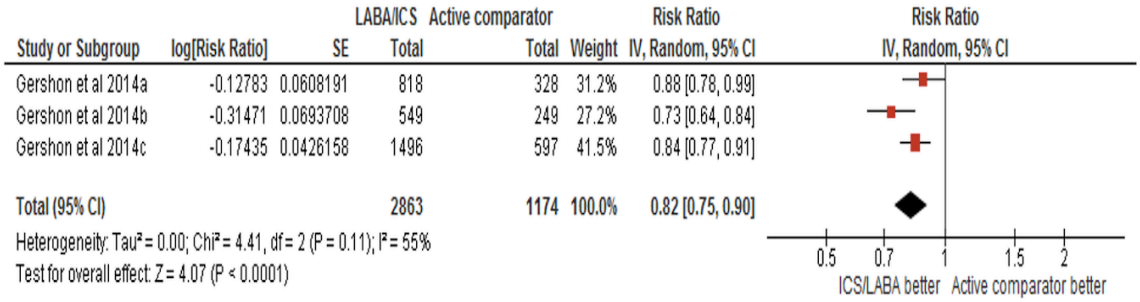

Figure 2.5: Risk for death or hospitalization; Forest plot describing the association between inhaled combination therapy of corticosteroid and long-acting beta2-agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap.

2.3.4.4 ASTHMA-COPD OVERLAP EXACERBATION

Su et al. [22] reported LAMA monotherapy or ICS/LABA combinations were associated with a lower risk of acute exacerbation [time-dependent model, 1 year: LAMA, HR=0.51, 95% CI: 0.49–0.54; ICS/LABA combinations, HR=0.61, 95% CI: 0.60-0.62; all P < 0.0001] than were those for LABAs or ICSs monotherapies in patients

with asthma-COPD overlap. Lim et al [27] found that ICS did not show a decrease in the risk of severe exacerbation (rate ratio (RR) =1.24, 95% CI: 0.44 - 3.46) compared with non-ICS treatment group of LABA, SABA or LAMA in patients with asthma-COPD overlap.

2.3.4.5 NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

Nontuberculous mycobacterial pulmonary disease (NTM-PD) in patients with asthma-COPD overlap was reported in one of the studies which compared current use of ICS with no use of ICS.[23] The authors observed that current use of ICS was associated with increased risk of NTM-PD compared with no-use; (OR=1.74, 95% CI 1.32 - 2.28; P < 0.001).[23]

2.3.4.6 FRACTURE RATES

One study reported fracture finding of patients with asthma-COPD overlap.[25] Hubbard et al. reported that the use of ICS was associated with increased risk of fracture (rate ratio (RR) = 2.24, 95% CI: 1.63-3.06) in subjects with both asthma and COPD diagnoses.[25] This finding is based on subset of patients who have both asthma and COPD.

2.3.4.7 SUBGROUP ANALYSIS

A subgroup analysis was performed comparing data based on users of LAMA or LABA monotherapies. The meta-analysis of the first subgroup when ICS/LABA were

compared to receipts of LAMA and LABA alone users gave a significant evidence of decreased risk of death or hospitalization due to asthma-COPD overlap which had an adjusted RRs of 0.80 (95% CI of 0.67, 0.97, p < 0.04 and I2 = 76%); and 0.84 (95% CI 0.77, 0.91 and p < 0.0001) respectively. Results for death or hospitalization due to asthma-COPD overlap when LABA/ICS were compared with LAMA or LABA monotherapies were found to be consistent when all studies were combined RR 0.82 (95% CI 0.75, 0.90; P < 0.001; Test for subgroup differences, I2 = 0%) (**Figure 2.6**).

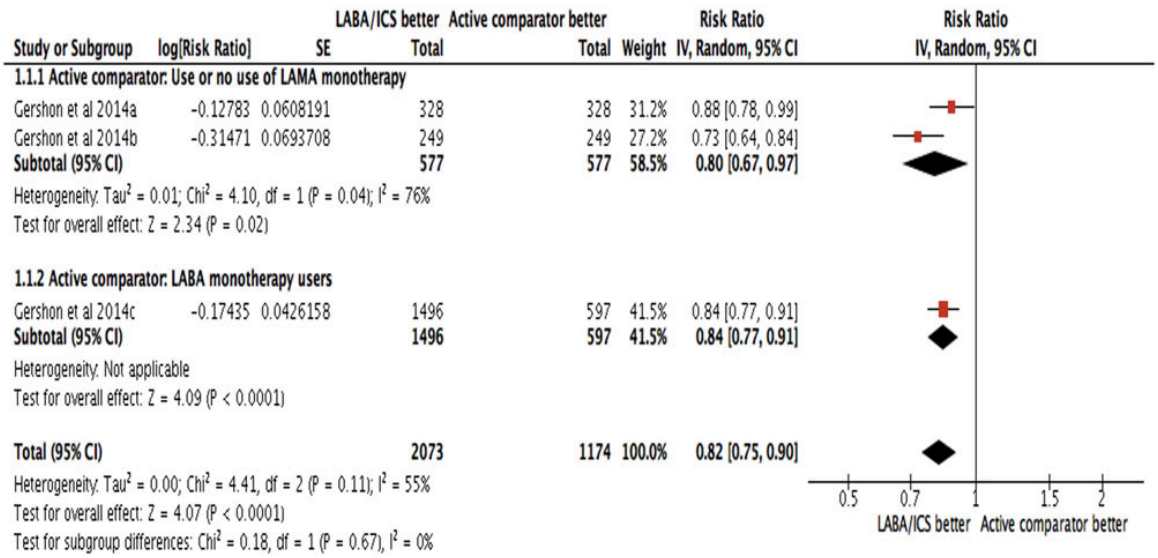

Figure 2.6: Risk for death or hospitalization; Forest plot subgroup analysis describing the association between inhaled combination therapy of corticosteroid and long-acting beta2-agonist (ICS/LABA) vs an active comparator (LABA, LAMA, or non-LAMA) and risk for death or hospitalization of asthma–COPD overlap.

2.4 DISCUSSION

Results of this systematic review and meta-analysis comprise of 10 studies, including three randomized controlled studies, six cohort studies and one nested control study resulting in three independent meta-analyses. In our meta-analysis, we observed that LABA was associated with decreased risk of myocardial infarction compared with non-LABA (comprised of either SABA, LAMA or SAMA); and the combination therapy of ICS/LABA was associated with lower risk of death or hospitalization due to asthma-COPD overlap compared with active comparator of either LABA or LAMA monotherapy. The result from the decline in FEV_1 meta-analysis remains inconclusive due to limited study power.

2.4.1 MYOCARDIAL INFARCTION

Through the meta-analysis, we aimed to assess the association between new users of inhaled LABA and the incidence of myocardial infarction (including acute MI) in patients with asthma-COPD overlap. The summary result yielded a significant association (Figure 3) which showed that patients with asthma-COPD overlap who were new users of LABA are associated with a reduced risk of a myocardial infraction compared with those patients with asthma-COPD overlap never treated with LABA. All included studies in the meta-analysis referred to subjects with asthma-COPD overlap as patients with both features of asthma and COPD as described by GINA/GOLD combination guideline.[6] On the basis of result presented in the meta-analysis, physicians might consider LABA either in formulation depending on their preference. However, given the lack of

randomized intervention studies of asthma-COPD overlap patients and few high qualities observational data coupled with lack of true placebo groups, we believe that it is premature to recommend the designation of LABA as an effective agent in reducing the incidence of myocardial infarction in asthma-COPD overlap patients. Furthermore, patients who are started on LABA may be more engaged with health care services and this could be reducing their risk of MI. Also, concerning the ongoing debate on the safety of LABAs in people with asthma, [30] the use of LABAs in people with any suspicion of an asthmatic component should be of great concern to prescribing physicians. More research is therefore needed to predict treatment response in individual ACO patients prescribed with LABAs.

2.4.2 PULMONARY FUNCTION TESTING (FEV_1)

Post bronchodilator (BD) spirometry test of forced expiratory volume in 1 second with pre- and post-bronchodilator results was provided in 3 of the included studies. However, only two studies, all RCTs, were included in the meta-analysis with a common exposure. In the meta-analysis conducted, patients with asthma-COPD overlap, treated with ICS monotherapy or its combination therapy of ICS/LABA were compared with asthma-COPD overlap patients not treated with ICS. We found no clear difference in decline in FEV1 (Figure 4) between the intervention (ICS and/or LABA) assessed and placebo. Given the lack of trials evaluating the effectiveness of ICS alone or its combination with ICS and the small number of asthma-COPD overlap patients involved in these published studies, no robust conclusions can be drawn due to lack of study

power. Nevertheless, judging from the confidence interval from our meta-analysis, we cannot totally rule out a difference. Even though ICS treatment is currently recommended for asthma-COPD overlap patients, its long-term use is however discouraged as it may cause various side effects.[31, 32]

One study that was not included in the meta-analysis, [21] reported that improvements at 12 weeks with tiotropium, a LAMA, were observed for their primary endpoint of FEV_1. The authors found out that patient with asthma-COPD overlap achieved spirometry improvements along with symptomatic benefits resulting in reduced need for rescue inhaler medication. Tiotropium, an antagonist of M1 and M3 muscarinic receptor subtypes, which induce relaxation of airway smooth muscle, is extensively used in COPD because of its observed benefits. On the other hand, large and high quality RCTs evaluating the efficacy of tiotropium therapy in asthmatics have shown considerable improvements in FEV_1 when LAMA is used as add-on therapy to ICS or ICS/LABA combinations.[33, 34] Thus, the clinical benefits noticed in both asthma and COPD patients suggest that LAMA (tiotropium) therapy may be a therapeutic option for patients with asthma-COPD overlap.

2.4.3 DEATH OR HOSPITALIZATION FOR ASTHMA-COPD OVERLAP

This meta-analysis focused on death or hospitalization for asthma-COPD overlap occurring during the exposure period of up to 30 days. Summary data from this study showed that there was a lower risk of death or hospitalization due to asthma-COPD overlap in the ICS/LABA group versus the non-LABA/ICS group (Figure 6). Subjects in

this study were referred to as COPD patients with co-diagnosis of asthma. COPD is characterized by a significant smoking history, airway obstruction that is persistent and progressive, lack of reversibility of airway obstruction, and neutrophil infiltration in the airways.[35] As described above, it is however believed that reversibility, eosinophilia, and bronchial hyperresponsiveness may be present in COPD patients. Based on eosinophilic pathology, ICS and combinations with LABA have been recommended as treatment options for asthma-COPD overlap patients because many clinicians have believed eosinophilia as a diagnostic criterion.[36, 37] Both GINA and GOLD have recommended well-defined treatment and management options for patients with asthma or COPD alone.[6] Combination therapy of ICS/LABA is recommended in a subset of COPD patients or for those with asthma-type symptoms who continue to have symptoms and/or exacerbations despite LABA/LAMA use, thus making the use of ICS/LABA more appealing in asthma-COPD overlap.

2.4.4 ASTHMA-COPD OVERLAP EXACERBATION

Su et al. [22] found that LAMA or ICS/LABA combinations were associated with a lower risk of acute exacerbation than were those for LABAs or ICSs monotherapies in patients with asthma-COPD overlap. On the contrary, Lim et al. [27] found that inhaled corticosteroids did not show a decrease in the risk of severe exacerbation compared with non-ICS treatment group of SABA, LABA or SAMA. The strength of evidence for these recommendations is mixed, however. Different factors may contribute to exacerbation in asthma, COPD or asthma-COPD overlap exacerbation. In the analysis of frequent

exacerbations in 2138 patients in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, they observe that the single best predictor of exacerbations was an exacerbation in the preceding year.[38] LABAs (salmeterol and formoterol) are first-line therapies in the treatment of COPD to manage symptoms and reduce exacerbations. Whilst, LABA monotherapy use in asthma is not encouraged due to their associated risk of mortality, it is preferred as an add-on to ICS in asthma. ICSs also reduce the severity of COPD exacerbation, but their frequent use is discouraged as its continuous use is associated with incidence of pneumonia.[39] Nevertheless, the likelihood that ICSs with or without LABA may provide benefit for eosinophilic asthma-COPD overlap patients cannot be either dismissed or ignored due to lack of large RCT studies, lack of quality observational data and insufficient evidence. Thus, further investigation is warranted to be confident of the benefits of ICS and/or LABA in this patient group.

2.4.5 NONTUBERCULOUS MYCOBACTERIAL PULMONARY DISEASE

One study compared incidence of nontuberculous mycobacterial pulmonary disease (NTM-PD) in patients with asthma-COPD overlap with current use of ICS and those with no use of ICS.[23] The authors observed that current use of ICS was associated with an increased risk of NTM-PD compared with no-use. Whilst, there have been studies on the associated risk of ICS use on the incidence of tuberculosis in asthmatic patients, little has been published on the potential risk of NTM-PD associated with ICS in asthma, COPD and especially in asthma-COPD overlap patients. However, in this particular

study, the population assessed is of prevalent users of medications which limit the generalizability of their result. Prevalent users are labelled as “survivors” of the early period of pharmacotherapy, a situation which can introduce substantial selection bias in comparative effectiveness research studies.

2.4.6 FRACTURE RATES

Safety concerns of fractures and osteoporosis relating to long-term use of ICSs have been documented in the literature as clinical studies have shown that accelerated bone resorption occurs at all doses of ICS use.[40] Only one study reported fracture finding of patients with asthma-COPD overlap.[25] Hubbard et al. found out that the use of ICS was associated with increased risk of fracture in subjects with asthma-COPD overlap.[25] Asthma-COPD overlap patients who have any asthmatic features might benefit from inhaled glucocorticoids, thus long-term use of ICS and its associated risk of fracture cannot be discounted. Nevertheless, further studies are needed to assess whether and at what dose long term use of ICS increases the risk of fracture among asthma-COPD overlap patients dispensed respiratory medications.

There are limitations that needed to be considered when interpreting the results. First and foremost is the small number of studies included in the final reviews and the meta-analyses. This is primarily due to the fact that asthma-COPD overlap is a new disease and its classification as a complete separate disease is still debatable. Another limitation is the variations in the intervention or the primary exposure drug used. Even though, the effective dosage and duration of action of these drugs may differ, we ensured

that we were analyzing the same class of medication based on their therapeutic activity and duration of action. Also, there was considerable heterogeneity (I2 = 55%) between the data synthesized from one of the studies. Different active comparators used in the analysis may partly explained this heterogeneity, as there were not enough studies to conduct informative active subgroup analysis or meta-regression based on different active comparators. In this regard, there are currently four registered clinical trials that are either active or recruiting to evaluate the comparative safety and effectiveness of triple combinations of LABA/LAMA/ICS and double combinations of LABA/LAMA medications in asthma-COPD overlap patients. These ongoing clinical trials, along with any data from yet-to-be published studies, may highlight distinctive findings on the safety and efficacy of inhaled medications in treating patients with asthma-COPD overlap. Finally, we did not perform our search in the grey literature. Given the paucity of articles extracted in this review, we do not expect that this additional search would have contributed to our body of evidence.

2.5 CONCLUSION

This systematic review and meta-analysis primarily focused on the safety and effectiveness of inhaled corticosteroids and/or bronchodilators-based therapies when compared with placebo or active comparators in patients with asthma-COPD overlap and its associated risk of cardiorespiratory outcomes. In our meta-analysis, we observed that LABA was associated with decreased risk of myocardial infarction; and the combination therapy of ICS/LABA was associated with lower risk of death or hospitalization due to

asthma-COPD overlap. The result from the decline in FEV_1 meta-analysis remains inconclusive due to limited study power. Future studies should include high quality data and larger number of patients which would help further characterizes the safety and efficacy of inhaled corticosteroids and bronchodilator based therapies in treating patients with a suspected overlap between asthma and COPD.

CHAPTER 3

GENDER DIFFERENCES IN INHALED PHARMACOTHERAPY UTILIZATION IN PATIENTS WITH OBSTRUCTIVE AIRWAY DISEASES (OADS): A POPULATION-BASED STUDY

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3.1 INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the two most common categories of respiratory diseases characterized by airway obstruction.[1, 2] Recently a new phenotype, referred to as asthma-COPD overlap (ACO), has been identified with its first guidelines for treatment and management in effect since 2015.[3] Gender differences exist in most common health conditions and especially in lung diseases such as asthma and COPD.[4] These assertions have been evident by many studies showing significant differences in medical treatments between females and males with the same respiratory condition such as asthma and COPD.[5-7] Although the mechanisms of gender differences are not fully understood, many population studies and cluster analyses have shown that gender, race, environment, genetics and specific phenotypes have played important roles in asthma symptoms and management. [8-10]

The airflow obstruction in patients with obstructive airway diseases (OADs) is either fixed or reversible by medication.[11] The clinical guidelines for asthma, COPD and asthma-COPD overlap convey equal treatment between males and females.[1] For patients with asthma, the Global Initiative for Asthma (GINA) guideline recommends treating everyone with combination therapy of inhaled corticosteroid/long-acting $beta_2$-agonist (ICS/LABA) on an as-needed basis, even for mild patients (GINA step 1 and step 2).[1]

The clinical guideline for COPD proposes building up treatment from short-acting $beta_2$-agonist (SABA) to single LABA or long-acting muscarinic antagonist (LAMA) to combination therapy of LABA/LAMA, then step-up to ICS/LABA/LAMA triple therapy

in those with frequent acute exacerbation chronic obstructive pulmonary disease (AECOPD) or persistent symptoms; whist the asthma-COPD overlap guideline advocates treatment with asthma medication and to continue steadily with COPD medications as the disease progresses to lessen the risk of exacerbations.[2] Furtherance to this suggestion, a recent systematic review concluded that patients with asthma-COPD overlap may benefit from combination therapy of inhaled corticosteroids/long-acting beta$_2$-agonist (ICS/LABA) combination therapy which appears to reduce the risk of death or hospitalization.[12]

Over the years, gender-specific epidemiological studies and clinical trials have been lacking in detailing differences in pharmacotherapy utilization in patients with obstructive airways diseases which may have important implications in symptoms and disease management.[13, 14] However, this phenomenon has long been established in cardiovascular disease and is labelled as Yentl syndrome stating female receive generally less treatment (across the spectrum of medical and interventional therapy) for ischaemic heart disease than their male equivalents. [15, 16]

Whilst it is evident that recommendations for treatment with inhaled pharmacotherapy for asthma, COPD and asthma-COPD overlap have changed tremendously over several decades, gender differences in inhaled pharmacotherapy of asthma, COPD and asthma-COPD overlap in both randomized control trials and observational studies have not been demonstrated before. Therefore, we sought to investigate gender differences in new-users of ICS monotherapy, ICS/LABA combination therapy, LABA monotherapy, LAMA monotherapy, SABA monotherapy and short-

acting muscarinic antagonist (SAMA) monotherapy in patients with asthma, COPD or asthma-COPD overlap.

3.2 METHOD

3.2.1 DATA SOURCES

We conducted a retrospective observational cohort study using primary care records from CPRD. The CPRD is a United Kingdom (UK) based database which is representative of UK population that contains de-identified, longitudinal data, with approximately 700 total contributing general practitioner (GP) primary care practices and more than 14 million acceptable (good quality) patients.[17] Patients' data are available for demographics, symptoms and diagnoses, primary care prescriptions, test results, referrals to specialist and lifestyle information (smoking, alcohol). Approximately half of the source population (study population) is linked to hospital records (Hospital Episode Stats, HES) and death certificate (Office of National Statistics, ONS).[18] Our study was conducted in compliance with the ethical principles of the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice (GCP) and received approval from the Health Research Ethics Board at Memorial University. The study protocol was approved by the CPRD Independent Scientific Advisory Committee (ISAC 18_005RA). Generic ethical approval for observational research using the CPRD with approval from ISAC has been granted by a Health Research Authority (HRA) Research

Ethics Committee. Patient informed consent was not necessary since the data were anonymized for research purposes.

3.2.2 STUDY POPULATION AND IDENTIFICATION OF INHALED PHARMACOTHERAPIES

The study population included patients who were registered with up-to-standard practice and active between January 1, 1998 and July 31, 2018 inclusive (**Figure 3.1**). This population comprised of male and female patients in CPRD database with an incident read code (see supplementary file) for asthma and/or COPD defined as at least one diagnostic record for either disease and a new-user of ICS, SABA, LABA, combination therapy of ICS/LABA, SAMA or LAMA (see supplementary file). Patients with asthma-COPD overlap were defined as having; 1) COPD readcode and 2) asthma readcode and 3) an ex or current smoker (if never smoked, exposure to wood smoke, biofuels, random gas or second-hand smoke) before the index date (the date of first prescription of inhaled pharmacotherapy). To identify new-users of inhaled pharmacotherapy, patients with a record of taking any inhaler drug within 365 days before their first medication prescription were excluded. Recent validation studies in the CPRD GOLD database have shown that patients with asthma or COPD can be accurately identified from CPRD database using specific diagnostic codes.[19, 20]

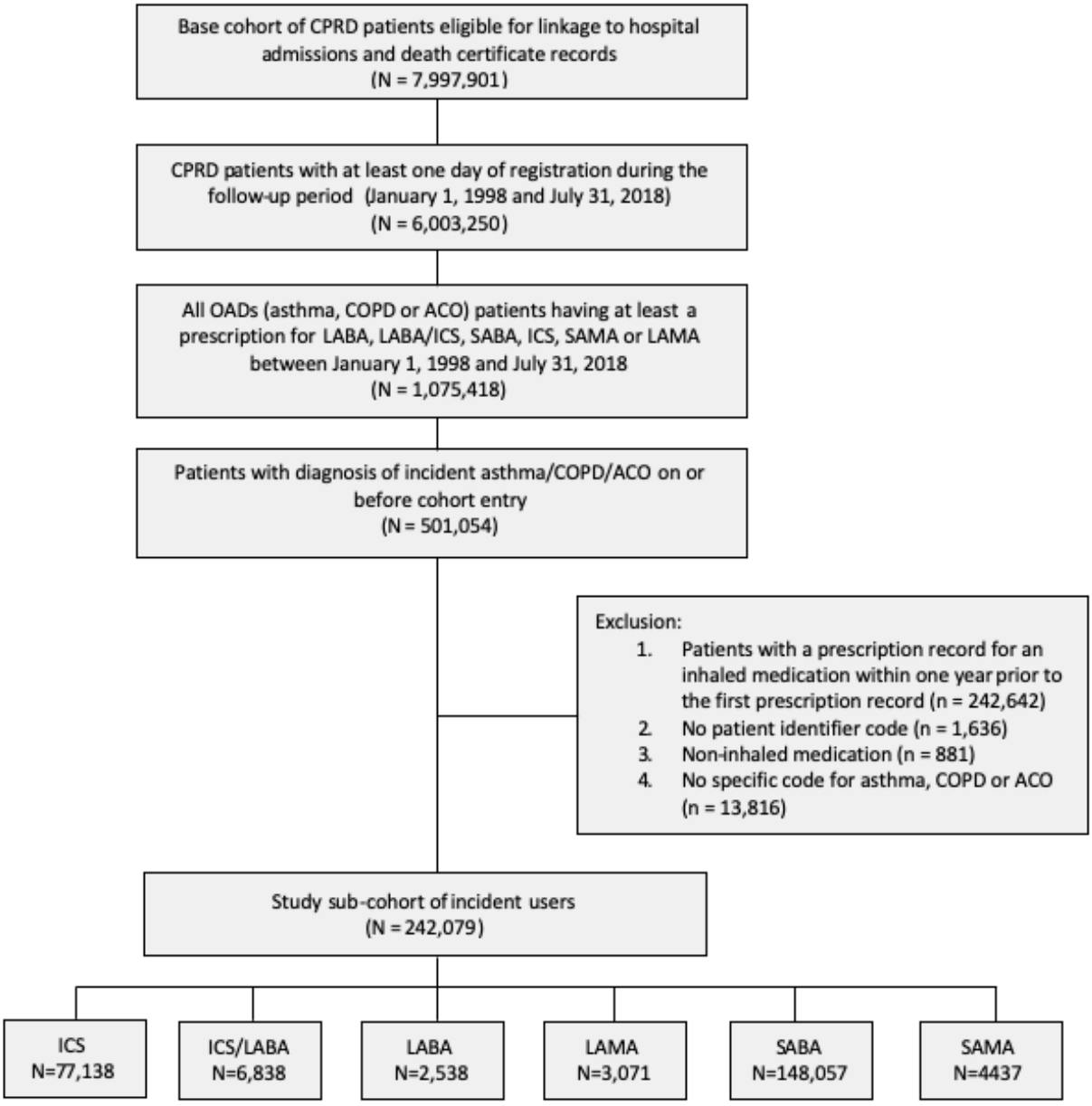

Figure 3.1: Flowchart of study cohort formation.

3.2.2 EXPOSURE AND OUTCOMES

The primary exposure variable of interest was gender which was defined as either male or female based on medical records from the patient's general practitioner. The outcomes of interests were new-users of the following mutually exclusive categories of inhaled pharmacotherapies:

1. ICS monotherapy (budesonide, fluticasone, mometasone, beclomethasone, ciclesonide and flunisolide);
2. ICS/LABA combination therapy (fluticasone propionate/formoterol fumarate, Budesonide/formoterol fumarate, beclomethasone dipropionate/formoterol fumarate, fluticasone furoate/vilanterol, fluticasone propionate/salmeterol xinafoate, budesonide/formoterol fumarate and mometasone furoate/ formoterol fumarate);
3. LABA monotherapy (salmeterol xinafoate, indacaterol maleate, olodaterol, vilanterol and formoterol fumarate);
4. LAMA monotherapy (tiotropium bromide, aclidinium bromide and umeclidinium bromide);
5. SABA monotherapy (salbutamol, terbutaline sulfate, fenoterol hydrobromide, rimiterol, pirbuterol, reproterol and orciprenaline sulfate); or
6. SAMA monotherapy (ipratropium bromide and oxitropium bromide).

New-users were defined using a 1-year washout period whereby no prescription for any agent in the aforementioned categories was recorded in the previous 365 days. We

considered only first treatment, therefore, any subsequent switches, discontinuations or new therapies were not examined in our analysis. Since recommendations on inhaled pharmacotherapy for patients with obstructive lung diseases may have changed over the years, we also considered calendar year in our analysis; (1. First decade spanning January 1, 1998 to December 31, 2007 and (2. Second decade spanning January 1, 2008 to July 31, 2018.

3.2.3 STATISTICAL ANALYSIS

Descriptive statistics for asthma, COPD and asthma-COPD overlap including count/percentage and mean/standard deviation were provided for categorical and continuous variables, respectively. For categorical variables with more than two categories, type 3 *p-values* (a *p-value* indicating the overall effect of all levels of a categorical variable) were also calculated. An interaction term between gender and a variable indicating OAD types (asthma, COPD or asthma-COPD overlap) was introduced into multivariable models to examine the association between gender and a pharmacotherapy for patients with asthma, COPD and asthma-COPD overlap respectively. The initial multivariable model included clinical important variables and all variables which were significant at p=0.20 in the univariate analysis. Then we started by removing the least significant variable one at a time, until all the variables in the final multivariable model are either clinically important or significant at p=0.05. The strength of an association was measured as an Odd Ratio (OR), 95% Confidence Interval

(95%CI). Data analysis was conducted using SAS (version 9.4, SAS Institute Inc.) on IBM cluster.

3.3 RESULTS

We identified a total number of 242,079 new users of inhaled pharmacotherapies of which 85% had asthma, 10% had COPD and 5% had asthma-COPD overlap. Among them, around 67% were identified in the first decade (January 1, 1998 – December 31, 2007) and around 34% were identified in the second decade (January 1, 2008 – July 31, 2018). The average age of the study population was 52 (±22) years, 113,712 (47%) were females and 128,367 (53%) were males. **Table 3.1** below summarizes the characteristics of patients with obstructive airway diseases. In relation to other respiratory drugs received before cohort entry, more than 28,000 patients received oral corticosteroids with very few patients receiving methylxanthine (0.5%).

Table 3.1: Baseline characteristics among patients diagnosed with asthma, COPD and asthma-COPD overlap

Characteristics	**Asthma**	**COPD**	**Asthma-COPD Overlap**	**Overall**
	N = 205,596	N = 24,672	N = 11,811	N = 242,079
Age (mean, STD)	46.86 (±19.6)	79.38 (±12.6)	76.08 (±15.9)	51.60 (±22.0)
Gender				
Male	92,849 (46.2%)	14,350 (58.2%)	6,513 (55.1%)	128,367 (53%)
Female	112,747 (54.8%)	10,322 (41.8%)	5,298 (44.9%)	113,712 (47%)
Year of cohort entry				
January 1998 – December 2007	143,333 (69.7%)	11,210 (45.4%)	6,417 (54.3%)	160,960 (66.5%)
January 2008 – July 2018	62,263 (30.3 %)	13,462 (54.6%)	5,394 (45.7%)	81,119 (33.5%)
Body mass index (BMI)				
Underweight	16,841 (11.2%)	1,251 (5.6%)	479 (4.4%)	18,571 (10.2%)
Normal	59,896 (40.0%)	8,751 (39.5%)	3,885 (36.1%)	72,532 (39.7%)
Overweight	42,006 (28.0%)	7,101 (32.0%)	3,755 (34.9%)	52,862 (28.9%)
Obese	31,086 (20.8%)	5,070 (22.9%)	2,654 (24.6%)	38,810 (21.2%)
%Rx received as initial treatment				
ICS	71,024 (34.6%)	3,245 (13.2%)	2,869 (24.3%)	77,138 (31.9%)
ICS/LABA	3,737 (1.8%)	2,084 (8.5%)	1,017 (8.6%)	6,838 (2.8%)
LABA	1,253 (0.6%)	875 (0.4%)	410 (3.4%)	2,538 (1.1%)
LAMA	97 (0.1%)	2436 (9.9%)	538 (4.7%)	3,071 (1.3%)
SABA	128,379 (62.4%)	13,609 (55.2%)	6,069 (51.4%)	148,057 (61.1%)
SAMA	1,106 (0.5%)	2,423 (9.8%)	908 (7.6%)	4,437 (1.8%)
Index of deprivation				
Least deprived	46,363 (22.6%)	3,760 (15.3%)	1,873 (15.9%)	51,996 (21.5%)
Less deprived	43,752 (21.3%)	4,673 (19.0%)	2,292 (19.4%)	50,717 (21.0%)

Deprived	42,186 (20.5%)	4,915 (16.0%)	2,320 (19.7%)	49,421 (20.4%)
More deprived	38,377 (18.7%)	5,257 (21.3%)	2,606 (22.1%)	46,240 (19.1%)
Most deprived	34,681 (16.9%)	6,026 (24.4%)	2,714 (22.9%)	43,421 (18.0%)
Smoking status				
No	89,199 (56.4%)	2,493 (10.4)	2,199 (19.1)	93,891 (48.5%)
Yes	38,991 (24.6%)	11,214 (46.8)	4,220 (36.6)	54,425 (28.1%)
Ex-smoker	29,998 (19.0)	10,246 (42.8)	5,112 (44.3)	45,356 (23.4%)
Respiratory drugs before cohort entry				
Oral corticosteroid				
Yes	21,803 (10.6)	4,562 (18.5)	2,446 (20.7)	28,811 (11.9%)
No	183,793 (89.4)	20,110 (81.5)	9,365 (79.3)	213,268 (88.1%)
Methylxanthine				
Yes	574 (0.3%)	331 (1.3%)	241 (2.0%)	1,146 (0.5%)
No	205,022 (99.7%)	24,341 (98.7%)	11,570 (98.0%)	240,933 (99.5%)
Other drugs before cohort entry				
NSAIDs				
Yes	24,211 (11.8%)	3,771 (15.3%)	1,798 (15.2%)	29,780 (12.3%)
No	181,385 (88.2%)	20,901 (84.7%)	10,013 (84.8%)	212,299 (87.7%)
Opioids				
Yes	6,219 (3.0%)	2,429 (9.9%)	1,025 (8.7%)	9,673 (4.0%)
No	199,377 (97.0%)	22,243 (90.1%)	10,786 (91.3%)	232,406 (96.0%)
Acetaminophen				
Yes	12,782 (6.2%)	4,245 (17.2%)	1,637 (13.9%)	18,664 (7.7%)
No	192,814 (93.8%)	20,427 (82.8%)	10,0174 (85.1%)	223,415 (92.3%)
Comorbidity in year before cohort entry				
0	164,782 (80.2%)	7,771 (31.5%)	4,569 (38.7%)	177,122 (73.2%)
1	26,980 (13.1%)	7,332 (29.7%)	3,403 (28.8%)	37,715 (15.6%)

>1	13,834 (6.7%)	9,569 (38.8%)	3,839 (32.5%)	27,242 (11.2%)
Physician visits in year before cohort entry				
1 – 17	184,396 (89.7%)	16,077 (65.2%)	8,270 (70.0%)	208,743 (86.2%)
18 – 35	18,440 (9.0%)	6,885 (27.9%)	2,896 (24.5%)	28,221 (11.7%)
>36	2,760 (1.3%)	1,710 (6.9%)	645 (5.5%)	5,115 (2.1%)
No. of hospitalization in year before cohort entry				
0	176,156 (85.7%)	16,226 (65.8%)	8,643 (73.2%)	201,025 (83.0%)
1	20,662 (10.1%)	5,027 (20.4%)	1,939 (16.4%)	27,628 (11.4%)
>1	8,778 (4.2%)	3,419 (13.8%)	1,229 (10.4%)	13,426 (5.6%)

ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist; LABA: long-acting beta$_2$-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; COPD: chronic obstructive pulmonary disease; CI: confidence interval; ACO: asthma-COPD overlap; Rx: prescription; STD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table 3.2 shows results from the univariate analyses of factors associated with different inhaled pharmacotherapies. Increasing age was significantly associated with increased prescription of all inhaled pharmacotherapies, except ICS and SABA prescriptions. In comparison to females, males were significantly associated with increased prescriptions of ICS/LABA, LABA, LAMA and SAMA, and with decreased prescriptions of ICS, and SABA. In comparison to patients entering cohort between January 1998 – December 2007, those entering cohort between January 2008 – July 2018 showed significantly higher rates of ICS, LABA and SAMA, and significantly lower rates of ICS/LABA, LAMA, and SABA. Other variables which were significantly associated with the six inhaled pharmacotherapies included body mass index (BMI), index of deprivation, smoking status, other drugs (NSAID, opioids, Acetaminophen), comorbidity, and several disease severity indictors (prescription of methylxanthine, oral corticosteroid and number of hospitalization). However, prescription of ICS/LABA was not significantly associated with Index of deprivation.

Table 3.2: Univariate (unadjusted) analyses of factors associated with different inhaled pharmacotherapies

Factors	**Pharmacotherapies**					
	ICS	**ICS/LABA**	**LABA**	**LAMA**	**SABA**	**SAMA**
Age	0.95 (0.95-0.96)**	1.70 (1.67-1.74)**	2.19 (2.11-2.27)**	2.84 (2.74-2.94)**	0.82 (0.81-0.83)**	3.34 (3.24-3.45)**
Gender						
Female	1	1	1	1	1	1
Male	0.97 (0.95-0.99)*	1.19 (1.13-1.25)**	1.28 (1.19-1.39)**	1.83 (1.70-1.97)**	0.94 (0.92-0.95)**	1.49 (1.41-1.59)**
Year of cohort entry						
January 1998 – December 2007	1	1	1	1	1	1
January 2008 – July 2018	3.86 (3.77-3.94)**	0.45 (0.43-0.47)**	2.68 (2.41-2.98)**	0.04 (0.04-0.05)**	0.39 (0.38-0.39)**	1.43 (1.34-1.53)**
OAD diagnoses						
Asthma	1	1	1	1	1	1
COPD	0.29 (0.28-0.30)**	4.98 (4.72-5.27)**	6.0 (5.49-6.54)**	5.45 (5.24-5.65)**[#]	0.74 (0.72-0.76)**	20.14 (18.73-21.65)**
Asthma-COPD Overlap	0.61 (0.58-0.63)**	5.09 (4.74-5.47)**	5.86 (5.24-6.57)**	4.62 (4.40-4.83)**[#]	0.64 (0.61-0.66)**	15.40 (14.07-16.85)**
p-value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Body mass index (BMI)						
Underweight	1	1	1	1	1	1
Normal	0.78 (0.75-0.81)**	1.95 (1.73-2.20)**	1.63 (1.35-1.96)**	1.59 (1.36-1.86)**	1.10 (1.07-1.14)**	1.49 (1.30-1.71)**
Overweight	0.75 (0.72-0.78)**	2.28 (2.02-2.58)**	1.81 (1.50-2.19)**	1.80 (1.53-2.11)**	1.09 (1.05-1.13)**	1.71 (1.49-1.97)**
Obese	0.69 (0.67-0.72)**	2.34 (2.11-2.70)**	1.72 (1.42-2.09)**	1.95 (1.66-2.30)**	1.16 (1.12-1.21)**	1.52 (1.31-1.75)**

p-value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Index of deprivation						
Least deprived	1	1	1	1	1	1
Less deprived	1.02 (0.99-1.04)	0.98 (0.91-1.05)	1.06 (0.93-1.20)	1.31 (1.17-1.47)**	0.96 (0.94-0.98)*	1.26 (1.14-1.39)**
Deprived	0.97 (0.95-0.99)*	1.02 (0.94-1.09)	1.10 (0.97-1.24)	1.27 (1.13-1.43)**	1.00 (0.97-1.02)	1.25 (1.13-1.39)**
More deprived	0.93 (0.90-0.95)**	10.97 (0.90-1.04)	1.32 (1.17-1.49)**	1.36 (1.21-1.53)**	1.02 (1.00-1.05)	1.44 (1.30-1.59)**
Most deprived	0.92 (0.89-0.94)**	0.98 (0.91-1.06)	1.29 (1.13-1.46)**	1.51 (1.35-1.70)**	1.00 (0.97-1.02)	1.95 (1.78-2.15)**
p value (type 3)	< 0.0001	0.7061	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Smoking status						
No	1	1	1	1	1	1
Yes	0.72 (0.70-0.75)**	1.73 (1.58-1.90)**	2.30 (1.99-2.66)**	12.00 (9.77-14.73)**	0.91 (0.88-0.94)**	5.46 (4.78-6.23)**
Ex-smoker	0.64 (0.61-0.66)**	2.57 (2.36-2.80)**	2.51 (2.17-2.91)**	16.61 (13.56-20.34)**	0.86 (0.83-0.89)**	6.03 (5.28-6.89)**
p value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Other drugs						
NSAIDs						
No	1	1	1	1	1	1
Yes	1.09 (1.07-1.12)**	0.89 (0.83-0.96)*	0.78 (0.70-0.86)**	0.97 (0.87-1.08)	0.97 (0.95-0.99)*	0.73 (0.68-0.79)**
Opioids						
No	1	1	1	1	1	1
Yes	1.60 (1.52-1.67)**	0.49 (0.45-0.54**	0.55 (0.47-0.64)**	0.28 (0.25-0.31)**	0.95 (0.92-0.99)*	0.48 (0.43-0.54)**
Acetaminophen						

No	1	1	1	1	1	1
Yes	1.16 (1.12-1.20)**	0.68 (0.63-0.73)**	0.65 (0.58-0.74)**	0.36 (0.33-0.39)**	1.12 (1.08-1.15)**	0.44 (0.41-0.48)**
Comorbidity						
0	1	1	1	1	1	1
1	0.80 (0.78-0.82)**	2.23 (2.10-2.37)**	2.22 (2.02-2.44)**	4.99 (4.53-5.51)**	0.90 (0.88-0.92)**	3.48 (3.23-3.74)**
>1	0.52 (0.51-0.54)**	3.26 (3.07-3.46)**	2.75 (2.49-3.04)**	12.50 (11.45-13.64)**	0.93 (0.91-0.96)**	5.29 (4.92-5.68)**
p value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Indicators for disease severity measured in the year before cohort entry						
Rx of methylxanthine						
No	1	1	1	1	1	1
Yes	0.60 (0.53-0.68)**	0.44 (0.34-0.56)**	0.16 (0.12-0.20)**	0.91 (0.55-1.49)	3.12 (2.76-3.52)**	0.19 (0.15-0.23)**
Rx of oral corticosteroid						
No	1	1	1	1	1	1
Yes	0.75 (0.73-0.77)**	0.56 (0.53 0.60)**	0.51 (0.46-0.56)**	0.72 (0.65-0.79)**	1.55 (1.51-1.59)**	0.62 (0.57-0.67)**
No. of hospitalization						
0	1	1	1	1	1	1
1	0.87 (0.85-0.90)**	1.83 (1.72-1.96)**	1.58 (1.42-1.77)**	2.88(2.64-3.14)**	0.89(0.87-0.92)**	2.00(1.85-2.16)**
>1	0.74 (0.71-0.77)**	2.45 (1.73-1.96)**	2.23 (1.96-2.53)**	4.73(4.30-5.21)**	0.86 (0.83-0.89)**	2.59 (2.35-2.84)**
p value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Physician visits						

1 – 17	1	1	1	1	1	1
18 – 35	0.60 (0.58-0.61)**	2.33 (2.19-2.47)**	1.76 (1.59-1.95)**	5.29 (4.89-5.71)**	1.08 (1.05-1.11)**	2.09 (1.94-2.25)**
>36	0.36 (0.33-0.38)**	3.07 (2.75-3.43)**	1.63 (1.30-2.05)**	9.26 (8.22-10.44)**	1.25 (1.18-1.32)**	2.33 (2.01-2.71)**
p value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Comorbidities						
0	1	1	1	1	1	1
1	0.80 (0.78-0.82)**	2.23 (2.10-2.37)**	2.22 (2.02-2.44)**	4.99 (4.53-5.51)**	0.90 (0.88-0.92)**	3.48 (3.23-3.74)**
>1	0.52 (0.51-0.54)**	3.26 (3.07-3.46)**	2.75 (2.49-3.04)**	12.50 (11.45-13.64)**	0.93 (0.91-0.96)**	5.29 (4.92-5.68)**
p value (type 3)	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

ICS: inhaled corticosteroid; SABA: short-acting beta$_2$-agonist; LABA: long-acting beta$_2$-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; COPD: chronic obstructive pulmonary disease; CI: confidence interval; ACO: asthma-COPD overlap; STD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drugs; **: $p < 0.0001$; *: $p < 0.05$; $^{\#}$: model value; Rx: prescription.

Table 3.3 shows adjusted results from multivariable analysis after controlling for all potential confounders in **Table 3.2**. Among the patients diagnosed with asthma, male patients were significantly less likely to be a new user of ICS monotherapy (adjusted OR 0.97; 95%CI 0.95-0.99, p=0.01) and more likely to be prescribed ICS/LABA combination therapy (adjusted OR 1.15; 95% CI 1.08-1.23, p<0.0001) than female patients. Among patients with COPD, males were more likely to be prescribed a LABA (adjusted OR 1.29; 95% CI 1.12-1.49, p=0.0005), LAMA (adjusted OR 1.21; 95% CI, 1.10-1.33, p<0.0001), and SAMA (adjusted OR 1.11; 95% CI, 1.01-1.21, p=0.02) and significantly less likely to be prescribed a SABA (adjusted OR 0.84; 95% CI, 0.80-0.89, p<0.0001) than female patients. Similar associations were also observed among patients diagnosed with ACO, in which male patients had significantly higher rates in initial prescription of LABA (adjusted OR 1.26; 95% CI, 1.03-1.55, p=0.03), LAMA (adjusted OR 1.27; 95% CI, 1.05-1.53, p=0.01) and SAMA (adjusted OR 1.28; 95% CI, 1.11-1.48, p=0.0008) and significantly lower rate in SABA (adjusted OR 0.89, 95% CI, 0.82-0.96, p=0.003) than female patients.

Table 3.3: Multivariable analyses of gender differences in inhaled pharmacotherapies by three obstructive airway diseases

Pharmacotherapies[#]		**Asthma**		**COPD**		**Asthma-COPD overlap**	
		OR: 95% CI	aOR: 95% CI)	OR: 95% CI	aOR: 95% CI	OR: 95% CI	aOR: 95% CI
ICS							
	Female	1	1	1	1	1	1
	Male	1.03 (1.01-1.05)*	0.97 (0.95-0.99)*	0.99 (0.92-1.07)	0.98 (0.90-1.07)	0.89 (0.82-0.97)*	0.91 (0.83-1.00)
ICS/LABA							
	Female	1	1	1	1	1	1
	Male	0.98 (0.92-1.05)	1.15 (1.08-1.23)**	1.07 (0.98-1.17)	1.06 (0.97-1.18)	1.11 (0.97-1.26)	1.09 (0.96-1.25)
LABA							
	Female	1	1	1	1	1	1
	Male	0.94 (0.83-1.05)	1.04 (0.92-1.18)	1.27 (1.10-1.46)*	1.29 (1.12-1.49)*	1.23 (1.01-1.50)*	1.26 (1.03-1.55)*
LAMA							
	Female	1	1	1	1	1	1
	Male	1.14 (0.77-1.70)	1.40 (0.93-2.10)	1.20 (1.11-1.31)**	1.21 (1.10-1.33)**	1.33 (1.11-1.59)*	1.27 (1.05-1.53)*
SABA							
	Female	1	1	1	1	1	1
	Male	0.97 (0.95-0.99)*	1.00 (0.98-1.02)	0.87 (0.83-0.91)**	0.84 (0.80-0.89)**	0.93 (0.86-0.99)*	0.89 (0.82-0.96)*
SAMA							
	Female	1	1	1	1	1	1
	Male	1.12 (0.99-1.26)	1.13 (0.98-1.30)	1.08 (0.99-1.17)	1.11 (1.01-1.21)*	1.22 (1.06-1.40)*	1.28 (1.11-1.48)*

**: $p < 0.0001$; *: $p < 0.05$; OR: unadjusted odds ratio; aOR: adjusted odds ratio; ICS: inhaled corticosteroid; SABA: short-acting $beta_2$-agonist; LABA: long-acting $beta_2$-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; COPD: chronic obstructive pulmonary disease; CI: confidence interval; ACO: asthma-COPD overlap; [#]: Adjusted for all factors listed in Table 2.

3.4 DISCUSSION

Using a large population-based cohort of asthma, COPD and asthma-COPD overlap patients from a period of January 1, 1998 to July 31, 2018, we found significant differences in inhaled pharmacotherapies between females and males among patients with obstructive airway diseases. Adjusted multivariable analyses showed, males in comparison to females with COPD or asthma-COPD overlap were more likely to be a new-user of a LABA, LAMA, and SAMA and less likely to be a new-user of a SABA. Also, males with asthma were more likely to be a new user of ICS/LABA and less likely to start an ICS.

There are several medications that are currently available for the treatment of asthma but no differential preferences between females and males have been suggested in clinical practice guidelines of asthma and COPD globally.[1, 2] The GINA guideline recommends that all or most asthma patients should have an ICS/LABA therapy in their regimen. In COPD however, the treatment option is to avoid ICS if possible as increased use of ICS alone increases the risk of pneumonia in these patients.[21, 22] Noticeably, among patients with asthma, female patients have a significant, albeit small, increase of ICS monotherapy use as initial treatment in comparison with the males in our study. Although the exact reasons for this observed gender differences are not fully understood, the significant increase use of ICS monotherapy among female patients with asthma could be partially explained by more frequent reports of asthma symptoms in female patients than males. In the American Lung Association Asthma Clinical Research Centers (ALA-ACRC) trials to determine if sex differences in asthma control or symptom profiles exist,

they observed that females were more likely to report specific symptoms such as nocturnal awakenings, activity limitations, and shortness of breath compared to males.[23]

In contrast to ICS monotherapy initiation, males with asthma received more ICS/LABA as first-line therapy compared to females. It is plausible that male asthmatics were being treated aggressively compared to females as the former were more likely to receive more step-up treatment or superior treatment than the later. It is also interesting that whilst it is known that females have a worse perception of asthma, feel it as more symptomatic and suffer a greater impact on their quality of life (QoL), our finding demonstrated they are less likely to receive ICS/LABA than their male counterparts initially.[24] Nevertheless, we found no gender difference in either COPD or asthma-COPD overlap patients prescribed ICS monotherapy, or the combination therapy of ICS/LABA.

The observed gender differences could be partially explained that the average physician recognizes symptoms in males and respond to them more aggressively than they would have done to females with either COPD alone or asthma-COPD overlap. In an observational study to objectively measure and compare reported sleep disturbances due to symptoms in males and females, the authors reported that sleep disturbances were significantly more prevalent in males with COPD compared with controls; whereas there was no significant difference in females.[25] Indeed, it is perceived that COPD is seen as male-dominated disease.[26] Alternatively, gender differences may be partially explained by differences in disease characteristics. Papaioannou *et al.* found that female patients were characterized by milder forms of COPD disease relative to males, and comorbidities

were more prevalent in males than in females.[27] As such, it is possible that females presenting with COPD were being treated more with asthma medications. Yet, the COPD GOLD clinical guideline reports no differential treatment between genders.[2]

We observed similar differences among patients with asthma, COPD and asthma-COPD overlap in our study who were new users of rescue medications. Female patients with either COPD or asthma-COPD overlap were more like to receive SABA compared to males. This is consistent with Dunn *et al.* study which found a trend toward increased use of asthma rescue pharmacotherapy in females vs males (36.2% vs 13.1%; p=0.051).[28] Even though we found that males were less likely to receive rescue medication of SABA, on average, they were on more superior therapy (SAMA) compared to females. This observation may be due to the fact that common respiratory infections in COPD are responsible for most of the incidents of worsened COPD.[29] Furthermore, males are more susceptible to bacteria and virus infections, infectious complications after surgery, severe sepsis and septic shock.[30-33]

This study has strengths and limitations. A major strength of our study is the size of our study population which consists of more than 240,000 patients. Another, strength is the quality of our cohort and its robust capture of medication data. The CPRD is a high-quality database which is representative of approximately 14 million acceptable patients. This attribute makes the study representative of the overall United Kingdom population of obstructive airway patients diagnosed with asthma, COPD and asthma-COPD overlap.

Among limitations, is the potential for medication misclassification as the CPRD database does not capture prescriptions from specialists or prescriptions given in a hospital setting. Given most of these agents would be initially prescribed or continued by

GP's, the degree of misclassification is likely very low. Another limitation of this study is the lack of information on lung function tests such as FEV_1 and FEV_1/FVC ratio due to large missing values or its unavailability in entirety even though we adjusted for multiple important disease severity indicators such as age, body mass index, material deprivation, smoking status, comorbidities, oral corticosteroid use (indicator for exacerbation), number of hospitalizations, GPs visits and treatment (comedications). Finally, on the validity of the asthma-COPD overlap subgroup. Just as the clinical definition of asthma or COPD is still debatable, as things stand, there is not a standard definition for patients with asthma-COPD overlap. However, we defined these patients as having; 1) COPD readcode and 2) asthma readcode and 3) an ex or current smoker (if never smoked, exposure to wood smoke, biofuels, random gas or second-hand smoke) before the index date. The readcodes for both asthma and COPD in the CPRD have been extensively validated and used in several studies.

3.5 CONCLUSION

Albeit in a more specific population, our findings are consistent with van der Verde *et al whom found* that overall prescription rates were substantially higher in females than in males with diverse regional and ethnic differences and called for renewed efforts to close expanding gender treatment gap.[34] Our findings are novel and highlights GPs potential unconscious bias in management of obstructive airway disease patients. In conclusion, we observed an overall gender difference in first time drug use to

treat patients with asthma, COPD or asthma-COPD overlap who are new users of inhaled pharmacotherapies from January-01, 1998 to July-31, 2018. Adjusting for proxies of disease severity, smoking and socioeconomic (material deprivation) status did not change the association by gender.

CHAPTER 4

RISKS OF MAJOR ADVERSE CARDIOVASCULAR EVENTS ASSOCIATED WITH B2-AGONISTS FOR THE TREATMENT OF ASTHMA, COPD, AND ASTHMA-COPD OVERLAP

This manuscript has been submitted to *a speciality journal* and is currently under review.

J. Amegadzie, JM Gamble, J. Farrell, Z. Gao (Submitted May 26, 2021). Risks of Major Adverse Cardiovascular Events associated with Inhaled Beta2-adrenergic agonists for the Treatment and Management of Asthma, COPD, and Asthma-COPD Overlap: A Nested Case-Control study. *International Journal of Epidemiology*

4.1 INTRODUCTION

Asthma and chronic obstructive pulmonary diseases (COPD) are the two main diagnoses of Obstructive Airways Diseases (OADs).[1, 2] Beta $(\beta)_2$-adrenergic agonists are frontline treatment for these diseases.[3] They exert their pharmacologic effects via β_2-adrenoceptors that are predominantly present on airway smooth muscles but also exist on cardiac muscles, vascular endothelium, eosinophils and lymphocytes.[4] β_2-adrenoceptors agonists including long-acting and short-acting β_2-agonists (LABA and SABA) are typically designed to mimic the functions of epinephrine by producing autonomic responses within the airway smooth muscle and to limit the stimulation to β_2-adrenoceptors outside the airway smooth muscles as much as possible to reduce adverse effects.[3] However, a lack of selectivity for β_2-adrenoceptors may result in "off-target" effects such as tachycardia, tremors, headaches and increase in cardiac ectopy.[5-8] These effects are thought to be partially mediated by β_2-adrenoceptors desensitization or exacerbation of airway inflammation, and may lead to further cardiovascular sequelae.[9]

Epidemiological studies conducted on the effectiveness and safety β_2-agonists, including a large randomized controlled trial (RCT) report inconclusive findings because of large drop-out rates, low events rates, inclusion of patients with no record of OAD diagnosis or showed varied conclusions with respect to their effectiveness and safety.[10-17] Prior to these studies, studies of adverse cardiovascular events, including sudden cardiac death, fatal myocardial infarction and arrhythmia resulting from β_2-agonists use have accumulated over the last six decades among patients with asthma and COPD.[18-21] Furtherance to this, recent combined analysis of safety trials of LABA by Busse et al. concluded that adding a LABA to an inhaled glucocorticoid (ICS) was safe.[22]

However, this study is limited on the premise that patients recruited were hesitance to take part in trials investigating risk of death and also fraught with exclusion of patients with previous life-threatening events from their analysis.

It thus remains uncertain whether new initiation of β_2-agonists-based medications is associated with a differential risk of cardiovascular events. To advance our understanding of the cardio-respiratory safety of β_2-agonists, we conducted a nested case-control study among current and new users LABA, SABA or ICS/LABA combination therapy on the risk of major adverse cardiovascular event (MACE) among patients with asthma, COPD and asthma-COPD overlap using a large population-based cohort from real world setting.

4.2 METHODS

4.2.1 SOURCE POPULATION

We conducted a nested case-control study using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD is representative of UK's population that contains de-identified, longitudinal data, with approximately 700 contributing general practitioner (GP) primary care practices and more than 14 million acceptable (good quality) patients.[23, 24] The Patients' data are available for demographic characteristics, symptoms, diagnoses, primary care prescriptions, laboratory tests, lifestyle information, referrals to specialists and hospitals. Prescriptions prescribed by GPs are automatically coded into computer records based on the British National

Formulary.[25] Approximately half of the source population is linked to hospital (Hospital Episode Stats, HES) and death certificate (Office of National Statistics [ONS]) records.[26] This dataset has been widely used to investigate a broad range of health related topics including the safety and effectiveness of respiratory medications.[27-30] Our study was approved by the Health Research Ethics Board at Memorial University and by the CPRD Independent Scientific Advisory Committee (ISAC 18_005RA).

4.2.2 COHORT DEFINITION

Our source cohort included all HES/ONS-linked individuals in the CPRD aged ≥18 with a diagnosis of asthma, COPD, or asthma-COPD overlap and a new prescription for a LABA, SABA, ICS/LABA, ICS or short-or long acting muscarinic antagonist (SAMA, LAMA) between 1-January-1998 and 31-July-2018. In order to assess only new-users, patients with a record of taking any inhaler drug within 365 days before their first medication prescription were excluded. The date of cohort entry was defined as the date of first prescriptions for any of these inhaled drugs. For subjects who initiated LAMA (tiotropium), cohort entry was defined as the date of the first prescription on or after 25-September-2003 (that is at least one year after the drug was available in the UK) separately for LAMA case events and their matched controls. Patients were followed from the date of study-cohort entry until an event of MACE, emigration from a CPRD practice site, end of coverage in the database, end of the study period (31-July-2018) or which ever occurred first.

An incident Read code in CPRD database was used to define a patient with asthma and/or COPD (see **APPENDIX II**). Detailed information on exclusion criteria are shown in **Figure 1**. Recent validation studies in the CPRD GOLD database have shown that patients with asthma or COPD can be accurately identified from CPRD database using specific diagnostic codes.[31, 32] Three separate sub-cohorts were created based on OAD diagnosis; namely asthma, COPD or asthma-COPD overlap.

4.2.3 NESTED CASE-CONTROL

For each of the three OAD sub-cohorts, a nested case-control study was carried out to investigate our primary endpoint of MACE. The nested case-control analytic approach was chosen because of the time-varying nature of exposure, the size of the cohort, and the long duration of follow-up.[33] MACE were defined as the first occurrence of non-fatal heart failure, non-fatal myocardial infarction, non-fatal arrhythmia, non-fatal stroke, or any cardiovascular-related mortality after the date of cohort-entry. In order to assess only incidents cases, patients with MACE events occurring before the date of cohort-entry were excluded. Our event definitions were based on International Classification of Disease Version 10 codes (linked HES/ONS data). Thus, the index date for cases was the date of event for MACE.

Consequently, for each event occurring during the follow-up, we used risk-set sampling method to match the event with a random sample from the risk set; primarily, members of the cohort who were being followed and were event-free at the index date of

the case. These risk sets, which allow exposure to be measured at the time of the event occurrence, are identical to those used in a Cox proportional-hazards model. For each of the three OAD sub-cohorts, a case was randomly matched up to 10 controls within each sub-cohort on the basis of sex, age (±1 year), date of cohort entry (±180 days) and duration of follow-up. The index date for the cases was the same as the index date for their matched controls.

4.2.4 EXPOSURE ASSESSMENT

All drugs exposures were identified in the prescription files through the use of gemscript codes between cohort entry and index date, and were classified 4 mutually exclusive exposure groups of interest as;

1) Current and new use of LABA was defined by a prescription duration plus a 30-day grace period overlapping the index date;
2) Current and new use of SABA was defined by a prescription duration plus a 30-day grace period overlapping the index date;
3) Current and new use of ICS/LABA was defined by a prescription duration plus a 30-day grace period overlapping the index date;
4) Current and new use of inhaled non-β_2-agonists-based drugs (i.e. ICS, SAMA or LAMA) – reference category; was defined by a prescription whose duration plus a 30-day grace period overlapping the index date.

A 30-day grace period added to the end of a prescription to allow for refill time. This 30-day grace period also accounted for non-adherence.

4.2.5 POTENTIAL CONFOUNDERS

In addition to all matching factors, the models were further adjusted for several potential confounders measured at study-cohort entry including body mass index smoking status, alcohol abuse, blood pressure, material deprivation, number of physician visits, comorbidities, Charlson comorbidity index, cardiovascular drugs and drugs prolonging QT interval.

We also adjusted in our final model the following: 1) the use of other respiratory or antibiotics drugs as a measure of COPD (also asthma or asthma-COPD overlap) severity including the use of methylxanthines, oral corticosteroid and respiratory antibiotics; 2) moderate or severe exacerbation which was defined by a new prescription for prednisolone or hospitalization for asthma, COPD or asthma-COPD overlap; 3) other drugs used in the year before cohort entry including aspirin, acetaminophen, opioids and non-steroidal anti-inflammatory drugs in the year before cohort entry.

4.2.6 STATISTICAL ANALYSIS

Descriptive statistics to summarize the characteristics of the cohort, cases and matched controls were provided. For categorical variables with more than two categories,

type 3 p-values (a p-value indicating the overall effect of all levels of a categorical variable) were also calculated. Conditional logistic regression was used to estimate odds ratios and 95% confidence interval for the risk of MACE associated with inhaled β_2-agonists-based drugs (LABA, SABA or ICS/LABA) as compared with ICS, LAMA or SAMA drugs. In nested case-control analysis, conditional logistic regression is used to compute odds ratio that are unbiased estimators of hazard ratios (HRs), with little or no loss in precision.[33, 34]

To investigate the possible modification effects of β-blocker use, an interaction term between a drug group variable and a variable indicating β-blocker type (cardioselective or non-cardioselective) was introduced into multiple regression models. Data analysis was conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC).

4.2.7 SECONDARY ANALYSIS

We also investigated the risk of each disease of the five major cardiovascular events of MACE including HF, MI, stroke, arrhythmia and cardiovascular death. Risk-set sampling was done independently for each outcome.

4.2.8 SENSITIVITY ANALYSIS

We conducted series of sensitivity analyses to explore the robustness of our study design, potential mediating effects and results. The cohort population was restricted to add-on or switchers therapy approach. Also, since the length of the grace period is

uncertain, sensitivity analyses were conducted by varying the grace period to 0, 45 and 60 days.

4.3 RESULTS

A total of 180 567 patients met the study inclusion criteria (see **Figure 1**), which included 2095, 111 829, 5614, 55 287, 2239 and 3502 new users of LABA, SABA, ICS/LABA, ICS, LAMA and SAMA users respectively. During this time, 686 patients experienced MACE of which 359, 239 and 88 cases were observed among patients with asthma, COPD and asthma-COPD overlap respectively. The mean age at cohort entry with MACE case patients were 63.8, 74.3 and 72.3 years for asthma, COPD and asthma-COPD overlap respectively (see **Table 1** for detailed patient characteristics).

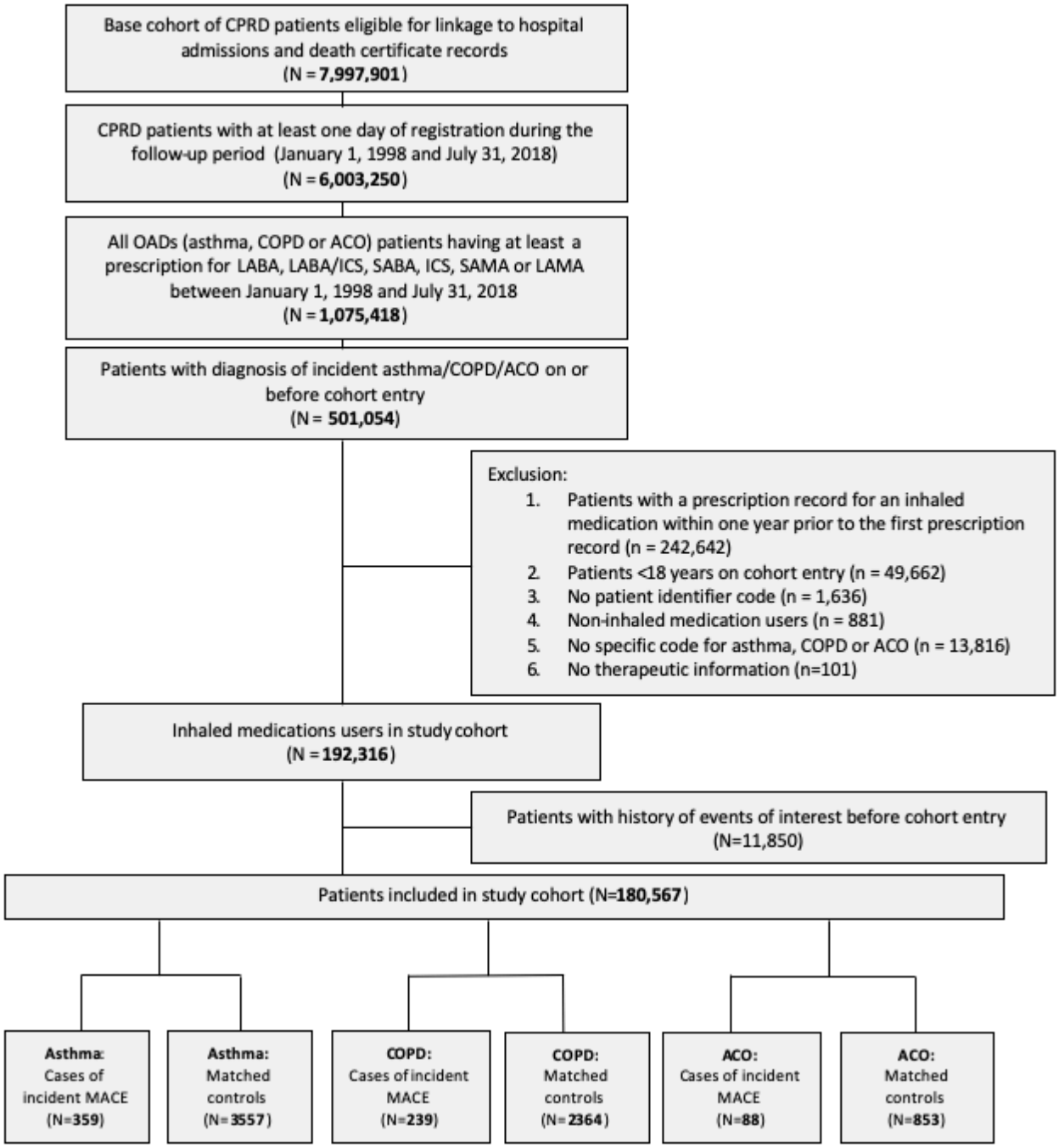

Figure 4.1: Flowchart of Number of Patients in the Base and Study Cohort

Abbreviations: CPRD, Clinical Practice Research Datalink; OADs, obstructive airway diseases; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; Rx, prescription.

Table 4.1: Baseline characteristics of Primary Case Patients (major adverse cardiovascular events) and Matched Controls, stratified by patients diagnosed with Asthma, COPD and Asthma-COP Overlap respectively

Primary Outcome	**Major Adverse Cardiovascular Events (MACE)**					
Types of OADs	Asthma		COPD		Asthma-COPD Overlap	
Characteristics	**Cases** (N=359)	**Controls** (N=3557)	**Cases** (N=239)	**Controls** (N=2364)	**Cases** (N=88)	**Controls** (N=853)
Age (years) at inhaled medication initiation	63.8 (±17.9)	63.2 (±17.7)	74.3 (±9.3)	74.0 (±8.9)	72.3 (±10.5)	72.1 (±9.9)
Sex						
Men	173(48.2)	1712(48.1)	156(65.3)	1540(65.1)	60 (59.0)	585 (68.6)
Women	186 (51.8)	1845(51.9)	83(34.7)	824(34.9)	28 (41.0)	268 (31.4)
Body mass index (kg/m^2)						
Underweight	17(4.7)	133(3.7)	25(10.5)	231(9.8)	5(5.7)	57(6.7)
Normal	80(22.3)	963(27.1)	66(27.6)	698(29.5)	18(20.5)	245(28.7)
Overweight	100(27.9)	1131(31.8)	74(30.9)	709(30.0)	32(36.3)	282(33.1)
Obese	109(30.4)	837(23.5)	38(15.9)	458(19.4)	26(29.5)	171(20.0)
Unknown/missing	53(14.8)	493(13.9)	36(15.1)	268(11.3)	7(8.0)	98(11.5)
Smoking status						
Current	58(16.2)	544(15.3)	106(44.4)	944(39.9)	24(27.3)	382(44.8)
Former	109(30.4)	1023(28.8)	103(43.1)	1069(45.2)	48(54.5)	174(20.4)
None	172(47.9)	1796(50.5)	17(7.1)	274(11.6)	16(18.2)	275(32.2)
Unknown/missing	20(5.6)	194(5.5)	13(5.4)	77(3.3)	0(0.0)	22(2.6)
Alcohol abuse						
None	62(17.3)	558(15.7)	42(17.6)	88(3.7)	6(6.8)	23(2.7)
Former	6(1.7)	64(1.8)	8(3.3)	401(17.0)	14(15.9)	135(15.8)
Current	236(65.7)	2363(66.4)	152(63.6)	1594(67.4)	60(68.2)	583(68.4)

Unknown/missing	55(15.3)	272(7.6)	37(15.5)	281(11.9)	8(9.1)	112(13.1)
Average systolic blood pressure	137.1 (±19.6)	137.0(±19.4)	137.4 (±20.1)	139.8 (±17.8)	139.7 (±23.4)	139.9 (±19.6)
Measure of deprivation						
Least deprived	71(19.8)	868(24.4)	36(15.1)	385(16.3)	13(14.8)	139(16.3)
Less deprived	88(24.5)	827(23.3)	46(19.3)	467(19.8)	8(9.1)	166(19.5)
Deprived	78(21.7	770(21.6)	53(22.2)	511(21.6)	19(21.6)	199(23.3)
More deprived	69(19.2)	589(16.5)	48(20.1)	483(20.4)	28(31.8)	183(21.5)
Most deprived	53(14.8)	500(14.1)	56(23.4)	516(21.9)	20(22.7)	166(19.5)
Unknown/missing	0(0.0)	5(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Charlson Index						
0	202(56.3)	2436(68.5)	107(44.8)	1196(50.6)	35(39.8)	468(54.9)
1	68(18.9)	473(13.3)	42(17.6)	426(18.0)	23(26.1)	151(17.7)
≥ 2	89(24.8)	648(18.2)	90(37.7)	742(31.4)	30(34.1)	234(27.4)
Medications in year before cohort entry						
CV drugs						
ACE inhibitors	134(37.3)	840(23.62)	106 (44.4)	893 (37.8)	35(39.8)	303(35.5)
Angiotensin receptor blockers	24(6.7)	216(6.1)	22 (9.2)	190 (8.0)	9(10.2)	56(6.6)
β-blocker						
Cardioselective	50 (13.9)	313 (8.8)	59 (24.7)	377 (16.0)	10 (11.4)	83 (9.7)
Non-cardioselective	10 (2.8)	51 (1.4)	5 (2.1)	34 (1.4)	0 (0.0)	15 (1.8)
Loop diuretics	64(17.8)	334(9.4)	71 (29.7)	420 (17.8)	29(33.0)	127(14.9)
Thiazide diuretics	68(18.9)	608(17.1)	49 (20.5)	443 (18.7)	23(26.1)	177(20.8)
Digoxin	32(8.9)	98(2.8)	28 (11.7)	115 (4.9)	8(9.1)	48(5.6)
Nitrates	52(14.5)	261(7.3)	45 (18.8)	297 (12.6)	13(14.8)	93(10.9)
Drugs prolonging QT interval						
Macrolides	45(12.5)	395(11.1)	28 (11.7)	323 (13.7)	10(11.4)	101(11.8)
Antiarrhythmic	15(4.2)	43(1.2)	10 (4.2)	61 (2.6)	5(5.7)	19(2.2)

Other drugs						
Aspirin	105(29.3)	615(17.3)	86 (36.0)	746 (31.6)	37(42.1)	253(29.7)
Acetaminophen	55(15.3)	417(11.7)	57 (23.9)	411 (17.4)	21(23.9)	139(16.3)
NSAIDs	54(15.0)	663(18.6)	36 (15.1)	354 (15.0)	14(15.9)	124(14.5)
Opioids	36(10.0)	242(6.8)	28 (11.7)	195 (8.3)	14(15.9)	67(7.9)
Insulin	142(39.6)	1264(35.5)	111 (46.4)	1012 (42.8)	38(43.2)	363(42.6)
Comorbidities in the year before cohort entry						
Hyperlipidemia	42(11.7)	371(10.4)	29 (12.1)	322 (13.6)	11(12.5)	99(11.6)
Hypertension	165(46.0)	1342(37.7)	125 (52.3)	1142 (48.3)	48(54.6)	387(45.4)
Congenital CVA	9(2.5)	81(2.3)	23 (9.6)	119 (5.0)	6(6.8)	27(3.2)
Thyroid disease	29(8.1)	289(8.1)	19 (8.0)	177 (7.5)	9(10.2)	68(8.0)
Liver disease	5(1.4)	51(1.4)	6 (2.5)	34 (1.4)	5(5.7)	11(1.3)
CHF	13(3.6)	74(2.1)	14 (5.9)	90 (3.8)	7(8.0)	34(4.0)
Diabetes	55(15.3)	356(10.0)	38 (15.9)	284 (12.0)	11(12.5)	89(10.4)
Dementia	10(2.8)	56(1.6)	11 (4.6)	54 (2.3)	5(5.7)	23(2.7)
Renal disease	35(9.8)	224(6.3)	33 (13.8)	306 (12.9)	10(11.4)	71(8.3)
Atherosclerosis and PVD	29(8.1)	209(5.9)	35 (14.6)	261 (11.0)	14(15.9)	87(10.2)
Respiratory events and medications						
Physician visits per year						
1 – 17	103(28.7)	1337(37.6)	37(15.5)	468(19.8)	17(19.3)	197(23.1)
18 – 35	78(21.7)	1007(28.3)	55(23.0)	684(28.9)	18(20.5)	247(29.0)
>36	178(49.6)	1213(34.1)	147(61.5)	1212(61.3)	53(60.3)	409(48)
Moderate or severe exacerbation	77(21.5)	473(13.3)	51 (21.3)	394 (16.7)	20(22.7)	181(21.2)
Oral corticosteroid	75(20.9)	473(13.3)	50 (20.9)	392 (16.6)	19(21.6)	181(21.2)
Methylxanthines	5(1.4)	33(0.9)	0(0.0)	33 (1.4)	0(0.0)	34(4.0)
Respiratory antibiotics	153(42.6)	1423(40.0)	119 (49.8)	1181 (50.0)	41(46.6)	404(47.4)

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive

pulmonary disease; ACO, asthma-COPD overlap; NSAIDs, nonsteroidal anti-inflammatory drugs; CV, cardiovascular; ACE, angiotensin-converting enzyme; CVA, cerebrovascular accident; CHF, congestive heart failure; PVD, peripheral vascular disease.

Table 2 presents the result of the primary analyses for the association between new use of inhaled β_2-agonists-based drugs and the incidence of MACE. Among patients with asthma alone or asthma-COP overlap, new use of ICS/ LABA was not significantly associated with risk of MACE in comparison to new use of ICS. Also, new use of SABA was not significantly associated with increased risk of MACE in comparison to new use of ICS. However, among COPD patients, in comparison to new use of SAMA, an increased risk of major adverse cardiovascular events was observed among new use of the SABA (adjusted HR, 2.02 [1.13 – 3.59]), ICS/LABA (adjusted HR, 2.08 [1.04 – 4.16]), and LABA (adjusted HR, 2.38 [1.04 - 5.47]) were associated with . Similarly, among patients with asthma-COPD overlap, new use of SABA was associated with increased risk of MACE (adjusted HR, 2.57 [1.26 – 5.24]) compared with new use of ICS. However, there was no association between new of β_2-agonists-based drugs compared with new users of LAMA or ICS among COPD patients. Subsequently, no interaction term between a β-blockers use variable and a drug group variable was statistically significant in the multiple regression models of MACE. Notably in our analyses of associations, not all exposure or treatment groups were displayed. Thus, cells with fewer than 5 events are not shown, in accordance with confidentiality policies of the CPRD.

Table 4.2: Association Between Use of inhaled β2-agonists-based Drugs and the Incidence of Major Adverse Cardiovascular Events

OADs / Treatment	**Major Adverse Cardiovascular events**		**Adjusted Hazard Ratio** (95% CI)	***p* – value** (type 3)
	Case Patients *no. %*	Controls *no. %*		

Asthma					
1.	ICS (reference)	86 (24.0)	956 (26.9)	1.00	0.08
	SABA	262 (73.0)	2407 (67.7)	1.29 (0.96-1.73)	
	ICS/LABA	7 (2.0)	93 (2.6)	0.75 (0.33-1.73)	
COPD					
1.	ICS (reference)	33 (13.8)	344 (14.6)	1.00	0.175
	SABA	153 (64.0)	1430 (60.5)	1.07 (0.67-1.70)	
	ICS/LABA	26 (10.9)	220 (9.3)	1.10 (0.60-2.02)	
	LABA	12 (5.0)	96 (4.1)	1.26 (0.60-2.68)	
2.	SAMA (reference)	15 (6.3)	274 (11.6)	1.00	0.175
	SABA	153 (64.0)	1430 (60.5)	2.02 (1.13-3.59)*	
	ICS/LABA	26 (10.9)	220 (9.3)	2.08 (1.04-4.16)*	
	LABA	12 (5.0)	96 (4.1)	2.38 (1.04-5.47)*	
3.	LAMA (reference)	12 (7.7)	211 (10.84)	1.00	0.578
	SABA	125 (63.8)	1183 (60.8)	1.47 (0.83-2.62)	
	ICS/LABA	23 (11.73)	180 (9.3)	1.76 (0.86-3.61)	
	LABA	7 (3.6)	55 (2.8)	1.76 (0.66-4.70)	
Asthma-COPD Overlap					
1.	ICS (reference)	13 (14.8)	213 (25.0)	1.00	0.085
	SABA	57 (64.8)	456 (53.5)	2.57 (1.26-5.24)*	
	ICS/LABA	7 (8.0)	72 (8.4)	1.78 (0.62-5.11)	
2.	SAMA (reference)	8 (9.1)	69 (8.1)	1.00	0.085
	SABA	57 (64.8)	456 (53.5)	1.09 (0.48-2.50)	
	ICS/LABA	7 (8.0)	72 (8.4)	0.76 (0.24-2.36)	

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ACO, asthma-COPD overlap.
*: $p < 0.05$

4.4.1 SECONDARY ANALYSIS

Analyses of individual components of MACE revealed no association between new use of SABA compared to new use of ICS for all the major components for patients who are asthmatics as shown in **Table 3**. Similar results were found whereby current and new use of SABA was not associated with increased risk of heart failure and arrhythmia compared with current and new use of ICS among patients with COPD.

Table 4.3: Secondary Outcomes of Individual Components of Major Adverse Cardiovascular Events

OADs / Treatment	Heart Failure		Adjusted Hazard Ratio (95% CI)	*p* – value (type 3)
	Case Patients *no. %*	Controls *no. %*		
Asthma				
1. ICS (reference)	18 (22.0)	211 (26.4)	1.00	0.53
SABA	61 (74.4)	539 (67.5)	1.66 (0.88-3.12)	
COPD				
1. ICS (reference)	14 (18.7)	150 (20.2)	1.00	0.150
SABA	45 (60.0)	413 (55.7)	1.28 (0.64-2.56)	
ICS/LABA	10 (13.3)	64 (8.6)	1.90 (0.73-4.94)	
OADs / Treatment	**Arrhythmia**		**Adjusted Hazard Ratio** (95% CI)	***p* – value** (type 3)
	Case Patients *no. %*	Controls *no. %*		
Asthma				
1. ICS (reference)	48 (22.1)	506 (23.5)	1.00	0.91
SABA	164 (75.6)	1544 (71.8)	1.10 (0.74-1.64)	
COPD				
1. ICS (reference)	18 (13.7)	185 (14.2)	1.00	0.432
SABA	87 (66.4)	802 (66.4)	1.07 (0.59-1.94)	
LABA	7 (5.3)	53 (4.1)	1.45 (0.56-3.74)	
2. SAMA (reference)	9 (6.9)	137 (10.5)	1.00	0.432
SABA	87 (66.4)	802 (66.4)	1.76 (0.84-3.66)	
ICS/LABA	10 (7.6)	123 (9.5)	1.22 (0.46-3.21)	
LABA	7 (5.3)	802 (66.4)	2.37 (0.82-6.90)	
OADs / Treatment	**Myocardial Infarction**		**Adjusted Hazard Ratio** (95% CI)	***p* – value** (type 3)
	Case Patients *no. %*	Controls *no. %*		
Asthma				0.68

1. ICS (reference)	15 (27.3)	155 (28.3)	1.00	
SABA	36 (65.5)	350 (64.0)	1.07 (0.55-2.09)	
OADs / Treatment	**Stroke**		**Adjusted Hazard Ratio** (95% CI)	***p* – value** (type 3)
	Case Patients *no. %*	Controls *no. %*		
Asthma				
2. ICS (reference)	14 (24.6)	177 (31.7)	1.00	0.90
SABA	41 (71.9)	361 (64.6)	1.43 (0.69-2.96)	
OADs / Treatment	**Cardiovascular Death**		**Adjusted Hazard Ratio** (95% CI)	***p* – value** (type 3)
	Case Patients *no. %*	Controls *no. %*		
Asthma				
1. ICS (reference)	12 (33.3)	113 (38.2)	1.00	0.99
SABA	21 (58.3)	16 (54.1)	1.11 (0.49-2.53)	

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ACO, asthma-COPD overlap; N/A, not applicable.

4.4.2 SENSITIVITY ANALYSIS

The results of the sensitivity analyses are summarized in **Figure 2.** The results of our sensitivity analyses for MACE were consistent with those of our primary analyses among asthma patients when the analyses were repeated by varying the grace period by 0 day (adjusted HR 1.28 [0.96 - 1.71]), 45 days (adjusted HR, 1.33 [1.02 - 1.74]), 60 days (adjusted HR, 1.47 [1.14 - 1.89]) and with add-on or switchers (adjusted HR, 1.17 [0.92 - 1.49]). The HR generated in our primary analyses (adjusted HR, 1.29 [0.96 - 1.73]) for

asthma was similar to the one generated in our fixed-effect analysis (adjusted HR, 1.24 [1.11 - 1.37]). Similarly, the HR generated in our primary analyses (adjusted HR, 1.07 [0.67 - 1.70]) for COPD was similar to the one generated in our fixed-effect analysis (adjusted HR, 1.09 [0.91 - 1.31]).

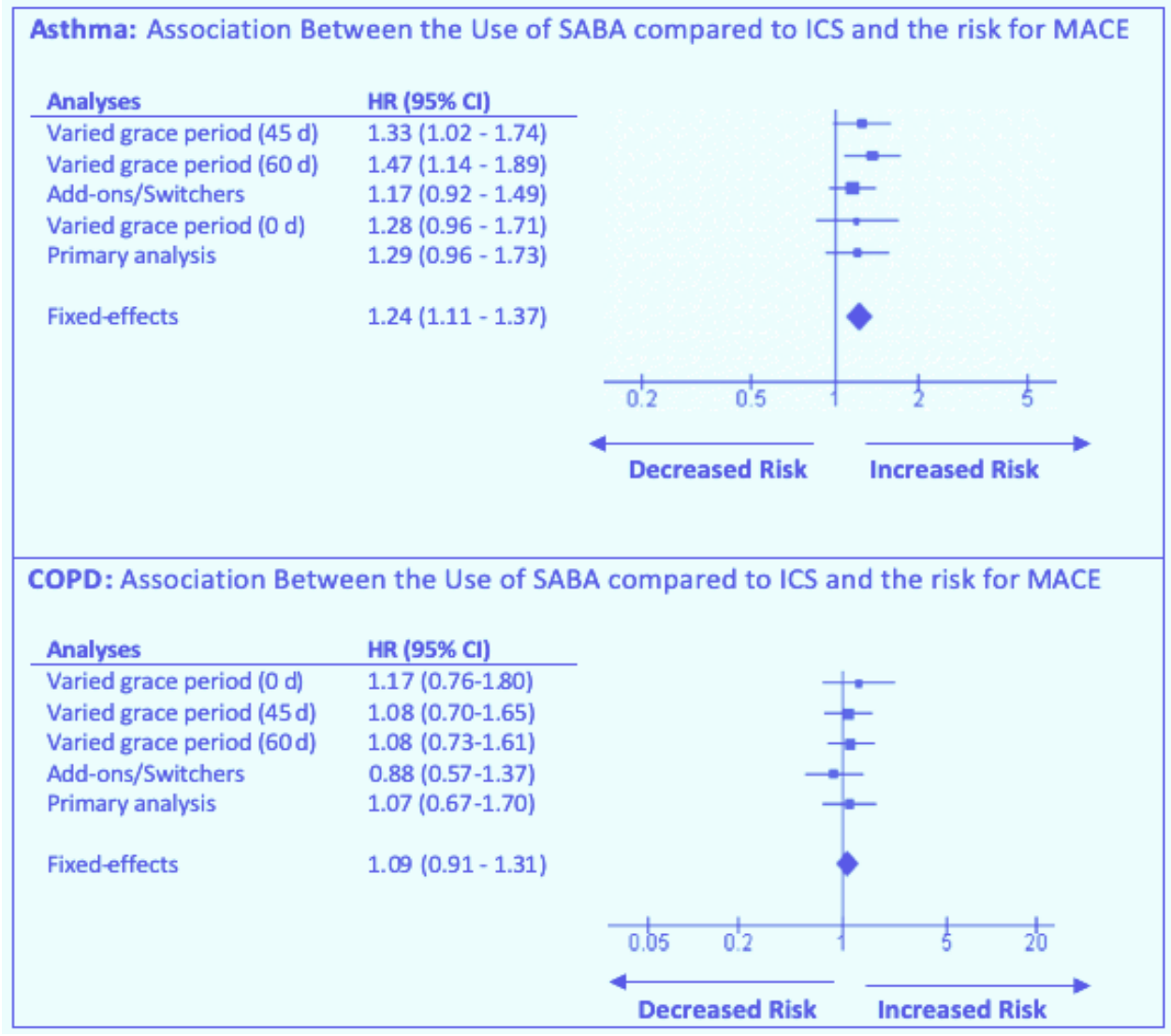

Figure 4.2: Sensitivity Analyses for the Association Between the Use of SABA compared to ICS and the risk for Major Adverse Cardiovascular Event.

4.5 DISCUSSION

Our findings suggest the use of SABA, LABA or ICS/LABA is associated with a 2-fold increased risk of MACE compared with use of SAMA among patients diagnosed with COPD. Similarly, patients with asthma-COPD overlap who are new users of SABA are approximately 2.6 times more likely to suffer MACE compared with patients using ICS. On the other hand, our findings suggest that use of SABA or ICS/LABA combination therapy was not associated with an increased risk of MACE compared with ICS among patients with asthma. Furthermore, we did not observe any significant association between the use of β_2-agonists-based drugs and incidences of the individual components of MACE.

Our findings are consistent with results from a recent meta-analysis of RCTs showing an increased risk of cardiac failure among patients with stable COPD and receiving LABA therapy than patients receiving placebo (odds ratio, OR 1.70, 95% CI, 1.00 - 2.90).[35] Additional network meta-analysis results indicated that LABAs combined with LAMAs resulted in an increased risk of cardiac failure in patients with COPD compared with placebo (OR 2.32, 95% CI, 1.10 – 5.09).[35] Also, in another meta-analysis of 43 randomized trials, the authors reported that inhaled LABA increased the risk of cardiac failure (relative risk [RR] 1.71, 95% CI 1.04 – 2.84, I^2 27.5%).[36] Furthermore, a recent nested-case control study indicated that new use of LABAs or LAMAs in patients with COPD is associated with an approximate 1.5-fold increase in severe cardiovascular risk, irrespective of prior CVD status and history of exacerbation.[37] With the increased risks associated with LABA use, GPs need to be

very mindful and monitor for cardiovascular symptoms within 30 days of new initiations of LABA treatment for COPD.

Another meta-analysis of RCTs also reported increased risk of cardiovascular event associated with β_2-agonists-based drugs (RR 2.54, 95% CI, 1.59–4.05) compared to placebo.[38] In this study, initiation of β_2-agonists treatment increases heart rate and reduces potassium concentrations compared to placebo. Just as in asthma, β_2-agonists such as SABAs are recommended as the initial treatment for the relief of symptoms and exercise limitations in COPD.[2] Nonetheless, the efficacy of SABAs in COPD is however less than in asthma as a result of limited or no reversibility observed in COPD patients. Pertaining to patients with asthma-COPD overlap, we observed that patients on rescue medication of SABA are 2.6 times more like to experience MACE compared with ICS. Given the lack of randomized intervention studies of asthma-COPD overlap, it is difficult to provide firm treatment guidance for these patients. It is indicated that treatment with inhaled glucocorticoids should be continued in patients with long-standing asthma even if a component of irreversible airway obstruction develops.[39]

Previous studies of risk of cardiovascular diseases associated with β_2-agonists mainly included prevalent users [40], limited to elderly patients only [14, 16] or lacked statistical power [41-43]. Our study is novel in that we examined a single prescription drug use after new initiation of β_2-agonists therapy and the risk of MACE since the advent of β_2-agonists on the market. Although, a thorough discussion on the potential mechanism of cardiovascular effects associated with β_2-agonist use is beyond the scope of our study, the use of SABAs or LABAs, acting as autonomous nervous system agents is suspected to cause sympathetic overstimulation by activating both β_2-adrenoceptors and

cardiac muscle.[44, 45] Also, the presence of moderate amount of β_2-adrenoreceptors with percentages ranging from 14 to 40% in ventricular myocardium and from 20 to 55% in atrial tissue explain why β_2-agonists can induce a number of adverse effects on cardiac function. [46]

The present study has several strengths. First, we assembled a large population-based cohort of patients initiating β2-agonist-based drugs, ICS, SAMA or LAMA therapies. Even though, our study is observational in nature and thus susceptible to potential confounding, we used rigorous matching and statistical adjustment to minimize residual confounding and to control for a large number of potential confounders. Second, the use of a new-user design eliminated biases related to the inclusion of prevalent users. Third, consistent results with varied time-window in our sensitive analyses further confirmed the robustness of our results. Another strength is the generalizability of the results from our cohort, which is representative of the overall United Kingdom population of patients diagnosed with asthma, COPD and asthma-COPD overlap.

Among limitations, first, is the possibility that patients using SAMA would be healthier and have less severe disease than those receiving ICS/LABA or LABA. However, we addressed this issue by including multiple disease severity related covariates in our final models. A second limitation is the inability to examine individual agents of β_2-agonist agents to preclude which agents may be responsible for CV events. However, in a study that compared the cardiac effects of formoterol, salbutamol and fenoterol, Bremmer et al found that all β_2-agonist agents increased heart rate and Corrected-QT interval, decreased Q-S_2 interval and plasma potassium levels compared with placebo.[47]

4.6 CONCLUSION

New initiation of β_2-agonist therapy including SABA, LABA or ICS/LABA combination therapy was associated with an increased risk of major adverse cardiovascular events respectively among patients diagnosed with COPD. Similarly, patients with asthma-COPD overlap who are new users of SABA were more likely to suffer major adverse cardiovascular events. The decision to prescribe β2-agonist-based drugs should be premised on consideration of patient benefit and increased risk of major adverse cardiovascular events.

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Author contributions

JEA, J-MG, JF and ZG conceived the study. Data analysis and interpretation was carried out by JEA, J-MG, JF and ZG. JEA, J-MG, JF and ZG drafted the manuscript, commented on and approved the final version of the manuscript. ZG is responsible for the study management and coordination and he is also the study guarantor.

Conflict of interest: none to be declared

Disclaimer

The study funder was not involved in the study design or the writing of the protocol.

CHAPTER 5

ASSOCIATION OF B2-AGONISTS-BASED DRUGS WITH ALL-CAUSE MORTALITY OR PNEUMONIA IN PATIENTS WITH ASTHMA, COPD OR ASTHMA-COPD OVERLAP

J. Amegadzie, JM Gamble, J. Farrell, Z. Gao (This manuscript is ready to be submitted) Association of β2-agonists-based drugs with All-cause Mortality or Pneumonia in patients with Asthma, COPD or Asthma-COPD overlap

5.1 INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are two common obstructive airways disease (OAD) that affect the lung. COPD on the other hand is ranked as the 4th leading cause of death in 2019 and considered as a major worldwide killer [1, CDC] as well as causing considerable morbidity and costs.[2, 3] β2-agonists are recommended by existing guidelines for treatment and management of lung diseases are widely used in the management of asthma, COPD or asthma-COPD overlap.[4-6] β2-agonists such as long-or short-acting β2-agonists (SABA) and the combination therapy of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABA) – ICS/LABA are indicated in asthma to improve lung function by enhancing bronchial airway smooth muscle by triggering β2-adrenergic receptors.[4] In spite of the promising bronchodilatory effect, there is a great deal of evidence in regard to their pro-inflammatory effects on inflammatory cells and cytokine systems, which have been demonstrated both in vitro and in vivo, in normal and asthmatic populations.[7-9] Furthermore, systemically absorbed and rapid onset bronchodilators medications have been implicated for morbidity mostly observed in COPD which may be partly due to adverse effects of β2-agonists or intrinsic medication effect.[10]

With more and more β2-agonists-based drugs prescribed to patients [11, 12], there has been a need to understand the safety and risk of adverse effects. There are a few studies focusing on the risk of cardiovascular disease (CVD) associated with inhaled β2-agonists.[13-15] Nevertheless, the information on risk of all-cause mortality and pneumonia is limited and results are not consistent. Previously, there has been debate whether LABA monotherapy should be avoided for moderate and severe COPD. Notably,

the TORCH (Towards a Revolution in COPD Health) trial, a multicentre, randomised, double-blind trial of more than 6100 patients with moderate-to-severe COPD showed a nonsignificant trend toward reduced total mortality (all-cause mortality) in the salmeterol group compared with the placebo group.[16] Even though this did not reach statistical significance, there was actually an increase in COPD deaths and respiratory deaths in the salmeterol group compared with the placebo group. Also, in a systematic review study comprising of 26 trials including 2,630 participants with asthma comparing salmeterol to placebo, all-cause mortality was higher with regular salmeterol than placebo but the increase was not significant (Odds Ratio 1.33 [95% CI: 0.85, 2.10]).[17] Although the interpretation is that there were no clinically meaningful events of death, this would be largely incorrect because of the lack of power. Pharmacotherapy treatment and management of COPD with inhaled β2-adrenergic–receptor agonists have been centered on improving lung function and relieving symptoms.[5] These drugs, in principle, also reduce exacerbations, but there is no convincing evidence so far to suggest that this therapy substantially affects mortality.

β2-agonists in combination with corticosteroids is one of the most frequently used forms of inhaled respiratory medication for obstructive airway diseases, including asthma and COPD.[11] Although, they are indicated for symptomatic relief and prevention of acute exacerbation of COPD, it can increase the risk for pneumonia which is one of the major causes of acute exacerbation, especially in COPD. In a recent network-meta-analysis assessing the risk of pneumonia including 134 692 adults with COPD, the authors observed that 24 treatments were more harmful, including two agents of β2-agonists that increased risk of pneumonia versus placebo; commonly, a β2-agonists based

combination therapy, with the most harmful agent been fluticasone/salmeterol with a SUCRA (surface under the cumulative ranking curve) of 89%.[18] Also, a recent study among COPD patients found that the risk of pneumonia is higher with LABA.[19] The increase risks of pneumonia observed in these two studies were as a result of likely due to the ICS component within ICS/LABA combination products. Thus, investigation of the effects of LABA on the risk of pneumonia poses challenge due to common ICS and LABA combination treatment among COPD patients.

Given the importance and increasing use of β2-agonists based drugs in asthma, COPD and asthma-COPD overlap, there is a need to assess whether these drugs are associated with an increased risk of all-cause-mortality and hospitalization for pneumonia. The objective of this large population-based study was to determine whether new use of LABA, SABA or ICS/LABA, when compared with use of ICS, LAMA or SAMA is associated with an increased risk of all-cause-mortality or hospitalization for pneumonia in patients with asthma, COPD and asthma-COPD overlap.

5.2 METHODS

5.2.1 SOURCE POPULATION

This study was conducted using the United Kingdom Clinical Practice Research Datalink (CPRD) linked to both the Hospital Episode Statistics (HES) and Office of National Statistics databases which is representative of the geographical distribution of the UK's population that contains de-identified and longitudinal data. The CPRD is a United Kingdom (UK) based database that includes more than 14 million acceptable (good quality) patients from more than 700 total contributing general practitioner (GP)

primary care practices.[20, 21] Patients' data are available for demographics, symptoms and diagnoses, primary care prescriptions (drugs and devices), test results (e.g. spirometry), referrals to specialist (secondary care), lifestyle information (BMI [body mass index], smoking, alcohol, exercise) hospitalization dates, primary and secondary diagnoses (coded using International Classification of Diseases, 10thRevision [ICD-10]), and related procedures. Patients' prescriptions data written by GPs are coded into computer records based on the British National Formulary. Data routinely collected in the CPRD is regularly audited and has been shown to be of high validity (median proportion of patients with confirmed diagnoses is 89%).[22] The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (ISAC 18_005RA) and by the Health Research Ethics Board at Memorial University, St. John's, Canada.

5.2.2 STUDY COHORT

The study cohort included all males and females diagnosed with asthma, COPD or asthma-COPD overlap in the CPRD aged 18 or over with first-ever prescription for a LABA, SABA, combination therapy ICS/LABA, ICS, long-or short acting muscarinic antagonist (LAMA, SAMA). We used incident Read code in CPRD database to define patient with asthma, COPD or asthma-COPD overlap (see **APPENDIX II**). Validation studies on asthma and COPD in the CPRD GOLD database have shown that these patients can be accurately identified from CPRD database using specific diagnostic

codes.[23, 24] Patients with asthma-COPD overlap were defined as having; 1) COPD read code and 2) asthma read code and 3) an ex or current smoker (if never smoked, exposure to wood smoke, biofuels or second-hand smoke) before the receipt of first prescription. In assessing only new-users, we excluded all patients with a record of taking any inhaler drug within 365 days before their first medication prescription. Cohort entry was defined as the date of first prescriptions during any time period from 1-January-1998 to 31-July-2018. To exclude confounding associated with severe patients being the first to be prescribed the newest bronchodilator on the market; we only included OAD patients who initiated LAMA (tiotropium) at least one year after the drug was available in the UK (25-September-2002). Thus, we defined cohort entry as the date of the first prescription on or after 25-September-2003 separately for LAMA cases and their respective controls. Detailed information on the study cohort is shown in **Figure 1**. Patients were followed from the date of study-cohort entry until an event all-cause-mortality or pneumonia occurred, emigration from a CPRD practice site, end of coverage in the database, end of the study period (July 31, 2018) or which ever occurred first.

5.2.3 CASE-CONTROL SELECTION

The study cohorts as defined above were analyzed by adopting the nested case-control analyses, in which cases were defined by our primary outcomes of all-cause mortality or pneumonia. Because of the time-varying nature of exposure, the size of the cohort, and the long duration of follow-up, the nested case-control approach was chosen.

Most essentially, the nested case-control analysis is computationally equally efficient just like a time-dependent survival analysis whilst producing identical estimates.[25] To assess only incidents cases, patients with event of hospitalization for pneumonia occurring before the date of cohort-entry were excluded. Events definitions were based on International Classification of Disease Version 10 codes (linked HES/ONS data). Thus, the index date was the date of event for all-cause-mortality or admission for pneumonia.

For each case occurring during the study follow-up, a risk-set sampling method to match the case with a random sample from the risk set was used. Thus, each members of the cohort who were being followed and who were event-free at the time of the case occurrence were matched accordingly. The adoption of the risk sets, allows exposure to be measured at the time of the cases occurrence, which are identical to those executed in a Cox proportional-hazards model. For each case, we randomly selected up to 10 controls within the cohort on the basis of sex, age (±1 year), date of cohort entry (±180 days) and duration of follow-up. The case's index date became the index date for those matched controls selected at random at risk-set.

5.2.4 EXPOSURE ASSESSMENT

Cases and controls were classified into 1 of 4 mutually exclusive categories on the basis of their exposure status at index date;

5) Current and new use of LABA monotherapy was defined by a prescription duration plus a 30-day grace period overlapping the index date;

6) Current and new use of SABA monotherapy was defined by a prescription duration plus a 30-day grace period overlapping the index date;
7) Current and new use of combination therapy ICS/LABA was defined by a prescription duration plus a 30-day grace period overlapping the index date;
8) Not exposed was the reference category for all comparisons and comprised all patients with a prescription of ICS, SAMA or LAMA whose duration plus a 30-day grace period overlapped the index date.

The grace period was to account for non-adherence to the prescribed inhaled pharmacotherapy (for example, late make-up for missed doses and/or refills).

5.2.5 COVARIATES

Covariates included all matching factors (age, sex, and duration of follow-up) used in the study design as well as the following potential confounders measured 365 days prior to study-cohort entry which included BMI, smoking status, alcohol abuse, systolic blood pressure, material deprivation, number of physician visits (measure of health utilization), comorbidities (hyperlipidemia, hypertension, congenital CVA (cerebrovascular accident), thyroid disease, liver disease, congestive heart failure [CHF], diabetes, dementia, renal disease, atherosclerosis and peripheral vascular disease[PVD]) Charlson comorbidity index, prescription drugs (macrolides, anti-arrhythmia, ACE (angiotensin converting enzyme) inhibitors, angiotensin receptor blockers, beta-blockers, loop diuretics, thiazide diuretics, digoxin, aspirin, acetaminophen, opioids and non-steroidal anti-inflammatory drugs and nitrates).

We also adjusted for the use of respiratory or antibiotics drugs as a measure of disease severity which included the use of methylxanthines, oral corticosteroid and respiratory antibiotics. We defined moderate or severe exacerbation as a new prescription for prednisolone or hospitalization for asthma, COPD or asthma-COPD overlap.

5.2.6 STATISTICAL ANALYSIS

Nested case-control analyses for asthma, COPD and asthma-COPD overlap were conducted separately. Descriptive statistics was used to summarize the characteristics of the cases and their matched controls. Categorical variables with more than two categories, type 3 p-values (a p-value indicating the overall effect of all levels of a categorical variable) were also calculated. We used conditional logistic regression to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals for all-cause-mortality and hospitalization for pneumonia with new use of LABA, SABA or ICS/LABA versus ICS, SAMA or LAMA. All our models were adjusted for the covariates listed above. Data analysis was conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC) on IBM cluster.

5.2.7 SENSITIVITY ANALYSES

We explored series of sensitivity analyses to examine the robustness of our study design and results. Our study population was restricted to switchers or add-on therapy for instances whereby the day a patient receives a second inhaler medication they will begin

to contribute time at risk to the exposure groups of interest. We also repeated the primary analysis by varying the grace period to 0, 45 and 60 days.

5.3 RESULTS

We identified 185 407 patients who were eligible for the study (**Figure 1**) which comprises of 2221, 114 600, 5977, 56 174, 2585 and 3850 new users of LABA, SABA, ICS/LABA combination therapy, ICS, LAMA and SAMA respectively. In this cohort, 334 all-cause-mortality were identified including 139, 153 and 42 cases of asthma, COPD and asthma-COPD overlap respectively and 505 new events of hospitalization for pneumonia representing 332, 133 and 40 cases of asthma, COPD and asthma-COPD overlap cases respectively. The mean ± SD age at cohort entry with all-cause-mortality case patients were 69.6 ±14.8, 75.9 ±9.7 and 75.9 ±8.0 years for asthma, COPD and asthma-COPD overlap respectively and those for pneumonia case patients were 53.1 ±19.9, 72.7 ±9.3 and 72.4 ±14.3 years for asthma, COPD and asthma-COPD overlap respectively. Baseline characteristics of case patients for both all-cause-mortality and pneumonia are presented in **Table 1** and **Table 2** respectively. Among cases with all-cause-mortality, controls were less likely to be females compared to males. However, pneumonia case patients were more likely to be female diagnosed with asthma whilst in COPD and asthma-COPD patients, cases more likely to be males. With all-cause mortality, case patients were more likely to be obese except patients with COPD. Also, cases were more likely to be current smokers, most deprived, with at least 2 or more

comorbidity (Charlson Index), prescribed more loop diuretics, aspirin, opioids and insulin. However, the baseline characteristics among case patients with systolic blood pressure, deprived (material deprivation) and NSAIDs prescription were quite balanced across OADs groups. Nonetheless, all our matching variables were balanced among cases and their matched controls.

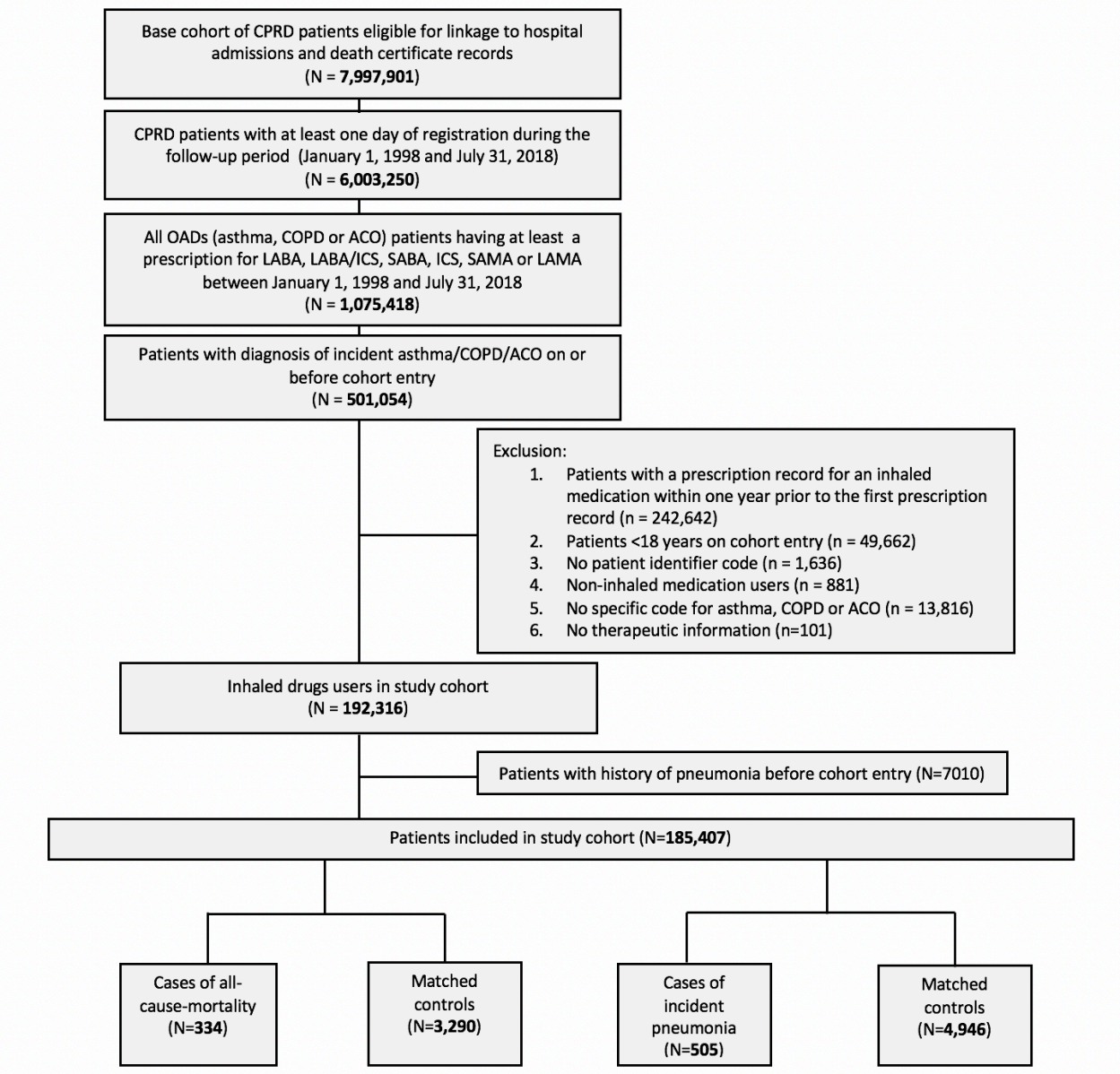


Figure 5.1: Flowchart of Number of Patients in the Base and Study Cohort

Abbreviations: CPRD, Clinical Practice Research Datalink; OADs, obstructive airway diseases; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; Rx, prescription.

Table 5.1: Baseline characteristics of All-Cause Mortality Case Patients and Matched Controls

Primary Outcome	**All-Cause Mortality**					
Types of OADs	Asthma		COPD		Asthma-COPD Overlap	
Characteristics	**Cases** (N=139)	**Controls** (N=1387)	**Cases** (N=153)	**Controls** (N=1503)	**Cases** (N=42)	**Controls** (N=400)
Age (years) at inhaled medication initiation	69.6 (±14.8)	69.1 (±14.7)	75.9(±9.7)	75.2(±9.1)	75.9(±8.0)	75.4(±7.5)
Sex						
Men	75(54.0)	747(53.9)	96(62.8)	941(62.6)	26(61.9)	243(60.8)
Women	64(46.0)	640(46.1)	57(37.3)	562(37.4)	16(38.1)	157(39.3)
Body mass index (kg/m^2)						
Underweight	9(6.5)	63(4.5)	19(12.4)	169(11.2)	8(19.0)	37(9.2)
Normal	25(18.0)	384(27.7)	48(31.4)	469(31.2)	6(14.3)	115(28.8)
Overweight	39(28.1)	449(32.4)	41(36.8)	406(27.0)	13(31.0)	130(32.5)
Obese	30(21.6)	284(20.5)	17(11.1)	204(13.6)	15(35.7)	75(18.8)
Unknown/missing	36(25.8)	207(14.9)	28(18.3)	255(17.0)	0(0.0)	43(10.7)
Smoking status						
Current	33(23.7)	184(13.3)	68(44.5)	602(40.1)	17(40.5)	115(28.8)
Former	43(30.9)	437(31.5)	56(36.6)	611(40.7)	18(42.9)	188(47.0)
None	50(36.0)	657(47.4)	19(12.4)	192(12.7)	7(16.6)	82(20.5)
Unknown/missing	13(9.4)	109(7.8)	10(6.5)	98(6.5)	0(0.0)	15(3.7)
Alcohol abuse						
None	16(11.5)	213(15.4)	19(12.4)	254(16.9)	9(21.4)	69(17.2)
Former	0(0.0)	13(0.9)	5(3.3)	36(2.4)	0(0.0)	9(2.3)
Current	90(64.8)	919(66.3)	97(63.4)	960(63.9)	33(78.6)	272(68.0)
Unknown/missing	33(23.7)	242(17.4)	32(20.9)	253(16.8)	0(0.0)	50(12.5)
Average systolic blood pressure	141.4 (±19.1)	140.0(±19.8)	137.7(±21.7)	141.4(±19.5)	140.6(±25.6)	141.1(±20.2)
Measure of deprivation						

Least deprived	34(24.5)	327(23.6)	23(15.0)	206(13.7)	5(11.9)	60(15.0)
Less deprived	24(17.3)	325(23.4)	27(17.7)	314(20.9)	7(16.7)	85(21.3)
Deprived	33(23.7)	305(22.0)	35(22.9)	308(20.5)	7(16.7)	75(18.8)
More deprived	23(16.6)	229(16.5)	32(20.9)	324(21.6)	13(31.0)	101(25.3)
Most deprived	25(18.0)	201(14.5)	36(23.5)	351(23.3)	10(23.8)	79(19.8)
Unknown/missing	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Charlson Index						
0	66(47.5)	871(62.8)	71(46.4)	818(54.4)	17(40.5)	209(52.3)
1	26(18.7)	221(15.9)	33(21.6)	278(18.5)	8(19.1)	61(15.3)
≥ 2	47(33.8)	295(21.3)	49(32.0)	407(27.1)	17(40.5)	130(32.5)
Medications in year before cohort entry						
ACE inhibitors	52(37.4)	408(29.4)	54(35.3)	506(33.7)	14(33.3)	146(36.5)
Angiotensin receptor blockers	10(7.2)	73(5.3)	13(8.5)	100(6.7)	0(0.0)	24(6.0)
Beta-blockers	20(14.4)	159(11.5)	21(13.7)	204(13.6)	# ...	# ...
Loop diuretics	24(17.3)	166(12.0)	41(26.8)	280(18.6)	10(23.8)	81(20.3)
Thiazide diuretics	35(25.2)	296(21.3)	25(16.3)	314(20.9)	9(21.4)	91(22.8)
Digoxin	7(5.0)	46(3.3)	11(7.2)	77(5.1)	# ...	# ...
Nitrates	17(12.2)	131(9.4)	29 (19.0)	186(12.4)	5(11.9)	55(13.8)
Macrolides	22(15.8)	163(11.8)	23(15.0)	177(11.8)	5(11.9)	43(10.8)
Aspirin	42(30.2)	325(23.4)	47(30.7)	449(29.9)	16(38.1)	123(30.8)
Acetaminophen	22(15.8)	198(14.3)	46(30.1)	299(19.9)	11(26.2)	65(16.3)
NSAIDs	29(20.9)	289(20.8)	26(17.0)	246(16.4)	5(11.9)	57(14.3)
Opioids	19(13.7)	108(7.8)	22(14.4)	127(8.5)	9(21.4)	36(9.0)
Insulin	47(33.8)	451(32.5)	59(38.6)	560(37.3)	18(42.9)	166(41.5)
Comorbidities in the year before cohort entry						
Hyperlipidemia	14(10.1)	123(8.9)	14(9.2)	153(10.2)	6(14.3)	42(10.5)
Hypertension	72(51.8)	581(41.9)	60(39.2)	676(45.0)	18(42.9)	188(47.0)
Congenital CVA	# ...	# ...	9(5.9)	52(3.5)	0(0.0)	12(3.0)
Thyroid disease	10(7.2)	103(7.4)	9(5.89)	98(6.5)	# ...	# ...
Liver disease	5(3.6)	17(1.2)	0(0.0)	26(1.7)	# ...	# ...

CHF	5(3.6)	41(1.3)	13(8.5)	79(5.3)	0(0.0)	11(3.1)
Diabetes	20(14.4)	151(10.9)	21(13.7)	158(10.5)	5(11.9)	50(12.5)
Dementia	# ...	# ...	# ...	# ...	# ...	# ...
Renal disease	13(9.4)	81(5.84)	12(7.8)	131(8.7)	5(11.9)	44(11.0)
Atherosclerosis and PVD	17(12.2)	97(7.0)	22(14.4)	152(10.1)	7(16.7)	50(12.5)
Respiratory events and medications in the year before cohort entry						
Physician visits per year						
1 – 17	47(33.8)	512(36.9)	39(25.5)	419(27.9)	7(16.7)	97(24.3)
18 – 35	26(18.7)	386(27.8)	32(20.9)	436(29.0)	8(19.1)	116(29.0)
>36	66(47.5)	489(35.3)	82(53.6)	648(43.1)	27(64.3)	187(46.8)
Moderate or severe exacerbation	28(20.1)	186(13.4)	42(27.5)	293(19.5)	11(26.2)	77(19.3)
Oral corticosteroid	28(20.1)	185(13.4)	41(26.8)	292(19.4)	11(26.2)	77(19.3)
Methylxanthines	# ...	# ...	6(3.9)	33(2.2)	# ...	# ...
Respiratory antibiotics	64(46.0)	529(38.1)	83(54.3)	732(48.7)	21(50.0)	173(43.3)

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ACO, asthma-COPD overlap; NSAIDs, nonsteroidal anti-inflammatory drugs; CV, cardiovascular; ACE, angiotensin-converting enzyme; CVA, cerebrovascular; CHF, congestive heart failure; PVD, peripheral vascular disease.

#; Cells with fewer than 5 events are not shown, in accordance with confidentiality policies of the Clinical Practice Research Datalink.

Table 5.2: Baseline characteristics of Pneumonia Cases and Matched Controls categorized according to OAD diagnoses

Primary Outcome	**Pneumonia**					
Types of OADs	Asthma		COPD		Asthma-COPD Overlap	
Characteristics	**Cases** (N=332)	**Controls** (N=3289)	**Cases** (N=133)	**Controls** (N=1296)	**Cases** (N=40)	**Controls** (N=361)

Age (years) at inhaled medication initiation	53.1 (±19.9)	52.4 (±19.6)	72.7 (±9.3)	72.3 (±9.9)	72.4(±14.3)	73.2(±10.5)
Sex						
Men	120(36.1)	1179(35.9)	76(57.1)	754(58.2)	22(55.0)	199(55.1)
Women	212(63.9)	2110(64.2)	57(42.9)	542(41.8)	18(45.0)	162(44.9)
Body mass index (kg/m^2)						
Underweight	17(4.7)	179(3.7)	16(12.0)	131(10.1)	7(17.5)	33(9.1)
Normal	94(22.3)	1011(27.1)	47(35.3)	383(29.6)	9(22.5)	105(29.1)
Overweight	86(27.9)	919(31.8)	28(21.1)	363(28.0)	10(25.0)	120(33.2)
Obese	87(30.4)	666(23.5)	23(17.3)	257(19.8)	8(20.0)	71(19.7)
Unknown/missing	48(14.8)	514(13.9)	19(14.3)	162(12.5)	6(15.0)	32(8.9)
Smoking status						
Current	87(16.2)	618(15.3)	73(54.9)	551(42.5)	9(22.5)	107(44.8)
Former	76(30.4)	814(28.8)	46(34.6)	556(42.9)	20(50.0)	177(20.4)
None	147(47.9)	1682(50.5)	8(6.0)	138(10.7)	21(52.5)	66(32.2)
Unknown/missing	22(5.6)	175(5.5)	6(4.5)	51(3.9)	0(0.0)	11(2.6)
Alcohol abuse						
None	65(19.6)	478(15.7)	32(24.1)	232(17.9)	5(12.5)	57(15.8)
Former	0(0.0)	44(1.8)	5(3.8)	55(4.3)	0(0.0)	13(3.6)
Current	219(66.0)	2196(66.4)	73(54.9)	839(64.7)	27(67.5)	250(69.3)
Unknown/missing	48(14.4)	571(7.6)	23(17.2)	170(13.1)	6(15.0)	41(11.3)
Average systolic blood pressure	130.0 (±19.5)	130.5(±19.1)	136.2 (±20.4)	139.2 (±18.0)	136.9(±16.5)	137(±16.8)
Measure of deprivation						
Least deprived	77(19.8)	799(24.4)	21(15.8)	205(15.8)	5(12.5)	52(14.4)
Less deprived	62(24.5)	776(23.3)	23(17.3)	268(19.8)	13(32.5)	91(25.2)
Deprived	69(21.7	697(21.6)	21(15.8)	264(21.6)	6(15.0)	74(20.5)
More deprived	62(19.2)	559(16.5)	31(23.3)	284(20.4)	6(15.0)	73(20.2)
Most deprived	62(14.8)	453(14.1)	37(27.8)	275(21.9)	10(25.0)	71(19.7)
Unknown/missing	0(0.0)	5(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Charlson Index						
0	226(68.1)	2558(77.8)	61(45.9)	704(54.3)	18(45.0)	200(55.4)

1	49(14.8)	309(9.4)	18(13.5)	223(17.2)	12(30.0)	67(18.6)
≥ 2	57(17.2)	422(12.8)	54(40.6)	369(28.5)	10(25.0)	94(26.0)
Medications in year before cohort entry						
ACE inhibitors	67(20.2)	509(15.5)	42(31.6)	451(34.8)	13(32.5)	140(38.8)
Angiotensin receptor blockers	18(5.4)	119(3.6)	9(6.8)	99(7.6)	6(15.0)	28(7.8)
Beta-blockers	26(7.8)	238(7.2)	25(18.8)	203(15.6)	5(12.5)	52(14.4)
Loop diuretics	28(8.4)	171(5.2)	35(26.3)	196(15.2)	10(25.0)	60(16.6)
Thiazide diuretics	46(13.9)	377(11.5)	20(15.0)	247(19.1)	7(17.5)	90(24.9)
Digoxin	7(2.1)	36(1.1)	8(6.0)	47(3.6)	# ...	# ...
Nitrates	18(5.4)	134(4.1)	15(11.3)	143(11.0)	5(12.5)	48(13.3)
Macrolides	65(19.6)	380(11.5)	29(21.8)	206(15.9)	5(12.5)	56(15.5)
Aspirin	55(16.6)	334(10.2)	42(31.6)	358(27.6)	12(30.0)	116(32.1)
Acetaminophen	36(10.8)	279(8.5)	29(21.8)	252(19.4)	10(25.0)	58(16.1)
NSAIDs	62(18.7)	536(16.3)	24(18.1)	194(15.0)	10(25.0)	52(14.4)
Opioids	28(8.4)	155(4.7)	22(16.5)	110(8.5)	6(15.0)	42(11.6)
Insulin	141(42.5)	1059(32.2)	62(46.6)	547(42.2)	19(47.5)	158(43.8)
Comorbidities in the year before cohort entry						
Hyperlipidemia	28(8.4)	216(6.6)	16(12.0)	185(14.3)	5(12.5)	55(11.6)
Hypertension	97(29.2)	816(24.8)	56(42.1)	635(49.0)	18(45.0)	180(49.9)
Congenital CVA	6(1.8)	59(1.8)	7(5.3)	49(3.9)	0(0.0)	7(1.9)
Thyroid disease	25(7.5)	226(6.9)	6(4.5)	107(8.3)	5(12.5)	36(10.0)
Liver disease	5(1.5)	38(1.2)	# ...	# ...	# ...	# ...
CHF	5(1.5)	41(1.3)	5(3.8)	36(2.8)	# ...	# ...
Diabetes	31(9.3)	219(6.7)	15(11.3)	144(11.1)	7(17.5)	38(10.5)
Dementia	5(1.5)	36(1.1)	# ...	# ...	12(3.3)	5(1.4)
Renal disease	17(5.1)	157(4.8)	17(12.8)	139(10.7)	5(12.5)	37(10.3)
Atherosclerosis and PVD	14(4.2)	94(2.9)	20(15.0)	143(11.0)	5(12.5)	35(9.7)
Respiratory events and medications in the year before cohort entry						
Physician visits per year						

1 – 17	98(29.5)	1403(42.7)	27(20.3)	265(20.5)	5(12.5)	64(17.7)
18 – 35	89(26.8)	933(28.4)	30(22.6)	379(29.2)	12(30.0)	108(29.9)
>36	145(43.7)	953(29.0)	76(57.1)	652(50.3)	23(57.5)	189(52.4)
Moderate or severe exacerbation	83(25.0)	372(11.3)	35(26.3)	254(19.6)	11(27.5)	93(25.8)
Oral corticosteroid	79(23.8)	371(11.3)	35(26.3)	252(19.4)	11(27.5)	92(25.5)
Methylxanthines	# ...	# ...	# ...	# ...	# ...	# ...
Respiratory antibiotics	193(58.1)	1250(38.0)	78(58.7)	661(51.0)	22(55.0)	179(49.6)

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; NSAIDs, nonsteroidal anti-inflammatory drugs; CV, cardiovascular; ACE, angiotensin-converting enzyme; CVA, cerebrovascular; CHF, congestive heart failure; PVD, peripheral vascular disease.

#; Cells with fewer than 5 events are not shown, in accordance with confidentiality policies of the Clinical Practice Research Datalink.

Table 3 presents the result of the primary analyses for the association between new use of inhaled β2-agonists-based drugs and the risk of all-cause-mortality and pneumonia. Due to suppressed results because of small cell sizes, in our analyses of associations, not all exposure or treatment groups were displayed. Cells with fewer than 5 events are not shown, in accordance with confidentiality policies of the CPRD.

5.3.1 β2-AGONIST-BASED DRUGS AND THE RISK FOR ALL-CAUSE-MORTALITY

Compared with current and new use of ICS, current and new use of SABA was associated with increased risk of all-cause-mortality (adjusted HR, 1.82 [1.04 – 3.20]) and current and new use of LABA was associated with increased risk of all-cause-mortality (adjusted HR, 2.77 [1.22 – 6.31]) among COPD patients. However, there was no association of increased risk of all-cause-mortality between current and new use of ICS/LABA (adjusted HR, 1.83 [0.83 – 4.03]) and LABA (adjusted HR, 2.19 [0.96 – 5.01]) compared with current and new use of ICS and SAMA respectively among COPD patients. Compared with current and new use of ICS, similar results were observed with current and new use of SABA (adjusted HR, 1.11 [0.70 – 1.76]) among asthmatics and SABA (adjusted HR, 1.10 [0.41 – 2.96]) among asthma-COPD overlap patients.

5.3.2 β2-AGONIST-BASED DRUGS AND HOSPITALIZATION FOR PNEUMONIA

As indicated in **Table 3**, among OADs diagnosed with asthma, compared with current and new use of ICS, current and new use of SABA (adjusted HR, 1.26 [0.93 – 1.72]) and ICS/LABA (adjusted HR, 0.87 [0.36 – 2.06]) were not associated with increased or decreased risk for hospitalization for pneumonia. Similar results were found among patients with COPD who were current and new users of SABA (adjusted HR, 0.81 [0.45 – 1.44]) and ICS/LABA (adjusted HR, 0.84 [0.36 – 1.98]) compared with current and new users of ICS. Also, current and new use of SABA was not associated with either increased or decreased risk of hospitalization for pneumonia compared with ICS (adjusted HR, 1.73 [0.58 – 5.18]) and SAMA (adjusted HR, 0.86 [0.27 – 2.71]) among asthma-COPD overlap patients.

Table 5.3: Association Between Use of inhaled β2-agonists-based Drugs with All-Cause-Mortality and Incidence of Pneumonia.

OADs / Treatment		All-Cause-Mortality		Adjusted Hazard Ratio (95% CI)
		Case Patients *no. %*	Controls *no. %*	
Asthma				
1.	ICS (reference)	40 (28.8)	425 (30.6)	1.00
	SABA	90 (64.8)	878 (63.3)	1.11 (0.70-1.76)
COPD				
2.	ICS (reference)	18 (11.8)	283 (18.8)	1.00
	SABA	94 (61.4)	845 (56.2)	1.82 (1.04-3.20)*
	ICS/LABA	13 (8.5)	114 (7.6)	1.83 (0.83-4.03)
	LABA	12 (7.8)	66 (4.4)	2.77 (1.22-6.31)*
3.	SAMA (reference)	16 (10.5)	195 (13.0)	1.00
	SABA	94 (61.4)	845 (56.2)	1.44 (0.82-2.54
	ICS/LABA	13 (8.5)	114 (7.6)	1.45 (0.66-3.19)

	LABA	12 (7.8)	66 (4.4)	2.19 (0.96-5.01)
Asthma-COPD Overlap				
3.	ICS (reference)	9 (21.4)	104 (26.0)	1.00
	SABA	22 (52.4)	202 (50.5)	1.10 (0.41-2.96)

OADs / Treatment		**Pneumonia**		**Adjusted Hazard Ratio** (95% CI)
		Case Patients *no. %*	Controls *no. %*	
Asthma				
1.	ICS (reference)	72 (21.7)	768 (23.4)	1.00
	SABA	251 (75.6)	2405 (73.1)	1.26 (0.93-1.72)
	ICS/LABA	7 (2.1)	71 (2.2)	0.87 (0. 36-2.06)
COPD				
2.	ICS (reference)	21 (15.8)	193 (14.9)	1.00
	SABA	84 (63.2)	808 (62.3)	0.81 (0.45-1.44)
	ICS/LABA	12 (9.0)	111 (8.6)	0.84 (0.36-1.98)
Asthma-COPD Overlap				
4.	ICS (reference)	6 (15.0)	69 (19.1)	1.00
	SABA	26 (65.0)	204 (56.5)	1.73 (0.58-5.18)
5.	SAMA (reference)	5 (12.5)	35 (9.7)	1.00
	SABA	26 (65.0)	204 (56.5)	0.86 (0.27-2.71)

Abbreviations: ICS, inhaled corticosteroid; SABA, short-acting beta2-agonist; LABA, long-acting beta2-agonist; SAMA, short-acting muscarinic antagonist; LAMA, long- acting muscarinic antagonist; LAMA, long-acting muscarinic antagonist; COPD, chronic obstructive pulmonary disease; CI, confidence interval; ACO, asthma-COPD overlap.

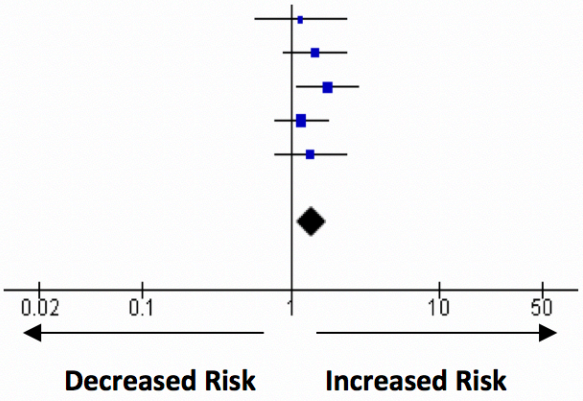
5.3.3 SENSITIVITY ANALYSES

Results from our sensitivity analyses are depicted in **Figure 2.** Overall, the results of our sensitivity analyses for all-cause-mortality were consistent with those of our primary analyses when the analyses were repeated by varying the grace period by 0 day (adjusted HR 1.30 [0.61 - 2.77]), 45 days (adjusted HR, 1.46 [0.88 – 2.43]), 60 days

(adjusted HR, 1.84 [1.12 – 3.03]) and with add-on or switchers (adjusted HR, 1.19 [0.71 - 1.99]). The HR generated in our primary analyses for COPD (adjusted HR, 1.44 [0.82 - 1.54]) was similar to the one generated in our fixed-effect analysis (adjusted HR, 1.38 [1.10 – 1.73]). In regard to patients with asthma, the HR generated in our primary analyses (adjusted HR, 1.11 [0.70-1.76]) was similar to the one generated in our fixed-effect analysis (adjusted HR, 1.17 [0.99 - 1.38]).

COPD: Association Between the Use of SABA compared to SAMA and the risk for All-Cause Mortality

Analyses	HR (95% CI)
Varied grace period (0 d)	1.30 (0.61 – 2.77)
Varied grace period (45 d)	1.46 (0.88 – 2.43)
Varied grace period (60 d)	1.84 (1.12 – 3.03)
Add-ons/Switchers	1.19 (0.71 - 1.99)
Primary analysis	1.44 (0.82 - 1.54)
Fixed-effects	1.38 (1.10 - 1.73)



Asthma: Association Between the Use of SABA compared to ICS and the risk for All-Cause Mortality

Analyses	HR (95% CI)
Varied grace period (0 d)	1.40 (0.74-2.65)
Varied grace period (45 d)	1.24 (0.87-1.78)
Varied grace period (60 d)	1.38 (0.99-1.92)
Add-ons/Switchers	0.97 (0.72-1.31)
Primary analysis	1.11 (0.70-1.76)
Fixed-effects	1.17 (0.99 - 1.38)

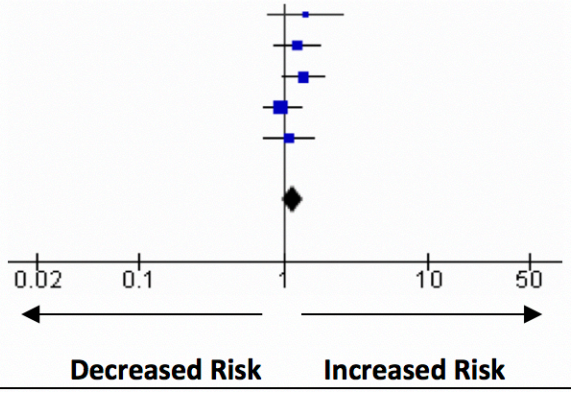


Figure 5.2: Sensitivity Analyses for the Association Between the Use of SABA compared to SAMA or ICS and the risk for All-Cause-Mortality in COPD and Asthma patients respectively

5.4 DISCUSSION

This real world population based nestle case-control study suggests that among patients with COPD who newly started inhaled β2-agonists-based drugs, the use of either SABA or LABA monotherapy was associated with 1.8-fold and 2.8-fold increase in mortality respectively, compared with ICS monotherapy. In regard to risk of pneumonia, our findings indicate that use of β2-agonists-based drugs (SABA or ICS/LABA) is not associated with an increased risk of pneumonia compared with use of ICS among patients diagnosed with asthma alone or COPD alone. Our findings also offer insight into the optimal treatment of patients with asthma-COPD overlap who are newly treated with β2-agonists-based drugs and the risk of pneumonia. In this group of patients, we did not observe any potential risk of pneumonia. Finally, our findings remained consistent in several sensitivity analyses that explored overall robustness of our study design and results.

In our study, COPD patients who newly started SABA alone are 1.8-fold more likely to die compared with ICS. It is argued that SABA use in COPD tends to increase with increasing COPD severity. This argument has been highlighted by a study conducted in the United State using clinical practice data which reported a mean SABA use of 3.3 puffs/day observed in patients with less severe airflow limitation (≥50% predicted forced expiratory volume in 1 s [FEV_1]), compared with 5.2 puffs/day in patients with more severe airflow limitation (< 50% predicted FEV_1).[27] Whilst it is believed that high supplementary SABA use was an indicator for a significant modest risk of exacerbation and hospitalization,[28, 29] a recent analyses of pooled longitudinal data from 23 randomised controlled of more than 23,000 patients on mono-and dual-bronchodilators

revealed that COPD patients in spite of their severity status used approximately 4 SABA puffs per day.[30] Noteworthy, the efficacy of SABA monotherapy use in COPD is however less than in asthma as a result of limited or no reversibility observed in COPD patients. Thus, the increased use of SABA monotherapy use in COPD is rather an indicator of its ineffectiveness than its association with disease severity. We believe that SABA should be used in combination with other treatments or replaced with a more superior treatment, preferably, a SAMA (or combination with SABA) in the initial treatment for symptom relief, improvement in FEV_1 and to prevent acute exacerbation of COPD. Our assertion is currently backed by clinical guidelines which recommend treatments with LAMA or LABA/ICS over regular short-acting β2-agonist for patients with exacerbations or persistent breathlessness, otherwise referred to as patients with moderate or severe COPD.[3, 31]

The strength of our association is consistent with a meta-analysis of RCTs that did observe a 2.5-fold increased risk of death in COPD patients using a LABA monotherapy compared with placebo.[26] In our study, we observed a 2.8-fold in all-cause mortality with new use of LABA compared with SAMA. Our study takes into full cognizant that not a single long-acting β2-agonists bronchodilator is recommended over another in the clinical management guidelines. Notwithstanding, few studies have comparatively assessed different LABAs. Even though, the use of ICS (study comparator) in COPD is a potential risk for pneumonia, recent studies have demonstrated the effectiveness of ICS among COPD patients with significant eosinophilia or frequent exacerbators. In recent past however, studies comparing LABA monotherapies with LAMAs were not adequately designed or powered to demonstrate the clinical effectiveness of LABA

monotherapy leading to inconclusive results. Even though, it is an acceptable fact that there is no cure for COPD, acceptable pharmacotherapy is essential in reducing the frequency and severity of symptoms. That being so, bronchodilators which alter airway smooth muscle tone, are paramount to the management of COPD symptoms and exacerbations.

Our findings indicate that use of β2-agonist-based drugs is not associated with increased risk of pneumonia compared with ICS among obstructive airways disease patients with asthma or COPD alone. Our findings also contribute new knowledge to the treatment of patients with asthma-COPD overlap and the potential risk of pneumonia. This is of particular concern in regards to patients with the overlap disease whereby, studies of asthma medications have excluded patients with COPD and vice versa. Perhaps the risk of β2-agonist-based drugs is more fully understood in respect to pneumonia.

The present study has several strengths. First, we assembled a large population-based cohort of patients initiating β2-agonist-based drugs, ICS, SAMA or LAMA therapies. Even though, our study is observational in nature and thus susceptible to potential confounding, we used rigorous matching and statistical adjustment to minimize residual confounding, including adjustment for body mass index, alcohol abuse, multiple socio-economic (matched on age and sex and adjusted for material deprivation), smoking status and blood pressure. Thus, the use of the CPRD and HES/ONS databases allowed us to control for a large number of potential confounders. Second, the use of a new-user design eliminated biases related to the inclusion of prevalent users. Third, we observed consistent results with varied time-window in our sensitive analyses, which addressed

concerns related to possible residual confounding and the overall strength of our study design.

Among limitations, first, is the potential for medication misclassification as the CPRD database does not capture prescriptions from specialists or prescriptions given in a hospital setting. Given most of these agents would be initially prescribed or continued by GPs, the degree of misclassification is likely very low. A second limitation of this study is the lack of information on lung function tests such as FEV1 and FEV1/FVC (force vital capacity) ratio due to large missing values or its unavailability in entirety even though we adjusted for multiple important covariates including age, body mass index, material deprivation, smoking status, comorbidities, oral corticosteroid use (indicator for exacerbation), number of hospitalizations, GPs' visits, respiratory antibiotics, moderate-severe exacerbation and treatment (comedications). Finally, due to observational nature of our study design, residual confounding cannot be overruled. Encouraging however is the fact that we observed similar results from our sensitivity analyses using different exposure definitions and grace periods.

5.5 CONCLUSION

Starting LABA monotherapy or SABA monotherapy treatment was associated with an increased risk of all-cause mortality in patients with COPD. On the hand, we observed no association with SABA, LABA or LABA/ICS use and the risk of pneumonia in patients with asthma, COPD or asthma-COPD overlap.

Acknowledgements

This study is based in part on data from the Clinical Practice Research Datalink (CPRD-GOLD) obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone.

Author contributions

JEA, J-MG, JF and ZG conceived the study. Data analysis and interpretation was carried out by JEA, J-MG, JF and ZG. JEA, J-MG, JF and ZG drafted the manuscript, commented on and approved the final version of the manuscript. ZG is responsible for the study management and coordination and he is also the study guarantor.

Conflict of interest: none to be declared

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Disclaimer

The study funder was not involved in the study design or the writing of the protocol.

CHAPTER 6

PLANNING FOR FUTURE STUDY

VALIDATION OF ASTHMA-COPD OVERLAP RECORDING IN HEALTHCARE RECORDS: PROTOCOL FOR A SYSTEMATIC REVIEW

A VERSION OF THIS PROTOCOL HAS BEEN PUBLISHED IN THE BMJ-OPEN JOURNAL, 2019

J. Amegadzie, O. Badejo, JM Gamble, M. Wright, J. Farrell, B. Jackson, K. Sultana, M. Hashmi, Z. Gao (2019). Validated methods to identify patients with asthma-COPD overlap in healthcare databases of asthma-COPD overlap recording in healthcare records: a systematic review protocol. *BMJ Open. 2019 Mar 13;9(3):e024306*

6.1 INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are the 2 most common obstructive airway diseases (OADs). Recently a new phenotype, referred to as asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap (ACO), has been identified with its first guidelines for treatment and management in effect since 2015.[1] The Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) described asthma-COPD overlap as "persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD", and pointed out that asthma-COPD overlap includes different clinical phenotypes with several underlying mechanisms.[2] Whilst there have been varied definitions of asthma-COPD overlap in the literature, most of the discussions on asthma-COPD overlap have primarily focused on reviewing the evidential features of asthma and COPD coexisting at biological,[3] epidemiological levels,[4, 5] and on its clinical significance.[6, 7]

Just as the basic definitions of asthma and COPD are still debatable,[8, 9] the primary definition of asthma-COPD overlap is not yet clear. The first guideline for identification of asthma-COPD overlap was proposed in the combination of GINA and GOLD guidelines in 2015.[1] The Spanish COPD guideline (GesEPOC) was the first clinical practice guideline to recognize the asthma-COPD overlap phenotype, calling it the mixed asthma-COPD phenotype.[10] The GesEPOC and the Spanish Guideline on the Management of Asthma (GEMA) recently came out with a consensus to unify the criteria for the diagnosis of asthma-COPD overlap.[11] The GesEPOC/GEMA consensus defined

the presence of asthma-COPD overlap in a given patient based on three elements: significant smoking exposure, chronic airflow limitation and asthma.

In advancing a clearer diagnostic criteria for asthma-COPD overlap, Miravitlles[12] proposed "the five commandments of asthma-COPD overlap diagnosis": 1) A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma. 2) A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from "pure" COPD, which he categorized as the most frequent type of patient with ACO. 3) Some patients who smoke and develop COPD may have a genetic type 2 immune responses (Th2) background (even in the absence of a previous history of asthma), which can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO. 4) A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV_1 change) has reversible COPD but is not an asthmatic. Finally, on the 5^{th} commandment, a patient with COPD and a very positive bronchodilator test (>400 mL FEV_1 change) is more likely to have some features of asthma and could also be classified as ACO.

In asthma-COPD overlap, combination pharmacotherapy treatment consisting of long-acting β_2-agonists/inhaled corticosteroids (ICS) may be the first choice of treatment in patients with a history suggestive of the overlap disease.[2] In spite of the uncertainties concerning asthma-COPD overlap definition, there is broad agreement that patients with features of both asthma and COPD experience frequent exacerbations, have poor quality of life, a more rapid decline in lung function and high mortality, and consume a disproportionate amount of healthcare resources than asthma or COPD alone.[1]

There are various kinds of healthcare databases accessible for healthcare research. These databases generally fall into two divisions; administrative (e.g., hospital billing data) and electronic health records (EHRs).[13] The increased use of these two categories of databases has added to the popularity of population-based epidemiology and health outcomes research studies. However, the basic functional use of healthcare databases includes but is not limited to hospital billing, administration, provision of care, laboratory procedures, pharmacy dispensing and physician practice.[13] Recently, there has been an increased use of these healthcare databases for epidemiological studies and population outcome studies as researchers have identified these databases as very useful avenues for clinical research.[14-16]

These databases primarily collect longitudinal information in connection with a patient's demographics, important information regarding healthcare resource utilization such as hospitalizations, referrals to specialists or secondary care, drug prescription, laboratory tests, imaging and lifestyle.[17, 18] Thus, the types of information contained in these databases have become extremely important. The availability of these healthcare databases provide great opportunity and benefits over several major limitations of randomized controlled trials (RCTs) such as lower cost, increased generalizability and increased statistical power due to larger sample size.[13] The applications of these healthcare datasets in observational studies have become desirable as they are well-suited in hypothesis generation and in advancing previously tested hypotheses.[13]

Algorithms to identify cases in these hierarchically coded healthcare databases can be developed by a single code, combination of multiple codes or sets of codes. As noted by Nissen et al [19] the accuracy of diagnoses recorded in these large databases may be

low, which would introduce bias into studies using the data. They developed an algorithm, to increase the ability to identify case definitions for asthma in the Clinical Practice Research Datalink (CPRD) database, using a diagnosis plus spirometry plus specific medication. They found out that extra information on asthma medication prescription (PPV 83.3%), evidence of reversibility testing (PPV 86.0%) or a combination of all three selection criteria (PPV 86.4%) did not result in a higher PPV.[19] Even though validation of codes or algorithms to correctly identify patients with diseases or medical conditions may be time consuming and labour intensive, unless these algorithms are validated for research, the quality of studies generated from EHRs may be debatable. Identification of properly-validated algorithms to identify patients with different health states (diseases and conditions) will inform more accurate patient selection in future studies.

To determine the validity of any health outcome, a clear understanding of the data and the algorithms to be used to identify health outcomes in these databases is required. This can be ascertained using questionnaires completed by a patient or physician, medical charts review, medical notes, manual review or an independent second database.[19, 20] We will conduct a systematic review to evaluate the current body of evidence that have used algorithms or codes based on information in healthcare databases to identify patients with asthma-COPD overlap.

6.1.2 RESEARCH QUESTION

The primary objectives of this systematic review are to evaluate and summarize current methods of identifying asthma-COPD overlap.

Specifically, the questions of interest are;

1. What type of healthcare databases have been used to obtain information on the diagnosis of asthma-COPD overlap?
2. Which algorithms have been extensively used to define and correctly identify patients with asthma-COPD overlap?
3. What are the estimates (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV]) of these algorithms to correctly identify patients with asthma COPD overlap in healthcare databases?

6.2 METHODS

6.2.2 LITERATURE SEARCH

MEDLINE, EMBASE and the Web of Science will be systematically searched for published peer-reviewed articles. We will utilize a search strategy based on a combination of: (1) key-words, Medical Subject Headings (MeSH) and title/abstract (tiab) to identify records in association with “asthma AND COPD”; (2) terms to identify articles probably containing validity or accuracy measures and (3) a search strategy likely to contain studies on the combination of terms and asthma-COPD overlap definitions by Miravitllesc[12] Don Sin *et al*[21] and GesEPOC.[11] In addition, reference lists of

primary articles will be reviewed to find relevant articles. An experienced librarian from the Health Science Library (HSL) of Memorial University along with one of the authors will independently conduct a comprehensive search in MEDLINE, EMBASE and web of science to identify potential articles. The MEDLINE, EMBASE and web of science searches will be independently reviewed by a more senior librarian and another one of the authors.

This systematic review protocol has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and the PRISMA flow diagram from Moher *et al*[22] can be found in **Figure 1.3**. The PRISMA flow diagram will allow for more transparent flow of information through the different phases of our systematic review. This protocol has been published in the PROSPERO International Prospective Register of Systematic Reviews with registration number CRD42018087472.

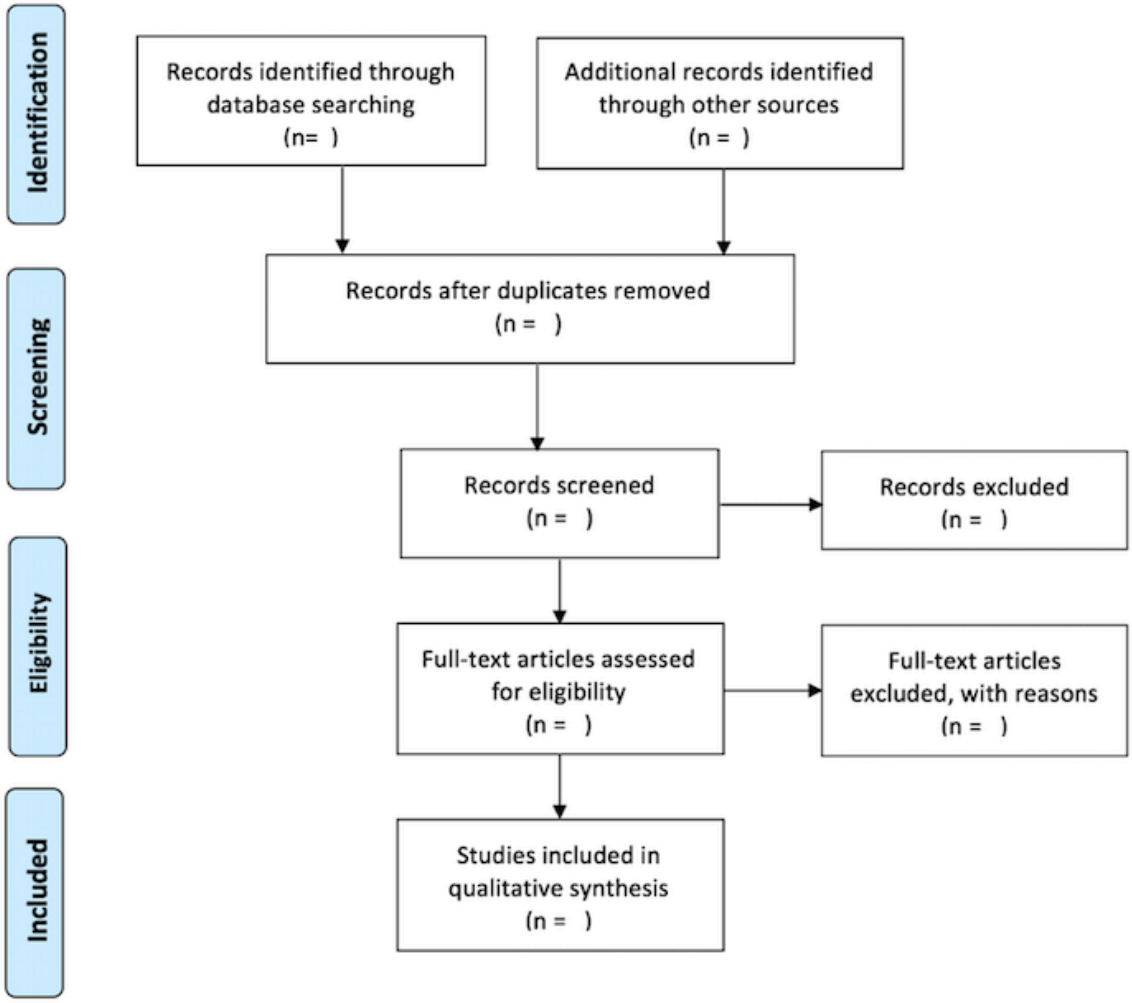


Figure 6.1: Study Screening Process: PRISMA flow diagram from Moher et al.

6.2.3 INCLUSION CRITERIA

Any full-text, peer-reviewed articles published in English before September 2018, that validated the recording of asthma COPD overlap in a healthcare database will be considered for inclusion. We aim to focus on databases, in which the diagnosis of asthma-COPD overlap is primarily based on clinical features, spirometry results, prescription

data, radiography and laboratory data. The included studies will be considered if the validated algorithm is compared with an external reference standard such as questionnaires completed by physicians, medical charts review, medical notes, manual review or an independent second database. For each study, we require the presence of at least one study measure such as specificity, sensitivity, positive predictive value and negative predictive value. Also, for our inclusion criteria, we will include algorithms developed from single codes, algorithms formed of multiple case characteristics (e.g. disease code plus spirometry code plus prescription code) and algorithms generated by natural language processing (NLP) or machine-learning (e.g. Read code, ICD-9 or ICD-10).

6.2.4 EXCLUSION CRITERIA

Studies without validation of asthma-COPD overlap recording, conference abstracts, surveys and disease registries will be excluded. In addition, studies involving pharmacovigilance databases (spontaneous reporting, signal detection) will be excluded.

6.2.5 SELECTION PROCESSES

Two independent reviewers will scan titles and abstracts of identified articles and relevant articles will be retrieved based on our research questions and inclusion/exclusion criteria. Discrepancies in determining whether the study met our inclusion criteria during the full-text review will be resolved by consensus between the reviewers. If a consensus could not be reached, arbitration will be decided by a third reviewer.

6.2.6 DATA EXTRACTION

The following information will be extracted from each of the included studies by two reviewers independently.

1. Study characteristics (including title, year, country, journal of publication, date of publication and information on the author);
2. Data source, population;
3. Type of healthcare database used (including electronic health record, hospitalization discharge data, etc);
4. Sample characteristics;
5. Clinical event or outcome;
6. Algorithms; the modality of algorithm development (eg, using logistic regression, Classification and Regression Trees, expert opinion etc.,);
7. Gold standard of validation;
8. Characteristic of the test measure(s) used to determine validity;

6.2.7 RISK OF BIAS ASSESSMENT

Quality assessment of the design and methods on all included primary studies will be assessed using a checklist developed by Benchimol *et al*. [23] Using Standards for Reporting of Diagnostic accuracy (STARD) [24] criteria as a guide, they created a 40-item checklist of items with which to assess the quality of validation studies of health administrative data and to report studies that validated algorithms or codes for identifying patients with different health states (diseases and conditions).

Two reviewers will independently assess the quality of these studies and report potential bias in a descriptive form. Disagreements will be resolved by discussion or arbitration with a third reviewer. However, no subgroup analysis or publication bias assessment is anticipated.

6.2.8 DATA SYNTHESIS

All records will be de-duplicated and screened using Covidence (https://www.covidence.org); a web-based software platform that streamlines the production of systematic reviews and EndNote (Version X7, Thomson Reuters) software will be used to manage the study articles and references. An overview for the validation of asthma-COPD overlap recording will be summarized in narrative composition and in tables describing the methods and results of the included studies. Possibly, validation statistic will be aggregated and stratified by kind of healthcare database, the type of EHR coding and country of origin. However, no formal meta-analysis is planned. These results may include specificity, sensitivity, PPV and NPV of studies that met our inclusion criteria. Where they are not reported, these test results such as 95% CI, PPV and NPV will be calculated if possible.

6.3 CONCLUSION

Preliminary systematic searches of databases revealed that no single study has validated asthma-COPD overlap in any kind of database either administrative or electronic health records.

CHAPTER 7

VALIDATION OF ASTHMA-COPD OVERLAP SYNDROME IN THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

This is an ongoing project to assess the utility of various search algorithms to best locate GP confirmed asthma-COPD overlap cases in United Kingdom electronic primary care records and to validate these algorithms has been stalled due to COVID-19 pandemic. The overall aim of this study is to determine the positive predictive value (PPV) of four algorithms among patients assumed to have been diagnosed with asthma-COPD overlap syndrome within CPRD GOLD.

Data collections which started very well eventually broke down as GPs are not allowed to see patients in person in the United Kingdom.

Currently, there is no definite time schedule when GPs will start seeing individual patients in person.

CHAPTER 8

GENERAL DISCUSSION AND CONCLUSION

8.1. SUMMARY OF RESEARCH

The objectives of this research were:

- To determine the comparative safety and effectiveness of current pharmacotherapies consisting of LABA and/or ICS in patients with asthma–COPD overlap.
- To investigate gender differences in new-users of ICS, SABA, LABA, ICS/LABA, SAMA or LAMA among patients with asthma, COPD or asthma-COPD overlap.
- To determine whether the use of inhaled LABA, SABA or combination therapy of inhaled corticosteroids ICS/LABA compared with ICS, SAMA or LAMA is associated with major adverse cardiovascular events.
- To determine whether new use of LABA, SABA or ICS/LABA, when compared with use of ICS, LAMA or SAMA is associated with an increased risk of all-cause-mortality or hospitalization for pneumonia in patients with asthma, COPD and asthma-COPD overlap.

Primarily, this research work focused on "Pharmaco-epidemiological study of cardio-respiratory safety of β2-agonists for the treatment and management of asthma, COPD and

asthma-COPD overlap". Using United Kingdom Clinical Practice Research Datalink (CPRD) of over 250 000 patient's data, I conducted a retrospective cohort study to investigate gender differences in new-users of ICS, SABA, LABA, ICS/LABA, SAMA or LAMA and a nested case-control study to test the association between β2-agonist-based medications and safety events for cardio-respiratory outcomes. These cardio-respiratory outcomes include all-cause mortality, arrhythmia, heart failure, myocardial infarction, pneumonia, stroke and cardiovascular death. Furthermore, I performed a systematic review of the literature to provide a general overview of what the comparative effectiveness and safety of inhaled corticosteroids and bronchodilators and meta-analyzed the association between LABA vs non-LABA use and ICS/LABA vs no use and the risk of myocardial infarction and death/hospitalization respectively.

8.2 SUMMARY OF RESULTS

The findings identified in this research are supported, to different degrees, by evidence presented in the literature review and individual chapters. The results presented in this thesis are based on detailed assessment of the project aims and objectives. Findings from the systematic review and meta-analyses on comparative safety and effectiveness of current pharmacotherapies consisting of LABA and/or ICS in patients with asthma–COPD overlap revealed that LABA is associated with decreased risk of myocardial infarction in comparison to non-LABA; and the combination therapy of ICS/LABA appears to reduce the risk of death or hospitalization compared to placebo.[1]

In a cohort study of new users or inhaled bronchodilators and ICS, we observed significant gender differences in new-users of ICS, ICS/LABA, LABA, LAMA, SABA and SAMA among obstructive airways disease patients including asthma, COPD and asthma-COPD overlap from January-01, 1998 to July-31, 2018.[2] In this particular study, further adjustment for proxies of disease severity, calendar year, smoking and material deprivation did not change the association by gender. This study received considerable attention of over 137 manuscript downloads and 386 views within two weeks of being published. This study was novel and revealed GPs potential unconscious bias in management of obstructive airway disease patients on the premise that no differential preferences between females and males have been suggested in clinical practice guidelines globally on the basis of available treatment and management of asthma, COPD or asthma-COPD overlap.[3-5]

The research to estimate the risk of all-cause mortality and CR safety outcomes associated with exposure to β2-agonists among cohorts of new users of bronchodilator

medications diagnosed with asthma, COPD and asthma-COPD overlap was directed towards the aspects of observational study of real-world clinical settings. This study being a safety outcome research, it is believed a randomized controlled trial study, cannot address this question fully. Our findings suggest, new initiation of LABA, SABA or ICS/LABA compared to SAMA in COPD or SABA compared to ICS in asthma-COPD overlap is associated with an increased risk of MACE. However, among asthmatics, β2-agonists compared to ICS were not associated with risk of MACE. In assessing individual components of MACE, our findings revealed no association between the use of β2-agonists-based drugs and incidences of the individual components.

For all-cause mortality, patients with COPD who newly started inhaled β2-agonists-based, the use of either SABA or LABA monotherapy was associated with increased risk in mortality compared with ICS monotherapy. In regard to risk of pneumonia, our findings indicate that use of β2-agonists-based drugs (SABA or ICS/LABA) was not associated with an increased risk of pneumonia compared with use of ICS among patients diagnosed with asthma alone or COPD alone.

8.3 STRENGTHS OF THE RESEARCH

The research work included in this thesis has several strengths. The strengths include:

- The size of our study population which consists of more than 250 000 patients. Thus, this large random population-based data and nested case-control analysis methodology serve to minimize the extent to which bias and confounders affect our outcome. Also, study power calculations using type I error rate of 5%, conducted using STATA and command prompt *stpower cox* indicated that this research will have at least a 100% power to detect a 5.20% difference in CR outcomes associated with SABAs or 76.0% power to detect a 5.90% difference in CR outcomes associated with LABA (see **APPENDIX II** for power calculations).
- Another strength is the quality of our cohort and its robust capture of medication data over 14 million acceptable patients of high quality in the CPRD database assessed.[6]
- Unlike other databases, the CPRD database is endowed with several variables which were used to control for potential confounding and also in our matching variables. Even though, our study is observational in nature and thus susceptible to potential confounding, this attribute of CPRD database enabled us to employ rigorous matching and statistical confounding adjustment to minimize residual confounding.
- This research study incorporated the use of a new-user design thereby eliminating biases related to the inclusion of prevalent users in all our objectives assessed using the CPRD database.

8.4 LIMITATION

Measurement error can be categorized into classification error or misclassification. However, due to the nature of my study, I will like to do a brief discussion on misclassification bias that may be inherent in my study and how this bias was resolved using the CPRD database. The United Kingdom Clinical Practice Research Datalink (CPRD), database was the first European electronic health database established in Europe (previously known as Value Added Medical Products [VAMP] database and then the General Practice Research Database [GPRD]). CPRD was established in 1987 as a tool for conducting public health research. Data quality checks to eliminate bias are performed by CPRD databases at regular intervals on three levels: (1) practitioner recording, (2) data extraction, and (3) maintenance of the database. [146]

Nondifferential exposure misclassification usually occurs when the proportion of patients misclassified on exposure does not depend on the status of the variable being analyzed as per disease status. [147] More so, nondifferential disease misclassification occurs when the proportion of patients misclassified on disease does not depend on the status of these patients with respect to their exposure. Consequently, bias introduced by independent nondifferential misclassification of a binary exposure or disease is predictable in direction, namely, toward the null value leading to insignificant result or effects. [147]

In my gender study, the exposure variable is sex (male or female). Thus, you are either a male or a female. It is less subject to the effect of misclassification. The three obstructive airway diseases types (including asthma, COPD or asthma-COPD overlap) in

this study was used as a stratification variable to study the medication prescription difference between males and females in each of the diseases. The main outcome variable was medication prescriptions, which are determined by gemscript codes. The misclassification of medication prescriptions is more likely to be non-differential misclassification between males and females, which leads to our statistical tests toward null hypothesis. The validation study using CPRD databases showed the PPV of asthma and COPD recording in the CPRD to be above 83%.

For the MACE and all-cause-mortality/pneumonia study of my thesis project, the main exposure variable is medication prescription (ICS, ICS/LABA, LABA, LAMA, SABA or SAMA) and the main outcome variables are MACE and all-cause-mortality/pneumonia. Again, the three obstructive airways diseases types (Asthma, COPD and ACO) was used as a stratification variable in all these studies. The misclassification of our outcome variables (MACE, all-cause-mortality/pneumonia) are less likely to happen because these outcome events are based on hospitalization information and official death certificate. The misclassification of our main exposure variable (medication prescriptions) could happen in any electronic datasets. However, it is more likely to be non-differential misclassification which is predicable in the direction, namely, towards null value.

The effects of nondifferential misclassification of disease are similar to that of nondifferential misclassification of exposure. In addition, the bias in the risk difference is a simple function of the sensitivity and specificity which are used to calculate positive predictive value. Nondifferential misclassification of a binary disease outcome usually produce bias toward the null, also leading to nonsignificant results. My study produced

significant results in major adverse cardiovascular event and also all-cause-mortality outcomes assessed. Therefore, the impact of nondifferential misclassification is very low in my study.

The research study presented in this thesis also has several other limitations. These include:

- The results from the systematic review and meta-analysis of the safety and effectiveness of current pharmacotherapies consisting of LABA and/or ICS in patients with asthma–COPD overlap should be interpreted with caution due to the small number of studies included in the final reviews and the meta-analyses.[1]
- A potential limitation is the possibility for medication misclassification as the CPRD database does not capture prescriptions dispensed and the likelihood whether those medications dispensed were actually adhered to.
- An important limitation is the lack of information on diagnostic tests such as eosinophils, neutrophils and lung function tests. This information were either unavailable or missing in entirety.
- The description and possible definition of patients with asthma-COPD overlap were entirely based on CPRD coded description and those found in the literature. Caution must therefore be exercised when interpreting results from patients with the overlap disease.

8.5 IMPLICATION FOR FUTURE RESEARCH

There are a number of possible directions that future research may take, but the following recommendations would begin to provide a firm evidence base for treatment recommendations especially in the asthma-COPD overlap patients:

- Validation of asthma-COPD overlap patients in real-world clinical database setting. Research in this direction will not only promote efficient and clinical identification of these patients but will also establish treatment guidelines for this group of patients whose conditions are thought to be worse than asthma or COPD alone patients.
- Possible double-blind randomized controlled trials comparing response to common β2-agonists and/or ICS in COPD and asthma-COPD overlap, as determined by blood eosinophil levels and lung function tests. Possibly interventions would include:
    - Inhaled corticosteroid - including long term response and
    - ICS/LABA therapies and other combination double and triple therapies.

One critical clinical question which the above studies would help to answer is the role of ICS in patients with the asthma-COPD overlap and COPD patients. Our study provides some insight suggestive of the fact that the use of ICS/LABA in asthma-COPD overlap was not associated with increased risk of pneumonia. It is therefore clinically prudent to look at potential beneficial role of ICS and/or β2-agonists in these overlap group of patients.

8.6 CONCLUSION

This research has confirmed the existence of an overall gender difference in first time drug use to treat patients with asthma, COPD or asthma-COPD overlap who were new-users of inhaled pharmacotherapies. Consequently, COPD treatment initiation with LABA, SABA or ICS/LABA and initiating SABA treatment for asthma-COPD overlap within 30 days is associated with risk of MACE. Also, starting LABA monotherapy or SABA monotherapy treatment was associated with an increased risk of all-cause mortality in patients with COPD. In contrast, among asthmatics, β_2-agonists were not associated with risk of MACE. We also observed no association with SABA, LABA or LABA/ICS use and the risk of pneumonia in patients with asthma, COPD or asthma-COPD overlap.

REFERENCES

1. Postma, D.S., et al., *Revisiting the Dutch hypothesis.* Journal of Allergy and Clinical Immunology, 2015. **136**(3): p. 521-529.
2. Postma, D.S. and H.M. Boezen, *Rationale for the Dutch hypothesis. Allergy and airway hyperresponsiveness as genetic factors and their interaction with environment in the development of asthma and COPD.* Chest, 2004. **126**(2 Suppl): p. 96S-104S; discussion 159S-161S.
3. Postma, D.S., et al., *Asthma and chronic obstructive pulmonary disease: common genes, common environments?* Am J Respir Crit Care Med, 2011. **183**(12): p. 1588-94.
4. Suissa, S., et al., *Inhaled corticosteroids in COPD and the risk of serious pneumonia.* Thorax, 2013. **68**(11): p. 1029-36.
5. Kraft, M., *Asthma and chronic obstructive pulmonary disease exhibit common origins in any country!* Am J Respir Crit Care Med, 2006. **174**(3): p. 238-40; discussion 243-4.
6. Holgate, S.T., *A brief history of asthma and its mechanisms to modern concepts of disease pathogenesis.* Allergy Asthma Immunol Res, 2010. **2**(3): p. 165-71.
7. Karamanou, M. and G. Androutsos, *Aretaeus of Cappadocia and the first clinical description of asthma.* Am J Respir Crit Care Med, 2011. **184**(12): p. 1420-1.
8. *The Global Asthma Report 2018, Global Asthma Network, Auckland, New Zealand (2018).*

https://scholar.google.com/scholar?q=The%20Global%20Asthma%20Report%202018. **Accessed on February 14th, 2021**.

9. Canada, S., *http://www.statcan.gc.ca.qe2a-proxy.mun.ca/pub/82-625-x/2015001/article/14179-eng.htm.* Statistics CanadaAsthma, 2014 (2015) Accessed 6th January, 2021.

10. McCracken, J.L., et al., *Diagnosis and Management of Asthma in Adults: A Review.* JAMA, 2017. **318**(3): p. 279-290.

11. GINA, *Global Initiative for Asthma, 2020 update.* https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf Accessed on 29th December, 2020. **Updated 2020**.

12. C., B., *An Essay on Bronchitis: With a Supplement Containing Remarks on Simple Pulmonary Abscess, Etc.* 2nd ed. London: J Callow.

13. *A Treatise on the Diseases of the Chest, and on Mediate Auscultation.* Med Chir Rev, 1829. **10**(20): p. 420-422.

14. Sakula, A., *R T H Laënnec 1781--1826 his life and work: a bicentenary appreciation.* Thorax, 1981. **36**(2): p. 81-90.

15. Briscoe, W.A. and E.S. Nash, *THE SLOW SPACE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASES.* Ann N Y Acad Sci, 1965. **121**: p. 706-22.

16. *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1789-1858.

17. Canada, S., *Statistics Canada . Canada at a glance—2018—population.* Available from: https://www150-statcan-gc-ca.qe2a-proxy.mun.ca/n1/pub/12-581-x/2018000/pop-eng.htm. **Accessed on January 6, 2021**.

18. Prevention., C.f.D.C.a., *Centers for Disease Control and Prevention. National Center for Health Statistics Data brief 63: Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998–2009. [Accessed on Jan 1 2021].* . http://www.cdc.gov.qe2a-proxy.mun.ca/nchs/data/databriefs/db63_tables.pdf#2.

19. Fletcher, C. and R. Peto, *The natural history of chronic airflow obstruction.* Br Med J, 1977. **1**(6077): p. 1645-8.

20. Fletcher, C.M., *The natural history of chronic bronchitis.* Community Health (Bristol), 1975. **7**(2): p. 70-8.

21. Peto, R., et al., *The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation.* Am Rev Respir Dis, 1983. **128**(3): p. 491-500.

22. GOLD, *copd gold guidelines 2020.* https://goldcopd.org/wp-content/uploads/2020/03/GOLD-2020-POCKET-GUIDE-ver1.0_FINAL-WMV.pdf, 2020 Report. **Accessed December 30th, 2020**.

23. Vogelmeier, C.F., et al., *Goals of COPD treatment: Focus on symptoms and exacerbations.* Respir Med, 2020. **166**: p. 105938.

24. ACOS, *Asthma-COPD overlap syndrome.* https://goldcopd.org/wp-content/uploads/2016/04/GOLD_ACOS_2015.pdf Accessed on the 24th January, 2019.

25. Postma, D.S. and K.F. Rabe, *The Asthma-COPD Overlap Syndrome.* N Engl J Med, 2015. **373**(13): p. 1241-9.

26. Leung, J.M. and D.D. Sin, *Asthma-COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets.* BMJ, 2017. **358**: p. j3772.

27. Miravitlles, M., et al., *Spanish COPD Guidelines (GesEPOC) 2017. Pharmacological Treatment of Stable Chronic Obstructive Pulmonary Disease.* Archivos de Bronconeumologia, 2017. **53**(6): p. 324-335.

28. Nanda, A. and A.N. Wasan, *Asthma in Adults.* Med Clin North Am, 2020. **104**(1): p. 95-108.

29. Barisione, G., et al., *Beta-Adrenergic Agonists.* Pharmaceuticals (Basel), 2010. **3**(4): p. 1016-1044.

30. Raherison, C. and P.O. Girodet, *Epidemiology of COPD.* Eur Respir Rev, 2009. **18**(114): p. 213-21.

31. Gentry, S. and B. Gentry, *Chronic Obstructive Pulmonary Disease: Diagnosis and Management.* Am Fam Physician, 2017. **95**(7): p. 433-441.

32. Suissa, S., S. Dell'Aniello, and P. Ernst, *Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study.* Lancet Respir Med, 2018. **6**(11): p. 855-862.

33. Miravitlles, M., *Diagnosis of asthma-COPD overlap: Is it possible a global definition?* Pulmonology, 2018. **24**(3): p. 143-145.

34. Kim, S.H., et al., *Perceptions of severe asthma and asthma-COPD overlap syndrome among specialists: A questionnaire survey.* Allergy, Asthma and Immunology Research, 2018. **10**(3): p. 225-235.

35. Plaza, V., et al., *Consensus on the Asthma-COPD Overlap Syndrome (ACOS) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA).* Arch Bronconeumol, 2017. **53**(8): p. 443-449.

36. Salpeter, S.R., *Cardiovascular safety of beta(2)-adrenoceptor agonist use in patients with obstructive airway disease: a systematic review.* Drugs Aging, 2004. **21**(6): p. 405-14.

37. Paggiaro, P. and E. Bacci, *Montelukast in asthma: a review of its efficacy and place in therapy.* Ther Adv Chronic Dis, 2011. **2**(1): p. 47-58.

38. Morjaria, J.B., A. Rigby, and A.H. Morice, *Inhaled Corticosteroid use and the Risk of Pneumonia and COPD Exacerbations in the UPLIFT Study.* Lung, 2017. **195**(3): p. 281-288.

39. Hines, K.L. and R.S. Peebles, Jr., *Management of the Asthma-COPD Overlap Syndrome (ACOS): a Review of the Evidence.* Curr Allergy Asthma Rep, 2017. **17**(3): p. 15.

40. Feng, J.X., et al., *Relationship between Fractional Exhaled Nitric Oxide Level and Efficacy of Inhaled Corticosteroid in Asthma-COPD Overlap Syndrome Patients with Different Disease Severity.* Journal of Korean medical science, 2017. **32**(3): p. 439-447.

41. Hsu, E. and T. Bajaj, *Beta 2 Agonists*, in *StatPearls*. 2021, © 2021, StatPearls Publishing LLC.: Treasure Island FL.

42. Abosamak, N.E.R. and M.H. Shahin, *Beta 2 Receptor Agonists/Antagonists*, in *StatPearls*. 2021, © 2021, StatPearls Publishing LLC.: Treasure Island FL.

43. Billington, C.K., R.B. Penn, and I.P. Hall, *beta2 Agonists.* Handb Exp Pharmacol, 2017. **237**: p. 23-40.

44. Cazzola, M., M.G. Matera, and C.F. Donner, *Inhaled beta2-adrenoceptor agonists: cardiovascular safety in patients with obstructive lung disease.* Drugs, 2005. **65**(12): p. 1595-610.

45. Bristow, M.R., *beta-adrenergic receptor blockade in chronic heart failure.* Circulation, 2000. **101**(5): p. 558-69.

46. Bristow, M.R., et al., *Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure.* Circ Res, 1986. **59**(3): p. 297-309.

47. Xiao, R.P., et al., *Recent advances in cardiac beta(2)-adrenergic signal transduction.* Circ Res, 1999. **85**(11): p. 1092-100.

48. Sears, M.R., *Adverse effects of beta-agonists.* J Allergy Clin Immunol, 2002. **110**(6 Suppl): p. S322-8.

49. Andreas, S., et al., *Effect of long-acting β(2)-agonists olodaterol and formoterol on heart rate and blood pressure in chronic obstructive pulmonary disease patients.* Pulm Pharmacol Ther, 2018. **52**: p. 1-6.

50. Salpeter, S.R., T.M. Ormiston, and E.E. Salpeter, *Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis.* Chest, 2004. **125**(6): p. 2309-21.

51. Tricco, A.C., et al., *Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis.* BMJ Open, 2015. **5**(10): p. e009183.

52. Lulich, K.M., et al., *Adverse reactions to beta 2-agonist bronchodilators.* Med Toxicol, 1986. **1**(4): p. 286-99.

53. Edgell, H., et al., *Short-term cardiovascular and autonomic effects of inhaled salbutamol.* Respir Physiol Neurobiol, 2016. **231**: p. 14-20.

54. Au, D.H., et al., *The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists.* Am J Respir Crit Care Med, 2000. **161**(3 Pt 1): p. 827-30.

55. Zhang, B., et al., *The pattern of risk of myocardial infarction in patients taking asthma medication: a study with the General Practice Research Database.* J Hypertens, 2009. **27**(7): p. 1485-92.

56. Fingleton, J., et al., *Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults.* J Allergy Clin Immunol, 2015. **136**(3): p. 601-9.

57. Beasley, R., et al., *Call for withdrawal of LABA single-therapy inhaler in asthma.* Lancet, 2010. **376**(9743): p. 750-1.

58. Kuehn, B.M., *FDA offers advice to reduce risks of long-acting beta-agonists in asthma care.* JAMA, 2010. **303**(14): p. 1353-4.

59. Sears, M.R., *Safety of long-acting beta-agonists: are new data really required?* Chest, 2009. **136**(2): p. 604-607.

60. Cates, C.J. and M.J. Cates, *Regular treatment with salmeterol for chronic asthma: serious adverse events.* Cochrane Database Syst Rev, 2008(3): p. CD006363.

61. Wood-Baker, R., B. Cochrane, and M.T. Naughton, *Cardiovascular mortality and morbidity in chronic obstructive pulmonary disease: the impact of bronchodilator treatment.* Intern Med J, 2010. **40**(2): p. 94-101.

62. Soler-Cataluna, J.J., et al., *Consensus document on the overlap phenotype COPD-asthma in COPD.* Arch Bronconeumol, 2012. **48**(9): p. 331-7.

63. Louie, S., et al., *The asthma-chronic obstructive pulmonary disease overlap syndrome: pharmacotherapeutic considerations.* Expert Rev Clin Pharmacol, 2013. **6**(2): p. 197-219.

64. Menezes, A.M.B., et al., *Increased risk of exacerbation and hospitalization in subjects with an overlap phenotype: COPD-asthma.* Chest, 2014. **145**(2): p. 297-304.

65. Sin, D.D., et al., *What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion.* Eur Respir J, 2016. **48**(3): p. 664-73.

66. van Boven, J.F., et al., *Comorbidome, Pattern, and Impact of Asthma-COPD Overlap Syndrome in Real Life.* Chest, 2016. **149**(4): p. 1011-20.

67. Koblizek, V., et al., *Phenotypes of COPD patients with a smoking history in Central and Eastern Europe: the POPE Study.* Eur Respir J, 2017. **49**(5).

68. Asthma, G.I.f., *Global Strategy for Asthma Management and Prevention* Availbable from: www. ginasthma. org, 2018 Global Initiative for Asthma. **2018 Update**.

69. Afonso, A., et al., *A methodological comparison of two European primary care databases and replication in a US claims database: inhaled long-acting beta-2-*

agonists and the risk of acute myocardial infarction. Eur J Clin Pharmacol, 2016. **72**(9): p. 1105-16.

70. Brode, S.K., et al., *The risk of mycobacterial infections associated with inhaled corticosteroid use.* European Respiratory Journal, 2017. **50**(3).
71. Gershon, A.S., et al., *Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease.* JAMA - Journal of the American Medical Association, 2014. **312**(11): p. 1114-1121.
72. Hubbard, R., et al., *Use of inhaled corticosteroids and the risk of fracture.* Chest, 2006. **130**(4): p. 1082-8.
73. Ishiura, Y., et al., *A comparison of the efficacy of once-daily fluticasone furoate/vilanterole with twice-daily fluticasone propionate/salmeterol in asthma-COPD overlap syndrome.* Pulmonary Pharmacology and Therapeutics, 2015. **35**: p. 28-33.
74. Lim, H.S., et al., *Responsiveness to inhaled corticosteroid treatment in patients with asthma-chronic obstructive pulmonary disease overlap syndrome.* Annals of Allergy, Asthma and Immunology, 2014. **113**(6): p. 652-657.
75. Magnussen, H., et al., *Improvements with tiotropium in COPD patients with concomitant asthma.* Respiratory Medicine, 2008. **102**(1): p. 50-56.
76. Su, V.Y.F., et al., *Use of ICS/LABA Combinations or LAMA Is Associated with a Lower Risk of Acute Exacerbation in Patients with Coexistent COPD and Asthma.* Journal of Allergy and Clinical Immunology: In Practice, 2018.

77. Uddin, M.J., et al., *Evaluating different physician's prescribing preference based instrumental variables in two primary care databases: a study of inhaled long-acting beta2-agonist use and the risk of myocardial infarction.* Pharmacoepidemiol Drug Saf, 2016. **25 Suppl 1**: p. 132-41.

78. Cazzola, M., et al., *β2-agonist therapy in lung disease.* Am J Respir Crit Care Med, 2013. **187**(7): p. 690-6.

79. Cazzola, M. and M.G. Matera, *Tremor and β(2)-adrenergic agents: is it a real clinical problem?* Pulm Pharmacol Ther, 2012. **25**(1): p. 4-10.

80. Taylor, D.R., M.R. Sears, and D.W. Cockcroft, *The beta-agonist controversy.* Med Clin North Am, 1996. **80**(4): p. 719-48.

81. Billington, C.K., R.B. Penn, and I.P. Hall, *β(2) Agonists.* Handb Exp Pharmacol, 2017. **237**: p. 23-40.

82. Dong, Y.H., et al., *Comparative Cardiovascular and Cerebrovascular Safety of Inhaled Long-Acting Bronchodilators in Patients with Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study.* Pharmacotherapy, 2016. **36**(1): p. 26-37.

83. Calverley, P.M., et al., *Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease.* N Engl J Med, 2007. **356**(8): p. 775-89.

84. Xia, N., H. Wang, and X. Nie, *Inhaled Long-Acting β2-Agonists Do Not Increase Fatal Cardiovascular Adverse Events in COPD: A Meta-Analysis.* PLoS One, 2015. **10**(9): p. e0137904.

85. Wilchesky, M., et al., *Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study.* Chest, 2012. **142**(2): p. 298-304.

86. Wilchesky, M., et al., *Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort.* Chest, 2012. **142**(2): p. 305-311.

87. Juniper, E.F., et al., *Development and validation of a questionnaire to measure asthma control.* Eur Respir J, 1999. **14**(4): p. 902-7.

88. Gershon, A., et al., *Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease.* JAMA Intern Med, 2013. **173**(13): p. 1175-85.

89. Tashkin, D.P., et al., *A 4-year trial of tiotropium in chronic obstructive pulmonary disease.* N Engl J Med, 2008. **359**(15): p. 1543-54.

90. Lockett, M.F., *DANGEROUS EFFECTS OF ISOPRENALINE IN MYOCARDIAL FAILURE.* Lancet, 1965. **2**(7403): p. 104-6.

91. Busse, W.W., et al., *Combined Analysis of Asthma Safety Trials of Long-Acting β(2)-Agonists.* N Engl J Med, 2018. **378**(26): p. 2497-2505.

92. Herrett, E., et al., *Data Resource Profile: Clinical Practice Research Datalink (CPRD).* Int J Epidemiol, 2015. **44**(3): p. 827-36.

93. Quint, J.K., et al., *Recruitment of patients with Chronic Obstructive Pulmonary Disease (COPD) from the Clinical Practice Research Datalink (CPRD) for research.* NPJ Prim Care Respir Med, 2018. **28**(1): p. 21.

94. Hamilton, W., *Using CPRD data for public health research.* Br J Gen Pract, 2018. **68**(672): p. 334.

95. McDonald, L., et al., *Performing studies using the UK Clinical Practice Research Datalink: to link or not to link?* Eur J Epidemiol, 2018. **33**(6): p. 601-605.

96. Price, D.B., et al., *Comparative Safety Profile of the Fixed-Dose Combination Corticosteroid and Long-acting β(2)-Agonist Fluticasone Propionate/Formoterol Fumarate: A 36-Month Longitudinal Cohort Study in UK Primary Care.* Drugs, 2020. **80**(1): p. 47-60.

97. Amegadzie, J.E., et al., *Gender Differences in Inhaled Pharmacotherapy Utilization in Patients with Obstructive Airway Diseases (OADs): A Population-Based Study.* Int J Chron Obstruct Pulmon Dis, 2020. **15**: p. 2355-2366.

98. Suissa, S., S. Dell'Aniello, and P. Ernst, *Comparative Effectiveness of Initial LAMA versus LABA in COPD: Real-World Cohort Study.* COPD, 2021. **18**(1): p. 1-8.

99. Nissen, F., et al., *Validation of asthma recording in the Clinical Practice Research Datalink (CPRD).* BMJ Open, 2017. **7**(8): p. e017474.

100. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

101. Essebag, V., et al., *Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure.* BMC Med Res Methodol, 2005. **5**(1): p. 5.

102. Suissa, S., *The Quasi-cohort approach in pharmacoepidemiology: upgrading the nested case-control.* Epidemiology, 2015. **26**(2): p. 242-6.

103. Wu, J., et al., *Correlation of Inhaled Long-Acting Bronchodilators With Adverse Cardiovascular Outcomes in Patients With Stable COPD: A Bayesian Network*

Meta-Analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol, 2019. **74**(3): p. 255-265.

104. Li, C., et al., *Relationship of inhaled long-acting bronchodilators with cardiovascular outcomes among patients with stable COPD: a meta-analysis and systematic review of 43 randomized trials.* Int J Chron Obstruct Pulmon Dis, 2019. **14**: p. 799-808.

105. Wang, M.T., et al., *Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study.* JAMA Intern Med, 2018. **178**(2): p. 229-238.

106. Lee, C.H., et al., *Inhaled bronchodilators and the risk of tachyarrhythmias.* Int J Cardiol, 2015. **190**: p. 133-9.

107. De Vries, F., et al., *Use of β2 agonists and risk of acute myocardial infarction in patients with hypertension.* British Journal of Clinical Pharmacology, 2008. **65**(4): p. 580-586.

108. Suissa, S., T. Assimes, and P. Ernst, *Inhaled short acting beta agonist use in COPD and the risk of acute myocardial infarction.* Thorax, 2003. **58**(1): p. 43-6.

109. Martin, R.M., et al., *Risk of non-fatal cardiac failure and ischaemic heart disease with long acting beta 2 agonists.* Thorax, 1998. **53**(7): p. 558-62.

110. Bremner, P., et al., *A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol.* Eur Respir J, 1993. **6**(2): p. 204-10.

111. *Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1736-1788.

112. Gershon, A.S., et al., *Quantifying health services use for chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **187**(6): p. 596-601.

113. Gershon, A.S., et al., *Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in ontario, Canada, 1996 to 2007: a population-based study.* Arch Intern Med, 2010. **170**(6): p. 560-5.

114. Agarwal, S.K. and G.D. Marshall, Jr., *Beta-adrenergic modulation of human type-1/type-2 cytokine balance.* J Allergy Clin Immunol, 2000. **105**(1 Pt 1): p. 91-8.

115. Lazarus, S.C., et al., *Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial.* JAMA, 2001. **285**(20): p. 2583-93.

116. Panina-Bordignon, P., et al., *Beta2-agonists prevent Th1 development by selective inhibition of interleukin 12.* J Clin Invest, 1997. **100**(6): p. 1513-9.

117. Rottenkolber, M., et al., *Time trends of period prevalence rates of patients with inhaled long-acting beta-2-agonists-containing prescriptions: a European comparative database study.* PLoS One, 2015. **10**(2): p. e0117628.

118. Punekar, Y.S., et al., *Rescue medication use as a patient-reported outcome in COPD: a systematic review and regression analysis.* Respir Res, 2017. **18**(1): p. 86.

119. Onishi, K., *Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease.* J Cardiol, 2017. **70**(2): p. 128-134.

120. Suissa, S., S. Dell'Aniello, and P. Ernst, *Long-Acting Bronchodilator Initiation in COPD and the Risk of Adverse Cardiopulmonary Events: A Population-Based Comparative Safety Study.* Chest, 2017. **151**(1): p. 60-67.

121. Fournier, J.P., et al., *Tramadol use and the risk of hospitalization for hypoglycemia in patients with noncancer pain.* JAMA Intern Med, 2015. **175**(2): p. 186-93.

122. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

123. Dransfield, M.T., et al., *Disease severity and symptoms among patients receiving monotherapy for COPD.* Prim Care Respir J, 2011. **20**(1): p. 46-53.

124. Jenkins, C.R., et al., *Reliever salbutamol use as a measure of exacerbation risk in chronic obstructive pulmonary disease.* BMC Pulm Med, 2015. **15**: p. 97.

125. Punekar, Y.S., et al., *Bronchodilator reliever use and its association with the economic and humanistic burden of COPD: a propensity-matched study.* J Med Econ, 2017. **20**(1): p. 28-36.

126. Donohue, J.F., et al., *Correlations between FEV1 and patient-reported outcomes: A pooled analysis of 23 clinical trials in patients with chronic obstructive pulmonary disease.* Pulm Pharmacol Ther, 2018. **49**: p. 11-19.

127. COPD, N.G.o., *National Institute for Health and Care Excellence.* https://www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/chronic-obstructive-pulmonary-disease Accessed on February 16, 2021.

128. Salpeter, S.R., N.S. Buckley, and E.E. Salpeter, *Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD.* J Gen Intern Med, 2006. **21**(10): p. 1011-9.

129. ACOS, *Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and asthma-COPD overlap syndrome.* GINA and GOLD, 2015. **2015 update**.

130. GINA, *Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and asthma-COPD overlap* Global Initiative for astrhma, 2017 update, 2017.

131. Piras, B. and M. Miravitlles, *The overlap phenotype: the (missing) link between asthma and COPD.* Multidiscip Respir Med, 2012. **7**(1): p. 8.

132. Shaya, F.T., et al., *Burden of concomitant asthma and COPD in a Medicaid population.* Chest, 2008. **134**(1): p. 14-9.

133. Shaya, F.T., et al., *Burden of COPD, asthma, and concomitant COPD and asthma among adults: racial disparities in a medicaid population.* Chest, 2009. **136**(2): p. 405-411.

134. Barrecheguren, M., C. Esquinas, and M. Miravitlles, *How can we identify patients with asthma-COPD overlap syndrome in clinical practice?* Arch Bronconeumol, 2016. **52**(2): p. 59-60.

135. Juhn, Y.J., *Risks for infection in patients with asthma (or other atopic conditions): is asthma more than a chronic airway disease?* J Allergy Clin Immunol, 2014. **134**(2): p. 247-57; quiz 258-9.

136. Bhatt, S.P., *Diagnosis of Chronic Obstructive Pulmonary Disease: Breathing New Life into an Old Debate.* Ann Am Thorac Soc, 2018. **15**(2): p. 163-165.

137. Miravitlles, M., et al., *[Spanish COPD Guidelines (GesEPOC): Pharmacological treatment of stable COPD].* Aten Primaria, 2012. **44**(7): p. 425-37.

138. Baarnes, C.B., et al., *Identifying possible asthma-COPD overlap syndrome in patients with a new diagnosis of COPD in primary care.* npj Primary Care Respiratory Medicine, 2017. **27**.

139. Schneeweiss, S. and J. Avorn, *A review of uses of health care utilization databases for epidemiologic research on therapeutics.* J Clin Epidemiol, 2005. **58**(4): p. 323-37.

140. Yeh, J.J., et al., *Association of asthma-chronic obstructive pulmonary disease overlap syndrome with coronary artery disease, cardiac dysrhythmia and heart failure: a population-based retrospective cohort study.* BMJ Open, 2017. **7**(10): p. e017657.

141. de Jong, R.G., et al., *Comparability of the age and sex distribution of the UK Clinical Practice Research Datalink and the total Dutch population.* Pharmacoepidemiol Drug Saf, 2016. **25**(12): p. 1460-1464.

142. Nissen, F., et al., *Validation of asthma recording in electronic health records: a systematic review.* Clin Epidemiol, 2017. **9**: p. 643-656.

143. Sin, D.D., *Asthma-COPD Overlap Syndrome: What We Know and What We Don't.* Tuberc Respir Dis (Seoul), 2017. **80**(1): p. 11-20.

144. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* J Clin Epidemiol, 2009. **62**(10): p. 1006-12.

145. Amegadzie, J.E., et al., *Comparative safety and effectiveness of inhaled bronchodilators and corticosteroids for treating asthma-COPD overlap: a systematic review and meta-analysis.* J Asthma, 2021. **58**(3): p. 344-359.

146. Brian L. Strom; Stephen E. Kimmel and Sean Hennessy.Pharmacopeidemiology. Published by John and Wiley Sons Ltd 2020

147. Kenneth J. Rothman; Sander Greenland and Timothy L. Lash. Modern Epidemiology Third Edition. 2008 Lippincott Williams and Wilkins.

APPENDIX I:

NEWFOUNDLAND AND LABRADOR
HREB
HEALTH RESEARCH ETHICS BOARD

Ethics Office
Suite 200, Eastern Trust Building
95 Bonaventure Avenue
St. John's, NL
A1B 2X5

January 27, 2017

Joseph Emil Amegadzie
Clinical Epidemiology Unit
Medical Educational Center
Room 4M133
Faculty of Medicine
Memorial University

Dear Mr. Amegadzie:

Researcher Portal File # 20171567
Reference # 2017.024

RE: "Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of ß2-agonists for the Treatment and Management of Asthma-COPD Overlap Syndrome"

Your application received a delegated review by a sub-committee of the Health Research Ethics Board (HREB). ***Full approval*** of this research study is granted for one year effective **January 27, 2017**.

This is your ethics approval only. Organizational approval may also be required. It is your responsibility to seek the necessary organizational approval from the Regional Health Authority (RHA) or other organization as appropriate. You can refer to the HREA website for further guidance on organizational approvals.

This is to confirm that the HREB reviewed and approved or acknowledged the following documents (as indicated):

- Application, approved
- Letter to data custodian, approved

MARK THE DATE

This approval will lapse on January 27, 2018. It is your responsibility to ensure that the Ethics Renewal form is submitted prior to the renewal date; you may not receive a reminder. The Ethics Renewal form can be found on the Researcher Portal as an Event form.

If you do not return the completed Ethics Renewal form prior to date of renewal:

- ***You will no longer have ethics approval***
- *You will be required to stop research activity immediately*
- *You may not be permitted to restart the study until you reapply for and receive approval to undertake the study again*

- *Lapse in ethics approval **may result in interruption or termination of funding***

You are solely responsible for providing a copy of this letter, along with your approved HREB application form; **to Research Grant and Contract Services** should your research depend on funding administered through that office.

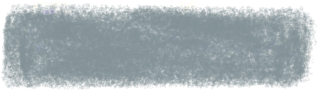
Modifications of the protocol/consent are not permitted without prior approval from the HREB. **Implementing changes without HREB approval may result in your ethics approval being revoked, meaning your research must stop**. Request for modification to the protocol/consent must be outlined on an amendment form (available on the Researcher Portal website as an Event form) and submitted to the HREB for review.

The HREB operates according to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2), the Health Research Ethics Authority Act (HREA Act) and applicable laws and regulations.

You are responsible for the ethical conduct of this research, notwithstanding the approval of the HREB.

We wish you every success with your study.

Sincerely,



Ms. Patricia Grainger (Chair, Non-Clinical Trials Health Research Ethics Board)
Dr. Joy Maddigan (Vice-Chair, Non-Clinical Trials Health Research Ethics Board)

APPENDIX II: Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of β2-agonists for the Treatment and Management of Asthma, COPD, and Asthma-COPD Overlap Syndrome.

ISAC APPLICATION FORM: PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY
1. Study Title[§] (*Please state the study title below)* **Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of β2-agonists for the Treatment and Management of Asthma, COPD, and Asthma-COPD Overlap Syndrome** [§]*Please note: This information will be published on the CPRD's website as part of its transparency policy.*
2. Has any part of this research proposal or a related proposal been previously submitted to ISAC? Yes * ☐ No ☒ **If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*
3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee) Yes* ☒ No ☐ **If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol:* **Canada Respiratory Research Network (CRRN), Ottawa, Canada**

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☒	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☒	Other*	☐

**If Other, please specify the type of study here and in the lay summary below:*

5. Health Outcomes to be Measured§

§*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- **Pneumonia**
- **Stroke**
- **Heart Failure**
- **Arrhythmia**
- **Myocardial Infarction**
- **All-cause mortality**
- **Cardiovascular mortality**
-
-

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Regulatory purposes	☐
Other*	☒		

If Other, please provide further information:* **Completion of PhD Thesis

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Zhiwei Gao; MD, PhD

Assistant Professor, Clinical Epidemiology

Academic Director, Statistics Canada Research Data Center, Memorial University

Memorial University of Newfoundland, Canada

Zhiwei.Gao@med.mun.ca

§*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC ☒ **CV number:** 009_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

8. Affiliation of Chief Investigator (full address)

Room: 4M130, Clinical Epidemiology Unit

Faculty of Medicine, Memorial University

300 Prince Phillip Drive,

St. John's, NL A1B 3V6

PHONE: +1 (709)8646523

9. Corresponding Applicant§

Please state the full name, affiliation(s) and e-mail address below:

Joseph Emil Amegadzie, BSc, MSc, PhD Researcher

Faculty of Medicine

Memorial University of Newfoundland, Canada

Joseph.amegadzie@med.mun.ca

§*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator ☐

CV has been previously submitted to ISAC ☒ **CV number:** 006_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators[§]

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

[§]*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: **William Midodzi, PhD., P. Stat**

Assistant Professor

Clinical Epidemiology Unit

Faculty of Medicine

Memorial University of Newfoundland, Canada

William.Midodzi@med.mun.ca

CV has been previously submitted to ISAC ☒ **CV number:** 007_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: **John-Michael Gamble, BScPharm. MSc., PhD.**

Clinical Associate Professor

University of Waterloo

School of Pharmacy

Kitchener, Ontario, Canada

jm.gamble@uwaterloo.ca

CV has been previously submitted to ISAC ☒ **CV number:** 008_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: **Jamie Farrell, BSc., MD, FRCPC**

Assistant Professor of Medicine (Respirology)

Department of Medicine

Memorial University of Newfoundland, Canada

Jamie.Farrel@med.mun.ca

CV has been previously submitted to ISAC ☒ **CV number:** 010_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator:

CV has been previously submitted to ISAC ☐ **CV number:**

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

This study is supported by a grant from the Canadian Respiratory Research Network (CRRN).

The authors have no conflict of interest to declare.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☒
> 3	☒	☐

Experience/Expertise available	**Yes**	**No**

Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Zhiwei Gao** **William Midodzi**	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **John-Michael Gamble** **William Midodzi** **Zhiwei Gao**	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)*	☐	☒

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1.0 Salpeter, S.R., *Cardiovascular safety of β2-adrenoceptor agonist use in patients with obstructive airway disease: A systematic review.* Drugs and Aging, 2004. **21**(6): p. 405-414.

2.0 Tricco, A.C., et al., *Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis.* BMJ Open, 2015. **5**(10): p. e009183.

3.0 Edgell, H., et al., *Short-term cardiovascular and autonomic effects of inhaled salbutamol.* Respir Physiol Neurobiol, 2016. **231**: p. 14-20.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☐	*Please specify name and country:*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☒	**Canadian Respiratory Research Network, Canada. A national research Network with their largest funders being the Canadian government and charity**
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	**Memorial University, Newfoundland, Canada**
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☐

A data set will be provided by the CPRD[¥€] ☒

CPRD has been commissioned to extract the data and perform the analyses[€] ☐

Other: ☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*

¥*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*

€*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher **Arlene Gallagher** Reference number (where available) Date of contact **30th January, 2017**

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher Reference number (where available) Date of contact

18. Site Location of Data

a) Processing location(s):

Location area - UK / EEA / Worldwide: Center for Health Informatics and Analytics (CHIA)

Organisation address: Center for Health Informatics and Analytics (CHIA)

Faculty of Medicine, Memorial University

300 Prince Phillip Drive,

St. John's, NL A1B 3V6

Canada

https://www.med.mun.ca/CHIA/Home.aspx

Data stored in CHIA IBM Spectrum Scale GPFS storage clusters with access restricted using RBAC (Role-based access control). Access is only allowed to users that are added to the required security group based on project approval.

Note: Please enter the location details of where the data for this study will be used (processed).

b) Storage Location(s)

Location area - UK / EEA / Worldwide: Center for Health Informatics and Analytics (CHIA)

Organisation address: Center for Health Informatics and Analytics (CHIA)

Faculty of Medicine, Memorial University

300 Prince Phillip Drive,

St. John's, NL A1B 3V6

Canada

https://www.med.mun.ca/CHIA/Home.aspx

Note: Please enter the location details of where the data for this study will be stored.

c) Territory of analysis - UK / EEA / Worldwide:

Faculty of Medicine,

Memorial University

St. John's, Newfoundland, Canada

Note: Please enter the details of where the data for this study will be analysed.

SECTION D: INFORMATION ON DATA LINKAGES

19. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset, PROMS data, the Pregnancy Register, Cancer Registration, SACT and CPES data and the Mental Health Services Data Set **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher **Arlene Gallagher** Reference number (where available) Date of contact **30th January, 2017**

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

20. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data

☒ HES Admitted Patient Care

☐ HES Outpatient

☐ HES Accident and Emergency

☐ HES Diagnostic Imaging Dataset ☐ HES PROMS (Patient Reported Outcomes Measure) **

☐ CPRD Mother Baby Link

☐ Pregnancy Register

☐ NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data *

☐ NCRAS Cancer Patient Experience Survey (CPES) data*

☐ NCRAS Systemic Anti-Cancer Treatment (SACT) data*

☐ Mental Health Services Data Set (MHDS)

☐ Practice Level Index of Multiple Deprivation (Standard)

☐ Practice Level Index of Multiple Deprivation (Bespoke)

☒ Patient Level Index of Multiple Deprivation***

☐ Patient Level Townsend Score ***

**Applicants seeking access to NCRAS data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only available for non-commercial purposes, such as academic research, or in connection with delivering services to the NHS.*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher **Arlene Gallagher** Reference number (where available) Date of contact **30th January, 2017**

21. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **<u>not</u>** be included in this count)* **3**

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

22. Is linkage to a <u>local</u>¥ dataset with <1 million patients being requested?

Yes * ☐ No ☒

**If yes, please provide further details:*

¥ *Data from defined geographical areas i.e. non-national datasets.*

23. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

* *If yes, please provide further details:*

24. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

25. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

* *Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

** *No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

26. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☒

Is the questionnaire a validated instrument? Yes ☐ No ☒

If yes, has permission been obtained to use the instrument? Yes ☐ No ☒

Please provide further information:

Other (please describe)

[ψ] Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

27. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

28. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

29. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.

- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: **Zhiwei Gao** Date: **2nd April, 2018** e-Signature (type name): **ZHIWEI GAO**

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
A. Study Title§ §*Please note: This information will be published on CPRD's website as part of its transparency policy* **Pharmaco-Epidemiological Study of Cardio-Respiratory Safety of β2-agonists for the Treatment and Management of Asthma, COPD and Asthma-COPD Overlap Syndrome**
B. Lay Summary (Max. 200 words) § §*Please note: This information will be published on CPRD's website as part of its transparency policy* Asthma and chronic obstructive pulmonary disease (COPD) are two common diseases that affect the lung. Bronchodilator, an inhaler medicine used to open the airways of the lung are recommended by existing guidelines for treatment and management of lung diseases. Asthma-COPD overlap syndrome also known as ACOS is a new disease of the lung that has recently been described. Just as the basic definitions of asthma and COPD are sometimes debated, the primary definition of ACOS is not yet clear, however, patients with ACOS consume more and higher doses of inhaler medications. Currently, there is a lack of knowledge about the increased level of exposure to medications that are used to open the airways of the lung and the impact of these medications on the risk of Cardio-Respiratory (CR) diseases, a serious illness relating to the action of both heart and lungs. To address these knowledge gap, we propose to use

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
routinely collected health information from the Clinical Practice Research Datalink to identify patients who have developed CR illness and compare them with otherwise similar people who do not have this illness to see whether CR is a side effect of using inhaled medications.
C. Technical Summary (Max. 200 words) [§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* To date, there is limited evidence examining the association between inhaled β_2-agonist medications and the risk of Cardio-Respiratory (CR) events in patients with Asthma-COPD Overlap Syndrome (ACOS). To address these limitations and knowledge gap, this research proposes to use an existing database of detailed healthcare records of new-users of bronchodilator medications for patients with physician diagnosed asthma and COPD. In particular, the impact of inhaled β_2-agonist medications on CR outcomes /events which include all-cause-mortality, pneumonia and major adverse cardiovascular events (including non-fatal myocardial infarction (MI), non-fatal stroke, heart failure (HF), arrhythmia or cardiovascular mortality) in patient with ACOS would be assessed. The primary analysis will be conducted using conditional logistic regression for time-matched nested case-control design in patients with incident asthma, COPD or ACOS as identified by diagnostic codes among new users of inhaled β_2-agonists controlling for potential confounders. The effect modification will also be examined by introducing an interaction term between beta-agonists exposure level and one of potential effect modifiers each time.
D. Objectives, Specific Aims and Rationale **Objectives, Specific Aims:** The objective of this research is to estimate the risk of CR safety outcomes associated with exposure to β_2-agonists among cohorts of new users of bronchodilator medications. These cohorts include patients prescribed with LABA and SABA diagnosed with OADs. The CR safety events

include all-cause-mortality, pneumonia and major adverse cardiovascular events (including non-fatal myocardial infarction (MI), non-fatal stroke, heart failure (HF), arrhythmia or cardiovascular mortality).

Primary research questions:

1. Does exposure to inhaled short-acting β_2-agonists (SABA) and/or long-acting β_2-agonists (LABA) increase or decrease the risk of all-cause mortality or hospitalization for CR events compared to no exposure to short and/or long-acting β_2-agonists based medications?

For primary research question;

i. Will compare LABA to LA anticholinergics
ii. Will compare LABA to SA anticholinergics
iii. Will compare SABA to LA anticholinergics
iv. Will compare SABA to SA anticholinergics
v. Will compare all β_2-agonists to anticholinergics
vi. Will compare all β_2-agonists to inhaled corticosteroid therapy.

Secondary research questions:

2. Does exposure to long-acting or short-acting β_2-agonists increase or decrease the risk of hospitalization or mortality due to cardio-respiratory events in ACOS patients compared to those diagnosed with asthma and COPD alone?
3. Does the effect of exposure to long-acting or short-acting β_2-agonists increase or decrease the risk of hospitalization or mortality due to cardio-respiratory events contingent on the order of asthma and COPD diagnosis?

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

For our secondary research questions;

i. Will compare LABA to LA anticholinergics
ii. Will compare LABA to SA anticholinergics
iii. Will compare SABA to LA anticholinergics
iv. Will compare SABA to SA anticholinergics
v. Will compare all β_2-agonists to anticholinergics
vi. Will compare all β_2-agonists to inhaled corticosteroid therapy.

For the secondary research questions; the patients with asthma or COPD alone will be used as the reference group for patients with ACOS.

Justification for these hypotheses are based on safety outcomes of adverse effects of β_2-agonists-based medications as found either in the literature or clinical trials or post-market safety surveillance. Pharmacoepidemiological studies on short-term cardiovascular and autonomic effects of inhaled salbutamol in asthma found an association between acute salbutamol use and risk of sympathetic activities such as heart rate (HA) and muscle sympathetic nervous activity (MSNA) suggesting that salbutamol could contribute to cardiovascular morbidity/mortality in individuals using inhaled β_2-agonists.[4] On the other hand, an adjusted OR of 3.2 (CI 1.61 – 6.35) for AMI was found in patients from the USA receiving SABA in the 3 months prior to the AMI compared to non-users which was more pronounced in new users (aOR 7.32, CI 2.34 – 22.8).[5] Heavy long-term users of SABA (at least 13 prescription in the year before) living in the UK had an increased AMI risk compared to users receiving less than 3 prescriptions

(relative rate 1.6).[6] Also, a recent open label trial on treatment responsiveness of phenotypes of symptomatic airways obstruction in adults revealed that ACOS patients who use LABA/ICS or LABA alone in 12 months had the highest incidence of CVD morbidities.[7] In recent past, there have also been calls for the withdrawal of single therapy of LABA in asthma.[8, 9] Prior to this, safety warnings about the use of salmeterol were issued in North America[10] as a result of serious adverse events.[11, 12] In a recent network-meta-analysis for pneumonia including 54 RCTs and 21 treatments, salmeterol and fluticasone combination had the greatest risk of pneumonia compared to placebo (SUCRA = 89%).[13] In a meta-analysis of 13 single-dose randomized placebo control trials in patients with asthma and COPD, a single dose of β_2-agonists (such as formoterol, salmeterol, terbutaline and salbutamol) increased the heart rate by 9.12 beats/ min (CI 5.32 to 12.92).[14] For trials lasting from 3 days to 1 year, β_2-agonists treatment significantly increased the risk for cardiovascular event (RR, 2.54; CI 1.59 to 4.05) compared to placebo.[14] This is also due to the fact that OAD patients share other risk factors with CVD patients due to advanced age and decrease in physical activities caused by lung disease.

Thus, these questions represent clinically relevant safety events and more importantly, this research will inform patients, clinicians and policy-makers of the safety of β_2-agonists-based medications in everyday clinical practice among this new and understudied populations of OADs especially patients with the overlap syndrome.

E. Study Background

β_2-agonists are effective bronchodilators primarily due to their ability to relax airway smooth muscle (ASM). B2-agonist is a class of drugs that act on the β_2 adrenergic receptor. Traditionally inhaled short-acting β_2-agonists like salbutamol, fenoterol and terbutaline provide rapid as-needed symptom relief and short-term prophylactic protection against bronchoconstriction induced by exercise or other stimuli. Over

the past 50 years, case reports of adverse cardiovascular events, including sudden cardiac death, fatal myocardial contraction and arrhythmia resulting from β_2-agonists use have accumulated.[15-19] In general, there is still controversy as to whether long-acting β_2-agonists may increase the risk of asthma mortality.[20, 21] In any case they can induce adverse effects, such as increased heart rate, palpitations, transient decrease in Pa_{02} and tremor.[22, 23]

A study done to forecast the burden of OADs in Canada has projected that almost 1 in 8 individuals in Ontario will have asthma by the year 2022, suggesting that asthma will continue to be a major burden on individuals and the health care system.[24] Also, in Alberta, Canada, patients with acute exacerbation of OADs who are 55 years of age or older present to one of more than 100 EDs in the province about every 37 minutes.[25] OADs are serious chronic lung disease that affects between 7% and 10% of the adult population; in 2012, approximately 2.4 million Canadians aged 12 years and older (8.1%) reported being given a diagnosis of asthma alone by a health professional. It is estimated that nearly 2 million ED asthma visits occur annually in the United States alone, and 80% to 90% of the patients with acute asthma.[26] Two types of bronchodilators are generally considered to be equivalent choices in the treatment of OADs,[1, 2] however, recent data published by the PROTECT study found out that the Period Prevalence Rates (PPRs) of patients with LABA-containing medications increased in all databases (58.2% - 185.1%) from 2002-2009.[27]

The Global Initiative for Asthma (GINA) guideline for initial treatment to ensure efficacy and safety for patients with features of asthma, recommends management with controller therapy including inhaled corticosteroids, but not long-acting bronchodilators alone.[1] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline for management of patients with COPD also recommends initial treatment with bronchodilators or combination therapy, but not ICS alone.[2] This stepwise

approach is in recognition of the presence of chronic airways disease, syndromic categorization as characteristic asthma or COPD, and by spirometry confirmation of chronic airflow limitation.

Epidemiology studies[28] of asthma and COPD have shown that the two diseases over period of time may develop physiological features that are quite similar. Rapid rate of decline in pulmonary function, characteristic of subjects with COPD, may be seen in asthmatic patients as well.[29] Therefore, it has been recognized that with time there is development of permanent irreversible change in a small proportion of asthmatics with persistent severe disease. This has recently been termed Asthma/COPD Overlap Syndrome (ACOS).[3] Recently, the updated GINA/GOLD guidelines for ACOS, recommended first line of pharmacotherapy treatment as ICS and further add-ons of LABA or long-acting muscarinic antagonists (LAMA) as the disease progresses.[3] In these patients, the default is to start treatment for asthma, that is, an ICS at low or moderate doses plus LABA, which is to consider the potential life-saving role of ICS in asthma. LAMA treatment plus ICS/LABA can be considered as the disease progresses as in COPD.

The safety and effectiveness of pharmacotherapy treatment for this overlap syndrome is poorly recognized and given less attention in part because clinical trials have consistently ignored this condition, as evidenced by strict inclusion and exclusion criteria that either exclude asthma patients from COPD studies or COPD patients from asthma studies. Despite these shortcomings, the effect and impact of bronchodilators on the cardiovascular system has been documented for patients with COPD, rheumatoid arthritis as well as organ transplantations.[30-32] However, the incidence and severity of cardiovascular adverse events associated with the use of inhaled bronchodilators have not been documented in the context of ACOS. This is of particular concern because this population with features of the overlap

syndrome experience frequent exacerbations, has poor quality of life, a more rapid decline in lung function and high mortality, and consumes a disproportionate amount of medications than asthma or COPD alone.[33] Additionally, chronic bronchitis and lung function have been identified as independent predictors of the occurrence of coronary artery disease.[34, 35] Also, findings indicate that β_2 stimulants, especially in parenteral administration such as inhalation, can induce adverse effects such as ischemic heart disease, a comorbid factor, and once present can predict all-cause mortality in patients with severe OADs.[36] Evidence from several studies examining patients receiving inhaled therapy with ICS, LABA and LAMA for obstructive airways diseases (OADs) especially in COPD or asthma have showed varied conclusions in respect to their effectiveness and safety.[30, 37, 38]

In summary, this study will add novel information to the body of evidence on the impact of β_2-agonists based medications on the risk of CR events/outcomes among cohorts of new users of bronchodilator medications in patients with history of physician diagnosed OADs. In particular, the impact of CR outcome in patient with ACOS would be assessed and the results from this proposed study will represent the first and novel findings

F. Study Type

This is a ***hypothesis testing research*** study to test the association between ***β_2-agonist-based therapies*** and safety events. These safety events are fully described under 'background' and *justified* in 'objectives and specific aim sections'.

G. Study Design

To study the effect of bronchodilator use preceding a CR-event while simultaneously controlling for potential confounding effect of changes in the treatment of OADs over time, this study proposes to use a time-matched nested case-control (NCC) approach (see *figure 1*).[39] The NCC design yields a case-

control study embedded in an existing cohort with incidence density sampling application, where controls for each case are randomly selected from the risk set corresponding to the case.[40, 41]

H. Feasibility counts

Feasibility count taking into account subjects eligible for linked HES or ONS provided by the CPRD Knowledge centre indicates;

58,448 patients had a prescription for SABA

47,939 patients had a prescription for LABA

138,081 patients had a prescription of ICS

42,864 patients had a prescription for SAMA

67,258 patients had a prescription for LAMA

Based on a patient count estimate provided by CPRD in February 2017, we expect a base cohort of approximately 354,590 patients. However, the base cohort did not take into account feasibility count of subjects prescribed with combination therapies.

I. Sample size considerations

Sample size calculation is based on Schoenfeld method.[42] Schoenfeld method allows the power of an NCC design to be directly connected to the power of a cohort study.[43] Based on a patient count estimate provided by CPRD in February 2017, ~ 138,081 patients will have been exposed to ICS; ~ 42,864 patients will have been exposed to SAMA; ~ 67,258 patients will have been exposed to LAMA; ~ 58,448 patients will have been exposed to SABA and ~ 47,939 patients will have been exposed to LABA. Power calculations using type I error rate of 5%, conducted using Stata and command prompt *stpower cox* are summarized in *APPENDIX A* for our primary outcomes.

J. Data Linkage Required (if applicable):§

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

CPRD will supply the following linked data for patients who are eligible for linkage based on the latest release;

1. The basic HES data with coverage from 01/01/1998 up to most recent dataset has been requested for outcome assessment of pneumonia and cardiovascular-related hospital admissions (hospitalization) including hospitalization reasons. The admission date will be used to determine the date of outcome occurrence. Discharge dates of hospitalization will also be used to identify the date of comorbidities for covariate measures. Operational definitions for outcomes and covariates will be based on diagnostic codes (ICD-10 codes) in the HES.
2. The ONS mortality data with coverage from 01/01/1998 up to most recent dataset has been requested to identify the cause and date of death. Death certificate will be used to ascertain the cause of pneumonia and cardiovascular-related death. The date of death will be used to determine the date of occurrence of death for pneumonia and cardiovascular-related mortality. Operational definitions for cause of death will be based on ICD-10 codes in the ONS.
3. The SES data, Index of Multiple Deprivation 2015 has been requested to include a covariate in our statistical model indicating subjects' socio economic status. Quintiles of socioeconomic deprivation will be used to assess effect modifiers.

K. Study population

Source Population and Data Linkage

The source population will be patients in CPRD GOLD database with an incident code for asthma and/or COPD (Appendix B) defined as at least one diagnostic record for either disease or new-user of

bronchodilator drug (Appendix C). The incident code will be based on 365 days washout period, whereby patients with a record of taking any inhaler drug within 365 days before their first bronchodilator medication prescription will be excluded. Patients will be identified from January 1, 1998 up to the most recent dataset. Based on a patient count estimate provided by CPRD in February 2017, we expect a base cohort of approximately 354,590 patients. The Clinical Practice Research Datalink, CPRD is a UK based database which is representative of UK population that contains de-identified, longitudinal data, with ~700 total contributing GP primary care practices and more than 14 million acceptable (good quality) patients.[44] Patients' data are available for demographics, symptoms and diagnoses, primary care prescriptions (drugs and devices), test results (e.g. spirometry), referrals to specialist (secondary care), and lifestyle information (BMI, smoking, alcohol, exercise). Approximately half of the source population (study population) is linked to hospital records (Hospital Episode Stats, HES) and death certificate (Office of National Statistics, ONS). The CPRD will supply the following linked data for the patients in the cohort who are eligible for linkage based on linkage set 13; 1) basic HES data with coverage from 01/01/1998 up to most recent dataset; 2) ONS mortality data with coverage from 01/01/1998 up to most recent dataset; 3) SES data, Index of Multiple Deprivation 2015. Our study population will be drawn from among acceptable patients in who are registered with up-to-standard practice; all patients in the past 1 year with record of Read Code indicating a diagnosis of OAD or a Gemscript Code indicating newly prescription of an inhaler medication.

Cohort Selection

This will be population-based cohort of patients who received at least one prescription for β_2-agonists or anticholinergics bronchodilators or corticosteroids commonly used to treat OADs with incident physician recorded diagnosis of asthma and/or COPD. Our study population will consist of

cohort of patients with incident asthma, COPD and ACOS as identified by diagnostic codes and new users of bronchodilators. In this regard, we planned to define our study population to identify subjects who are first time users of bronchodilators. These subjects will further be categorized into patients who are also assigned diagnostic codes for either asthma alone, COPD alone or ACOS. Recent validation studies in the CPRD GOLD database have shown that patients with OADs can be accurately identified from GOLD database using specific diagnostic codes.[45-47]

Cohort Entry

The date of cohort entry will be defined as the date of 1st prescriptions for a bronchodilator or ICS for OADs treatment during any time period from January 1, 1998 up to the most recent dataset available.

Cohort Exit

The date of cohort exit will be defined as the earliest of the dates of any of the Cardio-Respiratory outcomes of interest, death from any other cause, emigration from a CPRD practice site, end of the study or which ever occurred first.

Index date

Index date of subjects will be the date of the event of interest of all-cause mortality, pneumonia or major cardiovascular events (including AMI, HF, or stroke).

Case Patients and Control Selection: ICD-10 codes and admission dates from the HES data and mortality dates from the ONS data will be used to identify cases. For subjects with multiple outcomes, the first occurrence of event will be taken as the case event. In connection with the point previously mentioned, we will be running additional secondary analysis whereby the case-control selection process is run separately for each outcome of interest. Each case will be matched to 10 controls available within the cohort on the basis of three factors: (1) all matched controls for each case had a duration of follow-up at least as long as

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the time to the event of the corresponding case (this will be achieved by assuring that each control is in the cohort and therefore at risk for the at the date of the case (event of interest), a date designated as the index date); (2) to control for secular trends in inhaled β_2-agonist use, the matched controls will have the same calendar year of cohort entry as the case; (3) the controls will be matched to the cases for age within a year of the date of birth. In addition, the controls will be required to receive at least one prescription of drug for OADs treatment in the year before the index date. Multiple sample risk sets for controls will be used as per nested case-control sampling method.
L. Selection of comparison group(s) or controls For the primary analyses, an active comparator will be used as a reference group. Specifically, any exposure to any inhaled medication that is not a beta-2-agonist during the 365 days prior to the index dates (i.e. no use of inhaled β_2-agonists as the reference).
M. Exposures, Health Outcomes[§] and Covariates [§]*Please note: Summary information on health outcomes (as included on the ISAC application form above) will be published on CPRD's website as part of its transparency policy* **Exposure Assessment**: All inhaled β_2-agonists prescription dispensed to the cases and their matched controls during the year before their index date will be identified, as well as at any time between cohort entry and the index date. All drugs exposures will be identified in the prescription files through the use of Gemscript codes. Contribution to person-time at risk will be the day an individual receives any medications to one of the three mutually exclusive exposure groups of interest: 1) Long-acting β_2-agonists (salmeterol, indacaterol, olodaterol, vilanterol and formoterol) alone or in combination with ICS; 2) short-acting β_2-agonists (salbutamol, terbutaline, fenoterol, rimiterol, pirbuterol, reproterol and orciprenaline); 3) other inhaled-non-β_2-agonists-based therapies – reference category. Individuals will contribute person-

time at risk to one of the aforementioned drug exposure groups until they discontinue, switched categories, experience an event of interest, leave the database or on the last available follow-up date, whichever occurs earliest. Each prescription will be analyzed to quantify the number of canisters dispensed and the corresponding defined daily units (dosing) according to the World Health Organisation Drug Utilization Research Group. A single prescription will be required, as there is no biological rationale why early events could not occur with short duration of exposure. If we are unable to determine the expected medication supplied or dispensed, we will use a 90-day duration. In accounting for non-adherence of prescriptions dispensed, a portion of follow-up time following the end of the expected medication supply that will be equivalent to 50% of the prescription duration during the period of exposure will be included.

***Outcomes*:** Our primary endpoints of interest are 1) all-cause mortality 2) pneumonia and 3) major adverse cardiovascular events. Pneumonia and major adverse cardiovascular events will consist of a diagnosis recorded in the ONS data or HES data. Since mortality outcomes are only available in the subcohort data linked to ONS (death certificate), we will use this linked subcohort to assess cause-specific mortality for pneumonia and cardiovascular mortality. Major adverse cardiovascular events will be defined as the first occurrence of non-fatal MI, non-fatal stroke, heart failure, arrhythmia or any cardiovascular-related mortality. Outcome assessment of cardiovascular-related admissions and mortality will be based on READ codes contained in the GOLD data linked to the sub-cohort of ICD-10 codes in the HES/ONS data (see Appendix D for codes). These outcomes definition were based on validated READ codes in the CPRD data and ICD-10 codes in the HES or ONS linkage data.[48-50]. Our research will utilize the full study cohort identified from the GOLD database to maximize precision.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
***Risk Factors and Confounders*:** A variety of potential confounders and risk factors in each of the two drug-endpoint associations of interest will be adjusted. Different statistical models estimating the relationship between β_2-agonists exposure and each outcome will be identified and use for adjustment of the crude estimate of effect. As it seems unrealistic to assume that exposures and confounders remain constant throughout follow-up,[51] potential confounders (i.e. co-medications, comorbidities, and health behaviours) will be assessed. Pre-defined covariates for each drug outcome relationship of interest such as age, sex, systemic hypertension, diabetes, hyperlipidemia, ischemic heart disease, disease duration and severity of OADs will be measured (please refer to Appendix E for list of covariates). For COPD severity, lung function value of FEV_1, the number of COPD exacerbations and prescription for other respiratory drugs (such as methylxanthines and oral steroids as indicators of severity for COPD) used during year before cohort entry will be measured at baseline period. Also, for asthma severity, indicators such as prescription of oral steroids (prednisolone), PEF value < 33% (best or predicted), exacerbation frequency, ED/hospitalization re-admission which is associated with increased disease severity will be measured one year prior to cohort entry. It is unknown as to best ACOS severity ranges determinants. These patients have permanent or fixed obstruction similar to COPD cases. We will compare these patients on a number of factors including FEV_1/GOLD range as this is globally accepted. Exacerbations, ER visits and hospitalization factors will also be considered. ACOS severity will be classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grading system: mild-to-moderate, $FEV_1 \geq 50\%$ predicted; and severe-to-very severe, $FEV_1 < 50\%$ predicted. Furthermore, based on the number of exacerbations to define severity, subjects will be defined as stable (no hospitalization or emergency department visitation), mild (>0 and <1 event), moderate (≥1 and <2

events), severe (≥2 and <3 events), and very severe (≥3 events) groups.

Also, in the analysis, severity of OADs will be controlled by matching on age and duration of disease, and by adjusting for OADs treatment based on the number of prescription in the 12 months before the index date.

N. Data/ Statistical Analysis

The primary analysis will be conducted using conditional logistic regression for time-matched nested case-control design in patients with incident asthma, COPD or ACOS as identified by diagnostic codes among new users of inhaled β_2-agonists. Current exposure to inhaled β_2-agonists will be considered as any prescription dispensed in the 1-month period before the index date as there is no justification why the outcomes of interest will not occur during this time-axis. In order to assess the effect of *new-use* of inhaled β_2-agonists, subjects who are currently exposed and who have not received β_2-agonists of any form during the 2 – 12 months before the index date will be considered. However, we will also look at a 90-day exposure period or durations, because most of these medications are usually prescribed for 3 months at a time. Baseline patient characteristics will be described using appropriate statistics at the time of initiation of an individual's first new inhaler therapy during the study period. Conditional logistic regression will provide an accurate estimate of the rate ratio based on computation of Odds Ratios (ORs), and 95% confidence interval (CI).

To control for disease severity, adjusted estimates will be obtained by including in the model the number of hospitalizations and prescriptions of inhaled β_2-agonists, inhaled corticosteroids, antibiotics and anticholinergics during the 12 months before cohort entry. Multiple sample risk-sets as per the NCC sampling method which allows subjects to be used as controls will be employed as measure against immeasurable-time or time-window bias.[52] For the analysis comparing inhaled β_2-agonists-based

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therapies, the exposure contrasts of interest are: 1) Main analysis of LABA vs LA anticholinergics, LABA vs SA anticholinergics, SABA vs LA anticholinergics, SABA vs SA anticholinergics, All Beta-2 vs anticholinergics, All Beta-2 vs placebo (no-anticholinergics); 2) A sub-analysis of ACOS vs asthma alone, ACOS vs COPD alone. 3) A sub-analysis contingent on the order of asthma and COPD diagnosis. The primary analysis will be conducted using conditional logistic regression for time-matched nested case-control design in patients with incident asthma, COPD or ACOS as identified by diagnostic codes among new users of inhaled β_2-agonists controlling for potential confounders including acute lower respiratory tract infection (pneumonia), history of stroke, history of heart failure, history of MI, smoking status, dose response, BMI, and quintiles of SES. In order to estimate the risk of Beta-2 in ACOS vs asthma lone or COPD alone, a two-way interaction term between beta$_2$-agonists exposure level and OAD diagnosis (asthma alone, COPD alone, ACOS) will be introduced into multivariate models and assessed. On the ordering of OAD diagnosis, a two-way interaction term between beta$_2$-agonists exposure level and the order of OAD diagnosis will be assessed. Also, to investigate the sex and age group specific associations, a three-way interaction term between beta$_2$-agonists exposure level, sex (female vs. male) and age group variable (<35, 35-40, 40-60, 60-80, >80 years) will be introduced into the multivariate models. Also, variables available within the GOLD data as well those used in studies examining bronchodilator drugs and outcomes will be identified and included in the model for adjustment. All analysis will be performed by using SAS (SAS Institute Inc.) statistical software.
O. Plan for addressing confounding **Sensitivity Analyses**

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
1. The main analysis will be repeated using alternative methods to define drug exposure over time. The cohort population will be restricted to monotherapy users, then add-on or switchers therapy approach whereby the day an individual receives a second inhaler medication they will begin to contribute time at risk to the exposure groups of interest. 2. Dose-response effect will be obtained by stratifying individuals into two categories, ≤ 0.5 and > 0.5 average daily units dispensed during a given time window and each contrasted against no use. **Case-Time-Control Analysis** For the secondary analyses, this will be varied using Case-Time-Control study. The case-time-control design is a strategy that was developed to tackle the problem of **confounding by indication** in the nonexperimental assessment of intended or known effects of drugs.[53, 54] To optimize this procedure, current exposure to β_2-agonists of each case subjects will be contrasted with periods prior to the current one as well as in control subjects (i.e. those recruited according to the NCC design). That is, for each subjects, the year prior to AMI hospitalization or all-cause mortality will be subdivided into 12 consecutive 30-day periods. Conditional logistic regression will be used to estimate ORs with 95% CIs. Suissa [53] showed that dividing the case-crossover exposure odds ratio by the control-crossover odds ratio, produces an odds ratio adjusted for time-trend. Analysis will be restricted to cases that transiently used β_2 adrenergic receptor agonists (less than 6 control periods).
P. Plans for addressing missing data Variables with missing data will be coded with an "unknown" category
Q. Patient or user group involvement (if applicable) Not applicable

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Upon the completion of the study analyses, the new knowledge and findings generated will be communicated to appropriate knowledge-users, including research, policy-makers and healthcare professionals such as CRRN, CTS etc. Results found in this healthcare research will be published in high impact journals (*BMJ, CMAJ*), as well as subspecialty (*Chest, Epidemiology, American Heart*) and/or methodological journals (*Pharmacoepidemiology and Drug Safety*) as per appropriate field of study. We will disseminate the results of this work through the more typical scientific methods including presentations at national and international scientific conferences such as the Canadian Association for Population Therapeutics (CAPT), International Society for Pharmacoepidemiology (ISPE), Society for Epidemiological Research (SER), among others. In all, we anticipate a minimum of 4 papers published based on the specific objectives.

S. Limitations of the study design, data sources, and analytic methods

1. Residual confounding may be introduced into the analysis as a result of incomplete adjustment for unmeasured baseline covariates; however, the GOLD database in particular, measures numerous confounders that are not available in typical computerized health databases.
2. Immeasurable-time bias due to incorrect time-window.[52] This is as a result of cases and controls not properly matched on duration of exposure opportunity time which may lead to time-window bias. In this case, the opportunity of follow-up in the control is greater than cases or vice versa. *This situation will be corrected by using "multiple risk-set sampling method" to match on*

duration of follow-up. This ensures that the opportunity for follow-up for both cases and controls are the same.

3. Drug exposure misclassification is a potential as the CPRD database does not capture prescriptions from specialists or prescriptions given in a hospital setting. Given most of these agents would be initially prescribed or continued by GP's, the degree of misclassification is likely very low.
4. There is a potential risk of diagnostic misclassification given the nature of the data available. However, we intend to minimise this trend by conducting a validation study of ACOS within the CPRD database to correctly define and identify patients with the overlap syndrome. The diagnosis of CVD within the CPRD database has been validated in other studies.

T. References

1. (GINA), G.I.f.A., *Global Strategy for Asthma Management and Prevention.* National Institute for Heart, Lung and Blood, 2015. **2015 update**(Revised 2014).
2. GOLD, *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease.* GOLD, Inc, 2015. **Update 2015**.
3. ACOS, *Diagnosis of Diseases of Chronic Airflow Limitation: Asthma COPD and asthma-COPD overlap syndrome.* GINA and GOLD, 2015. **2015 update**.
4. Abramson, M.J., et al., *Accuracy of asthma and COPD diagnosis in Australian general practice: a mixed methods study.* Prim Care Respir J, 2012. **21**(2): p. 167-73.
5. Salpeter, S.R., T.M. Ormiston, and E.E. Salpeter, *Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis.* Chest. **125**(6): p. 2309-21.
6. Edgell, H., et al., *Short-term cardiovascular and autonomic effects of inhaled salbutamol.* Respir Physiol Neurobiol, 2016. **231**: p. 14-20.

7. Au, D.H., et al., *The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists.* Am J Respir Crit Care Med, 2000. **161**(3 Pt 1): p. 827-30.
8. Zhang, B., et al., *The pattern of risk of myocardial infarction in patients taking asthma medication: a study with the General Practice Research Database.* J Hypertens, 2009. **27**(7): p. 1485-92.
9. Fingleton, J., et al., *Treatment responsiveness of phenotypes of symptomatic airways obstruction in adults.* Journal of Allergy and Clinical Immunology, 2015. **136**(3): p. 601-609.
10. Beasley, R., et al., *Call for withdrawal of LABA single-therapy inhaler in asthma.* The Lancet, 2010. **376**(9743): p. 750-751.
11. Kuehn, B.M., *FDA offers advice to reduce risks of long-acting β-agonists in asthma care.* JAMA - Journal of the American Medical Association, 2010. **303**(14): p. 1353-1354.
12. *New safety warning for salmeterol in US.* Pharmaceutical Journal, 2003. **271**(7263): p. 229.
13. Cates, C.J. and M.J. Cates, *Regular treatment with salmeterol for chronic asthma: Serious adverse events.* Cochrane Database of Systematic Reviews, 2008(3).
14. Kelly, H.W., *The U.S. Food and Drug Administration (FDA) and the safety of salmeterol in children.* Pediatric Asthma, Allergy and Immunology, 2008. **21**(2): p. 105-107.
15. Tricco, A.C., et al., *Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis.* BMJ Open, 2015. **5**(10): p. e009183.
16. Salpeter, S.R., *Cardiovascular safety of β2-adrenoceptor agonist use in patients with obstructive airway disease: A systematic review.* Drugs and Aging, 2004. **21**(6): p. 405-414.

17. Lulich, K.M., et al., *Adverse reactions to beta 2-agonist bronchodilators.* Med Toxicol, 1986. **1**(4): p. 286-99.

18. Lockett, M.F., *DANGEROUS EFFECTS OF ISOPRENALINE IN MYOCARDIAL FAILURE.* Lancet, 1965. **2**(7403): p. 104-6.

19. Kurland, G., J. Williams, and N.J. Lewiston, *Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma.* J Allergy Clin Immunol, 1979. **63**(6): p. 407-11.

20. Robin, E.D. and R. McCauley, *Sudden cardiac death in bronchial asthma, and inhaled beta-adrenergic agonists.* Chest, 1992. **101**(6): p. 1699-702.

21. Raper, R., M. Fisher, and D. Bihari, *Profound, reversible, myocardial depression in acute asthma treated with high-dose catecholamines.* Crit Care Med, 1992. **20**(5): p. 710-2.

22. Nelson, H.S., et al., *The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol.* Chest, 2006. **129**(1): p. 15-26.

23. Beasley, R., et al., *Call for withdrawal of LABA single-therapy inhaler in asthma.* Lancet, 2010. **376**(9743): p. 750-1.

24. Cazzola, M. and M.G. Matera, *Tremor and beta(2)-adrenergic agents: is it a real clinical problem?* Pulm Pharmacol Ther, 2012. **25**(1): p. 4-10.

25. Cazzola, M., et al., *Pharmacology and therapeutics of bronchodilators.* Pharmacol Rev, 2012. **64**(3): p. 450-504.

26. To, T., et al., *Is asthma a vanishing disease? A study to forecast the burden of asthma in 2022.* BMC Public Health, 2013. **13**: p. 254.

27. McKenna, P., et al., *Management of acute exacerbation of COPD in rural Alberta emergency departments.* Can J Rural Med, 2015. **20**(1): p. 7-14.

28. Rowe, B.H., et al., *Rates and correlates of relapse following ED discharge for acute asthma: a Canadian 20-site prospective cohort study.* Chest, 2015. **147**(1): p. 140-9.

29. Rottenkolber, M., et al., *Time trends of period prevalence rates of patients with inhaled long-acting beta-2-agonists-containing prescriptions: a European comparative database study.* PLoS One, 2015. **10**(2): p. e0117628.

30. Juniper E.F, O.B.P.M., Guyact G.H, Ferrie P.J, King D.R. , *Development and Validation of a questionnaire to measure Asthma Control.* European respiratory Journal 1999. **14**: p. 902-907.

31. Jarernsiripornkul, N., et al., *Patient reporting of potential adverse drug reactions: a methodological study.* Br J Clin Pharmacol, 2002. **53**(3): p. 318-25.

32. Huiart, L., et al., *Oral corticosteroid use and the risk of acute myocardial infarction in chronic obstructive pulmonary disease.* Can Respir J, 2006. **13**(3): p. 134-8.

33. Wallberg-Jonsson, S., M.L. Ohman, and S.R. Dahlqvist, *Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden.* J Rheumatol, 1997. **24**(3): p. 445-51.

34. Becker, D.M., et al., *Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients.* Am J Med, 1988. **85**(5): p. 632-8.

35. Kauppi P, K.H.e.a., *Overlap syndrome of asthma and COPD predicts low quality of life.* J Asthma, 2011. **48**(3): p. 279-85.

36. Haider, A.W., et al., *The association of chronic cough with the risk of myocardial infarction: the Framingham Heart Study.* Am J Med, 1999. **106**(3): p. 279-84.

37. Zureik, M., et al., *Association between peak expiratory flow and the development of carotid atherosclerotic plaques.* Arch Intern Med, 2001. **161**(13): p. 1669-76.

38. Antonelli Incalzi, R., et al., *Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease.* Eur Respir J, 1997. **10**(12): p. 2794-800.

39. P, N.E.D.V.B.X.R., *Short-acting beta-agonist prescription fills as a marker for asthma morbidity.* Chest Journal, 2005. **128**(2): p. 602-8.

40. Salpeter, S.R., T.M. Ormiston, and E.E. Salpeter, *Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis.* Chest, 2004. **125**(6): p. 2309-21.

41. Suissa, S., *Novel approaches to pharmacoepidemiology study design and statistical analysis.* In: Strom BL, ed Pharmacoepidemiolgy, Wiley and Sons, 2000. **3rd ed**(2000:785-805).

42. Pearce, N., *Incidence density matching with a simple SAS computer program.* Int J Epidemiol, 1989. **18**(4): p. 981-4.

43. Richardson, D.B., *An incidence density sampling program for nested case-control analyses.* Occup Environ Med, 2004. **61**(12): p. e59.

44. Schoenfeld, D.A., *Sample-size formula for the proportional-hazards regression model.* Biometrics, 1983. **39**(2): p. 499-503.

45. Ohneberg, K., et al., *Analysis of Clinical Cohort Data Using Nested Case-control and Case-cohort Sampling Designs. A Powerful and Economical Tool.* Methods Inf Med, 2015. **54**(6): p. 505-14.

46. Gallagher, A.M., et al., *The Impact of the Choice of Data Source in Record Linkage Studies Estimating Mortality in Venous Thromboembolism.* PLoS One, 2016. **11**(2): p. e0148349.

47. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

48. Rothnie, K.J., et al., *Validation of the Recording of Acute Exacerbations of COPD in UK Primary Care Electronic Healthcare Records.* PLoS One, 2016. **11**(3): p. e0151357.

49. Hammad, T.A., et al., *Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database.* Pharmacoepidemiol Drug Saf, 2008. **17**(12): p. 1197-201.

50. Herrett, E., et al., *Validation and validity of diagnoses in the General Practice Research Database: a systematic review.* Br J Clin Pharmacol, 2010. **69**(1): p. 4-14.

51. Khan, N.F., S.E. Harrison, and P.W. Rose, *Validity of diagnostic coding within the General Practice Research Database: a systematic review.* Br J Gen Pract, 2010. **60**(572): p. e128-36.

52. Soriano, J.B., et al., *Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database.* Eur J Epidemiol, 2001. **17**(12): p. 1075-80.

53. Arbogast P, V.W.T., *In: Velentgas P and Dreyer NA, eds. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide.* Rockville, MD: Agency for Healthcare Research and Quality. **Publication No. 12(13)-EHC099**: p. 135-144.

54. Suissa, S., et al., *Time-window bias in case-control studies: statins and lung cancer.* Epidemiology, 2011. **22**(2): p. 228-31.

55. Suissa, S., *The case-time-control design.* Epidemiology, 1995. **6**(3): p. 248-53.

56. Suissa, S., *The case-time-control design: further assumptions and conditions.* Epidemiology, 1998. **9**(4): p. 441-5.

57. Newhouse, M.T., et al., *Cardiovascular safety of high doses of inhaled fenoterol and albuterol in acute severe asthma.* Chest, 1996. **110**(3): p. 595-603.

58. Jara, M., C. Wentworth, 3rd, and S. Lanes, *A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD.* BMJ Open, 2012. **2**(3).

59. Lin, H.W., et al., *Inhaled Pharmacotherapy and Stroke Risk in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide Population Based Study Using Two-Stage Approach.* PLoS One, 2015. **10**(7): p. e0130102.

60. Tsai, M.J., et al., *Long-acting Inhaled Bronchodilator and Risk of Vascular Events in Patients With Chronic Obstructive Pulmonary Disease in Taiwan Population.* Medicine (Baltimore), 2015. **94**(51): p. e2306.

61. Jara, M., et al., *Comparative safety of long-acting inhaled bronchodilators: a cohort study using the UK THIN primary care database.* Drug Saf, 2007. **30**(12): p. 1151-60.

62. Carmargo CA, Barr RG, Chen R, Speizer FE, *Prospective study of inhaled corticosteroid use, cardiovascular mortality in asthmatic women.*Chest. 2006 Sep;134(3): 546-551. Epub 2008

63. DiSantostefano RL, Sampson T, Le HV, Hinds D, Davia KJ, Barkerly ND, *Risk of pneumonia with*

inhaled corticosteroid versus long-acting bronchodilator regimens in chronic obstructive pulmonary disease: a new-user cohort study. PLoS One. 2014 May 30;9(5):e97149

64. Sin DD, Tu JV, *lack of association between ipratropium bromide and mortality in elderly patients with chronic obstructive airways disease*: Thorax. 200 Mar;55(3):194-7

65. Jara M, Wentwirth O 3rd, Lance S, *A new user cohort study comparing the safety of long-acting inhaled bronchodilators in COPD.* BMJ Open. 2012 May 22;2(3). pii: e000841.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Amendment – 28th January, 2020

Whilst analyzing our dataset, we observed interesting gender differences in inhaled corticosteroids (ICS), short-or long-acting beta2-agonist (SABA or LABA), ICS/LABA, short-or long-acting muscarinic antagonist (SAMA or LAMA) among patients with Asthma, COPD and Asthma-COPD Overlap Syndrome.

Although we anticipated gender differences in inhaled pharmacotherapy in patients with Obstructive Airways Diseases (OADs), we did not elaborate this in our study protocol. We have decided to highlight one of our secondary research questions below in addition to all our stated research questions in the protocol.

D. Objectives, Specific Aims and Rationale

Secondary research questions:

4. Does gender difference exist between any of our six categories of inhaled pharmacotherapies among patients who are newly treated for asthma, COPD and asthma-COPD overlap?

N. Data/ Statistical Analysis

To examine gender differences between pharmacotherapies, multivariate logistic regression will be used to assess significant associations between gender and each of the inhaled pharmacotherapies.

Amendment – 28th December, 2020

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

In analyzing our dataset, we observed that ICS and its combination therapy ICS/LABA consist of almost 50% of our exposure being assessed. Even though ICS/LABA, ICS or LABA are part of exposure variables already requested from ISAC, we deem it appropriate to amend our protocol to capture our objective on the safety or effectiveness of ICS/LABA, ICS or LABA and accompanying survivorship (mortality), severe exacerbation and lung function among patients with Asthma, COPD and Asthma-COPD Overlap Syndrome.

This is being done to fully capture the apparent benefit and exposure of our study population of patients on ICS/LABA, LABA or ICS we did not elaborate this in our study protocol. We have decided to highlight one of our secondary research questions/objectives below in addition to all our stated research questions in the protocol.

Once again, the patient population is the same (patients with asthma, COPD and ACOS). Likewise, the drug groups are the same as in the protocol. Since this secondary research question was not highlighted in the current protocol, we here want to have your approval to enable us to tailor our subsequent analyses and discussion in this regard.

D. Objectives, Specific Aims and Rationale

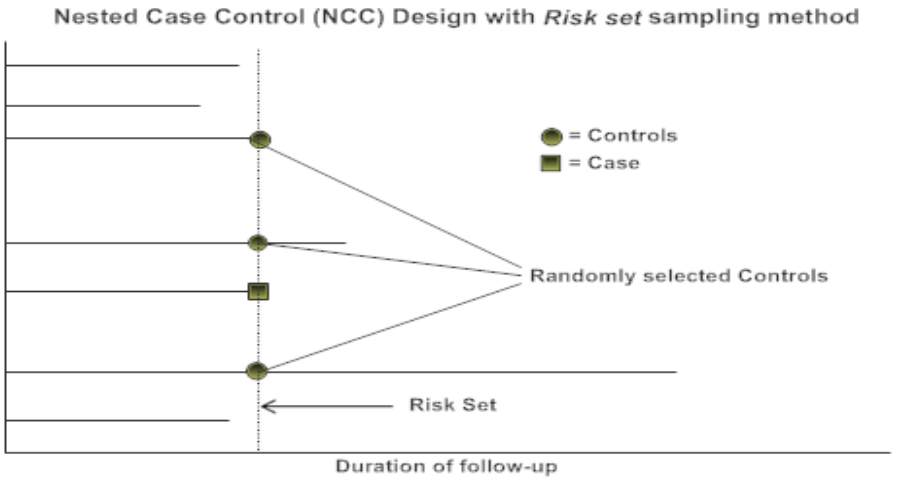
Secondary research questions/objectives:

Examine the effects of additional ICS to LABA (i.e. ICS/LABA) among COPD or ACOS patients on survival (mortality), exacerbation and lung function.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
N. Data/ Statistical Analysis To examine additional benefit of ICS to LABA, Cox regression model will be used to assess significant association between the use of ICS/LABA vs LABA, ICS/LABA vs ICS alone and ICS vs LABA on survivorship, severe exacerbation or lung function.

List of Appendices *(Submit all appendices as separate documents to this application)*

APPENDIX A*: Figure 1*: Schematic design of a Nested Case Control Study



1. The opportunity of exposure is the same for both cases and controls
2. Therefore, matching on duration of follow-up guarantees the same opportunity time for cases and matched controls

Cohort Entry : 1st Rx for a bronchodilator or ICS at t = 0 and begins to contribute person-time
Exposure time window: Inhaled Beta-2 agonists(Exposure) or ICS(Unexposed) Rx in 30-day period prior to index date
Index Date : Date of event of interest (i.e Case = ■)
Study Exit : When a subject becomes a case (■), death from any other cause, emigration, end of the study or which ever occurred first.

Table 1: Power Calculations for Cardio-Respiratory Safety Events of Interest in OADs Patients Exposed to β_2-agonists

Outcome	Exposure	Expected Event Rate	Power for HR of 1.1	Power for HR of 1.25	Power for HR of 1.50	Power for HR of 1.75	Power for HR of 2.0
Mortality	SABA	10.30[57]	1	1	1	1	1
Mortality	LABA	13.50[58]	0.98	1	1	1	1
Hospitalization	SABA	7.00[57]	1	1	1	1	1
Hospitalization	LABA	9.34[58]	0.92	1	1	1	1
Stroke	SABA	5.20[59]	1	1	1	1	1
Stroke	LABA	1.26[60]	0.23	0.82	0.99	1	1
MI	LABA	1.21[61]	0.23	0.81	0.99	1	1
Pneumonia	LABA	1.48[58]	0.27	0.88	0.99	1	1
HF	LABA	5.90[61]	0.76	0.99	1	1	1
Mortality	ICS	3.3[62]	0.89	0.99	1	1	1
Pneumonia	ICS	4.87[63]	0.97	1	1	1	1
Mortality	SAMA	3.27[64]	0.43	0.99	1	1	1
Mortality	LAMA	5.48[65]	0.82	0.99	1	1	1
MI	LAMA	1.27[65]	0.29	0.90	1	1	1
Stroke	LAMA	1.64[65]	0.35	0.96	1	1	1
Pneumonia	LAMA	1.27[65]	0.29	0.90	1	1	1
HF	LAMA	3.40[65]	0.63	0.99	1	1	1

All the above calculations were based on assumed two-sided alpha of 0.05 and expected event rates from previous studies; and a cohort consisting ~ 58,448 individuals exposed to short-acting β_2-agonists (SABA); ~ 47,939 individuals exposed to long-acting β_2-agonists (LABA); ~ 138,081 individuals exposed to ICS; ~ 42,864 individuals exposed to SAMA and ~ 67,258 individuals exposed to LAMA

Appendix B: READ codes for asthma and/or COPD in the CPRD

Read Code	Description/Read Term
H331.00	Intrinsic Asthma
66YP.00	Asthma night-time symptoms
H330.11	Allergic asthma
H330.12	Childhood asthma
H330.13	Hay fever with asthma
H330.14	Pollen asthma
H35y600	Sequoiosis (red-cedar asthma)
663O.00	Asthma not disturbing sleep
9OJB.00	Asthma monitoring invit SMS (short message service)
9NI8.00	Asthma outreach clinic
663e100	Asthma severely restricts exercise
8793.00	Asthma control step 0
9N1d.00	Seen in asthma clinic
2126200	Asthma resolved
173A.00	Exercise induced asthma
66Ys.00	Asthma never causes night symptoms
663t.00	Asthma causes daytime symptoms 1 to 2 times per month
663..11	Asthma monitoring
663q.00	Asthma daytime symptoms
H33z000	Status asthmaticus NOS
8798.00	Asthma control step 5
663h.00	Asthma – currently dormant
663n.00	Asthma treatment compliance satisfactory
9OJA.11	Asthma monitored
661M100	Asthma self-management plan agreed

663e.00	Asthma restricts exercise
663V200	Moderate asthma
H33..11	Bronchial asthma
388t.00	Royal college of physicians asthma
68C3.00	Asthma screening
9OJ6.00	Asthma monitor 3rd letter
66Yz500	Telehealth asthma monitoring
H335.00	Chronic asthma with fixed airflow
H330.00	Extrinsic (atopic) asthma
663V300	Severe asthma
1784.00	Asthma trigger – emotion
66YQ.00	Asthma monitoring by nurse
661N100	Asthma self-management plan review
663w.00	Asthma limits walking up hills or stairs
679J000	Health education - asthma self management
663u.00	Asthma causes daytime symptoms 1 to 2 times per week
H33z100	Asthma attack
66YE.00	Asthma monitoring due
663O000	Asthma never disturbs sleep
H330000	Extrinsic asthma without status asthmaticus
1O2..00	Asthma confirmed
66YR.00	Asthma monitoring by doctor
H333.00	Acute exacerbation of asthma
H47y000	Detergent asthma
H331111	Intrinsic asthma with asthma attack
9hA..00	Exception reporting: asthma quality indicators
H33..00	Asthma
H33z200	Late-onset asthma

8CR0.00	Asthma clinical management plan
8HTT.00	Referral to asthma clinic
8791.00	Further asthma - drug prevent
8797.00	Asthma control step 4
8B3j.00	Asthma medication review
663r.00	Asthma causes night symptoms 1 to 2 times per month
TJF7300	Adverse reaction to theophylline (asthma)
663x.00	Asthma limits walking on the flat
1783.00	Asthma trigger - warm air
1781.00	Asthma trigger – pollen
1787.00	Asthma trigger – seasonal
H33z.00	Asthma unspecified
H332.00	Mixed asthma
H334.00	Brittle asthma
178..00	Asthma trigger
H33z111	Asthma attack NOS
663s.00	Asthma never causes daytime symptoms
663P200	Asthma limits activities most days
663V000	Occasional asthma
H312000	Chronic asthmatic bronchitis
H33zz12	Allergic asthma NEC
H33zz11	Exercise induced asthma
9OJ3.00	Asthma monitor offer default
66Y9.00	Step up change in asthma management plan
1785.00	Asthma trigger – damp
663N100	Asthma disturbs sleep weekly
9OJB000	Asthma monitoring SMS text message 1st invitation
173c.00	Occupational asthma

H331100	Intrinsic asthma with status asthmaticus
663P.00	Asthma limiting activities
663V.00	Asthma severity
38DT.00	Asthma control questionnaire
663P100	Asthma limits activities 1 to 2 times per week
8795.00	Asthma control step 2
66Yp.00	Asthma review using Roy Colleg of Physicians three questions
H330111	Extrinsic asthma with asthma attack
663m.00	Asthma accident and emergency attendance since last visit
663y.00	Number of asthma exacerbations in past year
663V100	Mild asthma
1782.00	Asthma trigger - tobacco smoke
1780.00	Aspirin induced asthma
H3B..00	Asthma-chronic obstructive pulmonary disease overlap syndrom
663N000	Asthma causing night waking
9OJB100	Asthma monitoring SMS text message 2nd invitation
H331000	Intrinsic asthma without status asthmaticus
G581.11	Asthma – cardiac
H330100	Extrinsic asthma with status asthmaticus
9OJ5.00	Asthma monitor 2nd letter
9OJ9.00	Asthma monitoring deleted
663P000	Asthma limits activities 1 to 2 times per month
8796.00	Asthma control step 3
8794.00	Asthma control step 1
13Y4.00	Asthma society member
1J70.00	Suspected asthma
8CMA000	Patient has a written asthma personal action plan
9OJ..11	Asthma clinic administration

H331.11	Late onset asthma
66YK.00	Asthma follow-up
9hA1.00	Excepted from asthma quality indicators: Patient unsuitable
TJF7z00	Adverse reaction to antiasthmatic NOS
66Y5.00	Change in asthma management plan
TJF7.00	Adverse reaction to antiasthmatics
663N.00	Asthma disturbing sleep
663W.00	Asthma prophylactic medication used
9OJA.00	Asthma monitoring check done
9OJC.00	Asthma monitoring invitation email
H330z00	Extrinsic asthma NOS
38B8.00	Severe asthma exacerbation risk assessment
66Yq.00	Asthma causes night time symptoms 1 to 2 times per week
14Ok000	At risk of severe asthma exacerbation
173d.00	Work aggravated asthma
178B.00	Asthma trigger – exercise
66Yr.00	Asthma causes symptoms most nights
9OJZ.00	Asthma monitoring admin.NOS
9OJ2.00	Refuses asthma monitoring
9NNX.00	Under care of asthma specialist nurse
1788.00	Asthma trigger - cold air
6AP..00	Review of patient at risk of asthma
66YC.00	Absent from work or school due to asthma
U60F61A	[X] Adverse reaction to antiasthmatic NOS
U60F615	[X] Adverse reaction to theophylline - asthma
U60F611	[X] Adverse reaction to antiasthmatics
663p.00	Asthma treatment compliance unsatisfactory
663v.00	Asthma causes daytime symptoms most days

H35y700	Wood asthma
66Yz000	Asthma management plan declined
663N200	Asthma disturbs sleep frequently
663j.00	Asthma - currently active
178A.00	Asthma trigger - airborne dust
663e000	Asthma sometimes restricts exercise
663f.00	Asthma never restricts exercise
H331z00	Intrinsic asthma NOS
H33z011	Severe asthma attack
9hA2.00	Excepted from asthma quality indicators: Informed dissent
1789.00	Asthma trigger - respiratory infection
663Q.00	Asthma not limiting activities
9OJ..00	Asthma monitoring admin
212G.00	Asthma resolved
H330011	Hay fever with asthma
9OJ7.00	Asthma monitor verbal invite
9OJ1.00	Attends asthma monitoring
663U.00	Asthma management plan given
9OJ8.00	Asthma monitor phone invite
9OJ4.00	Asthma monitor 1st letter
66YA.00	Step down change in asthma management plan
8H2P.00	Emergency admission, asthma
66Yu.00	Number days absent from school due to asthma in past 6 month
66YJ.00	Asthma annual review
663d.00	Emergency asthma admission since last appointment
1786.00	Asthma trigger – animals
COPD	

9h51.00	Excepted from COPD quality indicators: Patient unsuitable
9h52.00	Excepted from COPD quality indicators: Informed dissent
9kf2.00	COPD structured smoking assessment declined - enh serv admin
8H2R.00	Admit COPD emergency
661N300	COPD self-management plan review
9h5..00	Exception reporting: COPD quality indicators
66Yf.00	Number of COPD exacerbations in past year
9NgP.11	On COPD (chr obstruc pulmonary disease) supportv cre pathway
8CeD.00	Preferred place of care for next exacerbation of COPD
9e03.00	GP OOH service notified of COPD care plan
66Yi.00	Multiple COPD emergency hospital admissions
66YI.00	COPD self-management plan given
8Hkw.00	Referral to COPD community nursing team
66YL.11	COPD follow-up
9kf..00	COPD - enhanced services administration
9kf1.00	Refer COPD structured smoking assessment - enhanc serv admin
661M300	COPD self-management plan agreed
66Ye.00	Emergency COPD admission since last appointment
9kf0.11	COPD patient unsuitable for pulmonary rehabilitation
66Yd.00	COPD accident and emergency attendance since last visit
9kf1.11	Referred for COPD structured smoking assessment
9kf0.00	COPD patient unsuitable for pulmonary rehab - enh serv admin
9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
8IEZ.00	Chronic obstructive pulmonary disease rescue pack declined
9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
H36..00	Mild chronic obstructive pulmonary disease
38Dg.00	Chronic obstructive pulmonary disease assessment test
66Yg.00	Chronic obstructive pulmonary disease disturbs sleep

8CE6.00	Chronic obstructive pulmonary disease leaflet given
66YD.00	Chronic obstructive pulmonary disease monitoring due
H37..00	Moderate chronic obstructive pulmonary disease
H38..00	Severe chronic obstructive pulmonary disease
9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite
9Oi..00	Chronic obstructive pulmonary disease monitoring admin
66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
14OJ.00	At risk of chronic obstructive pulmonary disease
9NgP.00	On chronic obstructive pulmonary disease supprtv cre pathway
H3y..11	Other specified chronic obstructive pulmonary disease
2126F00	Chronic obstructive pulmonary disease resolved
8CMV.00	Has chronic obstructive pulmonary disease care plan
9Nk7000	Seen in chronic obstructive pulmonary disease clinic
38Dd.00	Clinical chronic obstructive pulmonary disease questionnaire
1I70.00	Chronic obstructive pulmonary disease excluded by spirometry
8CR1.00	Chronic obstructive pulmonary disease clini management plan
679V.00	Health education - chronic obstructive pulmonary disease
H39..00	Very severe chronic obstructive pulmonary disease
66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
1J71.00	Suspected chronic obstructive pulmonary disease
66YL.00	Chronic obstructive pulmonary disease follow-up
9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
8CMW500	Chronic obstructive pulmonary disease care pathway
8BMW.00	Issue of chronic obstructive pulmonary disease rescue pack
66YB200	Telehealth chronic obstructive pulmonary disease monitoring
66YB.00	Chronic obstructive pulmonary disease monitoring

H3...00	Chronic obstructive pulmonary disease
66YM.00	Chronic obstructive pulmonary disease
Hyu3100	[X]Other specified chronic obstructive pulmonary disease
66YB100	Chronic obstructive pulmonary disease 6 monthly review
66YB100	Chronic obstructive pulmonary disease 3 monthly review
H3z..11	Chronic obstructive pulmonary disease NOS
H3A..00	End stage chronic obstructive airways disease
H3...11	Chronic obstructive airways disease NOS
H3y..00	Other specified chronic obstructive airways disease
H312200	Acute exacerbation of chronic obstructive airways disease
H312200	Chronic obstructive airways disease
663K.00	Airways obstructn irreversible

Appendix C: Gemscript Codes to identify asthma and/or COPD medications in the CPRD

prodcode	gemscriptcode	Productname	drugsubstancename
47638	00402021	Neovent 25microgram/dose Inhaler CFC (Kent Pharmaceuticals Ltd) salmeterol xinafoate	Salmeterol Xinafoate
35165	92979020	Serevent 50microgram disks with Diskhale (GlaxoSmithKline UK Ltd) Salmeterol xinafoate	Salmeterol Xinafoate
7270	90173020	Salmeterol 25microgram/dose inhaler CFC free salmeterol xinafoate 25microgram/actuation	Salmeterol Xinafoate
549	74018020	Serevent 25microgram/dose inhaler (GlaxoSmithKline UK Ltd) salmeterol xinafoate	Salmeterol Xinafoate
57694	16929021	Vertine 25microgram/dose inhaler CFC free (Teva UK Ltd) salmeterol xinafoate	Salmeterol Xinafoate
2224	74020020	Serevent 50microgram/dose Accuhaler (GlaxoSmithKline UK Ltd) salmeterol xinafoate	Salmeterol Xinafoate

54742	4199020	Salmeterol 25microgram/dose inhaler CFC free (A A H Pharmaceuticals Ltd) salmeterol	Salmeterol Xinafoate
50051	21883020	Serevent 25microgram/dose Evohaler (Waymade Health Care Plc) salmeterol xinafoate	Salmeterol Xinafoate
35825	92985020	Serevent 50microgram disks (GlaxoSmithKline UK Ltd) salmeterol xinafoate 50microgram	Salmeterol Xinafoate
57544	02702020	Serevent 50microgram/dose Accuhaler (Waymade Health Care Plc) salmeterol xinafoate	Salmeterol Xinafoate
719	74015020	Salmeterol 50microgram/dose dry powder inhaler salmeterol xinafoate 50microgram/1 dose	Salmeterol Xinafoate
465	74013020	Salmeterol 25microgram/dose inhaler salmeterol xinafoate 25microgram/1 dose	Salmeterol Xinafoate
35503	92977020	Salmeterol 50microgram inhalation powder blisters salmeterol xinafoate 50microgram	Salmeterol Xinafoate
35542	9291020	50microgram inhalation powder blisters with device salmeterol xinafoate	Salmeterol Xinafoate
56478	02704020	Serevent 50microgram/dose Accuhaler (DE Pharmaceuticals) salmeterol xinafoate	Salmeterol Xinafoate
3297	74014020	Salmeterol 50micrograms disk salmeterol xinafoate 50microgram Disc inhalation	Salmeterol Xinafoate
910	74019020	Serevent diskhaler 50microgram inhalation powder (Glaxo Welldone UK Ltd) Salmeterol	Salmeterol Xinafoate
37432	94307020	Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd) Formoterol Fumarate Formoterol fumarate	Formoterol fumarate dihydrate
6525	80413020	Formoterol 12microgram inhalation powder capsules with device Formoterol Fumarate dihydrate Formoterol fumarate dihydrate	Formoterol fumarate dihydrate

		12microgram	
66448	52510021	Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Waymade Healthcare Plc)	Formoterol fumarate dihydrate
1975	85747020	Oxis 6 Turbohaler (AstraZeneca UK Ltd) Formoterol fumarate dehydrate 6microgram/1dose inhalation Formoterol fumarate dihydrate 6microgram/1dose Inhalation Oxi	Formoterol fumarate dihydrate
66547	02723020	Oxis 12 Turbohaler (DE Pharmaceuticals) Formoterol fumarate dehydrate 12microgram/1dose Formoterol fumarate dihydrate 12microgram/1dose	Formoterol fumarate dihydrate
35725	92823020	Formoterol Easyhaler 12micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	Formoterol fumarate dihydrate
10968	80411020	Foradil 12microgram inhalation powder capsules with device (Novartis Pharmaceuticals UK Ltd) Formoterol	Formoterol fumarate dihydrate
57558	02718020	Oxis 6 Turbohaler (Lexon (UK) Ltd) Formoterol fumarate dihydrate 6microgram/1dose Inhalation powder	Formoterol fumarate dihydrate
62535	44185021	Duaklir 340micrograms/dose / 12micrograms/dose Genuair (AstraZeneca UK Ltd) Formoterol fumarate	Formoterol fumarate dihydrate

7133	85743020	Formoterol 12micrograms/dose dry powder inhaler Formoterol dihydrate 12microgram/1dose Formoterol fumarate dihydrate 12microgram/1dose	Formoterol fumarate dihydrate
67238	32398020	Foradil 12microgram inhalation powder capsules with device (Sigma Pharmaceuticals Plc) Formoterol fumarate	Formoterol fumarate dihydrate
1974	85749020	Oxis 12 Turbohaler (AstraZeneca UK Ltd) Formoterol fumarate dehydrate 12microgram/1dose inhalation powder Formoterol fumarate dihydrate 12microgram/1dose Inhalation powder	Formoterol fumarate dihydrate
9711	85742020	Formoterol 6micrograms/dose dry powder inhaler Formoterol fumarate dihydrate 6microgram/1dose Inhalation powder Inhalation	Formoterol fumarate dihydrate
25784	89766020	Atimos Modulite 12micrograms/dose inhaler (Chiesi Ltd) Formoterol fumarate dihydrate 12microgram/1dose Pressurised inhalation Inhalation	Formoterol fumarate dihydrate
14306	89764020	Formoterol 12micrograms/dose inhaler CFC free Formoterol Fumarate Dihydrate 12micrograms/actuation Inhaler Cfc-free Inhalation	Formoterol fumarate dihydrate
56482	02721020	Oxis 12 Turbohaler (Waymade Healthcare Plc) Formoterol fumarate dihydrate 12microgram/1dose Inhalation powder	Formoterol fumarate dihydrate
1957	52235020	Ventolin 5mg Nebules (GlaxoSmithKline UK Ltd) Salbutamol sulfate 2mg/1ml Nebuliser liquid Inhalation	Salbutamol sulfate
16577	88298020	Easyhaler Salbutamol sulfate 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd) Salbutamol 200microgram/1dose	Salbutamol sulfate
42830	98212020	Ventolin 100micrograms/dose Evohaler (GlaxoSmithKline UK Ltd) Salbutamol sulfate 100microgram/1dose Pressurised inhalation	Salbutamol sulfate

48741	02651020	Ventolin 100micrograms/dose Evohaler (Mawdsley-Brooks & Company Ltd) Salbutamol sulfate	Salbutamol sulfate
882	67866020	Salbutamol 200microgram inhalation powder capsules Salbutamol sulfate 200microgram Inhalation powder	Salbutamol sulfate
30212	53424020	Salbutamol cyclohaler Salbutamol Sulphate Cyclohaler	Salbutamol sulfate
8	59553020	Salbutamol 100microgram/1dose Pressurised inhalation	Salbutamol sulfate
510	52229020	Ventolin 5mg/ml respirator solution (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
49591	02653020	Salbutamol 100micrograms/dose inhaler CFC free (Sandoz Ltd) Salbutamol	Salbutamol sulfate
5753	69628020	Salbutamol 400micrograms disc Salbutamol Sulphate 400micrograms	Salbutamol sulfate
34311	50518020	Salbutamol 100microgram/inhalation Inhalation powder (Berk Pharmaceuticals Ltd)	Salbutamol sulfate
1741	86841020	Salbutamol 100micrograms/dose breath actuated inhaler CFC free Salbutamol sulfate	Salbutamol sulfate
7935	70528020	Maxivent 100microgram/inhalation Inhalation powder (Ashbourne Pharmaceuticals Ltd)	Salbutamol sulfate
3443	81503020	Salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)	Salbutamol sulfate
34162	59498020	Salbutamol 2.5mg/2.5ml Nebuliser liquid (Galen Ltd)	Salbutamol sulfate
53297	02658020	Ventolin 200micrograms/dose Accuhaler (Sigma Pharmaceuticals Plc)	Salbutamol sulfate
31	52213020	Ventolin 100microgram/inhalation Inhalation powder (Glaxo Wellcome UK Ltd)	Salbutamol sulfate
48742	02645020	Ventodisks 400microgram (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
942	68159020	Aerolin 100micrograms/dose Autohaler (3M Health Care Ltd)	Salbutamol sulfate
3163	69627020	Salbutamol 200micrograms disc Salbutamol Sulphate 200micrograms	Salbutamol sulfate
5889	79551020	Salamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)	Salbutamol sulfate
9651	85793020	Asmasal 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)	Salbutamol sulfate
17	59554020	Salbutamol 100micrograms/dose inhaler CFC free Salbutamol sulfate 100microgram/1dose Pressurised inhalation	Salbutamol sulfate

5170	81157020	Salamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)	Salbutamol sulfate
1950	68215020	Ventodisks 400microgram/blister Disc (Allen & Hanburys Ltd)	Salbutamol sulfate
66793	69338020	Salbutamol rondo 100micrograms/actuation inhaler and spacer	Salbutamol sulfate
14525	80501020	Salbutamol 100micrograms/inhalation vortex inhaler	Salbutamol sulfate
22512	!6452101	SALBUTAMOL Inhaler	Salbutamol sulfate
30118	61514020	Salbutamol 100micrograms/dose inhaler CFC free (Teva UK Ltd)	Salbutamol sulfate
49370	02643020	Ventodisks 200microgram (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
1882	68214020	Ventodisks 200microgram/blister Disc (Allen & Hanburys Ltd)	Salbutamol sulfate
58269	16419021	AirSalb 100micrograms/dose inhaler CFC free (Sandoz Ltd)	Salbutamol sulfate
50315	02638020	Salbutamol 200microgram inhalation powder blisters with device	Salbutamol sulfate
30240	68160020	Aerolin autohaler 100microgram/actuation Pressurised inhalation (3M Health Care Ltd)	Salbutamol sulfate
20675	!9131025	SALBUTAMOL ROTAHALER COMPLETE UNIT	Salbutamol sulfate
27793	70349020	Salbutamol cyclohaler type 5 insufflator Inhalation powder (Bristol-Myers Squibb Pharmaceuticals Ltd)	Salbutamol sulfate
50503	02659020	Ventolin 200micrograms/dose Accuhaler (Mawdsley-Brooks & Company Ltd)	Salbutamol sulfate
33817	63650020	Salbutamol 100micrograms/dose inhaler CFC free (Actavis UK Ltd)	Salbutamol sulfate
66395	57278021	Salbutamol 100micrograms/dose inhaler CFC free (Mawdsley-Brooks & Company Ltd)	Salbutamol sulfate
22430	84022020	Spacehaler salbutamol 100microgram/inhalation Spacehaler (Celltech Pharma Europe Ltd)	Salbutamol sulfate
34702	50525020	Salbutamol 100microgram/inhalation Inhalation powder(C P Pharmaceuticals Ltd)	Salbutamol sulfate
60923	02661020	Salamol 100micrograms/dose Easi-Breathe inhaler (DE Pharmaceuticals)	Salbutamol sulfate
25218	!8504810	SALBUTAMOL CFC/FREE B/A	Salbutamol sulfate
48809	02641020	Ventodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
34310	61776020	Salbutamol 100micrograms/dose inhaler CFC free (A A H Pharmaceuticals Ltd)	Salbutamol sulfate

64801	02646020	Salbutamol 100micrograms/dose inhaler CFC free (Mylan Ltd)	Salbutamol sulfate
113181	88296020	Easyhaler Salbutamol sulfate 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	Salbutamol sulfate
33373	63926020	Salbutamol 200 Cyclocaps (Teva UK Ltd) Salbutamol sulfate	Salbutamol sulfate
898	52215020	Ventolin evohaler 100 100microgram/inhalation Pressurised inhalation (Glaxo Wellcome UK Ltd)	Salbutamol sulfate
44713	50537020	Salbutamol 100microgram/inhalation Inhalation powder (Celltech Pharma Europe Ltd)	Salbutamol sulfate
5740	79575020	Airomir 100micrograms/dose Autohaler (Teva UK Ltd)	Salbutamol sulfate
5516	79690020	Salamol 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)	Salbutamol sulfate
67040	02647020	Salbutamol 100micrograms/dose inhaler CFC free (Alliance Healthcare (Distribution) Ltd)	Salbutamol sulfate
38079	94863020	Salbutamol 100micrograms/dose dry powder inhalation cartridge with device	Salbutamol sulfate
30230	79713020	Salbutamol 100micrograms/actuation breath actuated inhaler	Salbutamol sulfate
2978	69894020	Salbutamol 200micrograms/dose dry powder inhaler	Salbutamol sulfate
1952	52219020	Ventolin 400microgram Rotacaps (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
49368	02639020	Ventodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
958	84965020	Ventolin easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	Salbutamol sulfate
34134	68156020	Aerolin 400 100microgram/actuation Inhalation powder (3M Health Care Ltd)	Salbutamol sulfate
31933	50543020	Salbutamol 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	Salbutamol sulfate
48519	02648020	Ventolin 100micrograms/dose Evohaler (Waymade Healthcare Plc)	Salbutamol sulfate
40655	69361020	Salbuvent 100microgram/actuation Inhalation powder (Pharmacia Ltd)	Salbutamol sulfate
42858	98214020	Ventolin 200micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
13038	83865020	Pulvinal Salbutamol 200micrograms/dose dry powder inhaler (Chiesi Ltd)	Salbutamol sulfate
28508	54287020	Salbutamol 100microgram/inhalation Inhalation powder (IVAX Pharmaceuticals UK Ltd)	Salbutamol sulfate
2850	67867020	Salbutamol 400microgram inhalation powder capsules	Salbutamol sulfate

7017	88294020	Salbutamol 100micrograms/dose dry powder inhaler	Salbutamol sulfate
66924	53356021	Salbutamol 100micrograms/dose inhaler CFC free (DE Pharmaceuticals)	Salbutamol sulfate
66972	15632021	Salbutamol 100micrograms/dose inhaler CFC free (AM Distributions (Yorkshire) Ltd)	Salbutamol sulfate
38214	94865020	Salbutamol 100micrograms/dose dry powder inhalation cartridge	Salbutamol sulfate
48490	02650020	Ventolin 100micrograms/dose Evohaler (DE Pharmaceuticals)	Salbutamol sulfate
38097	56098020	Salbutamol cyclocaps 200microgram Inhalation powder (DuPont Pharmaceuticals Ltd)	Salbutamol sulfate
46551	77674020	Salbutamol 100microgram/inhalation Inhalation powder (Neo Laboratories Ltd)	Salbutamol sulfate
4497	52214020	Ventolin accuhaler 200 200microgram/actuation Inhalation powder (Glaxo Wellcome UK Ltd)	Salbutamol sulfate
13996	86269020	Salamol 100microgram/inhalation Inhalation powder (Sandoz Ltd)	Salbutamol sulfate
4665	84485020	Salbulin 100micrograms/dose inhaler (3M Health Care Ltd)	Salbutamol sulfate
38416	56099020	Salbutamol cyclocaps 400microgram Inhalation powder (DuPont Pharmaceuticals Ltd)	Salbutamol sulfate
49369	02642020	Salbutamol 200microgram inhalation powder blisters	Salbutamol sulfate
957	79689020	Salamol easi-breathe 100microgram/actuation Pressurised inhalation (IVAX Pharmaceuticals UK Ltd)	Salbutamol sulfate
34619	62351020	Salbutamol 100microgram/inhalation Inhalation powder (Kent Pharmaceuticals Ltd)	Salbutamol sulfate
34029	53423020	Salbutamol 400micrograms inahalation capsules	Salbutamol sulfate
48547	41350020	Salamol 100micrograms/dose inhaler CFC free (Arrow Generics Ltd)	Salbutamol sulfate
38226	94869020	Salbulin Novolizer 100micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)	Salbutamol sulfate
38136	94867020	Salbulin Novolizer 100micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)	Salbutamol sulfate
61591	02652020	Salbutamol 100micrograms/dose inhaler CFC free (Phoenix Healthcare Distribution Ltd)	Salbutamol sulfate

57524	02655020	Ventolin 200micrograms/dose Accuhaler (Dowelhurst Ltd)	Salbutamol sulfate
2851	52218020	Ventolin 200microgram Rotacaps (GlaxoSmithKline UK Ltd)	Salbutamol sulfate
33089	63418020	Salbutamol 100micrograms/dose inhaler (Kent Pharmaceuticals Ltd)	Salbutamol sulfate
52799	02640020	Salbutamol 400microgram inhalation powder blisters with device	Salbutamol sulfate
32050	63930020	Salbutamol 400 Cyclocaps (Teva UK Ltd)	Salbutamol sulfate
1087	86061020	Asmasal 95micrograms/dose Clickhaler (Focus Pharmaceuticals Ltd)	Salbutamol sulfate
2655	79415020	Airomir 100micrograms/dose inhaler (Teva UK Ltd)	Salbutamol sulfate
31082	70320020	Salbuvent 5mg/ml Respirator solution (Pharmacia Ltd)	Salbutamol sulfate
1698	69893020	Salbutamol 100micrograms/dose breath actuated inhaler	Salbutamol sulfate
57249	02654020	Asmavent 100micrograms/dose inhaler CFC free (Kent Pharmaceuticals Ltd)	Salbutamol sulfate
6462	69895020	Salbutamol 95micrograms/dose dry powder inhaler	Salbutamol sulfate
50956	02657020	Ventolin 200micrograms/dose Accuhaler (DE Pharmaceuticals)	Salbutamol sulfate
862	52877020	Salbulin Inhalation powder (3M Health Care Ltd)	Salbutamol sulfate
50557	39799020	Ventolin 200micrograms/dose Accuhaler (Lexon (UK) Ltd)	Salbutamol sulfate
21859	57680020	Asmaven 100microgram Inhalation powder (Berk Pharmaceuticals Ltd)	Salbutamol sulfate
1093	52885020	Salamol 100microgram/actuation Inhalation powder (IVAX Pharmaceuticals UK Ltd)	Salbutamol sulfate
28577	52223020	Ventolin 50microgram/ml Injection (Allen & Hanburys Ltd)	Salbutamol sulfate
30204	53422020	Salbutamol 200micrograms inahalation capsules	Salbutamol sulfate
235	48447020	Bricanyl 250micrograms/dose inhaler (AstraZeneca UK Ltd)	Terbutaline sulfate
42886	98210020	Bricanyl 500micrograms/dose Turbohaler (AstraZeneca UK Ltd)	Terbutaline sulfate
3763	03195007	TERBUTALINE RESPULES INH	Terbutaline sulfate
2758	58865020	Bricanyl Refill canister (AstraZeneca UK Ltd)	Terbutaline sulfate
67326	02685020	Bricanyl 500micrograms/dose Turbohaler (DE Pharmaceuticals)	Terbutaline sulfate
67543	02682020	Bricanyl 500micrograms/dose Turbohaler (Waymade Healthcare Plc)	Terbutaline sulfate
1619	74122020	Terbutaline 500micrograms/dose dry powder inhaler	Terbutaline sulfate
1628	66884020	Terbutaline 250micrograms/actuation refill canister	Terbutaline sulfate
1620	66882020	Terbutaline 250micrograms/dose inhaler	Terbutaline sulfate

907	48448020	Bricanyl turbohaler 500 500microgram Turbohaler (AstraZeneca UK Ltd)	Terbutaline sulfate
52410	02688020	Bricanyl 500micrograms/dose Turbohaler (Necessity Supplies Ltd)	Terbutaline sulfate
7954	48449020	Bricanyl 250micrograms/dose spacer inhaler (AstraZeneca UK Ltd)	Terbutaline sulfate
1794	48393020	Berotec 100microgram/actuation Inhalation powder (Boehringer Ingelheim Ltd)	Fenoterol hydrobromide
4842	61821020	Fenoterol 100microgram/actuation inhaler	Fenoterol hydrobromide
2020	48391020	Berotec 200micrograms/dose inhaler (Boehringer Ingelheim Ltd)	Fenoterol hydrobromide
5185	61819020	Fenoterol 200micrograms/dose inhaler	Fenoterol hydrobromide
8572	66535020	Rimiterol inhaler	Rimiterol hydrobromide
10858	52870020	Pulmadil auto Inhalation powder (3M Health Care Ltd)	Rimiterol hydrobromide
12563	53826020	Exirel Inhalation powder (3M Health Care Ltd)	Pirbuterol
16236	72193020	Pirbuterol acetate inhaler	Pirbuterol
12486	48475020	Bronchodil 500microgram/dose Inhalation powder (Viatris Pharmaceuticals Ltd)	Reproterol hydrobromide
15165	66477020	Reproterol 500micrograms/dose inhaler	Reproterol hydrobromide
8508	48103020	Alupent 750microgram/inhalation Inhalation powder (Boehringer Ingelheim Ltd)	Orciprenaline sulfate
8151	72219020	Orciprenaline 750micrograms/inhalation Aerosol refill	Orciprenaline sulfate
8149	48107020	Alupent 750microgram/inhalation Aerosol refill (Boehringer Ingelheim Ltd)	Orciprenaline sulfate
461	72218020	Orciprenaline 750micrograms/inhalation inhaler	Orciprenaline sulfate
1959	65884020	Pulmicort 0.5mg Respules (AstraZeneca UK Ltd) Budesonide 250microgram/1ml Nebuliser liquid inhalation Inhalation 250microgram/1ml Nebuliser liquid Inhalation Budesonide 250microgram/1ml Nebuliser liquid Inhalation	Budesonide
49711	02876020	Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd) Budesonide 200microgram/1dose Pressurised inhalation Inhalation	Budesonide

454	53685020	Pulmicort 200micrograms/dose inhaler (AstraZeneca UK Ltd) Budesonide 200microgram/1dose Pressurised inhalation Inhalation Budesonide 200microgram/1dose Pressurised inhalation Inhalation	Budesonide
17670	90421020	Easyhaler Budesonide 100micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd) Budesonide 100microgram/1dose Inhalation powder Inhalation	Budesonide
56498	02858020	Pulmicort 200 Turbohaler (Waymade Healthcare Plc) Budesonide 200microgram/1dose Inhalation powder Inhalation Budesonide 200microgram/1dose Inhalation powder Inhalation	Budesonide
1642	52570020	Budesonide 400micrograms/dose dry powder inhaler Budesonide	Budesonide
35510	92711020	Budesonide 200micrograms/dose dry powder inhalation cartridge with device	Budesonide
909	64256020	Budesonide 200micrograms/dose inhaler Budesonide 200microgram/1dose Pressurised inhalation	Budesonide
2092	52569020	Budesonide 200micrograms/dose dry powder inhaler Budesonide	Budesonide
8433	64258020	Budesonide 100micrograms/actuation inhaler Budesonide 100micrograms/actuation Aerosol Inhaler	Budesonide
67239	02867020	Pulmicort 400 Turbohaler (Waymade Healthcare Plc) Budesonide 400microgram/1dose Inhalation powder Inhalation Budesonide 400microgram/1dose Inhalation powder Inhalation Budesonide 400microgram/1dose Inhalation powder Inhalation	Budesonide
3570	73584020	Budesonide 200micrograms/actuation refill canister Budesonide 200micrograms/actuation Refill Canister Inhalation	Budesonide
16054	87972020	Budesonide 200micrograms/actuation breath actuated powder inhaler Budesonide 200micrograms/actuation Breath Actuated Dry Powder Inhaler Inhalation	Budesonide
39879	96157020	Budesonide 200micrograms/dose inhaler CFC free Budesonide 200microgram/1dose Pressurised inhalation Inhalation	Budesonide

908	73579020	Pulmicort 400 Turbohaler (AstraZeneca UK Ltd) Budesonide 400microgram/1dose Inhalation powder Inhalation 03020000 Corticosteroids (for Respiratory Conditions)	Budesonide
35724	92729020	Budelin Novolizer 200micrograms/dose inhalation powder refill (Meda Pharmaceuticals Ltd)	Budesonide
39099	96231020	Pulmicort 100micrograms/dose inhaler CFC free (AstraZeneca UK Ltd) Budesonide 100microgram/1dose Pressurised inhalation	Budesonide
18537	86508020	Budesonide 200microgram inhalation powder capsules Budesonide 200microgram	Budesonide
7788	52571020	Budesonide 100micrograms/dose dry powder inhaler Budesonide 100microgram/1dose Inhalation powder Inhalation	Budesonide
67322	02850020	Pulmicort 100 Turbohaler (Waymade Healthcare Plc)Budesonide 100microgram/1dose Inhalation powder Inhalation	Budesonide
14700	73583020	Budesonide 400micrograms/actuation inhaler Budesonide 400micrograms/actuation Aerosol Inhaler	Budesonide
35631	92727020	Budelin Novolizer 200micrograms/dose inhalation powder (Meda Pharmaceuticals Ltd)Budesonide 200microgram/1dose Inhalation powder	Budesonide
960	73580020	Pulmicort 100 Turbohaler (AstraZeneca UK Ltd)Budesonide 100microgram/1dose Inhalation powder	Budesonide
23741	87974020	Novolizer budesonide 200microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd	Budesonide
35602	92719020	Budesonide 200micrograms/dose dry powder inhalation cartridge Budesonide 200micrograms Dry Powder Inhalation Cartridge(refill)	Budesonide
959	64257020	Budesonide 50micrograms/dose inhaler Budesonide 50microgram/1dose Pressurised inhalation	Budesonide
60937	02859020	Pulmicort 200 Turbohaler (Dowelhurst Ltd)Budesonide 200microgram/1dose Inhalation powder	Budesonide
40057	96233020	Pulmicort 200micrograms/dose inhaler CFC free(AstraZeneca UK Ltd) Budesonide 200microgram/1dose Pressurised inhalation	Budesonide

27188	90423020	Easyhaler Budesonide 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd) Budesonide 200microgram/1dose Inhalation	Budesonide
947	73585020	Budesonide 50micrograms/actuation refill canister Budesonide 50micrograms/actuation Refill Canister	Budesonide
10321	84348020	Budesonide 400microgram inhalation powder capsules Budesonide 400microgram	Budesonide
30649	90425020	Easyhaler Budesonide 400micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd) Budesonide	Budesonide
67315	02866020	Budesonide 400micrograms/dose Turbohaler (Waymade Healthcare Plc	Budesonide
956	73578020	Pulmicort 200 Turbohaler (AstraZeneca UK Ltd)Budesonide	Budesonide
2125	53686020	Pulmicort 200microgram Refill canister(AstraZeneca UK Ltd) Budesonide	Budesonide
4545	53691020	Pulmicort LS 50microgram Refill canister (AstraZeneca UK Ltd) Budesonide 50microgram	Budesonide
39102	96155020	Budesonide 100micrograms/dose inhaler CFC free Budesonide 100micrograms	Budesonide
1680	53690020	Pulmicort LS 50micrograms/dose inhaler(AstraZeneca UK Ltd) Budesonide	Budesonide
37447	93259020	Fluticasone propionate 50microgram inhalation powder blisters Fluticasone propionate	Fluticasone Propionate
1518	74986020	Flixotide 50microgram/actuation Inhalation powder(Allen & Hanburys Ltd)Fluticasone Propionate	Fluticasone Propionate
4131	74459020	Fluticasone 100microgram Disc Fluticasone Propionate 100microgram Disc	Fluticasone Propionate
7638	74460020	Fluticasone 250microgram Disc Fluticasone Propionate 250microgram Disc Inhalation	Fluticasone Propionate
4688	74991020	Fluticasone 50microgram/actuation Pressurised inhalation Fluticasone Propionate	Fluticasone Propionate
7948	79604020	Fluticasone propionate 250micrograms/dose dry powder inhaler	Fluticasone Propionate
5975	76450020	Fluticasone 125micrograms/dose inhaler CFC free Fluticasone propionate	Fluticasone Propionate
36021	93257020	Fluticasone propionate 50microgram inhalation powder blisters with device	Fluticasone Propionate

911	79577020	Flixotide accuhaler 250 250microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	Fluticasone Propionate
9164	75180020	Fluticasone propionate 50micrograms/dose dry powder inhaler Fluticasone propionate	Fluticasone Propionate
42994	98222020	Flixotide 250micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	Fluticasone Propionate
42928	98218020	Flixotide 100micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd)	Fluticasone Propionate
35905	93287020	Fluticasone propionate 250microgram inhalation powder blisters Fluticasone propionate	Fluticasone Propionate
35986	93265020	Flixotide 50microgram disks (GlaxoSmithKline UK Ltd) Fluticasone propionate 50microgram Inhalation powder 4132	Fluticasone Propionate
4132	74992020	Fluticasone 125microgram/actuation Pressurised inhalation Fluticasone Propionate	Fluticasone Propionate
42985	98216020	Flixotide 50micrograms/dose Accuhaler(GlaxoSmithKline UK Ltd) Fluticasone propionate 50microgram/1dose Inhalation powder	Fluticasone Propionate
35392	93297020	Flixotide 500microgram disks with Diskhaler(GlaxoSmithKline UK Ltd) Fluticasone propionate 500microgram Inhalation powder	Fluticasone Propionate
35374	93299020	Flixotide 500microgram disks (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
5718	78907020	Flixotide 125micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	Fluticasone Propionate
36290	93263020	Flixotide 50microgram disks with Diskhaler (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
2282	79605020	Fluticasone propionate 500micrograms/dose dry powder inhaler	Fluticasone Propionate
56484	02904020	Flixotide 250micrograms/dose Accuhaler (Waymade Healthcare Plc) Fluticasone propionate	Fluticasone Propionate
7602	74458020	Fluticasone 50microgram Disc Fluticasone Propionate	Fluticasone Propionate
36462	93295020	Fluticasone propionate 500microgram inhalation powder blisters Fluticasone propionate	Fluticasone Propionate

5885	75181020	Fluticasone propionate 100micrograms/dose dry powder inhaler Fluticasone propionate	Fluticasone Propionate
53057	02951020	Flixotide 50micrograms/dose Evohaler (Lexon (UK) Ltd)	Fluticasone Propionate
57525	02909020	Flixotide 250micrograms/dose Accuhaler (Stephar (U.K.) Ltd) Fluticasone propionate	Fluticasone Propionate
1424	74455020	Flixotide 250microgram Disc (Allen & Hanburys Ltd) Fluticasone Propionate	Fluticasone Propionate
56499	02912020	Flixotide 500micrograms/dose Accuhaler (Waymade Healthcare Plc) Fluticasone propionate 500microgram/1dose	Fluticasone Propionate
5309	78909020	Flixotide 50micrograms/dose Evohaler (GlaxoSmithKline UK Ltd)	Fluticasone Propionate
35700	93293020	Fluticasone propionate 500microgram inhalation powder blisters with device	Fluticasone Propionate
1426	75187020	Flixotide 500microgram Disc(Allen & Hanburys Ltd) Fluticasone Propionate 500microgram Disc Inhalation	Fluticasone Propionate
57555	02930020	Flixotide 125micrograms/dose Evohaler (Dowelhurst Ltd) Fluticasone propionate 125microgram/1dose Pressurised inhalation	Fluticasone Propionate
2951	75179020	Fluticasone 250microgram/actuation Pressurised inhalation Fluticasone Propionate	Fluticasone Propionate
8635	74453020	Flixotide 50microgram Disc (Allen & Hanburys Ltd) Fluticasone Propionate 50microgram Disc Inhalation	Fluticasone Propionate
1676	74987020	Flixotide 125microgram/actuation Inhalation powder (Allen & Hanburys Ltd) Fluticasone	Fluticasone Propionate
49772	02943020	Fluticasone 250micrograms/dose Evohaler (Sigma Pharmaceuticals Plc) Fluticasone propionate	Fluticasone Propionate
1412	75190020	Flixotide 250microgram/actuation Inhalation powder (Allen & Hanburys Ltd) Fluticasone Propionate	Fluticasone Propionate
43074	98224020	Flixotide 500micrograms/dose Accuhaler (GlaxoSmithKline UK Ltd) Fluticasone propionate 500microgram/1dose	Fluticasone Propionate
56474	02932020	Flixotide 125micrograms/dose Evohaler (DE Pharmaceuticals)	Fluticasone Propionate
35638	93273020	Fluticasone propionate 100microgram inhalation powder blisters with device	Fluticasone Propionate

36090	93281020	Flixotide 100microgram disks (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
5223	76452020	Fluticasone 50micrograms/dose inhaler CFC free Fluticasone propionate 50microgram/1dose Pressurised inhalation Inhalation Fluticasone propionate 50microgram/1dose Pressurised inhalation Inhalatio	Fluticasone Propionate
3989	74454020	Flixotide 100microgram Disc (Allen & Hanburys Ltd) Fluticasone Propionate 100microgram Disc Inhalation	Fluticasone Propionate
3289	74985020	Flixotide 25micrograms/dose inhaler (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
5683	78908020	Flixotide 250micrograms/dose Evohaler (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
57579	02897020	Flixotide 50micrograms/dose Accuhaler (DE Pharmaceuticals) Fluticasone propionate 50microgram/1dose	Fluticasone Propionate
4926	75192020	Flixotide accuhaler 100 100microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	Fluticasone Propionate
35611	93291020	Flixotide 250microgram disks (GlaxoSmithKline UK Ltd) Fluticasone propionate 250microgram Inhalation powder	Fluticasone Propionate
16305	57311020	Flixotide 2mg/2ml Nebules (GlaxoSmithKline UK Ltd) Fluticasone propionate 1mg/1ml Nebuliser liquid Inhalation Fluticasone propionate 1mg/1ml Nebuliser liquid Inhalation	Fluticasone Propionate
67237	02934020	Flixotide 125micrograms/dose Evohaler (Lexon (UK) Ltd) Fluticasone propionate	Fluticasone Propionate
5822	76451020	Fluticasone 250micrograms/dose inhaler CFC free Fluticasone propionate 250microgram/1dose Fluticasone propionate 250microgram/1dose	Fluticasone Propionate
35772	93275020	Fluticasone propionate 100microgram inhalation powder blisters Fluticasone propionate	Fluticasone Propionate
2440	79578020	Flixotide accuhaler 500 500microgram/inhalation Inhalation powder (Allen & Hanburys Ltd)	Fluticasone Propionate

5580	75191020	Flixotide accuhaler 50 50microgram/inhalation Inhalation powder(Allen & Hanburys Ltd)	Fluticasone Propionate
56475	02895020	Flixotide 50micrograms/dose Accuhaler (Sigma Pharmaceuticals Plc)	Fluticasone Propionate
35225	93279020	Flixotide 100microgram disks with Diskhaler (GlaxoSmithKline UK Ltd) Fluticasone propionate 100microgram	Fluticasone Propionate
56477	02898020	Flixotide 100micrograms/dose Accuhaler (Waymade Healthcare Plc) Fluticasone propionate 100microgram/1dose Inhalation powder	Fluticasone Propionate
51815	02938020	Flixotide 250micrograms/dose Evohaler (Waymade Healthcare Plc) Fluticasone propionate 250microgram/1dose Pressurised inhalation	Fluticasone Propionate
2723	74990020	Fluticasone 25micrograms/dose inhaler Fluticasone propionate 25microgram/1dose Pressurised inhalation Fluticasone propionate 25microgram/1dose Pressurised inhalation	Fluticasone Propionate
67253	02896020	Flixotide 50micrograms/dose Accuhaler (Mawdsley-Brooks & Company Ltd) Fluticasone propionate 50microgram/1dose	Fluticasone Propionate
36401	93285020	Fluticasone propionate 250microgram inhalation powder blisters with device	Fluticasone Propionate
35461	93289020	Flixotide 250microgram disks with Diskhaler (GlaxoSmithKline UK Ltd) Fluticasone propionate	Fluticasone Propionate
7891	75184020	Fluticasone 500microgram Disc Fluticasone Propionate 500microgram Disc	Fluticasone Propionate
14294	88500020	Qvar 50micrograms/dose Easi-Breathe inhaler (Teva UK Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
33258	60178020	Beclometasone 250micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	Beclometasone Dipropionate
4759	69249020	Beclometasone 100microgram inhalation powder capsules Beclometasone dipropionate	Beclometasone Dipropionate
2148	69624020	Beclometasone 400microgram disc Beclometasone Dipropionate 400micrograms Disc Beclometasone Dipropionate 400micrograms Disc Inhalation	Beclometasone Dipropionate

54399	10729020	Qvar 100 Autohaler (Sigma Pharmaceuticals Plc) Beclometasone dipropionate	Beclometasone Dipropionate
57589	02831020	Becloforte 250micrograms/dose inhaler (Dowelhurst Ltd) Beclometasone dipropionate 250microgram/1dose	Beclometasone Dipropionate
31774	58818020	Beclometasone 50micrograms/dose inhaler(Mylan Ltd) Beclometasone dipropionate 50microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
16148	91167020	Clenil Modulite 250micrograms/dose inhaler (Chiesi Ltd) Beclometasone dipropionate 250microgram/1dose	Beclometasone Dipropionate
1551	56477020	Beclazone 250 inhaler (Teva UK Ltd) Beclometasone dipropionate 250microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
1406	48324020	Becotide 50 inhaler (GlaxoSmithKline UK Ltd)Beclometasone dipropionate 50microgram/1dose	Beclometasone Dipropionate
24898	84019020	Spacehaler BDP 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd) Beclometasone Dipropionate 100microgram/actuation	Beclometasone Dipropionate
1242	69244020	Beclometasone 250micrograms/dose inhaler Beclometasone dipropionate	Beclometasone Dipropionate
62341	02839020	Becotide 50 inhaler (Dowelhurst Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
1258	67266020	Becotide 200 inhaler (GlaxoSmithKline UK Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
16158	1161020	Clenil Modulite 50micrograms/dose inhaler (Chiesi Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
99	57212020	Becotide 100 inhaler(GlaxoSmithKline UK Ltd) Beclometasone dipropionat	Beclometasone Dipropionate
13037	80128020	Pulvinal Beclometasone Dipropionate 200micrograms/dose dry powder inhaler (Chiesi Ltd)	Beclometasone Dipropionate
54207	10721020	Qvar 50 inhaler (DE Pharmaceuticals) Beclometasone dipropionate	Beclometasone Dipropionate

21005	91159020	Beclometasone 250micrograms/dose inhaler CFC free Beclometasone dipropionate	Beclometasone Dipropionate
2160	74421020	Beclometasone 50micrograms/dose breath actuated inhaler Beclometasone dipropionate 50microgram/1dose	Beclometasone Dipropionate
67234	02845020	Becotide 100 inhaler (Waymade Healthcare Plc) Beclometasone dipropionate Beclometasone dipropionate	Beclometasone Dipropionate
14524	81511020	Bdp 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd) Beclometasone Dipropionate	Beclometasone Dipropionate
14321	91157020	Beclometasone 200micrograms/dose inhaler CFC free Beclometasone Dipropionate 200micrograms/actuation	Beclometasone Dipropionate
9477	85796020	Asmabec 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd) Beclometasone Dipropionate 100microgram/actuation Spacehaler Inhalation	Beclometasone Dipropionate
51681	10726020	Becodisks 400microgram Disc (Allen & Hanburys Ltd) Beclometasone Dipropionate 400microgram Disc Inhalation	Beclometasone Dipropionate
47943	99655020	Beclazone easi-breathe (roi) 100microgram/actuation Pressurised inhalation (Ivax Pharmaceuticals Ireland) Beclometasone Dipropionate	Beclometasone Dipropionate
25204	60177020	Beclometasone 100micrograms/dose inhaler (A A H Pharmaceuticals Ltd) Beclometasone dipropionate 100microgram/1dose Pressurised inhalation Inhalation	Beclometasone Dipropionate
4499	54706020	Aerobec 250microgram/actuation Pressurised inhalation (Meda Pharmaceuticals Ltd)	Beclometasone Dipropionate
11732	86878020	Beclometasone 50micrograms/dose breath actuated inhaler CFC free	Beclometasone Dipropionate
14567	85881020	Asmabec 250 Clickhaler (Focus Pharmaceuticals Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
9577	85879020	Asmabec 50 Clickhaler (Focus Pharmaceuticals Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
51415	10720020	Qvar 50 inhaler (Mawdsley-Brooks & Company Ltd) Beclometasone dipropionate	Beclometasone Dipropionate

33849	63536020	Beclometasone 100microgram/actuation Inhalation powder (Neo Laboratories Ltd)	Beclometasone Dipropionate
1734	74422020	Beclometasone 100micrograms/dose breath actuated inhaler Beclometasone dipropionate	Beclometasone Dipropionate
3743	48110020	Filair 50 inhaler (Meda Pharmaceuticals Ltd)Beclometasone dipropionate 50microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
3993	54871020	Filair Forte 250micrograms/dose inhaler (Meda Pharmaceuticals Ltd) Beclometasone dipropionate 250microgram/1dose	Beclometasone Dipropionate
13815	82720020	Beclazone 100microgram/actuation Inhalation powder (Actavis UK Ltd) Beclometasone dipropionate 100microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
30238	61523020	Beclometasone 50microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd) Beclometasone dipropionate 50microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
17654	89688020	Easyhaler Beclometasone 200micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd) Beclometasone dipropionate 200microgram/1dose	Beclometasone Dipropionate
11198	81505020	Beclometasons 50 micrograms/actuation vortex inhaler Beclometasone Dipropionate 50micrograms/actuation Vortex Metered Dose Inhaler Inhalation Beclometasone Dipropionate 50micrograms/actuation Vortex Metered Dose Inhaler Inhalation	Beclometasone Dipropionate
15326	91155020	Beclometasone 100micrograms/dose inhaler CFC free Beclometasone dipropionate 100microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
5522	79503020	Beclometasone 100micrograms/dose dry powder inhaler Beclometasone dipropionate 100microgram/1dose	Beclometasone Dipropionate
3927	48111020	Filair 100 inhaler (Meda Pharmaceuticals Ltd)Beclometasone dipropionate 100microgram/1dose Pressurised inhalation	Beclometasone Dipropionate
56493	10722020	Qvar 50micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc) Beclometasone dipropionate 50microgram/1dose	Beclometasone Dipropionate
1727	84967020	Becotide easi-breathe 50microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	Beclometasone Dipropionate

5521	77000020	Beclometasone 200micrograms/dose dry powder inhaler Beclometasone dipropionate 200microgram/1dose	Beclometasone Dipropionate
3363	57934020	Becloforte 400microgram disks with Diskhaler (GlaxoSmithKline UK Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
35580	93039020	Beclometasone 100microgram inhalation powder blisters with device Beclometasone dipropionate 100microgram	Beclometasone Dipropionate
1885	81155020	Beclazone 200 inhaler (Teva UK Ltd) Beclometasone dipropionate 200microgram/1dose Pressurised inhalation Inhalation	Beclometasone Dipropionate
63585	75217020	Beclometasone 50micrograms/dose inhaler (Almus Pharmaceuticals Ltd)	Beclometasone Dipropionate
9233	69250020	Beclometasone 200microgram inhalation powder capsules	Beclometasone Dipropionate
14757	80127020	Pulvinal Beclometasone Dipropionate 100micrograms/dose dry powder inhaler (Chiesi Ltd)	Beclometasone Dipropionate
3947	53710020	Becotide 100microgram Rotacaps (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
35288	93057020	Beclometasone 400microgram inhalation powder blisters	Beclometasone Dipropionate
35293	93047020	Beclometasone 200microgram inhalation powder blisters with device	Beclometasone Dipropionate
1725	79400020	Beclazone 50 Easi-Breathe inhaler (Teva UK Ltd)	Beclometasone Dipropionate
53480	10735020	Qvar 100 Autohaler (Stephar (U.K.) Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
18848	88502020	Qvar 100micrograms/dose Easi-Breathe inhaler (Teva UK Ltd)	Beclometasone Dipropionate
2992	56475020	Beclazone 50 inhaler (Teva UK Ltd)	Beclometasone Dipropionate

19389	85795020	Asmabec 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
13290	91163020	Clenil Modulite 100micrograms/dose inhaler (Chiesi Ltd)	Beclometasone Dipropionate
34919	60176020	Beclometasone 50micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	Beclometasone Dipropionate
1100	56476020	Beclazone 100 inhaler (Teva UK Ltd)	Beclometasone Dipropionate
28073	61525020	Beclometasone 250microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)	Beclometasone Dipropionate
2600	74423020	Beclometasone 250micrograms/dose breath actuated inhaler Beclometasone dipropionate	Beclometasone Dipropionate
1243	79402020	Beclazone 250 Easi-Breathe inhaler (Teva UK Ltd)	Beclometasone Dipropionate
35430	93051020	Becodisks 200microgram with Diskhaler (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
50129	10737020	Qvar 100micrograms/dose Easi-Breathe inhaler (DE Pharmaceuticals)	Beclometasone Dipropionate
41412	69256020	Beclometasone 400micrograms/actuation inhaler Beclometasone Dipropionate	Beclometasone Dipropionate
41269	63923020	Beclometasone 400 Cyclocaps (Teva UK Ltd)	Beclometasone Dipropionate
2892	57935020	Becloforte 400microgram disks (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
35118	93059020	Becodisks 400microgram with Diskhaler (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
7964	63531020	Beclometasone 50microgram/actuation Inhalation powder (Neo Laboratories Ltd)	Beclometasone Dipropionate

9571	81507020	Beclometasone 250micrograms/actuation vortex inhaler Beclometasone Dipropionate	Beclometasone Dipropionate
1552	84970020	Becloforte easi-breathe 250microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	Beclometasone Dipropionate
19031	81510020	Bdp 100microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
34794	65723020	Beclometasone 200micrograms/dose inhaler (A A H Pharmaceuticals Ltd)	Beclometasone Dipropionate
20825	84020020	Spacehaler BDP 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
2229	68209020	Becodisks 100microgram Disc (Allen & Hanburys Ltd)	Beclometasone Dipropionate
896	84968020	Becotide easi-breathe 100microgram/actuation Pressurised inhalation (Allen & Hanburys Ltd)	Beclometasone Dipropionate
10090	86870020	Beclometasone 50micrograms/actuation extrafine particle cfc free inhaler	Beclometasone Dipropionate
5804	76999020	Beclometasone 250micrograms/dose dry powder inhaler Beclometasone dipropionate	Beclometasone Dipropionate
56471	02827020	Becodisks 200microgram (Mawdsley-Brooks & Company Ltd)	Beclometasone Dipropionate
61664	26859021	Clenil Modulite 250micrograms/dose inhaler (Waymade Healthcare Plc)	Beclometasone Dipropionate
34739	67073020	Beclometasone 50micrograms/dose inhaler (Teva UK Ltd)	Beclometasone Dipropionate
48340	38603020	Clenil Modulite 100micrograms/dose inhaler (Mawdsley-Brooks & Company Ltd)	Beclometasone Dipropionate
35408	93045020	Becodisks 100microgram (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate

62518	27040021	Beclometasone 100micrograms/dose inhaler CFC free (Ennogen Healthcare Ltd)	Beclometasone Dipropionate
28640	59873020	Beclometasone 100microgram/actuation Inhalation powder (Actavis UK Ltd)	Beclometasone Dipropionate
38	69246020	Beclometasone 100micrograms/dose inhaler	Beclometasone Dipropionate
11497	77001020	Beclometasone 400micrograms/dose dry powder inhaler	Beclometasone Dipropionate
7653	69251020	Beclometasone 400microgram inhalation powder capsules	Beclometasone Dipropionate
29325	58817020	Beclometasone 250micrograms/dose inhaler (Mylan Ltd)	Beclometasone Dipropionate
21482	58819020	Beclometasone 100micrograms/dose inhaler (Mylan Ltd)	Beclometasone Dipropionate
35652	93041020	Beclometasone 100microgram inhalation powder blisters	Beclometasone Dipropionate
28761	84018020	Spacehaler BDP 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
26063	67076020	Beclometasone 100micrograms/dose inhaler (Teva UK Ltd)	Beclometasone Dipropionate
51480	10736020	Qvar 100 Autohaler (DE Pharmaceuticals)	Beclometasone Dipropionate
35107	93055020	Beclometasone 400microgram inhalation powder blisters with device	Beclometasone Dipropionate
35071	93053020	Becodisks 200microgram (GlaxoSmithKline UK Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
4365	69622020	Beclometasone 100micrograms disc	Beclometasone Dipropionate

39200	95879020	AeroBec Forte 250 Autohaler (Meda Pharmaceuticals Ltd)	Beclometasone Dipropionate
67735	99657020	Beclazone easi-breathe (roi) 250microgram/actuation Pressurised inhalation (Ivax Pharmaceuticals Ireland)	Beclometasone Dipropionate
18394	81509020	Bdp 50microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
34315	59874020	Beclometasone 250microgram/actuation Inhalation powder (Actavis UK Ltd)	Beclometasone Dipropionate
895	79401020	Beclazone 100 Easi-Breathe inhaler (Teva UK Ltd)	Beclometasone Dipropionate
5992	79502020	Beclometasone 50micrograms/dose dry powder inhaler	Beclometasone Dipropionate
3119	79444020	Becloforte integra 250microgram/actuation Inhaler with compact spacer (Glaxo Laboratories Ltd)	Beclometasone Dipropionate
50287	10725020	Qvar 100 inhaler (DE Pharmaceuticals)	Beclometasone Dipropionate
3075	53712020	Becotide 400microgram Rotacaps (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
67265	02826020	Becodisks 200microgram (Lexon (UK) Ltd)	Beclometasone Dipropionate
3018	69245020	Beclometasone 50micrograms/dose inhaler	Beclometasone Dipropionate
3150	86871020	Beclometasone 100micrograms/actuation extrafine particle cfc free inhaler	Beclometasone Dipropionate
19401	79501020	Beclometasone 250micrograms/actuation inhaler and compact spacer	Beclometasone Dipropionate
49367	38602020	Clenil Modulite 50micrograms/dose inhaler (Mawdsley-Brooks & Company Ltd)	Beclometasone Dipropionate

4413	86884020	Qvar 100 Autohaler (Teva UK Ltd)	Beclometasone Dipropionate
32874	59872020	Beclometasone 50microgram/actuation Inhalation powder (Actavis UK Ltd)	Beclometasone Dipropionate
30210	67080020	Beclometasone 250micrograms/dose inhaler (Teva UK Ltd)	Beclometasone Dipropionate
2335	86874020	Qvar 100 inhaler (Teva UK Ltd)	Beclometasone Dipropionate
46157	63918020	Beclometasone 200 Cyclocaps (Teva UK Ltd)	Beclometasone Dipropionate
4601	85880020	Asmabec 100 Clickhaler (Focus Pharmaceuticals Ltd)	Beclometasone Dipropionate
16151	91165020	Clenil Modulite 200micrograms/dose inhaler (Chiesi Ltd)	Beclometasone Dipropionate
2159	54705020	AeroBec 50 Autohaler (Meda Pharmaceuticals Ltd)	Beclometasone Dipropionate
52806	10732020	Qvar 100 Autohaler (Lexon (UK) Ltd)	Beclometasone Dipropionate
35106	93043020	Becodisks 100microgram with Diskhaler (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
1537	53711020	Becotide 200microgram Rotacaps (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
1259	69255020	Beclometasone 200micrograms/dose inhaler	Beclometasone Dipropionate
9599	82719020	Beclazone 50microgram/actuation Inhalation powder (Actavis UK Ltd)	Beclometasone Dipropionate
1236	48309020	Becloforte 250micrograms/dose inhaler (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate

3546	86873020	Qvar 50 inhaler (Teva UK Ltd)	Beclometasone Dipropionate
35113	93049020	Beclometasone 200microgram inhalation powder blisters	Beclometasone Dipropionate
14736	80129020	Pulvinal Beclometasone Dipropionate 400micrograms/dose dry powder inhaler (Chiesi Ltd)	Beclometasone Dipropionate
8111	48310020	Becloforte vm 250microgram/actuation VM pack (Allen & Hanburys Ltd)	Beclometasone Dipropionate
3220	86883020	Qvar 50 Autohaler (Teva UK Ltd) Beclometasone dipropionate	Beclometasone Dipropionate
883	68210020	Becodisks 200microgram Disc (Allen & Hanburys Ltd)	Beclometasone Dipropionate
35299	93063020	Becodisks 400microgram (GlaxoSmithKline UK Ltd)	Beclometasone Dipropionate
2893	69623020	Beclometasone 200micrograms disc Beclometasone Dipropionate 200micrograms Disc Inhalation	Beclometasone Dipropionate
4803	82721020	Beclazone 250microgram/actuation Inhalation powder (Actavis UK Ltd)	Beclometasone Dipropionate
56462	02818020	Becodisks 400microgram (Waymade Healthcare Plc)	Beclometasone Dipropionate
1861	54707020	AeroBec 100 Autohaler (Meda Pharmaceuticals Ltd)	Beclometasone Dipropionate
34859	63539020	Beclometasone 250microgram/actuation Inhalation powder (Neo Laboratories Ltd)	Beclometasone Dipropionate
51234	10727020	Qvar 100 inhaler (Waymade Healthcare Plc)	Beclometasone Dipropionate
27679	61524020	Beclometasone 100microgram/actuation Pressurised inhalation (Approved Prescription Services Ltd)	Beclometasone Dipropionate

15706	81506020	Beclometasone 100 micrograms/actuation vortex inhaler	Beclometasone Dipropionate
14590	85797020	Asmabec 250microgram/actuation Spacehaler (Celltech Pharma Europe Ltd)	Beclometasone Dipropionate
48709	10734020	Qvar 100micrograms/dose Easi-Breathe inhaler (Sigma Pharmaceuticals Plc)	Beclometasone Dipropionate
9921	86879020	Beclometasone 100micrograms/dose breath actuated inhaler CFC free	Beclometasone Dipropionate
10254	84120020	Mometasone 400micrograms/dose dry powder inhaler Mometasone furoate 400microgram/1dose Inhalation powder	Mometasone Furoate
17590	80362020	Asmanex 400micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)	Mometasone Furoate
16018	80792020	Mometasone 200micrograms/dose dry powder inhaler	Mometasone Furoate
16433	85228020	Asmanex 200micrograms/dose Twisthaler (Merck Sharp & Dohme Ltd)	Mometasone Furoate
21224	88720020	Alvesco 80 inhaler (Takeda UK Ltd) Ciclesonide 80microgram/1dose Pressurised inhalation	Ciclesonide
7356	88708020	Ciclesonide 80micrograms/dose inhaler CFC free	Ciclesonide
6839	88722020	Alvesco 160 inhaler (Takeda UK Ltd)	Ciclesonide
10102	88716020	Ciclesonide 160micrograms/dose inhaler CFC free	Ciclesonide
60920	10891020	Atrovent 20micrograms/dose inhaler CFC free (Sigma Pharmaceuticals Plc)	Ipratropium Bromide
43105	98206020	Atrovent 40microgram Aerocaps with Aerohaler (Boehringer Ingelheim Ltd)	Ipratropium Bromide
3306	58545020	Atrovent Forte 40micrograms/dose inhaler (Boehringer Ingelheim Ltd)	Ipratropium Bromide
43090	98208020	Atrovent 40microgram Aerocaps (Boehringer Ingelheim Ltd)	Ipratropium Bromide
1697	75004020	Atrovent 20micrograms/dose Autohaler (Boehringer Ingelheim Ltd) Ipratropium bromide 20microgram/1dose Pressurised inhalation	Ipratropium Bromide
1409	63608020	Ipratropium bromide 20micrograms/dose inhaler	Ipratropium Bromide
57557	10892020	Atrovent 20micrograms/dose inhaler CFC free (Lexon (UK) Ltd) Ipratropium bromide 20microgram/1dose Pressurised inhalation	Ipratropium Bromide
2994	72270020	Atrovent aerocaps 40microgram Inhalation powder (Boehringer Ingelheim Ltd)	Ipratropium Bromide

23709	88636020	Ipratropium 500micrograms/2ml nebuliser liquid Steri-Neb unit dose vials (Teva UK Ltd)	Ipratropium Bromide
6522	87822020	Ipratropium bromide 20micrograms/dose inhaler CFC free	Ipratropium Bromide
50810	39925020	Atrovent 20micrograms/dose inhaler CFC free (DE Pharmaceuticals)	Ipratropium Bromide
4268	63612020	Ipratropium bromide 40micrograms/dose inhaler Ipratropium bromide 40microgram/1dose Pressurised inhalation	Ipratropium Bromide
6512	87824020	Atrovent 20micrograms/dose inhaler CFC free (Boehringer Ingelheim Ltd)	Ipratropium Bromide
11779	72265020	Ipratropium bromide 40microgram inhalation powder capsules with device	Ipratropium Bromide
6081	63609020	Ipratropium bromide 20micrograms/dose breath actuated inhaler	Ipratropium Bromide
534	48252020	Atrovent 20micrograms/dose inhaler (Boehringer Ingelheim Ltd)	Ipratropium Bromide
8333	72266020	Ipratropium bromide 40microgram inhalation powder capsules	Ipratropium Bromide
9681	72269020	Atrovent aerohaler 40microgram Inhalation powder (Boehringer Ingelheim Ltd) Ipratropium bromide 40microgram Inhalation powder Antimuscarinic Bronchodilators Inhalation Antimuscarinic Bronchodilators	Ipratropium Bromide
6050	84108020	Spiriva 18 microgram Capsule (Boehringer Ingelheim Ltd) Tiotropium Bromide 18 Microgram Capsule Inhalation	Tiotropium Bromide
36869	94073020	Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Boehringer Ingelheim Ltd)	Tiotropium Bromide
51967	21580020	Spiriva 18microgram inhalation powder capsules (Mawdsley-Brooks & Company Ltd)	Tiotropium Bromide
35000	92699020	Spiriva 18microgram inhalation powder capsules (Boehringer Ingelheim Ltd)	Tiotropium Bromide
34995	92697020	Spiriva 18microgram inhalation powder capsules with HandiHaler (Boehringer Ingelheim Ltd)	Tiotropium Bromide
64232	44715021	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free (AM Distributions (Yorkshire) Ltd)	Tiotropium Bromide
50577	21583020	Spiriva 18microgram inhalation powder capsules with HandiHaler (DE Pharmaceuticals)	Tiotropium Bromide

36864	94071020	Tiotropium bromide 2.5micrograms/dose solution for inhalation cartridge with device CFC free	Tiotropium Bromide
746	73050020	Tiotropium 18 microgram Capsule inhalation Tiotropium Bromide 18 Microgram	Tiotropium Bromide
61582	26397021	Spiriva Respimat 2.5micrograms/dose solution for inhalation cartridge with device (Waymade Healthcare Plc)	Tiotropium Bromide
35011	92695020	Tiotropium bromide 18microgram inhalation powder capsules Tiotropium Bromide Monohydrate 18 MicrogramsInhalation Powder Capsules (refill) 18 MicrogramsInhalation Powder Capsules (refill)	Tiotropium Bromide
35014	92693020	Tiotropium bromide 18microgram inhalation powder capsules with device Tiotropium Bromide Monohydrate 18 Micrograms Inhalation Powder Capsules With Device	Tiotropium Bromide
2437	74071020	Oxitropium bromide 100micrograms/dose inhaler Oxitropium bromide 100microgram/1dose Pressurised inhalation	Oxitropium Bromide
9658	74072020	Oxitropium bromide 100micrograms/dose breath actuated inhaler	Oxitropium Bromide
3039	74069020	Oxivent 100micrograms/dose inhaler (Boehringer Ingelheim Ltd)	Oxitropium Bromide
3850	75001020	Oxivent 100micrograms/dose Autohaler (Boehringer Ingelheim Ltd)	Oxitropium Bromide
49227	44134020	Aclidinium bromide 375micrograms/dose dry powder inhaler Aclidinium bromide	Aclidinium Bromide
49228	44135020	Eklira 322micrograms/dose Genuair (AstraZeneca UK Ltd) Aclidinium bromide 375microgram/1dose	Aclidinium Bromide
63992	44771021	Eklira 322micrograms/dose Genuair (Waymade Healthcare Plc)	Aclidinium bromide
37432	94307020	Fostair 100micrograms/dose / 6micrograms/dose inhaler (Chiesi Ltd)	Beclometasone dipropionate/Formoterol fumarate dihydrate
37470	94305020	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose inhaler CFC free	Beclometasone dipropionate/Formoterol fumarate dihydrate

65894	60895021	Beclometasone 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	Beclometasone dipropionate/Formoterol fumarate dihydrate
62030	29629021	Beclometasone 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	Beclometasone dipropionate/Formoterol fumarate dihydrate
65658	60896021	Fostair NEXThaler 200micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)	Beclometasone dipropionate/Formoterol fumarate dihydrate
61644	29630021	Fostair NEXThaler 100micrograms/dose / 6micrograms/dose dry powder inhaler (Chiesi Ltd)	Beclometasone dipropionate/Formoterol fumarate dehydrate
50739	14019020	Symbicort 400/12 Turbohaler (Mawdsley-Brooks & Company Ltd)	Budesonide/Formoterol fumarate dehydrate
6796	86176020	Budesonide 200micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	Budesonide/Formoterol fumarate dihydrate
61782	27233021	DuoResp Spiromax 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Teva UK Ltd)	Budesonide/Formoterol fumarate dihydrate
51759	00048020	Symbicort 200/6 Turbohaler (Mawdsley-Brooks & Company Ltd)	Budesonide/Formoterol fumarate dihydrate
7013	81547020	Symbicort 100/6 Turbohaler (AstraZeneca UK Ltd)	Budesonide/Formoterol fumarate dihydrate
68034	00049020	Symbicort 200/6 Turbohaler (Necessity Supplies Ltd)	Budesonide/Formoterol fumarate dehydrate
51570	00046020	Symbicort 200/6 Turbohaler (DE Pharmaceuticals)	Budesonide/Formoterol fumarate dihydrate
53491	00047020	Symbicort 200/6 Turbohaler (Sigma Pharmaceuticals Plc)	Budesonide/Formoterol fumarate dihydrate

71284	78502021	Fobumix Easyhaler 320micrograms/dose / 9micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	Budesonide/Formoterol fumarate dihydrate
71371	00050020	Symbicort 100/6 Turbohaler (Waymade Healthcare Plc)	Budesonide/Formoterol fumarate dihydrate
71915	78958021	Fobumix Easyhaler 160micrograms/dose / 4.5micrograms/dose dry powder inhaler (Orion Pharma (UK) Ltd)	Budesonide/Formoterol fumarate dihydrate
10218	86175020	Budesonide 100micrograms/dose / Formoterol 6micrograms/dose dry powder inhaler	Budesonide/Formoterol fumarate dihydrate
6325	81548020	Symbicort 200/6 Turbohaler (AstraZeneca UK Ltd)	Budesonide/Formoterol fumarate dihydrate
6780	79213020	Symbicort 400/12 Turbohaler (AstraZeneca UK Ltd)	Budesonide/Formoterol fumarate dihydrate
53237	14017020	Symbicort 400/12 Turbohaler (DE Pharmaceuticals)	Budesonide/Formoterol fumarate dihydrate
6746	76616020	Budesonide 400micrograms/dose / Formoterol 12micrograms/dose dry powder inhaler	Budesonide/Formoterol fumarate dehydrate
50945	00054020	Symbicort 100/6 Turbohaler (Mawdsley-Brooks & Company Ltd)	Budesonide/Formoterol fumarate dihydrate
71354	14020020	Symbicort 400/12 Turbohaler (Necessity Supplies Ltd)	Budesonide/Formoterol fumarate dihydrate
61666	27378021	DuoResp Spiromax 320micrograms/dose / 9micrograms/dose dry powder inhaler (Teva UK Ltd)	Budesonide/Formoterol fumarate dihydrate
49114	00053020	Symbicort 100/6 Turbohaler (Sigma Pharmaceuticals Plc)	Budesonide/Formoterol fumarate dihydrate
51209	44172020	Fluticasone 125micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free	Fluticasone propionate/Formoterol fumarate dihydrate

64638	52509021	Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Waymade Healthcare Plc)	Fluticasone propionate/Formoterol fumarate dihydrate
48666	44175020	Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	Fluticasone propionate/Formoterol fumarate dihydrate
66448	52510021	Flutiform 250micrograms/dose / 10micrograms/dose inhaler (Waymade Healthcare Plc)	Fluticasone propionate/Formoterol fumarate dihydrate
68175	52511021	Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Waymade Healthcare Plc)	Fluticasone propionate/Formoterol fumarate dihydrate
50689	44177020	Flutiform 50micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	Fluticasone propionate/Formoterol fumarate dihydrate
51270	44176020	Fluticasone 50micrograms/dose / Formoterol 5micrograms/dose inhaler CFC free	Fluticasone propionate/Formoterol fumarate dehydrate
50036	44173020	Flutiform 125micrograms/dose / 5micrograms/dose inhaler (Napp Pharmaceuticals Ltd)	Fluticasone propionate/Formoterol fumarate dihydrate
49868	44174020	Fluticasone 250micrograms/dose / Formoterol 10micrograms/dose inhaler CFC free	Fluticasone propionate/Formoterol fumarate dihydrate
51394	02760020	Seretide 500 Accuhaler (Waymade Healthcare Plc)	Salmeterol xinafoate/Fluticasone propionate

6616	86896020	Salmeterol 25micrograms with fluticasone 50micrograms CFC free inhaler	Salmeterol Xinafoate/Fluticasone Propionate
5942	85657020	Salmeterol 50micrograms with fluticasone 250micrograms CFC free inhaler	Salmeterol Xinafoate/Fluticasone Propionate
67101	60670021	Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler (A A H Pharmaceuticals Ltd)	Salmeterol xinafoate/Fluticasone propionate
13273	85660020	Fluticasone propionate 100micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	Salmeterol xinafoate/Fluticasone propionate
5864	86898020	Salmeterol 25micrograms with fluticasone 250micrograms CFC free inhaler	Salmeterol Xinafoate/Fluticasone Propionate
51861	02764020	Seretide 500 Accuhaler (Mawdsley-Brooks & Company Ltd)	Salmeterol xinafoate/Fluticasone propionate
53230	02755020	Seretide 250 Accuhaler (DE Pharmaceuticals)	Salmeterol xinafoate/Fluticasone propionate
11410	85662020	Fluticasone propionate 500micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	Salmeterol xinafoate/Fluticasone propionate
61280	02753020	Seretide 250 Accuhaler (Waymade Healthcare Plc)	Salmeterol xinafoate/Fluticasone propionate

6938	85656020	Salmeterol 50micrograms with fluticasone 100micrograms dry powder inhaler	Salmeterol Xinafoate/Fluticasone Propionate
62126	02747020	Seretide 100 Accuhaler (DE Pharmaceuticals)	Salmeterol xinafoate/Fluticasone propionate
68983	71438021	Aerivio Spiromax 50micrograms/dose / 500micrograms/dose dry powder inhaler (Teva UK Ltd)	Salmeterol xinafoate/Fluticasone propionate3666
5558	85658020	Salmeterol 50micrograms with fluticasone 500micrograms CFC free inhaler	Salmeterol Xinafoate/Fluticasone Propionate
55677	02763020	Seretide 500 Accuhaler (Lexon (UK) Ltd)	Salmeterol xinafoate/Fluticasone propionate
13040	85661020	Fluticasone propionate 250micrograms/dose / Salmeterol 50micrograms/dose dry powder inhaler	Salmeterol xinafoate/Fluticasone propionate
6569	86897020	Salmeterol 25micrograms with fluticasone 125micrograms CFC free inhaler	Salmeterol Xinafoate/Fluticasone Propionate
638	79544020	Seretide 250 Accuhaler (GlaxoSmithKline UK Ltd)	Salmeterol xinafoate/Fluticasone propionate
665	85668020	Seretide 100 Accuhaler (GlaxoSmithKline UK Ltd)	Salmeterol xinafoate/Fluticasone propionate

63945	02757020	Seretide 250 Accuhaler (Lexon (UK) Ltd)	Salmeterol xinafoate/Fluticasone propionate
68495	02765020	Seretide 500 Accuhaler (Necessity Supplies Ltd)	Salmeterol xinafoate/Fluticasone propionate
51593	02766020	Seretide 500 Accuhaler (DE Pharmaceuticals)	Salmeterol xinafoate/Fluticasone propionate
53283	02745020	Seretide 100 Accuhaler (Waymade Healthcare Plc)	Salmeterol xinafoate/Fluticasone propionate
50560	02756020	Seretide 250 Accuhaler (Sigma Pharmaceuticals Plc)	Salmeterol xinafoate/Fluticasone propionate
59899	21595021	Fluticasone furoate 184micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler	Fluticasone furoate/Vilanterol
59327	21598021	Relvar Ellipta 92micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)	Fluticasone furoate/Vilanterol
59439	21597021	Fluticasone furoate 92micrograms/dose / Vilanterol 22micrograms/dose dry powder inhaler	Fluticasone furoate/Vilanterol
59573	21596021	Relvar Ellipta 184micrograms/dose / 22micrograms/dose dry powder inhaler (GlaxoSmithKline UK Ltd)	Fluticasone furoate/Vilanterol

Appendix D: CPRD READ and ICD-10 codes for outcomes of Interest

Code	**Description/Read Term**

PNEUMONIA	
H20..11	Chest infection - viral pneumonia
Q310300	Congenital pneumonia due to Escherichia coli
A789311	HIV disease resulting in Pneumocystis jirovecii pneumonia
H24y300	Pneumonia with Q-fever
Q310.00	Congenital pneumonia
H24z.00	Pneumonia with infectious diseases EC NOS
Hyu0A00	[X]Other bacterial pneumonia
H2B..00	Community acquired pneumonia
A380300	Septicaemia due to streptococcus pneumoniae
Hyu0D00	[X]Pneumonia in viral diseases classified elsewhere
H222.11	Pneumonia due to haemophilus influenzae
H247000	Pneumonia with candidiasis
4JRC.00	Atypical pneumonia screening test
H200.00	Pneumonia due to adenovirus
43n1.00	Mycoplasma pneumoniae antibody level
H24y100	Pneumonia with nocardiasis
H22y200	Pneumonia – Legionella
H22y.00	Pneumonia due to other specified bacteria
H21..00	Lobar (pneumococcal) pneumonia
H220.00	Pneumonia due to klebsiella pneumoniae
Hyu0H00	[X]Other pneumonia, organism unspecified February 2009
Q310400	Congenital pneumonia due to pseudomonas
A3C0300	Sepsis due to Streptococcus pneumoniae
43eG.00	Chlamydia pneumoniae IgG level
H241.00	Pneumonia with cytomegalic inclusion disease

H243.00	Pneumonia with whooping cough
H24..00	Pneumonia with infectious diseases
H20..00	Viral pneumonia
A3BXB00	Klebsiella pneumoniae/cause/disease classifd/oth chapters
H564.00	Bronchiolitis obliterans organising pneumonia
A789300	HIV disease resulting in Pneumocystis carinii pneumonia
H22y100	Pneumonia due to proteus
H261.00	Basal pneumonia due to unspecified organism
H25..00	Bronchopneumonia due to unspecified organism
H571.00	Rheumatic pneumonia
Q310500	Congenital pneumonia due to viral agent
H56y100	Interstitial pneumonia
H24y000	Pneumonia with actinomycosis
H530200	Gangrenous pneumonia
H231.00	Pneumonia due to mycoplasma pneumoniae
H233.00	Chlamydial pneumonia
H060A00	Acute bronchitis due to mycoplasma pneumoniae
H223000	Pneumonia due to streptococcus, group B
H2y..00	Other specified pneumonia or influenza
AB24.11	Pneumonia - candidal
H21..11	Chest infection - pneumococcal pneumonia
H201.00	Pneumonia due to respiratory syncytial virus
H20y.00	Viral pneumonia NEC
Hyu0B00	[X]Pneumonia due to other specified
H22y000	Pneumonia due to escherichia coli
H243.11	Pneumonia with pertussis
H262.00	Postoperative pneumonia
H270100	Influenza with pneumonia, influenza virus identified

H564.11	Cryptogenic organising pneumonia
H2z..00	Pneumonia or influenza NOS
H240.00	Pneumonia with measles
H242.00	Pneumonia with ornithosis
Q310y00	Other specified congenital pneumonia
H530300	Abscess of lung with pneumonia
4JUK.00	Mycoplasma pneumoniae detected
H22z.00	Bacterial pneumonia NOS
H25..11	Chest infection - unspecified bronchopneumonia
AyuK900	[X]Mycoplasma pneumoniae [PPLO]cause/dis classifd/oth chaptr
H232.00	Pneumonia due to pleuropneumonia like organisms
H22..11	Chest infection - other bacterial pneumonia
H270.11	Chest infection - influenza with pneumonia
H24y200	Pneumonia with pneumocystis carinii
H224.00	Pneumonia due to staphylococcus
Hyu0C00	[X]Pneumonia in bacterial diseases classified elsewhere
H222.00	Pneumonia due to haemophilus influenzae
Q310200	Congenital pneumonia due to group B haemolytic streptococcus
H270000	Influenza with bronchopneumonia
H247z00	Pneumonia with systemic mycosis NOS
H22y011	E.coli pneumonia
H247.00	Pneumonia with other systemic mycoses
H470312	Aspiration pneumonia due to vomit
H20z.00	Viral pneumonia NOS
H24y.00	Pneumonia with other infectious diseases EC
A3BXA00	Mycoplasma pneumoniae [PPLO] cause/dis classifd/oth chaptr
A3By400	Pleuropneumonia-like organism (PPLO) infection
A54x400	Herpes simplex pneumonia

H24y400	Pneumonia with salmonellosis
H22yz00	Pneumonia due to bacteria NOS
H23..00	Pneumonia due to other specified organisms
H202.00	Pneumonia due to parainfluenza virus
H223.00	Pneumonia due to streptococcus
H2C..00	Hospital acquired pneumonia
43n7.00	Chlamydia pneumoniae IgA level
Q310600	Congenital pneumonia due to Chlamydia
H244.00	Pneumonia with tularaemia
Hyu0800	[X]Other viral pneumonia
H2...00	Pneumonia and influenza
A730.00	Ornithosis with pneumonia
F00y400	Meningitis due to klebsiella pneumoniae
H270.00	Influenza with pneumonia
H23z.00	Pneumonia due to specified organism NOS
A116.00	Tuberculous pneumonia
H540100	Other bacterial pneumonia
H22..00	Other aspiration pneumonia as a complication of care
SP13100	Pneumonia due to unspecified organism
H26..00	Pneumonia with varicella
H24y700	[X]Klebsiella pneumoniae/cause/disease classifd/oth chapters
AyuKA00	Influenza with pneumonia NOS
H270z00	Pneumonia with other infectious diseases EC NOS
H24yz00	Aspiration pneumonia
H23..11	Chest infection - pneumonia organism OS
H56y000	Endogenous lipoid pneumonia
H540000	Hypostatic pneumonia
Q310000	Congenital pneumonia due to staphylococcus

H471000	Lipoid pneumonia (exogenous)
Q310100	Congenital pneumonia due to group A haemolytic streptococcus
Q310z00	Congenital pneumonia NOS
H22yX00	Pneumonia due to other aerobic gram-negative bacteria
A022200	Salmonella pneumonia
H24y500	Pneumonia with toxoplasmosis
43eH.00	Chlamydia pneumoniae IgM level
H221.00	Pneumonia due to pseudomonas
AB41500	Histoplasma duboisii with pneumonia
H260.00	Lobar pneumonia due to unspecified organism
H24y600	Pneumonia due to human metapneumovirus
A551.00	Pneumonia with typhoid fever
H230.00	Postmeasles pneumonia
AB40500	Pneumonia due to Eaton's agent
H246.00	Histoplasma capsulatum with pneumonia
H246.00	Pneumonia with aspergillosis
H247100	Pneumonia with coccidioidomycosis
STROKE	
8HTQ.00	Referral to stroke clinic
G663.00	Brain stem stroke syndrome
662M.00	Stroke monitoring
C315100	Mitochond encephalopathy, lact acidosis & strokelike episode
8Hd6.00	Admission to stroke unit
7P24200	Delivery of rehabilitation for stroke
13YA.00	Stroke group member
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
ZV12511	[V]Personal history of stroke

661M700	Stroke self-management plan agreed
L440.12	Stroke in the puerperium
38G3.00	Hyperten, abnorm renal/liver funct, stroke, BLED score
662e.00	Stroke/CVA annual review
9N0p.00	Seen in stroke clinic
G61..12	Stroke due to intracerebral haemorrhage
G64..13	Stroke due to cerebral arterial occlusion
9h21.00	Excepted from stroke quality indicators: Patient unsuitable
14AK.00	H/O: Stroke in last year
1M4..00	Central post-stroke pain
6F...00	Stroke prevention
9Om4.00	Stroke/transient ischaemic attack monitoring telephone invte
SN20z00	Heat stroke or sunstroke NOS
12C4.00	FH: CVA/stroke
662e.11	Stroke annual review
38DM.11	ABCD2 stroke risk score
9Om0.00	Stroke/transient ischaemic attack monitoring first letter
662o.00	Haemorrhagic stroke monitoring
662M100	Stroke 6 month review
9Om2.00	Stroke/transient ischaemic attack monitoring third letter
1154500	No significant family history of CVA or stroke
8HBJ.00	Stroke / transient ischaemic attack referral
8IEC.00	Ref multidisciplinary stroke function improvement declined
14A7.00	H/O: CVA/stroke
8HHM.00	Ref to multidisciplinary stroke function improvement service
388I.00	Stroke risk
9h2..00	Exception reporting: stroke quality indicators
1JA1011	Suspected stroke

G66..00	Stroke and cerebrovascular accident unspecified
38DM.00	Age, BP, clinical feat, duration, diabetes 2 stroke rsk scre
661N700	Stroke self-management plan review
38Go.00	QStroke 10 year risk of stroke calculator
SN20100	Sunstroke
Gyu6C00	[X]Sequelae of stroke,not specfd as h'morrhage or infarction
9Om..00	Stroke/transient ischaemic attack monitoring administration
38DE.00	Cong heart fail, hypertens, age, diab, stroke 2 risk score
9Om1.00	Stroke/transient ischaemic attack monitoring second letter
9Om3.00	Stroke/transient ischaemic attack monitoring verbal invitati
G664.00	Cerebellar stroke syndrome
G66..12	Stroke unspecified
8OAC.00	Provision of written information about stroke
ZLEP.00	Discharge from stroke serv
9h22.00	Excepted from stroke quality indicators: Informed dissent
SN20000	Heat stroke, unspecified
662M200	Stroke initial post discharge review
MYOCARDIAL INFARCTION	
G30X.00	Acute transmural myocardial infarction of unspecif site
G311011	MI - myocardial infarction aborted
G305.00	Lateral myocardial infarction NOS
G52y300	Septic myocarditis - pneumococcal
G520000	Acute aseptic myocarditis of the newborn
G520z00	Acute myocarditis in diseases EC, NOS
Q494.00	Transient myocardial ischaemia of newborn

G362.005	Ventric septal defect/curr comp fol acut myocardal infarctn
G380.00	Postoperative transmural myocardial infarction anterior wall
G52..00	Acute myocarditis
A364300	Meningococcal myocarditis
G384.00	Postoperative subendocardial myocardial infarction
P6y7.00	Myocardial bridge of coronary artery
G32..00	Old myocardial infarction
S710112	Myocardial contusion
G31y300	Transient myocardial ischaemia
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
14A4.00	H/O: myocardial infarct >60
14A..12	H/O: myocardial problem
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G52z.00	Acute myocarditis NOS
G311000	Myocardial infarction aborted
G52yz00	Other acute myocarditis NOS
G310.00	Postmyocardial infarction syndrome
G52y200	Idiopathic myocarditis NOS
G30yz00	Other acute myocardial infarction NOS
G520100	Acute myocarditis - coxsackie
G30z.00	Acute myocardial infarction NOS
G306.00	True posterior myocardial infarction
G550.00	Endomyocardial fibrosis
7L12300	Myocardial perfusion scan
G520500	Acute myocarditis - toxoplasmosis
P6yy500	Congenital anomaly of myocardium
5C02000	Radionuc myocard perfusn stress study us Tc-99m MIBI normal

14A3.00	H/O: myocardial infarct <60
G52y400	Septic myocarditis - staphylococcal
A17y100	Tuberculosis myocardium
Gyu5G00	[X]Acute myocarditis, unspecified
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G520600	Acute myocarditis - tuberculous
G304.00	Posterior myocardial infarction NOS
G5y8.00	Rheumatoid myocarditis
7P07500	Myocardial perfusion scan
Gyu5F00	[X]Other acute myocarditis
G5y7.00	Sarcoid myocarditis
G360.00	Haemopericardium/current comp folow acut myocard infarct
43Gm.00	Myocardial antibody level
A32y100	Diphtheritic myocarditis
G34y100	Chronic myocardial ischaemia
G5y0.00	Myocarditis NOS
9hM0.00	Exc myocard infarction quality indicators: informed dissent
G52y700	Toxic myocarditis
G30..00	Acute myocardial infarction
8HQE.11	Refer for myocardial perfusion scan
G520700	Acute myocarditis - meningococcal
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G52y111	Giant cell myocarditis
G353.00 7	Subsequent myocardial infarction of other sites
G52y600	Septic myocarditis NOS
G381.00	Postoperative transmural myocardial infarction inferior wall

G383.00	Postoperative transmural myocardial infarction unspec site
G5y1.00	Myocardial degeneration
G38..00	Postoperative myocardial infarction
ZV71900	[V]Observation for suspected myocardial infarction
G36..00	Certain current complication follow acute myocardial infarct
G35..00 316	Subsequent myocardial infarction
8HQE.00 15	Refer for radionuclide myocardial perfusion study
G30y.00	Other acute myocardial infarction
315A.00	Myocardial oxygen consumption
G344.00	Silent myocardial ischaemia
323Z.00	ECG: myocardial infarct NOS
9hM..00	Exception reporting: myocardial infarction quality indicator
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site
7P07300	Myocardial positron emission tomography
323..00	ECG: myocardial infarction
G308.00	Inferior myocardial infarction NOS
Gyu5J00	[X]Myocarditis in viral diseases classified elsewhere
14AH.00	H/O: Myocardial infarction in last year
G30B.00	Acute posterolateral myocardial infarction
G1y0.00	Rheumatic myocarditis
G35X.00	Subsequent myocardial infarction of unspecified site
3222.00	ECG:shows myocardial ischaemia
G38z.00	Postoperative myocardial infarction, unspecified

3232.00	ECG: old myocardial infarction
A93y100	Syphilitic myocarditis
G30X000	Acute ST segment elevation myocardial infarction
A742300	Coxsackie myocarditis
G32..11	Healed myocardial infarction
G32..12	Personal history of myocardial infarction
S312300	Closed fracture distal femur, supracondylar
Gyu3600	[X]Subsequent myocardial infarction of unspecified site
G30..17426	Silent myocardial infarction
G30..15	MI - acute myocardial infarction
G30..13	Cardiac rupture following myocardial infarction (MI)
G351.00	Subsequent myocardial infarction of inferior wall
G350.00	Subsequent myocardial infarction of anterior wall
G52y000	Acute myocarditis, unspecified
322Z.00	ECG: myocardial ischaemia NOS
Gyu3500	[X]Subsequent myocardial infarction of other sites
G012.00	Acute rheumatic myocarditis
G520300	Acute myocarditis - influenzal
3221.00	ECG: no myocardial ischaemia
14AT.00	History of myocardial infarction
G307100	Acute non-ST segment elevation myocardial infarction
B241200	Malignant neoplasm of myocardium
G301z00	Anterior myocardial infarction NOS
G301.00	Other specified anterior myocardial infarction
G52y.00	Other acute myocarditis
G303.00	Acute inferoposterior infarction
G311.12	Impending infarction
G30y200	Acute septal infarction

G300.00	Acute anterolateral infarction
G64z300	Right sided cerebral infarction
3234.00	ECG:posterior/inferior infarct
G302.00	Acute inferolateral infarction
9hM1.00	Exc myocar infarction quality indicators: patient unsuitable
G301100	Acute anteroseptal infarction
G307.003299	Acute subendocardial infarction
G86y600	Lymph vessel infarction
G311.00	Preinfarction syndrome
G301000	Acute anteroapical infarction
3233.0018	ECG: antero-septal infarct.
3235.00	ECG: subendocardial infarct
G307000	Acute non-Q wave infarction
3236.001	ECG: lateral infarction
G30y000	Acute atrial infarction
G311z00	Preinfarction syndrome NOS
32B2.00	ECG: Q wave abnormal
32B..00	ECG: Q wave
32B3.00	ECG: Q wave pathological
32F3.00	ECG: T wave flattened
326Z.00	ECG: ectopic beats NOS
321Z.00	ECG - general - NOS
32G2.00	ECG: U wave abnormal
32B2.00	ECG: Q wave abnormal
32B..00	ECG: Q wave
G30..12	Coronary thrombosis
1JH..009609	Suspected deep vein thrombosis
G82z.00	Embolism and thrombosis NOS

G82y.00	Other embolism and thrombosis
K138400	Renal artery stent thrombosis
L414.11	DVT - deep venous thrombosis, postnatal
G82zz00	Embolism and thrombosis NOS
G5yy800	Right ventricular thrombosis
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G30..14	Heart attack
ARRHYTHMIA	
G57..11	Cardiac arrhythmias
Gyu5a00	[X]Other specified cardiac arrhythmias
F256000	Hypsarrhythmia
328..00	ECG: ventricular arrhythmia
G559.00	Arrhythmogenic right ventricular cardiomyopathy
3281.00	ECG: no ventricular arrhythmia
G577.00	Sinus arrhythmia
327..00	ECG: supraventricular arrhythmia
1J62.00691	Suspected arrhythmia
G57yA00	Re-entry ventricular arrhythmia
328Z.00	ECG: ventricular arrhythmia
G57z.00	Cardiac dysrhythmia NOS
G57yz00	Other cardiac dysrhythmia
G57..00	Cardiac dysrhythmias
Q491.00	Neonatal cardiac dysrhythmia
G57y700	Sinus tachycardia
L263.12	Fetal bradycardia
G570000	Paroxysmal atrial tachycardia

TJC0.00	Adverse reaction to cardiac rhythm regulators
3282.00	ECG: ventricular tachycardia
SLC0.00	Cardiac rhythm drug poisoning
2426.00	O/E - pulse rate tachycardia
2422.00	O/E - pulse rate - bradycardia
G57y000	Persistent sinus bradycardia
HEART FAILURE	
8CL3.00	Heart failure care plan discussed with patient
8HTL.00	Referral to heart failure clinic
662W.00	Heart failure annual review
9Or0.00	Heart failure review completed
8IB8.00	Referral to heart failure exercise programme not indicated
G580400	Congestive heart failure due to valvular disease
8Hk0.00	Referred to heart failure education group
8IE1.00	Referral to heart failure exercise programme declined
1O1..00	Heart failure confirmed
8HgD.00	Discharge from heart failure nurse service
ZRad.00	New York Heart Assoc classification heart failure symptoms
8I98.00	Heart failure rehabilitation programme not available
9N6T.00	Referred by heart failure nurse specialist
G58z.00	Heart failure NOS
8HHz.00	Referral to heart failure exercise programme
9hH..00	Exception reporting: heart failure quality indicators
G583.00	Heart failure with normal ejection fraction
68B6.00	Heart failure screen
SP11111	Heart failure as a complication of care
679X.00	Heart failure education

9N0k.00	Seen in heart failure clinic
9Or2.00	Heart failure monitoring verbal invite
8IE0.00	Referral to heart failure education group declined
2126400	Heart failure resolved
G5y4z00	Post cardiac operation heart failure NOS
8CMK.00	Has heart failure management plan
67D4.00	Heart failure information given to patient
9hH1.00	Excepted heart failure quality indicators: Informed dissent
8HTL000	Referral to rapid access heart failure clinic
G583.11	HFNEF - heart failure with normal ejection fraction
G580.12	Right heart failure
1J60.00	Suspected heart failure
8Hg8.00	Discharge from practice nurse heart failure clinic
2JZ..00	On optimal heart failure therapy
9N4w.00	Did not attend heart failure clinic
G580000	Acute congestive heart failure
9Or5.00	Heart failure monitoring third letter
1I10.00	Heart failure excluded
9Or..00	Heart failure monitoring administration
106198	Heart failure self-management plan agreed
G58..00	Heart failure
9m5..00	High risk of heart failure screening invitation
9N2p.00	Seen by community heart failure nurse
G580100	Chronic congestive heart failure
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G582.00	Acute heart failure
G580.00	Congestive heart failure
8HBE.00	Heart failure follow-up

662p.00	Heart failure 6 month review
9N4s.00	Did not attend practice nurse heart failure clinic
9Or4.00	Heart failure monitoring second letter
388D.00	New York Heart Assoc classification heart failure symptoms
9Or1.00	Heart failure monitoring telephone invite
8HHb.00	Referral to heart failure nurse
14AM.00	H/O: Heart failure in last year
G583.12	Heart failure with preserved ejection fraction
8CeC.00	Preferred place of care for next exacerbation heart failure
9Or3.004513	Heart failure monitoring first letter
14A6.00	H/O: heart failure
8CMW800	Heart failure clinical pathway
679W100	Education about deteriorating heart failure
8H2S.00	Admit heart failure emergency
662T.00	Congestive heart failure monitoring
8B29.00	Cardiac failure therapy

APPENDIX E: List of Covariates for our events of interest

Arrhythmia	**Heart Failure**	**Myocardial Infarction**	**Stroke**	**Pneumonia**
Age at cohort entry	Age at cohort entry	Age at cohort entry	Age at cohort entry	Age at cohort entry
BMI: < 20 20-25 25-30 >30	BMI: < 20 20-25 25-30 >30	BMI: < 20 20-25 25-30 >30	BMI: < 20 20-25 25-30 >30	BMI: < 20 20-25 25-30 >30

Missing data	Missing data	Missing data	Missing data	Missing data
Alcohol abuse: Never Former Current Missing data	Alcohol abuse: Never Former Current Missing data	Alcohol abuse: Never Former Current Missing data	Alcohol abuse: Never Former Current Missing data	Alcohol abuse: Never Former Current Missing data
History of: Atherosclerosis Hypertension Hyperlipidaemia Congenital cardiovascular abnormalities Diabetes Renal disease Thyroid disease	History of: Atherosclerosis Hypertension Hyperlipidaemia Congenital cardiovascular abnormalities Diabetes Renal disease Thyroid disease	History of: Atherosclerosis Hypertension Hyperlipidaemia Congenital cardiovascular abnormalities Diabetes Renal disease Thyroid disease	History of: Hyperlipidaemia Peripheral arterial disease Acute coronary syndrome MI Heart failure Angina Atrial fibrillation Coronary Artery bypass graft	History of: Coronary artery diseasea Heart failure Diabetes mellitus Cerebrovascular disease Dementia
Age at index date	Age at index date	Age at index date	Age at index date	Age at index date
Sex	Sex	Sex	Sex	Sex
Smoking status: Never Former Current Missing data	Smoking status: Never Former Current Missing data	Smoking status: Never Former Current Missing data	Smoking status: Never Former Current Missing data	Smoking status: Never Former Current Missing data
Socioeconomic status [Index of Multiple Deprivation]	Socioeconomic status [Index of Multiple Deprivation]	Socioeconomic status [Index of Multiple Deprivation]	Socioeconomic status [Index of Multiple Deprivation]	Socioeconomic status [Index of Multiple Deprivation]

Prior use of; OCS Methylxanthines	Prior use of; OCS Methylxanthines	Prior use of; OCS Methylxanthines	Prior use of; OCS Methylxanthines	Prior use of; OCS Methylxanthines
Prior use Cardiovascular drugs: ACE inhibitors Angiotensin receptor blockers β-blockers Thiazide diuretics Loop diuretics Antiarrhythmics Digoxin (digitalis) Nitrates Non-aspirin antiplatelets Statins	Prior use Cardiovascular drugs: ACE inhibitors Angiotensin receptor blockers β-blockers Thiazide diuretics Loop diuretics Antiarrhythmics Digoxin (digitalis) Nitrates Non-aspirin antiplatelets Statins	Prior use Cardiovascular drugs: ACE inhibitors Angiotensin receptor blockers β-blockers Thiazide diuretics Loop diuretics Antiarrhythmics Digoxin (digitalis) Nitrates Non-aspirin antiplatelets Statins	Drug use: ACE inhibitors Angiotensin receptor blockers β-blockers Calcium channel blocker Lipid lowering medication Antiplatelet Nitrates Anticoagulant	Drug use: Oxygen Antipsychotics Acid suppressants Immunosuppressants Influenza vaccination Pneumococcal vaccination
Prior use of Drugs prolonging QT interval: Antibiotics Antidepressants Antipsychotics Phosphodiesterase 3 inhibitor Antihistamine Anticancer GI stimulant	Prior use of Drugs prolonging QT interval: Antibiotics Antidepressants Antipsychotics Phosphodiesterase 3 inhibitor Antihistamine Anticancer GI stimulant	Prior use of Drugs prolonging QT interval: Antibiotics Antidepressants Antipsychotics Phosphodiesterase 3 inhibitor Antihistamine Anticancer GI stimulant	Stroke risk factors: Positive family history Dyslipidemia Hypertension Diabetes	Other comorbidities: Malignancy (excluding nonmelanoma skin cancer) disease Chronic liver disease Chronic renal disease Stroke Osteoporosis

Antidepressant Cholinesterase inhibitor Antifungal Psychedelic Antiemetic Antilipemic	Antidepressant Cholinesterase inhibitor Antifungal Psychedelic Antiemetic Antilipemic	Antidepressant Cholinesterase inhibitor Antifungal Psychedelic Antiemetic Antilipemic		
Other medications: Insulin Aspirin NSAIDs Acetaminophen Opioids	Other medications: Insulin Aspirin NSAIDs Acetaminophen Opioids	Other medications: Insulin Aspirin NSAIDs Acetaminophen Opioids	Other medications: Insulin NSAIDs Acetaminophen Opioids	Other medications: Insulin NSAIDs Acetaminophen Opioids

APPENDIX III: Validation of Asthma-COPD Overlap Syndrome in the Clinical Practice Research Datalink (CPRD.

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

30. Study Title[§] (*Please state the study title below)*

Validation of Asthma-COPD Overlap Syndrome in the Clinical Practice Research Datalink (CPRD)

[§]*Please note: This information will be published on the CPRD's website as part of its transparency policy.*

31. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes * ☐ No ☒

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

32. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes* ☒ No ☐

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :* Canada Respiratory Research Network (CRRN)

33. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☒

Health/Public Health Services Research	☒	Other*	☐

If Other, please specify the type of study here and in the lay summary below:

34. Health Outcomes to be Measured§

§*Please note: This information will be published on CPRD's website as part of its transparency policy.*

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Positive Predictive Value (PPV)
-
-
-
-
-
-

[Please add more bullet points as necessary]

35. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

36. Chief Investigator§

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Zhiwei Gao; MD, PhD

Assistant Professor, Clinical Epidemiology

Academic Director, Statistics Canada Research Data Center, Memorial University

Memorial University of Newfoundland, Canada

Zhiwei.Gao@med.mun.ca

§*Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy*

CV has been previously submitted to ISAC ☒ **CV number:** 009_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

37. Affiliation of Chief Investigator (full address)

Room: 4M130, Clinical Epidemiology Unit

Faculty of Medicine, Memorial University

300 Prince Phillip Drive,

St. John's, NL A1B 3V6

PHONE: +1 (709)8646622

38. Corresponding Applicant[§]

Please state the full name, affiliation(s) and e-mail address below:

Joseph Emil Amegadzie, BSc, MSc, PhD Researcher

Faculty of Medicine

Memorial University of Newfoundland, Canada

Joseph.amegadzie@med.mun.ca

[§]*Please note: The name and organisation of the corresponding applicant and their organisation name will be published on CPRD's website as part of its transparency policy*

Same as chief investigator ☐

CV has been previously submitted to ISAC ☒ **CV number:** 006_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

39. List of all investigators/collaborators[§]

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

[§]*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: **William Midodzi, PhD., P. Stat**

Assistant Professor

Clinical Epidemiology Unit

Faculty of Medicine

Memorial University of Newfoundland, Canada

William.Midodzi@med.mun.ca

CV has been previously submitted to ISAC ☒ **CV number:** 007_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: **John-Michael Gamble, BScPharm. MSc., PhD.**

Clinical Associate Professor

University of Waterloo

School of Pharmacy

Kitchener, Ontario, Canada

jm.gamble@uwaterloo.ca

CV has been previously submitted to ISAC ☒ **CV number:** 008_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

Other investigator: **Jamie Farrell, BSc., MD, FRCPC**

Assistant Professor of Medicine (Respirology)

Department of Medicine

Memorial University of Newfoundland, Canada

Jamie.Farrel@med.mun.ca

CV has been previously submitted to ISAC ☒ **CV number:** 010_18

A new CV is being submitted with this protocol ☐

An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

40. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

This study is supported by a grant from the Canadian Respiratory Research Network (CRRN), with a collaboration with Clinical Practice Research Datalink (CPRD), a centre of Medicines and Healthcare products Regulatory Agency (MHRA).

CRRN is a national research network with their largest funders being the Canadian government and charity.

Funding for this project was sourced via CRRN Young Investigator Award, 2017.

The authors have no conflict of interest to declare.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

41. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☒
> 3	☒	☐

Experience/Expertise available	**Yes**	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Zhiwei Gao** **William Midodzi**	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* **Zhiwei Gao** **William Midodzi** **John-Michael Gamble**	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)*	☐	☒

42. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

1. Nissen, F., et al., *Validation of asthma recording in the Clinical Practice Research Datalink (CPRD).* BMJ Open, 2017. **7**(8): p. e017474.
2. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.
3. Piras, B. and M. Miravitlles, *The overlap phenotype: the (missing) link between asthma and COPD.* Multidiscip Respir Med, 2012. **7**(1): p. 8

SECTION C: ACCESS TO THE DATA

43. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☐	*Please specify name and country:*
Government / NHS	☐	*Please specify name and country:*
Charity	☐	*Please specify name and country:*
Other	☒	**Canadian Respiratory Research Network, Canada. A national research Network with their largest funders being the Canadian government and charity**
None	☐	

44. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	***Memorial University, Newfoundland, Canada***
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

45. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☐

A data set will be provided by the CPRD¥€ ☐

CPRD has been commissioned to extract the data and perform the analyses€ ☐

Other: ☐

If Other, please specify: GPs will be contacted by CPRD personnel to fill out electronic questionnaires. CPRD personnel will be solely in charge of this process.

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*

***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*

¥*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*

€*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher: Brooke Jackson Reference number (where available) Date of contact

46. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.

Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher Reference number (where available) Date of contact

SECTION D: INFORMATION ON DATA LINKAGES

47. Does this protocol seek access to linked data

Yes* ☐ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset PROMS data and the Pregnancy Register **must** also discuss this with a member of the CPRD Research team before submitting an ISAC*

application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements ***before*** *submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

48. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

- ☐ ONS Death Registration Data
- ☐ HES Admitted Patient Care
- ☐ HES Outpatient
- ☐ HES Accident and Emergency
- ☐ HES Diagnostic Imaging Dataset
- ☐ MINAP (Myocardial Ischaemia National Audit Project)
- ☐ Cancer Registration Data*
- ☐ PROMS (Patient Reported Outcomes Measure)**
- ☐ CPRD Mother Baby Link
- ☐ Pregnancy Register

- ☐ Practice Level Index of Multiple Deprivation (Standard)
- ☐ Practice Level Index of Multiple Deprivation (Bespoke)
- ☐ Patient Level Index of Multiple Deprivation***
- ☐ Patient Level Townsend Score ***
- ☐ Other**** *Please specify:*

**Applicants seeking access to cancer registration data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*

***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only accessible by academics*

**** 'Patient level IMD and Townsend scores will not be supplied for the same study*

*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher: Brooke Jackson Reference number (where available) Date of contact

49. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should* ***<u>not</u>*** *be included in this count)* 1

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

50. Is linkage to a <u>local</u>[¥] dataset with <1 million patients being requested?

Yes * ☐ No ☒

**If yes, please provide further details:*

[¥] *Data from defined geographical areas i.e. non-national datasets.*

51. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

52. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

53. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

54. Does this protocol involve requesting any additional information from GPs?

Yes* ☒ No ☐

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☒ No ☐

Is the questionnaire a validated instrument? Yes ☐ No ☒

If yes, has permission been obtained to use the instrument? Yes ☐ No ☐

Please provide further information:

Other (please describe)

[ψ] *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

55. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

56. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

57. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;
- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Zhiwei Gao Date:27/01/2019 e-Signature (type name): Zhiwei Gao

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
D. Study Title§ §*Please note: This information will be published on CPRD's website as part of its transparency policy* Validation of Asthma-COPD Overlap Syndrome in the Clinical Practice Research Datalink (CPRD*)*
E. Lay Summary (Max. 200 words)§ §*Please note: This information will be published on CPRD's website as part of its transparency policy* Our study is to assess the utility of various search procedures or algorithms to best locate general practitioner (GP) confirmed asthma-COPD (Chronic Obstructive Pulmonary Disease) overlap syndrome (ACOS) cases, using independent expert verification of the GP view and validate these procedures in the primary care medical records database of the Clinical Practice Research Datalink (CPRD GOLD). This will be done by the collection of information provided by GPs through a questionnaire. This information will then be examined by two independent expert respiratory physicians, giving a reliable diagnosis to be compared with the recording of patients with a possible diagnosis of asthma-COPD overlap syndrome within the CPRD database. According to published clinical guidelines, cases of asthma-COPD overlap

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
syndrome are a subset of patients with respiratory disease who have features of both asthma and COPD. Our study when performed, would help to establish the best possible method to locate individuals with asthma-COPD overlap syndrome within the CPRD and inform more accurate patient selection in future studies.
F. Technical Summary (Max. 200 words) [§] [§]*Please note: This information will be published on CPRD's website as part of its transparency policy* The overall aim of our study is to determine the positive predictive value (PPV) of four algorithms among patients assumed to have been diagnosed with asthma-COPD overlap syndrome within CPRD GOLD. In order to achieve this, a cross-sectional study consisting of patients with possible diagnosis of asthma-COPD overlap syndrome will be constructed using these algorithms in which 200 cases will be randomly selected. Diagnostic information about these patients will be filled out by GPs via online questionnaire. The information collected from the GPs will be reviewed by two independent respiratory physicians whose opinions will be considered as the gold standard to assess PPV of an asthma-COPD overlap syndrome within CPRD. The main analysis is calculation of PPV's for each of our four algorithms. PPV is denoted as the proportion of true positives among those assumed to have been diagnosed with asthma-COPD overlap syndrome.
U. Objectives, Specific Aims and Rationale **Aim:** To assess the utility of various search algorithms to best locate GP confirmed ACOS cases in United Kingdom electronic primary care records and to validate these algorithms. The outcome of interest is asthma-COPD overlap syndrome diagnosis within the CPRD database.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
Objectives: To determine the PPV of the recording of asthma-COPD overlap syndrome diagnosis of adults within the CPRD GOLD database. **Rationale:** In undertaking this study, we will be able to assess how accurately the algorithms are able to locate asthma-COPD overlap syndrome patients within the CPRD, by adopting a gold standard comprised of independent expert verification of the GP view. Thus, identification of properly-validated algorithms to locate patients with asthma-COPD overlap from CPRD databases will inform more accurate patient selection in future studies.
V. Study Background Asthma and chronic obstructive pulmonary disease (COPD) are the two most common obstructive airway diseases (OADs). Recently a new phenotype, referred to as asthma-COPD overlap syndrome (ACOS) or asthma-COPD overlap (ACO) has been identified with its first guidelines for treatment and management in effect since 2015. [1] In clinical practice, asthma-COPD overlap is therefore characterized by presenting features of both asthma and COPD.[1] Most clinical practice guidelines identify patients with asthma-COPD overlap syndrome for the presence of the following factors: 1) bronchial obstruction with a strong, although incomplete, reversibility to bronchodilation tests; 2) cigarette smoke exposure; 3) history of atopy or asthma. Other diagnostic features include a good response to corticosteroid treatment, eosinophilic airway and systemic inflammation and a high concentration of nitric oxide.[2] An airflow limitation that is persistent is the main functional criterion required for the diagnosis of both ACOS and COPD. An indication of a post-bronchodilator of

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
FEV_1/FVC less than the lower limit of normal (LLN) is also generally considered. The GOLD guidelines suggest the use of a fixed cut-off of 0.70, but stressed that they may be overdiagnosis in the older age groups because of deteriorating health. Accordingly, the American Thoracic Society (ATS) further recommends, a significant bronchodilator response, an increase by FEV_1 and/or FVC >200 mL or 12% from baseline for ACOS diagnosis.[3] The British guideline on the management of asthma recommends that the diagnosis in asthmatics should be based on the recognition of a characteristic pattern of symptoms and signs and the absence of an alternative explanation. The diagnosis is then confirmed or rejected based on spirometry and/or a trial of treatment with corticosteroids. [4] Algorithms based on patient's information of diagnosis, medication and spirometry to locate cases in hierarchically coded healthcare databases such as the Clinical Practice Research Datalink (CPRD) can be developed by a single code, combination of multiple codes or sets of codes. As noted by Nissen et al. [19] the accuracy of diagnoses recorded in these large databases may be low, which would introduce bias into studies using the data. Unless the algorithms are validated for research, the quality of studies generated from Electronic Health Records (EHRs) may be debatable. They developed an algorithm, to increase the ability to locate case definitions for asthma in the CPRD database, using a diagnosis plus spirometry plus specific medication. They found out that extra information on asthma medication prescription (PPV 83.3%), evidence of reversibility testing (PPV 86.0%) or a combination of all three selection criteria (PPV 86.4%) did not result in a higher PPV.[5]

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
Furtherance to this recommendations, COPD, which has a lot of symptoms in common with asthma can be identified with high PPV from the CPRD datasets using diagnostic Read codes alone (PPV=86.5%) or combined with COPD medications plus spirometry (PPV=89.4%) [6]. To determine the validity of any health outcome, a clear understanding of the data and the algorithms to be used to identify health outcomes in these databases is required. This can be ascertained using questionnaires completed by a patient or physician, medical charts review, medical notes, manual review or an independent second database.[5, 7] To date, there has not been any validation of asthma-COPD overlap syndrome undertaken in any electronic database anywhere as it is evident that clinical examination necessary for the diagnosis of the asthma-COPD overlap syndrome is time and resource demanding. It would be important for epidemiological studies to be able to obtain accurate records of ACOS diagnosis within electronic databases of primary health-care records. The aim of this study is therefore to understand and quantify how accurate the algorithms are able to locate asthma-COPD overlap syndrome patients within the CPRD. When subsequent studies are therefore to be performed, it will be better understood how well the data truly reflects diagnoses of ACOS. The CPRD database has been extensively used in obstructive airways disease (OADs) studies such as COPD and asthma because it captures a broad range of patients and goes back a long time. The current study will focus on the accuracy of asthma-COPD overlap syndrome recordings in adults in CPRD, by measuring the PPV of four different algorithms within the CPRD database and comparing it to a gold standard diagnosis given by two (2) independent respiratory physicians reviewing the answers of the GP questionnaire.

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

W. Study Type

This is a methodological study.

X. Study Design

This is a validation study of algorithms to ascertain asthma-COPD overlap syndrome (ACOS). A cross-sectional study consisting of patients with asthma-COPD overlap syndrome will be constructed and compare database information (CPRD GOLD) with information collected by questionnaire filled in by GPs. We will therefore locate patients from CPRD GOLD with potential ACOS according to our four algorithms listed below and then randomly select cases to be validated by GP questionnaire.

Algorithms to Identify Asthma-COPD Overlap Syndrome (ACOS)

1. Specific "Asthma-chronic obstructive pulmonary disease overlap syndrome" code only
2. COPD code + Asthma code + smoking history code + prescription of inhaled asthma and/or COPD therapy
3. Asthma code + COPD code + evidence of reversibility testing (spirometry or trial of treatment) *or variable PEFR* + smoking history code
4. COPD code and asthma code + evidence of reversibility testing (spirometry or trial of treatment) *or variable PEFR*

Random sample of individuals to be included in the study will be constructed from all participants registered in CPRD on or after 1 January 2004 who meet our inclusion criteria (see below). For the main

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
analysis, we include all patients selected by at least one algorithm listed above and in Appendix 2. It is however possible an individual will be selected by more than one algorithm depending on the Read codes used in their medical record. Individuals will be randomly selected from whatever algorithm that they meet the criteria for. However, a patient may still be eligible to be selected for another algorithm if they meet the criteria of a different algorithm. Based on previous validation studies conducted in the CPRD, [5] we have chosen this strategy (as opposed to an individual being eligible for a single algorithm only and thus cannot be selected for another algorithm) because we want to test the validity of the diagnostic algorithms that we will use to accurately identify ACOS patients.
Y. Feasibility counts Not applicable
Z. Sample size considerations The number of records for whom either a COPD and/or asthma monitoring plan was started exceeds 600,000; and the total number of OADs-related consultations exceeds 10,000,000 in the CPRD database. Based on the above assumption, and an estimated PPV of 0.85 for an algorithm and an accuracy of the PPV (95% CI ± 0.08), 200 questionnaires will be sent. However, similar studies on both COPD and asthma had response rates of 73.2% and 69.4% respectively. [5, 6] Based upon the 73.2% and 69.4% response rates we expect there to be more than 230 available questionnaires in order to achieve 200 completed.
AA. Data Linkage Required (if applicable):§

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable*'**
§*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy* The data linkage of CPRD-GOLD to Index of Multiple Deprivation is required to gather more information on the socio-economic status of the studied records. The Index of Multiple Deprivation on patient level data will be the most appropriate for this study; however, if this is not available, then the Index of Multiple Deprivation on practice level will be used instead. Once responses (validations) are obtained for coded patients that a linkage could be applied subsequently to those specific patients.
BB. Study population **Inclusion Criteria** At cohort entry, subjects have to be ≥40 years. Also, the study patient fits in one of the ACOS algorithms with acceptable user status registered in CPRD. Patients have to be alive at least 24 months of the last data collection and latest data build date for inclusion in the analysis so that CPRD can access their medical records and any supporting information. The patient's registered GP practice is "up to standard" at study start 1/1/2004. From this date onwards, the Quality and Outcomes Framework (QOF) came in effect. **Exclusion Criteria:** • The patient does not fit the criteria of an algorithm group and missing information on age • Younger than 40 years
CC. Selection of comparison group(s) or controls

Applicants must complete all sections listed below

Sections which do not apply should be completed as '*Not Applicable*'

Since this is a validation study, there will be no comparison group. Our study algorithms will consist of only patients with a possible recording of asthma-COPD overlap syndrome.

DD. Exposures, Health Outcomes[§] and Covariates

[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

Exposure: Individuals will be randomly selected from whatever algorithm that identifies them with ACOS. However, a patient may still be eligible to be chosen for another algorithm that they meet the criteria of (see appendix 2).

Also, a code list for both COPD and asthma diagnosis to locate cases of the overlap syndrome can be found in Appendix 3.

Covariates for stratification analysis:

- Age (40-44, 45-54, 55-64 and ≤ 65)
- Gender (male, female)
- Body Mass Index (< 18.5kg/m^2, [underweight], 18.5-24 kg/m^2 [normal], 25-29kg/m^2 [overweight], ≥ 30kg/m^2 [obese])
- Race/ethnicity
- Education attainment

- Cigarette smoking status
- Other comorbid conditions
- Family history
- Atopy history
- MDI

Outcome: Recording of asthma-COPD overlap syndrome diagnosis according to any of our specified algorithms listed above and in Appendix 2; and verified by the gold standard.

The "gold standard diagnosis" would be based on description of asthma-COPD overlap syndrome outlined in the GINA/GOLD clinical guideline. [1]

Our validation study questionnaire is a two-page structured questionnaire which will be sent online to GPs based on a random sample of patients in their respective practices who fit in a certain algorithm to obtain information for the "gold standard". Contact has been made with CPRD personnel who will be in charge of study questionnaire and its distribution to GPs for data collection. A draft of the questionnaire can be found in Appendix 1.

EE. Data/ Statistical Analysis

The main analysis will be the calculation of the proportion of true positives (i.e. PPV) in each of our four predefined algorithms. The gold standard will consist of the opinion of two respiratory physicians independently reviewing the questionnaires and any supporting information provided. The "gold

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
standard diagnosis" would be based on description of asthma-COPD overlap syndrome outlined in the GINA/GOLD clinical guideline. [1] If there is a disagreement of diagnosis, the case would be discussed by the two experts. If an agreement cannot be found, a third opinion will be sought. Our analysis will be stratified based on our covariates list (see covariates list above), which will be used to assess potential effect modification or confounding by covariates.
FF. Plan for addressing confounding Not applicable.
GG. Plans for addressing missing data In our validation study, we plan to do a complete case analysis, assuming that the probability of data being missing is independent of accuracy of the ACOS diagnosis, conditional on covariates. If the amount of missing data is small, any violation of the assumption is very unlikely to importantly affect the results. However, we anticipate a low degree of missing data for our covariates.
HH. Patient or user group involvement (if applicable) Not applicable
II. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication Upon the completion of the study analyses, the new knowledge and findings generated will be communicated to appropriate knowledge-users, including research, policy-makers and healthcare

professionals such as Canadian Respiratory Research Network (CRRN), Canadian Thoracic Society (CTS) etc. Results found in this healthcare research will be published in high impact journals (*British Medical Journal, Canadian Medical Association Journal*), as well as subspecialty (*Chest, Epidemiology*).

JJ. Limitations of the study design, data sources, and analytic methods

1. Using a GP questionnaire as the source of patient information in order to obtain a gold standard to validate the overlap syndrome diagnosis can be problematic as the GP can consult the electronic health record to see if there was ACOS diagnosis. This could lead to an overestimation of the PPV.
2. Incomplete diagnostic information will lead to missing data which we will be unaware. This could lead to some inaccuracy in PPV or classification of ACOS probability.
3. Only patients who are alive will be assessed, as GP's no longer have access to the patient records after death. This excludes the records of the deceased patients and could result in survival bias.
4. Miscoding accidents could lower the PPV.
5. Response rate for the questionnaire might be lower than expected, and the sample size of the completed questionnaires could be too small.
6. By focusing on the PPV, we will not be able to accurately assess the NPV, specificity or sensitivity. By preselecting the population of possible ACOS cases, the NPV, specificity and sensitivity would be artificially manipulated. The NPV is the Negative Predictive Value: the proportion of negative results that are true negatives

7. We are also assuming that the probability of data being missing is independent of accuracy of the ACOS diagnosis. However, we anticipate little missing relevant data in this study based on past researches in asthma and COPD. Additionally, the covariates are needed for stratification analysis only, rather than for adjustment. We anticipate the impact of missing data to be small.

8. Not all GP practices contribute to CPRD, and patients might refuse to participate in the CPRD programme. This can result in selection bias.

KK. References

1. Asthma, G.I.f., *Global Strategy for Asthma Management and Prevention* Availbable from: www. ginasthma. org, 2018 Global Initiative for Asthma. **2018 Update**.
2. Sin, D.D., et al., *What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion.* Eur Respir J, 2016. **48**(3): p. 664-73.
3. Cosio, B.G., et al., *Defining the Asthma-COPD Overlap Syndrome in a COPD Cohort.* Chest, 2016. **149**(1): p. 45-52.
4. British Thoracic Society Scottish Intercollegiate Guidelines, N., *British Guideline on the Management of Asthma.* Thorax, 2008. **63 Suppl 4**: p. iv1-121.
5. Nissen, F., et al., *Validation of asthma recording in electronic health records: a systematic review.* Clin Epidemiol, 2017. **9**: p. 643-656.
6. Quint, J.K., et al., *Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD).* BMJ Open, 2014. **4**(7): p. e005540.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
7. Nissen, F., et al., *Validation of asthma recording in the Clinical Practice Research Datalink (CPRD).* BMJ Open, 2017. **7**(8): p. e017474.

APPENDIX VI: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7, 8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8, 9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, 10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, 11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11-13

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19, 20
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

APPENDIX V: MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition	Yes	4, 5
Hypothesis statement	Yes	3
Description of Study Outcome(s)	Yes	5
Type of exposure or intervention used	Yes	4
Type of study design used	Yes	4
Study population	Yes	4
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)	Yes	6
Search strategy, including time period included in the synthesis and keywords	Yes	6
Effort to include all available studies, including contact with authors	Yes	6
Databases and registries searched	Yes	5, 6
Search software used, name and version, including special features used (eg, explosion)	Yes	6
Use of hand searching (eg, reference lists of obtained articles)	Yes	6
List of citations located and those excluded, including justification	Yes	5, 6
Method for addressing articles published in languages other than English	Yes	6
Method of handling abstracts and unpublished studies	Yes	6
Description of any contact with authors	Yes	6
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	5, 6
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	6, 7
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	6, 7
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	7, 8

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	8
Assessment of heterogeneity	Yes	9
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	8, 9
Provision of appropriate tables and graphics	Yes	6
Reporting of Results		
Table giving descriptive information for each study included	Yes	9
Results of sensitivity testing (eg, subgroup analysis)	Yes	14
Indication of statistical uncertainty of findings	Yes	11, 14
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	14, 19
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	6, 19
Assessment of quality of included studies	Yes	14, 19
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	19, 20
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	19
Guidelines for future research	Yes	20
Disclosure of funding source	Yes	20

APPENDIX VI

MEDLINE SEARCH STRATEGY USED TO IDENTIFY ARTICLES

1. Search ("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]
2. Search asthma AND (COPD OR chronic obstructive pulmonary disease)
3. Search ((asthma AND (COPD OR chronic obstructive pulmonary disease))) OR (("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh])
4. Search "Adrenergic beta-2 Receptor Agonists"[Mesh]
5. Search "Adrenergic beta-2 Receptor Agonists"[Mesh] OR beta-2 adrenergic receptor agonists OR beta 2 agonists OR muscarinic antagonists OR inhaled corticosteroids OR ICS OR inhaledcorticosteroids OR cholinergic antagonists OR beclomethasone dipropionate OR budesonide OR flunisolide OR fluticasone propionate OR mometasone furoate OR triamcinolone acetonide OR ciclesonide OR Formoterol OR salmeterol OR formoterol OR vilanterol
6. Search (("Adrenergic beta-2 Receptor Agonists"[Mesh] OR beta-2 adrenergic receptor agonists OR beta 2 agonists OR muscarinic antagonists OR inhaled corticosteroids OR ICS OR inhaledcorticosteroids OR cholinergic antagonists OR beclomethasone dipropionate OR budesonide OR flunisolide OR fluticasone propionate OR mometasone furoate OR triamcinolone acetonide OR ciclesonide OR Formoterol OR salmeterol OR formoterol OR vilanterol)) AND (((asthma[tiab] AND (COPD[tiab] OR chronic obstructive pulmonary disease[tiab]))) OR (("Asthma"[Mesh]) AND "Pulmonary Disease, Chronic Obstructive"[Mesh]))

EMBASE SEARCH STRATEGY USED TO IDENTIFY ARTICLES

No.	Query	Results	Date
#7	((('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt) OR (asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti)) AND (('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic antagonists' OR 'cholinergic antagonists' OR 'cholinergic receptor blocking agents') OR (budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline))	2046	1 Jun 2018
#6	('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic antagonists' OR 'cholinergic antagonists' OR 'cholinergic receptor blocking agents') OR (budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline)	116522	1 Jun 2018
#5	budesonide OR fluticasone OR mometasone OR beclomethasone OR ciclesonide OR flunisolide OR ipratropium OR tiotropium OR salmeterol OR indacaterol OR olodaterol OR vilanterol OR formoterol OR salbutamol OR terbutaline OR fenoterol OR rimiterol OR pirbuterol OR reproterol OR orciprenaline	88013	1 Jun 2018
#4	'beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists' OR 'inhaled corticosteroid' OR 'ics' OR 'muscarinic	40278	1 Jun 2018

	antagonists' OR 'cholinergic antagonists' OR 'cholinergic receptor blocking agents'		
#3	(('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt) OR (asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti)	9765	1 Jun 2018
#2	asthma:ab,ti AND (copd:ab,ti OR chronic) AND obstructive AND pulmonary AND disease:ab,ti	9692	1 Jun 2018
#1	('asthma'/exp OR asthma) AND 'chronic obstructive pulmonary disease':jt		

WEB OF SCIENCE (WOS) SEARCH STRATEGY USED TO IDENTIFY ARTICLES

((((('asthma OR asthma) AND 'chronic obstructive pulmonary disease') OR ((((asthma AND (copd OR chronic)) AND obstructive) AND pulmonary) AND disease)) AND (((((((('beta 2 adrenergic receptor stimulating agent' OR 'beta 2 agonists') OR 'inhaled corticosteroid') OR 'ics') OR 'muscarinic antagonists') OR 'cholinergic antagonists') OR 'cholinergic receptor blocking agents') OR ((((((((((((((((((budesonide OR fluticasone) OR mometasone) OR beclomethasone) OR ciclesonide) OR flunisolide) OR ipratropium) OR tiotropium) OR salmeterol) OR indacaterol) OR olodaterol) OR vilanterol) OR formoterol) OR salbutamol) OR terbutaline) OR fenoterol) OR rimiterol) OR pirbuterol) OR reprotool) OR orciprenaline)))

APPENDIX VII: Risk of bias assessment in individual observational studies

Study	No active Comparator	Channeling bias	Depletion of Susceptible	Lack of Statistical Power	Residual confounding	Immortal time	Time-lag	Time-window
Afonso et al., 2016					♦			
Brode et al., 2017					♦	♦		
Gershon et al., 2014					♦			
Hubbard et al., 2006		♦	♦	♦	♦	♦		
Lim et al., 2014				♦	♦	♦		
Su et al., 2018					♦			
Uddin et al., 2016					♦			
Yeh et al., 2018					♦			

♦Indicates presence of bias or methodological issue in the study