EFFECTIVENESS OF INHALED CORTICOSTEROIDS IN PREVENTING MORBIDITY AND
MORTALITY IN INDIVIDUALS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE
AND THE IMPACT OF COEXISTING ASTHMA

by

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a devastating illness that affects 4.3% of the population of British Columbia over the age of 45 years. Asthma is known to coexist in 10-20% of individuals with obstructive lung disease, and adds to the substantial burden of illness posed by COPD alone. Inhaled corticosteroids (ICS) are currently recommended for the management of COPD among individuals with frequent exacerbations; however, the ability of inhaled corticosteroids to reduce death and hospitalizations among individuals with COPD is controversial. Less is known about the effectiveness of ICS among individuals who are afflicted with both COPD and asthma.

Methods: We used a retrospective cohort study design and administrative data to estimate the relative effectiveness of ICS in reducing hospitalizations or death among individuals with concomitant asthma and COPD, compared with individuals with COPD alone. We used an extended Cox model to estimate this association, with a time-varying measure of exposure to ICS.

Results: We did not find any association between ICS and hazard of death or hospitalization among individuals with COPD alone (HR = 0.99; 95% CI: 0.94 – 1.05), however the hazard was 18% lower (HR = 0.82; 95% CI: 0.69-0.99) among individuals with concomitant disease.

Conclusions: Individuals with combined COPD and asthma show significant benefit from the use of ICS and are more responsive to the effects of ICS than individuals with COPD alone.

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List of Abbreviations

ACG®	Adjusted Clinical Groups
ATS	American Thoracic Society
BC	British Columbia
BC GPAC	British Columbia Guidelines and Protocols Advisory Committee
BCLHD	British Columbia Linked Health Database
CMA	Continuous multiple availability
COPD	Chronic Obstructive Pulmonary Disease
CTS	Canadian Thoracic Society
DAG	Directed Acyclic Graph
DNA	Deoxyribonucleic Acid
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HDAC2	Histone deacetylase 2
HRQL	Health related quality of life
ICD-9	International Classification of Diseases – version 9
ICD-10	International Classification of Diseases – version 10
ICS	Inhaled Corticosteroids
IQR	Interquartile range
ISOLDE	Inhaled Steroids in Obstructive Lung Disease in Europe
IV	Instrumental variables
LABA	Long acting beta agonist
MSM	Marginal structural model
MSP	Medical Services Plan
RCT	Randomized Controlled Trial

SD	Standard Deviation
TORCH	TOWards a Revolution in COPD Health
TRISTAN	Trial of Inhaled Steroids And long-acting β_2 agonists

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1 Introduction

1.1 Overview

Chronic obstructive pulmonary disease (COPD) is a devastating illness characterized by progressive airway obstruction. It affects 4.3 percent of British Columbia (BC) residents over the age of 45 years,¹ and is projected to be the third leading cause of death by the year 2020.² The disease has no cure and places an enormous burden on the health care system due to a lifetime of treatment required to alleviate individuals' symptoms.

COPD and asthma are known to coexist in 10-20% of individuals with obstructive lung disease.³ Although the two diseases share similar clinical characteristics, their combined presence is associated with a much higher burden of disease than the combined burden of both individually.⁴

Inhaled corticosteroids (ICS) have been demonstrably effective in reducing morbidity and mortality in persons affected by asthma;⁵ however, there is no consensus as to the effectiveness of the drug in reducing these outcomes among individuals with COPD.^{6,7} Despite the additional burden posed by individuals with concomitant COPD and asthma, little is known about the effectiveness of ICS in reducing morbidity or mortality in this population with combined disease.

1.2 Overarching objectives

The thesis describes much of the background research that was undertaken in order to design and conduct the study of ICS effectiveness among individuals afflicted with COPD, with and without coexisting asthma. The broad objectives of the thesis were: to review the literature regarding the disease area of COPD and coexisting asthma; to review evidence of ICS treatment effectiveness; to identify sources of bias that could affect observational studies of ICS effectiveness; and to identify analytical techniques to reduce these sources of bias. Ultimately, the goal of the thesis was to use this information to design and conduct a study that compares

estimates of ICS effectiveness among COPD-afflicted individuals with and without coexisting asthma, and to interpret the findings of the study in the context of what is known.

1.3 Responsibilities

The candidate was responsible for conceiving the specific study question, designing the methodology study described in this thesis, coding and analyzing all data, and for the authorship of the entire document. The candidate and members of the thesis committee jointly conceived of conducting a study in the area of COPD and identified appropriate sources of data to inform the study. Prescription claims, physician billing and hospitalization data were made available through an existing dataset provided by the BC Linked Health Database to Dr. Carleton who also provided some study variables partially coded for the purpose of a different study by Dr. Robert Prosser.

Members of the thesis committee provided methodological and statistical expertise in the conduct of the research and the interpretation of the results (Drs. Adrian Levy and Andrew Briggs) and clinical expertise and guidance and the interpretation of the results (Drs. Robert Levy and Bruce Carleton). Students in the Department of Healthcare and Epidemiology and the Thesis Screening Panel provided feedback and guidance on some aspects of the study design.

For literary convention, and to reflect the inputs of all involved in the study, the first person plural is used throughout the thesis, although it is recognized that the candidate is responsible for the contents of the thesis.

1.4 Structure of thesis

The remainder of the thesis will be structured as follows. Chapter two introduces the disease area of COPD – its current definition, epidemiology, burden of illness, management, and the role of ICS in disease management. We also present what is known about coexisting COPD and asthma. In chapter three, we discuss major methodological challenges in pharmacoepidemiological studies and analytic approaches to minimizing the impact of these

challenges. The specific objectives of the study are stated in chapter four. Chapter five contains a detailed description of the methods applied in the study with the results of the study described in chapter six. Chapter seven is the discussion section of the thesis, in which the results of the study are interpreted in the context of what is currently known, and what is still not well understood. Additionally, we critically evaluate the internal and external validity of the study and discuss the extent to which the study results represent the true effectiveness of ICS in a population of individuals with coexisting asthma and COPD, compared with individuals with COPD alone. We conclude the thesis with potential directions for future research in the field.

2 Background on COPD

2.1 Definition of COPD

COPD includes three pathologic subtypes: chronic bronchitis, characterized by excessive mucous secretion,⁸ chronic bronchiolitis, characterized by inflammation of the peripheral airways,⁹ and emphysema, characterized by the destruction of the lung alveoli.¹⁰ These pathological subtypes are difficult to diagnose, and most patients have all three pathologic conditions in varying degrees.⁹ For this reason, the formal definition of COPD, according to the 2007 CTS guidelines is defined functionally:

“COPD is a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, systemic manifestations, and increasing frequency and severity of exacerbations.”¹¹

Physicians in BC are currently referred to the 2007 CTS guidelines¹¹ as a guide for diagnosing and treating COPD, with additional recommendations published by the BC Guidelines and Protocols Advisory Committee (BC GPAC).¹² Both guidelines emphasize the need for diagnosing COPD at an early stage, using targeted spirometric testing in high-risk patients. The BC GPAC recommends using the criteria of 1) FEV_1 ¹ less than 80% of the predicted value (based on age, height, sex and race) and 2) FEV_1/FVC ² <0.7 postbronchodilator, indicative of a positive diagnosis of COPD.¹² Additional disease staging guidelines incorporating clinical symptoms are shown in Table 2.1.

¹ Forced Expiratory Volume in 1 second: The volume of air that can be forced out in one second after taking a deep breath

² Forced Vital Capacity: The total volume of air that can be forced out after taking a deep breath

2.2 Natural History of untreated COPD

2.2.1 Lung Function

The hallmark of COPD is the progressive decline in lung function over time. Studies by Burrows and Earle,¹³ and Fletcher and Peto¹⁴ were among the first to characterize the temporal decline in lung function among individuals with COPD. Their studies showed that the rate of lung function decline changed over time, with more rapid decline associated with more severe disease. Furthermore, they found that smoking cessation retarded the rate of decline such that, eventually, it slowed to the age-related rate of decline observed among non-smokers without COPD (Figure 2.1). The Lung Health Study, which enrolled individuals at high risk for developing COPD, validated this finding in an experimental setting, finding a difference in the rate of lung function decline between two arms of its study: lung function declined an average of 62.3mL/year among patients receiving usual care, compared with an average decline of 47.0mL/year among patients who received a smoking intervention along with usual care.¹⁵ Untreated, the rate of lung function decline in COPD-afflicted patients ranges from 47mL/year to 69mL/year¹⁶⁻¹⁹ (values observed in the placebo arms of clinical trials of treatment for COPD, measured using FEV₁), with larger rates of decline occurring among patients of greater disease severity.

2.2.2 Exacerbations

The symptoms of stable COPD are punctuated by periods of intense symptom severity, called exacerbations. Acute exacerbations are characterized by sustained (48 hours or more) worsening of shortness of breath and coughing leading to an increase in the use of maintenance medication and/or supplementation with additional medications.²⁰ They are the most frequent cause of medical visits, hospital visits and death among patients with COPD,²⁰ and the most common cause is a viral or bacterial infection.¹²

An increased rate of decline in lung function is associated with frequent exacerbations history of respiratory tract infections.^{21,22} Recovery from an exacerbation may take weeks or

months^{22,23} and a significant proportion of individuals may never show complete resolution of lung function or symptoms.²⁴ This incomplete recovery may partially explain the accelerated rate of decline in lung function among individuals experiencing frequent exacerbations. The proposed mechanism is illustrated in Figure 2.2.

Individuals with severe COPD tend to have more exacerbations than those with moderate or mild COPD,²⁵ implying that the frequency of exacerbations increases over time. Although this increase in frequency has yet to be confirmed in longitudinal studies,²⁵ it has been demonstrated that the severity of exacerbation (characterized by increase in symptoms, recovery time and likelihood of hospitalization) increases over time.²⁵

2.3 Pulmonary and systemic inflammation in COPD

Airway inflammation is a major component of COPD that causes dyspnea, wheezing, and hyperinflation of the lungs. The inflammation evident in COPD arises from an abnormal inflammatory response in the central and peripheral airways and the lung parenchyma.⁹ The prolonged and chronic nature of the inflammation causes the bronchial tissue to become scarred and unable to fully expand, and produces symptoms such as bronchoconstriction, hypersecretion of mucus, and pain.⁹

The principal cells involved in the inflammatory process of COPD are T lymphocytes, mononuclear cells, neutrophils, macrophages, and scanty eosinophils.^{9,26} The specific roles of these cells in the inflammatory process, and their effect on lung function is described elsewhere.^{27,28} Of importance to the current study is that the cell types evident in the lungs of individuals with COPD differ from those that exist in normal inflammatory response, as well as those presenting in other respiratory diseases.

The inflammatory process affecting individuals with COPD is not limited to that occurring in the airways. The CTS and Global Initiative for Chronic Obstructive Lung Disease (GOLD) definitions of COPD describe “systemic manifestations”²⁰ and “extrapulmonary effects”⁸ associated with COPD. Elevated levels of systemic inflammatory markers – C-reactive protein,

fibrinogen, leucocytes, tumor necrosis factor- α , and interleukins 6 and 8 – have been found in patients with COPD,²⁹ supporting the notion that individuals with COPD experience systemic effects of the disease. This is further corroborated by the observation that COPD-afflicted individuals often have multiple comorbid medical conditions, including skeletal muscle abnormalities, hypertension, diabetes, coronary artery disease, heart failure, pulmonary infections, cancer, autoimmune disorders, weight loss and nutritional abnormalities and pulmonary vascular disease.^{30,31} Although this association between systemic inflammation and COPD has been established, it remains to be determined whether the systemic effects that coexist with COPD are caused in part by the abnormal inflammatory processes associated with COPD or whether they arise independently due to the same insult that caused the pulmonary inflammation.^{30,31}

2.4 COPD and asthma

Asthma is another respiratory disease that is characterized by restricted airflow. According to the Canadian guidelines on adult asthma,

“Asthma is characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli. Inflammation and its resultant effects on airway structure are considered to be the main mechanisms leading to the development and maintenance of asthma”⁵

The “Dutch Hypothesis,” suggested in 1961 by a group of researchers in the Netherlands, proposes that the two diseases share genetic origins and should be considered as a single disease.³² Although some facets of the argument are sound,³³ the weight of evidence lines up against the hypothesis.³⁴ In contemporary clinical practice, the diseases are considered distinct and are defined and managed differently. Although features of the two diseases appear similar, we will highlight some of the principal differences.

Functionally, COPD and asthma can be differentiated from one another based on spirometric tests of lung function. The test is administered twice: once before and once after administering a bronchodilator. Compared with individuals who have COPD, those with asthma

typically have a greater improvement in FEV₁ from the baseline 15 minutes after use of an inhaled short-acting β_2 -agonist.¹² According to the 2007 CTS guidelines, an improvement in FEV₁ of more than 0.4L can be suggestive of asthma.¹¹ An oral corticosteroid may also be administered to differentiate between the two diseases:¹² symptoms tend to improve with this treatment in individuals with asthma whereas those with COPD may not improve. Neither test is diagnostically definitive because individuals with COPD can have a partially reversible component to their disease, and individuals with asthma can have a partially irreversible component.^{5,11} Furthermore, the improvement in FEV₁ after the use of a bronchodilator is highly variable within individuals³⁵ – in a study of individuals with moderate to severe COPD, approximately 50% changed responder status (defined as an improvement in FEV₁ of more than 0.2L) when tested repeatedly over time.³⁵ Therefore, even when using spirometry testing to guide diagnosis, the distinction between asthma and COPD in cases with partial airflow reversibility can be difficult.

A major difference between asthma and COPD lies in their inflammatory profiles. As described in section 2.3, the cell types present in the inflammatory process of COPD differ from those in asthma. The inflammatory cells in asthma are primarily CD4+ cells and eosinophils, whereas those in COPD are mainly CD8+ cells and neutrophils. The relevance of this lies in the differential response of these cells to pharmacological treatments³⁶ such as ICS, which has been shown to be more effective in reducing eosinophilic inflammation than neutrophilic inflammation (see section 2.8).³⁶

The different inflammatory profiles in COPD and asthma result in different lung pathologies that manifest into different symptom presentation.³⁶ In asthma, airway smooth muscle contracts as a result of multiple bronchoconstrictor mediators being released from inflammatory cells. This causes episodic wheezing, breathlessness, and coughing.³⁷ In COPD, the airflow limitation arises from structural changes of small airways and closure of small airways as a

result of disrupted alveolar attachments, resulting in air trapping and dyspnea. This gives rise to the more constant feeling of breathlessness that is characteristic of COPD.³⁷

A summary of the key differences between COPD and asthma is presented in Table 2.2.

2.4.1 Co-existing COPD and Asthma

Some individuals are described by clinicians as having “COPD-like” asthma and others as having “asthma-like” COPD. However, the two diseases can coexist.^{8,11} Between 10% and 20% of people with obstructive lung disease have are believed to have both asthma and COPD,³ although given the difficulties in diagnostic definitions, this value is not well defined. A common scenario resulting in the coexistence of both diseases is when asthmatic individuals develop COPD later in life, typically after many years of smoking. Some evidence exists suggesting that asthma is a risk factor for COPD, with higher rates of COPD occurring in asthmatics who smoke than in non-asthmatic smokers.³⁸

The coexistence of asthma and COPD creates a challenge in disease management because of differences in guidelines for the two respiratory diseases.^{5,11} There is a paucity of information regarding the effectiveness of treatment among individuals with concomitant asthma and COPD, as this sub-population is typically excluded from randomized controlled trials (RCT) in both disease areas. One RCT was recently conducted exclusively in patients with coexisting disease, measuring the efficacy of an anticholinergic in improving lung function. The authors reported a beneficial effect of tiotropium on lung function and symptomatic relief compared with placebo.³⁹ With respect to effectiveness of therapies in reducing outcomes such as death or hospitalizations in this population, more research is needed.

Little else is known about co-existing COPD and asthma. The remainder of the introduction focuses on what is known about COPD because the study objectives focus on this population – specifically the comparative effectiveness of ICS across subgroups of this disease.

2.5 Epidemiology of COPD

2.5.1 Incidence and Prevalence

In BC, COPD is reported to affect 4.3% of the population aged over 45 years.¹ In 2003/2004 there were 8,000 new cases of COPD in BC (0.5% of the BC population over the age of 45 years).¹ Worldwide, reported prevalence and incidence estimates vary substantially. Some reasons for this variability will be discussed in section 2.5.2.

2.5.2 Challenges in estimating true prevalence and incidence of COPD

Choosing a method to identify individuals afflicted with COPD that is both sensitive and specific poses a considerable challenge.⁴⁰ The estimates reported in section 2.5.1 were generated based on the criteria of two physician visits or one hospitalization per year, as recorded in administrative records. Administrative databases contain numeric codes that uniquely identify diseases (International Classification of Diseases – ICD). The study investigators used the ICD codes corresponding to “chronic bronchitis”, “emphysema”, and “chronic airway obstruction, not elsewhere classified” to identify cases (Table 2.3). A fourth ICD-9 code – 490: “bronchitis, not specified as acute or chronic” includes both COPD patients (chronic bronchitis) and non-COPD patients (acute bronchitis); however, it is impossible to determine the patient diagnosis from this code alone. In an analysis of the RAMQ database in Quebec, this code represented 63% of the four ICD codes potentially representing COPD.⁴¹ The use of this ambiguous code greatly reduces the specificity of the diagnoses of COPD in administrative databases. Inclusion of this diagnostic code inflates the estimate of COPD incidence and prevalence by including cases of acute bronchitis; however exclusion of the code may provide an underestimate. Additional discussion regarding the validity of recording data into administrative databases is discussed further in section 3.1.2.3.

The use of health services utilization to determine incidence and prevalence – including through analysis of administrative databases and surveys of patient-reported diagnosis – may underestimate the true values. Because airflow restriction in COPD occurs gradually over time,

rather than with sudden onset, individuals may progressively restrict their activity levels than to seek medical attention, particularly when the disease is in a mild state. Analysis of the Third National Health and Nutrition Examination Survey indicated that 63.3% of subjects with documented low lung function had no prior or current reported diagnosis of any obstructive lung disease,⁴² suggesting that COPD is a highly under-diagnosed disease, and that records of physician visits underestimate disease prevalence. Conversely, spirometric screening is thought to yield a high number of false positive results, and produces an overestimate of prevalence.⁴³ The burden of obstructive lung disease initiative (BOLD) is presently undertaking a study to estimate the prevalence of COPD in countries around the world in a standardized fashion, incorporating spirometry as well as clinical symptoms and exposure history.⁴⁴

Another major challenge in comparing prevalence and incidence of COPD across jurisdictions and over time lies in the definition of the disease. Historically, there was no standard definition of COPD – the major guidelines published different definitions in different jurisdictions. Applying the spirometry guidelines of the ATS and the ERS on a study population in Northern Italy resulted in airways obstruction prevalence of 57% using the ATS definitions compared with 12% using the ERS guidelines.⁴⁵ Until recently, there was no international consensus on the definition of COPD. In 1997, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed and comprised an international panel of experts to raise awareness of COPD and to improve prevention and treatment. GOLD developed a consensus definition, severity grading system and disease management guidelines. Several national societies have adopted the GOLD disease definition;⁴⁶ the CTS has recently done so.¹¹ This common definition will facilitate global comparisons of COPD prevalence, but until it has been adopted internationally, inter-country comparisons will remain unreliable.⁴⁷

For estimating disease incidence, disease registries are a superior resource because incident cases can be captured at diagnosis; however, such registries do not exist for COPD⁴⁸ and few estimates of COPD incidence exist.^{49,50}

2.5.3 Risk factors

There are many component causes⁵¹ that may contribute to the development of COPD. Smoking is the most commonly cited attributable cause, but is neither necessary nor sufficient for developing the disease: 10 to 20% of individuals diagnosed with COPD have never been smokers,⁵² and 80 to 90% of smokers never develop COPD.⁵³ Exposure to noxious gases and air pollution has been linked to the development of COPD, as well as occupational exposures to grain, isocyanates, cadmium, coal, other mineral dust, and welding fumes.⁵³

There is evidence that a genetic component contributes to COPD susceptibility,^{48,53} with the α -1-antitrypsin gene commonly cited.^{8,20,53,54} Several regions of the genome have been identified that contain genes associated with increased risk of COPD,⁸ but results of these genetic association studies have been inconsistent, and no genes other than α -1-antitrypsin have been definitively identified as influencing the development of COPD.⁸

Women are thought to be more susceptible to COPD than men: upon diagnosis and in age- and severity-matched studies, females tend to have smoked fewer pack-years than their male counterparts.⁵⁵⁻⁶⁰

Associations between nutrition (low levels of vitamins C and E), socioeconomic status, and lower respiratory infections during childhood have also been linked with development of COPD later in life.⁵³

2.6 Burden of illness

2.6.1 Individual burden of illness

The health-related quality of life (HRQL) of COPD-afflicted individuals is severely compromised, even in the early stages of disease.⁶¹ As the disease progresses, the health status of individuals deteriorates.⁶² Individuals develop increasingly severe feelings of breathlessness and are frequently unable to participate in daily activities or attend work; as a result, they often feel isolated and depressed.⁴⁹ In the Confronting COPD study, one quarter of

the subjects described themselves as having to “stop for breath every few minutes when walking even on level ground” or were “too breathless to leave the house”.⁶³

The intensified symptoms experienced during acute exacerbations affect the HRQL of individuals throughout the period of the exacerbation, and continue to reduce HRQL throughout recovery and between exacerbations,⁶⁴ due to incomplete recovery and anxiety surrounding future exacerbations.⁴⁹

2.6.2 Societal burden of illness

The morbidity and mortality associated with COPD has been steadily increasing over recent decades.^{2,8,40,48,65} Projections of the global burden of illness suggest that by 2020, COPD will become the third leading cause of death worldwide, and the fifth leading cause of morbidity.² In Canada, the number of deaths from COPD increased by 95% between 1980 and 1995.⁶⁵ In 1998, it accounted for 4% of all deaths in Canada, the 4th highest among men and 7th highest among women.⁶⁶ The cause-specific mortality rate for COPD is likely underestimated.^{49,50} Statistics Canada records only the underlying cause of death in the National Mortality Database,⁶⁵ omitting deaths where COPD was an intermediate or contributing cause. Inaccuracies in the diagnosis, in chart completion, or chart transcription would also contribute to underestimates, as well omissions due to un-diagnosed cases of COPD.⁴²

2.6.3 Economic Burden of illness

Although COPD poses a considerable societal burden, there is little information regarding the total economic burden of disease in Canada.⁶⁷ Estimates of direct annual costs from other countries have ranged from USD\$200 to \$10,800 (year unknown) per patient per year depending on country, disease severity, and study methodology.⁴⁸ The Confronting COPD study, based on a telephone interview of 401 self-reported COPD patients, used micro-costing to estimate an annual direct medical cost of CDN\$1998 (2003) per patient.⁶⁷ A 1998 report by Health Canada estimated CDN\$467 million as the total cost of hospital care and

pharmacotherapy for treating persons with COPD.⁶⁸ This figure excluded the cost of physician visits and of ancillary services.

The economic burden of COPD is estimated to be 50% greater than the burden of asthma.⁴ Among individuals with concomitant COPD and asthma, the direct medical costs are estimated to be greater than that of either disease alone (5.25 times the burden of asthma, and 3.5 times the burden of COPD), as well as greater than the additive combination of the individual costs.⁴

2.6.4 COPD Hospitalizations

COPD-related hospitalizations are the largest contributor to the direct medical costs of the disease.⁶⁹ A study of the American National Medical Expenditure Survey estimated the cost of inpatient hospitalization and emergency department care in the United States to account for 73% of total COPD-related expenditures.⁷⁰ The Confronting COPD study in Canada attributed 57% of the mean annual direct medical cost per patient to inpatient hospitalizations and emergency room visits.⁶⁷

Individuals with COPD are typically admitted to hospital between one and four times per year, depending on severity, with between 46% and 86% of patients making at least two visits in a year.⁷¹ In BC, 9% of patients discharged from a hospital following an acute exacerbation are re-admitted within two weeks of discharge.¹

2.7 Disease Management

2.7.1 Stable COPD

COPD cannot be cured. The goals of disease management focus on slowing the progression of disease, alleviating the symptoms, preventing exacerbations, improving exercise tolerance, HRQL, and survival.¹¹ Smoking cessation is the only intervention that is able to slow this accelerated rate of decline.¹⁵ Other treatments – pharmacologic therapy, pulmonary rehabilitation, oxygen therapy, and surgical interventions – are used as disease severity increases, illustrated in Figure 2.3.

Pharmacologic treatment – bronchodilators and ICS – alleviate symptoms, improve HRQL and have been shown to reduce the occurrence of exacerbations⁷², however have not been shown to modify the rate of decline in lung function. Bronchodilators act on the airway smooth muscle, widening the airways, improving airflow, and reducing dynamic hyperinflation at rest and during exercise. The action of ICS will be discussed in greater detail in section 2.8.

Non-pharmacologic treatment is also important in COPD management. Supplemental oxygen therapy is provided for individuals who have low levels of blood oxygen at rest. It has been shown to improve exercise tolerance and HRQL, and is the only therapy that has been shown to improve survival among COPD patients in an experimental setting.⁷² Pulmonary rehabilitation – which includes exercise training, nutritional counseling, and education – has been shown to have beneficial effects on exercise capacity, HRQL, duration and frequency of hospitalizations, and feelings of anxiety and depression.⁸ Surgical interventions have yielded positive results in some COPD patients, however, these interventions are expensive, show unattractive cost-effectiveness ratios in most subgroups,⁷³ and have a high risk of post-operative complications, and are not recommended for the routine management of COPD.⁸

2.7.2 Acute Exacerbations

Management of exacerbations of COPD depends on their cause and severity. Most exacerbations are caused by viral or bacterial infections;¹² however, for approximately one-third of severe exacerbations, the cause is unknown.⁸ For less severe exacerbations that can be managed at home, recommended treatment involves bronchodilator therapy, a possible course of antibiotics if necessary, and oral corticosteroids if the exacerbation is not resolved within hours.⁸ For more severe exacerbations that must be managed in hospital, standard treatment may involve controlled oxygen therapy, intravenous methylxanthines, intravenous glucocorticosteroids, and/or noninvasive mechanical ventilation.⁸

2.8 Inhaled Corticosteroids

ICS are currently recommended in combination with long acting beta agonists for individuals with moderate to severe COPD.¹¹ Among individuals with infrequent exacerbations, ICS/LABA is only recommended for individuals who do not respond to bronchodilators alone, whereas this combination is recommended for all individuals who experience frequent exacerbations.¹¹

Glucocorticoids (e.g. cortisol, cortisone) are types of corticosteroids naturally produced by the adrenal glands that regulate the metabolism of carbohydrates and proteins and provide anti-inflammatory effects.⁷⁴ Synthetic glucocorticoids are prescribed to counteract the body's inflammatory process; however, their effects also include suppression of the immune response, altered metabolism, reduced serum calcium levels, and regulation of mood and behaviour.⁷⁵ Therefore, prolonged exposure is avoided. When administered topically, the systemic effects of the glucocorticoids are substantially reduced, improving the safety and side-effect profile of the drugs, and allowing for continued use.⁷⁴ Inhaled corticosteroids are topically administered glucocorticoids used for treatment of respiratory disease. They can be inhaled using a dry powder inhaler, pressurized metered-dose inhaler, or nebulas.⁷⁶

2.8.1 Mechanism of action

Glucocorticoids bind with steroid receptors in the cell cytoplasm and then enter the nucleus and bind to deoxyribonucleic acid (DNA). A cascade of events leads to a reversal of the inflammatory response.⁷⁵

One mechanism of ICS action of particular relevance is through histone acetylation.⁷⁷ COPD patients have been observed to have impaired function of histone deacetylase 2 (HDAC2) due to cigarette smoking and oxidative stress.⁷⁸ The impaired function is thought to reduce the responsiveness to the beneficial effects of ICS,⁷⁸ which provides some rationale behind why ICS has been shown to provide less symptom relief in individuals with COPD than in asthmatics.

ICS is associated with significant reductions in airway inflammation, allowing for improved air exchange.⁷⁹ Beneficial effects of ICS on lung function have been seen within one week of treatment initiation.^{80,81} Evidence of long term benefits of ICS on lung function decline, death, symptom relief, and exacerbation frequency, will be reviewed in detail in sections 2.8.4 and 2.8.5.

2.8.2 Historical and current recommended use of ICS

Historically, there is little consensus on the role of ICS in the management of COPD. Only recently is consensus emerging.^{6,7} The 1992 CTS guidelines state that that

“[a]lthough there is clear evidence of airway inflammation in COPD it is less clear that COPD patients, in general, benefit from steroids either taken systemically or inhaled.... If the patient is deemed steroid responsive ... one could also consider the use of inhaled steroids. However, data on the response to inhaled steroids in COPD are conflicting^{82,83} and more research is required.”⁸⁴

Between 1992 and 2003, no updated guidelines were provided by the CTS regarding use of ICS in management of COPD. The 1995 updates of the American Thoracic Society (ATS) and European Respiratory Society (ERS) noted that the beneficial effects of ICS on lung function and symptoms had not been established, and therefore until recently, no consensus existed as to their effectiveness.^{85,86}

Following the publication of several large-scale clinical trials measuring the efficacy of ICS in COPD, the CTS recommendations released in 2003 suggested high-dose ICS for moderate-to-severe patients and patients with high frequencies of exacerbation (e.g. 3 acute exacerbations in 3 years),²⁰ and recommended that ICS be initiated according to the step-wise approach (Figure 2.3). Informed by additional studies of the effectiveness of ICS as well as combined ICS with long-acting β -agonists (ICS/LABA) combination therapy, the CTS published updated guidelines in 2007, recommending ICS/LABA use for individuals with moderate to severe COPD, and depending on frequency of exacerbations (Figure 2.4).¹¹

2.8.3 Trends in ICS Utilization

Despite a lack of guidance from the governing bodies in BC, Canada, or internationally, the number of ICS dispensations for COPD increased through the 1990s. In England, the prescribed daily dose of ICS nearly doubled, from 69.9 million per quarter in 1992 to 124.7 million per quarter in 1998.⁸⁷ Scottish data between 1999 and 2002 showed an increase in dispensations of 10%.⁸⁸ This increase in dispensation can be partially attributed to the increasing prevalence of the disease; however, the proportion of COPD patients using ICS also increased during the 1990s. An analysis of baseline clinical trial data suggested that the proportion of COPD patients taking ICS in 1987 was 13.2% and rose to 41.4% in 1995.⁸⁹ A population-based study found a similar increase in ICS dispensations among the elderly, with a reported increase of ICS prescription fills from 42.4% to 53.1% of elderly patients with COPD.²⁰

2.8.4 ICS Efficacy in COPD

The goal of pharmacologic therapy in COPD management is to slow the rate of decline in lung function, ultimately reducing COPD-related mortality. Although no individual clinical trial has shown a reduction in mortality,^{16-19,26,80,81,90-94} a recent pooled analysis⁹⁵ of 5085 subjects enrolled in seven randomized controlled trials^{16-19,80,81,92} (the Inhaled Steroid Effects Evaluation in COPD (ISEEC) study) found that participants randomized to ICS had a lower risk of mortality (HR 0.75; 95% Confidence Interval (CI): 0.57 to 0.99) compared with placebo. The ISEEC study investigators also analyzed the decline in FEV₁ among these same seven RCTs⁹⁶ and concluded that in the first six months of treatment, ICS use was associated with a significant increase in FEV₁, compared with placebo. This was quantified as an average increase in post-bronchodilator FEV₁ of 42mL among men, and a 29mL increase among women. Although the finding at 6 months was statistically significant, the magnitude of the change in FEV₁ was acknowledged to be clinically insignificant – 112mL has previously been identified as the minimum change in FEV₁ that results in an appreciable change in perceived dyspnea.⁹⁷

Furthermore, after six months, the investigators found no difference – statistical or clinically meaningful – in the rate of FEV₁ decline between the ICS and placebo arms.

Investigators have examined the effect of ICS on other outcomes and observed that subjects randomized to ICS (either alone, or in combination with long-acting β -agonists^{80,81,92,94}) experience fewer exacerbations^{17,18,92}, less severe exacerbations^{81,90} and improved HRQL^{17,92}. A systematic review of nine randomized trials reported that the overall rate of exacerbations was 30% lower in subjects randomized to ICS than to placebo (RR=0.70; 95% CI: 0.58 to 0.84).⁹⁸

The severity of recruited patients varied between studies, and there was evidence to suggest that the choice of study population affected the measured effect sizes. The Copenhagen City Heart Study investigators enrolled patients between 30 and 70 years of age with a baseline post-bronchodilator FEV₁ in the ICS group of 86.2% predicted (SD: 20.6%).¹⁸ (Table 2.1 contains COPD staging definitions based on values of FEV₁.) The EUROSCOP study investigators also recruited younger (30-65 years) patients with mild-to-moderate COPD (100% > FEV₁ > 50%). The baseline post-bronchodilator FEV₁ of the ICS group was 76.8% predicted (SD:12.4%).¹⁹ Neither of these studies was able to detect a treatment effect on respiratory symptoms or exacerbation frequency.²⁰ The baseline post-bronchodilator FEV₁ of the ICS group enrolled in the Lung Health Study was 68.5% predicted (SD: 12.8%). This study detected improvements in the ICS arm in terms of reduced number of outpatient visits for respiratory conditions and reduced symptoms. The largest effect sizes were observed in the studies which enrolled the most severe subjects. The ISOLDE study¹⁷ enrolled patients with a baseline FEV₁ in the ICS group of 50.3% predicted and reported a 25% reduction in median exacerbation rate. Szafranski *et al*⁸¹, Calverley *et al*⁹², the TRISTAN study,⁸⁰ and the TORCH study⁹⁴ enrolled subjects with mean baseline FEV₁ values that were all below 45% predicted.

In each of these studies, significant reductions in exacerbation rates were observed for ICS alone³ as well as ICS/LABA combination treatment.

Improvements in health status have been shown to become progressively wider between ICS and placebo groups after study enrollment,¹⁷ suggesting that there was a cumulative benefit of ICS. This has been attributed to a reduction in exacerbations, leading to improved health over the long term.⁷⁹

2.8.5 ICS Effectiveness in COPD

While randomized controlled trials are designed to measure drug efficacy – whether a medication has the ability to bring about the intended effect – observational studies measure a drug's effectiveness – whether, in a 'real world' setting, a drug in fact achieves its desired effect.⁹⁹

RCTs are generally viewed as the reference standard for the evaluation of drug efficacy^{100,101} due to the random allocation of individuals to treatment. This ensures that exposed and unexposed groups are mostly balanced in terms of known and unknown confounders, and that any residual differences are due to chance. Observational studies are prone to imbalances in the exposed and unexposed groups, particularly in studies of intended effects of drugs. This is because in the 'real world' setting, patients and physicians select treatment based on clinical need, therefore causing exposed and unexposed groups to differ in clinical symptoms.¹⁰²

Despite these limitations, many observational studies of the intended effects of ICS among COPD-afflicted individuals have been conducted because they are able to measure exposures and outcomes in a large number of subjects over an extended period of time – studies that would be prohibitively expensive to conduct as RCTs. These studies applied strategies to reduce the amount of bias and confounding incurred from the non-randomized treatment

³ Exception: Szafranski *et al* did not find a significant reduction in exacerbation rates for ICS alone

allocation using large administrative databases to estimate the effectiveness of ICS in reducing death, hospitalizations, or both, among individuals with COPD.

The earliest of these observational studies to emerge found a 24% reduction in repeat hospitalizations (95% CI: 20-29%), and a 29% reduction in risk of mortality (95% CI: 22-35%) among subjects over 65 years, following discharge from a first hospitalization for COPD.¹⁰³ This apparent reduction in mortality among ICS users was supported by subsequent observational studies,^{104,105} suggesting that ICS use caused a significant reduction in mortality; however, it was later realized that these results may have been subject to “immortal time” bias (discussed in detail in section 3.1.2). In two separate studies,^{106,107} Suissa demonstrated the effect of “immortal time” bias on the effect estimate using an administrative database of Saskatchewan Health. He analysed the data in two ways: first using the methods of previous studies,^{103,104} and then using methods free of immortal time bias. The re-analysis produced substantial increases in the point estimates of ICS effectiveness, resulting in non-significant effect sizes.^{106,107}

Numerous studies of ICS effectiveness have since been conducted, some free of immortal time bias,¹⁰⁸⁻¹¹³ and others still susceptible to the problem.¹¹¹ Outcomes in these observational studies were all global-clinical rather than physiologic or functional¹¹⁴ – hospitalizations, death, and combined hospitalization or death. Unfortunately, the effect sizes associated with ICS use in these studies remain incongruent, even among those free of immortal time bias. Table 2.4 summarizes the results of these observational studies. The studies with published acknowledgement of immortal time bias are presented separately from those without. Some results listed in the table refer to the same study, with different methods applied to produce the effect estimate.

Using hospitalizations as an outcome, no observational studies free of immortal time bias demonstrated a reduction in risk.¹⁰⁸⁻¹¹⁰ The nested case-control study of de Melo *et al*¹⁰⁸ found an increase in risk of hospitalizations in all categorizations of exposure: any use in the year

prior to hospitalization, any use in the 15-60 days prior, and any use in the 61-365 days prior. The authors also investigated the effectiveness of ICS according to dose, and found counter-intuitive (and likely confounded) results of higher risk among higher dose. Individuals taking ICS in the highest dose category were reported to have a risk of hospitalization that was 2.9 times that of unexposed individuals (95% CI: 1.5-5.9). Although it is possible that ICS is associated with increased risk of hospitalizations, the elevated risk of hospitalization among the exposed group is likely a result of confounding by severity (described in section 3.1), resulting in an artificially elevated estimate of risk in the exposed group.

Among the studies using death as a primary endpoint, all studies except for that of Mapel *et al*¹¹² similarly reported no benefit of ICS. Mapel *et al*¹¹² used three study designs – Cox proportional hazards, propensity score-matched cohort, and a nested case-control study – to investigate ICS effectiveness. The authors used permutations of exposure and non-exposure to ICS and LABA to produce five different exposure categories (combined ICS/LABA in one inhaler was treated separately from ICS and LABA being used concurrently) during a baseline period of 1 year prior to cohort entry. All three study designs identified statistically significant or borderline significant reductions in the risk of death among any exposure category. Other studies employing similar techniques yielded null results. A main difference between the study conducted by Mapel *et al* and other studies was that Mapel *et al* used a time-fixed exposure to ICS, based on exposure at baseline, whereas other studies used time-dependent exposures. Mapel *et al* argued that the use of a time-fixed exposure misclassifies unexposed individuals as exposed, biasing the results upward, and producing an inflated measure of ICS effectiveness. However, due to the hierarchical nature of treatment and the authors' definition of cohort entry, the study design excluded the person years of event-free exposure to SABA preceding the use of ICS among those classified as ICS users. This has been described in detail by Suissa¹¹⁵ as excluded immortal time (section 3.1.2), which leads to an overestimate of the event rate in the unexposed (because of the excluded event-free person years in the unexposed group) and

thus underestimates the rate ratio. The magnitude of the bias has not been estimated, and it is therefore unclear whether the study results analyzed free from immortal bias would still yield a beneficial effect of ICS.

Among the studies with a combined endpoint of death and hospitalization, there was only one result (from a nested case-control study) that indicated a favourable effect of ICS.¹¹¹ The effect measure was an odds ratio which was meant to estimate the relative risk of death or hospitalization. While the odds ratio approximates the risk ratio when the incidence of outcome is low, it tends to underestimate the risk ratio when outcomes are more frequent.¹¹⁶ The incidence of death or hospitalization during this time period was 53.5%¹⁰⁷ – a value at which the odds ratio substantially underestimates the relative risk. However, the point estimate estimated by the authors was 0.71 (95% CI: 0.56-0.90), and even with the underestimate produced by the odds ratio, this still may have suggested a protective effect of ICS. Odds ratios were also used in studies using hospitalization or death alone as an end-point, but because the incidence of hospitalization alone and death alone was not as high as the combined end-point, the odds ratio did not underestimate the relative risk to the extent that it did when using the combined outcome.

Although we noted the flaws in the studies that reported a protective effect, the studies detecting a null, or even harmful effect, were also subject to bias. These studies are all subject to some of the common challenges of pharmacoepidemiology that are discussed in greater detail in section 3.1. The most prominent challenge in these studies is controlling for the severity of disease. Uncontrolled studies can result in overestimates of event rates in the exposed, thus overestimating the rate ratio, and at times suggesting harmful effects of drugs.

2.8.6 Heterogeneity of response to ICS

The pathological heterogeneity of COPD poses a significant challenge in assessing the effectiveness of ICS.¹¹⁷ Historically, COPD was defined as an umbrella term for three distinct disease pathologies: chronic bronchitis, chronic bronchiolitis and emphysema, each of which

has distinct pathologies and different inflammatory processes, suggesting that the response to treatment might differ between these groups. Coexisting asthma also contributes to the heterogeneity of the disease because of the additional differences in lung pathology and inflammation profile of asthma compared with COPD (section 2.4). The different systemic manifestations that may arise concurrently also affect the symptoms and outcomes associated with COPD, and may affect an individual's response to therapy. Another source of heterogeneity within the population of COPD is the exposure to cigarette smoke. The pathology of COPD among current and former smokers differs from that among non-smokers,¹¹⁸ and the rate of lung function decline is known to differ between current and former smokers.^{15,60}

In order to minimize the heterogeneity of the population in studies of persons with COPD, RCTs generally have strict entry and exclusion criteria. Among RCTs estimating the efficacy of ICS among persons with COPD, frequent exclusion criteria include: individuals with a history of asthma,^{17,80,81,92-94,119} individuals with bronchodilator reversibility of more than 10-15% of baseline FEV₁,^{17,19,26,80,94} individuals with conditions that could have lead to death within the timeframe of the study,^{80,81,92,94,119} and individuals with no history of smoking.^{16,17,19,26,90,91,80,81,92,94,119}

A benefit of observational studies is that the sample size can be large, providing the ability to analyze effectiveness within subgroups, while maintaining a large enough sample size to detect differences (providing that internal validity is adequate). Published observational studies have typically included sensitivity analyses, investigating the effect of changing certain operationalized definitions, or looking at effectiveness with or without certain subgroups. Vollmer *et al*¹¹³ measured the effectiveness of ICS among subgroups according to smoking history and co-existing asthma. Although differences between these groups were not tested statistically, the point estimates of ICS effectiveness were generally lower among individuals with coexisting asthma than among individuals without, and the point estimates were also lower in never smokers than in current or former smokers. Fan *et al*¹¹⁰ also investigated the

difference in ICS effectiveness with and without individuals with prior history of asthma. The estimates were also not compared statistically, but the point estimates of ICS effectiveness in reducing mortality were more favourable when asthmatics were included in the cohort.

It has been suggested that observational studies should entirely omit individuals with history of asthma because they are considered to be asthmatics misdiagnosed with COPD.¹¹⁷ Several studies have attempted to exclude asthma either using hospital and physician visit records to identify individuals with prior history of asthma, or using the assumption that asthma is rare in an older age-group¹²⁰ and the majority of obstructive lung disease is due to COPD.¹⁰³ If patients who are truly asthmatic and do not have COPD are included in a study cohort, evidence suggests that the effect size will be underestimated; however, given that there exists a subgroup of COPD patients with coexisting asthma, we argue that these individuals should be included and the effectiveness in this subgroup should be estimated separately.

2.9 Summary

It is known that COPD is a heterogeneous disease with varying pathophysiological characteristics, symptoms, and responsiveness to medication; however, little is known about the comparative effect sizes of ICS within well-defined sub-groups of the disease. Concomitant COPD and asthma is a subgroup of COPD that places a significantly higher burden on the health care system. We know that ICS is effective in asthmatics, but little is known about its effectiveness in individuals with COPD as well as asthma. In this study, we estimate the effectiveness of ICS among individuals with concomitant COPD and asthma, compared with COPD-afflicted individuals with no history of asthma.

2.10 Figures and Tables

FEV₁: Forced Expiratory Volume in one second

Figure 2.1: Representation of decline in lung function over time associated with smoking, adapted from Fletcher and Peto.¹⁴

Figure 2.2: Theoretical representation of the decline in lung function over time. The upper line represents exacerbation-free decline and the lower line is punctuated by exacerbations and incomplete recovery. Modified from Jones⁷⁹

AECOPD: acute exacerbation of COPD; MRC: Medical Research Council; PRN: as needed; Rx: treatment.

Figure 2.3: Stepwise approach to therapy for COPD (copied from 2007 CTS guidelines with permission).¹¹

Figure 2.4 Recommended pharmacotherapy for stable COPD according to disease severity and exacerbation frequency (copied from 2007 CTS guidelines with permission)¹¹

Table 2.1 COPD disease severity based on CTS classification by symptoms, disability and impairment of lung function (copied from 2007 CTS guidelines).¹¹

Stage	Symptoms	Lung Function
Mild COPD	Shortness of breath from COPD when hurrying on the level or walking up a slight hill (MRC 2)	$FEV_1 \geq 80\%$, $FEV_1/FVC < 0.7$
Moderate COPD	Shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes) on the level (MRC 3 to 4)	$50\% \geq FEV_1 < 80\%$ predicted, $FEV_1/FVC < 0.7$
Severe COPD	Shortness of breath from COPD resulting in the patient too breathless to leave the house, breathless when dressing or undressing (MRC 5), or the presence of chronic respiratory failure or clinical signs of right heart failure	$30\% \geq FEV_1 < 50\%$ predicted, $FEV_1/FVC < 0.7$
Very severe COPD	n/a	$FEV_1 < 30\%$ predicted, $FEV_1/FVC < 0.7$

Abbreviations: FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; MRC: Medical Research Council dyspnea scale

Table 2.2 Differences between asthma and COPD (adapted from several sources^{11,33,37}).

	Asthma	COPD
Inflammatory profile		
Predominant inflammatory cells	Mast cells Eosinophils CD4+ cells	Neutrophils CD8+ cells
Clinical Symptoms		
Frequency	Intermittent and variable	Persistent
Age of onset	Usually < 40 years	Usually > 40 years
Smoking history	Not casual	Usually > 10 pack years
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Physiology		
Spirometry	Often normalizes	Never normalizes
Airflow obstruction	Usually intermittent airflow obstruction but often has a less reversible obstruction Improvement in airway obstruction with bronchodilators and corticosteroids Airway remodeling (epithelial injury and fibrosis)	Progressive airflow obstruction Smaller bronchodilator and corticosteroid response Emphysema (lung destruction) frequent.

Table 2.3 International Classification of Disease (ICD) codes corresponding to COPD

ICD-9 code	Description	ICD-10 code	Description
491	Chronic bronchitis	J41	Simple and mucopurulent chronic bronchitis
		J42	Unspecified chronic bronchitis
492	Emphysema	J43	Emphysema
496	Chronic airway obstruction, not elsewhere classified	J44	Other chronic obstructive pulmonary disease

Table 2.4 Summary of effect estimates from observational studies of ICS in COPD, according to presence of immortal time bias, reported in peer-reviewed literature.

End Point	Effect Estimate of ICS compared with no ICS (Point estimate, 95% CI)	
	Immortal time bias	Free of immortal time bias
Death	HR = 0.71, 0.65-0.78 ¹⁰³	HR ^a = 1.10, 0.77-1.59 ¹¹⁰
		HR ^b = 0.85, 0.64-1.13 ¹¹⁰
	HR = 0.62, 0.45-0.85 ¹⁰⁴	
		HR ^c = 0.94, 0.81-1.09 ¹⁰⁷
	HR = 0.75, 0.68-0.82 ¹⁰⁵	
		HR = 0.76, 0.61-0.95 ¹¹²
	HR ^c = 0.66, 0.57-0.76 ¹⁰⁷	HR = 0.75, 0.58-0.97 ¹¹²
Hospitalization	HR ^c = 0.75, 0.62-0.90 ¹⁰⁷	OR = 0.66, 0.46-0.96 ¹¹²
		HR ^d = 1.09, 0.65-1.83 ¹¹³
		HR ^e = 0.76, 0.56-1.02 ¹¹³
	HR = 0.76, 0.71-0.80 ¹⁰³	OR = 1.07, 0.91-1.27 ¹⁰⁹
		HR ^a = 1.05, 0.81-1.37 ¹¹⁰
Death + Hospitalization		HR ^b = 1.13, 0.94-1.36 ¹¹⁰
		OR = 1.27, 1.08-1.48 ¹⁰⁸
	HR ^c = 0.69, 0.55-0.86 ¹⁰⁶	HR ^c = 1.00, 0.79-1.26 ¹⁰⁶
	HR = 0.69, 0.52-0.93 ¹¹¹	OR = 0.71, 0.56-0.90 ¹¹¹
		HR ^d = 1.09, 0.79-1.49 ¹¹³
		HR ^e = 1.02, 0.83-1.25 ¹¹³

Abbreviations: HR = hazard ratio; OR = odds ratio; CI = confidence interval; ICS = inhaled corticosteroids

^aLow-dose ICS

^bHigh-dose ICS

^cA study demonstrating the impact of immortal time bias

^dIncluding only current smokers, excluding asthma

^eIncluding only ex-smokers, excluding asthma

3 Pharmacoepidemiological Context

3.1 Methodologic challenges in pharmacoepidemiological studies

Due to the non-experimental nature of pharmacoepidemiological studies, several challenges arise in measuring effect sizes with precision and without bias. There are three broad categories of bias that distort the true estimate of effect between exposure and outcome in epidemiological and pharmacoepidemiologic studies: selection bias, information bias, and confounding.^{121,122}

3.1.1 Selection Bias

Selection bias exists in studies where there is a systematic difference in the characteristics of the exposed and unexposed samples, often due to the method used to identify study participants.^{99,121-123} If the likelihood of being included in the study sample is not equal across all factors in the target population, the resulting effect estimate may not accurately represent the true effect size. There are many types of selection bias. We will discuss one form that is prone to affecting pharmacoepidemiological studies conducted using administrative data, and briefly describe two types that are generally avoided when using administrative databases.

Individuals who are censored during the follow up period can contribute to a biased results if exposed and unexposed subjects exit the study in a non-differential manner.¹²⁴ In longitudinal studies, this is also called informative right censoring. In many of the observational studies of ICS effectiveness discussed in section 2.8.5, individuals were censored when they dis-enrolled from the drug plan used to collect the data. In BC, where health coverage is universal, this is unlikely to be related to either exposure or outcome because dis-enrollment would likely be due to a move outside of the province for a reason unrelated to exposure or outcome, and thus would not impose a bias on the results. The administrative drug database in BC, however, does not record drugs dispensed in hospital. Therefore, drug exposure among individuals admitted to long term care facilities cannot be determined, and individuals should be

censored upon admission. Because these individuals are typically sicker than non-hospitalized individuals, this does impose a bias. If the main study outcome is time to hospitalization, censorship due to death, may also impose bias. In studies of COPD patients, risk of death is positively associated with the risk of hospitalization, and represents a worse outcome. If the treatment of interest is effective in reducing mortality, the relative risk of hospitalization may appear larger in the exposed group than in the unexposed group because the exposed group lives long enough to be hospitalized, whereas the un-exposed individuals who die will be censored, 'event-free'. When informative censoring exists, a competing risks framework can be used to obtain unbiased effect estimates.¹²⁵ This is discussed in further detail in section 3.2.6.

Population-based administrative databases are excellent tools for reducing other forms of selection bias related to patient recruitment. In Canada, universal health coverage ensures that every citizen is covered by provincial health coverage and therefore is captured by the database. For this reason, administrative database studies are not prone to referral¹²² or self-selection bias.¹²²

3.1.2 Information Bias

Information bias refers to any error that arises from when a measurement does not accurately reflect what it is supposed to be measuring, and does so differentially between exposure or outcome categories.^{99,121-123} Scenarios resulting in misclassification of exposure, diagnosis, and outcomes, and the implications of these misclassifications are discussed in this section.

3.1.2.1 Exposure Misclassification

In pharmacoepidemiological studies, drug exposure is difficult to track, especially when using administrative drug databases to measure exposure.¹²⁶ When a prescription has been filled, it is typically assumed that the individual is subsequently exposed; however, this is not necessarily true. Non-consumption of medication following dispensation occurs in many ways: the medication is not taken at all, the medication is taken intermittently (often due to

forgetfulness or delay in re-filling a prescription), or the medication is taken at a dose different from that prescribed (e.g. pill splitting, change in frequency of daily pill-taking).¹²⁷ Because there is currently no way to track consumption with administrative data, this results in non-compliant individuals being misclassified as 'exposed' when they may be un-exposed, or exposed to a lower dose. By measuring compliance in addition to exposure, we can improve the characterization of drug consumption. While still imperfect in its ability to quantify when and how much medication is truly consumed, this approach accommodates for varying levels of compliance with prescribed dose across individuals. The continuous multiple availability (CMA) metric is useful in administrative database studies when there is no evidence of a clinically meaningful compliance cut-point.¹²⁸ The metric allows for multiple interval measures which are useful when longer-term duration of use or cumulative drug dosage are important aspects of exposure, and the "availability measures" rather than "gap measures" are desirable when studying cumulative drug dosage or dose-response relationships.¹²⁸

3.1.2.2 Immortal time bias

Immortal time bias is an issue relating to exposure misclassification that arises frequently in pharmacoepidemiological literature.¹¹⁵ There are two main types of immortal time bias: misclassified and excluded.¹²⁹ Misclassified immortal time bias is more common, and arises when individuals are assigned to exposure categories based on prescription fills that follow the cohort entry date. For example, in the study design of Sin and Tu¹⁰³, individuals were classified as 'exposed' if they filled a prescription for ICS in the ninety days following hospital discharge; however, follow-up time started upon discharge. The time spent unexposed was therefore misclassified as 'exposed' from the time of discharge to first fill, and was necessarily immortal since individuals must have lived long enough to fill the prescription. Excluded immortal time, on the other hand, occurs in scenarios when the exposed population enters the cohort at the time of (first) drug fill and the unexposed population enters the cohort at another point in disease history, such as at the time of diagnosis. If a step-wise approach to treatment exists,

then the exposed population will enter the cohort at a later stage in disease history, and will have immortal time between time of diagnosis and drug fill that was excluded from analysis. By excluding this immortal unexposed time, there will be fewer person-moments in the unexposed, and therefore the event rate in the unexposed will be artificially inflated, making the exposed group look relatively better compared to the unexposed group.¹²⁹ Appropriate cohort definition can avoid excluded immortal time, and use of time-varying exposure methodology will avoid misclassified immortal time.

3.1.2.3 Diagnostic Misclassification

Differential disease misclassification also leads to information bias. The study cohorts used in pharmacoepidemiological studies often include only one disease category and track time to event between exposure categories. Although there is no formal disease-free category, misclassification bias occurs when non-diseased individuals are included in the study cohort and are not balanced between exposure categories. In addition to the issues regarding individuals not being captured in administrative databases due to underutilization of the health system, or having an ambiguous ICS code associated with a visit (discussed in section 2.5.2), administrative records may also yield incorrect ICD codes, arising from infidelity of the transcription of the ICD code on the patient chart to the database, incorrect billing diagnostic codes despite correct clinical diagnoses, or incorrect diagnoses. The transcription from patient chart to database in hospital discharge databases is reportedly highly accurate,^{130,131} however, the frequency of incorrect billing codes and incorrect diagnoses are more difficult to ascertain, and has not been done for COPD. In addition to inaccuracies, there are also potential omissions from administrative databases due to the limitations of coding. In MSP billing databases, there is room for only one diagnostic code, meaning that patients suffering from two or more comorbid conditions can continue to visit a physician without ever being traced by the MSP database as having that disease. Medication use has been shown to provide good discrimination between COPD and asthma, as well as between COPD and other diseases.¹³²

Therefore, we expect that in the event that a disease-free individual is included in the study cohort, they would be more likely to be included in the non-exposed category than the exposed.

3.1.2.4 Outcome Misclassification

Outcomes suffer from the same potential for misclassification as previously discussed. Using administrative databases, health service utilization often serves as a proxy measure for a clinical outcome. In database studies, acute exacerbations are typically operationalized as one of: hospitalizations or emergency department visits with COPD as the first or second most responsible diagnostic code; or dispensation of an oral corticosteroid and antibiotic on the same day.¹⁰⁸ Non-exacerbations can be misclassified when individuals are admitted to hospital for a reason unrelated to COPD (e.g. diabetes) but COPD, a co-existing condition, is recorded as a responsible diagnosis. Conversely, an exacerbation may be missed (misclassified as no-event) if the individual did not fill an oral corticosteroid and antibiotic on the same day, or if they were admitted to hospital for an acute exacerbation but COPD was not recorded in the operationalized responsible diagnosis field. COPD is often mistaken for congestive heart failure upon admission to hospital and could be missed.^{133,134} Hospital over-crowding can also lead to missed acute exacerbations, as individuals may be less likely to be admitted. When misclassification is nondifferential across levels of exposure, which is likely in the scenarios described previously, it attenuates the strength of association between exposure and outcome (bias towards the null);¹²² however, differential misclassification of outcome that arises when exposure to a COPD drug increases the likelihood of being recorded as having COPD can change the size and even direction of the effect.

Death is also frequently used as an outcome. Although mortality databases are highly accurate in capturing deaths, the cause of death is typically reduced to a single field, which can lead to poor sensitivity in capturing cause-specific mortality in COPD.^{49,135} As with misclassified hospitalizations, this can lead to a biased effect estimate if the misclassification of death is differential across levels of exposure.

3.1.3 Confounding

In observational studies, individuals are not randomized to treatment arms. The observed and unobserved characteristics for the treatment groups are unlikely to be balanced. When characteristics associated with the outcome of interest are not distributed equally across treatment groups, this imposes a distortion and when not properly accounted for, yields effect sizes that are inaccurate.

To be considered a confounder, a covariate must 1) be a predictor of risk among the unexposed; 2) be a correlate of exposure in the population in the population serving as the source of subjects; and 3) not be an intermediate variable in the causal pathway under study.¹³⁶

It is important to ensure that non-confounders – particularly variables that lie on the causal pathway between exposure and outcome – are not adjusted for in analysis. Adjustment for non-confounders will actually impose additional bias to the results rather than correct for existing bias.¹³⁷ Directed acyclic graphs (DAG) are excellent tools for researchers to visually assess potentially confounding variables^{137,138} and prevent unnecessary adjustment.

Figure 3.1 presents a DAG identifying factors that have been shown to confound the relationship between ICS and COPD. Table 3.1 presents evidence of the association between these factors and exposure to ICS, as well as to risk of death or hospitalization.

Confounding by severity is a specific type of confounding that relates to differential disease severities in the exposed and unexposed groups. This generally occurs when a drug is indicated for use at an advanced stage of disease – often in chronic diseases. Confounding by severity differs from confounding by indication: with confounding by severity, all study subjects have the disease, but in varying levels of severity, whereas confounding by indication refers to scenarios where individuals may or may not have a disease that is a risk factor for the outcome.¹³⁹ When the outcome is associated with severity of disease, confounding by severity causes an increased event rate in the exposed category, compared with the unexposed. Presence of this confounding will increase the effect estimate, and may even suggest a harmful

effect of the drug. This does not pose a problem when the outcome is not related to severity of disease, for example, in studies of unintended harmful drug effects (e.g. the relative risk of development of glaucoma based on exposure to ICS).¹²² When it is necessary to adjust for confounders (through restriction, matching, stratification, or statistical modeling), proxy measures for severity, although imperfect, are used in order to balance exposed and unexposed groups according to severity. In studies of COPD, lung function is an excellent measure of severity with which to balance groups; however, these data are not available in administrative health databases.

Protopathic bias can be thought of as an extreme form of confounding by severity. Protopathic bias is not actually a confounder, but is discussed here because of its similarity to confounding by severity. It occurs when individuals become exposed immediately prior to an event because the medication relieves its early symptoms,¹³⁹ and is therefore problematic in studies of relief medication.¹³⁹ The causality in this association is reversed: the individuals are taking the medication *because* they are at high risk; they are not at high risk *because* they are taking the medication. By including this subset of high-risk individuals in the exposed population, it produces an elevated risk of death among the exposed and may result in a finding that suggests harmful effects of the drug. Conversely, 'reverse' protopathic bias can occur when an individual discontinues medication when they begin to feel prodromal symptoms. This yields an opposite consequence on the effect estimate: individuals are categorized as unexposed immediately before the outcome occurs, causing the event rate in the unexposed to be elevated. This yields an artificially low effect size.

Epidemiological studies are also subject to unmeasured and unknown confounders. These are underlying differences between exposure groups that are not captured by the data source, or that cannot be quantified by a measurable variable. The use of instrumental variables is a strategy that can account for unmeasured confounders (discussed in section 3.2.4), but when these are unavailable, the best that can be done is to acknowledge their existence and attempt to control for confounders that are measurable.

We will discuss analytic approaches that can reduce confounding in pharmacoepidemiological studies in section 3.2.

3.1.4 Effect modification

Effect modifiers are variables such that the effect of one variable (e.g. exposure) on another (e.g. outcome) varies across strata of the effect modifier (e.g. sex).¹⁴⁰ This can occur in situations where an exposure is necessary but not sufficient for an outcome: a third variable may need to be present in order for the exposure to be fully effective.¹⁴¹ In extreme examples, presence of a third variable may reverse the effect of the exposure. There is evidence to suggest that the presence of coexisting asthma modifies the effect of ICS in reducing hospitalizations and death among individuals with COPD.¹¹³ It is included as an effect modifier in the directed acyclic graph presented in Figure 3.1.

3.1.5 Summary of methodological challenges

Despite their limitations, observational studies are essential for understanding drug effectiveness in the general population. The aforementioned challenges of bias and confounding simply highlight the extent of methodological rigor that must be applied in analyzing drug effectiveness. In conjunction with the results of drug efficacy, a well-conducted observational study where the magnitude and direction of bias is well-documented, is critical in informing policy- and decision-makers whether a drug is being used effectively in the jurisdiction under study.

3.2 Pharmacoepidemiological modeling approaches

Many of the challenges discussed previously can be avoided by using an appropriate study design and careful analysis.¹⁴² We will discuss some of the strategies discussed in the literature that account for covariate imbalances,¹⁴³⁻¹⁴⁵ assuming a retrospective cohort study design using administrative data.

3.2.1 Multiple regression models

Simple regression models express an outcome variable as a function of an explanatory variable. In cases where the exposed and unexposed populations differ with respect to risk factors associated with the outcome, additional terms may be added to the model.¹⁴⁶ This is called multiple regression (where there is more than one explanatory variable), and can be applied to all types of regression models, including linear, logistic, Poisson, and Cox proportional hazards models.¹⁴⁷ By including the confounding variable in the regression model, a portion of the effect size is attributed to that variable, and the effect size associated with the exposure of interest is adjusted.

There are several limitations to this approach.^{148,149} First, this method does not correct of imbalances in unmeasured or immeasurable confounders, as they are, by definition, not measured, and therefore can not be entered into the model. When confounders are unmeasured or immeasurable, and there are no proxy measures for these confounders available, the results will be biased. A second limitation is that if the joint distributions of the covariates do not overlap, this will not be detected by the model, and the model will be calculated anyway, yielding ungeneralizable results. This is not a limitation if the joint distributions are checked and do in fact overlap – thus it is merely a caution. Finally, a fundamental assumption of any model is that it has been properly specified: if the model is mis-specified, the estimated effect sizes will be inaccurate.

3.2.2 Extended Cox models with time-dependent covariates

The Cox proportional hazards model¹⁴⁷ is the most widely used model for time-to-event analysis with multiple predictors and censored observations. The hazard of event occurrence is defined as the conditional probability of event occurring at time t , given survival to time t or later. Mathematically, it is expressed as

$$\lambda(t) = \frac{\lim_{\Delta t \rightarrow 0} P(t \leq T < t + \Delta t | T \geq t)}{\Delta t} \quad (1)$$

The Cox proportional hazards model provides an estimate of the comparative hazard rates between groups of individuals. The model assumes an underlying (baseline) hazard function, $\lambda_0(t)$, and assumes that for all groups of individuals, the hazard of outcome over time is a constant multiple of this hazard function. The hazard function of an individual, i , with covariates $\mathbf{X}_i = (X_1, X_2, X_3, \dots, X_p)$ is

$$\lambda_i(t) = \lambda_0(t)e^{[\mathbf{X}_i\boldsymbol{\beta}]} \quad (2)$$

where $\boldsymbol{\beta}$ is a vector of coefficients. Assuming that the baseline hazard is identical for all groups, the ratio of the hazard of death over time for individuals i and j with differing covariate values is computed as

$$\frac{\lambda_i(t)}{\lambda_j(t)} = \frac{\lambda_0(t)e^{[\mathbf{X}_i\boldsymbol{\beta}]}}{\lambda_0(t)e^{[\mathbf{X}_j\boldsymbol{\beta}]}} \quad (3)$$

Thus, for a one unit increase in a covariate, X_p with all other covariates equal, the hazard ratio can be reduced to e^{β_p} . The method has been extended to accommodate for variables that change with time and variables that interact with time. While the Cox proportional hazards model assumes that the baseline hazard for all individuals is proportional over time, the extended Cox model¹⁴⁷ is not limited by this restriction and allows covariate values to change over time.

The general form of the extended Cox model is

$$\lambda_i(t) = \lambda_0(t)e^{[\mathbf{X}_i\boldsymbol{\beta} + \mathbf{X}_i(t)\boldsymbol{\delta}]} \quad (4)$$

where $\lambda_0(t)$ is the baseline hazard and is a non-negative function of time, $\mathbf{X}_i$ is a vector of time-constant covariates, $\mathbf{X}_i(t)$ is a vector of time-varying covariates, and $\boldsymbol{\beta}$ and $\boldsymbol{\delta}$ are vectors of coefficients.

In RCTs of drug efficacy, an intention-to-treat approach is often taken, where an individual is assigned as being exposed or unexposed to a drug at baseline, regardless of changes to exposure status following baseline. This is done to preserve the randomization in RCTs and prevent the introduction of bias. In analyzing drug effectiveness, which is already subject to bias due to non-randomization of individuals to treatment, time-varying covariates better represent what occurs in a 'real world' setting. Extended Cox models (with time-dependent exposure) have been used in several of the observational studies of ICS effectiveness in COPD.^{106,107,110,113} The model allows individuals to change their exposure status during follow-up, and importantly, avoids immortal time bias (section 3.1.2). The underlying assumption of the extended Cox model with time-dependent exposure is that the change of exposure status is unrelated to the risk of subsequent event.¹⁵⁰ Violation of this assumption, for example becoming exposed to a drug because one is at higher risk of the outcome, will bias the effect size upward. Because of this assumption, the results of several studies of ICS effectiveness have been criticized in their ability to produce an unbiased effect size of ICS on COPD morbidity and mortality because of the association between ICS initiation and risk of outcome.^{151,152} When using this model, care must be taken to ensure that this assumption is not violated.

3.2.3 Propensity scores

Propensity scores have been used frequently to adjust for indicated use of medications across treatment groups.¹⁵³⁻¹⁵⁵ The propensity score was developed by Rosenbaum and Rubin¹⁵⁶ as "the conditional probability of assignment to a particular treatment given a vector of observed covariates." The propensity score is most often calculated using a logistic regression model, where the outcome is the probability of receiving a particular treatment, and covariates

associated with exposure to treatment are used as independent predictors; however, other methods such as neural networks, discriminant function analysis, and classification trees may also be used.¹⁵⁵ With a given model, a propensity score can be calculated for each individual, based on his or her associated covariates.

The propensity score is then incorporated as a covariate in a regression model to model the outcome of interest (e.g. death) to adjust for confounding by indication. The propensity score may be either continuous or categorized into an ordinal categorical variable, which may be used to stratify the regression model or used as a matching variable.

Although propensity scores allow for adjustment according to likelihood of receipt of treatment, unmeasured confounders (section 3.1.3), cannot be accounted for by propensity scores. However, because the groups may seem balanced by likelihood of medication receipt, they can give a false impression that exposure groups are balanced.¹⁵⁵

The use of propensity scores in research has increased exponentially over the past eight years, however, it is questionable whether its use has improved effect estimates substantially.¹⁵⁵ A comparison of effect estimates in 78 analyses using propensity scores and traditional multiple regression found only eight studies in which the propensity score analysis yielded a significantly different score than the multiple regression model.¹⁵⁷

3.2.4 Instrumental Variables

Instrumental variables (IV) are used extensively in econometrics, and have been used increasingly in the health care research literature as a method to adjust for unbalanced exposure groups.^{158,159} This method, unlike the propensity score method, has the ability to adjust for both measured and unmeasured confounders.¹⁵⁸ IVs are observable factors associated with the treatment but not with the outcome. For example, in a RCT, the randomization assignment (0 for placebo, 1 for drug) would be a perfect instrumental variable – it is perfectly correlated with the treatment (in this case exposure or non-exposure to the drug)

but is not associated with the outcome (e.g. time to death). The technique is performed using two equations:

$$X_i = \alpha_0 + \alpha_1 Z_i + \nu_i \quad (5)$$

$$Y_i = \beta_0 + \beta_1 X_i + \varepsilon_i \quad (6)$$

where Y_i is the outcome, X_i is the treatment received, Z_i is the instrumental variable and $\alpha_1 \neq 0$.

Equation 6 can then be substituted into equation 5 to yield:

$$Y_i = (\beta_0 + \beta_1 \alpha_0) + \beta_1 \alpha_1 Z_i + (\beta_1 \nu_i + \varepsilon_i) \quad (7)$$

The instrument must be related to the treatment, but not related to factors explaining the treatment, or to factors explaining the outcome. Mathematically, these criteria are summarized as:¹⁵⁸

- 1) $\rho_{X,Z} \neq 0$, non-zero correlation between the treatment and the instrument
- 2) $\rho_{Z,\nu} = 0$, zero correlation between the instrument and other factors explaining the exposure.
- 3) $\rho_{Z,\varepsilon} = 0$, zero correlation between the instrument and other factors explaining the outcome (main assumption).

When a strong instrument exists ($|\rho_{X,Z}|$ is close to 1) and assumptions have not been violated ($\rho_{Z,\nu} = 0$ and $\rho_{Z,\varepsilon} = 0$), IV modeling is an excellent way to adjust for known and unknown confounders in unbalanced exposure groups; however, when assumptions are violated, the effect estimates will be biased and imprecise (i.e. large standard error).¹⁵⁸ In pharmacoepidemiological studies using administrative databases, it is not always possible to find a variable that is associated with the exposure but not the outcome. Brookhart *et al*¹⁶⁰ used prescription claims database to estimate prescribing physician's preference for one drug relative to another. They used this as an instrument in their observational study of the

effectiveness of COX-2 inhibitors compared with nonselective nonsteroidal anti-inflammatory medications on gastrointestinal complications. While this is theoretically a good instrument, the proxy measure used to define physicians' prescribing preferences violates the assumptions, leading to a biased effect estimate.¹⁶¹

Not all types of observational studies are well-suited for IVs. In studies with time-varying exposure, individuals may change treatments throughout the study. The example of the COX-2 inhibitors assumes an intent-to-treat type analysis rather than a time-varying analysis of treatment. Identifying a time-varying instrument for time-varying exposure is not often possible.¹⁶¹ Another type of study that is ill-suited to IV models are those that study heterogeneous treatment effects.¹⁶¹ Additional assumptions are required to estimate the average causal effect of a treatment in the population.¹⁶¹ For example, there should be no additive effect modification by the instrument among the treated (and untreated) patients.¹⁶² Hernan *et al*¹⁶¹ warn against using IV analysis under these circumstances.

3.2.5 Marginal Structural Models

Marginal structural models (MSM) are able to adjust for time-dependent confounding of effect estimates in the presence of a time-dependent exposure.¹⁶³ First introduced by Robins,¹⁶³ this technique was used extensively in HIV/AIDS research, but infrequently outside that disease area. MSMs can be used instead of standard approaches to modeling time-dependent exposure (e.g. Cox regression with time-varying covariate) when the following conditions apply: 1) there exists a time-dependent covariate that is a risk factor for, or a predictor of, the event of interest and also predicts subsequent exposure, and 2) past exposure history predicts subsequent level of the covariate.¹⁶³ This tends to hold true when confounding by severity or indication exists, particularly when the treatment regimen changes over time according to a person's response to the treatment.

While this is a promising method for controlling for bias in studies of time-dependent exposure, this approach is limited to data-rich studies where values of intermediate variables

(such as CD4 lymphocyte count) exist. In studies using administrative data, without clinical variables, the ability to implement this model is limited.

3.2.6 Competing risks framework

Regardless of the modeling approach used, pharmacoepidemiologic studies may be limited in their ability to characterize the risk of experiencing non-fatal outcomes. Standard survival techniques can only be meaningfully interpreted when the outcome of interest is independent of the censoring mechanism. In studies where the outcome is time to hospitalization, censoring of deaths is typically not independent of the risk of hospitalization.

The competing risks framework allows for unbiased analysis of competing events by fitting cause-specific models separately for each type of failure.¹²⁵ Although the most frequently used method does not allow for controlling of confounders,¹⁶⁴ Lunn and McNeil¹⁶⁵ recently developed a method for dealing with competing risks using an adaptation of the Cox proportional hazards model. This method has yet to be incorporated into standard statistical software, in such a way as to accommodate for time-varying covariates and interaction across strata of a second variable.

3.2.7 Summary of pharmacoepidemiological modeling approaches

Several methods exist to account for confounding and bias in pharmacoepidemiological studies. Multiple regression models, with or without time-varying covariates, are the most commonly used methods for modeling the association between drug exposure and outcome. Propensity scores, while quantifying the likelihood of receipt of medication, may not improve significantly upon multiple regression mostly because they do not offer any advantage over multiple regression approaches in accounting for unmeasured confounders. In theory, the IV approach is an excellent tool for accounting for unmeasured confounding and therefore providing a method for balancing exposure categories. Unfortunately, the ability to identify valid instruments in pharmacoepidemiological research is highly limited, and furthermore, IV methods are not well-suited to address time-varying exposure or heterogeneity in treatment

response. MSMs can handle time-varying exposure as well as time-varying confounders; however, the use of these models is limited to data-rich environments with respect to clinical outcome measures; their use with administrative data sets is limited.

It seems that, while many advances are being made in pharmacoepidemiological modeling approaches, advanced models are only applicable in certain scenarios. In a study of time-varying exposure with administrative data, multiple regression with time-varying exposure is the most feasible approach. As it is a widely used approach, this allows for comparison of estimates with other studies employing the same technique; however, it does not avoid the problems of unmeasured confounders, model misspecification, or violation of assumptions. Care must be taken in minimizing these problems as much as possible and understanding their impact, in order to generate the least biased effect estimates.

3.3 Figures and Tables

LABA: long-acting beta-agonists; ICS: inhaled corticosteroids; ACG[®]: adjusted clinical group; LOS: length of stay in hospital; ICU: intensive care unit. Arrow heads indicate the direction of the association. The arrow head from “Asthma” points to the association between “Exposure to ICS” and “Hospitalization or Death”, indicating that it modifies the effect.

Figure 3.1 Directed acyclic graph of variables that potentially confound or modify the relationship between inhaled corticosteroids and death or hospitalization (see Table 3.1).

Table 3.1 Variables that potentially confound the association between exposure to inhaled corticosteroids and risk of death or hospitalization (see Figure 3.1)

Characteristic	Measurement	Association with exposure to ICS	Association with risk of death or hospitalization
<i>Demographic information</i>			
Age	10-year intervals	Younger individuals more likely to receive treatment ¹⁶⁶	Older individuals at advanced risk of death and hospitalization ¹⁶⁷
Sex	Binary: M/F	Women associated with asthma diagnosis ¹⁶⁸ who are more likely to receive ICS	Mortality and re-hospitalization for COPD higher in men than women ¹⁶⁷
<i>Hospitalization information</i>			
Admission to intensive care unit (ICU)	Binary: Y/N	Admission to ICU implies more severe disease; associated with ICS initiation	Admission to ICU implies more severe disease; higher risk of outcome
Length of stay	Days (continuous)	Longer LOS implies more severe disease; associated with ICS initiation	Longer LOS implies more severe disease; higher risk of outcome
Charlson comorbidity index	Number	Lower Charlson score associated with higher likelihood of ICS ¹⁶⁸	Higher Charlson comorbidity index associated with higher risk of death ¹⁶⁹
Adjusted Clinical Group (ACG®)	Binary: Y/N	Assumed to be similar to association with Charlson score	Belonging to ACG® group 4940 and 5070 are associated with higher risk of mortality and hospitalization ¹⁷⁰
<i>MSP information</i>			
History of asthma	Binary: Y/N	ICS is the mainstay of asthma treatment and is associated with higher likelihood of use ⁵	History of asthma implies better response to ICS, although unknown if this is 'cancelled out' by existing COPD
<i>Drug information</i>			
Prior use of long-acting beta agonist (LABA)	Binary: Y/N	Because of stepwise approach to COPD management, expect individuals already taking LABA to be more likely to take ICS ¹¹	Expect greater ICS effectiveness when used in conjunction with LABA
Prior use of anticholinergic	Binary: Y/N	Because of stepwise approach to COPD management, expect individuals already taking anticholinergics to be more likely to take ICS ¹¹	Expect greater ICS effectiveness when used in conjunction with LABA

4 Objectives

The overarching aim of this pharmacoepidemiologic study was to determine whether the effectiveness of ICS in persons with COPD differs in the presence of concomitant asthma. The specific objective was to compare the reduction in the hazard of hospitalizations or death conferred by ICS among COPD-afflicted individuals without coexisting asthma to the hazard reduction among individuals afflicted with both diseases.

5 Methods

5.1 Overview

We used a retrospective cohort study to estimate the effect of ICS on death or hospitalization among two subgroups of individuals afflicted with COPD: individuals afflicted with both COPD and asthma; and individuals afflicted with COPD but not with asthma. Data obtained from the BC Linked Health Database (BCLHD) between April 1, 1991 and March 31, 2001. We measured the intended effect of ICS treatment on the risk of re-hospitalization or death among individuals diagnosed with COPD, and individuals diagnosed with both asthma and COPD. We applied design features and statistical methods to account for common challenges in using observational data for pharmacoepidemiological studies discussed in section 3.1.

5.2 Data Quality

5.2.1 BC Linked Health Database

The BCLHD is a deterministically linked set of administrative databases that include information on health care resources used by all registered individuals in BC (approximately 97% of residents). The linked database integrates health service records, prescription data, population health data and census statistics anonymously at the individual level.¹⁷¹

General issues pertaining to the reliability and validity of administrative databases were discussed in section 3.1.2. There are no validation studies that validate the BCLHD against survey data for COPD. Validity of physician billing databases for identification of COPD in Québec administrative databases compared with survey data is reportedly low;⁶⁵ however, there is no gold standard against which to compare COPD prevalence, and survey data may overestimate COPD.⁴² Given the accuracy of Canadian hospital discharge databases compared with patient charts in other disease areas,^{130,131} as well as in respiratory disease,¹⁷²

the use of hospitalization data to identify patients with COPD is likely a reasonable representation of reality.

The validity of PharmaNet (College of Pharmacists) prescription refill data for reflecting adherence among individuals with heart failure taking beta-blockers was reportedly high.¹⁷³ No validation studies have been performed assessing the validity of the PharmaNet database in COPD patients; however, coding accuracy is reportedly high in other Canadian drug databases.¹⁷⁴ Therefore, although there is no certainty that the drugs were consumed, the PharmaNet database is likely accurate with respect to the dispensation of drugs.

5.3 Ethics

Ethical approval for this study was provided by the University of British Columbia Behavioural Research Ethics Board (Appendix 2).

5.4 Data Preparation

Data were received from the BCLHD in six files: data from the province's Medical Services Plan (MSP) (1991-1995; 1996-2001), hospital discharge data (1991-1995; 1996-2001), PharmaNet data (1996-2001) and Adjusted Clinical Group (ACG[®]) codes (1996-2001). Demographic and mortality statistics were included in these files. We queried the database using Structured Query Language (SQL) on an Oracle[®] database through the Toad[®] interface. We prepared the data, created new variables, and conducted all statistical analysis using R version 2.7.0 (© The R Foundation for Statistical Computing).

5.4.1 Data verification and transformation

In order to prepare the data for analysis, a series of checks of data integrity were undertaken. We first checked the records of ICS fills contained in the PharmaNet dispensing data. ICS are dispensed in containers (inhalers, nebules, or blisters) that contain anywhere between 8 to 240 units (e.g. inhalations) of medication, depending on the brand and packaging of the drug. We prepared a table containing, for each brand, possible packaging quantities, and minimum and maximum daily doses, and the corresponding days of supply that could be

delivered from one package. These data were obtained from the Compendium of Pharmaceuticals and Specialties in years concurrent with our study period.^{76,175} We cross-checked the 'quantity' and 'days' fields of the PharmaNet database with the values in the table. We reviewed the records for which the number of days supplied was outside the possible days calculated in our table, and records for which the quantity supplied was not a multiple of the possible packaging units. We used these records to prepare a standard set of rules to apply in order to detect and correct errors in data entry systematically. We identified records where the quantity dispensed was equal to 1, 2, 3 or 4 and the minimum possible supply was greater than 1, 2, 3, or 4 respectively. We changed these entries to be multiples of the number of units per canister (e.g. if one inhaler provides 200 doses, we changed the value of "1" to "200" and the value of "2" to "400"). We also identified records where the number of days provided was greater than the maximum possible days, calculated from the minimum daily dose, and the quantity supplied. We changed these values to the quantity dispensed divided by the minimum daily dose. We repeated this process for values that were below the minimum possible days supplied. We systematically investigated all records where the 'days' field was greater than 200. We corrected entries that were clearly typographical errors (e.g. 'days' supply' field was 2800 but all other fills for the same medication for that person were for 200 days). In total, approximately 1% of the dispensation 141,714 records were modified.

We adjusted the hospitalization data in two ways. First, we removed any hospitalizations for which the individual was not currently registered with MSP, as it was unclear whether drug data would be captured for these individuals. Second, we merged records for patients who were transferred between hospitals (these are entered as separate records). We applied a rule such that individuals who were discharged and re-admitted within one calendar day were considered as the same hospitalization. We did not use the 'transfer to' and 'transfer from' fields, because an initial inspection of these fields showed that they were not entered consistently (e.g. 'transfer to' field complete in one record but 'transfer from' field in subsequent record with same calendar date was empty). Because some individuals were transferred to

extended-care hospitals directly from acute-care hospitals, we tracked the level-of-care fields for each of the hospital admissions.

For privacy reasons, the month of death is provided, but not the day of death. We set the death dates to the last day of the month, to ensure that events that occurred in the same month as death could not appear to occur after the death date.

5.4.2 Cohort Definition

The source population was all residents in BC who were registered with MSP between the April 1, 1991 and May 2001. The study sample included a dynamic population of individuals who were continuously enrolled in MSP between April 1, 1996 and March 31, 2001 (Figure 2.1). Individuals entered the cohort upon discharge (to the community) from a first hospitalization for COPD between October 1, 1996 and March 31, 2001. We excluded individuals who were hospitalized for more than ninety days, because this was unlikely to be for an acute hospital episode. We cross-referenced hospitalization records between April 1, 1991 and September 30, 1996 to verify there were no prior hospitalizations for COPD. To be considered a hospitalization for COPD, the first or second most responsible diagnosis had to correspond to the ICD-9 codes used to define COPD (Table 2.3). We excluded the ICD-9 code '490' (bronchitis, not specified as acute or chronic) due its low specificity for COPD (discussed in section 2.5.2).⁴¹ Individuals were included in the cohort if they were aged 45 years or older at the time of discharge in order to exclude asthmatics who did not have COPD.¹²⁰

5.4.3 Exposure

Exposure to ICS was assessed using the PharmaNet database, which captures prescriptions dispensed from community pharmacies to all individuals enrolled in BC's MSP. Exposure to ICS was defined as prescriptions containing belomethasone dipropionate, budesonide, fluticasone propionate, or triamcinolone as any of the active ingredients, in which the administration route was inhalation. Nasal sprays and oral corticosteroids were excluded. Combination products, such as ICS/LABA inhalers, were included.

We tracked exposure using a time-dependent measure, in an effort to avoid immortal time bias.¹⁰⁷ We used the CMA¹²⁸ metric to measure compliance using the days' worth of medication dispensed, as recorded in the PharmaNet database.

We calculated the CMA for each individual from first recorded ICS fill until last recorded fill. The CMA following the last recorded fill was assumed to be the same as between the penultimate fill and the last. We used the CMA following the last recorded fill to define an 'expected next fill'. Individuals who did not fill a prescription on or before this day were then considered unexposed. Changing between brands of ICS was not considered to be discontinuation from ICS. We added a 30 day grace period to the end of the 'expected next fill' because of the imprecision of the death date in our data. At the time of discharge from hospital, the CMA was defined as 0 for those who had not yet filled an ICS prescription and for those who had filled prescriptions prior to hospitalization, the current level of CMA was used.

We used a counting process¹⁴⁷ to identify transition days when an individual's level of compliance changed. Table 5.1 shows an example of the counting process form of records for an individual who is 100% compliant for the first 90 days, 80% compliant for the next 100 days, and 50% for the following 200 days.

We categorized CMA according to the step function:

$$ICS = \begin{cases} 0 & \text{if } CMA = 0 \\ 1 & \text{if } 0 < CMA < 0.25 \\ 2 & \text{if } 0.25 \leq CMA < 0.5 \\ 3 & \text{if } 0.5 \leq CMA < 0.75 \\ 4 & \text{if } 0.75 \leq CMA \end{cases} \quad (8)$$

For the main analysis, we categorized ICS exposure according to the CMA:

$$ICS = \begin{cases} 0 & \text{if } CMA = 0 \\ 1 & \text{if } CMA > 0 \end{cases} \quad (9)$$

5.4.4 Asthma

We assumed that individuals with co-occurring COPD and asthma were diagnosed with asthma prior to COPD. Therefore, we assigned individuals to the coexisting asthma stratum if they had any history of a hospitalization or specialist visit coded for asthma (ICD-9 493.xx). We intentionally excluded general practitioner (GP) visits, because these records have poor discriminatory ability to distinguish between asthma and COPD;¹³² however, the definition of asthma was broadened to include GP visits in a sensitivity analysis (section 5.5.5).

5.4.5 Comorbidities

We used two measures of comorbidities in our analysis: the ACG[®] system¹⁷⁶ and the Charlson comorbidity index.¹⁶⁹ The ACG[®] system was developed by investigators at Johns Hopkins University. ACGs[®] are a set of 106 mutually exclusive health states defined by morbidity, age, and sex. Using administrative data, individuals are first assigned one or more Aggregated Diagnosis Groups (ADGs[®]) according to the ICD codes present in their resource history use. Based on the combination of ADGs[®], individuals are then assigned to an ACG[®]. In our study, the ACGs[®] were provided by the BC Ministry of Health, and incorporated all health service utilization data from the fiscal year prior to the index hospitalization. Two ACGs[®] (4940 – 6-9 Other ADG[®] Combinations, Age 35+, 4+ Major ADGs[®]; 5070 – 10+ Other ADG[®] Combinations, Age 18+, 4+ Major ADGs[®]) were identified in the literature as being significant predictors of death and future hospitalization.¹⁷⁰ We used this categorization to produce a single binary variable that coded for belonging to one of these two groups. To calculate the Charlson comorbidity index, we used an algorithm adapted for administrative databases.¹⁷⁷ We calculated the index using the diagnostic codes in the other 15 responsible diagnosis codes of the index hospitalization, as we did not have access to non-respiratory-related health services utilization of our study population, and, by definition, this was the first respiratory-related hospitalization of this study population. This likely underestimated the true value of the index. The Charlson index was developed specifically to predict mortality (within one year), and

weights presence of comorbid disease according to the associated risk of death.¹⁶⁹ We considered using both of these indices because they were calculated in very different ways, and captured different sets of health utilization data – the ACG[®] capturing data from the fiscal year prior to index hospitalizations, and the Charlson index capturing listed conditions at the time of discharge from the index hospitalization.

5.4.6 Outcomes

The primary outcome of interest was a second hospitalization for COPD or all-cause mortality. We chose to use a combined end-point because it is an effective method of handling competing risks (discussed in section 3.2.6), and reduces selection bias due to informative censoring arising from death (section 3.1.1). All-cause mortality, rather than cause-specific death, was used because of the poor sensitivity of death codes could underestimate the cause-specific mortality rate and there is potential for this misclassification to be differential across levels of exposure (discussed in section 3.1.2). Furthermore, given the systemic effects of COPD, some non-pulmonary deaths may be associated with COPD (e.g. heart failure), and thus a reduction in the frequency of these deaths among individuals exposed to ICS may reflect systemic anti-inflammatory properties of ICS.

5.4.7 Censoring

We administratively censored individuals on March 31, 2001 if they had not yet experienced an event. We also censored individuals if they de-registered from MSP, because after that date, there were no data on health service utilization or prescription fill data. Finally, we censored individuals upon entry to long-term care facilities. These events can occur on a pre-scheduled date, and do not reflect an exacerbation or death, for which the hospitalizations are meant to serve as a proxy measure, and furthermore, dispensations of medications by hospitals and long-term care facilities are not captured by PharmaNet and therefore, exposure status cannot be determined following admission.

5.5 Data Analysis

The data analysis was designed to: 1) describe the hospitalization and prescription fill data of the study cohort; 2) characterize ICS use temporally and to identify patient characteristics associated with ICS initiation; and 3) estimate factors associated with time to death or re-hospitalization, using an extended Cox model.

5.5.1 Descriptive statistics

We calculated descriptive statistics of the study cohort, subdivided by presence of co-existing asthma, including counts, percents, and parametric and non-parametric descriptive statistics of study covariates at baseline. We also calculated mean and median follow-up times for each stratum, and tested for differences in proportions of outcomes using standard statistical methods.¹⁷⁸

5.5.2 Characterization of ICS use

We calculated the number of ICS dispensations over the study period, as well as the most frequently dispensed brands and types of drug, stratified by presence of asthma. To characterize the timing of ICS initiation with respect to first hospitalization, we calculated the time to ICS initiation among the asthma and non-asthma sub-groups. We categorized individuals who were previously taking ICS upon hospitalization as initiating ICS at day 0, and treated ICS initiation as an event. We generated a life table to summarize days to event, taking into account censored observations.

5.5.3 Predictors of ICS use

We used a logistic model¹⁷⁹ to identify predictors of ICS within the three months (90 days) following a hospitalization so that we could compare these results with other observational studies (section 2.8.5). Three months is a time frame that is short enough to capture dispensations for which the hospitalization served as the impetus for ICS initiation, yet long enough that individuals who were given ICS in hospital (which would not be captured by PharmaNet) would re-fill within this time frame. For this analysis, we excluded individuals who

died within the three month period. The anticipated association between characteristics and likelihood of ICS initiation is included in the table of potential confounders, in Table 3.1. We fit a multiple logistic regression model to estimate the relationship between covariates and the likelihood of initiating ICS following hospitalization. We obtained a regression coefficient for each variable which represents the change in the odds of ICS initiation for 1-unit increase in the covariate value, or the change in odds for a change in category, compared with a reference.

We left all predictors in the final model to display all information. We recognize that this leads to model over-fitting; however, the purpose of the model was descriptive rather than predictive – the model is intended only for describing the data. We tested the significance of individual covariates to identify potentially predictive variables, and the significance of the association fitted by the model using the log likelihood ratio.

5.5.4 Association between ICS and time to re-hospitalization or death

We estimated and compared the unadjusted and adjusted association between exposure to ICS and the composite outcome of COPD hospitalizations or all-cause mortality in the two strata defined by presence of asthma.

5.5.4.1 Person Time

We first calculated the counts and proportion of events – censorship, all-cause mortality, and hospitalization – across exposure categories and sub-grouped according to presence of co-existing asthma. We then used person-time analysis¹⁸⁰ to calculate the crude event rate among exposed and unexposed person-years. The event rate was calculated as the number of outcomes divided by the person-years at risk. We used the ratio of these two event rates to determine the unadjusted measure of relative risk of re-hospitalization or death among exposed and unexposed populations, stratified by presence of co-existing asthma.

5.5.4.2 Cox Model¹⁴⁷

The choice of modeling approach to measure the association between exposure to ICS and death or hospitalization is discussed in more detail in sections 3.2.7 and 7.2. Briefly, we chose

to use the extended Cox model over other modeling approaches because it was the most suitable model given that we were using administrative data without any clinical data and based on its ability to model varying exposure over time, adjust for potentially confounding variables, and allow for stratification of the cohort based on presence of co-existing asthma.

In order to produce an adjusted estimate of ICS effectiveness, we compared the hazard of death or hospitalization among individuals exposed to ICS against individuals unexposed to ICS, at a given time, t .

5.5.4.3 Preliminary analysis

We calculated the smoothed hazard function of death or hospitalization over time for individuals with and without coexisting asthma in order to provide insight about the conditional failure rates in these two groups and to support the decision to use a non-parametric form of the Cox model.

5.5.4.4 Adjusted analysis of ICS effectiveness

The covariates considered in the model are listed in Table 3.1. We chose these variables based on the directed acyclic graph (Figure 3.1). Variables which, according to the directed acyclic graph, did not appear to be confounders, were not included in the model.

In the interest of developing a parsimonious model with high explanatory power, we removed variables from the model by comparing log likelihood ratios of nested models with and without the variables, and by testing the effect of removing that variable on changes to the estimates of other coefficients. We did not anticipate there being any interaction terms, other than the interaction between asthma and ICS. This was based on there being no evidence in the observational literature and no *a priori* reasoning for interaction in the selected variables. To model the interaction between ICS exposure and presence of co-existing asthma, we used strata by covariate interaction terms.¹⁴⁷

By fitting the extended Cox model, we obtained the log hazard ratios associated with each variable. Exponentiating the estimates produced the hazard ratios. For continuous variables,

the hazard ratio represents the change in hazard associated with a one-unit increase in the covariate at each point in time. Categorical variables were converted to dummy variables, giving each category its own hazard ratio, compared with the referent category. The hazard ratio associated with the ICS by asthma interaction was multiplied by the ICS hazard ratio to produce the hazard ratio associated with ICS in the stratum of individuals with coexisting asthma.¹⁴⁷ The significance of the individual regression estimates were tested using the Wald statistic,¹⁴⁷ which tests the null hypothesis that the regression estimate is equal to zero. We used the likelihood ratio test¹⁴⁷ to assess the significance of the association represented by the model.

5.5.5 Sensitivity Analyses

In order to understand the impact of changing operationalized definitions in the study design, and to quantify the potential effect of potential sources of bias (discussed in section 3.1), we conducted several sensitivity analyses. We investigated the impact of changing our definitions of cohort inclusion, exposures, and outcomes. Analyzing the sensitivity of our results to various parameters was essential in being able to draw robust conclusions regarding the relationship between exposure and outcomes.¹⁸¹

5.5.5.1 Cohort definition

The original analysis included individuals at the time of first hospitalization where the first or second responsible hospital discharge diagnostic code was COPD. We assessed the impact of restricting the cohort to individuals whose first diagnostic code was COPD, excluding those with a second responsible diagnostic code of COPD.

In a second analysis, we investigated the effect of broadening the definition of the asthma. Initially, individuals were categorized into the coexisting asthma and COPD stratum based on a prior specialist visit or hospitalization coded for asthma, intentionally excluding GP visits. This definition was broadened to include any prior physician visit coded for asthma.

5.5.5.2 Exposure

In the main analysis, individuals were considered to be exposed when they filled consecutive prescription fills, according to the methods of CMA calculation. In the literature, 75% compliance is frequently considered a cut-point of compliance. We investigated several compliance cut-points and estimated the effect sizes when creating cut-points of 10%, 25%, 50%, and 75% compliance.

We investigated the extent to which the use of time-varying exposure in the main analysis avoided exposure misclassification in this study. First, we eliminated the time-varying exposure between the time of hospital discharge and first ICS fill. This yields misclassified immortal time¹²⁹ and has been demonstrated to underestimate the risk of outcome in the exposed.¹⁰⁶ We changed the exposure status so that individuals who filled a prescription for ICS during the follow-up period were categorized as 'exposed' from the time of hospital discharge until first ICS fill, rather than changing from 'unexposed' between hospital discharge to first ICS fill to 'exposed' at the time of first ICS fill. Second, we additionally eliminated time-varying exposure following an ICS fill. In the main analysis, individuals become 'unexposed' if they stopped filling ICS prescriptions (section 5.4.3) in order to reflect discontinued use medication; however, in this sensitivity analysis, individuals filling any prescription for ICS were considered 'exposed' from first ICS fill to the end of the follow-up period. Therefore, an individual's exposure was considered time-fixed over the entire follow-up period – 'exposed' if they filled any prescription for ICS, and 'unexposed' if they did not fill any prescriptions for ICS.

5.5.5.3 Outcomes

Using the Cox-proportional hazards model, we limited the deaths to respiratory-specific deaths, using the ICD-10 equivalents of the death codes used in the analysis of Sin and Man.¹⁰⁵ We then measured the effectiveness of ICS in reducing the hazard of re-hospitalization alone, all-cause mortality alone, and cause-specific mortality alone, compared between strata of concomitant asthma.

5.6 Figures and Tables

Figure 5.1 Diagram describing study design including cohort entry, diagnostic classification, exposure classification, and identification of outcomes based on prior hospitalizations and health service utilization recorded in the medical service plan (MSP) database, hospitalization discharge records and drug dispensations.

Table 5.1 Example of counting process format of data

Subject identification	Interval (days)	Compliance	Covariate 2	Covariate 3	...
1	(0,90]	100%	x1	y1	
1	[90,190)	80%	x1	y1	
1	[190, 390)	50%	x1	y1	
...	...	...	...	...	

6 Results

6.1 Descriptive statistics

The study cohort consisted of 14,153 individuals who were first hospitalized for COPD between October 1, 1996 and March 31, 2001 (Figure 6.1), 14.4% (2041) of whom had a history of asthma (Table 6.1). Overall, there were more men (57.8%) than women, and the mean age was 73.7 years (SD 10.0 years). Within the subset of subjects with coexisting asthma and COPD, there were proportionally fewer men (47.1%) but the mean age was similar (73.1 years; SD 10.2 years).

More than half of the study cohort (59.7%) had a Charlson comorbidity index of one or more. 10.7% of the cohort had an index of two or three, which indicates that at the time of hospitalization, these individuals had three or more of the comorbid conditions that are associated with death within one year,¹⁶⁹ or had one or more of the serious comorbid conditions that are associated with a higher risk of death. These numbers were similar in the subset of individuals with concomitant COPD and asthma – 60.5% of this sample had a Charlson index of one or more, and 9.8% had an index greater than one. Based on health services utilization in the year prior to the index hospitalization, 14.9% of all subjects were assigned to either of the ACG® groups 5070 or 4940, meaning that they had six or more comorbid conditions, four of which were considered to be serious (e.g. malignancy).¹⁷⁰

An ICD code corresponding to COPD (Table 2.3) was listed as the first most responsible reason for hospitalization in 42.9% of the index hospitalizations, and as the second most responsible reason in 58.0% of the hospitalizations (0.9% had a code for COPD in both the first and second most responsible diagnosis fields). ‘Chronic airway obstruction, not elsewhere classified’ (ICD-9 code 496) was the most frequently recorded diagnostic code (23.8% of first most responsible diagnoses, and 45.4% of second most responsible diagnoses). Although pneumonia was not used as a criterion for cohort inclusion, it was recorded as the primary

diagnostic code in 11.3% of the index hospitalizations. Additional data describing diagnostic codes in the first and second most responsible diagnosis fields is presented in Table 1a, b of Appendix 1. Subjects were hospitalized for a median of five days (IQR: 3-9 days). 5.7% were admitted to ICU for a median of three days (IQR 1-5 days).

The median follow-up time was 14.4 months (mean of 17.8 months), until the re-hospitalization, death, or censoring, whichever came first. During this period, a total of 8540 study subjects filled a prescription for ICS. This represented 55.0% of the COPD-alone study sample and 92.2% of the COPD/asthma sample (Table 6.2). Of 59,135 prescriptions filled, Flovent® inhalers (250 µg/AEM) were most frequently dispensed, and the majority of dispensations were delivered using the MDI/dry powder formulation (90.4%). A summary of all drug dispensations is provided in Table 2 of Appendix 1.

6.2 Characterization of ICS use

Temporal characteristics of ICS initiation are presented as a life table in Table 6.3. Only the number of ICS-naïve subjects who were alive and uncensored *at the end* of each time interval is presented in the first column, although the cumulative proportion of individuals remaining ICS-naïve (presented in the third results column) was calculated using *all* person-time during that interval. 50.1% of all subjects (43.9% of COPD-only and 87.3% of COPD plus asthma) had filled an ICS prescription prior to their first hospitalization. The cumulative proportion of individuals who remained ICS naïve ninety days following hospital discharge was 49.8% among individuals with COPD only, and 10.0% among individuals with COPD and asthma. After two years, this proportion was 42.4% and 7.0%, respectively.

Among all individuals who were dispensed at least one prescription of ICS, the median level of compliance was 70.3% (IQR: 44.1%-96.1%), based on individuals' cumulative prescription refill compliance at the time of last fill (Table 6.4). The distribution of compliance was roughly Gaussian, with the most frequent compliance levels between 70% and 80%. Individuals who refilled their prescription prior to depleting their available supply had a cumulative refill

compliance that was calculated to be greater than 100%; however, because this represented a period of oversupply due to refill timing, these individuals were re-assigned a 100% level of refill compliance rather than a value greater than 100%. This resulted in a second peak in the distribution at 100%.

6.3 Predictors of ICS use

There were 5711 individuals who were ICS-naïve at the time of discharge from hospitalization and who did not die in the subsequent 90 days, 13.4% (764) of whom filled a first prescription for ICS in the ninety days following discharge. The estimates of the multiple logistic regression model show that there was a significant association between the likelihood of ICS initiation and sex, presence of asthma, and comorbid conditions (Table 6.5). The odds of ICS initiation during this 90 day period among individuals with concomitant asthma were approximately two times the odds among individuals without: 21.7% of ICS-naïve asthmatics filled within the ninety days following hospitalization, compared with 11.6% of ICS-naïve non-asthmatics. Men showed 25% lower odds of ICS initiation as compared with women (OR: 0.75; 95% CI: 0.64 - 0.88), and the presence of major comorbidities in the year prior to hospitalization (ACG® group) was associated with a 29% reduction in the odds of receiving ICS (OR: 0.71; 95% CI: 0.55 - 0.92).

Women and asthma were correlated ($\chi^2= 18.6$; $p < 0.001$); however, we retained both of these variables so as to present all information and because we do not intend to use these results for predictive purposes. There was a significant association between the likelihood of ICS initiation and the variables in the model; the log-likelihood ratio was 68.2, $p < 0.001$ for 12 degrees of freedom, suggesting that at least one regression coefficient was different from zero.

6.4 Association between ICS and time to re-hospitalization or death

Overall, there were 8385 (59.2%) censored observations due to MSP deregistration, entry to a long-term care facility, or reaching the end of the study period (Table 6.6). All other outcomes in the follow-up period were either death or second hospitalization, which were

combined into a single outcome in the main analysis, as they represent competing risks. Among individuals with COPD alone, 14.8% of outcomes following first hospitalization for COPD were deaths; 9.6% of outcomes were death among individuals with concomitant COPD and asthma. The lower proportion of deaths in the stratum of individuals with concomitant COPD and asthma may not represent fewer deaths during follow-up, but rather that individuals were re-hospitalized prior to death more frequently in this group. Re-hospitalizations represented 34.5% of outcomes in the COPD plus asthma stratum, and 24.5% of outcomes in the stratum of individuals with COPD.

Table 6.7 presents the crude rate ratios of death or hospitalization across ICS exposure categories. In the stratum containing individuals with COPD-only, the unadjusted event rate in the exposed group was 0.29 events per person year, and was 0.25 events per person year in the unexposed group, representing a rate ratio of 1.14 (95% CI: 1.07 – 1.21). Among individuals afflicted with both asthma and COPD, the unadjusted event rates were 0.30 and 0.32 in the exposed and unexposed categories, respectively, resulting in a rate ratio of 0.94 (95% CI: 0.79 – 1.12). The overall rate ratio (RR = 1.13; 95% CI: 1.08 – 1.19) was similar to that among the COPD-alone stratum.

Table 6.8 shows the hazard ratios and 95% CIs of the extended Cox model, estimating the adjusted association between ICS exposure and hazard of hospitalization or death. The adjusted hazard ratio was not significantly associated with ICS exposure at time t , in the stratum of individuals with COPD alone (HR=0.99; 95% CI: 0.94-1.05). In the stratum containing individuals afflicted with both COPD and asthma, the hazard ratio of exposure to ICS at time t compared with non-exposure was 18% lower than in the stratum of individuals with COPD alone (HR = 0.82; 95% CI: 0.69 – 0.99). This represents a significant difference in hazard ratios between strata, and a beneficial association between ICS exposure and hazard of death or hospitalization.

Except for prior use of LABA, and time spent in ICU, all of the anticipated confounding variables were found to be significantly associated with the hazard of death or hospitalization. Increased age was associated with higher hazard ratios, as was increased Charlson comorbidity index and increased length of stay. Men had a higher hazard ratio compared with women (1.16; 95% CI: 1.10 – 1.22), and individuals assigned to high-risk ACG[®] groups were associated with increased hazard of death or hospitalization (HR = 1.55; 95% CI: 1.45 – 1.65). Although prior use of LABA was not found to be significantly associated with the hazard ratio, because some evidence that suggests that ICS and LABA together are more effective than ICS alone, we chose to keep prior use of LABA in the model.

The log likelihood ratio of the model was 1079 with $p < 0.001$ on 15 degrees of freedom, suggesting that at least one regression coefficient is different from zero.

The hazard functions for each stratum are displayed presented in Figure 2.1. For most of the study period, the hazard of death or hospitalization was higher among individuals with coexisting asthma and COPD than among individuals with COPD alone. This figure does not take into account differences in exposure status. It simply indicates that individuals with coexisting disease have a different underlying hazard function than individuals with COPD alone.

6.5 Sensitivity Analyses

The sensitivity analyses are summarized in Table 6.9 according to changes in cohort definition, exposure, and outcomes. The hazard ratios and Wald statistics for the variables included in each analysis are provided in Appendix 1, Table 3 a-k. The log-likelihood ratios for each model had p-values less than 0.001, suggesting that in each model, at least one hazard ratio was different from one.

6.5.1 Cohort definition

In limiting the analysis to include only individuals for whom the index hospitalization had a first responsible diagnosis was COPD (rather than a first or second), we found a greater

effectiveness of ICS in the COPD-only stratum. The hazard ratio in this stratum was 0.92 (95% CI: 0.84-1.00). The hazard ratio associated with the COPD/asthma times ICS interaction term indicated that there was greater effectiveness in this stratum than in the COPD-only stratum (HR = 0.92; 95% CI: 0.70-1.21). The point estimate of ICS effectiveness in the COPD/asthma stratum, obtained by multiplying the ICS hazard ratio with the COPD/asthma-ICS interaction hazard ratio, was 0.846, which is similar to the estimate in the main analysis.

Changing the definition of co-existing asthma to include individuals with any history of physician visit or hospitalization with a responsible diagnostic code corresponding to asthma resulted in an increase in the number of individuals with co-existing asthma from 2041 to 5552 (39.2% of the cohort). Using this definition, the population defined as having coexisting COPD and asthma had a hazard ratio associated with ICS exposure that was lower than that among individuals with COPD alone (HR = 0.77; 95% CI: 0.68 – 0.86), consistent with the main analysis.

6.5.2 Exposure

We observed a trend in the point estimates of ICS effectiveness when we adjusted our definition of exposure as a function of compliance. When we required compliance to be greater than 75% in order to be considered exposed, and considered all compliance levels below 75% to be unexposed, ICS exposure was associated with an increased hazard of death or hospitalization in the COPD-only stratum (HR = 1.13; 95% CI: 1.05 – 1.22). Lowering this compliance threshold resulted in a lowered association between ICS and hazard of death or hospitalization in the COPD-only stratum: at the 50% compliance threshold, the hazard ratio associated with exposure was 1.09 (95% CI: 1.02 – 1.17); at 25% the hazard ratio was 1.08 (95% CI: 1.02 – 1.15) and at 10% it was 1.04 (95% CI: 0.98 – 1.10). In the asthma plus COPD stratum, the multiplicative combination of the stratum specific hazard ratio with the hazard ratio in the COPD-alone stratum yielded a similar decrease in effect estimates with decreasing cut-points.

Changing the time-varying exposure variable to a time-fixed exposure was done in two steps (section 5.5.5.2). In the first step, where we demonstrated the effect of including immortal time between the time of hospital discharge and first ICS, 1444 individuals who had been categorized as 'unexposed' in the main analysis were re-categorized as 'exposed' during this period, resulting in 918.2 person years of misclassified immortal time. The inclusion of this immortal time among the exposed resulted in a lower point estimate of ICS effectiveness in the COPD-only stratum (HR = 0.80; 95% CI: 0.75-0.85) and in the co-existing COPD and asthma stratum (HR = $0.85 * 0.80 = 0.68$) (Table 6.9), compared with the main analysis (Table 6.8). In the second step, where individuals who filled a prescription for ICS was categorized as 'exposed' for all time periods following first fill, 2144.4 person years were re-assigned as 'exposed' and 598 outcomes (deaths or hospitalizations) were re-assigned as 'exposed'. The combination of these two steps resulted in a time-fixed exposure variable rather than time-varying. The overall effect estimate suggested a reduction in the risk of hospitalization among individuals with COPD alone (HR = 0.88; 95% CI: 0.83 - 0.93) and no significant difference in effectiveness between individuals with COPD alone and individuals with combined COPD and asthma (HR = 0.97; 95% CI: 0.74 - 1.25) (Table 6.9).

6.5.3 Outcomes

The choice of outcome measure impacted the point estimates of effectiveness of ICS in the COPD-alone stratum, but the point estimate associated with ICS effectiveness was consistently lower in the stratum of coexisting COPD and asthma, regardless of outcome measure. ICS was associated with a 58% reduction in hazard of all-cause mortality (HR = 0.42; 95% CI: 0.39 – 0.46) in the COPD-alone stratum, and a 41% reduction in hazard of cause-specific mortality (HR = 0.59; 95% CI: 0.51 – 0.69). In the COPD plus asthma stratum, the point estimates of these hazard ratios were 0.25 and 0.26, respectively. The combined outcome of cause-specific mortality or hospitalization yielded a hazard ratio of 1.47 in the COPD-only stratum (95% CI: 1.37 – 1.58), and hospitalization alone resulted in a hazard ratio of 1.64 (95% CI: 1.52 – 1.77).

6.6 Figures and Tables

Abbreviations: MSP = Medical Services Plan; LOS = length of stay.

Figure 6.1 Flowchart of cohort inclusion among individuals discharged from a first hospitalization for COPD in BC between 1996 and 2001.

Figure 6.2 Estimated (smoothed) hazard function for death or hospitalization following discharge from first hospitalization for COPD in BC between 1996 and 2001.

Table 6.1 Characteristics of individuals discharged alive after a first hospitalization for COPD in BC between 1996 and 2001.

	COPD without Asthma		COPD with Asthma		All Subjects	
<i>n, %</i>	12112	100	2041	100	14153	100
Demographics						
Age - mean, SD	73.8	10.0	73.1	10.2	73.7	10.0
Sex - n male, %male	7222	59.6	961	47.1	8183	57.8
Comorbid Conditions						
Charlson Index - n, %						
0 - Total comorbid score = 0	4890	40.4	807	39.5	5697	40.3
1 - Total comorbid score = 1-2	5911	48.8	1034	50.7	6945	49.1
2 - Total comorbid score = 3-4	1110	9.2	176	8.6	1286	9.1
3 - Total comorbid score = 5-6	201	1.7	24	1.2	225	1.6
ACG® Group - n, %						
5070 - 4+ Major ADG®, 10+ conditions	1396	11.5	250	12.2	1646	11.6
4940 - 4 Major ADG®, 10 conditions	435	3.6	32	1.6	467	3.3
Index Hospitalization Data						
Most frequently coded primary diagnosis - n, %						
496 - Chronic airway obstruction, not elsewhere classified	2821	23.3	552	27.0	3373	23.8
491 - Chronic bronchitis	1780	14.7	366	17.9	2146	15.2
486 - Pneumonia	1386	11.4	218	10.7	1604	11.3
Most frequently coded secondary diagnosis - n, %						
496 - Chronic airway obstruction, not elsewhere classified	5596	46.2	825	40.4	6421	45.4
491 - Chronic bronchitis	888	7.3	177	8.7	1065	7.5
492 - Emphysema	649	5.4	68	3.3	717	5.1
Admission to intensive care unit - n, %	695	5.7	118	5.8	813	5.7
Length of Stay (days) - median, IQR						
In ICU (if admitted)	3	1 - 5	2	1 - 5	3	1 - 5
In hospital (total stay)	5	3 - 9	6	3 - 9	5	3 - 9

Abbreviations: ACG®: Adjusted Clinical Group; ADG®: Aggregated Diagnosis Group; ICU: intensive care unit; SD: standard deviation; IQR: inter-quartile range.

Table 6.2 Characteristics of drug dispensation to individuals discharged alive after a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

	COPD without Asthma		COPD with Asthma		All Subjects	
<i>Dispensations - n, %</i>	44851		14284		59135	
Use of ICS						
<i>Never dispensed ICS</i>	5454	45.0	159	7.8	5613	39.7
<i>At least one dispensation of ICS</i>	6658	55.0	1882	92.2	8540	60.3
<i>ICS Drug Type - n fills, % fills</i>						
ICS: MDI/dry powder	41008	91.4	12442	87.1	53450	90.4
ICS: nebulized	3282	7.3	1544	10.8	4826	8.2
Salmeterol + ICS	561	1.3	298	2.1	859	1.5
<i>Most frequently prescribed drugs - n fills, % fills</i>						
Flovent Inhaler	7163	16.0	2307	16.2	9470	16.0
Pulmicort Turbuhaler	6238	13.9	2246	15.7	8484	14.3
Becloforte Inhaler	6132	13.7	2013	14.1	8145	13.8
Drug use prior to 1st hospitalization						
<i>LABA - n, %</i>	638	5.3	433	21.2	1071	7.6
<i>Anticholinergics - n, %</i>	4052	33.5	1276	62.5	5328	37.6

Abbreviations: ICS: Inhaled corticosteroids; MDI: metered-dose inhaler; LABA: long-acting beta-agonist.

Table 6.3 Life table describing time to inhaled corticosteroid (ICS) initiation prior to and following discharge hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

Days	COPD without asthma			COPD with asthma			All Subjects		
	n at risk	n initiating ICS	% unexposed	n at risk	n initiating ICS	% unexposed	n at risk	n initiating ICS	% unexposed
Pre-hospitalization	12112	5314	56.1	2041	1782	12.7	14153	7096	49.9
1	6798	120	55.1	259	3	12.5	7057	123	49.0
2 - 30	5751	386	51.8	213	32	11.0	5964	418	45.9
31 - 60	5224	135	50.6	183	13	10.3	5407	148	44.7
61 - 90	4861	71	49.8	170	4	10.0	5031	75	44.1
91 - 180	4123	126	48.5	140	14	9.2	4263	140	42.8
181 - 365	3152	183	46.1	103	12	8.3	3255	195	40.6
365 - 730	1710	193	42.4	51	12	7.0	1761	205	37.3
731 - 1600	31	130	35.5	0	0	0	31	140	31.0

Abbreviations: ICS: Inhaled corticosteroids.

Table 6.4 Compliance with prescribed ICS dose (using cumulative multiple availability measure)¹²⁸ during follow-up from a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

	COPD without asthma	COPD with asthma	All subjects
Median	0.700	0.700	0.700
IQR	(0.430 - 0.962)	(0.474 - 0.954)	(0.441 - 0.961)

Abbreviations: IQR: Inter-quartile range.

Table 6.5 Odds ratios and 95% confidence intervals (CIs) of multiple logistic regression model of ICS initiation within ninety days of an index hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

	Odds Ratio	95% CI
<i>Intercept</i>	0.16	(0.11 - 0.23)
<i>Male (vs. Female)</i>	0.75	(0.64 - 0.88)
<i>Age (vs 45-54)</i>		
55-64	1.25	(0.86 - 1.84)
65-74	1.14	(0.79 - 1.62)
75-84	0.92	(0.64 - 1.31)
85-94	0.81	(0.54 - 1.23)
95-104	1.13	(0.37 - 3.41)
<i>Coexisting Asthma (vs. no coexisting asthma)</i>	2.06	(1.47 - 2.89)
<i>Prior use of LABA (vs. no prior use)</i>	0.65	(0.34 - 1.23)
<i>Prior use of anticholinergics (vs. no prior use)</i>	1.08	(0.88 - 1.33)
<i>Days spent in intensive care unit</i>	1.02	(0.97 - 1.08)
<i>ACG[®] = 5070 or 4940</i>	0.71	(0.55 - 0.92)
<i>Comorbidity Index (vs 0)</i>		
Charlson Index = 1	1.00	(0.84 - 1.18)
Charlson Index = 2	0.76	(0.56 - 1.05)
Charlson Index = 3	0.56	(0.24 - 1.30)

Abbreviations: ACG[®]: Adjusted Clinical Group

Table 6.6 Frequency of outcomes and censored observations during follow-up from a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

	COPD without asthma		COPD with asthma		All subjects	
	n	%	n	%	n	%
<i>Deaths</i>	1794	14.8	195	9.6	1989	14.1
<i>2nd Hospitalizations</i>	3075	25.4	704	34.5	3779	26.7
<i>Censored observations</i>	7243	59.8	1142	56.0	8385	59.2
<i>Total</i>	12112	100.0	2041	100.0	14153	100.0

Table 6.7 Rates and crude rate ratios (RRs) of death or hospitalization for exposure to inhaled corticosteroids (ICS) among individuals discharged alive from a first hospitalization in British Columbia (BC) between 1996 and 2001.

	Exposed			Unexposed			RR	95% CI
	Events	Person years	Event Rate (event·py-1)	Events	Person years	Event Rate (event·py-1)		
<i>COPD without Asthma</i>	2253	7763	0.29	2616	10270	0.25	1.14	1.07 - 1.21
<i>COPD with Asthma</i>	736	2455	0.30	163	511	0.32	0.94	0.79 - 1.12
<i>All subjects</i>	2989	10218	0.29	2779	10781	0.26	1.13	1.08 - 1.19

Abbreviations: CI: Confidence Interval.

Table 6.8 Adjusted estimates of ICS effectiveness among individuals discharged alive from a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001, using an extended Cox model with time-varying exposure. CI: Confidence Interval.

	Hazard Ratio	95% CI
Stratum-specific effectiveness of ICS		
<i>Exposure to ICS - COPD only stratum</i>	0.99	(0.94 - 1.05)
<i>Exposure to ICS * COPD plus asthma stratum</i>	0.82	(0.69 - 0.99)
Adjustment Variables		
<i>Male (vs. Female)</i>	1.16	(1.1 - 1.22)
<i>Age (vs 45-54)</i>		
55-64	1.39	(1.17 - 1.65)
65-74	1.84	(1.57 - 2.16)
75-84	2.26	(1.93 - 2.65)
85-94	2.73	(2.31 - 3.23)
95-104	3.19	(2.23 - 4.56)
<i>Length of Stay</i>	1.01	(1.01 - 1.01)
<i>Comorbidity Index (vs 0)</i>		
Charlson Index = 1	1.17	(1.11 - 1.24)
Charlson Index = 2	1.38	(1.26 - 1.51)
Charlson Index = 3	2.06	(1.73 - 2.46)
<i>ACG[®] = 5070 or 4940 (vs other)</i>	1.55	(1.45 - 1.65)
<i>Prior use of long acting beta agonists</i>	1.04	(0.94 - 1.16)
<i>Prior use of anticholinergics</i>	1.63	(1.54 - 1.72)

Abbreviations: ICS: Inhaled Corticosteroids; ACG[®]: Adjusted Clinical Group

Table 6.9 Sensitivity analyses of adjusted^a ICS effect estimates among individuals discharged alive from a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001, using an extended Cox model with time-varying exposure.

Cohort Definition	Hazard Ratio	95% CI
<i>Asthma as any prior HSU coded with 493</i>		
Exposure to ICS - COPD only stratum	1.06	(0.98 - 1.14)
Exposure to ICS * COPD plus asthma stratum	0.77	(0.68 - 0.86)
<i>First responsible diagnostic code of COPD only</i>		
Exposure to ICS - COPD only stratum	0.92	(0.84 - 1.00)
Exposure to ICS * COPD plus asthma stratum	0.92	(0.70 - 1.21)
Exposure	Hazard Ratio	95% CI
<i>Compliance ≥75%</i>		
Exposure to ICS - COPD only stratum	1.13	(1.05 - 1.22)
Exposure to ICS * COPD plus asthma stratum	1.07	(0.91 - 1.26)
<i>Compliance ≥50%</i>		
Exposure to ICS - COPD only stratum	1.09	(1.02 - 1.17)
Exposure to ICS * COPD plus asthma stratum	1.17	(1.01 - 1.36)
<i>Compliance ≥25%</i>		
Exposure to ICS - COPD only stratum	1.08	(1.02 - 1.15)
Exposure to ICS * COPD plus asthma stratum	1.05	(0.90 - 1.23)
<i>Compliance ≥10%</i>		
Exposure to ICS - COPD only stratum	1.04	(0.98 - 1.10)
Exposure to ICS * COPD plus asthma stratum	0.93	(0.78 - 1.10)
<i>No time varying exposure to first fill</i>		
Exposure to ICS - COPD only stratum	0.80	(0.75 - 0.85)
Exposure to ICS * COPD plus asthma stratum	0.85	(0.71 - 1.02)
<i>Time-fixed exposure</i>		
Exposure to ICS - COPD only stratum	0.88	(0.83 - 0.93)
Exposure to ICS * COPD plus asthma stratum	0.97	(0.75 - 1.25)
Outcomes	Hazard Ratio	95% CI
<i>Cause-specific death or hospitalization</i>		
Exposure to ICS - COPD only stratum	1.47	(1.37 - 1.58)
Exposure to ICS * COPD plus asthma stratum	0.86	(0.68 - 1.09)
<i>Hospitalization (death censored)</i>		
Exposure to ICS - COPD only stratum	1.64	(1.52 - 1.77)
Exposure to ICS * COPD plus asthma stratum	0.92	(0.71 - 1.19)
<i>All cause mortality</i>		
Exposure to ICS - COPD only stratum	0.42	(0.39 - 0.46)
Exposure to ICS * COPD plus asthma stratum	0.59	(0.48 - 0.74)
<i>Cause-specific mortality</i>		
Exposure to ICS - COPD only stratum	0.59	(0.51 - 0.69)
Exposure to ICS * COPD plus asthma stratum	0.44	(0.30 - 0.64)

^a Adjusted for same variables as main model: age, sex, length of stay, comorbidity index, ACG group, prior use of long acting beta agonists, prior use of anticholinergics
Abbreviations: CI: Confidence Interval; ICS: Inhaled Corticosteroids

7 Discussion

In this study of individuals with COPD discharged from a first hospitalization in BC between 1996 and 2001, we observed a difference in the effectiveness of ICS among individuals with COPD alone and individuals with concomitant COPD and asthma. The hazard ratio of death or hospitalization was 18% lower in the subset of individuals with concomitant COPD and asthma compared with the subset of individuals with COPD alone (HR = 0.82, 95% CI: 0.69 – 0.99). We did not detect a reduction in hazard of death or hospitalization associated with exposure to ICS in the COPD-only stratum (HR = 0.99; 95% CI: 0.94-1.05); however, the hazard ratio in the stratum of individuals with COPD and asthma suggested that there was a beneficial effect of ICS in this subgroup. Because co-existing asthma and COPD is characterized by partially reversible airflow, this may suggest that post-bronchodilator reversibility may be an important factor in identifying individuals with COPD who respond well to ICS.

7.1 Contextualization of results

Prior to this study, no other published studies have estimated the comparative effectiveness of ICS in a population of individuals with COPD alone and individuals with co-existing asthma and COPD. Two other observational studies explored the impact of a prior history of asthma;^{110,113} however, neither explicitly measured the difference in effectiveness between the two groups, and both studies used a broad definition of co-existing asthma, likely including individuals with “pure” asthma, rather than individuals with co-existing asthma and COPD. Although not explicitly quantified, the results of both studies suggested greater ICS effectiveness among individuals afflicted with COPD who had a prior history of asthma compared those with no history, which is consistent with the findings of the current study. There are no experimental studies to which the results can be compared, as there are no studies of ICS efficacy among individuals with concomitant asthma and COPD, nor are there subgroup analyses addressing this issue, because individuals with history of asthma and

individuals with bronchodilator reversibility of more than 10% of baseline FEV₁ are typically excluded from RCTs (discussed in section 2.8.6).

Patients with COPD are thought to have impaired HDAC2 function, consequently reducing the effectiveness of ICS (section 2.8.1).⁷⁸ Therefore, in theory, the comparatively greater effectiveness of ICS on the asthmatic component of the disease could be overridden by the impaired function of HDAC2. However, the results of this study suggest that this may not be the case, since ICS maintains its improved effectiveness in asthma compared with COPD, even when both diseases coexist.

Given the macro-level of our findings, it is injudicious to draw conclusions regarding the biological mechanisms that may or may not explain the effect modification we observed in our data.¹⁸² The previously suggested mechanism should be investigated further.

Causal relationships become more credible with the support of additional evidence and logical reasoning.¹⁸³ Additional studies should be conducted to strengthen the body of evidence supporting the causal relationship between ICS and reduced rates of death and hospitalization in asthmatics with COPD.

7.2 Choice of modeling approach

We implemented an extended Cox model with a time-varying covariate representing use of ICS. Cox models are a superior method for representing risk using censored longitudinal data,¹⁴⁷ and their extension to allow for time-varying covariates provides an analytic tool for reducing immortal time bias in pharmacoepidemiological studies.¹¹⁵

Because exposure changes over time, it means that the hazard ratio between two groups of individuals changes over follow-up time. As a result, the hazard ratio associated with ICS exposure applies only to the hazard ratio *at a specified time*, and the hazard ratio of an exposed group of individuals can only be assessed at specified times, compared with an unexposed group of individuals with equal baseline covariates. Therefore, these results cannot be used to predict the estimated time to event among individuals with known covariates.¹⁸⁴

This implies that the results from this study must be interpreted carefully: in the subpopulation of asthmatics with COPD, the hazard of death *at a specified time* is 19% lower among those exposed to ICS *at that time* compared with those who are not, assuming all baseline characteristics are equal; and in the subpopulation of individuals with COPD alone, the hazard of death is not different between exposure categories of ICS, *at a given time, t* (HR = 0.99; 95% CI: 0.94-1.05).

The major assumption in using a model with time-varying exposure is that the change in exposure occurs in a random fashion. This has been a criticism of other studies using time varying covariates in the estimation of ICS effectiveness in COPD.¹⁸⁵ Because frequent exacerbations are currently an indication for ICS initiation,¹¹ we anticipated that by restricting cohort entry to individuals at the time of discharge from their first hospitalization for COPD, ensuing changes in exposure status would be related to this common event, and not to a difference in underlying risk of death or re-hospitalization. Only 10.2% (1444) of subjects initiated ICS following hospitalization, with just 4.8% (680) initiating more than 90 days post-discharge (Table 6.3). Thus, the impetus for ICS initiation in these cases was likely the index hospitalization. Therefore, the use of a time-varying exposure is unlikely to have biased our results any more than a time-fixed exposure, and the time-varying exposure had the additional advantage of reducing immortal time bias, and incorporating discontinued use of ICS.

The choice to use this model over other modeling approaches discussed in section 3.2 was in part because of the limitations of administrative databases in pharmacoepidemiological research. The instrumental variable approach may have been more effective in reducing any unknown confounding; however, within the available data, we were unable to identify an instrument that was related to the exposure but not to the outcome. We were also unable to implement a marginal structural model due to the unavailability of a data source that captures one or more intermediate variables. Had an intermediate variable been available, such as

FEV₁, it could have been incorporated into the model to predict subsequent exposure, and may have reduced bias.

The choice not to use propensity scores approach was based on the fact that it does not significantly improve the accuracy of effect estimates when data is limited nor does it control for unmeasured confounders.¹⁵⁵ We did identify predictors of ICS use using a logistic regression model; however, due to the large number of individuals who filled their first prescription prior to the index hospitalization, the model only predicted use for 8.0% of individuals who filled one or more ICS prescriptions (Table 6.3).

7.3 Internal validity

Bias and confounding exist in all epidemiological studies. Confounding is particularly a concern in observational studies of effectiveness because individuals are not randomized to treatment groups and thus predictors of outcome may not be equally distributed across categories of exposure.¹²³ While some types of bias are avoidable through careful study design and analysis, many types are not. The direction and magnitude of the biases introduced in section 3.1 are discussed in this section in order to inform inferences regarding the results of the study.¹²³

7.3.1 Selection Biases

As administrative databases were used to form the study cohort, this study is mainly free of types of selection bias relating to subject recruitment; however, informative right-censoring of individuals may have contributed some amount of bias.

Because death and hospitalization are both events that are associated with COPD disease severity and are competing risks, we used a composite end point of death and hospitalization. This allowed for the measurement of hospitalizations as an outcome, while avoiding informative right censoring of deaths.

Censoring deaths only induces bias if the exposed and unexposed groups have different underlying mortality rates, yielding an over-estimate of event-free survival in the group with the

higher death rate. In the sensitivity analysis, the association between ICS and hazard of hospitalization alone in the COPD-only stratum was 1.47 (95% CI: 1.37-1.58) (Table 6.9), suggestive of a harmful effect of ICS on mortality. Further analysis of the differential censoring between exposure groups confirmed that there were proportionally more deaths among the unexposed (18.3%) than among the exposed (8.2%). This resulted in more 'hospitalization-free' person years in the un-exposed category, because individuals died before being hospitalized, and artificially inflated the hazard ratio.

We also censored individuals who entered long-term care facilities. This was a reasonable decision because these hospital admissions are typically pre-scheduled, do not represent an acute exacerbation, and because medication is supplied by the long-term care facility and data for these medications cease to be recorded in the PharmaNet database. However, the individuals who required long-term care and surgery likely represented a more advanced stage of disease and higher risk of death. As with the censorship of death, bias would be incurred if censorship occurred differentially between the exposed and unexposed groups. In this case, there were more censored events due to level-of-care in the exposed compared with the unexposed (3.9% in the exposed, and 1.5% in the unexposed). Assuming that individuals who were censored were at higher risk for events, our effect size would be biased downward, in favour of ICS. This difference was more marked in the asthma subpopulation (1.2% unexposed censored due to long-term care, versus 4.2% exposed censored). Therefore, the effect of differential censorship may account in some part for the lower effect size measured among those individuals with asthma; however because of the small number of censored observations due to surgery and long-term care, the change in effect size was small. We investigated the effect of changing these censored observations to 'events' and the point estimates of the hazard ratios changed by 0.01 units. Therefore, although theoretically the hazard ratios are biased downwards due to differential censoring of long-term care, the magnitude of the bias is very small, and has little effect on the estimates or conclusions that be drawn from the results.

7.3.2 Information Biases

Several potential sources of information bias were discussed in section 3.1.2: exposure misclassification (with special consideration of immortal time bias), diagnostic misclassification, and outcome misclassification. This section addresses the extent to which these were avoided in this study, and the impact of the biases on the effect estimates.

7.3.2.1 Immortal time bias

Given the concern about immortal time bias in studies of ICS effectiveness in COPD,¹²⁹ we were careful to design this study in such a way as to avoid it. By defining cohort entry at the time of discharge from hospital, rather than according to a hierarchical drug utilization benchmark, we avoided excluded immortal time.¹⁰⁷ To avoid misclassified immortal time, we used a time-varying exposure, with 'days' as the unit of time.¹⁰⁶

We conducted an analysis to investigate the impact of using a time-fixed exposure variable rather than time-varying exposure. Suissa¹⁰⁶ originally demonstrated this difference, using the work of Sin and Tu¹⁰³ as an exemplar. Suissa found that eliminating the misclassified immortal time changed the point estimate of ICS effectiveness from 0.69 in the analysis subject to immortal time bias to 1.00 in the analysis free of immortal time. Using the data from the current study, addition of immortal time (because the current study was designed to exclude it) changed the estimate of ICS effectiveness in the COPD-only stratum from 0.99 in the analysis free of immortal time to 0.80 in the analysis including it. We suspect that the magnitude of the change was not as large as that demonstrated by Suissa because his study enrolled individuals who were ICS-naïve upon discharge from hospital, and thus all individuals filling a prescription for ICS accumulated immortal time, whereas in the current study, approximately 50% of individuals who were categorized as exposed at any time had filled an ICS prescription prior to hospitalization, and thus did not accumulate immortal time. The second step in investigating the effect of using a time-fixed exposure variable involved categorizing individuals as 'exposed' between the time of first ICS fill and the end of follow-up, despite ICS discontinuation. Although

this does not represent immortal time bias, we will discuss it in this section as it relates to the use of time-fixed exposure. After changing exposure from 'unexposed' to 'exposed' for all time periods following an ICS fill, the point estimate of ICS effectiveness in the COPD-only stratum increased from 0.80 to 0.88, which was lower than the initial analysis, yet higher than in the first step. The anticipated direction of change of estimate depends upon the association between ICS discontinuation and outcome. Because there was a decrease in the number of unexposed person years, if the number of events were to remain the same, the event rate in the unexposed would increase, suggesting a larger benefit of ICS. However, the proportion of events among those who discontinued was higher than among those who did not, leading to an increase in the effect estimate when individuals were analyzed according to an intent to treat analysis.

7.3.2.2 Exposure Misclassification

Proper exposure classification using administrative data is challenging. In this study, exposure was assumed based on filled prescriptions for ICS; however, the actual consumption of the medication was never verified due to the administrative nature of the data. The use of the CMA metric accounted for hoarding because unused doses carry forward from one refill interval to the next,¹²⁸ preventing misclassification of individuals as unexposed during a perceived lapse in prescription fill. It is more likely that individuals were misclassified as exposed when they were truly unexposed than vice versa. Twenty-five percent of ICS users were less than 44.1% compliant (cumulative compliance) at the time of their last fill (Table 6.4), meaning that they were either taking less than half of the recommended daily dose throughout, or used the full recommended daily dose during periods of use, but on more than half of the days, they took no medication at all. The effect of this misclassification on the effect estimate is complicated, as it depends on when and how the misclassification occurred. If the level of compliance increases over time, with individuals becoming more compliant near the end of the study period, then these event-free periods of truly un-exposed person-time would inflate the

person-time denominator of the exposed category, leading to an underestimate of the hazard ratio (suggesting a protective effect of ICS). However, it is more likely that misclassified time occurred immediately prior to an event, causing events to be mistakenly assigned to the exposed category, thus inflating the event rate in the exposed category and overestimating the hazard ratio (towards a harmful effect of ICS). Without further analysis of the temporal trends in compliance, it is difficult to conclude the effect of exposure misclassification on the results.

The sensitivity analyses elucidated some additional aspects regarding the impact of exposure misclassification. When classification to the 'exposed' category was restricted to individuals with a compliance level greater than or equal to 75%, the hazard ratio was higher in both strata than in the original analysis (where exposure was defined as compliance greater than 0%) (Table 6.8). The hazard ratios became smaller as the compliance threshold used to define exposure was lowered. A similar trend was identified previously using increasing levels of dose to define exposure.¹⁰⁸ If we assume that compliance and dose are associated with risk of outcome (i.e. higher compliance among individuals with worse health), then these results are rational: periods of lower compliance were event-free, and the period of higher compliance were more strongly associated with events, thus inflating the hazard ratio.

7.3.2.3 Diagnostic Misclassification

Cohort entry was defined as the time of discharge from a first hospitalization for COPD, as captured by the first or second responsible diagnosis in the hospital discharge record. This choice was made because hospitalizations for COPD are not always captured in the first diagnostic field. This choice of including individuals with a first or second responsible diagnosis of COPD may have included resulted in the inclusion of individuals who were hospitalized for reasons unrelated to COPD. The top first- and second- responsible diagnoses for the index admissions are listed in Table 1 of Appendix 1. In the primary diagnostic field, most of the primary diagnostic codes were pulmonary in nature, however, cardiac diseases (heart failure, cardiac dysrhythmias, and acute myocardial infarction) ranked among the top ten (accounting

for 9.5% of the subjects). A sensitivity analysis including only first hospitalizations for which the primary diagnostic code was for COPD yielded an estimate of 0.92 (95% CI: 0.84-1.00) in the COPD-alone stratum (Table 6.9). The asthmatic subgroup was not found to be statistically different from the COPD group; however, the point estimate of effectiveness in the asthmatic group ($0.92 \times 0.92 = 0.846$) is in the same direction and of a similar magnitude as in the original analysis (Table 6.8). The lower hazard ratio found in the COPD-alone stratum suggests that differential diagnostic misclassification may have occurred in the original analysis, leading to an overestimate of the hazard ratio. This is corroborated by the fact that there were proportionally fewer events (39.0%) and more unexposed individuals (63.1%) in the group of individuals with COPD as a second diagnostic code than in those with COPD as the first (43.0% and 50.0% respectively).

Diagnostic misclassification may also have occurred with respect to the definition of asthma. In this study, individuals were categorized as having coexisting asthma if there was any record of a specialist visit or hospitalization for asthma prior to the index hospitalization. This definition resulted in 14.4% of the study sample to be considered to have co-existing asthma. This is consistent with the estimates that 10%-20% of the COPD population has co-existing asthma, but differs from the study by Vollmer *et al*¹³, where 42.5% of the study sample was categorized as having co-existing asthma, according to any prior health care utilization for which asthma was listed as the diagnostic code. These authors acknowledged that this was likely to include individuals who did not have truly co-existing disease, but rather individuals whose diagnosis of asthma was re-assessed and found to be truly COPD, and vice versa. The more stringent criteria requiring a specialist visit or hospital encounter for asthma categorization likely produced a more representative sample of individuals who were truly afflicted with both diseases. In a sensitivity analysis, the definition of asthma was broadened to match the definition used by Vollmer *et al*. Using this definition, 39.2% of the COPD population was categorized as having asthma. The point estimate of hazard of death or re-hospitalization

associated with ICS use in the coexisting COPD and asthma stratum was similar to that in the original analysis: ($HR = 1.06 \times 0.77 = 0.82$) (Table 6.9). The point estimate in the COPD-alone stratum increased when potential asthmatics were re-categorized to the asthma-plus COPD stratum. This finding suggests that any diagnostic misclassification in the study made with respect to categorization of asthma would not change the point estimate of effectiveness in the concomitant asthma plus COPD stratum, nor would it change the conclusion that ICS has greater effectiveness in this stratum, compared with the COPD alone stratum; however, it does suggest that the estimate in the COPD-only stratum would be slightly higher.

7.3.2.4 Outcome misclassification

Sensitivity analyses of the choice of outcome measures investigated the impact of changing the end-point from all-cause mortality or re-hospitalization to permutations of all-cause mortality, pulmonary-specific mortality and re-hospitalization (Table 6.9). While all-cause mortality is not subject to misclassification, the cause of death and cause of hospitalization may have been misclassified differentially between exposure categories.

Changing the outcome to pulmonary-specific mortality or re-hospitalization resulted in a hazard ratio of 1.47 (95% CI: 1.37-1.58), which suggests a harmful effect of ICS, and is higher than our original estimate of 0.99 in the COPD-only stratum. In the asthma subpopulation, the estimate also suggests a harmful effect ($HR = 1.47 \times 0.86 = 1.26$).

A higher hazard ratio associated with cause-specific death compared with all-cause mortality was also detected in the sensitivity analysis using death alone as an outcome (ignoring hospitalizations) (Table 6.9). This inflated risk that resulted from changing all-cause mortality to cause-specific mortality may be explained by a proportionally higher frequency of cause-specific deaths among the exposed compared with the unexposed. 39% of the deaths in the exposed category were respiratory-related, whereas only 24% of the unexposed category died due to respiratory-related causes. This difference in proportional cause-specific deaths may be due to poor sensitivity in recording respiratory-related deaths,¹⁸⁶⁻¹⁸⁸ and may

occur differentially if individuals who are taking COPD medication at the time of death are more likely to have their cause of death attributed to COPD than non-medicated individuals. If this difference in cause-specific mortality is indeed due to misclassification, the choice of using an all-cause mortality end-point rather than cause-specific mortality in measuring effectiveness of ICS in COPD is justified.

7.3.3 Confounding

This study employed techniques to identify confounders, and to reduce the degree of confounding by severity, protopathic bias (and reverse protopathic bias).

To be considered a confounder, a variable must be associated with the drug exposure and the outcome of interest, without being in the causal pathway between the drug exposure and the outcome.¹²² Using variables that we suspected, *a priori*, to be associated with ICS exposure, we measured the association between variables and exposure to ICS in our logistic regression analysis. The odds ratios presented in Table 6.5 suggest that sex, history of co-existing asthma, and presence of severe comorbid conditions (ACG®) were associated with exposure to ICS in the ninety days following discharge from hospitalization. The direction of these associations were consistent with the anticipated directions based on the literature, presented in Table 3.1. Although we did not detect significant associations in our analysis between ICS initiation and age, prior use of LABA, prior use of anticholinergics, or Charlson comorbidity index, data from the literature suggested that they are associated, and furthermore, these factors have been associated with death and hospitalizations in previous studies (Table 3.1). Therefore, we considered these variables to be potential confounders of the association between ICS exposure and outcome, and adjusted for them in the Cox models.

Disease severity was not explicitly captured in the administrative health databases. However, to reduce the amount of bias imposed from unbalanced severity levels across categories, we restricted the definition of cohort entry to individuals who had been admitted to hospital exactly one time with the responsible diagnostic code of COPD, since severity is

associated with frequency of acute exacerbations and hospitalizations.²⁵ We assumed that the change in severity over the median 14.4 of months of follow-up from the index hospitalization was similar across individuals, and therefore that the severity would be similar across individuals at any time during follow-up, except for periods of symptom exacerbation experienced by individuals with COPD.

Confounding by severity was likely minimized as a result of the study time frame. Between 1992 and 2003 there were no formal guidelines on when ICS should be administered with respect to disease severity.⁸⁴ The recommendation that ICS be restricted to those with moderate-to-severe COPD who experience frequent exacerbations was first published in the 2003 CTS guidelines;²⁰ prior to this, guidelines were unclear regarding ICS use in COPD management. The dataset used in this study captured data between 1996 and 2001, in the absence of recommendations to prescribe ICS to individuals with advanced disease, suggesting that ICS may not have been prescribed according to disease severity to the extent that it would be following publication of the guidelines. A study of Belgian physicians conducted in 2002 supports the conjecture that ICS was not being prescribed exclusively to individuals with advanced disease: 59.4% of general practitioners initiated ICS in *all* patients presenting with COPD, rather than initiating according to severity (32.8% and 7.3% initiated ICS “sometimes” or “in specific cases”, respectively, while 0.5% reported that they never initiated ICS).¹⁸⁹

As discussed in section 3.1.3, because ICS are not intended for use as relief medication, it is unlikely that protopathic bias affected the results (resulting in an overestimate of risk among the exposed). Of the individuals who were ever exposed to ICS, 89% had filled their first ICS prescription either prior to, or within one month of discharge from hospital (Table 6.3). Therefore, the protopathic bias would likely only affect the remaining 11% of ICS initiators. Other observational studies have not found strong indication of protopathic bias in ICS use.¹⁰⁸

On the contrary, reverse protopathic bias may have affected our results. The exposure field was coded such that individuals may 'discontinue' ICS use. This approach differs from other studies of ICS effectiveness, but is consistent with patterns of ICS use described in the literature, where between 47.6% and 67.0% of COPD patients were found to discontinue ICS use within 1 year.¹⁹⁰ It is known that patients experience withdrawal effects from systemic steroids, and some evidence that this is the case with ICS.¹⁹¹ In studies using administrative data, it is impossible to determine the direction of causation in a scenario where an individual discontinued ICS shortly before an event: the individual may have discontinued ICS because of his or her deterioration, or the individuals' health may have deteriorated because of ICS discontinuation. For this reason, we did not take any measures to correct for potential 'reverse protopathic bias' as we may be covering up important effects of ICS discontinuation.

It is likely that there are additional unknown factors that are associated with both the exposure and the outcome and that are not in the causal pathway; however, the known confounders were controlled for to the extent possible using administrative data, using methods of restriction in the design phase and adjustment in the analysis phase.

7.4 External validity

The sample population was all individuals aged greater than 45 years in BC registered with MSP who experienced a first hospitalization for COPD between 1996 and 2001, categorized by prior history of asthma, and by use of ICS (beclomethasone dipropionate, budesonide, fluticasone propionate, or triamcinolone). The target population, to whom the results are generalizable, are older individuals who have moderate COPD and have experienced at least one acute exacerbation.

The mean age of the study sample was 73.7 years (SD 10.0 years), and there were proportionally more men than women. Because COPD currently tends to be under-diagnosed among women,¹⁶⁸ in coming years, the target population may comprise more women. Because

the results were adjusted for sex, and there is sufficient representation of women in the data set, this should not affect their generalizability.

The operationalized definition of coexisting asthma and COPD used in this study is thought to represent the true population of individuals afflicted with both diseases because of the requirement that the physician visit be for a specialist. Therefore, we expect that these results are generalizable to the population of individuals who truly have both diseases, rather than to a population of individuals with COPD who were mis-diagnosed with asthma, or vice versa.

7.5 Future work

The current study estimated effectiveness of ICS using data between 1996 and 2001 among individuals with COPD alone and individuals with concomitant COPD and asthma. A complement to the current study would be to include a third population: individuals with asthma alone. This would allow comparison of effectiveness estimates in the group with concomitant disease with the effectiveness estimates in groups with each disease on its own. This would allow for comparison to see if individuals with concomitant asthma and COPD respond to ICS in a way that is more “asthma-like” or “COPD-like”.

Additional studies could be done to identify other sub-populations that may respond well to ICS, based on clinical measures such as FEV₁ reversibility and airway hyperresponsiveness, other exposures, such as smoking status, race, or presence of other comorbid conditions. These studies would contribute to a greater understanding of ICS mechanisms in COPD, and would provide a targeted treatment strategy for practitioners.

The drugs used during the study period were primarily delivered as monotherapy. Only one brand of drug existed that delivered a combined dose of ICS and LABA together, and it represented only 1.5% (885) of all ICS dispensations. The combined ICS/LABA therapy is currently the recommended delivery of ICS for the treatment of individuals with COPD,¹¹ Future studies could be conducted comparing ICS/LABA combination therapy with ICS monotherapy.

Germaine to the study of ICS in COPD is the issue of adverse events. Recent publications suggest that there is an increased risk of pneumonia among individuals using ICS.⁹⁴ Investigation of this issue was outside the scope of the current study, however, an observational study design could lend itself well to answering the question of whether ICS is associated with a greater risk of pneumonia.

7.6 Concluding statements

Prior to this study, the effectiveness of ICS had not been studied in a population of individuals with concomitant COPD and asthma. Currently, very little is understood regarding the diagnosis, management and treatment effectiveness in this subpopulation. Our findings suggest that ICS is more effective in this population than among individuals with COPD alone, and that use of ICS significantly reduces the hazard of death and hospitalization associated with the combined presence of asthma and COPD. Given the uncertain effectiveness of ICS in COPD, this finding suggests that there is at least one subpopulation of individuals afflicted with COPD that stands to benefit from ICS. Further research is needed to identify additional subpopulations that may benefit from treatment in the highly heterogeneous population of individuals afflicted with COPD. This will allow for targeted treatment of the disease, allowing for improved outcomes and a potential reduction of the considerable burden of illness attributable to death and hospitalization.

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Appendix 1: Additional Tables

Table 1a First most responsible ICD-9 codes for index hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

Diagnosis 1	Description	COPD without Asthma		COPD with Asthma		All Subjects	
		n	%	n	%	n	%
496	Chronic airway obstruction, not elsewhere classified	2821	23.3	552	27.0	3373	23.8
491	Chronic bronchitis	1780	14.7	366	17.9	2146	15.2
486	Pneumonia	1386	11.4	218	10.7	1604	11.3
428	Heart Failure	783	6.5	89	4.4	872	6.2
492	Emphysema	482	4.0	67	3.3	549	3.9
466	Acute bronchitis and bronchiolitis	266	2.2	44	2.2	310	2.2
427	Cardiac dysrhythmias	226	1.9	39	1.9	265	1.9
786	Symptoms involving respiratory system and other chest symptoms	202	1.7	36	1.8	238	1.7
482	Other bacterial pneumonia	182	1.5	19	0.9	201	1.4
410	Acute MI	179	1.5	21	1.0	200	1.4
	Other	3653	30.2	572	28.0	4225	29.9
	NA	152	1.3	18	0.9	170	1.2
	Total	12112	100.0	2041	100.0	14153	100.0

Table 1b Second most responsible ICD-9 codes for index hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

Diagnosis 2	Description	COPD without Asthma		COPD with Asthma		All Subjects	
		n	%	n	%	n	%
496	Chronic airway obstruction, not elsewhere classified	5596	46.2	825	40.4	6421	45.4
491	Chronic bronchitis	888	7.3	177	8.7	1065	7.5
492	Emphysema	649	5.4	68	3.3	717	5.1
428	Heart Failure	402	3.3	80	3.9	482	3.4
486	Pneumonia	311	2.6	40	2.0	351	2.5
	Other ill-defined and unknown causes - respiratory						
799	arrest?	203	1.7	34	1.7	237	1.7
401	Essential hypertension	206	1.7	30	1.5	236	1.7
427	Cardiac dysrhythmias	158	1.3	24	1.2	182	1.3
250	Diabetes	143	1.2	34	1.7	177	1.3
	Acute upper respiratory infections of multiple or						
465	unspecified sites	122	1.0	33	1.6	155	1.1
	Other	2088	17.2	380	18.6	2468	17.4
	NA	1346	11.1	316	15.5	1662	11.7
	Total	12112	100.0	2041	100.0	14153	100.0

Table 2: Dispensations of ICS, by DIN during follow-up from a first hospitalization for COPD in British Columbia (BC) between 1996 and 2001.

DIN	NAME	COPD without asthma		COPD with asthma		All Subjects	
		n	%	n	%	n	%
2213613	FLOVENT INHALERS - AEM INH-ORL 250MCG/AEM	7483	14.7%	2402	15.2%	9885	14.8%
851752	PULMICORT TURBUHALER 200 MCG/DOSE	7216	14.2%	2582	16.3%	9798	14.7%
2215055	BECLOFORTE INHALER - AEM INH 250MCG/AEM	6749	13.3%	2246	14.2%	8995	13.5%
2213605	FLOVENT INHALERS - AEM INH-ORL 125MCG/AEM	7528	14.8%	1438	9.1%	8966	13.4%
	ALTI-BECLOMETHASONE DIPROPIONATE INHALER						
872334	50MCG/MD	6484	12.7%	1211	7.6%	7695	11.5%
851760	PULMICORT TURBUHALER 400 MCG/DOSE	2519	5.0%	1254	7.9%	3773	5.7%
897353	BECLOFORTE 250MCG/AEM	2644	5.2%	838	5.3%	3482	5.2%
1978926	PULMICORT NEBUAMP 0.5 MG/ML	1890	3.7%	1064	6.7%	2954	4.4%
2174774	FLOVENT INHALERS - AEM INH-ORL 250MCG/ACTUATION	1872	3.7%	873	5.5%	2745	4.1%
1978918	PULMICORT NEBUAMP 0.25 MG/ML	1868	3.7%	586	3.7%	2454	3.7%
2174766	FLOVENT INHALERS - AEM INH-ORL 250MCG/ACTUATION	1603	3.2%	337	2.1%	1940	2.9%
2237246	FLOVENT DISKUS	494	1.0%	160	1.0%	654	1.0%
374407	VANCERIL AEM 50MCG	536	1.1%	114	0.7%	650	1.0%
2240836	ADVAIR 250 DISKUS	395	0.8%	143	0.9%	538	0.8%
2237247	FLOVENT DISKUS	167	0.3%	163	1.0%	330	0.5%
2240837	ADVAIR 500 DISKUS	159	0.3%	159	1.0%	318	0.5%
852074	PULMICORT TURBUHALER 100 MCG/DOSE	243	0.5%	25	0.2%	268	0.4%
2213591	FLOVENT INHALERS - AEM INH-ORL 50MCG/AEM	203	0.4%	32	0.2%	235	0.4%
2213729	BECLODISK - PWR INH 200MCG/BLISTER	113	0.2%	48	0.3%	161	0.2%
828548	BECLODISK PWR 200MCG/BLISTER	94	0.2%	13	0.1%	107	0.2%
2215047	BECLOVENT ROTACAPS - INH 200 MCG/CAP	83	0.2%	20	0.1%	103	0.2%
2229099	PULMICORT NEBUAMP 0.125 MG/ML	82	0.2%	11	0.1%	93	0.1%
1950002	BECLOVENT ROTACAPS - INH 200 MCG	68	0.1%	18	0.1%	86	0.1%
2174758	FLOVENT INHALERS - AEM INH-ORL 50MCG/ACTUATION	77	0.2%	6	0.0%	83	0.1%
790486	BRONALIDE INHAL 250MCG/AEM	43	0.1%	31	0.2%	74	0.1%
2237245	FLOVENT DISKUS	56	0.1%	6	0.0%	62	0.1%
1949993	BECLOVENT ROTACAPS 100 MCG	28	0.1%	29	0.2%	57	0.1%
2216531	BECLOVENT - AEM 50MCG/AEM	29	0.1%	10	0.1%	39	0.1%

DIN	NAME	COPD without asthma		COPD with asthma		All Subjects	
		n	%	n	%	n	%
828521	BECLODISK - PWR 100MCG/BLISTER	34	0.1%	2	0.0%	36	0.1%
2240835	ADVAIR 100 DISKUS	29	0.1%	0	0.0%	29	0.0%
768707	BECLOFORT INHALER	16	0.0%	4	0.0%	20	0.0%
893633	BECLOVENT AEM 50MCG/AEM	14	0.0%	5	0.0%	19	0.0%
2213583	FLOVENT INHALERS - AEM INH-ORL 25MCG/AEM	18	0.0%	1	0.0%	19	0.0%
634549	PULMICORT INHALER 200MCG	12	0.0%	3	0.0%	15	0.0%
2213710	BECLODISK - PWR INH 100MCG/BLISTER	14	0.0%	0	0.0%	14	0.0%
1926314	AZMACORT	6	0.0%	1	0.0%	7	0.0%
2174731	FLOVENT INHALERS - AEM INH-ORL 25MCG/ACTUATION	6	0.0%	1	0.0%	7	0.0%
2242030	QVAR 100 MCG	4	0.0%	1	0.0%	5	0.0%
2215039	BECLOVENT ROTACAPS - INH 100 MCG/CAPSULE	0	0.0%	3	0.0%	3	0.0%
545333	BECLOVENT ROTACAPS 200MCG	2	0.0%	0	0.0%	2	0.0%
2242029	QVAR 50 MCG	0	0.0%	1	0.0%	1	0.0%
Total		50881		15841		66722	

Table 3a Cox proportional hazards model using cause-specific deaths and hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001.

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.49	1.38	1.60
Male (vs. Female)	1.09	1.02	1.16
Age (vs 45-54)			
55-64	1.48	1.21	1.81
65-74	1.79	1.48	2.16
75-84	2.08	1.73	2.51
85-94	2.29	1.87	2.80
95-104	2.09	1.25	3.47
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.06	0.99	1.13
Charlson Index = 2	0.94	0.84	1.06
Charlson Index = 3	0.87	0.60	1.28
ACG = 5070 or 4940 (vs other)	1.39	1.27	1.51
Prior Use of LABA	1.03	0.92	1.16
Prior use of Anticholinergics	1.82	1.70	1.94
Asthma * ICS interaction term (vs. no Asthma)	0.89	0.70	1.13

Table 3b Cox proportional hazards model measuring time to re-hospitalization among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 (death is censored)

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.67	1.54	1.80
Male (vs. Female)	1.06	0.99	1.13
Age (vs 45-54)			
55-64	1.42	1.16	1.75
65-74	1.72	1.42	2.08
75-84	1.93	1.59	2.32
85-94	1.89	1.53	2.32
95-104	1.28	0.67	2.45
Length of Stay	1.01	1.00	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.06	0.99	1.14
Charlson Index = 2	0.93	0.82	1.06
Charlson Index = 3	0.93	0.63	1.39
ACG = 5070 or 4940 (vs other)	1.38	1.26	1.51
Prior Use of LABA	1.02	0.90	1.15
Prior use of Anticholinergics	1.78	1.66	1.91
Asthma * ICS interaction term (vs. no Asthma)	0.95	0.72	1.24

Table 3c Cox proportional hazards model measuring time to death (all-cause) among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	0.42	0.38	0.45
Male (vs. Female)	1.39	1.29	1.50
Age (vs 45-54)			
55-64	1.51	1.13	2.00
65-74	2.46	1.90	3.20
75-84	3.61	2.78	4.67
85-94	5.03	3.85	6.57
95-104	7.83	5.09	12.05
Length of Stay	1.01	1.01	1.02
Comorbidity Index (vs 0)			
Charlson Index = 1	1.41	1.30	1.53
Charlson Index = 2	2.07	1.85	2.32
Charlson Index = 3	2.11	1.57	2.84
ACG = 5070 or 4940 (vs other)	1.77	1.62	1.92
Prior Use of LABA	1.10	0.93	1.31
Prior use of Anticholinergics	1.52	1.40	1.64
Asthma * ICS interaction term (vs. no Asthma)	0.58	0.47	0.73

Table 3d Cox proportional hazards model measuring time to death (respiratory related) among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	0.58	0.50	0.68
Male (vs. Female)	1.40	1.22	1.60
Age (vs 45-54)			
55-64	2.03	1.07	3.87
65-74	3.24	1.77	5.94
75-84	5.39	2.96	9.81
85-94	7.87	4.27	14.51
95-104	10.86	4.48	26.32
Length of Stay	1.02	1.02	1.03
Comorbidity Index (vs 0)			
Charlson Index = 1	1.13	0.99	1.30
Charlson Index = 2	0.87	0.67	1.14
Charlson Index = 3	0.67	0.28	1.62
ACG = 5070 or 4940 (vs other)	1.28	1.08	1.53
Prior Use of LABA	1.55	1.21	1.98
Prior use of Anticholinergics	2.43	2.11	2.80
Asthma * ICS interaction term (vs. no Asthma)	0.41	0.28	0.61

Table 3e Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – compliance less than 75% was considered unexposed

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.69	1.57	1.81
Male (vs. Female)	1.17	1.11	1.23
Age (vs 45-54)			
55-64	1.40	1.18	1.67
65-74	1.80	1.53	2.11
75-84	2.23	1.90	2.61
85-94	2.74	2.31	3.25
95-104	3.35	2.34	4.80
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.10	1.24
Charlson Index = 2	1.40	1.28	1.53
Charlson Index = 3	1.32	1.02	1.73
ACG = 5070 or 4940 (vs other)	1.61	1.51	1.72
Prior Use of LABA	0.97	0.87	1.08
Prior use of Anticholinergics	1.49	1.41	1.57
Asthma * ICS interaction term (vs. no Asthma)	1.05	0.91	1.22

Table 3f Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – compliance less than 50% was considered unexposed

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.33	1.25	1.42
Male (vs. Female)	1.17	1.11	1.23
Age (vs 45-54)			
55-64	1.40	1.18	1.67
65-74	1.81	1.54	2.13
75-84	2.23	1.90	2.62
85-94	2.73	2.30	3.23
95-104	3.39	2.37	4.84
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.11	1.24
Charlson Index = 2	1.40	1.28	1.53
Charlson Index = 3	1.35	1.03	1.75
ACG = 5070 or 4940 (vs other)	1.62	1.51	1.73
Prior Use of LABA	0.97	0.87	1.08
Prior use of Anticholinergics	1.51	1.42	1.59
Asthma * ICS interaction term (vs. no Asthma)	1.20	1.03	1.39

Table 3g Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – compliance less than 25% was considered unexposed

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.17	1.10	1.24
Male (vs. Female)	1.16	1.10	1.23
Age (vs 45-54)			
55-64	1.41	1.19	1.68
65-74	1.84	1.57	2.17
75-84	2.26	1.93	2.65
85-94	2.75	2.32	3.26
95-104	3.35	2.34	4.80
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.11	1.24
Charlson Index = 2	1.39	1.27	1.52
Charlson Index = 3	1.32	1.01	1.72
ACG = 5070 or 4940 (vs other)	1.61	1.51	1.72
Prior Use of LABA	0.99	0.89	1.10
Prior use of Anticholinergics	1.55	1.46	1.64
Asthma * ICS interaction term (vs. no Asthma)	1.09	0.93	1.28

Table 3g Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – compliance less than 10% was considered unexposed

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.07	1.01	1.14
Male (vs. Female)	1.17	1.11	1.23
Age (vs 45-54)			
55-64	1.42	1.19	1.69
65-74	1.86	1.58	2.19
75-84	2.29	1.95	2.68
85-94	2.77	2.33	3.28
95-104	3.36	2.35	4.81
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.11	1.24
Charlson Index = 2	1.38	1.26	1.51
Charlson Index = 3	1.31	1.01	1.71
ACG = 5070 or 4940 (vs other)	1.60	1.50	1.71
Prior Use of LABA	1.01	0.91	1.13
Prior use of Anticholinergics	1.59	1.50	1.68
Asthma * ICS interaction term (vs. no Asthma)	0.94	0.79	1.12

Table 3h Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – individuals were categorized as exposed between time of hospital discharge and first ICS fill.

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	0.80	0.75	0.85
Male (vs. Female)	1.15	1.09	1.21
Age (vs 45-54)			
55-64	1.40	1.17	1.66
65-74	1.86	1.58	2.18
75-84	2.28	1.94	2.67
85-94	2.70	2.28	3.20
95-104	3.05	2.13	4.36
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.10	1.24
Charlson Index = 2	1.36	1.25	1.49
Charlson Index = 3	2.02	1.69	2.41
ACG = 5070 or 4940 (vs other)	1.52	1.42	1.63
Prior Use of LABA	1.06	0.96	1.18
Prior use of Anticholinergics	1.71	1.62	1.81
Asthma * ICS interaction term (vs. no Asthma)	0.85	0.71	1.02

Table 3i Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – time-fixed exposure

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	0.88	0.83	0.93
Male (vs. Female)	1.15	1.09	1.21
Age (vs 45-54)			
55-64	1.40	1.18	1.66
65-74	1.85	1.58	2.17
75-84	2.27	1.94	2.66
85-94	2.73	2.30	3.23
95-104	3.17	2.22	4.53
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.11	1.24
Charlson Index = 2	1.37	1.26	1.50
Charlson Index = 3	2.04	1.71	2.43
ACG = 5070 or 4940 (vs other)	1.53	1.43	1.64
Prior Use of LABA	1.05	0.94	1.16
Prior use of Anticholinergics	1.67	1.58	1.77
Asthma * ICS interaction term (vs. no Asthma)	0.97	0.75	1.25

Table 3j Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – – asthma was coded as prior history of any ICD-9 code of 493 – not limited to specialists

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	1.07	0.99	1.15
Male (vs. Female)	1.17	1.11	1.24
Age (vs 45-54)			
55-64	1.42	1.19	1.69
65-74	1.87	1.59	2.20
75-84	2.30	1.96	2.70
85-94	2.75	2.32	3.26
95-104	3.28	2.29	4.69
Length of Stay	1.01	1.01	1.01
Comorbidity Index (vs 0)			
Charlson Index = 1	1.17	1.11	1.24
Charlson Index = 2	1.38	1.26	1.51
Charlson Index = 3	1.30	1.00	1.69
ACG = 5070 or 4940 (vs other)	1.59	1.49	1.70
Prior Use of LABA	1.02	0.92	1.13
Prior use of Anticholinergics	1.59	1.50	1.69
Asthma * ICS interaction term (vs. no Asthma)	0.76	0.68	0.85

Table 3k Cox proportional hazards model measuring time to all-cause death or hospitalizations among individuals with COPD following a first hospitalization in British Columbia (BC) between 1996 and 2001 – cohort was restricted to individuals with a first diagnosis of 491, 492, 496.

	HR	lower 95% CI	upper 95% CI
Exposure to ICS	0.92	0.84	1.00
Male (vs. Female)	1.21	1.12	1.31
Age (vs 45-54)			
55-64	1.57	1.23	2.02
65-74	2.04	1.61	2.57
75-84	2.35	1.87	2.95
85-94	2.65	2.07	3.39
95-104	1.71	0.82	3.54
Length of Stay	1.01	1.01	1.02
Comorbidity Index (vs 0)			
Charlson Index = 1	1.04	0.95	1.13
Charlson Index = 2	1.07	0.93	1.24
Charlson Index = 3	0.83	0.53	1.32
ACG = 5070 or 4940 (vs other)	1.60	1.44	1.79
Prior Use of LABA	1.09	0.94	1.26
Prior use of Anticholinergics	1.67	1.54	1.82
Asthma * ICS interaction term (vs. no Asthma)	0.92	0.70	1.21

Appendix 2: Ethics approval

The University of British Columbia
Office of Research Services and Administration
Behavioural Research Ethics Board

Certificate of Approval

PRINCIPAL INVESTIGATOR Carleton, B.	DEPARTMENT Pharmaceutical Sciences	NUMBER B04-0927	
INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT UBC Campus ,			
CO-INVESTIGATORS: Camp, Patricia, Medicine; Dean, Charmaine, ; Fitzgerald, Mark, Medicine; Goring, Sarah, Health Care/Epidemiology; Levy, Adrian, Health Care/Epidemiology; Levy, Robert, Medicine; Maclure, Malcolm, Pharmacology/Therapeutics; Marra, Carlo, Pharmaceutical Sciences			
SPONSORING AGENCIES Canadian Institutes of Health Research			
TITLE: Modelling Trends and Regional Variations in Asthma Medication and Health Service Utilization to Improve Care			
APPROVAL DATE 06-03-02 <small>(yr/mo/day)</small>	TERM (YEARS) 1	AMENDMENT: Aug. 9, 2006, Co-PIs / Research method	AMENDMENT APPROVED: AUG 16 2006
<p>CERTIFICATION:</p> <p>The request for continuing review of an amendment to the above-named project has been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.</p> <p style="text-align: center;"><i>[Signature]</i></p> <p style="text-align: center;"><i>Approved on behalf of the Behavioural Research Ethics Board</i> by one of the following: Dr. Peter Suedfeld, Chair, Dr. Jim Rupert, Associate Chair Dr. Arminee Kazanjian, Associate Chair</p> <p>This Certificate of Approval is valid for the above term provided there is no change in the experimental procedures</p>

PROVIDENCE HEALTH CARE
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Providence Health Care Institutional Certificate of Final Approval

Principal Investigator: B. Carleton	Department: Pharmaceutical Sciences	Reference Number: BREB H04-80927
Sponsoring Agencies: Canadian Institute of Health Research		
Project Title: Modelling Trends and Regional Variations In Asthma Medication and Health Service Utilization to Improve Care		
Date Ethical Approval: March 2, 2006	Date Institutional Approval: MAR 02 2007	
<p>The UBC-BREB Research Ethics Board granted ethical approval for the above-referenced research project on the date stated above. I am now pleased to inform you that all necessary hospital department/facilities approvals and institutional agreements/contracts are now in place and that you have permission to begin your research at Providence Health Care</p> <p style="text-align: center;"> Dr. Yvonne Lefebvre Vice President Research and Academic Affairs, Providence Health Care President, Providence Health Care Research Institute</p> <p style="text-align: center;"><u>March 2, 2007</u> Date</p>		

St. Paul's Hospital
Holy Family Hospital
Mount St. Joseph's Hospital
St. Vincent's Hospital-Brock Fahrni Pavilion
St. Vincent's Hospital-Langara
Youville Residence